Synthesis of Oxygen Containing Functionalities: Use of the Acyloin and Metathesis Reactions in Organic Chemistry

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by

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Oriel College and the Chemistry Research Laboratory (CRL), Hilary 2012

For My Parents and Maziar

Declaration

The work described in this thesis is entirely my own, except where I have either acknowledged help from a named person or given reference to a published source or a thesis. Text taken from another source will be enclosed in quotation marks and a reference given.

Ali Jahanshahi Esfahani
Oxford, Hilary 2012

Abstract

Synthesis of Oxygen Containing Functionalities: Use of the Acyloin and Metathesis Reactions in Organic Chemistry

Ali Jahanshahi Esfahani Oriel College D-Phil degree Hilary Term 2012

1. In the first part of this thesis, the concept of a tether based intramolecular crossed-acyloin reaction mediated by heterogeneous lithium/ 4,4′-di-*tert*-butylbiphenyl (Li/DBB) reducing conditions was examined. The objective of the project was to accomplish an intramolecular crossed-acyloin reaction, by employing non-symmetric di-esters, linked with a suitable tether (diol) between the two acyl functionalities.

Chapter 1: Introduction – Acyloin Condensation

The concept of carbon-carbon coupling reactions between two carbonyl functionalities to synthesise *α*-hydroxyketone (acyloin) moieties is described. Generally, there are two methods, either by bimolecular reductive coupling of esters, known as acyloin condensation or the *umpolung* dimerisation of aldehydes, known as benzoin condensation. The background and recent developments in these reaction categories are discussed in this section. In addition, this section outlines the project's aims and describes the previous work conducted in the group.

Chapter 2: Results & Discussion – An Alternative Route to Crossed-acyloin

In this section, the tether based intramolecular crossed-acyloin reaction mediated by Li/DBB reducing conditions is introduced. This work is based on the hypothesis that a suitable tether, could promote an intramolecular crossed-acyloin reaction. The objective was successfully achieved through a series of competition experiments, which demonstrated that the application of *exo-exo* norbornenediol as a tether exclusively formed crossed-acyloin products. This discovery was accompanied by an investigation into regioselective crossed-acyloin reaction.

2. In the second part of this thesis, the Sharpless Asymmetric Epoxidation (SAE) desymmetrisation reaction of *σ*-symmetric diene 1,3-diols was examined. It was suggested that formation of the epoxide would trigger a stereoselective 5-*exo*-tet ring closure to deliver predominately *trans*-THF adducts.

Chapter 3: Introduction – Metal Mediated Synthetic Routes to *trans*-2,5-Disubstituted THFs

This section introduces the transition metal mediated cyclisation of bishomoallylic alcohol, to the corresponding *trans*-THF moieties. In particular, the development and application of three methods were highlighted; rhenium mediated (3+2) oxidative cyclisation, cobalt catalysed oxidative cyclisation and an π-allylpalladium complex catalysed reaction. In addition, the concept of the Sharpless Asymmetric Epoxidation (SAE) is introduced and the project objectives are outlined.

Chapter 4: Results & Discussion – A Novel Route Towards *trans*-THFs

The primary effort was to design a robust route to form the test substrate, *(3R,5S)*-hepta-1,6-diene-3,5-diol, which was accomplished in good yield by Ring Opening/Crossed metathesis (ROM) of silyl ether protected *(1R,3S)*-cyclopent-4-ene-1,3-diol. The experimental results have demonstrated that SAE of the diene 1,3 diol formed *trans*-THF.

Chapter 5: Experimental

Full experimental procedures and characterisation of the synthesised molecules are reported.

Acknowledgements

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Abbreviations

Å	Ångström	**Ac**	Acetyl
Ar	Aromatic group	**aq**	Aqueous
Bn	Benzyl	**Bu**	Butyl
***n*-BuLi**	Butyllithium	**C**	Celsius
cm^{-1}	Wavenumbers	**conc.**	Concentrated
COSY	Correlation spectroscopy	**DBB**	4,4'-Di-tert-butylbiphenyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	**DCC**	Dicyclohexylcarbodiimide
DET	Diethyl tartrate	**DIPT**	Diisopropyl tartrate
DMAP	4-(Dimethylamino)pyridine	**DMF**	*N,N*-dimethylformamide
DMT	Dimethyl tartrate	**DPPBA**	(1*R*,2*R*)-(+)-1,2-Diaminocyclohexane-*N,N*-bis(2-diphenylphosphinobenzoyl)
e.e.	Enantiomeric excess	**eq.**	Equivalents
ESI	Electrospray ionisation	**Et**	Ethyl
G	Gram(s)	**h.**	Hours(s)
HRMS	High resolution mass spectrometry	**Hz**	Hertz
IR	Infrared	***i*-**	Iso
J	Coupling constant	**LCA**	Lithocholic acid
Me	Methyl	**min**	Minute(s)
mL	Millilitres	**mol.**	Mole
MP	Melting point	**modp**	1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato
MOM	Methoxymethyl	**Ms**	Methanesulfonyl
MS	Mass spectrometry / Molecular sieves	***m/z***	Mass to charge ratio
Nmax	Peak infrared absorption	**NMP**	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance	**n.O.e.**	Nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy	**PG**	Protecting group
Ph	Phenyl	**pH**	$-\log [H_3O]^+$
Piv	Pivaloyl	**pK_a**	$-\log K_a$
PMB	*Para*-Methoxybenzyl	**ppm**	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate	**PolyCyc**	Polycyclic structure
Pr	Propyl	**R**	Generic organic substituent
R_f	Retention factor	**ROM**	Ring Opening/cross Metathesis
r.t.	Room temperature	**SAE**	Sharpless Asymmetric Epoxidation
SET	Single electron transfer	**SET**	Single electron transfer
TBAF	*tetra-n*-Butylammonium fluoride	***t*-**	Tertiary
TBDPS	*tert*-Butylphenylsilyl	**TBS**	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid	**TBHP**	*tert*-Butyl hydroperoxide
ThDP	Thiamine dipyrophosphate	**TFAA**	Trifluoroacetic acid anhydride
THP	Tetrahydropyran	**THF**	Tetrahydrofuran
TMO	Trimethylamine-*N*-oxide dihydrate	**TLC**	Thin layer chromatography
Ts	*Para*-Toluenesulfonyl	**TMS**	Trimethylsilyl

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Chapter 4: Results & Discussion – A Novel Route towards *trans*-THFs

Chapter 5 - Experimental

Chapter 1: Introduction – Acyloin Condensation

1.0 Acyloin: General Information

Acyloins (*α*-hydroxyketones) 1-**1** are a class of organic compounds with the formula RCHOHCOR, in which R represents an aliphatic or aromatic substituent. The term "acyloin" is commonly used as a trivial name for symmetrical or non-symmetrical *α*-hydroxyketones. The names for individual chemical compounds are derived by adding the suffix "*oin*" to the name of the corresponding acid: acetoin, propionoin *etc*. (Figure 1-**1**).

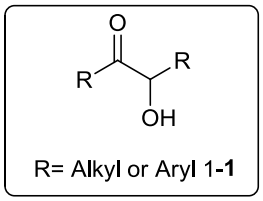


Figure 1-**1** – The acyloin structure.

The acyloin adduct exists in a large number of biologically active natural products such as beclometasone 1-**2** and paciltaxel (taxol) 1-**3** (Figure 1-**2**), which have both been developed in the pharmaceutical industry as a result of their inherent inflammatory and anti-tumour activities.[1,2]

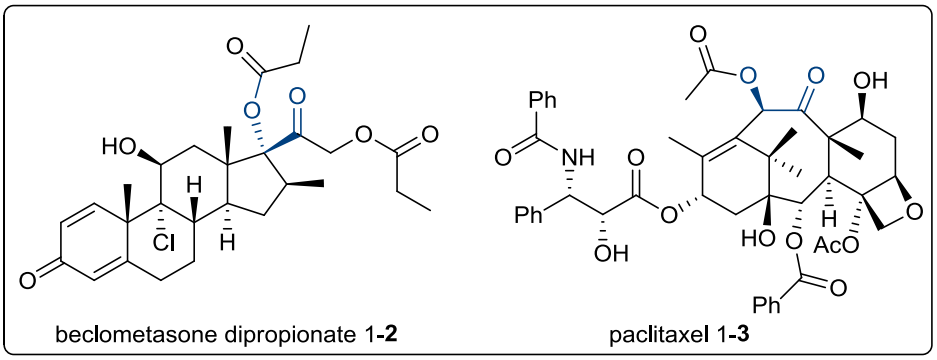


Figure 1-**2** – The structure of beclometasone and paclitaxel.

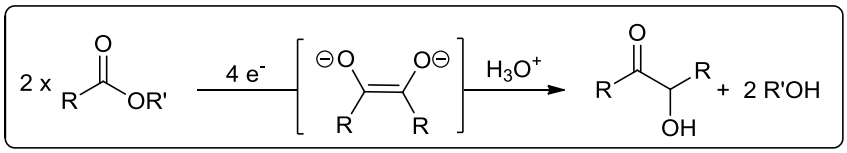
Various strategies have been developed with the aim of synthesising the acyloin subunit. These methods can be divided into two main categories; i) oxidative or reductive

transformation of functionalised carbon chains into an acyloin (*e.g.* Rubottom oxidation),[3]

ii) carbon-carbon coupling reactions. The following chapter presents two different methods to generate the acyloin adduct *via* a carbon-carbon bond formation; these methods include the acyloin and benzoin condensation.

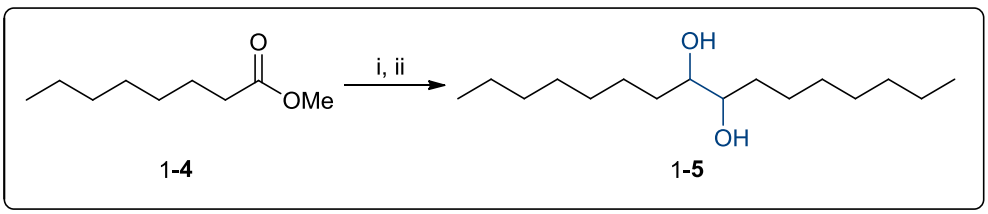
1.1 Acyloin Condensation

The acyloin condensation is the most common method for the preparation of *α*-hydroxyketones, in which a bimolecular reductive carbon-carbon coupling occurs between two esters mediated by single electron transfer (SET) from alkali metals such as lithium, sodium or potassium (Scheme 1-**1**).



Scheme 1-**1** – Acyloin condensation.

This reaction was discovered by Bouveault and Blanc in 1903, during the course of their investigations into the sodium-mediated reduction of aliphatic esters to the corresponding primary alcohols.[4] It was found that the reduction of methyl caprylate 1-**4** with sodium in aprotic solvents such as diethyl ether and benzene afforded glycol 1-**5** as the major product (Scheme 1-**2**).



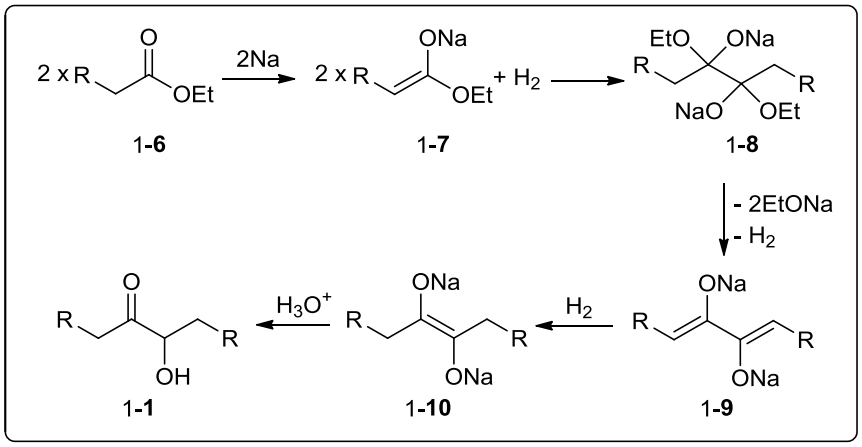
Reagent and Conditions: i) Na (10 eq.), Et_2O or benzene, 0-25 °C. ii) NH_4Cl (aq.).

Scheme 1-**2** – Reductive coupling of methyl caprylate 1-**4** to the corresponding glycol 1-**5**.

Bouveault and Locquin carried out further investigations by subjecting ethyl esters of acetic, propionic, butyric, isobutyric and trimethylacetic acids to sodium in dry ether at 0 °C, followed by warming to ambient temperature.[5] After stirring the reaction mixture for several days, they obtained the corresponding acyloins as the major product in good yields. It was postulated that the observation of *α*-diketones as by-products was due to tautologous oxidation of the acyloin upon work up or during the purification procedure.

1.2 Mechanism of the Acyloin Condensation

The first attempt to rationalise the mechanism of acyloin condensation was undertaken by Scheibler *et al.* in 1920, who suggested that the ester 1-**6** was deprotonated to form key intermediate enolate 1-**7** in the initial stage of the reaction (Scheme 1-**3**).[6]



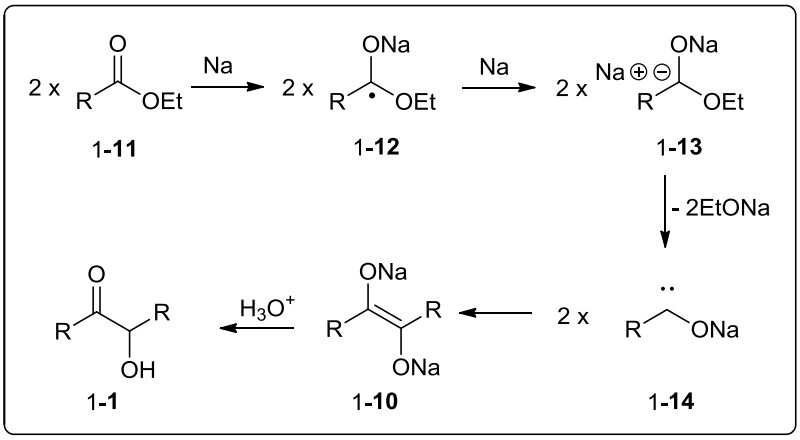
Scheme 1-**3** – Mechanism suggested by Scheibler *et al.* for enolisable esters

It was speculated that under the acyloin reaction conditions hydrogen gas was released upon formation of 1-**7**, which was subsequently reduced to form hemiacetal 1-**8**. Ene-diolate 1-**10** was formed by elimination of sodium alkoxide followed by hydrogen reduction of the bis-enolate 1-**9**. The acyloin product 1-**1** was delivered by protonation and tautomerisation of

1-**10** upon acidic quench (see Scheme 1-**3**).

However, this proposed mechanism has been disproved, primarily due to the lack of experimental evidence for the formation of hydrogen gas, and secondly because it did not rationalise the compatibility of non-enolisable esters with the reaction conditions.

An alternative mechanism was suggested by Scheibler *et al.* in 1923 for the formation of acyloins using non-enolisable esters as substrates (Scheme 1-**4**).[7] They suggested that the carbonyl functionality of the ester 1-**11** was reduced by a sodium-mediated SET to form the ketyl radical anion 1-**12**.

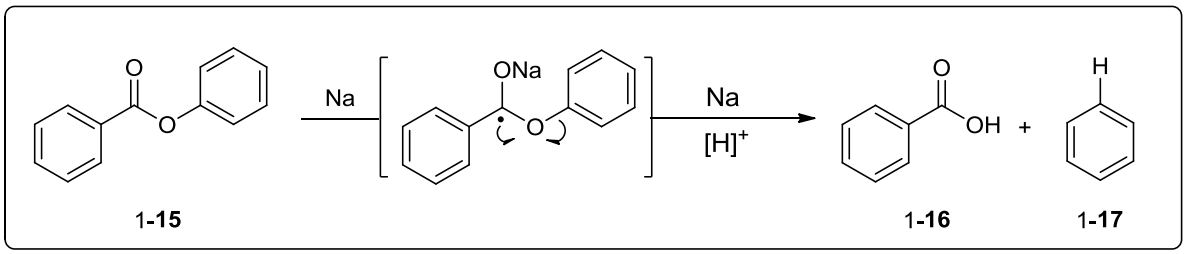


Scheme 1-**4 –** Mechanism suggested by Scheibler *et al.* for non-enolizable esters.

Carbene 1-**14** was subsequently formed by further SET reduction of 1-**12** followed by elimination of sodium alkoxide, which then dimerised to produce ene-diolate 1-**10**. Finally, the acyloin product 1-**1** was formed in a similar manner described in the previous mechanism (see Scheme 1-**4**).

