
# Complexity-Generating Cascade Reactions

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# Abstract

The development of complexity-generating reactions for the synthesis of molecules containing multiple quaternary centres has the potential to provide access to new 3D templates for the pharmaceutical and agrochemical industries as well as the efficient synthesis of biologically active natural products and fragments thereof. This thesis describes the development of radical cascade methodologies for the synthesis of complex spiro[4.4]nonanes, containing three adjacent quaternary centres, from linear precursors.

**Chapter 1** provides an introduction. The ambitious cascade cyclisation reaction which forms the basis of the work in this thesis is discussed along with its potential use in the generation of 3D templates and for natural product synthesis. An introduction to 3D templates and cascade reactions forms the majority of this chapter.

Initial studies on a simplified cascade reaction using samarium diiodide forms the basis of **Chapter 2**.

In **Chapter 3**, an efficient synthesis of cyclisation precursors is described along with oxidative radical cyclisation of these 1,3-dicarbonyl compounds using manganese(III) triacetate and copper(II) salts. The synthesis of unusual spirocyclic molecules is reported.

In tandem with the radical cyclisations, anionic cyclisations were briefly investigated and are reported in **Chapter 4**.

**Chapter 5** details the development of a visible light-mediated radical cyclisation cascade. An atom-economical method has been developed to form complex spiro[4.4]nonanes, bearing three contiguous all-carbon quaternary centres, in an efficient manner from readily accessible starting materials.

Full experimental details are reported for compounds reported in the thesis as well as NMR and other spectroscopic data for the spirocycles and other key compounds.

# Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated and does not include any collaborative work.

This thesis has not been previously submitted for a degree, diploma or any other qualification at the University of Oxford or elsewhere.

Kilian Garrec

October 2018

In memory of my dear friend and colleague, Dr Erin Shepherd.

“End? No, the journey does not end here. Death is just another path, one that we all must take. The grey rain-curtain of this world rolls back, and all turns to silver glass, and then you see it. […] White shores, and beyond, a far green country under a swift sunrise.”

- Gandalf [i]

[i] Fictional character. From "The Lord of the Rings: The Return of the King" by J. R. R. Tolkien.

# Acknowledgements

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# Contents

# Selected abbreviations

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| ACCN | 1,1'-azobis(cyclohexanecarbonitrile) |
| AIBN | 2,2'-azobis(2-methylpropionitrile) |
| Ar | aryl |
| ATRA | atom-transfer radical addition |
| ATRC | atom-transfer radical cyclisation |
| aq | aqueous |
| ax | axial |
| Bn | benzyl |
| brsm | based on remaining starting material |
| Boc | *tert*-butyloxycarbonyl |
| $^{t}$Bu | *tert*-butyl |
| b.p. | boiling point |
| CAN | ceric ammonium nitrate |
| cat. | catalytic |
| CDI | carbonyldiimidazole |
| CFL | compact fluorescent lamp |
| conc. | concentrated |
| COSY | correlation spectroscopy |
| d | day(s) |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DHP | dihydropyran |
| DIBAl-H | diisobutylaluminium hydride |

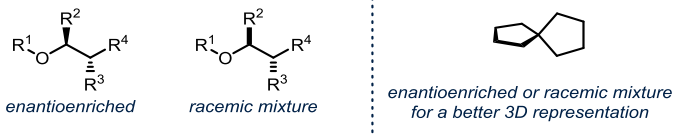
| | |
|---|---|
| DIPA | diisopropylamine |
| DIPEA | *N*,*N*-diisopropylethylamine, Hünig's base |
| DMF | dimethyl formamide |
| DMS | dimethyl sulphide |
| DMP | Dess–Martin periodinane |
| DMDO | dimethyldioxirane |
| DMSO | dimethylsulfoxide |
| *d.e*. | diastereomeric excess |
| *d.r*. | diastereomeric ratio |
| eq. | equivalent; or equatorial |
| ESI | electrospray ionisation |
| *e.e*. | enantiomeric excess |
| *e.r*. | enantiomeric ratio |
| FC | flash chromatography |
| FPT | freeze-pump-thaw |
| GC-MS | gas chromatography–mass spectrometry |
| h | hour(s) |
| HMBC | heteronuclear multiple bond correlation spectroscopy |
| HMDS | bis(trimethylsilyl)amine |
| HMPA | hexamethylphosphoramide |
| HRMS | high resolution mass spectrometry |
| HPLC | high-performance liquid chromatography |
| HSQC | heteronuclear single quantum coherence spectroscopy |
| Hz | Hertz |
| IBX | 2-iodoxybenzoic acid |
| IPA | isopropyl alcohol |

| | |
|---|---|
| IR | infrared |
| IS | internal standard |
| LDA | lithium diisopropylamide |
| LG | leaving group |
| *m*-CPBA | *meta*-chloroperbenzoic acid |
| MS | mass spectroscopy, molecular sieves |
| min | minute(s) |
| m.p. | melting point |
| Ms | methanesulfonyl |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |
| NIS | *N*-iodosuccinimide |
| NMI | 4-methylimidazole |
| NOS | *N*-hydroxysuccinimide |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| NOESY | nuclear Overhauser effect spectroscopy |
| PE | petroleum ether b.p. 30–40 °C or 40–60 °C |
| $PE_{30-40}$ | petroleum ether b.p. 30–40 °C |
| $PE_{40-60}$ | petroleum ether b.p. 40–60 °C |
| Pent. | pentane |
| PG | protecting group |
| Ph | phenyl |
| PMB | *para*-methoxybenzyl |
| Piv | pivaloyl |
| PPTS | pyridinium *p*-toluenesulfonate |

| | |
|---|---|
| PTSA | *p*-toluenesulfonic acid |
| *PTSC* | pre-transition state conformation |
| Py | pyridine |
| $R_f$ | retention factor |
| r.t. | room temperature |
| SAR | structure activity relationship |
| sat | saturated |
| SET | single electron transfer |
| TBDPS | *tert*-butyldiphenylsilyl |
| TES | triethylsilyl |
| Tf | trifluoromethanesulfonyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| THP | tetrahydropyranyl |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl or tetramethylsilane (in NMR context) |
| TOCSY | total correlation spectroscopy |
| TS | transition state |
| Ts | 4-methylbenzenesulfonyl |
| TTMSS | tris(trimethylsilyl)silane |
| UV | ultraviolet |

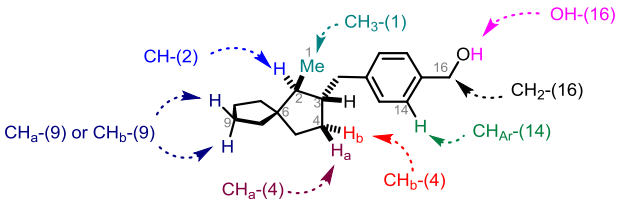
# Notes on convention

In this manuscript, solid and broken wedged bonds are used for a given enantiomer, solid and broken bold bonds are used for racemic mixtures. One notable exception is for their use in molecules drawn in 3D. In this case, wedged bonds can also be used to give a better view/understanding of the structure/conformation in space, whether racemic or enantioenriched molecules are depicted.[1]




Steps are described in schemes as **a.**, **b.**, **c.** *etc* meaning a quench and/or purification was/were performed after each step. Other identifiers such as i), ii), iii) *etc* indicates single-pot reactions.


Numbering of atoms on structures in not based on IUPAC numbering, but is usually chosen based on convenience and similarities with other compounds. CH-(X), $CH_2$-(X), $CH_3$-(X) or $CH_{Ar}$-(X) refer to the CH, $CH_2$, $CH_3$ or aromatic proton, respectively, of carbon labelled "X" on the structure. $CH_a$-(X) or $CH_b$-(X) refers to the diastereotopic proton labelled "$H_a$" or "$H_b$", respectively, on carbon labelled "X". If all protons on carbon "X" are labelled "H" then it was not determined which proton was $H_a$ and which one was $H_b$.




The reagent manganese(III) triacetate dihydrate has been used as its hydrated form during all our study but will be written as $Mn(OAc)_3$ in the text for simplicity (it will be written as the hydrated form in schemes as a reminder).

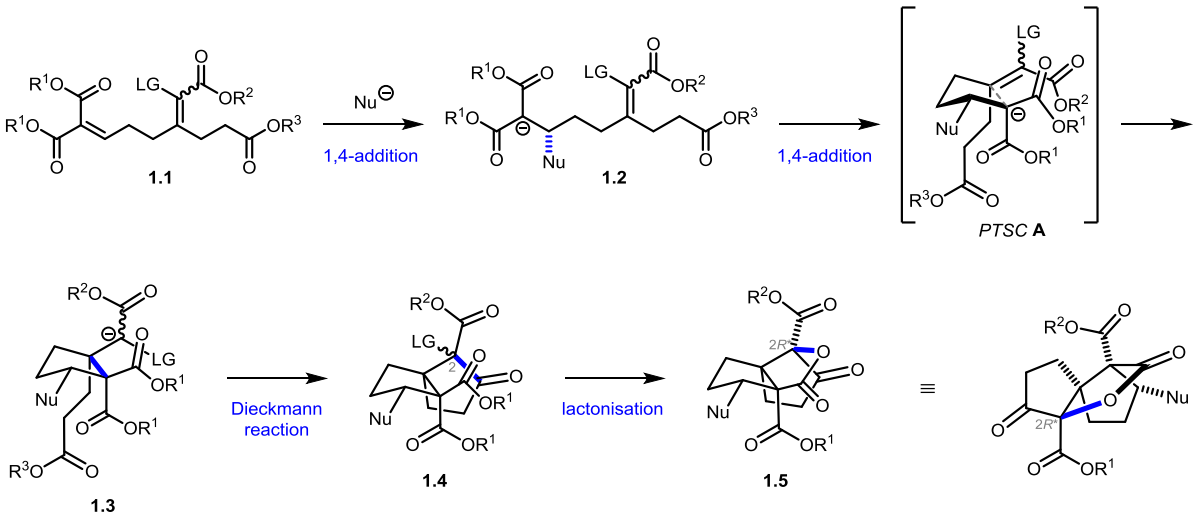
# 1 General Introduction

## 1.1 Project aims

As part of the EPSRC Centre for Doctoral Training Synthesis for Biology and Medicine (SBM CDT), two 16-week rotations were undertaken within the Burton group (discussed in **Section 2.1.1**) working on "Complexity-Generating Cascade Reactions" and within the Fletcher group (not discussed in this manuscript) working on "Asymmetric Chemistry with $Cp_2ZrMeCl$: A Methyl Nucleophile and New Opportunities with Benzynes and Cyclohexynes".[2] The Burton group project was then chosen as the substantive project.

### 1.1.1 Original project proposal

All-carbon quaternary centres are a central motif in a wide range of chemically and biologically important molecules,[3–6] but are still challenging to synthesise when adjacent to other stereocentres.[7–10] Previous work within the Burton group has allowed for the synthesis of bicyclic molecules with multiple adjacent quaternary centres using $Mn(OAc)_3$.[6,11] This complexity-generation oriented project aims to develop a methodology using an ambitious novel cascade reaction to readily assemble elaborate 3D templates with three adjacent all-carbon quaternary centres (**Scheme 1-1**).




**Scheme 1-1**: Proposed complexity-generating cascade reaction.

We propose that reacting a nucleophile (*e.g.* an organocuprate and suitable ligand) with compound **1.1** would lead to a chemoselective 1,4-addition onto the comparatively more electron deficient and sterically unencumbered Michael acceptor. The resulting anion **1.2** could undergo a subsequent 1,4-addition intramolecularly onto the second Michael acceptor *via* the proposed chair-like pre-transition state conformation (*PTSC*) **A**. Dieckmann cyclisation can occur between the anion and the pendant ester of **1.3** to provide a mixture of ester diastereomers at C(2) of ketone **1.4**. Depending on the choice of leaving group (LG), activation/heating of **1.4** could then trigger nucleophilic displacement of the leaving group by the adjacent ester to form the final (*R**)-C(2) γ-lactone **1.5**. This lactonisation would end the cascade and yield tricyclic compound **1.5**. This powerful sequence would generate three C-C bonds, one C-O bond, three rings, four stereocenters including three adjacent quaternary centres, all in a single pot. It is interesting to note that apart from the first stereoselective addition, all subsequent transformations are substrate controlled until **1.5** is obtained. We propose that similar reaction cascades could be envisaged using radical conditions or a combination of anionic and radical. In this case, the terminal ester ($CO_2R^3$) should be changed accordingly.

Product **1.5** could also be used in the total synthesis of complex natural products including terpene trilactones such as the ginkgolide family (discussed later, **Section 1.1.3**) or fragments thereof.[12]

The formation of quaternary centres is still a challenge for modern synthetic chemistry. A review by Overman and Quasdorf, postulated that out of the top 200 prescription drugs sold in the US in 2011, 12% contained at least one quaternary stereocentre.[13] However, they stated that “all of these drugs are derived from naturally occurring compounds (steroids, opioids or taxane diterpenoids), with a natural product precursor providing the quaternary stereocentres of the marketed drug in virtually every case”. This demonstrates one of the challenges facing the chemistry community to this day. In a medicinal chemistry context, substituents at quaternary centres are important for impacting the biological activity of drug candidates as they can influence the conformation of molecules to a certain extent, allowing specific interactions with a target protein.

### 1.1.2 **3D templates**

The pharmaceutical (and agrochemical) industry has realised the importance of increasing the complexity of their molecules to improve the biological activities on their targets.[14] The complexity usually increases with the size of the molecule which allows more specific interactions between a drug molecule and a host protein (for example, in a medicinal chemistry context).[15]

Drug candidates inspired by/coming from natural products are usually intrinsically more $sp^3$-rich than drug targets developed in a more traditional way (fragment based, for instance). The flatness of the latter can be explained by observing the well-established array of reactions enabling $sp^2$-$sp^2$ couplings such as Pd-catalysed cross-coupling reactions (Suzuki-Miyaura, Stille and more), which are used for quick, efficient and sometimes automated synthesis of libraries for screening.[16] For example in 2011, Roughley and Jordan described "The Medicinal Chemistry's Toolbox".[17] They found that more than 40% of carbon-carbon bond forming reactions during the small-scale synthesis of drug candidates were Suzuki cross-coupling (another 20% used other Pd-catalysed reactions). They explained that this prevalence and the robustness of the reaction could explain the reason that around 39% of the molecules surveyed contained at least one biaryl moiety.

The dominance of $sp^2$-rich molecules in this domain lead to the creation of the term "flatland" describing the flat nature of these molecules. Lovering and co-workers showed that increasing the saturation in drug candidates also increased the chances of success to turn them into drug molecules.[18] It has been observed during the past decades that the medicinal chemistry community is gradually stepping outside "flatland" and has switched to the synthesis of new $sp^3$-rich molecules to access unexplored chemical space.[18] Syntheses of 3D templates[19–21] and development of transition metal-catalysed $sp^2$-$sp^3$ and $sp^3$-$sp^3$ couplings,[22–25] for medicinal chemistry has therefore been growing and is still an important axis of research worldwide.

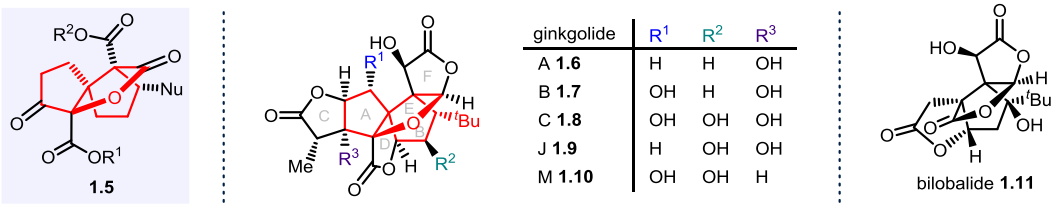
We propose that rigid spirocycles, such as **1.5**, would be an interesting 3D scaffold for the medicinal chemistry community. We could envisage the use of a variety of nucleophiles (Nu) to add to **1.1** to

obtain different analogues, while still possessing different handles (esters, lactone and ketone) for further derivatisation. Formation of other ring sizes could further expand the utility of the compounds. Changes of this sort would modify the angles at which the substituents are projecting into space enabling new interactions between the molecule and its host protein, for instance.

### 1.1.3 The ginkgolide family, overview and selected syntheses

#### 1.1.3.1 The ginkgolide family

Diterpenes from the ginkgolide family and bilobalide (**Scheme 1-2**, *middle* and *right*) have been isolated from the tree *Ginkgo biloba* L, predominantly from the root bark and the leaves.[26–33] It is the only tree remaining from the *Ginkgoaceae* family which appeared about 170 million years ago. This tree, sometimes referred as a "living fossil", produces interesting looking terpene trilactones such as the ginkgolides and bilobalide. For example, Ginkgolide B **1.7** possesses 20 carbons of which 11 are stereocentres. This molecule is characterised by a dense skeleton formed of six 5-membered rings with a central spiro[4.4]nonane core bearing an unprecedented *tert*-butyl group.




**Scheme 1-2**: Cyclisation product **1.5** (*left*), some members of the ginkgolide family with the tricyclic core of **1.5** highlighted (*middle*) and bilobalide **1.11** (*right*).

The structural complexity of this natural product, along with its diverse biological activity profile renders it a challenging synthetic target. We anticipate that product **1.5** could be used in the total synthesis of ginkgolide B **1.7**; or any other ginkgolide member of the family; or fragment/analogues of them for biological evaluation.

These molecules have been used for many millennia in Chinese traditional medicine and continue to be used currently all over the world. The Ginkgo biloba extract EGb 761 is produced from the leaves

of about 50 million trees grown for its production. This extract containing 6% of terpene trilactones (3.1% of ginkgolides and 2.9% of bilobalide) generated about half a billion dollars in sales in 2000.[34]

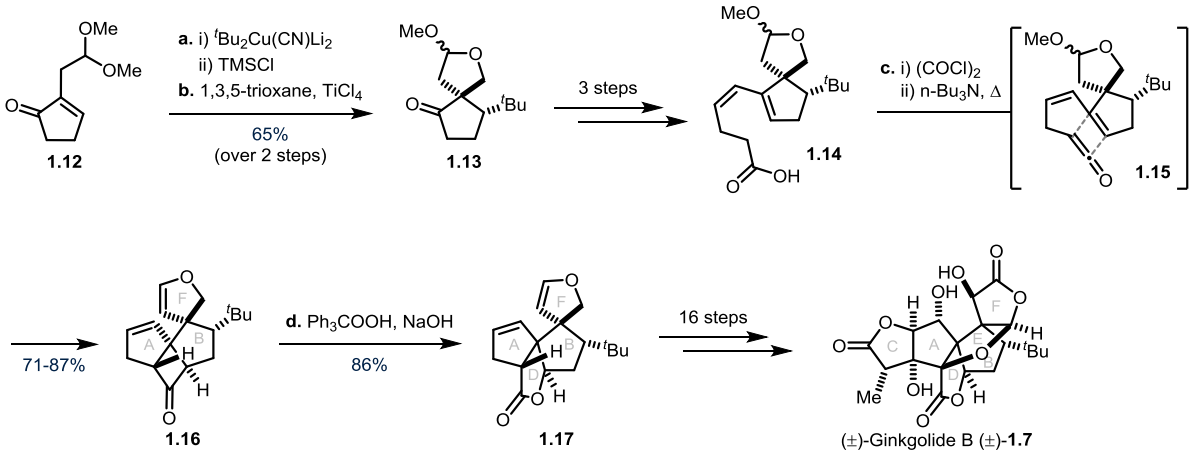
Extract EGb 761 has been studied in detail during the past five decades especially for its benefits for the central nervous system.[35–37] In particular, the ginkgolides were found to be antagonists of the platelet-activating factor (PAF) receptor, ginkgolide B **1.7** being the most potent of them.[38] Its use as a potential treatment of Alzheimer's disease has been the main focus of these studies. However, it is not clear which component(s) of the extract is responsible for the beneficial effects as, in comparison, very few studies have been carried out on isolated members of the ginkgolide family. Structure-activity relationship studies of the ginkgolides on the PAF receptor have been carried out using degradation products, elimination products or molecules derived directly from the natural products.[39] One notable exception is the use of derivatives synthesised by Corey and co-workers that gave insight into the pharmacophores of the family.[40]

#### 1.1.3.2 Selected syntheses

The ginkgolide structural motifs have attracted the attention of chemists.[39] Corey and co-workers synthesised racemic bilobalide (±)-**1.11** in 1987,[41,42] racemic ginkgolide A (±)-**1.6** and ginkgolide B (±)-**1.7** in 1988.[43,44] They also published an enantioselective route to a key intermediate in the total synthesis of ginkgolide B **1.7**.[45] Crimmins and co-workers published the formal synthesis and then total synthesis of racemic bilobalide (±)-**1.11** in 1992-93,[41,42] and racemic ginkgolide B (±)-**1.7** in 1999.[46–48] These syntheses have been previously reviewed,[39,49,50] therefore we will focus only on the methods used to introduce the *tert*-butyl group and form the spiro[4.4]nonane carbocyclic core of ginkgolide B **1.7**.

##### 1.1.3.2.1 Corey's synthesis of racemic ginkgolide B

The readily available α,β-unsaturated ketone **1.12** was doubly functionalised *via* 1,4-addition of cuprate $^{t}Bu_2Cu(CN)Li_2$, trapping as the TMS-enol ether and Mukayama aldol reaction sequence to form acetal **1.13** in 65% overall yield (**Scheme 1-3**, below).




**Scheme 1-3**: Corey and co-workers: Total synthesis of Ginkgolide B (±)-**1.7.**[43,44]

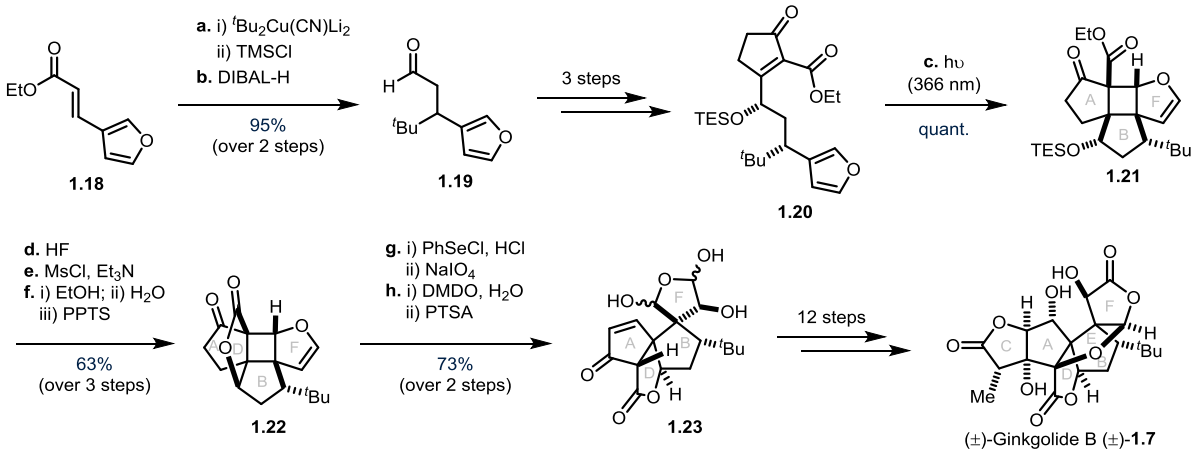
Reagents and conditions: (a) i) $^{t}Bu_2Cu(CN)Li_2$ (1.5 eq.), $Et_2O$, -78 °C, 50 min to -45 °C, 30 min; ii) TMSCl (5 eq.), $Et_3N$ (5 eq.), -45 °C, 45 min, then -10 °C, 5 min; (b) 1,3,5-trioxane (1.2 eq.), $TiCl_4$ (3.6 eq.), $CH_2Cl_2$, -78 °C, 2 h, then -45 °C, 1 h, 95% (over 2 steps); (c) oxalyl chloride (5 eq.), benzene, r.t., 2 h; ii) n-$Bu_3N$ (10 eq.), toluene, reflux, 3 h, 71-87%; (d) $Ph_3COOH$, 8:1 acetone/1 N $NaOH_{(aq)}$, -30 °C, 2 h, 86%.

The selectivity of the latter reaction is controlled by the bulky *tert*-butyl group leading to formation of only one isomer at the quaternary carbon, but as a mixture of anomeric isomers. Later in the synthesis, carboxylic acid **1.14** was treated with oxalyl chloride to give the corresponding acid chloride that formed ketene **1.15** upon treatment with tributylamine in toluene. Ketene-olefin [2+2] cycloaddition reaction on the least hindered side of the pendant cyclopentene occurred to efficiently form cyclobutane product **1.16** in an excellent 80% yield. This reaction elegantly set three stereocentres closing the A-ring and B-ring of the natural product in one step with concomitant elimination of the anomeric methoxy group. Careful choice of oxidant was required to trigger a Bayer-Villiger oxidation of the cyclobutanone into lactone **1.17** in the presence of two alkenes and to form the desired isomeric form of the γ-lactone. This highly advanced intermediate was carried forward in 16 additional steps to complete the total synthesis of the target natural product in racemic form.

#### 1.1.3.2.2 Crimmins' synthesis of racemic ginkgolide B

In Crimmins' synthesis, the crucial *tert*-butyl moiety was also introduced *via* 1,4-addition of cuprate $^{t}Bu_2Cu(CN)Li_2$ onto Michael acceptor **1.18** (obtained in one step by olefination from the

corresponding aldehyde) (**Scheme 1-4**, below). Reduction of the corresponding saturated ester with DIBAL-H gave aldehyde **1.19** in 95% yield over 2 steps.




**Scheme 1-4**: Crimmins and co-workers: Total synthesis of Ginkgolide B (±)-**1.7.**[46,48]

Reagents and conditions: (a) i) $^{t}Bu_2Cu(CN)Li_2$ (1.5 eq.), $Et_2O$, -78 °C to -45 °C, 2 h; ii) TMSCl (2 eq.), -45 °C to 0 °C, 30 min, quant.; (b) DIBAL-H (1.2 eq.), toluene, -78 °C, 15 min, 95%; (c) 450 W mercury lamp with uranium glass filter, hexane, 17 h, quant.; (d) $HF_{(aq)}$ (excess), MeCN, 0 °C to r.t., 1 h; (e) MsCl (1.2 eq.), $Et_3N$ (1.3 eq.), $CH_2Cl_2$, 0 °C, 45 min; (f) i) EtOH, 4 Å MS, EtOH, reflux, 26 h; ii) $H_2O$, reflux, 8 h; iii) concentrate, then PPTS, benzene, reflux (Dean-Stark apparatus), 16 h, 63% (3 steps); (g) i) PhSeCl (1 eq.), HCl-washed EtOAc, r.t., 1 h; ii) $NaHCO_3$ $NaIO_4$ (6 eq.), THF, $H_2O$, r.t., 2 h, 78%; (h) i) DMDO (1.5 eq.), acetone, $H_2O$, r.t., 8 h; ii) PTSA (0.2 eq.), r.t., 15 h, 94%.

Later in the synthesis, key precursor **1.20** was converted into tetracyclic compound **1.21** in quantitative yield upon exposure to light (366 nm). This intramolecular [2+2] photocycloaddition secured the configuration at three centres of the final natural product. Lactone **1.22** was formed by deprotection/mesyl activation of the TES-protected alcohol followed by cyclisation in ethanol at reflux with pyridinium *p*-toluenesulfonic acid in 63% overall yield. Ketone **1.22** was oxidised to the enone and then treatment with dimethyldioxirane and water followed by *p*-toluenesulfonic acid gave the ring-opened product **1.23** revealing the spirocyclic core of the final natural product in 76% (over 2 steps). Tetracyclic compound **1.23** was further elaborated in 12 steps to racemic ginkgolide B (±)-**1.7**.

The spirocycles of both routes were made using extremely elegant and efficient strategies. In both cases, the advanced starting materials were converted into complex products using powerful [2+2] cycloaddition reactions.

We expect that we could reach compounds of such complexity using the cascade reaction described in **Section 1.1.1**. This would offer an alternative method to make the core of the ginkgolides that could be used to access different analogues thereof. We therefore desired that the development of our study should take into consideration its applicability to the total synthesis of the ginkgolides (or related fragments) as far as possible.

## 1.2 Cascade reactions

### 1.2.1 Introduction to cascade reactions

The term “cascade” reaction, also known as “tandem” or “domino” reaction is, surprisingly, not defined by IUPAC. As a result, chemists tend to have slightly different definitions for this category of reactions. Our definition is the following: “a cascade reaction is a reaction during which multiple transformations/bonds are occurring in a single pot of constant conditions (*i.e*. not altered by the experimentalist). To satisfy the definition, these consecutive transformations also need to be dependent on the preceding one”. Cascade reaction should not be confused with one-pot reactions which involve a change in conditions in between the different transformations (*i.e.* addition of a reagent, change of temperature, exposure to light and more)

Performing cascade reactions has many benefits. For example, no purification in between transformations reduces drastically the non-chemical energy required, manpower required and also the amount of waste generated. The complexity generated compared to the starting material is usually greatly and quickly increased. The time saved by using such a strategy also enables shorter syntheses, hence speeding up research (drug discovery for example) progress.

The number of reviews concerning cascade reactions shows the appeal they hold for chemists.[51–60] The variety of transformations available to the chemist makes for an impressive number of combination possibilities for cascade reactions. Depending on which type of reaction is used, it is not always easy to sort them in distinct categories. They are sometimes organised in different categories

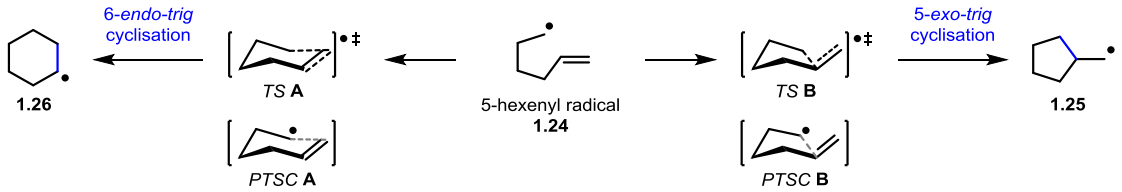
such as “nucleophilic, electrophilic, radical-mediated, pericyclic, and transition-metal-catalyzed process” based on the overall “major theme of the sequence”.[54] But sometimes also sorted using the types of the first transformation accomplished.[52,53]

Despite our project proposal being proposed as an anionic cascade, we mainly explored radical conditions to accomplish the desired type of cascade. As a consequence, the following section gives examples of intramolecular transformations that can be achieved using radical-only cascades, radical-anionic and radical-cationic cascade reactions. The first two reagents that will be discussed are tributyltin hydride (**Section 1.2.3.1**) and samarium diiodide (**Section 1.2.3.2**) as they were used in the early days of our investigation. A more substantial part will be devoted to manganese(III) triacetate as most of our efforts in this research study focussed on this reagent (**Section 1.2.3.3**). A classic cyclisation in radical chemistry is the cyclisation of 5-hexenyl radicals. It is important to understand the regio- and stereoselectivity of such radical cyclisations to predict the outcome of these processes. The following section aims to explain concisely the Beckwith-Houk model, a key predictive model used throughout this manuscript and in some selected cascade reaction examples (**Section 1.2.3**).

### 1.2.2 **Regioselectivity and stereoselectivity of 5-hexenyl radical cyclisations**

#### 1.2.2.1 Regioselectivity

Simple 5-hexenyl radicals such as **1.24** (**Scheme 1-5**, below) preferably undergo cyclisation in 5-*exo* mode to give primary radical **1.25** in keeping with Baldwin’s rules.[61] This can be surprising at first given the expected relative lower stability of primary radical **1.25** compared to secondary radical **1.26** resulting from the 6-*endo-trig* cyclisation process. Experimentally, Beckwith and co-workers found that the rate constant of the 5-*exo-trig* cyclisation was 48 times faster than its 6-*endo-trig* counterpart.[62]




**Scheme 1-5**: 5-*exo-trig* vs 6-*endo-trig* cyclisation transition states of 5-hexenyl radicals.

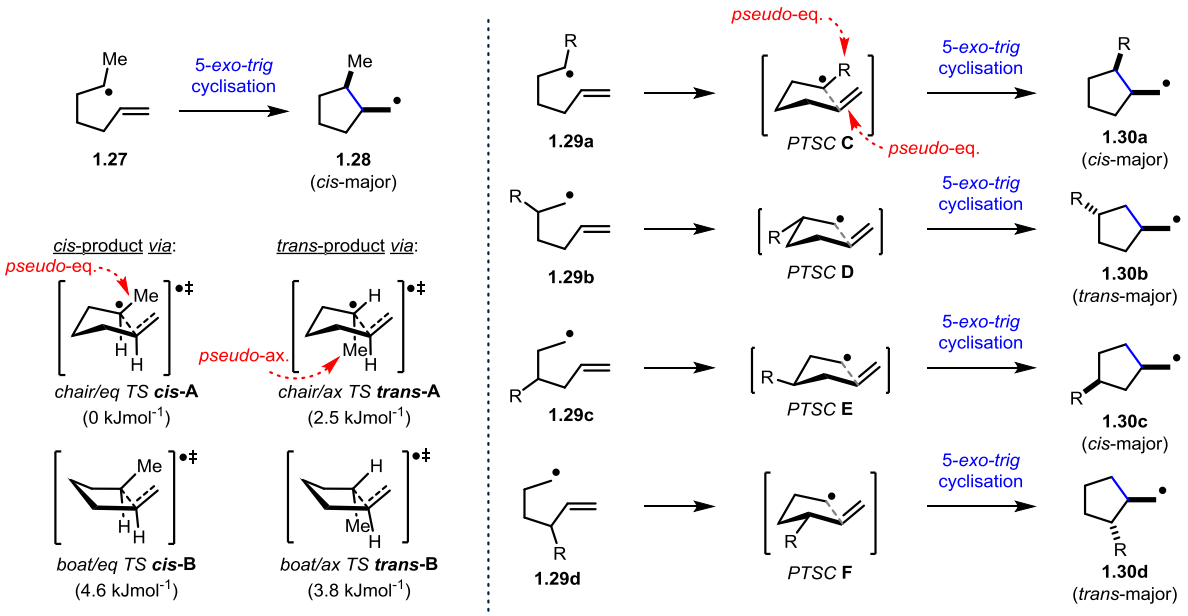
The kinetic preference for the 5-*exo* mode can be explained by a better overlap between the singly occupied molecular orbital (SOMO) and the lowest unoccupied molecular orbital (LUMO) of the alkene in the transition state *TS* **B** compared *TS* **A** for the 6-*endo-trig* cyclisation. The 6-*endo-trig* cyclisation pathway likely requires a build-up in strain to adopt the reactive conformation *PTSC* **A** to reach the ideal Bürgi-Dunitz angle.[63]

In this manuscript, the use of pre-transition state conformations (*PTSC*) is favoured over the use of transition states (*TS*) for simplicity and clarity as we judged that addition of substituents on the structure can make transition states confusing. In a *PTSC*, the grey dotted bond represents the bond formed during the cyclisation step; it is drawn as a visual aid only.

For the system shown above, Beckwith and Schiesser calculated that the difference of energy between the two transition states (*TS* **A** and *TS* **B**) was 25.5 kJmol$^{-1}$ in favour of *TS* **B**.[64] We shall see later that the relative rates of these two competing pathway can greatly depend on the substituents present on the molecule (see **Section 3.3**).

### 1.2.2.2 Stereoselectivity

Beckwith and Schiesser found, using computational analysis of cyclisations of different substituted 5-hexenyl radicals, that 5-*exo-trig* cyclisations occurred mainly *via* two transition states.[64] Considering the cyclisation of radical **1.27** to cyclopentane **1.28** (**Scheme 1-6**, *top left, below*), they found that this cyclisation proceeded *via* a chair-like transition state *TS* ***cis*-A** or *TS* ***trans*-A**. The former (*TS* ***cis*-A**) in which both the methyl group and the alkene are occupying *pseudo*-equatorial positions being favoured over the other where the methyl is occupying the *pseudo*-axial position.




**Scheme 1-6**: Houk and co-workers: transition states (relative energies in brackets) for the 5-*exo*-*trig* cyclisation (*left*);[65] Beckwith-Houk model for different substituted 5-hexenyl radicals (*right*).[62,65]

Houk and co-workers improved on the calculation and found two additional transition states for this cyclisation.[65] Boat-like transition states *TS* ***cis*-B** and *TS* ***tran*-B** were found to be higher in energy than the corresponding chair-like TS. Additionally, their improved calculations accurately predicted the **cis/trans** ratio of product for the considered reaction (theoretical: 0.42; experimental: 0.39).

Their calculations also accurately reflected the ***cis/trans*** ratio of other cyclisations previously described by Beckwith and co-workers (**Scheme 1-6**, *right*, above).[62] In each case, chair-like transition states analogous to *TS* ***cis*-A** were found to be the most favourable (lower in energy). This relatively simple model consisting of arranging substituents on the chair-like TS with the expected lowest energy (using A values for example)[66] is now accepted as a useful method to predict the stereochemical outcome of such cyclisations. One can easily predict that the 1- and 3-substituted 5-hexenyl radicals **1.29a/c** will produce the corresponding *cis*-products as major isomers whereas the 2- and 4-substituted counterparts **1.29b/d** will give the corresponding *trans*-diastereomers; results actually obtained for R = Me experimentally.[62] In addition to being predictive, this model suggested that the use of more sterically encumbering group could exacerbate the stereocontrol of these

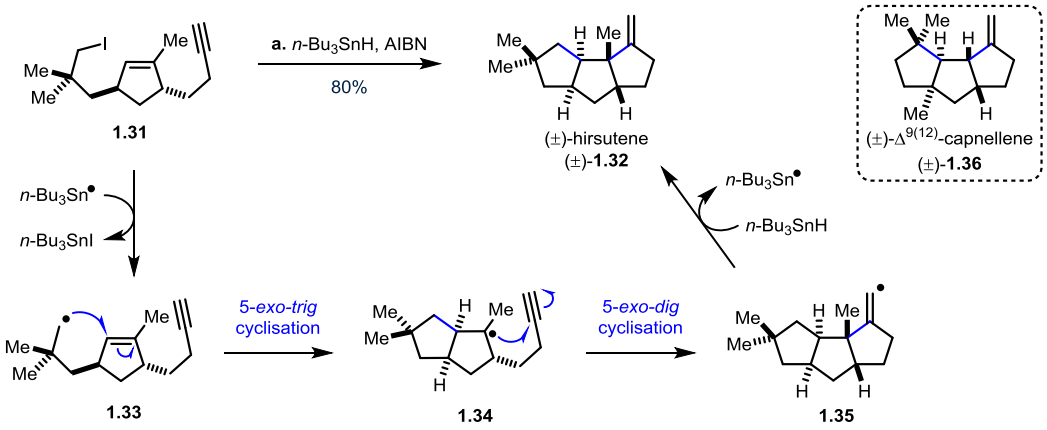
cyclisations. This model will be used throughout this manuscript and will be referred as the "Beckwith-Houk model".

### 1.2.3 Intramolecular cascade reaction examples

#### 1.2.3.1 Introduction to tributyltin hydride and its use in cascade reactions

Tributyltin hydride is a useful reagent in organic chemistry and was historically one of the first employed in radical cascade reactions. It has been used in conjunction with a radical initiator in substoichiometric amount such as AIBN, peroxides, or light irradiation to initiate radical chains. In a cascade reaction context, the tributyltin radical has mainly been used to initiate radical reaction by reduction of organic halides or by addition onto triple bonds.[51]

Curran and co-workers published the total synthesis of racemic hirsutene (±)-**1.32** from iodide **1.31** using a key and final *n*-$Bu_3SnH$-mediated radical cascade reaction (**Scheme 1-7**, below).[49,67] Radical **1.33** was obtained by reaction of iodide **1.31** with tributyltin radical (formed *in situ* using *n*-$Bu_3SnH$ and AIBN as initiator under reflux). Consecutive 5-*exo*-*trig*/6-*exo*-*dig* cyclisation formed vinyl radical **1.35**. Chain propagation with *n*-$Bu_3SnH$ gave the desired natural product in 80% yield in racemic form. This powerful transformation successfully formed two new stereocentres (one quaternary)

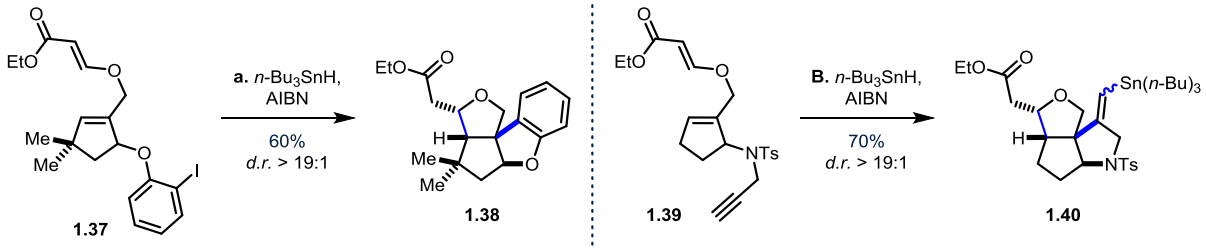



**Scheme 1-7**: Curran and co-workers: *n*-$Bu_3SnH$-mediated cascade cyclisation used in the total synthesis of racemic hirsutene (±)-**1.32**.[67]

Reagents and conditions: (a) *n*-$Bu_3SnH$ (1.3 eq.), AIBN (cat.), benzene (0.02 M), reflux, 1 h, 80%.

with the required *cis*-fused relationship between each cyclopentane rings. A similar approach was adopted for the synthesis of racemic capnellene (±)-**1.36** but using a tertiary bromide cyclisation precursor.[49,68]

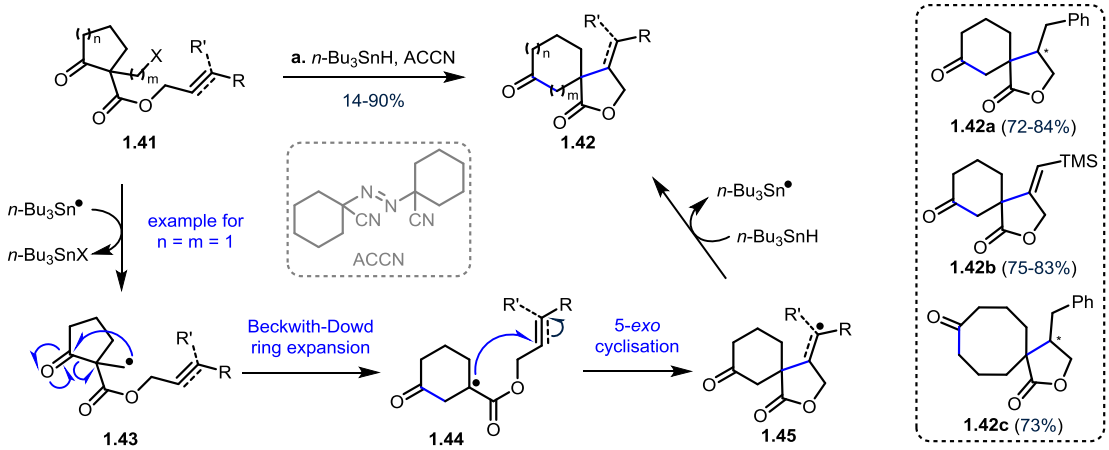
In a more recent example, Gharpure and co-workers formed polycyclic compounds such as **1.38** and **1.40** from the corresponding monocyclic precursors **1.37** and **1.39** *via* iodine abstraction from **1.37** or tributyltin radical addition onto the triple bond of **1.39** followed by double 5-*exo*-*trig* cyclisations.[69] These two molecules were obtained in relatively good yield and excellent diastereoselectivity. The outcome of the latter can be rationalised using the Beckwith-Houk model.




**Scheme 1-8**: Gharpure and co-workers: *n*-$Bu_3SnH$-mediated cascade reaction.[69]

Reagents and conditions: (a) *n*-$Bu_3SnH$ (1.9 eq.), AIBN (0.4 eq.), benzene, reflux, ~3 h, 60%; (b) *n*-$Bu_3SnH$ (2.0 eq.), AIBN (0.4 eq.), benzene, reflux, ~3 h, 70%.

The formation of spirocyclic compounds **1.42** of different sizes were studied by Lupton and co-workers from β-keto esters **1.41** with *n*-$Bu_3SnH$ and ACCN (1,1'-azobis(cyclohexanecarbonitrile)) in chlorobenzene at reflux.[70] The reaction proceeds *via* Beckwith-Dowd ring expansion of primary radical **1.43** followed by cyclisation in a 5-*exo* fashion onto the pendant alkene or alkyne of **1.44** provided radical **1.45** that gave the desired product **1.42** after hydrogen abstraction from *n*-$Bu_3SnH$. A variety of products were formed in modest to excellent yields such as oxaspiro[4.5]decanes **1.42a** (1:1 *d.r.* at C(*)) and **1.42b** (single isomer) or oxaspiro[4.7]dodecane **1.42c** in 73% (1:1 *d.r.* at C(*)) for example. Unfortunately, the final intramolecular addition onto the pendant alkenes led to the formation of diastereomers at C(*) (1:1 ratio).




**Scheme 1-9**: Lupton and co-workers: *n*-$Bu_3SnH$-mediated Beckwith-Dowd ring-expansion/*exo* cyclisation cascade reaction.[70]

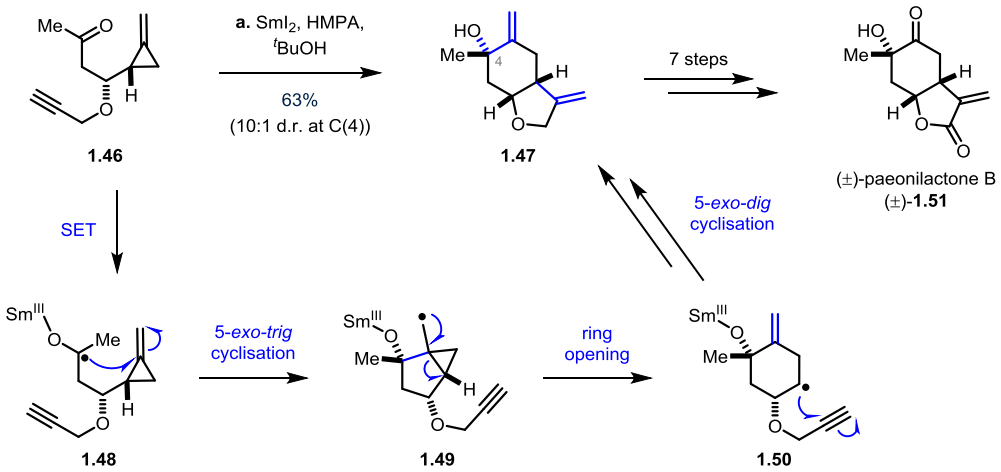
Reagents and conditions: (a) *n*-$Bu_3SnH$ (1.0 eq.), ACCN (0.1 eq.), $C_6H_5Cl$, reflux, 16 h, 14-90%; X = Br, I

Despite its versatility and the key role played in the expansion of radical chemistry, tributyltin hydride's toxicity and the amount of waste generated from its use considerably reduces its appeal to the community nowadays and prevents it from being used in the synthesis of pharmaceuticals.[71] We nevertheless used it in **Section 2.2.2** (page 31) as a starting point because of its reliability. Alternative reagents such as $TMS_3SiH$ (TTMSS) or *n*-$Bu_3GeH$, can be used instead.[71,72] In all cases, these reagents react *via* a *reductive* initiation and *reductive* termination. As a consequence, products formed during such reductive steps are usually relatively less functionalised than the corresponding starting materials.

### 1.2.3.2 Introduction to samarium diiodide and its use in cascade reactions

Samarium diiodide, also known as Kagan's reagent,[73] is a remarkable single electron transfer (SET) reducing agent known for imparting the chemo- and stereoselectivity in a number of reactions as well as for its functional group tolerance.[74,75] Its reducing ability can be modified by addition of different additives including water, alcohols, HMPA and more allowing tailoring of the reduction potential of the reagent.[76–78]

Kilburn and co-workers described the total synthesis of paeonilactone (±)-**1.51** in racemic form using a reductive polycyclisation of *exo*-alkene **1.46** using $SmI_2$ to form the core of the natural product **1.47** as a key step (**Scheme 1-10**, below).[79] The reaction proceeds *via* a 5-*exo*-*trig* cyclisation of radical **1.48** followed by cyclopropane opening of radical **1.49** leading to secondary radical **1.50**. Final 5-*exo*-*dig* cyclisation onto the terminal alkyne gives allylic alcohol **1.47** after a second SET/protonation sequence. This sophisticated cascade gave the core of the natural product in 63% yield (10:1 *d.r.* at C(4)) with the total synthesis being completed in 7 additional steps.

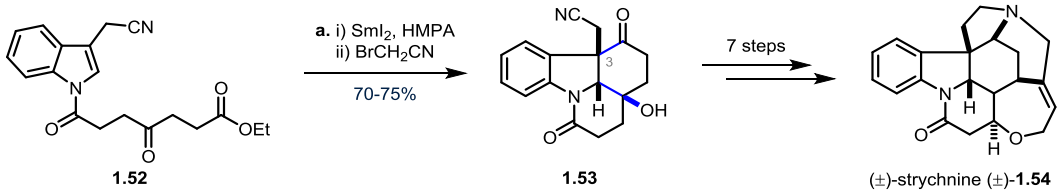



**Scheme 1-10**: Kilburn and co-workers: $SmI_2$-mediated cascade cyclisation used in the total synthesis of racemic paeonilactone (±)-**1.51**.[79]

Reagents and conditions: (a) $SmI_2$ (2.2 eq.), HMPA (21 eq.), $^t$BuOH (2 eq.), THF, 0 °C to r.t., 63%.

Reissig and co-workers showed that samarium diiodide could successfully convert ketone **1.52** into tertiary alcohol **1.53** in 70-75% yield (**Scheme 1-11**, below).[80] The reaction proceeds *via* single-electron reduction of the ketone by $SmI_2$ followed by 6-*endo*-*trig* cyclisation of the ketyl radical onto the indole alkene followed by further reduction by another equivalent of $SmI_2$. The resulting Sm(III) intermediate then cyclised onto the pendant ethyl ester to give the cyclohexanone ring fragment. HMPA was used as an additive to increase the reducing ability of Kagan's reagent. Bromoacetonitrile was also added in a one-pot procedure to increase the yield of the reaction. The researchers showed the efficient conversion of linear precursor **1.52** into diastereomerically pure **1.53** with $SmI_2$-HMPA

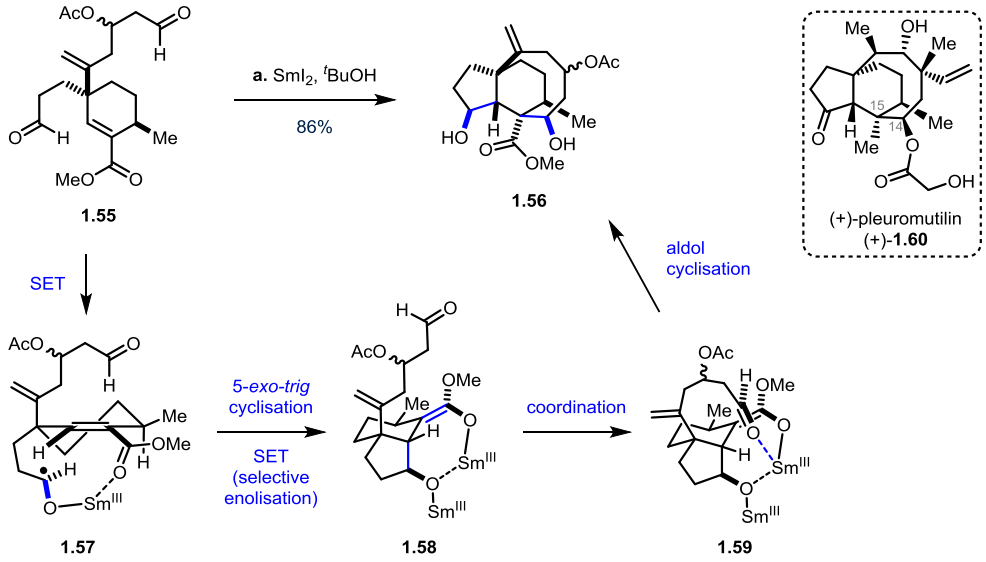
making in the process two new rings, three stereogenic centres (including one quaternary) in a radical/anionic cascade, and giving the core of strychnine **1.54**.




**Scheme 1-11**: Reissig and co-workers: $SmI_2$-mediated cascade cyclisation used in the formal synthesis of racemic strychnine (±)-**1.54**.[80]

Reagents and conditions: (a) i) $SmI_2$ (2.4 eq.), HMPA (10-12 eq.), THF, r.t., 5 min; ii) bromoacetonitrile (1.0-3.0 eq.), r.t., 12 h, 70-75%.

The coordinating ability of samarium(II) and samarium(III) species can lead to excellent diastereoselectivity in cascade reactions. For example, Procter and co-workers published the impressive transformation of dialdehyde **1.55** into complex tricyclic compound **1.56** with complete control of the formation of four contiguous stereocentres (**Scheme 1-12**, below).[81] The process is proposed to proceed *via* selective one electron reduction after coordination with the ester to form radical **1.57**. Cyclisation in a 5 *exo-trig* fashion gives an α-ester radical which can be reduced by




**Scheme 1-12**: Procter and co-workers: $SmI_2$-mediated radical-anionic cascade cyclisation used to access diol **1.56**, an approach to pleuromutilin **1.60**.[81]

Reagents and conditions: (a) $SmI_2$ (2.5 eq.), $^t$BuOH, 0 °C, 30 min, 86% (*d.r.* same as in the starting material).

another $SmI_2$ equivalent to form selectively enolate **1.58** thanks to the coordination to the initial chelated $SmI_3$. Coordination of the remaining aldehyde followed by aldol cyclisation provides **1.56** in an excellent 86% yield. This molecule was formed during a study towards the total synthesis of (±)-pleuromutilin (±)-**1.60**. Recently, Reisman and co-workers published the enantioselective total synthesis of (+)-pleuromutilin (+)-**1.60** using a samarium diiodide-mediated cyclisation (forming the C(14)-C(15) bond) as a key step.[82]

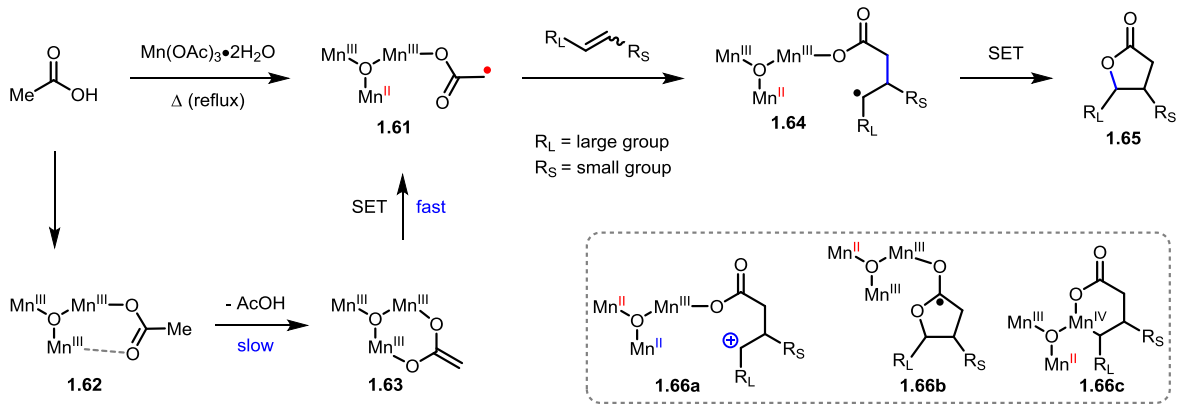
Samarium diiodide has been successfully used in an impressive number of total syntheses and other applications.[74,75] It is a particularly versatile reagent as it can be used in radical transformations (*e.g.* pinacol coupling, radical addition to unsaturations), polar transformations (*e.g.* Barbier reaction, Reformatsky reaction) as well as hybrid radical-anionic cascade transformations. **Section 2.3.2** (page 36) will describe our results using samarium diiodide in cascade reactions.

### 1.2.3.3 Introduction to manganese(III) acetate dihydrate and its use in cascade reactions

#### 1.2.3.3.1 Manganese(III) acetate dihydrate, a one-electron oxidant

Manganese(III) acetate is a single-electron transfer (SET) oxidant classically used to oxidise electron rich enolates/enol tautomers of mono- and 1,3-dicarbonyl compound as well as carboxylic acids.[83]

Heiba and co-workers,[84] and Bush and Finkbeiner[85] published the first examples of the use of $Mn(OAc)_3$ to form γ-lactones from alkenes in 1968 (**Scheme 1-13**). However, it was only in the mid-



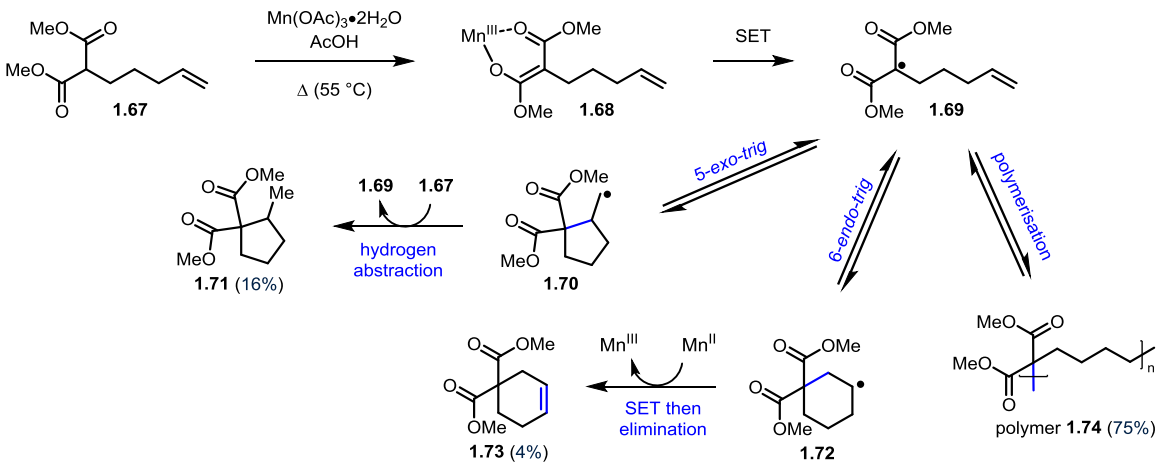

**Scheme 1-13:** Mn(III)-based formation of γ-lactones based on literature precedents.[84–88]

1980s that Fristad and Peterson proposed that the reaction proceeded through the tri-nuclear oxygen-centred cluster (bridged with acetates) $Mn_3O(OAc)_7$.[86–88]

Activation of acetate by an adjacent $Mn^{III}$ allows enolisation of **1.62** which gives **1.63** (rate-determining step). This is followed by a fast single-electron oxidation to give carbon-centred radical **1.61** which attacks the less hindered end of the alkene to give secondary radical **1.64**. The final step, formation of γ-lactone **1.65** by formal one-electron oxidation/cyclisation is not completely understood. However it is expected to be the result of the oxidation of radical **1.64** by a Mn(III) centre of the same cluster (*via* any **1.66a**-**c**). $Mn(OAc)_3$ (written as its monomeric form in this manuscript for simplification purposes) is known to be a slow oxidant of unactivated secondary (or primary) radicals; hence, oxidation is thought to occur from the same Mn cluster.[89]

In systems where the adduct radical formed is primary, secondary or not a γ-carboxy radical (such as **1.64**) then the slow oxidative termination step by $Mn(OAc)_3$ impacts the product distribution.

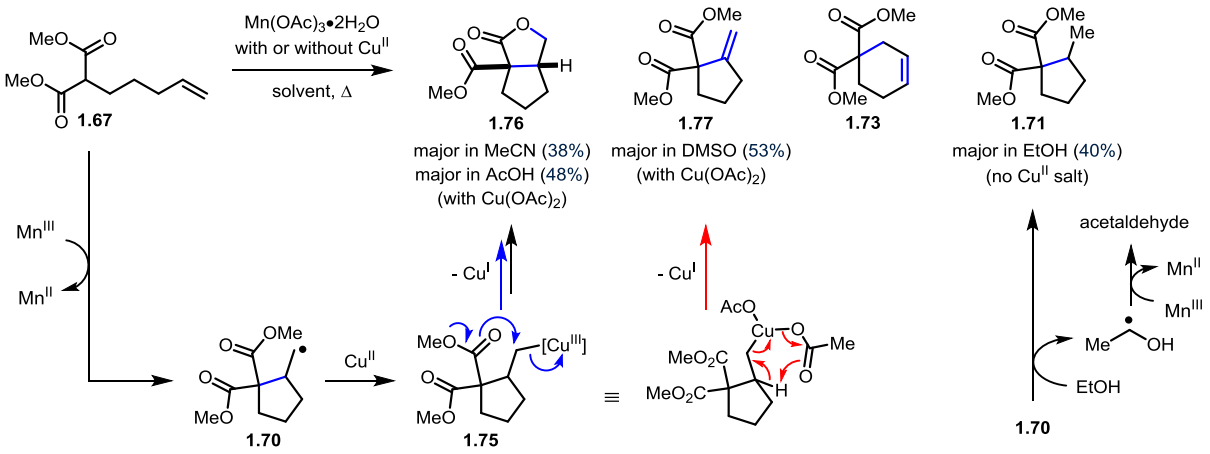
In the following example involving cyclisation of 5-hexenyl radical **1.67**, Snider and co-workers showed that the lack of an efficient termination step resulted in the formation of polymerisation product predominantly (75%) (**Scheme 1-14**).[90] The slow trapping of the 5-*exo-trig* and 6-*endo-trig* radical cyclisation products **1.70** and **1.72** allows reversion to ring-opened free radical **1.69** facilitating its polymerisation to **1.74**.




**Scheme 1-14:** Snider and co-workers: Mn(III)-based cyclisation of malonate **1.67** in absence of fast terminating agent.[90]

Snider found a small proportion of **1.73** from the oxidation/elimination process of secondary radical **1.72**. Primary radical **1.70** gave only hydrogen abstraction product **1.71** in 16% yield.

Copper(II) salts have been shown by Kochi and co-workers to react with alkyl radicals (bimolecular rate constant k = ~ $10^6$ $M^{-1}s^{-1}$).[91,92] Heiba and Dessau also found that Cu(II) salts could be used as a co-oxidant with $Mn(OAc)_3$ without incompatibility issues and that they react with alkyl radicals 350 times faster than $Mn(OAc)_3$ does.[93,94] This system has been successfully applied to numerous ketones and 1,3-dicarbonyl compound (diketones, β-keto esters, malonates and more).[89] Copper(II) acetate was used by Snider and co-workers in the previously presented reaction. They found that the solvent had a profound effect on the product nature and distribution. MeCN and AcOH were found to favour the formation of lactone **1.75** by attack of the pendant ester onto the α-carbon of Cu(III) intermediate **1.75** in a nucleophilic substitution fashion. DMSO favoured β-hydride elimination to form *exo*-alkene **1.77**. EtOH on its own (no Cu(II) salt added) was found to convert **1.70** to **1.71** *via* a proposed hydrogen atom abstraction process.[95]




**Scheme 1-15:** Snider and co-workers: Mn(III)-based cyclisation of malonate **1.67** in presence of Cu(II) acetate.[95]

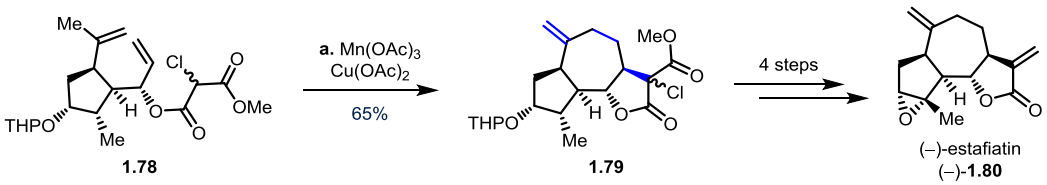
Inspired by Kochi and co-worker's work,[91,96] Burton and co-workers explored different Cu(II) salts in order to favour the nucleophilic substitution process.[97,98] It was found that weakly coordinating counteranion (*e.g.* in $Cu(OTf)_2$ and $Cu(BF_4)_2$) favoured the formation of substitution products over the formation of β-hydride elimination products.

From an experimental point of view, it is important to keep the reaction mixture oxygen-free to avoid formation of peroxide and other related by-products unless it is desired (see later in **Scheme 1-17**, in **Section 1.2.3.3.2**). It is common to use 2 eq. of $Mn(OAc)_3$ and 1 eq. of Cu(II) salt (or substoichiometric amount). The first equivalent of Mn(III) is consumed by the malonate while the second equivalent is use to re-oxidise the Cu(I) species obtained from the termination step back to Cu(II). There is normally an obvious colour change associated with this reaction (dark brown to clear blue/green) indicative of complete consumption of Mn(III).

### 1.2.3.3.2 $Mn(OAc)_3$-mediated cascade reactions

Unlike the previously presented reagents (*n*-$Bu_3SnH$ and $SmI_2$), $Mn(OAc)_3$ permits *oxidative* radical cyclisation reactions.[89] As discussed in the previous section; oxidative termination, using Cu(II) or Mn(III) in special cases, has been used to form formal carbocations that can be trapped by a nucleophiles or eliminate to obtain alkenes. Products made from these net two-electron oxidation processes usually shows greater potential for further functionalisation than with reductive radical cyclisations.

A Mn(III)-initiated 5-*exo*-*trig*/7-*endo*-*trig* cyclisation sequence was published by Lee and co-workers (**Scheme 1-16**, below) in their synthesis of estafiatin.[99] Their use of copper(II) acetate as a terminating agent enabled them to form *exo*-alkene **1.79** in 65% yield from chloromalonate **1.78**. The *trans*-fused [7,5] bicyclic relationship obtained followed the predictions of the Beckwith-Houk model. In this example, the chloride was used as a protecting group to avoid over-oxidation of the product.

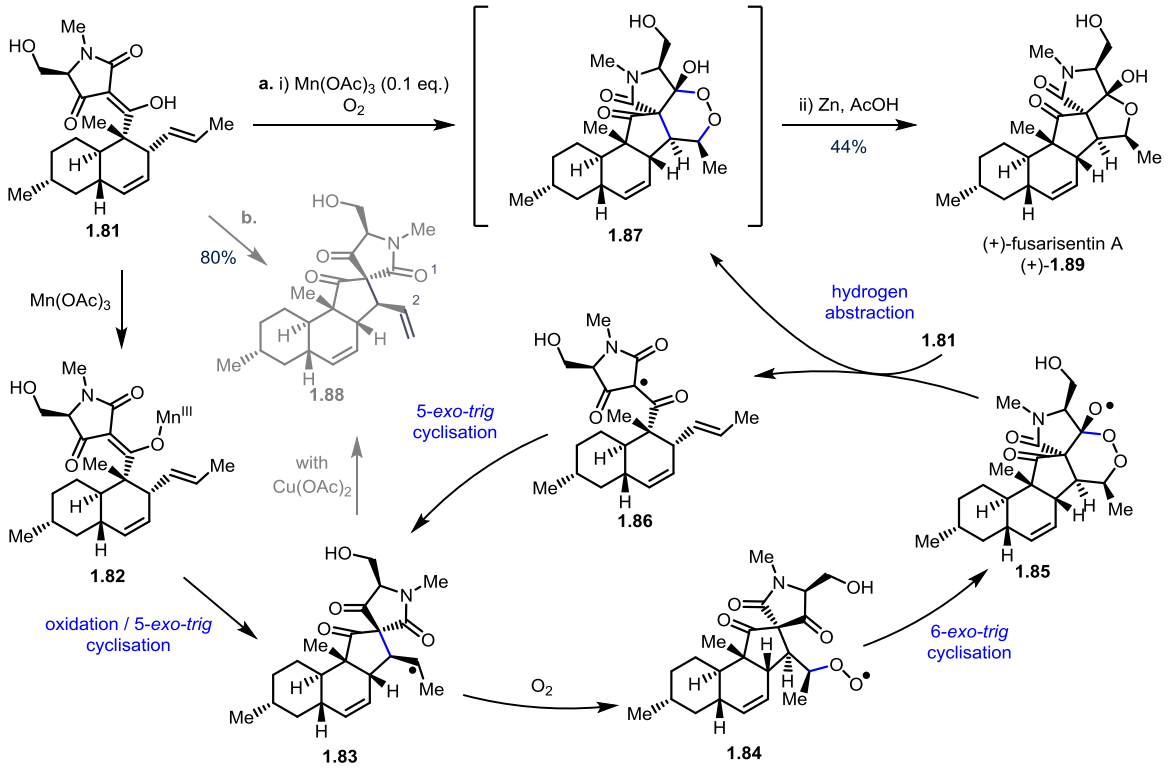



**Scheme 1-16**: Lee and co-workers: Mn(III)/Cu(II)-mediated cascade cyclisation used in the total synthesis of (–)-estafiatin (–)-**1.80**.[99]

Reagents and conditions: (a) $Mn(OAc)_3 \bullet 2H_2O$ (2.0 eq.), $Cu(OAc)_2 \bullet H_2O$ (1.0 eq.), EtOH, reflux, 65%.

In fact, without the chloride, the product would have been another enolisable unsymmetrical malonate compound. The chloride and THP protecting group were later removed using zinc powder in acetic acid (87%, not drawn) and further reactions gave the desired natural product (–)-estafiatin (–)-**1.80** in enantioenriched form.

In another example, Gao and co-workers showed that the use of the same combination of reagents on enol **1.81** gave terminal alkene **1.88** in 62% yield when acetic acid was used as a solvent (**Scheme 1-17**, below).[100] Formation of this product is proposed to be *via* a Mn(III)-enolate **1.82**, which cyclises to secondary radical **1.83** that was trapped by the Cu(II) salt forming the depicted Hofmann elimination product **1.88** *via* β-hydride elimination. However, the authors desired the participation of the oxygen O(1) to trap the Cu(III) intermediate at C(2). This problem was solved by running the experiment under air or an oxygen atmosphere using a substoichiometric amount of $Mn(OAc)_3$.

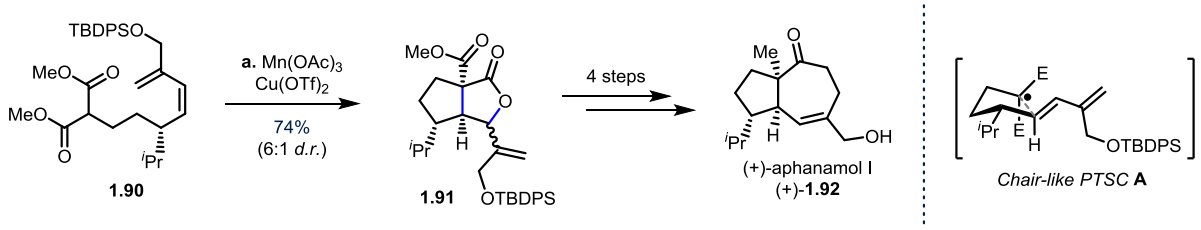



**Scheme 1-17**: Gao and co-workers: Mn(III)-mediated cascade cyclisation used in the total synthesis of (+)-fusarisetin A (+)-**1.89**.[100]

Reagents and conditions: (a) i) $Mn(OAc)_3 \bullet 2H_2O$ (0.1 eq.), air or $O_2$ (1 atm), degassed AcOH, r.t., 2 h; ii) activated Zn powder (30 eq.), $H_2O$, 50 °C, 2 h, 41% (over 2 steps); (b) $Mn(OAc)_3 \bullet 2H_2O$ (2.0 eq.), $Cu(OAc)_2$ (5.0 eq.), degassed AcOH, r.t., 2 h, 62%, 3.3:1 *d.r.*.

In the event, radical **1.83** was trapped by oxygen to form the *O*-centred radical **1.84** that underwent cyclisation into the nearby ketone to form **1.85**. A proposed hydrogen abstraction from the starting material **1.81** is believed to be responsible for the propagation of a chain reaction by forming radical **1.86**. The resulting peroxide product **1.87**, formed from the cascade reaction was reduced in a one-pot procedure with zinc in acetic acid (solvent of the cascade) to give their enantioenriched target natural product (+)-fusarisetin A (+)-**1.89** in 44% yield.

More recently, Burton and co-workers published a short synthesis of aphanamol I in racemic and enantiopure forms using a key Mn(III)-mediated oxidative radical cyclisation/lactonisation sequence to convert diene **1.90** into γ-lactone **1.91** (**Scheme 1-18**, below).[101] The cyclisation is believed to follow the Beckwith-Houk model, cyclising *via* the chair-like pre-transition state conformation *PTSC* **A** shown below (**Scheme 1-18**, *right*). The resulting vinyl radical is then trapped by copper(II) triflate and lactonisation happens to form the desired products **1.91** in 74% yield (6:1 *d.r.*). Advanced intermediate **1.91** was converted into the target natural product (+)-aphanamol I (+)-**1.92** in 4 additional steps.




**Scheme 1-18**: Burton and co-workers: Mn(III)-mediated cascade cyclisation used in the total synthesis of (+)-aphanamol I (+)-**1.92** (*left*); the chair-like PTSC proposed for the radical cyclisation (*right*).[101]

Reagents and conditions: (a) $Mn(OAc)_3 \bullet 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), MeCN, 80 °C , 30 min, 74% (6:1 *d.r.*).
E = $CO_2Me$; TBDPS = *tert*-butyldiphenylsilyl.

Manganese(III) acetate has been demonstrated to be powerful mild and selective single electron transfer oxidant useful to chemist in a multitude of reactions (cascade or not) and involved in key steps of numerous natural product syntheses.[83,89] This reagent has been used extensively in the Burton group,[6,11,98,102–107] and in the work described later in this thesis.

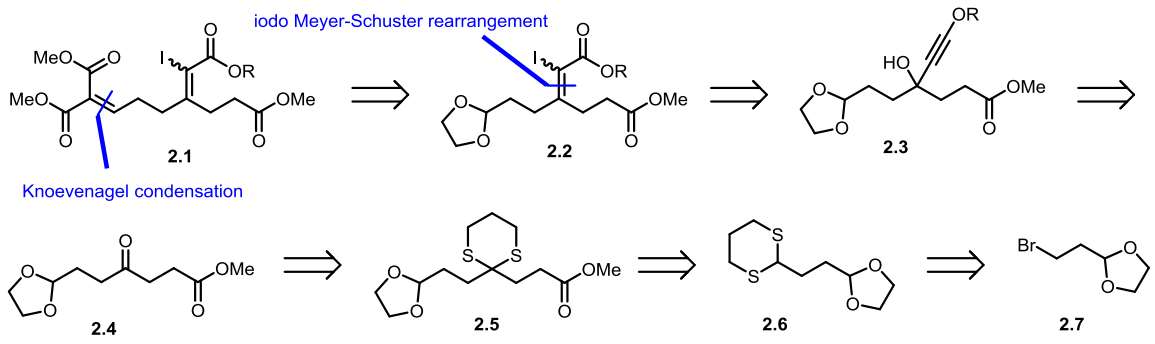
# 2 Early Challenges: Syntheses of Simplified Substrates and Their Cyclisations

## 2.1 SBM CDT rotations results

### 2.1.1 SBM CDT rotation results (Burton group)

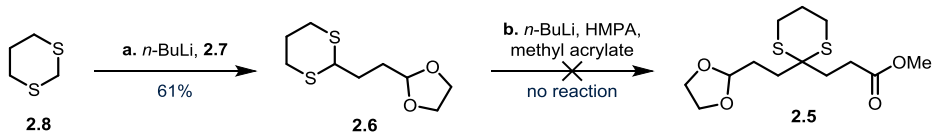
As presented in the introduction, the SBM CDT programme allowed for a 16-week rotation in the Burton group on the project described in this thesis to have a taste of its potential before later pursing it as a substantive project.

During the Burton group rotation, we decided to probe the synthesis of starting material **2.1** and the proposed anionic cascade cyclisation. The original retrosynthesis for **2.1**, is depicted in **Scheme 2-1** (below). We envisaged that alkylidene malonate **2.1** could come from a late stage Knoevenagel condensation of the aldehyde derived from **2.2**. We thought that the α-iodo α,β-unsaturated ester moieties could be accessed from an iodo Meyer-Schuster rearrangement of propargyl alcohol **2.3**.[108] This tertiary alcohol could come from ketone **2.4**; itself possibly derived from a dithiane double alkylation/deprotection sequence.




**Scheme 2-1**: Original retrosynthetic analysis of tetraester **2.1.**

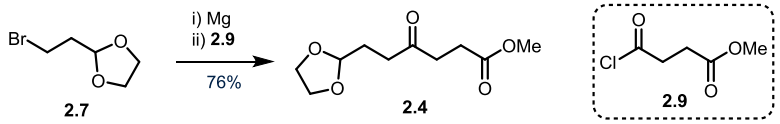
The design of this route was chosen to accommodate a variety of different electrophiles to gain access to analogues of **2.4** easily (**Scheme 2-2**). The synthesis began with alkylation of dithiane **2.8** with bromide **2.7** (61% yield). Lithiation of **2.6** was performed and the resulting reaction with methyl acrylate and HMPA failed to give the desired adduct **2.5**.




**Scheme 2-2**: Attempted synthesis of dithiane **2.5**.

Reagents and conditions: (a) *n*-BuLi (1.1 eq.), **2.7** (1.0 eq.), THF, -78 °C to r.t., 16 h, 61%; (b) *n*-BuLi (1.2 eq.), HMPA (2.0 eq.) then methyl acrylate (1.2 eq.), THF, -35 °C to r.t., 20 h.

In the meantime another more appealing strategy to obtain **2.4** was found and therefore the initial route was set aside. Starting from the previously commercially available **2.7**, we envisaged a lithium-halogen exchange or Grignard reagent formation would allow the direct formation of **2.4** by attack on a suitable 1,4-dicarbonyl compound. Salomon and co-workers showed that the Grignard reagent derived from **2.7** successfully underwent addition to the acid chloride **2.9** to give **2.4** in 60% yield.[109] We found that the nature of the solvent and temperature for the formation of the Grignard reagent was the key to a successful addition into the acyl chloride **2.9** as noted in the work by Bedoukian and Passaro (**Scheme 2-3**).[110]

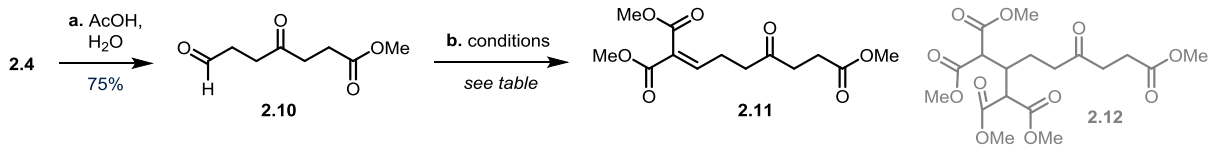



**Scheme 2-3:** Formation of ketone **2.4** from acid chloride **2.9**.

Reagents and conditions: Mg (1.1 eq.), THF, < 30 °C, 1 h, then **2.9** (0.8 eq.), -78 °C, 30 min, 76%.

In our hands, the formation of the Grignard reagent of **2.7** failed to initiate at reflux in $Et_2O$ whereas forming it in THF at reflux led to rapid decomposition. The greasy-looking mixture obtained, was attributed to a polymerisation process; supposedly formed by Mg-assisted opening of the acetal followed by Grignard reagent addition into the resulting oxocarbenium ion. Other optimization attempts (for example cross coupling using $Fe(acac)_3$,[111] changing the reagent addition order, and more) did not improve the yield of product.

Having ketone **2.4** in gram-quantities, we investigated both the iodo Meyer-Schuster rearrangement and Knoevenagel condensation in parallel, to determine the order in which these steps should be conducted.




| entry | conditions | yield[a] |
|---|---|---|
| 1 | L-proline (0.03 eq.) in DMSO, 3Å MS, rt, 16 h | - |
| 2 | $TiCl_4$ (2 eq.), pyridine (4 eq.) in THF, rt, 16 h | 7% |
| 3 | piperidine (0.02 eq.), AcOH (0.33 eq.), chloroform, 3Å MS, reflux, 16 h | traces |
| 4 | piperidine (0.1 eq.), AcOH (0.1 eq.), $C_6H_6$, Dean-Stark, reflux, 16 h | < 1% |

Table **2.1**: Knoevenagel attempts on aldehyde **2.10**.

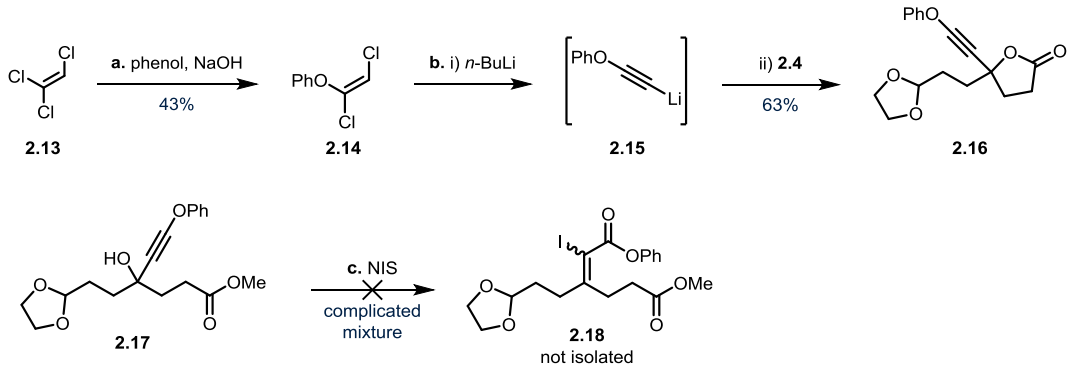
Reagents and conditions: (a) 3:1 AcOH/$H_2O$, 50 °C, 9 h, 75%; (b) dimethyl malonate (1.05 eq.), *see table*.

[a] isolated yields.

Hence, **2.4** was deprotected with AcOH in water to yield 1,4-dicarbonyl **2.10** in 75% yield.[109] Attempts at Knoevenagel condensation on **2.10** using dimethyl malonate are summarized in **Table** 2.1. It is important to note that 100% conversion of the starting material **2.10** was observed for entries 2-4 showing the expected good reactivity of this aldehyde-keto-ester. Unfortunately, proline catalysis gave an inseparable mixture of **2.11** and over-addition side product **2.12**, moreover in poor yield.[112] Titanium tetrachloride (entry 2) gave extensive starting material/product decomposition,[113] not a surprising result based on the Lewis acidity of the reagent. A difficult purification gave impure **2.11** in 7% yield which was then used as a reference sample. The last two entries (3-4) were performed using piperidinium acetate catalysed Knoevenagel conditions.[114,115] As previously observed, extensive decomposition occurred, leading to trace formation of product **2.11** (entry 3) and a token yield of < 1% of **2.11** (entry 4).

Approaching the middle part of our cyclisation cascade precursor **2.1**, the α-iodo α,β-unsaturated ester functionality was envisaged to be formed from ketone **2.4** in a two-step process involving an iodo Meyer-Schuster rearrangement of previously mentioned **2.17** (**2.3** with R = Me) based on a procedure developed by Reddy and co-workers.[108] Phenyl vinyl ether **2.14** was obtained in moderate yield from trichloroethylene **2.13** (**Scheme 2-4**, below). Treatment of dichloride **2.14** with *n*-BuLi

(2 eq.) formed lithium acetylide **2.15** that was then reacted in a one-pot procedure with ketone **2.4** at low temperature.




**Scheme 2-4:** Attempted synthesis of propargyl alcohol **2.18** *via* alcohol **2.17** to form of lactone **2.16**.
Reagents and conditions: (a) phenol (1.0 eq.), NaOH (1.0 eq.), DMSO, r.t., 16 h, 43%; (b) i) *n*-BuLi (2.05 eq.), $Et_2O$, -78 °C to -25 °C, 2 h, ii) **2.4** (0.95 eq.), $Et_2O$, -78 °C to r.t., 16 h, 63%; (c) NIS (2.0 eq.), $CH_2Cl_2$, r.t., 16 h.

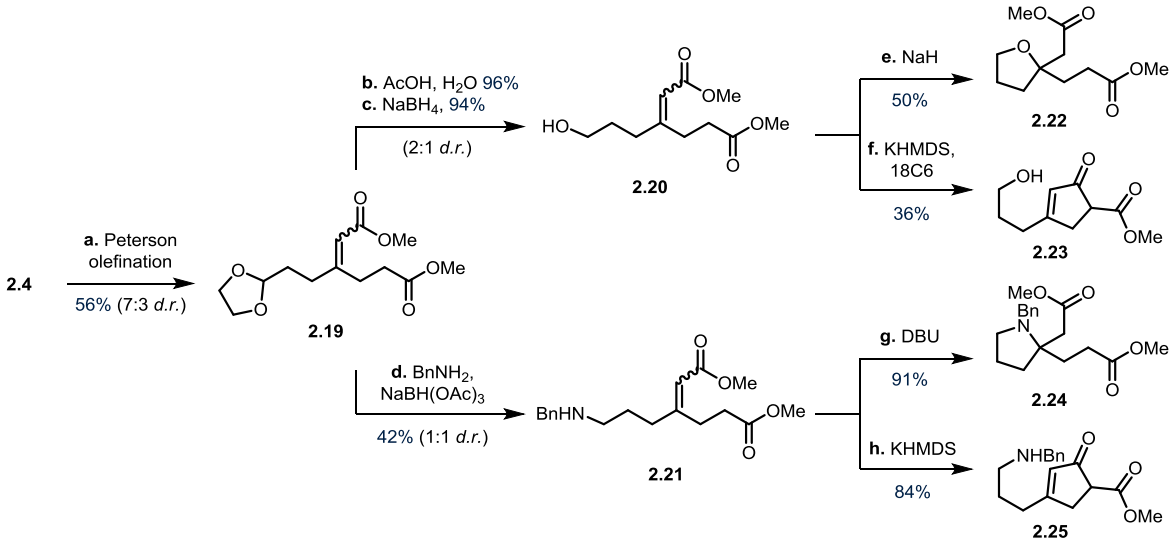
As we anticipated, tertiary alcohol **2.17** was not obtained when the reaction was allowed to warm up to room temperature. In fact, lactone **2.16** was obtained in reasonable yield (63%) as indicated by the loss of the ester methyl peak and the appearance of sharp IR stretches at 1776 and 2273 $cm^{-1}$, indicative of the appearance of a 5-membered lactone carbonyl and a triple bond respectively. Quenching the reaction with a solution of acetic acid in THF (precooled to -78 °C) helped reduce lactone formation but in an irreproducible manner. Unfortunately, the ratio of starting material **2.16**/alcohol **2.17**/lactone **2.16** seemed to depend on the scale, rate of addition and duration of reaction. Attempt at reacting alcohol **2.17** with NIS in $CH_2Cl_2$ only gave a complex mixture of products.

From these results, we realised that the Knoevenagel condensation strategy to gain access to the western fragment of our "ideal" cyclisation substrate **2.1** was not as straightforward as we expected. We therefore decided to simplify the α,β-unsaturated ester by removing the iodide, aiming to facilitate the starting material synthesis.

### 2.1.2 Heyao Shi's SBM CDT rotation results (Burton group)

Heyao Shi continued this project and focused on the polycyclisation of alcohol **2.20** and amine **2.21** (**Scheme 2-5**, below). These substrates could be obtained in 2 or 3 steps respectively from ketone **2.4** in reasonable yields. Reversibility issues were encountered during anionic cyclisation attempts as well as regiochemistry issues for the Dieckmann cyclisation step.

He found that monocyclised products **2.22** and **2.23** could be formed from the hetero-Michael addition of the alcohol/amine moieties onto the α,β-unsaturated ester in moderate yield. It was also discovered that the ester of the Eastern fragment could interfere when a stronger base was used to form monocyclised products **2.23** and **2.25** in excellent yields (> 80%). These products were obtained from addition of the enolate of the unconjugated ester into the conjugated one. Interestingly, the 84% yield obtained when amine **2.21** was treated with KHMDS to form β-ketoester **2.25** strongly suggests a reversible 1,4-addition of the amine onto the Michael acceptor. This would lead to the isomerisation of the double bond, allowing the yield to rise above the theoretical maximum of 50% expected from this reaction using a 1:1 mixture of alkene isomers.



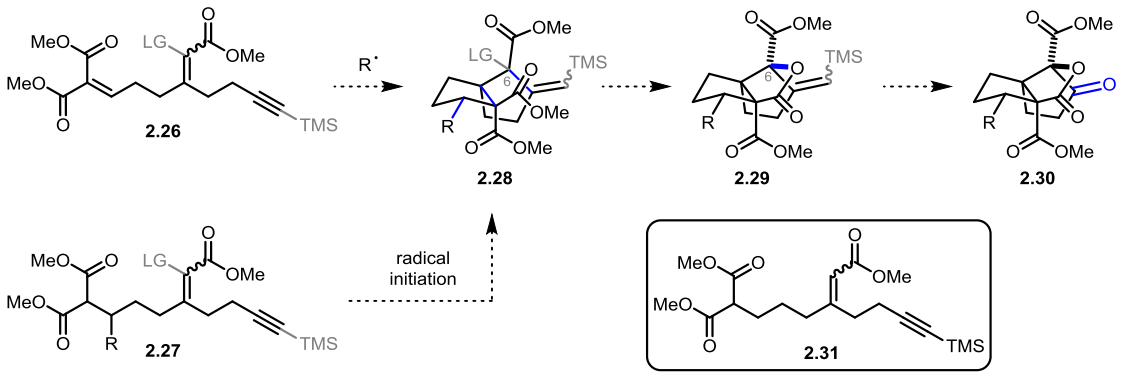

**Scheme 2-5:** Selected results of the work undertaken by Heyao Shi (SBM CDT rotation).

Reagents and conditions: (a) $TMSCH_2CO_2Me$ (3.2 eq.), LDA (3.2 eq.), THF, -78 °C, 2 h, 56% (7:3 *d.r.*); (b) 3:1 $AcOH/H_2O$, 50 °C, 9 h, 75%; (c) $NaBH_4$ (1.1 eq.), THF, r.t., 1 h, 94% (2:1 *d.r.*); (d) $BnNH_2$ (2.0 eq.), $NaBH(OAc)_3$ (4.0 eq.), $CH_2Cl_2$, r.t., 10 h, 42% (10:9 *d.r.*); (e) NaH (1.3 eq.), 1,4-dioxane, 100 °C, 4 h, 50%; (f) KHMDS (2.2 eq.), 18-crown-6 (2.2 eq.), THF, -78 °C, 1 h, 36%; (g) DBU (10.0 eq.), toluene, r.t., 48 h, 91%; (h) KHMDS (1.1 eq.), THF, r.t., 84%.

These interesting results were of use for developing future work in the project.

## 2.2 New focus: radical route

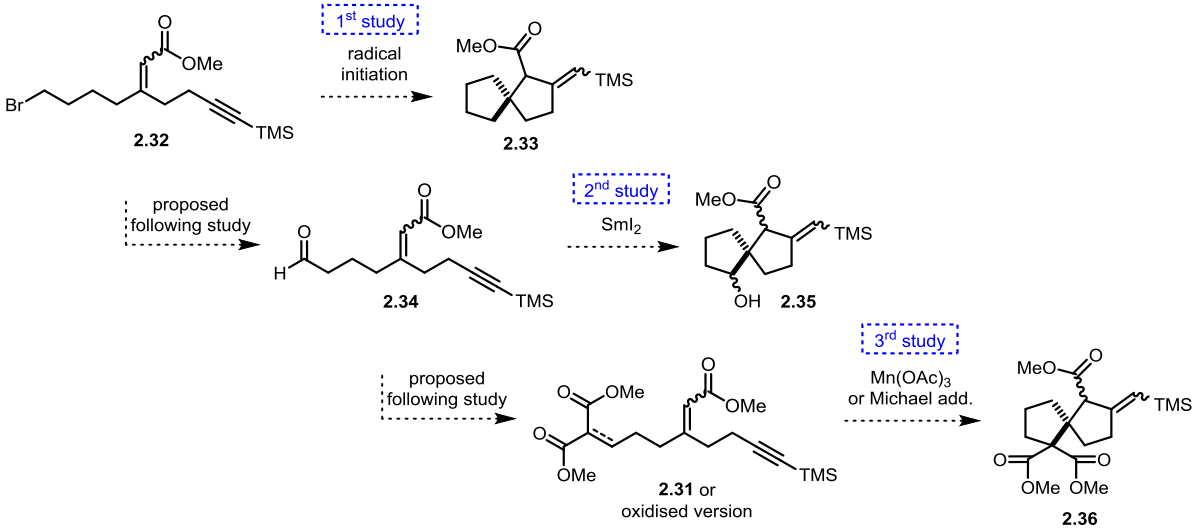
From work conducted during the two SBM CDT rotations (**Sections 2.1.1** and **2.1.2**), we decided to simplify our system (**Scheme 2-6**). Heyao Shi could not trigger the formation of a second ring by resubjecting the products to a variety of reaction conditions. This made us think that anionic conditions were possibly unsuitable to form such a sterically hindered spirocyclic system. The use of radical conditions was preferred as we thought it would have the best chance for this sterically demanding transformation. Neutral free radicals lack the solvation sphere that anions have as an additional hindrance for the cyclisation step. Hence, we chose to focus on the use of radical conditions for our desired transformation; having ginkgolide B **1.7** in mind as a guiding molecule, the eastern fragment was changed into an alkyne **2.26** as this could lead to the formation of alkene **2.28** that could be later transformed into ketone **2.30** (by ozonolysis for example). It was also decided that the use of malonate **2.27** would considerably simplify our initial study by removing the first Michael addition step. Starting with R = H in malonate **2.27** and leaving aside the leaving group for now gave us our new target substrate **2.31**.




**Scheme 2-6:** New simplified targeted substrates to be used in radical conditions and target molecule **2.31**.

R = alkyl, aryl

Given the low yields obtained in Knoevenagel condensation coupled with the length of the synthesis, we initialy decided to pursue cyclisations on simpler substrates (**Scheme 2-7**). We could tackle reactions resembling the originally proposed highly challenging cascade reaction later in the project.

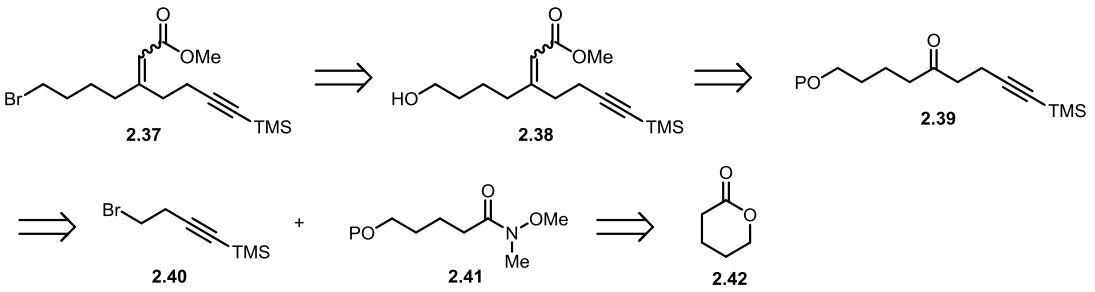



**Scheme 2-7:** Proposed sequence of studies of increasing complexity.

The first cyclisation shown in **Scheme 2-7** was initially selected in this project. It was chosen so that the route to bromide **2.32** could be used to form aldehyde **2.34** and then with only minor modifications could lead to **2.31**. The cyclisations of these substrates could be explored to form interesting spirocycles (**2.33**, **2.35** and **2.36**) and help inform us about the challenges involved with these reactions.

### 2.2.1 Synthesis of bromide 2.32

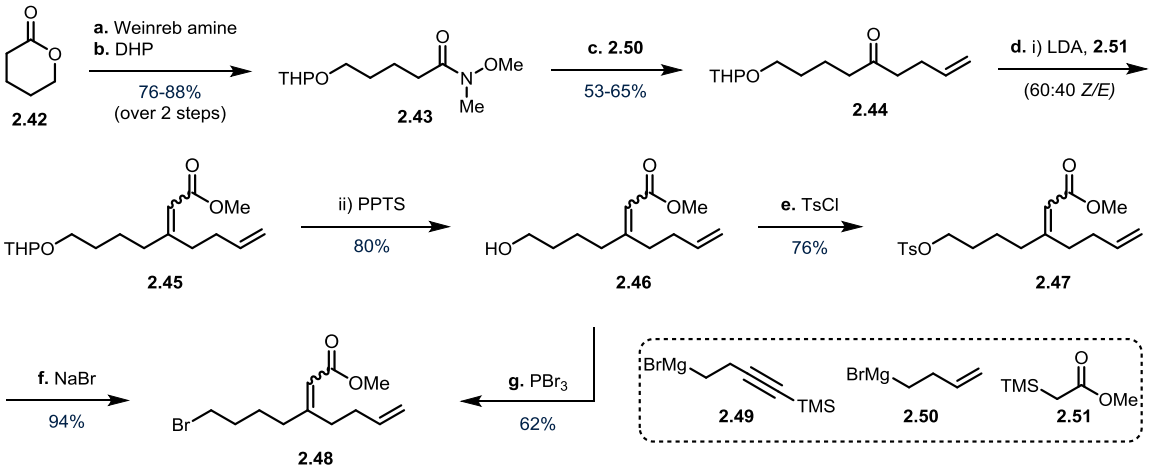
We envisaged a simple disconnection to cyclisation precursor **2.32** where the bromide would be derived from alcohol **2.38** (**Scheme 2-8**). This alcohol was envisaged to be the product of an olefination/deprotection sequence of ketone **2.39**. This unsymmetrical ketone was disconnected to Weinreb amide **2.41** and the Grignard reagent of bromide **2.40**. Finally, protected alcohol **2.41** would be obtained by opening of δ-valerolactone **2.42** with *N,O*-dimethylhydroxylamine hydrochloride followed by protection of the resulting primary alcohol.




**Scheme 2-8:** Disconnection strategy to form bromide **2.32**.

P: protecting group

Opening of δ-valerolactone **2.42** with *N,O*-dimethylhydroxylamine hydrochloride and protection of the resulting alcohol **2.43** as a THP ether went smoothly in excellent yield (**Scheme 2-9**, below). Unfortunately, despite being described in multiple publications,[116–118] we could not prepare the key Grignard reagent **2.49** from **2.40**. We originally thought this failure was due to potential impurities in **2.49** so we synthesised it using three different routes but this did not circumvent the problem; either no initiation or complete decomposition was obtained in all cases during the Grignard reagent formation.




**Scheme 2-9:** Synthesis of bromide **2.48**.

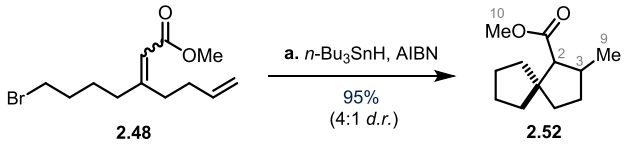
Reagents and conditions: (a) *N,O*-dimethylhydroxylamine hydrochloride (2.5 eq.), $^{i}$PrMgCl (5.0 eq.), THF, -20 °C, 2 h, 91%; (b) DHP (1 eq.), PPTS (0.1 eq.), $CH_2Cl_2$, r.t., 83-97%; (c) but-3-en-1-ylmagnesium bromide (1.5 eq.), THF, 0 °C, 1 h, 53-65%; (d) i) LDA (4.5 eq.), **2.51** (4.5 eq.), THF, -78 °C to 0 °C, 2 h; ii) PPTS (0.1 eq.), MeOH, r.t., 3 d, 80%; (e) TsCl (2.2 eq.), pyridine (2.2 eq.), $CH_2Cl_2$, r.t., 30 h, 76%; (f) NaBr (5.0 eq.), DMF, r.t., 48 h, 94%; (g) $PBr_3$ (0.5 eq.), $Et_2O$, -10 °C to r.t., 16 h, 62%.

We decided to continue this study with the alkene derivative homoallyl bromide instead. In fact, the corresponding Grignard reagent **2.50** could be formed uneventfully and reacted with Weinreb amide **2.43** cleanly but in moderate yield to deliver the resulting ketone **2.44**. Treatment of this ketone

using the Peterson olefination conditions found by Heyao Shi during his SBM CDT rotation project provided us with the α,β-unsaturated ester **2.45** as a mixture of isomers. Subsequent deprotection (in a one-pot sequence) gave primary alcohol **2.46** in very good yield (80% from ketone **2.44**). Finally, bromide **2.48** could be obtained in 71% yield from a tosylation/bromide displacement sequence (71% over 2 steps) or in 62% a single step using phosphorus tribromide.

### 2.2.2 Cyclisation of bromide 2.48

Alkyl bromides are classic substrates for radical initiations using tributyltin hydride and a radical initiator,[119,120] and we found that treatment of our bromide **2.48** (0.04 M) with slow addition of tributyltin hydride (1.2 eq., 0.6 eq./h) in the presence of AIBN in benzene at reflux gave the non-polar bicyclic product **2.52** in excellent yield (95%, 4:1 *d.r.*) after 4 h.



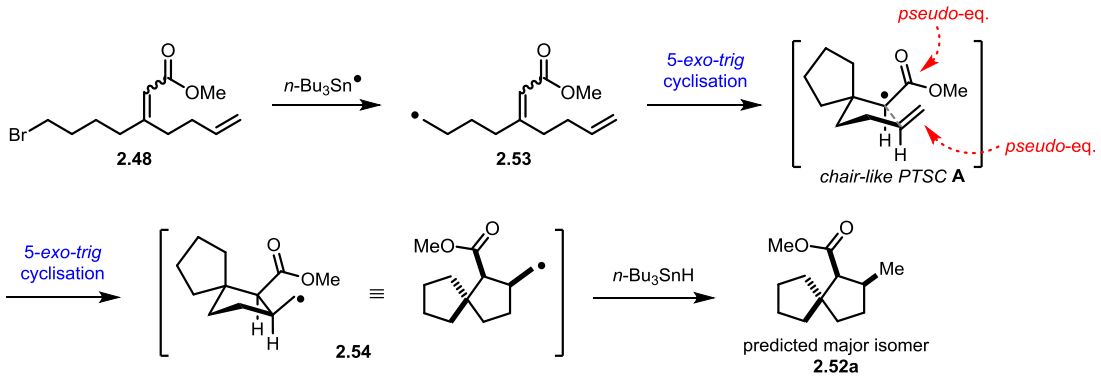

**2.48** **2.52**

**Scheme 2-10:** Cyclisation of bromide **2.48** to spiro[4.4]nonane **2.52**.

Reagents and conditions: (a) *n*-$Bu_3SnH$ (1.2 eq.), AIBN (0.05 eq.), $C_6H_6$ (0.04 M), reflux, 4 h, 95% (4:1 *d.r.*).

When this reaction was performed by adding all the reagents together at once, a mixture of products **2.52**, starting material **2.48** and other $UV_{254\ nm}$-active products was obtained. Based on $^1$H NMR, we hypothesised that these latter UV-active spots were reduced starting material. This was due to appearance of two new triplet (small *J* coupling, undetermined) resonance in the $^1$H NMR spectrum corresponding to α,β-unsaturated alkene protons that were found in 2:1 ratio (as with the starting bromide **2.48**). Spirocycle **2.52** was obtained in 4:1 *d.r.* but the relative stereochemistry of the newly formed centres could not be determined. In fact, $^1$H NMR nOe experiments conducted on the mixture of both isomers lead to inconclusive results. However, we expect *syn*-isomer **2.52a** to be the major product of the reaction (**Scheme 2-11**, below) assuming no isomerisation occurred. We expect the second 5-*exo*-*trig* cyclisation of radical **2.53** to adopt mainly the chair-like pre-transition state

conformation *PTSC* **A** based on the Beckwith-Houk model, where all substituents are in equatorial position.

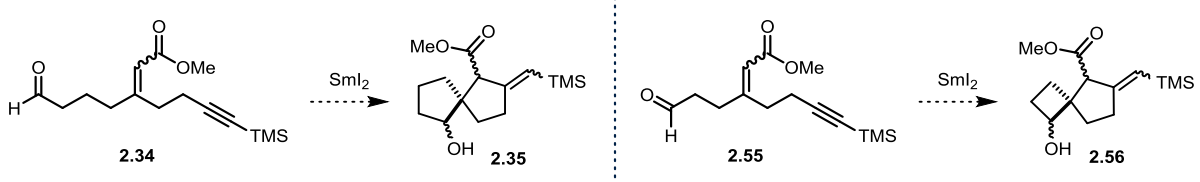



**Scheme 2-11:** Proposed major product for the cyclisation of bromide **2.48**.

These results were promising since we knew we could make spirocentres of this sort in excellent yield. We wanted to add some complexity to the reaction in order to obtain interesting compounds that could be used as possible 3D templates in the future. We therefore decided to move on to the synthesis of aldehyde **2.34** and explore its cyclisation.

## 2.3 Use of aldehydes cyclisation precursors

We next turned our attention to the aldehyde derivative **2.34** and the shorter chain analogue **2.55** as molecules of choice for the next phase of this project (**Scheme 2-12**, below). Aldehyde **2.34** was chosen as we would expect it to form the spiro[4.4]nonane **2.35** *via* two consecutive 5-*exo*-*trig* radical cyclisation upon treatment with Kagan's reagent ($SmI_2$). Aldehyde **2.55** would also be used to assess the feasibility of forming spiro[3.4]octane **2.56**, but more importantly its use as a key intermediate in the synthesis of the next study substrate (using a Knoevenagel condensation).

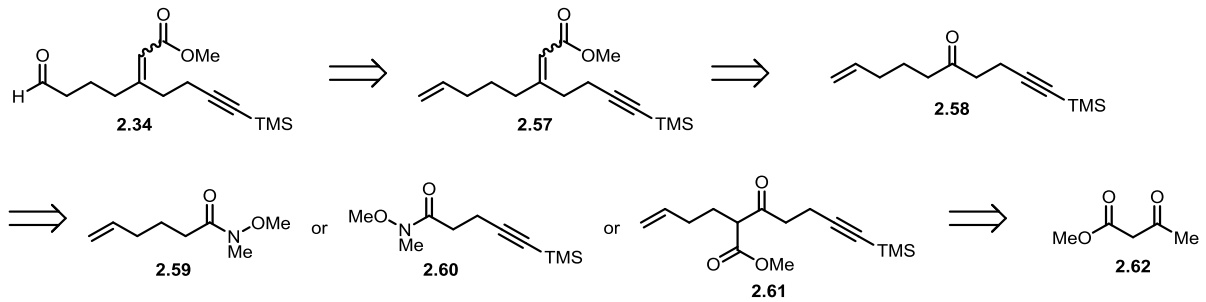



**Scheme 2-12:** Aldehydes **2.34**.and **2.55** and their desired cyclisation products **2.35** and **2.56** used in this study.

We decided it was worth persevering in synthesising the TMS-alkyne moiety of **2.32** instead of using a terminal alkene as was previously used (bromide **2.48**). Limiting ourselves to the use of a terminal alkene would result in reduced potential for further functionalisation. Using $SmI_2$ would result in a methyl group after cyclisation. In contrast, using an alkyne would produce alkene-containing products **2.56** and **2.35**, having much greater potential for further derivatisation.

### 2.3.1 Syntheses of aldehydes 2.34 and 2.55

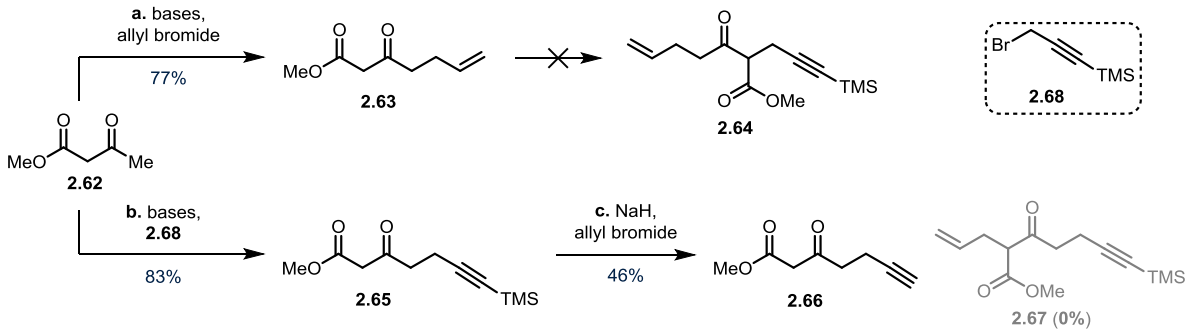
The new starting materials were disconnected as follows (**Scheme 2-13**, below). The aldehyde moiety was expected to come from a regioselective alkene cleavage. Alkene **2.57** would come from the classic olefination disconnection from ketone **2.58**, a structural motif we had experience in synthesising. We avoided using Weinreb amide **2.59** because it required use of Grignard reagent **2.49** that we previously failed to prepare. Disconnecting on the other side of the ketone functional group gave Weinreb amide **2.60** that would come from not readily available starting material, therefore another strategy was selected. A disconnection that led to a Krapcho decarboxylation gave rise to β-keto ester **2.61** as a candidate that would arise from α and γ alkylation of methyl acetoacetate **2.62** using two readily available electrophiles. A similar strategy could be envisaged for the other aldehyde **2.55** which led us to explore this route.




**Scheme 2-13:** Retrosynthetic analysis of aldehyde **2.34**.

γ-Alkylations of the dianion of methyl acetoacetate **2.62** (generated with NaH and *n*-BuLi) with allyl bromide or TMS-propargyl bromide **2.68** gave good yields of products **2.63** and **2.65** (77% and 83% respectively) (**Scheme 2-14**, below). Unfortunately, alkyne **2.68** failed to react with the mono-anion of **2.63** to form **2.64**. Likewise, the α-alkylation product **2.67** was not observed when the reaction of

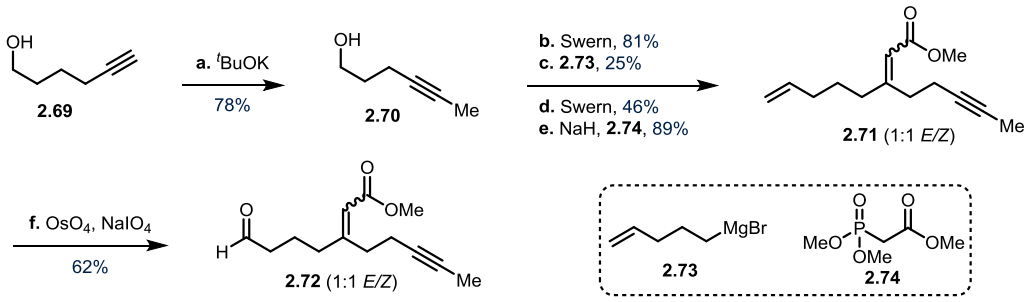
**2.65**, NaH and allyl bromide was attempted. Instead, the deprotected product **2.66** was isolated in 46% yield.




**Scheme 2-14:** Attempts to access aldehyde **2.55** *via* the Krapcho decarboxylation route.

Reagents and conditions: (a) NaH (1.25 eq.), *n*-BuLi (1.1 eq.), allyl bromide (1.0 eq.), THF, 0 °C, 2.5 h, 77%; (b) NaH (1.25 eq.), *n*-BuLi (1.1 eq.), **2.68** (1.0 eq.), THF, 0 °C, 2 h, 83%; (c) NaH (1.2 eq.), allyl bromide (1.0 eq.), THF, 0 °C to r.t., 3 h, 46%.

A reliable route towards our target aldehydes was yet to be identified. We eventually settled on the idea of a non-redox efficient sequence (**Scheme 2-15**, below). For practical reasons, we assessed the feasibility of our new route by synthesising alkyne **2.72** as a $SmI_2$-mediated cyclisation precursor. Terminal alkyne **2.69** was isomerised with potassium *tert*-butoxide and the resulting alcohol **2.70** was oxidised to the corresponding aldehyde using Swern conditions.[121] This aldehyde was treated with Grignard reagent **2.73**[122] to provide a secondary alcohol in low yield that was subsequently oxidised (Swern conditions) and olefinated (Horner-Wadsworth-Emmons reaction) with trimethyl phosphonoacetate **2.74**.[123]

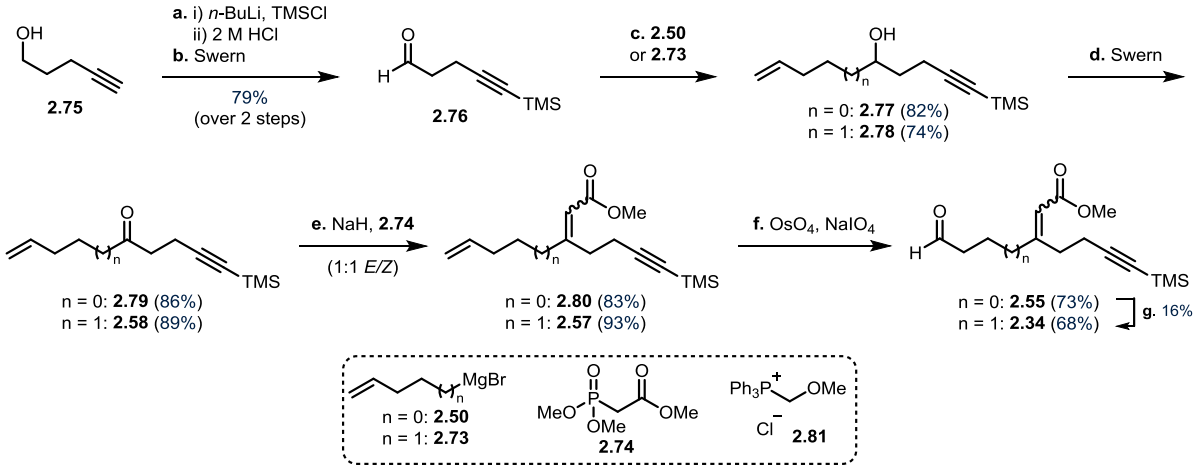



**Scheme 2-15:** Synthesis of alkyne **2.72**.

Reagents and conditions: (a) $^t$BuOK (2.0 eq.), DMSO, 0 °C, 4.5 h, 78%; (b) $(COCl)_2$ (1.1 eq.), DMSO (2.2 eq.), $Et_3N$ (5.0 eq.), $CH_2Cl_2$, -78 °C to r.t., 1.3 h, 81%; (c) **2.73** (2.4 eq.), THF, -78 °C, 1.5 h; 25%; (d) $(COCl)_2$ (1.1 eq.), DMSO (2.2 eq.), $Et_3N$ (5.0 eq.), $CH_2Cl_2$, -78 °C to r.t., 2.3 h, 46%; (e) **2.74** (4.5 eq.), NaH (4.5 eq.), THF, 50 °C, 16 h, 89% (1:1 *E*/*Z* mix.); (f) $OsO_4$ (0.02 eq.), $NaIO_4$ (4.0 eq.), 2,6-lutidine (2.0 eq.), 3:1 1,4-dioxane/$H_2O$, r.t., 45 min, 62% (1 :1 *E*/*Z* mix.).

These conditions provided α,β-unsaturated ester **2.71** as a mixture of the 2 alkene isomers in equal proportion. Lemieux–Johnson oxidation (Jin's modification)[124] of diene **2.71** cleaved the most electron-rich alkene to the corresponding aldehyde **2.72** in a satisfactory yield of 62%. This aldehyde **2.72** sample (30 mg) was kept in the freezer under argon atmosphere for future use.

This long but reliable route was replicated uneventfully to synthesise both aldehydes **2.55** and **2.34** from the common intermediate **2.76** (**Scheme 2-16**). The Grignard additions proceeded smoothly this time, giving the corresponding alcohols **2.77** and **2.78** in yields over 70%. All the subsequent steps gave similar or better yields than our methyl-alkyne substrate. Chronologically, aldehyde **2.55** was the first to be made and was then used as a substrate in a 1-carbon homologation using phosphonium salt **2.81** in a Wittig olefination. Unfortunately, product **2.34** was isolated in only 16% at that time. We later realised that decomposition could be occurring due to long reaction duration (16 h) which could explain this low yield. Because of that poor yield, the route described in




**Scheme 2-16:** Syntheses of aldehydes **2.55** and **2.34**.

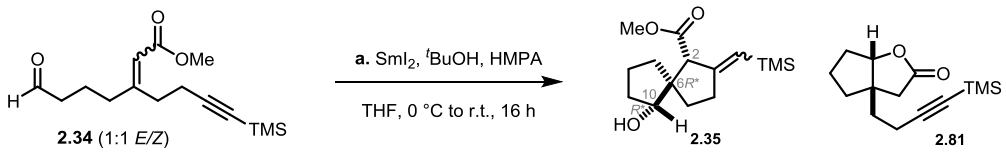
Reagents and conditions: (a) i) *n*-BuLi (2.2 eq.), TMSCl (3.0 eq.), -78 °C to r.t., 2.5 h; ii) 2 M HCl, r.t., 15 min, quant.; (b) $(COCl)_2$ (1.1 eq.), DMSO (2.2 eq.), $Et_3N$ (5.0 eq.), $CH_2Cl_2$, -78 °C to r.t., 2 h, 79%; (c) **2.50** (1.0 eq.) or **2.73** (2.0 eq.), THF, -78 °C, 1.5 h or 5 h; 82% (**2.77**) or 74% (**2.78**); (d) $(COCl)_2$ (1.1 eq.), DMSO (2.2 eq.), $Et_3N$ (5.0 eq.), $CH_2Cl_2$, -78 °C to r.t., 30 min or 40 min, 86% (**2.79**) or 89% (**2.58**); (e) **2.74** (3.0 eq.), NaH (3.0 eq.), THF, 50 °C, 25 h or 3 d, 83% (**2.80**) (1:1 *E*/*Z* mix.) or 93% (**2.57**) (1:1 *E*/*Z* mix.); (f) $OsO_4$ (0.02 eq.), $NaIO_4$ (4.0 eq.), 2,6-lutidine (2.0 eq.), 3:1 1,4-dioxane/$H_2O$, r.t., 20 min or 30 min, 73% (**2.55**) (1:1 *E*/*Z* mix.) or 68% (**2.34**) (1:1 *E*/*Z* mix.); (g) i) **2.81** (1.6 eq.), *n*-BuLi (1.5 eq.), THF, r.t., 1 h; ii) 2 M HCl, 16 h, 16%.

**Scheme 2-16** was eventually utilised for the other cyclisation precursor. The aldehydes could now be synthesised in 34% (for **2.55**) and 33% (for **2.34**) respectively, over 6 steps.

Aldehydes **2.55** and **2.34** are unexpectedly unstable. It is only once we were ready to cyclise aldehyde **2.34** with $SmI_2$ (see next section) that we realised that they decomposed overnight in the freezer under an argon atmosphere forming a complicated mixture. Likewise, aldehyde **2.55** and aldehyde **2.72** had both turned into black mixtures under the same storage conditions. We later found that aldehydes **2.55** and **2.34** were relatively stable once frozen separately in benzene (aldehyde **2.72** was not synthesised again in the event). This was not especially convenient as we had to thaw/concentrate the samples for every use, but still easier than synthesising them fresh every time.

### 2.3.2 Cyclisations of aldehydes with $SmI_2$

Kagan's reagent ($SmI_2$) was prepared from samarium metal and diiodoethane in THF based on Kagan's original procedure.[73] We turned our attention to the reductive cyclisation of **2.55** and **2.34** using literature conditions for a very similar system (making spiro[4.5]decanes).[123] We started by studying aldehyde **2.34** as a spiro[4.4]nonane should be readily formed. The results are presented in **Table 2.2** (below).



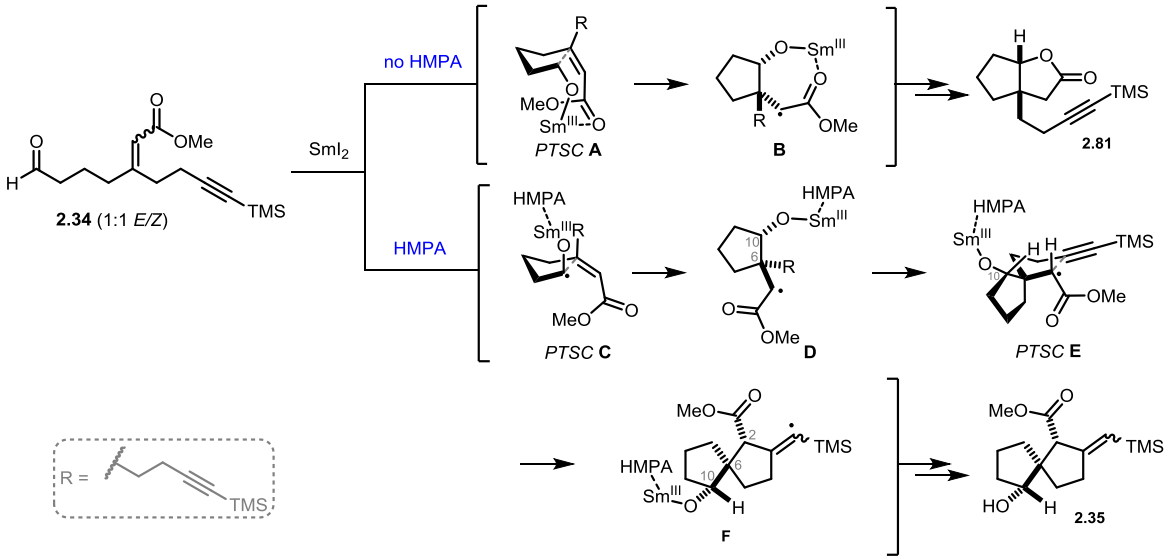

| entry[a] | $SmI_2$ (eq.) | $^t$BuOH (eq.) | HMPA (eq.) | product(s) (yield)[b] |
|---|---|---|---|---|
| 1 | 4.0 | - | - | **2.81** (30%) |
| 2 | 4.0 | 2.0 | - | **2.81** (60%) |
| 3 | 4.0 | 2.0 | 4.0 | **2.35**[c] (39%) + **2.81** (11%) |
| 4 | 4.0 | - | 4.0 | **2.35**[c] (30%) |

**Table 2.2**: Cyclization attempts with aldehyde **2.34**, $SmI_2$ and additives.

[a] reaction mixtures degassed using 3 freeze-pump-thaw cycles; [b] isolated yields; [c] corrected yield from a mixture of 2 desired diastereomers (2:1 ratio) + an undetermined alkyne of same molecular weight (25% by weight of the purified sample).

Treatment of aldehyde **2.34** (1:1 *E*/*Z* mix.) with $SmI_2$ (4.0 eq.) in THF gave a complicated mixture of products from which bicyclic lactone **2.81** could be isolated in 30% yield (entry 1). Adding *tert*-butanol (2 eq.) doubled the yield of **2.81** to 60% (entry 2). The formation of lactone **2.81** could be rationalised by a chelation-controlled 5-*exo*-trig cyclisation (see *PTSC* **A**→**B** in **Scheme 2-17**, *top*). In fact, the resulting secondary samarium(III) alkoxide **B**, possibly coordinating the ester to give a chelated intermediate, could aid the lactonisation. Chelation is probably also the reason for obtaining the required configuration at the secondary alcohol centre to allow lactonisation. No tricyclic product has been identified suggesting that radical **B** undergoes reduction before cyclisation onto the alkyne occurs.

Addition of 4 eq. of HMPA drastically changed the outcome of the reaction (entry 3). Lactone **2.81** was only isolated in 11% along with a mixture of only two diastereomers of **2.35** in a 2:1 ratio (39%). To complete the set of conditions, we decided to omit *tert*-butanol (entry 4) and observed a decrease in yield for both products (30% of **2.35** and traces of **2.81**) in analogy to entries 1-2.

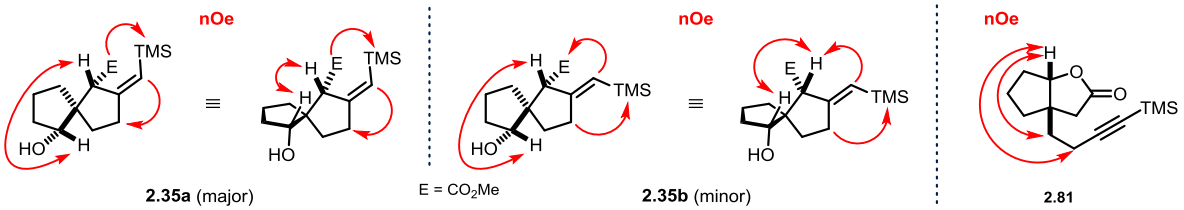



**Scheme 2-17:** Possible 5-*exo*-trig cyclization selectivity explanation with (*bottom*) or without (*top*) HMPA of **2.34**.

In contrast to product **2.81** formation, when HMPA was used, it was thought to coordinate to the samarium(III) alkoxide intermediate leading to *PTSC* **C** that minimised dipolar repulsion therefore reducing the propensity towards chelation between the samarium(III) alkoxide and the ester during

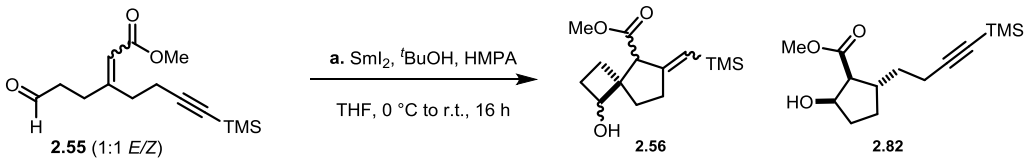
the first cyclisation *PTSC* **C→D** (**Scheme 2-17**, *bottom*).[123] This proposed arrangement would explain the *anti*-relationship between the alcohol at C(10) and the C(6) substituent in structure **D**. Once the first cyclisation has occurred, a modified Beckwith-Houk model arrangement *PTSC* **E** can be hypothesised where the more hindering part of the cyclopentane labelled C(10) in the structure as well as the methyl ester are placed in a *pseudo*-equatorial position; this again conveniently keeps them apart for the second cyclisation **E→F**.

The purification of these reaction mixtures containing HMPA were especially challenging because of the presence of a multitude of by-products. Products **2.35** could not be isolated cleanly to allow calculation of a meaningful yield. Instead, they could be isolated along with a TMS-alkyne-containing product of unknown structure as an impurity (25% based on $^1$H NMR integrations). We thought this would be acceptable as a MS analysis of this product (from its TLC plate spot) showed the same *m/z* as our expected products. Another purification by column chromatography provided us with a sample of only our desired products for full characterisation. The relative configuration of both spiro[4.4]nonanes **2.35** were determined using $^1$H NMR nOe analysis on a ~1:1 mixture of **2.35** isomers. Fortunately, the key protons CH-(2), $CH_2$-(4), CH-(10) and alkene protons of both isomers were properly resolved in the $^1$H NMR spectrum (in $CDCl_3$) allowing an unambiguous assignment of these isomers (**Scheme 2-18**, below).




**Scheme 2-18:** Indicative nOe interations observed for spirocycles **2.35a**/**b** (*left* and *middle*) and fused bicycle **2.81** (*right*).

With these interesting results, we decided to try the more challenging cyclisation of aldehyde cyclization precursor **2.55** (Table 2.3, below) using the conditions that gave the best results with the previous substrate (Table 2.2, above, entries 2-3).

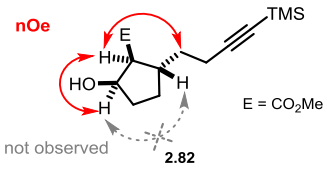



| entry[a] | $SmI_2$ (eq.) | $^t$BuOH (eq.) | HMPA (eq.) | product (yield)[b] |
|---|---|---|---|---|
| 1[c] | 4.0 | 2.0 | - | **2.82** (17%) |
| 2[c] | 4.0 | 2.0 | 4.0 | -[d] |

**Table 2.3**: Cyclization reactions with aldehyde **2.55**, $SmI_2$ and additives.

[a] reaction mixtures degassed using 3 freeze-pump-thaw cycles; [b] isolated yields; [c] complex mixture obtained; [d] no identifiable product was obtained.

Treatment of aldehyde **2.55** with $SmI_2$ (4 eq.) and *tert*-butanol (2 eq.) gave a complex mixture of products from which a compound containing alcohol, alkyne and ester stretches in the infrared spectrum (3470, 2176 and 1720 $cm^{-1}$ respectively) was isolated in poor yield (17%). This compound was assigned to cyclopentane **2.82** from its analytical data. Formation of **2.82** could be explained by a 5-*endo*-*trig* radical cyclisation instead of the expected 4-*exo*-*trig* cyclisation. Once again, the alcohol has been shown to be *syn* to the ester (nOe analyses, **Scheme 2-19**, below) showing a possible chelation of the ester promoting the 5-*endo*-trig cyclization. This is in accordance with the results obtained with addition of HMPA (entry 2) where a complex mixture of products was obtained (no identifiable products by $^1$H NMR).




**Scheme 2-19:** Indicative nOe interations observed for cyclopentane **2.82**.

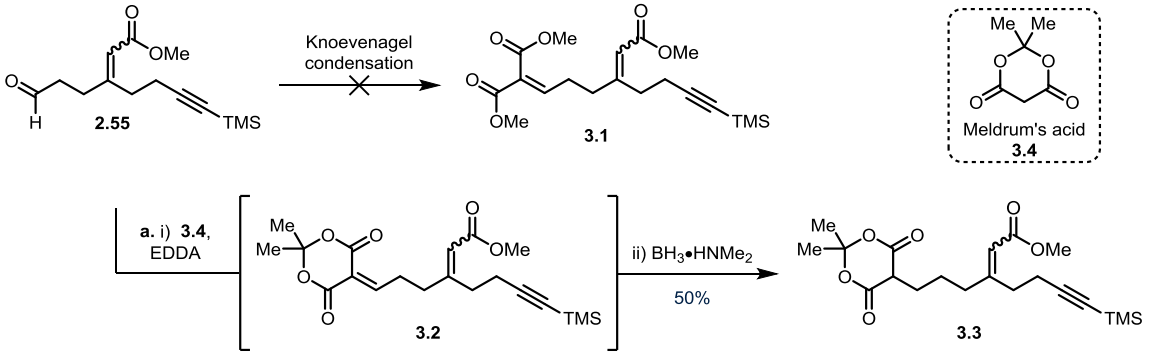
Having briefly explored spirocyclisation under reductive conditions, we moved to examining oxidative radical cyclisation.

# 3 Cyclisation Study using Manganese(III) Triacetate Dihydrate

## 3.1 Cyclisation of Meldrum's acid derivatives

### 3.1.1 Preparation of the substrates

Due to the inherent difficulties of performing Knoevenagel condensation reactions of malonates with non-aromatic aldehydes, we have yet to find any conditions for the synthesis of alkylidene malonate **3.1** from aldehyde **2.55** (**Scheme 3-1**). Instead, we found that aldehyde **2.55** could be reacted with Meldrum's acid **3.4** in a presence of an amine complex (EDDA) leading to intermediate **3.2** that was then reduced with a borane amine complex to Meldrum's acid derivative **3.3** (Meldrum's acid analogue of **2.31** in **Scheme 2-6** (page 28)) in 56% yield.[125]




**Scheme 3-1:** Synthesis of Meldrum's acid derivative **3.3**.

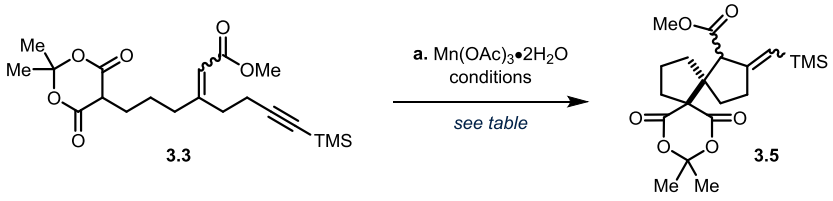
Reagents and conditions: (a) i) Meldrum's acid (1.55 eq.), ethylenediamine diacetate (EDDA) (0.25 eq.), EtOH, r.t., 55 min; ii) $BH_3$•$HNMe_2$, r.t., 1.25 h, 56% (55:45 *E*/*Z* mix.).