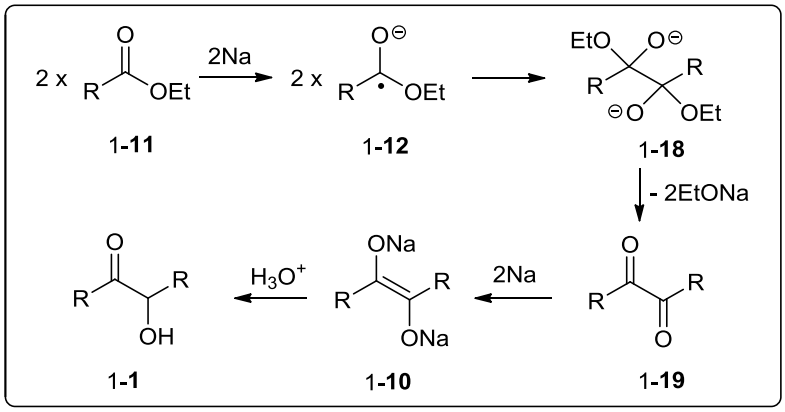
In 1925, Blicke observed the formation of a red-coloured precipitate when two moles of phenyl benzoate 1-**15** were subjected to one mole of sodium in diethyl ether.[8] Benzene 1-**16** and benzoic acid 1-**17** were isolated as the major products and the presence of benzoin and benzil were deduced by qualitative analysis. It was postulated that the red colour was an

indication of a sequential electron addition, *i.e.* a radical reaction. Their hypothesis was that an insufficient concentration of electrons in the reaction mixture caused radical decomposition of the substrate to form benzene and benzoic acid (Scheme 1-**5**).



Scheme 1-**5** – Radical decomposition of phenyl benzoate.

The mechanism of acyloin condensation was revised by McElvin in 1931.[9] By subjecting a series of ethyl esters to the heterogeneous lithium in diethyl ether conditions, no correlation between the property of the substituent on the esters and the rate of the reaction rate was established. As a result, a unified mechanism for the acyloin condensation was formulated, in which the reaction was suggested to be a combination of both reduction and condensation pathways, involving *α*-diketone 1-**19** as the key intermediate (Scheme 1-**6**), contradicting the previous perception that 1-**19** was the result of atmospheric air oxidation of an acyloin.



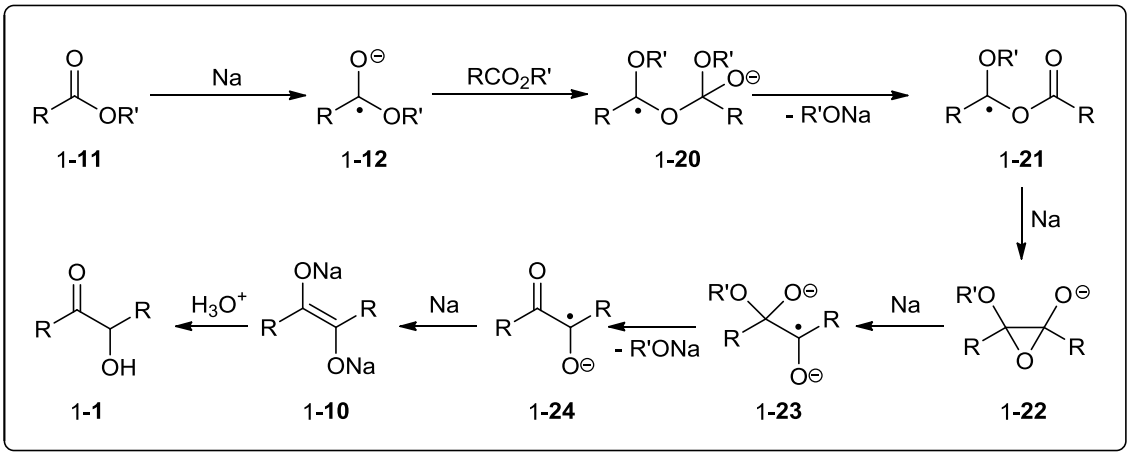
Scheme 1-**6** – Mechanism suggested by McElvin *et al.*

The mechanism proposed by McElvin involved the formation of the ketyl radical anion 1-**12** from 1-**11** *via* a SET reduction. Compound 1-**12** undergoes dimerisation to form 1-**18**, which

undergoes elimination to form *α*-diketone 1-**19**. Addition of two electrons to 1-**19** delivered the ene-diolate 1-**10,** which upon acidic quench was protonated and tautomerised to form the acyloin product 1-**1** (see Scheme 1-**6**).

Years later in 1975, Bloomfield *et al.* proposed an alternative mechanism for the acyloin condensation, [10] arguing that the mechanism proposed by McElvin was incomplete as it did not account for all reported results in the literature. Indeed, it is important to stress that the sodium-mediated reduction of esters also produces carboxylic acids, alcohols, aldehydes and other anomalous by-products.

Therefore, a mechanism which did not involve an *α*-diketone 1-**19** as an intermediate and could explain the formation of most reaction products was proposed (Scheme 1-**7**).



Scheme 1-**7 –** Mechanism suggested by Bloomfield *et al*.

It was suggested that the reaction was initiated by the SET reduction of the ester 1-**11** to form ketyl radical anion 1-**12**. The key oxybriged dimer intermediate 1-**20** was formed *via* nucleophilic attack by the oxygen anion of 1-**12** on an un-reacted ester 1-**11** followed by elimination of sodium alkoxide to deliver ester 1-**21**. Epoxide 1-**22** was subsequently formed *via* SET reduction of 1-**21** followed by ring closure, which underwent a reduction/elimination

process to form radical anion 1-**24** *via* 1-**23**. Finally, SET reduction of 1-**24** produced the ene-diolate 1-**10**, which was protonated and tautomerised to deliver acyloin 1-**1** (see Scheme 1-**7**). Bloomfield *et al.* acknowledged that even thier hypothsis could not count for the formation of all the by-products formed in the reaction, *"This paper presents some conclusions as to the mechanism of the acyloin condensation in order to stimulate thought and experimentation on this reaction. We are presently unable to carry out any further work toward this end"*.[10]

It is worth noting that the commonly accepted mechanism taught in undergraduate textbooks is based on McElvin's proposal. A complete understanding of the acyloin condensations mechanism is still to be achieved, as the reaction can be carried out in both homogeneous and heterogeneous conditions, increasing its complexity. The classical acyloin condensation is considered to be a heterogeneous reaction, which involves an inner sphere electron transfer reaction between the alkali metal and esters in refluxing aprotic solvents. By comparison, homogeneous conditions, which employ dissolved sodium in liquid ammonia involve SET reduction and occur at lower temperatures (Figure 1-**3**).

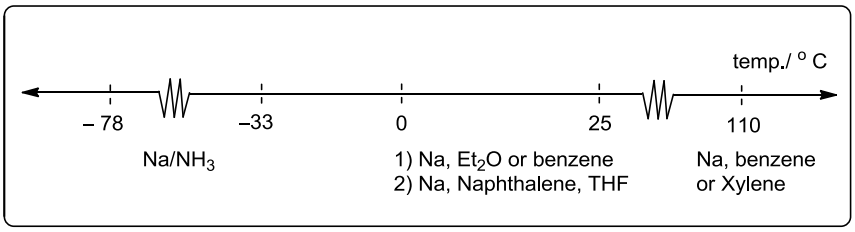


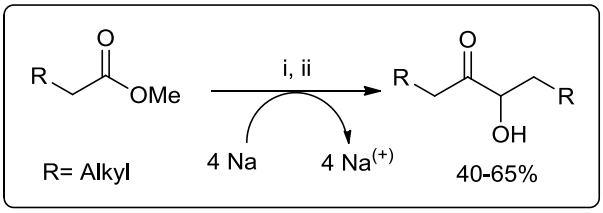
Figure 1-**3** – Different acyloin condensation reaction conditions.

Each set of conditions could favour a specific mode of reactivity, forming different intermediates and by-products which could interfere with the reaction to promote other competitive side-reactions. Consequently, the mechanism of the formation of the acyloin

could differ in each case. This complexity provides a plausible explanation for why the mechanism of the acyloin reaction has not been conclusively elucidated and speculation remains regarding the possible intermediates and pathways.

1.2.1 Heterogeneous Acyloin Condensation

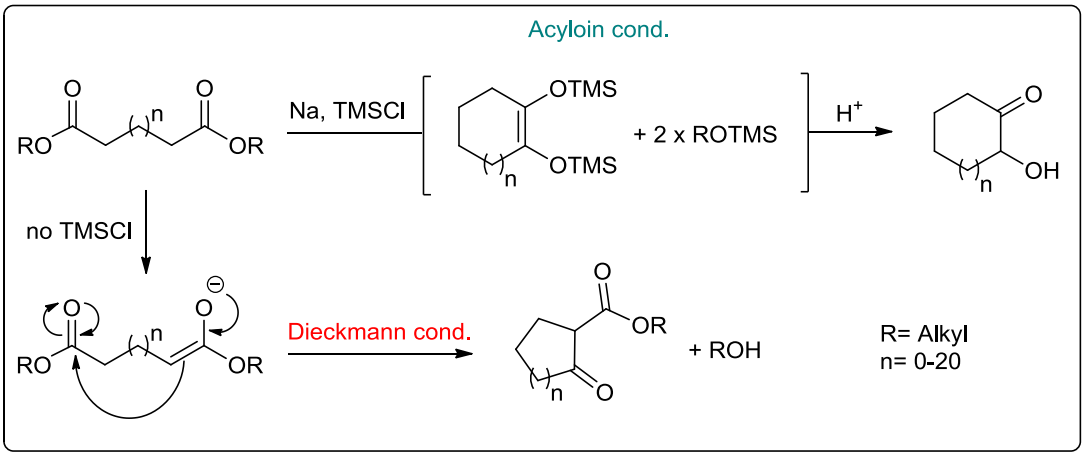
The very first synthetic application of the heterogeneous acyloin condensation employed aliphatic esters in the preparation of symmetrical acyloins. In 1935, Hansley reported the most robust heterogenous conditions by subjecting sodium to esters in refluxing aromatic solvents such as toluene and *m*-xylene, modifying the original conditions which employed sodium in ether at ambient temperature (Scheme 1-**8**).[11]



Reagent and Conditions: i) Na (5 eq.), PhMe or *m*-xylene, at reflux, 1 h. ii) NH_4Cl (aq.).

Scheme 1-**8** – Heterogenous acyloin conditions used by Hansley *et al.*

These new conditions provided higher yields compared to the previous methodology, due to an improved electron transfer process caused by the increased surface area once sodium becomes molten and finely dispersed in the hot solvent. Thus, the reaction proved to be valuable synthetic tool for intramolecular acyloin reactions, in particular for the construction of small, medium and large carbocyclic systems (Scheme 1-**9**).



Scheme 1-**9** – TMSCl as trapping agent to subdue Dieckmann condensation side reaction.

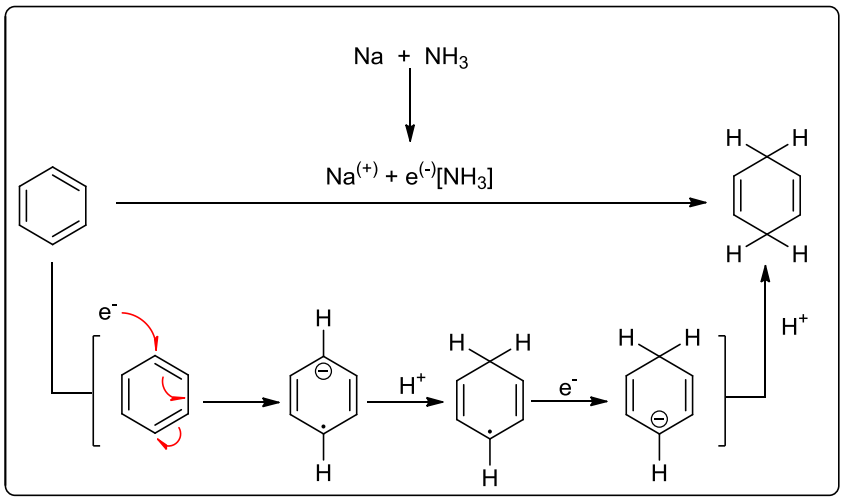
Previous observations on the acyloin condensation have indicated that a competitive Dieckmann condensation side reaction (see Scheme 1-**9**) was involved, in which the residual sodium alkoxide reacted with the ester to form the aldol product. This could be avoided by addition of chlorotrimethylsilane (TMSCl) as a trapping reagent, which subdued the enolisation process and improved the yield of the reaction (see Scheme 1-**9**).[12]

1.2.2 Homogeneous Acyloin Condensation

1.2.2.1 Dissolving metal Based Procedure

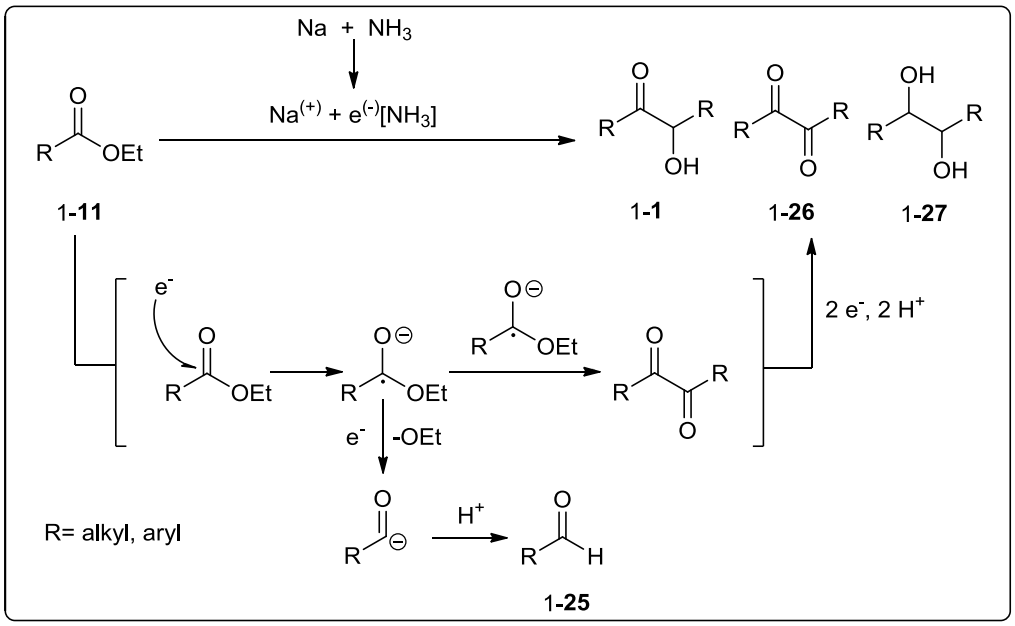
The homogeneous sodium in ammonia conditions were discovered by Wooster and Godfrey in 1937.[13] The reductive reagent employed in the reaction was a solution of dissolved sodium in water and liquid ammonia, conducted at –33 °C. It was thought that the reaction between water and sodium metal produced hydrogen, which was responsible for the reduction of aromatic structures such as benzene and toluene. Years later in 1944, this *'nascent' hydrogen* theory was revised by Birch, who formulated the most commonly

accepted mechanism (Scheme 1-**10**). [14] It was proposed that the electrons produced from the oxidation of alkali-metal were solvated in an ammonia medium, which in turn reduced aromatic structures *via* a SET reduction process (Scheme 1-**10**).



Scheme 1-**10** – The Birch reduction.

In 1940, the first application of the homogeneous Na/NH_3 acyloin condensation was reported by Mayo *et al.* who subjected a series of aliphatic and aromatic esters 1-**11** to the Birch reduction conditions to deliver acyloin products in poor yield. Aldehydes 1-**25**, *α*-diketones 1-**26** and glycols 1-**27** were isolated as by-products (Scheme 1-**11**).[15]



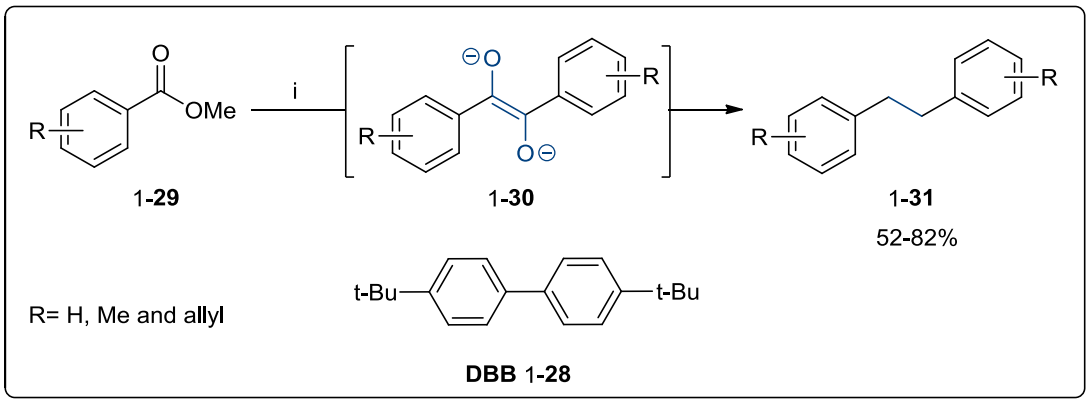
Scheme 1-**11** – Application of the Birch reduction conditions to the acyloin condensation.

However, the high concentration of ammonia in the reaction produced a number of disadvantages. Firstly, ammonia acted both as a medium and proton source in the reaction, which resulted in the formation of by-products such as aldehyde 1-**25** and glycol 1-**27**. Furthermore, the reaction conditions required handling of toxic ammonia gas (with a boiling point of –33 °C) at high pressure, making these conditions undesirable for large scale synthesis.