Despite the acceptable 56% yield, this reaction proved to be difficult to control. Choosing when to quench the reaction with borane dimethylamine complex proved to be a difficult task as diene **3.2** was unstable on silica and gave a multitude of spots by TLC analysis. For this reason, knowing when this species was consumed was a challenge and quenching the reaction too early resulted in a reduced yield. At the same time, leaving the reaction stirring for too long resulted in the decomposition of the (*Z*)-isomer of our alkene product. This was problematic as we ideally needed **3.3** in consistent *E*/*Z* ratio for the cyclisation study. Once optimised, we were limited to a 'blind'

quench of the reaction after 1 h at room temperature. Moreover, this reaction required an excess of Meldrum's acid which was difficult to separate from our desired products **3.3** on TLC as both were streaking on silica. We also found that cyclisation precursor **3.3** was mildly unstable and would form an appreciable amount of very polar degradation products after a week when stored neat in a freezer under argon atmosphere. Attempts to isolate diene **3.2** were unsuccessful.

### 3.1.2 Results of cyclisation of Meldrum's acid derivative 3.3

Having access to Meldrum's acid derivative **3.3**, we subjected it to a variety of cyclisation conditions. Compound **3.3** (55:45 *E*/*Z* mixture) was first subjected to conditions developed by Snider and co-workers for the cyclisation of Meldrum's acid derivatives.[125] The use of $Mn(OAc)_3$ (2.0 eq.) and $Cu(OAc)_2$ (1.0 eq.) in EtOH at room temperature led to a complex mixture of products from which **3.5** could be isolated as a mixture of 4 diastereomers in 24% yield (see **Table 3.1**, entry 1). When Cu(II)




| entry | SM *E*/*Z* ratio | $Mn(OAc)_3 \bullet 2H_2O$ (eq.) | dilution (M)[a] | solvent | yield[b] |
|---|---|---|---|---|---|
| 1[c] | 55:45 | 2.0 | 0.05 | EtOH (dry) | 23% |
| 2 | 55:45 | 2.0 | 0.05 | EtOH (dry) | 14% |
| 3[c] | 55:45 | 2.0 | 0.05 | MeCN (dry) | 35% |
| 4 | 55:45 | 2.0 | 0.05 | MeCN (dry) | 46% |
| 5 | 55:45 | 2.0 | 0.05 | MeCN (wet) | 41% |
| 6 | 55:45 | 2.0 | 0.10 | MeCN (dry) | 31% |
| 7 | 55:45 | 1.0 | 0.05 | MeCN (dry) | 44% |
| 8[d] | 55:45 | 0.5 | 0.05 | MeCN (dry) | 33% |
| 9[e] | 74:26 | 2.0 | 0.05 | MeCN (dry) | 27% |

**Table 3.1**: Cyclisation reactions of alkyne **3.3** with Mn(III) and additives.

Reagents and conditions: (a) $Mn(OAc)_3 \bullet 2H_2O$ (*see table*), solvent (degassed using $N_2$ sparging) (*see table*), r.t., 22-25 h. Reactions performed on > 70 mg unless otherwise stated; [a] relative to **3.3**; [b] isolated yields as a mixture of 4 diastereomers in ~47:36:10:7 ratio for entries using MeCN as solvent (undetermined for EtOH entries); [c] with $Cu(OAc)_2 \bullet H_2O$ (1.0 eq.) as an additive; [d] 28% of **3.3** (74:26 E/Z mix.) was recovered; [e] reaction performed on 33 mg scale.

salt was omitted, **3.5** was isolated in 14% yield (entry 2). Opposite results were obtained when MeCN was used as the reaction solvent but an important increase in yield was obtained with 35% with Cu(II) salt and 46% without (entries 3 and 4). $Mn(OAc)_3$ and $Cu(OAc)_2$ are hydrated complexes but dry solvents were still used in order to control the amount of water in the system. When MeCN was used from the bottle (wet), we observed a 5% decrease in yield (41%, entry 5) and a 10% decrease when the concentration with respect to starting material was doubled (entry 6).

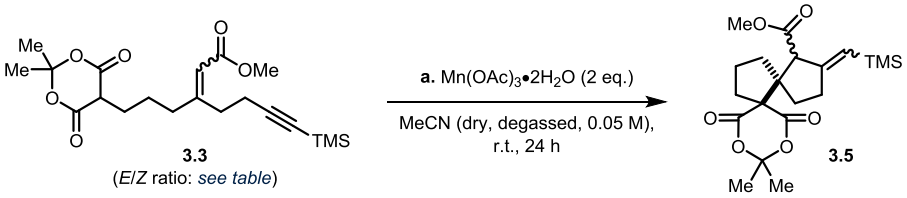
We propose that only 1 eq. of $Mn(OAc)_3$ is required in order to form the one electron oxidation product of **3.3** (if a chain process occurs). In fact, when 1 eq. of $Mn(OAc)_3$ was used, a similar yield (44%) was obtained. While the initiation step was clear, the termination was less so. As briefly discussed in **Section 1.2.3.3.1**, neither Mn(III) nor Cu(II) salts can oxidise vinyl radicals.[89] In the absence of an obvious hydrogen atom donor, we speculated that it had to come from another starting material molecule *via* a radical chain reaction process. The use of a substoichiometric amount of $Mn(OAc)_3$ (0.5 eq.) gave a lower 33% yield of **3.5** (entry 8) which does not rule out the possibilities of a chain process. However interestingly, the unreacted starting material **3.3** was recovered in a different 74:26 *E/Z* ratio than we started with (55:45), in 28% yield. A depletion of (*Z*)-**3.3** implies that this isomer was consumed faster than (*E*)-**3.3** and resubmission of this mixture to our best conditions (conditions of entry 4) resulted in an intriguing 27% yield. From this result, we saw a clear dependence of the yield upon the isomer ratio used. We hypothesized that the consumption of (*Z*)-**3.3** had to be more productive (making **3.5**) as well being faster or, in other words: (*Z*)-**3.3** cyclises better than (*E*)-**3.3**.

Given that a mixture containing 45% of (*Z*)-**3.3** gave 46% yield of **3.5** (entry 4) and that a mixture containing 26% of (*Z*)-**3.3** gave 27% yield of **3.5** (entry 9), we envisaged that the use of pure (*Z*)-**3.3** could theoretically form product **3.5** in near quantitative yield.

The above hypothesis brought a new challenge to this project. We required both alkene isomers of **3.3** in pure form in order to test the above hypothesis and due to the difficulties in separating the *E*/*Z*

isomers of cyclisation substrate **3.3** (or precursors of it) we embarked on new synthetic route towards **3.3**. This decision was based on promising yields for this polycyclisation reaching almost 50% and possibly much higher if our hypothesis was correct.

After the successful preparation of both geometrical isomers in ≥ 95% purity (the route will be described in more detail in **Section 3.2.2**, page 48), we subjected them to the previously described reaction conditions (**Table 3.2**, below). (*Z*)-**3.3** gave **3.5** in better yield (60%, entry 4) than (*E*)-**3.3** (31%, entry 3), hence confirming that (*Z*)-**3.3** was a better cyclisation precursor.

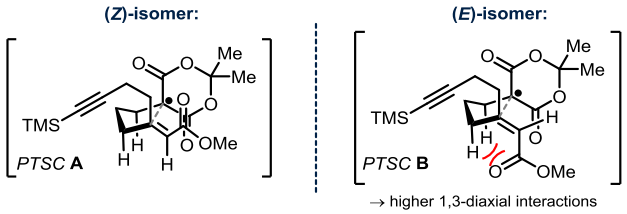



| entry | SM *E*/*Z* ratio | yield[a] |
|---|---|---|
| 1 | 55:45 | 46% |
| 2[b] | 74:26 | 27% |
| 3 | > 95:5 | 31% |
| 4 | 5:95 | 60% |

**Table 3.2**: Hypothesis interrogation for the cyclisation of (*Z*)- and (*E*)-**3.3** with Mn(III) and additives. Reactions performed on > 70 mg unless otherwise stated; [a] isolated yields as a mixture of 4 diastereomers in ~47:36:10:7 ratio; [b] reaction performed on 33 mg scale.

These results are both interesting as it is a considerable improvement in terms of yield, but also disappointing as we were expecting a greater discrepancy (better yield for entry 4 and lower for entry 3) between the reactivity of these two isomers.

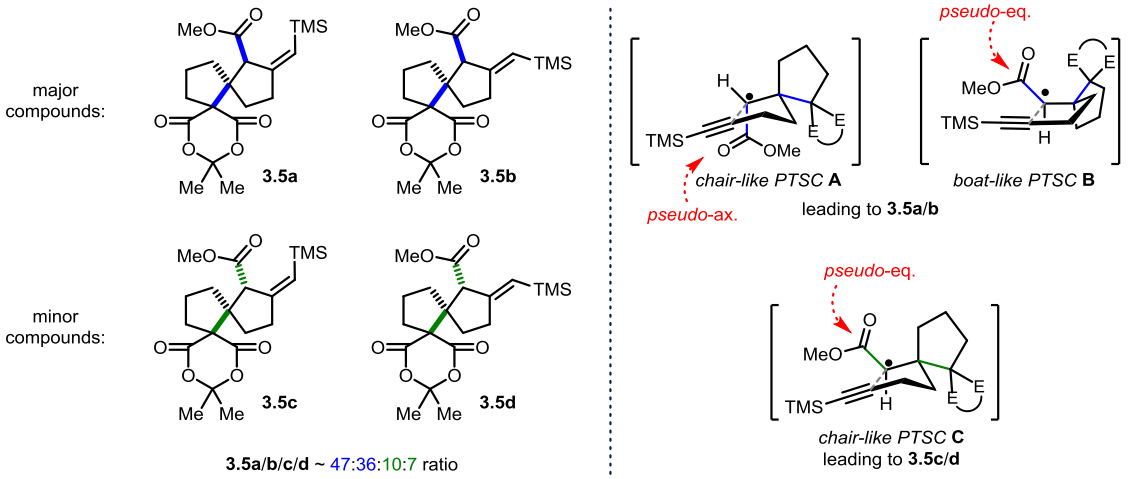
The greater results obtained with (*Z*)-**3.3** can be rationalised by the lower steric hindrance observed in the proposed chair-like pre-transition state conformation in the first cyclisation (**Scheme 3-2**, *left*, below). The (*E*)-isomer suffers from a greater 1,3-diaxial interaction between the *pseudo*-axial ester group and the hydrogen compared to the two axial hydrogens for the (*Z*)-isomer.




**Scheme 3-2:** Comparison of the pre-transition state conformations for the first cyclisation of (*Z*)- and (*E*)-**3.3** after initiation with $Mn(OAc)_3$.

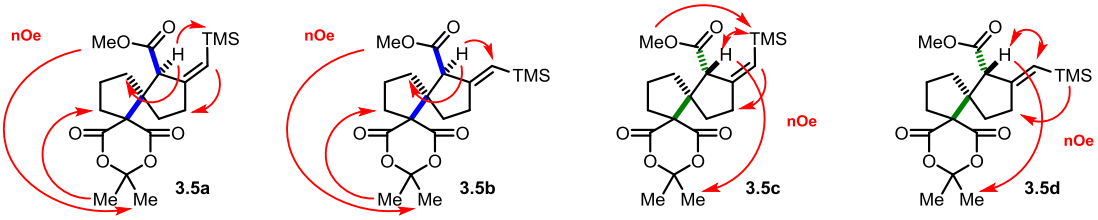
For all the entries in **Table 3.1** and **Table 3.2**, spirocycle **3.5** was obtained as a mixture of 4 diastereomers. The product distribution in all cases was approximately 47:36:10:7 in MeCN (**Scheme 3-3**, *right*, below). The distributions in EtOH were not determined as these older experiments were lacking a $Na_2S_2O_{3\,(aq)}$ quench in their procedure. This quenching procedure developed in the group, was paramount to analyse the reactions by $^1$H NMR as it removed paramagnetic Cu(II) species.

Although we were unable to separate all 4 diastereomers, a mixture of both major isomers, and both minor isomers could be isolated and $^1$H NMR nOe experiments were used to determine their stereochemistry (**Scheme 3-4**, below).




**Scheme 3-3:** Product distribution of **3.5** (*left*) and comparison of the proposed pre-transition state conformations of the second cyclisation of (*Z*)- and (*E*)-**3.3** after initiation with $Mn(OAc)_3$ (*right*).

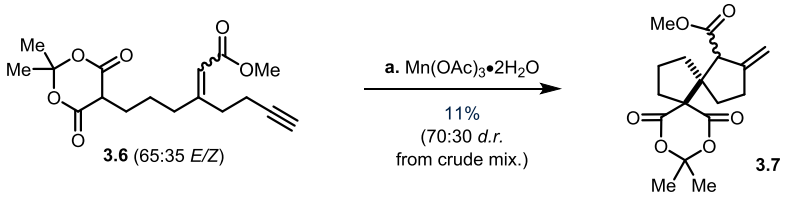
We found that the major isomers (**3.5a**/**b**) only differ in the configuration at the alkene and this was also the case for the minor isomers (**3.5c**/**d**) which confirmed an expected low selectivity during the termination hydrogen atom transfer step.




**Scheme 3-4:** Indicative nOe interations observed for meldrum's acid derivatives **3.5a-d**.

However, the selectivity at the α-ester centre was opposite to what we could predict. Considering an adapted Beckwith-Houk model to cyclisation on alkynes, we could envisage the chair-like pre-transition state conformation *PTSC* **C** (**Scheme 3-3**, *bottom-right*) where we keep both the Meldrum's acid and the ester moieties in *pseudo*-equatorial to be the lowest in energy. This is proposed to minimise the overall energy of the system and it was expected to be the major reaction pathway forming **3.5c/d**. However, the experimental data shows the opposite selectivity. This is comparing with *PTSC* **A** (*top-right*) where the ester is now in a *pseudo*-axial, which is expected to be higher in energy (for simple systems). The boat-like *PTSC* **B** could also contribute to the formation of the major compounds. It is important to note that the Beckwith-Houk model was based on cyclisation of 5-hexenyl radicals but no analogous research has been done on alkynes. Given that the previous predictions described (**Section 2.3.2**) were in keeping with the modified model, we proposed that the Meldrum's acid part of the molecule interacts with the rest during the cyclisation.

Terminal alkyne **3.6** could be obtained using the previously described Knoevenagel/reduction from the corresponding terminal alkyne aldehyde starting material. We obtained **3.6** in a 65:35 *E/Z* ratio that was used in the cyclisation reaction. The TLC of the crude mixture was complex, however we isolated the expected *exo*-alkene products **3.7** in 70:30 *d.r.* in 11% yield.




**Scheme 3-5:** Cyclisation of terminal alkyne **3.6** to *exo*-alkene **3.7**.

Reagents and conditions: (a) i) $Mn(OAc)_3 \bullet 2H_2O$ (2.0 eq.), MeCN (0.05 M), r.t., 20 h, 11%.

We envisaged that this lower yield could be explained by a poor termination step, as compared to the previous TMS-alkyne system, the resulting vinyl radical produced at the end will be much less sterically hindered. This would open numerous side-reaction pathways including radical-radical dimerization, intermolecular reactions with starting material or even with the desired product, *etc.*

Instead of optimising the reaction, we decided to focus on other systems (described in later sections of this manuscript), that were giving more promising results.

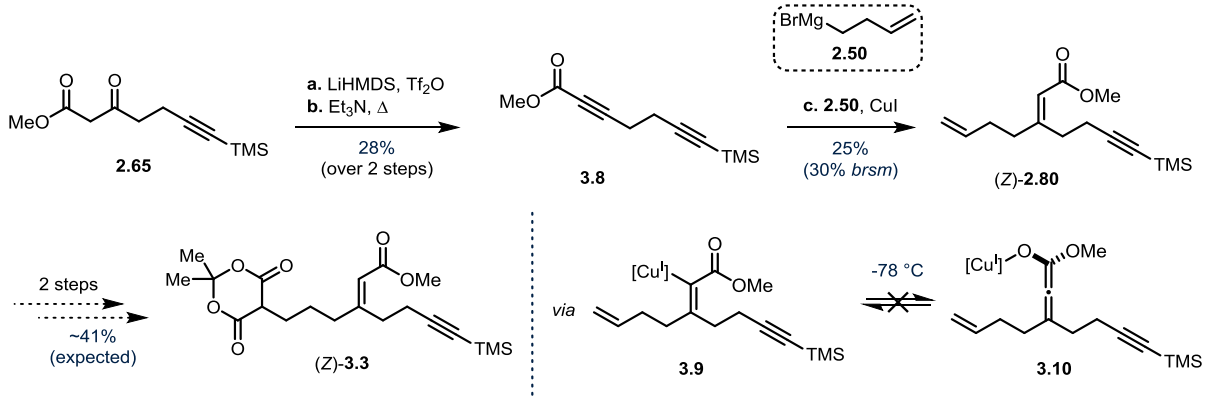
## 3.2 New syntheses of cyclisation precursors

This section aims to discuss how we developed an efficient route to **2.31** and, as a consequence, a route to both isomers of Meldrum's acid derivative **3.3** described in the previous section. In this section, we will present a series of reactions that inspired us towards the development of a unified route for the syntheses of the desired products.

### 3.2.1 Stereoselective synthesis of alkenes by the carbocupration of alkynes

One efficient method for the stereoselective syntheses of alkenes is the carbocupration of alkynes. Such reactions can be extremely selective if the quenching temperature is controlled.[126–130] In our system, we attempted to intercept our route to **3.3** at the alkene stage (previously discussed **Scheme 2-15**, page 34 and **Scheme 3-1**, page 41). Retrosynthesis yielded key synthons **3.8** and Grignard reagent **2.50** for the construction of **3.3** (**Scheme 3-7**, below).

Alkyne **3.8** was prepared in poor yield using a triflation/elimination procedure described by Lepore and co-workers.[131] The alkyne was subsequently treated with Grignard reagent **2.50** in the presence of copper(I) iodide and TMEDA at -78 °C in THF to form vinyl copper(I) species **3.9**. This was expected to be conformationally stable and not in equilibrium with allene **3.10** provided that the temperature did not exceed -30 °C.[126–128] The reaction was therefore quenched at -78 °C using MeOH (precooled to -78 °C) *via* cannula. This reaction gave (*Z*)-**2.80** as the only observable geometrical isomer in a low, but unoptimised 25% yield.




**Scheme 3-6:** Formal synthesis of isomerically pure (Z)-**3.3** *via alkene* (*Z*)-**2.80**.

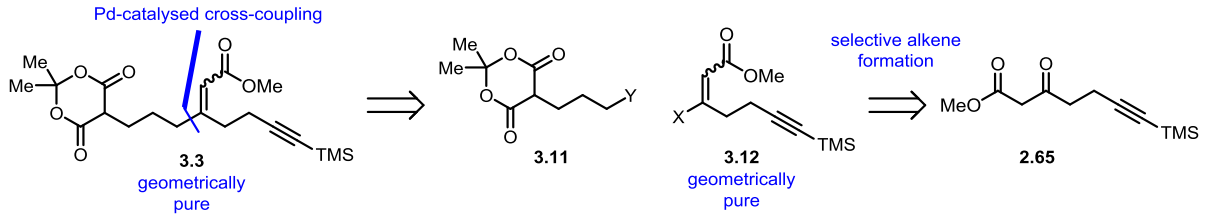
Reagents and conditions: (a) LiHMDS (2.0 eq.), $Tf_2O$ (1.0 eq.), THF, -78 °C, 2.5 h; (b) 1:10 $Et_3N$/THF, reflux, o.n., 28% (over 2 steps); (c) **2.50** (1.2 eq.), CuI (1.2 eq.), TMEDA (3.0 eq.), THF, -78 °C, 4.5 h, 25% (30% *brsm*).

This was a proof of concept that (*Z*)-**3.3** could be synthesised from (*Z*)-**2.80** using the previously described conditions. It was also discovered that the cuprate could be quenched with iodine to give a vinyl iodide,[126,128] and this could be a way to reintroduce the leaving group we omitted earlier in our study to simplify our system (discussed in **Section 2.2**)). One major drawback of this route was that it would not allow us to access the other isomer (*E*)-**3.3**.

We briefly explored other options to obtain alkyne **3.8** in synthetically useful quantity but without any success. However, the triflation/elimination strategy could be optimised by controlling the vinyl triflate geometry as reported by Lepore. In his report, good yields of alkyne were achieved when the triflate and the proton are anti to each other.[131] We then realised that we could directly use the intermediate vinyl triflate as a coupling partner in a Pd-catalysed cross-coupling reaction instead of obtaining the desired olefin *via* an alkyne synthesis followed by hydroalkylation.

### 3.2.2 Stereoselective synthesis of alkenes by Suzuki cross-coupling reaction

As described in the previous section, the inspiration for this new route comes from the intermediate triflate that precedes alkyne **3.8**. Nevertheless, a number of different methods are available for the selective formation of coupling coupling partners **3.12** for our new disconnection (**Scheme 3-7**, below). We were therefore not limited to just enol triflates as a coupling partner **3.12**.

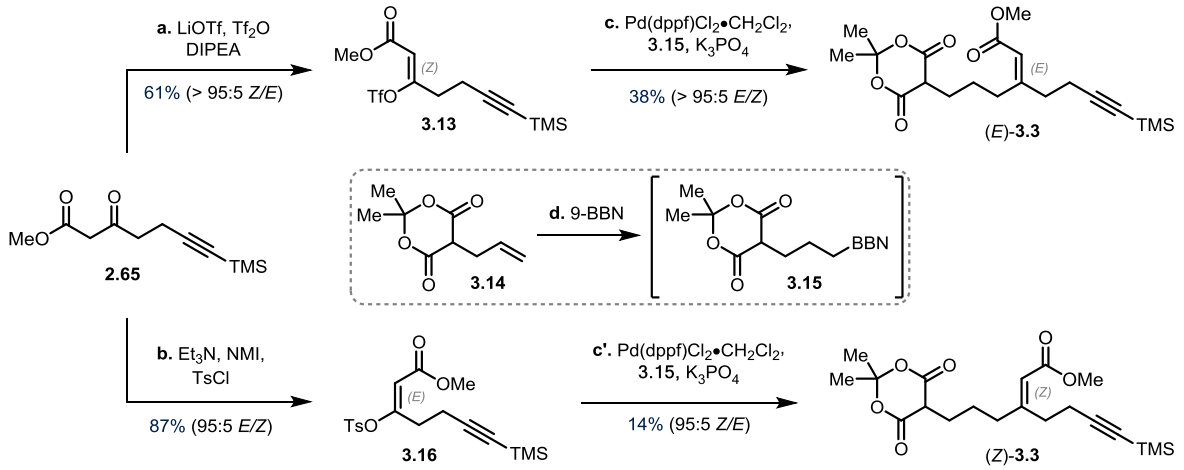



**Scheme 3-7:** Disconnection sequence utilising a Pd-catalysed cross-coupling reaction to form geometrically pure **3.3**.

A quick literature survey revealed that different methods were available to form **3.12** (different X groups) in a selective manner. For example, selective formation of vinyl halides have been reported but mainly utilises alkynes as starting materials. Examples using alkyl propiolate derivatives,[132–134] propiolic acid[135] or terminal alkynes[136] have been published.

We decided to prepare **3.12** (X = OTf) as routes to both geometrical isomers had been previously reported.[137–139] Additionally, these triflates are commonly used as substrates in cross coupling reactions using palladium complexes[140–143] or iron complexes[144,145] as catalysts. The 9-BBN-derived fragment **3.11** (Y = BBN) was identified as a potential coupling partner. We anticipated it could be prepared by hydroboration of the corresponding alkene and used *in situ*.[140,141] Apparent advantages for this strategy are the convergence and potentially efficient syntheses of both fragments. An additional advantage of this disconnection was the direct incorporation of the Meldrum's acid moiety in our molecule which renders the oxidative cleavage/Knoevenagel condensation/reduction strategy obsolete.

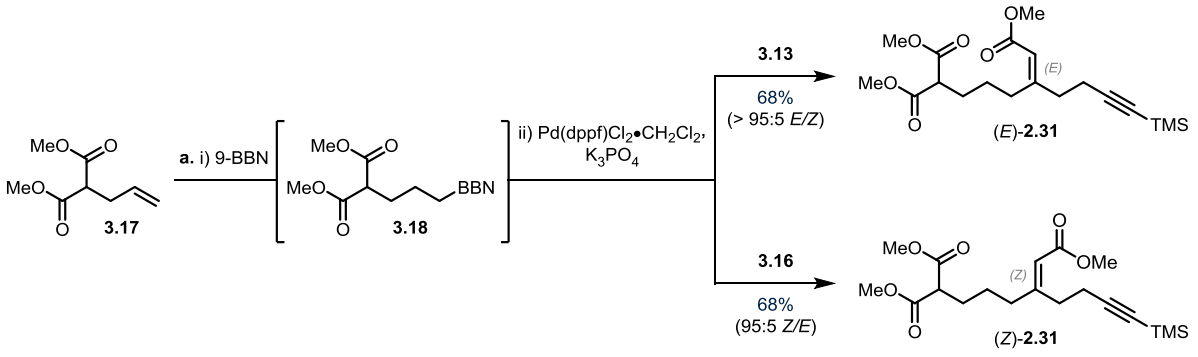
We found that (*Z*)-enol triflate **3.13** could be synthesized in a good 61% yield and with excellent selectivity using LiOTf as a chelating agent.[137] It was also discovered that the other isomer could not be synthesised using aqueous $NH_4OH$ as base as described by Frantz and co-workers as we observed a concomitant undesired TMS deprotection.[139] Instead, we found that tosylate **3.16** could be formed according to Tanabe and co-worker's work with good selectivity (95:5 *E*/*Z*) and excellent yield.[146] Published conditions for the one-pot hydroboration/Suzuki cross-coupling procedure were used to obtain (*E*)-**3.3** in a moderate 38% yield.[141] Similar conditions provided the other isomer (*Z*)-**3.3** in a lower 14% yield.




**Scheme 3-8:** Synthesis of geometrically enriched (*Z*)- and (*E*)-**3.3**.

Reagents and conditions: (a) LiOTf (2.0 eq.), DIPEA (1.1 eq.), $Tf_2O$ (2.0 eq.), $CH_2Cl_2$, 0 °C, 30 min, 61% (> 95:5 *Z*/*E* mix.); (b) *N*-methylimidazole (NMI) (1.5 eq.), $Et_3N$ (1.5 eq.), TsCl (1.5 eq.), PhCl, r.t., 1.3 h, 87% (95:5 *E*/*Z* mix.); (c) i) **3.14** (1.3 eq.), 9-BBN (2.6 eq.), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), $Pd(dppf)Cl_2•CH_2Cl_2$ (0.05 eq.), 1,4-dioxane/$H_2O$, 85 °C, 16 h, 38% (> 95:5 *E*/*Z* mix.); (c') i) **3.14** (1.3 eq.), 9-BBN (2.0 eq.), THF, 0 °C to r.t., 7 h; ii) $K_3PO_4$ (2.5 eq.), $Pd(dppf)Cl_2•CH_2Cl_2$ (0.05 eq.), 1,4-dioxane/$H_2O$, 75 °C, 6.5 h, 14% (95:5 *Z*/*E* mix.); (d) see first part of step c or c'.

Chronologically, these conditions were found to work satisfactorily to synthesise malonate derivatives (*Z*)-**2.31** and (*E*)-**2.31** and were then applied to form **3.3**. These conditions gave both isomers with an identical 68% yield using the same pseudohalides (**3.13** and **3.16**) and hydroborated dimethyl allylmalonate **3.17**. Gas was given off when 9-BBN was added to Meldrum's acid **3.14** which could indicate the formation of undesired adducts quenching 9-BBN while this was not observed in the malonate case. This could be explained by its more acidic α-proton (Meldrum's acid: p$K_a$ 7.3 in




**Scheme 3-9:** Synthesis of malonates (*E*)-**2.31** and (*Z*)-**2.31**.

Reagents and conditions: (a) i) dimethyl allylmalonate **3.17** (1.5 eq.), 9-BBN (1.6 eq.), degassed THF, 0 °C to r.t., 4 h; ii) for (*E*)-**2.31**: $K_3PO_4$ (2.5 eq.), triflate **3.13** or tosylate **3.16** (1.0 eq.), $Pd(dppf)Cl_2•CH_2Cl_2$ (0.05 eq.), degassed 1,4-dioxane/$H_2O$, 85 °C, < 5 h, 68% (> 95:5 *E*/*Z* mix.) for (*E*)-**2.31**, 68% (95:5 *Z*/*E* mix.) for (*Z*)-**2.31**.

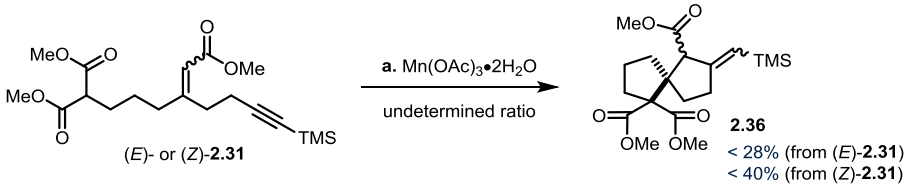
DMSO) compared to one of the malonate derivative (dimethyl malonate: p$K_a$ 15.9 in DMSO).[147]

The compounds (*E*)- and (*Z*)-**2.31** could now be synthesised efficiently utilising the unified strategy as shown in **Scheme 3-9**. We therefore decided to continue the studies on malonates due to their ease of preparation and stability. Nevertheless, this provided enough material **3.3** to test our hypothesis (**Table 3.2**, page 44).

## 3.3 Cyclisation of malonates trisubstituted α,β-unsaturated esters

### 3.3.1 Alkyne-containing substrates

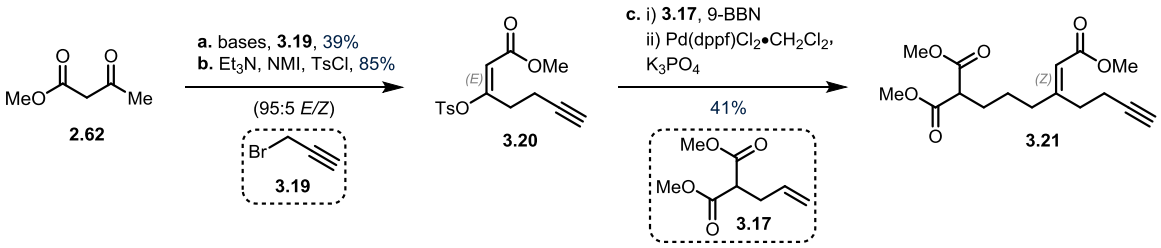
Compounds (*E*)-**2.31** and (*Z*)-**2.31** were both treated with the previously successful conditions using $Mn(OAc)_3$ (2 eq.) in MeCN (0.05 M) at reflux. Surprisingly, no conversion was observed after 24 h and only about 10-15% conversion after 7 days. Importantly, our recovered starting material was obtained without any erosion of the geometrical purity. This implied that the first cyclisation did not occur under these conditions as a reversible first addition would lead to isomerisation of our alkene double-bond. Acetic acid, another widely utilised solvent for these reactions,[89] also failed to induce any reaction and no consumption of starting material was observed after 12 days at reflux. Unexpectedly, dry ethanol performed much better leading to isolation of impure **2.36** from (*E*)-**2.31** and (*Z*)-**2.31** respectively (**Scheme 3-10**, below) after only 18 h at 75 °C. These reactions again showed a better yield for the (*Z*)-isomer compared to the (*E*)-isomer and the major isomer of **2.36** could be obtained pure and was the sole product to be fully characterised. The yields shown for these reactions (**Scheme 3-10**) are therefore for reference only.




**Scheme 3-10:** Cyclisation of malonate alkynes (*E*)- and (*Z*)-**2.31** to spirocycle **2.36**.

Reagents and conditions: (a) $Mn(OAc)_3•2H_2O$ (2.0 eq.), dry EtOH (0.05 M), 75 °C, 16 h, < 28% from (*E*)-**2.31**, < 40% from (*Z*)-**2.31**.

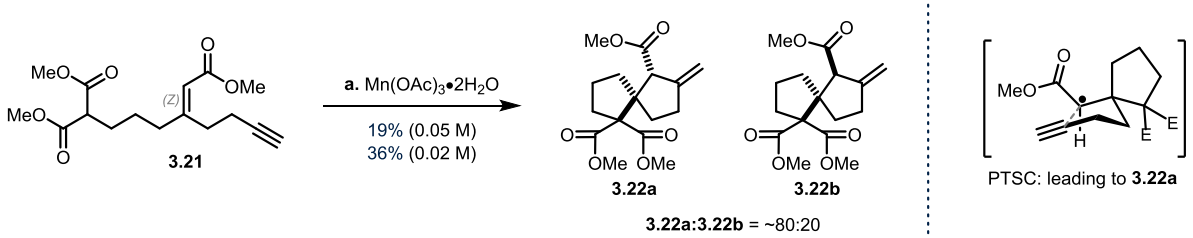
Due to the difficulty purifying the mixture of diastereomers, we decided to use the terminal alkyne **3.21** as substrate to remove the possibility of *E*/*Z* isomerism in the product (see synthesis in **Scheme 3-11**, below).




**Scheme 3-11:** Synthesis alkyne **3.21**.

Reagents and conditions: (a) NaH (1.25 eq.), *n*-BuLi (1.1 eq.), propargyl bromide **3.19** (1.0 eq.), THF, 0 °C, 2 h, 39%; (b) *N*-methylimidazole (NMI) (1.5 eq.), $Et_3N$ (1.5 eq.), TsCl (1.5 eq.), PhCl, r.t., 2.3 h, 85% (95:5 *E*/*Z* mix.); (c) i) **3.17** (1.5 eq.), 9-BBN (1.6 eq.), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), $Pd(dppf)Cl_2•CH_2Cl_2$ (0.05 eq.), 1,4-dioxane/$H_2O$, 85 °C, 3.5 h, 41%.

We proposed that EtOH was able to quench our vinyl radical before other undesired pathways could occur. Pleasingly, we found that we could obtain *exo*-alkenes **3.22a**/**b** from pure (*Z*)-**3.21** in a poor 19% yield at 0.05 M that increased to 36% when the reaction concentration was reduced to 0.02 M (**Scheme 3-12**, *left*).




**Scheme 3-12:** Cyclisation of malonate alkyne **3.21** and predicted favoured PTSC.

Reagents and conditions: (a) $Mn(OAc)_3•2H_2O$ (2.0 eq.), dry EtOH (0.05 M or 0.02 M), 75 °C, 4 h or 6 h, 19% (80:20 *d.r.*) or 36% (80:20 *d.r.*).

Both reactions provided the product as a mixture of isomers in 80:20 ratios. The major isomer **3.22a** was probably formed *via* the proposed favoured *PTSC* where both the malonate moieties and the ester are in *pseudo*-equatorial positions in the chair-like *PTSC* (**Scheme 3-12**, *right*).

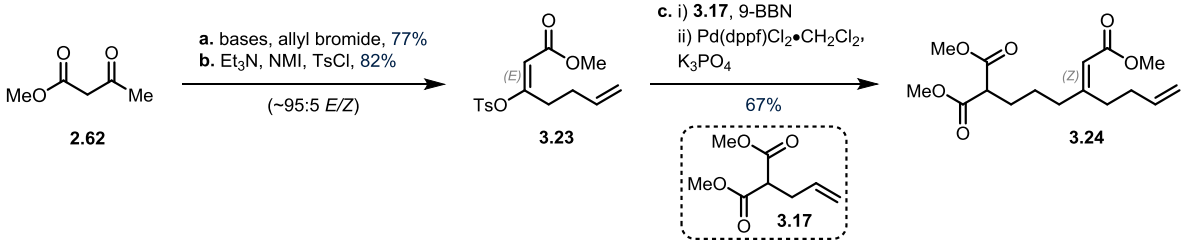
The selectivity of these reactions with the malonate western part is in striking contrast with the results obtained using the Meldrum's acid derivatives where the ester was pointing in the other direction.

This study on the polycyclisation of alkynes was kept short due to the poor yields obtained. We instead focussed on studying the polycyclisation reactions using terminal alkenes as the cyclisation precursors with the Mn(III)/Cu(II) strategy employed by Burton and others.[89,102] The study discussed in the next section led to important discoveries giving insight into why previous reactions were low yielding.

### 3.3.2 Use of terminal alkene-containing substrates

As discussed previously, Cu(II) salts have been used to efficiently terminate radical processes in the presence of $Mn(OAc)_3$. We envisaged that the Mn(III)/Cu(II) system could be used on alkene **3.24** to synthesise previously obtained *exo*-alkenes **3.22a**/**b**.

Alkene **3.24** had the advantage of being efficiently synthesised using our developed strategy (**Scheme 3-13**). We could obtain **3.24** as a pure (*Z*)-isomer after purification by flash-chromatography purification in 67% overall yield from readily available methyl acetoacetate **2.62**.



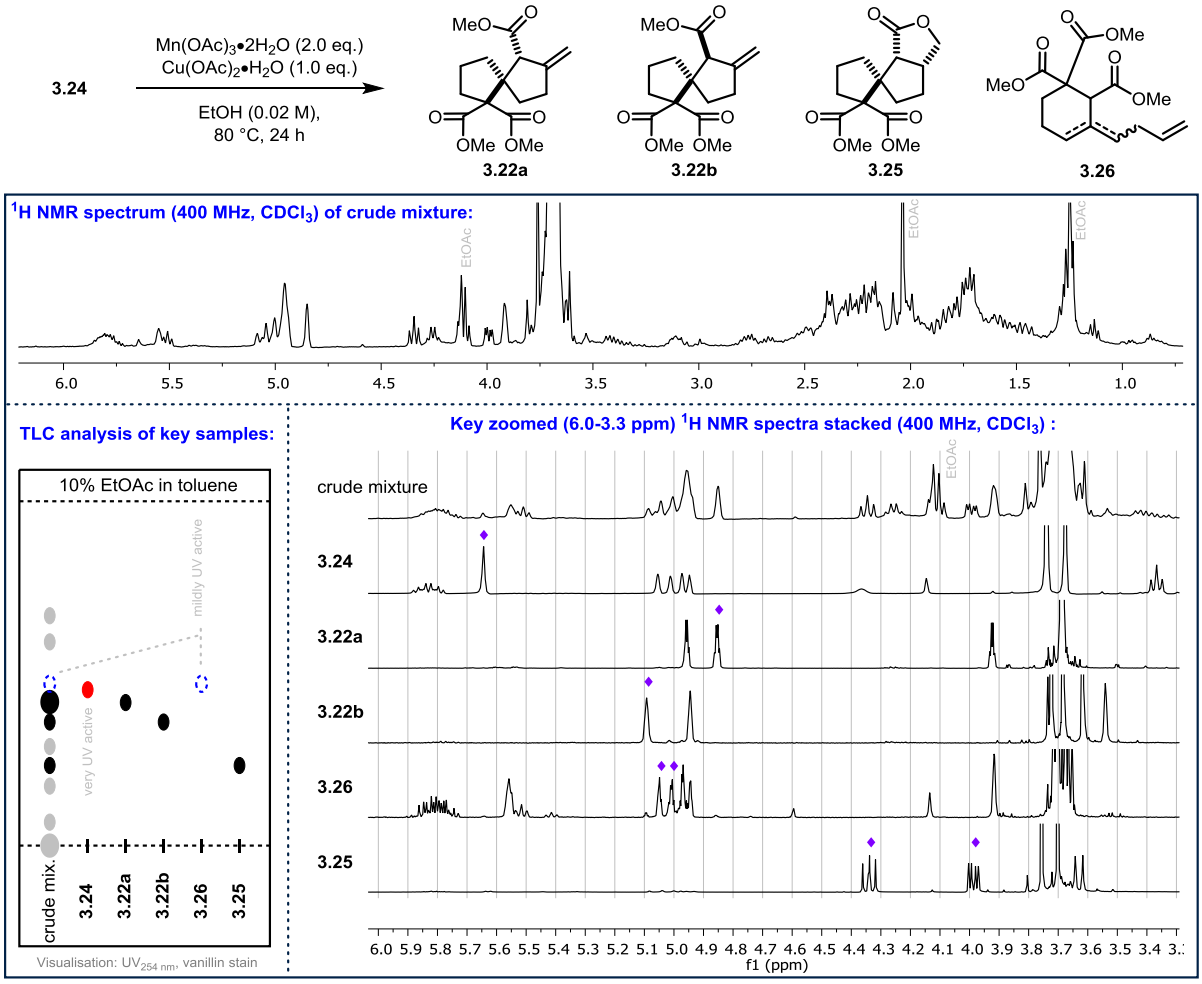

**Scheme 3-13:** Synthesis alkene **3.24**.

Reagents and conditions: (a) NaH (1.25 eq.), *n*-BuLi (1.1 eq.), allyl bromide (1.0 eq.), THF, 0 °C, 2.5 h, 77%; (b) *N*-methylimidazole (NMI) (1.5 eq.), $Et_3N$ (1.5 eq.), TsCl (1.5 eq.), PhCl, r.t., 4.5 h, 82% (95:5 *E*/*Z* mix.); (c) i) **3.17** (1.5 eq.), 9-BBN (1.6 eq.), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), $Pd(dppf)Cl_2•CH_2Cl_2$ (0.05 eq.), 1,4-dioxane/$H_2O$, 85 °C, 3.5 h, 67%.

The conditions that gave our *exo*-alkene in the greatest yield in the previous study were used as a test reaction with Cu(II) salts as an additive. Simple (relative to our previous systems studied) TLC and

$^1$H NMR of the crude reaction mixture were obtained for the reaction presented in **Scheme 3-14** (below).

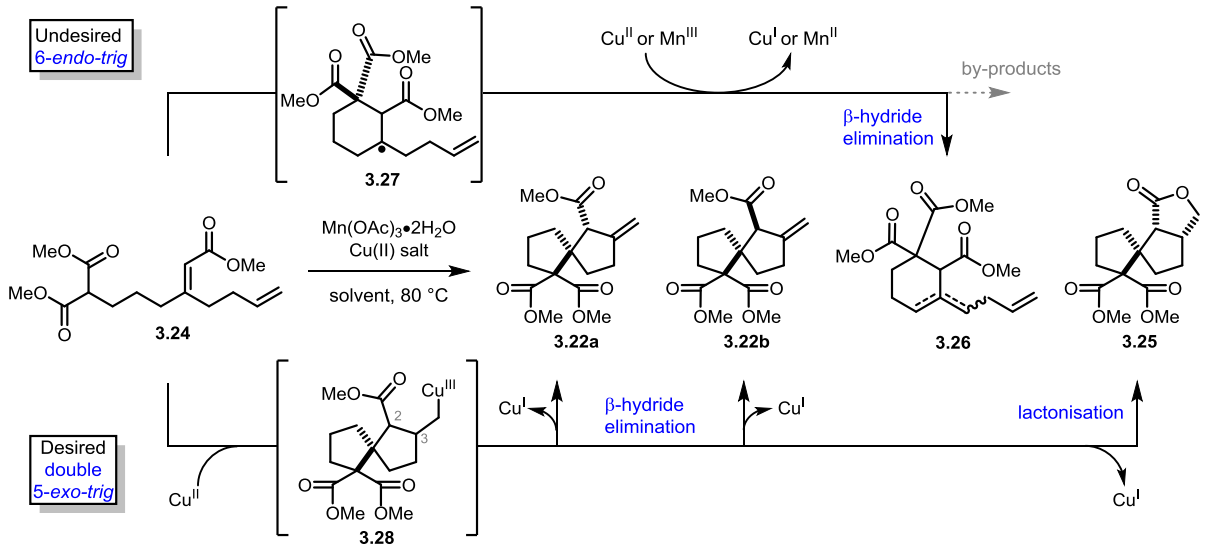
While this $^1$H NMR of the crude mixture shows a multitude of compounds, the desired bicyclic *exo*-alkenes **3.22a/b** were quickly identified. The tricyclic γ-lactone **3.25** was also found and was expected to be formed under this set of reaction conditions.[90] The dotted spot presented on the TLC (*bottom-left*) was of particular interest as we knew from its MS analysis that it had the same *m/z* as our desired *exo*-alkene but still showed terminal alkenes peaks in the $^1$H NMR spectrum. The need for good quantities of **3.22** for the anionic cyclisation study that will be discussed in **Section 4** drove our motivation to try to optimise this reaction.




**Scheme 3-14:** Cyclisation of **3.24** with Mn(III) and Cu(II), $^1$H NMR of crudes (*top*), TLC comparison of the reaction crude and key samples (*bottom-left*) and comparison of $^1$H NMR of the crude and key samples (*bottom-right*).

We wished to isolate both **3.22** isomers together but the dotted spot and the starting material (if any remained) always co-eluted during flash-column chromatography purification. Consequently, we were forced to collect them together. Preparative-TLC purification were performed relatively late in our optimisation (discussed later) which allowed isolation and some characterisation of the unknown impurity (cropped $^{1}$H NMR spectrum in **Scheme 3-14**, *bottom-right*). Based on all the elements of analysis in hand, we hypothesised that it was the mixture of alkenes **3.26**. If this assumption was correct, this meant that an important competing pathway was lowering our yields.

Mechanistically, radical initiation at the malonate centre of **3.24** followed by double 5-*exo-trig* cyclisation and trapping of the resulting primary radical by Cu(II) salt leads to Cu(III) intermediate **3.27** (**Scheme 3-15**, below). Depending on the isomer, it can form **3.22a** or **3.22b** *via* β-hydride elimination. If the substituents at C(2) and C(3) are in *syn*-relationship, *cis*-fused γ-lactone **3.25** can be formed. Finally, based on our hypothesis, a competing 6-*endo-trig* cyclisation gives tertiary radical **3.27** that can be oxidised by copper(II) or manganese(III) salts to form the mixture of alkenes **3.26** after β-hydride elimination.




**Scheme 3-15:** Cyclisation of malonate **3.24** with Mn(III) and Cu(II), an explanation of the formation of key products.

Promisingly, we found that the mixture of products could be formed in up to 67% combined NMR yield[ii] (entry 2, **Table 3.3**, below). In general, modest 5-*exo*/6-*endo* selectivities were obtained (70:30 to 40:60 5-*exo*:6-*endo*).

The formation of lactone **3.25** was greatly reduced in DMSO (entries 8-10), as observed by Snider and co-workers and Burton and co-workers.[90,98] The use of $Cu(OTf)_2$ gave more 6-*endo* product, especially in DMSO (entry 10) as well as forming more lactone **3.25**. It accompanied a switch in distribution of *exo*-alkenes **3.22** with **3.22b** now being the major alkene isomer (entries 4, 7).

This switch can be explained by the consumption of the isomer of **3.28** where both C(2) and C(3) substituents are in a *cis*-relationship to form γ-lactone **3.25**. As previously mentioned in the introduction (**Section 1.2.3.3.1**, page 17), $Cu(OTf)_2$ favours nucleophilic substitution processes over the β-hydride elimination. In this case, the same phenomenon happens. Lactonisation happens more efficiently than the elimination to form *exo*-alkene **3.22a**, therefore **3.22b** was found to be the major *exo*-alkene. Using DMSO as the reaction solvent showed excellent *d.r.* (up to 96:4) for the formation of our desired *exo*-alkenes **3.22** (entries 8-10). No other γ-lactones (neither *trans*-fused nor the other *cis*-fused) were observed.

All of these results gave us a better understanding of the major problem our cyclisations had been suffering from the use of Meldrum's acid derivative **3.3**: the 6-*endo*-*trig*/5-*exo*-*trig* selectivity.

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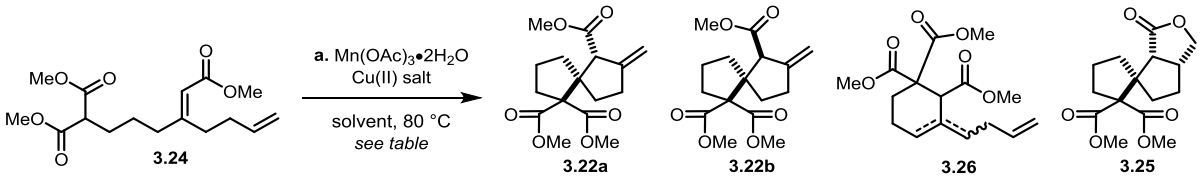
[ii] Determining yields accurately to optimise this reaction was a difficult task. Compounds **3.22a**/**b**, **3.26** and **3.24** were isolated together by flash-column chromatography and their ratios determined from the integrations of $^1$H NMR spectra (purified sample). No stain revealed lactone **3.25** on TLC (except $KMnO_4$ when an extremely concentrated sample was used) so it was rarely isolated, its approximated yield was therefore determined from on its integration in the crude $^1$H NMR mixture. Peaks labelled with diamonds on the $^1$H NMRs in **Scheme 3-14** were used for that purpose as they were not overlapping. Other methods of analysis were considered to obtain more accurate yields but this one was kept because of time constraints. We were aware that using this method would generate errors on the integrations and therefore yields. Comparisons of different ratios in the crude sample and in the purified sample were carried out in order to flag any problems arising in the purification.

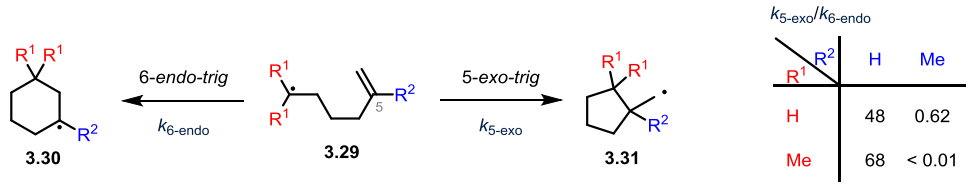



| entry[a] | solvent | (dilution) | Cu(II) salt | combined NMR yield[b,c] | **3.22**:**3.26**:**3.25** ratio[c] | **3.22a**:**3.22b** ratio[c] | 5-*exo*:6-*endo*[c] |
|---|---|---|---|---|---|---|---|
| 1[d] | AcOH | (0.02 M) | $Cu(OAc)_2$ | 50% | 20:54:26 | 50:50 | 46:54 |
| 2 | | (0.02 M) | $Cu(OAc)_2$ | 67% | 43:31:26 | 81:19 | 69:31 |
| 3[e] | EtOH | (0.2 M) | $Cu(OAc)_2$ | 53% | 36:42:22 | 74:26 | 58:42 |
| 4[f] | | (0.2 M) | $Cu(OTf)_2$ | 65% | 18:47:35 | 38:62 | 53:47 |
| 5 | | (0.02 M) | $Cu(OAc)_2$ | 66% | 32:40:28 | 56:44 | 60:40 |
| 6 | MeCN | (0.2 M) | $Cu(OAc)_2$ | 48%[i] | 23:39:38 | 50:50 | 61:39 |
| 7[g] | | (0.2 M) | $Cu(OTf)_2$ | 62% | 15:41:44 | 14:86 | 59:41 |
| 8 | | (0.02 M) | $Cu(OAc)_2$ | 52% | 49:48: 3 | 96: 4 | 52:48 |
| 9 | DMSO | (0.2 M) | $Cu(OAc)_2$ | 59% | 54:42: 4 | 89:11 | 58:42 |
| 10[h] | | (0.2 M) | $Cu(OTf)_2$ | 42% | 40:59: 1 | 87:13 | 41:59 |

**Table 3.3**: Cyclisation attempts of alkene **3.24** with Mn(III) and Cu(II).

Reagents and conditions: (a) $Mn(OAc)_3•2H_2O$ (2.0 eq.), $Cu(OAc)_2•H_2O$ or $Cu(OTf)_2$ (*see table*), solvent (*see table*), 80 °C, from 16 h to 7 d. Reactions performed on 100 mg scale except for entry 3 and 5 (50 mg); [a] the reactions were analysed by TLC when the reaction mixture turned blue (or green when using DMSO), usually between 16 h and 3 d (noticeable exception: 7 d for entry 5); [b] **3.22a/b** + **3.26** + **3.25**; [c] determined using a combination of $^1$H NMR crude ratios and the mass of isolated mixture of **3.22a/b** + **3.26**; [d] 17% of unreacted **3.24**; [e] 5% of unreacted **3.24**; [f] 15% of unreacted **3.24**; [g] 6% of unreacted **3.24**; [h] 13% of unreacted **3.24**.

This presence of competing 6-*endo-trig* cyclisation may not be that surprising considering that the first cyclisation is a polarity-mismatch process forming two adjacent quaternary centres. Beckwith and co-workers have shown that adding a methyl group at the 5-position (relative to the radical, see $R^2$ = Me) could drastically affect the rate of 5-*exo-trig* cyclisation relative to the rate of 6-*endo-trig* cyclisation (**Scheme 3-16**, below) making the 6-*endo* process faster and predominant.[62,148,149]

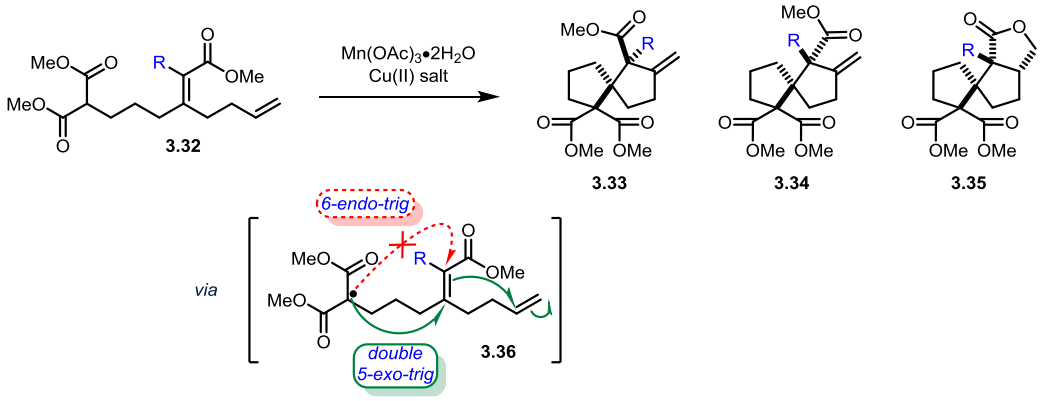



**Scheme 3-16:** Beckwith and co-workers: Effect of adding a methyl group at the 5-position on the relative rate constants $k_{5\text{-exo}}/k_{6\text{-endo}}$.[62,148,149]

We therefore decided to try to slow down the 6-*endo-trig* cyclisation pathway by adding another "blocking" substituent on our starting material, hence using a tetrasubstituted alkene. This will be the focus of the next section.

## 3.4 Use of tetrasubstituted alkene Michael acceptors as cyclisation precursors

As discussed in the previous section, our new goal was to prevent or reduce cyclisation *via* the 6-*endo-trig* pathway by introduction of a fourth substituent on the internal alkene (R in **3.32**).




**Scheme 3-17:** Cyclisation of tetrasubstituted malonate **3.32** with Mn(III) and Cu(II), an explanation of the formation of key products.

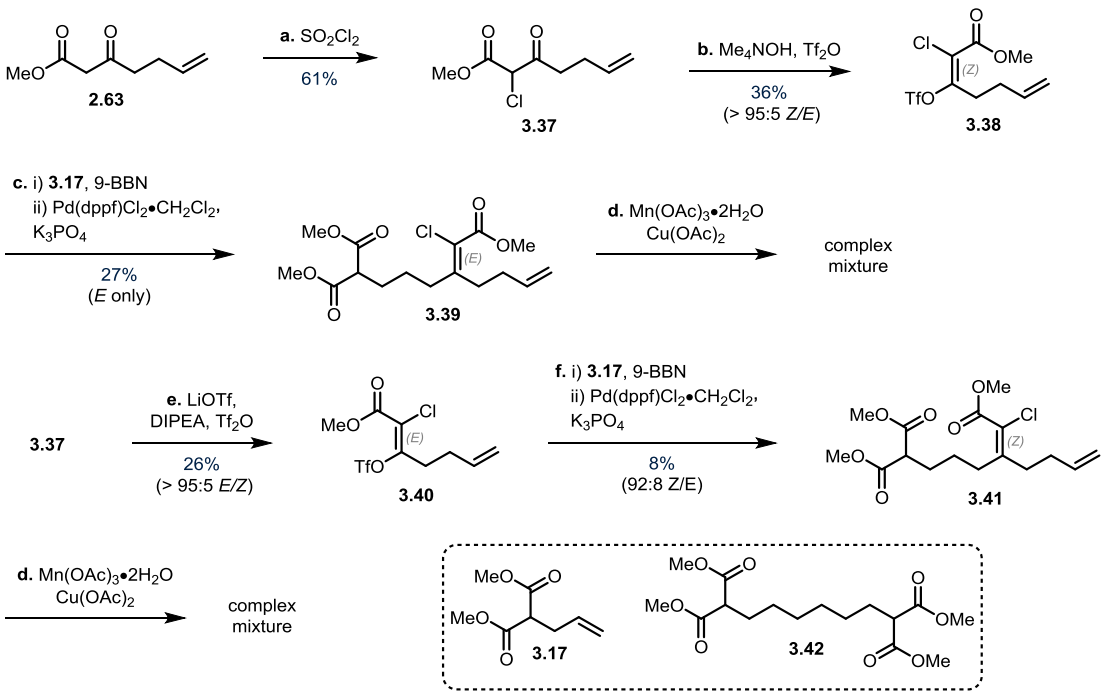
A drawback of this strategy is that the stereochemistry at the C(2) centre is fixed during the second 5-*exo-trig* cyclisation. Therefore, depending on the choice of R-group, we could form two isomers **3.33** and **3.34** that are not interconvertible by enolisation unlike in previous systems.

### 3.4.1 Halogens as blocking group

We thought that either a chloride or a bromide group would be ideal as the allyl chloride/bromide-containing spiro[4.4]nonane formed could be used as leaving group in a lactonisation reaction (in analogy to the proposed reaction in **Scheme 2-6**, page 28). This would make both products **3.33** and **3.34** (R = Cl or Br) converge to a single lactone *exo*-alkene (not drawn).

Attempts to synthesise the bromide analogue were not successful. First, the triflation was unselective and then the coupling reaction gave a complex mixture of products using our previously

described conditions. However, we synthesised of a moderate amount of chloride **3.39** starting by the chlorination of acetoacetate **2.63** with sulfuryl chloride in moderate yield. The corresponding chloride **3.37** underwent triflation using Frantz procedure to form unstable vinyl triflate **3.39**,[138] and subsequently coupled to form cyclisation precursor **3.39** in low yield. Cyclisation was attempted using $Mn(OAc)_3/Cu(OAc)_2$ in DMSO (0.2 M) at 80 °C until the mixture became blue/green (48 h). These conditions were chosen because they resulted in no lactone formation and good *d.r.* of compounds **3.22** in our previous study. Unfortunately, we observed a complex mixture of products in low yield. A difficult purification led to the isolation of impure compounds having characteristic *exo*-alkene peaks by $^1$H NMR spectroscopic analysis and an expected *m/z* by mass spectrometric analysis but in too low quantities to be synthetically promising (< 4% yield), some low quantities (< 4%) of what we associated as the corresponding lactone were also observed.




**Scheme 3-18:** Synthesis vinyl chlorides **3.38** and **3.41** and their attempted cyclisations with Mn(III) and Cu(II).

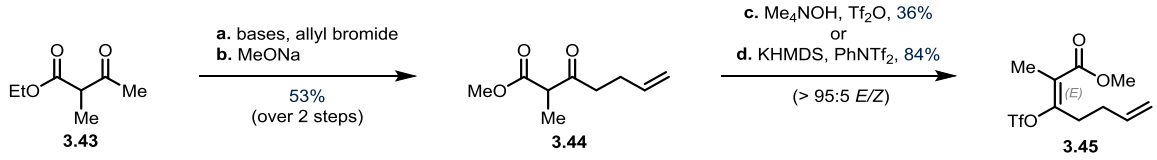
Reagents and conditions: (a) $SOCl_2$ (1.05 eq.), $CH_2Cl_2$, r.t., 2.75 h, 61%; (b) $Me_4NOH$ (5.0 eq.), $Tf_2O$ (2.5 eq.), hexane/$H_2O$, 0-10 °C, 15 min, 36% (> 95:5 *Z*/*E* mix.); (c) i) **3.17** (1.5 eq.), 9-BBN (1.6 eq.), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), $Pd(dppf)Cl_2•CH_2Cl_2$ (0.05 eq.), 1,4-dioxane/$H_2O$, 85 °C, o.n., 36%; (d) $Mn(OAc)_3•2H_2O$ (2.0 eq.), $Cu(OAc)_2•H_2O$ (1.0 eq.), DMSO (0.2 M), 48 h, complex mix.; (e) LiOTf (2.0 eq.), DIPEA (1.5 eq.), $Tf_2O$ (1.1 eq.), $CH_2Cl_2$, 0 °C, 1 h, 26% (> 95:5 *E*/*Z* mix.); (f) i) **3.17** (1.5 eq.), 9-BBN (1.6 eq.), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), $Pd(dppf)Cl_2•CH_2Cl_2$ (0.05 eq.), 1,4-dioxane/$H_2O$, 85 °C, 4 h, 8% (92:8 *Z*/*E* mix.).

The other isomer **3.41** was synthesised in extremely low yield but enough to test its reactivity. Homo-coupled product **3.42** was one of the major components present in the coupling reaction crude mixture (based on $^{1}$H NMR). Once again, a very complex mixture of products was obtained.

### 3.4.2 **Methyl as blocking group**

The introduction of a methyl substituent as a blocking group could obviate the observed promiscuous reactivity of **3.39** and **3.41** under Mn(III) cyclisation conditions as discussed previously. However, the introduction of an alkyl group also prevents enolisation at this position, which could potentially hamper our synthetic efforts towards the creation of tricyclic 3D-templates and Ginkgolide B.

α-Methyl acetoacetate **3.44** could be obtained by methylation of known acetoacetate **2.63** (MeI, $K_2CO_3$, 29%) or by allylation of ethyl acetoacetate **3.43** followed by transesterification in good yield (53% over 2 steps) (**Scheme 3-19**). Triflation of **3.44** using KHMDS/$PhNTf_2$ in near-freezing DMF lead to significantly better yields of **3.45** than the previous method using $Me_4NOH$ and $Tf_2O$ (84% compared to 36% yield).[138] Preliminary cyclisations showed a great potential for this substrate, as a consequence we decided to optimise the following coupling reaction conditions.

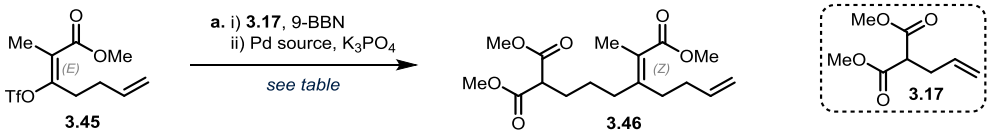



**Scheme 3-19:** Synthesis of vinyl triflate **3.45**.

Reagents and conditions: (a) NaH (1.25 eq.), *n*-BuLi (1.1 eq.), allyl bromide (1.0 eq.), THF, 0 °C, 1.6 h, 70%; (b) MeONa (0.05 eq.), MeOH, r.t., o.n., 75%; (c) $Me_4NOH$ (5.0 eq.), $Tf_2O$ (2.5 eq.), hexane/$H_2O$, 0-10 °C, 1 h, 36% (> 95:5 *E*/*Z* mix.); (d) KHMDS (1.2 eq.), $PhNTf_2$ (1.1 eq.), DMF, < -40 °C, 3.5 h, 84% (> 95:5 *E*/*Z* mix.).

Optimisation of the coupling to form tetrasubstituted alkene **3.46** was performed (**Table 3.4**). Our first attempt using previously developed conditions gave a low 27% yield of tetrasubstituted alkene **3.46** (entry 1). Denis Hartmann (MSc student, 2017-2018, Burton group) found that changing the temperature and palladium source had profound effects on his coupling yields (side-project

supervised by KG). Lowering the temperature to 50 °C or using $Pd(PPh_3)_4$ gave similar results (entries 2 and 3) but combining them both led to a substantial improvement with a 61% isolated yield of malonate **3.46** (entry 4).




| entry[a] | eq. of **3.17**[b] | eq. of 9-BBN[b] | Pd source | temp. | yield[c,d] |
|---|---|---|---|---|---|
| 1[e] | 1.5 | 1.6 | $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ | 85 °C | 27% |
| 2 | 1.5 | 1.6 | $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ | 50 °C | 28% |
| 3 | 1.5 | 1.6 | $Pd(PPh_3)_4$ | 85 °C | 24% |
| 4 | 1.5 | 1.6 | $Pd(PPh_3)_4$ | 50 °C | 61% |
| 5 | 1.6 | 1.5 | $Pd(PPh_3)_4$ | 50 °C | 80% |
| 6 | 1.6 | 1.5 | $Pd(PPh_3)_4$ | 30 °C | 77% |
| 7 | 1.6 | 1.5 | $Pd(OAc)_2$ + 2 $PPh_3$ | 50 °C | 76% |
| 8 | 1.6 | 1.5 | $Pd(OAc)_2$ + 3 $PPh_3$ | 50 °C | 75% |

**Table 3.4**: Optimisation of the Suzuki coupling to form tetrasubstituted alkene **3.46**.

Reagents and conditions: (a) i) **3.17** (see table), 9-BBN (see table), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), Pd source (0.05 eq.), 1,4-dioxane/$H_2O$, o.n., see table.

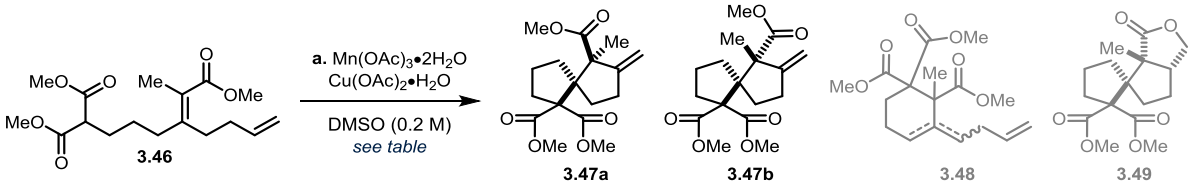
[a] coupling reactions performed on 0.77 mmol unless otherwise stated; [b] relative to **3.45**; [c] isolated yields as a single alkene isomer; [d] isomerisation occurred for entries 3-7 (90:10 to 85:15 *Z*/*E* mix. obtained) and entry 8 (65:35 *Z*/*E* mix. obtained); [e] reaction performed on 0.34 mmol scale.

The reaction conditions employed for the cross-coupling between **3.17** and **3.45** using an excess of 9-BBN were based on previous studies.[141] We were concerned that the excess 9-BBN could lead to undesired side-reactions and it was found that adding malonate **3.17** in excess (relative to 9-BBN) gave an additional yield increase to 80% (entry 5 versus entry 4). Lowering the temperature to 30 °C (entry 6) or using systems aiming to form more reactive 14-electron or 16-electon species with palladium(II) acetate and triphenylphosphine in 1:2 or 1:3 ratio (entries 7-8) gave slightly lower yields.

We found that our Suzuki coupling conditions using $Pd(PPh_3)_4$ isomerised our products. However, the ratio of product was still considered reasonable after an overnight reaction as **3.46** was isolated in 85:15 *Z*/*E* mixture or better for entries 3-6. The use of $Pd(OAc)_2$ (0.05 eq.) and $PPh_3$ (0.15 eq.) lead to

substantially more isomerisation (up to 65:35 *Z*/*E* mixture for entry 8) which we propose to result from background addition/elimination of some non-ligated $PPh_3$ onto the α,β-unsaturated ester of the product leading to the gradual erosion of the geometrical purity. Conditions in entry 5 using excess malonate **3.17** to 9-BBN, $Pd(PPh_3)_4$ at 50 °C were consequently chosen for future substrate syntheses.

From the previous study (**Table 3.3**, page 57), we decided to start using copper(II) acetate in DMSO (0.2 M) at 80 °C for 2 main reasons. First, the absence of γ-lactone **3.25** under with these conditions made us think it would reduce the number of expected products in this new system. Secondly, it gave good *d.r.* of *exo*-alkenes. The diastereoselectivity of the reaction is paramount as it is not possible to convert the cyclised products to a single isomer by enolisation.




| entry[a] | temp. | reaction time | isolated yield of *exo*-alkenes[b] | **3.47a**:**3.47b**[c] | approx. yield of lactone **3.49**[d] |
|---|---|---|---|---|---|
| 1 | 80 °C | 16 h | 50% | 3:1 | 13% |
| 2 | 40 °C | 4 d | 54% | 4.5:1 | traces |
| 3[e] | r.t. | 12 d | 59% | 5:1 | traces |

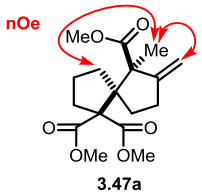
**Table 3.5**: Cyclisation attempts of tetrasubstituted alkene **3.46** with Mn(III) and Cu(II).

Reagents and conditions: (a) $Mn(OAc)_3•2H_2O$ (2.0 eq.), $Cu(OAc)_2•H_2O$ (1.0 eq.), DMSO (0.2 M), see table.
[a] coupling reactions performed on ≥ 50 mg; [b] isolated as a mixture of **3.47a** and **3.47b**, yields were corrected if some alkene **3.46** was remaining; [c] determined by $^1$H NMR on the crude mixture; [d] approximate $^1$H NMR yield determined using integrations ratios of ester peaks of the crude mixture; [e] the reaction did not run to completion.

The methyl blocking group was successful in suppressing 6-*endo*-*trig* process and two *exo*-alkenes **3.47a** (major) and **3.47b** (minor) were obtained in 3:1 *d.r.* and 50% yield after an overnight reaction (**Table 3.5**, entry 1). TLC analysis of the crude mixture (revealed using vanillin stain) showed an impressive improvement with the additional blocking group as only 2 spots (and starting material

**3.46** when some remained) were observed. The relative stereochemistry of spiro[4.4]nonane **3.47a** was determined using $^{1}$H NMR NOESY analysis (**Scheme 3-20**, below).

Lactone **3.49** was formed noticeably at 80 °C (13%, $^{1}$H NMR yield), something that was not expected from our previous study. However, it was difficult to isolate as it stained poorly on TLC under a variety of conditions. It was later synthesised using a different route (see **Section 5.3**) so that we could compare $^{1}$H NMR of the pure sample and give an approximate NMR yield.




**3.47a**

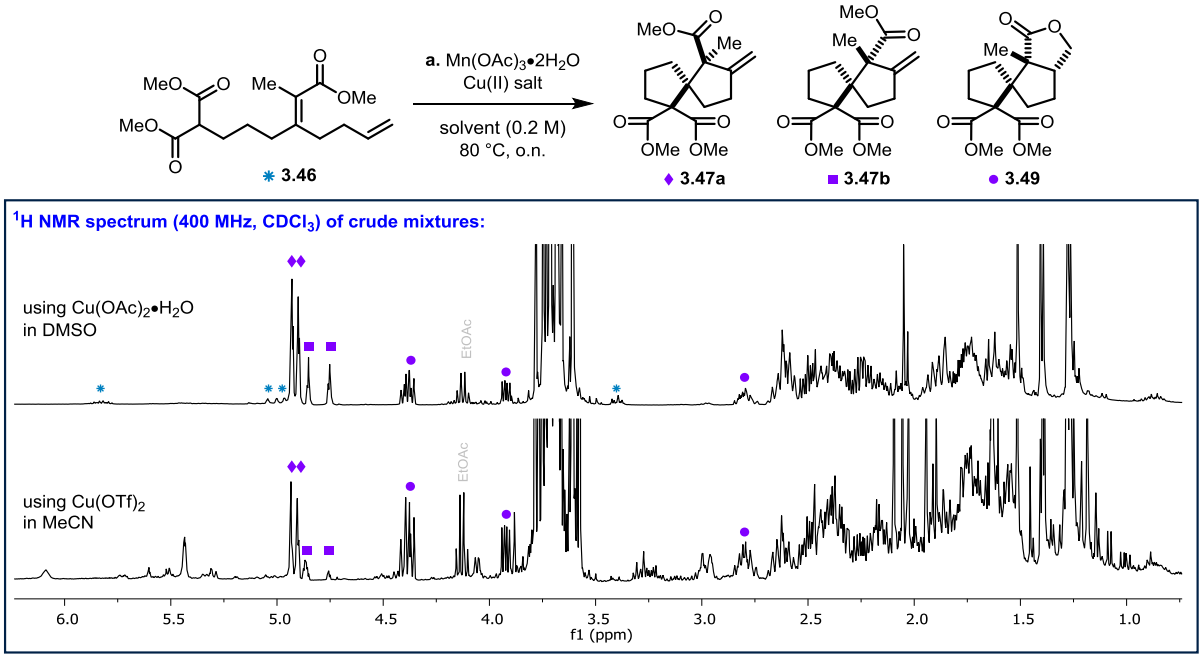
**Scheme 3-20:** Indicative nOe interations observed for spiro[4.4]nonanes **3.47a**.

Lowering the reaction temperature to 40 °C (entry 2) and then to room temperature (entry 3) led to a slight improvements of the yield and *d.r.* in both cases and pleasingly, lactone **3.49** was only observed in trace proportions at lower temperatures in $^{1}$H NMR spectra of the reaction crude mixture. These improvements came at a cost: the rate of the reaction dropped drastically. However, lowering the temperature also significantly reduced the rate of the reactions. While it took only 16 h at 80 °C, the reaction times rose to 4 days at 40 °C and we decided to stop the room temperature reaction after 12 days as no further improvement was observed by TLC analysis. Whilst the slowest reaction gave the best yield (59%), 40 °C was preferred as longer reaction times were prohibitive.

The starting material **3.46** and minor isomer **3.47b** were inseparable by column chromatography so it was important that reactions were run to completion.

Despite the fact that the easy interpretation of the $^{1}$H NMR spectra of the crude mixture for these reactions (for example, crude of entry 1, see *top* in **Scheme 3-21**, below) only moderate yields were obtained. We could not explain where the mass balance was (more thorough extractions did not help improving these yields). Another condition tested using copper(II) triflate in 0.2 M MeCN at 80 °C (conditions giving the most lactone in our previous study) also gave our desired products **3.47a**/**b** in

just 16% yield (12:1 *d.r.*) and lactone **3.49** in ~15% yield but with the formation of other alkene by-products (see *bottom,* **Scheme 3-21**). The poor mass recovery lost in these reactions could be the result of undesired insoluble by-product lost during the extraction process.




**Scheme 3-21:** Representative $^{1}$H NMR spectra (crude mixtures) of cyclisations of alkene **3.46**.

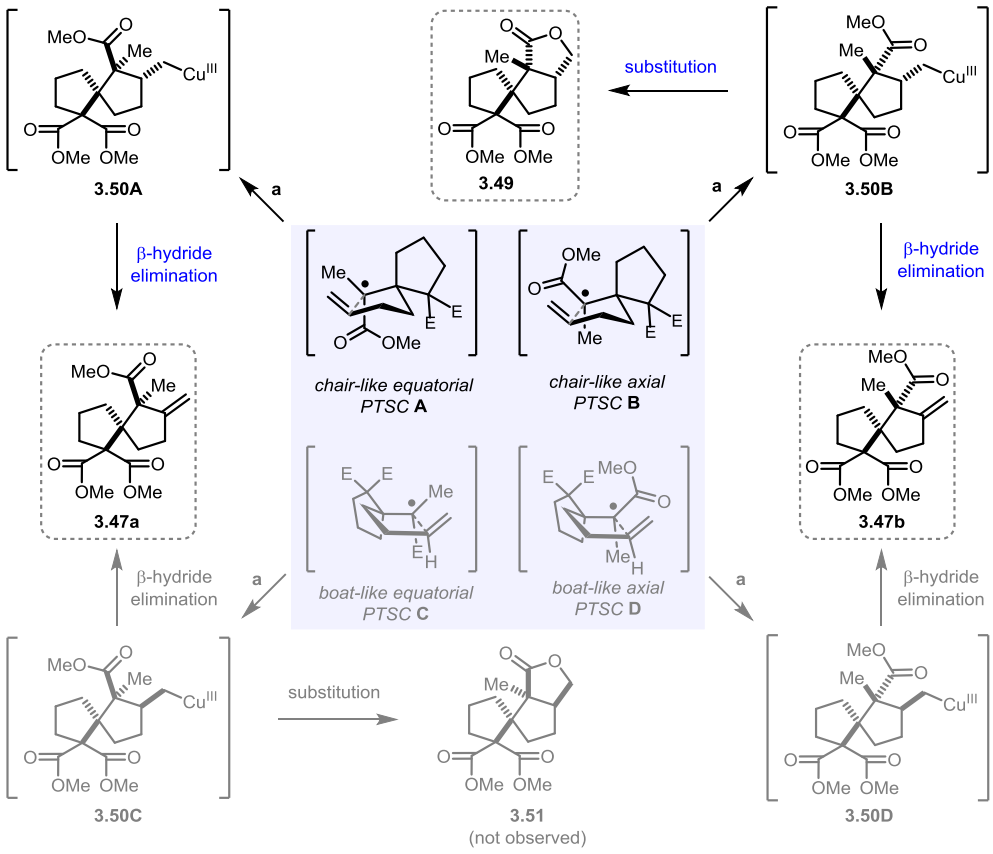
Reagents and conditions: (a) *top crude* $Mn(OAc)_3 \bullet 2H_2O$ (2.0 eq.), $Cu(OAc)_2 \bullet H_2O$ (1.0 eq.), DMSO (0.2 M), 80 °C, o.n; (a) *bottom crude* $Mn(OAc)_3 \bullet 2H_2O$ (2.0 eq.), $Cu(OTf)_2$ (1.0 eq.), MeCN (0.2 M), 80 °C, o.n.

The reactions in DMSO suggests that the methyl group successfully helped blocking any 6-*endo-trig* cyclisation from occurring as no other alkene products were observed based on $^{1}$H NMR spectroscopic analysis. However, we might be missing other species (dimers, trimers and more) that are lacking any alkene protons as the lower shift region of the $^{1}$H NMR spectra contains a number of overlapping multiplets. This would explain the relatively low yields obtained despite apparently excellent $^{1}$H NMR spectraof the crude mixtures.

Using the Beckwith-Houk model on our system, we expect chair-like *PTSC* **A** to be the lowest in energy. In fact, the methyl group possesses a higher A value (1.7 kcalmol$^{-1}$) than the methyl ester (1.27 kcalmol$^{-1}$) and therefore is expected to be in *pseudo*-equatorial in the most stable *PTSC* **A**.[66] β-Hydride elimination of the Cu(III) intermediate **3.50A** leads to the observed major *exo*-alkene

**3.47a**. The second lowest in energy *PTSC* **B** could either form *exo*-alkene **3.47b** or lactone **3.49** depending on the reaction pathway.

For completeness, the two other diastereomeric Cu(III) intermediates **3.50C** and **3.50D** could be obtained from the supposedly higher in energy boat-like *PTSC* **C** and **D**, respectively. They could theoretically be responsible for the formation of lactone **3.51** (not observed) and in part for formation of *exo*-alkene products **3.47a**/**b** (expected to be negligible).

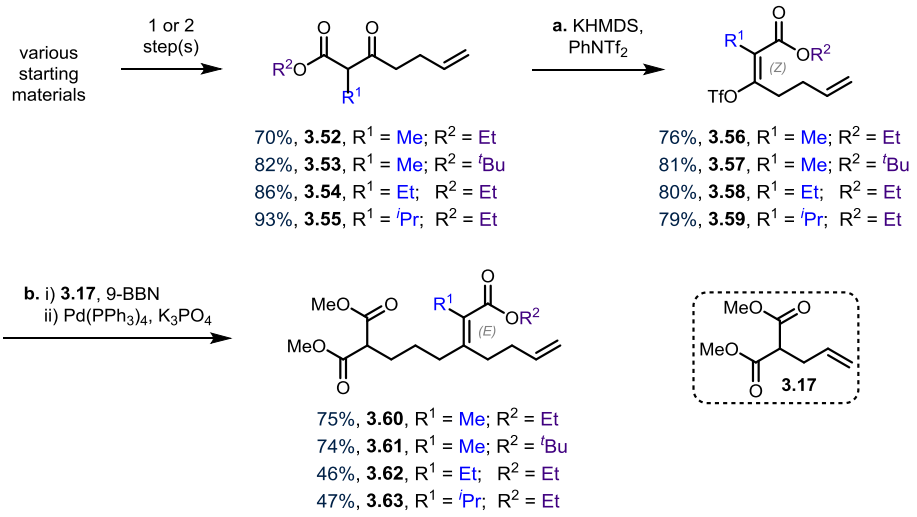



**Scheme 3-22:** Proposed pre-transition state conformations accounting for the formation of spirocycles **3.47a**/**b** and tricyclic lactone **3.49**.
**a** = 5-*exo*-*trig* cyclisation followed by trapping with Cu(II) salt; E = $CO_2Me$,

### 3.4.3 Preliminary investigation of tetrasubstituted alkene cyclisations with Mn(III)/Cu(II)

We wanted to explore the effect of variating the blocking group and the ester group on the diastereoselectivity of this reaction. We therefore synthesised tetrasubstituted alkenes **3.60**, **3.61**, **3.62** and **3.63** using our optimised conditions. Methyl ester **3.60** and *tert*-butyl ester **3.61** were obtained in good 74-75% yields and the more sterically demanding substrates **3.62** and **3.63** gave

relatively good yields (46-47%) for the cross-coupling reaction. However, we found that *tert*-butyl ester **3.61** underwent significantly more isomerisation (60:40 *Z*/*E* mixture) than the other substrates (85:5 to 90:10 *Z*/*E* mixture) but was used nevertheless.



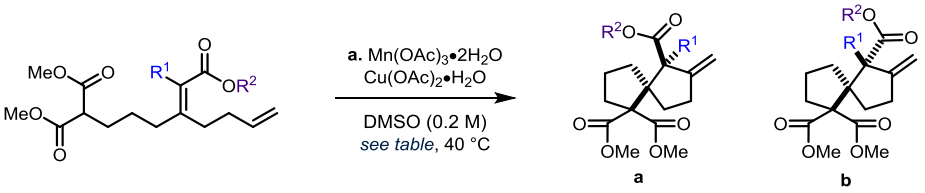

**Scheme 3-23:** Syntheses of tetrasubstituted alkene **3.60**, **3.61**, **3.62** and **3.63**.

Reagents and conditions: (a) KHMDS (1.2 eq.), $PhNTf_2$ (1.1 eq.), DMF, < -40 °C, 1.5-2 h, 76% (**3.56**, *E* only), 81% (**3.57**, 90:10 *E*/*Z* mix.), 80% (**3.58**, *E* only), 79% (**3.59**, *E* only.); (b) i) **3.17** (1.6 eq.), 9-BBN (1.5 eq.), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), $Pd(PPh_3)_4$ (0.05 eq.), 1,4-dioxane/$H_2O$, 50 °C, o.n., 75% (**3.60**, 90:10 *Z*/*E* mix.), 74% (**3.61**, 60:40 *Z*/*E* mix.), 46% (**3.62**, 85:15 *Z*/*E* mix.), 47% (**3.63**, 90:10 *Z*/*E* mix.).

Results of the cyclisation carried out on these substrates are presented in **Table 3.6** (below).

We did not observe any correlation between the size of the ester groups ($R^2$) and the *d.r.* of the reaction (entries 1-3) but the desired products were all isolated in similar yields (about 50%). However, when the size of the blocking group ($R^1$) was increased from methyl to ethyl (entry 2 vs entry 4), *exo*-alkene **3.66a** was isolated from a complex mixture after 9 days as the sole isomer in a much lower 22% yield. Further increasing the steric bulk from ethyl to isopropyl (entry 4 vs entry 5) led to the formation of a complex mixture lacking any *exo*-alkene peaks in the crude $^1$H NMR spectrum after 9 days of reaction.

Considering the complexity of the transformation, we could argue that obtaining our desired *exo*-alkene products in roughly 50% yield (entries 1-3) is reasonable.



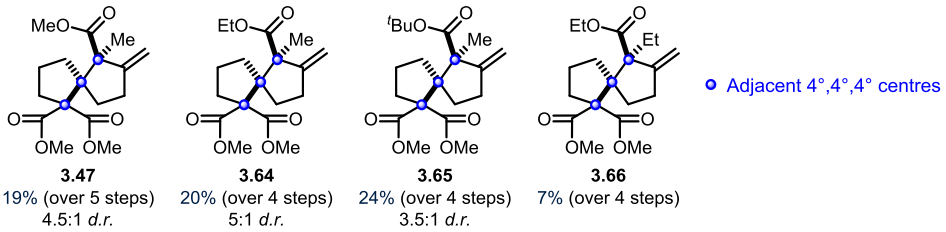

| entry[a] | substrate[b] | $R^1$ | $R^2$ | products | reaction time | yield[c] | **a**:**b** ratio[d] |
|---|---|---|---|---|---|---|---|
| 1 | **3.46** | Me | Me | **3.47a/b** | 4 d | 54% | 4.5:1 |
| 2 | **3.60** | Me | Et | **3.64a/b** | 4 d | 49% | 5:1 |
| 3 | **3.61** | Me | $^t$Bu | **3.65a/b** | 4 d | 48% | 3.5:1[e] |
| 4 | **3.62** | Et | Et | **3.66a/b** | 9 d | 22% | **a** only[f] |
| 5 | **3.63** | $^i$Pr | Et | **3.67a/b** | 9 d | -[g] | - |

**Table 3.6**: Cyclisation attempts of tetrasubstituted alkene **3.46** with Mn(III) and Cu(II).

Reagents and conditions: (a) $Mn(OAc)_3•2H_2O$ (2.0 eq.), $Cu(OAc)_2•H_2O$ (1.0 eq.), DMSO (0.2 M), 40 °C, *see table*. [a] reactions performed on 0.36-0.41 mmol scale; [b] see **Scheme 3-23** for the substrate *E*/*Z* ratios, **3.46** 85:15 *Z*/*E* mix.; [c] isolated as a mixture of **a** and **b**, yields were corrected when some alkene starting material was isolated with the desired products; [d] determined by $^1$H NMR on the crude mixture unless otherwise stated; [e] determined on the purified sample instead as the $^1$H NMR of the crude was complicated in the considered region; [f] **3.66b** was not observed; [g] complex mixture of products obtained.

## 3.5 Conclusion

In summary, the new route (alkylation/triflation/coupling) described in **Section 3.2.2** (page 48) allowed us to gain access to malonate substrates. We then aimed to find conditions that would allow clean reactions to occur. When we changed the alkyne moieties to alkenes, we obtained for the first time a mixture of products that we tentatively assigned as comprising undesired 6-*endo-trig* cyclisation products. While this has never been confirmed unambiguously, it prompted us to attempt the polycyclisation reaction on substrates with an extra blocking group. This blocking group strategy was successful in limiting the undesired 6-*endo-trig* cyclisations, thus greatly simplifying the outcome of the reaction and greatly improving its synthetic utility compared to previous experiments. For example, the introduction of a methyl group in combination with reaction conditions employing $Cu(OAc)_2$ in DMSO gave a clean reaction, and applying such conditions to related substrates allowed the expeditious syntheses of various complex spirocycles (**Scheme 3-24**).



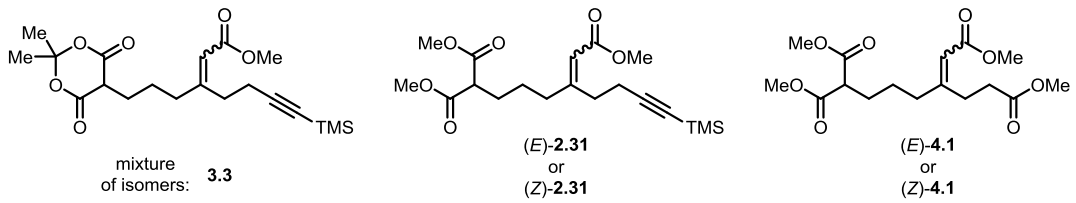

**Scheme 3-24:** Overall yields obtained for the syntheses of **3.47**, **3.64**, **3.65** and **3.66**.

Unfortunately, the *d.r.* was not profoundly affected by the ester group. Changes of the blocking group gave impressive differences but at the expense of yield. Consequently, we seemed to be limited to a methyl group (in the alkyl series). Despite the promising results obtained from this study, we therefore decided to pursue a light-mediated strategy that was considered to offer more potential in the synthesis of our desired spirocyclic systems (see **Section 5**).

The goal of this PhD research was to find an interesting scaffold that our industrial sponsors could potentially use as a 3D template for their research. Despite being a powerful cyclisation that can make remarkably hindered molecules efficiently (**Scheme 3-24**, above), we think some issues need to be addressed. We envisaged that the current chemistry developed using $Mn(OAc)_3$ had serious drawbacks that could dissuade industrial uses. First, the lengthy reaction times would be prohibitive to industry as this would slow down the synthesis of new targets (for an SAR study for example). Second, this process utilises super stoichiometric amounts of metals, something we would prefer to avoid if possible due to the amount of waste that would be generated.

# 4 Base-Catalysed Cyclisation Study

Our initial project proposal involved anionic species as intermediates in the cyclisation but we have mainly discussed radical processes up to now, this is because it was hard to obtain good quantities of cyclisation precursors derived from Meldrum's acid such as **3.3** (page 42). We nevertheless attempted a few cyclisations of this precious alkyne but without any success.

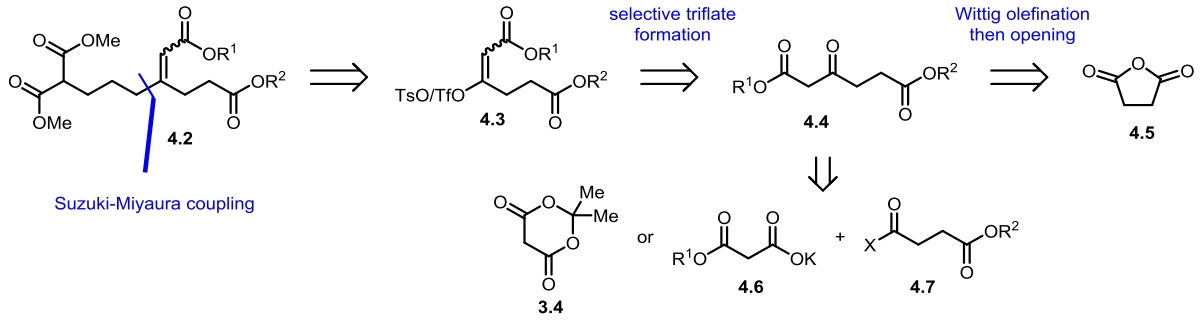



**Scheme 4-1:** Possible substrates for proposed anionic cyclisations.

Upon discovering our new route which allowed us to obtain alkenes (*E*)-**2.31** and (*Z*)-**2.31** in gram quantities, we could also envisage synthesising tetraesters (*E*)-**4.1** and (*Z*)-**4.1** which were compounds much closer to the proposed cyclisation at the outset of the project. The base-mediated studies of these two classes of compounds were relatively short for reasons that will be discussed below and carried out almost at the same time. For this reason, they will be described together.

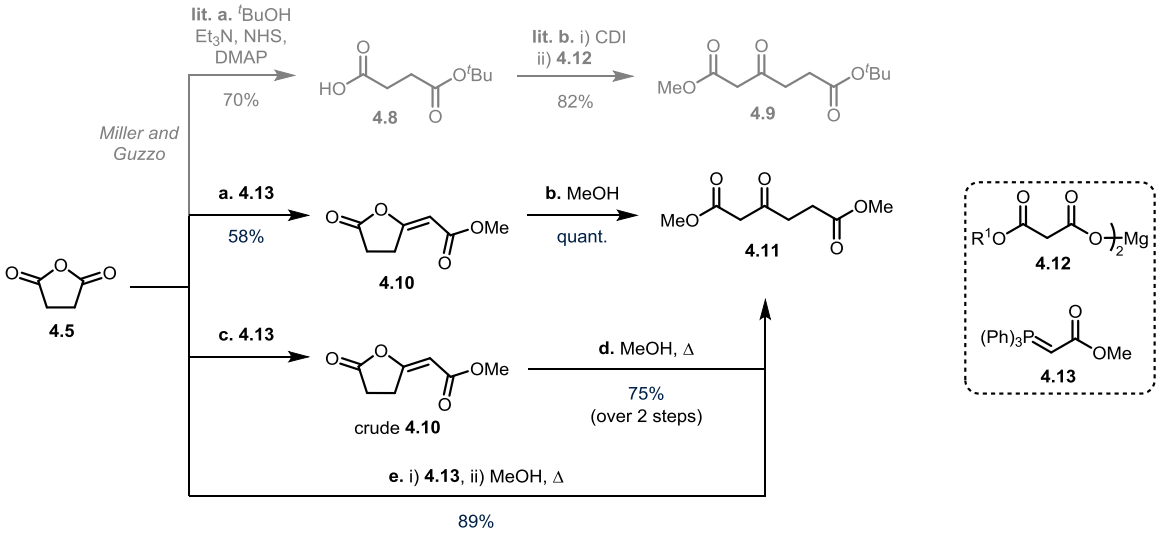
## 4.1 Syntheses of tetraesters (*E*)-4.1 and (*Z*)-4.1

Given the success we had synthesising alkynes (*E*)-**2.31** and (*Z*)-**2.31**, we decided to adopt similar a similar strategy to access compounds such as **4.2** (**Scheme 4-2**). A Pd-mediated Suzuki cross-coupling reaction would bring us back to triflates **4.3** that we envisaged could be formed in a selective manner in analogy to our previous work from β-keto ester **4.4**. These tricarbonyl compounds are known and usually formed by a decarboxylative coupling of a monoester malonate salt such as **4.6** (or sometimes Meldrum's acid **3.4**) and an activated carbonyl substrate such as **4.7**.[150–153] Inspired by these methods we thought **4.2** could be formed from succinic anhydride **4.5**.




**Scheme 4-2**: Proposed retrosynthesis analysis of tetraester **4.2**.

The synthesis of **4.9** described by Miller and Guzzo used an opening of succinic anhydride **4.5** with $^t$BuOH to form **4.8** (**Scheme 4-3**, *grey*).[150] The acid **4.2** was then converted into **4.9** using Masamune's conditions in good yield.[153] Application of methods described in the literature only gave low yield of β-keto ester **4.11** in our hands. However, we wondered if we could use the corresponding Wittig olefination product **4.10** as a substrate for a similar opening to form **4.9** or **4.11**.



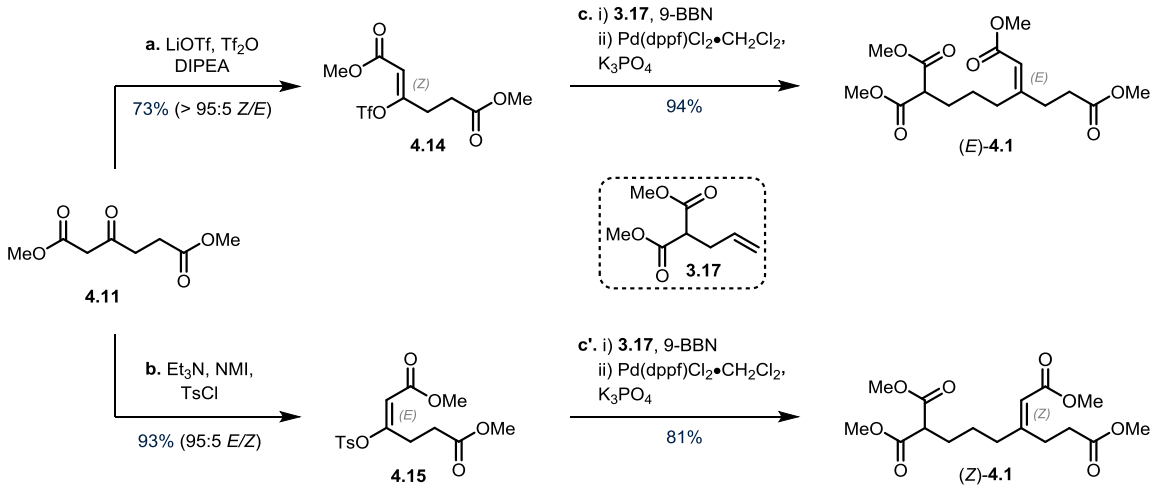

**Scheme 4-3:** Miller and Guzzo: Synthesis fo **4.9** (*top, grey*);[150] Our synthesis of **4.11** (*bottom, black*).

Reagents and conditions: (lit. a) $^t$BuOH (3.0 eq.), $Et_3N$ (0.3 eq.), *N*-hydroxysuccinimide (NHS) (0.3 eq.), DMAP (0.1 eq.), toluene, reflux, 1 h, 71%; (lit. b) i) CDI (1.1 eq.), THF, 0 °C to r.t., 1 h; ii) **4.12** (1.1 eq.), THF, r.t., 2 d, 82%; (a) **4.13** (1.0 eq.), toluene, 50 °C, 17 h, 58%; (b) MeOH (0.5 M), r.t., o.n., quant.; (c) **4.13** (1.0 eq.), toluene, 50 °C, 17 h, then concentrated down; (d) MeOH (0.5 M), r.t., 16 h then 50 °C, 6 h, 75% (over 2 steps); (e) i) **4.13** (1.0 eq.), toluene, 50 °C, 17 h; ii) MeOH (0.25 M), r.t., 54 h then 45 °C, o.n., 89%.

Wittig olefination of succinic anhydride **4.5** with ylide **4.13** gave **4.10** in reasonable yield. This compound was then opened with dry methanol in quantitative yield. The stability of **4.10** to flash chromatography was found to be the reason for the low yield obtained. We consequently decided to

use the crude mixture of **4.10** (toluene was simply removed under reduced pressure) for the methanolysis step and obtained an improved 75% yield of **4.11** over 2 steps. An even better yield was obtained when methanol was added to the reaction flask after the Wittig olefination was finished (89%).

Applying the previously described enolisation conditions to this β-keto ester gave enol triflate **4.14** and the stereo-complimentary tosylate **4.15**. Coupling went especially smoothly despite the use of an excess of 9-BBN in this reaction. It was actually the discrepancy between the yields obtained for these tetraesters (94% and 81%) and for the previous trisubstituted α,β-unsaturated ester alkene/alkyne equivalents (41-68%, **Section 3.3**) that made us realise that excess 9-BBN was responsible for lower yields.




**Scheme 4-4:** Syntheses of tetraesters (*E*)-**4.1** and (*Z*)-**4.1**.

Reagents and conditions: (a) LiOTf (2.0 eq.), DIPEA (2.2 eq.), $Tf_2O$ (1.8 eq.), $CH_2Cl_2$, 0 °C, 3.5 h, 73% (> 95:5 *Z*/*E* mix.); (b) *N*-methylimidazole (NMI) (1.5 eq.), $Et_3N$ (1.5 eq.), TsCl (1.5 eq.), PhCl, r.t., 5 h, 93% (95:5 *E*/*Z* mix.); (c) i) **3.17** (1.5 eq.), 9-BBN (1.6 eq.), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), Pd(dppf)$Cl_2$•$CH_2Cl_2$ (0.05 eq.), 1,4-dioxane/$H_2O$, 85 °C, 3.3 h, 94%; (c') i) **3.17** (1.5 eq.), 9-BBN (1.6 eq.), THF, 0 °C to r.t., 7 h; ii) $K_3PO_4$ (2.5 eq.), Pd(dppf)$Cl_2$•$CH_2Cl_2$ (0.05 eq.), 1,4-dioxane/$H_2O$, 75 °C, 6.5 h, 81%.

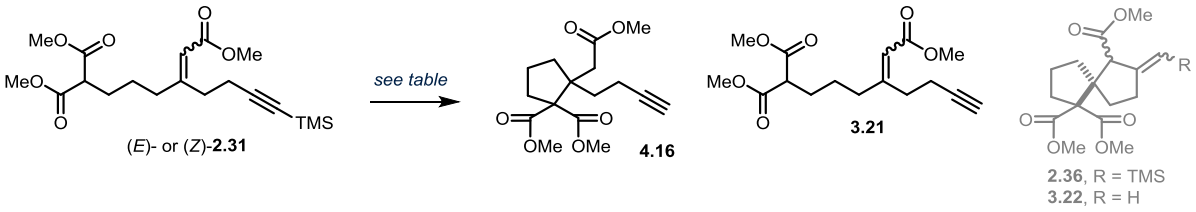
## 4.2 Attempted cylisations

Cyclisation attempts of the alkyne derivatives are summarised in the following table (**Table 4.1**). We generally found that using base in non-protic solvents tended to isomerise the starting material (entries 1-3). No reaction was observed with NaH in THF (50 °C), *n*-BuLi in THF (50 °C), or with DBU in $CH_2Cl_2$ (35 °C) on TMS-alkyne (*Z*)-**2.31** or terminal alkyne **3.21**.

A few different conditions and reagents were screened for activativation of the triple bond. For example, $InCl_3$ in *o*-xylene at reflux resulted in decomposition of (*E*)-**2.31** and a complex reaction mixture for (*Z*)-**2.31**.[154] Gold(I), titanium(IV),[155] or palladium(II)-activation[156] left our starting materials untouched in most cases.

Alkyne (*Z*)-**2.31** was deprotected with TBAF in excellent 96% yield but with a concomitant partial isomerisation of the alkene in only 15 min at 0 °C. This reaction was originally used in an attempt to synthesise pure (*Z*)-**3.21** for our Mn(III)-cyclisation study. In an attempt to use TBAF as a base to promote the anionic cyclisation, the reaction was warmed up to r.t. and then 50 °C lead to decomposition products. Potassium carbonate in MeOH was tested for the deprotection on both TMS-protected alkynes (entries 5-6). The terminal alkyne **3.21** was quickly observed as a mixture of alkene isomers with concomitant appearance of another spot (later confirmed as cyclopentane **4.16**) and a large spot on the baseline of the TLC plate. We later found that warming up improved conversion and we could isolate triester **4.16** in 44% yield using 1.5 equivalent of base (entry 8). Reducing the amount of base to 0.7 equivalent improved the yield to 65% (entry 9). Polar compound formation was observed again. No *exo*-alkene-containing products (**2.36** nor **3.22**) have been observed in this study. Triester **4.16** was resubmitted to $K_2CO_3$/MeOH conditions and was found to be stable as the polar compound spot was only barely visible by TLC analysis after 5 days.

In analogy to results obtained using radical conditions, the (*E*)-isomer (*E*)-**2.31** was generally giving less clean reactions compared to (*Z*)-isomer (*Z*)-**2.31** (entries 1-2, 5-6 and other reactions not shown in this manuscript).



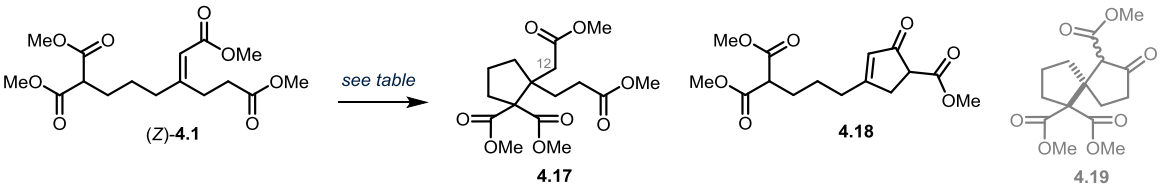

| entry | isomer tested | conditions | yield[a] 4.16 | yield[a] 3.21 | observations[b] |
|---|---|---|---|---|---|
| 1 | *Z* or *E* | $K_2CO_3$ (1.0 eq.), DMF (0.1 M), r.t., 48 h | - | - | extremely clean; **2.31** (~50:50 E/Z) |
| 2 | *Z* | $^t$BuOK (0.20 eq.), THF (0.12 M), r.t., 48 h | - | - | clean; **2.31** (25:75 E/Z) |
| 3 | *E* | | - | - | impurities formed; **2.31** (35:65 E/Z) |
| 4 | *Z* | TBAF (1.5 eq.), THF (0.06 M), 0 °C, 15 min | - | 96% (~34:66 *E:Z*) | - |
| 5 | *Z* | $K_2CO_3$ (1.5 eq.), MeOH (0.05 M), r.t., 40 h | 31% | 14% (~60:40 *E:Z*) | polar products formed |
| 6 | *E* | | 10% | - | polar products formed |
| 7[c] | *Z* | | 26% | 21% (~55:45 *E:Z*) | polar products formed |
| 8 | *Z* | $K_2CO_3$ (1.5 eq.), MeOH (0.1 M), r.t to 35 °C,[d] 3 d | 44% | - | polar products formed |
| 9 | *Z* | $K_2CO_3$ (0.7 eq.), MeOH (0.1 M), r.t to 35 °C,[d] 3 d | 65% | - | polar products formed |

**Table 4.1**: Attempted cyclisations of alkynes in basic conditions.

[a] isolated yield except for entries 5-7 ($^1$H NMR yield); [b] ratios based on $^1$H NMR, the rest is based on TLC; [c] unprotected alkyne **3.21** was used; [d] the reaction was first stirred at r.t. overnight and then heated.

The ester derivative (*Z*)-**4.1** was also treated with base and similar results as the previous alkyne substrates (**Table 4.2**, below) were observed. Aprotic solvents gave isomerisation of the double bond (entries 1-2) and/or decomposition (entries 1-5). Conditions using $K_2CO_3$ or MeONa in MeOH gave 53% and 48% of **4.17** respectively (entries 6-7).

Conditions developed in the Burton group using $Mn(OAc)_3$ and KI were also used to try to form **4.17** containing an iodide at C(12) (that could be possibly used for a subsequent cyclisation) but a complicated mixture of product that could not be characterised was obtained.[103]




| entry | conditions | yield[a] | | observations[b] |
|---|---|---|---|---|
| | | **4.17** | **4.18** | |
| 1 | $^{t}$BuOK (0.20 or 1.0 eq.), THF (0.12 M), 65 °C, 48 h | - | - | **4.1** (~40:60 E/Z) polar products formed |
| 2 | $^{t}$BuOK (1.2 eq.), DMF (0.05 M), r.t., 5 h | - | - | **4.1** (~50:50 E/Z) polar products formed |
| 3 | $^{t}$BuOK (1.2 eq.), DMSO (0.05 M), r.t., 20 min | - | 17% | polar products formed |
| 4 | DBU (1.0 eq.), $CH_2Cl_2$ (0.05 M), r.t., 26 h | - | - | polar products formed |
| 5 | NaH (1.2 eq.), THF (0.05 M), 60 °C, 16 h | - | - | polar products formed |
| 6 | $K_2CO_3$ (1.5 eq.), MeOH (0.05 M), r.t., 40 h | 53% | - | polar products formed |
| 7 | NaOMe (1.0 eq.), MeOH (0.05 M), r.t., 26 h | 48% | - | polar products formed |
| 8 | NaHMDS (1.0 eq.), THF (1.0 M), -78 °C, 5 h | - | - | no by-product formation; ((*Z*)-**4.1** recovered)[c] |
| 9 | NaHMDS (1.0 eq.), THF (1.0 M), -78 °C then r.t, 5 h | - | - | polar products formed |

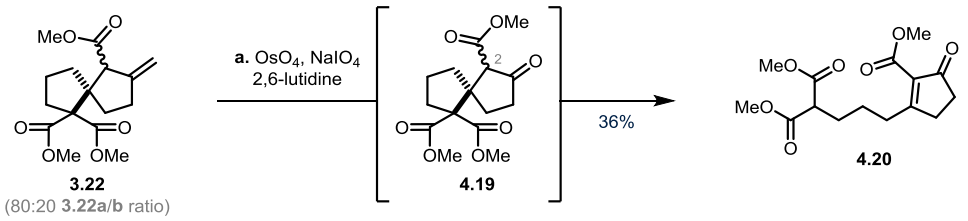
**Table 4.2**: Attempted cyclisations of tetraester (*Z*)-**4.1** in basic conditions.

[a] isolated yields; [b] ratios based on $^{1}$H NMR, the rest is based on TLC; [c] no isomerisation observed.

A common feature of all reactions entries 1-7,9 was the prevalence of polar species on the TLC (elutes only slightly in pure EtOAc). These polar species were attributed to a polymerisation process of some sort. Again, we submitted **4.17** to our $K_2CO_3$/MeOH conditions to find that it was also stable. The use of base at low temperature showed no by-product formation. This is important for what will be discussed in **Section 5** (page 77).

Having **4.17** in hand, we attempted to cyclise it using $^{t}$BuOK in DMSO (conditions of entry 3) only to obtain a mixture of isomerised starting material (*E*)-**4.1** and (*Z*)-**4.1**, **4.18** and polar compounds based on TLC. This proved the expected reversibility of the addition. Michael acceptor **4.18** was treated with $K_2CO_3$/MeOH (conditions of entry 6) but complete decomposition to polar materials was observed.

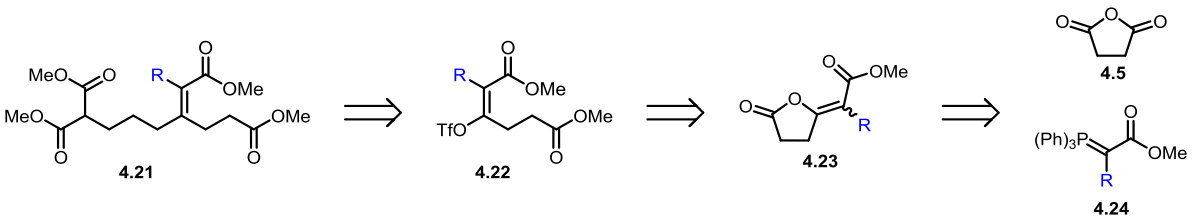
With no idea where to expect products **4.19** to be on TLC, it was difficult to envisage an efficient screening of conditions. So we decided the new goal was to prepare a sample of it in a different way. With the radical-mediated cyclisations going in parallel, we had access to precious alkenes **3.22a/b** that we submitted to Jin's modification of the Lemieux-Johnson oxidation.[124] Electron deficient cyclopentene **4.20** was isolated in 36% yield. This made us realise that we had overlooked something important in the design of the previous anionic cyclisation. In fact, desired product **4.19** is a β-keto ester that therefore possesses a more acidic proton than our starting material. The combined strain of the crowded double adjacent quaternary centre-containing spirocycle **4.19** combined with the ease of deprotonation, we expect that 2,6-lutidine, despite being a weak base (p$K_a$ 6.7),[157] acts as a general base to catalyse the opening to form **4.20**.




**Scheme 4-5:** Syntheses of tetraesters (*E*)-**4.1** and (*Z*)-**4.1**.

Reagents and conditions: (a) $OsO_4$ (0.02 eq.), $NaIO_4$ (4.0 eq.), 2,6-lutidine (2.0 eq.), 3:1 1,4-dioxane/$H_2O$, r.t., 4.5 h, 36%.

Given the above results, we thought an option to prevent this ring-opening/retro-Michael addition was to make sure this acidic *H*-C(2) proton is not present in our product. In other words, we need to introduce a blocking group on the alkene again and form compounds such as tetrasubstituted alkene **4.21** (**Scheme 4-6**, below).




**Scheme 4-6:** Proposed retrosynthetic analysis of tetrasubstituted alkene **4.21**.

At the time of this study, we did not know how easy it would be to do so but based on the Mn(III)-initiated cyclisation of malonate alkenes described in **Section 3.4** (page 58), we know that

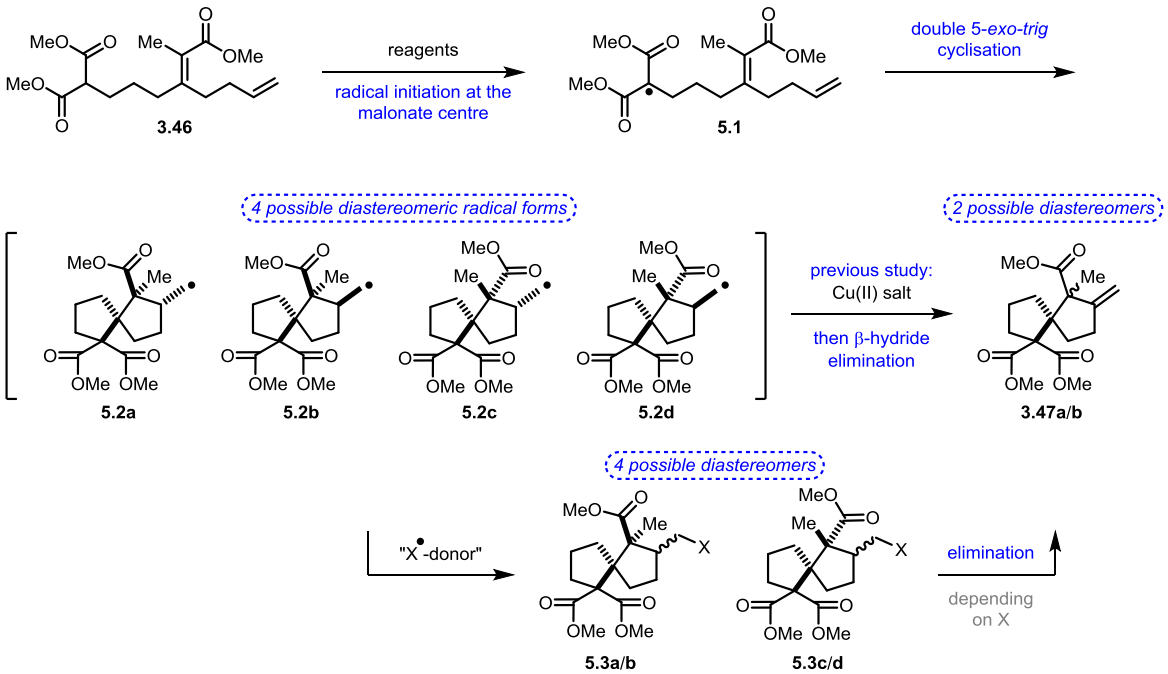
adding an alkyl group should be possible. This strategy will come with the same drawbacks as we previously described.

Due to time constraints, we had to halt the project at that stage. We expect that the extremely efficient route developed to form tetraester (*Z*)-**4.1** (67% overall yield over 3 steps) or (*E*)-**4.1** (61% overall yield over 3 steps) will provide compounds such as **4.21** (R = alkyl).

# 5 Visible Light-Induced Cyclisation Study.

## 5.1 Introduction

It was our intention to avoid the use of superstoichiometric amounts of metal salts in order to reduce waste and make the key methodology more user- and environmentally friendly. We could envisage a variety of reagent combinations leading to radical initiations at the malonate centre, forming for example radical **5.1** (**Scheme 5-1**, below). Assuming no competitive 6-*endo-trig* cyclisation process takes place, we can expect 4 isomeric forms of radical **5.2** (**a**-**d**) to be formed from malonate radical **5.1**, resulting in 4 diastereomers **5.3a**-**d** of products. This is something that we took into consideration and judged as a potential important limiting factor when using an alkene moieties on the eastern part of the molecules (**3.46**, for instance). In our previous system, the use of Cu(II) salt generated an *exo*-alkene reducing the number of stereoisomeric products; only two possible isomers **3.47a**/**b** can be obtained.



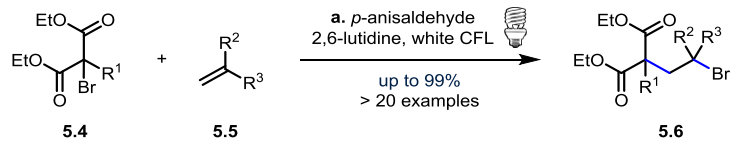

**Scheme 5-1:** The potentially complex mixtures of radical intermediates formed in the radical cyclisation process. Their reaction with Cu(II) salts, or *via* a proposed 2-step sequence to form *exo*-alkenes **3.47a**/**b**.

Another method to limit the number of stereogenic centres is to use terminal alkynes substrates (*e.g.* **3.21** in **Section 3.3.1**). Previously, we had managed to synthesise alkene derivatives cyclisation precursors in much better yields than terminal alkynes. This last reason was an important contributor in our decision process, especially given the time-scale limitations on our research. Finally, given the amount of material of **3.46** and analogues available from previous work, we decided it would be ideal to have a method that would allow for compounds such as **5.3a**-**d** to be formed from **5.2a**-**d**. It was also considered that by choosing X appropriately, **5.3a**-**d** could be converted into known compounds **3.47a/b** if desired/necessary.

Atom transfer radical addition reactions have been shown by Curran and co-workers to be an efficient way to build carbon-carbon bonds and we elected to investigate such process under tin-free conditions.[158,159]

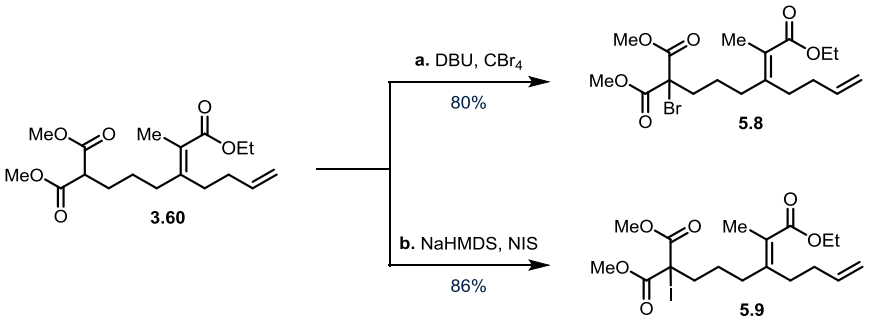
We chose halogens (X = Br or I) as bromomalonates[158,160–164] and iodomalonates[158,165–169] are ubiquitous as precursors of radical cyclisations. We knew from our anionic study that we could envisage forming our cyclisation precursors at low temperature without forming polar by-products or isomerisation of the internal double bond. Finally, base or oxidative elimination could be used to simplify our mixture of **5.3a**-**d** to *exo*-alkenes **3.47a**/**b** if desired.

Melchiorre and co-workers described the visible-light mediated atom-transfer radical addition (ATRA) of bromomalonates onto alkenes using *p*-anisaldehyde as a organo-photocatalyst onto alkenes and regular household compact fluorescent lamps (CFLs) were used as the light source in this study (**Scheme 5-2**, below).[161]




**Scheme 5-2:** Melchiorre and co-workers:[161] Organo-photocatalytic atom-transfer radical additions to alkenes using bromomalonates and *p*-anisaldehyde under visible light irradiation. $R^1$ = H, Me; $R^2$ = alkyl; $R^3$ = alkyl, OTMS. Reagents and conditions: (a) *p*-anisaldehyde (0.2 eq.), 2,6-lutidine (1.0 eq.), degassed (3x FPT cycles) MeCN, 23 W white CFL light, 12-95 h, up to 99%.

We proposed to use chemistry analogous to this on our substrates. We performed test brominations on previously described malonate **3.46** and found it could be brominated in excellent yields on 50-mg scale to form bromomalonate **5.7** (not drawn) in 91% yield with NaHMDS/NBS or 97% yield with DBU/$CBr_4$, both reactions in THF (-78 °C). Test reactions using Melchiorre's conditions gave extremely clean reaction based on the $^1$H NMR spectra of the crude reaction mixtures on the first attempts. We therefore decided to continue with this methodology. We switched to the ethyl α,β-unsaturated ester **3.60** (**Scheme 5-3**) as it was faster and cheaper to make than trimethyl ester **3.46**.




**Scheme 5-3:** Syntheses of bromomalonate **5.8** and iodomalonate **5.9**.

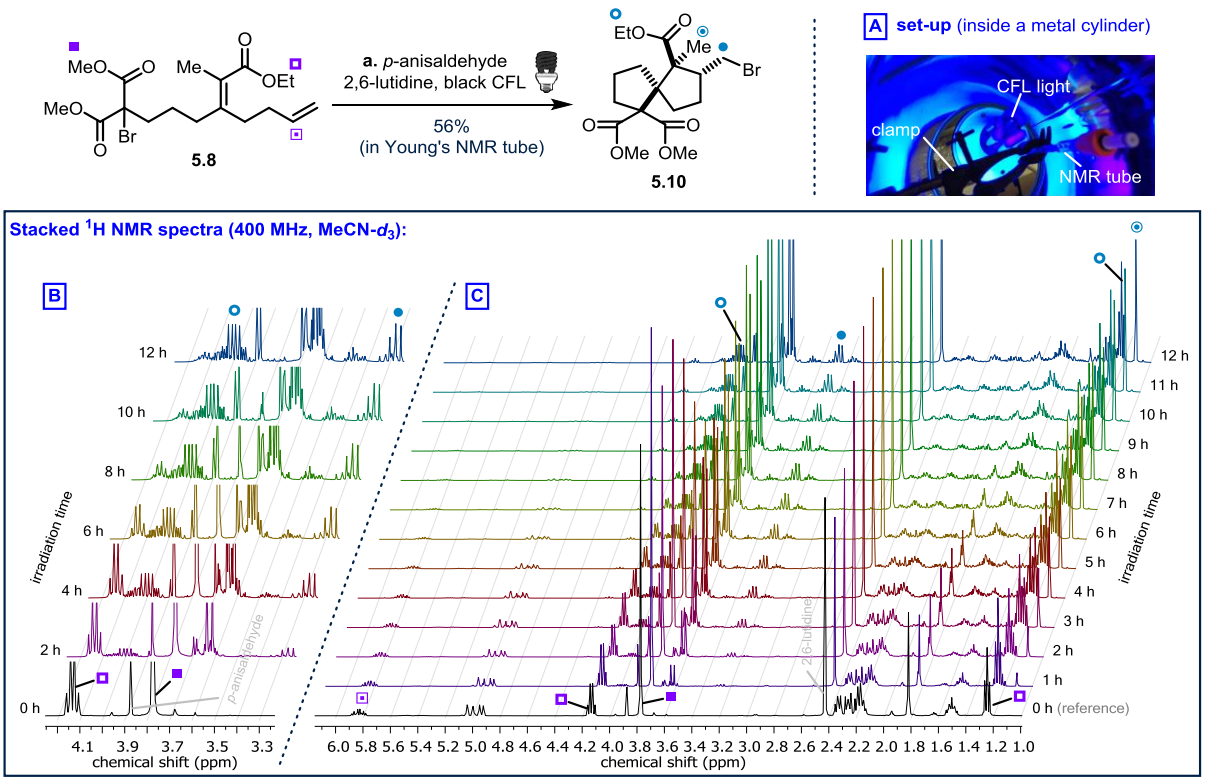
Reagents and conditions: (a) DBU (1.1 eq.), $CBr_4$ (1.1 eq.), THF, -78 °C, 40 min, 80%;
(b) NaHMDS (1.0 eq.), NIS (1.1 eq.), THF, -78 °C, 2.5 h, 86%.

Bromomalonate **5.8** could be formed in good yield (80%) by deprotonation with DBU at -78 °C and quenching with carbon tetrabromide. The use of NaHMDS in THF (-78 °C) and quenching with NIS gave iodomalonate **5.9** in good yield (86%).

## 5.2 Cyclisation of bromomalonate 5.8

Melchiorre and co-workers noted that oxygen inhibits the previously described ATRA as it is an efficient triplet state quencher;[161] therefore, the reactions were carried out in Young's NMR tubes under inert atmosphere. MeCN-$d_3$ was used as solvent to allow us to follow the progress of the reaction by $^1$H NMR spectroscopy while avoiding undesired introduction of oxygen in the system. The major drawbacks were that the combination of dilution and scale would have to be chosen in order to achieve an appropriate reaction volume for NMR analysis (minimum 0.40 mL to maximum 0.9 mL in a classic 5 mm NMR tube) and that the reaction could not be stirred/shaken.

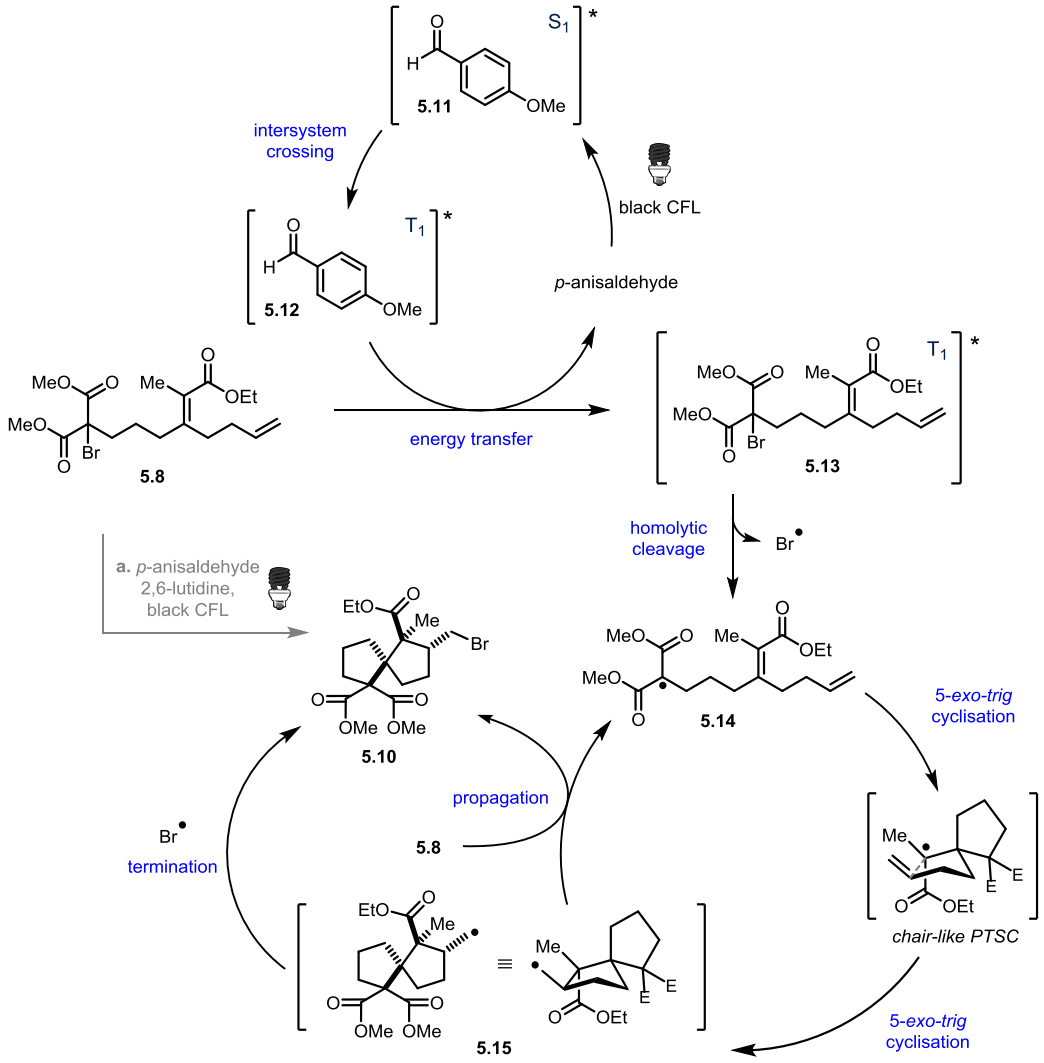
A stock solution of freshly distilled *p*-anisaldehyde (0.2 eq.) and 2,6-lutidine (1.0 eq.) in MeCN-$d_3$ was degassed using 3 freeze-pump-thaw (FPT) cycles and added to substrate **5.8** in a Young's NMR tube and sealed under argon atmosphere. The tube was placed at 0.5 cm away from a 30 W white CFL and irradiated for a known duration at a time. After each irradiation period, the sample was brought to the NMR spectrometer (covered with aluminium foil) and a $^1$H NMR spectrum was recorded. We found that the extent of reaction would reach a plateau after about 24 h. In contrast, the use of a 15 W black CFL increased the rate of the reaction. Complete consumption of starting bromomalonate **5.8** was observed after 12 h of irradiation (measurements were taken at 1 h increments) (**Scheme 5-4**).




**Scheme 5-4:** NMR study of the cyclisation of bromomalonate **5.8** under black CFL irradiation with *p*-anisaldehyde; [A] picture of the set-up used with the black CFL turned on (seen from above), $N_2$ flow inside the can (not pictured) used to keep the air inside below 28 °C; [B] stacked $^1$H NMR spectra every 2 h (clipped vertically for clarity; zoom: 4.25-3.25 ppm); [C] stacked $^1$H NMR spectra every 1 h (zoom: 6.1-1.0 ppm).

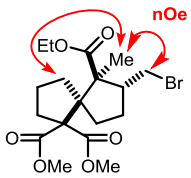
Reagents and conditions: (a) *p*-anisaldehyde (0.2 eq.), 2,6-lutidine (1.0 eq.), degassed (3x FPT cycles) MeCN-$d_3$ (0.27 M), 15 W black CFL light, ≤ 28 °C (outside temp.), 12 h (split in 1 h intervals), sealed in a Young's NMR tube (distance from the light: 0.5 cm), 56%.

The reaction was run in the set-up shown in **Scheme 5-4**[A] (viewed from above). The measured outside temperature was ≤ 28 °C when a strong nitrogen flow was run inside the set-up. The stacked $^1$H NMR obtained (see [B] and [C]) show a relatively clean disappearance of characteristic peaks of our starting material **5.8** and the progressive appearance of characteristic multiplets of product **5.10** which was isolated in 56% yield as a single isomer. Its relative configuration was determined using $^1$H NMR nOe analyses (**Scheme 5-6**, below).




**Scheme 5-5:** Proposed mechanism of the reaction with favoured transition state.

Reagents and conditions: (a) *p*-anisaldehyde (0.2 eq.), 2,6-lutidine (1.0 eq.), degassed (3x FPT cycles) MeCN-$d_3$, black CFL light. E = $CO_2Me$.




**5.10**

**Scheme 5-6:** Indicative nOe interations observed for spirocycle **5.10**.

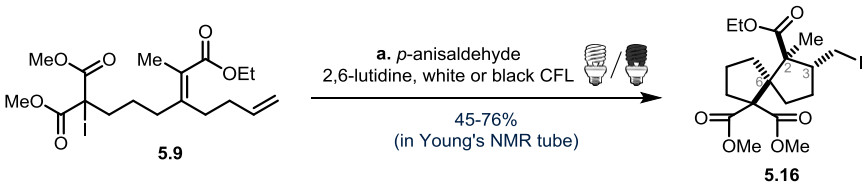
We propose that bromomalonate **5.8** undergoes homolytic fission to give free radical **5.13** after triplet sensitisation from the excited triplet state of *p*-anisaldehyde **5.12** (**Scheme 5-5**, above). This radical then undergoes consecutive 5-*exo*-*trig* cyclisations to give primary radical **5.15**. Product **5.10** can then be formed by abstraction of a bromine atom from starting bromomalonate **5.8** to start a chain reaction.

Encouraged by these excellent results, we decided to explore the chemistry of the parent iodide **5.9** using these types of conditions.

## 5.3 Cyclisation of iodomalonate 5.9

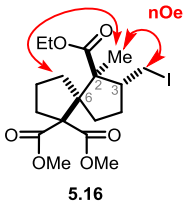
### 5.3.1 Early results

Given the promising results obtained with the cyclisation of bromomalonate **5.8**, we submitted iodomalonate **5.9** to the same reaction conditions (1 eq. of 2,6-lutidine, 0.2 eq. of *p*-anisaldehyde in degassed MeCN-$d_3$ (0.27 M) in a Young's NMR tube) using both white and black CFLs. We followed the reactions by $^1$H NMR experiments every 15 min for the first 2 h, then at longer irradiation intervals. To our delight, we found that using the 30 W white CFL gave a complete conversion after only 30 min whereas the 15 W black CFL did not lead to full conversion after 6 h which indicated to us that a different mechanism was taking place.




**Scheme 5-7:** Early results for the cyclisation of iodomalonate **5.9** under CFL irradiation with additives. Reagents and conditions: (a) *p*-anisaldehyde (0-0.5 eq.), 2,6-lutidine (0-2.4 eq.), degassed (3x FPT cycles) MeCN-$d_3$ (0.07-0.27 M), 15 W black CFL or 30 W white CFL, ≤ 28 °C (outside temp.), sealed in a Young's NMR tube (various distances from the CFL).

The configuration of primary iodide **5.16** was determined by $^1$H NMR NOESY analysis (**Scheme 5-8**, below) and was found to be the same as for the corresponding bromide **5.10**. The relative configuration at C(2) and C(6) were in keeping with previous results obtained using $Mn(OAc)_3$ (**Section 3.4**). Heating of iodide **5.16** neat to 140 °C for 1 h gave no cyclisation of the pendant ester to a γ-lactone (or any other decomposition product). This remarkable stability was also in keeping with the *trans*-relationship between the ethyl ester at C(2) and the $CH_2I$ group at C(3).




**Scheme 5-8:** Indicative nOe interations observed for spirocycle **5.16**.

To increase the scale and number of reactions that were able to run simultaneously, we investigated alternative reaction set-ups. We quickly realised that the distance from the light was very important in order to generate comparable results. Variation of yields were relatively minor (< 10%), but as we expected, the reaction times were highly impacted by this change (30 min to > 5 h). Indeed, we expect the rate of reaction to vary with quantity of photons absorbed (and therefore going through the glass reaction vessel). This was in keeping with a chain reaction process. We therefore decided to create a new set-up allowing for full control of our conditions while being able to run multiple reactions at a time.

### 5.3.2 New photochemistry set-up for controlled conditions

The main reason for creating a new set-up was to control the reaction time. This would become essential to reduce the work load during the optimisation (**Section 5.3.3**). We designed and 3D-printed a structure that could be bolted into a metallic cylinder (used by Aldrich/Merck to deliver sensitive/pyrophoric materials) (**Figure 5-1**). The cylinder provides a shield to protect chemicals/people around while the light is turned on. It also reflects the light back towards the sample for a better exposure. It was designed so that different types of extension could be attached for modular use of the set-up.

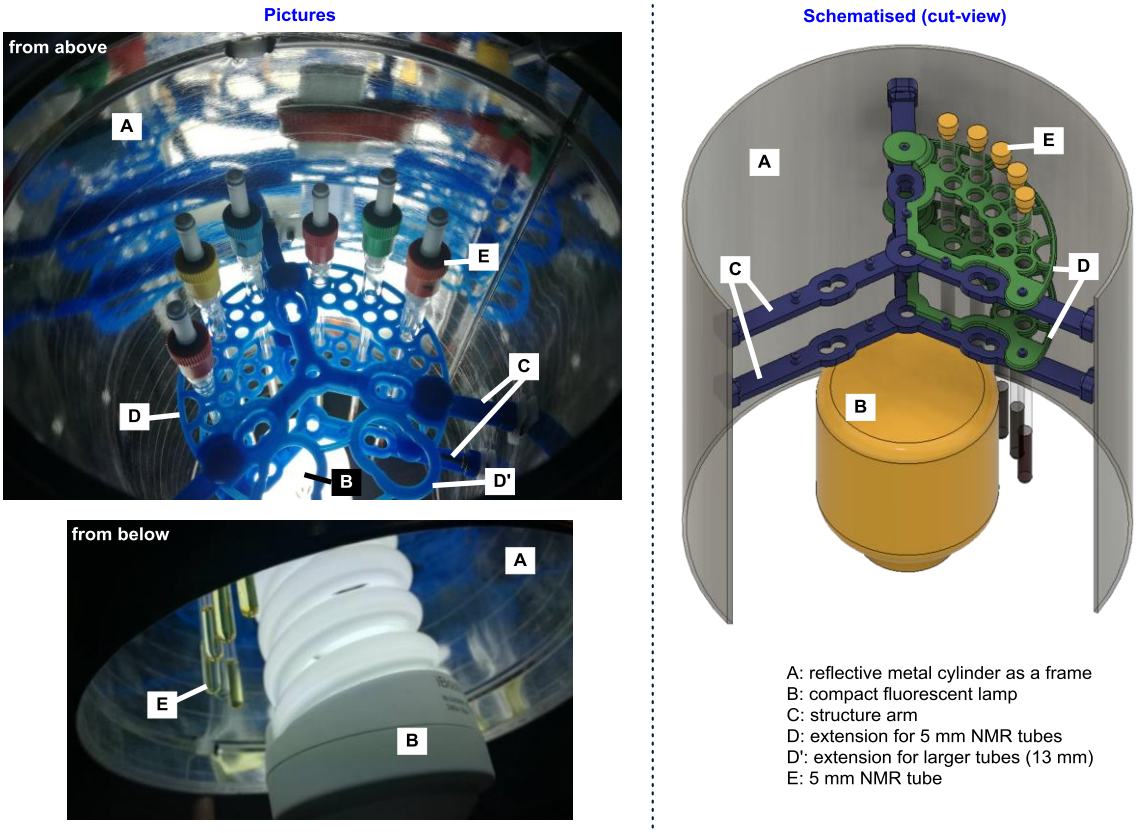



**Figure 5-1:** Pictures of the new set-up in use with a white CFL and 6 Young NMR tubes (*left*); Schematised cut-view of the new set up holding 5 NMR tubes (*right*).

For example, extension [D] can accommodate up to 6 NMR tubes at 2 different distances from the light source. Other extensions can be designed and 3D-printed (*e.g.* [D'] for larger tubes) to meet the need of the experiments. The extensions can be mixed and matched (see picture, *top-left*) allowing for quick screening of conditions keeping the lighting conditions identical. Temperatures below 30 °C

(26-28 °C in most cases using the 30 W white CFL) were measured at ≥ 1 cm of the light source when a strong flow of nitrogen gas was run into the set-up. More details can be found in **Section 7.4** (page 117).

### 5.3.3 Optimisation of cyclisation of iodomalonates

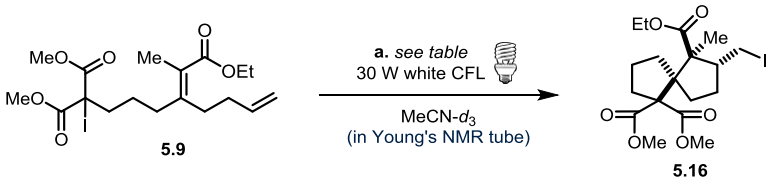
The previously described set-up was used to optimise the cyclisation of iodomalonate **5.9** to spiro[4.4]nonane **5.16** using GC-MS to measure yields relative to calibrated samples.

We first treated spirocycle **5.16** with our starting conditions (1 eq. of 2,6-lutidine, 0.2 eq. of *p*-anisaldehyde in degassed MeCN-$d_3$ (0.27 M) in a Young's NMR tube); no decomposition was observed after 2 h by $^1$H NMR spectroscopy. Increasing the exposure time of a cyclisation reaction was therefore unlikely to affect yields by decomposition of the product.

It was found that increasing the amount of *p*-anisaldehyde from 0.2 eq. (standard conditions, entry 1) to 1.0 eq. (entry 2) gave no improvement with about 65% yield of product **5.16** isolated (**Table 5.1**, below). Omitting *p*-anisaldehyde did not affect the yield (69% GC yield, 71% isolated yield, entry 3), which confirmed that the bromo- and iodomalonates were reacting *via* different mechanisms. This would indicate that the light causes direct homolytic fission of the C-I bond. Additional omission of 2,6-lutidine gave a lower 64% yield of **5.16** (60% isolated) (entry 4). We found that using more base was not improving the yield of product **5.16** (entry 5).

However, the degassing technique had a critical impact on the yield of the reaction. Sparging the reaction solvent for 1 h with nitrogen gas gave a low 10% yield of product **5.16** (mostly starting material recovered) after 3 h of irradiation (entry 6). The reaction was run for longer, allowing it to react to completion and gave spirocycle **5.16** in 37% yield (entry 7). The same yield was obtained when no degassing operation was performed (entry 8). Finally, conducting the reaction in non-degassed acetonitrile with no added additives gave 45% yield (entry 9). The set presented in this table showed that *p*-anisaldehyde was not necessary for the reaction to happen, lutidine had a small

positive impact on the yield and more importantly that a thoroughly degassed reaction mixture was essential to obtain good yields.



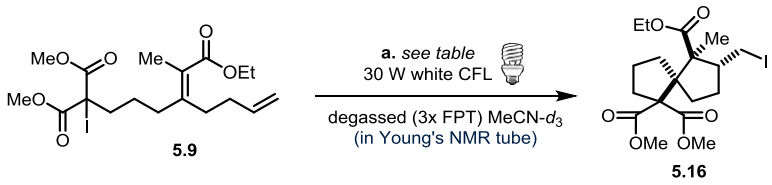

| entry[a] | solvent | base (eq.) | photosensitiser (eq.) | degassing method | yield[b] |
|---|---|---|---|---|---|
| 1 | MeCN-$d_3$ | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | 3x FPT cycles | 66% |
| 2 | MeCN-$d_3$ | 2,6-lutidine (1.0) | *p*-anisaldehyde (1.0) | 3x FPT cycles | 65% |
| 3 | MeCN-$d_3$ | 2,6-lutidine (1.0) | - | 3x FPT cycles | 69% (71%) |
| 4 | MeCN-$d_3$ | - | - | 3x FPT cycles | 64% (60%) |
| 5 | MeCN-$d_3$ | 2,6-lutidine (2.5) | - | 3x FPT cycles | 68% |
| 6 | MeCN-$d_3$ | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | sparging (1 h, $N_2$) | 10% |
| 7[c] | MeCN-$d_3$ | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | sparging (1 h, $N_2$) | 37% |
| 8[c] | MeCN-$d_3$ | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | none | 36% |
| 9 | MeCN-$d_3$ | - | - | none | 45% |

**Table 5.1**: Cyclisation of iodomalonate **5.9** to spirocycle **5.16** using GC-MS, effect of base, photosensitiser and degassing method.

Reagents and conditions: (a) *p*-anisaldehyde (*see table*), 2,6-lutidine (*see table*), MeCN-$d_3$ (0.27 M), 30 W white CFL, ≤ 28 °C (outside temp.), 3 h (unless otherwise stated), sealed in a Young's NMR tube (distance from the light: 1.0 cm).

[a] reaction performed on 25 to 50 mg scale; [b] GC yield against an internal standard, isolated yield in parentheses; [c] yield after 16 h; FPT= freeze-pump-thaw.

The second table (**Table 5.2**, below) confirmed that the photosensitiser was not necessary. All benzaldehyde derivatives tested gave the same yields (within experimental error) (entry 2-4) as the previous result without. A 4% yield drop was observed when the reaction was irradiated for much longer than necessary (16 h, entry 5). Using triethylamine as the base of the reaction resulted in a clean deiodination reaction of the starting material (entry 6). This could be explained by attack of the nitrogen of triethylamine at the iodide centre, using our starting material as an $I^+$ source. Finally, increasing the dilution to 0.05 M gave a small drop in yield consistent with a chain reaction process (entry 7).



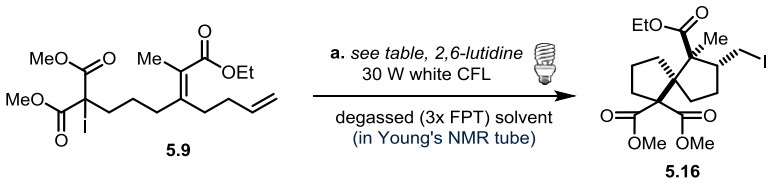

| entry[a] | solvent | base (eq.) | photosensitiser (eq.) | degassing method | yield[b] |
|---|---|---|---|---|---|
| 1 | MeCN-$d_3$ | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | 3x FPT cycles | 66% |
| 2 | MeCN-$d_3$ | 2,6-lutidine (1.0) | benzaldehyde (0.2) | 3x FPT cycles | 68% |
| 3 | MeCN-$d_3$ | 2,6-lutidine (1.0) | *p*-thioanisaldehyde (0.2) | 3x FPT cycles | 68% |
| 4 | MeCN-$d_3$ | 2,6-lutidine (1.0) | *p*-bromo-benzaldehyde (0.2) | 3x FPT cycles | 66% |
| 5[c] | MeCN-$d_3$ | 2,6-lutidine (1.0) | *p*-bromo-benzaldehyde (0.2) | 3x FPT cycles | 62% |
| 6[d] | MeCN-$d_3$ | $Et_3N$ (1.0) | *p*-bromo-benzaldehyde (0.2) | 3x FPT cycles | traces |
| 7[e] | MeCN-$d_3$ | 2,6-lutidine (1.0) | *p*-bromo-benzaldehyde (0.2) | 3x FPT cycles | 54% |

**Table 5.2**: Cyclisation of iodomalonate **5.9** to spirocycle **5.16** using GC-MS, additive screen.

Reagents and conditions: (a) photosensitiser (*see table*), base (*see table*), degassed (3x FPT cycles) MeCN-$d_3$ (0.27 M unless otherwise stated), 30 W white CFL, ≤ 28 °C (outside temp.), 3 h (unless otherwise stated), sealed in a Young's NMR tube (distance from the light: 1.0 cm).

[a] reaction performed on 25 to 50 mg scale, first entry was; [b] GC yield against an internal standard; [c] yield after 16 h of irradiation; [d] dehalogenated product **3.60** obtained instead; [e] concentration: 0.05 M.

The last table (**Table 5.3**, below) combines our results from a solvent screen. We found that the reaction could be performed in most solvents without suffering a drastic drop in yield. No significant trend emerged from this set even though more polar solvents gave better overall results. Three new solvents gave good yields of product **5.16** (entries 2-4). DMSO (65%, entry 4) and DMF (69%, entry 3) as solvents gave similar yields to reactions performed in deuterated acetonitrile (66%, standard conditions, entry 1). A slightly better yield was obtained in deuterated methanol (73%, entry 2). THF and benzene (entries 5-6) performed equally with about 56% yield. $CH_2Cl_2$ and EtOAc came last with yields around 50% (entries 7-8). This set was important because it made us realise the importance of the degassing technique used. Experimentally, we originally only sparged all solvents and ran the reactions but almost no conversion was observed after 3 h (previously reported for MeCN-$d_3$ in **Table 5.1**, entry 6). We therefore repeated all reaction using freeze-pump-thaw (FPT) cycles on each solvent to obtain these results.




| entry[a] | solvent | base (eq.) | photosensitiser (eq.) | degassing method | yield[b] |
|---|---|---|---|---|---|
| 1 | MeCN-$d_3$ | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | 3x FPT cycles | 66% |
| 2 | MeOD-$d_4$ | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | 3x FPT cycles | 73% |
| 3 | DMF | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | 3x FPT cycles | 69% |
| 4 | DMSO | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | 3x FPT cycles | 65% |
| 5 | benzene | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | 3x FPT cycles | 57% |
| 6 | THF | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | 3x FPT cycles | 56% |
| 7 | $CH_2Cl_2$ | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | 3x FPT cycles | 51% |
| 8 | EtOAc | 2,6-lutidine (1.0) | *p*-anisaldehyde (0.2) | 3x FPT cycles | 50% |
| 9 | $CDCl_3$ | 2,6-lutidine (1.0) | - | 3x FPT cycles | 63% |
| 10 | MeOD-$d_4$ | 2,6-lutidine (1.0) | - | 3x FPT cycles | 75% (70%)[c] |

**Table 5.3**: Cyclisation of iodomalonate **5.9** to spirocycle **5.16** using GC-MS, solvent screen.

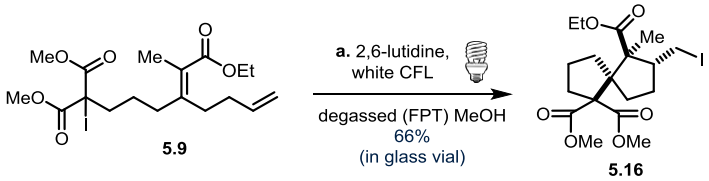
Reagents and conditions: (a) *p*-anisaldehyde (*see table*), 2,6-lutidine (1.0 eq.), degassed (3x FPT cycles) solvent (*see table*, 0.27 M), 30 W white CFL, ≤ 28 °C (outside temp.), 3 h (unless otherwise stated), sealed in a Young's NMR tube (distance from the light: 1.0 cm).

[a] reaction performed on 25 to 50 mg scale; [b] GC yield against an internal standard, isolated yield in parentheses.

Some of these solvents were deuterated to allow a quick analysis by $^1$H NMR spectroscopy before quenching the reactions and preparing samples for GC-MS analysis. It allowed us to check that the control experiments of each set ran to completion before irreversibly stopping all the others. We avoided as much as we could the use of TLC analysis during reaction as we did not want to risk any contamination of the reaction with oxygen. TLC was only performed on each experiment before stopping the reaction to check disappearance of iodomalonate **5.9**. This additional step was performed despite the upcoming GC-MS analysis. This is because iodomalonate **5.9** gave low responses during the MS ionisation so that determination of remaining starting material was not precise. NMR spectra could generally not be used for anything else than qualitative observations, such as disappearance of starting material, as the low amount of solvents in the tubes usually gave extremely poor shimming.

Combining the best conditions of each set, we decided to perform another reaction using only 2,6-lutidine (1.0 eq.) in deuterated methanol (0.27 M) degassed using FPT cycles. This gave a 75% GC yield and purification gave a satisfactory 70% isolated yield of **5.16** (entry 10). Deuterated chloroform was also tested as we realised that an NMR sample of starting iodomalonate **5.9** converted cleanly to expected products upon standing outside over less than a week. Nevertheless, a lower 63% yield was obtained.

With these new conditions in hand, we attempted the reaction in a glass vial using non-deuterated MeOH with magnetic stirring. We isolated 66% of a single isomer **5.16**, showing that this reaction could be used in a more standard set-up.

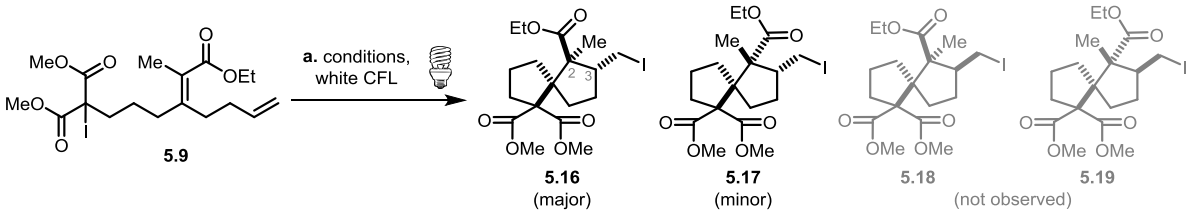



**Scheme 5-9:** Cyclisation reaction of iodomalonate **5.9** using optimised conditions in a glass vial.
Reagents and conditions: (a) 2,6-lutidine (1.0 eq.), degassed (3x FPT cycles) MeOH (0.27 M), 30 W white CFL, ≤ 28 °C (outside temp.), 16 h, in a glass tube (distance from the light: 5.0 ± 0.3 cm).

### 5.3.4 Other isomer(s) obtained in polycyclisation reactions of iodomalonates

The selectivity in the atom transfer reaction was surprising considering that previous Mn(III)-mediated cyclisations showed *d.r.* around 3.5:1 to 5:1 at the ester centre (**Section 3.4.3**, page 58). Therefore, we decided to investigate the presence of other minor isomers in more detail.

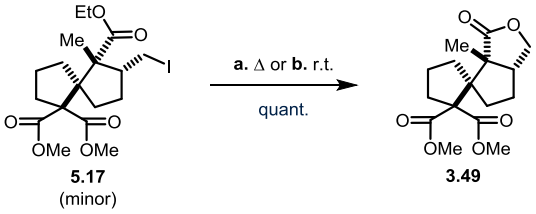
During our time-course $^{1}$H NMR experiments, we observed other multiplets that subsequently disappeared. We originally could not conclude if they were intermediates of the reaction or actual products/by-products decomposing. Later, we found that products originally observed by TLC analysis sometimes disappeared a few minutes to hours later. We hypothesised that another/other isomer(s) were formed but were unstable to the reaction conditions.




**Scheme 5-10:** Cyclisation reaction of iodomalonate **5.9** using optimised conditions in a glass vial.

Reagents and conditions: (a) different conditions, 30 W white CFL, ≤ 28 °C (outside temp.), 3-16 h.

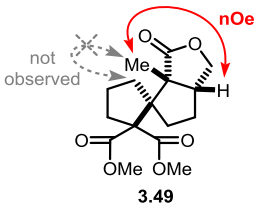
Minor C(2) diastereomer **5.17** was eventually isolated during the optimisation. We found that it was readily lactonising in quantitative yield to lactone **3.49** when heated neat to 140 °C (**Scheme 5-11**, below). Lactonisation of purified **5.17** was also relatively fast in solution at room temperature. In fact, full lactonisation was observed when a NMR sample (in $CDCl_3$) was left standing for 4 d at room temperature. This led to difficulties obtaining a clean $^1$H NMR of minor isomer **5.17** without any lactone **3.49** formed. We eventually managed to record NMR data with less than 10% of lactone by freshly preparing the sample and keeping it at -78 °C until the spectrum was acquired.




**Scheme 5-11:** Lactonisation of minor isomer **5.17**.

Reagents and conditions: (a) neat, 140 °C, 5 h, quant.; (a) $CDCl_3$, r.t., 4 d, quant.

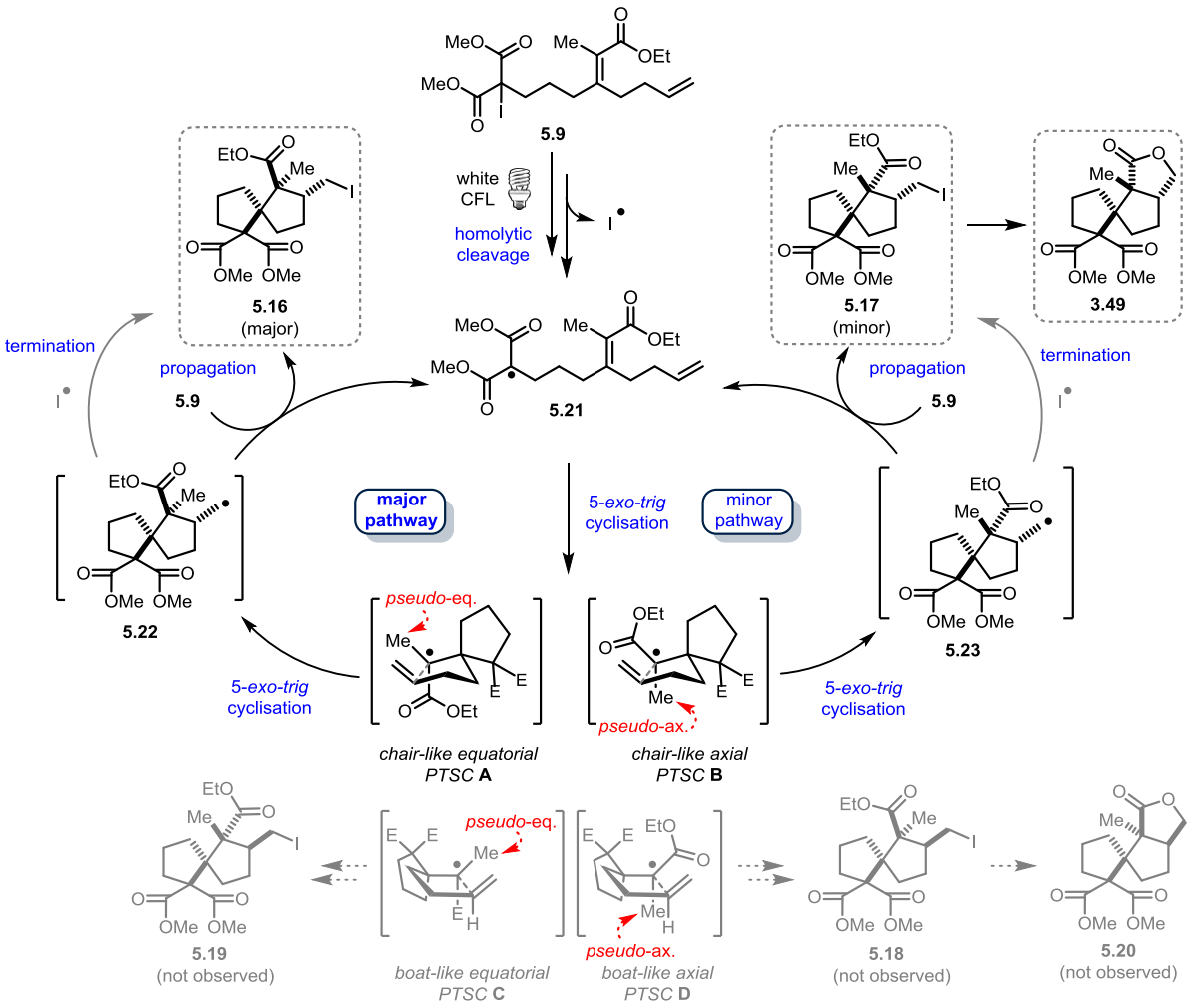
The minor isomer was not always observed in crude mixtures but it is not clear which conditions (solvents, presence of salts and more) triggered spontaneous lactonisation. However, we found that minor isomer **5.17** was less stable when in solution or left standing as part of a crude mixture than when it was concentrated down. $^1$H NMR NOESY experiments were in keeping with the structure proposed for lactone **3.49** (**Scheme 5-12**, below).




**Scheme 5-12:** Indicative nOe interations observed for spirocyclic lactone **3.49**.

Analysis of minor isomer **5.17** was attempted by GC-MS but no new peak was obtained on the GC chromatogram. The required temperature (about 300 °C) necessary to analyse major isomer **5.16** was deemed the reason for this absence of peak as we would expect minor isomer **5.17** to lactonise to **3.49** at these high temperatures. Unfortunately, lactone **5.17** failed to give any response by GC-MS analysis either. As was previously observed in **Section 3.3.2**, lactone **3.49** did not stain on TLC and eluted with impurities. As a result, it was never isolated from a crude mixture but always formed from isolated minor isomer **5.17**. For these reasons, we have not been able to measure accurately the *d.r.* at the quaternary carbon (C(2)) which is estimated to be 1:8 in MeOD-$d_4$ and $CDCl_3$. This approximate value was determined based on integral ratios in $^1$H NMR of crude mixtures of all considered species (**5.16**, **5.17** and **3.49**). This explains why we only reported GC-MS yields and isolated yields of major isomer **5.16** in the reaction optimisation in the previous section.

All these additional data helped us draw a more accurate picture of what happens in our reaction flask (**Scheme 5-13**, below). We propose a direct irradiation of iodide **5.16** leading to homolytic cleavage of the C-I bond to form free radical **5.14**. Double 5-*exo*-*trig* cyclisation follows leading to radical **5.22** when proceeding *via* chair-like *PTSC* **A** where all substituents are placed in *pseudo*-equatorial position. This forms major spiro[4.4]nonane **5.16** after propagation (or termination) step. Alternatively, chair-like *PTSC* **B** in which the methyl group (higher A value) is in *pseudo*-axial position would account for the formation of minor isomer **5.17** and its corresponding lactone **3.49**. Spirocycles **5.18/5.19** (or lactone **5.20**) have not been observed implying that boat-like *PTSCs* **C**/**D** are higher in energy. Chair-like transition states where the terminal alkene is *pseudo*-axial (not drawn) could also lead to the formation of these unobserved products.

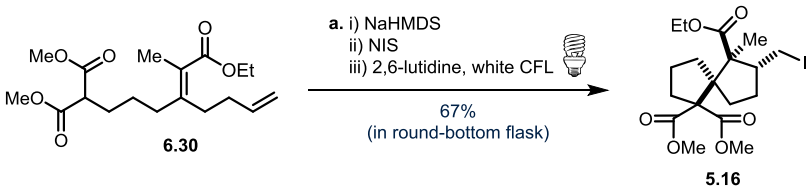



**Scheme 5-13:** Proposed mechanism of the cyclisation of iodomalonate **5.9** accounting for the formation of spirocycles **5.16** and **5.17** and tricyclic lactone **3.49**. E = ester.

Reagents and conditions: (a) different conditions, 30 W white CFL, ≤ 28 °C (outside temp.), 3-16 h.

### 5.3.5 One-pot iodination/polycyclisation procedure

Because of its light sensitivity, iodomalonate **5.9** had to be protected from light during its synthesis, isolation and storage. We therefore decided to complete the reaction in one pot to simplify the process. Malonate **3.60** was therefore treated with NaHMDS at -78 °C followed by NIS in degassed THF (3x FPT cycles). When the iodination reaction was considered complete by TLC analysis (it was usually left for 5 h for convenience), 2,6-lutidine was added, the flask was removed from the bath and placed next to the white CFL.




**Scheme 5-14:** one-pot iodination/cyclisation of malonate **3.60** to cyclised product **5.16**.
Reagents and conditions: (a) i) NaHMDS (1.0 eq.), degassed (3x FPT cycles) THF, -78 °C, 15 min; ii) NIS (1.1 eq.), 5 h; iii) 2,6-lutidine (1.0 eq.), 30 W white CFL, ≤ 25 °C (outside temp.), 16 h, in a round-bottom flask (distance from the light: 5.0 ± 0.3 cm).

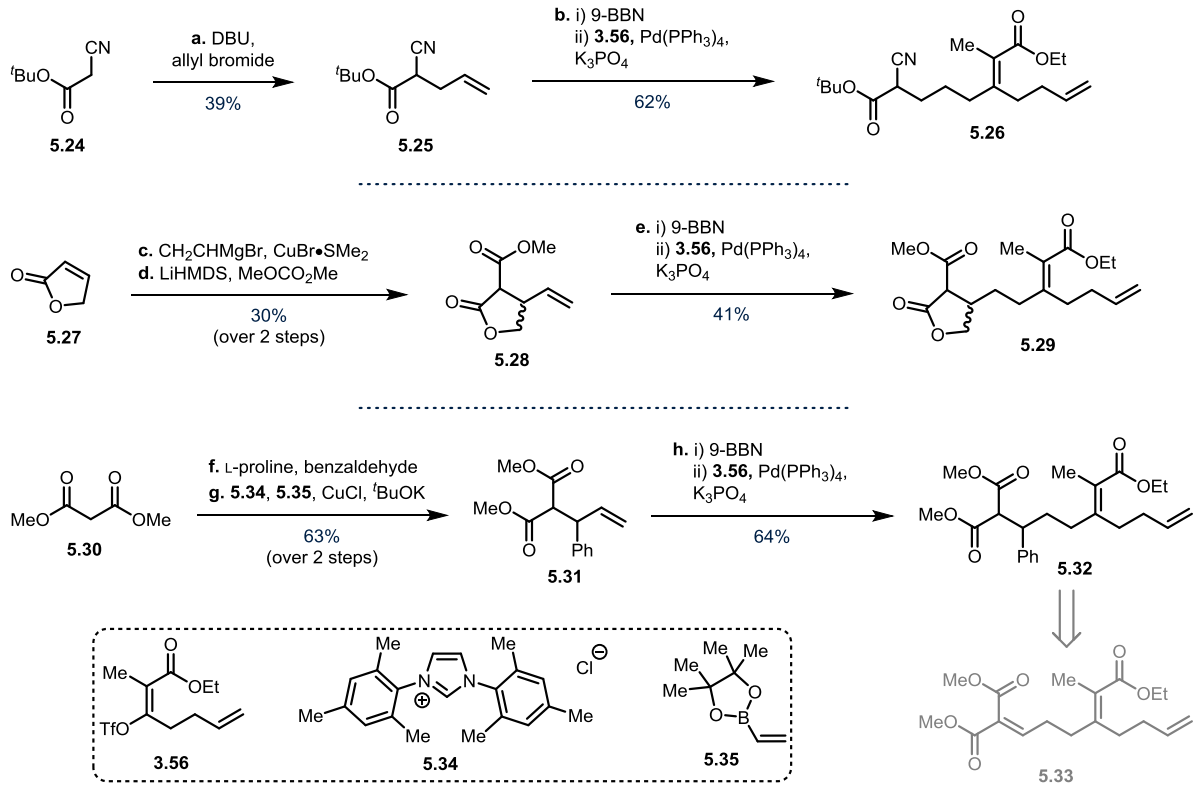
To our delight, primary iodide **5.16** was obtained in 67% isolated yield, which compared favourably with the iodination only (66% isolated yield when conducted in a vial). Other experiments showed that 2,6-lutidine (1.0 eq.) gave a 6% yield increase of **5.16**. This was unexpected as we already had the amine HMDS (1.0 eq., formed during the deprotonation of the malonate) in the reaction mixture. Because of time constraints, we focussed on the scope of both cyclisation and iodination/cyclisation reactions rather than optimising the reaction further.

### 5.3.6 **Scope**

#### 5.3.6.1 Choice of substrates and their syntheses

A number of malonates, iodomalonates and their derivatives were synthesised in preparation to the scoping of both iodination/cyclisation one-pot reaction and cyclisation reaction on its own.

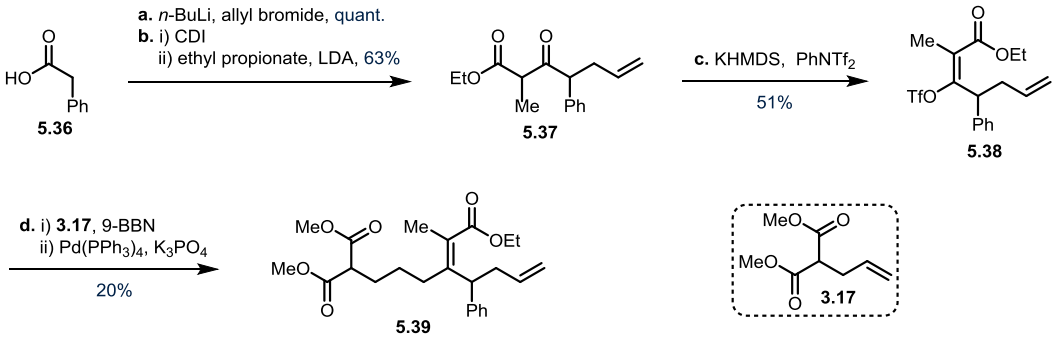
We decided to study the effect of the western part of the molecule. In that regard, β-keto nitrile **5.26** and malonates **5.29** and **5.32** were synthesised (**Scheme 5-15**, below). Malonate **5.32** was especially interesting to us. In fact, it imitates the reaction product of a mono-1,4-addition of a phenyl fragment to alkylidene malonate **5.33**. In turn, the cyclisation of **5.32** or its corresponding iodide would give us an idea of the diastereoselectivity to be expected for a complex cascade starting from **5.33**.




**Scheme 5-15:** Syntheses of malonates **5.26**, **5.29** and **5.32**.

Reagents and conditions: (a) DBU (1.0 eq.), allyl bromide (1.0 eq.), benzene, r.t., o.n., 39%; (b) i) **5.25** (1.6 eq.), 9-BBN (1.5 eq.), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), $Pd(PPh_3)_4$ (0.05 eq.), 1,4-dioxane/$H_2O$, 50 °C, o.n., 75% (*Z* only); (c) vinylmagnesium bromide (3.0 eq.), $CuBr•SMe_2$ (0.2 eq.), THF, -20 °C to -10 °C, 1 h, 47%; (d) LiHMDS (2.7 eq.), dimethyl carbonate (1.2 eq.), THF, -78 °C to r.t., o.n., 63%; (e) i) **5.28** (1.4 eq.), 9-BBN (1.3 eq.), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), $Pd(PPh_3)_4$ (0.05 eq.), 1,4-dioxane/$H_2O$, 50 °C, o.n., 41% (*Z* only); (f) L-proline (0.05 eq.), benzaldehyde (0.5 eq.), DMSO, r.t., 65 h, 79%; (g) CuCl (0.05 eq.), **5.34** (0.05 eq.), **5.35** (1.5 eq.), $^t$BuOK (1.5 eq.), THF, r.t., 16 h, 80%; (h) i) **5.25** (1.4 eq.), 9-BBN (1.3 eq.), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), $Pd(PPh_3)_4$ (0.05 eq.), 1,4-dioxane/$H_2O$, 50 °C, o.n., 64% (*Z* only).

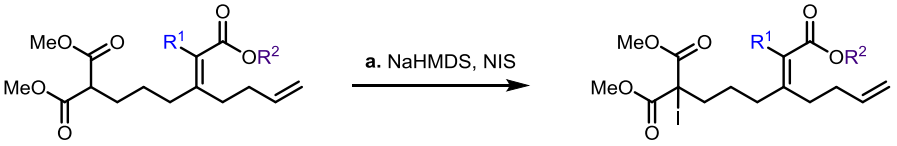
Compound **5.39** was also synthesised from phenylacetic acid **5.36** in 4 steps to test the effect that a phenyl group next to the α,β-unsaturated ester would have on the diastereoselectivity of the reaction (**Scheme 5-16**, below).




**Scheme 5-16:** Synthesis of malonate **5.39**.

Reagents and conditions: (a) *n*-BuLi (2.2 eq.), allyl bromide (1.2 eq.), THF, -78 °C to r.t., 1.75 h, quant.; (b) i) carbonyldiimidazole (CDI) (1.0 eq.), THF, r.t., 1 h; ii) ethyl propionate (2.0 eq.), LDA (4.0 eq.), THF, -78 °C to r.t., o.n., 63%; (c) KHMDS (1.2 eq.), $PhNTf_2$ (1.1 eq.), DMF, < -40 °C, 4 h, 51% (> 95:5 *E*/*Z* mix.); (d) i) **3.17** (1.6 eq.), 9-BBN (1.5 eq.), THF, 0 °C to r.t., 4 h; ii) $K_3PO_4$ (2.5 eq.), $Pd(PPh_3)_4$ (0.05 eq.), 1,4-dioxane/$H_2O$, 50 °C, o.n., 20% (*Z* only).

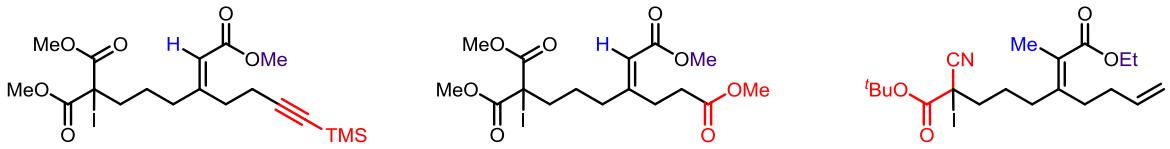
Because of time contraints and material availability, only some of them were iodinated. Iodinated products were usually obtained in good yields (**Scheme 5-17**, below). The only exception was β-Keto nitrile **5.46** which cyclised directly (discussed next section).




**3.46**, $R^1$ = Me; $R^2$ = Me
**3.61**, $R^1$ = Me; $R^2$ = $^t$Bu
**3.62**, $R^1$ = Et; $R^2$ = Et
**3.63**, $R^1$ = $^i$Pr; $R^2$ = Et

71%, **5.40**, $R^1$ = Me; $R^2$ = Me
84%, **5.41**, $R^1$ = Me; $R^2$ = $^t$Bu
64%, **5.42**, $R^1$ = Et; $R^2$ = Et
69%, **5.43**, $R^1$ = $^i$Pr; $R^2$ = Et

Other substrates made using conditions **a.**:



78% (from (*Z*)-**2.31**), **5.44**

46% (from (*Z*)-**4.1**), **5.45**

unstable (from **5.26**), **5.46**

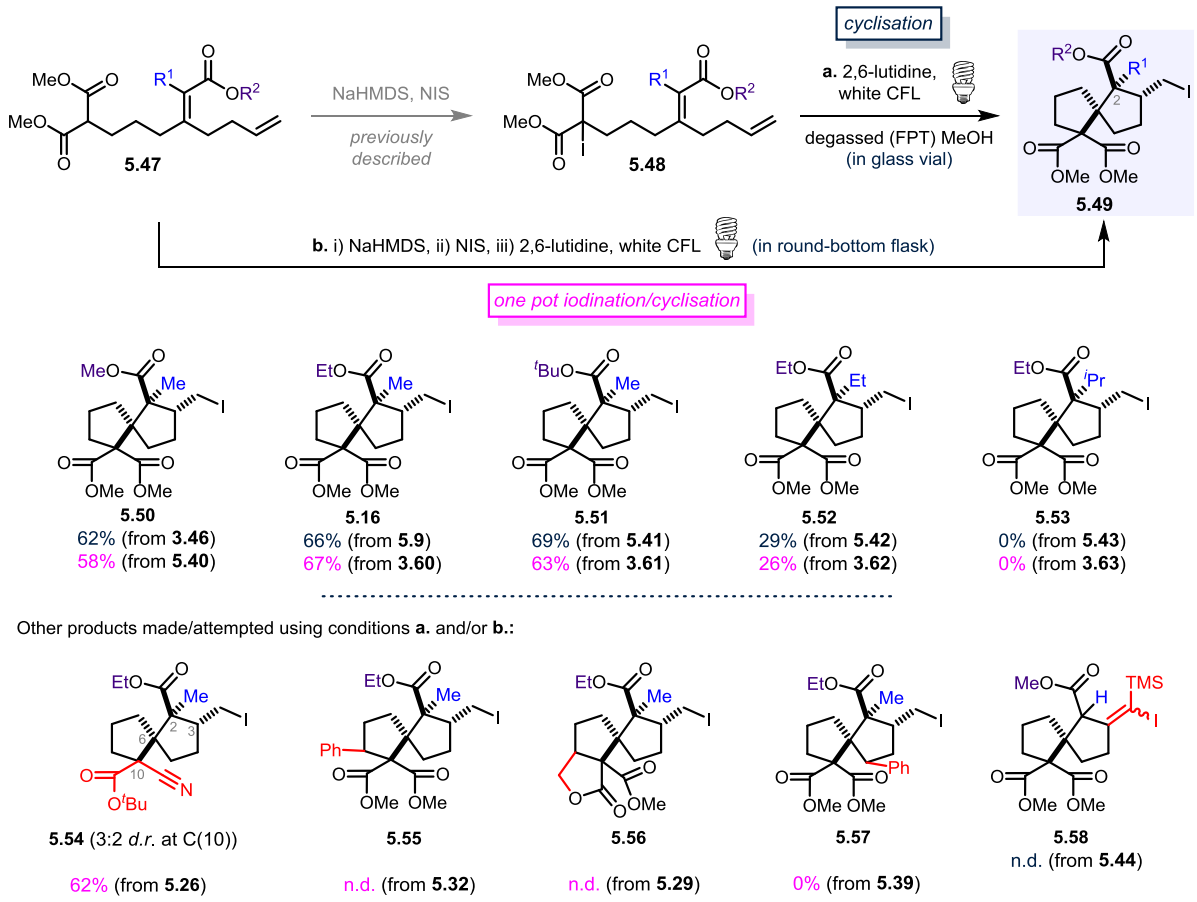
**Scheme 5-17:** Syntheses of iodomalonates **5.40**, **5.41**, **5.42**, **5.43**, **5.45** and **5.44**.

Reagents and conditions: (a) NaHMDS (1.0 eq.), NIS (1.1 eq.), THF, -78 °C, 2-5 h, 71% (**5.40**, *Z* only), 84% (**5.41**, 65:35 *Z*/*E* mix.), 64% (**5.42**, Z only), 69% (**5.43**, Z only), 78% (**5.44**, Z only), 46% (**5.45**, *Z* only).

### 5.3.6.2 Scope results

These substrates were subjected to the previous cyclisation conditions and conditions for one-pot iodination/cyclisation (**Scheme 5-18**, below). For reasons depicted in previous sections, only the major isomers were isolated and *d.r.* at the C(2) carbon of **5.49** were not determined.

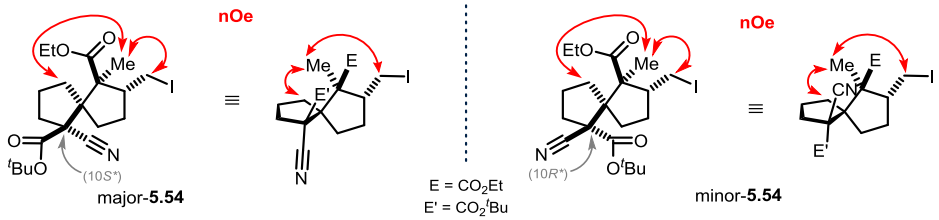
Spirocycles **5.50**, **5.16** and **5.51** were formed in good yields (62-69%) from their corresponding malonates. Similar results were obtained using the one-pot strategy (58-67%). In analogy to what was observed using Mn(III)/Cu(II) conditions (**Section 3.4.3**, page 65), an ethyl group as a blocking group gave a low 29% yield of cyclised product **5.52**. While increasing the bulk to an isopropyl group led to a complicated mixture and no trace of **5.53** was observed.




**Scheme 5-18:** Cyclisation and iodination/cyclisation scope.

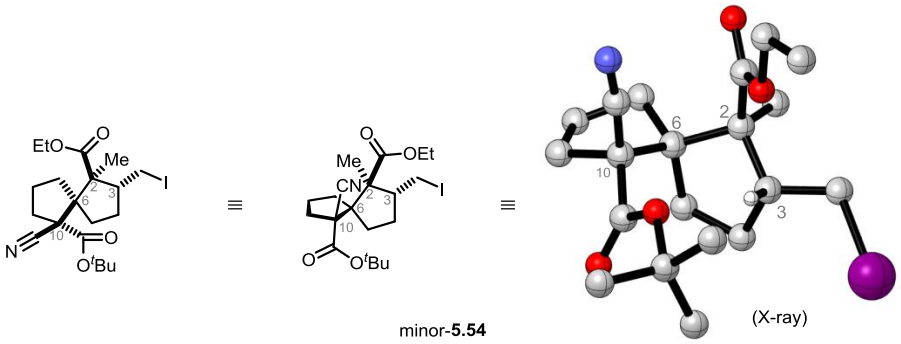
Reagents and conditions: (a) 2,6-lutidine (1.0 eq.), degassed (3x FPT cycles) MeOH (0.27 M), 30 W white CFL, ≤ 28 °C (outside temp.), 16 h, in a glass tube (distance from the light: 5.0 ± 0.3 cm); (b) i) NaHMDS (1.0 eq.), degassed (3x FPT cycles) THF, -78 °C, 15 min; ii) NIS (1.1 eq.), 5 h; iii) 2,6-lutidine (1.0 eq.), 30 W white CFL, ≤ 25 °C (outside temp.), 16 h, in a round-bottom flask (distance from the light: 5.0 ± 0.3 cm).

Using the one-pot procedure on β-keto nitrile **5.26** gave **5.54** as a 3:2 diastereomeric ratio at C(10) in 62% overall yield. The relative configuration at C(2), C(3) and C(6) was confirmed by $^{1}$H NMR NOESY analysis on both isomers (**Scheme 3-21**, above). However, the C(10) stereocentre could not be determined for these isomers using NMR spectroscopy techniques.




**Scheme 5-19:** Indicative nOe interations observed for spirocycles major- and minor-**5.54**.

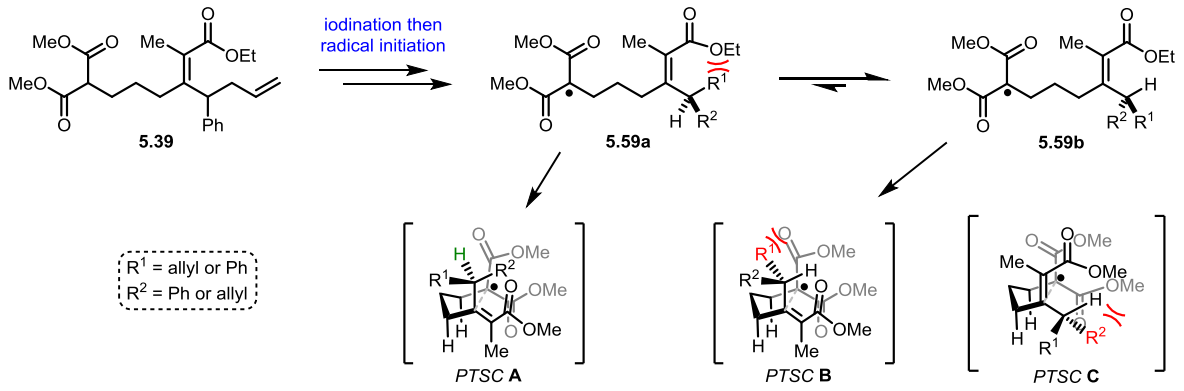
Fortunately, X-ray crystallography analysis could be obtained for crystalline compound minor-**5.54** allowing the unambiguous assignment (10*R**) of the relative configuration at carbon C(10).




**Scheme 5-20:** Crystal structure of minor-**5.54** (all protons but *H*-C(3) are hidden for simplicity).

A single one-pot iodination/cyclisation has been attempted on phenyl derivative **5.32** and lactone **5.56**. Unfortunately, characteristic resonances of C*H*$_2$I have been observed in the $^{1}$H NMR spectra of crude mixtures but the purification has proved unsuccessful. The other phenyl isomer **5.39** failed to cyclise under these conditions after 3 days of irradiation. We propose that radical **5.59a** once formed could cyclise *via* the pre-transition state conformation *PTSC* **A** (**Scheme 5-21**, below). Unfortunately, the conformation **5.59b** where the proton is eclipsing the alkene is going to be favoured as it reduces drastically the 1,3-allylic strain (Houk conformation).[170] The expected prevalence of conformer **5.59b** at room temperature forces the cyclisation to occur *via PTSC* **B** (or *PTSC* **C**, or boat-like *PTSC* (not

drawn)) where the allyl and phenyl substituent are shielding the alkene faces preventing any cyclisation.




**Scheme 5-21:** Proposed explanation for the cyclisation failure of **5.39**.

Based on these hypotheses, we expect that conducting the reaction at higher temperature could populate **5.59a** allowing the cyclisation to occur.

Finally, TMS-protected alkyne **5.44** formed a mixture of inseparable products. This may not be surprising as it does not possess the key methyl blocking group.

## 5.4 NMR analysis of spirocycles

On first appearance, $^{1}$H NMR spectra of the spiro[4.4]nonanes presented in the previous section appear challenging. Full assignment of each compound has been performed for each of the spirocycles only using usual an array of NMR experiments. In fact, we found that COSY, HSQC, HMBC and NOESY experiments were sufficient for the deconvolution of the $^{1}$H NMR and $^{13}$C NMR spectra. One example will be shown in this section emphasising the pieces of information that were used to assign all protons and carbons. Compound **5.50** has been chosen because it was found to show no overlap of proton multiplets in its $^{1}$H NMR spectrum (**Figure 5-2**), only a few carbons are close together in its $^{13}$C NMR spectrum (**Figure 5-3**). This was chosen to allow a clearer presentation of each 2D in one figure, without the need for a multitude of zooms thereof. Please note that for software reasons, shifts are as obtained from the raw data and not referenced to the solvent. This explains for a small difference with the values reported in the experimental section for which the

reference has been correctly set). Spectra reported here were measured in $CDCl_3$ at 500 MHz/126 MHz ($^1H/^{13}C$).

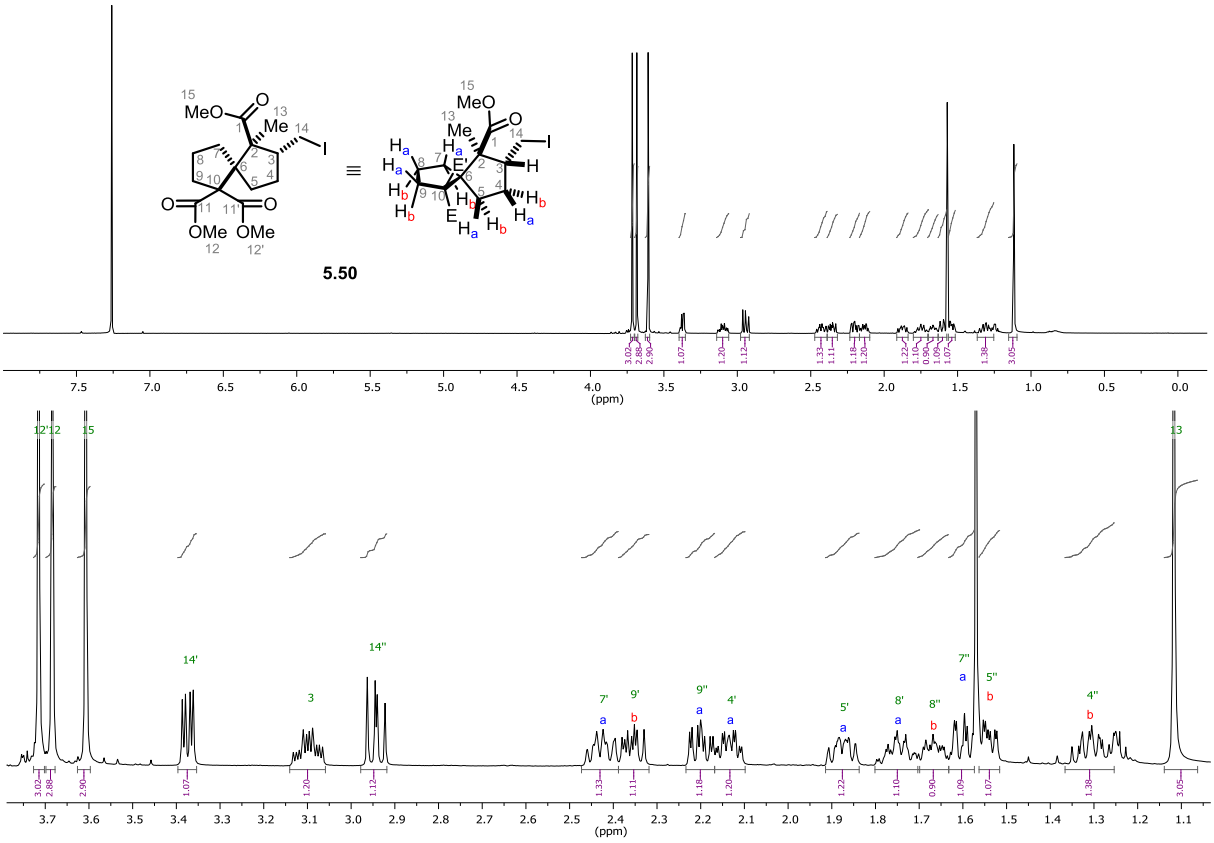



**Figure 5-2**: $^1H$ NMR spectrum ($CDCl_3$, 500 MHz) in full (*top*) and a 3.8-1.05 ppm zoom (*bottom*).

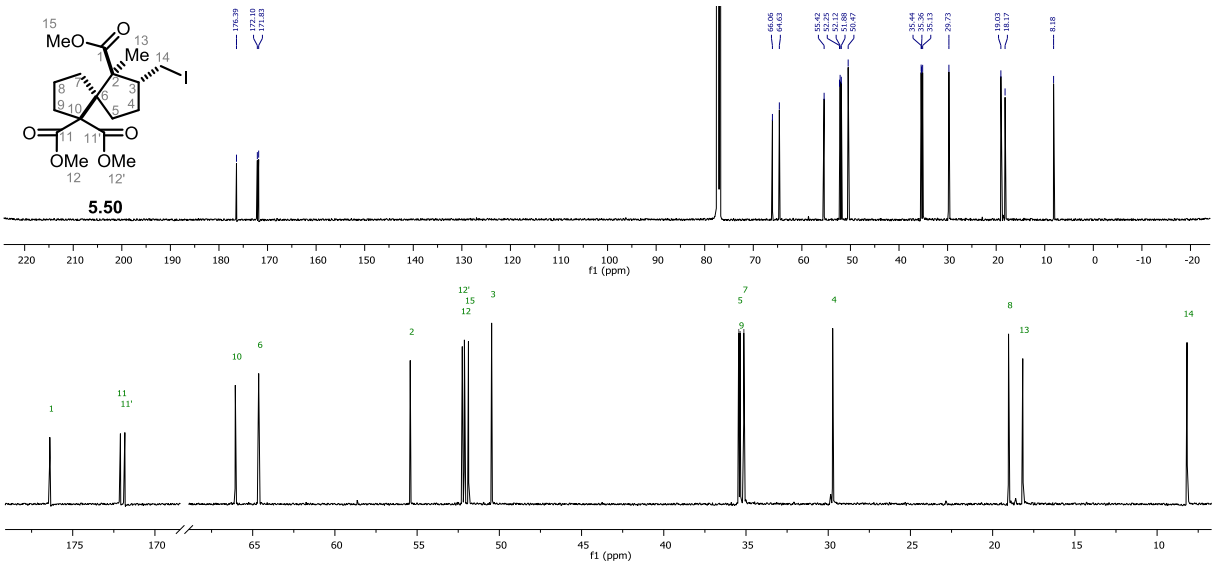



**Figure 5-3**: $^{13}C$ NMR spectrum ($CDCl_3$, 101 MHz) in full (*top*) and a cropped spectrum (165-70 ppm was hidden for clarity) (*bottom*).

As the deconvolution is not a linear analysis and requires analysing back and forth all experiment types. We highlighted on the side structure information obtained from the circled features on the 2D spectra for COSY, HSQC and HMBC. Protons “a” and “b” are labelled on the structures for clarity.

The HSQC experiment (**Figure 5-4**) was important to differenciate the diastereotopic protons and in particular the 35 ppm region containing C(5), C(7) and C(9). It conveniently highlighted proton CH-(3) as the 3.10 pmm as the only CH appart from the other methyl esters. Proton CH-(3) and diastereotopic $CH_2$-(14) were usually the starting point of the analysis. COSY experiment (**Figure 5-5**) revealed CH-(4) and then CH-(5). This revealed the full spin system of the right-hand side ring (as drawn below).

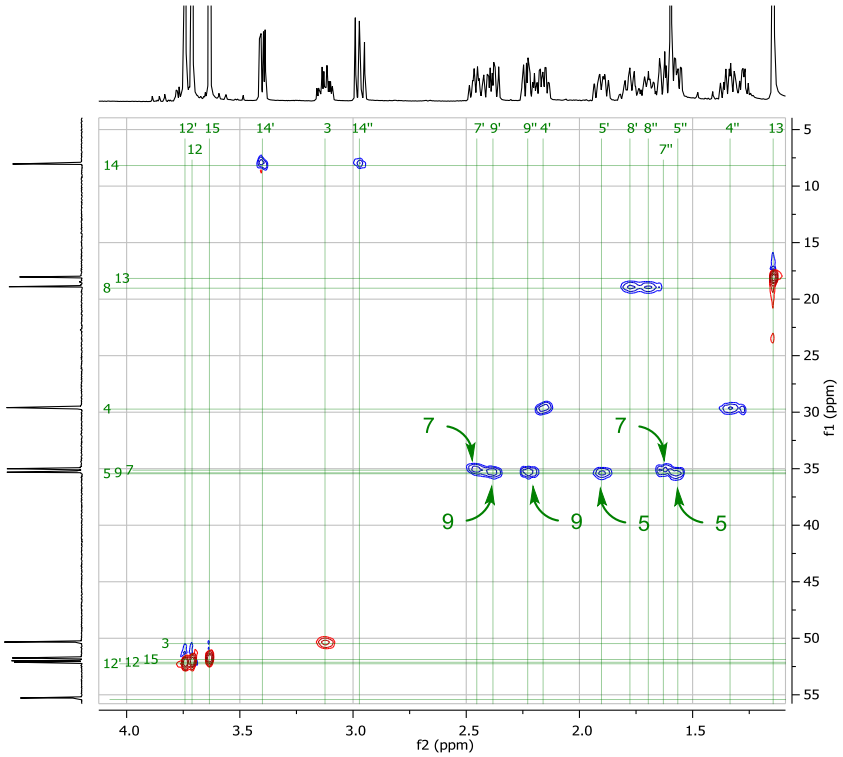



**Figure 5-4**: Zoom of the HSQC spectrum of spirocycle **5.50** in the area of interest.

COSY correlation on the left-hand side ring are can also be determined but have not been added for legibility of the figure. HMBC (**Figure 5-6**) has been an extremely important tool to assign all the quaternary carbons and check the connectivity, proving the spirocyclic nature of compound **5.50**. This experiement was also very important in order to discriminate $CH_2$-(7) and $CH_2$-(9) as COSY could not assign them.

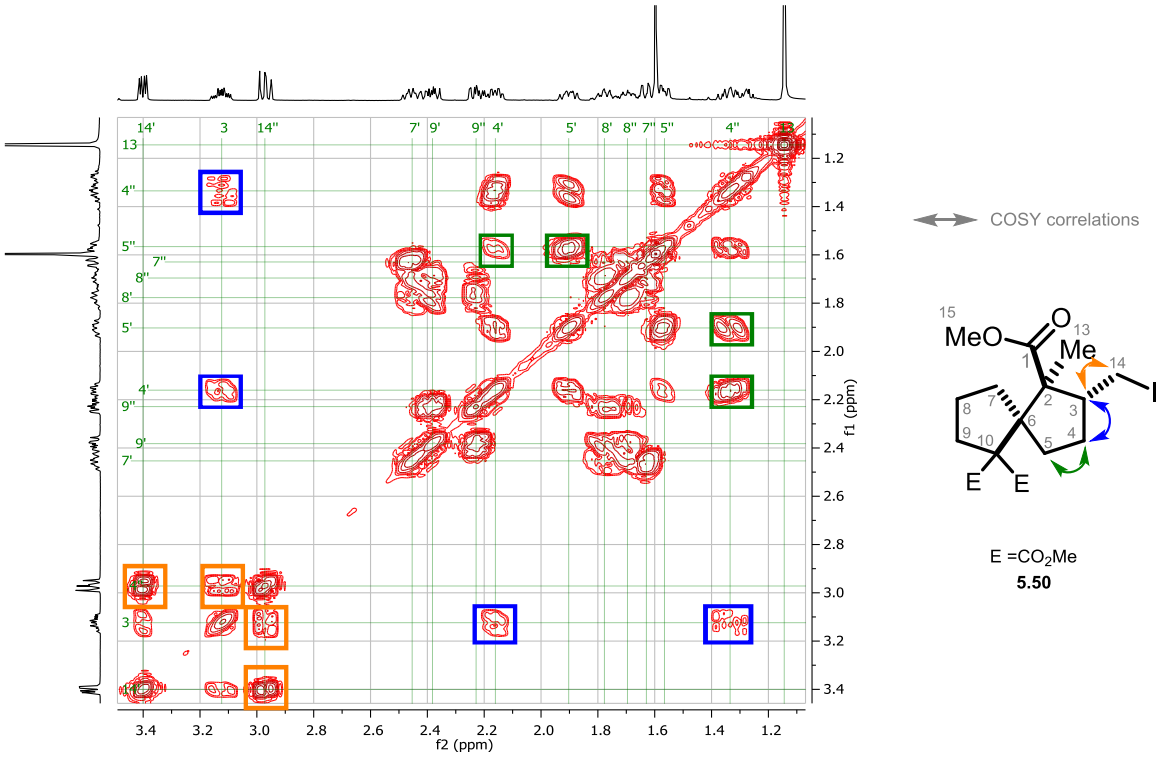



**Figure 5-5**: Zoom of the COSY spectrum of spirocycle **5.50** in the area of interest.

We found that HMBC 3-bond couping between $CH_2$-(9) to C(11) and C(11') was the easiest way to identify C(9) over C(7). Correlation from $CH_2$-(14) and $CH_2$-(4) revealed C(2) and C(6), respectively.

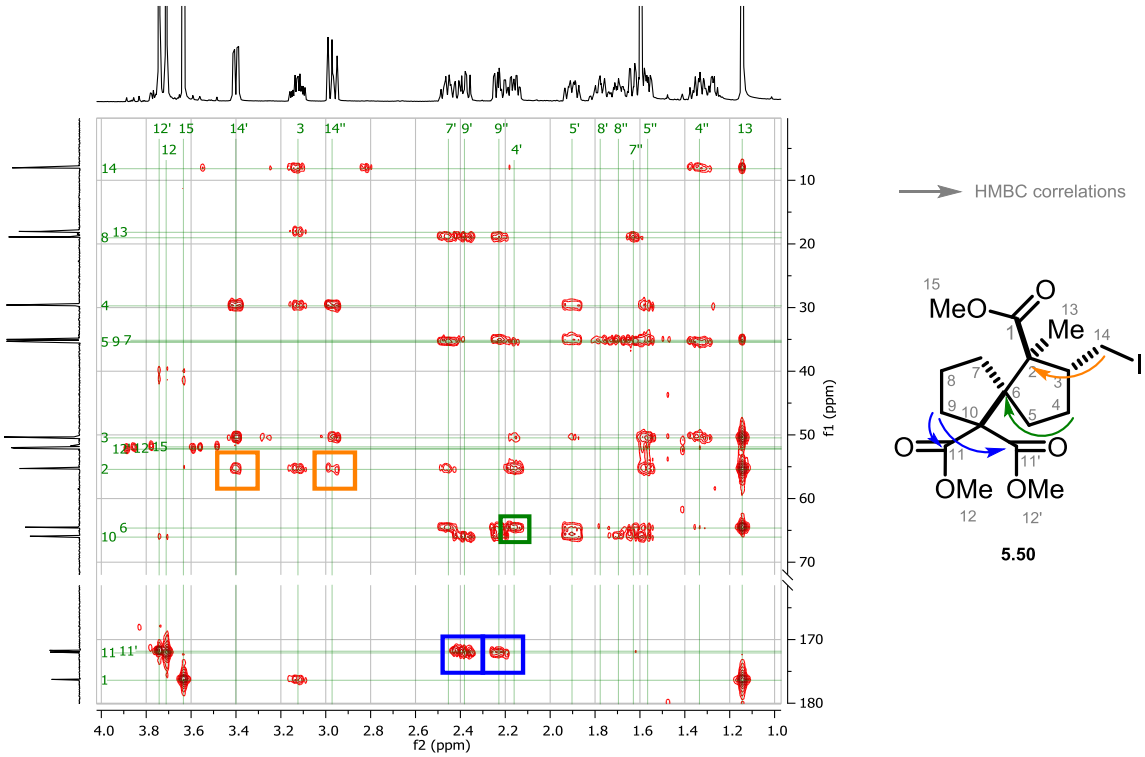



**Figure 5-6**: Zoom of the HMBC spectrum of spirocycle **5.50** in the area of interest.

NOESY experiment could then reveal the relative configuration of the molecule. We decided to present the NOESY spectrum data as its overlap with the previously described COSY spectrum (**Figure 5-7**). This is a particularly convenient way to quickly identify nOe interaction between protons on the same carbon and protons being on adjacent carbons. While on other molecules this could be counter-productive, this helps us filter nOe interactions that are further in space. The reason for excluding nOe interaction between protons on adjacent carbon is that the flexibility of 5-membered rings can make proton that are on adjacent carbons in *trans*-relationship closer in space than the corresponding *cis*-relationship; therefore giving ambiguous assignments.

Looking at only blue spots on the the figure, the key nOe interactions between $CH_2$-(14) and $CH_3$-(13) (orange squares) confirms the *cis*-relationship of the methyl and $CH_2I$ groups. The other key interaction is the cross-peaks between $CH_3$-(13) and $CH_a$-(7) (green squares) which sets the configuration of the C(6) as drawn.

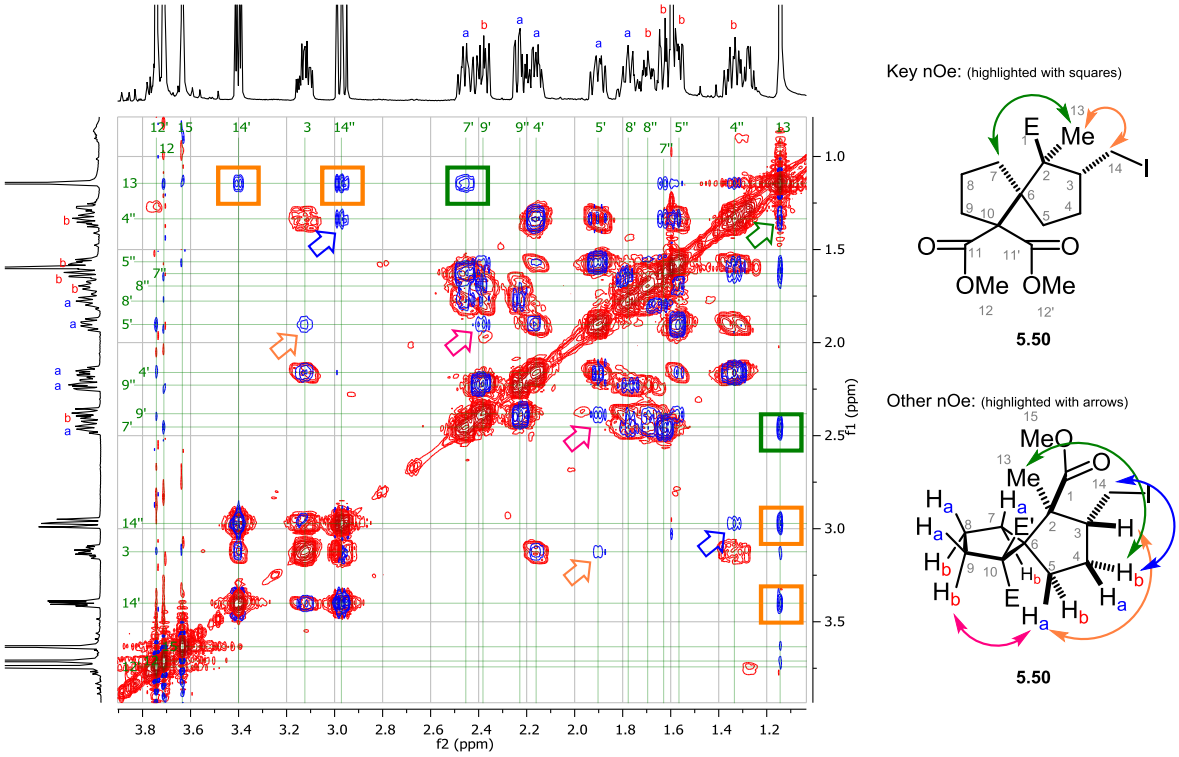
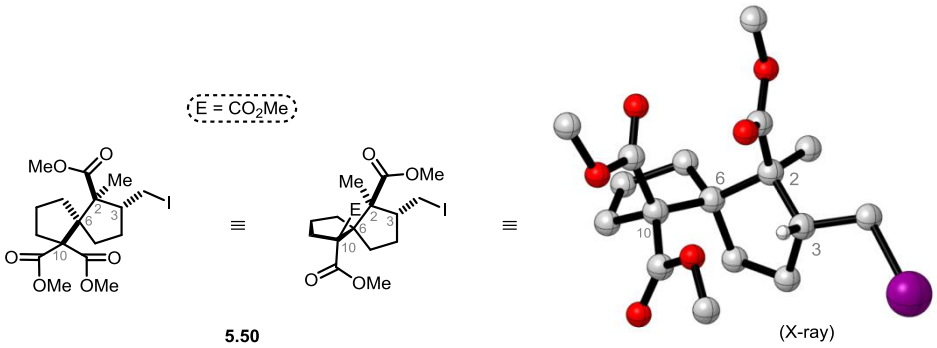



**Figure 5-7**: Overlap of zoom of the COSY (red) and NOESY (blue with red diagonal peaks) spectra of spirocycle **5.50** in the area of interest.

Other nOe interaction (some examples are highlighted with arrows in the spectrum) were used to fully assign diastereotopic protons as “a” or “b”.

X-ray crystallography analysis of iodide **5.50** confirmed the relative stereochemistry we determined using NOESY experiments (**Scheme 5-22**, below).

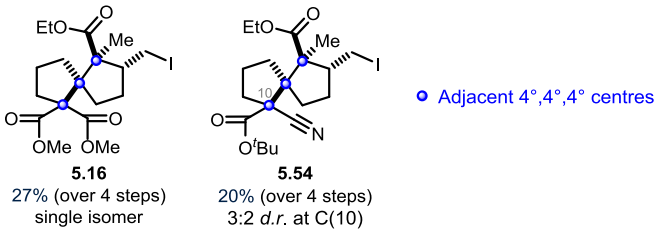



**5.50**

**Scheme 5-22:** Crystal structure of **5.50** (all protons but *H*-C(3) are hidden for simplicity).

## 5.5 Conclusion

Firstly, we developed a visible light induced atom-transfer radical addition (ATRA) of iodomalonates based on the work by Melchiorre and co-workers.[161] We discovered that no photosensitiser was required for iodomalonates, and that the cyclisations could be completed in a convenient one-pot fashion directly from the malonates, thus making it cheaper, simpler to set-up and also to purify. This allowing to expediently form complex spiro[4.4]nonanes bearing three all-carbon adjacent quaternary centres in good yields. For example, malonate **5.16** was formed in 27% overall yield over 4 steps from readily available ethyl 2-methylacetoacetate. Ketonitrile **5.54** could also be formed in 20% yield as a mixture of C(10) isomers from the same acetoacetate derivatives.

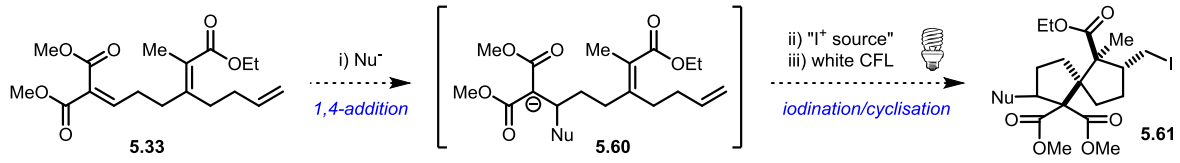



**Scheme 5-23:** Overall yields obtained for the syntheses of **5.16** and **5.54**.

We think that these compounds could be used as 3D templates in a variety of transformation to quickly build small libraries because of the multiple handles they possess.

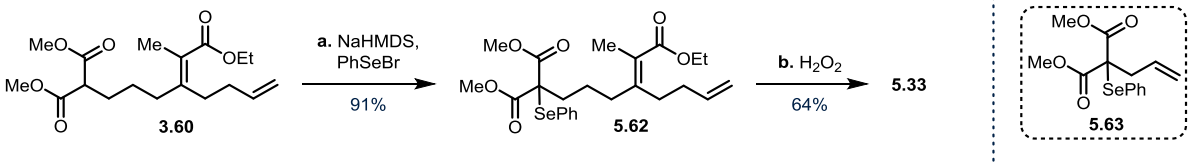
## 5.6 Efforts towards a 1,4-addition/iodination/cyclisation one-pot methodology

We wondered if we could increase the complexity one step further by performing a Michael addition onto the alkylidene malonate. With the right choice of reagent, we could envisage subjecting alkylidene malonate **5.33** to a suitable nucleophile could trigger a 1,4-addition onto the least hindered and more electron-poor alkene regioselectively. Based on our previously discussed work, we expect anion **5.60** to be stable at low temperature (-78 °C). Quenching with an appropriate $I^+$ source followed by exposure to light could in turn trigger cyclisation to spirocycle **5.61** in a single pot from **5.33**.




**Scheme 5-24:** Proposed 1,4-addition/iodination/cyclisation one-pot sequence.

Substrate **5.33** was synthesised by oxidising previously described compound **3.60** in a 2-step sequence (**Scheme 5-25**, below). First phenylselenide **5.62** was formed using the conditions we previously used to for iodomalonates using phenylselenyl bromide as electrophile in an excellent 91% yield. Secondly, oxidation to the selenoxide triggered a spontaneous elimination to the desired alkylidene malonate **5.33** in 64% yield.




**Scheme 5-25:** Selenoxide elimination strategy to form alkylidene malonate **5.33**.

Reagents and conditions: (a) NaHMDS (1.0 eq.), PhSeBr (1.1 eq.), THF, -78 °C, 2.5 h, 91%;
(b) $H_2O_2$ (11 eq.), $CH_2Cl_2$, 0 °C, 4 h, 61%.

Other attempts using **5.63** in our hydroboration/Suzuki cross-coupling sequence did not yield selenide **5.62** but removed the phenylselenyl group instead. Attempts to obtain compound **5.33** from bromomalonate **5.8** or iodomalonate **5.9** using DBU also failed; complex mixtures were obtained.

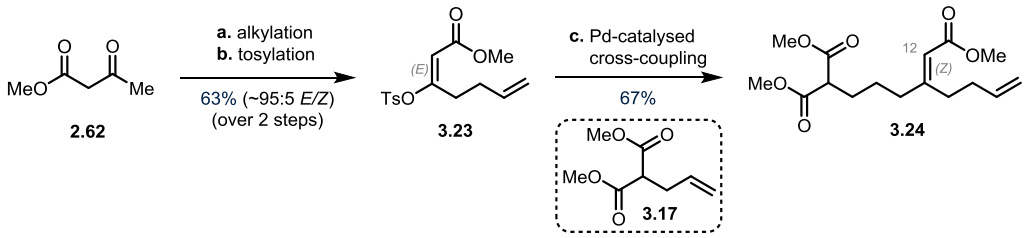
Because of a lack of time, no attempts of one-pot 1,4-additions/iodination/cyclisation reaction were carried out.

# 6 Conclusion and Future Work

In the this thesis, we have demonstrated that high yield of spiro[4.4]nonane could be formed using radical cyclisation cascades from linear starting materials. We manage to develop reaction conditions allowing for the construction of challenging carbon-carbon bonds making molecules possessing three adjacent quaternary centres and different handles for further functionalisation as potential 3D templates.

Given the initial issues faced in the early part of our research efforts, it was deemed necessary to simplify the ambitious cascade proposed as the basis of this project. We gradually increased the complexity of the cyclisations performed while exploring different reagents in order to initiate the radical cyclisations.

A long-standing problem was the synthesis of starting materials for this study. In fact, it was difficult to find a reliable and relatively short synthesis to obtain gram-quantities of cyclisation precursors. A key point in our study was the realisation that substrates such as **3.24** (**Scheme 6-1**, below) could be efficiently assembled stereoselectively from vinyl tosylate **3.23** and commercially available **3.17** *via* a Suzuki-Miyaura cross-coupling reaction. This reaction was found to be reliable and provided us with about a dozen different cyclisation substrates over the course of our research study.

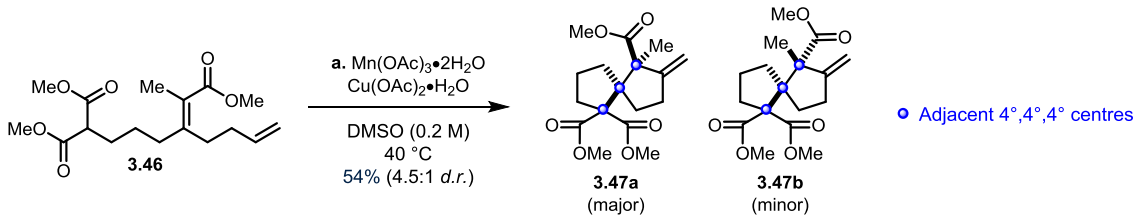



**Scheme 6-1:** Synthesis alkene **3.24**.

Reagents and conditions: see **Scheme 3-13**, page 53.

While substrate **3.24** was found to undergo double 5-*exo*-*trig* cyclisation as well as an undesired competitive 5-*exo*-*trig*/6-*endo*-*trig* process, we demonstrated that adding a methyl group as, what we referred to as, a “blocking group” at C(12) was a successful strategy in order to slow down the

undesired process and therefore improve the impurity profile of the reactions. The new improved starting materials, such as **3.46** (**Scheme 6-2**, below), were successfully converted into spiro[4.4]nonanes such as **3.47a**/**b** in a respectable yield of 53% given the complexity of the transformation. In fact, three all-carbon adjacent quaternary centres are being formed in this complex oxidative cyclisation cascade.



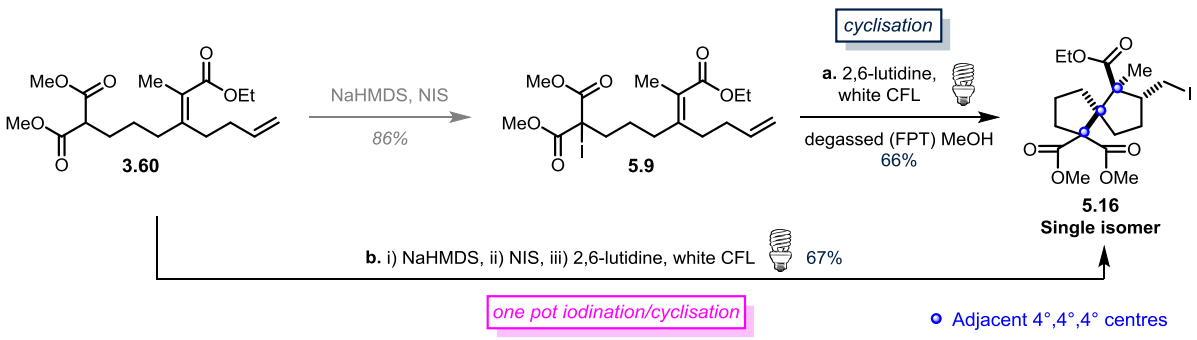

**Scheme 6-2:** Cyclisation of **3.46** using Mn(III)/Cu(II) conditions.

Reagents and conditions: $Mn(OAc)_3 \bullet 2H_2O$ (2.0 eq.), $Cu(OAc)_2 \bullet H_2O$ (1.0 eq.), DMSO (0.2 M), 40 °C, 4 d, 54% (4.5:1 *d.r.*).

More importantly, the cyclisation of different malonates using manganese(III) triacetate gave us a good understanding of the different pathway and intermediates formed during the polycyclisation process. This proved to be essential for the development of the next generation of radical cyclisation discussed in **Section 5**.

With the aim of rendering our cascade reaction more eco-friendly by avoiding the use of superstoichiometric amount of metals, we successfully developed a light-mediated atom transfer radical polycyclisation reaction using iodomalonates such as **5.9** (**Scheme 6-3**, below) using a household compact fluorescent lamp under catalyst- and metal-free conditions. Most of these reactions were performed at room temperature overnight and can expediently give complex spiro[4.4]nonanes (*e.g.* **5.16**) from the corresponding iodomalonate cyclisation precursor (*e.g.* **5.9**) or from the one-pot iodination/cascade cyclisation procedure from the "naked" malonate starting material (*e.g.* **3.60**). The one-pot procedure allowed us to form structurally interesting spirocycles bearing three all-carbon adjacent quaternary centres in up to 67% yield as single isomers without the need for isolation of any light-sensitive iodomalonates. The development a set-up of our own design

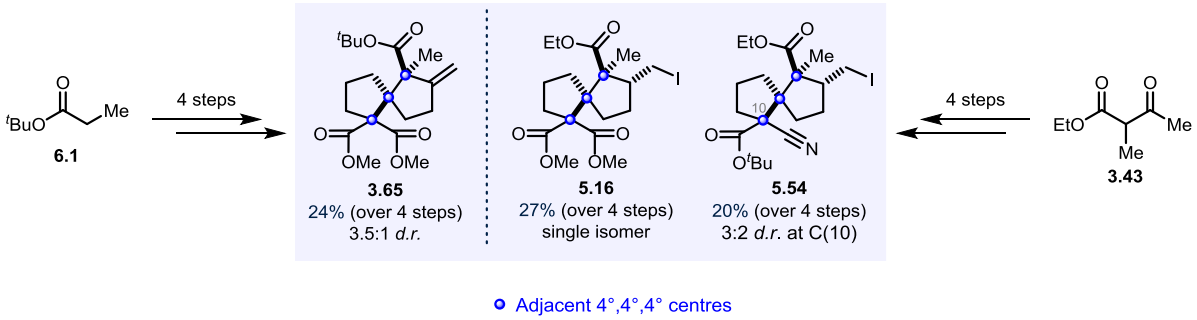
allowed us to run parallel reactions under identical conditions and considerably accelerate the optimisation process.




**Scheme 6-3:** Cyclisation and iodination/cyclisation scope to spiro[4.4]nonane **5.16**.

Reagents and conditions: see **Scheme 5-18**, page 96.

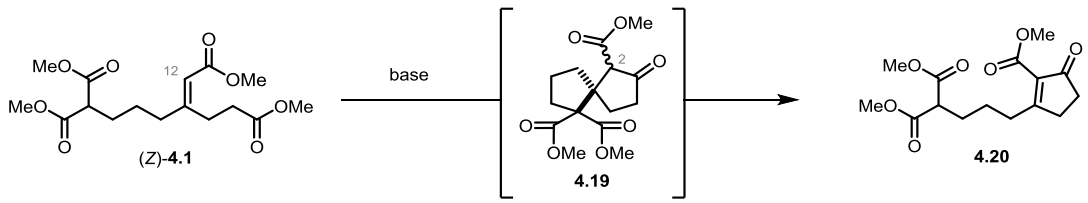
Future work should be focussed on expanding the scope of the reaction by exploring different groups in place of the esters as well as varying the linker sizes to achieve other spirocycle sizes such as spiro[4.5]decanes. Further derivatisation of spirocyles prepared during this study to show their potential use in other reactions would be of added value to emphasise their potential as 3D templates. Finally, the development of a one-pot 1,4-addition/iodination/radical cascade cyclisation reaction (as described in **Section 5.6**, page 104) would be of potential interest for industry and very close to the original project proposal (described in **Section 1.1**, page 1).




**Scheme 6-4:** Overall yields obtained for the syntheses of **3.65**, **5.16** and **5.54**.

The short anionic study performed highlighted challenges due to the reversibility of the desired consecutive Michael additions cyclisations. More importantly, it has demonstrated that the desired product **4.19** (**Scheme 6-5**, below) was unstable to basic conditions and decomposing *via* an initial

retro-Michael addition to give **4.20**. Efforts to prevent this should focus on adding a blocking group at C(12) on tetraester (*Z*)-**4.1.**




**Scheme 6-5:** Anionic study challenge

# 7 Experimental Section

## 7.1 General remarks

### 7.1.1 Equipment and techniques

Procedures using oxygen- and/or moisture-sensitive materials were performed with anhydrous solvents under an atmosphere of anhydrous argon in flame-dried flasks, using standard Schlenk techniques.

**Analytical thin-layer chromatography** was performed on precoated glass-backed plates (Silica Gel 60 $F_{254}$; Merck), and visualised using a combination of UV light (254 nm) and aqueous basic potassium permanganate stains or vanillin solution.

**Flash column chromatography** was carried out using Apollo Scientific silica gel 60 (0.040 – 0.063 nm), Merck 60 Å silica gel, VWR (40-63 µm) silica gel, or Sigma Aldrich silica gel. Pressure was applied at the column head *via* hand bellows or a flow of nitrogen with the solvent system used in parentheses. Column size information (Ø refers to the external diameter of the column used, L refers to the height of silica used once packed) and solvent volumes quoted are for reference only.

**Cooling** of reaction mixtures to 0 °C was achieved using an ice-water bath, -78 °C was achieved using a dry ice/acetone bath. Other low temperatures were obtained by adding dry ice to acetone at regular intervals with stirring in a Dewar to keep the desired temperature.

**NMR analysis**: Unless stated otherwise, solution NMR spectra were recorded at room temperature; $^{1}H$ and $^{13}C$ nuclear magnetic resonance experiments were carried out using Bruker DPX-200 (200/50 MHz), AVN-400 (400/101 MHz), DQX-400 (400/101 MHz) or AVC-500 (500/126 MHz) spectrometers. Chemical shifts are reported in ppm from the residual solvent peak. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are quoted in hertz (Hz). Resonances are

described as s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Coupling constant and resonance patterns are described as they *appear* in spectra. Labels $H_a$ and $H_b$ refer to diastereotopic protons attached to the same carbon and impart no stereochemical information unless the structure attached is explicitly labelled with $H_a$ and $H_b$ for the given carbon (see **Notes on Convention** for more information). Assignments were made with the assistance of gCOSY, DEPT-135, gHSQC and gHMBC or gHMQC NMR spectra. [Numbering and names of structures accompanying reported data is non-IUPAC, and solely for reference.]

**Low-resolution mass spectra** were recorded using a Walters LCT premier XE. High resolution mass spectra (EI and ESI) were recorded using a Bruker MicroTOF spectrometer by the internal service at the University of Oxford.

**Gas chromatography–mass spectrometry**: see **Section 7.5**, page 119.

**Infrared** measurements (neat, thin film) were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 4000-600 $cm^{-1}$.

**Light emission spectra measurements** (UV-visible) were recorded using an Ocean Optics USB2000.

**Glass vials** used with light-mediated reaction: Vial used for the cyclisation of iodomalonate with light are the following: 3.5 mL “Tall Screw Neck Vial - Neutral glass, tall form, with closure”, catalogue number T101/v2 from SAMCO.

**Crystallographic analyses** were performed by the Single Crystal X-ray Crystallography Services (internal service) at the University of Oxford.

### 7.1.2 **Chemicals**

Dry THF, $CH_2Cl_2$, $Et_2O$, PhMe, DMSO, benzene, hexane, pentane, acetonitrile and 1,4-dioxane were collected fresh from an mBraun SPS-800 solvent purification system having been passed through anhydrous alumina columns and then kept over 3 Å or 4 Å molecular sieves. All other dry solvents used were dried over 3 Å molecular sieves and stored under argon. All other solvents were used as purchased from Sigma Aldrich, Rathburn or Fisher Scientific.

Unless stated otherwise, commercially available reagents were purchased from Sigma-Aldrich, Fisher Scientific, Fluorochem, Apollo Scientific, Acros Organics, Strem Chemicals, Alfa Aesar or TCI UK and were used without purification. Petroleum ether $PE_{30\text{-}40}$ and $PE_{40\text{-}60}$ refers to light petroleum boiling in the range 30–40 °C and 40–60 °C respectively. Deuterated solvents were purchased from Sigma-Aldrich ($CDCl_3$, MeOD-$d_4$, MeCN-$d_3$, DMSO-$d_6$, benzene-$d_6$).

*p*-Anisaldehyde was freshly distilled before use.

## 7.2 Emission spectra of CFLs used

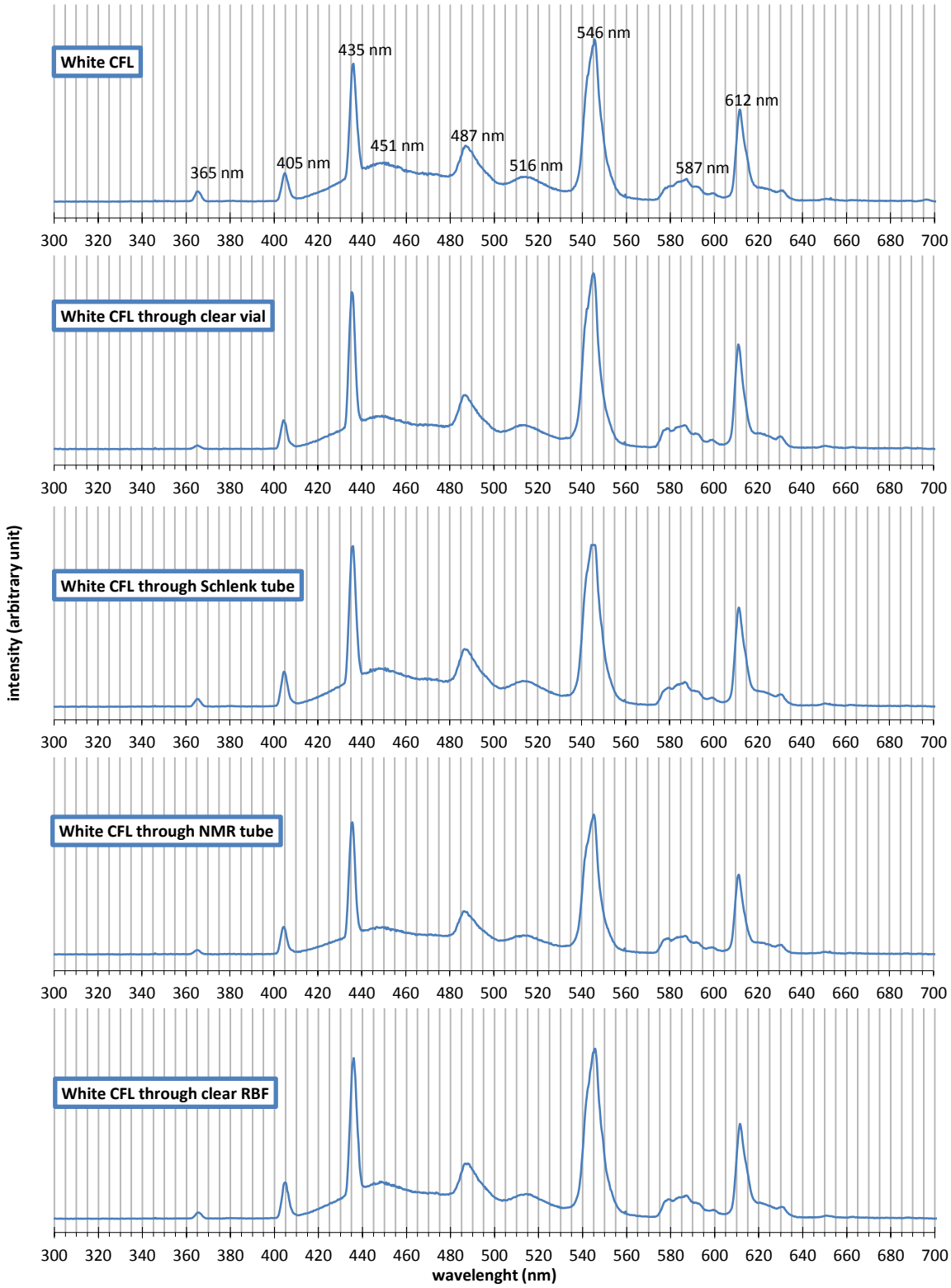



**Figure 7-1**: UV-visible emission spectra of the white CFL used in our study (*top*) and the light transmitted through different laboratory equipment used as reaction vessels in our study (*all but top*).

Emission spectra in the UV-visible region were recorder for the white CFL used in our study and compared with the light received inside different laboratory glassware used as reaction vessels in our study (**Figure 7-1**, above). No wavelengths were found to be significantly absorbed by the glassware. Similar measurements were taken with the black CFL used in our study (**Figure 7-2**, below).

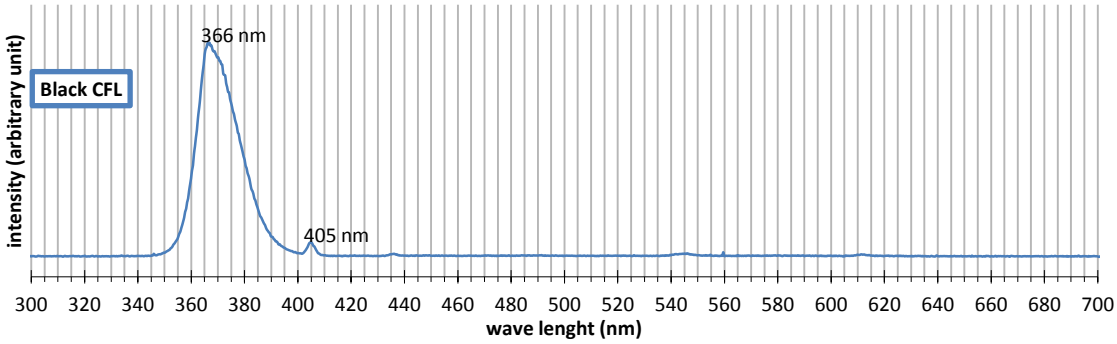



**Figure 7-2**: UV-visible emission spectra of the black CFL used in our study.

We found that the light mediated cyclisation reaction of iodomalonates happened when the tube was left in the fume hood with the lights turned on as well as with green LED strips; their emission spectra were also recorded (**Figure 7-3**, below).

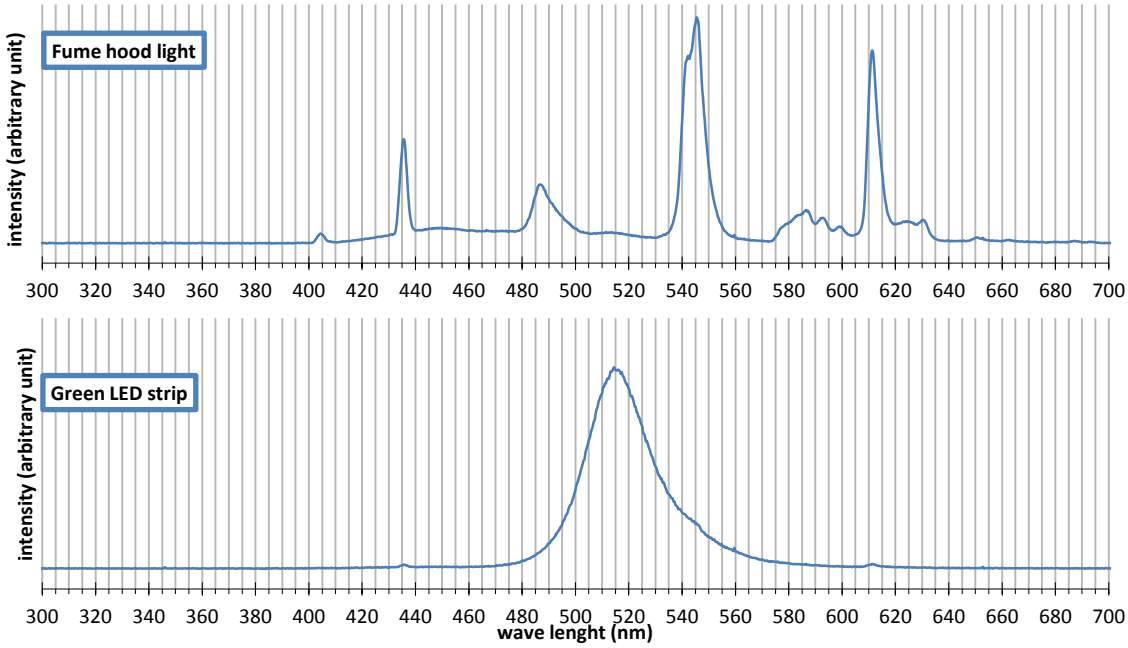



**Figure 7-3**: Other UV-visible emission spectra taken: laboratory lights (*top*) and green LED strip (*bottom*).

## 7.3 Bromomalonate $^{1}$H NMR study

The full range $^{1}$H NMR spectra (stacked) described in **Section 5.2** (**Scheme 5-4**, page 80) are presented below.

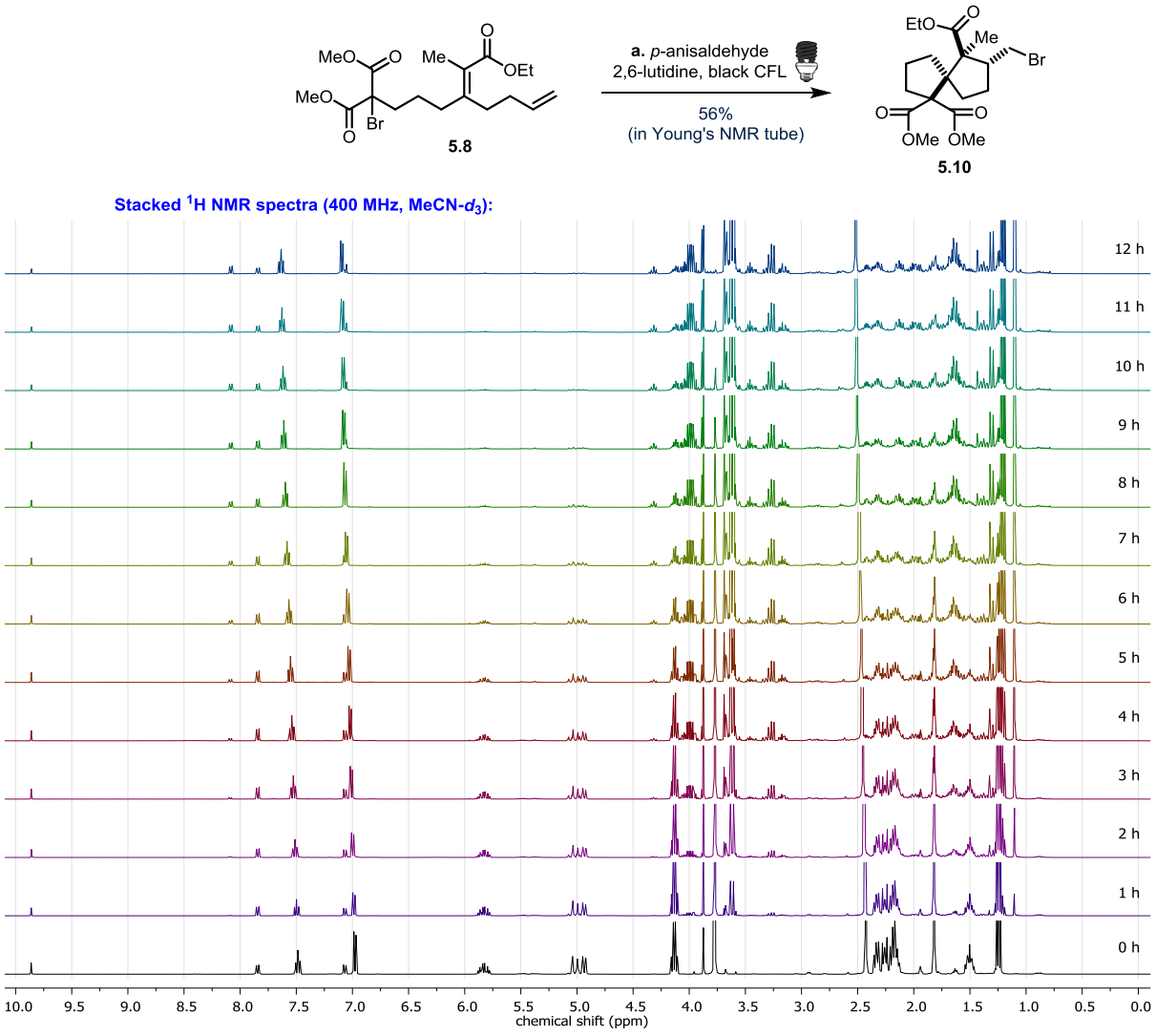



**Figure 7-4:** Full range $^{1}$H NMR spectra (stacked)) obtain for the light-mediated cyclisation of bromomalonate **5.8**.

## 7.4 Additional information about the optimisation set-up used in our light study

This part aims to give additional information on how the set-up was designed and created to help someone make another custom one for their use.

The set-up for optimisation was designed to be modular, maximise the number of experiments run at once while keeping identical conditions for each reaction. Knowing we wanted to perform the optimisation in NMR tubes with no stirring we could design the set-up using the following specifications: 1) being able to control the distance of a sample(s) from the light source; 2) avoiding unnecessary exposure of chemicals/equipment/people around the set-up to the light when in use; 3) not overheating/easy control of the temperature in the set-up; 4) easy to use; 5) not too voluminous.

The software used to design the parts was AUTODESK® FUSION 360™ (version: 2.0.4383; plan: Fusion 360 Ultimate, Student). The 3D models of parts were exported as stl files, gcodes for 3D printing were created using the open-source software ReplicatorG (version: 0040). Objects were printed using a Flashforge® Creator Pro 2015 3D-printer using 1.75 mm polylactic acid (PLA) filament as printing material. It was printed at 205 °C on a Kapton tape layer preheated to 60 °C with a 0.15 mm resolution (layer height); no raft/support was required.

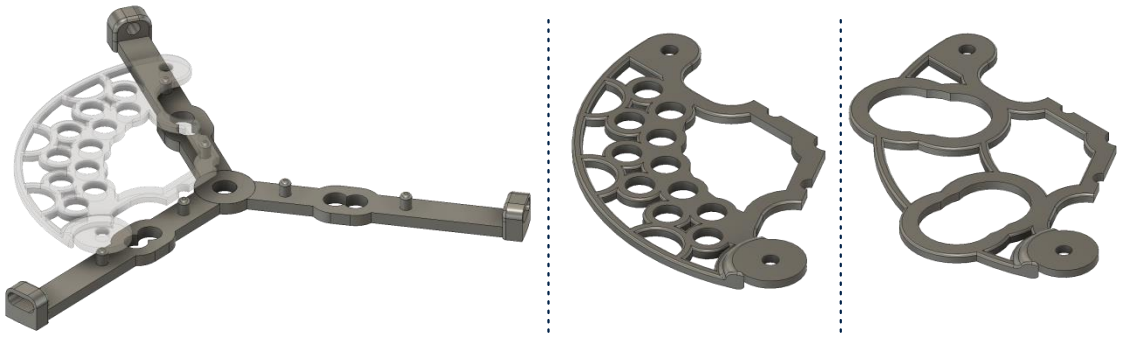


**Figure 7-5:** Structure arm with shadowed extension for 5 mm NMR tubes (*left*); Extension for 5 mm NMR tubes (*middle*); Extension for larger tubes (13 mm) (*right*).

The structure can itself hold 3 NMR tubes at different distances from the light source. The arm structure can hold 3 extensions. For example the extension for NMR tubes shown in **Figure 7-5** (*middle*) can hold up to 5 or 6 NMR tubes (depending on the distance chosen). Other extensions such

as shown on the right can hold two larger tubes (13 mm diameter) for larger scales at three different distances from the light source (*right*).

The design of the set-up can be adapted to accommodate other reaction vessels. Dimensions of the parts we made are given for reference (**Figure 7-6**).

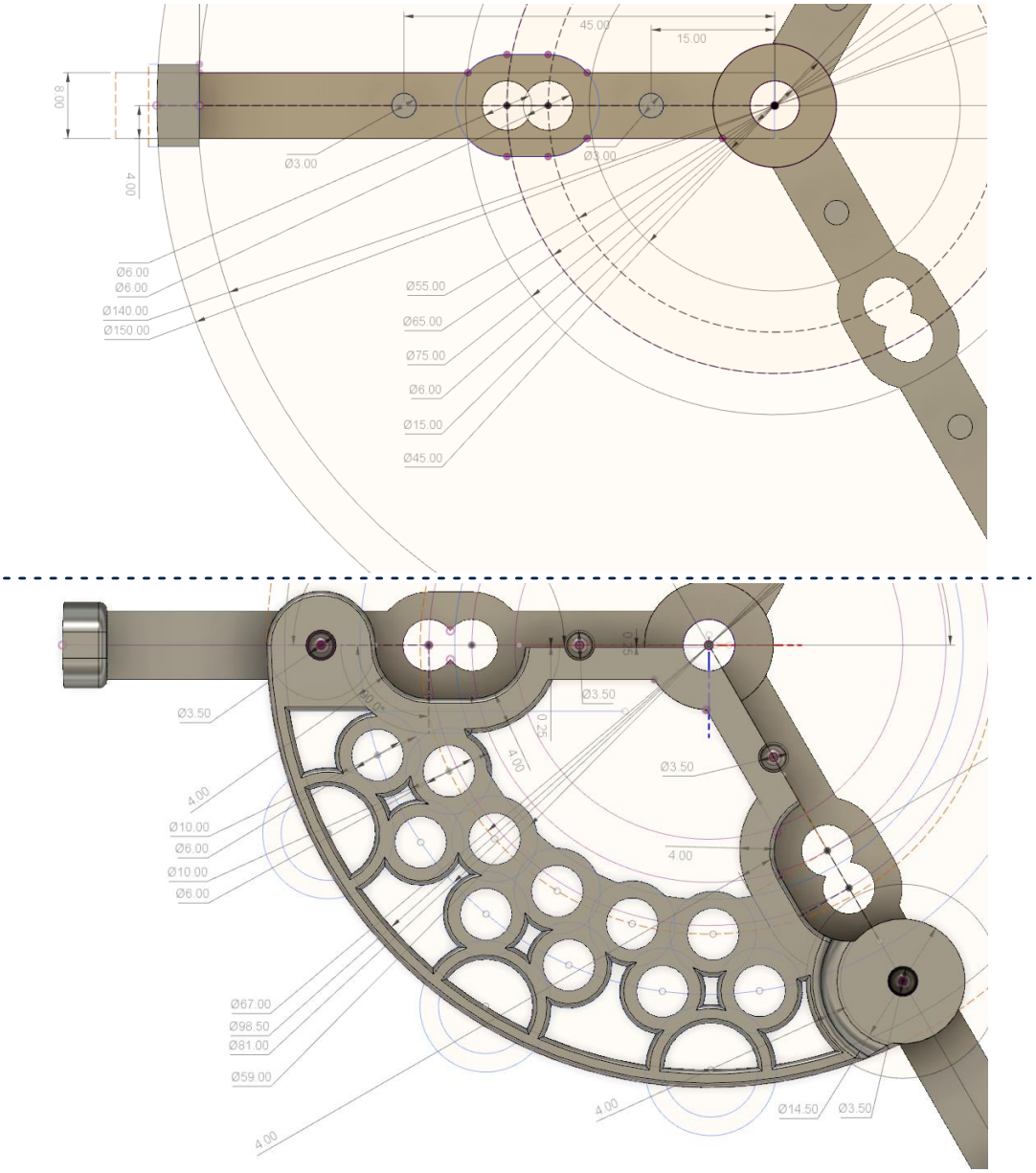



**Figure 7-6**: Main dimensions of the structure arm (*top*) and the extension for 5 mm NMR tubes (*bottom*).

The same objects could be made out of wood or metal if a 3D printer is not available.

## 7.5 GC-MS optimisation information.

Information about the GC-MS system used: GC-MS analyses were performed on a 7890B GC system equipped with a BPX5 column (30 m, 0.32 mm id, 0.25 µm film thickness), operated in split mode, with helium carrier gas. The detector was an Agilent 7200 quadrupole time of flight (Q-ToF) instrument equipped with a direct insertion probe supplied by Scientific Instrument Manufacturer (SIM) GmbH. Instrument control and data processing were performed using Agilent MassHunter software. Source conditions for EI were adjusted to maximise sensitivity.

Conditions used: Initial temperature of 40 °C for 2 min then heating 20 °C/min until reaching 300 °C then holding at 300 °C for 10 min. Flow: 2 mL/min. Pressure: 0.5 psi. Volume injected: 0.5 µL. Split: 5:1. Split flow: 6 mL/min.

Preparation of samples from a reaction mixture: Once the reaction was considered completed, it was diluted with MeCN to reach a concentration of product **5.16** of 200 ± 25 µg/mL (assuming a quantitative yield of product is obtained) using 2 successive dilutions (volumes depending on the scales). An equal amount of this solution and internal standard solution (200 µg/mL *p*-chloro-anisol in MeCN) were combined in a MS vial, stirred and used in the GC-MS instrument.

Calibration study and curve: The internal standard (IS) used in this study was *p*-chloro-anisol. Different samples containing 100 µg/mL of IS and 5-125 µg/mL of product **5.16** were analysed (**Table 7.1**).

We found that the plot of ratio of response factors of **5.16**/IS against ratio of concentration [**5.16**]/[IS] was linear for samples containing 10-125 µg/mL of product **5.16** (**Figure 7-7**). We therefore aimed to prepare a 200 µg/mL solution of compound **5.16** from the reaction mixture (therefore, obtaining a final concentration of 100 µg/mL in the sample). More concentrated samples were used when low yields were obtained to be in the linearity curve.

| [IS] (μg/mL) | [**5.16**] (μg/mL) | response factor of IS (x $10^7$) | response factor of **5.16** (x $10^7$) | ratio [**5.16**]/[IS] | ratio **5.16**/IS (response factor) |
|---|---|---|---|---|---|
| 100 | 5 | 3.53 | 2.70 | 0.05 | 0.765 |
| 100 | 10 | 4.05 | 4.33 | 0.10 | 0.107 |
| 100 | 20 | 3.82 | 0.91 | 0.20 | 0.238 |
| 100 | 30 | 3.80 | 1.62 | 0.30 | 0.427 |
| 100 | 40 | 3.56 | 2.05 | 0.40 | 0.574 |
| 100 | 50 | 3.57 | 2.67 | 0.50 | 0.748 |
| 100 | 60 | 3.38 | 3.48 | 0.60 | 1.030 |
| 100 | 75 | 3.28 | 4.02 | 0.75 | 1.224 |
| 100 | 100 | 3.33 | 5.91 | 1.00 | 1.773 |
| 100 | 125 | 3.50 | 7.28 | 1.25 | 2.079 |

**Table 7.1**: Sample analysis by GC-MS for calibration curve. IS = internal standard.

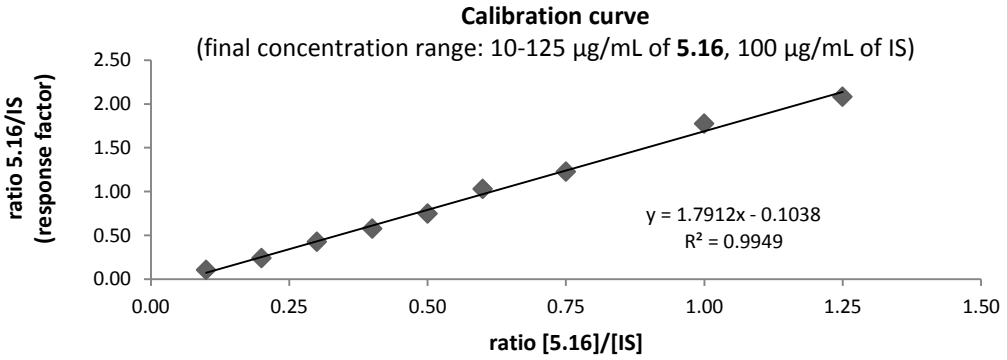



**Figure 7-7**: Calibration curve for the analysis of product **5.16** against the internal standard (IS) *p*-chloro-anisol by GC-MS.

Response factors of **5.16** and internal standard as well as the dilution used and scale of the reaction were used to obtain the approximated GC yields given in the optimisation section.

A set of values gave higher results than expected due to a systematic error arising from a different method to measure the starting material quantity used in the reaction. Repeat experiments were added in each set to flag any variability in the results. In this case, a correction factor determined from these control experiments was applied to lower the GC yield of the set containing the systematic error to match the other repeat experiment. Repeats of some of these experiments later confirmed the validity of these corrections.

Example of chromatograms: Examples of chromatograms obtained are shown below (**Figure 7-8** and **Figure 7-9**).

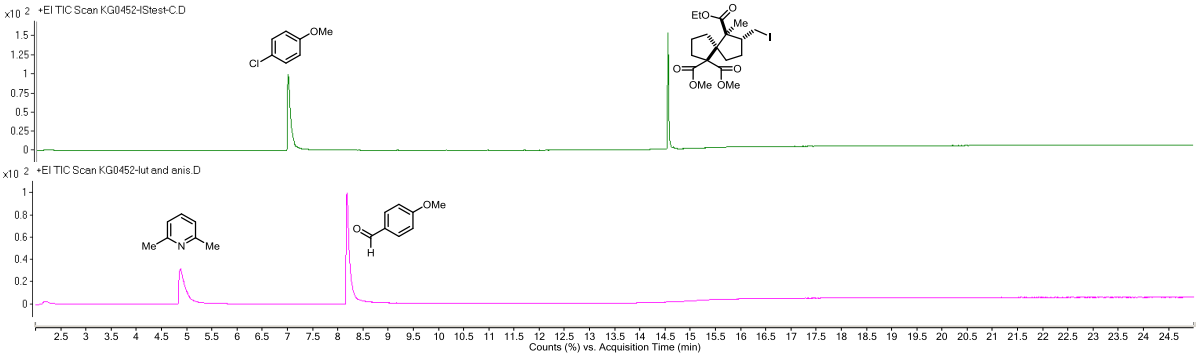



**Figure 7-8**: Chromatograms of IS and product **5.16** (*top*), and 2,6-lutidine and *p*-anisaldehyde (*bottom*).

The product peak labelled "P2" in **Figure 7-9** is a compound same *m/z* as our expected products but unknown structure. Heating of samples containing this compound neat at 140 °C for 4 h did not show any reduction in response factor and showing its stability to these conditions.

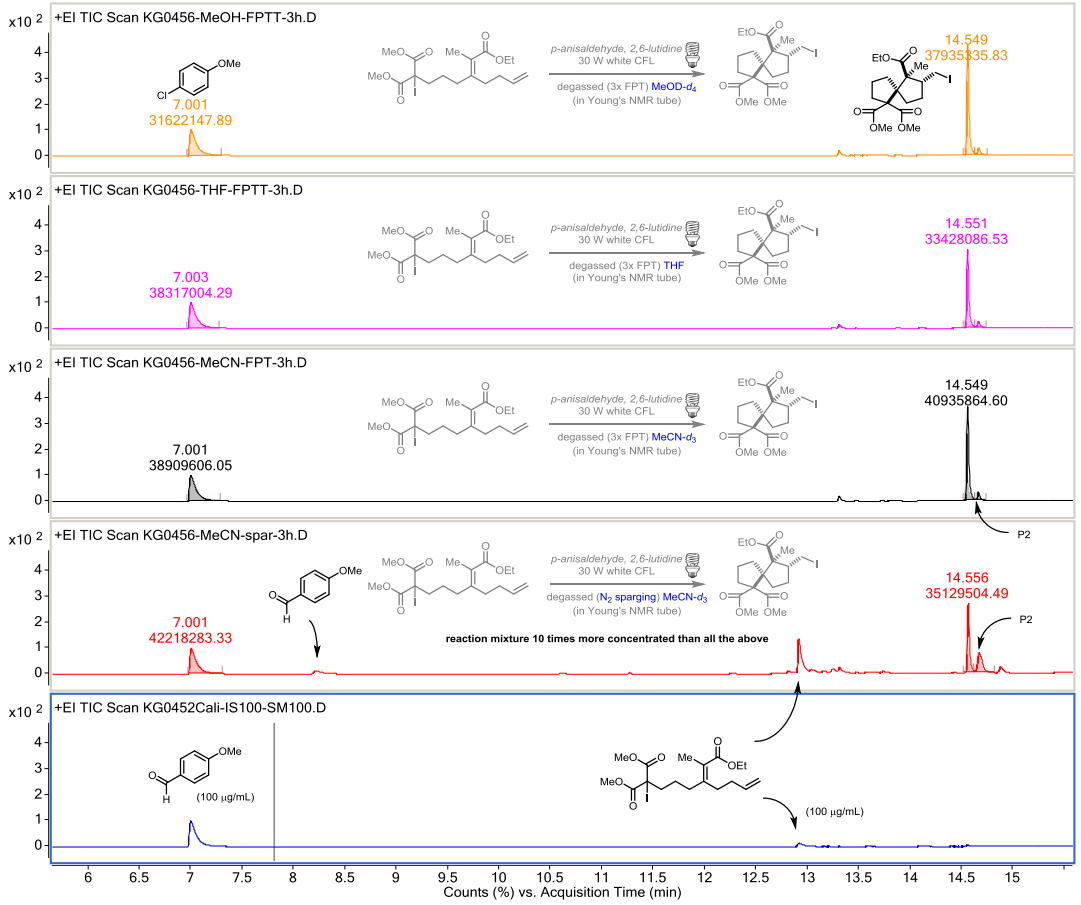



**Figure 7-9**: Chromatograms for some selected entries of the optimisation and comparison between reaction degassed using 3x FPT cycles or sparging in MeCN-$d_3$.

## 7.6 Syntheses of substrates and cyclisation products

### 7.6.1 General procedures

#### GP1: γ-alkylation of acetoacetates

In a flame-dried flask equipped with mechanical stirring when performed on large scale was added NaH (60% in mineral oil, 1.25 eq.) followed by dry THF (2.9 mL/mmol of acetoacetate). The suspension was cooled to 0 °C before the acetoacetate (1.0 eq.) was added over 15 min as a solution in dry THF (0.6 mL/mmol of acetoacetate). One hour later, *n*-BuLi solution (1.6 M or 2.5 M in hexane, 1.1 eq.) was added over 20 min and the resulting mixture was stirred for 20 min (yellow mixture obtained). Neat electrophile (1.0 eq.) was added and a creamy yellow mixture was obtained. The reaction was stirred at 0 °C (usually for about 2 h) before being quenched with saturated $NH_4Cl_{(aq)}$ (0.45 mL/mmol of acetoacetate) and water (0.45 mL/mmol of acetoacetate). The layers were separated and the aqueous layer was extracted with $Et_2O$. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification of the crude mixture was performed using flash-chromatography ($Et_2O$/PE or EtOAc/PE).

#### GP2: tosylation of acetoacetate to form the *trans*-alkene

According to the modified procedure of Nakatsuji *et al*.[146]

A flame-dried 50 mL round bottom flask under argon was charged (in this order) with the acetoacetate (1.0 eq.), dry chlorobenzene (1 mL/mmol of substrate, dried overnight over activated 4 Å molecular sieves), *N*-methylimidazole (1.5 eq.) in one portion, dry $Et_3N$ (1.5 eq.). Tosyl chloride (recrystallized, 1.5 eq.) was added as a solution in dry chlorobenzene (1 mL/mmol of substrate) over 15 min. The reaction was monitored by TLC analysisand was quenched with water (5 mL/mmol of substrate) when completed. NaCl was usually added to help the separation, the layers were separated and the aqueous layer was extracted with EtOAc (3x 5 mL/mmol of substrate). The combined organic layers were washed with 1 M $HCl_{(aq)}$ (3x 2 mL/mmol of substrate), dried ($Na_2SO_4$),

filtered and concentrated under reduced pressure. Purification by flash-chromatography (EtOAc/$PE_{30-40}$) afforded the desired product (usually *E*/*Z* ratio: >95:5 by $^1H$ NMR).

### GP3: triflation of acetoacetate to form the *trans*-alkene

**Method A:** According to the modified procedure of Babinski *et al*.[139] A flask equipped with a thermometer under argon was charged with the acetoacetate (1.0 eq.), hexane (0.42 mL/mmol of substrate), water (0.42 mL/mmol of substrate) and cooled to 0 °C. $Me_4NOH$ solution (25% w/w in water, 5.0 eq.) was added and the reaction was vigorously stirred for 5 min before triflic anhydride (2.5 eq.) was added dropwise (keeping the internal temperature below 10 °C). Extraction with EtOAc followed by concentration under reduced pressure provided the crude mixture. Purification of the crude mixture was performed using flash-chromatography.

**Method B:** According to the modified procedure of Munteanu *et al*.[138] A flame-dried multineck flask equipped with a thermometer was charged with the acetoacetate (1.0 eq.) and dry DMF (3.4 mL/mmol of substrate) under argon atmosphere. The mixture was cooled to -50 °C (internal temperature) (acetone/dry ice bath). KHMDS (0.5 M in toluene, 1.2 eq.) was added dropwise. The temperature was kept between -40 C and -60 °C throughout the addition. Once the addition completed, the clear solution was stirred for an additional 1 h. A solution of $PhNTf_2$ (1.1 eq.) in dry DMF (1.2 mL/mmol of substrate) was added slowly and stirred until TLC ($Et_2O$/PE) showed complete consumption of the substrate (usually 2-4 h). The reaction was diluted with $Et_2O$ then washed with citric $acid_{(aq)}$ solution (10% w/w, 3x 17 mL/mmol of substrate) then water (17 mL/mmol of substrate), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification of the crude mixture was performed using flash-chromatography.

### GP4: triflation of acetoacetate to form the *cis*-alkene

According to the modified procedure of Specklin *et al*.[137] A flame-dried flask under argon was charged with the acetoacetate (1.0 eq.), lithium triflate (2.0 eq.) and dry $CH_2Cl_2$ (30 mL/mmol of substrate) then cooled to 0 °C. Distilled Hünig's base (1.1 eq.) was added, the reaction was stirred at

0 °C for 20 min before triflic anhydride (1.1 eq.) was added over 20 s. TLC ($Et_2O/PE_{40-60}$) monitoring usually showed completion after about 30 min. The reaction was quenched with $NH_4Cl_{(aq)}$ (sat. sol., 30 mL/mmol of substrate), water added to dissolve the salts and the layers were separated. The aqueous layer was extracted with $CH_2Cl_2$ (2x 30 mL/mmol of substrate). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification of the crude mixture was performed using flash-chromatography.

### GP5: Pd-catalysed Suzuki cross-coupling

According to the modified procedure of Swidorski *et al*.[141] In a flame-dried flask under argon was added 9-BBN (0.5 M in THF, usually 1.5-1.7 eq.) to a cooled (0 °C) solution of dimethyl allylmalonate (usually 1.5-1.6 eq.) in dry degassed THF (5.5 mL/mmol of malonate substate). The ice bath was removed 5 min after the addition was completed and the reaction mixture was left stirring at room temperature for 4 h. A degassed solution of $K_3PO_{4(aq)}$ (1 M, 2.5-2.7 eq.) was added followed by a degassed solution of triflate or tosilate (1.0 eq.) in 1,4-dioxane (9 mL/mmol of tosylate/triflate) and finally the palladium source (usually 0.02-0.05 eq.) (by carefully opening the flask/adding the Pd source as a solid/closing the flask). The mixture was heated to 50-85 °C depending on the substrate until complete consumption of the tosylate or triflate was observed by TLC, usually < 8 h (but sometimes left overnight for convenience without deterioration of yield). The reaction was cooled to room temperature then water (10 mL/mmol of tosylate/triflate) and EtOAc (10 mL/mmol of tosylate/triflate) were added. The layers were separated and the aqueous phase was extracted with EtOAc (4x11 mL/mmol of tosylate/triflate). The combined organic layers were washed with brine (10 mL/mmol of tosylate/triflate), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Most of the time, two purifications by flash-chromatography were necessary to get pure product (the consecutive use of $Et_2O$/PE eluent system and EtOAc/toluene eluent system usually gave good separation).

### GP6: $Mn(OAc)_3$/Cu(II) cyclisation of malonates

To a dried round-bottom flask containing the malonate (1.0 eq.) under argon was added degassed (argon bubbling for 1 h) dry DMSO (5 mL/mmol of substrate). Solid $Mn(OAc)_3 \bullet 2H_2O$ (2.0 eq.) and the $Cu(OAc)_2 \bullet H_2O$ (1 eq.) were then added together as solids (by carefully opening the flask and introducing the solids quickly and closing). The reaction was heated to 40 °C until TLC showed complete consumption of the starting material and/or the DMSO solution turned blue/green. The reaction was quenched with $Na_2S_2O_{3\,(aq)}$ (sat. sol., freshly prepared, 4 mL/mmol of substrate), stirred until both layers were clear, then the layers were separated. The aqueous phase was extracted with EtOAc (3x 8 mL/mmol of substrate mL). The combined organic layers were washed once with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification of the crude mixture was performed using flash-chromatography.

### GP7: Iodination of malonates

According to the modified procedure of Tucker *et al*.[160] To a solution of the malonate (1.0 eq.) in dry THF (10 mL/mmol of substrate) in a flame-dried round bottomed flask under argon cooled to -78 °C was added dropwise NaHMDS solution (1 M in THF, 1.1 eq.) and stirred for 15 min. *N*-iodosuccinimide (1.1 eq.) was then added as a solid in one portion and the resulting mixture was stirred protected from any light (covered with aluminium foil) until TLC showed complete consumption of the substrate (usually < 3 h). The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (3 mL/mmol of substrate) and then warmed to room temperature. Water was added to dissolve the salts and extraction with $CH_2Cl_2$ (3x 20 mL/mmol of substrate) was done. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification of the crude mixture was performed using flash-chromatography.

### GP8: Cyclisation of iodomalonates

To the iodomalonate (1.0 eq.) in a flame-dried flask/vial or NMR tube at room temperature was added neat 2,6-lutidine (1.0 eq.) then the reaction vessel was flushed with argon. Dry and degassed

(3x freeze/pump/thaw cycles) MeOH (3.7 mL/mmol of substrate) was added and the vessel was sealed (electrical PVC tape). The reaction (with magnetic stirring) was irradiated using a white 30 W CFL light (at 5.0 cm distance for flasks and vials, at 1.0 cm for NMR tubes), using a mild $N_2$ flow on the outside of the reaction vessel (to keep it at room temperature). The reaction colour usually starts pale yellow and turns to orange. Once complete conversion was observed (TLC or $^1$H NMR when done in NMR tube with deuterated solvent), the reaction was concentrated under reduced pressure or with a nitrogen flow. Purification of the crude mixture was performed using flash-chromatography.

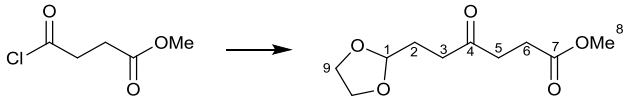
### GP9: One-pot iodination/cyclisation of malonates

To a solution of the malonate (1.0 eq.) in dry and degassed (3x freeze/pump/thaw cycles) THF (10 mL/mmol of substrate) in a flame-dried round-bottom flask under argon cooled to -78 °C was added dropwise NaHMDS solution (1 M in THF, 1.1 eq.) and stirred for 15 min. *N*-iodosuccinimide (1.1 eq.) was then added as a solid in one portion and the resulting mixture was stirred protected from any light (covered with aluminium foil) for 5 h. Neat 2,6-lutidine (1.0 eq.) was then added to the reaction. The reaction was removed from its dry ice/acetone bath and irradiated (with magnetic stirring) using a white 30 W CFL light (at 5.0 cm distance), using a mild $N_2$ flow on the outside of the reaction vessel (to prevent ice formation on the side of the vessel at the beginning and to keep it at room temperature after). The reaction colour usually starts brown or green after reacting with NIS and turn to clear/yellowish with white solids in suspension upon exposure to light. Once complete reaction was observed by TLC, the reaction was filtered (cotton wool and Celite©) concentrated down to dryness. Purification of the crude mixture was performed using flash-chromatography.

## 7.6.2 **Experimental characterisation and procedures**

### 7.6.2.1 Compounds described in schemes and tables

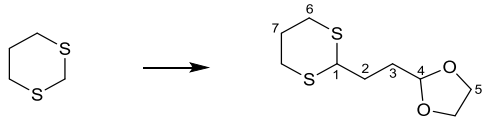
#### Methyl 6-(1,3-dioxolan-2-yl)-4-oxohexanoate (2.4)




According to the modified procedure of Lu *et al.*[109] and Bedoukian *et al.*:[110] To a 3-necked 100 mL RBF equipped with a thermometer (-10 to 100 °C), condenser and nitrogen inlet was added magnesium turnings (450 mg, 18.75 mmol, 1.3 eq.) and stirred overnight. Dry THF (12 mL) was then added followed by 0.5 mL of a solution of 2-(2-bromoethyl)-1,3-dioxolane **2.7** (3.0 g, 16.5 mmol, 1.2 eq.) in dry THF (6 mL) and a little crystal of iodine. After heating the mixture for a few seconds to about 60-65 °C, the Grignard reagent formation started (orange colour of iodine disappeared). The rest of the bromide was added to keep the internal temperature below 30 °C. The reaction was stirred at room temperature for 1 h, the thermometer was removed and the reaction was cooled to -78 °C. Methyl 4-chloro-4-oxobutyrate **2.9** (1.75 mL, 14.10 mmol, 1 eq.) as a solution in dry THF (7.5 mL) was added quickly in one portion and the resulting mixture was stirred for 30 min at -78 °C before being quenched with saturated $NH_4Cl_{(aq)}$ solution (30 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2x 100 mL). The combined organic layers were washed once with water (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to a colourless liquid (2.65 g). Purification by flash-chromatography (eluent: 50% EtOAc in $PE_{40\text{-}60}$) afforded the title product as a colourless liquid (2.33 g, 10.76 mmol, 76%).