1.2.2.2 Lithium/DBB Mediated Procedure

In 1989, Fry *et al.* reported the first application of homogeneous lithium/ 4,4'-di-*tert*-butylbiphenyl 1-**28** (DBB) conditions in the reductive coupling of aromatic esters 1-**29** to the corresponding di-benzyl products 1-**31** at lower temperature (Scheme 1-**12**). It was suggested that the reaction proceeded *via* a subsequent SET reduction between lithium metal, 1-**28** and starting material 1-**29** to form the key intermediate ene-diolate 1-**30**, which

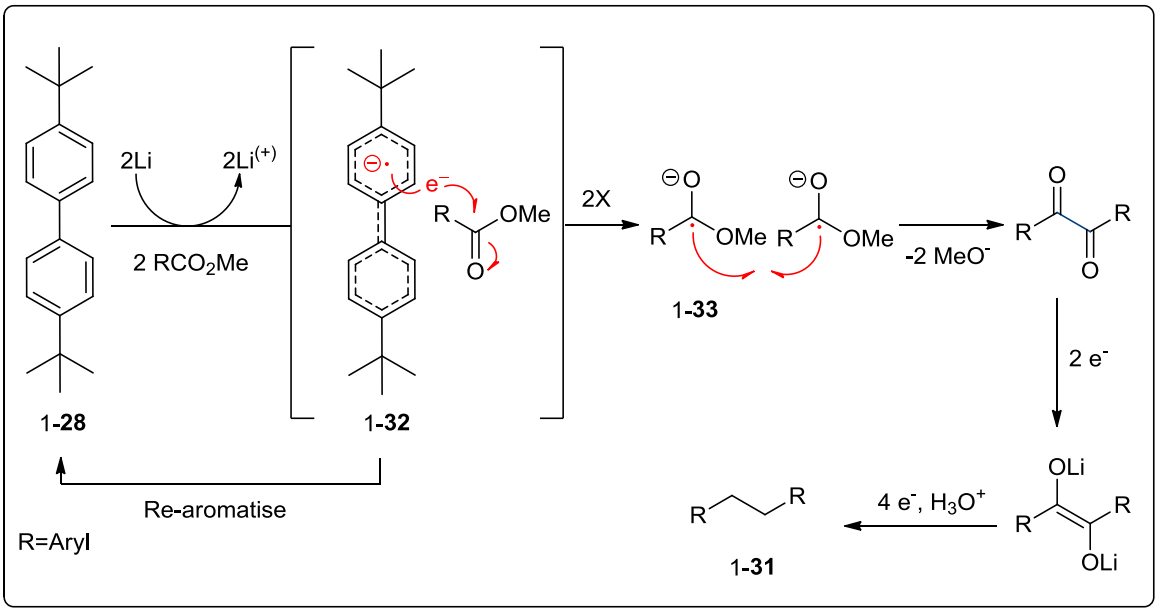
underwent further reduction in Li/DBB solution to yield alkane1-**31** (Scheme 1-**12**)[16]



Reagents and **conditions** i) Li (4.5 eq.), DBB (0.1 eq.), THF, r.t, 6-60 h.

Scheme 1-**12** – Application of the Li/DBB reduction conditions to C-C coupling between esters 1-**29**.

It was suggested that the redox reaction between lithium metal and DBB formed an arene radical anion 1-**32** as a potent reducing agent, which subsequently reduced the ester 1-**29** *via* a SET reduction process to form ketyl radical anion 1-**33** (Scheme 1-**13**).



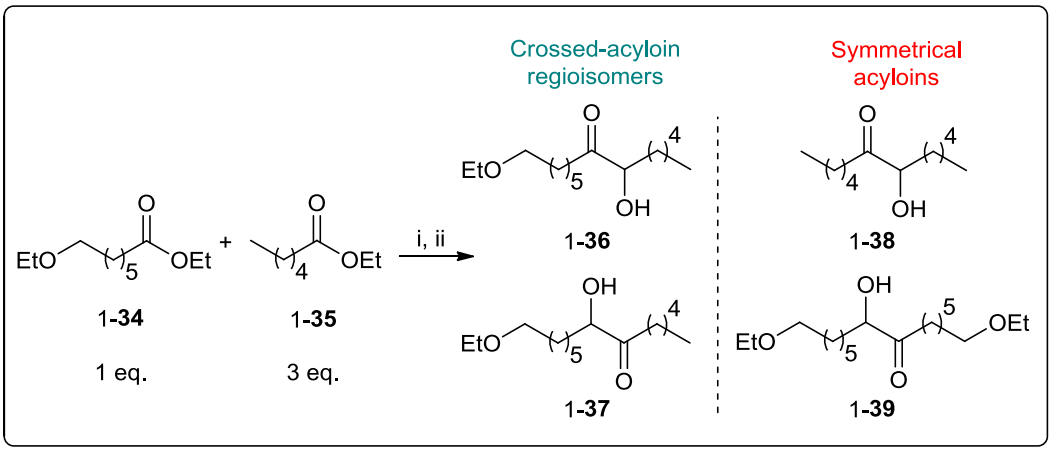
Scheme 1-**13** – Suggested mechanism for the Li/DBB mediated dimerisation of aromatic esters.

As previously described, the *α*-diketone intermediate was formed upon dimerisation of 1-**33** followed by elimination of the lithium alkoxide. It was speculated that the key ene-diolate

underwent deoxygenation by addition of 4 electrons and protons to generate alkane 1-**31** (see Scheme 1-**13**). It is worth noting that their suggestion did not match with the conditions used in the reaction. Indeed, according to the mechanism, the reaction would require at least 8 electrons, while only 4.5 equivalents of lithium metal were used in the presence of 10 mol% catalytic loading of DBB 1-**28** (see Scheme 1-**12**). Furthermore, their conditions required an extra sonication step of the Li/DBB solution in the presence of the aromatic ester, thus limiting the procedure's practicability; the reaction temperature having to be above the room temperature.

1.3 The Scope and Limitations of Acyloin Condensation

The acyloin condensation has been restricted to the formation of symmetrical acyloins, either was intermolecular cyclisation or by dimerisation of symmetrical esters. Indeed, in an uncontrolled environment when two different esters were subjected to typical acyloin conditions, the reaction produced two crossed-acyloin regioisomers and two symmetrical acyloin products in statistical yields: the two esters undergo a random dimerisation reaction to deliver a maximum yield of 50% of the two crossed-acyloin regioisomers. This method is consequently disfavoured as the isolation of the desired crossed-acyloin products would be complicated. A handful of attempts have been reported in the literature for the preparation of crossed-acyloins using the acyloin condensation. In 1946, Baudart tried to form exclusively crossed-acyloins by simply subjecting a mixture of ethyl 7-ethoxyheptanoate 1-**34** with an excess of ethyl hexanoate 1-**35** to sodium in refluxing *m*-xylene (Scheme 1-**14**).[17]

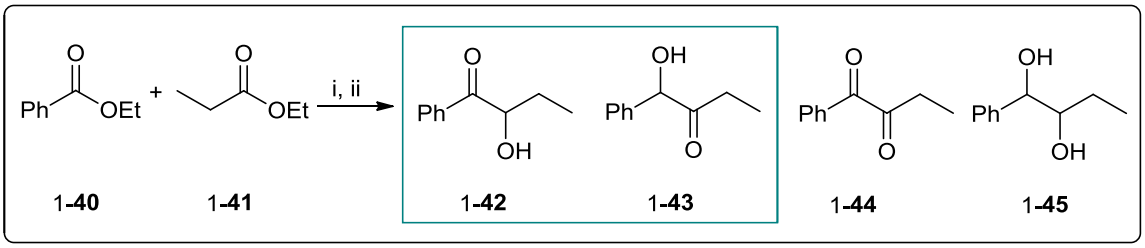


Reagent and Conditions: i) Na (9.0 eq.), *m*-xylene, 139 °C, 1 h. ii) NH_4Cl (aq.).

Scheme 1-14 – Crossed-acyloin method used by Baudart *et al*.

This method led to the formation of acyloins 1-**36**, 1-**37**, 1-**38** and 1-**39** in the ratio of (1:1:2:1). Meanwhile, repeating the reaction with an equal concentration of the two esters 1-**34** and 1-**35** resulted in a statistical product distribution of the crossed-acyloin and the symmetrical acyloin products in the ratio of (1:1).

In 1951, English *et al.* systematically investigated the effect of solvent, reaction time and ester concentration in the crossed-acyloin condensation reaction.[18] Ethyl benzoate 1-**40** and ethyl propionate 1-**41** were selected as model substrates in the heterogeneous acyloin condensation reaction. The optimal solvent was found to be benzene and the best yield was achieved by stirring the reaction mixture for 4 hours (Table 1-**1**, Entry **1**). Interestingly, an excess concentration only of ethyl propionate (Table 1-**1**, Entry **6**[b]) led to significant increase in the yield of the reaction. This result was rationalised by speculating that the corresponding ketyl radical anion intermediate of the ethyl propionate possessed greater reactivity than the ketyl radical anion of the ethyl benzoate, since the latter is relatively stable.



Entry	Conditions		Yield (%)		
	Solvents	Time	Crossed-acyloin 1-**42** and 1-**43**	α-Diketone 1-**44**	α-Glycol 1-**45**
1	benzene	4 h	16	10	10
2	ether	4 h	10	5.0	
3	*m*-xylene	4 h	7.5	6.0	
4	benzene	2 h	7.5	8.5	
5	benzene	8 h	9.5	3.5	3.0
6[a,b]	benzene	4 h	12[a](23)[b]		8.0[a](10)[b]

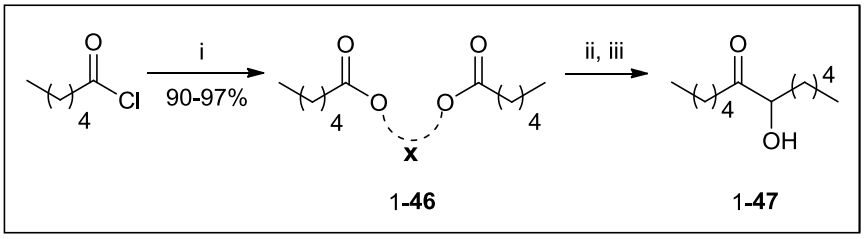
Reagent and Conditions: i) Na (4 eq.), at reflux, 1 h. ii) NH_4Cl (aq.).

Table 1-**1** – Variation of reaction parameter for crossed-acyloin condensation.

a) Using 2 eq. of 1-**40** and 1 eq. of 1-**41**, b) employing 1 eq. of 1-**40** and 2 eq. of 1-**41**.

The most successful protocol for the crossed-acyloin reaction was reported by Hutchinson *et al.* in 1993, who used a tether to link two different acyl groups to deliver a mixture of *α*-hydroxyketones: two crossed-acyloin products and two symmetrical acyloin products.[19] Their aim was to find a tether that promoted exclusive formation of the two crossed-acyloin regioisomers *via* an intramolecular reaction between two different acyl groups linked through the acyl oxygen. For comparison, they carried out an intermolecular acyloin condensation by subjecting methyl hexanoate to sodium in refluxing toluene, which furnished the symmetrical caproin 1-**47** in 68% yield (Table 1-**2**, Entry **1**). In order to find the optimal linker for the reaction, they employed a series of symmetrical di-esters using different linkers. The symmetrical di-esters 1-**46** were easily accessed by esterification of hexanoyl chlorides with the appropriate diol in the presence of triethylamine in dichloromethane. These were then

subjected to the heterogeneous acyloin condensation reaction conditions of sodium in refluxing toluene (Table 1-**2**).



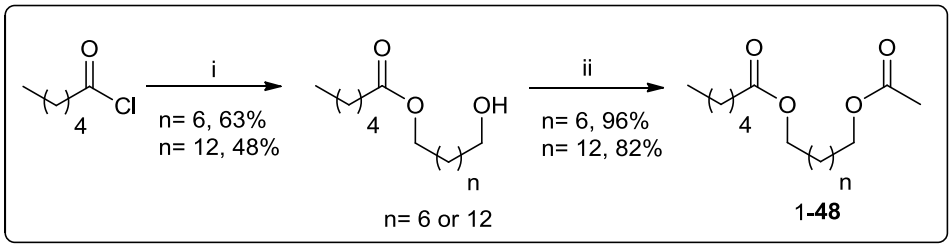
Entry	Substrate	Tether X	Yield (%) of 1-47
1	Methyl hexanoate	none	68
2	1-46a	$(i\text{-Pr})_2Si$	5
3	1-46b	$(CH_2)_2$	22
4	1-46c	$(CH_2)_3$	20
5	1-46d	$(CH_2)_5$	42
6	1-46e	$(CH_2)_8$	76
7	1-46f	$(CH_2)_{14}$	73

Reagents and **conditions:** i) Et_3N (2.2 eq.), CH_2Cl_2, r.t, 2 h. ii) Na (5.0 eq.), TMSCl (5.0 eq.), PhMe, 110 °C, 1 h. iii) NH_4Cl (aq.).

Table 1-**2** – Effect of different linker on the yield of the acyloin condensation.

As described in Table 1-**2** the outcome of their investigation showed that the yield of the acyloin condensation was highly dependent on the length of the tether. Indeed, the yields obtained with long tethers (Table 1-**2**, Entries **6** and **7**) were comparable with the yields from an intermolecular reaction, whereas shorter linkers gave poorer yields.

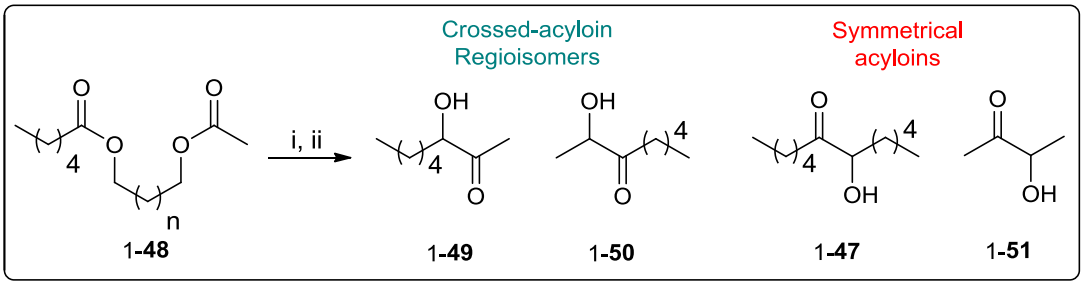
Armed with these results from the symmetrical acyloin, the linkers that delivered the highest yields were employed in a crossed-acyloin reaction. The non-symmetrical tethered di-ester 1-**48** was prepared in two steps by sequential esterification of the diol (Scheme 1-**15**).



Reagents and conditions: i) Et_3N (1.0 eq.), diol (1.0 eq.), CH_2Cl_2, r.t, 16 h.
ii) Et_3N (2.0 eq.), acetyl chloride (2.0 eq.), CH_2Cl_2, r.t, 16 h.

Scheme 1-**15 –** Synthesis of non-symmetrical tethered di-ester 1-**48**.

In order to establish a reference for the reaction, an equimolar mixture of methyl hexanoate and *n*-butyl acetate was subjected to the reaction conditions. As expected, the reaction formed a statistical mixture of the crossed-acyloins 1-**49** and 1-**50** in combined yield of 38% and capronoin 1-**47** in 20% yield (Table 1-**3**, Entry **1**). The other symmetrical acyloin product acetonin 1-**51,** observed by the crude ^{1}H-NMR spectroscopy, was lost in the aqueous work up procedure. The reduction of non-symmetrical di-esters linked with 8 and 14 carbon length chains delivered virtually the same result as in the case of the intermolecular reaction (see Table 1-**3**, Entry **2** and **3**).



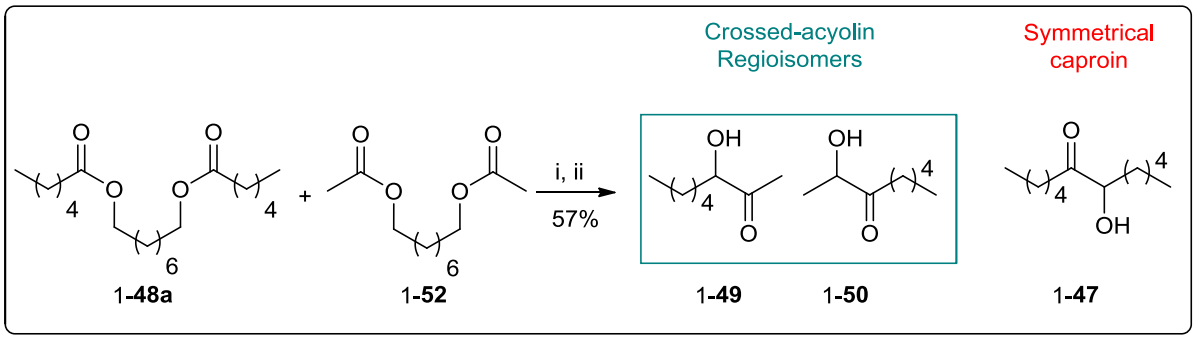
Entry	Substrate	Tether	Yield/ %	
			Crossed-acyloins 1-**49** and 1-**50**	Capronoin 1-**47**
1	Methyl hexanoate and *n*-butyl acetate	none	38	20
2	1-**48a**	n= $(CH_2)_6$	37(25)[a]	20(16)[a]
3	**1-48b**	n= $(CH_2)_{12}$	34	20

Reagents and conditions: i) Na (5.0 eq.), TMSCl (5.0 eq.), PhMe, 110 °C, 1 h. ii) NH_4Cl (aq.).