**$R_f$** 0.35 (50% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$, vanillin); **$\delta_H$** (400 MHz, $CDCl_3$) 4.88 (1H, t, *J*=4.2 Hz, CH-(1)), 3.77 – 3.97 (4H, m, 2 $CH_2$-(9)), 3.65 (3H, s, $CH_3$-(8)), 2.72 (2H, t, *J*=6.6 Hz, $CH_2$-(5)), 2.56 (2H, t, *J*=6.6 Hz, $CH_2$-(6)), 2.56 (2H, t, *J*=7.3 Hz, $CH_2$-(3)), 1.96 (2H, td, *J*=7.3, 4.2 Hz, $CH_2$-(2)); **$\delta_C$** (101 MHz, $CDCl_3$) 208.0 (C(4)), 173.3 (C(7)), 103.3 (C(1)), 65.1 (2 C(9)), 51.9 (C(8)), 37.1 (C(5)), 36.5 (C(3)), 27.8 (C(2 or 6)), 27.6 (C(2 or 6)); **$\nu_{max}$** (film, $CDCl_3$) 2889 (w), 1735 (s, C=O), 1715 (s, C=O), 1413, 1140, 1030; ***m/z*** ($ESI^+$) 239.1 ([M+$Na^+$], 100%), 217.1 ([M+$H^+$], 30%), 455.2 ([2M+$Na^+$], 25%); **HRMS** found 239.0891, $C_{10}H_{16}NaO_5^+$ requires 239.0890. Data are in accordance with the literature.[109]

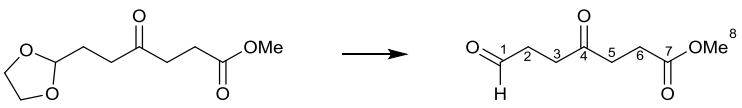
### 2-(2-(1,3-Dithian-2-yl)ethyl)-1,3-dioxolane (2.6)



According to the modified procedure of Stockman *et al.*:[171] To a stirred solution of 1,3-dithiane **2.8** (200 mg, 1.66 mmol, 1 eq., sublimed) in THF (2.5 mL, distilled over $CaH_2$) in an oven-dried 25 mL round-bottom flask was added *n*-butyllithium (730 µL, 1.83 mmol, 1.1 eq., 2.5 M in hexanes) dropwise under inert atmosphere at -40 °C. After stirring for 2 hours, the reaction was cooled to -78 °C and 2-(2-bromoethyl)-1,3-dioxolane **2.7** (301 mg, 1.66 mmol, 1 eq.) was added slowly. After 15 min, the reaction was allowed to warm to room temperature overnight. The reaction was quenched with water (5 mL) and diethyl ether (6 mL) was added. The layers were separated; the organic phase was washed once with brine (5 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to a yellowish liquid. Purification by flash-chromatography (eluent: 17% EtOAc in $PE_{40\text{-}60}$) gave the title product (207 mg, 0.94 mmol, 57%) as a white solid.

**$R_f$** 0.32 (17% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$, vanillin); **m.p.** 44-46 °C; **$\delta_H$** (400 MHz, benzene-$d_6$) 4.76 (1H, t, *J*=4.2 Hz, CH-(4)), 3.89 (1H, t, *J*=6.6 Hz, CH-(1)), 3.51 – 3.24 (4H, m, 2 $CH_2$-(5)), 2.38 – 2.27 (4H, m, 2 $CH_2$-(6)), 2.16 – 2.00 (4H, m, $CH_2$-(2), $CH_2$-(3)), 1.62 – 1.35 (2H, m, $CH_2$-(7)); **$\delta_C$** (101 MHz, benzene-$d_6$) δ 104.1 (C(4)), 64.9 (2 C(5)), 47.5 (C(1)), 31.5 (C(2 or3)), 30.3 (C(2 or3)), 30.1 (2 C(6)), 26.1 (C(7)); **$\nu_{max}$** (film, $CDCl_3$) 2890, 1138; ***m/z*** (ESI$^+$) 221.1 ([M+H$^+$], 100%), 243.0 ([M+Na$^+$], 40%); **HRMS** found 221.06665, $C_9H_{17}O_2S_2^+$ requires 221.06655.

### Methyl 4,7-dioxoheptanoate (2.10)

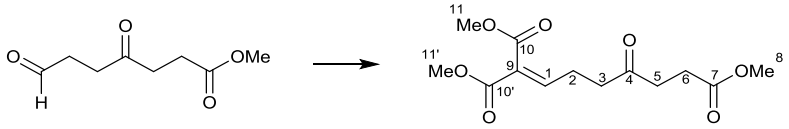


According to the modified procedure of Lu *et al.*:[109] A mixture of methyl 6-(1,3-dioxolan-2-yl)-4-oxohexanoate **2.4** (675 mg, 3.12 mmol) in 3:1 AcOH/water (50 mL) was heated to 50 °C for 9 h. Upon

completion by TLC (60% EtOAc in $PE_{40-60}$), solvents were removed under reduce pressure. The obtained colourless crude (liquid) was purified by flash-chromatography (eluent: 60% EtOAc in $PE_{40-60}$) to provide the title aldehyde as a colourless liquid (405 mg, 2.35 mmol, 75%).

**$R_f$** 0.41 (60% EtOAc in $PE_{40-60}$, $KMnO_4$, vanillin); **$\delta_H$** (400 MHz, $CDCl_3$) 9.78 (1H, s, CH-(1)), 3.66 (3H, s, $CH_3$-(8)), 2.79 (2H, t, J=6.5 Hz, $CH_2$-(5)), 2.78 (2H, m, $CH_2$-(3)), 2.60 (2H, t, J=6.5 Hz, $CH_2$-(6)); **$\delta_C$** (101 MHz, $CDCl_3$) 206.9 ((C(4)), 200.5 (C(1)), 173.3 (C(7)), 52.0 (C(8)), 37.6 ($CH_2$), 37.1 ($CH_2$), 34.8 ($CH_2$), 27.9 (C(6)); **$\nu_{max}$** (film, $CDCl_3$) 1732 (s, C=O), 1712 (s, C=O), 1409, 1197, 1104; ***m/z*** ($ESI^+$) 227.1 ([M+MeOH+$Na^+$], 100%). Data are in accordance with the literature.[109]

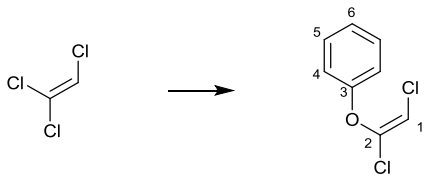
### Trimethyl 5-oxohept-1-ene-1,1,7-tricarboxylate (2.11)




According to the modified procedure of Ivanova *et al*.:[113] To THF (2 mL) was added $TiCl_4$ (1 M solution in $CH_2Cl_2$, 0.58 mL, 0.58 mmol, 2 eq.) dropwise at 0 °C. When the fumes where disappeared, a solution of methyl 4,7-dioxoheptanoate **2.10** (50 mg, 0.29 mmol, 1 eq.) in THF (1.7 mL) was added dropwise to this canary yellow solution followed by dimethyl malonate (35 µL, 0.30 mmol, 1.05 eq.) and pyridine (93 µL, 1.16 mmol, 4 eq.) at 0 °C. The reaction turned red during the last addition. The mixture was allowed to warm to room temperature overnight. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ solution then the aqueous layer was extracted with EtOAc (1x) and $Et_2O$ (1x, stable emulsion). The combined organic layers were washed with water (1x), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to an orange crude mixture (90 mg). Purification by flash-chromatography (eluent: 33% EtOAc in $PE_{40-60}$) yield the title product as a colourless liquid (5.7 mg, 0.02 mmol, 7%).

**$R_f$** 0.53 (63% EtOAc in $PE_{40-60}$, $KMnO_4$, vanillin, $UV_{254\ nm}$); **$\delta_H$** (400 MHz, $CDCl_3$) 7.01 (1H, t, J=7.8 Hz, CH-(1)), 3.83 (3H, s, $CH_3$-(11 or 11')), 3.77 (3H, s, $CH_3$-(11 or 11')), 3.68 (3H, s, $CH_3$-(8)), 2.77 – 2.53 (8H, m, $CH_2$-(2), $CH_2$-(3), $CH_2$-(5), $CH_2$-(6)); **$\delta_C$** (101 MHz, $CDCl_3$, reported on the basis of available HSBC data) 221.7 (C(4)), 148.5 (C(1)), 52.4 ($OCH_3$), 52.4 ($OCH_3$), 51.9 ($OCH_3$), 40.8 ($CH_2$), 37.0 ($CH_2$), 27.7 ($CH_2$), 23.8 ($CH_2$); **$\nu_{max}$** (film, $CDCl_3$) 1731 (s, C=O), 1721 (s, C=O), 1438 (w), 1412 (w), 1226 (m); ***m/z*** ($ESI^+$) 309.1 ([M+$Na^+$], 100 %), 287.1 ([M+$H^+$], 10 %); **HRMS** found 309.0938, $C_{13}H_{18}NaO_7^+$ requires 309.0945.

### (*E*)-((1,2-Dichlorovinyl)oxy)benzene (2.14)

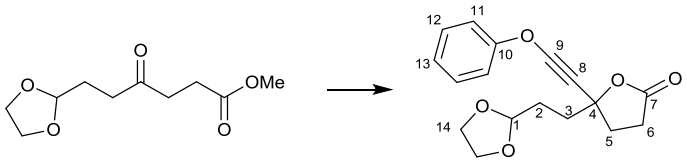



According to the modified procedure of Puri *et al.*:[108] To phenol (5.0 g, 53.1 mmol, 1.0 eq.) as a solution in dry DMSO (30 mL) was added sodium hydroxide (2.12 g, 53.1 mmol, 1.0 eq.) at room temperature. Argon was bubbled through the stirring solution for 5 minutes. After 4.5 hours a little part of sodium hydroxide was dissolved. A blast shield was placed, trichloroethylene (4.75 mL, 53.1 mmol, 1.0 eq.) was syringed and half of it was added dropwise to the reaction over 30 min. After 30 more minutes of stirring, the rest of trichloroethylene was added dropwise. After 3.5 h, the reaction was quenched with water (20 mL), $CH_2Cl_2$ (50 mL) was added and the layers were separated. The aqueous layer was extracting twice with $CH_2Cl_2$ (50 mL), the combined organic layers were washed with water (2x 20 mL), brine (3x 20 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to a colourless liquid crude (6 g). It was then purified by flash-chromatography (eluent: 100% $PE_{40-60}$) to provide the title compound (4.33 g, 22.90 mmol, 43%) as a colourless liquid.

**$R_f$** 0.75 (100% $PE_{40-60}$, $KMnO_4$, $UV_{254\ nm}$); **$\delta_H$** (400 MHz, $CDCl_3$) 7.38 (2H, t, *J*=7.8 Hz, 2 $CH_{Ar}$-(5)), 7.18 (1H, t, *J*=7.4 Hz, $CH_{Ar}$-(6)), 7.08 (2H, d, *J*=8.0 Hz, 2 $CH_{Ar}$-(4)), 5.97 (1H, s, CH-(1)); **$\delta_C$** (101 MHz, $CDCl_3$)

153.9 (C(3)), 140.1 ((C(2)), 129.9 (2 C(5)), 124.6 (C(6)), 117.2 (2 C(4)), 103.9 (C(1)); $\nu_{max}$ (film, $CDCl_3$) 1591, 1488, 1194, 1078. Data are in accordance with the literature.[172]

### 5-(2-(1,3-Dioxolan-2-yl)ethyl)-5-(phenoxyethynyl)dihydrofuran-2(3*H*)-one (2.16)

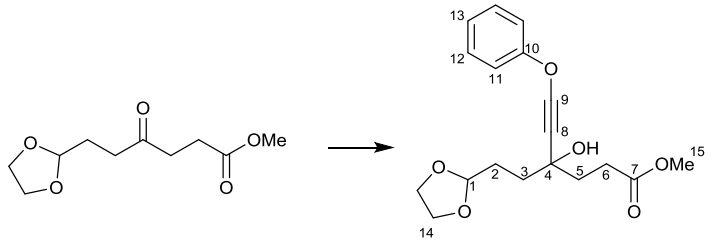



According to the modified procedure of Puri *et al.*:[Ref. 4] To a mixture of 1,2-dichlorovinyl phenyl ether **2.14** (184 mg, 0.97 mmol, 1.0 eq.) and $Et_2O$ (dry, 3.5 mL) in an oven-dried 10-mL RBF under argon atmosphere was added *n*-BuLi (0.84 mL, 2.37 M solution in hexanes, 2.00 mmol, 2.05 eq.) dropwise at -78 °C. The mixture was then kept between -20 and -30 °C for 2 h before being cooled down to -78 °C again. A white solid was observed on the side of the flask (LiCl). A solution of methyl 6-(1,3-dioxolan-2-yl)-4-oxohexanoate **2.4** (200 mg, 0.92 mmol, 0.95 eq.) in $Et_2O$ (dry, 1 mL) was added in one portion. After 5 min, the reaction was allowed to room temperature and stirred overnight. The reaction was quenched with saturated $NH_4Cl_{(aq)}$ solution, then extracted with EtOAc (4x). The combined organic layers were washed once with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to an orange oil crude. Purification by flash-chromatography (eluent: 75% EtOAc in $PE_{40\text{-}60}$) yield the title product as a yellowish oil (174.3 mg, 0.57 mmol, 63%).

$\mathbf{R_f}$ 0.54 (63% EtOAc in PE, $KMnO_4$, vanillin, $UV_{254\,nm}$); $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.40 – 7.34 (2H, m, 2 $CH_{Ar}$-(12)), 7.24 – 7.20 (2H, m, 2 $CH_{Ar}$-(11)), 7.20 – 7.15 (1H, m, $CH_{Ar}$-(13)), 4.97 (1H, t, *J*=4.0 Hz, CH-(1)), 4.00 – 3.84 (4H, m, 2 $CH_2$-(14)), 2.83 (1H, ddd, *J*=17.6, 10.2, 9.2 Hz, $CH_a$-(6)), 2.60 (1H, ddd, *J*=17.8, 9.0, 3.7 Hz, $CH_b$-(6)), 2.49 (1H, ddd, *J*=12.7, 9.2, 3.6 Hz, $CH_a$-(5)), 2.26 (1H, ddd, *J*=12.6, 10.2, 8.9 Hz, $CH_b$-(5)), 2.14 – 1.93 (4H, m, $CH_2$-(2), $CH_2$-(3); $\boldsymbol{\delta_C}$ (101 MHz, $CDCl_3$) 176.1 (C(7)), 155.6 (C(10)), 130.0 (2 C(12)), 125.0 (C(13)), 115.1 (2 C(11)), 103.7 (C(1)), 89.4 (C(9)), 82.0 (C(4)), 65.2 (2 C(14)), 43.8 (C(8)), 36.2 (C(3 or 5)), 35.6 (C(3 or 5)), 29.3 (C(2 or 6)), 29.2 (C(2 or 6)); $\nu_{max}$ (film, $CDCl_3$) 2272 (m,

C≡C-O), 1776 (s, ϒ-lactone C=O), 1488, 1197; ***m/z*** (ESI$^+$) 627.3 ([2M+Na$^+$], 100%), 325.1 ([M+Na$^+$], 85%), 303.1 ([M+H$^+$], 25%); **HRMS** found 325.1046, $C_{17}H_{18}NaO_5^+$ requires 325.1045.

### Methyl 4-(2-(1,3-dioxolan-2-yl)ethyl)-4-hydroxy-6-phenoxyhex-5-ynoate (2.17)

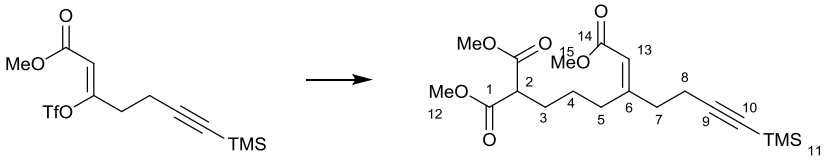



According to the modified procedure of Puri *et al.*:[108] To a mixture of 1,2-dichlorovinyl phenyl ether **2.14** (184 mg, 0.97 mmol, 1.0 eq.) and $Et_2O$ (dry, 3.6 mL) in an oven-dried 10-mL RBF under argon atmosphere was added *n*-BuLi (0.85 mL, 2.37 M solution in hexanes, 2.00 mmol, 2.05 eq.) dropwise at -78 °C. The mixture was then kept between -20 and -30 °C for 2 h before being cooled down to -78 °C again. No colour change but white solid was observed on the side of the flask (LiCl). A solution of methyl 6-(1,3-dioxolan-2-yl)-4-oxohexanoate **2.4** (200 mg, 0.92 mmol, 0.95 eq.) in $Et_2O$ (dry, 1 mL) was added in one portion. 0.3 mL of aliquot was taken and quenched in a -78 °C solution of AcOH in THF (0.6 M, 0.16 mL, ~4 eq.), diluted with $Et_2O$ (1 mL) then water (0.5 mL) to dissolve white salts. The organic layer was dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to the NMR sample. This was done after 1 min, 5 min, 10 min, 20 min, 40 min, 1.5 h, 3 h and the rest was quenched using appropriate amount of AcOH. Purification by preparative-TLC ($SiO_2$, eluent: 75% EtOAc in $PE_{40\text{-}60}$) on 50 mg of crude mixture gave the title product for characterisation as a colourless oil (12 mg, unknown yield).

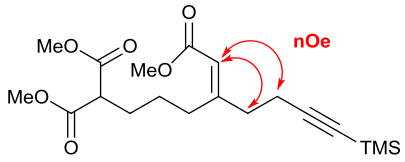
**$R_f$** 0.74 (63% EtOAc in PE, $KMnO_4$, vanillin, $UV_{254\ nm}$); **$\delta_H$** (400 MHz, $CDCl_3$) 7.39 – 7.33 (2H, m, 2 $CH_{Ar}$-(12)), 7.25 – 7.19 (2H, m, 2 $CH_{Ar}$-(11)), 7.15 (1H, tt, *J*=7.4, 1.1 Hz, $CH_{Ar}$-(13)), 4.96 (1H, dd, *J*=4.8, 3.9 Hz, CH-(1)), 4.02 – 3.85 (4H, m, 2 $CH_2$-(14)), 3.68 (3H, s, $CH_3$-(15)), 3.32 (1H, s, OH-C(4)), 2.77 – 2.62 (2H, m, $CH_2$-(3)), 2.14 – 1.95 (4H, m, $CH_2$-(2), $CH_2$-(6)), 1.90 – 1.83 (2H, m, $CH_2$-(5)); **$\delta_C$** (101 MHz, $CDCl_3$) 174.6 (C(7)), 155.8 (C(10)), 129.7 (2 C(12)), 124.5 (C(13)), 114.9 (2 C(11)), 104.2 (C(1)), 88.0

(C(9)), 70.2 (C(4)), 65.0 (2 C(14)), 51.8 (C(15)), 46.5 (C(8)), 37.7 (C(6)), 36.9 (C(5)), 29.8 (C(3)), 29.1 (C(2)); $\nu_{max}$ (film, $CDCl_3$) 3456 (br, OH), 2267 (m, C≡C-O), 1735 (s, C=O), 1589 (w), 1488 (m), 1175 (s); ***m/z*** ($ESI^+$) 357.1 ([M+$Na^+$], 100%), 691.3 ([2M+$Na^+$], 70%); **HRMS** found 357.1306, $C_{18}H_{22}NaO_6^+$ requires 357.1309.

### Trimethyl (*E*)-5-(4-(trimethylsilyl)but-3-yn-1-yl)hex-5-ene-1,1,6-tricarboxylate ((*E*)-2.31)



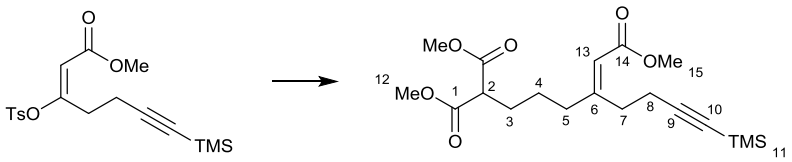

Prepared according to general procedure GP5 using 9-BBN (0.5 M in THF, 16.6 mL, 8.31 mmol, 1.6 eq.), dimethyl 2-allylmalonate **3.17** (1.25 mL, 7.79 mmol, 1.5 eq.), $K_3PO_{4(aq)}$ (1 M, 13 mL, 13.0 mmol, 2.5 eq.), methyl (*Z*)-3-(((trifluoromethyl)sulfonyl)oxy)-7-(trimethylsilyl)hept-2-en-6-ynoate **3.13** (1.86 g, 5.19 mmol, 1.0 eq.) and Pd(dppf)$Cl_2$-$CH_2Cl_2$ complex (212.0 mg, 0.26 mmol, 0.05 eq.). The mixture was heated to 85 °C until complete consumption of the **3.13** was observed by TLC (25% $Et_2O$ in $PE_{40\text{-}60}$), usually < 5 h. Crude: black liquid. Purification by flash-chromatography (eluent: 0% to 1% EtOAc in $CH_2Cl_2$; column size: Ø = 5.5 cm, L = 6 cm) followed by a second purification by flash-chromatography (eluent: 20% $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 5.5 cm, L = 10.5 cm) afforded the title product as colourless liquid (95:5 *E*/*Z* mix.1.36 g, 3.55 mmol, 68%).



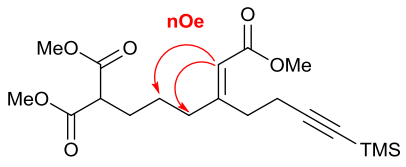

**$R_f$** 0.25 (25% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\ nm}$, vanillin); **$\delta_H$** /ppm (501 MHz, $CDCl_3$) 5.68 (1H, s, CH-(13)), 3.74 (6H, s, 2 $CH_3$-(12)), 3.68 (3H, s, $CH_3$-(15)), 3.42 (1H, t, *J*=7.5 Hz, CH-(2)), 2.66 – 2.60 (2H, m, $CH_2$-(5)), 2.40 – 2.32 (4H, m, $CH_2$-(7), $CH_2$-(8)), 1.98 – 1.92 (2H, m, $CH_2$-(3)), 1.49 (2H, td, *J*=10.4, 6.2 Hz, $CH_2$-(4)), 0.13 (9H, s, 3 $CH_3$-(11)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 169.9 (2 C(1)), 166.7 (C(14)), 160.9 (C(6)), 116.8 (C(13)), 105.6 (C(9)), 86.1 (C(10)), 52.6 (2 C(12)), 51.5 (C(2)), 51.1 (C(15)), 37.0 (C(7)), 31.4 (C(5)), 28.8 (C(3)), 26.2 (C(4)) , 18.7 (C(8)), 0.2 (3 C(11)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2175 (w, C≡C),

1751 (s, C=O), 1736 (s, C=O), 1719 (s, C=O), 1646 (m), 1435, 1337, 1279, 1248, 1215, 1158, 1041; ***m/z*** ($ESI^-$) 381.1 ($[M-H]^-$, 100%); **HRMS** ($ESI^+$) found 383.1884, $C_{19}H_{31}O_6{}^{28}Si^+$ requires 383.1884.

### Trimethyl (*Z*)-5-(4-(trimethylsilyl)but-3-yn-1-yl)hex-5-ene-1,1,6-tricarboxylate ((*Z*)-2.31)



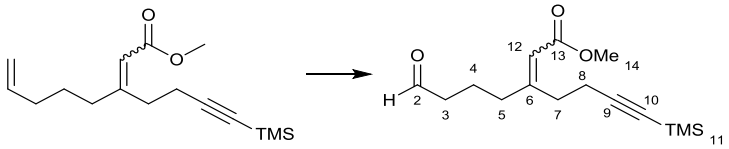

Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 25.2 mL, 12.61 mmol, 1.7 eq.), dimethyl 2-allylmalonate **3.17** (1.9 mL, 11.83 mmol, 1.6 eq.), $K_3PO_{4(aq)}$ (1 M, 20 mL, 20.0 mmol, 2.7 eq.), methyl (*E*)-3-(tosyloxy)-7-(trimethylsilyl)hept-2-en-6-ynoate **3.16** (2.79 g, 7.33 mmol, 1.0 eq.) and Pd(dppf)$Cl_2$-$CH_2Cl_2$ complex (322.0 mg, 0.39 mmol, 0.05 eq.). The mixture was heated to 85 °C until complete consumption of the **3.16** was observed by TLC (25% $Et_2O$ in $PE_{40\text{-}60}$), usually < 8 h. Crude: black liquid. Purification by flash-chromatography (eluent: 50% $CH_2Cl_2$ in $PE_{30\text{-}40}$; column size: Ø = 9 cm, L = 7 cm) followed by a second purification by flash-chromatography (eluent: 20% $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 9 cm, L = 10.5 cm) afforded the title product as colourless liquid (1.97 g, 5.15 mmol, 68%).




***R<sub>f</sub>*** 0.27 (25% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\ nm}$, vanillin); **$\delta_H$** /ppm (501 MHz, $CDCl_3$) 5.68 (1H, t, *J*=1.3 Hz, CH-(13)), 3.75 (6H, s, 2 $CH_3$-(12)), 3.68 (3H, s, $CH_3$-(15)), 3.37 (1H, t, *J*=7.5 Hz, CH-(2)), 2.79 (2H, t, *J*=7.4 Hz, $CH_2$-(7)), 2.42 (2H, t, *J*=7.3 Hz, $CH_2$-(8)), 2.27 (2H, td, *J*=7.6, 1.3 Hz, $CH_2$-(5)), 1.97 – 1.85 (2H, m, $CH_2$-(3)), 1.5 – 1.5 (2H, m, $CH_2$-(4)), 0.13 (9H, s, 3 $CH_3$-(11)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 169.7 (2 C(1)), 166.6 (C(14)), 161.6 (C(6)), 116.5 (C(13)), 106.5 (C(9)), 85.4 (C(10)), 52.7 (2 C(12)), 51.6 (C(2)), 51.1 (C(15)), 38.4 (C(5)), 30.9 (C(7)), 28.5 (C(3)), 25.2 (C(4)), 19.2 (C(8)), 0.2 (3 C(11)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2920 (s), 2851 (s), 2174 (w, C≡C), 1739 (s), 1730, (m), 1646 (w), 1458, 1436, 1245; ***m/z*** ($ESI^+$)

405.2 ([M+Na]$^+$, 100%), 383.2 ([M+H]$^+$, 50%); ***m/z*** (ESI$^-$) 381.1 ([M-H]$^-$, 100%); **HRMS** (ESI$^+$) found 383.1882, $C_{19}H_{31}O_6{}^{28}Si^+$ requires 383.1884.

### Methyl 3-(4-oxobutyl)-7-(trimethylsilyl)hept-2-en-6-ynoate (2.34)

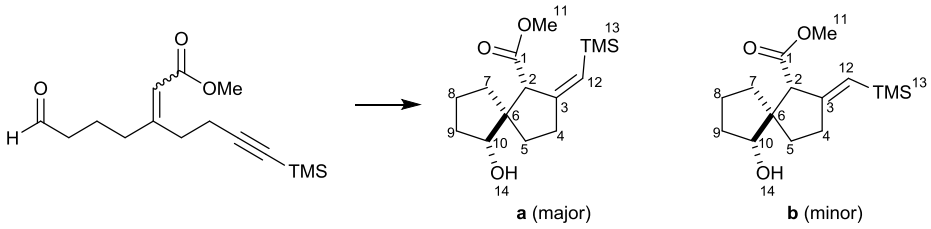



According to the modified procedure of Shen *et al*.[173] A 150 mL flask was charged (in this order) with methyl 3-(4-(trimethylsilyl)but-3-yn-1-yl)octa-2,7-dienoate **2.57** (1:1 *E/Z* mix., 2.18 g, 7.8 mmol, 1.0 eq.) , 1,4-dioxane/water (3:1 v/v, 80 mL), 2,6-lutidine (1.8 mL, 15.7 mmol, 2.0 eq.), $OsO_4$ (2.5 wt% in $^t$BuOH, 1.6 g, 0.16 mmol, 0.02 eq.) and $NaIO_4$ (6.7 g, 31.3 mmol, 4.0 eq.). The resulting pink creamy suspension was stirred until completion was observed 30 min later by TLC (30% $Et_2O$ in $PE_{30\text{-}40}$). The reaction was quenched with addition of $Na_2S_2O_{3\,(aq)}$ (sat. sol., 9.0 mL). $CH_2Cl_2$ (*ca.* 50 mL) and water (*ca.* 80 mL) were added. The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3x 125-150 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification by flash-chromatography (eluent: 30% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title product as a mixture of *E/Z* alkenes (1:1 ratio) as a colourless liquid (1.48 g, 5.28 mmol, 68%).

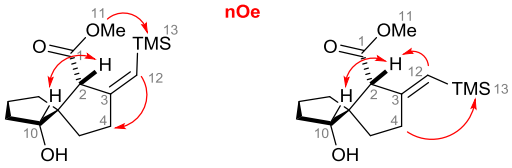
Analysed as a *E/Z* mixture (1:1 ratio): $\mathbf{R_f}$ 0.50 (30% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\,nm}$, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 9.79 (2H, t, *J*=1.6 Hz, CH-(2)), 9.78 (2H, t, *J*=1.6 Hz, CH-(2)), 5.73 (1H, s, CH-(12$^{trans}$)), 5.70 (1H, t, *J*=1.4 Hz, CH-(12$^{cis}$)), 3.69 (3H, s, $CH_3$-(14)), 3.68 (3H, s, $CH_3$-(14)), 2.80 (2H, t, *J*=7.3 Hz, $CH_2$-(7$^{cis}$)), 2.68 – 2.61 (2H, m, $CH_2$-(5$^{trans}$)), 2.51 (2H, td, *J*=7.3, 1.5 Hz, $CH_2$-(3$^{trans}$)), 2.47 (2H, td, *J*=7.3, 1.5 Hz, $CH_2$-(3$^{cis}$)), 2.44 (2H, t, *J*=7.3 Hz, $CH_2$-(8$^{cis}$)), 2.44 – 2.33 (4H, m, $CH_2$-(7$^{trans}$), $CH_2$-(8$^{trans}$)), 2.28 (2H, td, *J*=7.8, 1.4 Hz, $CH_2$-(5$^{cis}$)), 1.83 (2H, p, *J*=7.4 Hz, $CH_2$-(4$^{cis}$)), 1.81 (2H, p, *J*=7.4 Hz, $CH_2$-(4$^{trans}$)), 0.13 (9H, s, 3 $CH_3$-(11)), 0.13 (8H, s, 3 $CH_3$-(11)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 202.4 (C(2)), 201.7 (C(2)), 166.7 (C(13)), 166.6 (C(13)), 161.3 (C(6)), 160.8 (C(6)), 117.0 (C(12)), 116.8 (C(12)), 106.4 (C(9)), 105.5 (C(9)), 86.2 (C(10)), 85.5 (C(10)), 51.2 (C(14)), 51.1 (C(14)), 43.6 (C(3$^{trans}$)) 43.2 (C(3$^{cis}$)), 38.0 (C(5$^{cis}$)),

36.9 (C($7^{trans}$)), 31.2 (C($5^{trans}$)), 30.9 (C($7^{cis}$)), 20.9 (C($4^{trans}$)), 19.8 (C($4^{cis}$)), 19.3 (C($8^{cis}$)), 18.7 (C($8^{trans}$)), 0.2 (3 C(11)), 0.2 (3 C(11)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2953, 2921, 2850, 2175 (w), 1717 (s, C=O), 1645 (m), 1435, 1249, 1168 (m), 1041, 840 (s), 760; ***m/z*** ($ESI^+$) 303.0 ($[M+Na]^+$, 100%), 281.1 ($[M+H]^+$, 50%); **HRMS** ($ESI^+$) found 303.1386, $C_{15}H_{24}O_3{}^{23}Na^{28}Si^+$ requires 303.1387.

### Methyl 6-hydroxy-2-((trimethylsilyl)methylene)spiro[4.4]nonane-1-carboxylate (2.35)



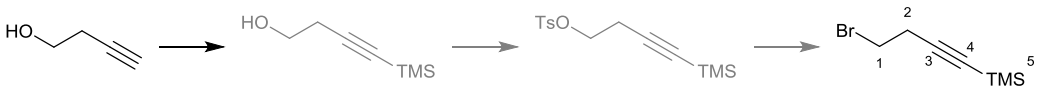

According to the modified procedure of Inui *et al*.[123] A flame-dried 25 mL round-bottomed flask was charged with methyl 3-(4-oxobutyl)-7-(trimethylsilyl)hept-2-en-6-ynoate **2.34** (50.0 mg, 0.18 mmol, 1.0 eq.), wet $^t$BuOH (34 µL, 0.36 mmol, 2.0 eq.), HMPA (124 µL, 0.71 mmol, 4.0 eq.) and dry THF (8.6 mL). The mixture was degassed using 3 freeze/thaw cycles ($N_2$ used to refill) and cooled to 0 °C. $SmI_2$ (1 M solution in THF, 7.1 mL, 0.71 mmol, 4.0 eq.) were slowly added to the reaction. The first drops were consumed to give a colourless solution then turned purple and finally dark blue. Electrical PVC tape was added on the Suba-Seal® septa to limit the possible entry of oxygen in the reaction flask. The reaction was kept at 0 °C for at least 1 h and then the ice was allowed to melt overnight. After 16 h, the reaction (greenish-blue colour) was quenched with a 4:1 mixture of sat. $NaHCO_{3(aq)}$/sat. $Na_2S_2O_{3(aq)}$ (2 mL), diluted with water (4 mL) and extracted EtOAc (3x10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Purification by flash-chromatography (eluent: 30% $Et_2O$ in $PE_{40\text{-}60}$) afforded the title product as colourless liquid as a mixture 2:1:1 **2.35a**/**2.35b**/impurity (26.2 mg, 0.09 mmol, 39% corrected yield). Further purification (flash-chromatography, eluent: 100% $CH_2Cl_2$) gave a sample of the desired diastereomers for full characterisation.




(major in crude) (minor in crude)

**2 diastereomers:** Analysed as a mix of 2 diastereomers (~ 1:1 ratio): $\mathbf{R_f}$ 0.53 (20% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$); $\mathbf{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.58 – 5.55 (1H, m, CH-(12$^{maj}$)), 5.48 (1H, dt, *J*=4.1, 2.0 Hz, CH-(12$^{min}$)), 3.84 – 3.80 (1H, m, CH-(10)), 3.77 (1H, dd, *J*=7.0, 4.5 Hz, CH-(10)), 3.67 (3H, s, $CH_3$-(11)), 3.67 (3H, s, $CH_3$-(11)), 3.11 (1H, q, *J*=1.3 Hz, CH-(2$^{maj}$)), 3.08 (1H, d, *J*=2.5 Hz, CH-(2$^{min}$)), 2.77 – 2.69 (1H, m, $CH_a$-(4$^{maj}$)), 2.58 – 2.49 (1H, m, $CH_a$-(4$^{min}$)), 2.40 (2H, dtdd, *J*=17.2, 8.5, 3.9, 2.3 Hz, $CH_b$-(4$^{maj}$), $CH_b$-(4$^{min}$)), 2.11 – 2.01 (2H, m, $CH_a$-(9$^{maj}$), $CH_a$-(9$^{min}$)), 2.01 – 1.97 (1H, m, $CH_a$-(5$^{min}$)), 1.97 – 1.93 (1H, m, $CH_a$-(5$^{maj}$)), 1.93 – 1.87 (1H, m, $CH_b$-(5$^{min}$)), 1.87 – 1.80 (2H, m, $CH_b$-(5$^{maj}$)), 1.75 – 1.69 (2H, m, $CH_a$-(8$^{maj}$), $CH_a$-(8$^{min}$)), 1.69 – 1.48 (6H, m, $CH_b$-(9$^{maj}$), $CH_b$-(9$^{min}$), $CH_b$-(8$^{maj}$), $CH_b$-(8$^{min}$), $CH_2$-(7)), 1.51 – 1.43 (2H, m, $CH_2$-(7)), 1.39 (1H, d, *J*=5.7 Hz, OH-(14)), 1.38 (1H, d, *J*=4.5 Hz, OH-(14)), 0.09 (11H, s, $CH_3$-(13$^{min}$)), 0.07 (11H, s, $CH_3$-(13$^{maj}$)); $\mathbf{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 173.5 (C(3)), 173.4 (C(3)), 159.6 (C(1$^{maj}$)), 158.9 (C(1$^{min}$)), 124.6 (C(12$^{maj}$)), 123.7 (C(12$^{min}$)), 78.7 (C(7$^{maj}$)), 78.1 (C(7$^{min}$)), 61.5 (C(2$^{min}$)), 59.1 (C(6$^{maj}$)), 57.5 (C(2$^{maj}$)), 57.2 (C(6$^{min}$)), 51.6 (C(11)), 51.6 (C(11)), 35.3 (C(4$^{maj}$)), 32.6 (C(8$^{maj}$), C(8$^{min}$)), 32.0 (C(10)), 31.1 (C(10)), 30.9 (C(4$^{min}$)), 30.3 (C(5$^{min}$)), 28.5 (C(5$^{maj}$)), 20.4 (C(9)), 20.3 (C(9)), -0.3 (3 C(13$^{maj}$)), -0.4 (3 C(13$^{min}$)); $\mathbf{\nu_{max}}$ /cm$^{-1}$ (film, $CDCl_3$) 3437 (br s, OH), 2953, 1733 (with shoulder, s, C=O), 1623 (m, C=C), 1434, 1247 (s), 1193 (s), 861, 838 (s); ***m/z*** (ESI$^+$) 305.2 ([M+Na]$^+$, 100%), 283.2 ([M+H]$^+$, 35%); **HRMS** (ESI$^+$) found 305.1543, $C_{15}H_{26}O_3{}^{23}Na^{28}Si^+$ requires 305.1543.

### (4-Bromobut-1-yn-1-yl)trimethylsilane (2.40)




Step 1: To an oven-dried 500 mL flask equipped charged with but-3-yn-1-ol (5.0 g, 71.34 mmol, 1.0 eq.) in dry THF (~200 mL) under $N_2$ was added an *n*-BuLi solution (2.28 M in hexane, 69 mL, 156.94 mmol, 2.2 eq.) over 25 min at -78 °C. After 1 h at -78 °C, TMSCl (27 mL, 214.0 mmol, 3.0 eq.) were added over 15 min. The cold bath was then removed the reaction was allowed to warm to

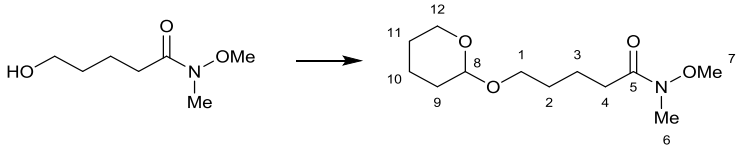
room temperature. TLC (25% $Et_2O/PE_{30-40}$, vanillin) showed complete conversion. The reaction was quench by addition of $HCl_{(aq)}$ (2 M sol., 110 mL) and the resulting clear yellowish biphasic was stirred for 15 min. The layers were separated and the aqueous phase was extracted with $Et_2O$. The combined organic layers were washed with saturated $NaHCO_{3(aq)}$ and brine, were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford 4-(trimethylsilyl)but-3-yn-1-ol that was used without purification.

Step 2: To an oven-dried 100 mL flask equipped charged with crude 4-(trimethylsilyl)but-3-yn-1-ol (73% of the previous crude, 8.0 g, 56.22 mmol, 1.0 eq.) in dry $CH_2Cl_2$ (55 mL) cooled at 0 °C under $N_2$ was added TsCl (16.0 g, 84.34 mmol, 1.5 eq.) in one portion followed by dry pyridine (6.8 g, 84.34 mmol, 1.5 eq.). The ice bath was allowed to melt and after 3 d at room temperature the reaction diluted in $Et_2O$ (300 mL) and washed with $HCl_{(aq)}$ (1 M sol., 4x100 mL) then brine (4x100 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford 4-(trimethylsilyl)but-3-yn-1-yl 4-methylbenzenesulfonate that was used without purification.

Step 3: To an oven-dried 500 mL flask equipped charged with crude 4-(trimethylsilyl)but-3-yn-1-yl 4-methylbenzenesulfonate (all the previous crude) and dry DMF (~200 mL) then NaBr (29.0 g, 281.1 mmol, 5.0 eq.) at room temperature. The resulting cloudy mixture was stirred for 4 d. Water was added followed by extraction with pentane. The combine pentane layers were washed with water, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to an orange liquid crude. Purification by flash-chromatography (eluent: 100% $PE_{30-40}$) afforded the title product as colourless liquid (8.45 g, 41.18 mmol, 76% (over 3 steps)).

$\mathbf{R_f}$ 0.60 (100% $PE_{30-40}$, $MnO_4$); $\boldsymbol{\delta_H}$ /ppm (400 MHz, $CDCl_3$) 3.42 (2H, t, J=7.6 Hz, $CH_2$-(1)), 2.77 (2H, t, J=7.6 Hz, $CH_2$-(2)), 0.15 (9H, s, 3 $CH_3$-(5)); $\boldsymbol{\delta_C}$ /ppm 101 MHz, $CDCl_3$) 103.3 (C(3)), 87.1 (C(4)), 29.3 (C(1)), 24.4 (C(2)), 0.1 (3 C(5)). Spectroscopic data is consistent with literature.[174]

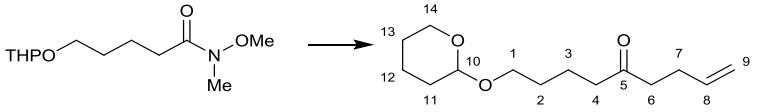
### *N*-Methoxy-*N*-methyl-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanamide (2.43)




According to the modified procedure of Pietruszka *et al*.[175] In an oven-dried flask was stirred a mixture of 5-hydroxy-*N*-methoxy-*N*-methylpentanamide **7.1** (500 mg, 3.10 mmol, 1.0 eq.), pyridinium *p*-toluenesulfonate (78 mg, 0.31 mmol, 0.1 eq.), 3,4-dihydro-2*H*-pyran (0.42 mL, 4.65 mmol, 1.5 eq.) in dry $CH_2Cl_2$ (45 mL) at room temperature for 2 d. After addition of water (30 mL), the layer were separated and the aqueous layer was extracted with $CH_2Cl_2$ (4 times, 25 mL each). The combined layers were dried ($Na_2SO_4$) and concentrated under reduce pressure to afford 0.85 g of crude (colourless liquid). The crude was purified by flash chromatography (eluent: 50% to 100% EtOAc in $PE_{40\text{-}60}$) and afforded the title product as a colourless liquid (620 mg, 2.53 mmol, 83%).

**$R_f$** 0.60 (100% $Et_2O$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 4.55 (1H, dd, *J*=4.5, 2.8 Hz, CH-(8)), 3.84 (1H, ddd, *J*=11.3, 7.8, 3.7 Hz, $CH_a$-(12)), 3.74 (1H, dt, *J*=9.6, 6.4 Hz, $CH_a$-(1)), 3.66 (3H, s, $CH_3$-(6)), 3.50 - 3.45 (1H, m, $CH_b$-(12)), 3.38 (1H, dt, *J*=9.6, 6.3 Hz, $CH_b$-(1)), 3.15 (3H, s, $CH_3$-(7)), 2.44 (2H, t, *J*=7.4 Hz, $CH_2$-(4)), 1.87 - 1.77 (1H, m, $CH_a$-(10)), 1.76 - 1.59 (5H, m, $CH_2$-(3), $CH_2$-(11), $CH_a$-(9)), 1.59 - 1.43 (4H, m, $CH_2$-(2), $CH_b$-(10), $CH_b$-(9)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 174.6 (broad, C(5)), 98.9 (C(8)), 67.3 (C(1)), 62.4 (C(12)), 61.3 (C(6)), 32.2 (broad, C(7)), 31.7 (broad, C(4)), 30.8 (C(9)), 29.5 (C(11)), 25.6 (C(2)), 21.6 (C(3)), 19.7 (C(10)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2940 (m), 2870 (w), 1663 (s, C=O), 1466 (w), 1440 (w), 1413 (w), 1384 (m), 1200 (w), 1178 (w), 1157 (w), 1137 (m), 1119 (m); ***m/z*** ($ESI^+$) 268.1 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 268.1518, $C_{12}H_{23}O_4N^{23}Na^+$ requires 268.1519.

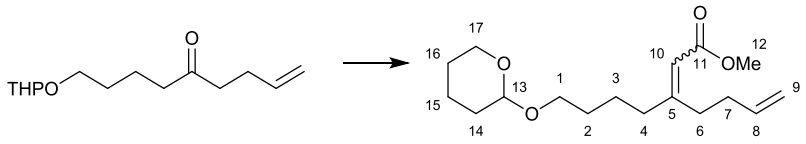
### 9-((Tetrahydro-2H-pyran-2-yl)oxy)non-1-en-5-one (2.44)



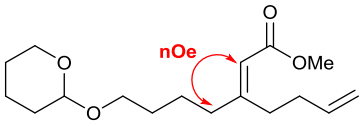

[The Grignard reagent was prepared according to the procedure of Williams *et al*.[122] An oven-dried 50 mL double-necked flask under nitrogen was charged with the *N*-methoxy-*N*-methyl-5-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanamide **2.43** (1.00 g, 4.08 mmol, 1.0 eq.) in dry THF (20 mL) and cooled to 0 °C. To the cooled solution was added but-3-en-1-ylmagnesium bromide solution (Grignard reagent in $Et_2O$, 6.12 mmol, 1.5 eq.) dropwise over 15 min. The mixture turned cloudy (white) after the addition of about 70% of the Grignard reagent. The reaction was stirred at 0 °C and monitored by TLC (70% EtOAc in $PE_{30\text{-}40}$). After 1 h, the reaction was quenched at 0 °C, by the addition of saturated $NH_4Cl_{(aq)}$ (2 mL dropwise then 8 mL quickly). The layers were separated and the aqueous phase was extracted with $Et_2O$. The combined organic layers were washed once with water and brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Purification by flash-chromatography (eluent: 0 to 25% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title product as a colourless liquid (0.64 g, 2.66 mmol, 65%).

**$R_f$** 0.33 (20% $Et_2O$ in $PE_{30\text{-}40}$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.75 (1H, ddt, *J*=17.1, 10.2, 6.5 Hz, CH-(8)), 4.97 (1H, dq, *J*=17.1, 1.6 Hz, $CH_a$-(9)), 4.92 (1H, dt, *J*=10.2, 1.6 Hz, $CH_b$-(9)), 4.51 (1H, dd, *J*=4.5, 2.8 Hz, CH-(10)), 3.80 (1H, ddd, *J*=11.0, 7.7, 3.5 Hz, $CH_a$-(14)), 3.69 (1H, dt, *J*=9.6, 6.4 Hz, $CH_a$-(1)), 3.47 - 3.42 (1H, m, $CH_b$-(14)), 3.33 (1H, dt, *J*=9.6, 6.3 Hz, $CH_b$-(1)), 2.46 (2H, t, *J*=7.4 Hz, $CH_2$-(6)), 2.40 (2H, t, *J*=7.3 Hz, $CH_2$-(4)), 2.27 (2H, dtd, *J*=8.7, 6.7, 1.6 Hz, $CH_2$-(7)), 1.77 (1H, qd, *J*=7.7, 3.4 Hz, $CH_a$-(12)), 1.68 - 1.58 (3H, m, $CH_a$-(11), $CH_2$-(3)), 1.58 - 1.43 (4H, m, $CH_b$-(11), $CH_b$-(12), $CH_2$-(13), $CH_2$-(2)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 210.1 (C(5)), 137.2 (C(8)), 115.2 (C(9)), 98.9 (C(10)), 67.2 (C(1)), 62.3 (C(14)), 42.6 (C(4)), 41.8 (C(6)), 30.8 (C(11)), 29.3 (C(2)), 27.8 (C(7)), 25.5 (C(13)), 20.7 (C(3)), 19.7 (C(12)); **$\nu_{max}$** /$cm^{-1}$ (neat) 2940 (s), 1713 (s), 1136 (m), 1120, 1075, 1032 (s); ***m/z*** ($ESI^+$) 263.1 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 263.1618, $C_{14}H_{24}O_3{}^{23}Na^+$ requires 263.1618.

### Methyl 3-(4-((tetrahydro-2H-pyran-2-yl)oxy)butyl)hepta-2,6-dienoate (2.45)

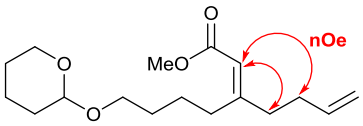



In an oven-dried 25 mL flask under nitrogen, *n*-BuLi (2.10 M in hexane, 1.43 mL, 3.01 mmol, 4.5 eq.) was added dropwise in a -78 °C solution of diisopropylamine (0.43 mL, 3.01 mmol, 4.5 eq.) in dry THF (6.8 mL). The solution turned to light yellow after 25 min stirring at -78 °C. Methyl 2-(trimethylsilyl)acetate **2.51** (0.49 mL, 3.01 mmol, 4.5 eq.) as a solution in THF (0.6 mL) was then added and stirred for an additional 15 min at -78 °C, the solution became dark yellow. The ketone 9-((tetrahydro-2H-pyran-2-yl)oxy)non-1-en-5-one **2.44** (161 mg, 0.67 mmol, 1.0 eq.) as a solution in THF (0.6 mL) was then added in one portion quickly to the reaction and stirred at -78 °C for 1 h (TLC monitoring: 20% $Et_2O$ in $PE_{30\text{-}40}$) before being quenched with $HCl_{(aq)}$ (3 M sol., 12 mL). The layers were separated and the aqueous phase was extracted with $Et_2O$ (4x 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Purification by flash-chromatography (eluent: 0 to 10% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title product as a mixture of *E/Z* alkenes (3:2 ratio) as colourless liquid (172 mg, 0.58 mmol, 86%).



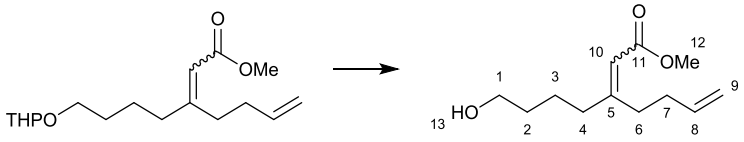

**(*Z*)-isomer (major) : $R_f$** 0.33 (10% $Et_2O$ in $PE_{30\text{-}40}$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.84 (1H, ddt, *J*=16.9, 10.1, 6.6 Hz, CH-(8)), 5.66 (1H, t, *J*=1.4 Hz, CH-(10)), 5.04 (1H, dq, *J*=17.2, 1.7 Hz, $CH_a$-(9)), 4.96 (1H, ddt, *J*=10.2, 2.2, 1.2 Hz, $CH_b$-(9)), 4.57 (1H, dd, *J*=4.5, 2.8 Hz, CH-(13)), 3.85 (1H, ddd, *J*=11.2, 7.7, 3.7 Hz, $CH_a$-(17)), 3.75 (1H, dt, *J*=9.8, 6.4 Hz, $CH_a$-(1)), 3.68 (3H, s, $CH_3$-(12)), 3.55 - 3.46 (1H, m, $CH_b$-(17)), 3.39 (1H, dt, *J*=9.8, 6.1 Hz, $CH_b$-(1)), 2.69 (2H, t, *J*=8.2 Hz, $CH_2$-(6)), 2.26 - 2.20 (2H, m, $CH_2$-(7)), 2.20 - 2.15 (2H, m, $CH_2$-(4)), 1.82 (1H, qd, *J*=7.9, 3.3 Hz, $CH_a$-(16)), 1.75 - 1.68 (1H, m, $CH_a$-(14)), 1.66 - 1.46 (8H, m, $CH_2$-(2), $CH_2$-(3), $CH_b$-(14), $CH_b$-(16), $CH_2$-(15)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 166.9 (C(11)), 163.8 (C(5)), 138.2 (C(8)), 115.5 (C(10)), 114.9 (C(9)), 99.0 (C(13)), 67.3 (C(1)), 62.5 (C(17)), 51.0 (C(12)), 38.3 (C(4)), 32.8 (C(7)), 31.6 (C(6)), 30.9 (C(14)), 29.5 (C(3)), 25.6 (C(15)), 24.4 (C(2)), 19.8 (C(16)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2942 (w),

2868 (w), 1718 (s, C=O), 1642 (m), 1435 (w), 1149 (s), 1120 (w), 1033 (m); ***m/z*** ($ESI^+$) 319.2 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 319.1880, $C_{17}H_{28}O_4{}^{23}Na^+$ requires 319.1880.



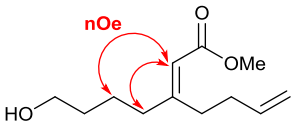

**(*E*)-isomer (minor):** $R_f$ 0.22 (10% $Et_2O$ in $PE_{30\text{-}40}$); $\delta_H$ /ppm (500 MHz, $CDCl_3$) 5.77 (1H, ddt, *J*=16.6, 10.3, 6.3 Hz, CH-(8)), 5.63 (1H, s, CH-(10)), 5.02 (1H, dq, *J*=17.2, 1.6 Hz, $CH_a$-(9)), 5.01 - 4.93 (1H, m, $CH_b$-(9)), 4.56 (1H, dd, *J*=4.5, 2.6 Hz, CH-(13)), 3.85 (1H, ddd, *J*=11.2, 7.6, 3.4 Hz, $CH_a$-(17)), 3.74 (1H, dt, *J*=9.6, 6.5 Hz, $CH_a$-(1)), 3.66 (3H, s, $CH_3$-(12)), 3.53 - 3.43 (1H, m, $CH_b$-(17)), 3.39 (1H, dt, *J*=9.8, 6.5 Hz, $CH_b$-(1)), 2.65 - 2.61 (4H, m, $CH_2$-(4)), 2.26 - 2.14 (4H, m, $CH_2$-(6), $CH_2$-(7)), 1.81 (1H, qd, *J*=7.9, 3.9 Hz, $CH_a$-(16)), 1.72 - 1.66 (1H, m, $CH_a$-(14)), 1.66 - 1.61 (2H, m, $CH_2$-(2)), 1.63 - 1.44 (4H, m, $CH_2$-(3), $CH_b$-(14), $CH_b$-(16), $CH_2$-(15)); $\delta_C$ /ppm (126 MHz, $CDCl_3$) 166.9 (C(11)), 163.7 (C(5)), 137.4 (C(8)), 115.5 (C(10)), 115.4 (C(9)), 99.0 (C(13)), 67.4 (C(1)), 62.4 (C(17)), 50.9 (C(12)), 37.6 (C(6)), 31.9 (C(4)), 31.8 (C(7)), 30.9 (C(14)), 29.9 (C(2)), 25.6 (C(3) or C(15)), 25.3 (C(3) or C(15)), 19.8 (C(16)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2940 (w), 2867 (w), 1718 (s, C=O), 1641 (m), 1434 (w), 1146 (s), 1169 (w), 1032 (m); ***m/z*** ($ESI^+$) 319.2 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 319.1881, $C_{17}H_{28}O_4{}^{23}Na^+$ requires 319.1880.

### Methyl 3-(4-hydroxybutyl)hepta-2,6-dienoate (2.46)




According to the modified procedure of Crimmins *et al.*[176] In an oven-dried 5 mL flask was stirred a mixture of the THP-protected alcohol methyl 3-(4-((tetrahydro-2*H*-pyran-2-yl)oxy)butyl)hepta-2,6-dienoate **2.45** (50 mg, 0.17 mmol, 1.0 eq.), pyridinium *p*-toluenesulfonate (4.2 mg, 0.02 mmol, 0.1 eq.) in methanol (2 mL) at room temperature. After 40 h, TLC (30% $Et_2O$ in $PE_{30\text{-}40}$) didn't show any remaining starting protected alcohol. The reaction was quenched by the addition of saturated $NaHCO_{3\,(aq)}$ (*ca* 0.5 mL) the concentrated down to remove the methanol. The heterogeneous mix

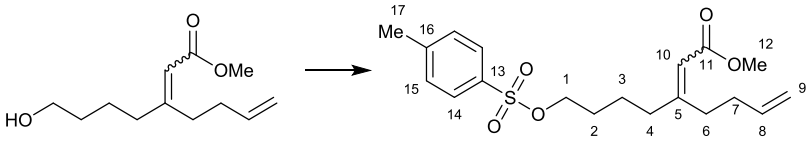
obtained was extracted with $Et_2O$ (4x 2 mL). The combined organic layers were washed once with water (2 mL) and brine (2 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a light yellow oil/liquid. Purification by flash-chromatography (eluent: 50% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title product as a mixture of *E/Z* alkenes as a colourless liquid (29.9 mg, 0.14 mmol, 83%).



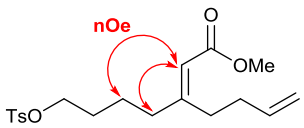

**(*Z*)-isomer (major):** $\mathbf{R_f}$ 0.36 (50% $Et_2O$ in $PE_{30\text{-}40}$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.84 (1H, ddt, *J*=16.9, 10.2, 6.6 Hz, CH-(8)), 5.66 (1H, t, *J*=1.3 Hz, CH-(10)), 5.04 (1H, ddt, *J*=17.0, 1.6 Hz, $CH_a$-(9)), 4.96 (1H, ddt, *J*=10.2, 2.2, 1.3 Hz, $CH_b$-(9)), 3.68 (3H, s, $CH_3$-(12)), 3.67 - 3.63 (2H, m, $CH_2$-(1)), 2.69 (2H, t, *J*=8.1, 7.7 Hz, $CH_2$-(6)), 2.25 - 2.20 (2H, m, $CH_2$-(7)), 2.20 - 2.16 (2H, m, $CH_2$-(4)), 1.57 (4H, d, *J*=8.2 Hz, $CH_2$-(2), $CH_2$-(3)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 166.9 (C(11)), 163.6 (C(5)), 138.1 (C(8)), 115.6 (C(9)), 115.0 (C(10)), 62.7 (C(1)), 51.0 (C(12)), 38.2 (C(4)), 32.8 (C(7)), 32.4 (C(2)), 31.5 (C(6)), 23.9 (C(3)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 3357 (br s, OH), 2937 (w), 2865, 1717 (s, C=O), 1640 (m), 1435 (w), 1233, 1194 (w), 1149 (m), 1063, 1029; ***m/z*** ($ESI^+$) 235.1 ($[M+Na]^+$, 100%), 213.1 ($[M+H]^+$, 20%); **HRMS** ($ESI^+$) found 235.1307, $C_{12}H_{20}O_3{}^{23}Na^+$ requires 235.1305.

**(*E*)-isomer (minor):** $\mathbf{R_f}$ 0.23 (50% $Et_2O$ in $PE_{30\text{-}40}$); $\boldsymbol{\delta_H}$ /ppm (400 MHz, $CDCl_3$) 5.83 – 5.73 (1H, m, CH-(8)), 5.65 (1H, s, CH-(10)), 5.04 (1H, dd, *J*=17.1, 1.7 Hz, $CH_a$-(9)), 5.00 (1H, dd, *J*=10.2, 1.5 Hz, $CH_b$-(9)), 3.71 (2H, t, *J*=6.0 Hz, 1), 3.68 (3H, s, $CH_3$-(12)), 2.64 – 2.54 (2H, m, $CH_2$-(4)), 2.31 – 2.15 (4H, m, $CH_2$-(6), $CH_2$-(7)), 2.02 (1H, d, *J*=14.8 Hz, HO-(13)), 1.69 – 1.51 (4H, m, $CH_2$-(2), $CH_2$-(3)); $\boldsymbol{\delta_C}$ /ppm (101 MHz, $CDCl_3$) 167.1 (C(11)), 164.5 (C(5)), 137.4 (C(8)), 115.5 (C(9)), 115.2 (C(10)), 62.0 (C(1)), 51.1 (C(12)), 37.9 (C(6)), 32.3 (C(4)), 31.8 (C(7)), 31.5 (C(2)), 24.7 (C(3)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 3391 (br s, OH), 2934 (w), 2861, 1718 (s, C=O), 1641 (m), 1435 (w), 1226 (w), 1163 (m), 1062, 1031; ***m/z*** ($ESI^+$) 235.1 ($[M+Na]^+$, 100%), 213.1 ($[M+H]^+$, 30%); **HRMS** ($ESI^+$) found 235.1307, $C_{12}H_{20}O_3{}^{23}Na^+$ requires 235.1305.

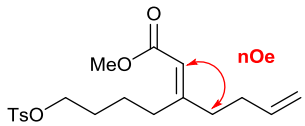
### Methyl 3-(4-(tosyloxy)butyl)hepta-2,6-dienoate (2.47)




According to the modified procedure of Moussa *et al*.[177] An oven-dried 10 mL flask equipped charged with methyl 3-(4-hydroxybutyl)hepta-2,6-dienoate **2.46** (351 mg, 1.65 mmol, 1 eq.) and $CH_2Cl_2$ (4.0 mL) was cooled to 0 °C. Tosyl chloride (690 mg, 3.62 mmol, 2.2 eq.) and pyridine (0.3 mL, 3.62 mmol, 2.2 eq.) were added and the reaction was allowed to warm to room temperature. After 2 d, the reaction was diluted with $Et_2O$ (50 mL), washed with $HCl_{(aq)}$ (1 M sol., 3x10 mL), ), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a light yellow oil/liquid. Purification by flash-chromatography (eluent: 30% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title product as an inseparable mixture of E/Z alkenes as a colourless liquid (460 mg, 1.26 mmol, 76%).

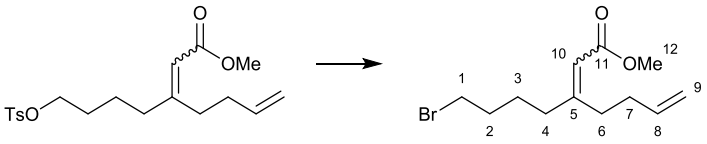



<u>Analysed as a *Z*/*E* mixture (70:30 ratio):</u> $\mathbf{R_f}$ 0.40 (30% $Et_2O$ in $PE_{30\text{-}40}$); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 1715 (s, C=O), 1641 (m), 1358 (s), 1189 (w), 1174 (s), 1149 (w), 1033 (m); ***m/z*** ($ESI^+$) 367.1 ($[M+H]^+$, 100%), 389.1 ($[M+Na]^+$, 75%), 757.3 ($[2M+Na]^+$, 10%); **HRMS** ($ESI^+$) found 367.1576, $C_{19}H_{27}O_5{}^{32}S^+$ requires 367.1574; **(*Z*)-isomer (major): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 7.81 – 7.76 (2H, m, 2 $CH_{Ar}$-(15)), 7.37 – 7.32 (2H, m, 2 $CH_{Ar}$-(14)), 5.82 (1H, ddt, *J*=16.9, 10.1, 6.6 Hz, CH-(8)), 5.57 (1H, t, *J*=1.3 Hz, CH-(10)), 5.02 (1H, dq, *J*=17.0, 1.6 Hz, $CH_a$-(9)), 4.96 (1H, ddt, *J*=10.2, 2.2, 1.2 Hz, $CH_b$-(9)), 4.03 (2H, t, *J*=5.7 Hz, $CH_2$-(1)), 3.68 (3H, s, $CH_3$-(12)), 2.66 – 2.61 (2H, m, $CH_2$-(6)), 2.45 (3H, s, $CH_3$-(17)), 2.21 – 2.14 (2H, m, $CH_2$-(7)), 2.09 (2H, td, *J*=7.6, 1.3 Hz, $CH_2$-(4)), 1.67 – 1.62 (2H, m, $CH_2$-(2)), 1.52 – 1.45 (2H, m, $CH_2$-(3)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 166.7 (C(11)), 162.8 (C(5)), 144.9 (C(16)), 137.9 (C(8)), 133.2 (C(13)), 130.0 (2 C(15)), 128.0 (2 C(14)), 115.9 (C(10)), 115.1 (C(9)), 70.2 (C(1)), 51.0 (C(12)), 37.6 (C(4)), 32.8 (C(7)), 31.4 (C(6)), 28.5 (C(2)), 23.5 (C(3)), 21.8 (C(17));




**(*E*)-isomer (minor): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 7.81 – 7.76 (2H, m, 2 $CH_{Ar}$-(15)), 7.37 – 7.32 (2H, m, 2 $CH_{Ar}$-(14)), 5.77 – 5.72 (1H, m, CH-(8)), 5.64 (1H, s, CH-(10)), 5.03 (1H, dd, *J*=16.9, 1.5 Hz, $CH_a$-(9)), 4.99 (1H, dq, *J*=10.2, 1.7, 0.9 Hz, $CH_b$-(9)), 4.04 (2H, t, *J*=6.3 Hz, $CH_2$-(1)), 3.66 (3H, s, $CH_3$-(12)), 2.59 – 2.54 (2H, m, $CH_2$-(4)), 2.44 (3H, s, $CH_3$-(17)), 2.21 – 2.14 (4H, m, $CH_2$-(6), $CH_2$-(7)), 1.73 – 1.67 (2H, m, $CH_2$-(2)), 1.52 – 1.45 (2H, m, $CH_2$-(3)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 166.8 (C(11)), 162.9 (C(5)), 144.8 (C(16)), 137.3 (C(8)), 133.3 (C(13)), 130.0 (2 C(15)), 128.0 (2 C(14)), 115.9 (C(10)), 115.6 (C(9)), 70.5 (C(1)), 51.0 (C(12)), 37.5 (C(6)), 31.8 (C(7)), 31.4 (C(4)), 28.9 (C(2)), 24.4 (C(3)), 21.8 (C(17)).

### Methyl 3-(4-bromobutyl)hepta-2,6-dienoate (2.48)

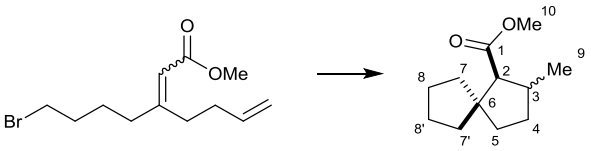



According to the modified procedure of Lin *et al.*[178] In an oven-dried 25 mL flask was stirred a mixture of methyl 3-(4-(tosyloxy)butyl)hepta-2,6-dienoate **2.47** (*Z*/*E* mixture (70:30 ratio), 440 mg, 1.20 mmol, 1.0 eq.), anhydrous sodium bromide (618 mg, 6.00 mmol, 5.0 eq.) in DMF (12 mL) at room temperature under nitrogen. After 16 h, TLC (30% $Et_2O$ in $PE_{30\text{-}40}$) didn't show any remaining starting tosylate. The reaction was extracted with pentane. The combined organic layers were washed with water and brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a colourless liquid. Purification by flash-chromatography (eluent: 5% $Et_2O$ in $PE_{40\text{-}60}$) afforded the title product as a colourless liquid (70:30 *E*/*Z* mix.,309 mg, 1.12 mmol, 94%).

Analysed as a Z/E mixture (70:30 ratio): **$R_f$** 0.37 (5% $Et_2O$ in $PE_{40\text{-}60}$); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 1715 (s, C=O), 1641 (m), 1434 (m), 1231 (w), 1193 (w), 1150 (s) 913 (m); ***m/z*** ($ESI^+$) 297.0 ($[M+Na]^+$, 100%), 275.0 ($[M+H]^+$, 65%); **HRMS** ($ESI^+$) found 275.0642, $C_{12}H_{20}O_2{}^{79}Br^+$ requires 275.0641**. (*Z*)-isomer (major): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.84 (1H, ddt, *J*=16.9, 10.2, 6.6 Hz, CH-(8)), 5.68 - 5.65 (1H, m, CH-

(10)), 5.04 (1H, dp, *J*=17.0, 1.5 Hz, $CH_a$-(9)), 4.98 - 4.95 (1H, m, $CH_b$-(9)), 3.68 (3H, s, $CH_3$-(12)), 3.41 (2H, t, *J*=6.6 Hz, $CH_2$-(1)), 2.72 - 2.68 (2H, m, $CH_2$-(6)), 2.26 - 2.20 (2H, m, $CH_2$-(7)), 2.20 - 2.15 (2H, m, $CH_2$-(4)), 1.86 (2H, dt, *J*=14.8, 6.6 Hz, $CH_2$-(2)), 1.67 - 1.60 (2H, m, $CH_2$-(3)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 166.7 (C(11)), 162.9 (C(5)), 137.9 (C(8)), 115.8 (C(10)), 115.0 (C(9)), 51.0 (C(12)), 37.4 (C(7)), 33.4 (C(1)), 32.7 (C(4)), 32.2 (C(2)), 31.4 (C(6)), 26.0 (C(3)); **(*E*)-isomer (minor): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.81 - 5.74 (1H, m, CH-(8)), 5.68 - 5.65 (1H, m, CH-(10)), 5.04 (1H, dp, *J*=17.0, 1.5 Hz, $CH_a$-(9),), 5.02 - 4.98 (1H, m, $CH_b$-(9)), 3.68 (3H, s, $CH_3$-(12)), 3.44 (2H, t, *J*=6.8 Hz, $CH_2$-(1)), 2.66 - 2.62 (2H, m, $CH_2$-(4)), 2.26 - 2.20 (4H, m, $CH_2$-(6), $CH_2$-(7)), 1.94 - 1.90 (2H, m, $CH_2$-(2)), 1.67 - 1.60 (2H, m, $CH_2$-(3)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 166.8 5C(11)), 163.0 (C(5)), 137.3 (C(8)), 115.8 (C(10)), 115.5 (C(9)), 51.0 (C(12)), 37.5 (C(7)), 33.7 (C(1)), 32.7 (C(2)), 31.7 (C(6)), 31.1 (C(4)), 27.0 (C(3)).

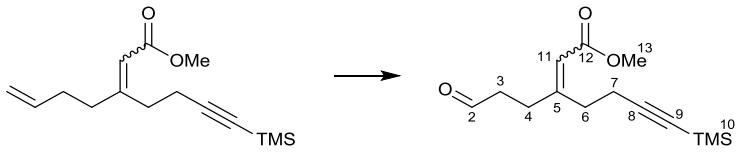
### Methyl 2-methylspiro[4.4]nonane-1-carboxylate (2.52)




According to the modified procedure of Beckwith *et al*.[178] An oven-dried 25 mL 2-necked flask equipped with a condenser was charged with methyl 3-(4-bromobutyl)hepta-2,6-dienoate **2.48** Z/E mixture (70:30 ratio), 100 mg, 0.36 mmol, 1.0 eq.), AIBN (3.0 mg, 18 µmol, 0.05 eq.) and dry benzene (8.0 mL). Argon was passed through the solution for 40 min to obtain a degassed mixture. The mixture was heated to reflux and then tributyltin hydride (1 M solution in hexane, 0.44 mL, 0.44 mmol, 1.2 eq.) was added at a rate of 0.22 mL/h using a syringe pump. TLC (5% $Et_2O$ in $PE_{30\text{-}40}$) showed a complete reaction after 4 h. The reaction was cooled down then concentrated under reduced pressure and purified by flash-chromatography (eluent: 5% $Et_2O$ in pentane) using KF silica. It afforded the title product as a mixture of isomers (4:1 d.r., 66.7 mg, 0.34 mmol, 95%).

Analysed as a mixture of isomers (4:1 *d.r.*): **$R_f$** 0.54 & 0.63 (5% $Et_2O$ in $PE_{30\text{-}40}$); **major isomer: $\delta_H$** /ppm (500 MHz, $CDCl_3$) 3.66 (3H, s, $CH_3$-(10)), 2.42 - 2.30 (1H, m, CH-(3)), 2.21 (1H, d, *J*=9.8 Hz, CH-(2)), 1.90 - 1.81 (1H, m, $CH_a$-(4)), 1.75 - 1.67 (1H, m, 1 CH-(7 or 7')), 1.65 - 1.44 (7H, m), 1.38 - 1.33 (2H, m, 2 CH-(7 or 7')), 1.20 (1H, ddt, *J*=12.6, 9.3, 8.4 Hz, $CH_b$-(4)), 1.00 (3H, d, *J*=6.6 Hz, $CH_3$-(9)); **major isomer: $\delta_C$** /ppm (500 MHz, $CDCl_3$) 175.5 (C(1)), 61.2 (C(2)), 54.5 (C(4)), 51.3 (C(10)), 40.0 (C(5)), 39.6 (C(7 or 7')), 37.5 (C(3)), 35.3 (C(7 or 7')), 32.4 (C(4)), 24.4 (C(8 or 8')), 23.9 (C(8 or 8')), 20.3 (C(9)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2950 (m), 2868 (w), 1732 (s, C=O), 1455, 1434, 1373, 1254, 1192, 1155 (m), 1034; ***m/z*** ($ESI^+$) 197.2 ($[M+H]^+$, 100%), 219.1 ($[M+Na]^+$, 65%); **HRMS** ($ESI^+$) found 197.15375, $C_{12}H_{21}O_2^+$ requires 197.15361.

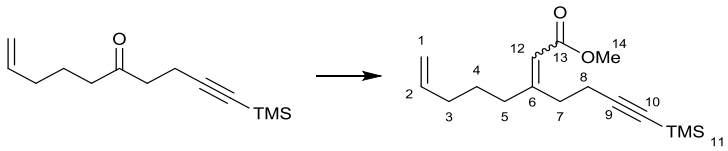
### Methyl 3-(3-oxopropyl)-7-(trimethylsilyl)hept-2-en-6-ynoate (2.55)




According to the modified procedure of Shen *et al*.[173] A 50 mL flask was charged (in this order) with methyl 3-(4-(trimethylsilyl)but-3-yn-1-yl)hepta-2,6-dienoate **2.80** (1:1 E/Z mix., 1.04 g, 3.95 mmol, 1.0 eq.) , 1,4-dioxane/water (3:1 v/v, 40 mL), 2,6-lutidine (0.90 mL, 7.90 mmol, 2.0 eq.), $OsO_4$ (2.5 wt% in $^t$BuOH, 0.80 g, 0.08 mmol, 0.02 eq.) and $NaIO_4$ (3.39 g, 15.80 mmol, 4.0 eq.). The resulting pink creamy suspension was stirred until completion was observed 20 min later by TLC (30% $Et_2O$ in $PE_{30\text{-}40}$). The reaction was quenched with addition of $Na_2S_2O_{3\,(aq)}$ (sat. sol., 4.5 mL). $CH_2Cl_2$ and water were added. The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification by flash-chromatography (eluent: 30% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title product as a mixture of E/Z alkenes (1:1 ratio) as a yellow liquid (764 mg, 2.87 mmol, 73%).

Analysed as a *E/Z* mixture (1:1 ratio): $\mathbf{R_f}$ 0.43 (30% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\,nm}$, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 9.80 (1H, t, *J*=1.3 Hz, CHO-($2^{cis}$)), 9.80 (1H, t, *J*=1.3 Hz, CHO-($2^{trans}$)), 5.74 (1H, t, *J*=1.3 Hz, CH-($11^{trans}$)), 5.67 (1H, t, *J*=1.4 Hz, CH-($11^{cis}$)), 3.69 (3H, s, $CH_3$-(13)), 3.69 (3H, s, $CH_3$-(13)), 2.89 (2H, dd, *J*=8.4, 7.0 Hz, $CH_2$-($4^{trans}$)), 2.82 (2H, t, *J*=7.2 Hz, $CH_2$-($6^{cis}$)), 2.68 – 2.62 (4H, m, 2 $CH_2$-(3)), 2.62 – 2.58 (2H, m, $CH_2$-($4^{cis}$)), 2.47 (2H, t, *J*=7.3 Hz, $CH_2$-($7^{cis}$)), 2.43 – 2.35 (4H, m, $CH_2$-($6^{trans}$), $CH_2$-($7^{trans}$)), 0.13 (9H, s, 3 $CH_3$-(10)), 0.13 (9H, s, 3 $CH_3$-(10)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 201.4 (C($2^{trans}$)), 200.5 (C($2^{cis}$)), 166.6 (C($12^{trans}$)), 166.4 (C($12^{cis}$)), 160.3 (C($5^{cis}$)), 159.9 (C($5^{trans}$)), 117.5 (C($11^{trans}$)), 116.7 (C($11^{cis}$)), 106.3 (C($8^{cis}$)), 105.3 (C($8^{trans}$)), 86.4 (C($9^{trans}$)), 85.7 (C($9^{cis}$)), 51.2 (2 C(13)), 42.7 (C($3^{trans}$)), 41.5 (C($3^{cis}$)), 37.4 (C($6^{trans}$)), 31.2 (C($6^{cis}$)), 31.0 (C($4^{cis}$)), 24.9 (C($4^{trans}$)), 19.3 (C($7^{cis}$)), 18.7 (C($7^{trans}$)), 0.2 (3 C(10)), 0.1 (3 C(10)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2956, 2175, 1718 (s, C=O), 1647 (m), 1435, 1249 (w), 1173 (m), 843 (s); ***m/z*** ($ESI^+$) 321.2 ([M+MeOH+Na]$^+$, 100%); **HRMS** ($ESI^+$) found 289.1231, $C_{14}H_{22}O_3{}^{23}Na^{28}Si^+$ requires 289.1230.

### Methyl 3-(4-(trimethylsilyl)but-3-yn-1-yl)octa-2,7-dienoate (2.57)

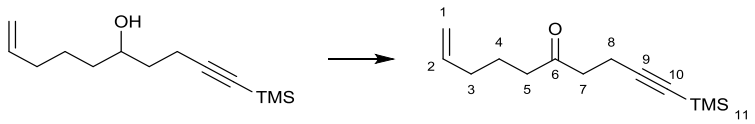



According to the modified procedure of Inui *et al*.[123] To a dried (heat gun under high vacuum) 500 mL flask charged with sodium hydride (60% in mineral oil, 1.0 g, 25.2 mmol, 3.0 eq.) and dry THF (*ca.* 250 mL) was added dropwise trimethyl phosphonoacetate (4.1 mL, 25.2 mmol, 3.0 eq.) at room temperature. The foamy mixture was stirred for 45 min before 1-(trimethylsilyl)dec-9-en-1-yn-5-one **2.58** (1.87 g, 8.4 mmol, 1.0 eq.) was added quickly (< 10 s) as a solution in THF (5 mL) at room temperature. The reaction was heated to 50 °C for 3 d and gave a complete conversion (TLC, 5% $Et_2O$ in $PE_{30\text{-}40}$). The reaction was quenched with addition of $NH_4Cl_{(aq)}$ (sat. sol., 70 mL). The layers were separated and the aqueous phase was extracted with $Et_2O$ (3x150 mL). The combined organic layers were washed with brine (2 x), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to

give a biphasic crude (assumed to be phosphonate and product). Purification by flash-chromatography (both phases together, eluent: 0% to 5% $Et_2O$ in $PE_{30-40}$) afforded the title product as a mixture of *E/Z* alkenes (1:1 ratio) as a yellowish liquid (2.18 g, 7.83 mmol, 93%).

Analysed as a *E/Z* mixture (1:1 ratio): $\mathbf{R_f}$ 0.54 (5% $Et_2O$ in $PE_{30-40}$, $UV_{254\ nm}$, $KMnO_4$); $\mathbf{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.83 (1H, ddt, *J*=17.0, 10.3, 6.7 Hz, CH-($2^{trans}$)), 5.79 (1H, ddt, *J*=17.0, 10.3, 6.7 Hz, CH-($2^{cis}$)), 5.69 (1H, t, *J*=1.4 Hz, CH-($12^{cis}$)), 5.68 (1H, s, CH-($12^{trans}$)), 5.02 (2H, dq, *J*=17.2, 1.7 Hz, 2 $CH_a$-(1)), 4.98 (1H, ddt, *J*=7.7, 2.2, 1.2 Hz, $CH_b$-(1)), 4.96 (1H, ddt, *J*=7.8, 2.2, 1.2 Hz, $CH_b$-(1)), 3.71 – 3.66 (6H, m, 2 $CH_3$-(14)), 2.80 (2H, t, *J*=7.4 Hz, $CH_2$-($7^{cis}$)), 2.65 – 2.58 (2H, m, $CH_2$-($5^{trans}$)), 2.43 (2H, t, *J*=7.3 Hz, $CH_2$-($8^{cis}$)), 2.37 (4H, d, *J*=1.7 Hz, $CH_2$-($7^{trans}$), $CH_2$-($8^{trans}$)), 2.28 – 2.22 (2H, m, $CH_2$-($5^{cis}$)), 2.11 (2H, qt, *J*=7.3, 1.2 Hz, $CH_2$-($3^{trans}$)), 2.07 (2H, qt, *J*=7.3, 1.2 Hz, $CH_2$-($3^{cis}$)), 1.63 – 1.50 (4H, m, 2 $CH_2$-(4)), 0.14 (9H, s, 3 $CH_3$-(11)), 0.13 (9H, s, 3 $CH_2$-(11)); $\mathbf{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 166.8 (C($13^{trans}$)), 166.8 (C($13^{cis}$)), 162.7 (C($6^{cis}$)), 162.0 (C($6^{trans}$)), 138.5 (C($2^{trans}$)), 138.2 (C($2^{cis}$)), 116.2 (C($12^{trans}$)), 116.1 (C($12^{cis}$)), 115.3 (C($1^{cis}$)), 114.9 (C($1^{trans}$)), 106.6 (C($9^{cis}$)), 105.8 (C($9^{trans}$)), 86.0 (C($10^{trans}$)), 85.3 (C($10^{cis}$)), 51.1 (C(14)), 51.0 (C(14)), 38.4 (C($5^{cis}$)), 37.2 (C($7^{trans}$)), 34.1 (C($3^{trans}$)), 33.4 (C($3^{cis}$)), 31.7 (C($5^{trans}$)), 31.1 (C($7^{cis}$)), 27.9 (C($4^{trans}$)), 26.8 (C($4^{cis}$)), 19.3 (C($8^{cis}$)), 18.8 (C($8^{trans}$)), 0.2 (3 C($11^{cis}$)), 0.2 (3 C($11^{trans}$)); $\mathbf{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2951, 2176 (m), 1719 (s, c=O), 1643, 1435, 1249, 1225, 1190, 1169, 1149, 1042, 913, 840 (s), 760; ***m/z*** ($ESI^+$) 279.1 ($[M+H]^+$, 100%), 301.2 ($[M+Na]^+$, 60%); **HRMS** ($ESI^+$) found 279.1777, $C_{16}H_{27}O_2{}^{28}Si^+$ requires 279.1777.

### 1-(Trimethylsilyl)dec-9-en-1-yn-5-one (2.58)

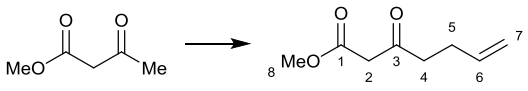



According to the modified procedures of Hötling *et al*.[121] A dried (heat gun under $N_2$ flow) 250 mL 3-necked flask charged with dry $CH_2Cl_2$ (ca. 100 mL) and dry DMSO (1.5 mL, 20.1 mmol, 2.2 eq.) was cooled to -78 °C before neat oxalyl chloride (0.9 mL, 10.5 mmol, 1.1 eq.) was added slowly (bubbling occurred) and stirred for 30 min. Neat 1-(trimethylsilyl)dec-9-en-1-yn-5-ol **2.78** (2.15 g, 9.6 mmol,

1.0 eq.) was then slowly added and stirred for 60 min. $Et_3N$ (6.6 mL, 47.9 mmol, 5.0 eq.) was added quickly (< 1 min) and then the acetone/dry ice bath was removed and the reaction was allowed to warm to room temperature. TLC (20% $Et_2O$ in $PE_{30\text{-}40}$) after 30 min showed no remaining starting material. The reaction was quenched with water (40 mL) and the layers were separated. The aqueous phase was extracted with $CH_2Cl_2$ (4x 15 mL). Combined organic layers were dried ($Na_2SO_4$), filtered and concentrated. Purification by flash-chromatography (eluent: 15% to 20% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title compound as a yellow liquid (1.89 g, 8.5 mmol, 89%).

**$R_f$** 0.69 (20% $Et_2O$ in $PE_{30\text{-}40}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.76 (1H, ddt, *J*=17.0, 10.2, 6.7 Hz, CH-(2)), 5.01 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-(1)), 4.97 (1H, dq, *J*=10.3, 2.2, 1.2 Hz, $CH_b$-(1)), 2.63 (2H, dd, *J*=8.7, 6.5 Hz, $CH_2$-(7)), 2.49 – 2.45 (2H, m, $CH_2$-(8)), 2.43 (2H, t, *J*=7.4 Hz, $CH_2$-(5)), 2.06 (2H, qt, *J*=6.6, 1.4 Hz, $CH_2$-(3)), 1.69 (2H, p, *J*=7.4 Hz, $CH_2$-(4)), 0.13 (9H, s, 3 $CH_3$-(11)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 208.8 (C(6)), 138.0 (C(2)), 115.4 (C(1)), 105.9 (C(9)), 85.2 (C(10)), 42.1 (C(5)), 41.7 (C(7)), 33.2 (C(3)), 22.9 (C(4)), 14.6 (C(8)), 0.2 (C(11)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2958, 2177 (m), 1716 (s, C=O), 1411, 1368, 1250 (m), 913, 840 (s), 760; ***m/z*** ($ESI^+$) 245.2 ($[M+Na]^+$, 100%), 223.2 ($[M+H]^+$, 60%); **HRMS** ($ESI^+$) found 245.1333, $C_{13}H_{22}O^{23}Na^{28}Si^+$ requires 245.1332.

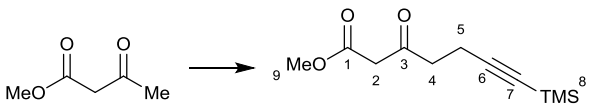
### Methyl 3-oxohept-6-enoate (2.63)




Prepared according to general procedure GP1 using NaH (60% in mineral oil, 6.43 g, 160.9 mmol, 1.25 eq.), methyl acetoacetate (13.9 mL, 128.9 mmol, 1.0 eq.), *n*-BuLi solution (2.50 M in hexane, 57 mL, 141.6 mmol, 1.1 eq.) and allyl bromide (11.1 mL, 128.9 mmol, 1.0 eq.). Reaction was stirred at 0 °C for 2.5 h before being quenched. Purification by flash-chromatography (eluent: 0% to 15% to 25% (500 mL each) $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 6.5 cm, L = 7 cm) afforded the title product as a yellow liquid (15.6 g, 99.9 mmol, 77%).

Analysed as the keto/enol mixture (~1:0.1 ratio): **$R_f$** 0.59 (35% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\,nm}$ and $KMnO_4$); **keto form (major): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.78 (1H, ddt, *J*=16.7, 10.2, 6.5 Hz, CH-(6)), 5.03 (1H, dq, *J*=17.2, 1.7 Hz, $CH_a$-(7)), 4.98 (1H, dq, *J*=9.3, 1.4 Hz, $CH_b$-(7)), 3.72 (3H, s, $CH_3$-(8)), 3.44 (2H, s, $CH_2$-(2)), 2.63 (2H, t, *J*=7.3 Hz, $CH_2$-(4)), 2.33 (2H, tdt, *J*=7.3, 6.5, 1.5 Hz, $CH_2$-(5)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 202.0 (C(3)), 167.7 (C(1)), 136.6 (C(6)), 115.7 (C(7)), 52.5 (C(8)), 49.2 (C(2)), 42.2 (C(4)), 27.5 (C(5)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 1746 (s, C=O), 1716 (s, C=O), 1437, 1408, 1319, 1270, 1255, 1202, 1158; ***m/z*** ($ESI^+$) 179.0 ($[M+Na]^+$, 100%). Data in accordance with literature.[179]

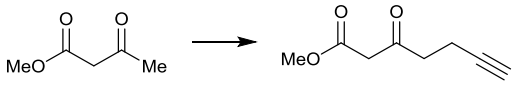
### Methyl 3-oxo-7-(trimethylsilyl)hept-6-ynoatedienoate (2.65)




Prepared according to general procedure GP1 using NaH (60% in mineral oil, 4.3 g, 107.3 mmol, 1.25 eq.), methyl acetoacetate **2.62** (9.3 mL, 116.2 mmol, 1.0 eq.), *n*-BuLi solution (1.49 M in hexane, 63 mL, 94.4 mmol, 1.1 eq.) and (3-bromoprop-1-yn-1-yl)trimethylsilane **2.68** (16.4 g, 85.8 mmol, 1.0 eq.) Reaction was stirred at 0 °C for 2 h before being quenched. Purification by flash-chromatography (eluent: 20% $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 7 cm, L = 11 cm) afforded the title product as a yellow liquid (16.0 g, 70.8 mmol, 83%).

Analysed as the keto/enol mixture (~1:0.1 ratio): **$R_f$** 0.65 (35% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\,nm}$ and $KMnO_4$); **keto form (major): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 3.73 (3H, s, $CH_3$-(9)), 3.47 (2H, s, $CH_2$-(2)), 2.81 – 2.75 (2H, m, $CH_2$-(4)), 2.52 – 2.46 (2H, m, $CH_2$-(5)), 0.12 (9H, s, 3 $CH_2$-(8)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 200.7 (C(3)), 167.5 (C(1)), 105.1 (C(6)), 85.6 (C(7)), 52.5 (C(9)), 49.1 (C(2)), 42.0 (C(4)), 14.5 (C(5)), 0.2 (C(8)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2958, 2177 (m, C≡C), 1750 (s, C=O), 1720 (s, C=O), 1322, 1250 (m), 843 (s); ***m/z*** ($ESI^+$) 249.0 ($[M+Na]^+$, 100%), 227.2 ($[M+H]^+$, 8%); **HRMS** ($ESI^+$) found 249.0917, $C_{11}H_{18}O_3{}^{23}Na^{28}Si^+$ requires 249.0917.

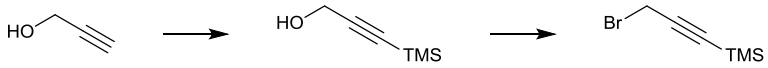
### Methyl 3-oxohept-6-ynoate (2.66)




Prepared according to general procedure GP1 using NaH (60% in mineral oil, 1.0 g, 25.1 mmol, 1.25 eq.), methyl acetoacetate (2.17 mL, 20.1 mmol, 1.00 eq.), *n*-BuLi solution (1.47 M in hexane, 15.0 mL, 22.1 mmol, 1.10 eq.), propargyl bromide (80% w/w in toluene, 22.1 mmol, 1.10 eq.) diluted in dry THF (5 mL). The reaction was stirred at 0 °C for 2 h before being quenched. Purification by flash-chromatography (eluent: 100% $PE_{40\text{-}60}$ (200 mL) to start then 25% $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 5 cm, L = 9 cm) afforded the title product as a yellow liquid (1.20 g, 7.8 mmol, 39%).

Analysed as the keto/enol mixture (~1:0.1 ratio): $\mathbf{R_f}$ 0.51 (50% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\ nm}$ and vanillin); **keto form (major):** $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) δ 3.75 (3H, s), 3.49 (2H, s), 2.81 (2H, t, *J*=7.2 Hz), 2.48 (2H, td, *J*=7.2, 2.7 Hz), 1.96 (1H, t, *J*=2.7 Hz)z; $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 200.5, 167.5, 82.6, 69.2, 52.6, 49.1, 41.8, 13.0; $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 3287 (m, C≡C-H), 1742 (s, C=O), 1716 (s, C=O), 1437, 1408, 1320, 1275, 1197, 1134, 1084, 1022; ***m/z*** ($ESI^+$) 177.0 ($[M+Na]^+$, 100%). Data is consistent with literature.[180]

### (3-Bromoprop-1-yn-1-yl)trimethylsilane (2.68)




According to the modified procedure of Kolundžić *et al*.[181]

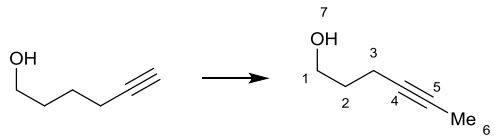
Step 1: In a flame-dried 1 L triple-necked flask equipped with an addition funnel and $N_2$ inlet was added *n*-butyllithium (1.48 M in hexane, 240 mL, 355 mmol, 2.05 eq., *via* addition funnel) over 30 min to a cooled (-78 °C) mixture of propargyl alcohol (10.0 mL, 171 mmol, 1.0 eq.) in dry THF (200 mL). After 2 h at -78 °C, neat TMSCl (45 mL, 355 mmol, 2.05 eq.) was added over 6 min to the white suspension. The cold bath was removed once it stopped bubbling and the reaction was

allowed to warm to room temperature. (Because of a very thick suspension formed, manual swirling of the flask was sometimes necessary at that point if the stirrer bar was not correctly chosen). After 1 h at r.t., the reaction was quench by addition of $HCl_{(aq)}$ (2 M sol., 200 mL) and the resulting biphasic mixture was stirred overnight. Careful neutralisation with solid $NaHCO_3$ was followed by layer separation. The aqueous phase was extracted with $Et_2O$ (3x 200 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure (40 mbar, ~25 °C bath) to afford crude 3-(trimethylsilyl)prop-2-yn-1-ol (24 g) that was used without purification.

Step 2: In a flame-dried 250 mL flask was dissolved crude 3-(trimethylsilyl)prop-2-yn-1-ol (24 g) in dry $Et_2O$ (130 mL) under $N_2$. $PBr_3$ (5.6 mL, 60 mmol, 0.35 eq.) was added and the reaction mixture was stirred overnight at r.t.. Quenching with $NaHCO_{3(aq)}$ (sat. sol.) was followed by layer separation. The aqueous phase was extracted with $Et_2O$ (3x200 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure (60 mbar, ~25 °C bath) to afford a liquid crude. Purification by flash-chromatography (eluent: 100% pentane; column size: Ø = 10 cm, L = 10 cm) afforded the title product as a colourless liquid (25.75 g, 135 mmol, 79% over 2 steps).

**$R_f$** 0.83 (35% $Et_2O$ in $PE_{30\text{-}40}$, $KMnO_4$, vanillin); **$\delta_H$** /ppm (400 MHz, $CDCl_3$) 3.91 (2H, s), 0.18 (9H, s). Data were identical to commercial material.

### Hex-4-yn-1-ol (2.70)

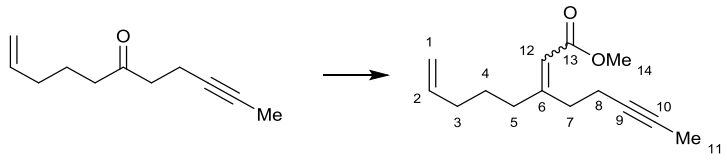



According to the modified procedures of Hötling *et al*.[121] In an oven-dried 50 mL flask; to a solution of 5-hexyn-1-ol (1.0 g, 10.2 mmol, 1.0 eq.) in dry DMSO (30 mL) was added $^t$BuOK (2.3 g, 20.4 mmol, 2.0 eq.) in portions at room temperature. Stirring was continued for 4.5 h before being quenched at 0 °C with $HCl_{(aq)}$ (2 M sol.), water was added to dissolve the salts and the layers were separated. The

aqueous phase was extracted with $Et_2O$ (3x 50 mL). Combined organic layers were washed water (3x 25 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a yellow liquid. Purification by flash-chromatography (eluent: 75% $Et_2O$ in $PE_{30-40}$) afforded the title product as a yellow liquid (779 mg, 7.9 mmol, 78%).

**$R_f$** 0.30 (50% $Et_2O$ in $PE_{30-40}$, $KMnO_4$, slightly less polar than the SM); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 3318 (br s, OH), 2946 (m), 2920 (m) 2875 (w), 1436 (m) 1056 (s), 1036; **$\delta_H$**/ppm (400 MHz, $CDCl_3$) 3.75 (2H, q, *J*=6.1, 5.4 Hz, $CH_2$-(1)), 2.25 (2H, tq, *J*=6.8, 2.6 Hz, $CH_2$-(3)), 1.77 (3H, t, *J*=2.6 Hz, $CH_3$-(6)), 1.73 (2H, tt, *J*=7.0, 6.1 Hz, $CH_2$-(2)), 1.62 (1H, t, *J*=5.4 Hz, OH-(7)); **$\delta_C$** /ppm (101 MHz, $CDCl_3$) 78.6 (C(5)), 76.4 (C(4)), 62.2 (C(1)), 31.6 (C(2)), 15.5 (C(3)), 3.6 (C(6)). Spectroscopic data consistent with literature.[121]

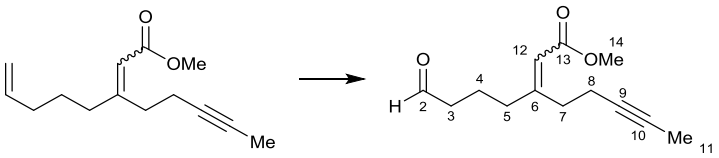
### Methyl 3-(pent-3-yn-1-yl)octa-2,7-dienoate (2.71)




According to the modified procedure of Inui *et al*.[123] To a dried (heat gun under high vacuum) 5 mL flask charged with sodium hydride (60% in mineral oil, 55 mg, 1.37 mmol, 4.5 eq.) and dry THF (1 mL) was added dropwise trimethyl phosphonoacetate **2.74** (0.22 mL, 1.37 mmol, 4.5 eq.) at room temperature. The foamy mixture was diluted with dry THF (2 mL) and stirred for 45 min before undec-1-en-9-yn-6-one **7.2** (50 mg, 0.30 mmol, 1.0 eq.) was added dropwise as a solution in THF (1 mL) at room temperature. Low conversion was observed after overnight stirring. The reaction was heated to 50 °C overnight and gave a complete conversion (TLC, 5% $Et_2O$ in $PE_{30-40}$). The reaction was quenched with addition of $NH_4Cl_{(aq)}$ (sat. sol., 2 mL). The layers were separated and the aqueous phase was extracted with a lot of $Et_2O$. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification by flash-chromatography (eluent: 5% $Et_2O$ in $PE_{30-40}$) afforded the title product as a mixture of E/Z alkenes (1:1 ratio) as a colourless liquid (58.8 mg, 0.27 mmol, 89%).

Analysed as a *E/Z* mixture (1:1 ratio): $\mathbf{R_f}$ 0.50 (5% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\ nm}$, $KMnO_4$); $\mathbf{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=16.9, 10.1, 6.6 Hz, CH-(2)), 5.79 (1H, ddt, *J*=16.9, 10.1, 6.6 Hz, CH-(2)), 5.68 (1H, t, *J*=1.3 Hz, CH-(12)), 5.67 (1H, t, *J*=1.3 Hz, CH-(12)), 5.02 (2H, dq, *J*=17.2, 1.7 Hz, 2 $CH_a$-(1)), 4.98 (1H, ddt, *J*=8.0, 2.4, 1.3 Hz, $CH_b$-(1)), 4.96 (1H, ddt, *J*=8.0, 2.4, 1.3 Hz, $CH_b$-(1)), 3.68 (6H, s, 2 $CH_3$-(14)), 2.77 (2H, t, *J*=7.5 Hz, $CH_2$-($7^{cis}$)), 2.64 – 2.59 (2H, m, $CH_2$-($5^{trans}$)), 2.36 – 2.26 (6H, m, $CH_2$-($7^{trans}$), 2 $CH_2$-(8)), 2.25 – 2.19 (2H, m, $CH_2$-($5^{cis}$)), 2.11 (2H, qt, *J*=7.2, 1.1 Hz, $CH_2$-(3)), 2.07 (2H, qt, *J*=7.4, 1.4 Hz, $CH_2$-(3)), 1.77 (3H, t, *J*=2.4 Hz, $CH_3$-(11)), 1.76 (3H, t, *J*=2.5 Hz, $CH_3$-(11)), 1.62 – 1.50 (4H, m, 2 $CH_2$-(4)); $\mathbf{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 166.9 (C(13)), 166.8 (C(13)), 162.8 (C(6)), 162.5 (C(6)), 138.6 (C(2)), 138.2 (C(2)), 116.0 (C(12)), 115.z9 (C(12)), 115.2 (C(1)), 114.9 (C(1)), 78.6 (C≡C), 77.9 (C≡C), 76.7 (C≡C), 76.3 (C≡C), 51.1 (C(14)), 51.0 (C(14)), 38.2 (C($5^{cis}$)), 37.6 (C ($7^{trans}$)), 34.1 (C(3)), 33.4 (C(3)), 31.8 (C($5^{trans}$)), 31.6 (C($7^{cis}$)), 27.9 (C(4)), 26.8 (C(4)), 18.2 (C(8)), 17.6 (C(8)), 3.6 (C(11)) 3.6 (C(11)); $\mathbf{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2921, 2862, 2175, 2040, 1719 (s, C=O), 1643 (m), 1435 (m), 1377, 1226, 1170 (m), 1150 (w); ***m/z*** ($ESI^+$) 243.2 ($[M+Na]^+$, 100%), 221.2 ($[M+H]^+$, 65%); **HRMS** ($ESI^+$) found 221.1539, $C_{14}H_{21}O_2^+$ requires 221.1536.

### Methyl 3-(4-oxobutyl)oct-2-en-6-ynoate (2.72)

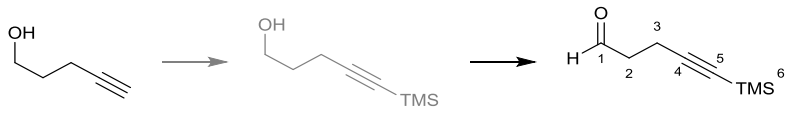



According to the modified procedure of Shen *et al*.[173] A 5 mL flask was charged (in this order) with methyl 3-(pent-3-yn-1-yl)octa-2,7-dienoate **2.71** (1:1 E/Z mix., 48.5 mg, 0.22 mmol, 1.0 eq.), 1,4-dioxane/water (3:1 v/v, 2.2 mL), 2,6-lutidine (51 µL, 0.44 mmol, 2.0 eq.), $OsO_4$ (2.5 wt% in $^tBuOH$, 45 mg, 4.4 µmol, 0.02 eq.) and $NaIO_4$ (188 mg, 0.88 mmol, 4.0 eq.). The resulting pink creamy suspension was stirred until completion was observed 45 min later by TLC (10% or 30% $Et_2O$ in $PE_{30\text{-}40}$). The reaction was quenched with addition of $Na_2S_2O_{3\ (aq)}$ (sat. sol., 0.25 mL). $CH_2Cl_2$ and water were added. The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$. The

combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification by flash-chromatography (eluent: 30% $Et_2O$ in $PE_{30-40}$) afforded the title product as a mixture of E/Z alkenes (1:1 ratio) as a yellow liquid (30.2 mg, 0.14 mmol, 62%).

Analysed as a *E/Z* mixture (1:1 ratio): $\mathbf{R_f}$ 0.44 (30% $Et_2O$ in $PE_{40-60}$, $UV_{254\,nm}$, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 9.79 (1H, t, *J*=1.5 Hz, CHO-(2)), 9.78 (1H, t, *J*=1.4 Hz, CHO-(2)), 5.72 (1H, d, *J*=1.4 Hz, CH-(12)), 5.70 – 5.67 (1H, m, CH-(12)), 3.69 (3H, s, $CH_3$-(14)), 3.69 (3H, s, $CH_3$-(14)), 2.76 (2H, t, *J*=7.4 Hz, $CH_2$-($7^{cis}$)), 2.66 – 2.61 (2H, m, $CH_2$-($5^{trans}$)), 2.50 (2H, td, *J*=7.3, 1.6 Hz, $CH_2$-(3)), 2.47 (2H, td, *J*=7.3, 1.6 Hz, $CH_2$-(3)), 2.33 (6H, m, $CH_2$-($7^{trans}$), 2 $CH_2$-(8)), 2.28 – 2.24 (2H, m, $CH_2$-($5^{cis}$)), 1.82 (4H, h, *J*=7.7 Hz, 2 $CH_2$-(4)), 1.76 (3H, t, *J*=2.4 Hz, $CH_3$-(11)), 1.75 (3H, t, *J*=2.7 Hz, $CH_3$-(11)); $\boldsymbol{\delta_C}$ /ppm (101 MHz, $CDCl_3$) 202.4 (C(2)), 201.7 (C(2)), 166.8 (C(13)), 166.6 (C(13)), 161.5 (C(6)), 161.3 (C(6)), 116.6 (2 C(12)), 78.4 (C≡C), 77.7 (C≡C), 77.4 (C≡C), 76.5 (C≡C), 51.1 (C(14)), 51.1 (C(14)), 43.6 (C(3)), 43.2 (C(3)), 37.9 (C($5^{cis}$)), 37.4 (C($7^{trans}$)), 31.4 (C($7^{cis}$)), 31.2 (C($5^{trans}$)), 20.9 (C(4)), 19.8 (C(4)), 18.2 (C(8)), 17.5 (C(8)), 3.6 (C(11)), 3.6 (C(11)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2950, 2921, 1717 (s , C=O), 1645 (m), 1435 (w), 1230, 1170 (s); ***m/z*** (Ammonia Cl) 223.1333 ($[M+H]^+$, 100%), 240.1599 ($[M+NH_4]^+$, 50%); **HRMS** (Ammonia Cl) found 223.1333, $C_{13}H_{19}O_3^+$ requires 223.1329.

### 5-(Trimethylsilyl)pent-4-ynal (2.76)




Step 1: According to the modified procedure of Palais *et al*.[182] An oven-dried 1 L flask equipped with an oven-dried addition funnel was charged with 4-pentyn-1-ol (11.1 mL, 119 mmol, 1.0 eq.) and dry THF (ca. 400 mL). under argon atmosphere and then cooled to -78 °C. n-BuLi solution (2.42 M in hexane, 109 mL, 2.6 mmol, 2.2 eq.) was then added via addition funnel over 25 min (yellow to orange clear solution obtained) and stirred for an additional 1 h 20 min. TMSCl (neat, 39 mL, 356 mmol, 3.0 eq.) was then slowly added via syringe over 15 min (exothermic, cloudy white mix

obtained). Once the acetone/dry ice bath stopped bubbling, the bath was removed and the reaction was allowed to warm to room temperature. TLC (25% $Et_2O$ in $PE_{30\text{-}40}$) after 2.5 h showed no remaining starting material. The reaction was quenched with $HCl_{(aq)}$ (2 M sol., 220 mL), stirred for 15 min and then the layers were separated. The aqueous phase was extracted with $Et_2O$ (3x 200 mL). Combined organic layers were washed twice with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a yellow liquid. Purification by flash-chromatography (eluent: 35% $Et_2O$ in $PE_{30\text{-}40}$) afforded the 5-(trimethylsilyl)pent-4-yn-1-ol intermediate as a yellow liquid (19 g, quant.).

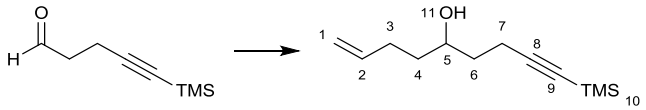
**$R_f$** 0.23 (25% $Et_2O$ in $PE_{30\text{-}40}$, $KMnO_4$). $^1H$ NMR is consistent with literature.[183]

Step2: According to the modified procedure of Hötling *et al*.[121] A dried (heat gun under $N_2$ flow) 2 L 3-necked flask charged with dry $CH_2Cl_2$ (*ca.* 1.0-1.2 L) and dry DMSO (18.5 mL, 257 mmol, 2.2 eq.) was cooled to -78 °C before neat oxalyl chloride (11.0 mL, 129 mmol, 1.1 eq.) was added slowly (bubbling occurred) and stirred for 40 min. Neat 5-(trimethylsilyl)pent-4-yn-1-ol intermediate (18.3 g, 117 mmol, 1.0 eq.) was then added over 10 min (cloudy white mix obtained) and stirred for 40 min. $Et_3N$ (*ca.* 81 mL, 585 mmol, 5.0 eq.) was added quickly (< 3 min) and then the acetone/dry ice bath was removed and the reaction was allowed to warm to room temperature. TLC (25% $Et_2O$ in $PE_{30\text{-}40}$) after 2 h showed no remaining starting material. The reaction was quenched with water (500 mL) and the layers were separated. The aqueous phase was extracted with $CH_2Cl_2$ (1x 300 mL, 2x 150 mL). Combined organic layers were washed with brine (200 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a yellow liquid. Purification by flash-chromatography (eluent: 15% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title compound as a yellow liquid (14.3 g, 93 mmol, 79%).

**$R_f$** 0.68 (25% $Et_2O$ in $PE_{30\text{-}40}$); **$\delta_H$** /ppm (400 MHz, $CDCl_3$) 9.78 (1H, t, J=1.2 Hz, CHO-(1)), 2.69 - 2.62 (2H, m, $CH_2$-(2)), 2.58 - 2.52 (2H, m, $CH_2$-(3)), 0.13 (9H, s, 3 $CH_3$-(6)); **$\delta_C$** /ppm (101 MHz, $CDCl_3$) 200.5 (C(1)), 104.8 (C(4)), 85.9 (C(5)), 42.6 (C(2)), 13.2 (C(3)), 0.1 (3 C(6)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2960 (w), 2177 (m), 1729 (m, C=O), 1250 (m), 842 (s), 760; ***m/z*** (Ammonia Cl) 155.0888 ($[M+H]^+$, 100%),

172.1152 ([M+$NH_4$]$^+$, 30%); **HRMS** (Ammonia Cl) found 155.0888, $C_8H_{15}O^{23}Na^{28}Si^+$ requires 154.0814. Spectroscopic data is consistent with literature.[121]

### 9-(Trimethylsilyl)non-1-en-8-yn-5-ol (2.77)



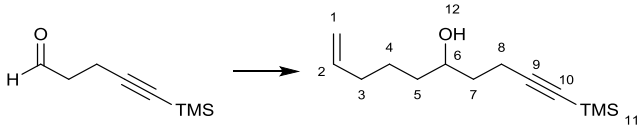

Grignard reagent prepared according to the modified procedure of Williams *et al*.[122] In an oven-dried double-necked flask equipped with a condenser was refluxed magnesium turnings (710 mg, 29.6 mmol, 1.2 eq.) and iodine (1 crystal) in dry $Et_2O$ (2.5 mL) under argon atmosphere until the brown colour disappeared (2 min). A solution of 4-bromo-1-butene (2.5 mL, 24.6 mmol, 1.0 eq.) in dry $Et_2O$ (7.5 mL) was added at a rate that maintained solvent refluxing. Upon complete addition, stirring was continued for 2 h at room temperature.

The Grignard reagent mixture was cooled to -78 °C and then a solution of 5-(trimethylsilyl)pent-4-ynal **2.76** (3.07 g, 19.7 mmol, 0.8 eq.) as a solution in dry THF (9 mL) was added dropwise (the mixture became thick and cloudy), The reaction was diluted with dry $Et_2O$ (10 mL). The reaction allowed warming up to room temperature (acetone/dry ice bath removed) and TLC (20% $Et_2O$ in $PE_{30\text{-}40}$) showed complete conversion after 1.5 h. The reaction was quenched with $NH_4Cl_{(aq)}$ (sat. sol., 8 mL), water (*ca.* 30 mL) was added to dissolve the salts, the layers were separated and the aqueous phase was extracted with $Et_2O$ (2x50 mL) and ethyl acetate (2x50 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated to a yellow oil. Purification by flash-chromatography (eluent: 20% $Et_2O$ in hexane) afforded the title product as a clear liquid (3.42g, 16.25 mmol, 82%).

$\mathbf{R}_f$ 0.29 (20% $Et_2O$ in hexane, $KMnO_4$); $\boldsymbol{\delta}_\mathbf{H}$ /ppm (500 MHz, $CDCl_3$) 5.83 (1H, ddt, *J*=16.9, 10.1, 6.6 Hz, CH-(2)), 5.05 (1H, dq, *J*=17.2, 1.7 Hz, $CH_a$-(1)), 4.97 (1H, dq, *J*=10.1, 1.8, 1.2 Hz, $CH_b$-(1)), 3.77 (1H, dddd, *J*=10.1, 8.5, 6.2, 4.7 Hz, CH-(5)), 2.40 – 2.32 (2H, m, $CH_2$-(7)), 2.27 – 2.08 (2H, m, $CH_2$-(3)), 1.87 (1H, d, *J*=4.7 Hz, OH-(11)), 1.69 (1H, dtd, *J*=14.5, 7.3, 3.5 Hz, $CH_a$-(6)), 1.66 – 1.59 (1H, m, $CH_b$-(6)),

1.56 (2H, td, *J*=8.0, 6.2 Hz, $CH_2$-(4)), 0.14 (9H, s, 3 $CH_3$-(10)); $\delta_C$ /ppm (126 MHz, $CDCl_3$) 138.5 (C(2)), 115.0 (C(1)), 107.1 (C(8)), 85.5 (C(9)), 70.8 (C(5)), 36.4 (C(6)), 35.8 (C(4)), 30.11 (C(3)), 16.7 (C(7)), 0.2 (3 C(10)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 3353 (br. s, OH), 2957, 2925, 2174, 1249, 1054, 911, 841 (s); ***m/z*** (Ammonia Cl) 211.1516 ($[M+H]^+$, 100%); **HRMS** ($ESI^+$) found 211.1516, $C_{12}H_{23}O^{28}Si^+$ requires 211.1513.

### 1-(Trimethylsilyl)dec-9-en-1-yn-5-ol (2.78)



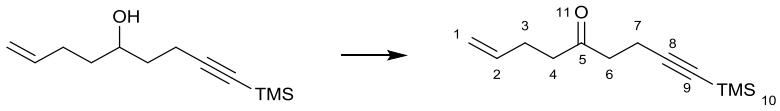

Grignard reagent prepared according to the modified procedure of Williams *et al*.[122] In an oven-dried 100 mL 3-necked flask equipped with a condenser was refluxed magnesium turnings (778 mg, 32.4 mmol, 2.5 eq.) and iodine (2 crystals) in dry $Et_2O$ (50 mL) under argon atmosphere until the brown colour disappeared (5-10 min). Neat 5-bromo-1-pentene (3.07 mL, 25.9 mmol, 2.0 eq.) was added at a rate that maintained solvent refluxing. Upon complete addition, refluxed was continued for an additional 10 min using a warm water bath and then 1 h at room temperature.

The Grignard mixture was cooled to -78 °C and then a solution of 5-(trimethylsilyl)pent-4-ynal **2.76** (2.00 g, 13.0 mmol, 1.0 eq.) as a solution in dry THF (20 mL) was added dropwise. The reaction was quenched after 5 h at -78 °C with $NH_4Cl_{(aq)}$ (sat. sol., 25 mL) at -78 °C. Once at r.t., the layers were separated and the aqueous phase was extracted with $Et_2O$. The combined organic layers were washed once with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to a yellow liquid. Purification by flash-chromatography (eluent: 20% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title product as a colourless liquid (2.15 g, 9.58 mmol, 74%).

$R_f$ 0.40 (20% $Et_2O$ in $PE_{40\text{-}60}$, $KMnO_4$); $\delta_H$ /ppm (500 MHz, $CDCl_3$) 5.80 (1H, ddt, *J*=17.0, 10.2, 6.6 Hz, CH-(2)), 5.01 (1H, dq, *J*=17.2, 1.7 Hz, $CH_a$-(1)), 4.95 (1H, ddt, *J*=10.2, 2.2, 1.3 Hz, $CH_b$-(1)), 3.74 (1H, ttd, *J*=9.5, 5.9, 3.2 Hz, CH-(6)), 2.36 (2H, td, *J*=7.0, 1.0 Hz, $CH_2$-(8)), 2.13 – 2.02 (2H, m, $CH_2$-(3)), 1.86 – 1.80

(1H, m, OH-(12)), 1.69 (1H, dtd, *J*=13.8, 7.3, 3.5 Hz, $CH_a$-(7)), 1.66 – 1.58 (1H, m, $CH_b$-(7)), 1.58 – 1.51 (1H, m, $CH_a$-(5)), 1.51 – 1.40 (3H, m, $CH_b$-(5), $CH_2$-(4)), 0.14 (9H, s, 3 $CH_3$-(11)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 138.8 (C(2)), 114.8 (C(1)), 107.2 (C(9)), 85.5 (C(10)), 71.2 (C(6)), 36.8 (C(4)), 35.9 (C(7)), 33.8 (C(3)), 25.0 (C(5)), 16.7 (C(8)), 0.2 (C(11)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 3329 (br. s, OH), 2931, 2861, 2174 (m), 1249 (m), 1054, 994, 911, 840 (s); ***m/z*** ($ESI^+$) 225.2 ($[M+H]^+$, 100%), 247.2 ($[M+Na]^+$, 50%); **HRMS** ($ESI^+$) found 247.1483, $C_{13}H_{24}O^{23}Na^{28}Si^+$ requires 247.1489.

### 9-(Trimethylsilyl)non-1-en-8-yn-5-one (2.79)

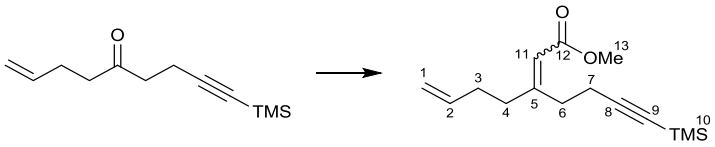



According to the modified procedures of Hötling *et al.*[121] A dried (heat gun under high vacuum) 500 mL 3-necked flask charged with dry $CH_2Cl_2$ (ca. 200 mL) and dry DMSO (2.6 mL, 35.6 mmol, 2.2 eq.) was cooled to -78 °C before neat oxalyl chloride (1.5 mL, 17.8 mmol, 1.1 eq.) was added slowly (bubbling occurred) and stirred for 40 min. Neat 9-(trimethylsilyl)non-1-en-8-yn-5-ol **2.77** (3.4 g, 16.2 mmol, 1.0 eq.) was then slowly added and stirred for 50 min. $Et_3N$ (11.9 mL, 80.8 mmol, 5.0 eq.) was added quickly (< 1 min). About 10 min later, the acetone/dry ice bath was removed and the reaction was allowed to warm to room temperature. TLC (20% $Et_2O$ in $PE_{30\text{-}40}$) after 40 min showed no remaining starting material. The reaction was quenched with water (20 mL) and the layers were separated. The aqueous phase was extracted with $CH_2Cl_2$ (4 x) and once $Et_2O$. Combined organic layers were washed once with water, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to a heterogeneous orange liquid crude. Purification by gravity-chromatography (eluent: 5% $Et_2O$ in $PE_{40\text{-}60}$) afforded the title compound as a yellowish liquid (2.9 g, 13.87 mmol, 86%).

$\boldsymbol{R_f}$ 0.58 (5% ethyl acetate in hexane, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.80 (1H, ddt, *J*=16.7, 10.2, 6.5 Hz, CH-(2)), 5.03 (1H, dq, *J*=17.2, 1.7 Hz, $CH_a$-(1)), 4.98 (1H, dq, *J*=10.1, 1.3 Hz, $CH_b$-(1)), 2.64 (2H,

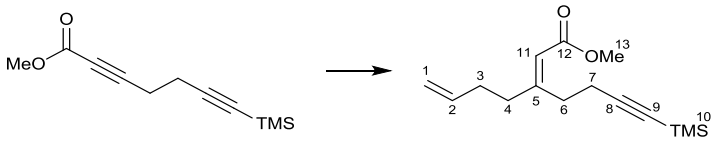
dd, *J*=8.4, 6.2 Hz, $CH_2$-(6)), 2.53 (2H, t, *J*=7.4 Hz, $CH_2$-(4)), 2.48 (2H, dd, *J*=8.2, 6.3 Hz, $CH_2$-(7)), 2.33 (2H, dtt, *J*=8.7, 7.3, 1.5 Hz, $CH_2$-(3)), 0.13 (9H, s, 3 $CH_3$-(10)); $\delta_C$ /ppm (126 MHz, $CDCl_3$) 208.1 (C(5)), 137.0 (C(2)), 115.5 (C(1)), 105.8 (C(8)), 85.27 (C(9)), 42.1 (C(4)), 41.7 (C(6)), 27.8 (C(3)), 14.6 (C(7)), 0.2 (3 C(10)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2960 (w), 2177 (m), 1717 (s, C=O), 1411, 1365, 1250 (m), 914, 841 (s); ***m/z*** (Ammonia Cl) 209.1358 ($[M+H]^+$, 100%); **HRMS** ($ESI^+$) found 209.1358, $C_{12}H_{21}O^{28}Si^+$ requires 209.1356.

### Methyl 3-(4-(trimethylsilyl)but-3-yn-1-yl)hepta-2,6-dienoate (2.80)




**Method 1** (from ketone **2.79**)**:** Mix of isomer: According to the modified procedure of Inui *et al*.[123] To a dried (heat gun under high vacuum) 250 mL flask charged with sodium hydride (60% in mineral oil, 576 mg, 14.40 mmol, 3.0 eq.) and dry THF (*ca.* 150 mL) was added dropwise a solution of trimethyl phosphonoacetate (2.3 mL, 14.40 mmol, 3.0 eq.) in dry THF (20 mL)at room temperature. Stirring was continued for 1.5 h before 9-(trimethylsilyl)non-1-en-8-yn-5-one **2.79** (1.00 g, 4.80 mmol, 1.0 eq.) was added dropwise as a solution in dry THF (5 mL) at room temperature. The reaction was heated to 50 °C for 25 h and gave a complete conversion (TLC, 5% $Et_2O$ in $PE_{30\text{-}40}$). The reaction was quenched with addition of $NH_4Cl_{(aq)}$ (sat. sol., 20 mL). The layers were separated and the aqueous phase was extracted with $Et_2O$ (3x 100 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to give a biphasic crude (assumed to be phosphonate and product). Purification by flash-chromatography (both phases together, eluent: 5% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title product as a mixture of *E/Z* alkenes (1:1 ratio) as a colourless liquid (1.05 g, 3.97 mmol, 89%).

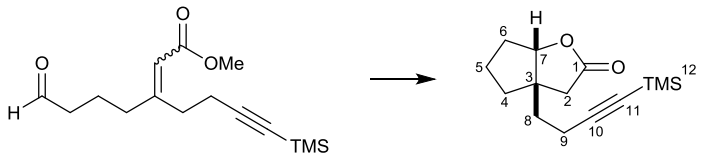
Analysed as a *E/Z* mixture (1:1 ratio): $\mathbf{R_f}$ 0.51 (5% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\ nm}$, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.83 (1H, ddt, *J*=16.8, 10.2, 6.8 Hz, CH-(2)), 5.78 (1H, ddt, *J*=16.5, 10.5, 6.5 Hz, CH-(2)), 5.68 (1H, s, CH-(11)), 5.68 (1H, s, CH-(11)), 5.04 (2H, dp, *J*=17.2, 1.7 Hz, 2 $CH_a$-(1)), 4.99 (1H, dq, *J*=10.2, 1.4 Hz, $CH_b$-(1)), 4.96 (1H, ddt, *J*=10.1, 2.0, 1.2 Hz, $CH_b$-(1)), 3.67 (3H, s, $CH_3$-(13)), 3.67 (3H, s, $CH_3$-(13)), 2.80 (2H, t, *J*=7.3 Hz, $CH_2$-($6^{cis}$)), 2.73 – 2.67 (2H, m, $CH_2$-($4^{trans}$)), 2.43 (2H, t, *J*=7.3 Hz, $CH_2$-($7^{cis}$)), 2.40 – 2.31 (6H, m, $CH_2$-($4^{cis}$), $CH_2$-($6^{trans}$), $CH_2$-($7^{trans}$)), 2.22 (4H, dtdd, *J*=7.9, 6.6, 5.0, 1.3 Hz, 2 $CH_2$-(3)), 0.13 (9H, s, 3 $CH_3$-(10)), 0.12 (9H, s, 3 $CH_3$-(10)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 166.7 (C(12)), 166.7 (C(12)), 162.0 (C(5)), 161.2 (C(5)), 137.9 (C(2)), 137.3 (C(2)), 116.5 (C(11)), 116.3 (C(11)), 115.5 (C(1)), 115.1 (C(1)), 106.6 (C(8)), 105.7 (C(8)), 86.0 (C(9)), 85.3 (C(9)), 51.0 (C(13)), 51.0 (C(13)), 38.2 (C($4^{cis}$)), 37.2 (C($6^{trans}$)), 32.7 (C(3)), 31.6 (C(3)), 31.5 (C($4^{trans}$)), 31.1 (C($6^{cis}$)), 19.2 (C($7^{cis}$)), 18.7 (C($7^{trans}$)), 0.2 (3 C(10)), 0.1 (3 C(10)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2954, 2176 (w), 1718 (s), 1643 (m), 1434, 1249, 1170, 1041, 839 (s); ***m/z*** ($ESI^+$) 287.1 ($[M+Na]^+$, 100%), 265.2 ($[M+H]^+$, 15%); **HRMS** ($ESI^+$) found 287.1437, $C_{15}H_{24}O_2{}^{23}Na^{28}Si^+$ requires 287.1438.



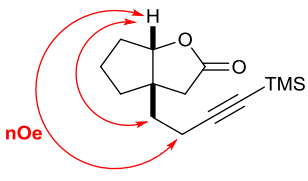

**Method 2** (from alkyne **3.8**): To a flame-dried 5 mL pear-shaped flask containing CuI (52.0 mg, 0.27 mmol, 1.2 eq.) and dry THF (0.4 mL) and dry TMEDA (stored over KOH, 0.1 mL, 0.66 mmol, 3.0 eq.) cooled to -40/-50 °C (dry ice in acetone) was added dropwise but-3-en-1-ylmagnesium bromide (2 M in $Et_2O$, 0.13 mL, 0.27 mmol, 1.2 eq.). The resulting mixture was stirred for 40 min and then cooled further to -78 °C. Methyl 7-(trimethylsilyl)hepta-2,6-diynoate **3.8** (46.1 mg, 0.22 mmol, 1.0 eq.) in dry THF (0.3 mL) was added dropwise and stirred for 4.5 h before the reaction was quenched at -78 °C with cold (-78 °C) MeOH (ca. 2 mL). The reaction flask was opened and water (1 mL) was added (blue mixture observed) followed by $NH_4Cl_{(aq)}$ (sat. sol., 1 mL). Extraction with EtOAc (5x 10 mL) and concentration of the combined organic layers provided the crude mixture. Purification by flash-chromatography (eluent: 5% $Et_2O$ in $PE_{30\text{-}40}$, column size: Ø = 1 cm, L = 12 cm)

afforded 22.3 mg of the title product as pure *Z* alkene as a mixture with remaining starting material **3.8** (65% pure product by weight, 14.4 mg, 0.05 mmol, 25% yield, 29% brsm).

### (3*aR**,6*aS**)-3a-(4-(Trimethylsilyl)but-3-yn-1-yl)hexahydro-2*H*-cyclopenta[*b*]furan-2-one (2.81)



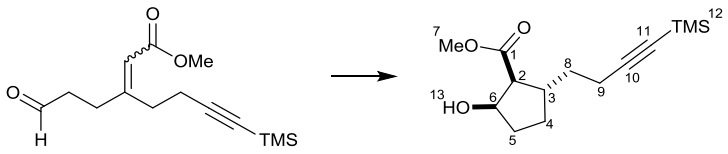

According to the modified procedure of Inui *et al*.[123] A flame-dried 25 mL round-bottomed flask was charged with methyl 3-(4-oxobutyl)-7-(trimethylsilyl)hept-2-en-6-ynoate **2.34** (50.0 mg, 0.18 mmol, 1.0 eq.), wet *t*-BuOH (34 µL, 0.36 mmol, 2.0 eq.) and dry THF (8.6 mL). The mixture was degassed (3 freeze-pump-thaw cycles, $N_2$ used to refill) and cooled to 0 °C. $SmI_2$ (1 M solution in THF, 7.1 mL, 0.71 mmol, 4.0 eq.) was slowly added to the reaction. The first drops were consumed to give a colourless solution then turned dark blue. Electrical PVC tape was added on the Suba-Seal® septa to limit the possible entry of oxygen in the reaction flask. The reaction was kept at 0 °C for at least 1 h and then the ice was allowed to melt overnight. After 16 h, the reaction (greenish-blue colour) was quenched with a 4:1 mixture of sat. $NaHCO_{3(aq)}$/sat. $Na_2S_2O_{3(aq)}$ (2 mL), diluted with water (4 mL) and extracted EtOAc (3x 10 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a yellow oil. Purification by flash-chromatography (eluent: 30% $Et_2O$ in $PE_{40\text{-}60}$) afforded the title product as colourless liquid (27.0 mg, 0.11 mmol, 60%).



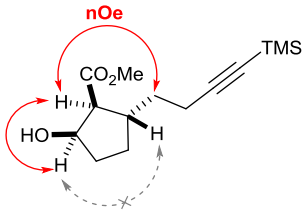

$\mathbf{R_f}$ 0.46 (100% $CH_2Cl_2$, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 4.63 – 4.60 (1H, m, CH-(7)), 2.70 (1H, d, *J*=18.4 Hz, $CH_a$-(2)), 2.44 (1H, d, *J*=18.3 Hz, $CH_b$-(2)), 2.36 – 2.20 (2H, m, $CH_2$-(9)), 2.06 – 1.97 (1H, m, $CH_a$-(6)), 1.83 (1H, ddd, *J*=13.7, 8.7, 6.8 Hz, $CH_a$-(8)), 1.78 – 1.59 (6H, m, $CH_2$-(4), $CH_2$-(5), $CH_b$-(6), $CH_b$-(8)), 0.14 (9H, s, 3 $CH_3$-(12)); $\boldsymbol{\delta_C}$ /ppm (101 MHz, $CDCl_3$) 176.9 (C(1)), 106.0 (C(10)), 91.0 (C(7)), 85.9 (C(11)), 49.9 (C(3)), 41.2 (C(2)), 38.5 (C(4)), 38.1 (C(8)), 32.9 (C(6)), 23.8 (C(5)), 16.5 (C(9)), 0.1 (3 C(12)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film,

$CDCl_3$) 2958, 2175 (w, C≡C), 1772 (s, C=O), 1249 (w), 1180 (m), 1036, 989, 963, 829 (s), 759; ***m/z*** ($ESI^+$) 273.1 ([M+Na]$^+$, 100%); **HRMS** ($ESI^+$) found 273.1283, $C_{14}H_{22}O_2{}^{23}Na^{28}Si^+$ requires 273.1281.

### Methyl (1*S**,2*R**,5*R**)-2-hydroxy-5-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopentane-1-carboxylate (2.82)



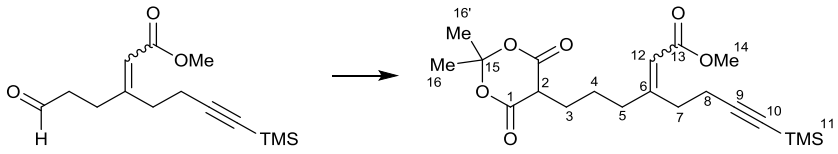

According to the modified procedure of Inui *et al.*[123] A flame-dried 25 mL round-bottomed flask was charged with methyl 3-(3-oxopropyl)-7-(trimethylsilyl)hept-2-en-6-ynoate **2.55** (47.4 mg, 0.18 mmol, 1.0 eq.), wet $^t$BuOH (34 µL, 0.36 mmol, 2.0 eq.) and dry THF (8.6 mL). The mixture was degassed (3 freeze-pump-thaw cycles, $N_2$ used to refill) and cooled to 0 °C. $SmI_2$ (1 M solution in THF, 7.1 mL, 0.71 mmol, 4.0 eq.) was slowly added to the reaction. The first drops were consumed to give a colourless solution then turned dark blue. Electrical PVC tape was added on the Suba-Seal® septa to limit the possible entry of oxygen in the reaction flask. The reaction was kept at 0 °C for at least 1 h and then the ice was allowed to melt overnight. After 16 h, the reaction (dark blue colour) was quenched with air (bubbled through until yellow clear mixture was obtained), diluted with water and extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification by flash-chromatography (eluent: 10% EtOAc in $CH_2Cl_2$) afforded the title product as colourless oil (8.2 mg, 0.03 mmol, 17%).