Table 1-**3 –** Effect of different linker on the yield of crossed-acyloin. a) High dilution conditions.

It was proposed that a highly diluted reaction with regard to the di-ester could promote an intramolecular reaction, but unfortunately this reaction also afforded a statistical mixture of acyloin products (see Table 1-**3**, Entry **2**[a]).

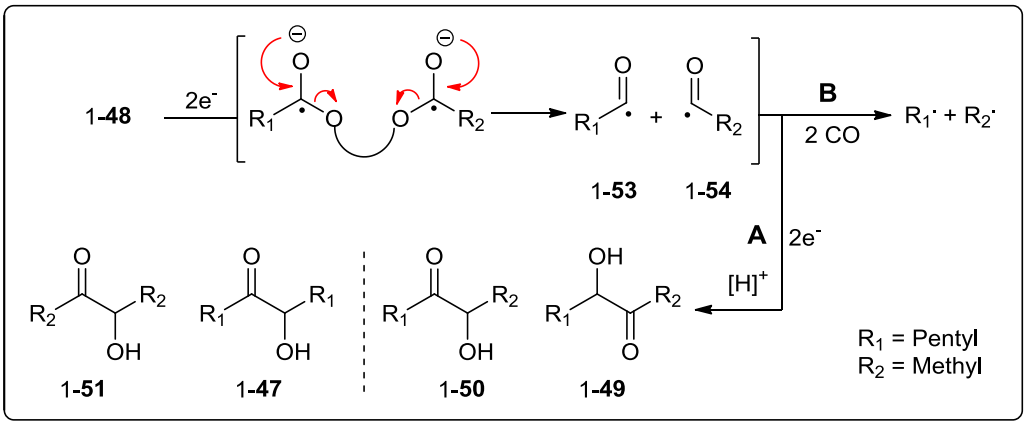
A crossover experiment was conducted between di-esters 1-**48a** and 1-**52**, which furnished a mixture of the crossed-acyloin products 1-**49** and 1-**50** in a combined yield of 40% and capronoin 1-**47** in 17% yield (Scheme 1-**16**).



Reagents and conditions: i) Na (5.0 eq.), TMSCl (5.0 eq.), PhMe, 110 °C, 1 h. ii) NH_4Cl (aq.).

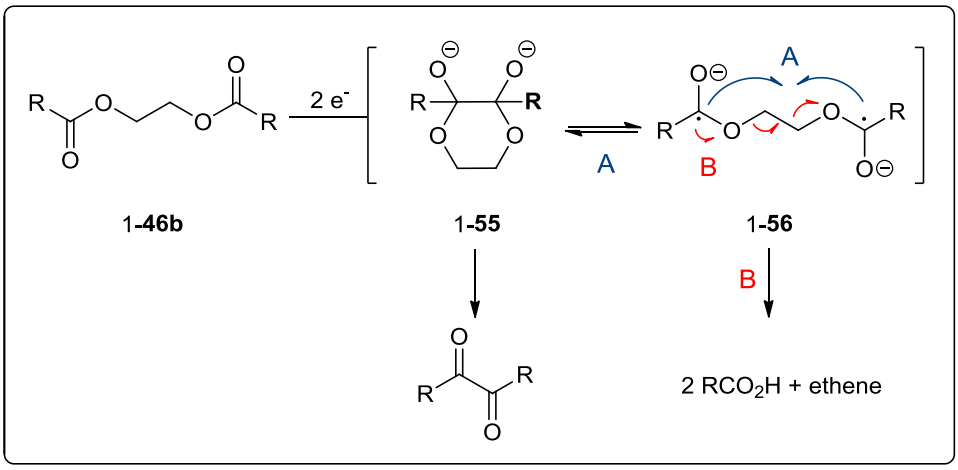
Scheme 1-**16** – Crossover experiment between di-esters 1-**48a** and 1-**52**.

These results indicated that the reaction proceeded through an alternative route, in which a fragmentation process occurred at the initial stage of the reaction after the addition of two electrons to the carbonyl functionalities. The resulting acyl radicals 1-**53** and 1-**54** could then either randomly dimerise (Path A, Scheme 1-**17**) to form the four acyloin products or decarbonylate to give carbon monoxide and alkyl radicals (Path B, Scheme 1-**17**).



Scheme 1-**17 –** Radical decomposition of the di-ester 1-**48**..

However, the authors acknowledged that the results obtained were not entirely consistent with a bimolecular intermolecular reaction, as high dilution experiments did not improve the yield of the intramolecular crossed-acyloin reaction. Furthermore, the authors provided an explanation for the poor yields observed in the case of the di-esters linked with shorter tethering units (Scheme 1-**18**).



Scheme 1-**18 –** Radical decomposition of the di-ester to the corresponding carboxylic acid.

In these cases, equilibrium between the cyclic intermediate 1-**55** (Path A, see Scheme 1-**18**) and the open chain 1-**56** could slow down and obstruct the recombination step and promote the decomposition of the di-ester to the parent carboxylic acids (Path B, see Scheme 1-**18**).

1.4 Application of the Acyloin Condensation

The acyloin condensation has been widely employed in the perfume industry for the preparation of macrocyclic ketones due to their pleasant fragrance.[20] Macrocylic musks are the oldest perfume ingredient and have been used for centuries as a major component in the perfume industry. The main source of musk in nature is from the skin of a deer (*Moschus moschiferus*) from Central Asia, or the American musk rat (*Ondarta zibethicus rivalicius*), from which they are isolated as a complex mixture and in minute quantities. Due to constant demand from the perfume industry, the synthesis of these natural products has attracted much attention from the synthetic organic chemistry community.

Pioneering work by Stoll *et al.* on the preparation of musk represents one of the most important results in early development and application of the acyloin condensation. This method has been used for the synthesis of macrocyclic musk such as civetone 1-**57**, and exaltone 1-**58** (Figure 1-**4**). [16,21,22]

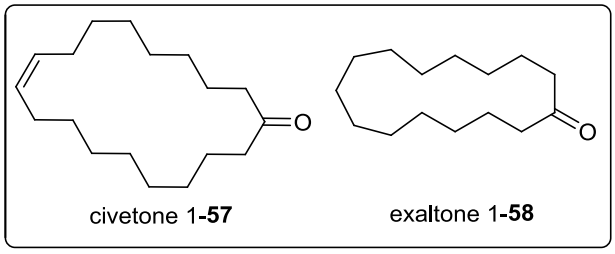
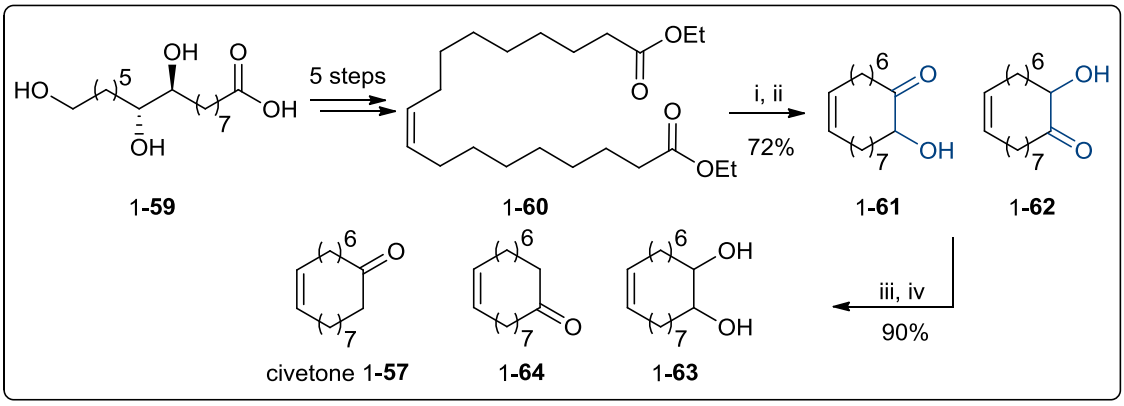


Figure 1-**4** – Natural musks civetone 1-**57** and exaltone 1-**58**.

Synthesis of civetone 1-**57** and dihydrocivetone 1-**63** were reported by Mathure *et al.* in 1963 using the easily accessible aleuritic acid 1-**59** as a starting material.[18] The acid was converted to the requisite diethyl heptadec-8-enedioate 1-**60** in five steps (Scheme 1-**19**). The α-ω di-ester 1-**60** was subjected to heterogeneous sodium in refluxing *m*-xylene to form the two acyloin regioisomers 1-**61** and 1-**62** in 72% yield. Acylation and subsequent reduction

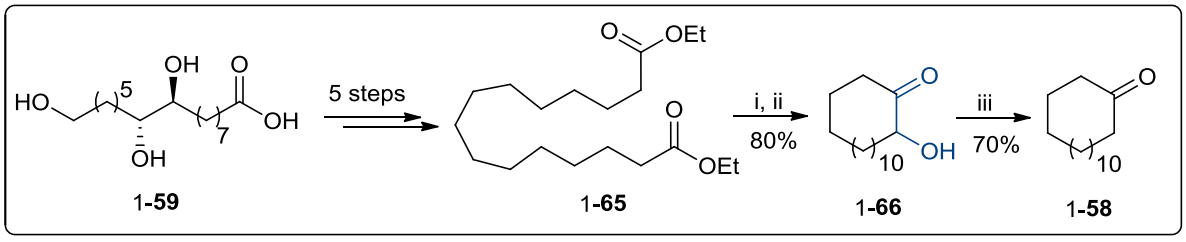
in a Ca/NH_3 solution, furnished a mixture of diol 1-**63** and ketones 1-**57** and 1-**64** as major products, which were separated by distillation (Scheme 1-**19**).



Reagents and **conditions:** i) Na (5.0 eq.), *m*-xylene, 139 °C, 0.5 h.
ii) NH_4Cl (aq.). iii) $(Ac)_2O$ (2.2 eq.), pyridine (2.2 eq.), r.t, 12 h. iv) Ca (4.0 eq.), NH_3, 2 h.

Scheme 1-**19** – The synthesis of civetone 1-**57** and dihydrocivetone 1-**63** by Mathure *et al*.

More recently in 2001, Ravi *et al*. employed the acyloin condensation in the synthesis of exaltone 1-**58** (Scheme 1-**20**).[16] The key intermediate 1-**65** was again obtained by conversion of aleuritic acid 1-**59** in five steps, including a chain contraction using the Hunsdiecker protocol.[23]



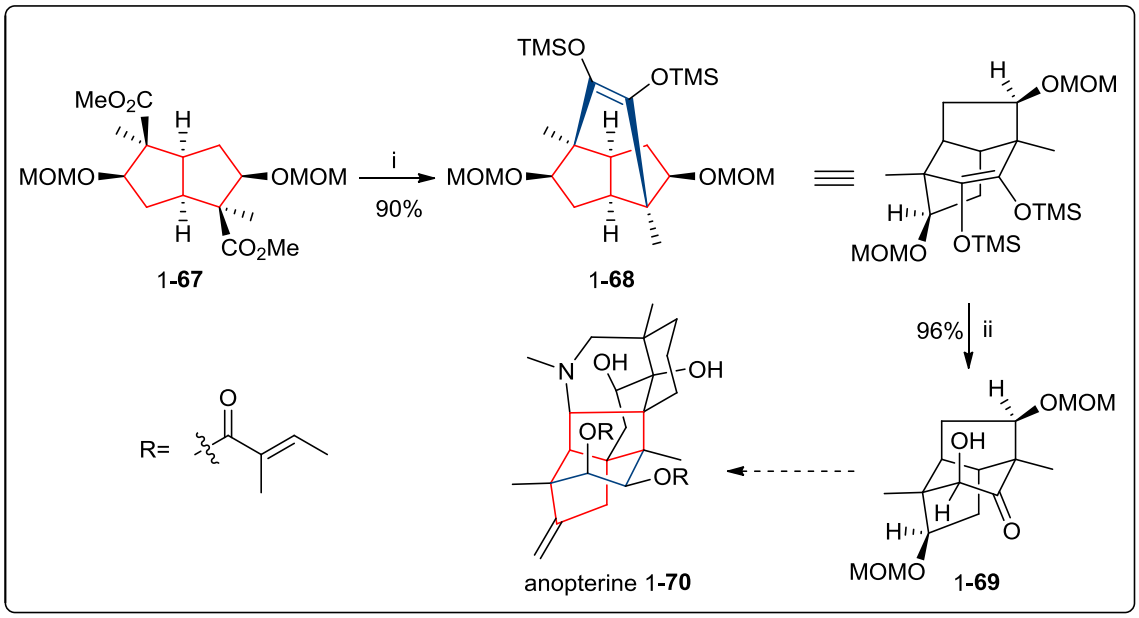
Reagents and **conditions:** i) Na (4.5 eq.), *m*-xylene, 139 °C, 2 h.
ii) NH_4Cl (aq.). iii) Zn (6.0 eq.), HCl (gas), dioxane, 90 °C, 6 h.

Scheme 1-**20** – The synthesis of exaltone 1-**58** by Ravi *et al*.

The di-ester 1-**65** was subjected to sodium in refluxing *m*-xylene to form the desired acyloin in 80% yield, which was subsequently deoxygenated by using the Clemmensen reduction procedure to deliver 1-**58** in 70% yield (see Scheme 1-**20**).

An acyloin cyclisation reaction has also been applied in the formal synthesis of anopterine

1-**70**, which is known to exhibit a high level of antitumor activity.[24] The core structure of 1-**70** represents a congested polycyclic system containing an isomer of adamantine. Sieburt *et al.* used an acyloin cyclisation reaction for the closure of the two-carbon bridge between the two five-membered rings of decahydronaphthalene 1-**67** (Scheme 1-**21**).



Reagents and **conditions:** i) Na (5.0 eq.), TMSCl (5.0 eq.) PhMe, 110 °C, 6 h. ii) HF (4.0 eq.), MeCN, r.t, 3 h.

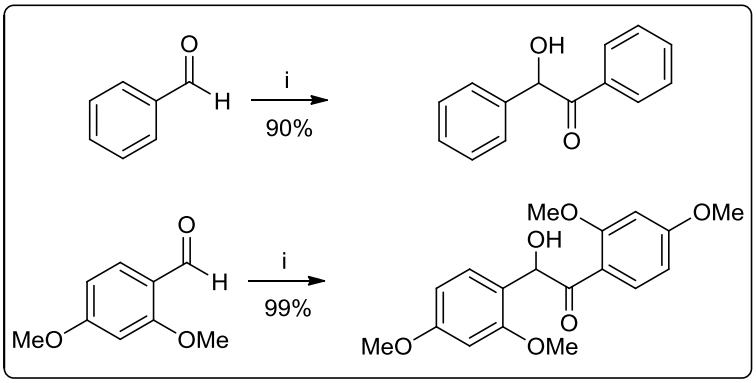
Scheme 1-**21 –** Application of the acyloin condensation in the synthesis of anopterine 1-**70**.

Di-ester 1-**67** was subjected to sodium in refluxing toluene in the presence of TMSCl under an atmosphere of argon forming the bis-trimethylsilyloxy alkene 1-**68** in 90% yield. Interestingly, 1-**68** was stable and did not hydrolyse upon acidic quench or during purification on silica. The authors proposed that the sterically hindered environment, imposed by the MOM ethers on both sides of the enediol disilyl ether group, could provide a stabilising effect, which prevented the deprotection. Treatment of 1-**68** with hydrofluoric acid in acetonitrile delivered the desired acyloin 1-**69** in 96% yield (see Scheme 1-**21**).

1.5 Variants of the Acyloin Condensation

1.5.1 Benzoin Condensation

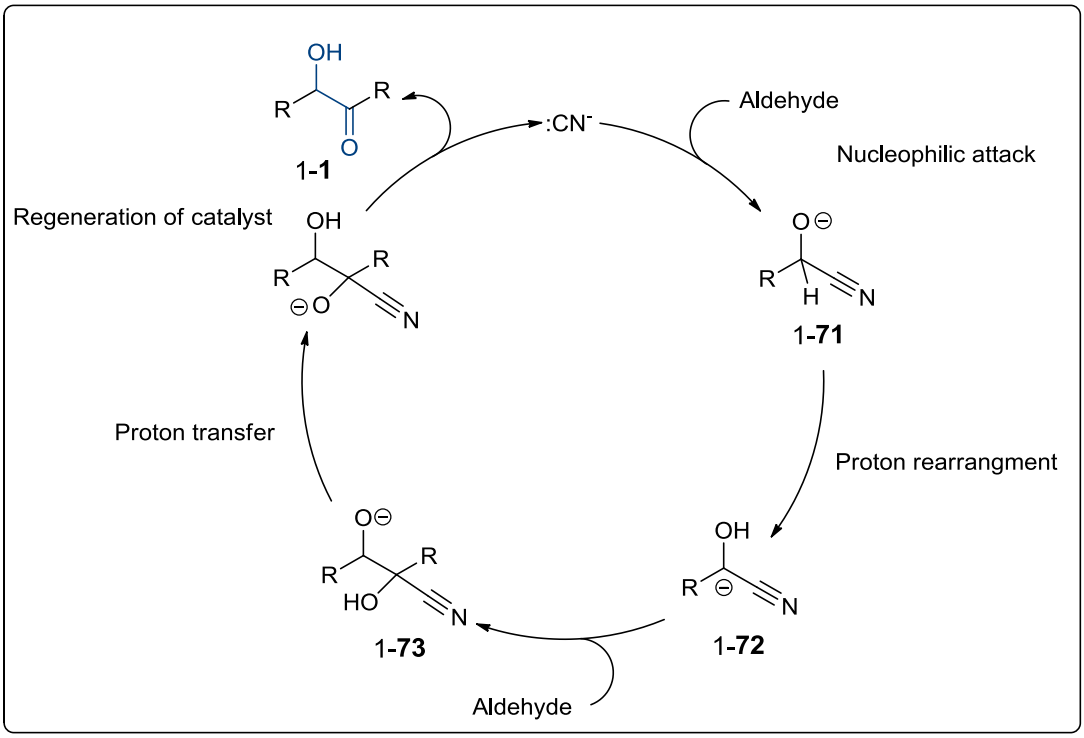
The cyanide-catalysed benzoin condensation, discovered by Liebig and Wöhler in 1832, is a typical example of *umpolung* chemistry, as the electrophilic carbonyl carbon of one molecule of benzaldehyde affects a nucleophilic attack on another unreacted benzaldehyde molecule.[25] The reaction is limited to dimerisation of aromatic aldehydes, due to the fact that enolisable aliphatic aldehydes tend to undergo aldol condensation under basic conditions (Scheme 1-**22**).