**$R_f$** 0.44 (10% EtOAc in $CH_2Cl_2$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (400 MHz, $CDCl_3$) 4.42 (1H, tt, *J*=5.0, 2.4 Hz, CH-(3)), 3.74 (2H, s, $CH_3$-(12)), 3.04 – 2.96 (1H, m, OH-(13)), 2.52 – 2.41 (1H, m, CH-(6)), 2.40 (1H, dd, *J*=10.1, 4.7 Hz, CH-(2)), 2.28 (1H, ddd, *J*=17.0, 9.0, 6.0 Hz, $CH_a$-(8)), 2.21 (1H, ddd, *J*=17.0, 8.8, 6.7 Hz, $CH_b$-(8)), 2.13 (1H, dtd, *J*=12.9, 8.5, 6.7 Hz, $CH_a$-(5)), 1.92 – 1.80 (2H, m, $CH_a$-(4), $CH_a$-(7)), 1.76 (1H, dddd, *J*=13.7, 8.4, 5.7, 2.8 Hz, $CH_b$-(4)), 1.50 (1H, dtd, *J*=13.2, 9.0, 6.0 Hz, $CH_b$-(7)), 1.29 (1H, dddd, *J*=13.1, 9.6, 7.6, 5.7 Hz, $CH_b$-(5)), 0.14 (9H, s, 3 $CH_3$-(11)); **$\delta_C$** /ppm (126 MHz,

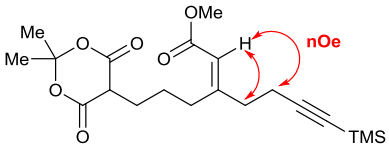
$CDCl_3$) 175.1 (C(1)), 107.1 (C(10)), 84.8 (C(9)), 74.5 (C(3)), 55.3 (C(2)), 52.0 (C(12)), 40.4 (C(6)), 34.6 (C(7)), 33.8 (C(4)), 29.0 (C(5)), 18.8 (C(8)), 0.3 (3 C(11)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 3470 (br s, OH), 2955, 2176 (w, C≡C), 1720 (s, C=O), 1437 (w), 1249, 1202, 1164 (w), 1037 (m), 842 (s); ***m/z*** (Ammonia Cl) 269.1557 ($[M+H]^+$, 100%); **HRMS** (Ammonia Cl) found 269.1557, $C_{14}H_{25}O_3{}^{28}Si^+$ requires 269.1567.

### Methyl 3-(3-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)propyl)-7-(trimethylsilyl)hept-2-en-6-ynoate (3.3)




According to the modified procedure of Snider *et al.*[125] In a dried pear-shaped 10 mL were added methyl 3-(3-oxopropyl)-7-(trimethylsilyl)hept-2-en-6-ynoate **2.55** (1:1 *E*/*Z* mix., 1.90 g, 7.13 mmol, 1.0 eq.), dry ethanol (10 mL), Meldum's acid **3.4** (1.54 g, 10.70 mmol, 1.50 eq.) and ethylenediamine diacetate (321 mg, 1.78 mmol, 0.25 eq.). The mixture was stirred for 55 min at room temperature before borane dimethylamine complex (420 mg, 7.13 mmol, 1.0 eq.) were added. Bubbling was observed. The reaction was quench after 1 h 15 min with $HCl_{(aq)}$ (1 M sol., 12 mL) then water was added to dissolve the salts then extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a yellow sticky liquid (3.7 g). Purification by flash-chromatography (eluent: 50% $Et_2O$ in $PE_{40\text{-}60}$; column size: Ø = 5.5 cm, L = 6.5 cm) afforded the title product as a mixture of *E/Z* alkenes (55:45 *E*/*Z* mix. ratio) as colourless liquid (1.58 g, 4.00 mmol, 56%).

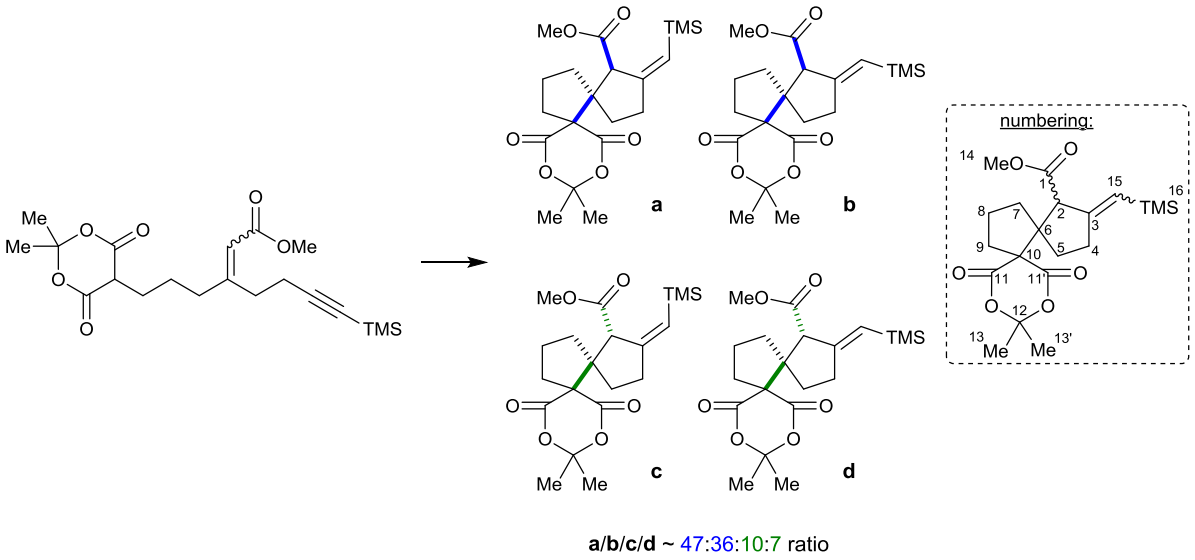
$\mathbf{R_f}$ 0.17 (*E*-isomer) and 0.20 (*Z*-isomer) (50% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\,nm}$, vanillin and $KMnO_4$); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2954, 2175 (w), 1786 (s, C=O), 1748 (s, C=O), 1715 (s, C=O), 1645 (w), 1435, 1383, 1295, 1205, 1165, 842 (s); ***m/z*** ($ESI^+$) 394.5 ($[M+H]^+$, 100%); **HRMS** ($ESI^+$) found 417.1722, $C_{20}H_{30}O_6{}^{23}Na^{28}Si^+$ requires 417.1704;




**(*E*)-isomer** (analysed as the isolated isomer): **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.71 (1H, s, CH-(12)), 3.90 (1H, t, *J*=5.3 Hz, CH-(2)), 3.64 (3H, s, $CH_3$-(14)), 2.67 (2H, dd, *J*=8.6, 6.7 Hz, $CH_2$-(5)), 2.39 – 2.36 (4H, m, $CH_2$-(7), $CH_2$-(8)), 2.10 (2H, td, *J*=7.3, 5.2 Hz, $CH_2$-(3)), 1.86 (3H, s, $CH_3$-(16)), 1.75 – 1.74 (3H, m, $CH_3$-(16')), 1.76 – 1.69 (2H, m, $CH_2$-(4)), 0.12 (9H, s, 3 $CH_3$-(11)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 166.9 (C(13)), 165.9 (2 C(1)), 161.2 (C(6)), 116.9 (C(12)), 105.5 (C(9 or 10)), 105.0 (C(9 or 10)), 86.1 (C(15)), 51.0 (C(14)), 45.6 (C(2)), 36.8 (C(7)), 30.5 (C(5)), 28.7 (C(16')), 26.4 (C(16)), 25.5 (C(4)), 25.2 (C(3)), 18.7 (C(8)), 0.1 (3 C(11));

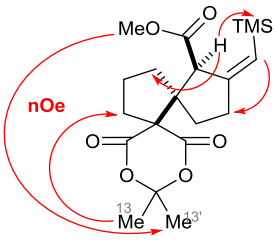
**(*Z*)-isomer** (analysed from a *E*/*Z* mixture): **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.69 (1H, s, CH-(12)), 3.66 (3H, s, $CH_3$-(14)), 3.53 (1H, t, *J*=5.0 Hz, CH-(2)), 2.78 (2H, t, *J*=7.3 Hz, $CH_2$-(7)), 2.41 (2H, t, *J*=7.4 Hz, $CH_2$-(8)), 2.29 (2H, td, *J*=7.6, 1.4 Hz, $CH_2$-(5)), 2.11 – 2.07 (2H, m, $CH_2$-(3)), 1.78 (3H, s, $CH_3$-(16)), 1.75 (3H, s, $CH_3$-(16')), 1.66 – 1.59 (2H, m, $CH_2$-(4)), 0.11 (9H, s, 3 $CH_3$-(11)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 166.6 (C(13)), 165.4 (2 C(1)), 161.4 (C(6)), 116.5 (C(12)), 106.4 (C(9 or 10)), 105.1 (C(9 or 10)), 85.4 (C(15)), 51.1 (C(14)), 46.1 (C(2)), 38.6 (C(5)), 30.9 (C(7)), 28.5 (C(16')), 26.9 (C(16)), 26.0 (C(3)), 24.1 (C(4)), 19.2 (C(8)), 0.2 (3 C(11)).

### Methyl 9,9-dimethyl-7,11-dioxo-2-((trimethylsilyl)methylene)-8,10-dioxadispiro[4.0.5$^6$.3$^5$]tetradecane-1-carboxylate (3.5a/b/c/d)

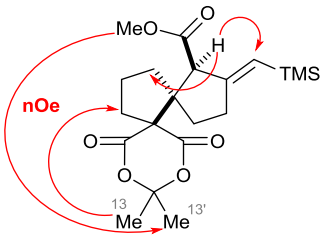



**a**/**b**/**c**/**d** ~ 47:36:10:7 ratio

According to the modified procedure of Snider *et al.*[125] To a dried 10 mL round-bottom flask was added methyl 3-(3-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)propyl)-7-(trimethylsilyl)hept-2-en-6-ynoate **3.3** (55:45 *E*/*Z* mix., 100.0 mg, 0.25 mmol, 1.0 eq.) before being purged with argon. To this flask was added dry and degassed (argon bubbling for 15 min) acetonitrile (5.4 mL). Solid $Mn(OAc)_3 \bullet 2H_2O$ (135.9 mg, 0.51 mmol, 2.0 eq.) was then added by opening the flask, introducing it quickly and closing. The flask was sealed with electrical tape and the resulting heterogeneous mixture was stirred for 24 h at room temperature (reaction usually finished after 5-7 h). The reaction was quenched by addition of $Na_2S_2O_{3\,(aq)}$ (sat. sol., freshly prepared, 5 mL), stirred until both layers were clear and the layers were separated. The aqueous phase was extracted with EtOAc (3x 10 mL). The combined organic layers were washed once with brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification of the crude mixture by flash-chromatography (eluent: 50% $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 1.5 cm, L = 7 cm) afforded the title products as a ~47:36:10:7 mixture of 4 isomers as colourless liquid (46.2 mg, 0.12 mmol, 46%). This is a ~20:80 *S**/*R** mixture at the ester centre and ~40:60 *Z*/*E* mixture at the alkene.

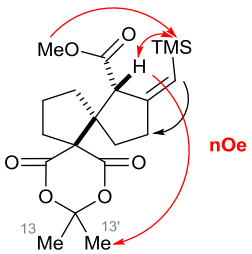


*cis*-alkene
(major)

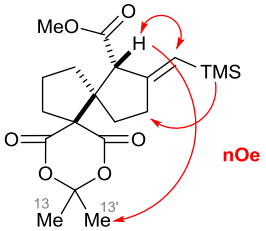


*trans*-alkene
(minor)

**2 Major isomers 3.5a/b** (analysed from a *E*/*Z* mixture): $\mathbf{R_f}$ 0.45 and 0.47 (50% $Et_2O$ in $PE_{30\text{-}40}$, vanillin, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.73 (1H, q, *J*=2.2 Hz, CH-($15^{trans}$)), 5.49 – 5.46 (1H, m, CH-($15^{cis}$)), 3.63 (3H, s, $CH_3$-($14^{trans}$)), 3.62 (3H, s, $CH_3$-($14^{cis}$)), 3.56 (1H, q, *J*=1.3 Hz, CH-($2^{cis}$)), 3.35 (1H, q, *J*=1.4 Hz, CH-($2^{trans}$)), 2.67 – 2.54 (1H, m, $CH_a$-($4^{cis}$)), 2.51 – 2.45 (1H, m, $CH_a$-($4^{trans}$)), 2.44 – 2.27 (8H, m, $CH_b$-($4^{cis}$), $CH_b$-($4^{trans}$), $CH_a$-($5^{cis}$), $CH_a$-($5^{trans}$), $CH_a$-($9^{cis}$), $CH_a$-($9^{trans}$)), 2.03 – 1.93 (4H, m, $CH_2$-($8^{cis}$), $CH_2$-($8^{trans}$)), 1.93 – 1.87 (3H, m, $CH_b$-($5^{trans}$), $CH_a$-($7^{cis}$), $CH_a$-($7^{trans}$)), 1.83 – 1.73 (3H, m, $CH_b$-($5^{cis}$), $CH_b$-($7^{cis}$), $CH_b$-($7^{trans}$)), 1.77 (3H, s, $CH_3$-($13'^{cis}$)), 1.76 (3H, s, $CH_3$-($13'^{trans}$)), 1.68 – 1.66 (3H, m, $CH_3$-($13^{cis}$)), 1.66 (3H, s, $CH_3$-($13^{trans}$)), 0.11 (9H, s, 3 $CH_3$-($16^{cis}$)), 0.07 (9H, s, 3 $CH_3$-($16^{trans}$)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 172.7 (C($1^{trans}$)), 172.3 (C($1^{cis}$)), 170.9 (C($11^{trans}$)), 170.5 (C($11^{cis}$)), 170.0 (C($11^{trans}$)), 170.0 (C($11^{cis}$)), 156.0 (C($3^{cis}$)), 155.8 (C($3^{trans}$)), 126.2 (C($15^{cis}$)), 125.6 (C($15^{trans}$)), 104.8 (C($12^{trans}$)), 104.8 (C($12^{cis}$)), 64.1 (C($10^{cis}$)), 63.4 (C($10^{trans}$)), 62.9 (C($2^{trans}$)), 58.0 (C($6^{cis}$)), 57.9 (C($2^{cis}$)), 57.9 (C($6^{trans}$)), 51.9 (C($14^{trans}$)), 51.7 (C($14^{cis}$)), 41.2 (C($9^{trans}$)), 40.8 (C($9^{cis}$)), 40.0 (C($7^{cis}$), (C($7^{trans}$)), 35.2 (C($5^{trans}$)), 33.1 (C($5^{cis}$)), 32.8 (C($4^{cis}$)), 30.6 (C($13^{trans}$)), 30.6 (C($13^{cis}$)), 29.6 (C($4^{trans}$)), 27.6 (C($13'^{cis}$)), 27.6 (C($13'^{trans}$)), 24.2 (C($8^{trans}$)), 23.6 (C($8^{cis}$)), -0.1 (3 C($16^{cis}$)), -0.5 (3 C($16^{trans}$)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2953, 1771 (m), 1736 (s), 1626 (w), 1434, 1392, 1380, 1323, 1283 (s), 1248 (m), 1204 (m), 1162, 1092, 1046, 1017, 839 (s); ***m/z*** ($ESI^+$) 417.2 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 417.1708, $C_{20}H_{30}O_6{}^{23}Na^{28}Si^+$ requires 417.1704.



*cis*-alkene
(major)

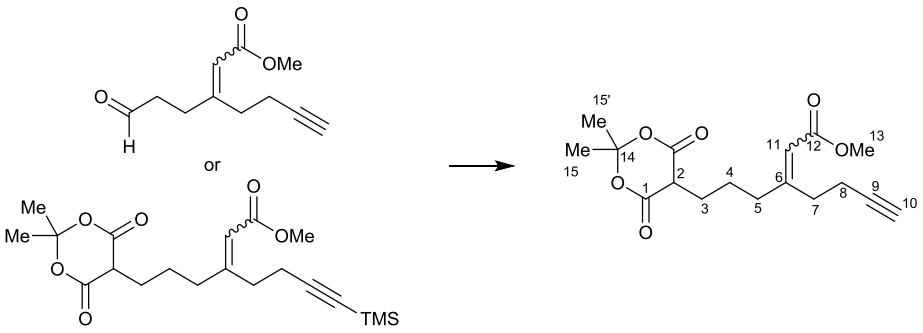


*trans*-alkene
(minor)

**2 Minor isomers 3.5c/d** (analysed from a *E*/*Z* mixture): $\mathbf{R_f}$ 0.45 and 0.47 (50% $Et_2O$ in $PE_{30\text{-}40}$, vanillin, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.56 (1H, q, *J*=2.2 Hz, CH-($15^{cis}$)), 5.48 (0.5H, td, *J*=2.5, 1.6 Hz, CH-($15^{trans}$)), 3.71 (1H, q, *J*=1.5 Hz, CH-($2^{cis}$)), 3.69 (1.5H, s, $CH_3$-($14^{trans}$)), 3.67 (3H, s, $CH_3$-($14^{cis}$)), 3.42 (0.5H, q, *J*=1.6 Hz, CH-($2^{trans}$)), 2.64 (1H, dddt, *J*=19.9, 9.8, 3.0, 1.7 Hz, $CH_a$-($4^{cis}$)), 2.53 – 2.47 (0.5H, m, $CH_a$-($4^{trans}$)), 2.44 – 2.31 (5H, m, $CH_b$-

($4^{cis}$), $CH_b$-($4^{trans}$), $CH_2$-($9^{cis}$), $CH_2$-($9^{trans}$)), 2.28 (0.5H, td, *J*=8.1, 4.5 Hz, $CH_a$-($7^{trans}$)), 2.17 – 2.03 (3H, m, $CH_2$-($5^{cis}$), $CH_2$-($5^{trans}$)), 2.03 – 1.87 (5H, m, $CH_2$-($7^{cis}$), $CH_2$-($8^{cis}$), $CH_2$-($8^{trans}$)), 1.83 – 1.77 (0.5H, m, $CH_b$-($7^{trans}$)), 1.69 (4.5H, s, $CH_3$-($13'^{cis}$), $CH_3$-($13'^{trans}$)), 1.61 (1.5H, s, $CH_3$-($13^{trans}$)), 1.61 (3H, s, $CH_3$-($13^{cis}$)), 0.08 (9H, s, 3 $CH_3$-($16^{cis}$)), 0.07 (4.5H, s, 3 $CH_3$-($16^{trans}$)); $\delta_C$ /ppm (126 MHz, $CDCl_3$) 173.1 ($C(1^{cis})$), 172.5 ($C(1^{trans})$), 170.6 ($C(11^{cis})$), 170.4 ($C(11^{cis})$), 170.2 ($C(11^{trans})$), 170.0 ($C(11^{trans})$), 156.8 ($C(3^{cis})$, $C(3^{trans})$), 125.9 ($C(15^{cis})$), 124.5 ($C(15^{trans})$), 104.6 ($C(12^{trans})$), 104.4 ($C(12^{cis})$), 68.92 ($C(6^{cis})$), 66.0 ($C(6^{trans})$), 62.4 ($C(10^{trans})$), 62.3 ($C(10^{cis})$), 60.5 ($C(2^{trans})$), 55.5 ($C(2^{cis})$), 51.9 ($C(14^{cis})$), 51.9 ($C(14^{trans})$), 37.0 ($C(7^{cis})$), 35.6 ($C(5^{trans})$), 35.3 ($C(7^{trans})$), 34.8 ($C(4^{cis})$), 34.4 ($C(9^{cis})$), 33.8 ($C(9^{trans})$), 33.4 ($C(5^{cis})$), 30.9 ($C(13^{trans})$), 30.9 ($C(13^{cis})$), 30.1 ($C(4^{trans})$), 27.3 ($C(13'^{trans})$), 27.1 ($C(13'^{cis})$), 23.0 ($C(8^{cis})$), 22.9 ($C(8^{trans})$), -0.5 (3 $C(16^{cis})$), -0.6 ($C(16^{trans})$); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2955, 2917, 2849, 1774 (m), 1740 (s), 1628 (w), 1279 (s), 1248, 1200, 1155, 840 (s); ***m/z*** ($ESI^-$) 393.2 ($[M-H]^-$, 100%); **HRMS** ($ESI^-$) found 393.1740, $C_{20}H_{29}O_6{}^{28}Si^-$ requires 393.1739.

### Methyl 3-(3-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)propyl)hept-2-en-6-ynoate (3.6)




**Method 1** (Knoevenagel/reduction route from **7.5**): According to the modified procedure of Snider *et al*.[125] In a dried pear-shaped 10 mL were added methyl 3-(3-oxopropyl)hept-2-en-6-ynoate **7.5** (1:1 *E*/*Z* mix., 450 mg, 2.32 mmol, 1.0 eq.), dry ethanol (7.2 mL), Meldum's acid **3.4** (500 mg, 3.47 mmol, 1.50 eq.) and ethylenediamine diacetate (104 mg, 0.58 mmol, 0.25 eq.). The mixture was stirred for 55 min at room temperature before borane dimethylamine complex (136 mg, 2.32 mmol, 1.0 eq.) was added. The reaction was quenched after 2.3 h with $NH_4Cl_{(aq)}$ (sat. sol., 5 mL), water (15 mL) then

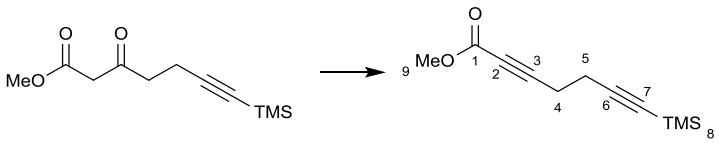
extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a yellow liquid (1.06 g). Purification by flash-chromatography (eluent: 50% $Et_2O$ in $PE_{40\text{-}60}$; column size: Ø = 2.5 cm, L = 10 cm) afforded a mixture of the title product with Meldrum's acid. Multiple washes of this mixture dissolved in $CH_2Cl_2$ with pH 8 water (HCl solution) gave the title product as an oil slowly crystalising (65:35 *E*/*Z* mix., 180 mg, 0.56 mmol, 24%).

**Method 2** (TMS deprotection route from **3.3**): To a vial was added methyl 3-(3-(2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl)propyl)-7-(trimethylsilyl)hept-2-en-6-ynoate **3.3** (55:45 *E*/*Z* mix., 100.0 mg, 0.25 mmol, 1.0 eq.), THF (dry, 0.3 mL) and AcOH (4 drops). The mixture was cooled to 0 °C before TBAF (1 M solution in THF, 0.33 mL, 0.33 mmol, 1.3 eq.) was slowly added. The reaction was allowed to warm up to room temperature. TBAF (1 M solution in THF, 0.99 mL, 0.99 mmol, 3.9 eq.) was slowly added at room temperature and stirred overnight. The reaction was quenched with $NH_4Cl_{(aq)}$ (sat. sol., *ca.* 1 mL) followed by water (to dissolve the salts) and $Et_2O$, and the layers were separated. The aqueous phase was extracted with $Et_2O$. The combined organic layers were concentrated with a $N_2$ flow. Purification of the crude mixture by flash-chromatography (eluent: 50% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title products as an amorphous solid (40:60 *E*/*Z* mix., 56.0 mg, 0.17 mmol, 69%).

Analysed as a *E/Z* mixture (~65:35 ratio): $\mathbf{R_f}$ 0.10 (100% $CH_2Cl_2$, $UV_{254\ nm}$, vanillin, $KMnO_4$); $\mathbf{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.75 – 5.71 (1.5H, m, CH-($11^{cis}$), CH-($11^{trans}$)), 3.89 (1H, t, *J*=5.2 Hz, CH-($2^{trans}$)), 3.68 (1.5H, s, $CH_3$-($13^{cis}$)), 3.65 (3H, s, $CH_3$-($13^{trans}$)), 3.53 (0.5H, t, *J*=5.0 Hz, CH-($2^{cis}$)), 2.81 (1H, t, *J*=7.3 Hz, $CH_2$-($7^{cis}$)), 2.68 (2H, dd, *J*=8.7, 6.8 Hz, $CH_2$-($5^{trans}$)), 2.42 – 2.36 (5H, m, $CH_2$-($7^{trans}$), $CH_2$-($8^{cis}$), $CH_2$-($8^{trans}$)), 2.30 (1H, td, *J*=7.7, 1.4 Hz, $CH_2$-($5^{cis}$)), 2.14 – 2.08 (3H, m, $CH_2$-($3^{cis}$), $CH_2$-($3^{trans}$)), 1.99 (1H, t, *J*=2.4 Hz, CH-($10^{trans}$)), 1.96 (0.5H, t, *J*=2.7 Hz, CH-($10^{cis}$)), 1.88 – 1.85 (3H, m, $CH_3$-($15^{trans}$)), 1.79 (1.5H, s, $CH_3$-($15^{cis}$)), 1.77 – 1.76 (1.5H, m, $CH_3$-($15'^{cis}$)), 1.76 – 1.75 (3H, m, $CH_3$-($15'^{trans}$)), 1.72 (2H, q, *J*=7.4 Hz, $CH_2$-($4^{trans}$)), 1.70 – 1.60 (1H, m, $CH_2$-($4^{cis}$)); $\mathbf{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 166.9 (C($12^{trans}$)), 166.6 (C($12^{cis}$)), 165.9 (2 C($1^{trans}$)), 165.4 (2 C($1^{cis}$)), 161.1 (C($6^{cis}$)), 161.0 (C($6^{trans}$)), 116.8 (C($11^{trans}$)), 116.7

(C(11$^{cis}$)), 105.1 (C(14$^{cis}$)), 105.1 (C(14$^{trans}$)), 83.7 (C(9$^{cis}$)), 82.9 (C(9$^{trans}$)), 69.6 (C(10$^{trans}$)), 69.1 (C(10$^{cis}$)), 51.1 (C(13$^{cis}$)), 51.1 (C(13$^{trans}$)), 46.1 (C(2$^{cis}$)), 45.6 (C(2$^{trans}$)), 38.5 (C(5$^{cis}$)), 36.6 (C(7$^{trans}$)), 30.8 (C(7$^{cis}$)), 30.6 (C(5$^{trans}$)), 28.8 (C(15'$^{trans}$)), 28.6 (C(15'$^{cis}$)), 26.9 (C(15$^{cis}$)), 26.4 (C(15$^{trans}$)), 26.0 (C(3$^{cis}$)), 25.5 (C(4$^{trans}$)), 25.2 (C(3$^{trans}$)), 24.2 (C(4$^{cis}$)), 17.8 (C(8$^{cis}$)), 17.1 (C(8$^{trans}$)); $\boldsymbol{\nu_{max}}$ /cm$^{-1}$ (film, $CDCl_3$) 3290 (s, C≡C-H), 3000, 2950, 2925, 2874, 1784 (s, C=O), 1746 (s, C=O), 1713 (s, C=O), 1644 (s, C=C), 1435, 1384, 1295 (s), 1270, 1204 (m), 1166 (m), 1135, 984 (m); ***m/z*** (ESI$^+$) 345.2 ([M+Na]$^+$, 100%); ***m/z*** (ESI$^-$) 321.1 ([M+H]$^-$, 100%); **HRMS** (ESI$^+$) found 321.1340, $C_{17}H_{21}O_6^-$ requires 321.1344.

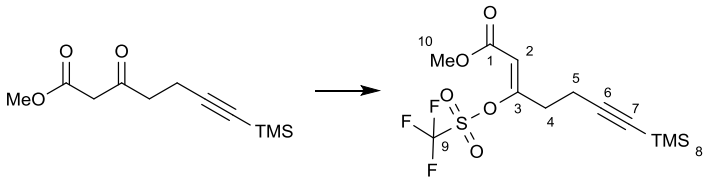
### Methyl 7-(trimethylsilyl)hepta-2,6-diynoate (3.8)



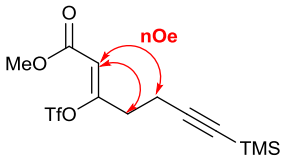

According to the modified procedure of Maity *et al*.[131] To a flame-dried 25 mL flask under argon containing dry THF (3.5 mL) and LiHMDS (1 M in toluene, 2.0 mL, 2.0 mmol, 2.0 eq.) cooled to -78 °C was added neat methyl 3-oxo-7-(trimethylsilyl)hept-6-ynoatedienoate **2.65** (226 mg, 1.0 mmol, 1.0 eq.) *via* syringe (0.5 mL THF was used to rinse the syringe). After 45 min, triflic anhydride (0.17 mL, 1.0 mmol, 1.0 eq.) was added over 7 min. After 2.5 h, the reaction was quenched with $NH_4Cl_{(aq)}$ (sat. sol., 3 mL) and the layers were separated. The aqueous layer was extracted with pentane. The combined organic layers were washed with $NH_4Cl_{(aq)}$ (half sat. sol.), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure and dissolved in dry THF (5.0 mL). dry $Et_3N$ (0.7 mL) was added and the mixture was heated to reflux overnight (no change by TLC). The mixture was cooled to room temperature and concentrated. Purification by flash-chromatography (eluent: 50% $CH_2Cl_2$ in $PE_{40\text{-}60}$, column size: Ø = 2 cm, L = 9 cm) afforded the title product as a yellow liquid (59 mg, 0.28 mmol, 28%).

**$R_f$** 0.40 (8% EtOAc in $PE_{40\text{-}60}$, $UV_{254\ nm}$, $KMnO_4$); **$\delta_H$** /ppm (501 MHz, $CDCl_3$) 3.76 (3H, s, $CH_3$-(9)), 2.56 (2H, ddd, *J*=7.9, 6.1, 1.7 Hz, $CH_2$-(5)), 2.49 (2H, ddd, *J*=8.2, 6.1, 1.7 Hz, $CH_2$-(4)), 0.15 (9H, s, 3 $CH_3$-(8)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 154.2 (C(1)), 103.9 (C(6)), 87.4 (C(3)), 86.7 (C(7)), 73.7 (C(2)), 52.8 (C(9)), 19.1 (C(5)), 19.1 (C(4)), 0.1 (3 C(8)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2242 (m, C≡C), 2179 (w, C≡C), 1715 (s, C=O), 1435 (w), 1263 (m), 1247 (s), 1077, 1042; ***m/z*** ($ESI^+$) 231.0 ($[M+Na]^+$, 100%), 209.0 ($[M+H]^+$, 10%); **HRMS** ($ESI^+$) found 231.0813, $C_{11}H_{16}O_2{}^{23}Na^{28}Si^+$ requires 231.0812.

### Methyl (*Z*)-3-(((trifluoromethyl)sulfonyl)oxy)-7-(trimethylsilyl)hept-2-en-6-ynoate (3.13)

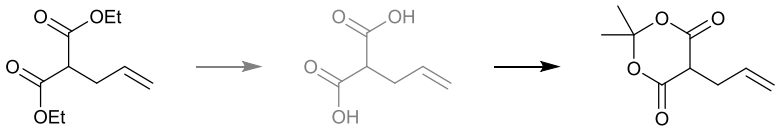



Prepared according to general procedure GP4, using methyl 3-oxo-7-(trimethylsilyl)hept-6-ynoatedienoate **2.65** (453 mg, 2.0 mmol, 1.0 eq.), lithium triflate (624 mg, 4.0 mmol, 2.0 eq.), Hünig's base (0.38 mL, 2.2 mmol, 1.1 eq.) and triflic anhydride (0.37 mL, 2.2 mmol, 1.1 eq.). After 30 min at 0 °C, TLC (10% or 35% $Et_2O$ in $PE_{40\text{-}60}$) shows completion of the reaction. Purification by flash-chromatography (eluent: 5% $Et_2O$ in $PE_{40\text{-}60}$, loading with pentane and minimum amount of $CH_2Cl_2$, column size: Ø = 5 cm, L = 7 cm) afforded the title product as a colourless liquid (493 mg, 1.38 mmol, 69%).




**$R_f$** 0.26 (10% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\ nm}$, $KMnO_4$); **$\delta_H$** /ppm (501 MHz, $CDCl_3$) 5.87 (1H, d, *J*=1.0 Hz, CH-(2)), 3.79 (3H, s, $CH_3$-(10)), 2.59 (2H, tt, *J*=6.6, 1.0 Hz, $CH_2$-(4)), 2.51 (2H, td, *J*=6.6, 1.3 Hz, $CH_2$-(5)), 0.14 (9H, s, 3 $CH_3$-(8)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 162.8 (C(1)), 156.7 (C(3)), 118.5 (q, *J*=320.0 Hz, C(9)), 112.9 (C(2)), 102.7 (C(6)), 87.9 (C(7)), 52.2 (C(10)), 33.9 (C(4)), 17.3 (C(5)), 0.0 (3 C(8)); **$\delta_F$** /ppm (377 MHz, $CDCl_3$) -74.53; **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2180 (w, C≡C), 1736 (s, C=O), 1684 (m, C=C), 1426 (s), 1200 (s), 1140; ***m/z*** ($ESI^+$) 381.0 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 381.0409, $C_{12}H_{17}O_5{}^{23}Na^{32}S^{28}Si^+$ requires 381.0410.

### 5-Allyl-2,2-dimethyl-1,3-dioxane-4,6-dione (3.14)



According to the modified procedure of Okada *et al*.[184] and Fortner *et al*.[185]

Step 1: A solution of diethyl 2-allylmalonate (9.0 mL, 45.4 mmol, 1.0 eq.) in $NaOH_{(aq)}$ (6 M, 23 mL, 138.0 mmol, 3.0 eq.) and EtOH (23 mL) was refluxed overnight. The yellowish solution was cooled down to r.t. then $HCl_{(aq)}$ (6 M, 50 mL) was added slowly with an ice bath followed by $Et_2O$ (50 mL). The layers were separated and the aqueous layer was extracted with $Et_2O$ (3x 50 mL). The combined organic layers were washed with brine (50 mL) and water (50 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure (then high vacuum for 1 h) to a white solid, 2-ally-malonic acid (5.6 g, 39.1 mmol, 86% crude) used in the next step without further purification.

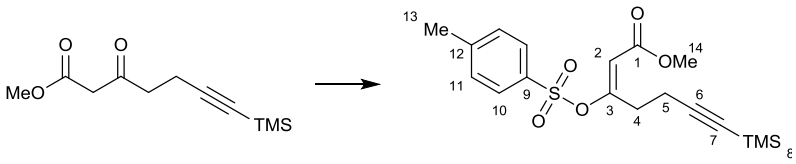
$\delta_H$ /ppm (400 MHz, MeOD-$d_4$) 5.82 (1H, ddt, *J*=17.1, 10.3, 6.8 Hz), 5.12 (1H, dq, *J*=17.1, 1.4 Hz), 5.04 (1H, ddt, *J*=10.3, 2.1, 1.4 Hz), 3.38 (1H, t, *J*=7.6 Hz), 2.58 (2H, ddt, *J*=7.6, 6.8, 1.3 Hz); $\delta_H$ /ppm (400 MHz, $D_2O$) 5.79 (1H, ddt, *J*=17.1, 10.3, 6.8 Hz), 5.17 – 5.01 (2H, m), 3.56 (0.5H, t, *J*=7.5 Hz), 2.59 – 2.53 (2H, m). Spectroscopic data is consistent with literature.[186]

Step 2: To crude 2-ally-malonic acid (5.6 g, 39.1 mmol, 1.0 eq.) in a flask under argon was added $Ac_2O$ (6.3 mL, 66.5 mmol, 1.7 eq.) followed by $H_2SO_4$ (conc., 0.1 mL). The heterogeneous mixture was stirred until all the solid was dissolved (~2 h at r.t.), then dry acetone (5.8 mL) was added and stirred overnight. To the dark mixture was added $Et_2O$ (75 mL) and water (75 mL). The layers were separated and the organic layer was kept. The organic layer was extracted with $NaHCO_{3(aq)}$ (2x 75 mL + 2x 50 mL). The combined aqueous layers from the extraction were acidified to pH 2-3 with $HCl_{(aq)}$ (4 M, ~70 mL) then extracted with $Et_2O$ (4x 100 mL). The combined organic layers were washed with brine (75 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was

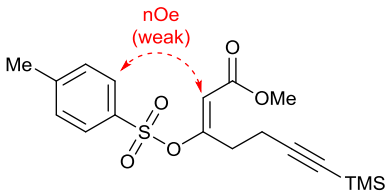
dissolved in $CHCl_3$ (60 mL), filtered and concentrated under reduce pressure to a white solid (6.9 g). Purer compound could be obtained adding $HCl_{(aq)}$ (conc. ~0.3 mL) to a saturated solution of the residue in methanol at r.t.. Filtration and washing of the filtered solid with water and drying provided pure 5-allyl-2,2-dimethyl-1,3-dioxane-4,6-dione in moderate quantities (1.75 g, 9.5 mmol, 24%).

**$R_f$** 0.10 (25% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, $KMnO_4$, vanillin); **m.p.** 69-70 °C; **$\delta_H$** /ppm (400 MHz, $CDCl_3$) 5.86 (1H, ddt, *J*=17.1, 10.3, 7.0 Hz), 5.23 (1H, dq, *J*=17.1, 1.5 Hz), 5.15 (1H, ddt, *J*=10.1, 1.8, 1.1 Hz), 3.59 (1H, t, *J*=5.1 Hz), 2.88 (2H, ddt, *J*=6.2, 5.0, 1.3 Hz), 1.79 (3H, d, *J*=0.9 Hz), 1.76 (3H, d, *J*=0.7 Hz); **$\delta_C$** /ppm (101 MHz, $CDCl_3$) 165.1, 132.7, 119.6, 105.1, 46.4, 30.5, 28.6, 27.1; ***m/z*** ($ESI^-$) 183.1 ($[M\text{-}H]^-$, 100%). Data is consistent with literature.[186]

### Methyl (*E*)-3-(tosyloxy)-7-(trimethylsilyl)hept-2-en-6-ynoate (3.16)



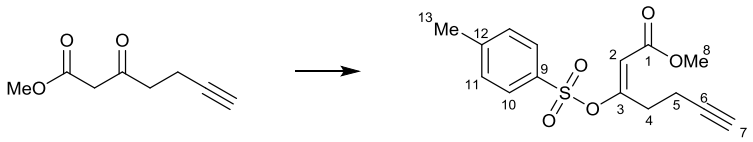

Prepared according to general procedure GP2 using methyl 3-oxo-7-(trimethylsilyl)hept-6-ynoatedienoate **2.65** (3.00 g, 13.2 mmol, 1.0 eq.), *N*-methylimidazole (1.60 mL, 19.8 mmol, 1.5 eq.), dry $Et_3N$ (2.74 mL, 19.8 mmol, 1.5 eq.) and tosyl chloride (recrystallized, 3.77 g, 19.8 mmol, 1.5 eq.). TLC (100% $CH_2Cl_2$, vanillin) showed no remaining ketoester **2.65** after 1 h 40 min at room temperature. Crude *E*/*Z* ratio: >95:5 by $^1H$ NMR. Purification by flash-chromatography (eluent: 50% $CH_2Cl_2$ in $PE_{30\text{-}40}$, column size: Ø = 3.5 cm, L = 12 cm) afforded the title product as a yellow oil (3.98 g, 10.5 mmol, 80%) (the *Z* isomer comes first and can be removed to obtain pure *E* isomer).




**$R_f$** 0.69 ($CH_2Cl_2$, $UV_{254\ nm}$, vanillin); **$\delta_H$** /ppm (501 MHz, $CDCl_3$) 7.87 – 7.77 (2H, m, 2 $CH_{Ar}$-(10), 7.41 – 7.31 (2H, m, $CH_{Ar}$-(11)), 5.83 (1H, s, CH-(2)), 3.70 (3H, s, $CH_3$-(14), 2.95 (2H, t, *J*=7.5 Hz, $CH_2$-(4)), 2.47 (3H, s, $CH_3$-(13)), 2.38 (2H, t, *J*=7.5 Hz, $CH_2$-(5)), 0.10 (9H, s, $CH_3$-(8)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 165.6

(C(1)), 163.5 (C(3)), 146.0 (C(12)), 132.8 (C(9)), 130.2 (2 C(11)), 128.4 (2 C(10)), 110.6 (C(2)), 104.5 (C(6)), 86.0 (C(7)), 51.8 (C(14)), 30.9 (C(4)), 21.9 (C(13)), 17.5 (C(5)), 0.1 (3 C(8)); $\nu_{max}$ /cm$^{-1}$ (film, $CDCl_3$) 2923, 2851, 2178 (w, C≡C), 1725 (s, C=O), 1656 (m, C=C), 1598, 1437, 1364, 1195, 1178, 1080, 1036, 1004; ***m/z*** (ESI$^+$) 403.0 ([M+Na]$^+$, 100%), 381.2 ([M+H]$^+$, 30%); **HRMS** (ESI$^+$) found 403.1005, $C_{18}H_{24}O_5{}^{23}Na^{32}S^{28}Si^+$ requires 403.1006.

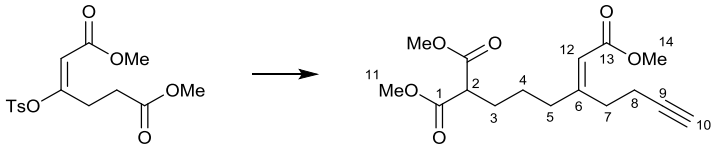
### Methyl (*E*)-3-(tosyloxy)hept-2-en-6-ynoate (3.20)



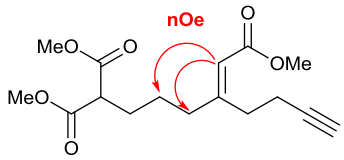

Prepared according to general procedure GP2 using methyl 3-oxohept-6-ynoate **2.66** (1.00 g, 6.49 mmol, 1.0 eq.), N-methylimidazole (0.78 mL, 9.73 mmol, 1.5 eq.), dry $Et_3N$ (1.31 mL, 9.73 mmol, 1.5 eq.) and tosyl chloride (recrystallized, 1.85 g, 9.73 mmol, 1.5 eq.). TLC (100% $CH_2Cl_2$, vanillin) after 2.3 h at room temperature showed complete consumption of the ketoester. Crude *E*/*Z* ratio: >95:5 by $^1$H NMR. Purification by flash-chromatography (eluent: 50% $CH_2Cl_2$ in $PE_{30\text{-}40}$, column size: Ø = 4 cm, L = 9 cm) afforded the title product as a yellowish oil (1.70 g, 5.51 mmol, 85%).

$\mathbf{R_f}$ 0.70 (100% $CH_2Cl_2$, $UV_{254\,nm}$, vanillin); $\delta_H$ /ppm (500 MHz, $CDCl_3$) 7.89 – 7.81 (2H, m, 2 $CH_{Ar}$-(10)), 7.42 – 7.35 (2H, m, 2 $CH_{Ar}$-(11)), 5.88 (1H, s, CH-(2)), 3.73 (3H, s, $CH_3$-(8)), 2.99 (2H, t, *J*=7.5 Hz, $CH_2$-(4)), 2.50 (3H, s, $CH_3$-(13)), 2.40 (2H, td, *J*=7.4, 2.7 Hz, $CH_2$-(5)), 1.95 (1H, t, *J*=2.7 Hz, CH-(7)); $\delta_C$ /ppm (126 MHz, $CDCl_3$) 165.5 (C(1)), 163.2 (C(3)), 146.0 (C(12)), 132.6 (C(9)), 130.1 (2 C(11)), 128.3 (2 C(10)), 110.6 (C(2)), 81.9 (C(6)), 69.4 (C(7)), 51.7 (C(8)), 30.5 (C(4)), 21.8 (C(13)), 15.9 (C(5)); $\nu_{max}$ /cm$^{-1}$ (film, $CDCl_3$) 3294 (m, C≡C-H), 1722 (s, C=O), 1653 (s, C=C), 1597, 1436, 1363 (s), 1192, 1176, 1078, 1036, 1002; ***m/z*** (ESI$^+$) 331.0 ([M+Na]$^+$, 100%), 309.0 ([M+H]$^+$, 40%); **HRMS** (ESI$^+$) found 309.0792, $C_{15}H_{17}O_5{}^{32}S^+$ requires 309.0791.

### Trimethyl (*Z*)-5-(but-3-yn-1-yl)hex-5-ene-1,1,6-tricarboxylate (3.21)

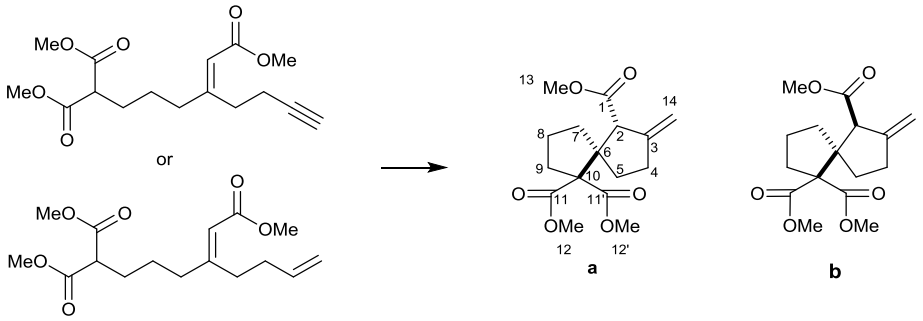



Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 16.4 mL, 8.20 mmol, 1.6 eq.), dimethyl 2-allylmalonate **3.17** (1.23 mL, 7.68 mmol, 1.5 eq.), $K_3PO_{4(aq)}$ (1 M, 12.0 mL, 12.80 mmol, 2.5 eq.), methyl (*E*)-3-(tosyloxy)hept-2-en-6-ynoate **3.20** (1.58 g, 5.12 mmol, 1.0 eq.) and Pd(dppf)$Cl_2$-$CH_2Cl_2$ complex (209 mg, 0.26 mmol, 0.05 eq.). The mixture was heated to 85 °C until complete consumption of the **3.20** was observed by TLC (40% $Et_2O$ in $PE_{40\text{-}60}$), after 3.5 h. Crude: black liquid. Two purifications by flash-chromatography (first: eluent: 30% to 60% $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 4.5 cm, L = 11 cm. second: eluent: 10% to 20% acetone in $PE_{30\text{-}40}$; column size: Ø = 5 cm, L = 10 cm) afforded the title product as colourless oily liquid (644 mg, 2.08 mmol, 41%).




**$R_f$** 0.31 (40% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\ nm}$, vanillin); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.69 (1H, t, *J*=1.4 Hz, CH-(12)), 3.74 (6H, s, 2 $CH_3$-(11)), 3.69 (3H, s, $CH_3$-(14)), 3.37 (1H, t, *J*=7.5 Hz, CH-(2)), 2.80 (2H, t, *J*=7.4 Hz, $CH_2$-(7)), 2.39 (2H, td, *J*=7.3, 2.6 Hz, $CH_2$-(8)), 2.27 (2H, td, *J*=7.7, 1.4 Hz, $CH_2$-(5)), 1.96 (1H, t, *J*=2.7 Hz, CH-(10)), 1.95 – 1.87 (2H, m, $CH_2$-(3)), 1.55 – 1.47 (2H, m, $CH_2$-(4)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 169.7(2 C(1)), 166.6 (C(13)), 161.2 (C(6)), 116.6 (C(12)), 83.7 (C(9)), 69.1 (C(10)), 52.7 (2 C(11)), 51.6 (C(2)), 51.2 (C(14)), 38.4 (C(5)), 30.8 (C(7)), 28.5 (C(3)), 25.2 (C(4)), 17.8 (C(8)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 3288 (m, C≡C-H), 2953, 1750 (s, C=O), 1732 (s, C=O), 1715 (s, C=O), 1644 (m, C=C), 1435 (m), 1331, 1272, 1227, 1192, 1170, 1154, 1089, 1070, 1029; ***m/z*** ($ESI^-$) 309.1 ($[M\text{-}Na]^-$, 100%); **HRMS** ($ESI^+$) found 311.1489, $C_{16}H_{23}O_3^+$ requires 311.1489.

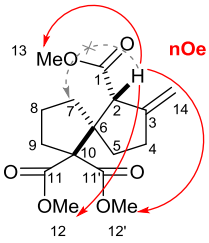
### Trimethyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (3.22a-b)



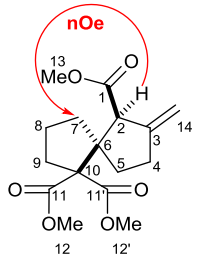

**Method 1** (from alkyne **3.21**): To a dried 25 mL round-bottom flask was added trimethyl (*Z*)-5-(but-3-yn-1-yl)hex-5-ene-1,1,6-tricarboxylate **3.21** (91.0 mg, 0.29 mmol, 1.0 eq.) before being purged with argon. To this flask was added dry and degassed (argon bubbling for 15 min) dry EtOH (over 4 Å MS, 14.5 mL). Solid $Mn(OAc)_3 \bullet 2H_2O$ (157 mg, 0.58 mmol, 2.0 eq.) was then added by opening the flask and introducing it quickly and closing. The reaction was heated to 75 °C for 6 h before being quench with $Na_2S_2O_{3\,(aq)}$ (sat. sol., freshly prepared, 5 mL), stirred until both layers were clear and the layers were separated. The aqueous phase was extracted with EtOAc (3x 10 mL). The combined organic layers were washed once with brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification of the crude mixture by flash-chromatography (eluent: 5% acetone in $PE_{30\text{-}40}$; column size: Ø = 1.8 cm, L = 15 cm) afforded the title products as a ~80:20 mixture **3.22a/3.22b** as colourless liquid (33.1 mg, 0.11 mmol, 36%).

**Method 2** (from alkene **3.24**): Alkenes **3.22** were obtained in various yields during the cyclisation study of linear precursor **3.24** initiated by $Mn(OAc)_3$ in presence of Cu(II) salts following general procedure GP6. Purification of **3.22** was rarely successful (presence of impurities of very similar $R_f$) therefore $^1$H NMR was used to determine NMR yields. This was made possible by the use of pure samples of both isomers of **3.22** obtained from **method 1**. Best NMR yield obtained using the following procedure: Following general procedure GP6 using trimethyl (*Z*)-5-(but-3-en-1-yl)hex-5-ene-1,1,6-tricarboxylate **3.24** (100 mg, 0.32 mmol, 1.0 eq.), $Mn(OAc)_3 \bullet 2H_2O$ (172 mg, 0.64 mmol, 2.0 eq.), $Cu(OAc)_2 \bullet H_2O$ (116 mg, 0.32 mmol, 1.0 eq.). The reaction was heated to 80 °C until TLC (10% EtOAc in toluene, vanillin) showed complete consumption of the starting material after 24 h.

Purification by flash-chromatography (eluent: 10% acetone in $PE_{40\text{-}60}$; column size: Ø = 1.7 cm, L = 12 cm) a mixture of **3.24** (minor), **3.24** (major) and 6-*endo*-cyclisation products in 0.09:1.00:0.86 ratio (56 mg of mixture, *i.e.* 29% NMR yield of **3.24** (major) and 3% NMR yield of **3.24** (minor)). Tricyclic lactone **3.25** was also obtained in 3% NMR yield.

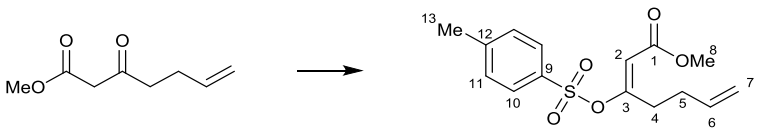



Major isomer: $\mathbf{R_f}$ 0.57 (50% $Et_2O$ in $PE_{30\text{-}40}$, vanillin, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 4.96 (1H, q, *J*=2.3 Hz, $CH_a$-(14)), 4.85 (1H, q, *J*=2.0 Hz, $CH_b$-(14)), 3.92 (1H, q, *J*=2.2 Hz, CH-(2)), 3.69 (3H, s), 3.69 (3H, s), 3.68 (3H, s), 2.52 (1H, qdq, *J*=9.8, 9.2, 7.0, 2.5, 2.1 Hz, $CH_a$-(4)), 2.35 – 2.26 (2H, m, $CH_b$-(4), $CH_a$-(9)), 2.27 – 2.19 (1H, m, $CH_b$-(9)), 2.22 – 2.15 (1H, m, $CH_a$-(7)), 1.87 (1H, dddd, *J*=12.6, 9.5, 8.4, 0.9 Hz, $CH_a$-(5)), 1.79 (1H, q, *J*=8.0, 7.3 Hz, $CH_b$-(7)), 1.76 – 1.68 (4H, m, $CH_b$-(5), $CH_2$-(8)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 173.9 (C(1)), 171.6, 171.2, 150.6 (C(3)), 108.0 (C(14)), 65.9 (C(10)), 59.3 (C(6)), 54.8 (C(2)), 52.4, 52.3, 51.7, 35.1 (C(5)), 33.5 (C(7)), 32.8 (C(9)), 31.1 (C(4)), 19.9 (C(8)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2953 (m), 1730 (C=O), 1656 (w), 1434, 1261 (m), 1296, 1169, 1091, 1049, 1021; ***m/z*** ($ESI^+$) 333.2 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 333.1306, $C_{16}H_{22}O_6{}^{23}Na^+$ requires 333.1309.




Minor isomer: $\mathbf{R_f}$ 0.53 (50% $Et_2O$ in $PE_{30\text{-}40}$, vanillin, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.10 – 5.08 (1H, m, $CH_a$-(14)), 4.96 – 4.94 (1H, m, $CH_b$-(14)), 3.72 (3H, s, $CH_3$-(12')), 3.68 (3H, s, $CH_3$-(12)), 3.62 (3H, s, $CH_3$-(13)), 3.54 (1H, t, *J*=1.3 Hz, CH-(2)), 2.63 – 2.55 (1H, m, $CH_a$-(4)), 2.55 – 2.47 (1H, m, $CH_a$-(9)), 2.43 – 2.39 (1H, m, $CH_b$-(9)), 2.39 – 2.34 (1H, m, $CH_b$-(4)), 2.34 – 2.28 (1H, m, $CH_a$-(5)), 1.77 – 1.70 (2H, m, $CH_a$-(7), $CH_a$-(8)), 1.70 – 1.64 (2H, m, $CH_b$-(5), $CH_b$-(8)), 1.64 – 1.59 (1H, m, $CH_b$-(7)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 173.2 (C(1)), 172.0 (C(11')), 171.0 (C(11)), 150.1 (C(3)), 109.6 (C(14)), 64.6 (C(10)), 59.3 (C(6)), 58.5 (C(2)), 52.4 (C(12), C(12')), 51.6 (C(13)), 37.9 (C(7)), 35.5 (C(9)), 31.6 (C(5)), 28.4 (C(4)), 19.3 (C(8)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2953 (m), 1732 (C=O), 1657 (w), 1434, 1259, 1201, 1157, 1097, 1030; ***m/z*** ($ESI^+$) 333.2 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 333.1305, $C_{16}H_{22}O_6{}^{23}Na^+$ requires 333.1309.

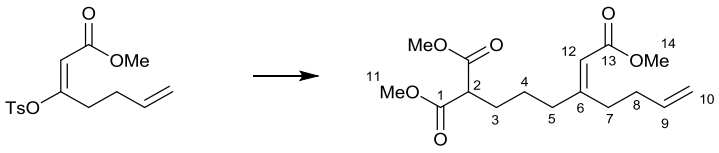
### Methyl (*E*)-3-(tosyloxy)hepta-2,6-dienoate (3.23)



Prepared according to general procedure GP2 using methyl 3-oxohept-6-enoate **2.63** (4.1 g, 26.4 mmol, 1.0 eq.), *N*-methylimidazole (3.2 mL, 39.6 mmol, 1.5 eq.), dry $Et_3N$ (5.5 mL, 39.6 mmol, 1.5 eq.) and tosyl chloride (recrystallized, 7.5 g, 39.6 mmol, 1.5 eq.). TLC (100% $CH_2Cl_2$, vanillin) showed no remaining ketoester after 4.5 h at r.t.. Purification by flash-chromatography (eluent: 0% then 30% then 50% then 60% then 90% (500 mL each) $CH_2Cl_2$ in $PE_{30\text{-}40}$, column size: Ø = 7 cm, L = 7.5 cm) afforded the title product as a clear liquid (6.7 g, 21.7 mmol, 82%).

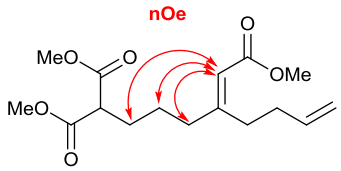
**$R_f$** 0.72 (100% $CH_2Cl_2$, $UV_{254\ nm}$, vanillin); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 7.86 – 7.78 (2H, m, $CH_{Ar}$-(10)), 7.40 – 7.36 (2H, m, 2 $CH_{Ar}$-(11)), 5.80 (1H, s, CH-(2)), 5.71 (1H, ddt, *J*=16.9, 10.2, 6.7 Hz, CH-(6)), 4.98 (1H, dq, *J*=17.2, 1.7 Hz, $CH_b$-(7)), 4.95 (1H, dq, *J*=10.2, 1.3 Hz, $CH_b$-(7)), 3.69 (3H, s, $CH_3$-(8)), 2.85 – 2.75 (2H, m, $CH_2$-(4)), 2.47 (3H, s, $CH_3$-(13)), 2.21 (2H, tdt, *J*=7.9, 6.5, 1.4 Hz, $CH_2$-(5)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 165.8 (C(1)), 165.3 (C(3)), 146.0 (C(12)), 136.4 (C(6)), 133.0 (C(9)), 130.1 (2 C(11)), 128.4 (2 C(10)), 115.9 (C(7)), 109.8 (C(2)), 51.7 (C(8)), 31.0 (C(4)), 30.6 (C(5)), 21.9 (C(13)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2952, 1722 (s, C=O), 1651 (s, C=C), 1598, 1436, 1362, 1193, 1178,1129, 1073, 1028; **HRMS** ($ESI^+$) found 311.0946, $C_{15}H_{19}O_5{}^{32}S^+$ requires 311.0948.

### Trimethyl (*Z*)-5-(but-3-en-1-yl)hex-5-ene-1,1,6-tricarboxylate (3.24)



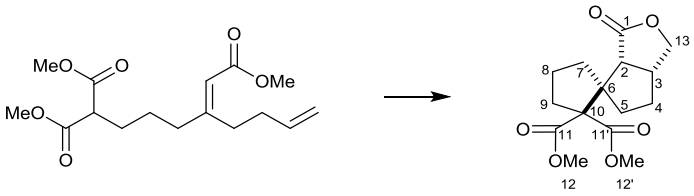
Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 47.0 mL, 23.4 mmol, 1.6 eq.), dimethyl 2-allylmalonate **3.17** (3.53 mL, 21.9 mmol, 1.5 eq.), $K_3PO_{4(aq)}$ (1 M, 36.5 mL, 36.5 mmol, 2.5 eq.), methyl (*E*)-3-(tosyloxy)hepta-2,6-dienoate **3.23** (4.53 g, 14.6 mmol, 1.0 eq.) in

1,4-dioxane (112 mL) and Pd(dppf)$Cl_2$-$CH_2Cl_2$ complex (360 mg, 0.44 mmol, 0.03 eq.). The mixture was heated to 85 °C until complete consumption of the **3.23** was observed by TLC (35% $Et_2O$ in $PE_{40\text{-}60}$), after 2 h. Crude: black liquid. Purification by flash-chromatography (eluent: 0% (500 mL) then 5% (1 L) then 10% (1 L) acetone in $PE_{30\text{-}40}$; column size: Ø = 6.5 cm, L = 11 cm) then purified again by flash-chromatography (eluent: $CH_2Cl_2$; column size: Ø = 6.5 cm, L = 6.5 cm) afforded the title product as colourless liquid (3.07 g, 9.8 mmol, 67%).




**$R_f$** 0.35 (35% $Et_2O$ in PE, $UV_{254\ nm}$, vanillin), 0.24 (10% acetone in $PE_{40\text{-}60}$, $UV_{254\ nm}$, vanillin), 0.33 ($CH_2Cl_2$, product spots streaks, $UV_{254\ nm}$, vanillin); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.83 (1H, ddt, *J*=16.9, 10.1, 6.6 Hz, CH-(9)), 5.65 (1H, d, *J*=1.4 Hz, CH-(12)), 5.04 (1H, dq, *J*=17.2, 1.7 Hz, $CH_a$-(10)), 4.96 (1H, ddt, *J*=10.1, 2.0, 1.3 Hz, $CH_b$-(10)), 3.74 (6H, s, 2 $CH_3$-(11)), 3.68 (3H, s, $CH_3$-(14)), 3.37 (1H, t, *J*=7.5 Hz, CH-(2)), 2.70 – 2.65 (2H, m, $CH_2$-(7)), 2.24 – 2.19 (2H, m, $CH_2$-(8)), 2.19 – 2.15 (2H, m, $CH_2$-(5)), 1.94 – 1.88 (2H, m, $CH_2$-(3)), 1.54 – 1.46 (2H, m, $CH_2$-(4)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 169.8 (2 C(1)), 166.8 (C(13)), 162.7 (C(6)), 138.0 (C(9)), 115.9 (C(12)), 115.1 (C(10)), 52.7 (2 C(11)), 51.6 (C(2)), 51.0 (C(14)), 37.9 (C(5)), 32.8 (C(8)), 31.5 (C(7)), 28.5 (C(3)), 25.3 (C(4)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2953, 2921, 2851, 1752 (m, C=O), 1734 (s, C=O), 1716 (s, C=O), 1642 (m, C=C), 1435 (m), 1231, 1194, 1147; ***m/z*** ($ESI^+$) 335.2 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 313.1642, $C_{16}H_{25}O_6^+$ requires 313.1646.

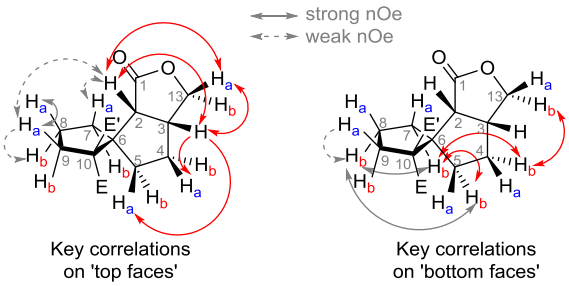
**Dimethyl (1*R*,3a'*R*,6a'*R*)-3'-oxohexahydrospiro[cyclopentane-1,4'-cyclopenta[*c*]furan]-2,2-dicarboxylate (3.25)**




Lactone **3.25** was obtained in various yields during the cyclisation study of linear precursor **3.24** to bicyclic product **3.22** initiated by $Mn(OAc)_3$.

The procedure that gave the best yield of lactone is the following:

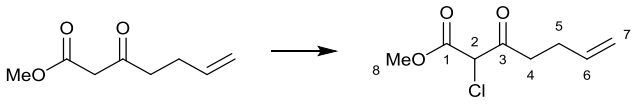
Prepared according to general procedure GP6 using dry MeCN (0.2 M) instead of DMSO as solvent, using trimethyl (*Z*)-5-(but-3-en-1-yl)hex-5-ene-1,1,6-tricarboxylate **3.24** (100 mg, 0.32 mmol, 1.0 eq.), $Mn(OAc)_3•2H_2O$ (172 mg, 0.64 mmol, 2.0 eq.), $Cu(OAc)_2•H_2O$ (116 mg, 0.32 mmol, 1.0 eq.). The reaction was heated to 80 °C until TLC (10% EtOAc in toluene, vanillin) showed complete consumption of the starting material after 24 h. Purification by flash-chromatography (eluent: 10% acetone in $PE_{40\text{-}60}$; column size: Ø = 1.7 cm, L = 12 cm) afforded the title tricyclic product as a yellowish liquid (26.8 mg, 0.09 mmol, 28%) along with the usual bicyclic products **3.22a/b** (36% combined).




**$R_f$** 0.25 (10% EtOAc in toluene, vanillin and $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 4.34 (1H, dd, *J*=9.4, 8.0 Hz, $CH_a$-(13)), 3.99 (1H, dd, *J*=9.4, 3.9 Hz, $CH_b$-(13)), 3.76 (3H, s, $CH_3$-(12)), 3.70 (3H, s, $CH_3$-(12)), 3.63 (1H, d, *J*=10.1 Hz, CH-(2)), 3.11 (1H, ddddd, *J*=10.1, 8.3, 8.0, 6.9, 3.9 Hz, CH-(3)), 2.39 (1H, ddd, *J*=13.9, 9.7, 4.5 Hz, $CH_a$-(9)), 2.27 – 2.20 (1H, m, $CH_a$-(7)), 2.07 – 1.96 (3H, m, $CH_b$-(9b), $CH_a$-(5), $CH_a$-(4)), 1.96 – 1.89 (1H, m, $CH_a$-(8)), 1.77 – 1.64 (1H, m, $CH_b$-(8)), 1.63 – 1.57 (1H, m, $CH_b$-(5)), 1.56 – 1.50 (1H, m, $CH_b$-(4)), 1.46 (1H, ddd, *J*=12.9,

9.1, 2.5 Hz, $CH_b$-(7)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 177.5 (C(1)), 171.2 (C(11), C(11')), 71.6 (C(13)), 66.1 (C(10)), 58.0 (C(6)), 53.1 (C(12')), 52.3 (C(12)), 48.3 (C(2)), 41.8 (C(3)), 37.6 (C(5)), 33.1 (C(7)), 31.5 (C(9)), 31.0 (C(4)), 20.3 (C(8)); **$\nu_{max}$** /$cm^{-1}$ (neat) 2954, 2921, 2851, 1759 (s, C=O), 1729 (s, C=O), 1454, 1434, 1376, 1250, 1220 (m), 1202, 1166 (s); ***m/z*** ($ESI^+$) 297.2 ($[M+H]^+$, 100%), 319.2 ($[M+Na]^+$, 70%); **HRMS** ($ESI^+$) found 297.1332, $C_{15}H_{21}O_6^+$ requires 297.1333.

### Methyl 2-chloro-3-oxohept-6-enoate (3.37)

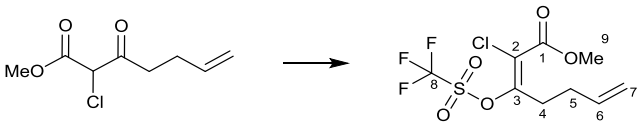



According to the modified procedure of De Kimpe *et al*.[187] To methyl 3-oxohept-6-enoate **2.63** (500 mg, 3.20 mmol, 1.0 eq.) in dry $CH_2Cl_2$ (2.6 mL) in a flame-dried 10 mL flask under argon atmosphere was added dropwise sulfuryl chloride (0.27 mL, 3.36 mmol, 1.05 eq.) at room temperature. The reaction was quenched with water after 2 h 45 min as no further conversion was observed by TLC (20% $Et_2O/PE_{40\text{-}60}$, $KMnO_4$, $UV_{254\ nm}$). The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3x). The combined organic layers were washed with $NaHCO_{3\ (aq)}$ (multiple times, until no gas was produced), brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a yellow oil (0.67 g). Purification by flash-chromatography (eluent: 7% (100 mL) then 11% (200 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2 cm, L = 10 cm) afforded the title product as a mixture of keto-enol forms as colourless liquid (369 mg, 1.94 mmol, 61%).

Analysed as the keto/enol mixture (~1:0.3 ratio): **$R_f$** 0.56 (20% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\ nm}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 12.32 (0.3H, t, *J*=1.1 Hz, OH-($9^{enol}$)), 5.84 (0.3H, ddt, *J*=17.0, 10.3, 6.5 Hz, CH-($6^{enol}$)), 5.79 (1H, ddt, *J*=17.0, 10.3, 6.5 Hz, CH-($6^{keto}$)), 5.09 (0.3H, dq, *J*=17.1, 1.7, 1.6 Hz, $CH_a$-($7^{enol}$)), 5.06 (1H, dq, *J*=17.0, 1.7 Hz, $CH_a$-($7^{keto}$)), 5.02 (1.3H, dq, *J*=10.1, 1.3 Hz, $CH_b$-($7^{keto}$), $CH_b$-($7^{enol}$)), 4.81 (1H, s, CH-($2^{keto}$)), 3.85 (1H, s, $CH_3$-($8^{enol}$)), 3.84 (3H, s, $CH_3$-($8^{keto}$)), 2.90 – 2.75 (2H, m, $CH_2$-($4^{keto}$)), 2.64 – 2.61 (0.6H, m, $CH_2$-($4^{enol}$)), 2.39 (2.6H, appears pt, *J*=7.4, 1.5 Hz, $CH_2$-($5^{keto}$),

$CH_2$-($5^{enol}$)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 198.3 (C($3^{keto}$)), 175.0 (C($3^{enol}$)), 170.0 (C($1^{enol}$)), 165.6 (C($1^{keto}$)), 136.7 (C($6^{enol}$)), 136.2 (C($6^{keto}$)), 116.1 (C($7^{keto}$)), 115.9 (C($7^{enol}$)), 96.8 (C($2^{enols}$)), 60.8 (C($2^{keto}$)), 53.9 (C($8^{keto}$)), 52.9 (C($8^{enol}$)), 38.3 (C($4^{keto}$)), 32.4 (C($4^{enol}$)), 29.8 (C($5^{enol}$)), 27.5 (C($5^{keto}$)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2923, 1728 (s with shoulder, C=O), 1643, 1606, 1437 (m), 1361, 1259, 1197, 1167, 1064; **HRMS** ($apci^+$) found 189.0321, $C_8H_{10}O_3{}^{35}Cl^+$ requires 189.0324.

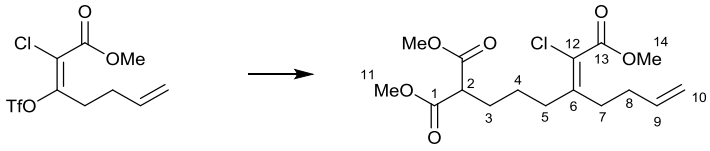
### Methyl (*Z*)-2-chloro-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate (3.38)




Prepared according to general procedure GP3 method A, using methyl 2-chloro-3-oxohept-6-enoate **3.37** (300 mg, 1.57 mmol, 1.0 eq.), $Me_4NOH$ solution (25% w/w in water, 2.87 mL, 7.87 mmol, 5.0 eq.) and triflic anhydride (0.66 mL, 3.93 mmol, 2.5 eq.). Reaction completed after 15 min (TLC, 20% $Et_2O$ in PE). Purification by flash-chromatography (eluent: 7% $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 2 cm, L = 10 cm) afforded the title product as a colourless liquid (180 mg, 0.56 mmol, 36%).

**$R_f$** 0.78 (20% $Et_2O$ in $PE_{30\text{-}40}$, $KMnO_4$, not vanillin, $UV_{254\ nm}$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.76 (1H, ddt, *J*=16.9, 10.1, 6.8 Hz, CH-(6)), 5.09 (1H, dq, *J*=17.2, 1.6 Hz, $CH_a$-(7)), 5.06 (1H, dq, *J*=10.2, 1.2 Hz, $CH_b$-(7)), 3.88 (3H, s, $CH_3$-(9)), 3.06 – 3.01 (2H, m, $CH_2$-(4)), 2.38 (2H, qt, *J*=7.0, 1.3 Hz, $CH_2$-(5)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 162.0 (C(1)), 158.1 (C(3)), 135.2 (C(6)), 119.4 (C(2)), 118.4 (q, *J*=320.3 Hz, C(8)), 117.1 (C(7)), 53.8 (C(9)), 32.4 (C(4)), 30.8 (C(5)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2981, 1733 (m, C=O), 1628 (w, C=C), 1426 (s), 1274, 1248, 1214 (s), 1136, 1045; **HRMS** ($ESI^+$) found 322.9963, $C_9H_{11}O_5{}^{35}ClF_3{}^{32}S^+$ requires 322.9962.

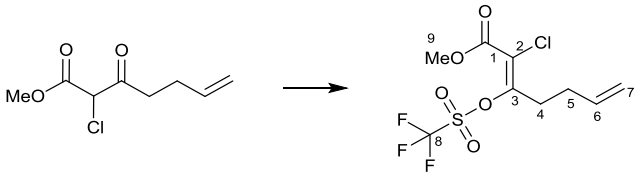
### Trimethyl (*E*)-5-(but-3-en-1-yl)-6-chlorohex-5-ene-1,1,6-tricarboxylate (3.39)




Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 1.64 mL, 0.818 mmol, 1.6 eq.), dimethyl 2-allylmalonate **3.17** (0.12 mL, 0.767 mmol, 1.5 eq.), $K_3PO_{4(aq)}$ (1 M, 1.27 mL, 1.27 mmol, 2.5 eq.), methyl (*Z*)-2-chloro-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.38** (165 mg, 0.511 mmol, 1.0 eq.) and Pd(dppf)$Cl_2$-$CH_2Cl_2$ complex (20.9 mg, 0.026 mmol, 0.05 eq.). The mixture was heated to 85 °C overnight. TLC (20% $Et_2O$ in $PE_{40\text{-}60}$) showed no remaining triflate. Crude: black liquid. Purification by flash-chromatography (eluent: 5% to 20% $Et_2O$ in $PE_{30\text{-}40}$) followed by a second purification by flash-chromatography (eluent: 7% EtOAc in toluene; column size: Ø = 2 cm, L = 11 cm) afforded the title product as colourless oil (47.2 mg, 0.14 mmol, 27%).

**$R_f$** 0.33 (20% $Et_2O$ in PE, $UV_{254\,nm}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.81 (1H, ddt, *J*=16.9, 10.1, 6.6 Hz, CH-(9)), 5.05 (1H, dq, *J*=17.0, 1.7 Hz, $CH_a$-(10)), 4.99 (1H, dq, *J*=10.1, 1.4 Hz, $CH_b$-(10)), 3.80 (3H, s, $CH_3$-(14)), 3.75 (6H, s, 2 $CH_3$-(11)), 3.41 (1H, t, *J*=7.6 Hz, CH-(2)), 2.62 – 2.55 (2H, m, $CH_2$-(7)), 2.44 – 2.35 (2H, m, $CH_2$-(5)), 2.27 – 2.18 (2H, m, $CH_2$-(8)), 2.03 – 1.92 (2H, m, $CH_2$-(3)), 1.57 – 1.49 (2H, m, $CH_2$-(4)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 169.7 (2 C(1)), 163.9 (C(13)), 153.2 (C(6)), 137.4 (C(9)), 119.4 (C(12)), 115.5 (C(10)), 52.7 (C(14)), 52.7 (2 C(11)), 51.3 (C(2)), 35.3 (C(5)), 33.6 (C(7)), 32.6 (C(8)), 28.8 (C(3)), 24.6 (C(4)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2954, 2921, 1752 (s with shoulder, C=O), 1733 (s, C=O), 1641 (s, C=C), 1605 (m, C=C), 1435 (m), 1284, 1198, 1150, 1031; **HRMS** ($apci^+$) found 347.1258, $C_{16}H_{24}O_6{}^{35}Cl^+$ requires 347.1256.

### Methyl (*E*)-2-chloro-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate (3.40)



Prepared according to general procedure GP4, using methyl 2-chloro-3-oxohept-6-enoate **3.37** (781 mg, 4.1 mmol, 1.0 eq.), lithium triflate (1.28 mg, 8.2 mmol, 2.0 eq.), Hünig's base (1.07 mL, 6.2 mmol, 1.5 eq.) and triflic anhydride (1.04 mL, 6.2 mmol, 1.1 eq.). After 1 h at 0 °C, TLC (5% $Et_2O$ in $PE_{40\text{-}60}$) showed no remaining starting material. Purification by flash-chromatography (eluent: 5% to 10% $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 5 cm, L = 7 cm) afforded the title product as a colourless liquid (347 mg, 1.08 mmol, 26%).

**$R_f$** 0.50 (5% $Et_2O$ in $PE_{30\text{-}40}$, $KMnO_4$, not vanillin, $UV_{254\ nm}$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.78 (1H, ddt, *J*=16.9, 10.1, 6.7 Hz, CH-(6)), 5.15 – 5.06 (2H, m, $CH_2$-(7)), 3.88 (3H, s, $CH_3$-(9)), 2.76 (2H, dd, *J*=8.5, 6.8 Hz, $CH_2$-(4)), 2.41 – 2.35 (2H, m, $CH_2$-(5)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 160.8 (C(1)) 153.6 (C(3)) 134.9 (C(6)) 121.2 (C(2)) 117.8 (q, *J*=320.4 Hz, C(8)) 117.2 (C(7)) 53.6 (C(9)) 32.2 (C(4)) 29.6 (C(5)); **$\delta_F$** /ppm (470 MHz, $CDCl_3$) -74.13; **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 1740 (s, C=O), 1630 (w, two bands, C=C), 1428 (s), 1269, 1249, 1207 (s), 1136, 1048; **HRMS** ($ESI^+$) found 344.9782, $C_9H_{10}O_5{}^{35}ClF_3{}^{23}Na{}^{32}S^+$ requires 344.9782.

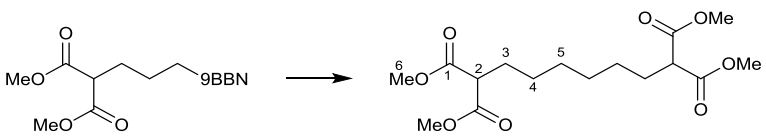
### Trimethyl (*Z*)-5-(but-3-en-1-yl)-6-chlorohex-5-ene-1,1,6-tricarboxylate (3.41)

Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 2.30 mL, 1.15 mmol, 1.6 eq.), dimethyl 2-allylmalonate **3.17** (0.17 mL, 1.05 mmol, 1.5 eq.), $K_3PO_{4(aq)}$ (1 M, 1.25 mL, 1.25 mmol, 2.5 eq.), methyl (*E*)-2-chloro-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.40**

(161 mg, 0.5 mmol, 1.0 eq.) and Pd(dppf)$Cl_2$-$CH_2Cl_2$ complex (20.4 mg, 0.025 mmol, 0.05 eq.). The mixture was heated to 85 °C until complete consumption of the **3.40** was observed by TLC (20% $Et_2O$ in $PE_{40\text{-}60}$) after 4 h. Purification by flash-chromatography (eluent: 20% $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 1.6 cm, L = 13 cm) followed by a second purification by flash-chromatography (eluent: 7% EtOAc in toluene; column size: Ø = 2 cm, L = 12 cm) afforded the title product as a Z/E mixture (92:8 ratio) as a yellowish oil (13.0 mg, 0.04 mmol, 8%).

**$R_f$** 0.20 (20% $Et_2O$ in PE, $UV_{254\ nm}$, $KMnO_4$, weak vanillin); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=16.7, 10.1, 6.5 Hz, CH-(9)), 5.06 (1H, dq, *J*=17.0, 1.6 Hz, $CH_a$-(10), 5.00 (1H, dq, *J*=10.1, 1.3 Hz, $CH_b$-(10)), 3.80 (3H, s, $CH_3$-(14)), 3.73 (6H, s, 2 $CH_3$-(11)), 3.39 (1H, t, *J*=7.5 Hz, $CH_2$-(2)), 2.54 – 2.49 (2H, m, $CH_2$-(5)), 2.46 – 2.40 (2H, m, $CH_2$-(7)), 2.26 – 2.17 (2H, m, $CH_2$-(8)), 1.96 – 1.91 (2H, m, $CH_2$-(3)), 1.55 – 1.48 (2H, m, $CH_2$-(4); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 169.8 (2 C(1)), 163.8 (C(13)), 153.4 (C(6)), 137.2 (C(9)), 119.4 (C(12)), 115.6 (C(10)), 52.7 (C(14)), 52.7 (2 C(11)), 51.4 (C(2)), 35.1 (C(7)), 33.8 (C(5)), 30.9 (C(8)), 28.8 (C(3)), 26.2 (C(4)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2920, 2849, 1732 (s with shoulder, C=O), 1719 (s, C=O), 1641 (s, C=C), 1605 (m, C=C), 1435 (m), 1255, 1221, 1150, 1034, 1003; ***m/z*** ($ESI^+$) 369.0 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 369.1075, $C_{16}H_{23}O_6{}^{35}Cl^{23}Na^+$ requires 369.1075.

### Tetramethyl octane-1,1,8,8-tetracarboxylate (3.42)

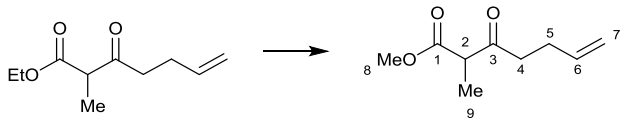



Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 2.30 mL, 1.15 mmol, 1.6 eq.), dimethyl 2-allylmalonate **3.17** (0.17 mL, 1.05 mmol, 1.5 eq.), $K_3PO_{4(aq)}$ (1 M, 1.25 mL, 1.25 mmol, 2.5 eq.), methyl (*E*)-2-chloro-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.40** (177.3 mg, 0.5 mmol, 1.0 eq.) and Pd(dppf)$Cl_2$-$CH_2Cl_2$ complex (20.4 mg, 0.025 mmol, 0.05 eq.). The mixture was heated to 85 °C until complete consumption of **3.40** was observed by TLC (20% $Et_2O$ in

$PE_{40-60}$) after 4 h. Purification by flash-chromatography (eluent: 20% $Et_2O$ in $PE_{30-40}$; column size: Ø = 1.6 cm, L = 13 cm) afforded the title product as yellow oil (22.9 mg, 0.06 mmol, 9%).

**$R_f$** 0.33 (50% $Et_2O$ in $PE_{30-40}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 3.72 (12H, s, 4 $CH_3$-(6)), 3.33 (2H, t, *J*=7.5 Hz, 2 CH-(2)), 1.86 (4H, td, *J*=7.6, 5.0 Hz, 2 $CH_2$-(3)), 1.35 – 1.21 (6H, m, 2 $CH_2$-(4), 2 $CH_2$-(5)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 170.0 (4 C(1)), 52.6 (4 C(6)), 51.8 (2 C(2)), 29.0 (2 C(4) or 2 C(5)), 28.9 (2-C(3)), 27.3 (2 C(4) or 2 C(5)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2953, 2927, 2857, 1732 (s, C=O), 1435, 1341, 1228, 1197, 1152, 1113, 1059, 1024; ***m/z*** ($ESI^+$) 369.2 ([M+Na]$^+$, 100%); **HRMS** ($ESI^+$) found 369.1518, $C_{16}H_{26}O_8{}^{23}Na^+$ requires 369.1520.

### Methyl 2-methyl-3-oxohept-6-enoate (3.44)




To a solution of ethyl 2-methyl-3-oxohept-6-enoate **3.52** (2.50 g, 13.57 mmol, 1.0 eq.) in MeOH (27 mL) at room temperature was added MeONa solution (25% w/w in MeOH, 0.68 mmol, 0.05 eq.) and stirred overnight. TLC (20% $Et_2O$ in $PE_{40-60}$, $KMnO_4$) showed complete consumption of the substrate. The reaction was quenched with AcOH (*ca* 40 mg). Water was added and the mixture was concentrated ($N_2$ flow, to remove MeOH) and extracted with $Et_2O$. The combined organic layers were washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification of the crude mixture by flash-chromatography (eluent: 10% $Et_2O$ in $PE_{30-40}$; column size: Ø = 6 cm, L = 7 cm) afforded the title product as a colourless liquid (1.73 g, 10.16 mmol, 75%).

Analysed as the keto/enol mixture (~1:0.03 ratio): **$R_f$** 0.43 (20% $Et_2O$ in $PE_{40-60}$, $UV_{254\ nm}$, $KMnO_4$); **keto-form (major): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.79 (1H, ddt, *J*=16.9, 10.2, 6.6 Hz, CH-(6)), 5.03 (1H, dq, *J*=17.0, 1.7 Hz, $CH_a$-(7)), 4.98 (1H, dq, *J*=10.2, 1.4 Hz, $CH_b$-(7)), 3.73 (3H, s, $CH_3$-(8)), 3.53 (1H, q, *J*=7.1 Hz, CH-(2)), 2.68 (1H, dt, *J*=17.7, 7.3 Hz, $CH_a$-(4)), 2.59 (1H, dt, *J*=17.7, 7.3 Hz, $CH_b$-(4)), 2.34 (2H,

qt, *J*=7.4, 1.5 Hz, $CH_2$-(5)), 1.34 (3H, d, *J*=7.3 Hz, $CH_3$-(9)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 205.1 (C(3), 171.1 (C(1), 136.9 (C(6), 115.6 (C(7), 52.9 (C(2), 52.5 (C(8), 40.6 (C(4), 27.6 (C(5), 12.9 (C(9)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2953, 1745 (s, C=O), 1715 (s, C=O), 1642, 1454, 1436, 1377, 1329, 1242, 1203, 1177, 1124, 1073; **HRMS** ($apci^+$) found 171.1017, $C_9H_{15}O_3^+$ requires 171.1016. Compound previously reported (no spectroscopic data available to compare).[188,189]

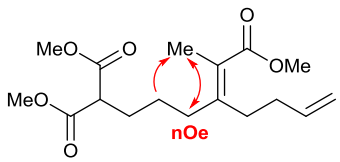
### Methyl (*E*)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate (3.45)


Prepared according to general procedure GP3 method B, using methyl 2-methyl-3-oxohept-6-enoate **3.44** (660 mg, 3.88 mmol, 1.0 eq.), KHMDS (0.5 M in toluene, 9.3 mL, 4.65 mmol, 1.2 eq.) and $PhNTf_2$ (1.52 g, 4.27 mmol, 1.1 eq.). TLC (20% $Et_2O$ in $PE_{30\text{-}40}$) showed complete reaction after 3.5 h. Crude: yellow liquid. Purification by flash-chromatography (eluent: 5% $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 6.5 cm, L = 8.5 cm) afforded the title product as a colourless liquid (987 mg, 3.26 mmol, 84%).

**$R_f$** 0.64 (20% $Et_2O$ in $PE_{30\text{-}40}$, $KMnO_4$, $UV_{254\,nm}$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.77 (1H, ddt, *J*=17.0, 10.1, 6.8 Hz, CH-(6)), 5.06 (1H, dq, *J*=17.0, 1.6 Hz, $CH_a$-(7)), 5.02 (1H, dq, *J*=10.2, 1.4, 1.3 Hz, $CH_b$-(7)), 3.80 (3H, s, $CH_3$-(9)), 2.88 (2H, tq, *J*=7.6, 1.1 Hz, $CH_2$-(4)), 2.33 (2H, tdt, *J*=7.7, 6.6, 1.3 Hz, $CH_2$-(5)), 2.01 (3H, t, *J*=1.1 Hz, $CH_3$-(10)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 166.9 (C(1)), 157.6 (C(3)), 136.0 (C(6)), 123.5 (C(2)), 118.4 (q, *J*=319.7 Hz, C(8)), 116.4 (C(7)), 52.6 (C(9)), 32.0 (C(4)), 31.0 (C(5)), 14.3 (C(10)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 1729 (s, C=O), 1662 (w, C=C), 1645 (w, C=C), 1415 (s), 1284, 1246, 1207 (s), 1137, 1100, 1021; **HRMS** ($ESI^+$) found 303.0511, $C_{10}H_{14}O_5F_3{}^{32}S^+$ requires 303.0509.

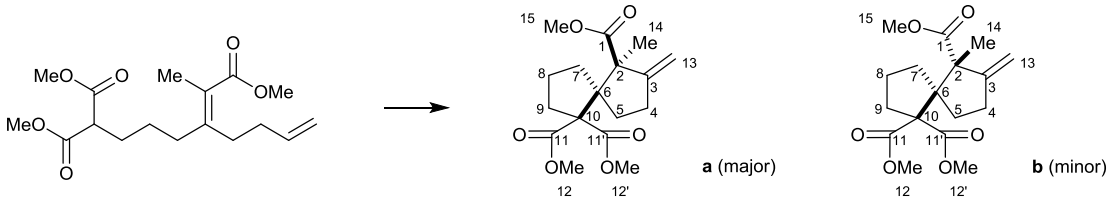
### Trimethyl (*Z*)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate (3.46)


Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 2.32 mL, 1.16 mmol, 1.5 eq.), dimethyl 2-allylmalonate **3.17** (0.20 mL, 1.23 mmol, 1.6 eq.), $K_3PO_{4(aq)}$ (1 M, 1.90 mL, 1.90 mmol, 2.5 eq.), methyl (E)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.45** (233 mg, 0.77 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (44.5 mg, 0.039 mmol, 0.05 eq.). The mixture was heated to 50 °C until complete consumption of the **3.45** was observed by TLC (20% $Et_2O$ in $PE_{40\text{-}60}$) after 17 h. Crude: black liquid. Purification by flash-chromatography (eluent: 7% EtOAc in toluene; column size: Ø = 5 cm, L = 9 cm) followed by a second purification by flash-chromatography (eluent: 5% (250 mL), 10% (350 mL), 20% $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 5 cm, L = 9 cm) afforded the title product as colourless liquid (185.2 mg, 0.57 mmol, 80%).

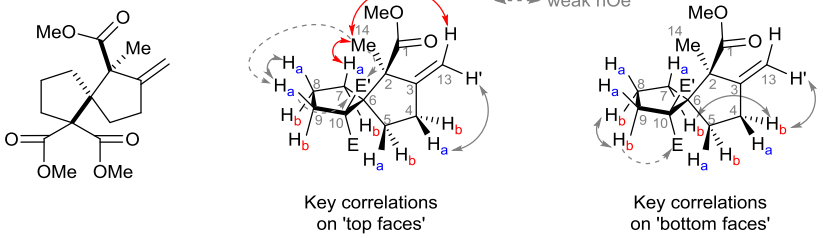



**$R_f$** 0.40 (5% EtOAc in toluene, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.30 (20% $Et_2O$ in PE, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=16.9, 10.1, 6.6 Hz, CH-(9)), 5.01 (1H, dq, *J*=17.0, 1.6 Hz, $CH_a$-(10)), 4.94 (1H, ddt, *J*=10.2, 2.2, 1.3 Hz, $CH_b$-(10)), 3.74 (6H, s, 2 $CH_3$-(11)), 3.70 (3H, s, $CH_3$-(14)), 3.38 (1H, t, *J*=7.6 Hz, CH-(2)), 2.40 – 2.34 (2H, m, $CH_2$-(7)), 2.20 – 2.12 (4H, m, $CH_2$-(5), $CH_2$-(8)), 1.97 – 1.90 (2H, m, $CH_2$-(3)), 1.84 (3H, s, $CH_3$-(15)), 1.47 – 1.39 (2H, m, $CH_2$-(4)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 170.1 (C(13)) 169.8 (2 C(1))) 149.1 (C(6)) 138.4 (C(9)) 123.9 (C(12)) 114.7 (C(10)) 52.7 (2 C(11)) 51.6 (C(2)) 51.5 (C(14)) 33.8 (C(7)) 33.4 (C(5)) 33.1 (C(8)) 29.1 (C(3)) 25.5 (C(4)) 15.6 (C(15)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2923, 1752, 1735 (s, C=O), 1715 (s, C=O), 1639 (m with shoulder, C=C), 1435 (m), 1279, 1223, 1193, 1152, 1103; ***m/z*** ($ESI^+$) 349.2 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 349.1615, $C_{17}H_{26}O_6{}^{23}Na^+$ requires 349.1622.

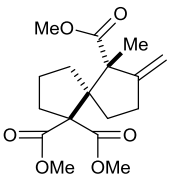
### Trimethyl (5*R**,6*S**)-6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (3.47)




Prepared according to general procedure GP6, using trimethyl (*Z*)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.46** (135 mg, 0.41 mmol, 1.0 eq.), $Mn(OAc)_3 \bullet 2H_2O$ (222 mg, 0.82 mmol, 2.0 eq.), $Cu(OAc)_2 \bullet H_2O$ (83 mg, 0.41 mmol, 1.0 eq.). The reaction was heated to 40 °C until TLC (10% EtOAc in toluene, vanillin) showed complete consumption of the starting material after 4 days. Purification by flash-chromatography (eluent: 5% EtOAc in toluene; column size: Ø = 2 cm, L = 13 cm) afforded the title product as a colourless oil as a mixture of diastereomers (4.5:1 *d.r.*, 73 mg, 0.22 mmol, 54%).

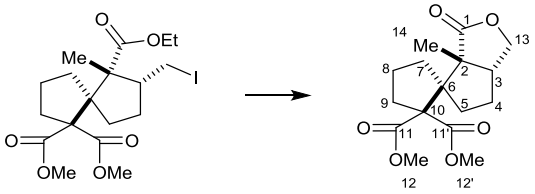



**Major isomer 3.47a** (analysed as a pure isomer)**:** $\mathbf{R_f}$ 0.41 (10% EtOAc in toluene, not $UV_{254\ nm}$, vanillin, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (600 MHz, $CDCl_3$) 4.92 (1H, t, *J*=2.0 Hz, CH'-(13)), 4.90 (1H, t, *J*=2.2 Hz, CH-(13)), 3.71 (3H, s, $CH_3$-(12')), 3.67 (3H, s, $CH_3$-(12)), 3.60 (3H, s, $CH_3$-(15)), 2.65 – 2.56 (2H, m, $CH_a$-(4), $CH_{a\ or\ b}$-(5)), 2.49 (1H, ddd, *J*=13.7, 9.8, 5.1 Hz, $CH_a$-(9)), 2.42 – 2.33 (1H, m, $CH_b$-(4)), 2.24 (1H, ddd, *J*=13.8, 11.1, 5.8 Hz, $CH_b$-(9)), 1.93 – 1.86 (1H, m, $CH_a$-(7)), 1.83 – 1.75 (1H, m, $CH_a$-(8)), 1.75 – 1.67 (1H, m, $CH_b$-(8)), 1.65 – 1.59 (1H, m, $CH_{a\ or\ b}$-(5)), 1.51 (1H, ddd, *J*=12.9, 8.6, 2.6 Hz, $CH_b$-(7)), 1.27 (3H, s, $CH_3$-(14)); $\boldsymbol{\delta_C}$ /ppm (151 MHz, $CDCl_3$) 175.1 (C(1)), 171.8 (C(11')), 171.6 (C(11)), 156.6 (C(3)), 107.2 (C(13)), 64.2 (C(10)), 63.0 (C(6)), 57.1 (C(2)), 52.2 (C(12)), 52.1 (C(12')), 51.7 (C(15)), 35.6 (C(9)), 33.2 (C(7)), 31.2 (C(5)), 29.4 (C(4)), 20.3 (C(14)), 19.4 (C(8)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 1725 (s, C=O, with shoulder), 1650 (w), 1433 (m, with shoulder), 1256, 1196, 1173, 1113, 1091, 1063; **HRMS** (apci$^+$) found 325.1645, $C_{17}H_{25}O_6^+$ requires 325.1646.



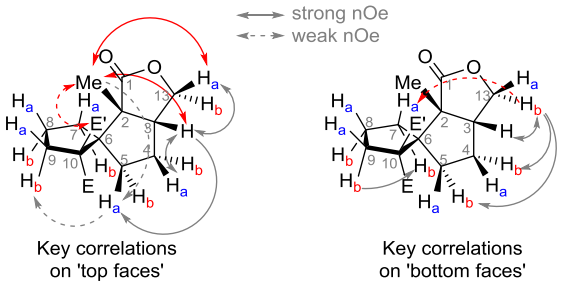
**Minor isomer 3.47b** (analysed as a mixture with **3.23** (*ca.* 10%) as an impurity): $\mathbf{R_f}$ 0.50 (10% EtOAc in toluene, not $UV_{254\,nm}$, vanillin, $KMnO_4$); $\mathbf{\delta_H}$ /ppm (600 MHz, $CDCl_3$) 4.84 (1H, t, *J*=2.2 Hz, CH'-(13)), 4.74 (1H, t, *J*=2.5 Hz, CH-(13)), 3.67 (3H, s, $CH_3$-(15)), 3.66 (3H, s, $CH_3$-(12)), 3.64 (3H, s, $CH_3$-(12)), 2.57 (1H, dddt, *J*=17.4, 10.2, 7.8, 2.6 Hz, $CH_a$-(4)), 2.46 – 2.39 (1H, m, $CH_a$-(7)), 2.39 – 2.31 (2H, m, $CH_b$-(4), $CH_a$-(9)), 2.28 (1H, ddd, *J*=13.8, 9.2, 4.2 Hz, $CH_b$-(9)), 2.22 (1H, dddd, *J*=13.5, 9.4, 7.9, 1.3 Hz, $CH_a$-(5)), 1.78 – 1.66 (3H, m, $CH_b$-(5), $CH_2$-(8)), 1.60 – 1.55 (1H, m, $CH_b$-(7)), 1.39 (3H, s, $CH_3$-(14)); $\mathbf{\delta_C}$ /ppm (151 MHz, $CDCl_3$) 175.5 (C(1)), 172.3 (C(11)), 171.7 (C(11')), 157.7 (C(3)), 105.5 (C(13)), 64.6 (C(10)), 64.3 (C(6)), 59.0 (C(2)), 52.2 (C(11 or 11' or 15)), 51.9 (C(11 or 11' or 15)), 51.7 (C(11 or 11' or 15)), 35.2 (C(9)), 34.6 (C(7)), 32.8 (C(5)), 29.3 (C(4)), 21.6 (C(14)), 19.5 (C(8)); $\mathbf{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2952, 1725 (s, with shoulder, C=O), 1651 (w), 1434, 1250, 1195, 1173, 1113, 1086, 1034; ***m/z*** ($ESI^+$) 671.3 ($[2M+Na]^+$, 100%), 347.1 ($[M+Na]^+$, 50%); **HRMS** ($ESI^+$) found 347.1464, $C_{17}H_{24}O_6{}^{23}Na^+$ requires 347.1465.

### Dimethyl (1*R**,3*a*'*R**,6*a*'*R**)-3*a*'-methyl-3'-oxohexahydrospiro[cyclopentane-1,4'-cyclopenta[*c*]furan]-2,2-dicarboxylate (3.49)



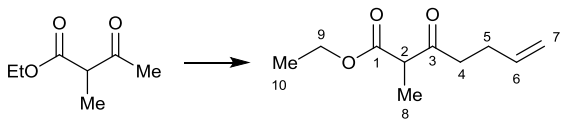
Neat 6-ethyl 1,1-dimethyl (5*R**,6*R**,7*R**)-7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate **5.17** (2.1 mg, 4.5 µmol) was heated to 140 °C in a vial under argon for 5 h. TLC (40% $Et_2O$ in PE, sample needs to be very concentrated, $KMnO_4$) showed a spot to spot reaction. $N_2$ flow on the sample (to remove any residual ethyl iodide formed) gave the title product as a colourless oil (1.5 mg, quant.).

[Lactone **3.49** was observed the reaction forming bicyclic compound **5.17** but was never isolated directly as it was coeluting with other unknown species. See experimental details and notes of compound **5.16**/**5.17** for more information.]




**$R_f$** 0.21 (40% $Et_2O$ in $PE_{40\text{-}60}$, slight $UV_{254\,nm}$ activity, weak vanillin, good $KMnO_4$), 0.60 (10% EtOAc in $CH_2Cl_2$, slight $UV_{254\,nm}$ activity, weak vanillin, good $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 4.39 (1H, dd, *J*=9.3, 8.4 Hz, $CH_a$-(13)), 3.94 (1H, dd, *J*=9.3, 5.1 Hz, $CH_b$-(13)), 3.80 (3H, s, $CH_3$-(12')), 3.73 (3H, s, $CH_3$-(12)), 2.82 (1H, tdd, *J*=8.7, 6.7, 5.1 Hz, CH-(3)), 2.52 – 2.41 (2H, m, $CH_a$-(5), $CH_a$-(7)), 2.36 (1H, ddd, *J*=14.0, 9.9, 3.7 Hz, $CH_a$-(9)), 2.18 (1H, ddd, *J*=14.0, 6.9, 3.8 Hz, $CH_b$-(9)), 2.06 (1H, dtd, *J*=13.3, 8.6, 3.2 Hz, $CH_a$-(4)), 2.03 – 1.90 (1H, m, CH-(8)), 1.78 – 1.69 (1H, m, CH-(8)), 1.66 (2H, ddd, *J*=12.9, 8.0, 2.7 Hz, $CH_b$-(5), $CH_b$-(7)), 1.58 – 1.55 (2H, m, $CH_b$-(4)), 1.53 (3H, s, $CH_3$-(14)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 180.1 (C(1)), 172.1 (C(11')), 171.5 (C(11)), 72.0 (C(13)), 65.0 (C(10)), 61.3 (C(6)), 55.4 (C(2)), 52.7 (C(12')), 52.2 (C(12)), 49.7 (C(3)), 36.2 (C(5)), 35.1 (C(9)), 34.4 (C(7)), 28.4 (C(4)), 21.1 (C(14)), 19.6 (C(8)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2987, 2953, 2922, 2852, 1762 (s, C=O), 1729 (s, C=O), 1460, 1434, 1376, 1259 (s), 1221, 1196, 1137, 1104, 1080 (s), 1020 (m); ***m/z*** ($ESI^+$) 333.2 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 333.1308, $C_{16}H_{22}O_6{}^{23}Na^+$ requires 333.1309.

### Ethyl 2-methyl-3-oxohept-6-enoate (3.52)

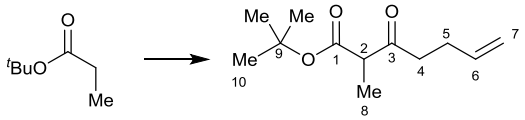


Prepared according to general procedure GP1 using NaH (60% in mineral oil, 3.21 g, 80.6 mmol, 1.25 eq.), ethyl 2-methyl-3-oxobutanoate (9.1 mL, 64.5 mmol, 1.0 eq.), *n*-BuLi solution (2.50 M in hexane, 28.4 mL, 70.9 mmol, 1.1 eq.) and allyl bromide (5.6 mL, 64.5 mmol, 1.0 eq.). Reaction was stirred at 0 °C for 1.6 h before being quenched. Purification by flash-chromatography (eluent: 0%

(250 mL) to 15% (500 mL) to 20% (500 mL) to 50% (800 mL) $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 7 cm, L = 7 cm) afforded the title product as a yellow liquid (8.4 g, 45.4 mmol, 70%).

Analysed as the keto/enol mixture (~1:0.1 ratio): **$R_f$** 0.47 (20% $Et_2O$ in $PE_{40\text{-}60}$, weak $UV_{254\ nm}$, $KMnO_4$), 0.63 (35% $Et_2O$ in $PE_{40\text{-}60}$, weak $UV_{254\ nm}$, $KMnO_4$); **keto form (major): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.79 (1H, ddt, *J*=16.8, 10.2, 6.5 Hz, CH-(6)), 5.03 (1H, dq, *J*=17.1, 1.6 Hz, $CH_a$-(7)), 4.98 (1H, dq, *J*=10.2, 1.4 Hz, $CH_b$-(7)), 4.18 (2H, qd, *J*=7.1, 1.1 Hz, $CH_2$-(9)), 3.51 (1H, q, *J*=7.1 Hz, CH-(2)), 2.68 (1H, dt, *J*=17.5, 7.4 Hz, $CH_a$-(4)), 2.60 (1H, dt, *J*=17.5, 7.2 Hz, $CH_b$-(4)), 2.37 – 2.31 (2H, m, $CH_2$-(5)), 1.33 (3H, d, *J*=7.2 Hz, $CH_3$-(8)), 1.26 (3H, t, *J*=7.1 Hz, $CH_3$-(10)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 205.2 (C(3)), 170.7 (C(1)), 136.9 (C(6)), 115.6 (C(7)), 61.5 (C(9)), 53.1 (C(2)), 40.6 (C(4)), 27.7 (C(5)), 14.2 (C(10)), 12.9 (C(8)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 1741 (s, C=O), 1714 (s, C=O), 1642 (w, C=C), 1193 (s), 1117; ***m/z*** ($ESI^+$) 207.0 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 207.0992, $C_{10}H_{16}O_3{}^{23}Na^+$ requires 207.0992.

### *tert*-Butyl 2-methyl-3-oxohept-6-enoate (3.53)

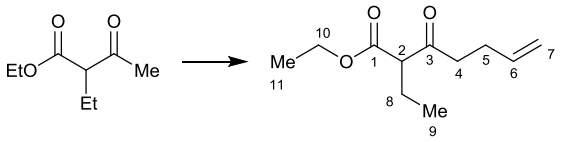



According to the modified procedure of Lanners *et al.*[190] Enolate solution preparation: To a flame-dried 150 mL flask containing a solution of diisopropylamine (13.8 mL, 98.65 mmol, 4.0 eq.) in dry THF (10 mL) at -78 °C under argon was added *n*-BuLi (2.5 M in hexane, 39.5 mL, 98.65 mmol, 4.0 eq.) over 7 min and stirred for 30 min. A solution of *tert*-butyl propionate (7.4 mL, 130.18 mmol, 2.0 eq.) in dry THF (7.5 mL) was added over 6 min and stirred for an additional 30 min. Activated acid solution: To a flame-dried 250 mL flask containing a solution of 4-pentenoic acid (2.51 mL, 24.65 mmol, 1.0 eq.) in dry THF (25 mL) at room temperature under argon was added in 2 portions every 10 min (gas evolution was observed). Stirring was continued for an additional 1 h and then cooled to -78 °C.

The enolate solution was added over 15 min via canula to the activated ester solution at -78 °C, stirred for 15 min and then the reaction was allowed to warm up to room temperature (bath removed) overnight. Quenching of the cloudy heterogeneous mixture was performed by addition $NH_4Cl_{(aq)}$ (sat. sol. 150 mL) followed by water to dissolve the remaining salts. Layers were separated and the aqueous was extracted with $Et_2O$ (2x 50 mL). The combined organic layers were washed with brine (50 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure (25 °C bath, 20 mbar). Purification of the crude mixture by flash-chromatography (eluent: 5% (500 mL), 10% (500 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 7 cm, L = 7 cm) afforded the title product as colourless liquid (4.31 g, 20.30 mmol, 82%).

Analysed as the keto/enol mixture (~1:0.05 ratio): **$R_f$** 0.73 (30% $Et_2O$ in $PE_{30\text{-}40}$, vanillin, $KMnO_4$); **keto form (major): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.80 (1H, ddt, *J*=16.9, 10.2, 6.5 Hz, CH-(6)), 5.03 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-(7)), 4.98 (1H, dq, *J*=10.2, 1.4 Hz, $CH_b$-(7)), 3.42 (1H, q, *J*=7.1 Hz, CH-(2)), 2.72 – 2.65 (1H, m, $CH_a$-(4)), 2.58 (1H, dt, *J*=17.3, 7.2 Hz, $CH_b$-(4)), 2.34 (2H, qt, *J*=7.1, 1.5 Hz, $CH_2$-(5)), 1.45 (8H, s, 3 $CH_3$-(10)), 1.28 (3H, dd, *J*=7.1, 1.3 Hz, $CH_3$-(8)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 205.5 (C(3)), 169.8 (C(1)), 137.0 (C(6)), 115.5 (C(7)), 81.9 (C(9)), 54.1 (C(2)), 40.6 (C(4)), 28.1 (3 C(10)), 27.7 (C(5)), 12.8 (C(8)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2980, 2939, 1737 (s, C=O), 1714 (s, C=O), 1456, 1369, 1252, 1153 (s); ***m/z*** ($ESI^+$) 235.0 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 235.1306, $C_{12}H_{20}O_3{}^{23}Na^+$ requires 235.1305. Data in accordance with the literature.[190]

### Ethyl 2-ethyl-3-oxohept-6-enoate (3.54)

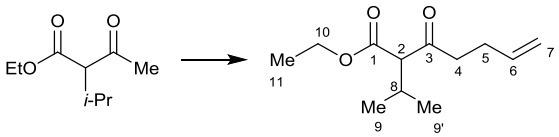



Prepared according to general procedure GP1 using NaH (60% in mineral oil, 1.56 g, 40.3 mmol, 1.25 eq.), ethyl 2-ethyl-3-oxobutanoate (5.2 mL, 32.2 mmol, 1.0 eq.), *n*-BuLi solution (2.50 M in

hexane, 14.2 mL, 35.5 mmol, 1.1 eq.) and allyl bromide (2.8 mL, 32.2 mmol, 1.0 eq.). Reaction was stirred at 0 °C for 65 min before being quenched. Purification by flash-chromatography (eluent: 0% (250 mL) to 10% (500 mL) to 15% (500 mL) to 50% (250 mL) $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 6 cm, L = 7 cm) afforded the title product as a yellow liquid (5.5 g, 27.6 mmol, 86%).

Analysed as the keto/enol mixture (~1:0.05 ratio): **$R_f$** 0.67 (30% $Et_2O$ in $PE_{30\text{-}40}$, weak $UV_{254\ nm}$, vanillin, $KMnO_4$); **keto form (major): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.78 (1H, ddt, *J*=16.9, 10.3, 6.5 Hz, CH-(6)), 5.02 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-(7)), 4.97 (1H, dq, *J*=10.2, 1.5 Hz, $CH_b$-(7)), 4.18 (2H, q, *J*=7.1 Hz, $CH_2$-(10)), 3.34 (1H, t, *J*=7.4 Hz, CH-(2)), 2.65 (1H, dt, *J*=17.6, 7.4 Hz, $CH_a$-(4)), 2.57 (1H, dt, *J*=17.7, 7.2 Hz, $CH_b$-(4)), 2.33 (2H, qt, *J*=7.4, 1.5 Hz, $CH_2$-(5)), 1.87 (2H, pd, *J*=7.4, 2.7 Hz, $CH_2$-(8)), 1.25 (3H, t, *J*=7.1 Hz, $CH_3$-(11)), 0.91 (3H, t, *J*=7.4 Hz, $CH_3$-(9)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 204.7 (C(3)), 169.9 (C(1)), 136.9 (C(6)), 115.5 (C(7)), 61.4 (C(10)), 60.9 (C(2)), 41.1 (C(4)), 27.6 (C(5)), 21.7 (C(8)), 14.3 (C(11)), 12.1 (C(9)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2970, 2930, 2879, 2857, 1741 (s, C=O), 1714 (s, C=O), 1642 (w, C=C), 1460, 1446, 1368, 1255, 1184 (s), 1132, 1023; ***m/z*** ($ESI^+$) 221.0 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 221.1149, $C_{11}H_{18}O_3{}^{23}Na^+$ requires 221.1148.

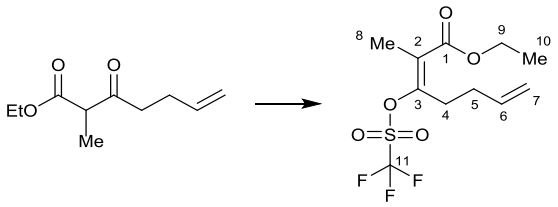
### Ethyl 2-isopropyl-3-oxohept-6-enoate (3.55)




Prepared according to general procedure GP1 using NaH (60% in mineral oil, 1.56 g, 40.3 mmol, 1.25 eq.), ethyl 2-isopropyl-3-oxobutanoate (5.8 mL, 32.2 mmol, 1.0 eq.), *n*-BuLi solution (2.50 M in hexane, 14.2 mL, 35.5 mmol, 1.1 eq.) and allyl bromide (2.8 mL, 32.2 mmol, 1.0 eq.). Reaction was stirred at 0 °C for 50 min before being quenched. Purification by flash-chromatography (eluent: 0% (250 mL) to 10% (500 mL) to 15% (500 mL) to 50% (250 mL) $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 6 cm, L = 7 cm) afforded the title product as a yellow liquid (6.3 g, 29.8 mmol, 93%).

**$R_f$** 0.68 (30% $Et_2O$ in $PE_{30\text{-}40}$, vanillin, $KMnO_4$, weak $UV_{254\ nm}$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.78 (1H, ddt, *J*=16.8, 10.2, 6.5 Hz, CH-(6)), 5.03 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-(7)), 4.97 (1H, dq, *J*=10.2, 1.4 Hz, $CH_b$-(7)), 4.17 (2H, q, *J*=7.1 Hz, $CH_2$-(10)), 3.21 (1H, d, *J*=9.6 Hz, CH-(2)), 2.64 (1H, dt, *J*=17.8, 7.4 Hz, $CH_a$-(4)), 2.57 (1H, ddd, *J*=17.8, 7.6, 6.8 Hz, $CH_b$-(4)), 2.43 (1H, dp, *J*=9.6, 6.7 Hz, $CH_2$-(8)), 2.37 – 2.30 (2H, m, $CH_2$-(5)), 1.26 (3H, t, *J*=7.1 Hz, $CH_3$-(11)), 0.96 (3H, d, *J*=6.6 Hz, $CH_3$-(9)), 0.90 (3H, d, *J*=6.7 Hz, $CH_3$-(9')); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 204.5 (C(3)), 169.2 (C(1)), 136.9 (C(6)), 115.6 (C(7)), 67.1 (C(2)), 61.3 (C(10)), 41.7 (C(4)), 28.8 (C(8)), 27.5 (C(5)), 20.7 (C(9')), 20.6 (C(9)), 14.3 (C(11)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2965, 1740 (s, C=O), 1713 (s, C=O), 1642 (w), 1467, 1369, 1290, 1226, 1183, 1120, 1031; **HRMS** ($ESI^+$) found 235.1306, $C_{12}H_{20}O_3{}^{23}Na^+$ requires 235.1305.

### Ethyl (*E*)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate (3.56)

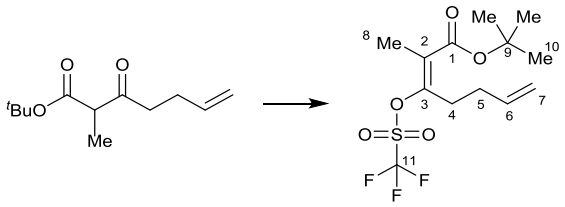



Prepared according to general procedure GP3 method B, using ethyl 2-methyl-3-oxohept-6-enoate **3.52** (4.05 g, 21.75 mmol, 1.0 eq.), KHMDS (0.5 M in toluene, 53 mL, 26.50 mmol, 1.2 eq.) and $PhNTf_2$ (8.67 g, 24.3 mmol, 1.1 eq.). TLC (20% $Et_2O$ in $PE_{30\text{-}40}$) showed complete reaction after 1.5 h. Purification by flash-chromatography (eluent: 5% to 10% $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 7.5 cm, L = 10 cm) afforded the title product as a pale yellow liquid (5.23 g, 16.53 mmol, 76%).

**$R_f$** 0.54 (10% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.77 (1H, ddt, *J*=16.9, 10.1, 6.7 Hz, CH-(6)), 5.06 (1H, dq, *J*=17.1, 1.6 Hz, $CH_a$-(7)), 5.02 (1H, dq, *J*=10.2, 1.3 Hz, $CH_b$-(7)), 4.25 (2H, q, *J*=7.1 Hz, $CH_2$-(9)), 2.90 – 2.84 (2H, m, $CH_2$-(4)), 2.37 – 2.31 (2H, m, $CH_2$-(5)), 2.00 (3H, d, *J*=1.0 Hz, $CH_3$-(8)), 1.32 (3H, t, *J*=7.1 Hz, $CH_3$-(10)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 166.5 (C(1)), 157.2 (C(3)), 136.0 (C(6)), 123.8 (C(2)), 118.6 (q, *J*=319.7 Hz, C(11)), 116.4 (C(7)), 61.8 (C(9)), 32.0 (C(4)), 31.0 (C(5)), 14.3 (C(8)), 14.2 (C(10)); **$\delta_F$** /ppm (470 MHz, $CDCl_3$) -74.63; **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2982, 1724 (s, C=O),

1418, 1246 (s), 1211 (s), 1140; ***m/z*** ($ESI^+$) 317.1 ($[M+H]^+$, 100%); **HRMS** ($ESI^+$) found 317.0666, $C_{11}H_{16}O_5F_3{}^{32}S^+$ requires 317.0665.

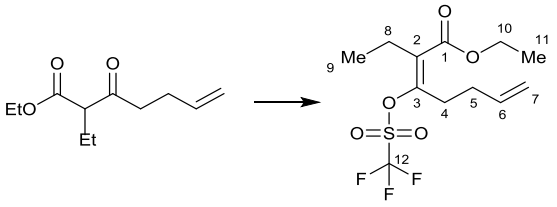
### *tert*-Butyl (*E*)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate (3.57)




Prepared according to general procedure GP3 method B, using *tert*-butyl 2-methyl-3-oxohept-6-enoate **3.53** (824 mg, 3.88 mmol, 1.0 eq.), KHMDS (0.5 M in toluene, 9.3 mL, 4.65 mmol, 1.2 eq.) and $PhNTf_2$ (1.52 g, 4.27 mmol, 1.1 eq.). TLC (10% $Et_2O$ in $PE_{30\text{-}40}$) showed complete reaction after 2 h. Purification by flash-chromatography (eluent: 5% (1 L) $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 5 cm, L = 7 cm) afforded the title product as a colourless liquid (~90:10 *E*/*Z* mix., 1.08 g, 3.14 mmol, 81%).

Analysed as a *E*/*Z* mixture (~90:10 ratio): $\mathbf{R_f}$ 0.64 (10% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\,nm}$, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.78 (1H, ddt, *J*=16.9, 10.2, 6.7 Hz, CH-(6)), 5.07 (1H, dq, *J*=17.5, 1.7 Hz, $CH_a$-(7)), 5.02 (1H, dq, *J*=10.3, 1.3 Hz, $CH_b$-(7)), 2.84 – 2.78 (2H, m, $CH_2$-(4)), 2.36 – 2.30 (2H, m, $CH_2$-(5)), 1.96 (3H, t, *J*=0.8 Hz, $CH_3$-(8)), 1.51 (9H, s, 3 $CH_3$-(10)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 165.7 (C(1)), 155.8 (C(3)), 136.1 (C(6)), 125.1 (C(2)), 118.4 (q, *J*=319.6 Hz, C(11)), 116.3 (C(7)), 82.8 (C(9)), 31.9 (C(4)), 31.0 (C(5)), 28.2 (3 C(10)), 14.6 (C(8)); $\boldsymbol{\delta_F}$ /ppm (470 MHz, $CDCl_3$) -74.70; $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 1718 (s, C=O), 1416, 1208 (s), 1138 (m); ***m/z*** ($ESI^+$) 367.1 ($[M+Na]^+$, 100%), 711.2 ($[2M+Na]^+$, 70%); **HRMS** ($ESI^+$) found 367.0802, $C_{13}H_{19}O_5F_3{}^{23}Na^{32}S^+$ requires 367.0798.

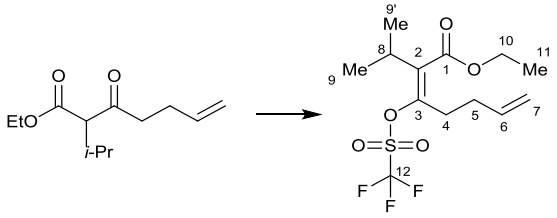
### Ethyl (*E*)-2-ethyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate (3.58)




Prepared according to general procedure GP3 method B, using ethyl 2-ethyl-3-oxohept-6-enoate **3.54** (769 mg, 3.88 mmol, 1.0 eq.), KHMDS (0.5 M in toluene, 9.3 mL, 4.65 mmol, 1.2 eq.) and $PhNTf_2$ (1.52 g, 4.27 mmol, 1.1 eq.). TLC (10% $Et_2O$ in $PE_{30\text{-}40}$) showed complete reaction after 1.5 h. Purification by flash-chromatography (eluent: 2.5% (250 mL) to 5% (500 mL) $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 5 cm, L = 7 cm) afforded the title product as a colourless liquid (1.03 g, 3.11 mmol, 80%).

**$R_f$** 0.49 (10% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.76 (1H, ddt, *J*=17.0, 10.2, 6.8 Hz, CH-(6)), 5.05 (1H, dq, *J*=16.6, 1.3 Hz, $CH_a$-(7)), 5.02 (1H, dq, *J*=10.2, 1.3 Hz, $CH_b$-(7)), 4.26 (2H, t, *J*=7.1 Hz, $CH_2$-(10)), 2.78 (2H, dd, *J*=8.6, 6.6 Hz, $CH_b$-(5)), 2.45 (2H, q, *J*=7.5 Hz, $CH_2$-(8)), 2.33 (2H, tdt, *J*=7.8, 6.8, 1.3 Hz, $CH_2$-(4)), 1.33 (3H, t, *J*=7.1 Hz, $CH_3$-(11)), 1.05 (3H, t, *J*=7.5 Hz, $CH_3$-(9)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 166.4 (C(1)), 155.0 (C(3)), 136.0 (C(6)), 130.0 (C(2)), 118.5 (q, *J*=319.7 Hz, C(12)), 116.4 (C(7)), 61.7 (C(10)), 32.0 (C(5)), 31.1 (C(4)), 22.0 (C(8)), 14.2 (C(11)), 12.8 (C(9)); **$\delta_F$** /ppm (470 MHz, $CDCl_3$) -74.70; **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2982, 2942, 2883, 1725 (s, C=O), 1417 (s), 1305, 1242, 1213 (s), 1141 (m); ***m/z*** ($ESI^+$) 331.1 ($[M+H]^+$, 100%); **HRMS** ($ESI^+$) found 331.0821, $C_{12}H_{18}O_5F_3{}^{32}S^+$ requires 331.0822.

### Ethyl (*E*)-2-isopropyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate (3.59)



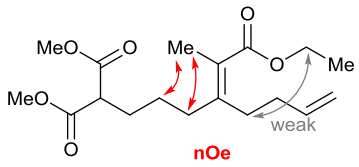
Prepared according to general procedure GP3 method B, using ethyl 2-isopropyl-3-oxohept-6-enoate **3.55** (824 mg, 3.88 mmol, 1.0 eq.), KHMDS (0.5 M in toluene, 9.3 mL, 4.65 mmol, 1.2 eq.) and $PhNTf_2$ (1.52 g, 4.27 mmol, 1.1 eq.). TLC (10% $Et_2O$ in $PE_{30\text{-}40}$) showed complete reaction after 1.5 h. Purification by flash-chromatography (eluent: 2.5% (250 mL) to 5% (500 mL) $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 5 cm, L = 7 cm) afforded the title product as a colourless liquid (1.05 g, 3.05 mmol, 79%).

**$R_f$** 0.53 (10% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.75 (1H, dddd, *J*=18.5, 10.2, 7.4, 6.0 Hz, CH-(6)), 5.08 – 4.99 (2H, m, $CH_2$-(7)), 4.27 (2H, qd, *J*=7.1, 1.5 Hz, $CH_2$-(10)), 3.03 (1H, pd, *J*=6.9, 1.5 Hz, CH-(8)), 2.50 (2H, ddd, *J*=7.8, 6.5, 1.5 Hz, $CH_2$-(4)), 2.33 – 2.28 (2H, m, $CH_2$-(5)), 1.33 (3H, td, *J*=7.1, 1.4 Hz, $CH_3$-(11)), 1.13 (6H, dd, *J*=6.8, 1.5 Hz, $CH_3$-(9), $CH_3$-(9')); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 166.3 (C(1)), 149.2 (C(3)), 135.9 (C(6)), 134.6 (C(2)), 118.5 (q, *J*=319.6 Hz, C(12)), 116.4 (C(7)), 61.5 (C(10)), 32.1 (C(4)), 30.9 (C(5)), 28.1 (C(8)), 20.7 (C(9), C(9')), 14.3 (C(11)); **$\delta_F$** /ppm (470 MHz, $CDCl_3$) -74.74; **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2979, 1730 (s, C=O), 1416 (s), 1276 (w), 1245, 1212 (s), 1142, 1033; ***m/z*** ($ESI^+$) 367.1 ($[M+Na]^+$, 100%), 345.1 ($[M+H]^+$, 60%); **HRMS** ($ESI^+$) found 367.0799, $C_{13}H_{19}O_5F_3{}^{23}Na^{32}S^+$ requires 367.0798.

### 6-Ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate (3.60)

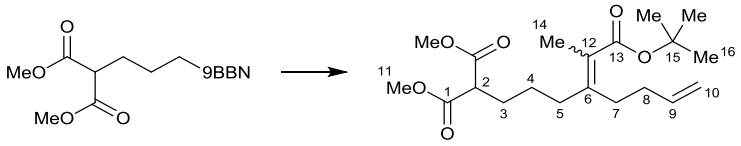
Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 4.64 mL, 2.32 mmol, 1.5 eq.), dimethyl 2-allylmalonate **3.17** (0.40 mL, 2.46 mmol, 1.6 eq.), $K_3PO_{4(aq)}$ (1 M, 3.8 mL,

3.80 mmol, 2.5 eq.), ethyl (*E*)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.56** (487 mg, 1.54 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (88 mg, 0.08 mmol, 0.05 eq.). The mixture was heated to 50 °C until complete consumption of the **3.56** was observed by TLC (20% $Et_2O$ in $PE_{40\text{-}60}$) after 17 h. Crude: yellow liquid. Purification by flash-chromatography (eluent: 7% EtOAc in toluene; column size: Ø = 5.5 cm, L = 10 cm) followed by a second purification by flash-chromatography (eluent: 5% (250 mL), 10% (350 mL), 20% (750 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 5.5 cm, L = 10 cm) afforded the title product as colourless liquid (90:10 *Z*/*E* mix., 391 mg, 1.15 mmol, 75%).

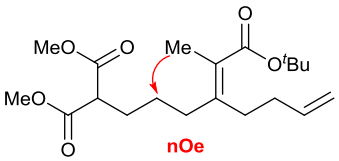



**$R_f$** 0.31 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\,nm}$, vanillin, $KMnO_4$), 0.50 (10% EtOAc in toluene, $UV_{254\,nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=16.9, 10.2, 6.6 Hz, CH-(9)), 5.01 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-(10), 4.95 (1H, ddt, *J*=10.2, 2.4, 1.3 Hz, $CH_b$-(10)), 4.17 (2H, q, *J*=7.1 Hz, $CH_2$-(15), 3.74 (6H, s, 2 $CH_3$-(11)), 3.38 (1H, t, *J*=7.6 Hz, CH-(2)), 2.35 (2H, dd, *J*=9.7, 6.4 Hz, $CH_2$-(7)), 2.20 – 2.15 (2H, m, $CH_2$-(8)), 2.15 – 2.10 (2H, m, $CH_2$-(5)), 1.98 – 1.90 (2H, m, $CH_2$-(3)), 1.84 (3H, s, $CH_3$-(14)), 1.47 – 1.39 (2H, m, $CH_2$-(4)), 1.28 (3H, t, *J*=7.1 Hz, $CH_3$-(16)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 169.7 (C(13)), 169.7 (2 C(1)), 148.0 (C(6)), 138.3 (C(9)), 124.2 (C(12)), 114.6 (C(10)), 60.2 (C(15)), 52.5 (2 C(11)), 51.5 (C(2)), 33.6 (C(7)), 33.1 (C(8)), 33.0 (C(5)), 29.0 (C(3)), 25.4 (C(4)), 15.5 (C(14)), 14.3 (C(16)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2979, 2954, 2869, 1753 (m, C=O), 1735 (s, C=O), 1709 (s, C=O), 1639 (w, C=C), 1436 (m, with shoulder), 1268, 1244, 1222, 1191, 1152, 1100 (s), 1066, 1021; ***m/z*** ($ESI^+$) 363.2 ($[M+Na]^+$, 100%), 703.32 ($[2M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 363.1775, $C_{18}H_{28}O_6{}^{23}Na^+$ requires 363.1778.

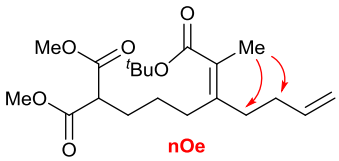
### 6-(*tert*-Butyl) 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate (3.61)




Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 4.64 mL, 2.32 mmol, 1.5 eq.), dimethyl 2-allylmalonate **3.17** (0.40 mL, 2.46 mmol, 1.6 eq.), $K_3PO_{4(aq)}$ (1 M, 3.8 mL, 3.80 mmol, 2.5 eq.), *tert*-butyl (*E*)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.57** (530 mg, 1.54 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (88 mg, 0.08 mmol, 0.05 eq.). The mixture was heated to 50 °C until complete consumption of the **3.57** was observed by TLC (20% $Et_2O$ in $PE_{40\text{-}60}$) after 17 h. Crude: black liquid. Purification by flash-chromatography (eluent: 7% EtOAc in toluene; column size: Ø = 5.5 cm, L = 10 cm) followed by a second purification by flash-chromatography (eluent: 5% (250 mL), 10% (350 mL), 20% (750 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 5.5 cm, L = 10 cm) afforded the title product as a mixture of alkene isomers (60:40 *Z/E* mix., 422 mg, 1.15 mmol, 74%).




(*Z*)-isomer (major)

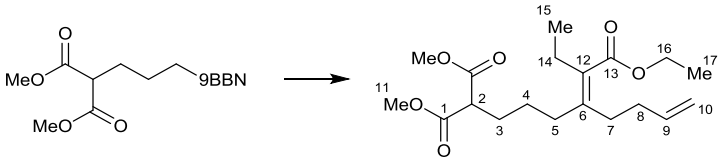



(*E*)-isomer (minor)

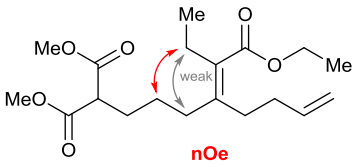
Analysed as a *Z/E* mixture (~1:0.62 ratio): $\mathbf{R_f}$ 0.39 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.59 (10% EtOAc in toluene, $UV_{254\ nm}$, vanillin, $KMnO_4$); $\mathbf{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.89 – 5.80 (2H, m, CH-($9^{cis}$), CH-($9^{trans}$)), 5.07 (1H, dd, *J*=17.1, 1.6 Hz, $CH_a$-($10^{trans}$)), 5.04 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-($10^{cis}$)), 5.01 – 4.96 (1H, m, $CH_b$-($10^{cis}$), $CH_b$-($10^{trans}$)), 3.76 (6H, s, 2 $CH_3$-($11^{cis}$)), 3.75 (4H, s, 2 $CH_3$-($11^{trans}$)), 3.40 (2H, t, *J*=7.6 Hz, CH-($2^{cis}$)), 3.40 (1H, t, *J*=7.8 Hz, CH-($2^{trans}$)), 2.36 – 2.28 (3H, m, $CH_2$-($7^{cis}$), $CH_2$-($5^{trans}$)), 2.22 – 2.16 (2H, m, $CH_2$-($8^{cis}$)), 2.15 (2H, d, *J*=2.2 Hz, $CH_2$-($8^{trans}$)), 2.14 – 2.09 (2H, m, $CH_2$-($5^{cis}$)), 1.99 – 1.91 (3H, m, $CH_2$-($3^{cis}$), $CH_2$-($3^{trans}$)), 1.83 (2H, s, $CH_3$-($14^{trans}$)), 1.82 (3H, s, $CH_3$-($14^{cis}$)), 1.51 (6H, s, 3 $CH_3$-($16^{trans}$)), 1.51 (8H, s, 3 $CH_3$-($16^{cis}$)), 1.49 – 1.40 (4H, m, $CH_2$-($4^{cis}$), $CH_2$-($4^{trans}$)); $\mathbf{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 169.8 (2 C($1^{trans}$)), 169.7 (2 C($1^{cis}$)), 169.7 (C($13^{cis}$)), 169.6 (C($13^{trans}$)), 144.8 (C($6^{trans}$)), 144.6 (C($6^{cis}$)), 138.4 (C($9^{cis}$)), 138.0 (C($9^{trans}$)), 125.9 (C($12^{cis}$)), $12^{trans}$)), 114.9 (C($10^{trans}$)), 114.5 (C($10^{cis}$)), 80.4 (C($15^{cis}$)), 80.3 (C($15^{trans}$)), 52.5 (C($11^{cis}$)), 52.5 (C($11^{trans}$)), 51.6 (C($2^{trans}$)), 51.5 (C($2^{cis}$)), 33.4 (C($5^{trans}$)),

33.2 (C($7^{cis}$)), 32.9 (C($8^{cis}$)), 32.6 (C($5^{cis}$)), 32.4 (C($7^{trans}$ or $8^{trans}$)), 31.8 (C($7^{trans}$ or $8^{trans}$)), 29.0 (C($3^{cis}$)), 29.0 (C($3^{trans}$)), 28.2 (3 C($16^{cis}$), 3 C($16^{trans}$)), 26.5 (C($4^{trans}$)), 25.5 (C($4^{cis}$)), 15.7 (C($14^{trans}$)), 15.7 (C($14^{cis}$)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2976, 2954, 2933, 1754 (m, C=O), 1736 (s, C=O), 1706 (s, C=O), 1639 (w, C=C), 1436, 1367, 1342, 1283, 1274, 1224, 1196, 1153, 1104 (s), 1065 (s); ***m/z*** (ESI$^+$) 391.2 ([M+Na]$^+$, 100%), 759.4 ([2M+Na]$^+$, 100%); **HRMS** (ESI$^+$) found 391.2101, $C_{20}H_{32}O_6{}^{23}Na^+$ requires 391.2091.

### 6-Ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)oct-5-ene-1,1,6-tricarboxylate (3.62)



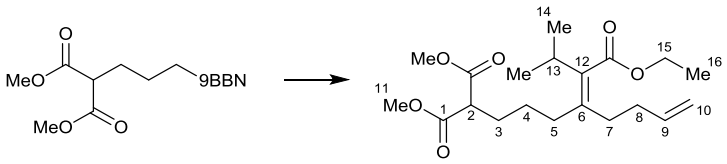

Prepared according to general procedure GP5, using using 9-BBN (0.5 M in THF, 4.64 mL, 2.32 mmol, 1.5 eq.), dimethyl 2-allylmalonate **3.17** (0.40 mL, 2.46 mmol, 1.6 eq.), $K_3PO_{4(aq)}$ (1 M, 3.8 mL, 3.80 mmol, 2.5 eq.), ethyl (*E*)-2-ethyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.58** (509 mg, 1.54 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (88 mg, 0.08 mmol, 0.05 eq.). The mixture was heated to 50 °C until complete consumption of the **3.58** was observed by TLC (20% $Et_2O$ in $PE_{40\text{-}60}$) after 15 h. Crude: black liquid. Purification by flash-chromatography (eluent: 7% EtOAc in toluene; column size: Ø = 5.5 cm, L = 9 cm) followed by a second purification by flash-chromatography (eluent: 5% (250 mL), 10% (250 mL), 20% (500 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 5 cm, L = 7 cm) afforded the title product as colourless liquid (85:15 *Z*/*E* mix., 252 mg, 0.71 mmol, 46%).



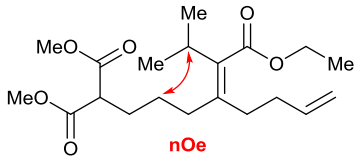

Analysed as a *Z*/*E* mixture (~1:0.15 ratio): $R_f$ 0.28 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.54 (10% EtOAc in toluene, $UV_{254\ nm}$, vanillin, $KMnO_4$); **(*Z*)-isomer (major): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.81 (1H, ddt, *J*=16.8, 10.1, 6.5 Hz, CH-(9)), 5.01 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-(10)), 4.94 (1H, ddt, *J*=10.1, 2.1, 1.2 Hz, $CH_b$-(10)), 4.19 (2H, qd, *J*=7.1, 1.6 Hz, $CH_2$-(16)), 3.74 (6H, s, 2 $CH_3$-(11)), 3.38 (1H, t, *J*=7.5 Hz, CH-(2)), 2.31 – 2.24 (4H, m, $CH_2$-(7), $CH_2$-(14)), 2.20 – 2.13 (2H, m, $CH_2$-(8)), 2.13 –

2.09 (2H, m, $CH_2$-(5)), 1.94 (2H, q, *J*=7.7 Hz, $CH_2$-(3)), 1.43 (2H, tt, *J*=10.8, 6.5 Hz, $CH_2$-(4)), 1.29 (3H, t, *J*=7.1 Hz, $CH_3$-(17)), 0.98 (3H, t, *J*=7.5 Hz, $CH_3$-(15)); $\delta_C$ /ppm (126 MHz, $CDCl_3$) 170.0 (C(13)), 169.8 (2 C(1)), 145.4 (C(6)), 138.4 (C(9)), 131.5 (C(12)), 114.7 (C(10)), 60.2 (C(16)), 52.7 (2 C(11)), 51.6 (C(2)), 33.5 (C(7)), 33.2 (C(8)), 32.2 (C(5)), 29.2 (C(3)), 26.4 (C(4)), 23.1 (C(14)), 14.4 (C(17)), 13.9 (C(15)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2956, 2873, 1753 (s, C=O), 1735 (s, C=O), 1711 (s, C=O), 1640, 1436 (m), 1343, 1293, 1244, 1218, 1152, 1107, 1025; ***m/z*** ($ESI^+$) 377.2 ([M+Na]$^+$, 100%), 731.4 ([2M+Na]$^+$, 100%); **HRMS** ($ESI^+$) found 377.1933, $C_{19}H_{30}O_6{}^{23}Na^+$ requires 377.1935.

### 6-Ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-7-methyloct-5-ene-1,1,6-tricarboxylate (3.63)

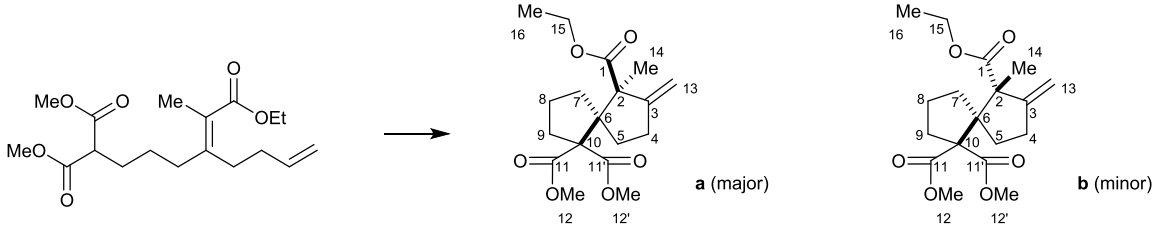



Prepared according to general procedure GP5, using using 9-BBN (0.5 M in THF, 4.64 mL, 2.32 mmol, 1.5 eq.), dimethyl 2-allylmalonate **3.17** (0.40 mL, 2.46 mmol, 1.6 eq.), $K_3PO_{4(aq)}$ (1 M, 3.8 mL, 3.80 mmol, 2.5 eq.), ethyl (*E*)-2-isopropyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.59** (530 mg, 1.54 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (88 mg, 0.08 mmol, 0.05 eq.). The mixture was heated to 50 °C until complete consumption of the **3.59** was observed by TLC (20% $Et_2O$ in $PE_{40\text{-}60}$) after 15 h. Crude: yellow liquid. Purification by flash-chromatography (eluent: 7% (500 mL) EtOAc in toluene; column size: Ø = 5.5 cm, L = 9 cm) followed by a second purification by flash-chromatography (eluent: 5% (250 mL), 10% (250 mL), 20% (500 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 5 cm, L = 7 cm) afforded the title product as colourless liquid (90:10 *Z*/*E* mix., 269 mg, 0.73 mmol, 47%).



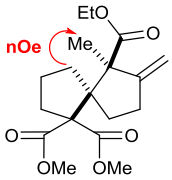

<u>Analysed as a *Z*/*E* mixture (~1:0.08 ratio):</u> **$R_f$** 0.26 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.48 (10% EtOAc in toluene, $UV_{254\ nm}$, vanillin, $KMnO_4$); **(*Z*)-isomer (major): $\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.77 (1H, ddt, *J*=16.7, 10.2, 6.2 Hz, CH-(9)), 4.99 (1H, dq, *J*=17.1, 1.6 Hz, $CH_a$-(10)), 4.96 – 4.92 (1H, m, $CH_b$-(10)), 4.19 (2H, q, *J*=7.1 Hz, $CH_2$-(16)), 3.74 (6H, s, 2 $CH_2$-(11)), 3.38 (1H, t, *J*=7.5 Hz, CH-(2)), 2.75 (1H, hept, *J*=6.8 Hz, CH-(14)), 2.13 (2H, dddd, *J*=9.4, 8.1, 5.4, 1.5 Hz, $CH_2$-(8)), 2.11 – 2.04 (4H, m, $CH_2$-(5), $CH_2$-(7)), 1.96 – 1.90 (2H, m, $CH_2$-(3)), 1.46 – 1.38 (2H, m, $CH_2$-(4)), 1.29 (3H, t, *J*=7.1 Hz, $CH_3$-(17)), 1.05 (6H, d, *J*=6.9 Hz, 2 $CH_3$-(15)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 170.3 (C(13)), 169.8 (2 C(1)), 138.3 (C(9)), 137.9 (C(6)), 136.9(C(12)), 114.7 (C(10)), 60.1 (C(16)), 52.7 (2 C(11)), 51.6 (C(2)), 33.6 (C(7)), 33.0 (C(8)), 30.4 (C(5)), 29.2 (C(3)), 28.6 (C(14)), 26.5 (C(4)), 21.7 (2 C(15)), 14.5 (C(17)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2958, 2937, 2872, 1753 (s, C=O), 1736 (s, C=O), 1716 (s, C=O), 1640 (w, C=C), 1458, 1436, 1269, 1244, 1218, 1196, 1175, 1148, 1128, 1031; ***m/z*** ($ESI^+$) 391.2 ($[M+Na]^+$, 100%), 759.4 ($[2M+Na]^+$, 95%); **HRMS** ($ESI^+$) found 391.2087, $C_{20}H_{32}O_6{}^{23}Na^+$ requires 391.2091.

### 6-Ethyl 1,1-dimethyl-6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (3.64a/b)

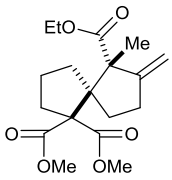



Prepared according to general procedure GP6, using 6-ethyl 1,1-dimethyl (Z)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.60** (140.8 mg, 0.41 mmol, 1.0 eq.), $Mn(OAc)_3 \bullet 2H_2O$ (222 mg, 0.82 mmol, 2.0 eq.), $Cu(OAc)_2 \bullet H_2O$ (83 mg, 0.41 mmol, 1.0 eq.). The reaction was heated to 40 °C until TLC (10% EtOAc in toluene, vanillin) showed complete consumption of the starting material after 4 days. Purification by flash-chromatography (eluent: 5% EtOAc in toluene; column size: Ø = 4 cm, L = 13 cm)

afforded the title product as a colourless oil as a mixture of diastereomers (5:1 *d.r.*, 68.4 mg corrected mass[iii], 0.20 mmol, 49% corrected yield).




**Major isomer 3.64a** (analysed as a pure isomer)**:** $\mathbf{R_f}$ 0.50 (10% EtOAc in toluene, not $UV_{254\ nm}$, vanillin, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (700 MHz, $CDCl_3$) 4.84 (1H, t, *J*=2.1 Hz, $CH_a$-(13)), 4.82 (1H, t, *J*=2.4 Hz, $CH_b$-(13)), 4.05 – 3.96 (2H, m, $CH_2$-(15)), 3.63 (3H, s, $CH_3$-(12')), 3.60 (3H, s, $CH_3$-(12)), 2.59 (1H, tdd, *J*=13.4, 10.1, 2.0 Hz, $CH_a$-(5)), 2.56 – 2.50 (1H, m, $CH_a$-(4)), 2.47 – 2.39 (1H, m, $CH_a$-(9)), 2.33 – 2.26 (1H, m, $CH_b$-(4)), 2.16 (1H, ddd, *J*=13.8, 11.1, 5.7 Hz, $CH_b$-(9)), 1.84 – 1.77 (1H, m, $CH_a$-(7)), 1.77 – 1.67 (1H, m, $CH_a$-(8)), 1.67 – 1.61 (1H, m, $CH_b$-(8)), 1.56 (1H, ddd, *J*=12.2, 8.8, 1.2 Hz, $CH_b$-(5)), 1.44 (1H, ddd, *J*=12.8, 9.1, 2.3 Hz, $CH_b$-(7)), 1.19 (3H, s, $CH_3$-(14)), 1.15 (3H, t, *J*=7.0 Hz, $CH_3$-(16)); $\boldsymbol{\delta_C}$ /ppm (176 MHz, $CDCl_3$) 174.3 (C(1)), 171.6 (C(11')), 171.4 (C(11)), 156.6 (C(3)), 106.8 (C(13)), 63.9 (C(10)), 62.7 (C(6)), 60.3 (C(15)), 57.0 (C(2)), 51.9 (C(12')), 51.9 (C(12)), 35.5 (C(9)), 33.1 (C(7)), 30.9 (C(5)), 29.2 (C(4)), 19.7 (C(14)), 19.2 (C(8)), 13.8 (C(16)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2953, 1722 (s, with shoulder, C=O), 1650, 1433 (m, with shoulder), 1253 (m), 1228 (m), 1193, 1174, 1110, 1089; ***m/z*** ($ESI^+$) 699.3 ($[2M+Na]^+$, 100%) 361.1 ($[M+Na]^+$, 55%); **HRMS** ($ESI^+$) found 361.1621, $C_{18}H_{26}O_8{}^{23}Na^+$ requires 361.1622.

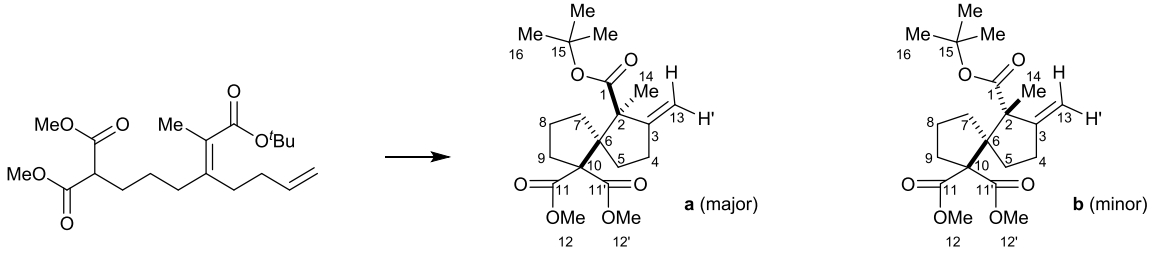



**Minor isomer 3.64b** (analysed as a mixture with **3.60** (*ca.* 30%) as an impurity): $\mathbf{R_f}$ 0.54 (10% EtOAc in toluene, no $UV_{254\ nm}$, vanillin, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (700 MHz, $CDCl_3$) 4.83 (1H, t, *J*=2.2 Hz, $CH_a$-(13)), 4.75 (1H, t, *J*=2.5 Hz, $CH_b$-(13)), 4.19 – 4.12 (2H, m, $CH_a$-(15)), 4.09 (1H, dq, *J*=10.8, 7.1 Hz, $CH_b$-(15)), 3.66 (3H, s, $CH_3$-(12')), 3.64 (3H, s, $CH_3$-(12)), 2.58 (1H, dddt, *J*=17.3, 10.0, 7.5, 2.6 Hz, $CH_a$-(4)), 2.46 (1H, dt, *J*=13.1, 9.7 Hz, $CH_a$-(7)), 2.40 – 2.34 (2H, m, $CH_a$-(9)), 2.32 (1H, dtd, *J*=13.9, 4.6, 2.1 Hz, $CH_b$-(4)), 2.25 (1H, ddd, *J*=13.8, 9.4, 3.9 Hz, $CH_b$-(9)), 2.17 (2H, ddd, *J*=13.3, 9.7, 7.3 Hz, $CH_a$-(5)), 1.80 – 1.72 (2H, m, $CH_2$-(5), $CH_a$-(8)), 1.72 – 1.66 (1H, m, $CH_b$-(8)), 1.60 (1H, ddd, *J*=13.1, 8.5, 2.6 Hz, $CH_b$-(7)), 1.38 (3H, s, $CH_3$-(14)), 1.25 (3H, t, *J*=7.2 Hz, $CH_3$-(16)); $\boldsymbol{\delta_C}$ /ppm (176 MHz, $CDCl_3$) 175.0 (C(1)), 172.4 (C(11')), 171.8 (C(11)), 157.8 (C(3)), 105.2 (C(13)), 64.7

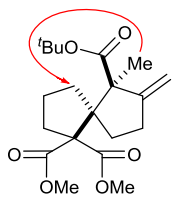
[iii] The major isomer was isolated pure: 56.7 mg (40% yield) but the minor isomer could only be isolated as a 3.5:1 mixture with some remaining starting material: 15.0 mg combined, 11.7 mg corrected mass.

(C(10)), 64.3 (C(6)), 60.5 (C(15)), 58.8 (C(2)), 52.2 (C(12')), 51.8 (C(12)), 35.2 (C(9)), 34.8 (C(7)), 33.1 (C(5)), 29.5 (C(4)), 21.2 (C(14)), 19.5 (C(8)), 14.2 (C(16)); $\nu_{max}$ /cm$^{-1}$ (film, $CDCl_3$) 2953, 1725 (s, with shoulder, C=O) 1650, 1434, 1376, 1248, 1226, 1191, 1109, 1090, 1030; ***m/z*** (ESI$^+$) 699.3 ([2M+Na]$^+$, 100%) 361.1 ([M+Na]$^+$, 65%); **HRMS** (ESI$^+$) found 361.1621, $C_{18}H_{26}O_8{}^{23}Na^+$ requires 361.1622.

### 6-(*tert*-Butyl) 1,1-dimethyl-6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (3.65a/b)




Prepared according to general procedure GP6, using 6-(*tert*-butyl) 1,1-dimethyl 5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.61** (60:40 *Z/E* mix., 151 mg, 0.41 mmol, 1.0 eq.), $Mn(OAc)_3 \bullet 2H_2O$ (222 mg, 0.82 mmol, 2.0 eq.), $Cu(OAc)_2 \bullet H_2O$ (83 mg, 0.41 mmol, 1.0 eq.). The reaction was heated to 40 °C until TLC (10% EtOAc in toluene, vanillin) showed complete consumption of the starting material after 4 days. Purification by flash-chromatography (eluent: 5% EtOAc in toluene; column size: Ø = 4 cm, L = 13 cm) afforded the title product as a colourless oil as a mixture of diastereomers (3.5:1 *d.r.*, 73.1 mg corrected mass[iv], 0.20 mmol, 48% corrected yield).



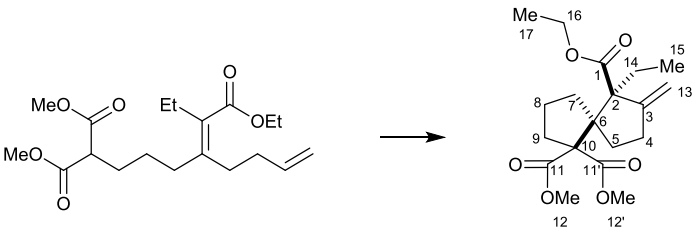

nOe on major isomer

**Mixture (3:1) of C(2)-isomers** (analysed as a mixture with **3.61** (*ca.* 15%) as an impurity): $R_f$ 0.56 (10% EtOAc in toluene, not $UV_{254\ nm}$, vanillin, $KMnO_4$); **Major isomer: $\delta_H$** /ppm (700 MHz, $CDCl_3$) 4.89 (1H, t, *J*=2.4 Hz, CH-(13)), 4.87 (1H, t, *J*=2.2 Hz, CH'-(13)), 3.67 (3H, s, $CH_3$-(12')), 3.63 (3H, s, $CH_3$-(12)), 2.91 (1H, tdd, *J*=12.5, 8.9, 1.9 Hz, $CH_b$-(5)), 2.61 (1H, ddd, *J*=14.0, 9.5, 4.9 Hz, $CH_a$-(9)), 2.46 (1H, dddd, *J*=16.9, 9.0, 3.4, 1.7 Hz, $CH_a$-(4)), 2.37 – 2.30 (1H, m, $CH_b$-(4)), 2.16 (1H, ddd, *J*=13.6, 11.1, 6.3 Hz, $CH_b$-(9)), 1.75 – 1.65 (2H, m,

[iv] The desired diastereomers were isolated as a mixture with some remaining starting material (15% based on $^1$H NMR).

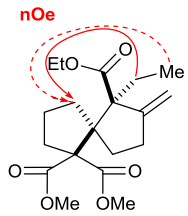
$CH_2$-(8)), 1.62 (1H, ddd, *J*=12.9, 8.1, 1.5 Hz, $CH_a$-(5)), 1.57 (1H, dddd, *J*=12.5, 10.5, 8.8, 1.9 Hz, $CH_a$-(7)), 1.49 (1H, ddd, *J*=13.0, 8.1, 2.6 Hz, $CH_b$-(7)), 1.38 (9H, s, 3 $CH_3$-(16)), 1.15 (3H, s, $CH_3$-(14)); **$\delta_C$** /ppm (176 MHz, $CDCl_3$) 173.4 (C(1)), 172.1 (C(11)), 171.7 (C(11')), 157.8 (C(3)), 106.7 (C(13)), 80.0 (C(15)), 63.8 (C(6)), 63.8 (C(10)), 57.8 (C(2)), 51.9 (C(12)), 51.8 (C(12')), 35.5 (C(9)), 33.4 (C(7)), 31.5 (C(5)), 29.5 (C(4)), 27.8 (3 C(16)), 21.2 (C(14)), 19.4 (C(8)); **Minor isomer** (partially assigned)**: $\delta_H$** /ppm (700 MHz, $CDCl_3$) 4.78 (1H, t, *J*=2.2 Hz, CH'-(13)), 4.72 (1H, t, *J*=2.5 Hz, CH-(13)), 3.64 (3H, s, $CH_3$-(12 or 12')), 3.60 (3H, s, $CH_3$-(12 or 12')), 2.55 (1H, dddt, *J*=12.9, 10.7, 5.6, 2.8 Hz, $CH_a$-(4)), 2.40 (1H, ddd, *J*=14.3, 7.2, 4.5 Hz), 2.21 – 2.18 (1H, m), 2.14 – 2.09 (1H, m), 2.03 – 1.98 (1H, m, $CH_a$-(5)), 1.83 – 1.77 (1H, m, $CH_b$-(5)), 1.75 – 1.70 (2H, m, $CH_2$-(8)), 1.69 – 1.63 (1H, m), 1.39 (9H, s, 3 $CH_3$-(16)), 1.30 (2H, s, $CH_3$-(14)); **$\delta_C$** /ppm (176 MHz, $CDCl_3$) 173.9 (C(1)), 172.5 (C(11 or 11')), 171.6 (C(11 or 11')), 158.3 (C(3)), 104.3 (C(13)), 80.5 (C(15)), 65.1 (C(6 or 10)), 64.2 (C(6 or 10)), 59.4 (C(2)), 52.2 (C(12 or 12')), 51.5 (C(12 or 12')), 35.5, 35.0, 34.2 (C(5)), 30.2 (C(4)), 28.2, 27.9 (3 C(16)), 20.3 (C(14)), 19.4 (C(8)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2972, 2952, 2883, 1720 (s, with shoulder, C=O), 1648 (w), 1456, 1448, 1433, 1367, 1251 (s), 1226, 1197, 1165 (s), 1110, 1089, 1061, 1041; ***m/z*** ($ESI^+$) 755.3 ($[2M+Na]^+$, 100%), 389.2 ($[M+Na]^+$, 25%); **HRMS** ($ESI^+$) found 389.1932, $C_{20}H_{30}O_6{}^{23}Na^+$ requires 389.1935.

### 6-Ethyl 1,1-dimethyl (5*R**,6*S**)-6-ethyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (3.66)



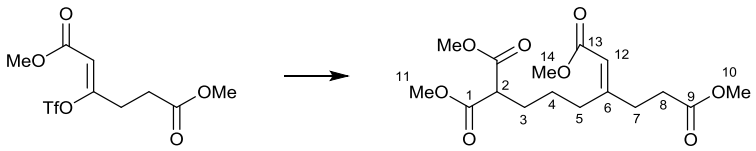

Prepared according to general procedure GP6, using 6-ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)oct-5-ene-1,1,6-tricarboxylate **3.62** (126 mg, 0.36 mmol, 1.0 eq.), $Mn(OAc)_3 \bullet 2H_2O$ (191 mg, 0.71 mmol, 2.0 eq.), $Cu(OAc)_2 \bullet H_2O$ (71 mg, 0.36 mmol, 1.0 eq.). The reaction was heated to 40 °C until TLC (10% EtOAc in toluene, vanillin) showed complete consumption of the starting material after 9 days.

Purification by flash-chromatography (eluent: 5% EtOAc in toluene; column size: Ø = 4 cm, L = 13 cm) afforded the title product (single isomer) as clear oil (27.2 mg, 0.08 mmol, 22%).



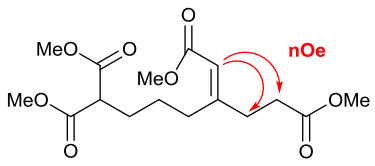

**$R_f$** 0.40 (10% EtOAc in toluene, not $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (700 MHz, $CDCl_3$) 4.97 (1H, t, *J*=2.3 Hz, $CH_a$-(13)), 4.90 (1H, t, *J*=2.3 Hz, $CH_b$-(13)), 4.14 (1H, dq, *J*=10.8, 7.1 Hz, $CH_a$-(16)), 4.03 (1H, dq, *J*=10.8, 7.2 Hz, $CH_b$-(16)), 3.66 (3H, s, $CH_3$-(12')), 3.65 (3H, s, $CH_3$-(12)), 2.49 – 2.45 (1H, m, $CH_a$-(7)), 2.45 – 2.41 (1H, m, $CH_a$-(9)), 2.41 – 2.35 (1H, m, $CH_a$-(4)), 2.35 – 2.29 (1H, m, $CH_b$-(4)), 2.21 – 2.16 (1H, m, $CH_a$-(14)), 2.15 (1H, q, *J*=5.8, 5.2 Hz, $CH_b$-(9)), 2.14 – 2.10 (1H, m, $CH_a$-(5)), 1.80 – 1.73 (1H, m, $CH_a$-(8)), 1.72 – 1.66 (1H, m, $CH_b$-(8)), 1.66 – 1.61 (1H, m, $CH_b$-(7)), 1.61 – 1.54 (1H, m, $CH_b$-(5)), 1.40 (1H, dq, *J*=14.2, 7.2 Hz, $CH_b$-(14)), 1.25 (3H, t, *J*=7.2 Hz, $CH_3$-(17)), 0.88 (3H, t, *J*=7.3 Hz, $CH_3$-(15)); **$\delta_C$** /ppm (176 MHz, $CDCl_3$) 173.0 (C(1)), 172.0 (C(11)), 171.6 (C(11')), 152.3 (C(3)), 107.9 (C(13)), 65.2 (C(10)), 64.6 (C(6)), 62.0 (C(2)), 60.2 (C(16)), 51.9 (C(12 or 12')), 51.6 (C(12 or 12')), 35.8 (C(9)), 34.1 (C(7)), 33.1 (C(5)), 30.2 (C(4)), 26.5 (C(14)), 18.9 (C(8)), 14.0 (C(17)), 10.4 (C(15)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2952, 2882, 1720 (s, with shoulder, C=O), 1457, 1433, 1258 (m), 1228 (m), 1196, 1169, 1114, 1098, 1070, 1032; ***m/z*** ($ESI^+$) 375.2 ([M+Na]$^+$, 100%); **HRMS** ($ESI^+$) found 375.1776, $C_{19}H_{28}O_3{}^{23}Na^+$ requires 375.1778.

### Trimethyl (*E*)-5-(but-3-en-1-yl)hex-5-ene-1,1,6-tricarboxylate ((*E*)-4.1)



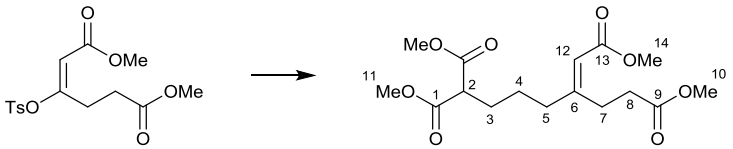

Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 7.8 mL, 3.89 mmol, 1.6 eq.), dimethyl 2-allylmalonate **3.17** (0.59 mL, 3.65 mmol, 1.5 eq.), $K_3PO_{4(aq)}$ (1 M, 5.7 mL, 5.70 mmol, 2.5 eq.), dimethyl (*Z*)-3-(((trifluoromethyl)sulfonyl)oxy)hex-2-enedioate **4.14** (779 mg, 2.43 mmol, 1.0 eq.) and Pd(dppf)$Cl_2$-$CH_2Cl_2$ complex (99 mg, 0.12 mmol, 0.05 eq.). The mixture was heated to 85 °C until complete consumption of the **4.14** was observed by TLC (25% $Et_2O$ in $PE_{40-60}$)

after 3.3 h. Crude: black liquid. Purification by flash-chromatography (eluent: 25% (200 mL) then 40% (500 mL) then 50% (500 mL) then 60% (500 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 9 cm, L = 10.5 cm) afforded the title product as yellowish liquid (711 mg, 2.28 mmol, 94%).

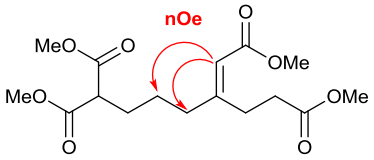



**$R_f$** 0.26 (50% $Et_2O$ in PE, $UV_{254\ nm}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.64 (1H, s, CH-(12)), 3.74 (6H, s, 2 $CH_3$-(11)), 3.68 (3H, s, $CH_3$-(10)), 3.67 (3H, s, $CH_3$-(14)), 3.42 (1H, t, *J*=7.5 Hz, CH-(2)), 2.66 – 2.61 (2H, m, $CH_2$-(5)), 2.47 (4H, s, $CH_2$-(7), $CH_2$-(8)), 1.98 – 1.92 (2H, m, $CH_2$-(3)), 1.55 – 1.46 (2H, m, $CH_2$-(4)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 172.9 (C(9)), 169.9 (2 C(1)), 166.6 (C(13)), 161.1 (C(6)), 116.1 (C(12)), 52.6 (2 C(11)), 52.0 (C(10)), 51.5 (C(2)), 51.1 (C(14)), 32.9 (C(7)), 32.1 (C(8)), 31.6 (C(5)), 28.8 (C(3)), 26.2 (C(4)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2954, 2923, 1733 (s, C=O), 1717 (m, C=O), 1645 (m, C=C), 1435 (m), 1347, 1200, 1155, 1066, 1023; ***m/z*** ($ESI^+$) 367.1 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 367.1357, $C_{16}H_{24}O_8{}^{23}Na^+$ requires 367.1363.

### Trimethyl (*Z*)-5-(2-methoxy-2-oxoethylidene)heptane-1,1,7-tricarboxylate ((*Z*)-4.1)

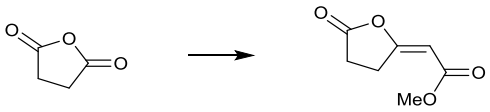



Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 47 mL, 23.4 mmol, 1.6 eq.), dimethyl 2-allylmalonate **3.17** (3.53 mL, 21.91 mmol, 1.5 eq.), $K_3PO_{4(aq)}$ (1 M, 36.5 mL, 36.5 mmol, 2.5 eq.), dimethyl (*E*)-3-(tosyloxy)hex-2-enedioate **4.15** (5.00 g, 14.60 mmol, 1.0 eq.) and Pd(dppf)$Cl_2$-$CH_2Cl_2$ complex (360 mg, 0.44 mmol, 0.03 eq.). The mixture was heated to 85 °C until complete consumption of the **4.15** was observed by TLC (60% $Et_2O$ in $PE_{40\text{-}60}$), after 3 h. Crude: black liquid. Purification by flash-chromatography (eluent: 25% (1 L) then 40% (1 L) then 55% (1 L) then 65% (1 L) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 7.5 cm, L = 12 cm) afforded the title product as colourless oil (4.05 g, 11.76 mmol, 81%).




**$R_f$** 0.30 (50% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\,nm}$, no vanillin); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.67 (1H, t, *J*=1.4 Hz, CH-(12)), 3.74 (6H, s, 2 $CH_3$-(11)), 3.68 (3H, s, $CH_3$-(14)), 3.67 (3H, s, $CH_3$-(10)), 3.36 (1H, t, *J*=7.4 Hz, CH-(2)), 2.88 – 2.83 (2H, m, $CH_2$-(7)), 2.51 – 2.46 (2H, m, $CH_2$-(8)), 2.19 (2H, td, *J*=7.6, 1.3 Hz, $CH_2$-(5)), 1.95 – 1.85 (2H, m, $CH_2$-(3)), 1.55 – 1.45 (2H, m, $CH_2$-(4)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 173.4 (C(9)), 169.7 (2 C(1)), 166.5 (C(13)), 161.1 (C(6)), 116.7 (C(12)), 52.7 (2 C(11)), 51.8 (C(10)), 51.5 (C(2)), 51.2 (C(14)), 38.0 (C(5)), 32.9 (C(8)), 28.4 (C(3)), 27.5 (C(7)), 25.2 (C(4)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2922, 2850, 1734 (s, C=O), 1718 (s, C=O), 1646 (m, C=C), 1435 (m), 1340, 1279, 1215, 1196, 1162, 1027; ***m/z*** ($ESI^+$) 367.2 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 345.1545, $C_{16}H_{25}O_8^+$ requires 345.1544.

### Methyl (*E*)-2-(5-oxodihydrofuran-2(3H)-ylidene)acetate (4.10)

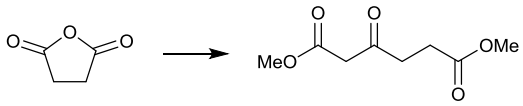



According to the modified procedure of Eagan *et al.*[191] In a flame-dried 50 mL round-bottomed flask equipped was dissolved methyl (triphenylphosphoranylidene)acetate **4.13** (5.00 g, 15.0 mmol, 1.0 eq.) in dry toluene (30 mL). To this solution was added succinic anhydride (1.50 g, 15.0 mmol, 1.0 eq.) in one portion. The heterogeneous mixture was heated to 50 °C for 16 h (after a few minutes the reaction mixture was homogeneous again). The reaction vessel was cooled to room temperature and the solvents were removed under reduced pressure to provide solids. The solid residue was purified by flash-chromatography (loaded with pentane + minimum amount of $CH_2Cl_2$, eluent: pentane first then 25% EtOAc in $PE_{40\text{-}60}$; column size: Ø = 9 cm, L = 8 cm) to afford the title product as off-white solid (1.34 g, 8.6 mmol, 58%).

**$R_f$** 0.50 (25% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$, vanillin); **m.p.** 85-88 °C; **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.72 (1H, t, *J*=2.2 Hz), 3.73 (3H, s), 3.39 (2H, ddd, *J*=10.8, 6.0, 2.1 Hz), 2.77 – 2.72 (2H, m); **$\delta_C$** /ppm (126 MHz,

$CDCl_3$) 173.6, 167.8, 167.2, 97.2, 51.5, 26.3, 26.2; ***m/z*** ($ESI^+$) 196.9 ($[M+Na+H_2O]^+$, 100%), 179.0 ($[M+Na]^+$, 55%). Data is consistent with literature.[191]

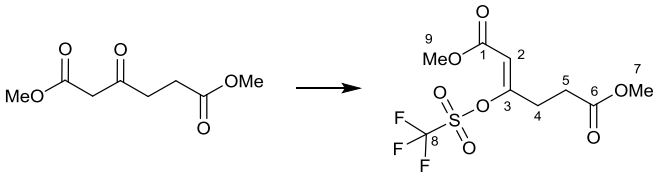
### Dimethyl 3-oxohexanedioate (4.11)



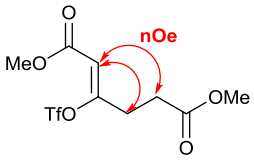

According to the modified procedure of Wu *et al*.[191] In a flame-dried 50 mL flask under argon was added methyl (triphenylphosphoranylidene)acetate **4.13** (1.67 g, 5.0 mmol, 1.0 eq.), followed by toluene (dry, 10 mL), succinic anhydride **4.5** (0.55 g, 5.5 mmol, 1.1 eq.). The heterogeneous mixture was stirred at 50 °C overnight (it became a solution after heated for 10 min). TLC (25% EtOAc in PE) showed complete consumption of succinic anhydride and appearance of a new compound (R*f* = 0.30, vanillin, $UV_{254\ nm}$). Methanol (dry, 10 mL) was added at room temperature and heated to 45 °C until full consumption of the previously formed product (usually about 16 h). The methanol and most of the toluene were removed under reduced pressure. The remainting mixture was loaded straight on silica column. Purification by flash-chromatography (eluent: 0% to 50% EtOAc in $PE_{40\text{-}60}$; column size: Ø = 5 cm, L = 7.0 cm) afforded the title product as colourless liquid (0.835 g, 4.44 mmol, 89%).

$\mathbf{R_f}$ 0.31 (60% $Et_2O$ in $PE_{40\text{-}60}$, $UV_{254\ nm}$, vanillin), $\mathbf{R_f}$ 0.21 (25% EtOAc in $PE_{40\text{-}60}$, $UV_{254\ nm}$, vanillin); $\boldsymbol{\delta_H}$ /ppm (400 MHz, $CDCl_3$) 3.73 (3H, s), 3.66 (3H, s), 3.51 (2H, s), 2.86 (2H, t, *J*=6.5 Hz), 2.61 (2H, t, *J*=6.5 Hz); $\boldsymbol{\delta_C}$ /ppm (101 MHz, $CDCl_3$) 201.1, 173.0, 167.5, 52.5, 52.0, 49.1, 37.5, 27.8; ***m/z*** ($ESI^+$) 211.0 ($[M+Na]^+$, 100%). Data is consistent with literature.[192]

### Dimethyl (*Z*)-3-(((trifluoromethyl)sulfonyl)oxy)hex-2-enedioate (4.14)

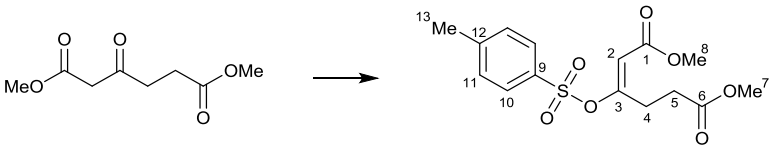


Prepared according to general procedure GP4, using dimethyl 3-oxohexanedioate **4.11** (1.5 g, 8.0 mmol, 1.0 eq.), lithium triflate (2.5 g, 16.0 mmol, 2.0 eq.), Hünig's base (1.53 mL, 8.8 mmol, 1.1 eq.) and triflic anhydride (1.6 mL, 9.6 mmol, 1.1 eq.). After 2.5 h at 0 °C, TLC (60% $Et_2O$ in $PE_{40\text{-}60}$) showed remaining starting material. It was therefore treated with an additional 1.1 eq. of Hünig's base and 1.0 mL of triflic anhydride (this was later found to be due to LiOTf not being fully anhydrous). Purification by flash-chromatography (eluent: 50% (500 mL) $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 5 cm, L = 8 cm) afforded the title product as a colourless liquid (1.85 g, 5.8 mmol, 73%).



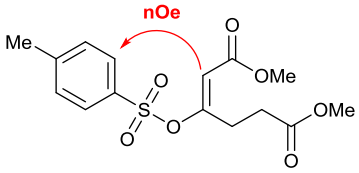

**$R_f$** 0.60 (60% $Et_2O$ in $PE_{30\text{-}40}$, $KMnO_4$, not vanillin, $UV_{254\ nm}$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.82 (1H, t, *J*=1.0 Hz, CH-(2)), 3.78 (3H, s, $CH_3$-(9)), 3.72 (3H, s, $CH_3$-(7)), 2.74 (2H, tt, *J*=6.6, 0.9 Hz, $CH_2$-(4)), 2.62 – 2.58 (2H, m, $CH_2$-(5)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 171.3(C(6)), 162.7 (C(1)), 157.0 (C(3)), 118.5 (q, *J*=320.0 Hz, C(8)), 112.6 (C(2)), 52.3 (C(7)), 52.3 (C(9)), 30.2 (C(5)), 29.9 (C(4)); **$\delta_F$** /ppm (471 MHz, $CDCl_3$) -74.51; **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 1734 (s, C=O), 1684 (w, C=O), 1426 (s), 1293, 1200, 1137, 918; ***m/z*** ($ESI^+$); **HRMS** ($ESI^+$) found 321.0250, $C_9H_{12}O_7F_3{}^{32}S^+$ requires 321.0252.

### Dimethyl (*E*)-3-(tosyloxy)hex-2-enedioate (4.15)



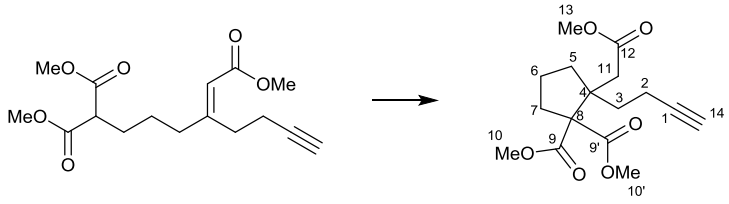
Prepared according to general procedure GP2 using dimethyl 3-oxohexanedioate **4.11** (3.17 g, 15.8 mmol, 1.0 eq.), N-methylimidazole (2.1 mL, 25.3 mmol, 1.5 eq.), dry $Et_3N$ (3.5 mL, 25.3 mmol,

1.5 eq.) and tosyl chloride (recrystallized, 4.82 g, 25.3 mmol, 1.5 eq.). TLC (50% $Et_2O$ in $PE_{40\text{-}60}$, vanillin) after 5 h at room temperature showed complete conversion. Crude *E*/*Z* ratio: >95:5 by $^1H$ NMR. Purification by flash-chromatography (eluent: 35% to 50% EtOAc in $PE_{30\text{-}40}$, column size: Ø = 7 cm, L = 7 cm) afforded the title product as a yellowish oil (5.04 g, 14.72 mmol, 93%).




**$R_f$** 0.40 (50% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 7.84 – 7.79 (2H, m, 2 $CH_{Ar}$-(10)), 7.41 – 7.35 (2H, m, 2 $CH_{Ar}$-(11)), 5.84 (1H, s, CH-(2)), 3.70 (3H, s, $CH_3$-(8)), 3.64 (3H, s, $CH_3$-(7)), 3.07 – 3.00 (2H, m, $CH_2$-(4)), 2.51 – 2.47 (2H, m, $CH_2$-(5)), 2.47 (3H, s, $CH_3$-(13)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 172.3 (C(6)), 165.6 (C(1)), 163.7 (C(3)), 146.2 (C(12)), 132.7 (C(9)), 130.2 (2 C(11)), 128.4 (2 C(10)), 110.2 (C(2)), 52.0 (C(7)), 51.9 (C(8)), 30.6 (C(5)), 27.1 (C(4)), 21.9 (C(13)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 1723 (s, C=O), 1653 (s, C=C), 1597 (w), 1437, 1364 (s), 1283, 1193, 1177, 1103, 1079, 1009; ***m/z*** ($ESI^+$) 365.0 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 365.0663, $C_{15}H_{18}O_7{}^{23}Na^{32}S^+$ requires 365.0665.

### Dimethyl 2-(but-3-yn-1-yl)-2-(2-methoxy-2-oxoethyl)cyclopentane-1,1-dicarboxylate (4.16)

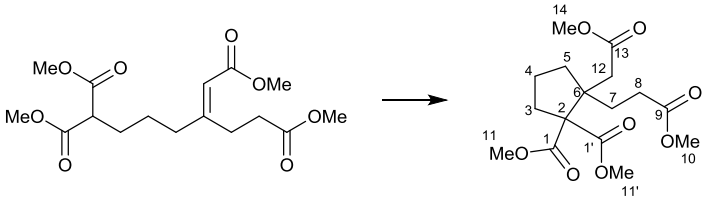



In a dried 10 mL flask was stirred $K_2CO_3$ (63 mg, 0.45 mmol, 0.7 eq.) and trimethyl (*Z*)-5-(4-(trimethylsilyl)but-3-yn-1-yl)hex-5-ene-1,1,6-tricarboxylate (*Z*)-**2.31** (250.0 mg, 0.66 mmol, 1.0 eq.) in wet MeOH (from bottle, 6.5 mL (0.1 M)) at room temperature for 17 h then heated to 35 °C for 48 h. The reaction was quenched with $NH_4Cl_{(aq)}$ (sat. sol., 2.5 mL) and water. The resulting water/methanol mixture was extracted with EtOAc (3x). The combined organic layers were washed with water (3x), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford an oil. Purification by

flash-chromatography (eluent: 20% to 30% $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2.0 cm, L = 11 cm) afforded the title product as colourless oil (132.5 mg, 0.43 mmol, 65%).

**$R_f$** 0.47 (40% $Et_2O$ in $PE_{30\text{-}40}$, vanillin); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 3.73 (3H, s), 3.69 (3H, s), 3.65 (3H, s), 2.83 (1H, d, *J*=14.3 Hz, $CH_a$-(11)), 2.44 (1H, d, *J*=14.3 Hz, $CH_b$-(11)), 2.45 – 2.38 (1H, m, $CH_a$-(7)), 2.35 (1H, dddd, *J*=16.6, 11.2, 5.4, 2.6 Hz, $CH_a$-(2)), 2.25 (1H, dddd, *J*=16.6, 10.6, 5.9, 2.6 Hz, $CH_b$-(2)), 2.15 (1H, ddd, *J*=14.5, 10.2, 5.8 Hz, $CH_b$-(7)), 2.03 (1H, ddd, *J*=13.1, 9.1, 5.7 Hz, $CH_a$-(5)), 1.92 (1H, t, *J*=2.6 Hz, CH-(14)), 1.95 – 1.85 (1H, m, $CH_b$-(5)), 1.85 – 1.74 (4H, m, $CH_2$-(3), $CH_2$-(6)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 172.2 (C(12)), 171.5 (C(9)), 171.5 (C(9')), 84.7 (C(1)), 68.3 (C(14)), 67.5 (C(8)), 52.6, 52.5, 51.7, 50.8 (C(4)), 38.4 (C(11)), 35.1 (C(5)), 35.0 (C(3)), 33.0 (C(7)), 20.0 (C(6)), 14.6 (C(2)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 3291 (w, C≡C-H), 2953, 1727 (s, C=O), 1457, 1434, 1257 (s), 1203, 1168, 1127, 1106, 1093, 1041, 1018; ***m/z*** ($ESI^+$) 333.2 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 311.1487, $C_{16}H_{23}O_6^+$ requires 311.1489.

### Dimethyl 2-(2-methoxy-2-oxoethyl)-2-(3-methoxy-3-oxopropyl)cyclopentane-1,1-dicarboxylate (4.17)

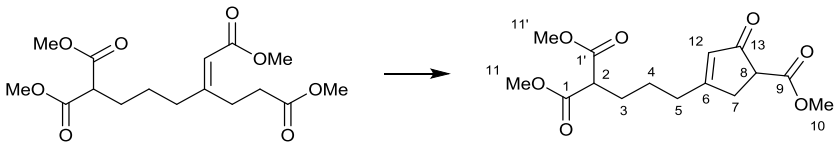



In a dried 25 mL flask was stirred $K_2CO_3$ (anhydrous, 140 mg, 0.98 mmol, 1.5 eq.) and trimethyl (*Z*)-5-(2-methoxy-2-oxoethylidene)heptane-1,1,7-tricarboxylate (*Z*)-**4.1** (225 mL, 0.65 mmol, 1.0 eq.) in dry MeOH (13 mL) at room temperature for 48 h. The reaction was quenched with $NH_4Cl_{(aq)}$ (sat. sol., 4 mL). The methanol was evaporated under reduced pressure then the resulting aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine (once), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a pinkish oil. Purification by flash-

chromatography (eluent: 30% $Et_2O$ in $PE_{30-40}$; column size: Ø = 2.2 cm, L = 13.5 cm) afforded the title product as colourless oil (119 mg, 0.35 mmol, 53%).

**$R_f$** 0.38 (50% $Et_2O$ in $PE_{30-40}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 3.72 (3H, s), 3.69 (3H, s), 3.65 (3H, s), 3.65 (3H, s), 2.86 (1H, d, *J*=14.2 Hz, $CH_a$-(11)), 2.54 (1H, ddd, *J*=15.8, 9.3, 7.7 Hz, $CH_a$-(2)), 2.49 – 2.38 (2H, m, $CH_a$-(7), $CH_b$-(2)), 2.44 (1H, d, *J*=14.2 Hz, $CH_b$-(11)), 2.16 (1H, ddd, *J*=14.7, 10.0, 5.8 Hz, $CH_b$-(7)), 2.02 (1H, ddd, *J*=12.0, 8.3, 5.0 Hz, $CH_a$-(5)), 1.87 (3H, ddd, *J*=9.3, 7.3, 3.0 Hz, $CH_b$-(5), $CH_2$-(3)), 1.84 – 1.75 (2H, m, $CH_2$-(6)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 174.2 (C(1)), 172.2 (C(12)), 171.5 (C(9')), 171.5 (C(9)), 67.4 (C(8)), 52.6, 52.5, 51.7, 51.7, 50.6 (C(4)), 38.4 (C(11)), 35.4 (C(5)), 33.1 (C(7)), 30.7 (C(3)), 30.1 (C(2)), 19.9 (C(6)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2954, 1726 (s, C=O), 1435 (w), 1256, 1196, 1165, 1096, 1043; ***m/z*** ($ESI^+$) 367.2 ($[M+Na]^+$, 100%), 345.2 ($[M+H]^+$, 10%); **HRMS** ($ESI^+$) found 345.1544, $C_{16}H_{25}O_8^+$ requires 345.1544.

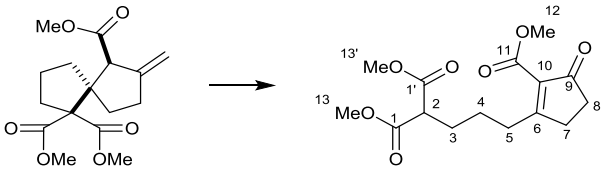
### Dimethyl 2-(3-(4-(methoxycarbonyl)-3-oxocyclopent-1-en-1-yl)propyl)malonate (4.18)




In a flame-dried 5 mL flask under argon, $^t$BuOK (anhydrous, 15 mg, 0.12 mmol, 1.2 eq.) was added in one portion to a solution of trimethyl (*Z*)-5-(2-methoxy-2-oxoethylidene)heptane-1,1,7-tricarboxylate (*Z*)-**4.1** (34.0 mg, 0.10 mmol, 1.0 eq.) in dry DMSO (2.0 mL (0.05 M)) at room temperature. After 4 h (a similar TLC was observed after 30 min reaction), the reaction was quenched with $NH_4Cl_{(aq)}$ (sat. sol., 1 mL) and diluted water (9 mL). The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water (2x), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification by flash-chromatography (eluent: 25% to 50% EtOAc in $PE_{30-40}$; column size: Ø = 1.5 cm, L = 8 cm) afforded the title product as clear oil (5.2 mg, 0.02 mmol, 17%).

**$R_f$** 0.21 (60% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.92 (1H, p, *J*=1.5 Hz, CH-(12)), 3.77 (3H, s, $CH_3$-(10)), 3.75 (6H, s, $CH_3$-(11), $CH_3$-(11')), 3.47 (1H, dd, *J*=7.1, 2.8 Hz, CH-(8)), 3.40 (1H, t, *J*=7.4 Hz, CH-(2)), 3.00 (1H, dtd, *J*=18.4, 1.8, 0.9 Hz, $CH_a$-(7)), 2.77 (1H, dddt, *J*=18.4, 7.2, 1.8, 0.9 Hz, $CH_b$-(7)), 2.49 (2H, td, *J*=7.3, 3.1 Hz, $CH_2$-(5)), 2.01 – 1.92 (2H, m, $CH_2$-(3)), 1.66 (2H, dt, *J*=15.6, 7.8 Hz, $CH_2$-(4)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 201.9 (C(13)), 181.7 (C(6)), 169.6 (C(1)), 169.6 (C(1')), 169.5 (C(9)), 127.8 (C(12)), 52.9 (C(10)), 52.8 (2 C(11)), 52.2 (C(8)), 51.4 (C(2)), 35.5 (C(7)), 33.1 (C(5)), 28.5 (C(3)), 24.7 (C(4)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2955, 2924, 2850, 1733 (s, C=O), 1704 (s, C=O), 1617 (m, C=C), 1436 (m), 1331, 1261, 1212, 1151 (m), 1060, 1019; ***m/z*** ($ESI^+$) 335.0 ($[M+Na]^+$, 100%), 313.0 ($[M+H]^+$, 55%) ; **HRMS** ($ESI^+$) found 313.1282, $C_{15}H_{21}O_7^+$ requires 313.1282.

### Dimethyl 2-(3-(2-(methoxycarbonyl)-3-oxocyclopent-1-en-1-yl)propyl)malonate (4.20)

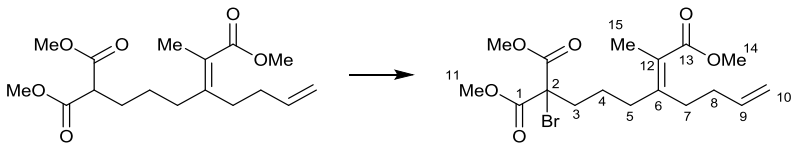



According to the modified procedure of Shen *et al.*[173] A 50 mL flask was charged with trimethyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate **3.22a/b** (80:20 *d.r.*, 16 mg, 0.052 mmol, 1.0 eq.), 1,4-dioxane/water (3:1 v/v, 0.6 mL), 2,6-lutidine (12 mg, 0.10 mmol, 2.0 eq.), $OsO_4$ (2.5 wt% in $^t$BuOH, 10.2 mg, 0.001 mmol, 0.02 eq.) and $NaIO_4$ (42.8 mg, 0.20 mmol, 4.0 eq.). The resulting mixture was stirred for 4.5 h. The reaction was quenched with addition of $Na_2S_2O_{3\,(aq)}$ (sat. sol., 0.5 mL). $CH_2Cl_2$ and water were added. The layers were separated and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification by flash-chromatography (eluent: 50% to 100% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title product as a colourless oil (5.8 mg, 0.019 mmol, 36%).

**$R_f$** 0.13 (75% $Et_2O$ in $PE_{30\text{-}40}$, vanillin); **$\delta_H$** /ppm (600 MHz, $CDCl_3$) 3.78 (3H, s, $CH_3$-(12)), 3.68 (6H, s, 2 $CH_3$-(13)), 3.35 (1H, t, *J*=7.3 Hz, CH-(2)), 2.74 (2H, t, *J*=7.7 Hz, $CH_2$-(5)), 2.62 – 2.60 (2H, m, $CH_2$-(7)),

2.44 – 2.41 (2H, m, $CH_2$-(8)), 1.90 (3H, q, *J*=7.6 Hz, $CH_2$-(3)), 1.6 – 1.5 (2H, m, $CH_2$-(4)); $\delta_C$ /ppm (101 MHz, $CDCl_3$) 203.4 (C(9)), 187.2 (C(6)), 169.5 (2 C(1)), 163.6 (C(11)), 132.8 (C(10)), 52.6 (2 C(13)), 51.9 (C(12)), 51.2 (C(2)), 34.9 (C(8)), 32.0 (C(5)), 30.2 (C(7)), 28.5 (C(3)), 25.2 (C(4)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2955, 2923, 2851, 1731 (s, C=O), 1712 (s, C=O), 1623 (m, C=C), 1435, 1353, 1293, 1249, 1225, 1158, 1085, 1064, 1022; ***m/z*** ($ESI^+$) 335.0 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 313.1284, $C_{15}H_{21}O_7^+$ requires 313.1282.

### Trimethyl (*Z*)-1-bromo-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate (5.7)

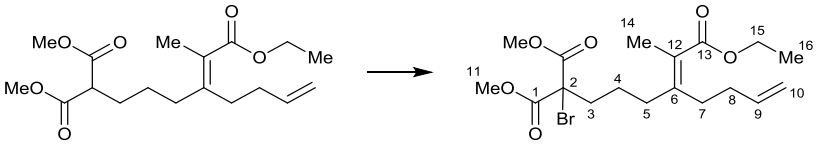



According to the modified procedure of Perreault *et al*.[193] To a solution of trimethyl (*Z*)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.46** (50 mg, 0.153 mmol, 1.0 eq.) in dry THF (1.3 mL) in a flame-dried round bottomed flask under argon cooled to -78 °C was added dropwise DBU (26 µL, 0.168 mmol, 1.1 eq.) and stirred for 30 min. Carbon tetrabromide (55.7 mg, 0.168 mmol, 1.1 eq.) was then added as a solid in one portion and the resulting mixture was stirred at -78 °C until TLC (10% EtOAc in toluene) showed complete consumption of the substrate (after 2.5 h). The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (0.5 mL) and then warmed to room temperature. Water was added to dissolve the salts and extraction with $CH_2Cl_2$ (3x 5 mL) was done. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification of the crude mixture by flash-chromatography (eluent: 0% (to remove $CBr_4$ and $CHBr_3$) then 50% $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2 cm, L = 6 cm) afforded the title product as a colourless liquid (60.3 mg, 0.149 mmol, 97%).

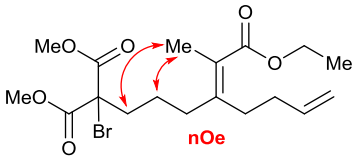
$\mathbf{R_f}$ 0.62 (10% EtOAc in toluene, $UV_{254\,nm}$, vanillin, $KMnO_4$); $\delta_H$ /ppm (500 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=16.8, 10.2, 6.6 Hz, CH-(9)), 5.02 (1H, dq, *J*=17.1, 1.6 Hz, CHa-(10)), 4.95 (1H, ddt, *J*=10.2, 2.1, 1.2 Hz,

$CH_b$-(10)), 3.82 (6H, s, 2 $CH_3$-(11)), 3.71 (3H, s, $CH_3$-(14)), 2.38 (2H, dd, *J*=9.6, 6.3 Hz, $CH_2$-(7)), 2.32 – 2.26 (2H, m, $CH_2$-(3)), 2.21 – 2.14 (4H, m, $CH_2$-(5), $CH_2$-(8)), 1.85 (3H, s, $CH_3$-(15)), 1.53 (2H, ddt, *J*=11.9, 8.0, 4.3 Hz, $CH_2$-(4)); $\delta_C$ /ppm (126 MHz, $CDCl_3$) 170.0 (C(13)), 167.5 (2 C(1)), 148.7 (C(6)), 138.4 (C(9)), 124.3 (C(12)), 114.8 (C(10)), 62.3 (C(2)), 54.1 (2 C(11)), 51.5 (C(14)), 38.3 (C(3)), 33.8 (C(7)), 33.2 (C(5)), 33.1 (C(8)), 23.7 (C(4)), 15.7 (C(15)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2954 2919, 1744 (s, with shoulder, C=O), 1715 (s, C=O), 1639 (w, C=C), 1435 (m, with shoulder), 1253 (m), 1226, 1194, 1103; ***m/z*** ($ESI^+$) 427.0 ($[M+Na]^+$, 100%); **HRMS** ($ESI^+$) found 427.0722, $C_{17}H_{25}O_6{}^{79}Br^{23}Na^+$ requires 427.0727.

### 6-Ethyl 1,1-dimethyl (*Z*)-1-bromo-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate (5.8)




According to the modified procedure of Perreault *et al*.[193] To a solution of 6-Ethyl 1,1-dimethyl (Z)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.60** (500 mg, 1.469 mmol, 1.0 eq.) in dry THF (12 mL) in a flame-dried round bottomed flask under argon cooled to -78 °C was added dropwise DBU (0.24 mL, 1.62 mmol, 1.1 eq.) and stirred for 30 min. carbon tetrabromide (538 mg, 1.62 mmol, 1.1 eq.) was then added as a solid in one portion and the resulting mixture was stirred at -78 °C until TLC (10% EtOAc in toluene) showed complete convertion (after 40 min). The reaction was quenched with saturated $NH_4Cl_{(aq)}$ (10 mL) and then warmed to room temperature. Water was added to dissolve the salts and extraction with $CH_2Cl_2$ (3x 50 mL) was done. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification of by flash-chromatography (eluent: 0% (400 mL, to remove $CBr_4$ and $CHBr_3$) then 8% EtOAc in pentane; column size: Ø = 5.5 cm, L = 8 cm) afforded the title product as a colourless liquid (493 mg, 1.18 mmol, 80%).




**$R_f$** 0.37 (10% EtOAc in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=16.8, 10.2, 6.6 Hz, CH-(9)), 5.02 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-(10)), 4.95 (1H, ddt, *J*=10.2, 2.2, 1.3 Hz, $CH_b$-(10)), 4.17 (2H, q, *J*=7.1 Hz, $CH_2$-(15)), 3.82 (6H, s, 2 $CH_3$-(11)), 2.36 (2H, dd, *J*=9.6, 6.3 Hz, $CH_2$-(7)), 2.31 – 2.27 (2H, m, $CH_2$-(3)), 2.17 (4H, ddd, *J*=10.7, 8.3, 5.7 Hz, $CH_2$-(5), $CH_2$-(8)), 1.85 (3H, s, $CH_3$-(14)), 1.57 – 1.49 (2H, m, $CH_2$-(4)), 1.29 (3H, t, *J*=7.1 Hz, $CH_3$-(16)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 169.8 (C(13)), 167.5 (2 C(1)), 147.7 (C(6)), 138.4 (C(9)), 124.7 (C(12)), 114.8 (C(10)), 62.4 (C(2)), 60.3 (C(15)), 54.1 (2 C(11)), 38.4 (C(3)), 33.7 (C(7)), 33.1 (C(8)), 33.1 (C(5)), 23.8 (C(4)), 15.7 (C(14)), 14.4 (C(16)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2955, 1745 (s, with shoulder, C=O), 1710 (s, C=O), 1639, 1436, 1367, 1254, 1225, 1192, 1102, 1026; ***m/z*** ($ESI^+$) 861.1 ($[2M+Na]^+$, 100%), 441.1 ($[M+Na]^+$, 100%), 419.1 ($[M+H]^+$, 80%); **HRMS** ($ESI^+$) 441.0881 found, $C_{18}H_{27}O_6{}^{79}Br^{23}Na^+$ requires 441.0883.

### 6-Ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-1-iodohept-5-ene-1,1,6-tricarboxylate (5.9)

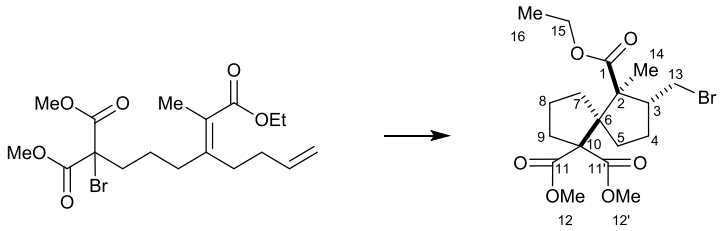

Prepared according to general procedure GP7, using 6-ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.60** (1.00 g, 2.94 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 3.2 mL, 3.23 mmol, 1.1 eq.) and *N*-iodosuccinimide (0.73 g, 3.23 mmol, 1.1 eq.). TLC (10% EtOAc in toluene, vanillin and $UV_{254\ nm}$) showed complete reaction after 2.5 h. Purification in the dark of the crude mixture by flash-chromatography (eluent: pentane (300 mL) then 8% (1 L) EtOAc in $PE_{40\text{-}60}$; column size: Ø = 4.5 cm, L = 8 cm) afforded the title product as colourless liquid (1.18 g, 2.53 mmol, 86%).

**$R_f$** 0.66 (10% EtOAc in toluene, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.32 (10% EtOAc in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=16.8, 10.2, 6.5 Hz, CH-(9)), 5.02 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-(10)), 4.95 (1H, ddd, *J*=10.2, 2.0, 1.1 Hz, $CH_b$-(10)), 4.18 (2H, q, *J*=7.1 Hz, $CH_2$-(15)), 3.80

(6H, s, 2 $CH_3$-(11)), 2.37 (2H, dd, *J*=9.6, 6.3 Hz, $CH_2$-(7)), 2.25 – 2.13 (6H, m, $CH_2$-(3), $CH_2$-(5), $CH_2$-(8)), 1.86 (3H, s, $CH_3$-(14)), 1.54 – 1.45 (2H, m, $CH_2$-(4)), 1.29 (3H, t, *J*=7.1 Hz, $CH_3$-(16)); $\delta_C$ /ppm (126 MHz, $CDCl_3$) 169.8 (C(13)), 168.8 (2 C(1)), 147.8 (C(6)), 138.4 (C(9)), 124.6 (C(12)), 114.8 (C(10)), 60.3 (C(15)), 54.1 (2 C(11)), 43.2 (C(2)), 40.3 (C(3)), 33.8 (C(7)), 33.1 (C(8)), 33.0 (C(5)), 26.2 (C(4)), 15.8 (C(14)), 14.4 (C(16)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2954, 1737 (s, C=O), 1711 (s, C=O), 1639, 1436 (with shoulder), 1249 (s), 1226, 1192, 1102 (s); ***m/z*** ($ESI^+$) 489.0 ($[M+Na]^+$, 100%), 955.1 ($[2M+Na]^+$, 100%), 467.1 ($[M+H]^+$, 90%); **HRMS** ($ESI^+$) found 489.0741, $C_{16}H_{27}O_6{}^{127}I^{23}Na^+$ requires 489.0744.

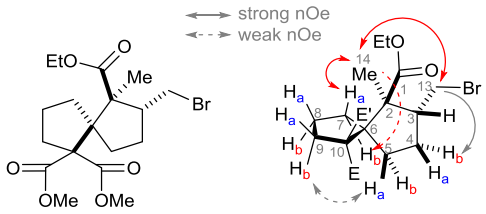
The alkene geometry was determined by analogy with bromide **5.8,** as the overlap of protons $CH_2$-(3,5 and 8) in iodide **5.9** made nOe from proton $CH_3$-(14) ambiguous.

### 6-Ethyl 1,1-dimethyl (5*R**,6*S**,7*R**)-7-(bromomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (5.10)




According to the modified procedure of Arceo *et al*.[161] To 6-ethyl 1,1-dimethyl (*Z*)-1-bromo-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **5.8** (50.0 mg, 0.12 mmol, 1.0 eq.) in a flame-dried Young's NMR tube at room temperature was added neat 2,6-lutidine (12 µL, 0.12 mmol, 1.0 eq.) and *p*-anisaldehyde (3 µL, 0.02 mmol, 0.20 eq.) under argon atmosphere. Dry and degassed (3x freeze/pump/thaw cycles) MeCN-$d_4$ (0.45 mL) was added and the vessel was sealed (electrical PVC tape). The reaction (with magnetic stirring) was irradiated using a black 15 W CFL light at a distance of 1.0 cm using a mild $N_2$ flow on the outside of the tube to keep it cool. Outside air temperature next to the tube (same distance from the lamp) showed 28 °C. The reaction colour started colourless and turned to clear orange over the course of the reaction. Once complete

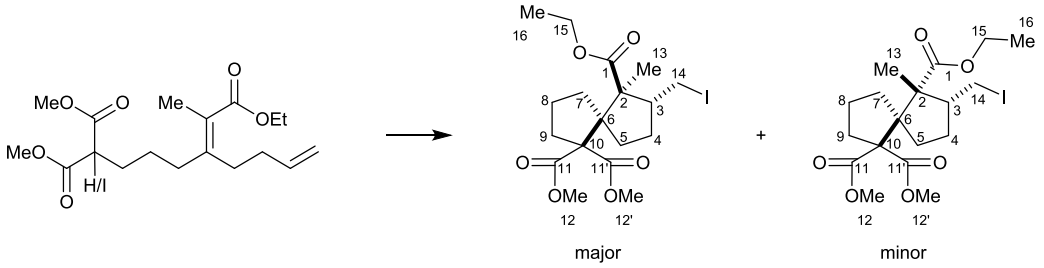
reaction was observed ($^1$H NMR) after 22 h, the reaction was concentrated down to dryness. Purification by flash-chromatography (eluent: 0% (100 mL) then 3.5% (100 mL) then 4.5% (100 mL) then 7% (100 mL) EtOAc in toluene; column size: Ø = 2.5 cm, L = 13.5 cm) afforded the title compound as a colourless oil (28.2 mg, 0.07 mmol, 56%).




**$R_f$** 0.38 (10% EtOAc in toluene, no $UV_{254\ nm}$, weak vanillin, $KMnO_4$); **$\delta_H$** /ppm (700 MHz, $CDCl_3$) 4.12 – 4.03 (2H, m, $CH_2$-(15)), 3.71 (3H, s, $CH_3$-(12)), 3.68 (3H, s, $CH_3$-(12')), 3.59 – 3.56 (1H, m, $CH_a$-(13)), 3.21 – 3.14 (2H, m, CH-(3), $CH_b$-(13)), 2.44 (1H, dddd, *J*=12.3, 11.2, 7.3, 1.2 Hz, $CH_a$-(7)), 2.37 (1H, ddd, *J*=14.2, 10.9, 7.7 Hz, $CH_b$-(9)), 2.22 (1H, ddd, *J*=14.2, 9.6, 3.1 Hz, $CH_a$-(9)), 2.12 – 2.05 (1H, m, $CH_a$-(4)), 1.93 (1H, dddd, *J*=13.3, 10.0, 7.5, 1.2 Hz, $CH_a$-(5)), 1.80 – 1.71 (1H, m, $CH_{a\ or\ b}$-(8)), 1.70 – 1.64 (1H, m, $CH_{a\ or\ b}$-(8)), 1.62 (1H, ddd, *J*=12.2, 8.9, 2.8 Hz, $CH_b$-(7)), 1.57 (1H, ddd, *J*=13.3, 8.1, 2.8 Hz, $CH_b$-(5)), 1.39 – 1.32 (1H, m, $CH_b$-(4)), 1.26 (3H, t, *J*=7.2 Hz, $CH_3$-(16)), 1.14 (3H, s, $CH_3$-(14)); **$\delta_C$** /ppm (176 MHz, $CDCl_3$) 175.9 (C(1)), 172.1 (C(11')), 171.9 (C(11)), 66.0 (C(10)), 64.3 (C(6)), 60.6 (C(15)), 55.5 (C(2)), 52.2 (C(12)), 52.1 (C(12')), 49.8 (C(3)), 35.9 (C(5)), 35.5 (C(9)), 35.3 (C(13)), 35.3 (C(7)), 28.1 (C(4)), 19.2 (C(8)), 18.4 (C(14)), 14.1 (C(16)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2951, 1721 (s, C=O), 1445, 1432 (w), 1262 (s), 1233, 1196 (w), 1178, 1133, 1111, 1089, 1027; ***m/z*** ($ESI^+$) 861.1 ($[2M+Na]^+$, 100%), 441.1 ($[M+Na]^+$, 100%), 419.1 ($[M+H]^+$, 90%); **HRMS** ($ESI^+$) found 441.0880, $C_{18}H_{27}O_6{}^{79}Br^{23}Na^+$ requires 441.0883.

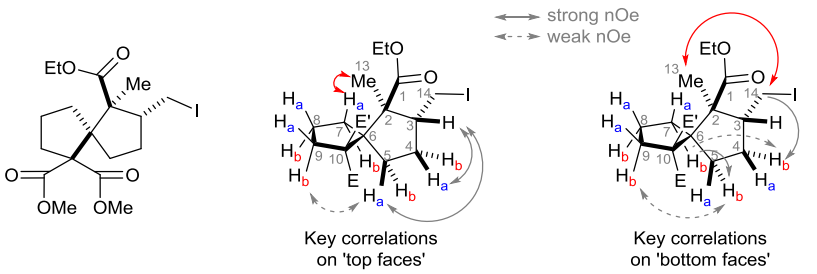
### 6-Ethyl 1,1-dimethyl (5*R**,6*S**,7*R**)-7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (5.16)

### 6-Ethyl 1,1-dimethyl (5*R**,6*R**,7*R**)-7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (5.17)

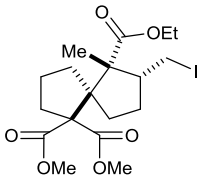



**Method 1** (from iodomalonate **5.9**): Prepared according to general procedure GP8, using 6-ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-1-iodohept-5-ene-1,1,6-tricarboxylate **5.9** (58.0 mg, 0.12 mmol, 1.0 eq.) and 2,6-lutidine (12 µL, 0.12 mmol, 1.0 eq.). Reaction vessel: 3.5 mL clear vial. The reaction was irradiated (with magnetic stirring) using a white 30 W CFL light (at 5.0 cm distance) for 16 h. Purification by flash-chromatography (eluent: 10% (300 mL) then 20% (300 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2 cm, L = 9 cm) afforded the major isomer **5.16** as a colourless oil (38.3 mg, 0.08 mmol, 66%) and the minor isomer **5.17** was usually not isolated (see note below), lactone **3.49** was also sometimes observed but not isolated.

**Method 2** (one-pot from malonate **3.60**): Prepared according to general procedure GP9, using ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.60** (70.0 mg, 0.21 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 0.23 mL, 0.23 mmol, 1.1 eq.), 2,6-lutidine (20 µL, 0.21 mmol, 1.0 eq.). Reaction vessel: 5 mL borosilicate round-bottom flask. The reaction was irradiated (with magnetic stirring) using a white 30 W CFL light (at 5.0 cm distance) for 13 h. Purification by flash-chromatography (eluent: 10% (300 mL) then 20% (300 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2 cm, L = 9 cm) afforded the major isomer **5.16** as a colourless oil (62.3 mg, 0.13 mmol, 67%) and the minor isomer **5.17** was usually not isolated (see note below), lactone **3.49** was also sometimes observed but not isolated.




**Major isomer (5.16):** $R_f$ 0.45 (10% EtOAc in toluene, weak $UV_{254\,nm}$, vanillin, $KMnO_4$); $\delta_H$ /ppm (700 MHz, $CDCl_3$) 4.06 (2H, qq, *J*=10.8, 7.2 Hz, $CH_2$-(15)), 3.71 (3H, s, $CH_3$-(12)), 3.67 (3H, s, $CH_3$-(12')), 3.38 (1H, dd, *J*=9.0, 3.6 Hz, $CH_a$-(14)), 3.13 (1H, tdd, *J*=11.4, 7.1, 3.6 Hz, CH-(3)), 2.93 (1H, dd, *J*=11.3, 9.0 Hz, $CH_b$-(14)), 2.43 (1H, ddd, *J*=12.5, 10.4, 6.6 Hz, $CH_a$-(7)), 2.36 (1H, ddd, *J*=14.1, 10.9, 7.7 Hz, $CH_b$-(9)), 2.20 (1H, ddd, *J*=14.2, 9.5, 3.0 Hz, $CH_a$-(9)), 2.12 (1H, dtd, *J*=12.7, 7.3, 2.8 Hz, $CH_a$-(4)), 1.93 (1H, dddd, *J*=13.4, 9.8, 7.5, 1.1 Hz, $CH_a$-(5)), 1.78 – 1.70 (1H, m, $CH_a$-(8)), 1.69 – 1.64 (1H, m, $CH_b$-(8)), 1.64 – 1.59 (2H, m, $CH_b$-(7)), 1.55 (1H, ddd, *J*=13.3, 8.1, 2.9 Hz, $CH_b$-(5)), 1.30 (1H, dddd, *J*=12.8, 10.9, 3.2, 1.4 Hz, $CH_b$-(4)), 1.26 (4H, t, *J*=7.2 Hz, $CH_3$-(16)), 1.11 (3H, s, $CH_3$-(13)); $\delta_C$ /ppm (176 MHz, $CDCl_3$) 175.8 (C(1)), 172.0 (C(11)), 171.9 (C(11')), 66.0 (C(10)), 64.7 (C(6)), 60.6 (C(15)), 55.6 (C(2)), 52.2 (C(12)), 52.0 (C(12')), 50.4 (C(3)), 35.5 (C(5) or C(7) or C(9)), 35.5 (C(5) or C(7) or C(9)), 35.4 (C(5) or C(7) or C(9)), 29.6 (C(4)), 19.1 (C(8)), 18.0 (C(13)), 14.1 (C(16)), 8.2 (C(14)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2952, 2876, 1723 (s, C=O), 1445, 1432, 1377, 1263 (s), 1196 (m), 1177, 1110, 1084, 1028; ***m/z*** ($ESI^+$) 955.0 ($[2M+Na]^+$, 100%), 489.0 ($[M+Na]^+$, 100%), 467.1 ($[M+H]^+$, 90%); **HRMS** ($ESI^+$) found 489.0740, $C_{18}H_{27}O_6{}^{127}I^{23}Na^+$ requires 489.0744.

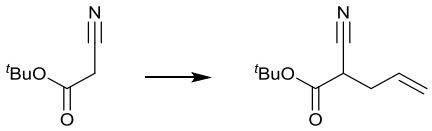


**Minor isomer (5.17):** $R_f$ 0.63 (40% $Et_2O$ in $PE_{30\text{-}40}$, weak $UV_{254\,nm}$, weak vanillin, $KMnO_4$); $\delta_H$ /ppm (600 MHz, $CDCl_3$) 4.10 (2H, qq, *J*=6.9, 3.7 Hz, $CH_2$-(15)), 3.75 (3H, d, *J*=0.6 Hz, $CH_3$-(12)), 3.68 (3H, d, *J*=0.6 Hz, $CH_3$-(12')), 3.21 (1H, dd, *J*=9.0, 3.3 Hz, $CH_a$-(14)), 3.04 (1H, dd, *J*=11.6, 9.0 Hz, $CH_b$-(14)), 2.85 (1H, tdd, *J*=11.3, 8.0, 3.3 Hz, CH-(3)), 2.42 – 2.32 (2H, m, $CH_a$-(7), $CH_a$-(9)), 2.12 (1H, ddd, *J*=14.4, 9.6, 2.4 Hz, $CH_b$-(9)), 2.04 (1H, dtd, *J*=12.6, 7.8, 5.6 Hz, $CH_a$-(4)), 1.91 – 1.83 (1H, m, $CH_b$-(4)), 1.80 – 1.73 (3H, m, $CH_2$-(5), $CH_a$-(8)), 1.70 – 1.62 (2H, m, $CH_b$-(8), $CH_b$-(7)), 1.35 (3H, s, $CH_3$-(13)), 1.28 (3H, t, *J*=7.1 Hz, $CH_3$-(16)); $\delta_C$ /ppm (data extracted from HSQC and HMBC, 176 MHz, $CDCl_3$) 173.5 (C(1)), 171.9 (C(11)), 170.9 (C(11)), 66.3 (C(10)), 64.3 (C(6)), 59.6 (C(15)), 58.2 (C(2)), 53.2 (C(3)), 51.5 (C(12')), 51.5 (C(12)), 37.5 (C(7)), 36.3

(C(5)), 35.1 (C(9)), 30.2 (C(4)), 19.1 (C(8)), 18.5 (C(13)), 13.6 (C(16)), 6.1 (C(14)); $\nu_{max}$ /cm$^{-1}$ (film, $CDCl_3$) 2952 (m), 2923 (m), 2874, 2852, 1727 (s, C=O), 1459 (m), 1434 (w), 1381, 1259 (s), 1183 (s), 1139, 1091 (s), 1050, 1027; ***m/z*** (ESI$^+$) 955.2 ([2M+Na]$^+$, 100%), 489.1 ([M+Na]$^+$, 95%); **HRMS** (ESI$^+$) found 489.0747, $C_{18}H_{27}O_6{}^{127}I^{23}Na^+$ requires 489.0745.

Note concerning the minor isomer **5.17**: Minor isomer **5.17** readily lactonises to lactone **3.49** at room temperature. The sample used for charactarisation was freshly purified and analysed straight away in order to minimise the amount of lactone present in the sample (still showing in the sample despite all the precautions taken).

### *tert*-Butyl 2-cyanopent-4-enoate (5.25)

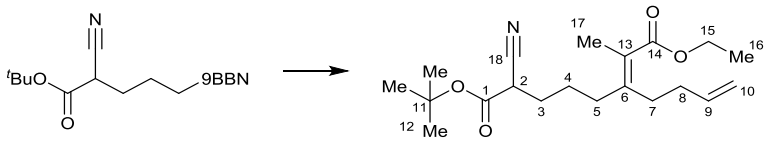



According to the modified procedure of Badiola *et al*.[194] To a solution of *tert*-butyl cyanoacetate **5.24** (3.0 mL, 21.0 mmol, 1.0 eq.) in dry benzene (100 mL) in a flame-dried round bottomed flask under argon at room temperature was slowly added DBU (3.13 mL, 21.0 mmol, 1.0 eq.) and stirred for 5 min. A solution of allyl bromide (1.73 mL, 21.0 mmol, 1.0 eq.) in dry benzene (21 mL) was then added over 20 min to give a yellow heterogeneous mixture that was stirred overnight. The reaction was quenched with $HCl_{(aq)}$ (1 M solution, 75 mL) and the layers were separated. The organic layer was washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to a yellow liquid. Purification of the crude mixture by flash-chromatography (eluent: 0% (200 mL), 5% (500 mL), 10% $Et_2O$ in pentane; column size: Ø = 5.5 cm, L = 8 cm) afforded the title product as a colourless liquid (1.50 g, 8.25 mmol, 39%).

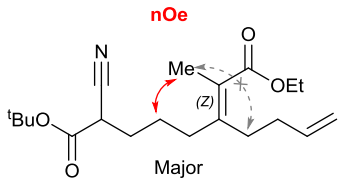
**$R_f$** 0.36 (10% $Et_2O$ in $PE_{30\text{-}40}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (400 MHz, $CDCl_3$) 5.81 (1H, ddt, *J*=17.1, 10.1, 7.0 Hz), 5.28 – 5.21 (2H, m), 3.46 (1H, dd, *J*=7.2, 6.3 Hz), 2.65 (2H, tdt, *J*=7.2, 2.4, 1.3 Hz), 1.49 (9H, s);

**$\delta_C$** /ppm (101 MHz, $CDCl_3$) 164.6, 131.7, 119.9, 116.6, 84.3, 38.5, 34.1, 28.0; **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2934 (w), 2251 (w, C≡N), 1738 (s, C=O), 1644 (w, C=C), 1479, 1443, 1395, 1370, 1342, 1279, 1259, 1152 (s). Data in accordance with the literature.[194]

### 8-(*tert*-Butyl) 1-ethyl (*Z*)-3-(but-3-en-1-yl)-7-cyano-2-methyloct-2-enedioate (5.26)




Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 6.6 mL, 3.31 mmol, 1.5 eq.), *tert*-butyl 2-cyanopent-4-enoate **5.25** (641 mg, 3.54 mmol, 1.6 eq.), $K_3PO_{4(aq)}$ (1 M, 5.5 mL, 5.53 mmol, 2.5 eq.), ethyl (*E*)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.56** (700 mg, 2.21 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (128 mg, 0.11 mmol, 0.05 eq.). The mixture was heated to 50 °C overnight, complete consumption of the **3.56** was observed by TLC (10% EtOAc in toluene, $UV_{254\ nm}$). Purification by flash-chromatography (eluent: 5% to 10% EtOAc in toluene; column size: Ø = 4 cm, L = 9 cm) followed by a second purification by flash-chromatography (eluent: 2.5% (400 mL), 5% (800 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 4 cm, L = 9 cm) afforded the title product as colourless oil as a mixture of alkene isomers (80:20 *Z/E* mix., 482 mg, 1.38 mmol, 62%).

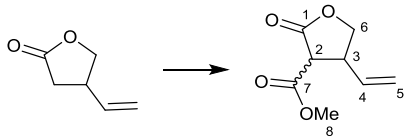



<u>Analysed as a *Z/E* mixture (4:1 ratio):</u> **$R_f$** 0.51 (10% EtOAc in toluene, $UV_{254\ nm}$ , vanillin, $KMnO_4$), 0.13 (10% $Et_2O$ in PE, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=16.9, 10.1, 6.6 Hz, CH-($9^{cis}$), CH-($9^{trans}$)), 5.08 – 4.99 (1H, m, $CH_a$-($10^{cis}$), $CH_a$-($10^{trans}$)), 4.95 (1H, dq, *J*=10.2, 1.3 Hz, $CH_b$-($10^{cis}$), $CH_b$-($10^{trans}$)), 4.18 (1.6H, q, *J*=7.1 Hz, $CH_2$-($15^{cis}$)), 4.18 (0.4H, q, *J*=7.1 Hz, $CH_2$-($15^{trans}$)), 3.41 (0.8H, t, *J*=6.9 Hz, CH-($2^{cis}$)), 3.43 (0.2H, t, *J*=7.4 Hz, CH-($2^{trans}$)), 2.37 (2H, dd, *J*=9.5, 6.4 Hz, $CH_2$-($7^{cis}$), $CH_2$-($^{trans}$)), 2.22 – 2.13 (4H, m, $CH_2$-($5^{cis}$), $CH_2$-($8^{cis}$), 2 $CH_2$-($^{trans}$)), 1.94 (2H, dt, *J*=8.5, 7.1 Hz, $CH_2$-($3^{cis}$), $CH_2$-($3^{trans}$)), 1.86 (3H, d, *J*=2.4 Hz, $CH_3$-($17^{cis}$), $CH_3$-($17^{trans}$)), 1.68 – 1.59 (2H, m, $CH_2$-($4^{cis}$), $CH_2$-($4^{trans}$)),

1.50 (7H, s, 3 $CH_3$-($12^{cis}$)), 1.49 (2H, s, 3 $CH_3$-($12^{trans}$)), 1.30 (0.6H, t, *J*=7.1 Hz, $CH_3$-($16^{trans}$)), 1.29 (2.4H, t, *J*=7.1 Hz, $CH_3$-($12^{cis}$)); $\delta_C$ /ppm (126 MHz, $CDCl_3$) 169.6 (C($14^{cis}$)), 169.4 (C($14^{trans}$)), 165.1 (C($1^{trans}$)), 164.9 (C($1^{cis}$)), 148.1 (C($6^{trans}$)), 147.1 (C($6^{cis}$)), 138.1 (C($9^{cis}$)), 137.6 (C($9^{trans}$)), 124.7 (C($13^{cis}$)), 124.6 (C($13^{trans}$)), 116.9 (C($18^{trans}$)), 116.7 (C($18^{cis}$)), 115.2 (C($10^{trans}$)), 114.7 (C($10^{cis}$)), 84.2 (C($11^{cis}$)), 83.9 (C($11^{trans}$)), 60.3 (C($15^{cis}$)), 60.2 (C($15^{trans}$)), 38.5 (C($2^{trans}$)), 38.4 (C($2^{cis}$)), 33.5 (C($7^{cis}$)), 33.2 (C($^{trans}$)), 33.0 (C($8^{cis}$)), 33.0 (C($^{trans}$)), 32.7 (C($5^{cis}$)), 31.8 (C($^{trans}$)), 29.8 (C($3^{cis}$)), 29.8 (C($3^{trans}$)), 27.8 (3 C($12^{cis}$), 3 C($12^{trans}$)), 25.9 (C($4^{trans}$)), 24.9 (C($4^{cis}$)), 15.6 (C($17^{cis}$)), 15.6 (C($17^{trans}$)), 14.3 (C($16^{trans}$)), 14.3 (C($16^{cis}$)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2979, 2933, 2871, 2249 (w, C≡N), 1739 (s, C=O), 1709 (s, C=O), 1640 (w, C=C), 1457, 1394, 1369, 1277 (m), 1256 (m), 1225, 1151 (s), 1100 (m), 1034; ***m/z*** ($ESI^+$) 721.5 ($[2M+Na]^+$, 100%), 372.2 ($[M+Na]^+$, 60%); **HRMS** ($ESI^+$) 372.2146 found, $C_{20}H_{31}O_4N^{23}Na^+$ requires 372.2145.

NMR peaks have been fully assigned for the major isomer, but only partially assigned for the minor isomer. This is because of the overlap of most signals. A very strong nOe correlation between $CH_3$-(17) and $CH_2$-(5) was seen but the overlap between $CH_2$-(5) and $CH_2$-(8) made it ambiguous. The nOe correlation between $CH_3$-(17) and $CH_2$-(4), the absence of a cross peak between $CH_3$-(17) and $CH_2$-(7) and the starting material geometry strongly suggests that the *cis* isomer is major compound of the mixture.

### Methyl 2-oxo-4-vinyltetrahydrofuran-3-carboxylate (5.28)

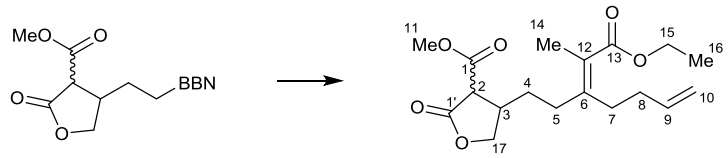



To a cooled (-78 °C) solution of LiHMDS (1 M in toluene, 26.7 mL, 26.70 mmol, 2.70 eq.) in dry THF (9 mL) was added a solution of 4-vinyldihydrofuran-2(3*H*)-one **7.7** (1.09 g, 9.72 mmol, 1.0 eq.) in dry THF (5.9 mL) over 15 min (*via* syringe pump). The clear solution was stirred for 10 min. Dimethyl carbonate (0.98 mL, 11.66 mmol, 1.20 eq.) was added quickly (over 10 sec) neat and the mixture was

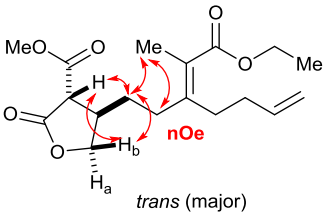
allowed to warm up to room temperature overnight. TLC didn't help determining when the reaction was complete as both **7.7** and **5.28** have same $R_f$ in the eluent systems we used. The reaction was quenched with $HCl_{(aq)}$ (1 M solution, 9 mL) and then extracted with $Et_2O$ (4x). The combined organic layers were washed with brine, dried ($Na_2SO_4$), filtered and carefully concentrated under reduced pressure to a yellow liquid containing mostly toluene (didn't interfear wih the purification). Purification of the crude mixture by flash-chromatography (eluent: 30% EtOAc in $PE_{40\text{-}60}$; column size: Ø = 7 cm, L = 7 cm; concentrated down at room temperature at 60 mbar) afforded the title product as a yellowish liquid as a mixture of 2 diastereomers (~10:1 *d.r.*, 1.04 g, 6.11 mmol, 63%).

Analysed as a *trans/cis* mixture (~10:1 ratio): **$R_f$** 0.45 (25% EtOAc in $PE_{30\text{-}40}$, $KMnO_4$); **NMR data for the major isomer: $\delta_H$** /ppm (600 MHz, $CDCl_3$) 5.75 (1H, ddd, *J*=17.1, 10.3, 7.6 Hz, CH-(4)), 5.27 (1H, dt, *J*=17.1, 1.0 Hz, $CH_a$-(5)), 5.23 (1H, dt, *J*=10.4, 0.9 Hz, $CH_b$-(5)), 4.52 (1H, dd, *J*=9.0, 8.0 Hz, $CH_a$-(6)), 4.01 (1H, t, *J*=9.1 Hz, $CH_b$-(6)), 3.82 (3H, s, $CH_3$-(8)), 3.64 (1H, tt, *J*=10.3, 9.1, 8.0, 7.6 Hz, CH-(3)), 3.42 (1H, d, *J*=10.1 Hz, CH-(2)); **$\delta_C$** /ppm (151 MHz, $CDCl_3$) 171.4 (C(1)), 167.5 (C(7)), 133.5 (C(4)), 119.4 (C(5)), 70.8 (C(6)), 53.3 (C(8)), 51.8 (C(2)), 44.2 (C(3)); **Partial NMR data for the minor isomer: $\delta_H$** /ppm (600 MHz, $CDCl_3$) 5.76 – 5.70 (m, CH-(4)), 5.27 – 5.24 (m, $CH_2$-(5)), 4.44 (1H, dd, *J*=8.8, 7.7 Hz, $CH_a$-(6)), 4.33 (1H, t, *J*=9.0 Hz, $CH_b$-(6)), 3.75 (3H, s, $CH_3$-(8)), 3.63 – 3.61 (m, CH-(2)), 3.52 – 3.45 (1H, m, CH-(3)); **$\delta_C$** /ppm (151 MHz, $CDCl_3$) 171.9 (C(1)), 166.9 (C(7)), 131.4 (C(4)), 120.6 (C(5)), 71.3 (C(6)), 52.8 (C(8)), 51.1 (C(2)), 43.7 (C(3)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 1778 (s, C=O, lactone), 1736 (s, C=O, ester), 1438, 1303, 1277 (m), 1215, 1153, 1130 (m), 1018 (s); ***m/z*** ($ESI^+$) 225.1 ($[M+MeOH+Na]^+$, 100%), 193.1 ($[M+Na]^+$, 90%); **HRMS** ($ESI^+$) 193.0472 found, $C_8H_{10}O_4{}^{23}Na^+$ requires 193.0471. NMR data consistent with the ethyl ester equivalent reported in the literature.[195]

### Methyl (*E*)-4-(3-(1-ethoxy-1-oxopropan-2-ylidene)hept-6-en-1-yl)-2-oxotetrahydrofuran-3-carboxylate (5.29)



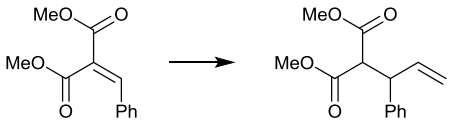

Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 4.0 mL, 2.0 mmol, 1.3 eq.), methyl 2-oxo-4-vinyltetrahydrofuran-3-carboxylate **5.28** (359 mg, 2.11 mmol, 1.4 eq.), $K_3PO_{4(aq)}$ (1 M, 3.8 mL, 3.8 mmol, 2.5 eq.), ethyl (*E*)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.56** (487 mg, 1.51 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (87 mg, 0.08 mmol, 0.05 eq.). The mixture was heated to 50 °C overnight. Purification by flash-chromatography (eluent: 15% to 25% EtOAc in $PE_{40\text{-}60}$; column size: Ø = 5 cm, L = 8 cm) followed by a second purification by flash-chromatography (eluent: 0% (100 mL) then 5% (250 mL) then 10% (250 mL) then 20% (500 mL) EtOAc in toluene; column size: Ø = 5 cm, L = 10 cm) afforded the title product as clear liquid (2:1 *trans/cis* ratio at C(2), 207.5 mg, 0.61 mmol, 41%).




**$R_f$** 0.36 (10% EtOAc in toluene, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.43 (25% EtOAc in $PE_{40\text{-}60}$, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.97 (1H, ddt, *J*=16.9, 10.2, 6.5 Hz, CH-($9^{trans}$), CH-($9^{cis}$)), 5.18 (1H, dt, *J*=15.2, 1.8 Hz, $CH_a$-($10^{trans}$)), 5.25 – 5.13 (1H, m, CH-($10^{cis}$)), 5.12 (1H, dd, *J*=10.1, 1.7 Hz, $CH_b$-($10^{trans}$)), 4.74 – 4.69 (1H, m, $CH_a$-($19^{trans}$), $CH_a$-($19^{cis}$)), 4.34 (2H, q, *J*=7.0 Hz, $CH_2$-($15^{trans}$), CH-($15^{cis}$)), 4.17 (0.3H, dd, *J*=9.1, 7.8 Hz, $CH_b$-($19^{cis}$)), 4.10 (1H, t, *J*=8.5 Hz, $CH_b$-($19^{trans}$)), 3.99 (2H, s, $CH_3$-($11^{trans}$)), 3.97 (1H, s, $CH_3$-($11^{cis}$)), 3.49 (0.3H, d, *J*=8.8 Hz, CH-($2^{cis}$)), 3.43 (1H, d, *J*=9.0 Hz, CH-($2^{trans}$)), 3.14 (1H, h, *J*=7.8 Hz, CH-($3^{trans}$), CH-($3^{cis}$)), 2.54 – 2.49 (2H, m, $CH_2$-($7^{trans}$)), 2.37 – 2.30 (2H, m, $CH_2$-($8^{trans}$)), 2.30 – 2.23 (2H, m, $CH_2$-($5^{trans}$)), 2.02 (1H, s, CH-($5^{cis}$)), 2.00 (2H, s, $CH_3$-($14^{trans}$)), 1.86 (1H, m, CH-($4^{cis}$)), 1.85 – 1.75 (2H, m, $CH_2$-($4^{trans}$)), 1.45 (1H, t, *J*=7.1 Hz, $CH_3$-($16^{cis}$)), 1.45 (2H, t, *J*=7.1 Hz, $CH_3$-($16^{trans}$)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 172.2 (C($1'^{cis}$)), 171.7 (C($1'^{trans}$)), 169.6 (C($13^{trans}$)), 169.1 (C($13^{cis}$)), 168.3 (C($1^{cis}$)), 168.1 (C($1^{trans}$)), 148.7 (C($6^{cis}$)), 146.5 (C($6^{trans}$)), 138.1 (C($9^{trans}$)), 137.6

(C(9$^{cis}$)), 125.0 (C(12$^{trans}$)), 124.8 (C(12$^{cis}$)), 115.5 (C(10$^{cis}$)), 115.0 (C(10$^{trans}$)), 72.2 (C(19$^{cis}$)), 71.9 (C(19$^{trans}$)), 60.5 (C(15$^{trans}$)), 60.4 (C(15$^{cis}$)), 53.4 (C(11$^{trans}$)), 53.2 (C(11$^{cis}$)), 52.5 (C(2$^{trans}$)), 52.4 (C(2$^{cis}$)), 40.4 (C(3$^{trans}$)), 40.3 (C(3$^{cis}$)), 33.6 (C(7$^{trans}$)), 33.5 (C($^{cis}$)), 33.1 (C(8$^{trans}$)), 31.9 (C($^{cis}$)), 31.9 (C($^{cis}$)), 31.7 (C(4$^{cis}$)), 31.1 (C(5$^{trans}$)), 30.5 (C(4$^{trans}$)), 15.7 (C(14$^{trans}$)), 15.6 (C(14$^{cis}$)), 14.4 (C(16$^{cis}$)), 14.4 (C(16$^{trans}$)); $\boldsymbol{\nu_{max}}$ /cm$^{-1}$ (film, $CDCl_3$)2979, 2955, 2929, 1781 (s, C=O), 1739 (s, C=O), 1707 (s, C=O), 1640 (w, C=C), 1438, 1275, 1217, 1148 (m), 1102 (m), 1021 (m); ***m/z*** (ESI$^+$) 699.3 ([2M+Na]$^+$, 100%), 361.2 ([M+Na]$^+$, 50%); **HRMS** (ESI$^+$) found 361.1624, $C_{18}H_{26}O_6{}^{23}Na^+$ requires 361.1622.

### Dimethyl 2-(1-phenylallyl)malonate (5.31)

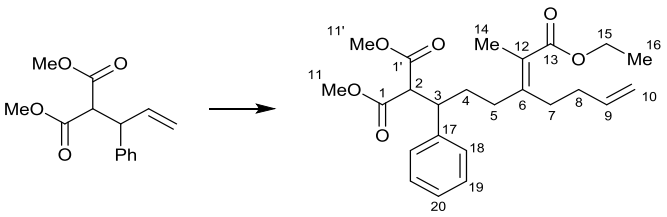



According to the modified procedure of Chong *et al*.[196] A dry flask was charged (in this order) with anhydrous CuCl (13.5 mg, 0.13 mmol, 0.05 eq.), 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride **5.34** (45.9 mg, 0.13 mmol, 0.05 eq.), $^t$BuOK (453 mg, 4.04 mmol, 1.5 eq.) and dry degassed ($N_2$ sparging, 1 h) THF (13.5 mL) at room temperature and stirred for 3.5 h. 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane **5.35** (624 mg, 4.05 mmol, 1.5 eq.) was then added neat in one portion foolowed by dimethyl 2-benzylidenemalonate **7.8** (594 mg, 2.70 mmol, 1.0 eq.) as a solid in one portion. Stirring was continued for 16 h, TLC (15% EtOAc in $PE_{40\text{-}60}$, $KMnO_4$) showed no remaining starting material. The resulting dark black mixture was filtered on a short Celite© and silica plug (0.5 cm hight each, Ø = 2 cm), eluted with $Et_2O$ (~40 mL) and was then concentrated under reduced pressure. Purification of the crude mixture by flash-chromatography (eluent: 5% (1 L) EtOAc in PE; column size: Ø = 4.5 cm, L = 6 cm) afforded the title product as a colourless liquid (535 mg, 2.15 mmol, 80%).

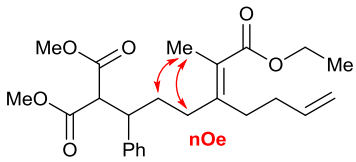
$\mathbf{R_f}$ 0.61 (15% EtOAc in $PE_{30\text{-}40}$, $UV_{254\ nm}$, $KMnO_4$, no vanillin); $\boldsymbol{\delta_H}$ /ppm (400 MHz, $CDCl_3$) 7.33 – 7.27 (2H, m), 7.24 – 7.19 (3H, m), 5.99 (1H, ddd, *J*=17.0, 10.2, 8.2 Hz), 5.16 – 5.06 (2H, m), 4.11 (1H, dd, *J*=11.1, 8.2 Hz), 3.87 (1H, d, *J*=11.1 Hz), 3.74 (3H, s), 3.49 (3H, s); $\boldsymbol{\delta_C}$ /ppm (101 MHz, $CDCl_3$) 168.2, 167.8,

139.9, 137.8, 128.6, 127.9, 127.1, 116.6, 57.4, 52.6, 52.4, 49.7; $\nu_{max}$ /cm$^{-1}$ (film, $CDCl_3$) 2954, 1758 (s, C=O), 1736 (s, C=O), 1454, 1261, 1243, 1197, 1160, 1145, 1125, 1077, 1061, 1026; ***m/z*** (ESI$^+$) 271.1 ([M+Na]$^+$, 100%), 519.2 ([2M+Na]$^+$, 60%). Data in accordance with the literature.[196]

### 6-Ethyl 1,1-dimethyl (*E*)-5-(but-3-en-1-yl)-2-phenylhept-5-ene-1,1,6-tricarboxylate (5.32)




Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 4.0 mL, 1.96 mmol, 1.3 eq.), dimethyl 2-(1-phenylallyl)malonate **5.31** (525 mg, 2.11 mmol, 1.4 eq.), $K_3PO_{4(aq)}$ (1 M, 3.8 mL, 3.77 mmol, 2.5 eq.), ethyl (*E*)-2-methyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **3.56** (487 mg, 1.51 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (87 mg, 0.08 mmol, 0.05 eq.). The mixture was heated to 50 °C until complete consumption of the **3.56** was observed (TLC: 20% $Et_2O$ in $PE_{40-60}$) after 16 h. Purification by flash-chromatography (eluent: 7% EtOAc in toluene; column size: Ø = 5 cm, L = 7 cm) followed by a second purification (eluent: 5% $Et_2O$ in $PE_{30-40}$; column size: Ø = 5.5 cm, L = 9 cm) afforded the title product as yellowish oil (402 mg, 0.96 mmol, 64%).

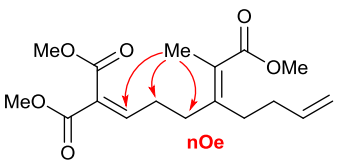



**$R_f$** 0.28 (20% $Et_2O$ in $PE_{30-40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.55 (10% EtOAc in toluene, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 7.35 – 7.31 (2H, m, 2 $CH_{Ar}$-(19)), 7.28 – 7.21 (3H, m, 2 $CH_{Ar}$-(18), $CH_{Ar}$-(20)), 5.76 (1H, ddt, *J*=16.9, 10.2, 6.7 Hz, CH-(9)), 4.96 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-(10)), 4.92 (1H, ddt, *J*=10.1, 2.2, 1.2 Hz, $CH_b$-(10)), 4.17 (2H, q, *J*=7.1 Hz, $CH_2$-(15)), 3.79 (3H, s, $CH_3$-(11')), 3.69 (1H, d, *J*=10.7 Hz, CH-(2)), 3.46 (3H, s, $CH_3$-(11)), 3.38 (1H, td, *J*=11.1, 2.6 Hz, CH-(3)), 2.30 (2H, t, *J*=7.9 Hz, $CH_2$-(7)), 2.11 – 2.03 (2H, m, $CH_2$-(8)), 2.00 – 1.93 (1H, m, $CH_a$-(5)), 1.84 – 1.80 (2H, m, $CH_a$-(4), $CH_b$-(5)), 1.74 – 1.68 (1H, m, $CH_b$-(4)), 1.66 (3H, s, $CH_3$-(14)), 1.29 (3H, t, *J*=7.1 Hz, $CH_3$-(16)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 169.9 (C(13)), 168.8 (C(1')), 168.2 (C(1)), 148.1 (C(6)), 140.2 (C(17)), 138.4

(C(9)), 128.7 (2 C(19)), 128.2 (2 C(18)), 127.4 (C(20)), 124.2 (C(12)), 114.7 (C(10)), 60.3 (C(15)), 58.5 (C(2)), 52.8 (C(11')), 52.4 (C(11)), 46.1 (C(3)), 33.7 (C(7)), 33.0 (C(8)), 31.8 (C(4)), 31.4 (C(5)), 15.4 (C(14)), 14.4 (C(16)); $\nu_{max}$ /cm$^{-1}$ (film, $CDCl_3$) 2952, 1757 (m, C=O), 1738 (s, C=O), 1710 (s, C=O), 1454, 1434, 1266, 1246, 1229, 1192, 1158, 1101; ***m/z*** (ESI$^+$) 439.2 ([M+Na]$^+$, 100%), 855.3 ([2M+Na]$^+$, 100%); **HRMS** (ESI$^+$) 439.2086 found, $C_{24}H_{32}O_6{}^{23}Na^+$ requires 439.2091.

### 6-Ethyl 1,1-dimethyl (*E*)-5-(but-3-en-1-yl)hepta-1,5-diene-1,1,6-tricarboxylate (5.33)

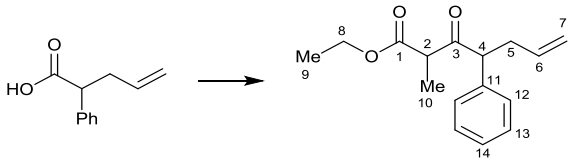

According to the modified procedure of Jagtap *et al.*[197] To a solution of 6-ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-1-(phenylselanyl)hept-5-ene-1,1,6-tricarboxylate **5.62** (30.0 mg, 0.06 mmol, 1.0 eq.) in dry $CH_2Cl_2$ (0.24 mL) in a vial at 0 °C was added $H_2O_2$ (30% w/w in $H_2O$, ~0.08 mL, ~0.64 mmol, ~10.7 eq.) and stirred for 4 h. TLC (20% EtOAc in toluene, $KMnO_4$, $UV_{254\ nm}$, vanillin) showed complete consumption of the starting material. The reaction was carefully quenched with $Na_2S_2O_{3\ (aq)}$ (sat. sol.) and was extracted with $CH_2Cl_2$. The combined organic layers were concentrated under a $N_2$ flow at room temperature. Purification of the crude mixture by flash-chromatography (eluent: 0% (50 mL), 20% (100 mL), 40% (100 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2.5 cm, L = 7 cm) afforded the title product as a colourless oil (13.0 mg, 0.04 mmol, 64%).




**$R_f$** 0.59 (40% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.61 (20% EtOAc in toluene, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 7.03 (1H, t, *J*=7.9 Hz, CH-(3)), 5.82 (1H, ddt, *J*=16.8, 10.2, 6.6 Hz, CH-(9)), 5.02 (1H, dq, *J*=17.1, 1.6 Hz, $CH_a$-(10)), 4.96 (1H, ddt, *J*=10.2, 2.2, 1.2 Hz, $CH_b$-(10)), 4.18 (2H, q, *J*=7.1 Hz, $CH_2$-(15)), 3.82 (3H, s, $CH_3$-(11 or 11')), 3.78 (3H, s, $CH_3$-(11' or 11)), 2.43 – 2.35 (4H, m, $CH_2$-(4), $CH_2$-(7)), 2.28 (2H, dd, *J*=9.9, 6.2 Hz, $CH_2$-(5)), 2.22 – 2.16 (2H, m, $CH_2$-(8)), 1.86 (3H, s, $CH_3$-(14)), 1.29 (3H, t, *J*=7.1 Hz, $CH_3$-(16)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 169.6 (C(13)), 165.7 (C(1 or 1')),

164.4 (C(1' or 1)), 148.7 (C(3)), 146.4 (C(6)), 138.2 (C(9)), 128.6 (C(2)), 125.4 (C(12)), 114.9 (C(10)), 60.4 (C(15)), 52.6 (C(11' or 11)), 52.5 (C(11 or 11')), 33.7 (C(7)), 33.1 (C(8)), 32.2 (C(5)), 28.1 (C(4)), 15.7 (C(14)), 14.4 (C(16)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2954, 1723 (relatively br s, C=O), 1641 (w, with shoulder, C=C), 1437, 1366, 1264 (s), 1225 (s), 1196, 1101, 1058; ***m/z*** ($ESI^+$) 699.3 ($[2M+Na]^+$, 100%), 361.1 ($[M+Na]^+$, 70%); **HRMS** ($ESI^+$) found 361.1618, $C_{18}H_{26}O_6{}^{23}Na^+$ requires 361.1622.

### Ethyl 2-methyl-3-oxo-4-phenylhept-6-enoate (5.37)



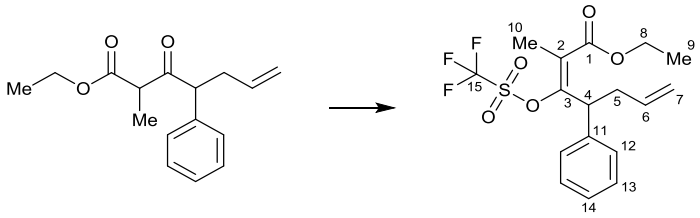

According to the modified procedure of Lanners *et al*.[190] Enolate solution preparation: To a flame-dried 50 mL flask containing a solution of diisopropylamine (4.8 mL, 34.04 mmol, 4.0 eq.) in dry THF (3.5 mL) at -78 °C under argon was added *n*-BuLi (1.47 M in hexane, 23.2 mL, 34.04 mmol, 4.0 eq.) over 5 min and stirred for 30 min. A solution of ethyl propionate (2.0 mL, 17.02 mmol, 2.0 eq.) in dry THF (2.6 mL) was added over 6 min, followed by dry THF (5 mL) and stirred for an additional 30 min. Activated acid solution: To a flame-dried 100 mL flask containing a solution of 2-phenylpent-4-enoic acid **7.9** (1.50 g, 8.51 mmol, 1.0 eq.) in dry THF (8.6 mL) at room temperature under argon was added CDI (1.38 g, 8.51 mmol, 1.0 eq) in 2 portions every 5 min (gas evolution was observed). Stirring was continued for an additional 1 h and then cooled to -78 °C.

The enolate solution was added over 15 min via canula to the activated ester solution at -78 °C, stirred for 15 min (orange hetereogeneous mix.) and then the reaction was allowed to warm up to room temperature (bath removed) overnight. Quenching of the cloudy heterogeneous mixture was performed by addition $NH_4Cl_{(aq)}$ (sat. sol. 55 mL) followed by water to dissolve the remaining salts. Layers were separated and the aqueous was extracted with $Et_2O$ (2x 20 mL). The combined organic layers were washed with brine (20 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced

pressure (25 °C bath, 20 mbar). Purification of the crude mixture by flash-chromatography (eluent: 2.5% (200 mL), 5% (400 mL), 10% (400 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 4.5 cm, L = 8.5 cm) afforded the title product as colourless liquid as a mixture of isomers (3:1 *d.r.*) and keto-enol forms (1.40 g, 5.38 mmol, 63%).

Analysed as a mixture of isomers (*ca.* 3:1 ratio) and its enol form: $\mathbf{R_f}$ 0.37 & 0.51 (10% $Et_2O$ in PE, vanillin, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 7.37 – 7.29 (2H, m, 2 $CH_{Ar}$-($13^{maj}$), 2 $CH_{Ar}$-($13^{min}$)), 7.29 – 7.25 (1H, m, $CH_{Ar}$-($14^{maj}$), $CH_{Ar}$-($14^{min}$)), 7.24 – 7.18 (2H, m, 2 $CH_{Ar}$-($12^{maj}$), 2 $CH_{Ar}$-($12^{min}$)), 5.64 (1H, ddtd, *J*=17.1, 10.2, 7.0, 1.0 Hz, CH-($6^{maj}$), CH-($6^{min}$)), 5.01 (1H, dtd, *J*=17.1, 3.3, 2.9, 1.6 Hz, $CH_a$-($7^{maj}$), $CH_a$-($7^{min}$)), 4.98 – 4.92 (1H, m, $CH_b$-($7^{maj}$), $CH_b$-($7^{min}$)), 4.18 – 4.07 (2H, m, $CH_2$-($8^{maj}$), $CH_2$-($8^{min}$)), 3.98 (0.75H, t, *J*=7.4 Hz, CH-($4^{maj}$)), 3.90 (0.25H, t, *J*=7.4 Hz, CH-($4^{min}$)), 3.55 (0.75H, q, *J*=7.0 Hz, CH-($2^{maj}$)), 3.55 (0.25H, q, *J*=7.2 Hz, CH-($2^{min}$)), 2.86 – 2.74 (1H, m, $CH_a$-($5^{maj}$), $CH_a$-($5^{min}$)), 2.43 (1H, dtt, *J*=14.3, 7.1, 1.3 Hz, $CH_b$-($5^{maj}$), $CH_b$-($5^{min}$)), 1.27 (0.75H, d, *J*=7.2 Hz, $CH_3$-($10^{min}$)), 1.24 (2.25H, t, *J*=7.2 Hz, $CH_3$-($9^{maj}$)), 1.15 (2.25H, d, *J*=7.0 Hz, $CH_3$-($10^{maj}$)), 1.07 (0.75H, t, *J*=7.1 Hz, $CH_3$-($9^{min}$)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 205.4 (C($3^{min}$)), 204.6 (C($3^{maj}$)), 170.4 (C($1^{maj}$)), 170.2 (C($1^{min}$)), 137.6 (C($11^{min}$)), $11^{maj}$)), 135.7 (C($6^{maj}$)), 135.5 (C($6^{min}$)), 129.2 (2 C($13^{maj}$)), 128.9 (2 C($13^{min}$)), 128.7 (C($12^{min}$)), 128.7 (C($12^{maj}$)), 127.7 (C($14^{maj}$)), 127.6 (C($14^{min}$)), 117.2 (C($7^{min}$)), 116.8 (C($7^{maj}$)), 61.5 (C($8^{maj}$)), 61.3 (C($8^{min}$)), 58.5 (C($4^{maj}$)), 57.6 (C($4^{min}$)), 52.8 (C($2^{min}$)), 51.3 (C($2^{maj}$)), 37.6 (C($5^{min}$)), 36.8 (C($5^{maj}$)), 14.2 (C($9^{maj}$)), 14.0 (C($9^{min}$)), 13.4 (C($10^{min}$)), 13.0 (C($10^{maj}$)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2987, 2940, 1743 (s, C=O), 1714 (s, C=O), 1642 (w, C=C), 1493, 1454 (m), 1375, 1325, 1193 (s), 1119, 1073, 1031; ***m/z*** ($ESI^+$) 543.3 ($[2M+Na]^+$, 100%), 283.1 ($[M+Na]^+$, 35%), 261.2 ($[M+H]^+$, 20%); **HRMS** ($ESI^+$) found 283.1305, $C_{16}H_{20}O_3{}^{23}Na^+$ requires 283.1305.

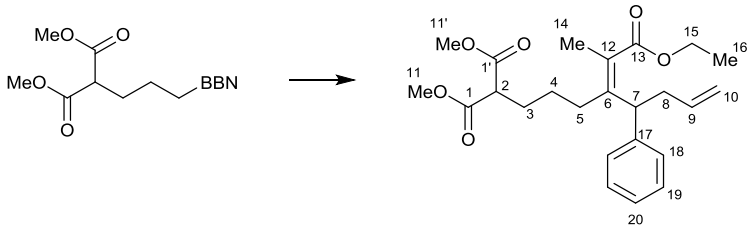
### Ethyl (*E*)-2-methyl-4-phenyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate (5.38)



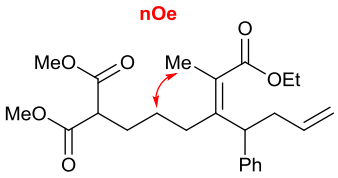
Prepared according to general procedure GP3 method B, using ethyl 2-methyl-3-oxo-4-phenylhept-6-enoate **5.37** (944 mg, 3.62 mmol, 1.0 eq.), KHMDS (0.5 M in toluene, 8.8 mL, 4.34 mmol, 1.2 eq.) and $PhNTf_2$ (1.45 g, 3.98 mmol, 1.1 eq.). TLC (10% $Et_2O$ in $PE_{30\text{-}40}$) showed complete reaction after 4 h. Purification by flash-chromatography (eluent: 0% (100 mL) then 3% (150 mL) then 5% (150 mL) then 7% (550 mL) $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 4.5 cm, L = 9 cm) followed by another flash-chromatography (eluent: 5% (900 mL) then 10% (1.5 L) $Et_2O$ in $PE_{40\text{-}60}$, column size: Ø = 7 cm, L = 10 cm) afforded the title product as a colourless liquid (720 mg, 1.83 mmol, 51%).

**$R_f$** 0.53 (10% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 7.36 – 7.31 (4H, m, 2 $CH_{Ar}$-(12), 2 $CH_{Ar}$-(13)), 7.30 – 7.26 (1H, m, $CH_{Ar}$-(14)), 5.76 (1H, ddt, *J*=17.0, 10.2, 6.8 Hz, CH-(6)), 5.14 (1H, dq, *J*=17.1, 1.6 Hz, $CH_a$-(7)), 5.06 (1H, dq, *J*=10.1, 1.2 Hz, $CH_b$-(7)), 4.71 (1H, t, *J*=7.9 Hz, CH-(4)), 4.28 (2H, q, *J*=7.1 Hz, $CH_2$-(8)), 2.83 – 2.71 (2H, m, $CH_2$-(5)), 2.03 (3H, s, $CH_3$-(10)), 1.34 (3H, t, *J*=7.1 Hz, $CH_3$-(9)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 167.3 (C(1)), 155.9 (C(3)), 137.4 (C(11)), 134.9 (C(6)), 128.6 (2 C(12)), 128.5 (2 C(13)), 127.6 (C(14)), 124.7 (C(2)), 118.5 (q, *J*=320.2 Hz, C(15)), 117.7 (C(7)), 62.0 (C(8)), 46.5 (C(4)), 34.2 (C(5)), 15.2 (C(10)), 14.2 (C(9)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2983, 1721 (s, C=O), 1644 (w, C=C), 1409 (s), 1274 (w), 1210 (s), 1175 (w), 1136 (m), 1097 (w), 1030 (m); ***m/z*** ($ESI^+$) 431.1 ($[M+K]^+$, 100%); **HRMS** ($ESI^+$) found 393.0977, $C_{17}H_{20}O_5F_3{}^{32}S^+$ requires 393.0978.

### 6-Ethyl 1,1-dimethyl (*Z*)-5-(1-phenylbut-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate (5.39)



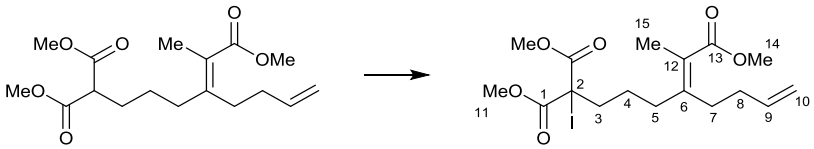

Prepared according to general procedure GP5, using 9-BBN (0.5 M in THF, 4.5 mL, 2.25 mmol, 1.5 eq.), dimethyl 2-allylmalonate **3.17** (0.39 mL, 2.42 mmol, 1.6 eq.), $K_3PO_{4(aq)}$ (1 M, 3.8 mL, 3.8 mmol, 2.5 eq.), ethyl (*E*)-2-methyl-4-phenyl-3-(((trifluoromethyl)sulfonyl)oxy)hepta-2,6-dienoate **5.38** (588 mg, 1.51 mmol, 1.0 eq.) and $Pd(PPh_3)_4$ (87 mg, 0.08 mmol, 0.05 eq.). The mixture was heated to 50 °C overnight, complete consumption of **5.38** was observed by TLC (20% $Et_2O$ in $PE_{40\text{-}60}$). Purification by flash-chromatography (eluent: 5% (200 mL) then 10% (300 mL) then 20% (600 mL) $Et_2O$ in $PE_{30\text{-}}$; column size: Ø = 4 cm, L = 7 cm) followed by a second purification by flash-chromatography (eluent: 0% (150 mL) then 5% (250 mL) then 7% (400 mL) EtOAc in toluene; column size: Ø = 5 cm, L = 8 cm) afforded the title product as colourless liquid (128 mg, 0.31 mmol, 20%).




**$R_f$** 0.20 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.50 (10% EtOAc in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 7.30 – 7.26 (4H, m, 2 $CH_{Ar}$-(18), 2 $CH_{Ar}$-(19)), 7.21 – 7.16 (1H, m, $CH_{Ar}$-(20)), 5.73 (1H, ddt, *J*=17.0, 10.2, 6.7 Hz, CH-(9)), 5.07 – 5.01 (1H, m, $CH_a$-(10)), 4.97 (1H, dd, *J*=10.3, 1.8 Hz, $CH_b$-(10)), 4.41 (1H, t, *J*=7.8 Hz, CH-(7)), 4.26 (2H, qd, *J*=7.2, 1.8 Hz, $CH_2$-(15)), 3.68 (3H, s, $CH_3$-(11)), 3.67 (3H, s, $CH_3$-(11)), 3.14 (1H, t, *J*=7.6 Hz, CH-(2)), 2.65 (1H, dt, *J*=14.1, 6.9 Hz, $CH_a$-(8)), 2.55 – 2.47 (1H, m, $CH_b$-(8)), 1.93 (1H, td, *J*=12.8, 5.1 Hz, $CH_a$-(5)), 1.85 (4H, s, $CH_b$-(5), $CH_3$-(14)), 1.77 – 1.69 (1H, m, $CH_a$-(3)), 1.69 – 1.61 (1H, m, $CH_b$-(3)), 1.33 (3H, t, *J*=7.1 Hz, $CH_3$-(16)), 1.21 – 1.10 (1H, m, $CH_a$-(4)), 0.59 (1H, ddt, *J*=17.5, 11.9, 5.2 Hz, $CH_b$-(4)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 170.9 (C(13)), 169.7 (2 C(1)), 146.7 (C(6)), 141.6 (C(17)), 136.7 (C(9)), 128.3 (2 C(18)), 128.3 (2 C(19)), 126.5 (C(20)), 125.9 (C(12)), 116.3 (C(10)), 60.6 (C(15)), 52.6 (2 C(11)), 51.3 (C(2)), 47.6 (C(7)), 35.3 (C(8)), 29.4 (C(3)), 28.7 (C(5)), 26.5 (C(4)), 16.2 (C(14)), 14.5 (C(16)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2954, 2929, 2871, 1753 (s, C=O),

1736 (s, C=O), 1714 (s, C=O), 1641 (w, C=C), 1495 (m), 1436, 1346, 1264, 1245, 1192 (m), 1148, 1100 (m), 1030, 1000; ***m/z*** ($ESI^+$) 439.2 ($[M+Na]^+$, 100%), 855.5 ($[2M+Na]^+$, 70%); **HRMS** ($ESI^+$) found 439.2071, $C_{24}H_{32}O_6{}^{23}Na^+$ requires 439.2091.

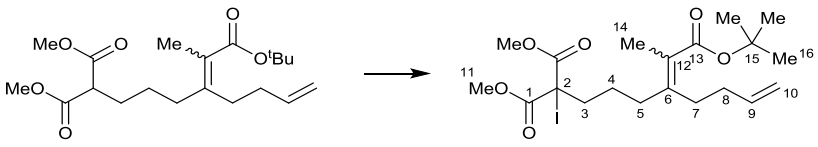
### Trimethyl (*Z*)-5-(but-3-en-1-yl)-1-iodohept-5-ene-1,1,6-tricarboxylate (5.40)




Prepared according to general procedure GP7, using trimethyl (*Z*)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.46** (200 mg, 0.61 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 0.67 mL, 0.67 mmol, 1.1 eq.) and *N*-iodosuccinimide (152 mg, 0.67 mmol, 1.1 eq.). TLC (20% $Et_2O$ in PE, vanillin, $UV_{254\ nm}$) showed complete reaction after 3 h. Purification in the dark of the crude mixture by flash-chromatography (eluent: 10% (200 mL), 20% (200 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2.5 cm, L = 8 cm) afforded the title product as colourless oil (196 mg, 0.43 mmol, 71%).

**$R_f$** 0.25 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.82 (1H, ddt, *J*=16.9, 10.2, 6.6 Hz, CH-(9)), 5.02 (1H, dq, *J*=17.1, 1.6 Hz, $CH_a$-(10)), 4.95 (1H, ddt, *J*=10.2, 2.2, 1.2 Hz, $CH_b$-(10)), 3.80 (6H, s, 2 $CH_3$-(11)), 3.72 (3H, s, $CH_3$-(14)), 2.38 (2H, dd, *J*=9.4, 6.5 Hz, $CH_2$-(7)), 2.18 (6H, ddt, *J*=10.0, 7.4, 5.1 Hz, $CH_2$-(3), $CH_2$-(5), $CH_2$-(8)), 1.86 (3H, s, $CH_3$-(15)), 1.54 – 1.45 (2H, m, $CH_2$-(4)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 170.0 (C(13)), 168.8 (2 C(1)), 148.8 (C(6)), 138.4 (C(9)), 124.2 (C(12)), 114.8 (C(10)), 54.1 (2 C(11)), 51.5 (C(14)), 43.2 (C(2)), 40.2 (C(3)), 33.8 (C(7)), 33.1 (C(8)), 33.1 (C(5)), 26.2 (C(4)), 15.7 (C(15)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2953, 1737 (s, with shoulder, C=O), 1639 (w, C=C), 1435 (m, with shoulder), 1251 (s), 1195 (m), 1104; ***m/z*** ($ESI^+$) 927.1 ($[2M+Na]^+$, 100%), 475.0 ($[M+Na]^+$, 75%); **HRMS** ($ESI^+$) found 475.0585, $C_{17}H_{25}O_6{}^{127}I^{23}Na^+$ requires 475.0588.

### 6-(*tert*-Butyl) 1,1-dimethyl 5-(but-3-en-1-yl)-1-iodohept-5-ene-1,1,6-tricarboxylate (5.41)

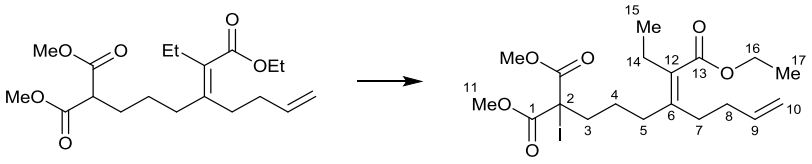


Prepared according to general procedure GP7, using 6-(*tert*-butyl) 1,1-dimethyl 5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.61** (60:40 *Z/E* mix., 147.0 mg, 0.40 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 0.44 mL, 0.44 mmol, 1.1 eq.) and *N*-iodosuccinimide (98.7 mg, 0.44 mmol, 1.1 eq.). TLC (20% $Et_2O$ in PE) showed complete reaction after 3 h. Purification in the dark of the crude mixture by flash-chromatography (eluent: 10% (200 mL), 20% (200 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2.5 cm, L = 8 cm) afforded the title product as colourless oil as a mixture of alkene isomers (65:35 *Z/E* mix., 166.5 mg, 0.34 mmol, 84%).

Analysed as a *Z/E* mixture (~1:0.5 ratio): $\mathbf{R_f}$ 0.33 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.90 – 5.81 (1.5H, m, CH-($9^{trans}$), CH-($9^{cis}$)), 5.06 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-($10^{trans}$)), 5.05 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-($10^{cis}$), 5.01 (0.5H, dq, *J*=10.3, 1.4 Hz, $CH_b$-($10^{trans}$)), 4.99 (1H, dq, *J*=10.3, 1.4 Hz, $CH_b$-($10^{cis}$)), 3.82 (6H, s, 2 $CH_3$-($11^{cis}$)), 3.82 (3H, s, 2 $CH_3$-($11^{trans}$)), 2.35 (3H, q, *J*=7.9 Hz, $CH_2$-($7^{cis}$), $CH_2$-($^{trans}$)), 2.24 – 2.18 (5H, m, $CH_2$-($8^{cis}$), $CH_2$-($3^{cis}$)), 2.18 – 2.12 (5H, m, $CH_2$-($5^{cis}$)), 1.84 (4.5H, d, *J*=1.6 Hz, $CH_3$-($14^{trans}$), $CH_3$-($14^{cis}$)), 1.52 (4.5H, s, 3 $CH_3$-($16^{trans}$)), 1.52 (9H, s, 3 $CH_3$-($16^{cis}$)), 1.56 – 1.47 (3.5H, m, $CH_2$-($4^{cis}$), $CH_2$-($4^{trans}$)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 169.6 (C($13^{cis}$)), 169.5 (C($13^{trans}$)), 168.7 (2 C($1^{trans}$)), 168.7 (2 C($1^{cis}$)), 144.2 (C($6^{cis}$)), 144.2 (C($6^{trans}$)), 138.4 (C($9^{cis}$)), 137.9 (C($9^{trans}$)), 126.2 (C($12^{trans}$)), 126.2 (C($12^{cis}$)), 115.0 (C($10^{trans}$)), 114.6 (C($10^{cis}$)), 80.5 (C($15^{cis}$)), 80.4 (C($15^{trans}$)), 54.0 (2 C($11^{cis}$)), 53.9 (2 C($11^{trans}$)), 43.8 (C($2^{trans}$)), 43.2 (C($2^{cis}$)), 40.2 (C($3^{cis}$)), 40.0 (C($3^{trans}$)), 33.3 (C($7^{cis}$)), 33.0 ($^{trans}$), 32.9 (C($8^{cis}$)), 32.4 (C($5^{cis}$)), 32.3 ($^{trans}$), 31.8 ($^{trans}$), 28.3 (3 C($16^{trans}$)) 28.2 (3 C($16^{cis}$)) , 26.9 (C($4^{trans}$)), 26.1 (C($4^{cis}$)), 15.8 (C($14^{cis}$), C($14^{trans}$)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 3005, 2954, 2932, 2868, 1738 (s, C=O), 1707 (s, C=O), 1640 (w, C=C), 1455, 1436, 1367, 1250 (s), 1169, 1106 (s); ***m/z*** ($ESI^+$) 1011.2 ($[2M+Na]^+$, 100%), 517.1 ($[M+Na]^+$, 60%); **HRMS** ($ESI^+$) found 517.1062, $C_{20}H_{31}O_6{}^{127}I^{23}Na^+$ requires 517.1058.

The full assignment by NMR of the minor isomer was not possible because of the strong overlap of $CH_2$-(3), $CH_2$-(5), $CH_2$-(7) and $CH_2$-(8) in $^1$H NMR and C(3), C(5), C(7) and C(8) in $^{13}$C NMR for both isomers.

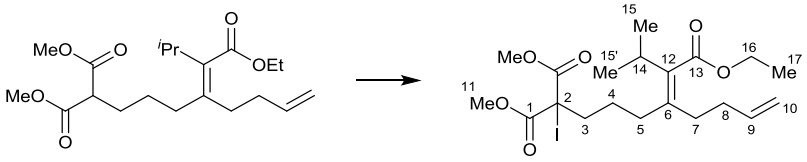
### 6-Ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-1-iodooct-5-ene-1,1,6-tricarboxylate (5.42)




Prepared according to general procedure GP7, using 6-ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)oct-5-ene-1,1,6-tricarboxylate **3.62** (46.8 mg, 0.13 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 0.15 mL, 0.15 mmol, 1.1 eq.) and *N*-iodosuccinimide (32.7 mg, 0.15 mmol, 1.1 eq.). TLC (20% $Et_2O$ in PE) showed complete reaction after 5 h. Purification in the dark of the crude mixture by flash-chromatography (eluent: 10% (200 mL), 20% (200 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2.5 cm, L = 8 cm) afforded the title product as colourless oil (40.3 mg, 0.08 mmol, 64%).