Reagents and conditions: i) KCN, DMF, 80 °C, 24 h.

Scheme 1-**22** – Benzoin condensation.

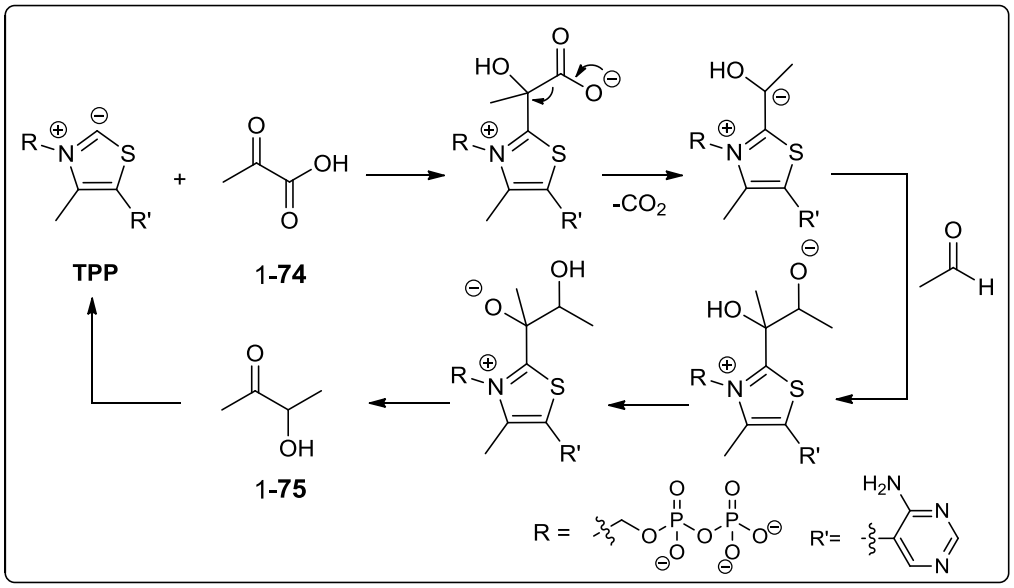
The commonly accepted mechanism of the cyanide-catalysed benzoin condensation was formulated by Lapworth (Scheme 1-**23**).[26] In the initial step of the reaction, cyanide ion is used as an *umpolung* reagent to yield the cyanohydrin 1-**71**, which tautomerises to form the key nucleophile intermediate carbanion 1-**72**. Nucleophilic addition to un-reacted aldehyde yield the benzoin precursor 1-**73**, which subsequently undergoes proton transfer followed by elimination of the cyanide to deliver the benzoin product 1-**1** (see Scheme 1-**23**).



Scheme 1-**23** – Mechanism of the benzoin condensation as proposed by Lapworth *et al*.

This well known reaction was made possible *via* the inherent properties of the cyanide ion. Indeed, cyanide is a good nucleophile due to its polarisability and low steric hindrance. Furthermore, its mesomeric electron withdrawing effect lowers the pK_a of intermediate 1-**71**, which facilitates formation of the reactive intermediate 1-**72**. Finally, cyanide is a stable anion which makes it a good leaving group. In principle, any catalyst that fulfils these criteria would be suitable for the benzoin condensation reaction. This is the case with coenzyme thiamine pyrophosphate (ThDP or vitamin B_1), which performs this task efficiently, by converting pyruvic acid 1-**74** into acetoin 1-**75**.

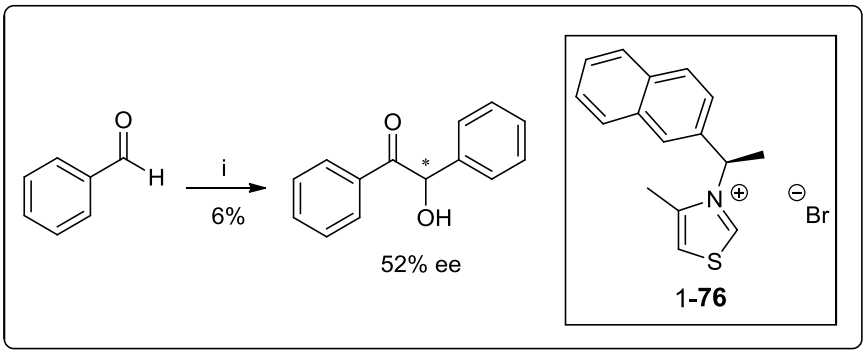
Mizuhara *et al*. demonstrated that the catalytic activity of the natural thiamine was based on its thiazolium unit, which served as an *umpolung* catalyst in a similar manner to cyanide in the benzoin condensation (Scheme 1-**24**). [27]



Scheme 1-**24 –** ThDP catalysed conversion of pyruvic acid into acetoin *in vivo.*

1.5.2 Carbene Catalysed Acyloin Condensation

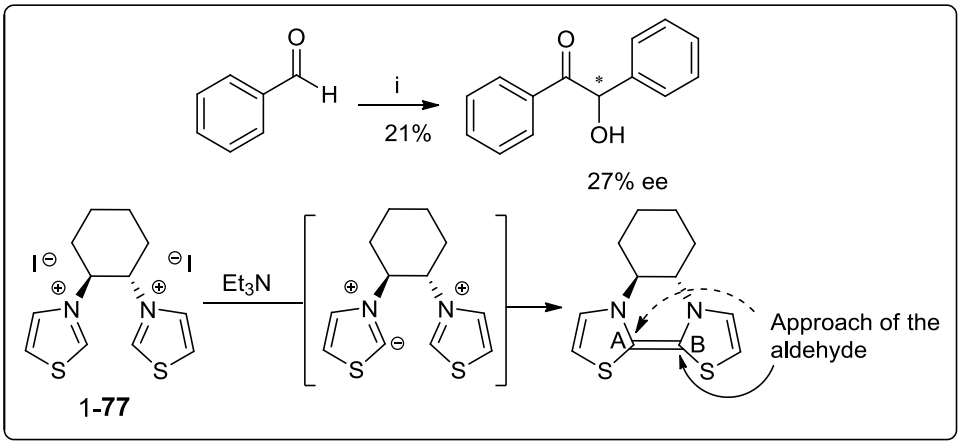
Following these results in 1943, Ukai *et al.* used thiazolium salts as *umpolung* catalysts for the benzoin condensation.[28] Since then, extensive research has been conducted into the development of synthetic catalysts that mimic enzymatic systems. Sheehan *et al.* in 1966 extended the methodology by introducing the asymmetric benzoin condensation reaction, employing chiral thiazolium salts 1-**76** as the precatalysts to induce chirality in the reaction.[29] However, the new reaction conditions furnished the desired benzoin product in only 6% yield and 52% enantiomeric excess (Scheme 1-**25**).



Reagents and conditions: i) 1-**76** (0.1 eq.), Et_3N (0.1 eq.), MeOH, 30 °C, 24 h.

Scheme 1-**25 –** Thiazolium salt catalysed chiral benzoin condensation.

In an attempt to improve the methodology, Lopez Calahora *et al*. used a rigid bi-dentate bis-thiazolium salt 1-**77** as a catalyst precursor.[30] Indeed, their suggestion was that by reacting two thiazole moieties in the catalyst, a planar structure would be obtained. This would result in a rotational restriction on the chiral *N*-substituent. Their hypothesis for inducing chirality was explained through a simultaneous discrimination between the two faces of the catalyst whether carbon A or B reacted with benzaldehyde (Scheme 1-**26**). Although the new catalyst helped to improve the yield of the reaction to 21%, the enantioselectivity of the reaction was halved to 21% (Scheme 1-**26**).

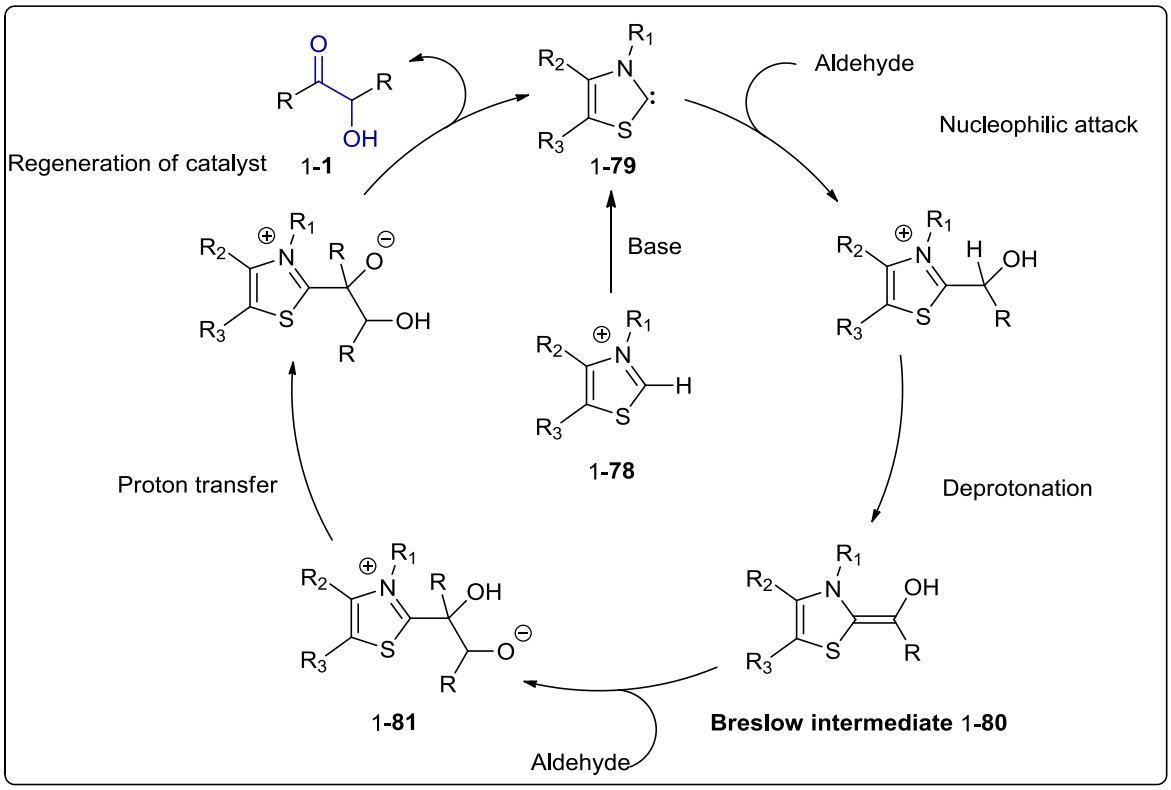


Reagents and conditions: i) 1-**77** (0.1 eq.), Et_3N (0.1 eq.), MeOH, 30 °C, 24 h.

Scheme 1-**26 –** Bis-thiazolium salt catalysed benzoin condensation.

The carbene mechanism of the thiazolium-ion catalysed benzoin condensation was

rationalised by Breslow following Lapworth's original proposal.[31] It was suggested that carbene 1-**79** was formed *in situ*, by deprotonation of the thiazolium salt 1-**78**, which reacted with an aldehyde to generate hydroxyenamine 1-**80**, commonly referred to as a Breslow intermediate (Scheme 1-**27**).

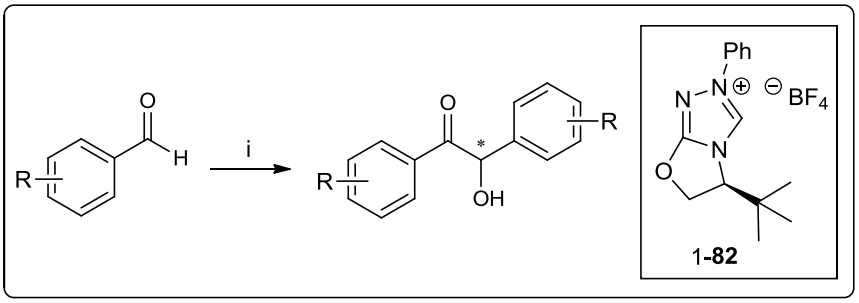


Scheme 1-**27** – Mechanism of carbene catalysed benzoin condensation proposed by Breslow *et al*.

Subsequently, 1-**80** acted as a nucleophile and attacked an un-reacted aldehyde to produce alkoxide 1-**81**, which undergoes proton transfer followed by elimination of the catalyst to deliver the benzoin product 1-**1** (see Scheme 1-**27**).

Enders *et al*. conducted an extensive investigation, in order to improve the yield and enantioselectivity of this methodology by screening various chiral triazolium salt precatalysts.[32] They discovered that enantiomeric excesses and catalytic activities varied profoundly with minor structural changes in the substitution pattern of the triazolium system.

These observations led to the development of bicyclic triazolium salt 1-**82** as a precatalyst, which exhibited the highest stereoselectivity in the asymmetric synthesis of benzoin (Table 1-**4**, Entry **1**). The scope of the reaction was extended to a wide range of aromatic aldehydes to generate the corresponding benzoin products (Table 1-**4**).



Entry	R	T/ °C	Yield/ %	e.e./ %
1	none	18	83	90
2	*p*-Me	18	16	93
3	*p*-MeO	18	8	95
4	*p*-Cl	18	80	64
5	*p*-Cl	0	44	89

Reagents and conditions: i) 1-**82** (0.1 eq.), *t*BuOK (0.1 eq.), THF, 16 h.

Table 1-4 – Asymmetric triazolium catalysed benzoin condensation reaction

The conclusion reached was that the yield and enantioselectivity of these acyloin products varied significantly due to the electronic effect of the substituents on the phenyl ring. Indeed, electron-rich aromatic aldehydes delivered the respective acyloins in moderate to excellent enantioselectivity (up to 95%) but in lower yields (see Table 1-**4**, Entries **2** and **3**). On the contrary, carrying out the reaction with electron-deficient aromatic aldehydes provided the corresponding acyloins with lower enantioselectivity but better yields (see Table 1-**4**, Entry **4**). It is worth noting that in the case of electron deficient aromatic aldehydes the enantioselectivity of the reaction improved significantly at lower temperature, although at the expense of the benzoin yield (see Table 1-**4**, Entry **5**).

It was proposed that the stereochemical outcome of the reaction could be explained by transition states 1-**83** and **1-84**, in which the *si*-face of the intermediate formed in the theoretical catalytic cycle would be blocked by the *t*-butyl group of the bicyclic catalyst (Figure 1-**5**).

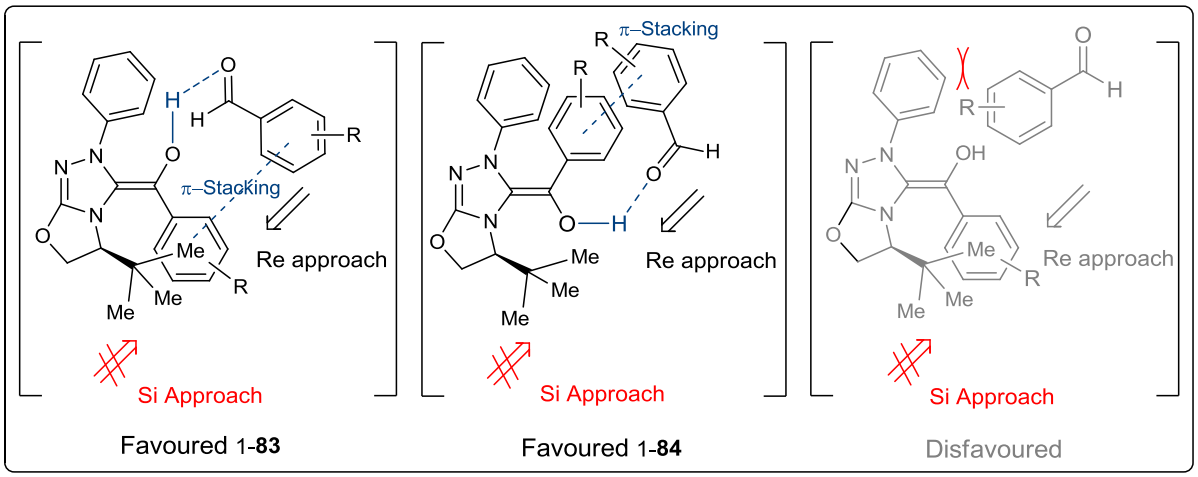


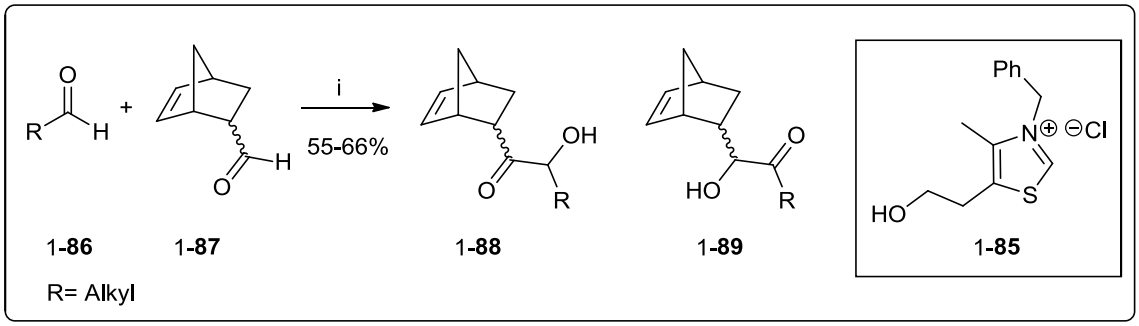
Figure 1-5 – Transition state for the asymmetric triazolium catalysed benzoin reaction.