**$R_f$** 0.29 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\,nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.81 (2H, ddt, *J*=16.8, 10.2, 6.5 Hz, CH-(9)), 5.02 (1H, dq, *J*=17.1, 1.7 Hz, $CH_a$-(10)), 4.95 (1H, ddt, *J*=10.2, 2.2, 1.2 Hz, $CH_b$-(10)), 4.20 (2H, q, *J*=7.1 Hz, $CH_2$-(16)), 3.80 (6H, s, 2 $CH_3$-(11)), 2.29 (4H, m, $CH_2$-(7), $CH_2$-(14)), 2.22 – 2.13 (6H, m, $CH_2$-(3), $CH_2$-(5), $CH_2$-(8)), 1.54 – 1.46 (2H, m, $CH_2$-(4)), 1.30 (3H, t, *J*=7.1 Hz, $CH_3$-(17)), 0.99 (3H, t, *J*=7.5 Hz, $CH_3$-(15)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 169.9 (C(13)), 168.8 (2 C(1)), 145.0 (C(6)), 138.3 (C(9)), 131.8 (C(12)), 114.8 (C(10)), 60.3 (C(16)), 54.1 (2 C(11)), 43.2 (C(2)), 40.3 (C(3)), 33.5 (C(7)), 33.2 (C(8)), 32.0 (C(5)), 27.0 (C(4)), 23.2 (C(14)), 14.5 (C(17)), 13.9 (C(15)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2954, 2933, 2872, 1738 (s, C=O), 1713 (m, C=O), 1640 (C=C), 1435, 1246 (m), 1222 (m), 1108 (m), 1025; ***m/z*** ($ESI^+$) 983.1 ($[2M+Na]^+$, 100%), 503.1 ($[M+Na]^+$, 65%); **HRMS** ($ESI^+$) found 503.0901, $C_{19}H_{29}O_6{}^{127}I^{23}Na^+$ requires 503.0901.

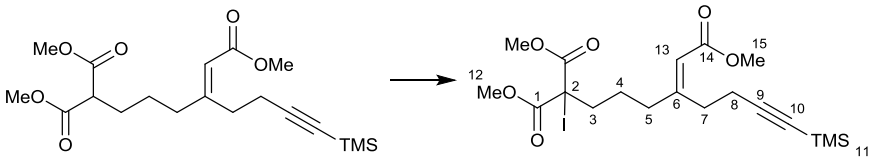
### 6-Ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-1-iodo-7-methyloct-5-ene-1,1,6-tricarboxylate (5.43)




Prepared according to general procedure GP7, using 6-isopropyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)oct-5-ene-1,1,6-tricarboxylate **3.63** (54.8 mg, 0.15 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 0.16 mL, 0.16 mmol, 1.1 eq.) and *N*-iodosuccinimide (36.8 mg, 0.16 mmol, 1.1 eq.). TLC (20% $Et_2O$ in PE) showed complete reaction after 5 h. Purification in the dark of the crude mixture by flash-chromatography (eluent: 10% (200 mL), 20% (200 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2.5 cm, L = 8 cm) afforded the title product as colourless liquid/oil (50.8 mg, 0.10 mmol, 69%).

**$R_f$** 0.34 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\,nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.78 (1H, ddt, *J*=16.7, 10.2, 6.3 Hz, CH-(9)), 5.00 (1H, dq, *J*=17.1, 1.6 Hz, $CH_a$-(10)), 4.94 (1H, ddt, *J*=10.1, 2.1, 1.2 Hz, $CH_b$-(10)), 4.20 (2H, q, *J*=7.1 Hz, $CH_2$-(16)), 3.79 (6H, s, 2 $CH_3$-(11)), 2.76 (1H, hept, *J*=6.9 Hz, CH-(14)), 2.21 – 2.17 (2H, m, $CH_2$-(3)), 2.16 – 2.11 (4H, m, $CH_2$-(5), $CH_2$-(8)), 2.11 – 2.06 (2H, m, $CH_2$-(7)), 1.54 – 1.44 (2H, m, $CH_2$-(4)), 1.30 (3H, t, *J*=7.1 Hz, $CH_3$-(17)), 1.07 (6H, d, *J*=6.9 Hz, 2 $CH_2$-(15)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 170.2 (C(13)), 168.8 (2 C(1)), 138.2 (C(9)), 137.6 (C(6)), 137.2 (C(12)), 114.8 (C(10)), 60.1 (C(16)), 54.1 (2 C(11)), 43.3 (C(2)), 40.4 (C(3)), 33.6 (C(7)), 33.0 (C(8)), 30.1 (C(5)), 28.7 (C(14)), 27.1 (C(4)), 21.7 (2 C(15)), 14.5 (C(17)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2956, 2933, 2871, 1737 (s, C=O), 1718 (s, C=O), 1640 (w, C=C), 1460, 1435 (m), 1249 (s), 1219 (m), 1180, 1157, 1126, 1030; ***m/z*** ($ESI^+$) 1011.2 ($[2M+Na]^+$, 100%), 517.1 ($[M+Na]^+$, 70%); **HRMS** ($ESI^+$) found 517.1060, $C_{20}H_{31}O_6{}^{127}I^{23}Na^+$ requires 517.1058.

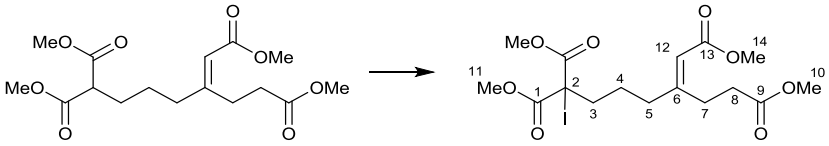
### Trimethyl (*Z*)-1-iodo-5-(4-(trimethylsilyl)but-3-yn-1-yl)hex-5-ene-1,1,6-tricarboxylate (5.44)



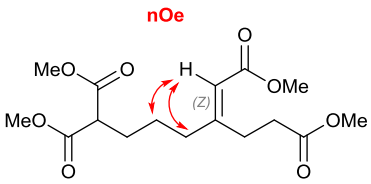

Prepared according to general procedure GP7, using trimethyl (*Z*)-5-(4-(trimethylsilyl)but-3-yn-1-yl)hex-5-ene-1,1,6-tricarboxylate (*Z*)-**2.31** (191 mg, 0.50 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 0.67 mL, 0.67 mmol, 1.35 eq.) and *N*-iodosuccinimide (151.4 g, 0.67 mmol, 1.35 eq.). TLC (10% EtOAc in toluene) showed complete reaction after 2 h. Purification in the dark of the crude mixture by flash-chromatography (eluent: 10% to 20% $Et_2O$ in $PE_{40\text{-}60}$; column size: Ø = 1.5 cm, L = 8 cm) afforded the title product as a colourless oil (202 mg, 0.38 mmol, 78%).

**$R_f$** 0.71 (10% EtOAc in toluene, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.31 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.69 (1H, t, *J*=1.4 Hz, CH-(13)), 3.81 (6H, s, 2 $CH_3$-(12)), 3.69 (3H, s, $CH_3$-(15)), 2.79 (2H, t, *J*=7.3 Hz, $CH_2$-(7)), 2.44 (2H, t, *J*=7.3 Hz, $CH_2$-(8)), 2.32 (2H, td, *J*=7.4, 1.3 Hz, $CH_2$-(5)), 2.19 – 2.13 (2H, m, $CH_2$-(3)), 1.62 – 1.52 (2H, m, $CH_2$-(4)), 0.13 (9H, s, 3 $CH_3$-(11)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 168.7 (C(1)), 166.6 (C(14)), 161.2 (C(6)), 116.6 (C(13)), 106.4 (C(9)), 85.5 (C(10)), 54.2 (2 C(12)), 51.2 (C(15)), 43.1 (C(2)), 39.7 (C(3)), 38.0 (C(5)), 30.9 (C(7)), 25.6 (C(4)), 19.2 (C(8)), 0.2 (3 C(11)); **$\nu_{max}$** /$cm^{-1}$ (neat) 2953, 2174 (w, C≡C), 1736 (s, C=O), 1718 (s, C=O), 1645 (m, C=C), 1434, 1247 (s), 1191, 1167 (s), 1135, 1078, 1040; ***m/z*** ($ESI^+$) 1039.1 ($[2M+Na]^+$, 100%), 531.0 ($[M+Na]^+$, 100%), 509.1 ($[M+H]^+$, 45%); **HRMS** ($ESI^+$) 531.0668 found, $C_{19}H_{29}O_6{}^{127}I^{23}Na^{28}Si^+$ requires 531.0670.

### Trimethyl (*Z*)-1-iodo-5-(2-methoxy-2-oxoethylidene)heptane-1,1,7-tricarboxylate (5.45)

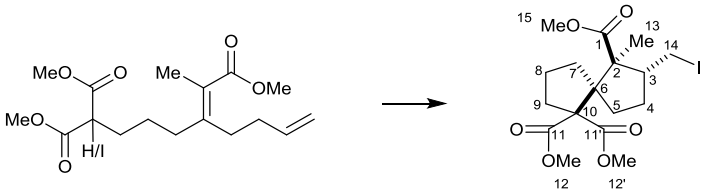


Prepared according to general procedure GP7, using trimethyl (Z)-5-(2-methoxy-2-oxoethylidene)heptane-1,1,7-tricarboxylate (*Z*)-**4.1** (1.10 g, 3.21 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 3.54 mL, 3.54 mmol, 1.1 eq.) and *N*-iodosuccinimide (0.79 g, 3.54 mmol, 1.1 eq.). TLC (10% EtOAc in toluene) showed complete reaction after 2 h. Purification in the dark of the crude mixture by flash-chromatography (eluent: 12.5% to 40% $Et_2O$ in $PE_{40\text{-}60}$; column size: Ø = 5 cm, L = 8 cm) afforded the title product as an orange liquid (0.70 g, 1.49 mmol, 46%).



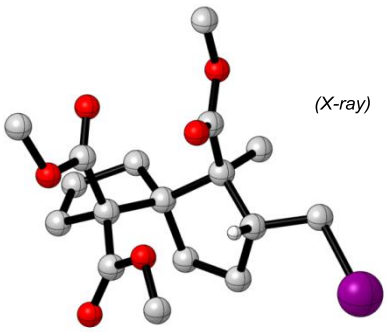

**$R_f$** 0.43 (10% EtOAc in toluene, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.42 (40% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (400 MHz, $CDCl_3$) 5.69 (1H, t, *J*=1.3 Hz, CH-(12)), 3.80 (6H, s, 2 $CH_3$-(11)), 3.69 (3H, s, $CH_3$-(14)), 3.68 (3H, s, $CH_3$-(10)), 2.86 (2H, dd, *J*=8.8, 7.2 Hz, $CH_2$-(7)), 2.50 (2H, dd, *J*=8.8, 7.2 Hz, $CH_2$(8)), 2.23 (2H, td, *J*=7.5, 1.3 Hz, $CH_2$-(5)), 2.19 – 2.11 (2H, m, $CH_2$-(3)), 1.62 – 1.52 (2H, m, $CH_2$-(4)); **$\delta_C$** /ppm (176 MHz, $CDCl_3$) 173.4 (C(9)), 168.7 (2 C(1)), 166.5 (C(13)), 160.7 (C(6)), 116.9 (C(12)), 54.2 (2 C(11)), 51.9 (C(10)), 51.2 (C(14)), 43.0 (C(2)), 39.6 (C(3)), 37.6 (C(5)), 32.9 (C(8)), 27.5 (C(7)), 25.7 (C(4)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2953, 2923, 2850, 1733 (s, C=O), 1719 (s, C=O), 1646 (w, C=C), 1435, 1247, 1224, 1194, 1163 (s), 1135, 1099, 1079, 1027; ***m/z*** ($ESI^+$) 493.0 ($[M+Na]^+$, 100%), 963.1 ($[2M+Na]^+$, 95%), 471.1 ($[M+H]^+$, 20%); **HRMS** ($ESI^+$) 493.0325 found, $C_{16}H_{23}O_8{}^{127}I^{23}Na^+$ requires 493.0330.

### Trimethyl (5*R**,6*S**,7*R**)-7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (5.50)

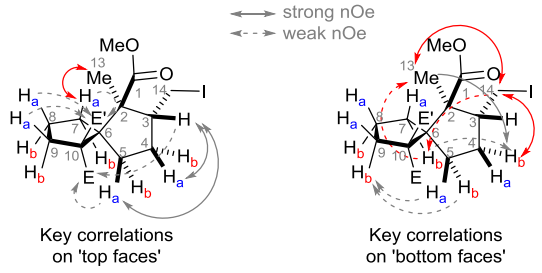



**Method 1** (from iodomalonate **5.40**): Prepared according to general procedure GP8, using trimethyl (*Z*)-5-(but-3-en-1-yl)-1-iodohept-5-ene-1,1,6-tricarboxylate **5.40** (57.7 mg, 0.13 mmol, 1.0 eq.) and 2,6-lutidine (13 µL, 0.13 mmol, 1.0 eq.). Reaction vessel: 3.5 mL clear vial. The reaction was irradiated (with magnetic stirring) using a white 30 W CFL light (at 5.0 cm distance) for 16 h. Purification by flash-chromatography (eluent: 5% (100 mL) then 10% (250 mL) then 15% (100 mL) then 20% (300 mL) then 40% $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2.5 cm, L = 8 cm) afforded the title product as a colourless oil (35.7 mg, 0.08 mmol, 62%).

**Method 2** (one-pot from malonate **3.46**): Prepared according to general procedure GP9, using trimethyl (*Z*)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.46** (89.0 mg, 0.27 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 0.30 mL, 0.30 mmol, 1.1 eq.), 2,6-lutidine (27 µL, 0.27 mmol, 1.0 eq.). Reaction vessel: 5 mL borosilicate round-bottom flask. The reaction was irradiated (with magnetic stirring) using a white 30 W CFL light (at 5.0 cm distance) for 16 h. Purification by flash-chromatography (eluent: 5% (100 mL) then 10% (250 mL) then 15% (100 mL) then 20% (300 mL) then 40% $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2.5 cm, L = 8 cm) afforded the title product as a colourless oil (71.6 mg, 0.16 mmol, 58%).



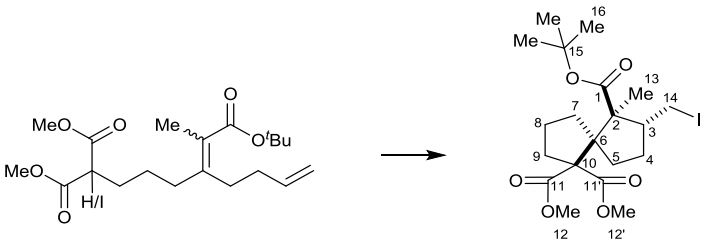
(*X-ray*)




**$R_f$** 0.40 (40% $Et_2O$ in $PE_{30\text{-}40}$, slight $UV_{254\ nm}$ if conc, weak vanillin, good $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 3.72 (3H, s, $CH_3$-(12)), 3.68 (3H, s, $CH_3$-(12')), 3.61 (3H, s, $CH_3$-(15)), 3.37 (1H, dd, *J*=9.0, 3.7 Hz,

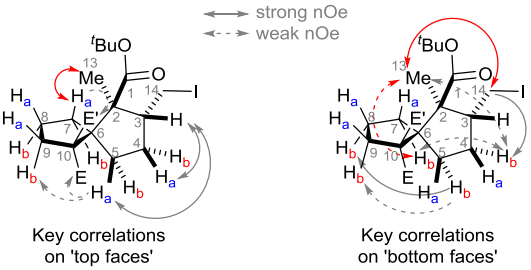
$CH_a$-(14)), 3.10 (1H, tdd, *J*=11.0, 6.8, 3.6 Hz, CH-(3)), 2.94 (1H, dd, *J*=11.4, 9.0 Hz, $CH_b$-(14)), 2.43 (1H, tdd, *J*=13.7, 8.0, 1.9 Hz, $CH_x$-(7)), 2.39 – 2.32 (1H, m, $CH_b$-(9)), 2.20 (1H, ddd, *J*=14.2, 9.5, 3.1 Hz, $CH_a$-(9)), 2.13 (1H, dtd, *J*=12.6, 7.1, 2.5 Hz, $CH_a$-(4)), 1.88 (1H, dddd, *J*=13.2, 10.5, 7.3, 1.4 Hz, $CH_a$-(5)), 1.80 – 1.70 (1H, m, $CH_a$-(8)), 1.70 – 1.63 (1H, m, $CH_b$-(8)), 1.63 – 1.57 (1H, m, $CH_b$-(7)), 1.56 – 1.52 (1H, m, $CH_b$-(5)), 1.31 (1H, tdd, *J*=12.3, 10.5, 7.7 Hz, $CH_b$-(4)), 1.12 (3H, s, $CH_3$-(13)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 176.4 (C(1)), 172.1 (C(11')), 171.8 (C(11)), 66.1 (C(10)), 64.6 (C(6)), 55.4 (C(2)), 52.3 (C(12)), 52.1 (C(12')), 51.9 (C(15)), 50.5 (C(3)), 35.4 (C(5)), 35.4 (C(9)), 35.1 (C(7)), 29.7 (C(4)), 19.0 (C(8)), 18.2 (C(13)), 8.2 (C(14)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2951, 1725 (s, C=O), 1432 (m, with shoulder), 1265 (m), 1196 (w), 1112, 1084; ***m/z*** ($ESI^+$) 927.2 ($[2M+Na]^+$, 100%), 475.1 ($[M+Na]^+$, 35%); **HRMS** ($ESI^+$) found 475.0587, $C_{17}H_{25}O_6{}^{127}I^{23}Na^+$ requires 475.0588.

### 6-(*tert*-Butyl) 1,1-dimethyl (5*R**,6*S**,7*R**)-7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (5.51)



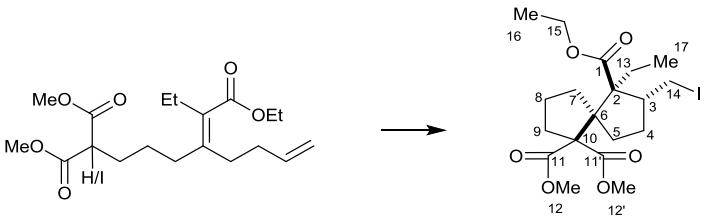

**Method 1** (from iodomalonate **5.41**): Prepared according to general procedure GP8, using 6-(*tert*-butyl) 1,1-dimethyl 5-(but-3-en-1-yl)-1-iodohept-5-ene-1,1,6-tricarboxylate **5.41** (65:35-*Z/E* mix., 62.9 mg, 0.13 mmol, 1.0 eq.) and 2,6-lutidine (13 µL, 0.13 mmol, 1.0 eq.). Reaction vessel: 3.5 mL clear vial. The reaction was irradiated (with magnetic stirring) using a white 30 W CFL light (at 5.0 cm distance) for 16 h. Purification by flash-chromatography (eluent: 5% (300 mL) then 10% (300 mL) then 30% (300 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2.5 cm, L = 8 cm) afforded the title product as a clear orange oil (43.6 mg, 0.09 mmol, 69%).

**Method 2** (one-pot from malonate **3.61**): Prepared according to general procedure GP9, using 6-(*tert*-butyl) 1,1-dimethyl 5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.61** (60:40 *Z/E* mix., 100.0 mg, 0.27 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 0.30 mL, 0.30 mmol, 1.1 eq.), 2,6-lutidine (27 µL, 0.27 mmol, 1.0 eq.). Reaction vessel: 5 mL borosilicate round-bottom flask. The reaction was irradiated (with magnetic stirring) using a white 30 W CFL light (at 5.0 cm distance) for 16 h. Purification by flash-chromatography (eluent: 5% (300 mL) then 10% (300 mL) then 30% (300 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2.5 cm, L = 8 cm) afforded the title product as a yellow oil (83.9 mg, 0.17 mmol, 63%).



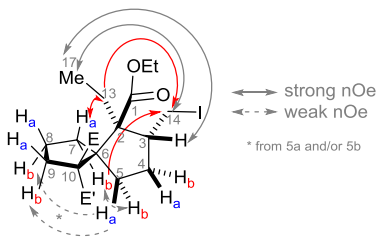

**$R_f$** 0.87 (40% $Et_2O$ in $PE_{30\text{-}40}$, weak $UV_{254\ nm}$, weak vanillin, $KMnO_4$), 0.55 (20% $Et_2O$ in $PE_{30\text{-}40}$, weak $UV_{254\ nm}$, weak vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 3.71 (3H, s, $CH_3$-(12)), 3.68 (3H, s, $CH_3$-(12')), 3.49 (1H, dd, *J*=8.3, 2.3 Hz, $CH_a$-(14)), 2.92 (1H, dd, *J*=11.3, 8.5 Hz, $CH_b$-(14)), 2.87 (1H, tdd, *J*=11.5, 11.5, 5.8, 2.5 Hz, CH-(3)), 2.34 (1H, dddd, *J*=12.4, 11.0, 7.2, 1.6 Hz, $CH_a$-(7)), 2.25 (2H, tdd, *J*=14.0, 7.2, 3.4 Hz, $CH_2$-(9)), 2.14 (1H, dtd, *J*=12.3, 6.7, 5.4, 1.5 Hz, $CH_a$-(4)), 1.94 – 1.85 (1H, m, $CH_a$-(5)), 1.84 – 1.74 (1H, m, $CH_a$-(8)), 1.73 – 1.60 (2H, m, $CH_b$-(8)), 1.60 – 1.54 (1H, m, $CH_b$-(7)), 1.51 (1H, ddd, *J*=12.5, 6.9, 1.5 Hz, $CH_b$-(5)), 1.45 (9H, s, 3 $CH_3$-(16)), 1.28 – 1.23 (1H, m, $CH_b$-(4)), 1.05 (3H, s, $CH_3$-(13)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 175.8 (C(1)), 172.3 (C(11)), 172.1 (C(11')), 80.7 (C(15)), 65.8 (C(10)), 64.2 (C(6)), 55.8 (C(2)), 52.1 (C(12)), 52.0 (C(12')), 51.7 (C(3)), 35.8 (C(5)), 35.1 (C(9)), 35.0 (C(7)), 29.4 (C(4)), 28.1 (3 C(16)), 19.4 (C(8)), 18.5 (C(13)), 8.6 (C(14)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2952, 1728 (s, with shoulder, C=O), 1432 (w), 1368 (w), 1272 (s), 1197 (m), 1165 (w), 1140 (w), 1111, 1085; ***m/z*** ($ESI^+$) 1011.3 ($[2M+Na]^+$, 100%), 517.2 ($[M+Na]^+$, 20%), 495.2 ($[M+H]^+$, 5%); **HRMS** ($ESI^+$) found 517.1055, $C_{20}H_{31}O_6{}^{127}I^{23}Na^+$ requires 517.1058.

### 6-Ethyl 1,1-dimethyl (5*R**,6*S**,7*R**)-6-ethyl-7-(iodomethyl)spiro[4.4]nonane-1,1,6-tricarboxylate (5.52)




**Method 1** (from iodomalonate **5.42**): Prepared according to general procedure GP8, using 6_ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-1-iodooct-5-ene-1,1,6-tricarboxylate **5.42** (35.0 mg, 0.07 mmol, 1.0 eq.) and 2,6-lutidine (7.8 mg, 0.07 mmol, 1.0 eq.). Reaction vessel: 3.5 mL clear vial. The reaction was irradiated (with magnetic stirring) using a white 30 W CFL light (at 5.0 cm distance) for 2 d. Purification by flash-chromatography (eluent: 10% then 20% then 40% then 60% then 80% (150 mL each) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 1.5 cm, L = 8 cm) afforded the title product as a colourless oil (9.1 mg, 0.02 mmol, 26%).

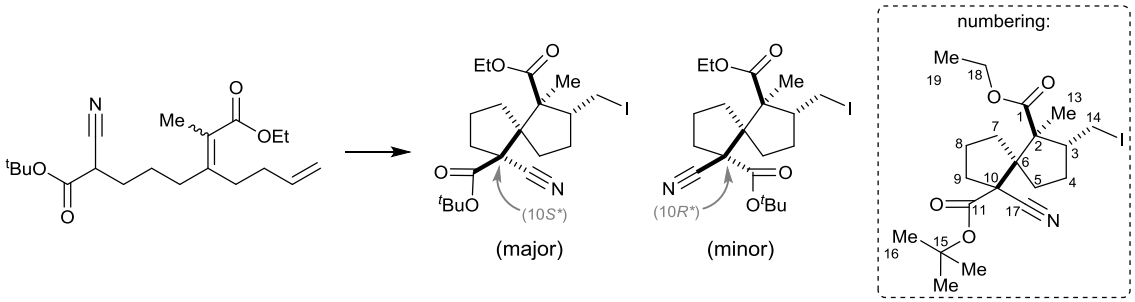
**Method 2** (one-pot from malonate **3.62**): Prepared according to general procedure GP9, using 6-ethyl 1,1-dimethyl (Z)-5-(but-3-en-1-yl)oct-5-ene-1,1,6-tricarboxylate **3.62** (69.4 mg, 0.20 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 0.22 mL, 0.22 mmol, 1.1 eq.), 2,6-lutidine (19 µL, 0.20 mmol, 1.0 eq.). Reaction vessel: 5 mL borosilicate round-bottom flask. The reaction was irradiated (with magnetic stirring) using a white 30 W CFL light (at 5.0 cm distance) for 2 d. Purification by flash-chromatography (eluent: 10% then 20% then 40% then 60% then 80% (150 mL each) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 1.5 cm, L = 8 cm) afforded the title product as a colourless oil (27.2 mg, 0.06 mmol, 29%).




**$R_f$** 0.45 (40% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 4.30 (1H, dq, *J*=10.9, 7.1 Hz, $CH_a$-(15)), 3.83 (1H, dq, *J*=11.0, 7.1 Hz, $CH_b$-(15)), 3.70 (3H, s, $CH_3$-(12)), 3.66 (3H, s, $CH_3$-(12')), 3.46 (1H, ddd, *J*=9.2, 3.0, 1.3 Hz, $CH_a$-(14)), 3.25 (1H, ddt, *J*=13.0, 6.5, 3.2 Hz, CH-(3)), 3.02 (1H, dd, *J*=12.8, 9.2 Hz, $CH_b$-(14)), 2.80 (1H, dt, *J*=12.1, 9.8 Hz,

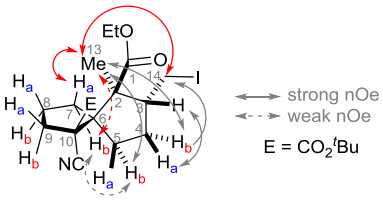
$CH_a$-(7)), 2.43 (1H, ddd, *J*=14.7, 11.6, 6.4 Hz, $CH_b$-(9)), 2.12 – 2.05 (1H, m, $CH_a$-(9)), 2.06 – 1.99 (2H, m, $CH_{a\ or\ b}$-(4), $CH_a$-(13)), 1.85 – 1.76 (1H, m, $CH_a$-(8)), 1.76 – 1.70 (1H, m, $CH_{a\ or\ b}$-(4)), 1.70 – 1.62 (1H, m, $CH_b$-(8)), 1.62 – 1.50 (3H, m, $CH_2$-(5), $CH_b$-(13)), 1.42 (1H, ddd, *J*=12.3, 8.3, 2.0 Hz, $CH_b$-(7)), 1.24 (3H, t, *J*=7.2 Hz, $CH_3$-(16)), 0.80 (3H, t, *J*=7.3 Hz, $CH_3$-(17)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 174.7 (C(1)), 172.7 (C(11)), 171.5 (C(11')), 66.8 (C(10)), 62.2 (C(6)), 61.9 (C(2)), 60.4 (C(15)), 52.1 (C(12), C(12')), 48.0 (C(3)), 38.0 (C(5)), 37.8 (C(7)), 35.6 (C(9)), 29.4 (C(4)), 25.7 (C(13)), 19.3 (C(8)), 14.3 (C(16)), 10.7 (C(17)), 10.0 (C(14)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2952, 2918, 2881, 1726 (s with shoulder, C=O), 1456, 1432, 1262 (s), 1228, 1207, 1175, 1120; ***m/z*** ($ESI^+$) 983.1 ($[2M+Na]^+$, 100%), 503.1 ($[M+Na]^+$, 45%); **HRMS** ($ESI^+$) found 503.0900, $C_{19}H_{29}O_6{}^{127}I^{23}Na^+$ requires 503.0901.

### 6-(*tert*-Butyl) 1-ethyl (1*S**,2*R**,5*R**)-6-cyano-2-(iodomethyl)-1-methylspiro[4.4]nonane-1,6-dicarboxylate (5.54)

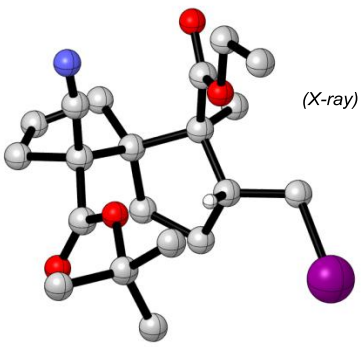


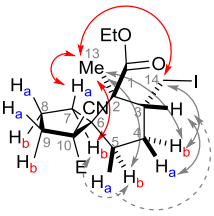

Prepared according to general procedure GP9, using 8-(*Tert*-butyl) 1-ethyl (*Z*)-3-(but-3-en-1-yl)-7-cyano-2-methyloct-2-enedioate **5.26** (80:20 *Z/E* mix., 95.0 mg, 0.27 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 0.30 mL, 0.30 mmol, 1.1 eq.), 2,6-lutidine (27 µL, 0.27 mmol, 1.0 eq.). Reaction vessel: 5 mL borosilicate round-bottom flask. The reaction was irradiated (with magnetic stirring) using a white 30 W CFL light (at 5.0 cm distance) for 16 h. Purification by flash-chromatography (eluent: 2.5% (150 mL) then 5% (150 mL) then 10% (150 mL) then 20% (150 mL) $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 2.5 cm, L = 8 cm) afforded the title product as a mixture of isomers at C(10) (3:2 *d.r.*, 80.7 mg,

0.17 mmol, 62%). Preparative TLC (eluent: 20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$ to reveal) was performed to obtain both compound separated for characterisation.




**Major isomer (major)-5.54:** $\mathbf{R_f}$ 0.56 (40% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, weak vanillin, $KMnO_4$), 0.45 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, weak vanillin, $KMnO_4$); $\mathbf{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 4.24 – 4.08 (2H, m, $CH_2$-(18)), 3.24 (1H, tdd, *J*=10.8, 7.7, 4.7 Hz, CH-(3)), 3.16 (1H, dd, *J*=9.4, 4.7 Hz, $CH_a$-(14)), 2.98 (1H, dd, *J*=10.6, 9.4 Hz, $CH_b$-(14)), 2.54 (1H, dt, *J*=12.6, 9.6 Hz, $CH_a$-(7)), 2.44 – 2.34 (2H, m, $CH_a$-(4), $CH_{a\ or\ b}$-(9)), 2.28 – 2.20 (2H, m, $CH_a$-(5), $CH_{a\ or\ b}$-(9)), 1.79 – 1.72 (2H, m, $CH_2$-(8)), 1.69 (1H, ddd, *J*=13.7, 9.5, 3.0 Hz, $CH_b$-(5)), 1.60 – 1.50 (1H, m, $CH_b$-(7)), 1.50 (9H, s, 3 $CH_3$-(16)), 1.44 (1H, ddt, *J*=13.0, 10.9, 9.2 Hz, $CH_b$-(4)), 1.30 (3H, t, *J*=7.1 Hz, $CH_3$-(19)), 1.15 (3H, s, $CH_3$-(13)); $\mathbf{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 175.1 (C(1)), 167.7 (C(11)), 120.5 (C(17)), 83.7 (C(15)), 65.1 (C(6)), 61.2 (C(18)), 55.7 (C(2)), 55.2 (C(10)), 50.9 (C(3)), 39.1 (C(9)), 37.3 (C(5)), 34.3 (C(7)), 30.2 (C(4)), 27.9 (3 C(16)), 19.8 (C(8)), 15.7 (C(13)), 14.1 (C(19)), 6.3 (C(14)); $\mathbf{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 2958, 2933, 2876, 2242 (w, C≡N), 1730 (s, C=O), 1477, 1456, 1393, 1368 1306, 1255 (m), 1195, 1155 (s), 1101, 1024; ***m/z*** ($ESI^+$) 973.2 ([2M+Na]$^+$, 100%), 498.1 ([M+Na]$^+$, 30%); **HRMS** ($ESI^+$) found 498.1108, $C_{20}H_{30}O_4N^{127}I^{23}Na^+$ requires 498.1112.

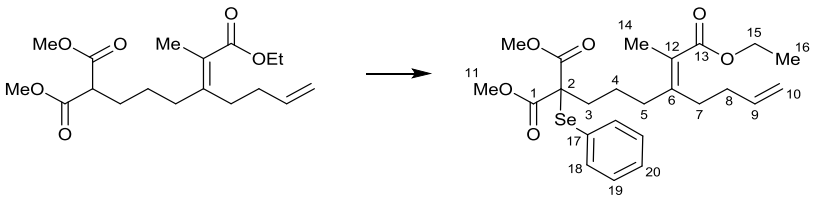



**Minor isomer (minor)-5.54:** $\mathbf{R_f}$ 0.61 (40% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, weak vanillin, $KMnO_4$), 0.51 (20% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\ nm}$, weak vanillin, $KMnO_4$); $\mathbf{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 4.32 (1H, dq, *J*=10.9, 7.2 Hz, $CH_a$-(18)), 4.21 (1H, dq, *J*=10.9, 7.2 Hz, $CH_b$-(18)), 3.40 (1H, dd, *J*=8.7, 3.2 Hz, $CH_a$-(14)), 3.05 (1H, tdd, *J*=11.4, 9.1, 3.3 Hz, CH-(3)), 2.91 (1H, dd, *J*=11.4, 8.7 Hz, $CH_b$-(14)), 2.58 – 2.52 (1H, m, $CH_{a\ or\ b}$-(9)), 2.49 (1H, d, *J*=4.5 Hz, $CH_a$-(5)), 2.47 – 2.40 (1H, m, $CH_a$-(7)), 2.32 (1H, ddd, *J*=13.4, 9.1, 3.6 Hz, $CH_{a\ or\ b}$-(9)), 2.10 (1H, dtd, *J*=13.4, 9.5, 5.5 Hz, $CH_a$-(4)), 1.91 – 1.83 (1H, m, $CH_{a\ or\ b}$-(8)), 1.80 – 1.72 (1H, m, $CH_{a\ or\ b}$-(8)), 1.72 –

1.66 (1H, m, $CH_b$-(7)), 1.66 – 1.59 (1H, m, $CH_b$-(5)), 1.58 (9H, s, 3 $CH_3$-(16)), 1.39 – 1.32 (1H, m, $CH_b$-(4)), 1.30 (3H, t, *J*=7.1 Hz, $CH_3$-(19)), 1.16 (3H, s, $CH_3$-(13)); $\delta_C$ /ppm (126 MHz, $CDCl_3$) 173.0 (C(1)), 167.2 (C(11)), 119.7 (C(17)), 84.6 (C(15)), 66.9 (C(6)), 61.1 (C(18)), 56.7 (C(2)), 54.0 (C(10)), 47.4 (C(3)), 38.8 (C(9)), 35.8 (C(5)), 31.3 (C(7)), 29.3 (C(4)), 27.9 (3 C(16)), 18.7 (C(8)), 16.8 (C(13)), 14.0 (C(19)), 7.3 (C(14)); $\nu_{max}$ /$cm^{-1}$ (film, $CDCl_3$) 2977, 2932, 2991, 2952, 2237 (w, C≡N), 1724 (s, C=O), 1477, 1458, 1368, 1304, 1276, 1256 (m), 1219, 1196, 1152 (s), 1122, 1088, 1023; ***m/z*** ($ESI^+$) 973.2 ($[2M+Na]^+$, 100%), 498.1 ($[M+Na]^+$, 20%); **HRMS** ($ESI^+$) found 498.1107, $C_{20}H_{30}O_4N^{127}I^{23}Na^+$ requires 498.1112.

### 6-Ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)-1-(phenylselanyl)hept-5-ene-1,1,6-tricarboxylate (5.62)

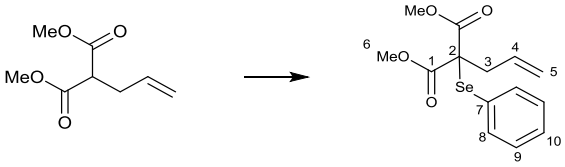



Prepared according to general procedure GP7, using PhSeBr instead of NIS. Reagents used: 6-ethyl 1,1-dimethyl (*Z*)-5-(but-3-en-1-yl)hept-5-ene-1,1,6-tricarboxylate **3.60** (50.0 mg, 0.15 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 0.16 mL, 0.16 mmol, 1.1 eq.) and phenylselenyl bromide (38.0 mg, 0.16 mmol, 1.1 eq.). TLC (10% EtOAc in toluene) showed complete reaction after 2.5 h. Purification by flash-chromatography (eluent: 0% (30 mL), 5% (60 mL), 10% (500 mL) EtOAc in pentane; column size: Ø = 1.5 cm, L = 7.5 cm) afforded the title product as a colourless oil (66.5 mg, 0.13 mmol, 91%).

$R_f$ 0.26 (10% EtOAc in $PE_{30\text{-}40}$, $UV_{254\ nm}$, vanillin, $KMnO_4$), 0.53 (10% EtOAc in toluene, $UV_{254\ nm}$, vanillin, $KMnO_4$); $\delta_H$ /ppm (500 MHz, $CDCl_3$) 7.56 – 7.54 (2H, m, 2 $CH_{Ar}$-(18)), 7.43 – 7.39 (1H, m, $CH_{Ar}$-(20)), 7.32 (2H, t, *J*=7.6 Hz, 2 $CH_{Ar}$-(19)), 5.83 (1H, ddt, *J*=16.9, 10.1, 6.6 Hz, CH-(9)), 5.03 (1H, dq, *J*=17.2, 1.7 Hz, $CH_a$-(10)), 4.96 (1H, dd, *J*=10.1, 1.9 Hz, $CH_b$-(10)), 4.19 (2H, q, *J*=7.1 Hz, $CH_2$-(15)), 3.73 (6H, s, 2 $CH_3$-(11)), 2.37 (2H, t, *J*=8.2, 7.7 Hz, $CH_2$-(7)), 2.18 (2H, q, *J*=7.6 Hz, $CH_2$-(8)), 2.07 (2H, t, *J*=7.7 Hz, $CH_2$-(5)), 1.92 – 1.88 (2H, m, $CH_2$-(3)), 1.84 (3H, s, $CH_3$-(14)), 1.58 – 1.50 (2H, m, $CH_2$-(4)), 1.30 (3H, t, *J*=7.2 Hz, $CH_3$-(16)); $\delta_C$ /ppm (176 MHz, $CDCl_3$) 169.8 (C(13)), 169.6 (2 C(1)), 148.2 (C(6)), 138.5 (C(9)),

138.0 (2 C(19)), 130.0 (C(20)), 129.1 (C(18)), 126.2 (C(17)), 124.4 (C(12)), 114.7 (C(10)), 60.3 (C(15)), 59.5 (C(2)), 53.2 (2 C(11)), 33.8 (C(7)), 33.8(C(3)), 33.3 (C(5)), 33.2 (C(8)), 23.6 (C(4)), 15.7 (C(14)), 14.4 (C(16)); $\nu_{max}$ /cm$^{-1}$ (film, $CDCl_3$) 2951, 1729 (s, C=O), 1711 (s), 1640 (w, C=C), 1438 (m), 1247, 1224, 1192, 1102; ***m/z*** (ESI$^+$) 519.1 ([M+Na]$^+$, 100%), 1015.3 ([2M+Na]$^+$, 75%); **HRMS** (ESI$^+$) found 513.1315, $C_{24}H_{32}O_6{}^{23}Na^{74}Se^+$ requires 513.1316.

### Dimethyl 2-allyl-2-(phenylselanyl)malonate (5.63)

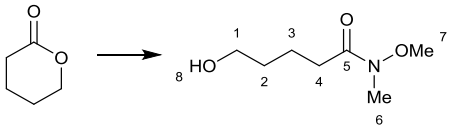



Prepared according to general procedure GP7, using PhSeBr instead of NIS. Reagents used: dimethyl 2-allylmalonate **3.17** (1.0 mL, 5.80 mmol, 1.0 eq.), NaHMDS solution (1 M in THF, 6.4 mL, 6.39 mmol, 1.1 eq.) and phenylselenyl bromide (1.50 g, 6.39 mmol, 1.1 eq.). TLC (10% EtOAc in toluene, $KMnO_4$) showed complete reaction after 3 h. Purification by flash-chromatography (eluent: 10% (500 mL), 20% (400 mL) $Et_2O$ in $PE_{40\text{-}60}$; column size: Ø = 5.5 cm, L = 5 cm) afforded the title product as a clear orange liquid (1.68 g, 5.66 mmol, 98%).

$\mathbf{R_f}$ 0.38 (20% $Et_2O$ in PE, $UV_{254\ nm}$, $KMnO_4$); $\delta_H$ /ppm (500 MHz, $CDCl_3$) 7.60 – 7.57 (2H, m, 2 $CH_{Ar}$-(9)), 7.43 – 7.39 (1H, m, $CH_{Ar}$-(10)), 7.35 – 7.30 (2H, m, 2 $CH_{Ar}$-(8)), 5.90 (1H, ddt, *J*=17.1, 10.2, 7.0 Hz, CH-(4)), 5.19 – 5.11 (2H, m, $CH_2$-(5)), 3.71 (6H, s, 2 $CH_{Ar}$-(6)), 2.72 (2H, dt, *J*=7.0, 1.3 Hz, $CH_2$-(3)); $\delta_C$ /ppm (126 MHz, $CDCl_3$) 169.3 (2 C(1)), 138.2 (2 C(9)), 132.7 (C(4)), 130.0 (C(10)), 129.1 (2 C(8)), 126.1 (C(7)), 119.4 (C(5)), 59.0 (C(2)), 53.1 (2 C(6)), 38.5 (C(3)); $\nu_{max}$ /cm$^{-1}$ (film, $CDCl_3$) 2952, 1726 (s, C=O), 1640 (w, C=C), 1476, 1435 (m), 1313, 1263 (s), 1234 (s), 1207 (s), 1126 (m), 1045; ***m/z*** (ESI$^+$) 679.0 ([2M+Na]$^+$, 100%), 351.0 ([M+Na]$^+$, 60%); **HRMS** (ESI$^+$) found 345.0168, $C_{14}H_{16}O_4{}^{23}Na^{74}Se^+$ requires 345.0166.

### 7.6.2.2 Other compounds

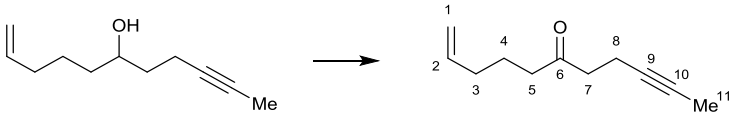
**5-Hydroxy-*N*-methoxy-*N*-methylpentanamide (7.1)**




According to the modified procedure of Palmes *et al* and Molander *et al*.[198,199] An oven-dried 100 mL round bottomed flask was charged with δ-valerolactone (1.2 mL, 10.0 mmol, 1.0 eq.), *N,O*-dimethylhydroxylamine hydrochloride (2.4 g, 25.0 mmol, 2.5 eq.) and dry THF (50 mL) and cooled to -20°C. To the flask was slowly added an isopropylmagnesium chloride solution (2M in THF, 25 mL, 50.0 mmol, 5.0 eq.) over a 30 min period at -20°C. The reaction was quenched by the addition of $NH_4Cl_{(aq)}$ (sat. sol., ca 25 mL) after 2 h. Water was then added until all salts were dissolved followed by extraction with EtOAc (3x 30 mL). The combined organic layers were washed once with brine (15 mL), dried ($Na_2SO_4$) and concentrated under reduce pressure to afford the title product as a colourless liquid (1.46 g, 9.06 mmol, 91%) that was used without further purification in the next step.

**$R_f$** 0.21 (100% EtOAc); **$\delta_H$** /ppm (400 MHz, $CDCl_3$) 3.67 (3H, s, $CH_3$-(6)), 3.63 (2H, t, *J*=6.3 Hz, $CH_2$-(1)), 3.17 (3H, s, $CH_3$-(7)), 2.46 (2H, t, *J*=7.1 Hz, $CH_2$-(4)), 2.18 – 2.06 (1H, m, HO-(8)), 1.73 (2H, qd, *J*=8.2, 7.2, 5.7 Hz, $CH_2$-(2)), 1.64 – 1.55 (2H, m, $CH_2$-(3)); ***m/z*** ($ESI^+$) 345.2 ($[2M+Na]^+$, 100%), 162.1 ($[M+H]^+$, 45%), 184.1 ($[M+Na]^+$, 20%). Data is consistent with literature.[199]

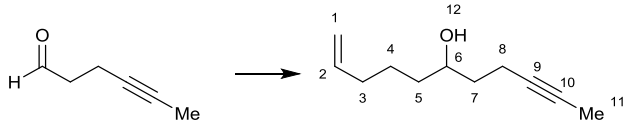
### Undec-1-en-9-yn-6-one (7.2)




According to the modified procedures of Hötling *et al*.[121] A dried (heat gun under high vacuum) 50 mL 2-necked flask charged with dry $CH_2Cl_2$ (20 mL) and dry DMSO (0.25 mL, 3.41 mmol, 2.2 eq.) was cooled to -78 °C before neat oxalyl chloride (0.15 mL, 1.70 mmol, 1.1 eq.) was added slowly (bubbling occurred) and stirred for 60 min. Undec-1-en-9-yn-6-ol **7.3** (257 mg, 1.55 mmol, 1.0 eq.) was then slowly added as a solution in $CH_2Cl_2$ (5 mL) and stirred for 60 min. $Et_3N$ (1.10 mL, 7.75 mmol, 5.0 eq.) was added quickly (< 1 min) and then the acetone/dry ice bath was removed and the reaction was allowed to warm to room temperature. TLC (80% $Et_2O$ in $PE_{30\text{-}40}$) after 2 h 40 min showed no remaining starting material. The reaction was quenched with water (10 mL) and the layers were separated. The aqueous phase was extracted with $CH_2Cl_2$ (4 x). Combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification by flash-chromatography (eluent: 5% $Et_2O$ in hexane) afforded the title compound as a colourless liquid (116 mg, 0.71 mmol, 46%).

**$R_f$** 0.40 (5% $Et_2O$ in hexane, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.76 (1H, ddt, *J*=16.9, 10.1, 6.6 Hz, CH-(2)), 5.01 (1H, dq, *J*=17.3, 1.8 Hz, $CH_a$-(1)), 4.98 – 4.96 (1H, m, $CH_b$-(1)), 2.58 (2H, dd, *J*=8.0, 6.5 Hz, $CH_2$-(7)), 2.42 (2H, t, *J*=7.4 Hz, $CH_2$-(5)), 2.40 – 2.35 (2H, m, $CH_2$-(8)), 2.06 (2H, qt, *J*=7.4, 1.2 Hz, $CH_2$-(3)), 1.74 (3H, t, *J*=2.5 Hz, $CH_3$-(11)), 1.69 (2H, p, *J*=7.5 Hz, $CH_2$-(4)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 209.3 (C(6)), 138.1 (C(2)), 115.4 (C(1)), 77.9 (C(10)), 76.2 (C(9)), 42.1 (C(5 or 7)), 42.1 (C(5 or 7)), 33.2 (C(3)), 22.8 (C(4)), 13.5 (C(8)), 3.6 (C(11)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2921, 1715 (s, C=O), 1438, 1415, 1371, 1085, 996, 913; ***m/z*** (Ammonia Cl) 165.1277 ($[M+H]^+$, 100%), 182.1538 ($[M+NH_4]^+$, 30%); **HRMS** ($ESI^+$) found 165.1277, $C_{11}H_{17}O^+$ requires 165.1274.

### Undec-1-en-9-yn-6-ol (7.3)

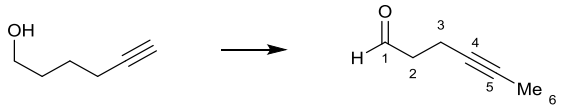



Grignard reagent prepared according to the modified procedure of Williams *et al*.[122] In an oven-dried 100 mL double-necked flask equipped with a condenser was refluxed magnesium turnings (621 mg, 25.6 mmol, 4.2 eq.) and iodine (2 crystals) in dry $Et_2O$ (50 mL) under argon atmosphere until the brown colour disappeared (5 min). Neat 5-bromo-1-pentene (1.78 mL, 15.0 mmol, 2.4 eq.) was added (0.3 mL first and refluxed to activate) at a rate that maintained solvent refluxing. Upon complete addition, refluxed was continued for an 15 min and then 1 h at r.t..

The Grignard mixture was cooled to -78 °C and then a solution of hex-4-ynal **7.4** (593 mg, 6.2 mmol, 1.0 eq.) as a solution in dry THF (20 mL) was added dropwise. The reaction was quenched after 1.5 h with $NH_4Cl_{(aq)}$ (sat. sol., 8 mL) at -78 °C, warmed up to r.t., the layers were separated and the aqueous phase was extracted with $Et_2O$ (4 x). The combined organic layers were washed with brine, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification by flash-chromatography (eluent: 20% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title product as a colourless liquid (257 mg, 1.55 mmol, 25%).

**$R_f$** 0.40 (20% $Et_2O$ in $PE_{40\text{-}60}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 5.81 (1H, ddt, *J*=16.9, 10.2, 6.7 Hz, CH-(2)), 5.01 (1H, dq, *J*=17.2, 1.7 Hz, $CH_a$-(1)), 4.95 (1H, ddt, *J*=10.1, 2.2, 1.1 Hz, $CH_b$-(1)), 3.79 – 3.71 (1H, m, CH-(6)), 2.33 – 2.20 (2H, m, $CH_2$-(8)), 2.08 (2H, dtdq, *J*=8.0, 5.4, 2.4, 1.4 Hz, $CH_2$-(3)), 1.79 (1H, d, *J*=4.6 Hz, OH-(12)), 1.77 (3H, t, *J*=2.6 Hz, $CH_3$-(11)), 1.69 – 1.61 (1H, m, $CH_a$-(7)), 1.60 – 1.50 (2H, m, $CH_a$-(5), $CH_b$-(7)), 1.50 – 1.42 (3H, m, $CH_b$-(5), $CH_2$-(4)); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 138.8 (C(2)), 114.8 (C(1)), 78.9 (C(10)), 76.5 (C(9)), 71.2 (C(6)), 36.9 (C(4)), 36.2 (C(7)), 33.8 (C(3)), 25.0 (C(5)), 15.5 (C(8)), 3.6 (C(11)); **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 3364 (br s), 3318 (br s), 2920 (s), 1436 (s), 1086 (m), 995 (w), 911 (s); ***m/z*** (Ammonia Cl) 167.1434 ($[M+H]^+$, 100%), 184.1690 ($[M+NH_4]^+$, 25%); **HRMS** (Ammonia Cl) found 167.1434, $C_{11}H_{19}O^+$ requires 167.1430.

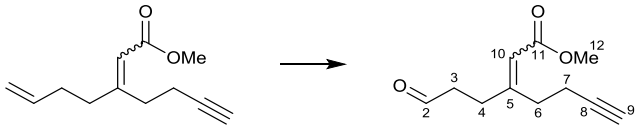
### Hex-4-ynal (7.4)




According to the modified procedures of Hötling *et al*.[121] A dried (heat gun under $N_2$ flow) 2 L 3-necked flask charged with dry $CH_2Cl_2$ (*ca.* 1.0 L) and dry DMSO (18.5 mL, 212 mmol, 2.2 eq.) was cooled to -78 °C before neat oxalyl chloride (9.2 mL, 107 mmol, 1.1 eq.) was added slowly (bubbling occurred) and stirred for 30 min. Neat hex-4-yn-1-ol intermediate **2.70** (9.3 g, 95 mmol, 1.0 eq.) was then added over 20 min and stirred for 40 min. $Et_3N$ (*ca.* 68 mL, 491 mmol, 5.0 eq.) was added quickly (< 3 min) and then the acetone/dry ice bath was removed and the reaction was allowed to warm to room temperature. TLC (80% $Et_2O$ in $PE_{30\text{-}40}$) after 1 h 40 min showed no remaining starting material. The reaction was quenched with water (300 mL) and the layers were separated. The aqueous phase was extracted with $CH_2Cl_2$ (4x 150-200 mL). Combined organic layers were washed with brine (200 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a yellow liquid. Purification by gravity-chromatography (eluent: 20% $Et_2O$ in $PE_{30\text{-}40}$) afforded the title compound as a yellow liquid (7.33 g, 76 mmol, 81%).

**$R_f$** 0.71 (80% $Et_2O$ in $PE_{30\text{-}40}$); **$\delta_H$** /ppm (400 MHz, $CDCl_3$) 9.79 (1H, t, *J*=1.3 Hz, CHO-(1)), 2.62 (2H, tdd, *J*=7.1, 1.3, 0.9 Hz, $CH_2$-(2)), 2.49 – 2.41 (2H, m, $CH_2$-(3)), 1.76 (3H, t, *J*=2.6 Hz, $CH_3$-(6)); ***m/z*** (Ammonia Cl) 114.0913 ($[M+NH_4]^+$, 100%); **HRMS** (Ammonia Cl) found 114.0913, $C_6H_{12}NO^+$ requires 114.0913. Spectroscopic data consistent with literature.[121]

### Methyl 3-(3-oxopropyl)hept-2-en-6-ynoate (7.5)




According to the modified procedure of Shen *et al*.[173] A 100 mL flask was charged (in this order) with methyl 3-(but-3-yn-1-yl)hepta-2,6-dienoate **7.6** (50:50 *E*/*Z* mix., 780 mg, 4.06 mmol, 1.0 eq.), 1,4-dioxane/water (3:1 v/v, 48 mL), 2,6-lutidine (0.95 mL, 8.11 mmol, 2.0 eq.), $OsO_4$ (2.5 wt% in $^{t}$BuOH, 825 mg, 0.08 mmol, 0.02 eq.) and $NaIO_4$ (3.47 g, 213.89 mmol, 4.0 eq.). The resulting thick suspension was stirred for 30 min. The reaction was quenched with $Na_2S_2O_{3\,(aq)}$ (sat. sol., 6 mL) followed by water (to dissolve the salts). Extracted with $CH_2Cl_2$ (3x). The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure (orange liquid obtained). Purification by flash-chromatography (eluent: 100% $CH_2Cl_2$ in $PE_{30\text{-}40}$; column size: Ø = 4 cm, L = 7 cm) afforded the title products as a yellowish liquid (50:50 *E*/*Z* mix., 460 mg, 2.37 mmol, 58%).

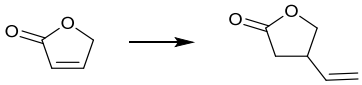
Analysed as a *E*/*Z* mixture (~1:1 ratio): $\mathbf{R_f}$ 0.33 and 0.40 (100% $CH_2Cl_2$, $UV_{254\,nm}$, vanillin, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 9.80 (2H, t, *J*=1.6 Hz, CH-($2^{cis}$), CH-($2^{trans}$)), 5.76 (1H, t, *J*=1.3 Hz, CH-($10^{cis}$)), 5.68 (1H, t, *J*=1.5 Hz, CH-($10^{trans}$)), 3.69 (3H, s), 3.69 (3H, s), 2.88 (2H, dd, *J*=8.4, 7.0 Hz, $CH_2$-($4^{cis}$)), 2.82 (2H, t, *J*=7.3 Hz, $CH_2$-($6^{trans}$)), 2.66 (4H, appears dddd, *J*=8.8, 7.4, 3.2, 1.7 Hz, $CH_2$-($3^{cis}$), $CH_2$-($3^{trans}$)), 2.59 (2H, ddt, *J*=8.2, 6.8, 1.4 Hz, $CH_2$-($4^{trans}$)), 2.43 (2H, td, *J*=7.3, 2.7 Hz, $CH_2$-($7^{trans}$)), 2.41 – 2.38 (4H, m, $CH_2$-($6^{cis}$), $CH_2$-($7^{cis}$)), 2.01 – 1.99 (1H, m, $CH_2$-($9^{cis}$)), 1.97 (1H, t, *J*=2.7 Hz, $CH_2$-($9^{trans}$)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 201.3 (C($2^{cis}$)), 200.6 (C($2^{trans}$)), 166.5 (C($11^{cis}$)), 166.4 (C($11^{trans}$)), 159.9 (C($5^{trans}$)), 159.7 (C($5^{cis}$)), 117.3 (C($10^{cis}$)), 116.9 (C($10^{trans}$)), 83.5 (C($8^{trans}$)), 82.6 (C($8^{cis}$)), 69.8 (C($9^{cis}$)), 69.3 (C($9^{trans}$)), 51.3 (C($12^{trans}$)), 51.2 (C($12^{cis}$)), 42.7 (C($3^{cis}$)), 41.5 (C($3^{trans}$)), 37.1 (C($6^{cis}$)), 31.1 (C($6^{trans}$)), 30.8 (C($4^{trans}$)), 24.9 (C($4^{cis}$)), 17.8 (C($7^{trans}$)), 17.0 (C($7^{cis}$)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 3289 (s, C≡C-H), 2839 (w, CHO), 2728 (w, CHO), 1713 (s, C=O), 1646 (s, C=C), 1435 (m), 1228, 1191, 1173, 1139, 1029, 645 (s); ***m/z*** ($ESI^+$) 249.0 ($[M+MeOH+H]^+$, 100%), 217.0 ($[M+Na]^+$, 25%); **HRMS** ($ESI^+$) found 217.0837, $C_{11}H_{14}O_3{}^{23}Na^+$ requires 217.0835.

### Methyl 3-(but-3-yn-1-yl)hepta-2,6-dienoate (7.6)


To a flame-dried 100 mL round-bottom flask was added Methyl 3-(4-(trimethylsilyl)but-3-yn-1-yl)hepta-2,6-dienoate **2.80** (50:50 *E*/*Z* mix., 1.46 g, 5.54 mmol, 1.0 eq.), THF (dry, 36 mL) and AcOH (0.12 mL). The mixture was cooled to 0 °C before TBAF (1 M solution in THF, 6.1 mL, 6.1 mmol, 1.1 eq.) was slowly added. The reaction was quenched after 45 min with $NH_4Cl_{(aq)}$ (sat. sol., *ca.* 10 mL) followed by water (to dissolve the salts) and the layers were separated. The aqueous phase was extracted with $Et_2O$. The combined organic layers were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to provide an orange liquid. Purification by flash-chromatography (eluent: 5% $Et_2O$ in $PE_{30\text{-}40}$; column size: Ø = 4.5 cm, L = 9 cm) afforded the title products as a yellowish liquid (50:50 *E*/*Z* mix., 823 mg, 4.28 mmol, 77%).

Analysed as a *E/Z* mixture (~1:1 ratio): $\mathbf{R_f}$ 0.43 (5% $Et_2O$ in $PE_{30\text{-}40}$, $UV_{254\,nm}$, vanillin, $KMnO_4$); $\boldsymbol{\delta_H}$ /ppm (500 MHz, $CDCl_3$) 5.83 (1H, ddt, *J*=17.0, 10.1, 6.7 Hz, CH-($2^{trans}$)), 5.78 (1H, ddt, *J*=16.6, 10.2, 6.2 Hz, CH-($2^{cis}$)), 5.70 (2H, q, *J*=1.4 Hz, CH-($10^{trans}$), CH-($10^{cis}$)), 5.04 (2H, dp, *J*=17.0, 1.6 Hz, $CH_a$-($1^{trans}$), $CH_a$-($1^{cis}$)), 4.99 (1H, dq, *J*=10.1, 1.3 Hz, $CH_b$-($1^{cis}$)), 4.96 (1H, ddt, *J*=10.1, 2.2, 1.1 Hz, $CH_b$-($1^{trans}$)), 3.68 (3H, s, $CH_3$-($12^{cis}$)), 3.68 (3H, s, $CH_3$-($12^{trans}$)), 2.81 (2H, t, *J*=7.5 Hz, $CH_2$-($6^{cis}$)), 2.73 – 2.68 (2H, m, $CH_2$-($4^{trans}$)), 2.42 – 2.38 (2H, m, $CH_2$-($7^{cis}$)), 2.38 – 2.35 (4H, m, $CH_2$-($6^{trans}$), $CH_2$-($7^{trans}$)), 2.34 – 2.30 (2H, m, $CH_2$-($4^{cis}$)), 2.26 – 2.19 (4H, m, $CH_2$-($3^{trans}$), $CH_2$-($3^{cis}$)), 1.99 (1H, t, *J*=2.4 Hz, $CH_2$-($9^{trans}$)), 1.96 (1H, t, *J*=2.7 Hz, $CH_2$-($9^{cis}$)); $\boldsymbol{\delta_C}$ /ppm (126 MHz, $CDCl_3$) 166.7 (C($11^{cis}$)), 166.7 (C($11^{trans}$)), 161.5 (C($5^{cis}$)), 161.0 (C($5^{trans}$)), 137.9 (C($2^{trans}$)), 137.2 (C($2^{cis}$)), 116.5 (C($10^{cis}$)), 116.4 (C($10^{trans}$)), 115.6 (C($1^{cis}$)), 115.1 (C($1^{trans}$)), 83.8 (C($8^{cis}$)), 83.0 (C($8^{trans}$)), 69.5 (C($9^{trans}$)), 69.0 (C($9^{cis}$)), 51.1 (C($12^{cis}$)), 51.1 (C($12^{trans}$)), 38.1 (C($4^{cis}$)), 37.0 (C($6^{trans}$)), 32.7 (C($3^{trans}$)), 31.6 (C($3^{cis}$)), 31.5 (C($4^{trans}$)), 31.0 (C($6^{cis}$)), 17.8 (C($7^{cis}$)), 17.1 (C($7^{trans}$)); $\boldsymbol{\nu_{max}}$ /$cm^{-1}$ (film, $CDCl_3$) 3301 (s, C≡C-H), 2119, 1715 (s, C=O), 1642 (s, C=C), 1434 (m), 1376, 1328, 1230, 1192, 1171, 1149, 1038, 997, 915, 866, 635 (s); ***m/z*** ($ESI^+$) 345.2 ($[M+Na]^+$, 100%); ***m/z*** ($ESI^-$) 321.1 ($[M+H]^-$, 100%); **HRMS** ($ESI^+$) found 193.1226, $C_{12}H_{17}O_2^+$ requires 193.1223.

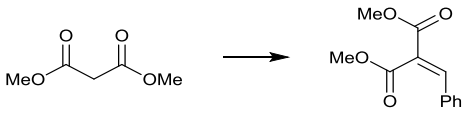
### 4-Vinyldihydrofuran-2(3*H*)-one (7.7)



According to the modified procedure of Taber *et al*.[200] To a yellow suspension of CuBr-$SMe_2$ complex (190 mg, 0.92 mmol, 0.2 eq.) in dry THF (15 mL) in a flame-dried round bottomed flask under argon cooled to -40 °C (internal temperature) was added dropwise vinylmagnesium bromide solution (1 M in THF, 13.9 mL, 13.92 mmol, 3.0 eq.). Once the addition was complete, the mixture was allowed to warm up to -20 °C (internal temperature), then a solution of furan-2(5*H*)-one **5.27** (0.33 mL, 4.64 mmol, 1.0 eq.) in dry THF (10 mL) was then added dropwise over 35 min (*via* syringe pump) keeping the temperature at -20 °C (±5 °C) and then allowed the mixture to warm up to -10 °C. TLC (25% EtOAc in $PE_{40\text{-}60}$) showed no remaining starting material after 1 h so the reaction was quenched with saturated $NH_4Cl_{(aq)}$ (30 mL) and then warmed to room temperature. Water (30 mL) was added to dissolve the salts and then extracted with $Et_2O$ (3x). The combined organic layers were dried ($Na_2SO_4$), filtered and carefully concentrated under reduced pressure. Purification of the crude mixture by flash-chromatography (eluent: 25% $Et_2O$ in pentane; column size: Ø = 2.5 cm, L = 9 cm) afforded the title product as a clear/yellowish liquid (243.9 mg, 2.17 mmol, 47%).

**$R_f$** 0.42 (25% EtOAc in $PE_{30\text{-}40}$, $KMnO_4$); **$\delta_H$** /ppm (400 MHz, $CDCl_3$) 5.77 (1H, ddd, *J*=17.1, 10.2, 7.6 Hz), 5.23 – 5.14 (2H, m), 4.44 (1H, dd, *J*=9.0, 7.6 Hz), 4.02 (1H, dd, *J*=9.0, 7.9 Hz), 3.28 – 3.17 (1H, m), 2.67 (1H, dd, *J*=17.4, 8.4 Hz), 2.39 (1H, dd, *J*=17.4, 9.0 Hz); **$\delta_C$** /ppm (101 MHz, $CDCl_3$) 176.6, 135.9, 117.6, 72.3, 40.0, 34.3; **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 2918, 1775 (s, C=O), 1418 1673, 1166 (s), 1015 (m). Data in accordance with the literature.[201]

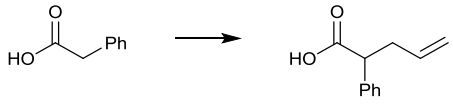
### Dimethyl 2-benzylidenemalonate (7.8)




According to the modified procedure of Smith III *et al*.[202] To a solution of L-proline (368 mg, 3.2 mmol, 0.1 eq.) in dry DMSO (85 mL) in a flame-dried round bottomed flask under argon at room temperature was added neat freshly distilled benzaldehyde (3.3 mL, 32.3 mmol, 1.0 eq.). After 5 min, dimethyl malonate (7.4 mL, 64.6 mmol, 2.0 eq.) was added and the mixture was left stirring for the week-end (65 h). EtOAc (30 mL) was added and the mixture was then washed with water (3x 30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Purification of the crude mixture by flash-chromatography (eluent: 2.5% (500 mL), 5% (1.5 L) EtOAc in $PE_{30\text{-}40}$; column size: Ø = 7.5 cm, L = 10 cm) afforded the title product as a clear oil that crystallized in the freezer (5.61 g, 25.47 mmol, 79%).

**$R_f$** 0.43 (15% $Et_2O$ in $PE_{30\text{-}40}$, $KMnO_4$); **$\delta_H$** /ppm (500 MHz, $CDCl_3$) 7.78 (1H, s), 7.45 – 7.36 (4H, m), 3.85 (3H, s), 3.85 (3H, s); **$\delta_C$** /ppm (126 MHz, $CDCl_3$) 167.3, 164.6, 143.1, 132.9, 130.8, 129.5, 129.0, 125.6, 52.9, 52.8; ***m/z*** ($ESI^+$) 243.0 ($[M+Na]^+$, 100%), 463.1 ($[2M+Na]^+$, 60%). Data in accordance with the literature.[202]

### 2-Phenylpent-4-enoic acid (7.9)




According to the modified procedure of Duguet *et al*.[203] To a solution of phenylacetic acid **5.36** (2.0 g, 14.7 mmol, 1.0 eq.) in dry THF (60 mL) in a flame-dried round bottomed flask under argon cooled to -78 °C was added *n*-BuLi (1.47 M in hexane, 22.0 mL, 32.3 mmol, 2.2 eq.) then warmed up to room temperature and stirred for 1 h 45 min (a pink heterogeneous mixture was obtained). Neat allyl bromide (1.45 mL, 17.6 mmol, 1.2 eq.) was added dropwise to give a clear solution that was stirred at

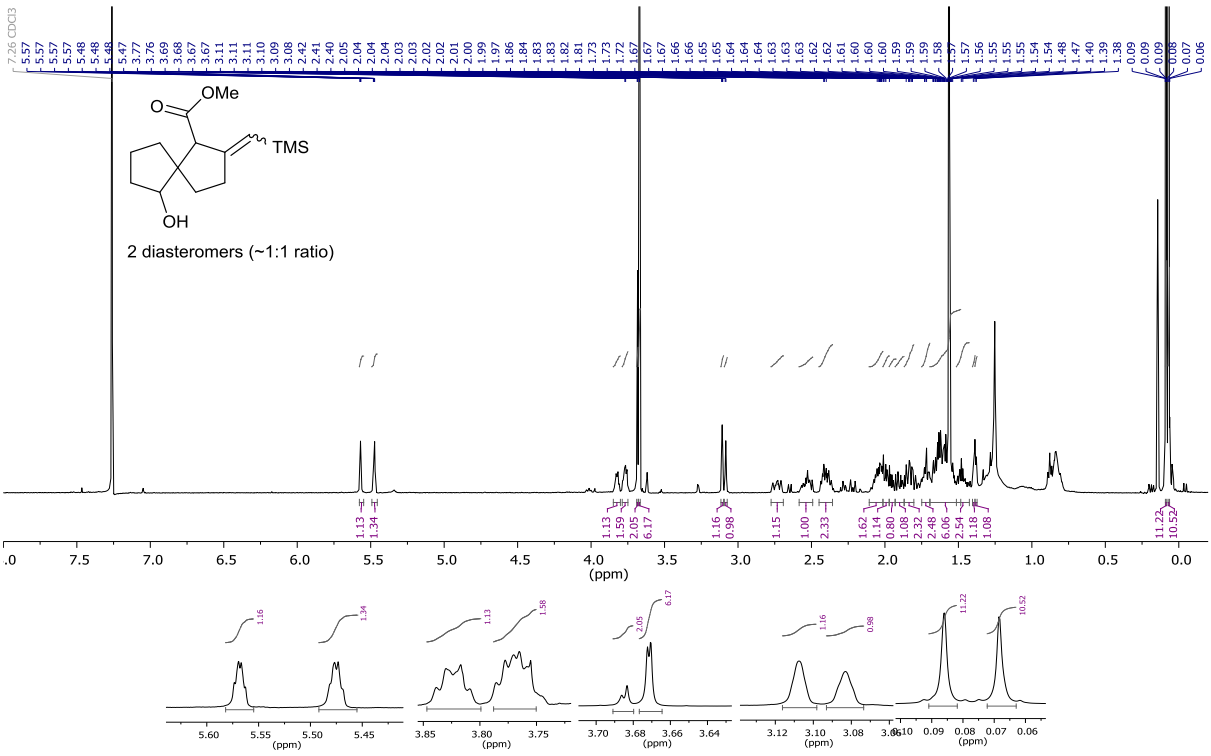
room temperature for 4 h. The reaction was quenched with $HCl_{(aq)}$ (1 M solution, 80 mL) and the layers were separated. The aqueous layer was exctracted with $Et_2O$ (3x 30 mL). The organic layer was washed with brine (100 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to pale yellow solid that was used without further purification (2.64 g, quant.).

**$R_f$** 0.37 (25% EtOAc + 3% acetic acid in $PE_{30\text{-}40}$, weak $UV_{254\ nm}$, $KMnO_4$); **$\delta_H$** /ppm (400 MHz, $CDCl_3$) 7.39 – 7.29 (5H, m), 5.75 (1H, ddt, *J*=17.1, 10.2, 6.8 Hz), 5.11 (1H, dq, *J*=17.1, 1.5 Hz), 5.04 (1H, ddt, *J*=10.2, 2.0, 1.1 Hz), 3.67 (1H, dd, *J*=8.4, 7.1 Hz), 2.85 (1H, dddt, *J*=14.3, 8.3, 7.0, 1.3 Hz), 2.56 (1H, dtt, *J*=14.5, 6.8, 1.4 Hz); **$\delta_C$** /ppm (101 MHz, $CDCl_3$) 179.6, 137.9, 135.0, 128.8, 128.2, 127.7, 117.4, 51.4, 37.2; **$\nu_{max}$** /$cm^{-1}$ (film, $CDCl_3$) 3031, 2671 (br. s, COOH), 1703 (s, C=O), 1642 (w, C=C), 1601, 1497, 1454, 1438, 1416, 1286, 1250, 1208. Data in accordance with the literature.[203]

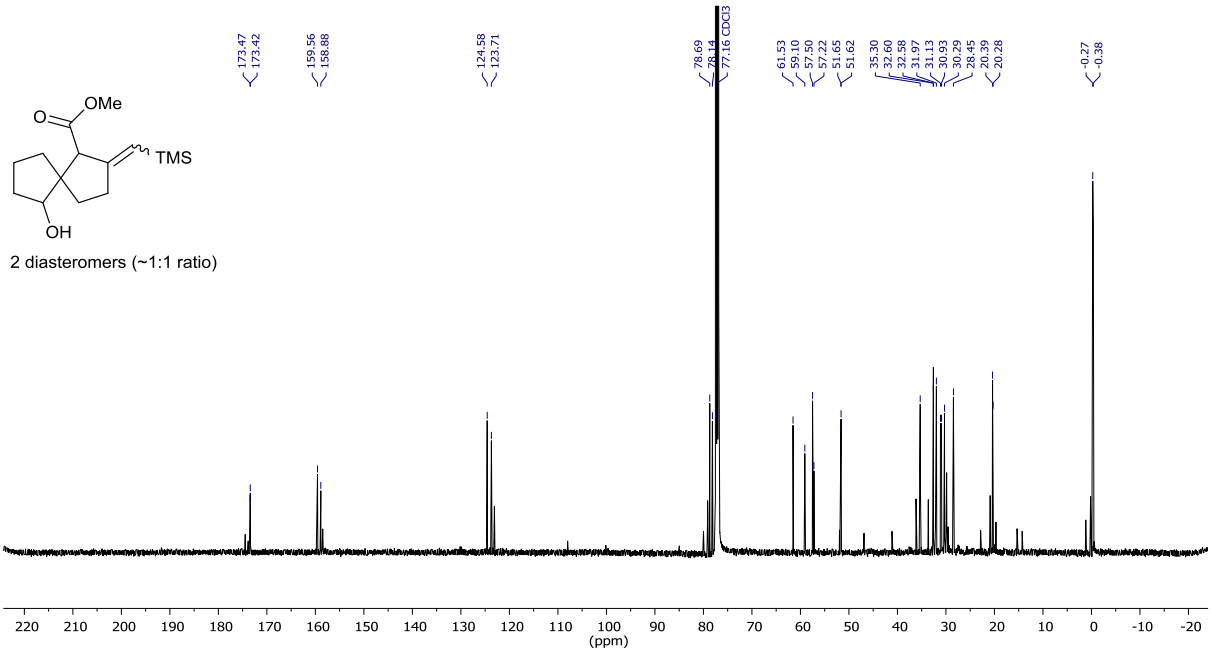
## 7.7 Selected spectra of key cyclisation products

### 7.7.1 Alcohol 2.35

Methyl 6-hydroxy-2-((trimethylsilyl)methylene)spiro[4.4]nonane-1-carboxylate (**2.35**)
($^1$H NMR, 500 MHz, $CDCl_3$)

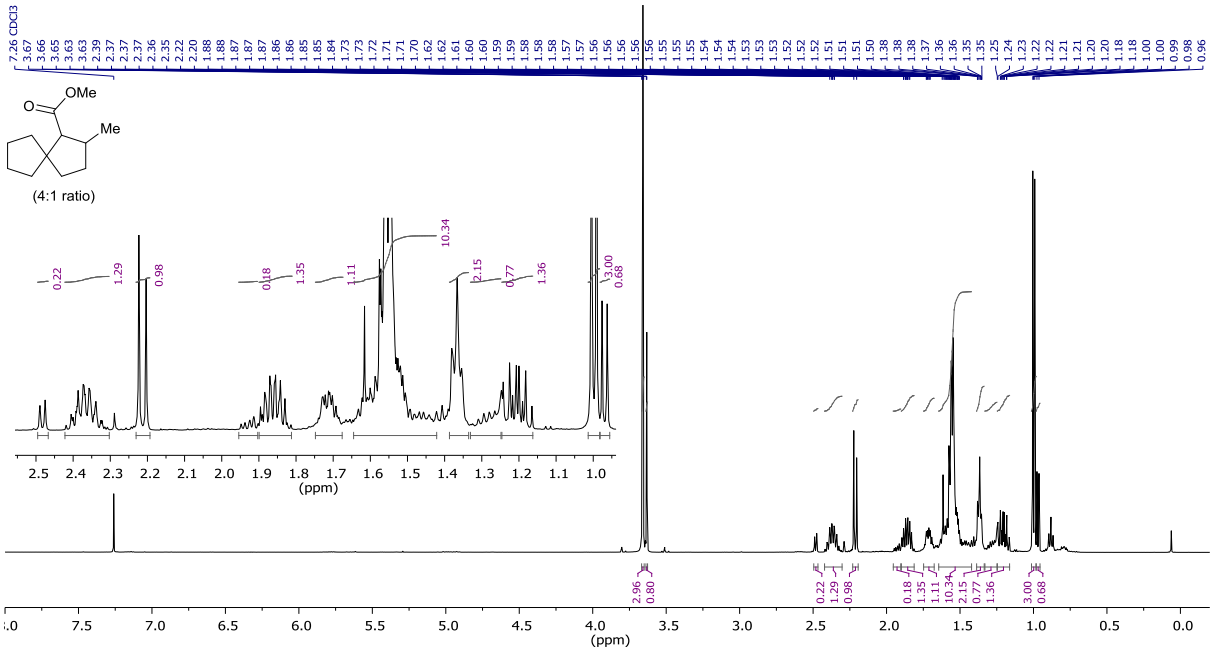



Methyl 6-hydroxy-2-((trimethylsilyl)methylene)spiro[4.4]nonane-1-carboxylate (**2.35**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)

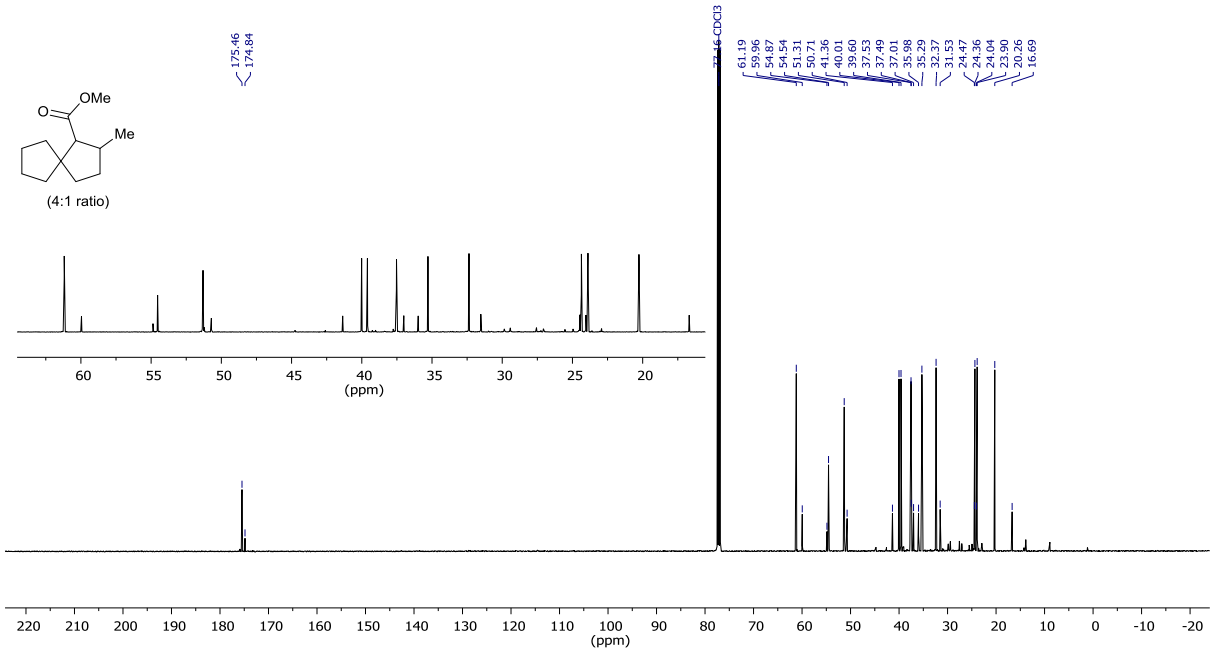


### 7.7.2 **Ester 2.52**

Methyl 2-methylspiro[4.4]nonane-1-carboxylate (**2.52**)
($^{1}$H NMR, 500 MHz, $CDCl_3$)

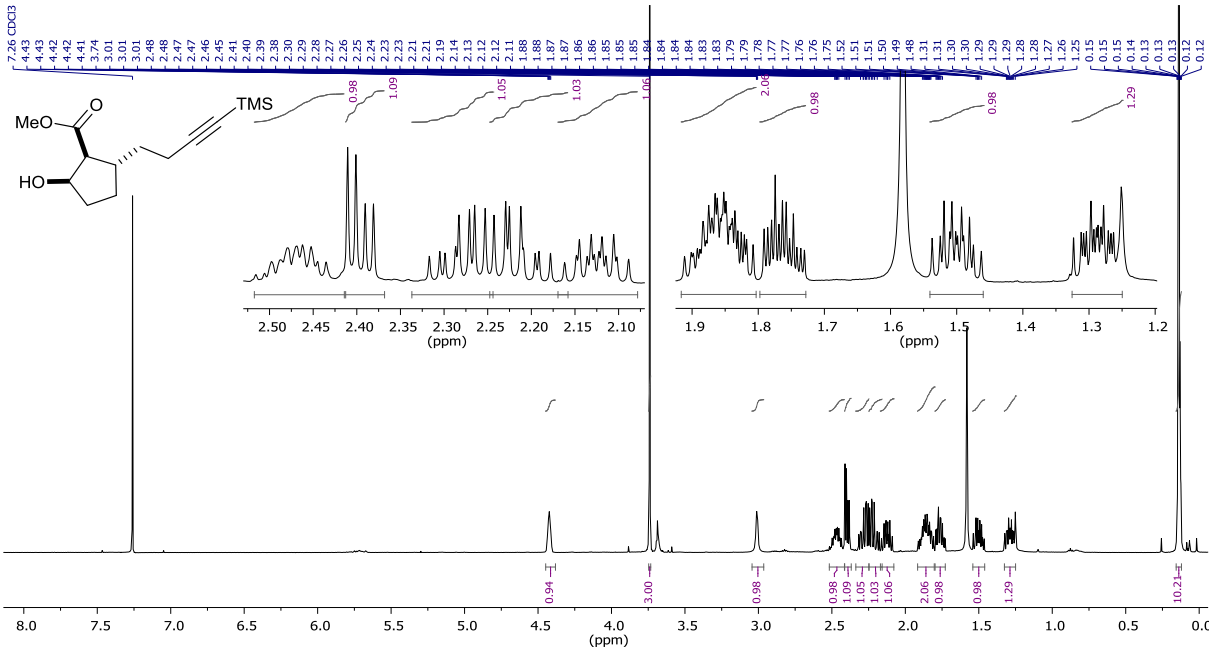



Methyl 2-methylspiro[4.4]nonane-1-carboxylate (**2.52**)
($^{13}$C NMR, 125 MHz, $CDCl_3$)

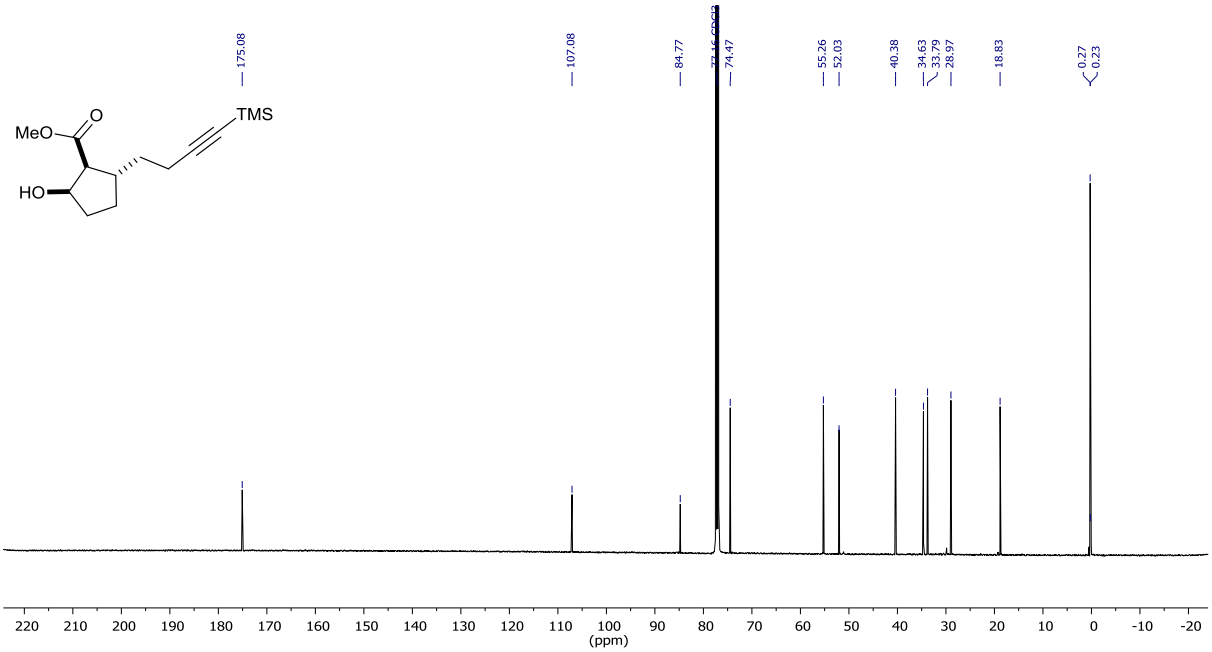


### 7.7.3 **Alcohol 2.82**

Methyl (1*S**,2*R**,5*R**)-2-hydroxy-5-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopentane-1-carboxylate (**2.82**) ($^1$H NMR, 500 MHz, $CDCl_3$)

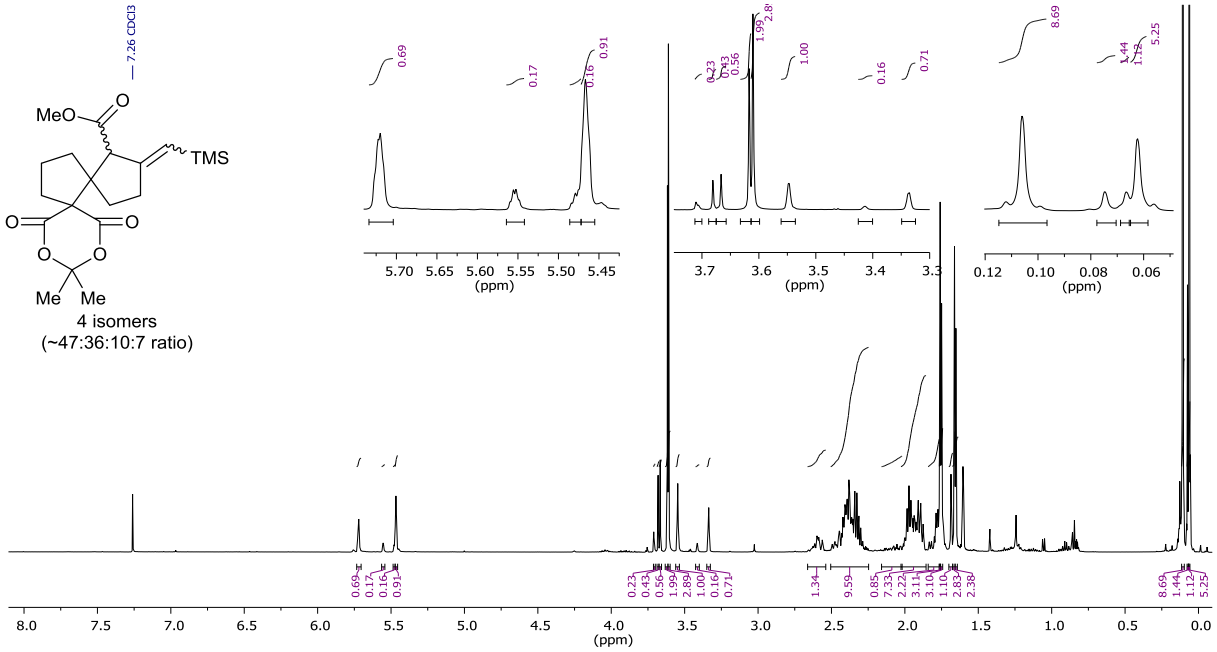



Methyl (1*S**,2*R**,5*R**)-2-hydroxy-5-(4-(trimethylsilyl)but-3-yn-1-yl)cyclopentane-1-carboxylate (**2.82**) ($^{13}$C NMR, 126 MHz, $CDCl_3$)

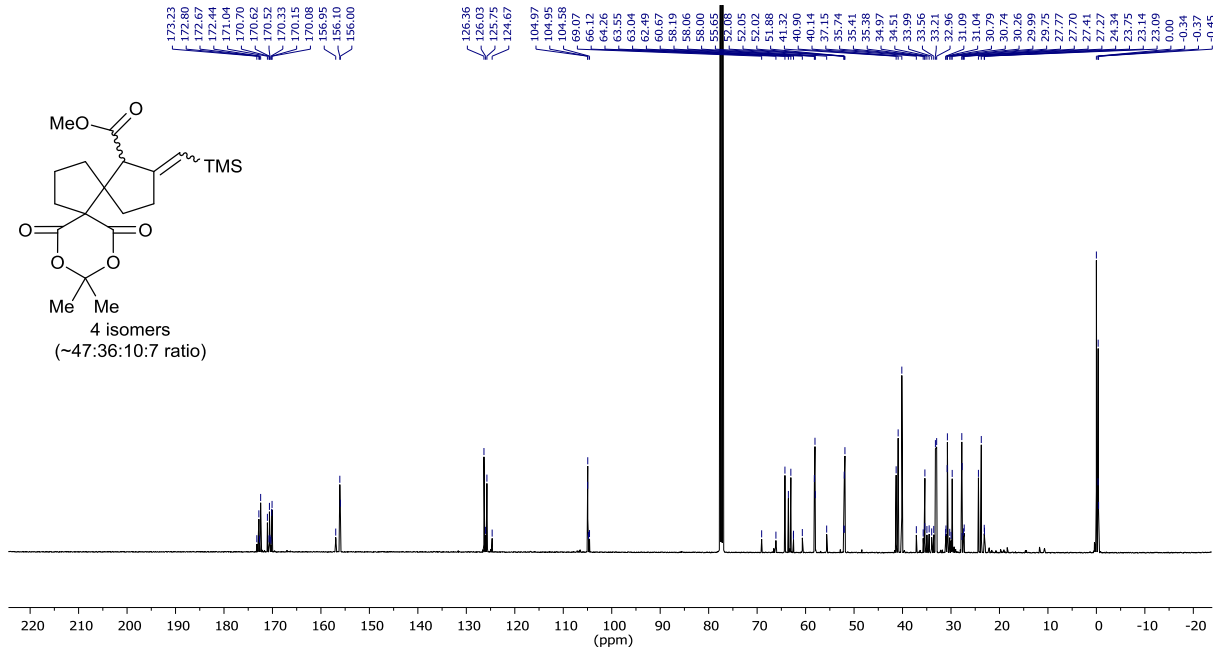


### 7.7.4 **Meldrum's acids 3.5a-d**

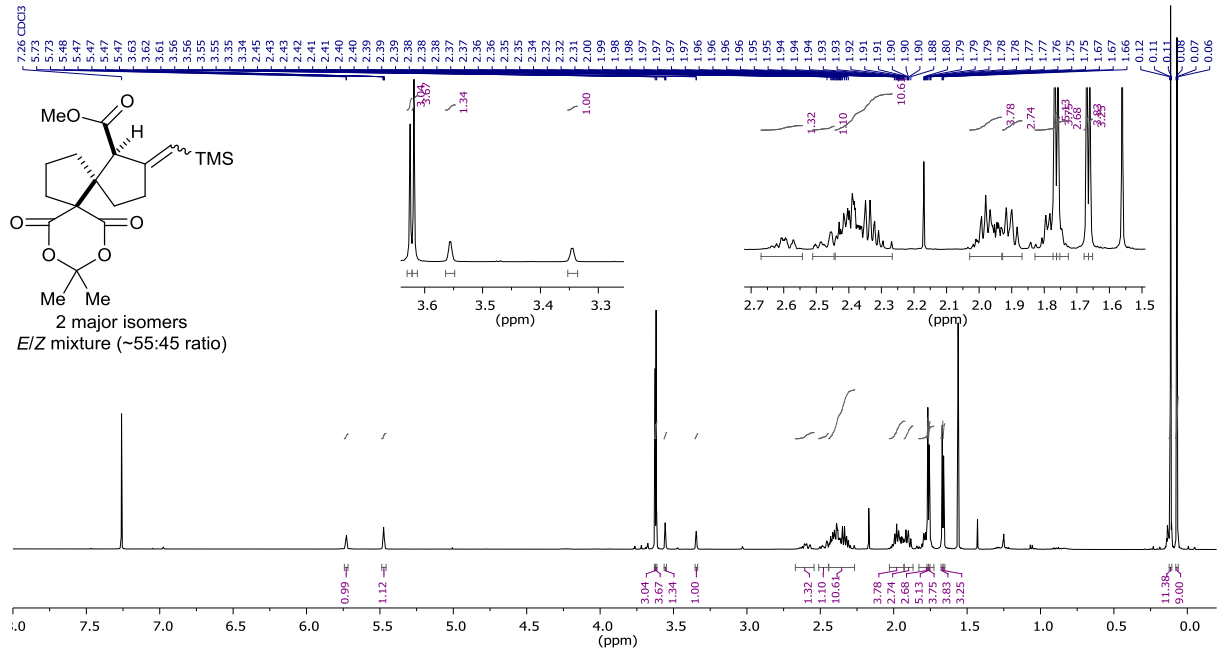
Methyl 9,9-dimethyl-7,11-dioxo-2-((trimethylsilyl)methylene)-8,10-dioxadispiro[4.0.5$^6$.3$^5$]tetradecane-1-carboxylate (**3.5**)
($^1$H NMR, 500 MHz, $CDCl_3$)



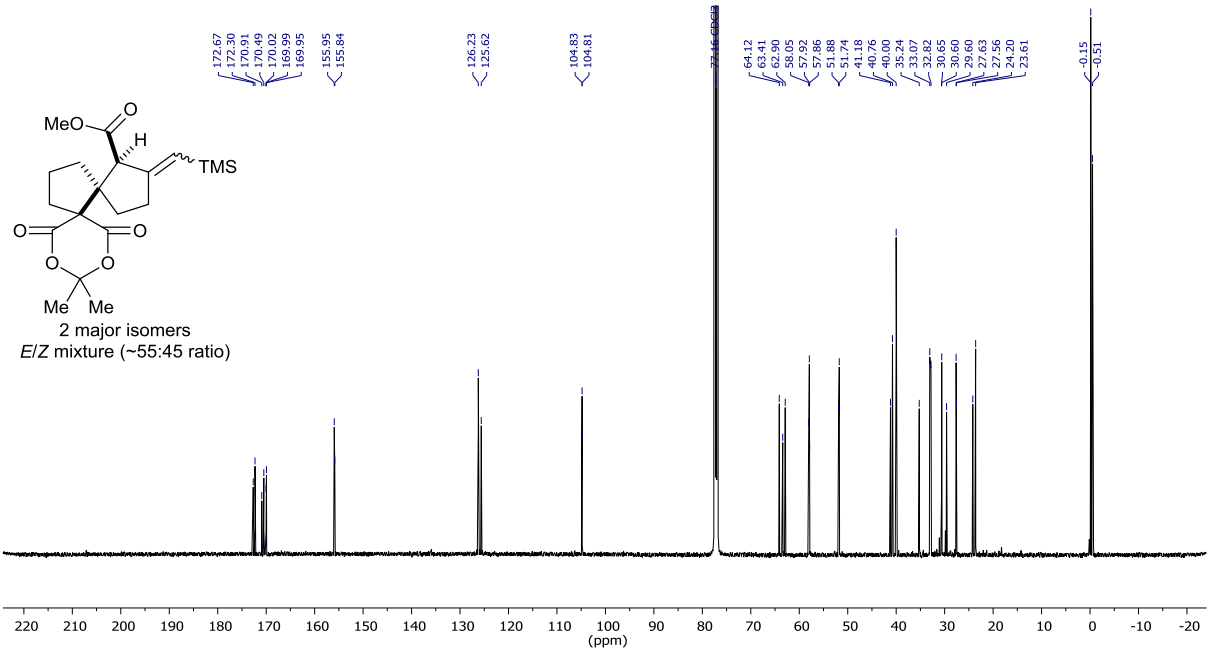

Methyl 9,9-dimethyl-7,11-dioxo-2-((trimethylsilyl)methylene)-8,10-dioxadispiro[4.0.5$^6$.3$^5$]tetradecane-1-carboxylate (**3.5**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)



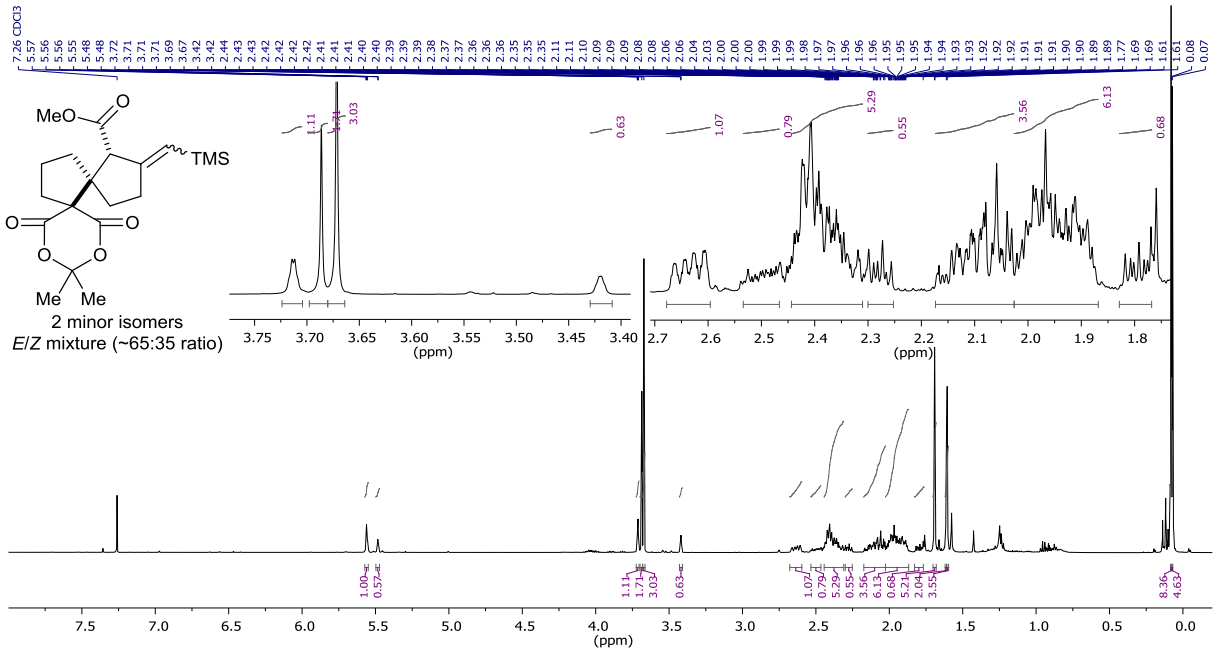
Methyl (1*R**,5*R**)-9,9-dimethyl-7,11-dioxo-2-((trimethylsilyl)methylene)-8,10-dioxadispiro[4.0.5$^6$.3$^5$]tetradecane-1-carboxylate (**3.5**)
($^1$H NMR, 500 MHz, $CDCl_3$)



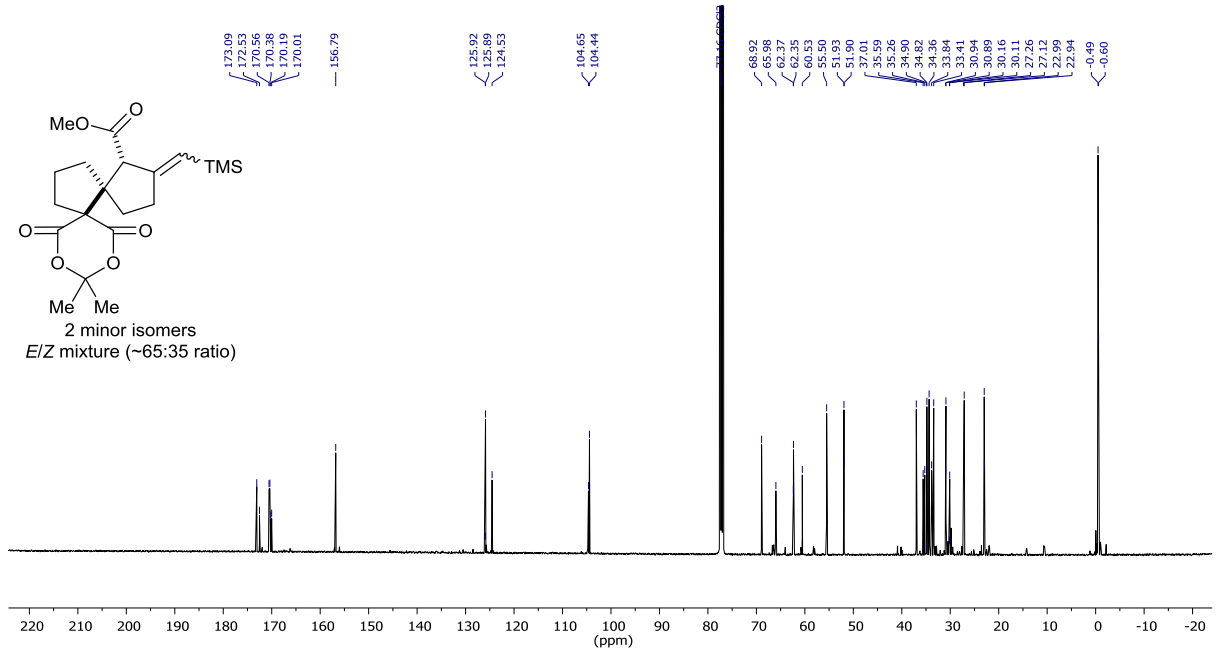

Methyl (1*R**,5*R**)-9,9-dimethyl-7,11-dioxo-2-((trimethylsilyl)methylene)-8,10-dioxadispiro[4.0.5$^6$.3$^5$]tetradecane-1-carboxylate (**3.5**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)



Methyl (1*S**,5*R**)-9,9-dimethyl-7,11-dioxo-2-((trimethylsilyl)methylene)-8,10-dioxadispiro[4.0.5$^6$.3$^5$]tetradecane-1-carboxylate (**3.5**)
($^1$H NMR, 500 MHz, $CDCl_3$)

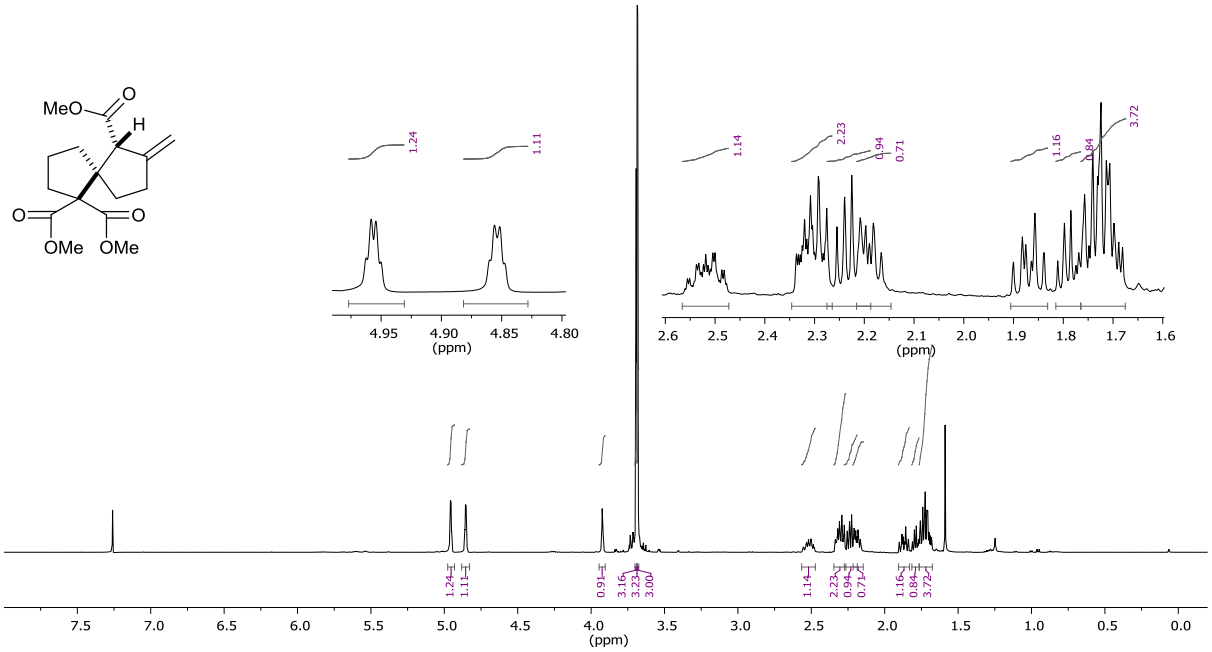



Methyl (1*S**,5*R**)-9,9-dimethyl-7,11-dioxo-2-((trimethylsilyl)methylene)-8,10-dioxadispiro[4.0.5$^6$.3$^5$]tetradecane-1-carboxylate (**3.5**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)

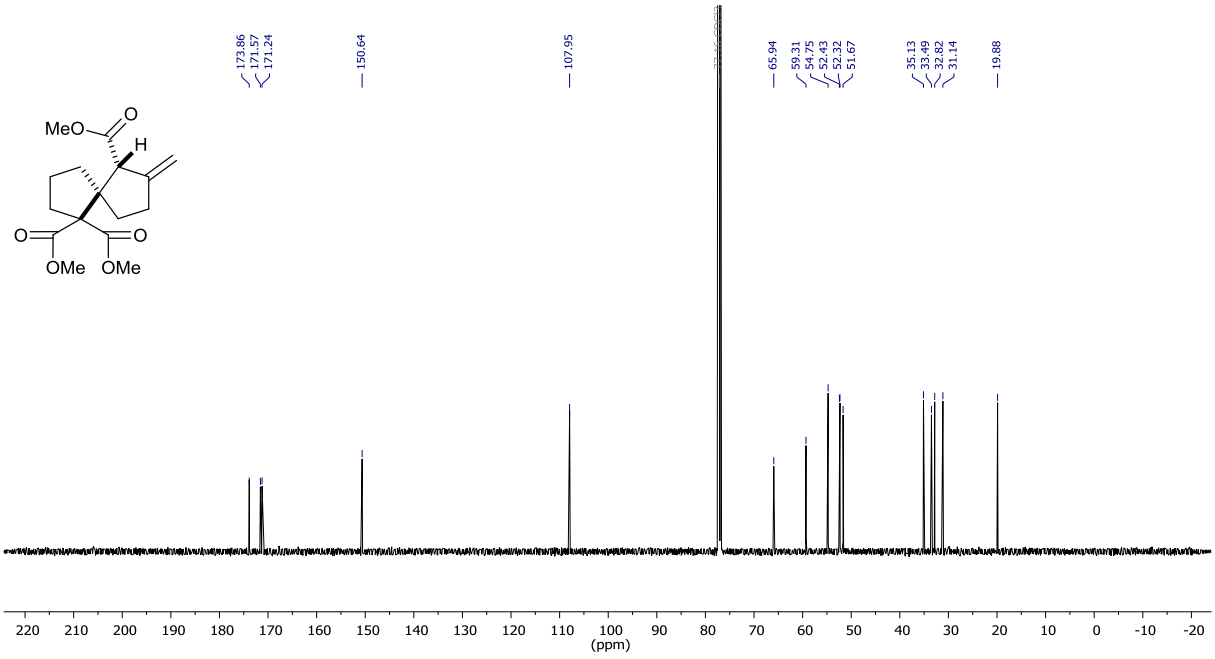


### 7.7.5 ***Exo*-alkenes 3.22a-b**

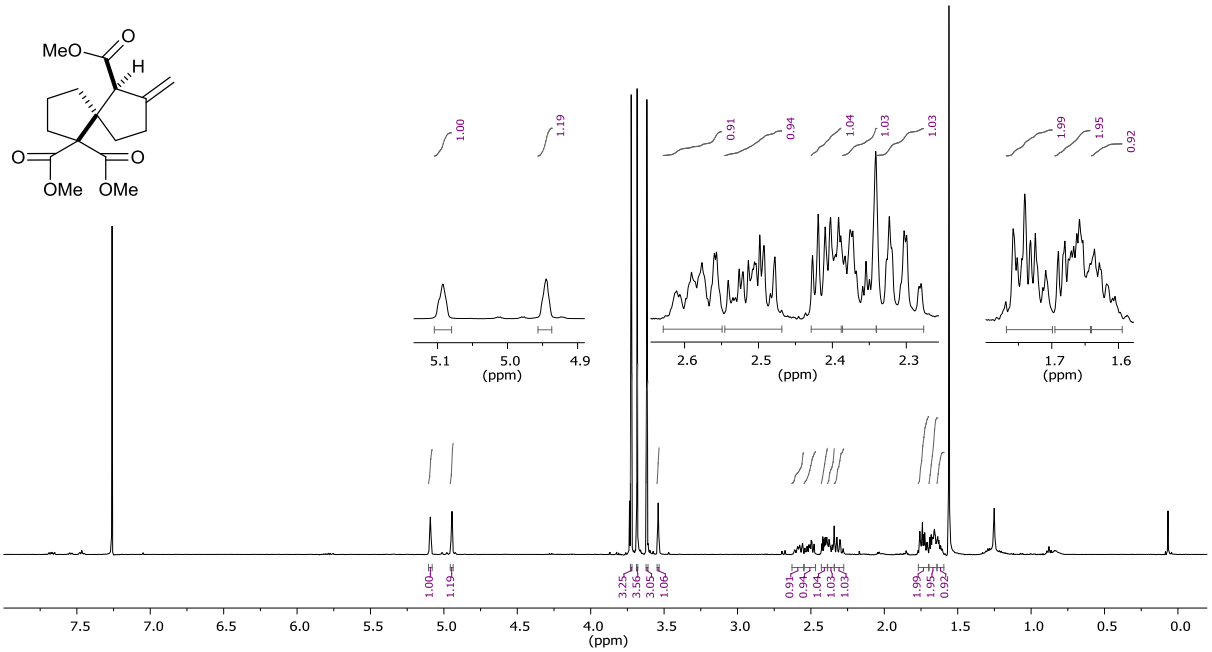
Trimethyl (5*R**,6*R**)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.22a**)
($^1$H NMR, 500 MHz, $CDCl_3$)



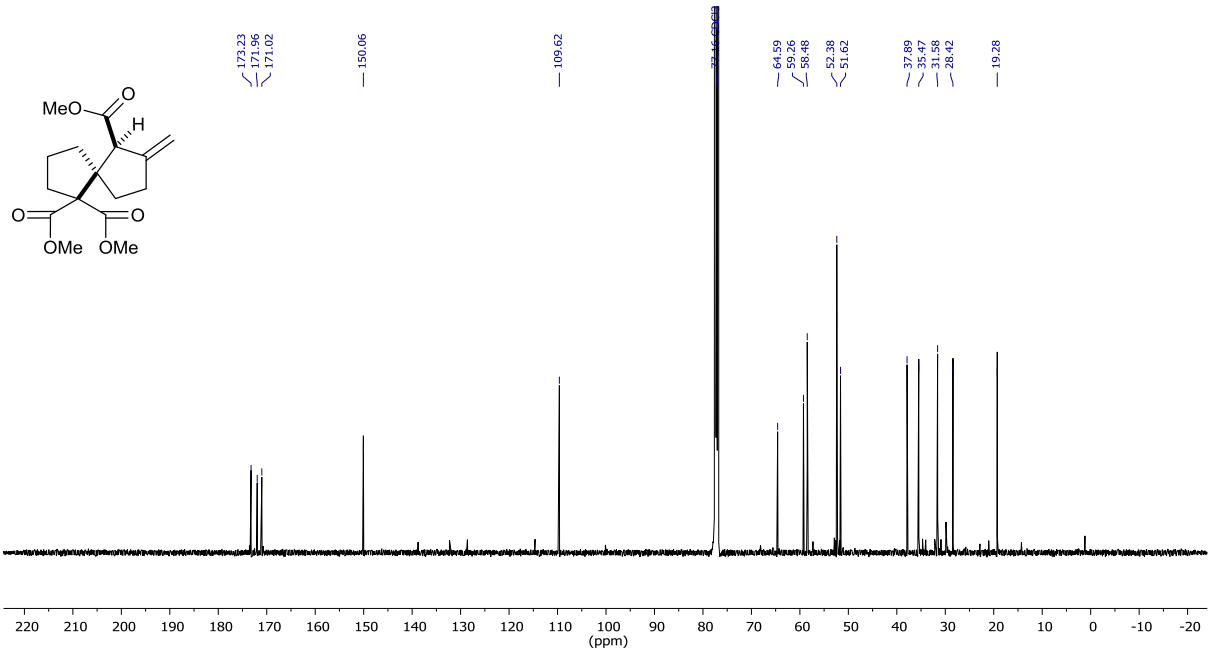

Trimethyl (5*R**,6*R**)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.22a**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)



Trimethyl (5*R**,6*S**)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.22b**)
($^{1}$H NMR, 500 MHz, $CDCl_3$)

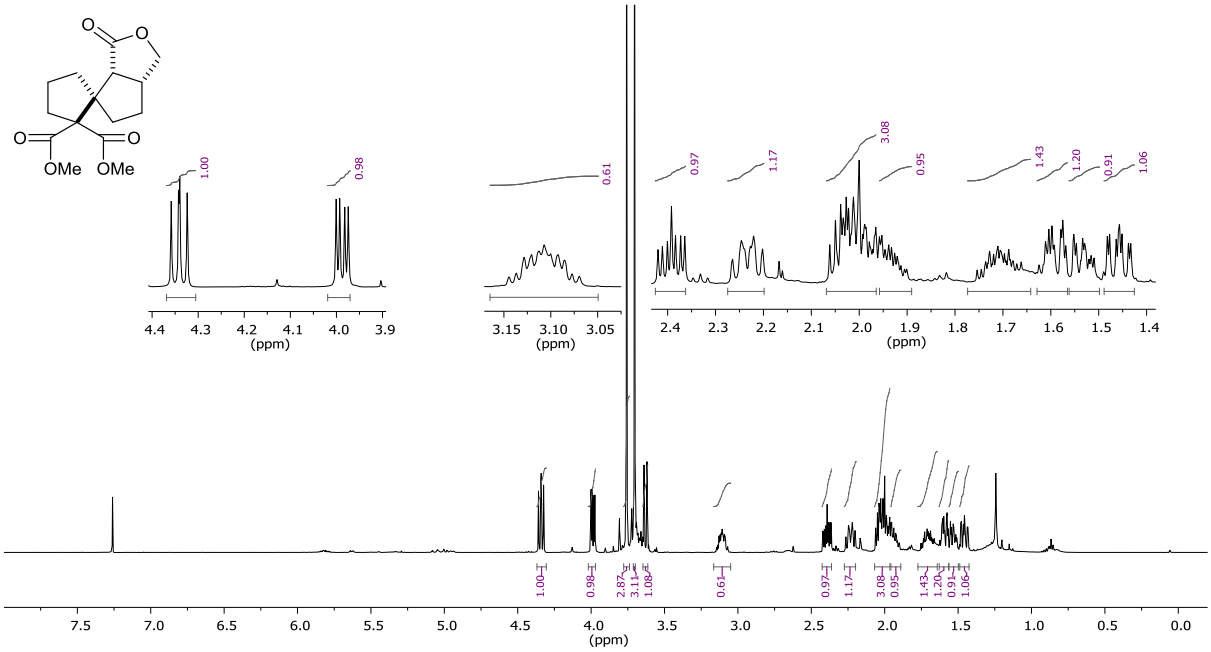



Trimethyl (5*R**,6*S**)-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.22b**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)

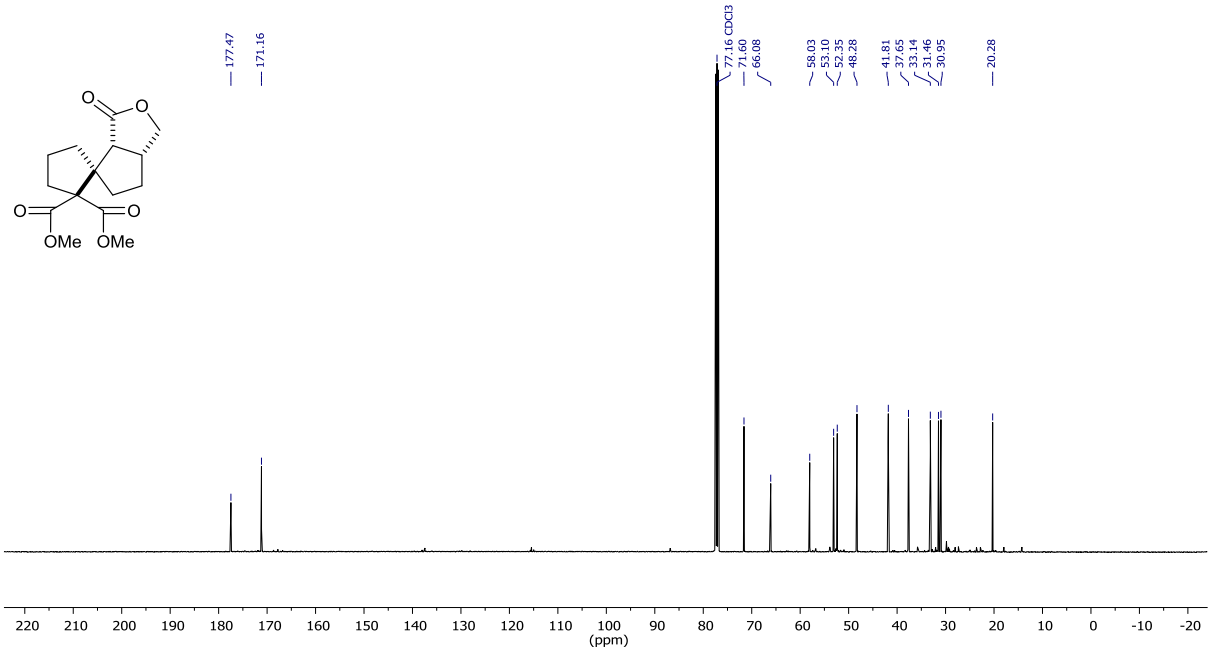


### 7.7.6 **Lactone 3.25**

Dimethyl (1*R**,3*a*'*R**,6*a*'*R**)-3'-oxohexahydrospiro[cyclopentane-1,4'-cyclopenta[*c*]furan]-2,2-dicarboxylate (**3.25**)
($^1$H NMR, 500 MHz, $CDCl_3$)

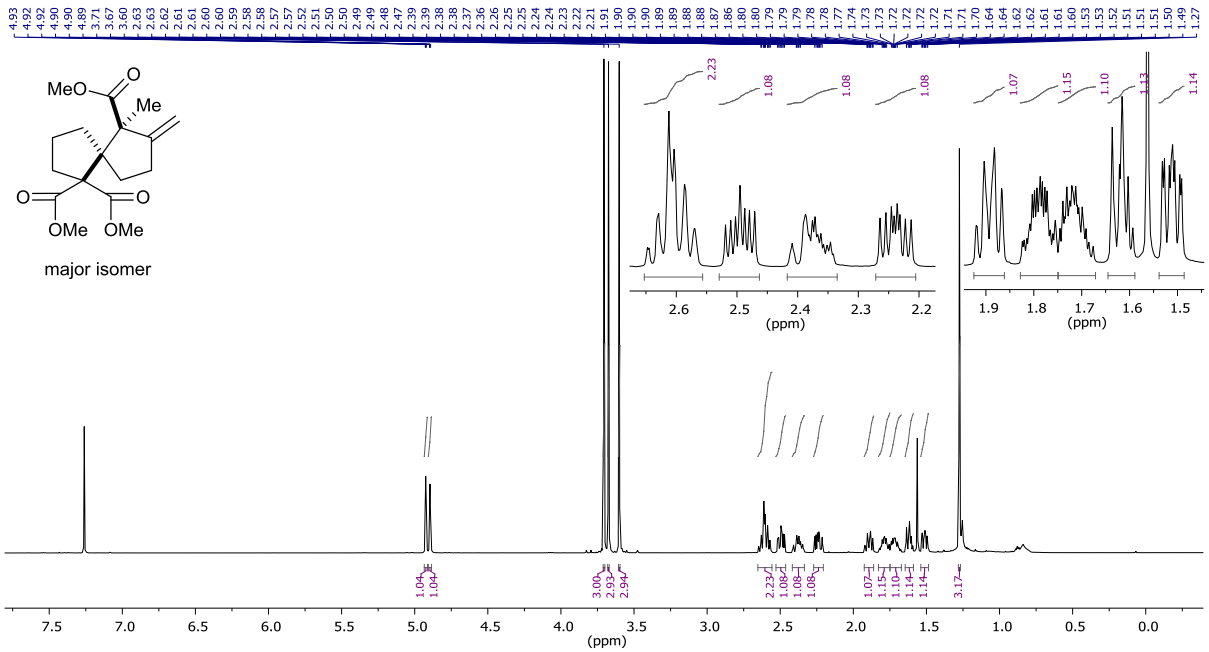



Dimethyl (1*R**,3*a*'*R**,6*a*'*R**)-3'-oxohexahydrospiro[cyclopentane-1,4'-cyclopenta[*c*]furan]-2,2-dicarboxylate (**3.25**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)

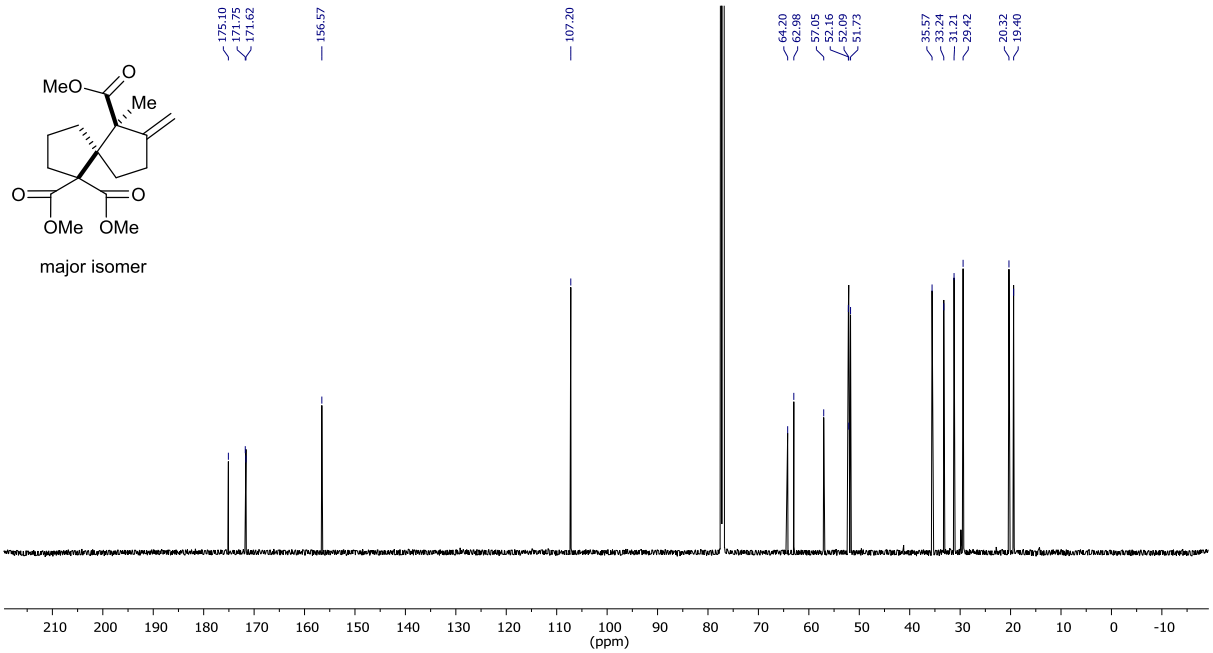


### 7.7.7 *Exo*-alkenes 3.47a-b

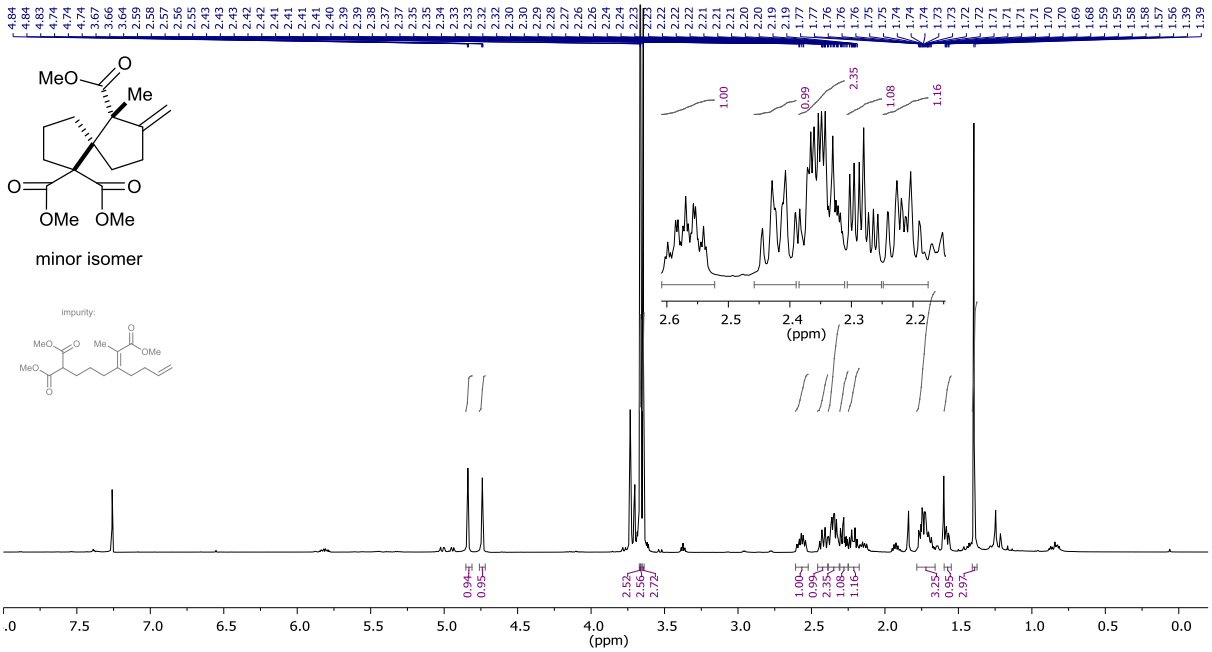
Trimethyl (5*R**,6*S**)-6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate **(3.47a)**
($^1$H NMR, 600 MHz, $CDCl_3$)



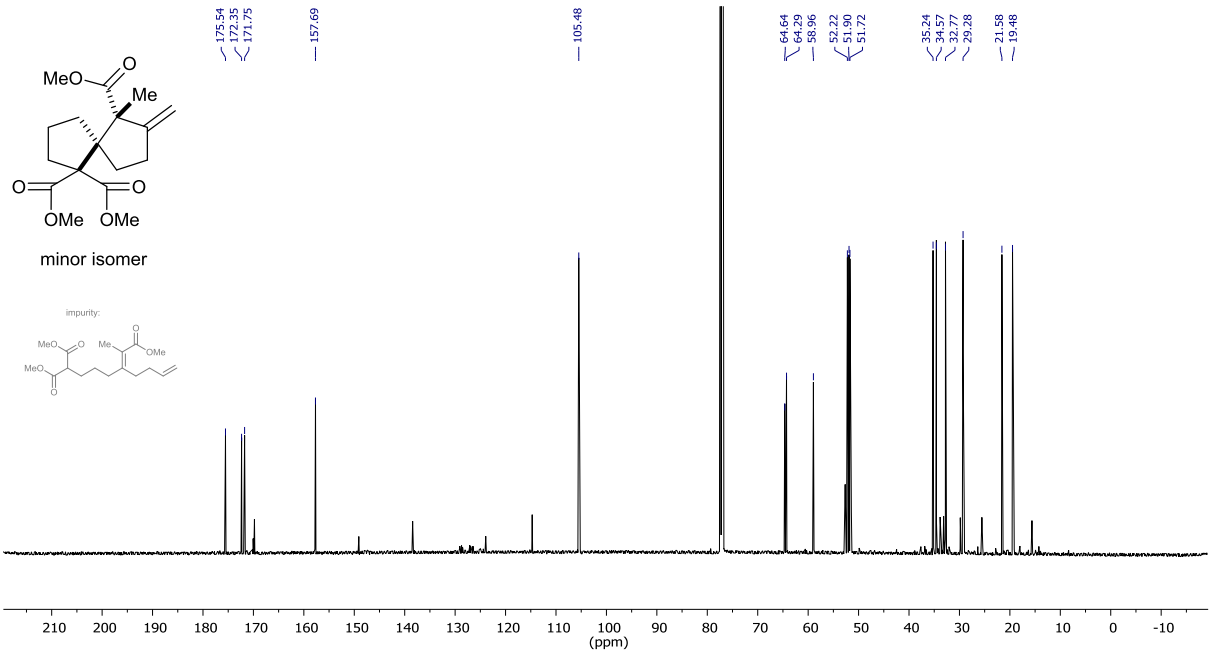

Trimethyl (5*R**,6*S**)-6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate **(3.47a)**
($^{13}$C NMR, 151 MHz, $CDCl_3$)



Trimethyl (5*R**,6*R**)-6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate **(3.47b)**
($^1$H NMR, 600 MHz, $CDCl_3$)

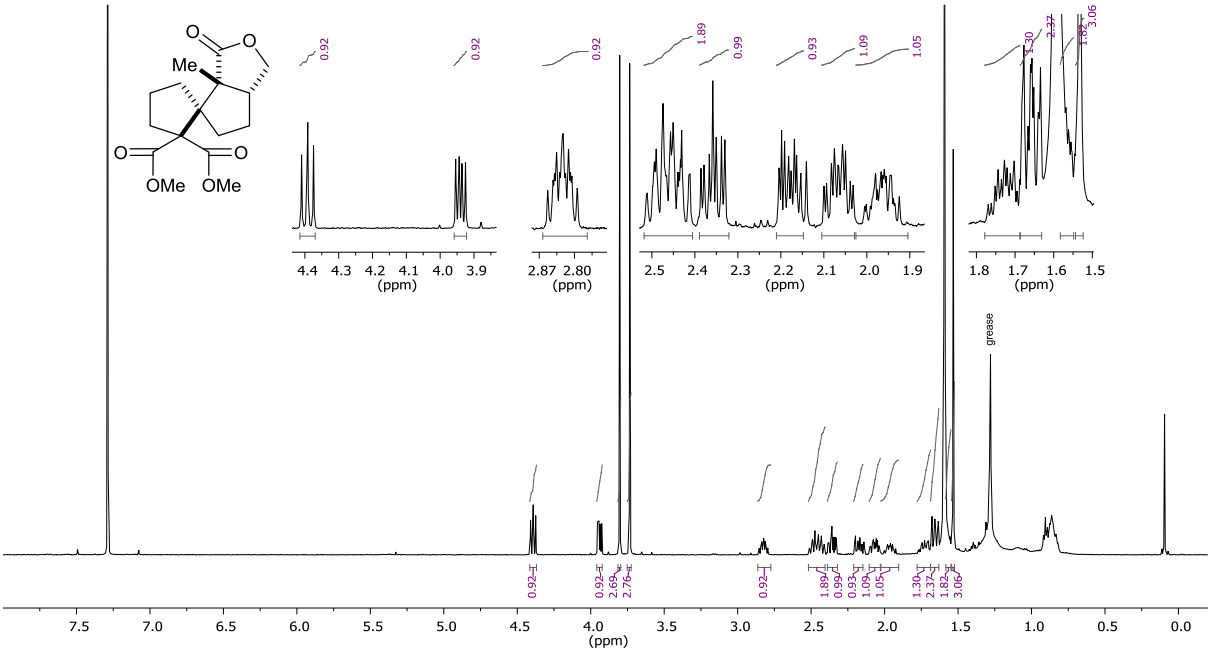



Trimethyl (5*R**,6*R**)-6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate **(3.47b)**
($^{13}$C NMR, 151 MHz, $CDCl_3$)

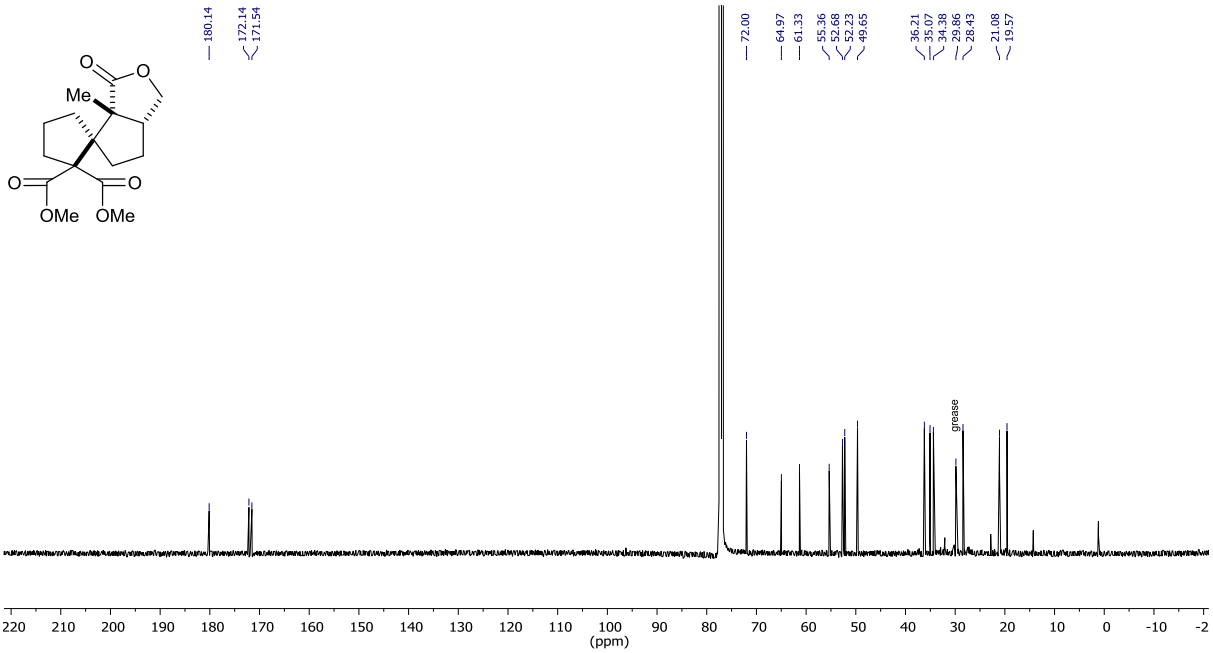


### 7.7.8 **Lactone 3.49**

Dimethyl (1*R**,3a*'R**,6a*'R**)-3a'-methyl-3'-oxohexahydrospiro[cyclopentane-1,4'-cyclopenta[*c*]furan]-2,2-dicarboxylate (**3.49**)
($^{1}$H NMR, 500 MHz, $CDCl_3$)

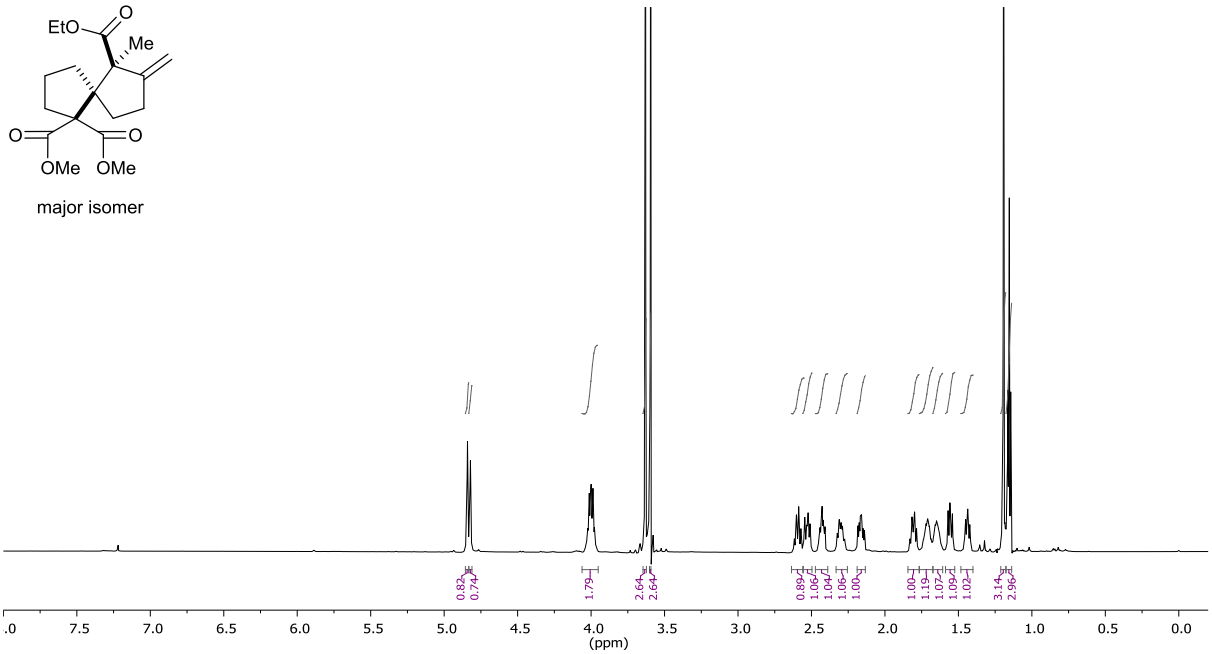



Dimethyl (1*R**,3a*'R**,6a*'R**)-3a'-methyl-3'-oxohexahydrospiro[cyclopentane-1,4'-cyclopenta[*c*]furan]-2,2-dicarboxylate (**3.49**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)

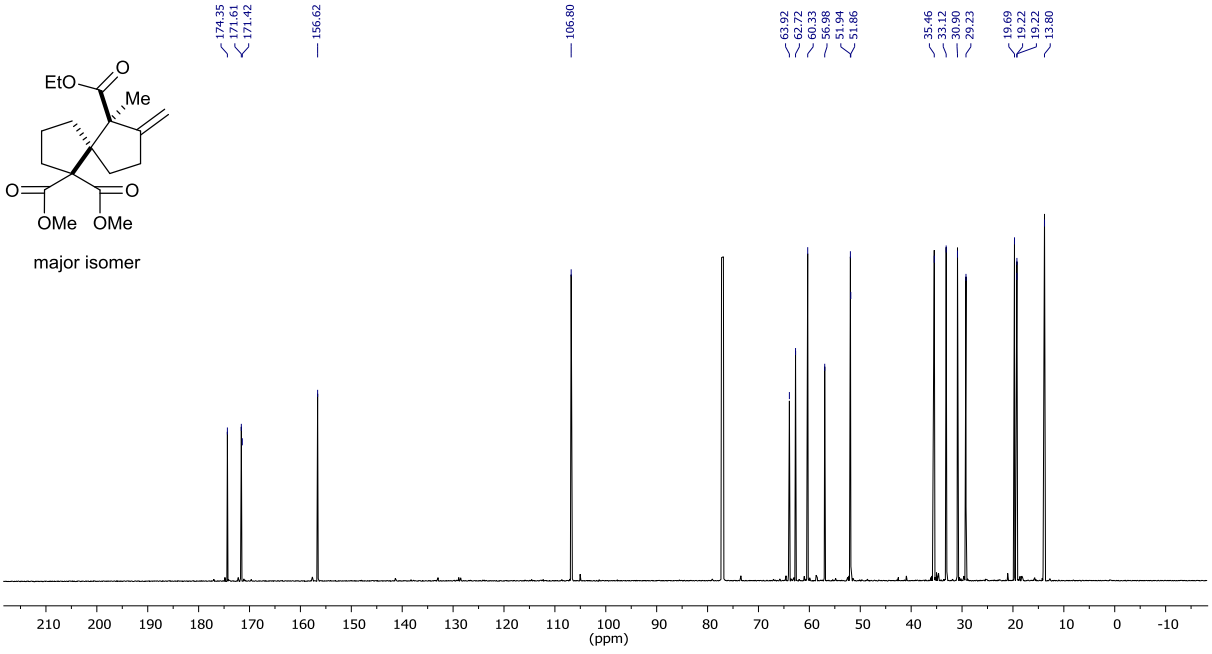


### 7.7.9 ***Exo*-alkenes 3.64a-b**

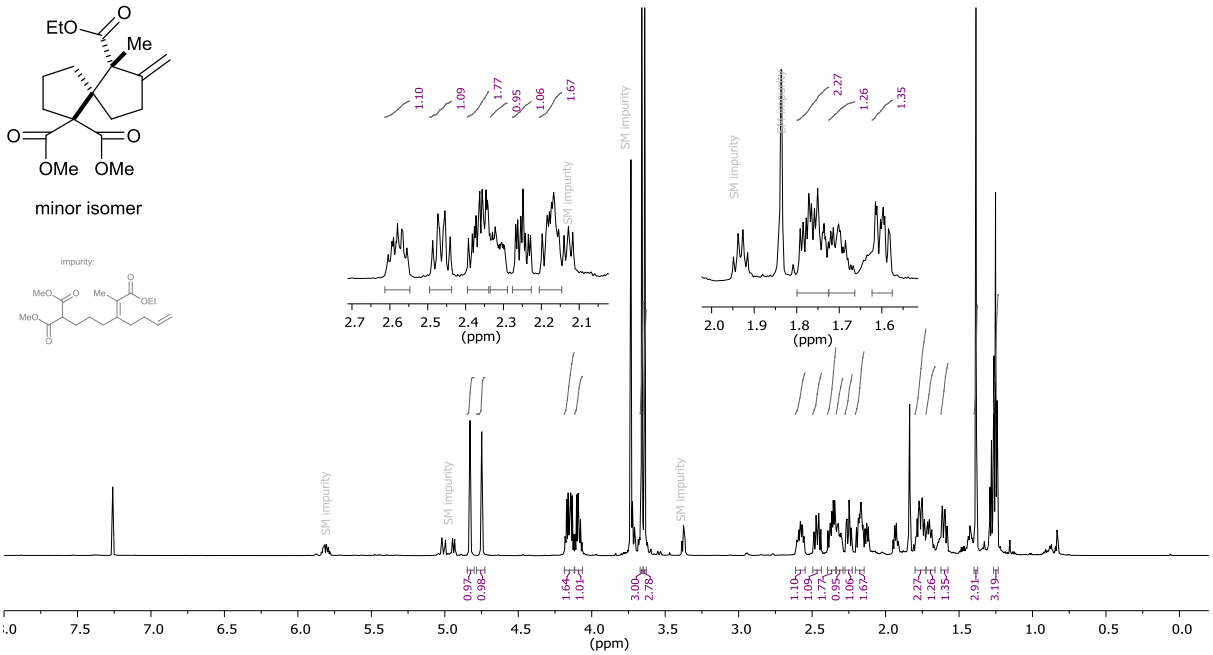
6-Ethyl 1,1-dimethyl (5R*,6S*)-6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.64a**) ($^{1}$H NMR, 700 MHz, $CDCl_3$)



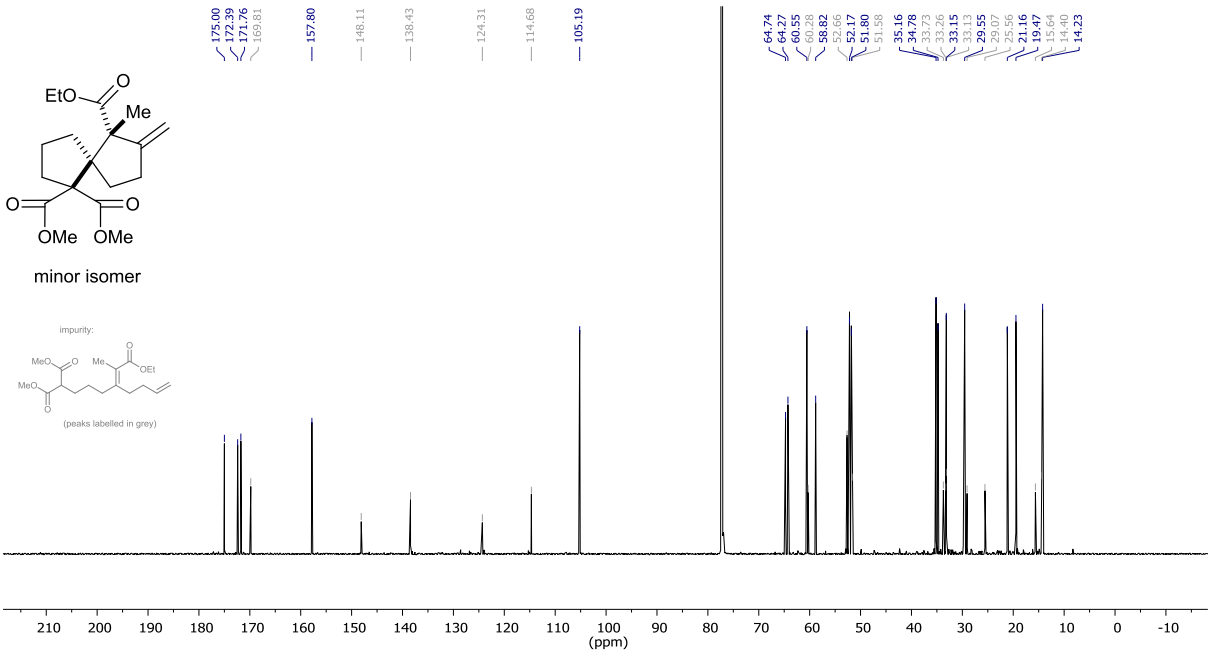

6-Ethyl 1,1-dimethyl (5R*,6S*)-6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.64a**) ($^{13}$C NMR, 176 MHz, $CDCl_3$)



6-Ethyl 1,1-dimethyl (5R*,6R*)-6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.64b**) ($^{1}$H NMR, 700 MHz, $CDCl_3$)

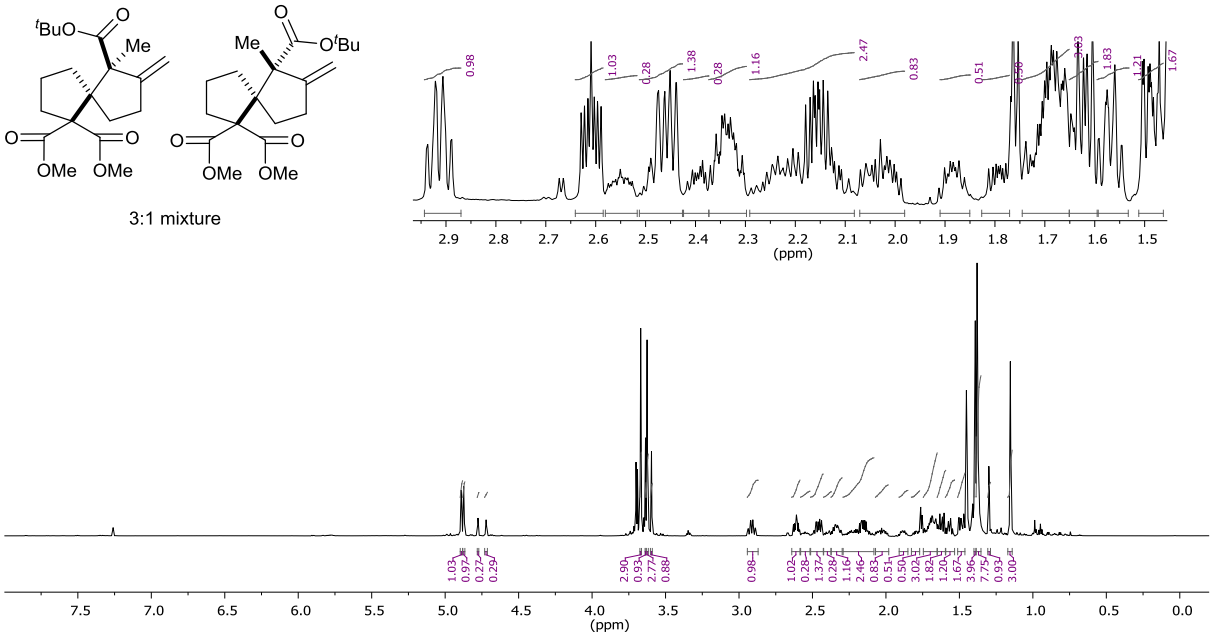



6-Ethyl 1,1-dimethyl (5R*,6R*)-6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.64b**) ($^{13}$C NMR, 176 MHz, $CDCl_3$)

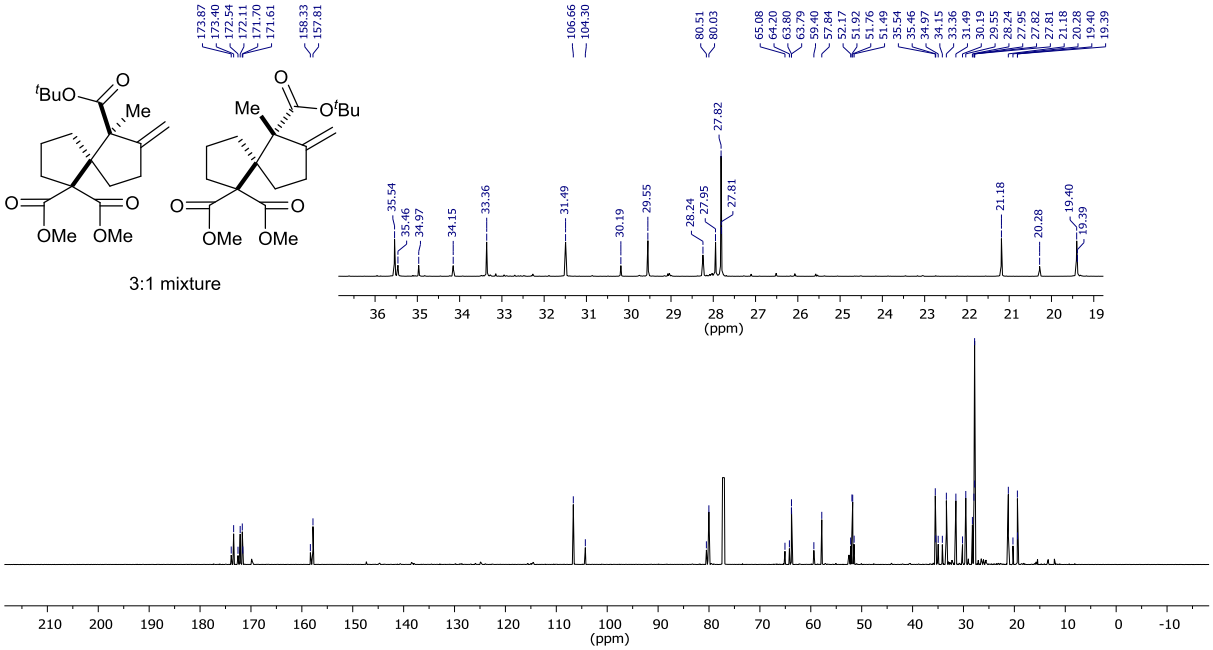


### 7.7.11 ***Exo*-alkenes 3.65a-b**

6-(*Tert*-butyl) 1,1-dimethyl 6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.65a**-**b**) ($^{1}$H NMR, 700 MHz, $CDCl_3$)

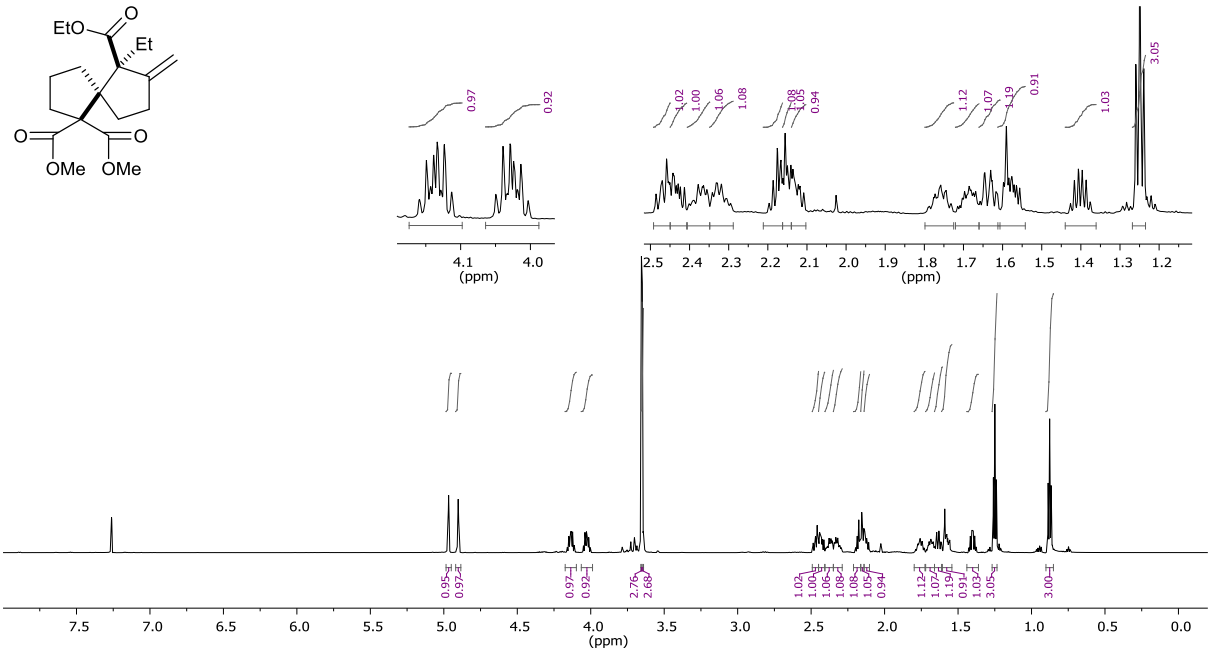



6-(*Tert*-butyl) 1,1-dimethyl 6-methyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.65a**-**b**) ($^{13}$C NMR, 176 MHz, $CDCl_3$)

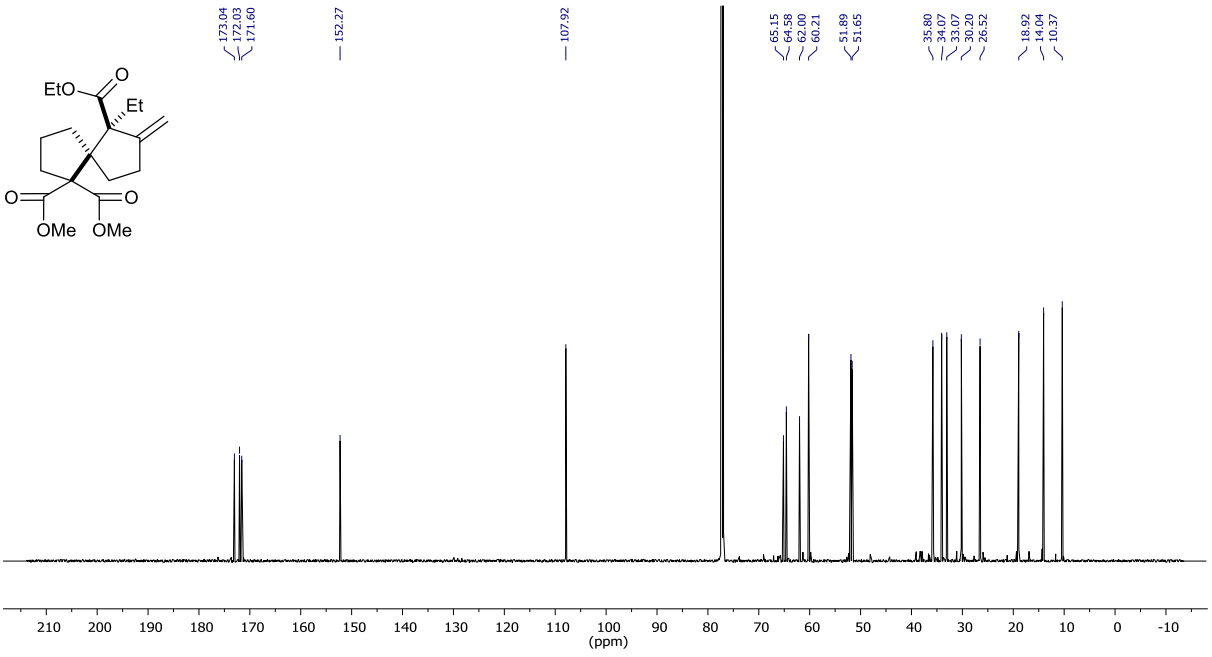


### 7.7.12 ***Exo*-alkenes 3.66**

6-Ethyl 1,1-dimethyl 6-ethyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.66**)
($^{1}$H NMR, 700 MHz, $CDCl_3$)

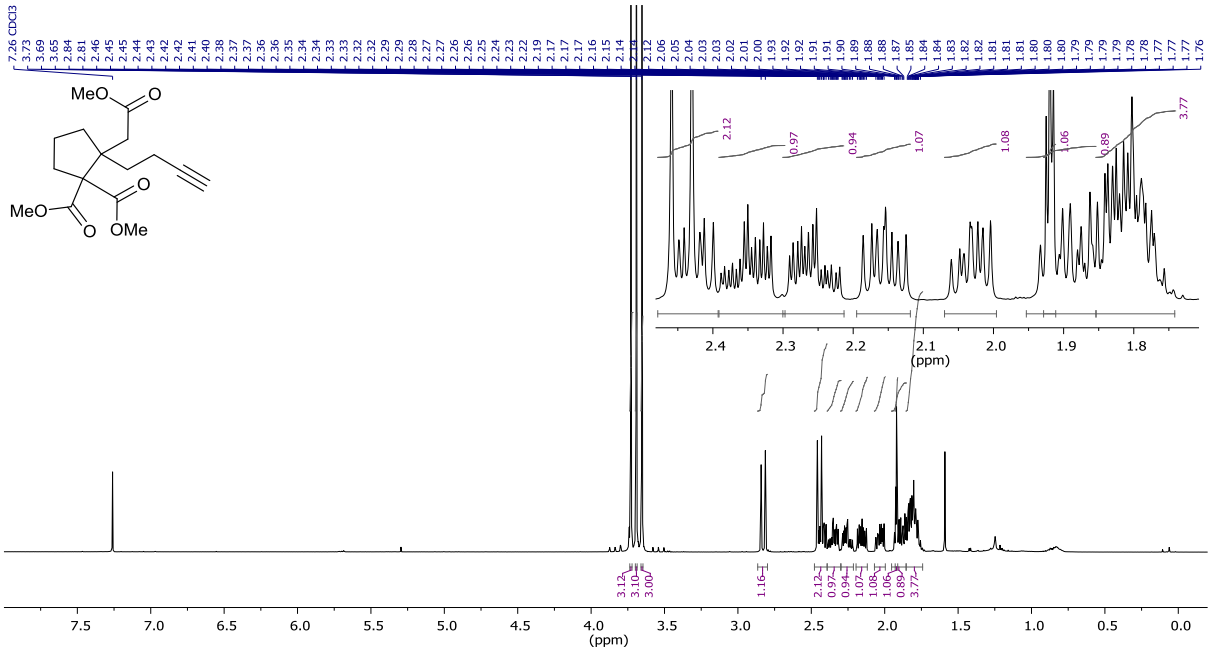



6-Ethyl 1,1-dimethyl 6-ethyl-7-methylenespiro[4.4]nonane-1,1,6-tricarboxylate (**3.66**)
($^{13}$C NMR, 176 MHz, $CDCl_3$)

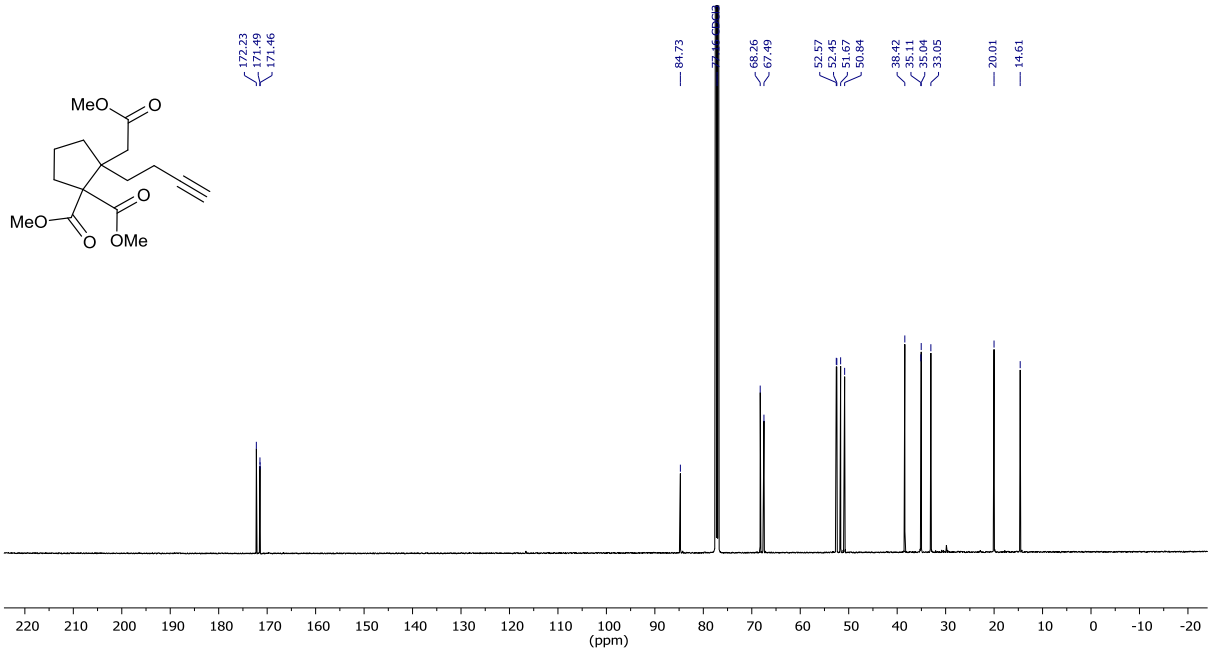


### 7.7.13 **Monocyclised product 4.16**

Dimethyl 2-(but-3-yn-1-yl)-2-(2-methoxy-2-oxoethyl)cyclopentane-1,1-dicarboxylate (**4.16**)
($^1$H NMR, 500 MHz, $CDCl_3$)

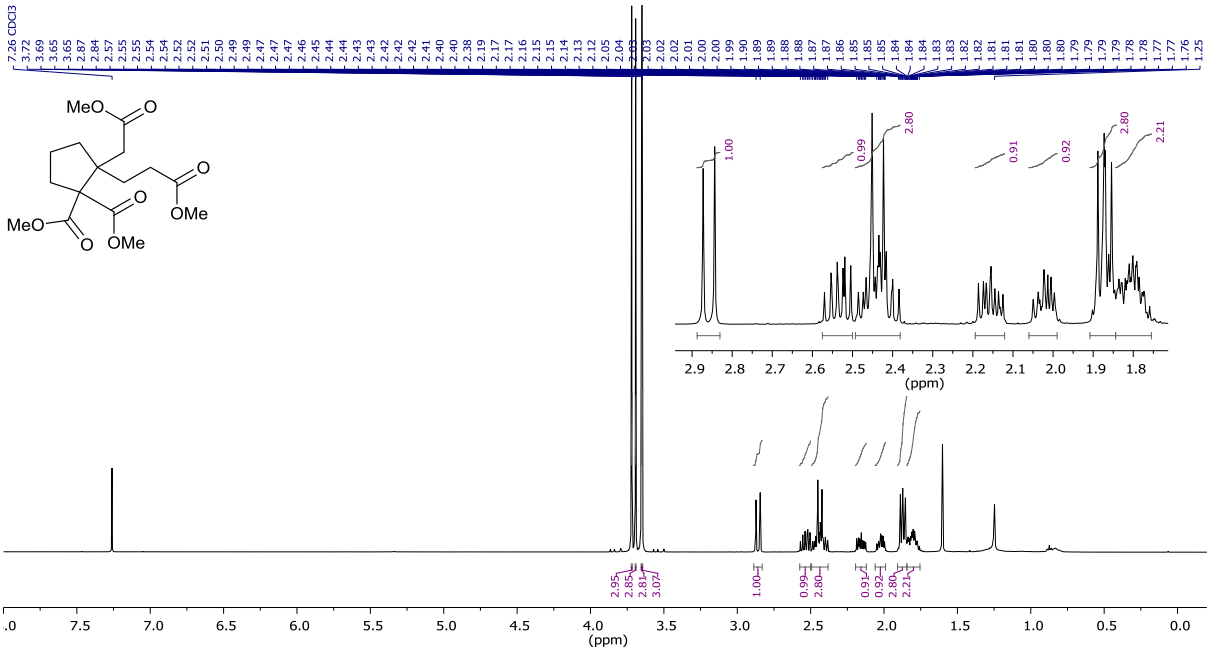



Dimethyl 2-(but-3-yn-1-yl)-2-(2-methoxy-2-oxoethyl)cyclopentane-1,1-dicarboxylate (**4.16**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)

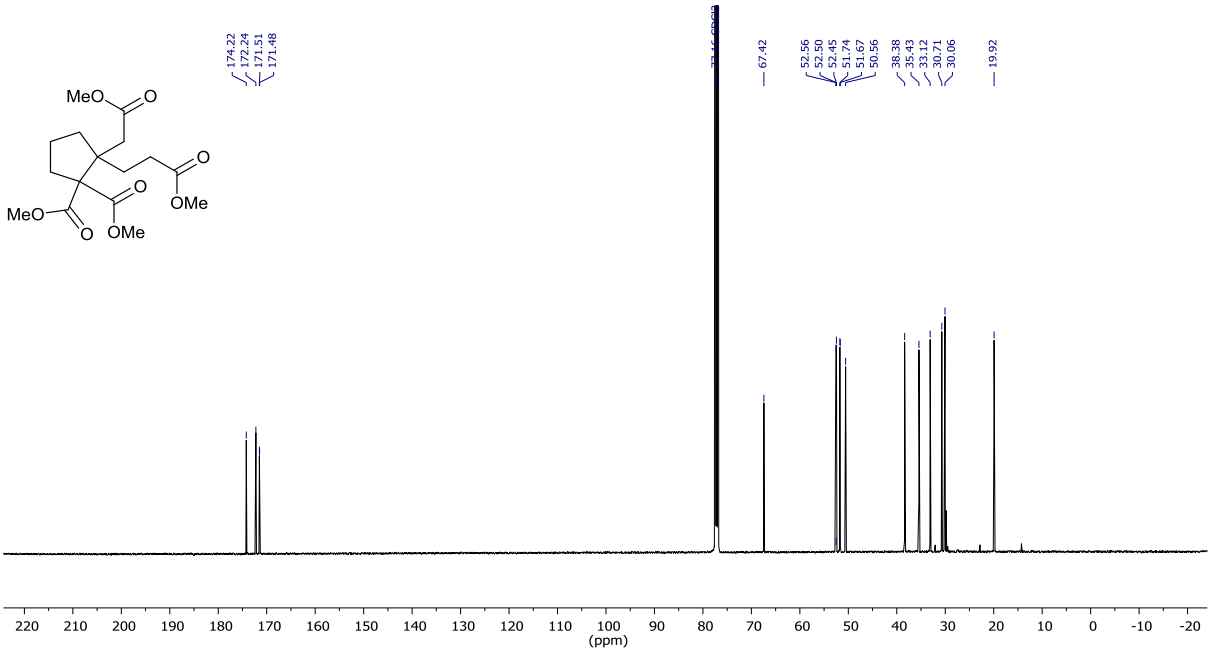


### 7.7.14 **Monocyclised product 4.17**

Dimethyl 2-(2-methoxy-2-oxoethyl)-2-(3-methoxy-3-oxopropyl)cyclopentane-1,1-dicarboxylate (**4.17**) ($^{1}$H NMR, 500 MHz, $CDCl_3$)

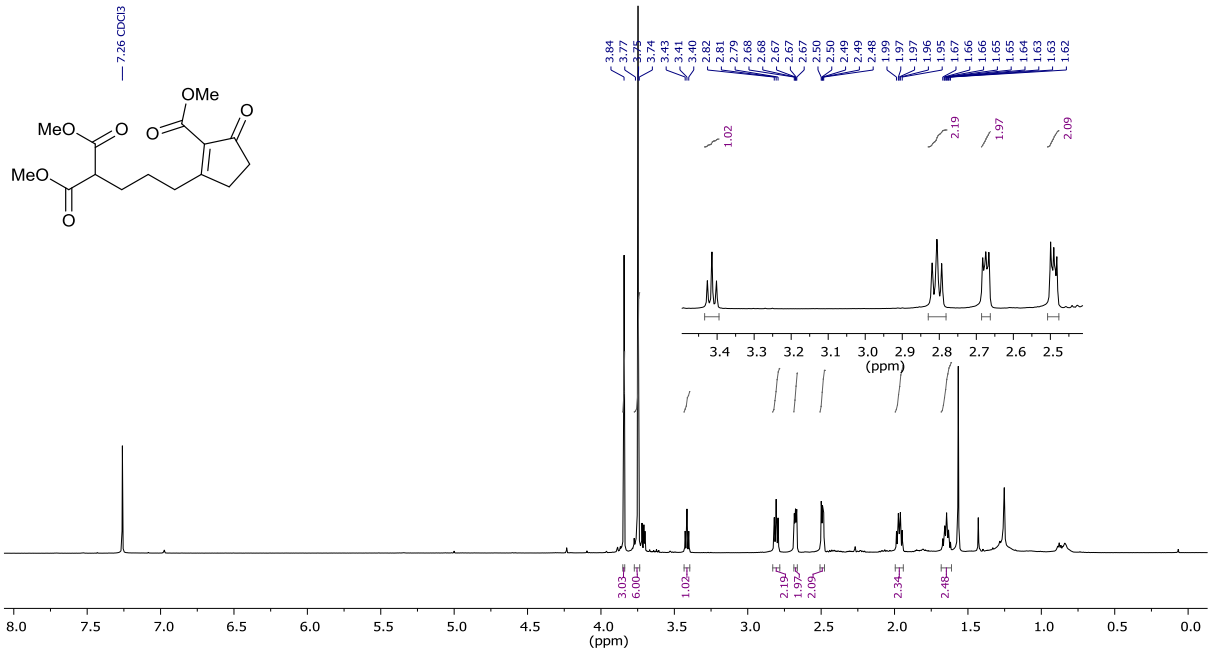



Dimethyl 2-(2-methoxy-2-oxoethyl)-2-(3-methoxy-3-oxopropyl)cyclopentane-1,1-dicarboxylate (**4.17**) ($^{13}$C NMR, 126 MHz, $CDCl_3$)

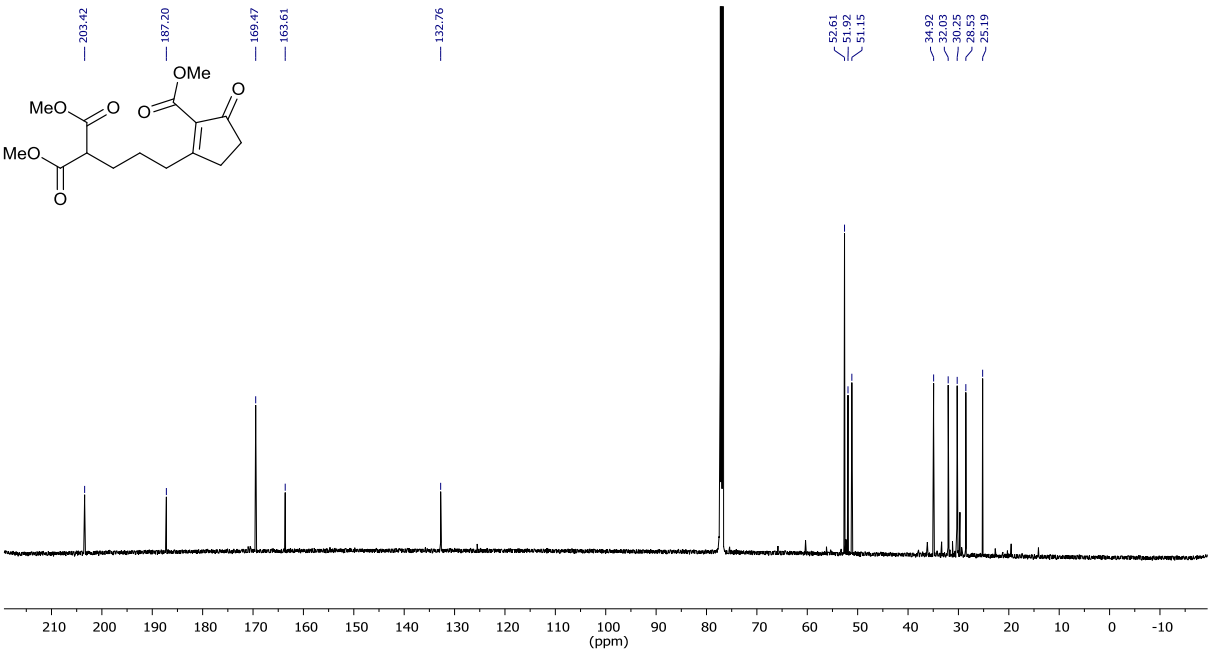


### 7.7.15 **Retro-Michael product 4.20**

Dimethyl 2-(3-(2-(methoxycarbonyl)-3-oxocyclopent-1-en-1-yl)propyl)malonate (**4.20**)
($^{1}$H NMR, 600 MHz, $CDCl_3$)

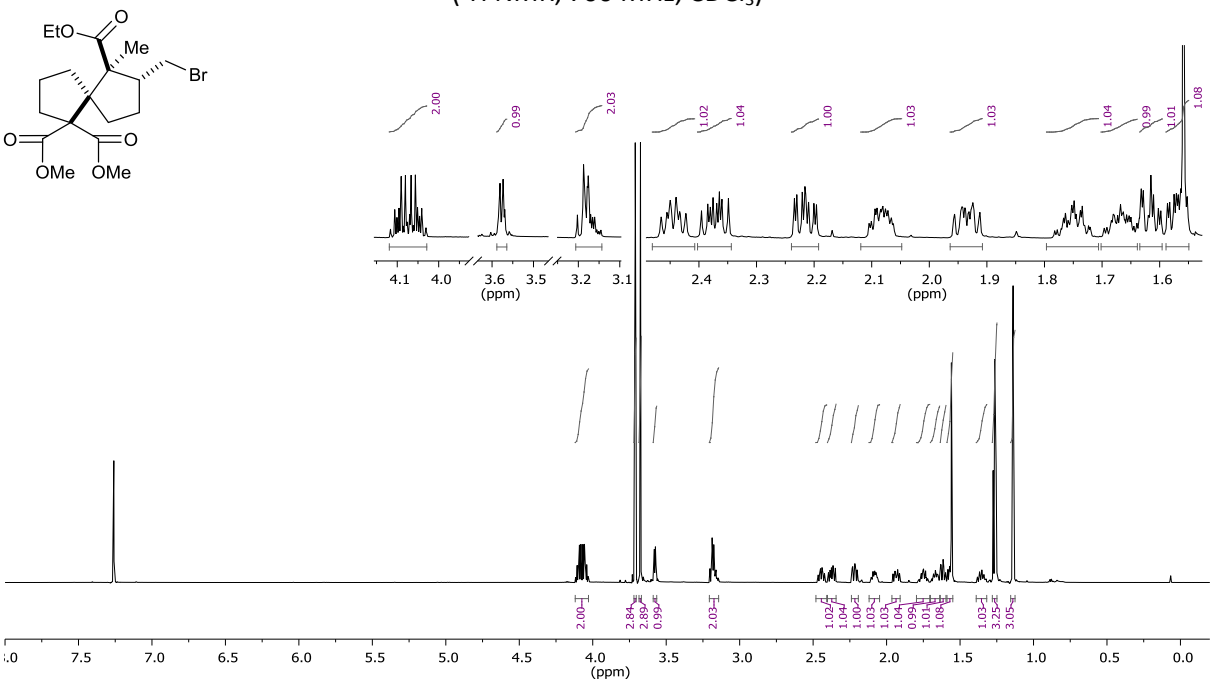



Dimethyl 2-(3-(2-(methoxycarbonyl)-3-oxocyclopent-1-en-1-yl)propyl)malonate (**4.20**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)

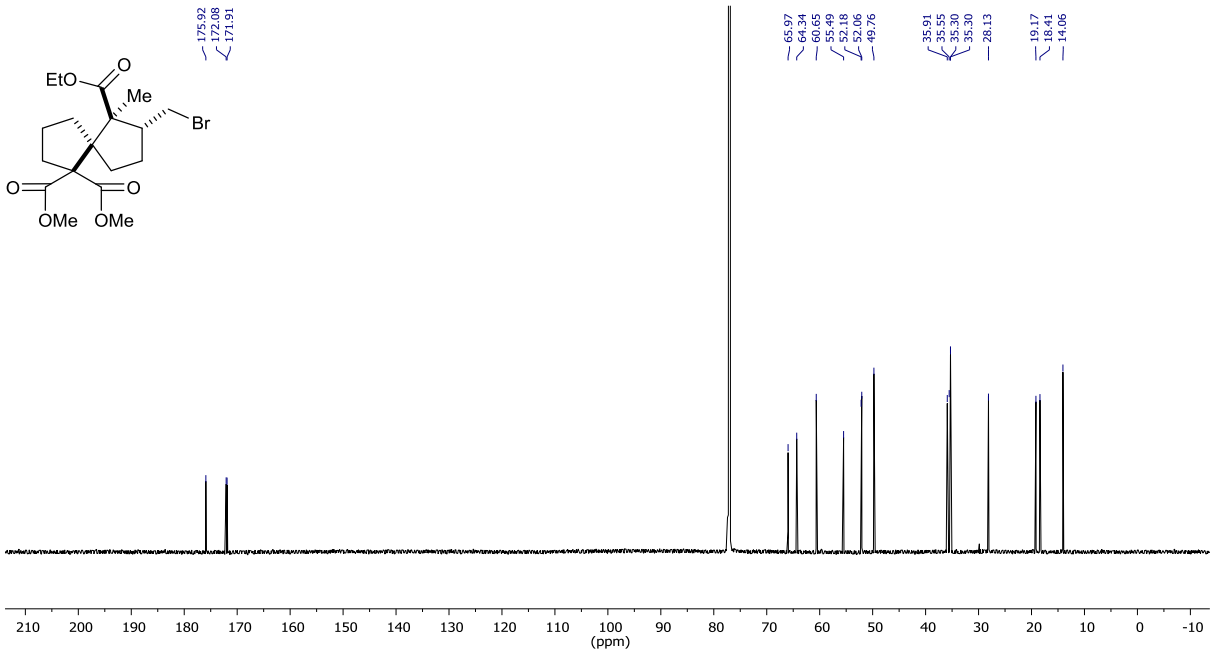


### 7.7.16 **Bromide 5.10**

6-Ethyl 1,1-dimethyl 7-(bromomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (**5.10**)
($^{1}$H NMR, 700 MHz, $CDCl_3$)

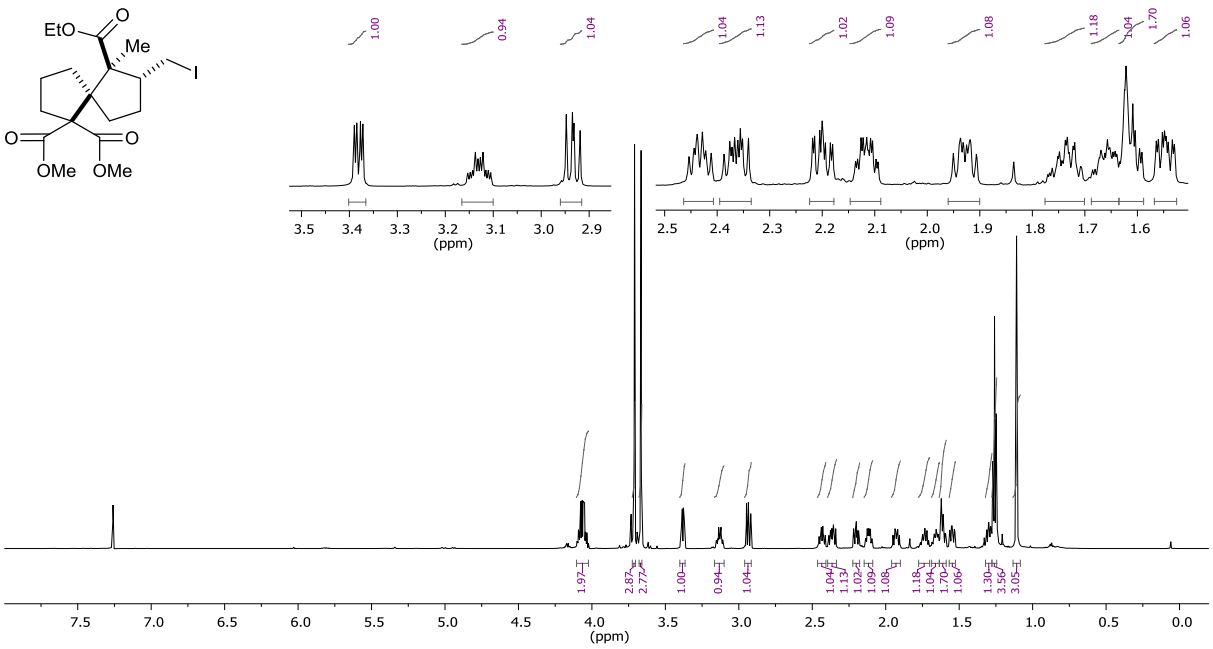



6-Ethyl 1,1-dimethyl 7-(bromomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (**5.10**)
($^{13}$C NMR, 176 MHz, $CDCl_3$)

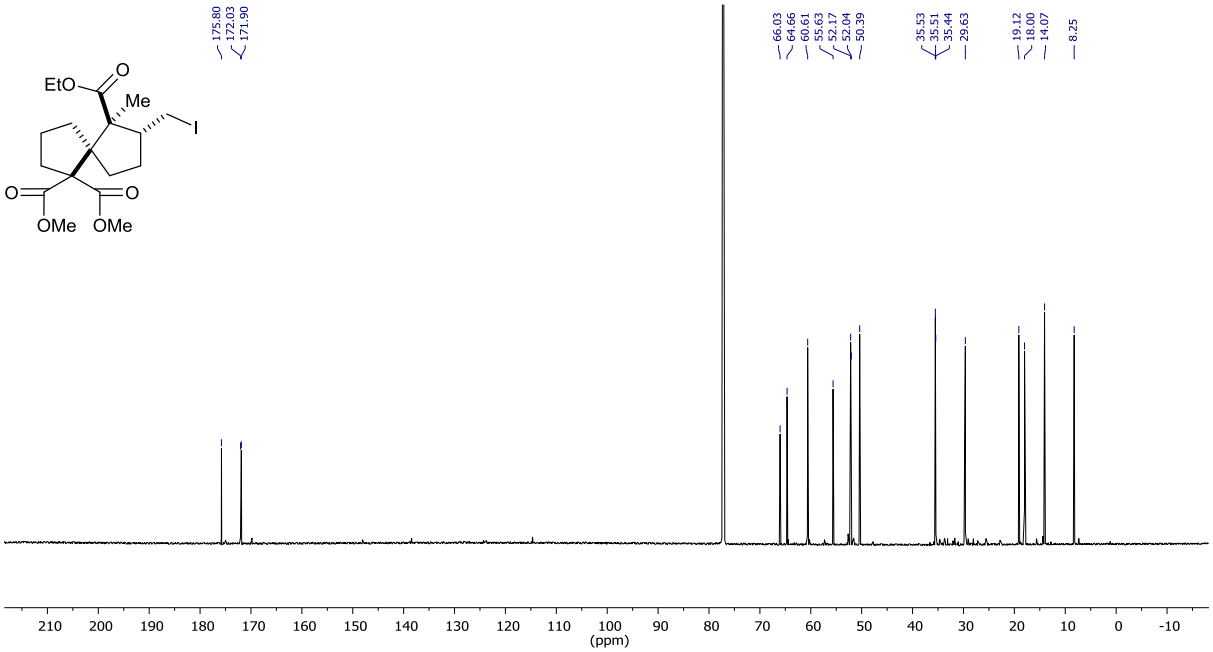


### 7.7.17 **Iodide 5.16**

6-Ethyl 1,1-dimethyl 7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (**5.16**)
($^{1}$H NMR, 700 MHz, $CDCl_3$)



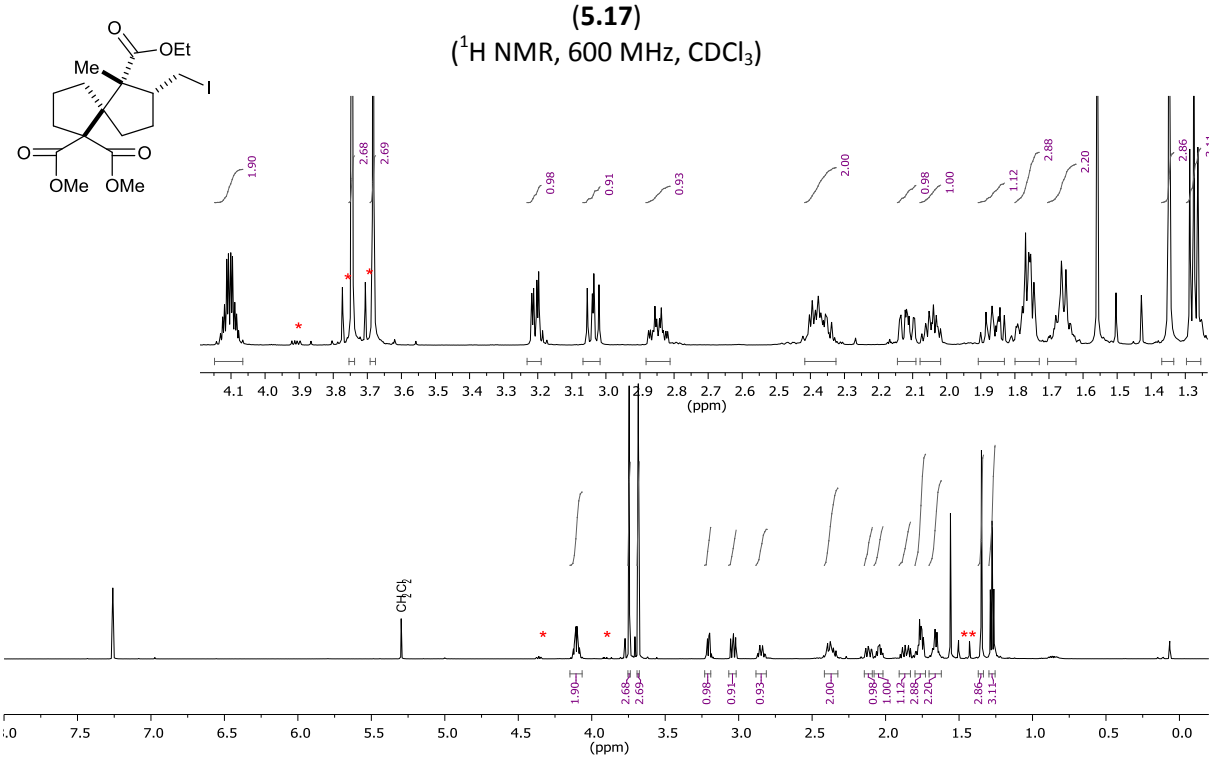

6-Ethyl 1,1-dimethyl 7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (**5.16**)
($^{13}$C NMR, 176 MHz, $CDCl_3$)



### 7.7.18 **Minor iodide 5.17**

6-Ethyl 1,1-dimethyl (5*R**,6*R**,7*R**)-7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (**5.17**)

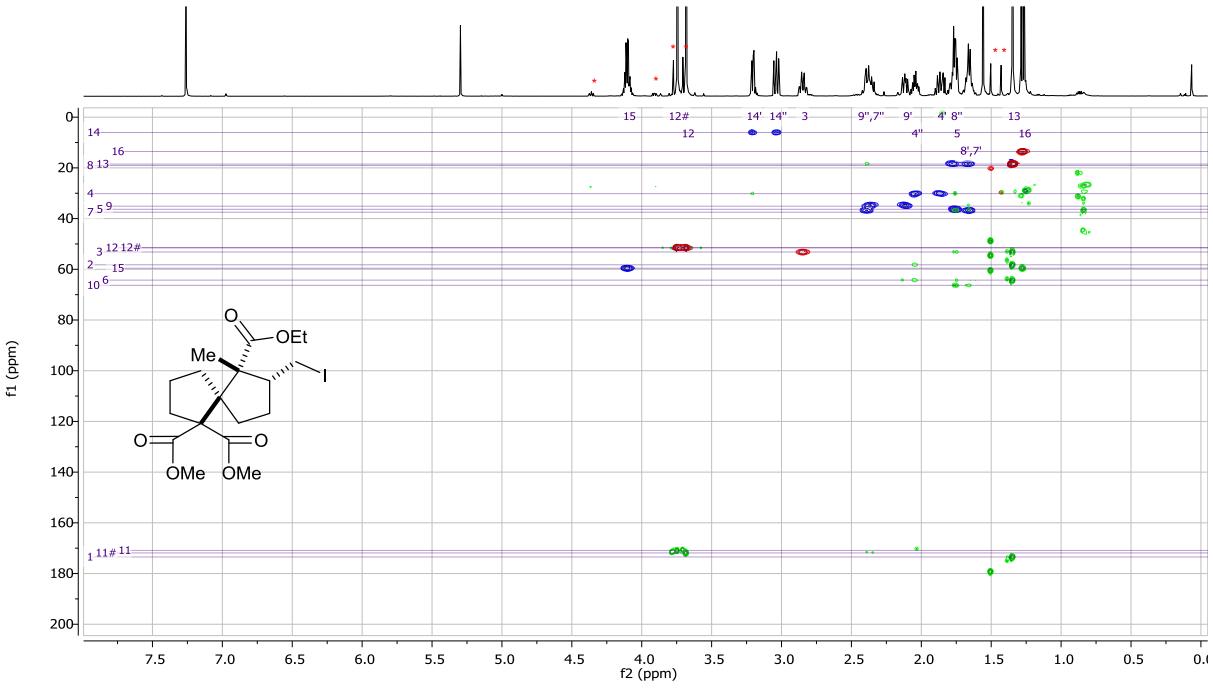
($^1$H NMR, 600 MHz, $CDCl_3$)



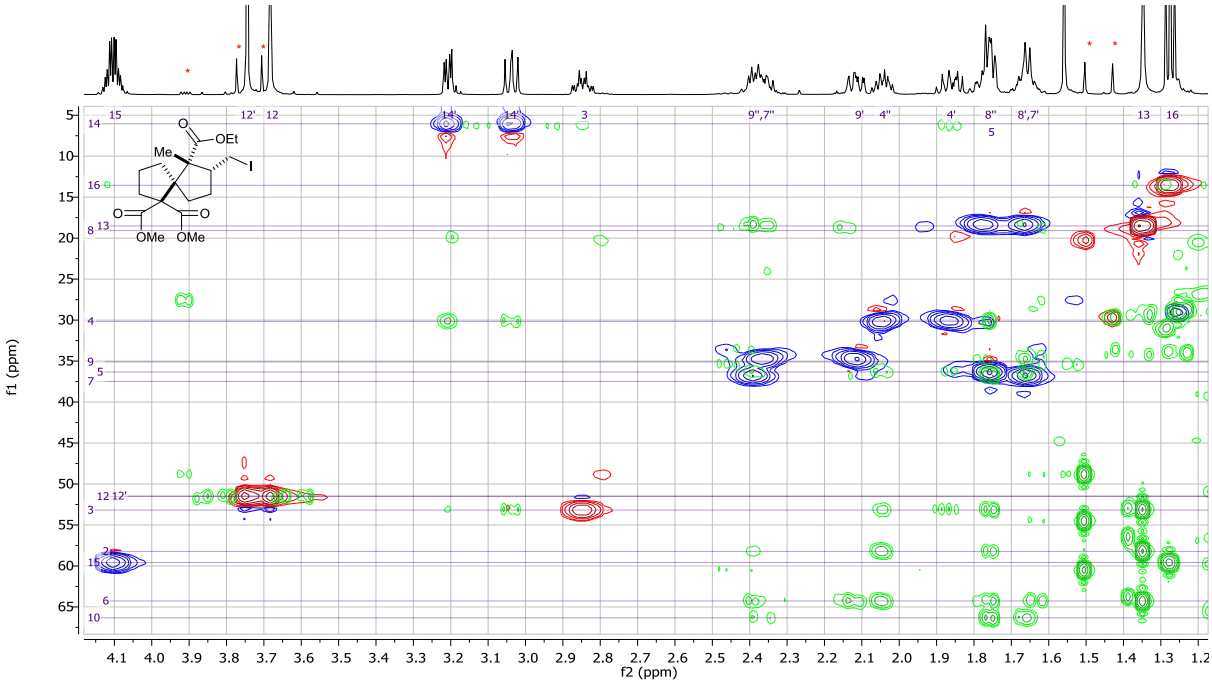

* = peaks from lactone **3.49**.

6-Ethyl 1,1-dimethyl (5*R**,6*R**,7*R**)-7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (**5.17**)

(HSQC (blue and red) and HMBC (green) spectra overlapped, 176 MHz, $CDCl_3$)



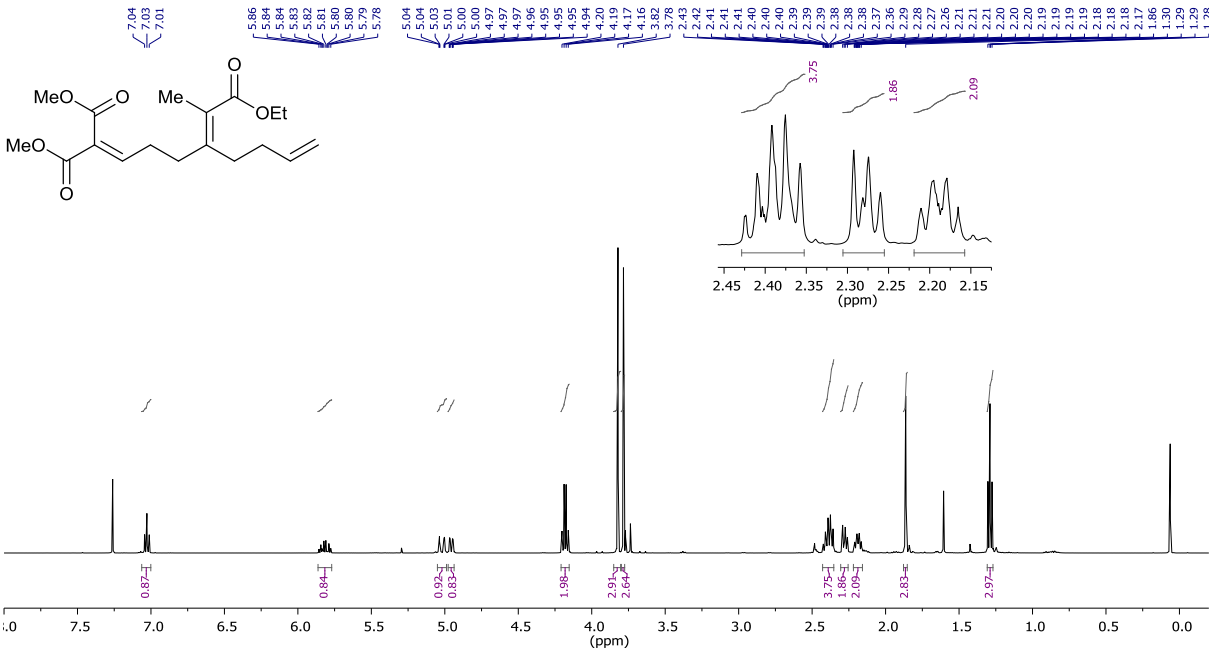

(zoom next page)



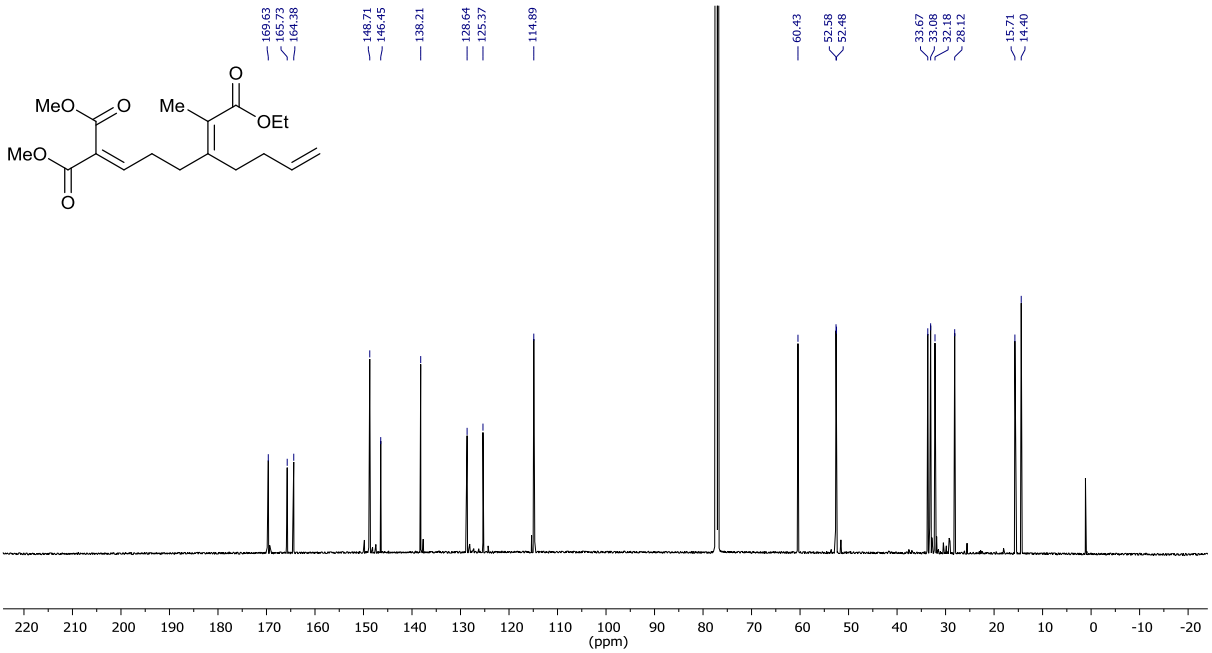

* = peaks from lactone **3.49**.

### 7.7.19 **Triene 5.33**

6-Ethyl 1,1-dimethyl (*E*)-5-(but-3-en-1-yl)hepta-1,5-diene-1,1,6-tricarboxylate (**5.33**)
($^{1}$H NMR, 500 MHz, $CDCl_3$)

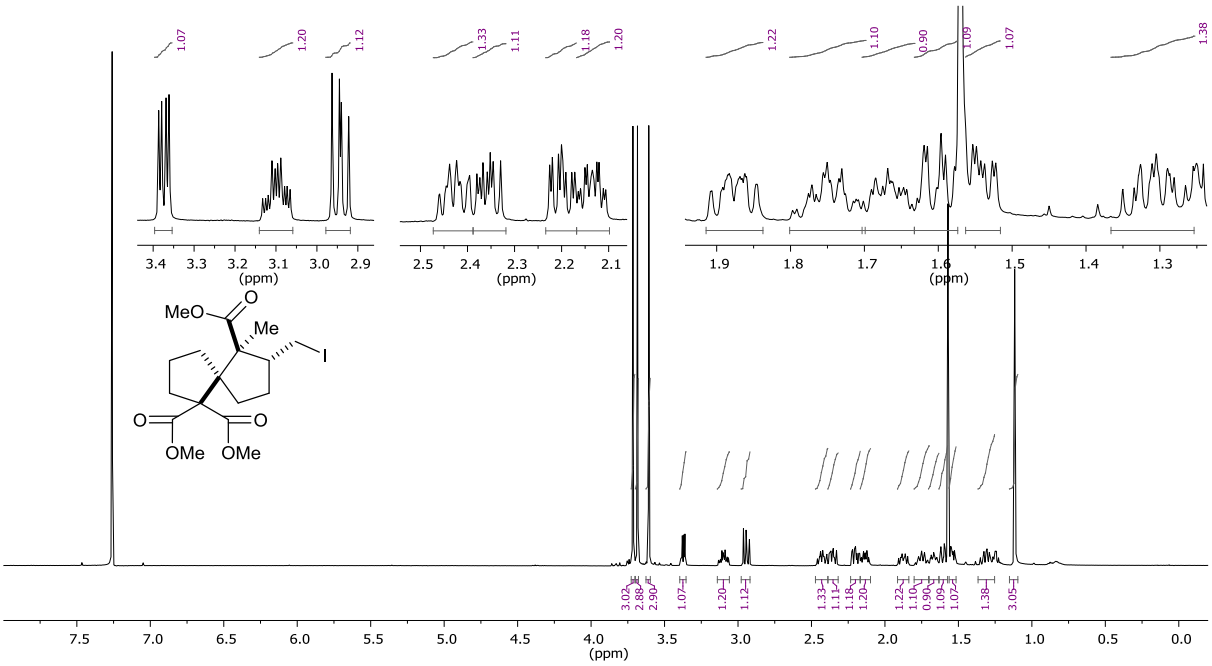



6-Ethyl 1,1-dimethyl (*E*)-5-(but-3-en-1-yl)hepta-1,5-diene-1,1,6-tricarboxylate (**5.33**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)

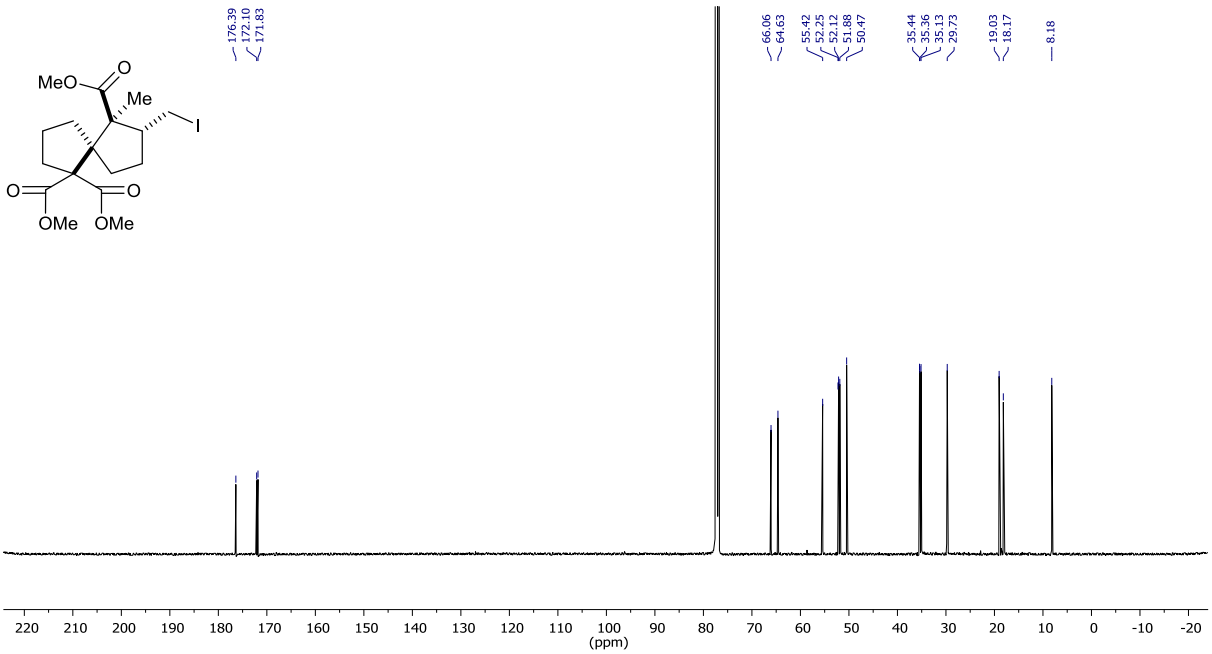


### 7.7.20 **Iodide 5.50**

Trimethyl (5*R**,6*S**,7*R**)-7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (**5.50**)
($^1$H NMR, 500 MHz, $CDCl_3$)

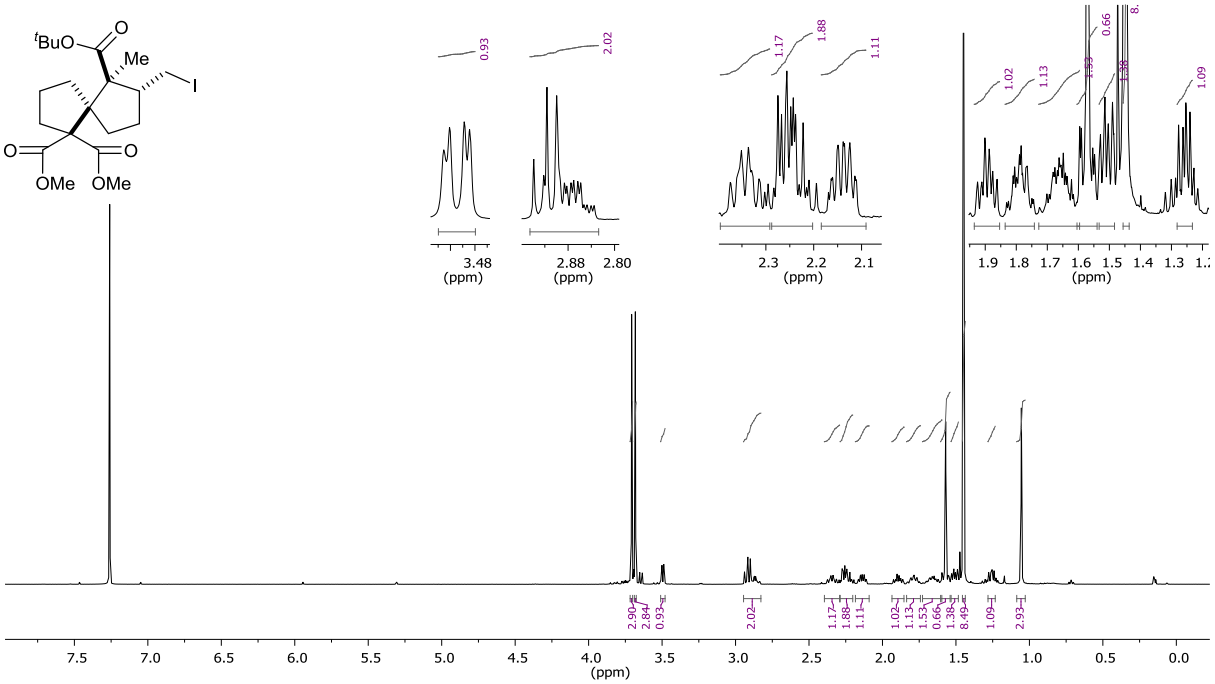



Trimethyl (5*R**,6*S**,7*R**)-7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (**5.50**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)

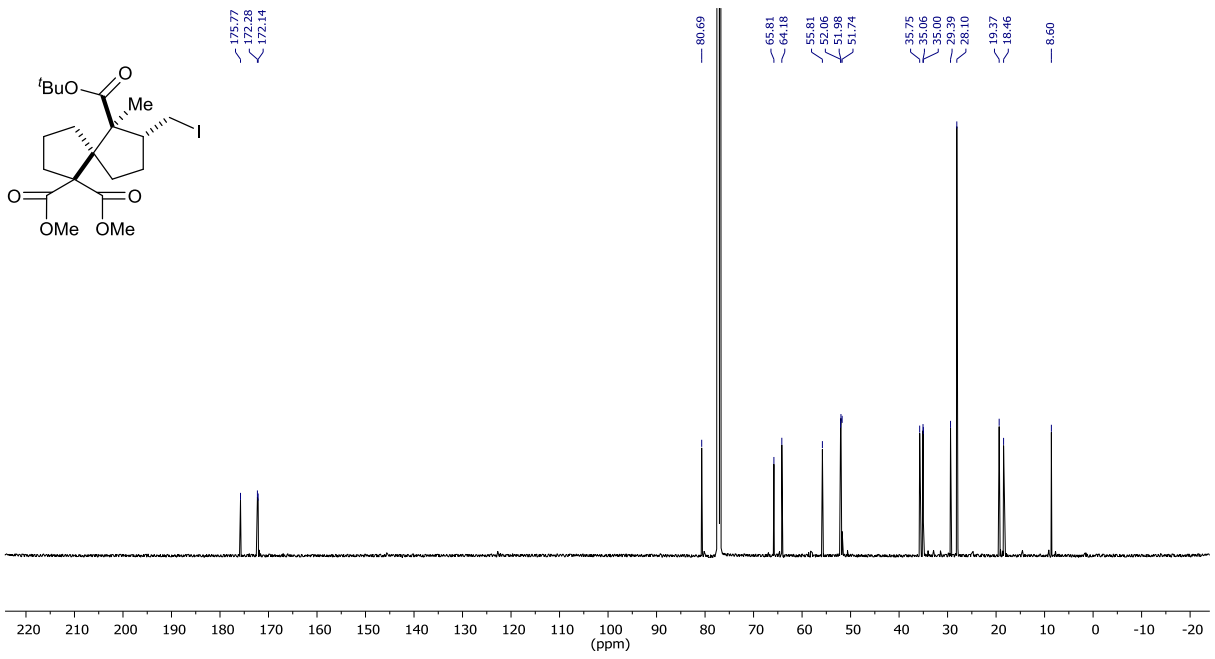


### 7.7.21 **Iodide 5.51**

6-(*Tert*-butyl) 1,1-dimethyl (5*R**,6*S**,7*R**)-7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (**5.51**)
($^{1}$H NMR, 500 MHz, $CDCl_3$)

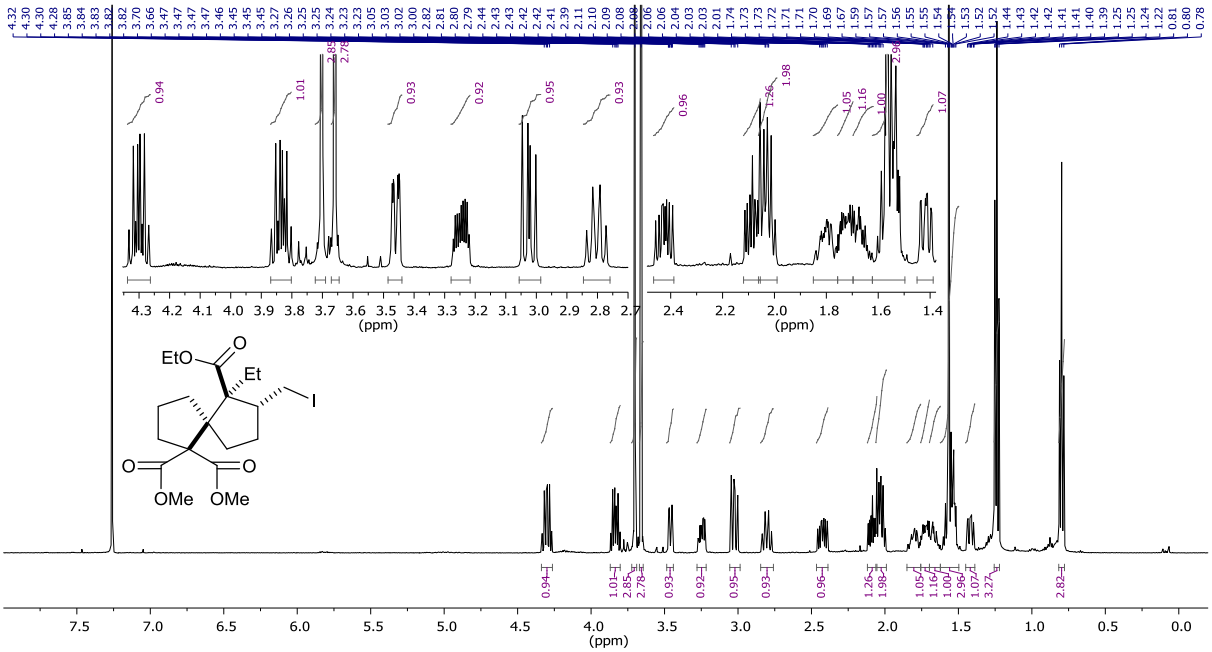



6-(*Tert*-butyl) 1,1-dimethyl (5*R**,6*S**,7*R**)-7-(iodomethyl)-6-methylspiro[4.4]nonane-1,1,6-tricarboxylate (**5.51**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)

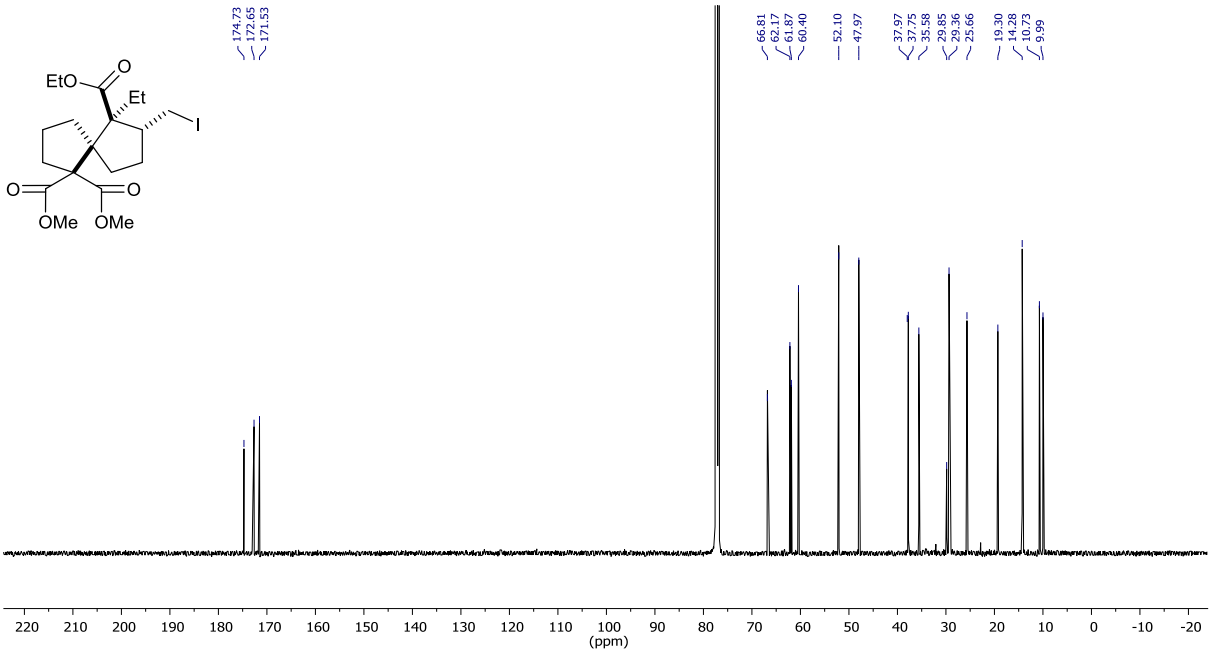


### 7.7.22 **Iodide 5.52**

6-ethyl 1,1-dimethyl (5*R**,6*S**,7*R**)-6-ethyl-7-(iodomethyl)spiro[4.4]nonane-1,1,6-tricarboxylate (**5.52**)
($^1$H NMR, 500 MHz, $CDCl_3$)

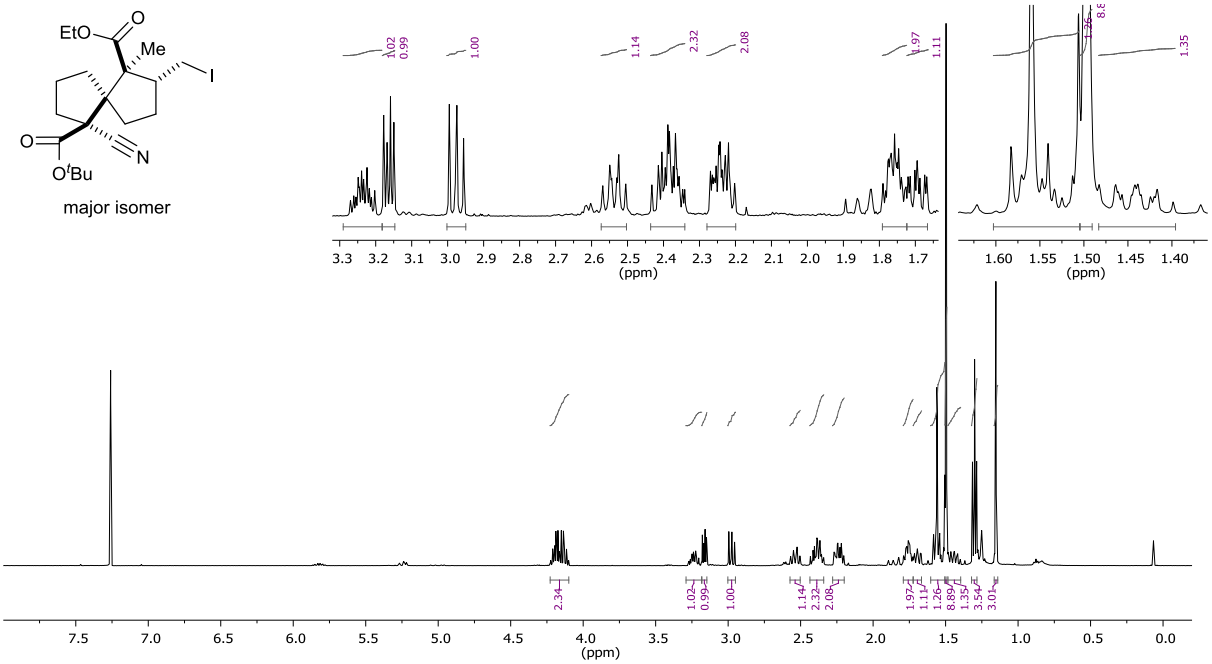



6-ethyl 1,1-dimethyl (5*R**,6*S**,7*R**)-6-ethyl-7-(iodomethyl)spiro[4.4]nonane-1,1,6-tricarboxylate (**5.52**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)

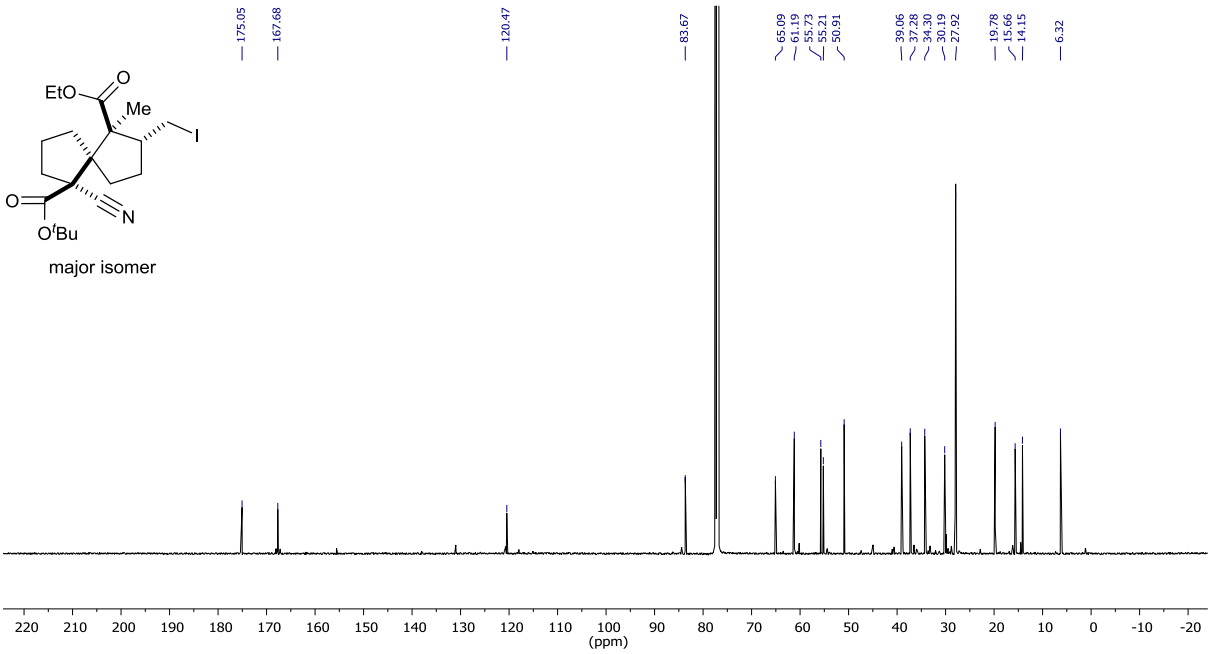


### 7.7.23 **Nitriles major- and minor-5.54**

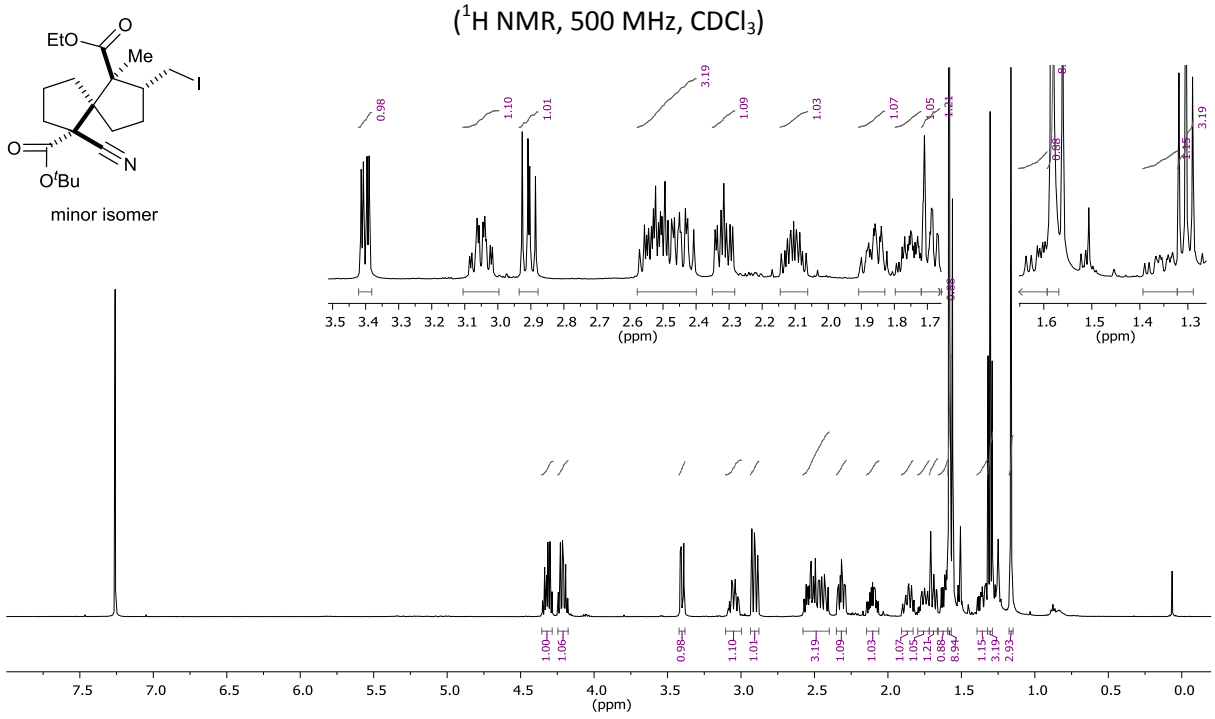
6-(*Tert*-butyl) 1-ethyl (1*S**,2*R**,5*R**,6*S**)-6-cyano-2-(iodomethyl)-1-methylspiro[4.4]nonane-1,6-dicarboxylate (**major-5.54**)
($^{1}$H NMR, 500 MHz, $CDCl_3$)



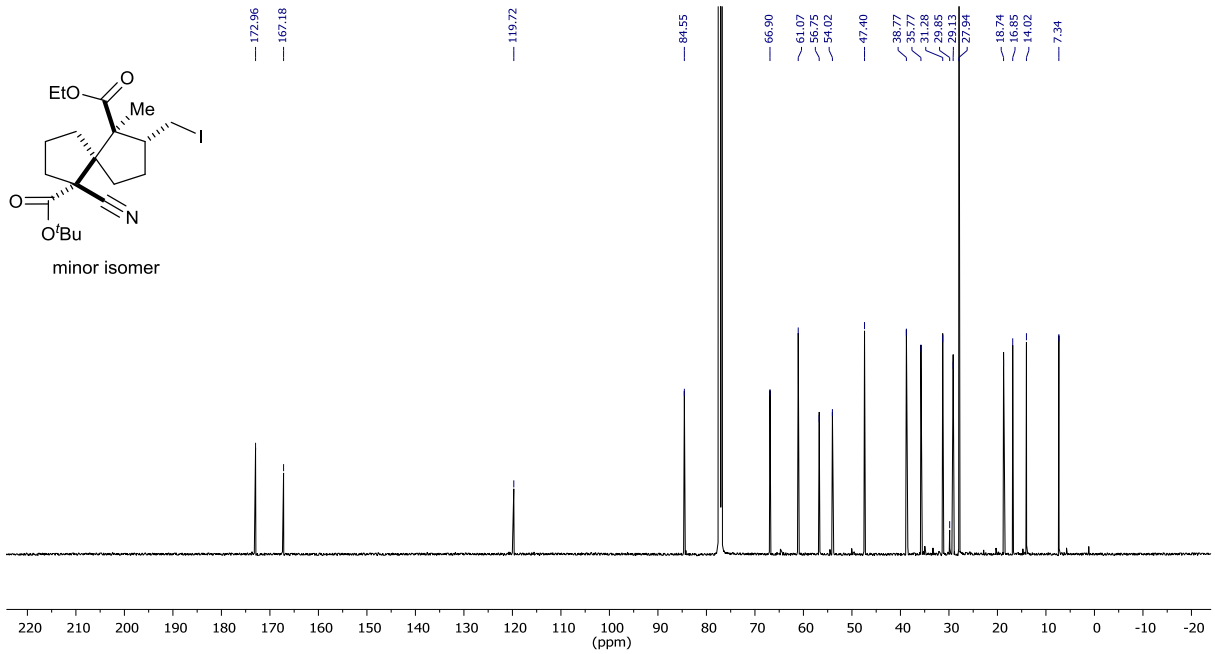

6-(*Tert*-butyl) 1-ethyl (1*S**,2*R**,5*R**,6*S**)-6-cyano-2-(iodomethyl)-1-methylspiro[4.4]nonane-1,6-dicarboxylate (**major-5.54**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)



6-(*Tert*-butyl) 1-ethyl (1*S**,2*R**,5*R**,6*S**)-6-cyano-2-(iodomethyl)-1-methylspiro[4.4]nonane-1,6-dicarboxylate (**minor-5.54**)
($^1$H NMR, 500 MHz, $CDCl_3$)




6-(*Tert*-butyl) 1-ethyl (1*S**,2*R**,5*R**,6*S**)-6-cyano-2-(iodomethyl)-1-methylspiro[4.4]nonane-1,6-dicarboxylate (**minor-5.54**)
($^{13}$C NMR, 126 MHz, $CDCl_3$)



## 7.8 Crystallographic data

### 7.8.1 X-ray data for 5.50

Table 1. Crystal data and structure refinement for 7034.

| | | |
|---|---|---|
| Identification code | 7034 | |
| Empirical formula | C17 H25 I O6 | |
| Formula weight | 452.29 | |
| Temperature | 150 K | |
| Wavelength | 1.54184 Å | |
| Crystal system | Monoclinic | |
| Space group | P 21/n | |
| Unit cell dimensions | a = 13.7816(3) Å | α= 90°. |
| | b = 8.59090(10) Å | β= 114.273(2)°. |
| | c = 16.6699(3) Å | γ = 90°. |
| Volume | 1799.18(6) Å$^3$ | |
| Z | 4 | |
| Density (calculated) | 1.670 Mg/m$^3$ | |
| Absorption coefficient | 14.244 mm$^{-1}$ | |
| F(000) | 912 | |
| Crystal size | 0.37 x 0.27 x 0.18 mm$^3$ | |
| Theta range for data collection | 3.525 to 76.667°. | |
| Index ranges | -17<=h<=16, -10<=k<=10, -15<=l<=21 | |
| Reflections collected | 16084 | |
| Independent reflections | 3769 [R(int) = 0.036] | |
| Completeness to theta = 73.811° | 100.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.07 and 0.02 | |
| Refinement method | Full-matrix least-squares on F$^2$ | |
| Data / restraints / parameters | 3768 / 0 / 217 | |
| Goodness-of-fit on F$^2$ | 1.0219 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0323, wR2 = 0.0853 | |
| R indices (all data) | R1 = 0.0327, wR2 = 0.0858 | |
| Largest diff. peak and hole | 0.81 and -1.54 e.Å$^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 7034. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 8382(2) | 384(2) | 4875(1) | 19 |
| C(2) | 7865(2) | 132(2) | 5517(1) | 17 |
| C(3) | 8737(2) | -56(2) | 6469(1) | 19 |
| C(4) | 8180(2) | 395(3) | 7068(2) | 27 |
| C(5) | 7160(2) | 1288(3) | 6496(1) | 22 |
| C(6) | 7200(2) | 1586(2) | 5588(1) | 16 |
| C(7) | 6069(2) | 1659(3) | 4845(2) | 23 |
| C(8) | 5650(2) | 3303(3) | 4856(2) | 33 |
| C(9) | 6601(2) | 4285(3) | 5431(2) | 25 |
| C(10) | 7616(2) | 3309(2) | 5579(2) | 18 |
| C(11) | 8532(2) | 3825(3) | 6442(2) | 22 |
| C(12) | 10351(2) | 3547(3) | 7374(2) | 33 |
| C(13) | 7139(2) | -1315(3) | 5259(2) | 24 |
| C(14) | 9241(2) | -1663(2) | 6652(2) | 27 |
| C(15) | 8249(2) | -71(3) | 3445(2) | 32 |
| C(21) | 7850(2) | 3726(2) | 4782(1) | 20 |
| C(22) | 8727(2) | 5527(3) | 4239(2) | 36 |
| O(31) | 8410(2) | 4607(3) | 6988(2) | 45 |
| O(32) | 9477(1) | 3290(2) | 6529(1) | 22 |
| O(33) | 9185(1) | 1116(2) | 5039(1) | 23 |
| O(34) | 7833(1) | -317(2) | 4100(1) | 26 |
| O(35) | 7418(2) | 3167(2) | 4061(1) | 26 |
| O(36) | 8517(1) | 4947(2) | 4969(1) | 26 |
| I(37) | 10503(1) | -1772(1) | 7962(1) | 31 |

Table 3. Bond lengths [Å] and angles [°] for 7034.

| | | | |
|---|---|---|---|
| C(1)-C(2) | 1.526(3) | C(13)-H(131) | 0.965 |
| C(1)-O(33) | 1.202(3) | C(13)-H(132) | 0.947 |
| C(1)-O(34) | 1.343(3) | C(13)-H(133) | 0.955 |
| C(2)-C(3) | 1.557(3) | C(14)-I(37) | 2.163(2) |
| C(2)-C(6) | 1.582(3) | C(14)-H(141) | 0.974 |
| C(2)-C(13) | 1.542(3) | C(14)-H(142) | 0.951 |
| C(3)-C(4) | 1.538(3) | C(15)-O(34) | 1.441(3) |
| C(3)-C(14) | 1.519(3) | C(15)-H(152) | 0.959 |
| C(3)-H(31) | 0.981 | C(15)-H(151) | 0.976 |
| C(4)-C(5) | 1.540(3) | C(15)-H(153) | 0.968 |
| C(4)-H(42) | 0.972 | C(21)-O(35) | 1.201(3) |
| C(4)-H(41) | 0.972 | C(21)-O(36) | 1.344(3) |
| C(5)-C(6) | 1.558(3) | C(22)-O(36) | 1.449(3) |
| C(5)-H(51) | 0.973 | C(22)-H(222) | 0.958 |
| C(5)-H(52) | 0.973 | C(22)-H(221) | 0.958 |
| C(6)-C(7) | 1.544(3) | C(22)-H(223) | 0.955 |
| C(6)-C(10) | 1.589(3) | | |
| C(7)-C(8) | 1.529(3) | C(2)-C(1)-O(33) | 124.54(19) |
| C(7)-H(71) | 0.985 | C(2)-C(1)-O(34) | 111.73(18) |
| C(7)-H(72) | 0.965 | O(33)-C(1)-O(34) | 123.73(19) |
| C(8)-C(9) | 1.523(4) | C(1)-C(2)-C(3) | 109.98(16) |
| C(8)-H(82) | 0.971 | C(1)-C(2)-C(6) | 113.08(16) |
| C(8)-H(81) | 0.964 | C(3)-C(2)-C(6) | 103.51(16) |
| C(9)-C(10) | 1.561(3) | C(1)-C(2)-C(13) | 110.84(17) |
| C(9)-H(91) | 0.973 | C(3)-C(2)-C(13) | 109.98(16) |
| C(9)-H(92) | 0.977 | C(6)-C(2)-C(13) | 109.20(16) |
| C(10)-C(11) | 1.539(3) | C(2)-C(3)-C(4) | 104.65(17) |

| | | | |
|---|---|---|---|
| C(10)-C(21) | 1.532(3) | C(2)-C(3)-C(14) | 113.37(17) |
| C(11)-O(31) | 1.198(3) | C(4)-C(3)-C(14) | 114.06(19) |
| C(11)-O(32) | 1.332(3) | C(2)-C(3)-H(31) | 106.6 |
| C(12)-O(32) | 1.445(3) | C(4)-C(3)-H(31) | 109.7 |
| C(12)-H(121) | 0.959 | C(14)-C(3)-H(31) | 108.1 |
| C(12)-H(122) | 0.986 | C(3)-C(4)-C(5) | 107.20(17) |
| C(12)-H(123) | 0.943 | C(3)-C(4)-H(42) | 110.4 |

| | | | |
|---|---|---|---|
| C(5)-C(4)-H(42) | 111.2 | C(6)-C(10)-C(11) | 114.82(18) |
| C(3)-C(4)-H(41) | 110.6 | C(9)-C(10)-C(21) | 103.36(17) |
| C(5)-C(4)-H(41) | 108.2 | C(6)-C(10)-C(21) | 115.59(17) |
| H(42)-C(4)-H(41) | 109.2 | C(11)-C(10)-C(21) | 111.03(17) |
| C(4)-C(5)-C(6) | 107.19(16) | C(10)-C(11)-O(31) | 123.7(2) |
| C(4)-C(5)-H(51) | 110.7 | C(10)-C(11)-O(32) | 113.09(18) |
| C(6)-C(5)-H(51) | 112.3 | O(31)-C(11)-O(32) | 123.2(2) |
| C(4)-C(5)-H(52) | 108.3 | O(32)-C(12)-H(121) | 110.8 |
| C(6)-C(5)-H(52) | 108.9 | O(32)-C(12)-H(122) | 109.4 |
| H(51)-C(5)-H(52) | 109.4 | H(121)-C(12)-H(122) | 110.3 |
| C(5)-C(6)-C(2) | 101.28(16) | O(32)-C(12)-H(123) | 109.5 |
| C(5)-C(6)-C(7) | 111.03(17) | H(121)-C(12)-H(123) | 108.6 |
| C(2)-C(6)-C(7) | 113.34(17) | H(122)-C(12)-H(123) | 108.3 |
| C(5)-C(6)-C(10) | 108.64(17) | C(2)-C(13)-H(131) | 109.3 |
| C(2)-C(6)-C(10) | 120.85(16) | C(2)-C(13)-H(132) | 107.0 |
| C(7)-C(6)-C(10) | 101.76(16) | H(131)-C(13)-H(132) | 109.1 |
| C(6)-C(7)-C(8) | 106.83(19) | C(2)-C(13)-H(133) | 111.5 |
| C(6)-C(7)-H(71) | 110.0 | H(131)-C(13)-H(133) | 109.5 |
| C(8)-C(7)-H(71) | 111.1 | H(132)-C(13)-H(133) | 110.4 |
| C(6)-C(7)-H(72) | 109.7 | C(3)-C(14)-I(37) | 110.71(15) |
| C(8)-C(7)-H(72) | 110.5 | C(3)-C(14)-H(141) | 111.1 |
| H(71)-C(7)-H(72) | 108.8 | I(37)-C(14)-H(141) | 107.0 |
| C(7)-C(8)-C(9) | 106.73(19) | C(3)-C(14)-H(142) | 110.6 |
| C(7)-C(8)-H(82) | 110.7 | I(37)-C(14)-H(142) | 108.0 |
| C(9)-C(8)-H(82) | 109.6 | H(141)-C(14)-H(142) | 109.3 |
| C(7)-C(8)-H(81) | 109.4 | O(34)-C(15)-H(152) | 107.7 |
| C(9)-C(8)-H(81) | 110.7 | O(34)-C(15)-H(151) | 109.3 |
| H(82)-C(8)-H(81) | 109.7 | H(152)-C(15)-H(151) | 109.8 |
| C(8)-C(9)-C(10) | 106.57(18) | O(34)-C(15)-H(153) | 109.6 |
| C(8)-C(9)-H(91) | 109.4 | H(152)-C(15)-H(153) | 110.2 |
| C(10)-C(9)-H(91) | 109.0 | H(151)-C(15)-H(153) | 110.1 |
| C(8)-C(9)-H(92) | 112.3 | C(10)-C(21)-O(35) | 125.4(2) |
| C(10)-C(9)-H(92) | 110.9 | C(10)-C(21)-O(36) | 110.50(18) |
| H(91)-C(9)-H(92) | 108.6 | O(35)-C(21)-O(36) | 123.6(2) |
| C(9)-C(10)-C(6) | 101.47(16) | O(36)-C(22)-H(222) | 107.0 |
| C(9)-C(10)-C(11) | 109.26(17) | O(36)-C(22)-H(221) | 109.5 |
| H(222)-C(22)-H(221) | 110.9 | C(12)-O(32)-C(11) | 116.1(2) |
| O(36)-C(22)-H(223) | 109.3 | C(15)-O(34)-C(1) | 114.88(19) |
| H(222)-C(22)-H(223) | 109.6 | C(22)-O(36)-C(21) | 115.3(2) |
| H(221)-C(22)-H(223) | 110.5 | | |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 7034. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 21(1) | 18(1) | 17(1) | -1(1) | 8(1) | 6(1) |
| C(2) | 20(1) | 15(1) | 16(1) | 0(1) | 8(1) | 1(1) |
| C(3) | 21(1) | 18(1) | 16(1) | 1(1) | 6(1) | 0(1) |
| C(4) | 32(1) | 34(1) | 18(1) | 4(1) | 13(1) | 4(1) |
| C(5) | 26(1) | 23(1) | 23(1) | 2(1) | 16(1) | -1(1) |
| C(6) | 17(1) | 16(1) | 18(1) | 1(1) | 9(1) | 1(1) |
| C(7) | 17(1) | 26(1) | 24(1) | 2(1) | 7(1) | 0(1) |
| C(8) | 21(1) | 30(1) | 47(2) | 5(1) | 13(1) | 6(1) |
| C(9) | 25(1) | 21(1) | 35(1) | 3(1) | 19(1) | 6(1) |
| C(10) | 21(1) | 14(1) | 22(1) | 1(1) | 13(1) | 1(1) |
| C(11) | 27(1) | 20(1) | 24(1) | -3(1) | 15(1) | -6(1) |
| C(12) | 33(1) | 36(1) | 24(1) | -5(1) | 4(1) | -9(1) |
| C(13) | 28(1) | 17(1) | 25(1) | -3(1) | 9(1) | -4(1) |
| C(14) | 32(1) | 18(1) | 21(1) | 2(1) | 2(1) | 4(1) |
| C(15) | 33(1) | 48(1) | 19(1) | -4(1) | 14(1) | 5(1) |
| C(21) | 20(1) | 18(1) | 24(1) | 5(1) | 12(1) | 5(1) |
| C(22) | 31(1) | 44(1) | 35(1) | 19(1) | 17(1) | -1(1) |
| O(31) | 38(1) | 60(1) | 46(1) | -35(1) | 26(1) | -15(1) |
| O(32) | 24(1) | 21(1) | 19(1) | -2(1) | 5(1) | 0(1) |
| O(33) | 22(1) | 28(1) | 22(1) | -1(1) | 12(1) | 1(1) |
| O(34) | 29(1) | 32(1) | 18(1) | -6(1) | 11(1) | -1(1) |
| O(35) | 31(1) | 28(1) | 20(1) | 3(1) | 12(1) | 3(1) |
| O(36) | 25(1) | 26(1) | 27(1) | 8(1) | 13(1) | -4(1) |
| I(37) | 31(1) | 32(1) | 24(1) | 8(1) | 4(1) | 4(1) |

Table 5. Hydrogen coordinates ( $x\ 10^4$) and isotropic displacement parameters ($Å^2 x\ 10^{-3}$) for 7034.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(31) | 9295 | 706 | 6535 | 21 |
| H(42) | 8648 | 1032 | 7556 | 33 |
| H(41) | 7977 | -529 | 7298 | 32 |
| H(51) | 7105 | 2250 | 6783 | 27 |
| H(52) | 6551 | 629 | 6408 | 26 |
| H(71) | 5611 | 873 | 4946 | 27 |
| H(72) | 6099 | 1450 | 4287 | 27 |
| H(82) | 5123 | 3299 | 5103 | 41 |
| H(81) | 5336 | 3705 | 4263 | 41 |
| H(91) | 6572 | 4469 | 5996 | 31 |
| H(92) | 6620 | 5290 | 5163 | 31 |
| H(121) | 10999 | 3124 | 7382 | 50 |
| H(122) | 10431 | 4672 | 7498 | 50 |
| H(123) | 10203 | 3057 | 7817 | 50 |
| H(131) | 6861 | -1493 | 5697 | 36 |
| H(132) | 7569 | -2172 | 5255 | 35 |
| H(133) | 6563 | -1193 | 4695 | 36 |
| H(141) | 9557 | -1914 | 6242 | 33 |
| H(142) | 8727 | -2433 | 6611 | 33 |
| H(152) | 7815 | -652 | 2931 | 49 |
| H(151) | 8982 | -444 | 3670 | 49 |
| H(153) | 8222 | 1027 | 3306 | 49 |
| H(222) | 9241 | 6345 | 4465 | 53 |
| H(221) | 8997 | 4698 | 4004 | 53 |
| H(223) | 8085 | 5935 | 3798 | 53 |

Table 6. Hydrogen bonds for 7034 [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| C(3)-H(31)...O(32) | 0.98 | 2.23 | 3.037(4) | 138 |

Symmetry transformations used to generate equivalent atoms:

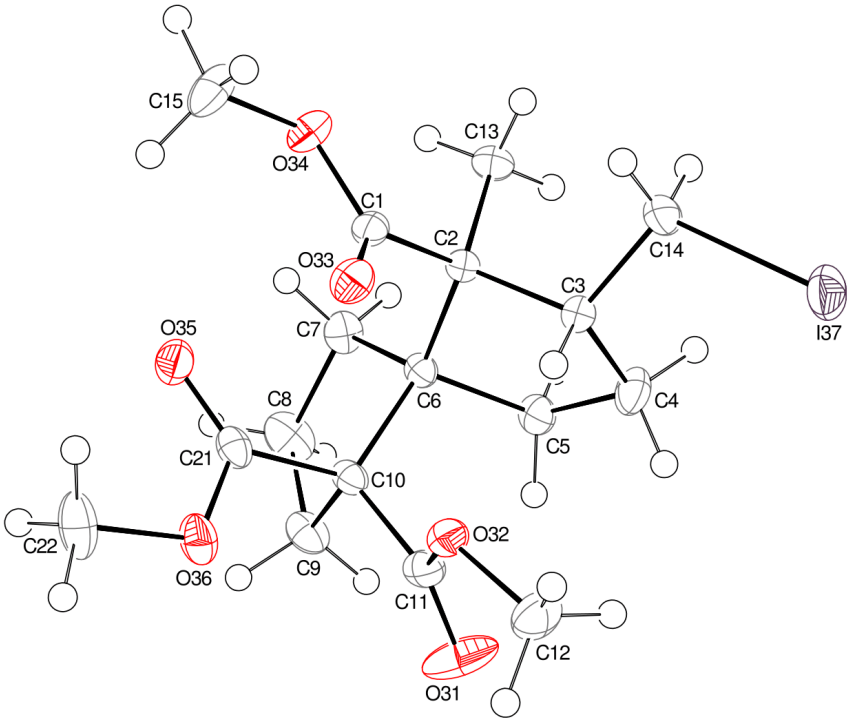


Table 1. Crystal data and structure refinement for 7035.

| | | |
|---|---|---|
| Identification code | 7035 | |
| Empirical formula | C20 H30 I N O4 | |
| Formula weight | 475.37 | |
| Temperature | 150 K | |
| Wavelength | 1.54184 Å | |
| Crystal system | Monoclinic | |
| Space group | P 21/c | |
| Unit cell dimensions | a = 8.0712(2) Å | α= 90°. |
| | b = 29.0078(5) Å | β= 104.878(2)°. |
| | c = 9.0523(2) Å | γ = 90°. |
| Volume | 2048.34(8) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.541 $Mg/m^3$ | |
| Absorption coefficient | 12.480 $mm^{-1}$ | |
| F(000) | 968 | |
| Crystal size | 0.33 x 0.16 x 0.15 $mm^3$ | |
| Theta range for data collection | 3.047 to 76.617°. | |
| Index ranges | -10<=h<=9, -36<=k<=32, -7<=l<=11 | |
| Reflections collected | 9209 | |
| Independent reflections | 4243 [R(int) = 0.033] | |
| Completeness to theta = 73.099° | 100.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.16 and 0.07 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3714 / 0 / 235 | |
| Goodness-of-fit on $F^2$ | 0.9991 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0296, wR2 = 0.0753 | |
| R indices (all data) | R1 = 0.0314, wR2 = 0.0772 | |
| Largest diff. peak and hole | 0.68 and -0.65 e.$Å^{-3}$ | |

Table 2. Atomic coordinates ( x $10^4$) and equivalent isotropic displacement parameters ($Å^2$x $10^3$) for 7035. U(eq) is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| C(1) | 7692(3) | 3194(1) | 5776(3) | 17 |
| C(2) | 9104(3) | 3492(1) | 5425(3) | 15 |
| C(3) | 9132(3) | 3504(1) | 3711(3) | 16 |
| C(4) | 10261(3) | 3927(1) | 3608(3) | 21 |
| C(5) | 10234(3) | 4242(1) | 4990(3) | 19 |
| C(6) | 8950(3) | 4020(1) | 5800(3) | 16 |
| C(7) | 9384(3) | 4134(1) | 7511(3) | 20 |
| C(8) | 8960(3) | 4645(1) | 7580(3) | 24 |
| C(9) | 7417(3) | 4729(1) | 6206(3) | 22 |
| C(10) | 7142(3) | 4274(1) | 5234(3) | 16 |
| C(11) | 6569(3) | 4398(1) | 3508(3) | 18 |
| C(13) | 10803(3) | 3301(1) | 6430(3) | 20 |
| C(14) | 9747(3) | 3058(1) | 3136(3) | 19 |
| C(15) | 4855(4) | 4115(1) | 1017(3) | 24 |
| C(16) | 6249(4) | 4203(1) | 199(3) | 30 |
| C(17) | 5732(3) | 4020(1) | 5632(3) | 20 |
| C(18) | 5195(3) | 2754(1) | 4865(3) | 23 |
| C(19) | 4269(3) | 2516(1) | 3423(3) | 27 |
| N(20) | 4613(3) | 3856(1) | 6005(3) | 29 |
| C(21) | 3519(4) | 4494(1) | 753(3) | 31 |
| C(22) | 4055(4) | 3642(1) | 603(3) | 34 |
| O(31) | 7666(3) | 3097(1) | 7072(2) | 24 |
| O(32) | 6539(2) | 3043(1) | 4540(2) | 19 |
| O(33) | 6970(3) | 4754(1) | 3009(2) | 28 |
| O(34) | 5595(2) | 4070(1) | 2702(2) | 19 |
| I(35) | 9343(1) | 3072(1) | 695(1) | 22 |

Table 3. Bond lengths [Å] and angles [°] for 7035.

| | | | |
|---|---|---|---|
| C(1)-C(2) | 1.527(3) | C(14)-H(141) | 0.969 |
| C(1)-O(31) | 1.211(3) | C(14)-H(142) | 0.954 |
| C(1)-O(32) | 1.334(3) | C(15)-C(16) | 1.519(4) |
| C(2)-C(3) | 1.558(3) | C(15)-C(21) | 1.515(4) |
| C(2)-C(6) | 1.581(3) | C(15)-C(22) | 1.521(4) |
| C(2)-C(13) | 1.542(3) | C(15)-O(34) | 1.495(3) |
| C(3)-C(4) | 1.546(3) | C(16)-H(163) | 0.966 |
| C(3)-C(14) | 1.524(3) | C(16)-H(162) | 0.958 |
| C(3)-H(31) | 0.979 | C(16)-H(161) | 0.955 |
| C(4)-C(5) | 1.555(3) | C(17)-N(20) | 1.145(4) |
| C(4)-H(42) | 0.966 | C(18)-C(19) | 1.497(3) |
| C(4)-H(41) | 0.974 | C(18)-O(32) | 1.459(3) |
| C(5)-C(6) | 1.554(3) | C(18)-H(182) | 0.956 |
| C(5)-H(51) | 0.964 | C(18)-H(181) | 0.955 |
| C(5)-H(52) | 0.966 | C(19)-H(191) | 0.942 |
| C(6)-C(7) | 1.533(3) | C(19)-H(192) | 0.946 |
| C(6)-C(10) | 1.596(3) | C(19)-H(193) | 0.945 |
| C(7)-C(8) | 1.526(3) | C(21)-H(212) | 0.949 |
| C(7)-H(72) | 0.971 | C(21)-H(211) | 0.949 |
| C(7)-H(71) | 0.966 | C(21)-H(213) | 0.957 |
| C(8)-C(9) | 1.537(3) | C(22)-H(222) | 0.968 |
| C(8)-H(81) | 0.968 | C(22)-H(221) | 0.948 |
| C(8)-H(82) | 0.970 | C(22)-H(223) | 0.964 |
| C(9)-C(10) | 1.572(3) | | |
| C(9)-H(92) | 0.960 | C(2)-C(1)-O(31) | 122.2(2) |
| C(9)-H(91) | 0.967 | C(2)-C(1)-O(32) | 114.1(2) |
| C(10)-C(11) | 1.554(3) | O(31)-C(1)-O(32) | 123.6(2) |
| C(10)-C(17) | 1.476(3) | C(1)-C(2)-C(3) | 114.99(19) |
| C(11)-O(33) | 1.205(3) | C(1)-C(2)-C(6) | 113.52(19) |
| C(11)-O(34) | 1.328(3) | C(3)-C(2)-C(6) | 102.40(18) |
| C(13)-H(133) | 0.961 | C(1)-C(2)-C(13) | 105.8(2) |
| C(13)-H(132) | 0.956 | C(3)-C(2)-C(13) | 110.95(19) |
| C(13)-H(131) | 0.958 | C(6)-C(2)-C(13) | 109.23(19) |
| C(14)-I(35) | 2.150(3) | C(2)-C(3)-C(4) | 103.72(19) |
| C(2)-C(3)-C(14) | 114.27(19) | C(8)-C(9)-H(92) | 110.3 |
| C(4)-C(3)-C(14) | 113.8(2) | C(10)-C(9)-H(92) | 109.9 |
| C(2)-C(3)-H(31) | 107.8 | C(8)-C(9)-H(91) | 112.5 |
| C(4)-C(3)-H(31) | 109.7 | C(10)-C(9)-H(91) | 108.9 |
| C(14)-C(3)-H(31) | 107.4 | H(92)-C(9)-H(91) | 108.5 |
| C(3)-C(4)-C(5) | 106.71(19) | C(9)-C(10)-C(6) | 102.82(18) |
| C(3)-C(4)-H(42) | 110.1 | C(9)-C(10)-C(11) | 109.25(19) |
| C(5)-C(4)-H(42) | 107.6 | C(6)-C(10)-C(11) | 116.22(19) |
| C(3)-C(4)-H(41) | 111.7 | C(9)-C(10)-C(17) | 106.82(19) |
| C(5)-C(4)-H(41) | 110.3 | C(6)-C(10)-C(17) | 113.0(2) |
| H(42)-C(4)-H(41) | 110.4 | C(11)-C(10)-C(17) | 108.17(19) |
| C(4)-C(5)-C(6) | 106.58(19) | C(10)-C(11)-O(33) | 122.5(2) |
| C(4)-C(5)-H(51) | 108.8 | C(10)-C(11)-O(34) | 111.5(2) |
| C(6)-C(5)-H(51) | 109.2 | O(33)-C(11)-O(34) | 125.9(2) |
| C(4)-C(5)-H(52) | 112.9 | C(2)-C(13)-H(133) | 110.6 |
| C(6)-C(5)-H(52) | 110.7 | C(2)-C(13)-H(132) | 110.4 |
| H(51)-C(5)-H(52) | 108.6 | H(133)-C(13)-H(132) | 107.7 |
| C(5)-C(6)-C(2) | 101.58(18) | C(2)-C(13)-H(131) | 110.1 |
| C(5)-C(6)-C(7) | 112.34(19) | H(133)-C(13)-H(131) | 109.4 |
| C(2)-C(6)-C(7) | 114.5(2) | H(132)-C(13)-H(131) | 108.6 |
| C(5)-C(6)-C(10) | 108.89(19) | C(3)-C(14)-I(35) | 111.02(16) |
| C(2)-C(6)-C(10) | 119.55(19) | C(3)-C(14)-H(141) | 111.2 |
| C(7)-C(6)-C(10) | 100.26(18) | I(35)-C(14)-H(141) | 108.0 |
| C(6)-C(7)-C(8) | 104.8(2) | C(3)-C(14)-H(142) | 109.2 |
| C(6)-C(7)-H(72) | 111.0 | I(35)-C(14)-H(142) | 106.5 |
| C(8)-C(7)-H(72) | 111.3 | H(141)-C(14)-H(142) | 110.7 |
| C(6)-C(7)-H(71) | 110.2 | C(16)-C(15)-C(21) | 112.8(2) |
| C(8)-C(7)-H(71) | 109.9 | C(16)-C(15)-C(22) | 110.6(2) |

| | | | |
|---|---|---|---|
| H(72)-C(7)-H(71) | 109.5 | C(21)-C(15)-C(22) | 112.1(2) |
| C(7)-C(8)-C(9) | 105.4(2) | C(16)-C(15)-O(34) | 111.1(2) |
| C(7)-C(8)-H(81) | 110.9 | C(21)-C(15)-O(34) | 107.8(2) |
| C(9)-C(8)-H(81) | 108.6 | C(22)-C(15)-O(34) | 101.8(2) |
| C(7)-C(8)-H(82) | 112.4 | C(15)-C(16)-H(163) | 110.5 |
| C(9)-C(8)-H(82) | 111.3 | C(15)-C(16)-H(162) | 110.7 |
| H(81)-C(8)-H(82) | 108.1 | H(163)-C(16)-H(162) | 108.6 |
| C(8)-C(9)-C(10) | 106.7(2) | C(15)-C(16)-H(161) | 108.3 |
| H(163)-C(16)-H(161) | 108.5 | C(15)-C(21)-H(212) | 109.8 |
| H(162)-C(16)-H(161) | 110.2 | C(15)-C(21)-H(211) | 110.7 |
| C(10)-C(17)-N(20) | 174.2(3) | H(212)-C(21)-H(211) | 111.5 |
| C(19)-C(18)-O(32) | 108.6(2) | C(15)-C(21)-H(213) | 108.5 |
| C(19)-C(18)-H(182) | 109.5 | H(212)-C(21)-H(213) | 108.3 |
| O(32)-C(18)-H(182) | 109.7 | H(211)-C(21)-H(213) | 108.0 |
| C(19)-C(18)-H(181) | 109.9 | C(15)-C(22)-H(222) | 112.3 |
| O(32)-C(18)-H(181) | 108.8 | C(15)-C(22)-H(221) | 109.8 |
| H(182)-C(18)-H(181) | 110.3 | H(222)-C(22)-H(221) | 107.3 |
| C(18)-C(19)-H(191) | 109.4 | C(15)-C(22)-H(223) | 111.4 |
| C(18)-C(19)-H(192) | 110.1 | H(222)-C(22)-H(223) | 107.8 |
| H(191)-C(19)-H(192) | 110.9 | H(221)-C(22)-H(223) | 108.1 |
| C(18)-C(19)-H(193) | 108.5 | C(18)-O(32)-C(1) | 114.5(2) |
| H(191)-C(19)-H(193) | 108.9 | C(15)-O(34)-C(11) | 121.5(2) |
| H(192)-C(19)-H(193) | 109.1 | | |

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 7035. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

| | $U^{11}$ | $U^{22}$ | $U^{33}$ | $U^{23}$ | $U^{13}$ | $U^{12}$ |
|---|---|---|---|---|---|---|
| C(1) | 20(1) | 17(1) | 13(1) | 1(1) | 6(1) | 1(1) |
| C(2) | 17(1) | 18(1) | 9(1) | 0(1) | 3(1) | 0(1) |
| C(3) | 20(1) | 18(1) | 9(1) | 1(1) | 5(1) | 0(1) |
| C(4) | 24(1) | 22(1) | 20(1) | -1(1) | 11(1) | -4(1) |
| C(5) | 18(1) | 21(1) | 19(1) | 0(1) | 6(1) | -4(1) |
| C(6) | 16(1) | 19(1) | 12(1) | -2(1) | 3(1) | -1(1) |
| C(7) | 21(1) | 25(1) | 11(1) | -3(1) | 0(1) | -3(1) |
| C(8) | 28(1) | 25(1) | 18(1) | -6(1) | 2(1) | -2(1) |
| C(9) | 25(1) | 21(1) | 19(1) | -5(1) | 5(1) | 0(1) |
| C(10) | 18(1) | 18(1) | 13(1) | 0(1) | 5(1) | -1(1) |
| C(11) | 17(1) | 20(1) | 16(1) | 0(1) | 2(1) | 1(1) |
| C(13) | 19(1) | 22(1) | 15(1) | 2(1) | 1(1) | 0(1) |
| C(14) | 26(1) | 21(1) | 13(1) | 2(1) | 7(1) | 3(1) |
| C(15) | 29(1) | 23(1) | 14(1) | 1(1) | -3(1) | 5(1) |
| C(16) | 41(2) | 33(2) | 15(1) | 2(1) | 10(1) | 6(1) |
| C(17) | 19(1) | 23(1) | 17(1) | -2(1) | 4(1) | 1(1) |
| C(18) | 23(1) | 27(1) | 21(1) | -3(1) | 10(1) | -7(1) |
| C(19) | 27(1) | 30(1) | 24(1) | -5(1) | 5(1) | -10(1) |
| N(20) | 22(1) | 36(1) | 30(1) | 1(1) | 11(1) | -2(1) |
| C(21) | 29(1) | 34(2) | 25(1) | 1(1) | -4(1) | 10(1) |
| C(22) | 44(2) | 26(2) | 26(2) | -5(1) | -3(1) | -2(1) |
| O(31) | 29(1) | 30(1) | 16(1) | 1(1) | 8(1) | -7(1) |
| O(32) | 20(1) | 24(1) | 15(1) | -1(1) | 5(1) | -6(1) |
| O(33) | 36(1) | 24(1) | 21(1) | 6(1) | 2(1) | -6(1) |
| O(34) | 23(1) | 20(1) | 14(1) | 1(1) | 2(1) | -1(1) |
| I(35) | 33(1) | 21(1) | 14(1) | -1(1) | 10(1) | 1(1) |

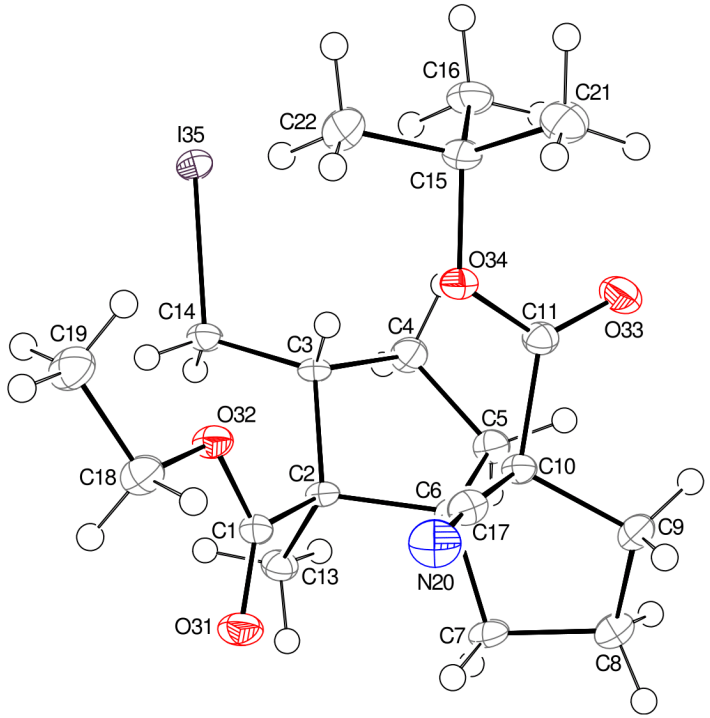
Table 5. Hydrogen coordinates ( x $10^4$) and isotropic displacement parameters ($Å^2$x $10^3$) for 7035.

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(31) | 7958 | 3559 | 3102 | 18 |
| H(42) | 11433 | 3831 | 3718 | 25 |
| H(41) | 9834 | 4094 | 2653 | 24 |
| H(51) | 11362 | 4244 | 5684 | 24 |
| H(52) | 9908 | 4555 | 4694 | 23 |
| H(72) | 10584 | 4074 | 7993 | 25 |
| H(71) | 8678 | 3953 | 8009 | 24 |
| H(81) | 9904 | 4834 | 7464 | 29 |
| H(82) | 8699 | 4728 | 8532 | 29 |
| H(92) | 7651 | 4981 | 5600 | 26 |
| H(91) | 6379 | 4798 | 6510 | 26 |
| H(133) | 11753 | 3486 | 6324 | 29 |
| H(132) | 10792 | 3305 | 7484 | 29 |
| H(131) | 10967 | 2989 | 6145 | 29 |
| H(141) | 10958 | 3009 | 3590 | 23 |
| H(142) | 9088 | 2806 | 3356 | 23 |
| H(163) | 7127 | 3969 | 461 | 44 |
| H(162) | 6770 | 4498 | 474 | 44 |
| H(161) | 5743 | 4190 | -876 | 44 |
| H(182) | 4407 | 2942 | 5227 | 27 |
| H(181) | 5712 | 2531 | 5621 | 27 |
| H(191) | 3400 | 2327 | 3620 | 41 |
| H(192) | 3806 | 2735 | 2656 | 41 |
| H(193) | 5061 | 2328 | 3091 | 41 |
| H(212) | 2636 | 4415 | 1225 | 47 |
| H(211) | 4030 | 4781 | 1117 | 47 |
| H(213) | 3024 | 4522 | -323 | 47 |
| H(222) | 3175 | 3575 | 1123 | 51 |
| H(221) | 3536 | 3628 | -462 | 50 |
| H(223) | 4905 | 3401 | 854 | 51 |

Table 6. Hydrogen bonds for 7035 [Å and °].

| D-H...A | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---|---|---|---|---|
| C(3)-H(31)...O(34) | 0.98 | 2.37 | 3.216(4) | 144 |
| C(5)-H(52)...O(33) | 0.97 | 2.54 | 3.153(4) | 122 |

Symmetry transformations used to generate equivalent atoms:



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