In this case, the second aldehyde molecule would approach the Breslow intermediate on its *re*-face. In addition, it was suggested that the phenyl substituent of the enol adduct could align with the approaching aldehyde through both π-stacking and hydrogen bonding interactions. This would lead to a favourable arrangement for the formation of the carbon-carbon bond for transition state 1-**83** and **1-84** (see Figure 1-**5**).

1.5.3 Synthesis of Crossed-Acyloins Mediated by Carbene Catalysed Benzoin Condensation

In 1980, Stetter *et al.* reported a method to generate crossed α-diketones *via* the corresponding crossed-acyloin, employing an achiral thiazolium catalyst 1-**85** for acyloin condensations of a series of different aliphatic aldehydes 1-**86** and norbornene

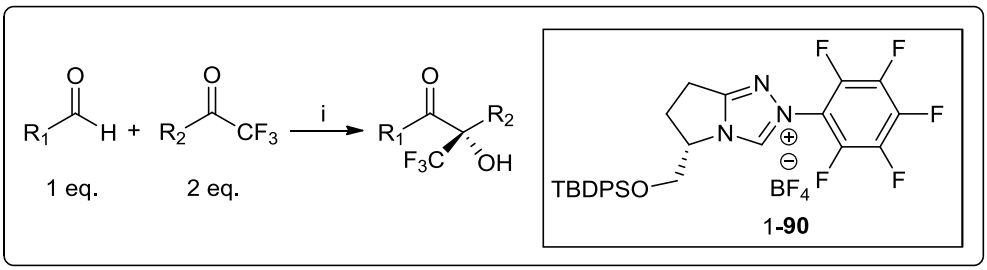
2-carboxaldehyde 1-**87**.[33] The reaction delivered two crossed-acyloin regioisomers 1-**88** and 1-**89** in good yields, when one of the substrates was used in excess (Scheme 1-**28**).



Reagents and conditions: i) 1-**85** (0.1 eq.), Et_3N (0.6 eq.), EtOH, 85 °C, 24 h.

Scheme 1-**28** – Thiazolium catalysed crossed-acyloin condensation reaction.

There have been several attempts reported in the literature to improve the thiazolium catalysed crossed-acyloin methodology. Recently, Enders *et al*. reported a method to generate enantiopure crossed-acyloins by employing the chiral triazolium salt 1-**90** as a precatalyst (Table 1-**5**).[34]



Entry	R_1	R_2	Yield/ %	e.e./ %
1	2-Furyl	4-$MeOC_6H_4$	69	82
2	2-Furyl	Phenyl	86	78
3	2-Pyridyl	Phenyl	73	62
4	2-Thienyl	4-BrC_6H_4	93	65

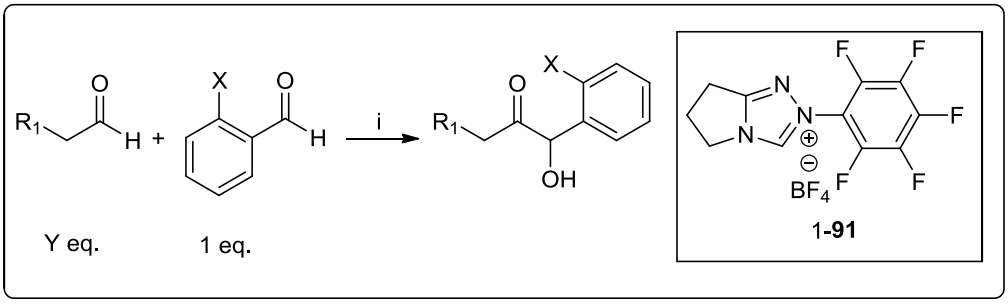
Reagents and conditions: i) 1-**90** (0.1 eq.), Hünig's base (1.0 eq.), THF, 0 °C, 24-48 h.

Table 1-**5** – Triazolium catalysed crossed-acyloin reaction.

They were able to obtain a wide range of aromatic crossed-acyloin products in moderate to satisfactory yields and enantioselectivities by subjecting a series of aromatic trifluoromethyl

ketones and aryl aldehydes to thiazolium catalysed crossed-acyloin conditions in the presence of 1-**90** at 0° C (see Table 1-**5**).

This work was followed up by Zeitler *et al.* in a chemoselective intermolecular crossed-acyloin reaction between various aliphatic and aromatic aldehydes.[35] It was postulated that subjecting less hindered aliphatic aldehydes to the achiral triazolium salt 1-**91**, followed by the addition of aromatic aldehydes would deliver crossed-acyloin products (Table 1-**6**).



Entry	R_1	Y/ eq.	X	Yield/ %
1	$PhCH_2$	1	CF_3	34
2	$PhCH_2$	1.7	CF_3	86
3	*n*-C_3H_7	1.7	Br	67
4	CH_3	2.5	Br	63
5	H	10	CF_3	78

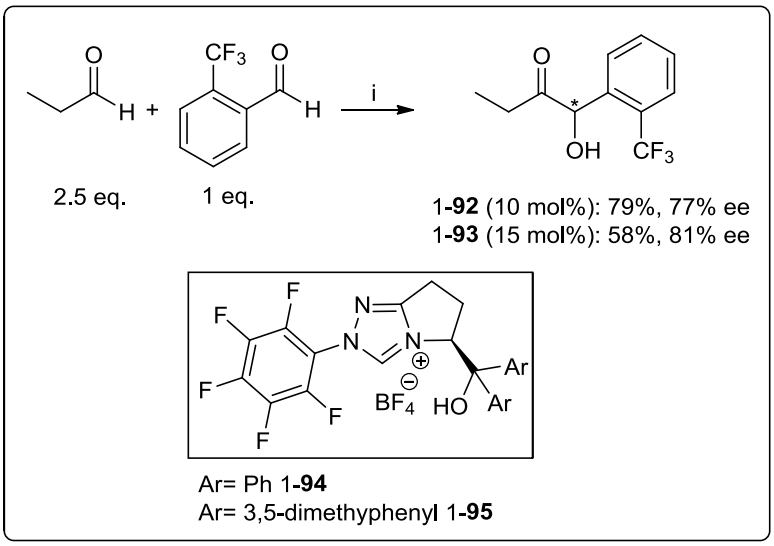
Reagents and conditions: i) 1-**91** (0.1 eq.), Rb_2CO_3 (0.1 eq.), THF, 18 °C, 40 h.

Table 1-6 – Triazolium catalysed crossed-acyloin reaction.

However, it was realised that the chemoselectivity and yields of these reactions were highly substrate-dependent and optimal yields could only be achieved by using an excess loading of the aliphatic aldehydes (Table 1-**6**, Entries **2** -**5**).

This methodology was extended to the enantioselective synthesis of crossed-acyloin 1-**92** and 1-**93**, by using chiral triazolium salts 1-**94** or 1-**95** as precatalysts. It was suggested that the combination of stereoelectronic properties of the catalyst and the substrate could provide

high stereoselectivity in the reaction (Scheme 1-**29**).



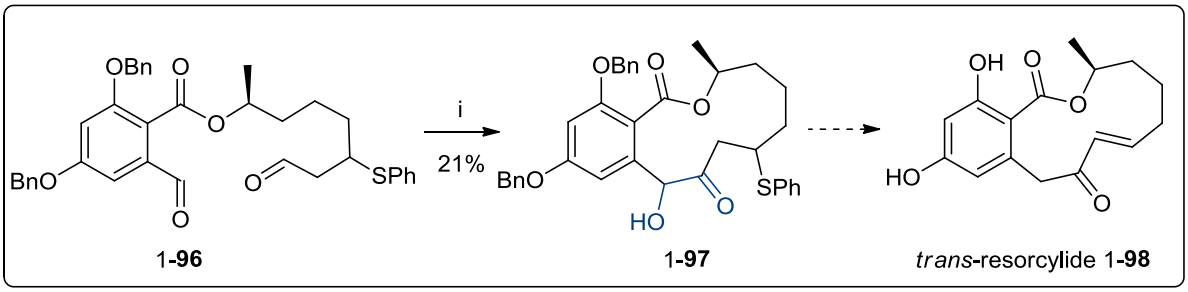
Reagents and conditions: i) 1-**94** (0.10 eq.) or 1-**95** (0.15 eq.), Rb_2CO_3 (0.10 eq.), THF, 18 °C, 40 h.

Scheme 1-**29 –** Enantioselective triazolium catalysed crossed-acyloin condensation reaction.

It was found that a 15 mol% catalytic loading of the chiral triazolium catalyst 1-**95** delivered higher enantioselectivity, albeit with lower yield (58% yield, 81% e.e.), whilst 1-**94** carrying phenyl substituents delivered higher yield but with poorer stereoselectivity (see Scheme 1-**29**).

1.5.4 Application of Carbene-based Benzoin Condensation in the Synthesis of Bioactive and Synthetically Useful Molecules

The triazolium catalysed crossed-acyloin protocol was employed by Miller *et al.* in a regioselective intramolecular macrocyclisation reaction in the formal synthesis of *trans*-resorcylide 1-**98**.[36] Crossed-acyloin product 1-**97** was obtained as a single regioisomer in moderate yield by subjecting di-aldehyde 1-**96** to a stoichiometric loading of 1-**85** in the presence of DBU in dichloromethane at room temperature (Scheme 1-**30**).



Reagents and conditions: i) 1-**85** (1.0 eq.), DBU (2.0 eq.), CH_2Cl_2, 22 °C, 1.5 h.

Scheme 1-**30** – Formal synthesis of *trans*-resorcylide by Miller *et al*.

Suzuki *et al*. also developed a method for the stereocontrolled synthesis of functionalised preanthraquinones; the structure presents polycyclic units which exist in various natural products such as tetracyclines 1-**99** and aquayamycin 1-**100** (Figure 1-**6**).[37]

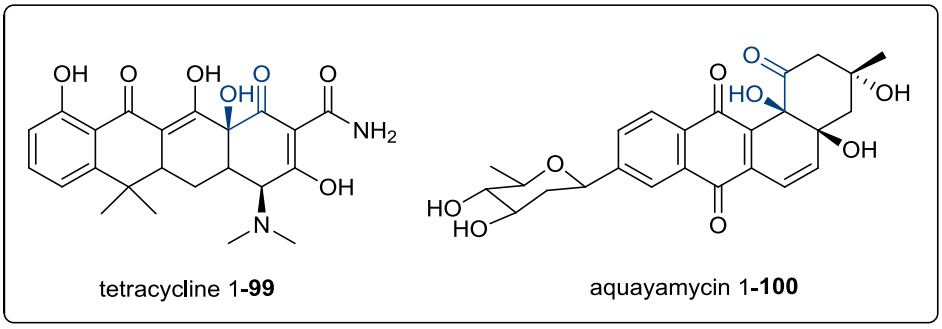
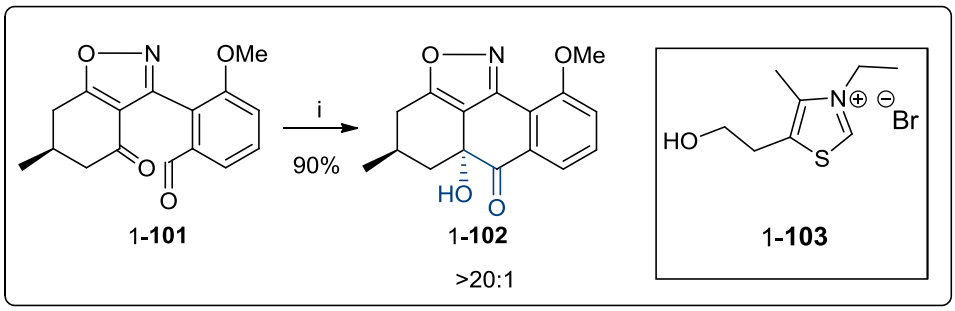


Figure 1-**6** – Structure of tetracycline 1-**99** and aquayamycin 1-**100**.

The core cyclic acyloin functionality was constructed by subjecting keto-aldehydes 1-**101** to a thiazolium catalysed acyloin procedure, which delivered a single regioisomer crossed-acyloin product 1-**102** in 90% yield and with good diastereoselectivity (Scheme 1-**31**).



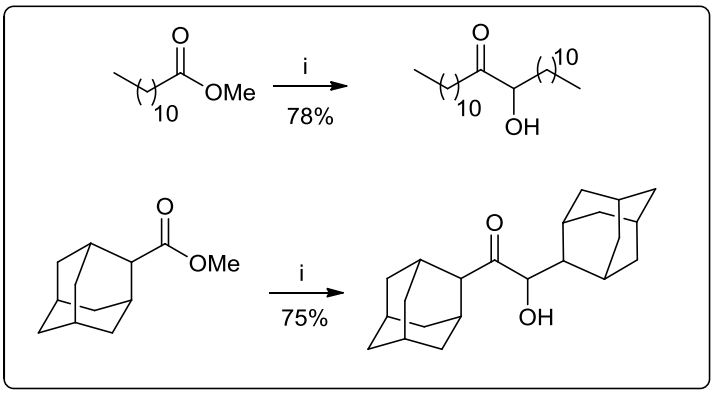
Reagents and conditions: i) 1-**103** (0.2 eq.), DBU (0.7 eq.), *t*-BuOH, CH_2Cl_2, 40 °C, 0.5 h.

Scheme 1-**31** – Synthesis of functionalised preanthraquinones by Suzuki *et al*.

1.6 Aims of This Research Project

As it was discussed in this chapter, one of the greatest challenges in the acyloin/benzoin condensation is to generate exclusively crossed-acyloin products. It was shown in the case of the reductive coupling of esters (acyloin condensation), the reaction proved to be limited to the dimerisation of symmetrical esters, even with a few attempts to exert control over the reaction. However, recent developments on the carbene-catalysed benzoin condensation has demonstrated the possibility to form crossed-acyloin adducts in good yields and stereoselectivity. It was shown that the scope of this reaction was highly substrate-dependent, and the reaction required excess loading of at least one of the aldehydes involved. These attributes may limit this methodology as a synthetic tool in organic chemistry.

Our intention was to develop a procedure to obtain crossed-acyloin products, by employing a tethered intramolecular crossed-acyloin approach, mediated by homogeneous Li/DBB conditions at – 78°C. Previous work in the Donohoe group* has demonstrated that exposure of various aliphatic and aromatic esters to Li/DBB reductive conditions at –78 °C generated acyloin products in good yields, with quantitative recovery of DBB (see Scheme 1-**32**).

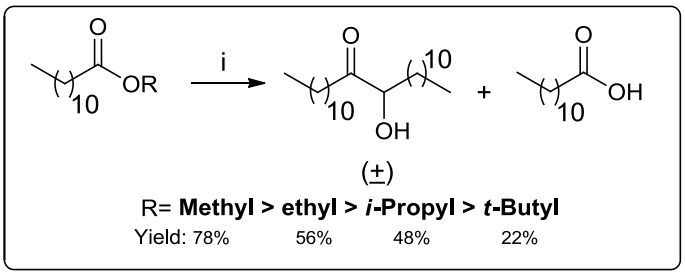


* Work carried out by Dr. Farrah Bhatti

Reagents and conditions i) Li (5.0 eq.), DBB (4.0 eq.), THF, –78 °C, 4.5 h. ii) NH_4Cl (aq.)

Scheme 1-32 – Li/DBB employed in acyloin condensation.

It is worth noting that the reaction worked well with un-substituted esters as well as with bulkier substrates such as the adamantyl group (see Scheme 1-**32**). Furthermore, it was shown that the yield of the reaction was also linked to the identity of alkyl group of the ester (Scheme 1-**33**). It was speculated that the esters which delivered lower yields underwent radical decomposition to form the corresponding carboxylic acids.



Reagents and conditions i) Li (45 eq.), DBB (4.5 eq.), THF, –78 °C, 4.5 h. ii) NH_4Cl (aq.).

Scheme 1-33 – Variation of yield in acyloin condensation dependent on the *O*-alkyl substituents.

With the successful results reported in the group for the Li/DBB mediated acyloin condensation, the aim of the research project was to extend this procedure to a tethered intramolecular crossed-acyloin condensation (Figure 1-**7**), which was previously attempted only under heterogenous conditions by Hutchinson *et al.* (page **16-20**).

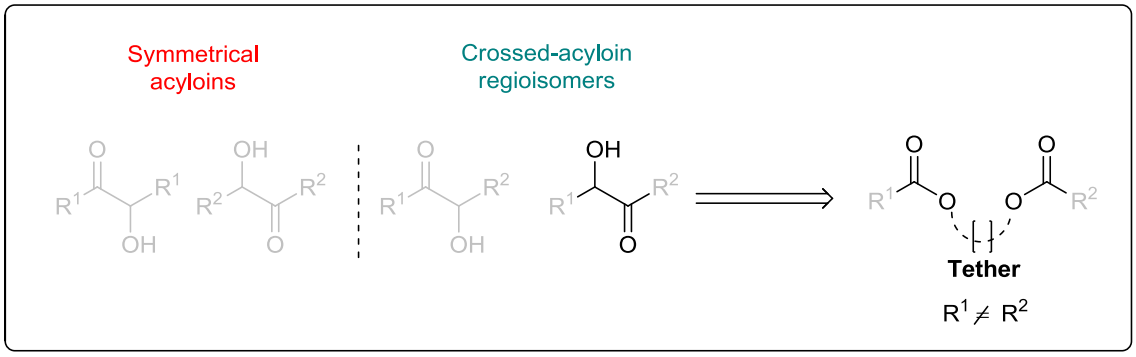


Figure 1-7 – Asymmetrically tethered di-ester in acyloin condensation.

In contrast, the new method would provide the opportunity to generate acyloin adducts under kinetically controlled conditions at –78 °C instead of the heterogeneous lithium in refluxing toluene procedure. In order to investigate the crossed-acyloin methodology, the following objectives were formulated:

- The primary effort was to find several methyl esters with distinctive chemical properties to be used as model substrate in the crossed-acyloin reaction.

- This objective was to be followed by screening for a suitable tether (linker), which would be compatible with Li/DBB reduction conditions, in order to achieve a chemoselective acyloin condensation (see Figure 1-**7**).

- Upon successful completion of these previous goals the next step would be to explore the possibility to achieve a regioselective crossed-acyloin condensation *i.e.* to form solely one crossed- acyloin product (see Figure 1-**7**).

- Finally, investigating the scope and limitation of the Li/DBB crossed acyloin condensation would be carried out.

This work is addressed in the following chapter.

Chapter 2: Results & Discussion –

An Alternative Route towards Crossed-Acyloins

2.0 An Alternative Route to Crossed-Acyloins

The aim of this project was to accomplish a chemo- and regioselective crossed-acyloin condensation, conducted under Li/DBB reduction conditions (see section **1.2.2.2**). Our strategy was to employ a tether based intramolecular acyloin condensation, following Hutchinson's methodology (see Scheme 1-**16**). Selection of a suitable diol, compatible with Li/DBB reduction conditions, would be the first step towards this aim. Our attention would then turn to improving the regioselectivity of the crossed-acyloin condensation by adjusting the reaction parameters. Finally, the scope and limitation of the crossed-acyloin condensation mediated by Li/DBB would be examined.

2.1 Intermolecular Acyloin Condensation

Initial efforts were directed towards finding two different esters with distinct chemical properties to be used as potential candidates in the crossed-acyloin reaction. The choice of methyl esters, partly due to their known reactivity in these conditions, was essential for the simplification of future NMR spectroscopic analysis of the reaction mixture (Figure 2-**1**).

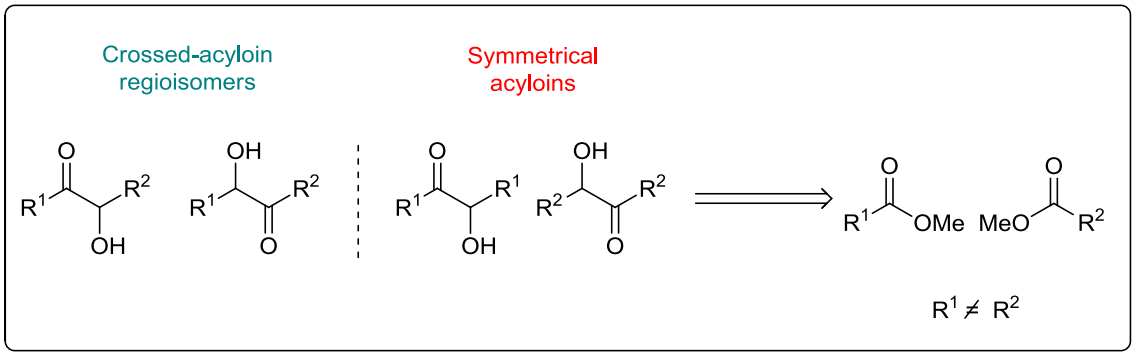
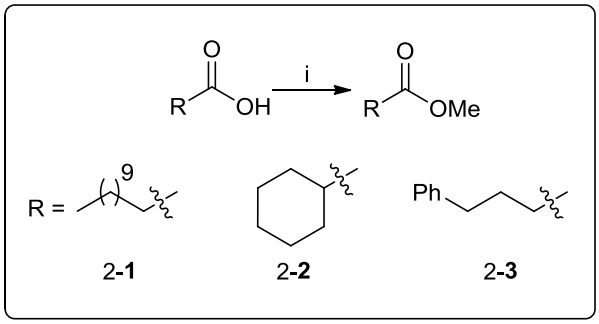


Figure 2-1 – Retrosynthetic analysis of the crossed-acyloin products and symmetrical acyloins.

2.1.1 Synthesis of Methyl Esters

Examining previous work in the group, especially with regards to analysis of the NMR spectrum and purification procedure, led to selection of the methyl esters of dodecanoate 2-**1**, cyclohexanecarboxylate 2-**2** and 4-phenylbutanoate 2-**3** as potential model substrates. Consequently, commercially available carboxylic acids were subjected to acidic esterification to yield the corresponding esters 2-**1**, 2-**2** and 2-**3** in excellent yields (Table 2-**1**, Entries 1-**3**).[38]



Entry	R	Product	Yield (%)
1	Undecyl	2-1	96
2	Cyclohexyl	2-2	95
3	Propylbenzyl	2-3	96

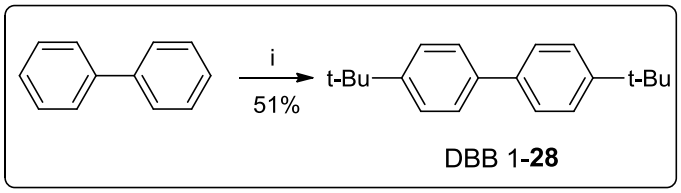
Reagents and conditions: i) H_2SO_4 (cat.), MeOH, r.t, 5 h.

Table 2-1 – Synthesis of methyl esters 2-**1**, 2-**2** and 2-**3**.

^{1}H-NMR studies indicated the formation of the diagnostic peak of methoxy group at δ 3.67 ppm in 2-**1**, 2-**2** and 2-**3,** as well as displaying the characteristic δ 174.2 ppm signal in the ^{13}C-NMR spectrum of the ester carbonyl. All the analytical data were consistent with those reported in the literature.[39,40]

2.1.2 Synthesis of Symmetrical Acyloins

The necessary electron-carrier DBB 1-**28** was prepared *via* a Friedel Crafts alkylation reaction. Subjecting commercially available biphenyl to a mixture of aluminium trichloride and *t*-butyl chloride in nitromethane at 0 °C provided the desired dialkylated product.[41] Upon recrystallisation in ethanol, 1-**28** was obtained in 51% yield as a white crystalline solid (Scheme 2-**1**).

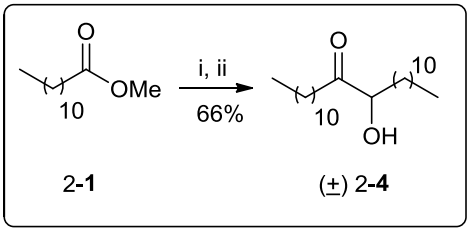


Reagents and conditions: i) $AlCl_3$ (1.0 eq.), *t*-butyl chloride (2.0 eq.), CH_3NO_2, 0-25 °C, 16 h.

Scheme 2-**1** – Synthesis of 1-**28**.

^{1}H-NMR analysis confirmed the formation of dialkylated product 1-**28** with two signals at δ 1.35 ppm (18 H) and at δ 7.55-7.44 ppm (8 H) with correct integration, which was consistent with the literature.[41]

In accordance with the procedure previously developed in the group, a solution of Li/DBB was prepared in a flame-dried Schlenk flask, by addition of Li to DBB in THF at 0 °C under an atmosphere of argon. The resulting teal-blue solution was stirred for four hours. The Li/DBB solution was then added dropwise to a solution of methyl ester 2-**1** in THF at –78 °C to furnish the acyloin 2-**4** in 66% yield as a white solid (Scheme 2-**2**).

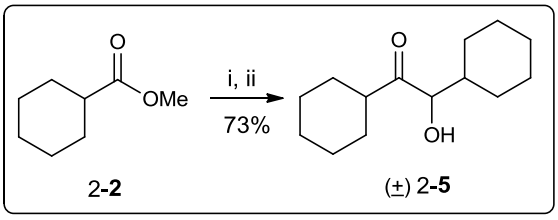


Reagents and conditions: i) Li (45 eq.), DBB (4.5 eq.), THF, –78 °C, 4.5 h ii) NH_4Cl (aq.).

Scheme 2-**2** – Reduction of ester 2-**1** to the corresponding acyloin 2-**4**.

The appearance of a multiplet at δ 4.19-4.15 ppm (1 H, CHOH) and a doublet at δ 3.50 ppm (1 H, CHOH) in the ^{1}H-NMR spectrum, as well as the characteristic signals for the ketone at δ 212.6 ppm and the carbinol at δ 76.4 in the ^{13}C-NMR spectrum, confirmed the presence of the acyloin functionality. In addition, IR spectroscopic analysis indicated the appearance of a broad O-H stretch at ν 3419 cm^{-1} and a ketone stretch at ν 1712 cm^{-1}, providing further confirmation of the formation of the acyloin moiety.[40]

Preparation of the second acyloin of interest was undertaken by exposing ester 2-**2** to the Li/DBB reduction conditions to form acyloin 2-**5** in 73% yield as a colourless oil (Scheme 2-**3**).

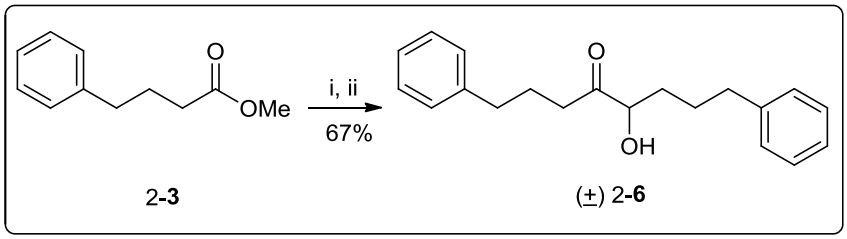


Reagents and conditions: i) Li (45 eq.), DBB (4.5 eq.), THF, –78 °C, 4.5 h. ii) NH_4Cl (aq.).

Scheme 2-**3** – Reduction of ester 2-**2** to the corresponding acyloin 2-**5**.

The presence of the characteristic acyloin signals in the ^{1}H-NMR spectrum at δ3.42 ppm (1H, CHOH, correlating to ν 3419 cm^{-1} in the IR spectrum) as a broad singlet and a doublet at δ 4.17 ppm (1H, CHOH), corresponded to the carbon signal at δ 79.3 ppm in the ^{13}C-NMR peak spectrum. In addition, the ketone peak appeared at δ 215.4 ppm, which was confirmed with the presence of carbonyl signal at ν 1731 cm^{-1} in the IR spectrum.[42]

The final symmetrical acyloin was generated by subjecting ester 2-**3** to analogous Li/DBB conditions, which delivered the desired product 2-**6** in 67% yield as colourless oil (Scheme 2-**4**).



Reagents and conditions: i) Li (45 eq.), DBB (4.5 eq.), THF, –78 °C, 4.5 h. ii) NH_4Cl (aq.).

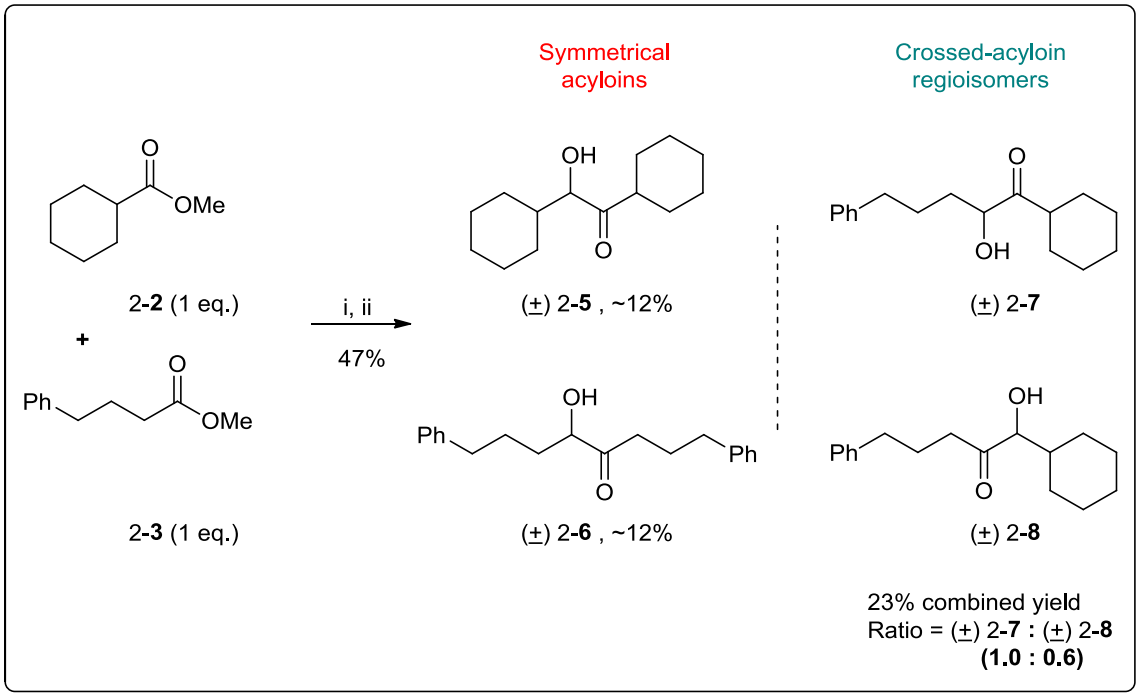
Scheme 2-**4** – Reduction of ester 2-**3** to the corresponding acyloin 2-**6**.

As expected, the appearance of a doublet of triplets at δ 4.16 ppm (1H, C<u>H</u>OH) and a broad singlet at δ 3.49 ppm (1H, CHO<u>H</u>) in the ^{1}H-NMR spectrum, and the typical carbonyl and carbinol signals at δ 212.0 ppm and δ 76.3 ppm respectively in the ^{13}C-NMR spectrum, were consistent with the formation of the α-hydroxyketone moiety. All analytical data were consistent with previous results in the group.[43]

The thin layer chromatographic (TLC) analysis revealed that in a 1:1 petrol:Et_2O solution mixture, the retention factor (R_f) for both acyloins 2-**4** and 2-**5** was 0.8, while in the case of acyloin 2-**6**, it was 0.4. The NMR studies indicated that the diagnostic signals of all the three acyloins 2-**4**, 2-**5** and 2-**6** appeared in the same region at δ 4.19-4.15 ppm. As expected, the non-selective crossed-acyloin condensation would form a mixture of crossed-acyloins and symmetrical acyloins, so due to convenient separation between acyloin 2-**5** and 2-**6** on silica gel, it was decided to select cyclohexanecarboxylate and 4-phenylbutanoate as the model substrates.

2.1.3 Synthesis of Crossed-acyloins

Initially, investigations into the intermolecular crossed-acyloin condensation was continued by subjecting an equimolar mixture of esters 2-**2** and 2-**3** to Li/DBB conditions, As expected, a statistical mixture of the acyloins 2-**5**, 2-**6**, 2-**7** and 2-**8** was generated. It is worth noting that in this case, the symmetrical acyloins 2-**5** (~12%) and 2-**6** (~12%) were isolated individually by flash column chromatography. By contrast, the reaction delivered the two crossed-acyloin regioisomers 2-**7** and 2-**8** in 23% as an inseparable mixture (Scheme 2-**5**).



Reagents and conditions: i) Li (45 eq.), DBB (4.5 eq.), THF, –78 °C, 4.5 h. ii) NH_4Cl (aq.).

Scheme 2-**5** – Reduction of esters 2-**2** and 2-**3** to corresponding acyloins 2-**5**, 2-**6**, 2-**7** and 2-**8**.

The ^{1}H-NMR analysis of the crossed-acyloin mixture 2-**7** and 2-**8** indicated the appearance of a multiplet at δ 4.30-4.27 ppm and a double doublet at δ 4.03 ppm corresponded to the carbinol functionaries in 2-**7** and 2-**8**. Furthermore, in the ^{13}C-NMR spectrum the presence of signals at δ 215.6 ppm (2-**7**, carbonyl), δ 212.5 ppm (2-**8**, carbonyl) followed by, δ 81.2 ppm

(2-**7**, CHOH) and δ 75.2 ppm (2-**8**, CHOH) confirmed the synthesis of the crossed-acyloins 2-**7** and 2-**8**.

The ratio between the symmetrical (2-**5** and 2-**6**) and crossed-acyloins (2-**7** and 2-**8**) was established by integration of the acyloin signals in the crude ^{1}H-NMR spectrum; signals at δ 4.30-4.27 ppm (2-**7**, CHOH), δ 4.17-4.15 ppm (2-**5** and 2-**6**, CHOH) and δ 4.03 ppm (2-**8**, CHOH), which confirmed the ratio of (2.1:1.6) for the symmetrical acyloins 2-**5** and 2-**6**: crossed acyloins 2-**7** and 2-**8** (Figure 2-**2**).

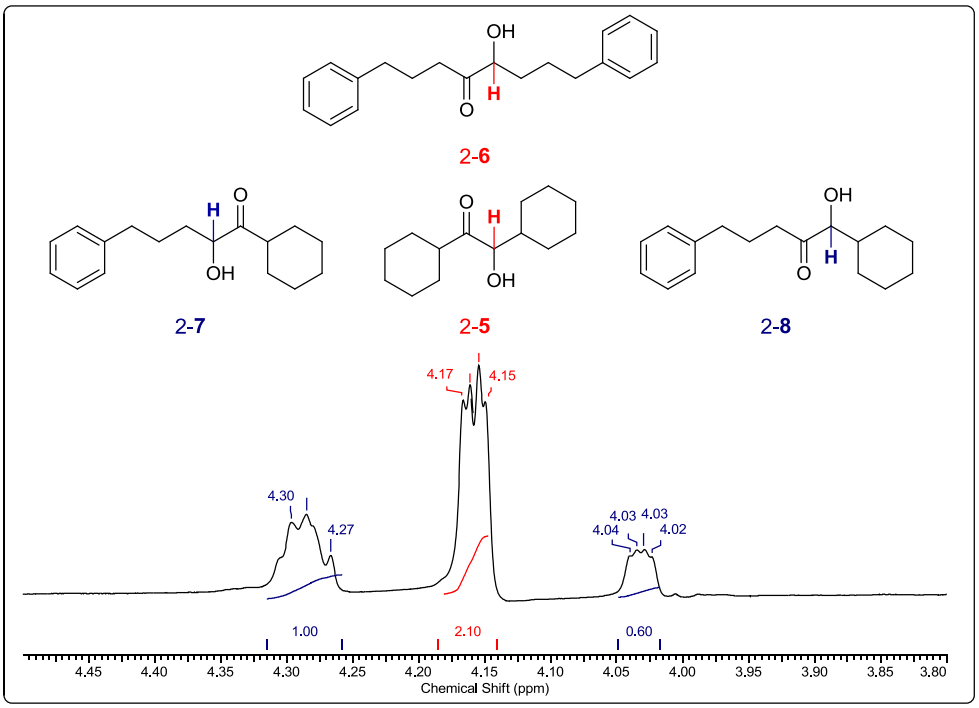


Figure 2-**2:** The appearance of a multiplet at δ 4.30-4.27 ppm (2-**7**, CHOH), a multiplet at δ 4.17-4.15 ppm (2-**5** and 2-**6**, CHOH) and a doublet at δ 4.03 ppm (2-**8**, CHOH) in the 200 MHz ^{1}H-NMR spectrum of the crude product mixture.

With the establishing the crossed-acyloin diagnostic NMR signals in hand, our attentions turned to examine the potential reactivity of the model substrates in an intramolecular crossed-acyloin reaction.

2.2 Tether-Based Intramolecular Acyloin Condensation

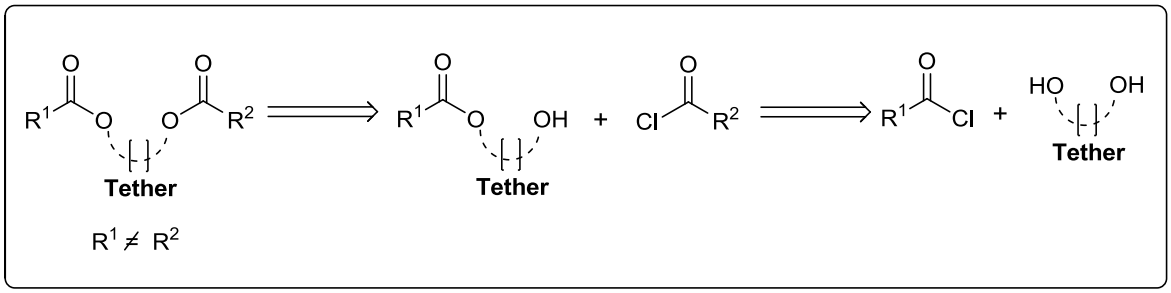


Figure 2-**3 –** Sequential synthesis of di-ester.

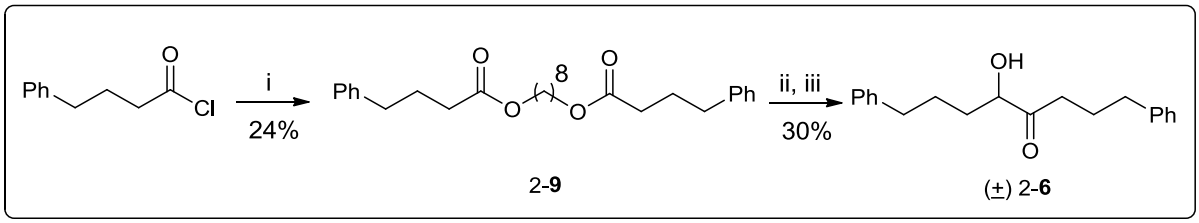
Having selected suitable substrates for the acyloin condensation, the possibility of introducing a tether compatible with Li/DBB reduction conditions, in order to control the chemoselectivity in the crossed-acyloin reaction was investigated. It was envisaged that the required substrates (di-esters) for this investigation could be easily accessed by esterification of two different acyl chlorides with the linker (diol), following literature procedure (see Figure 2-**3**).[18]

2.2.1 Unsubstituted Diols as Linkers

The initial objective was to establish a reference for the Li/DBB mediated tethered acyloin condensation, by repeating the reaction with simple unsubstituted diols as linkers, as previously reported in the literature.[18] The best yield and chemoselectivity in the tether-based heterogenous crossed-acyloin conditions was obtained by employing 1,8-octane diol as a linker (see Table 1-**2**, Entry **6**). In order to establish a reference for the homogeneous Li/DBB mediated crossed-acyloin condensation, 1,8-octane diol was initially selected as a tether.

2.2.1.1 1,8-Octane Diol as a Linker

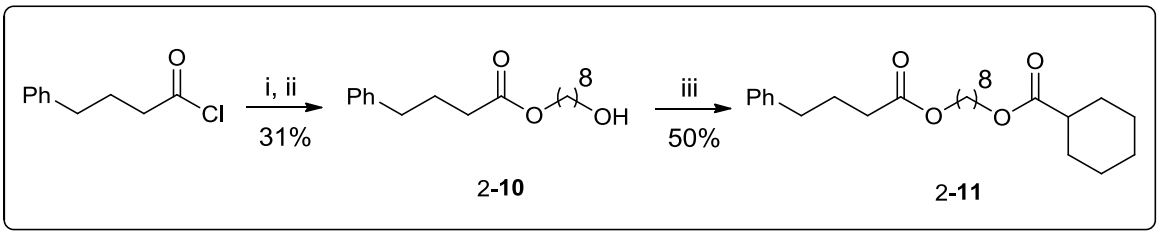
The yield and selectivity of di-esters linked with 1,8-octane diol under Li/DBB reducing conditions were studied. Initially, SET reduction of symmetrical di-ester 2-**9** was examined, in order to study the reaction and establish the yield. Thus, the symmetrical di-ester 2-**9** was generated first, by transformation of commercially available 4-phenylbutanoyl chloride to the requisite symmetrical di-ester 2-**9** in 24% yield (Scheme 2-**6**). Compound 2-**9** was then subjected to the Li/DBB reducing conditions to form symmetrical acyloin 2-**6** in 30% yield.[43] It is worth noting that the yield was significantly lower in these homogeneous conditions than in the case of previous observation in heterogeneous conditions reported by Hutchinson *et al.* (see Table 1-**2**, Entry **6**).



Reagents and conditions: i) Pyridine (2.5 eq.), diol (2.0 eq.), CH_2Cl_2, r.t, 16h.
ii) Li (10 eq.), DBB (4.0 eq.), THF, –78 °C, 4.5 h. iii) NH_4Cl (aq.).

Scheme 2-**6** – Reduction of di-ester 2-**9** to the corresponding acyloin 2-**6**.

The investigation was continued by application of 1,8-octane diol in an intramolecular crossed-acyloin condensation reaction. Thus, commercially available 4-phenylbutanoyl chloride was converted to the mono-ester 2-**10** in 31% yield (Scheme 2-**7**). The desired non-symmetrical di-ester 2-**11** was synthesised by esterification of 2-**10** with the commercially available cyclohexanecarbonyl chloride to deliver di-ester 2-**11** in 50% yield (Scheme 2-**7**).

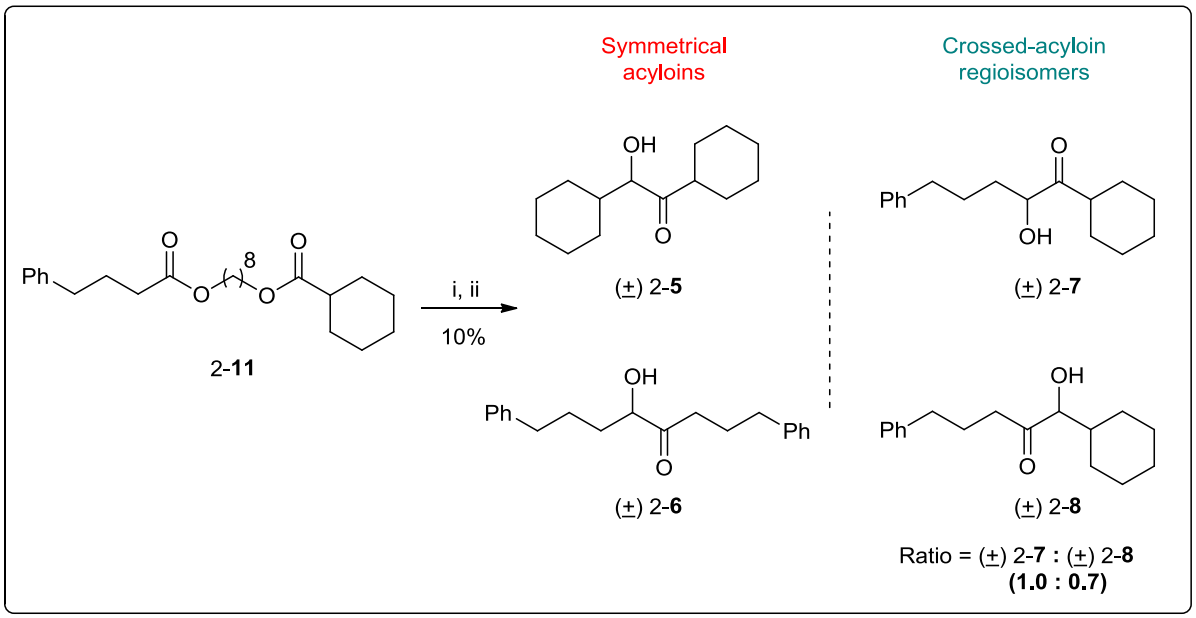


Reagents and conditions: i) Pyridine (1.2 eq.), diol (1.5 eq.), CH_2Cl_2, r.t, 3 h.
ii) Acid chloride, pyridine (2.5 eq.), CH_2Cl_2, r.t, 16 h.

Scheme 2-7 – Preparation of the non-symmetrical di-ester 2-**11**.

The appearance of four protons as a multiplet at δ 4.02-4.09 ppm (2-**11**, CO_2CH_2) in the ^{1}H-NMR spectrum confirmed the formation of 2-**11**. In addition, appearance of two distinct carbonyl peaks at δ 176.2 ppm and δ 173.6 ppm, further validated the key substrate 2-**11**.

This work was followed by exposure of di-ester 2-**11** to the Li/DBB reduction conditions to generate a mixture of acyloins 2-**5**, 2-**6**, 2-**7** and 2-**8** in a poor combined yield of only 10% (Scheme 2-**8**).



Reagents and conditions: i) Li (10 eq.), DBB (4.0 eq.), THF, –78 °C, 4.5 h. ii) NH_4Cl (aq.).

Scheme 2-8 – Reduction of di-ester 2-**11** to the corresponding acyloins 2-**5**, 2-**6**, 2-**7** and 2-**8**.

The ^{1}H-NMR spectrum of the crude acyloin mixture confirmed the formation of symmetrical acyloins (2-**5** and 2-**6**): crossed-acyloins (2-**7** and 2-**8**), in a ratio of 1:1, depicted in Figure 2-**4**.

Disappointingly, this outcome was similar to the *untethered* intermolecular acyloin condensation (see Scheme 2-**5**).

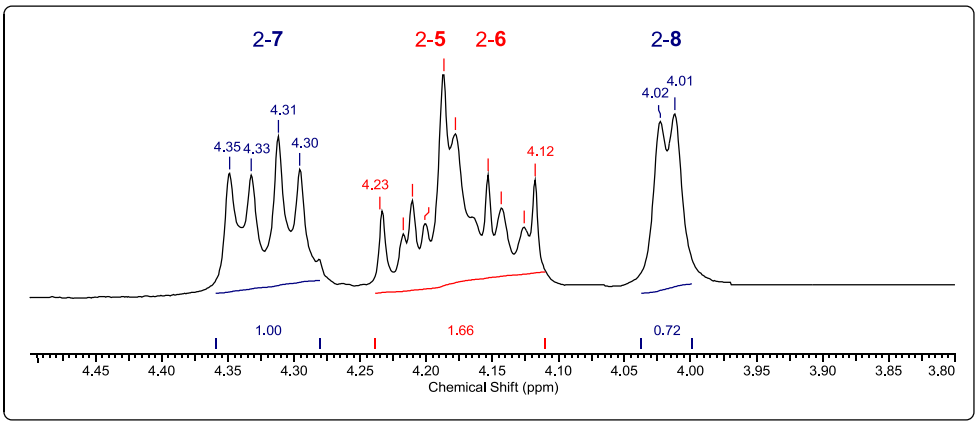


Figure 2-**4:** Depicts the appearance of a double doublet at δ4.32-4.31 ppm (2-**7**, CHOH), a multiplet at δ 4.23-4.12 ppm (2-**5** and 2-**6**, CHOH) and a doublet at δ 4.01 ppm (2-**8**, CHOH) in the 200 MHz ^{1}H-NMR spectrum of the crude mixture.

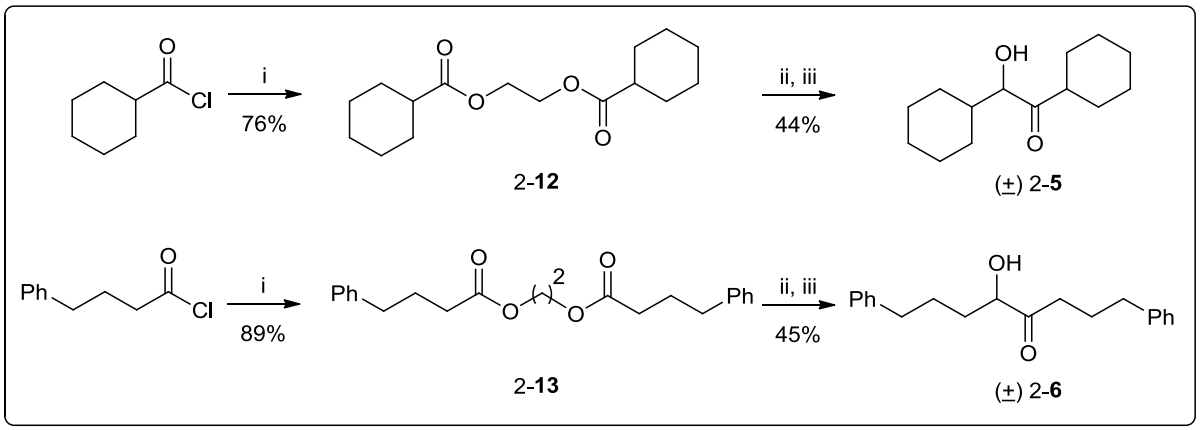
These results demonstrated that the difference between the homogenous Li/DBB reduction conditions and the heterogenous sodium in refluxing toluene procedure (see Table 1-**3**, Entry 2), which achieved this transformation with a better yield (57%) with the 1,8-octane diol linker. It was suggested that the yield and selectivity of the reaction might be improved by employing a shorter linker such as ethylene glycol, which provides closer proximity for the carbon-carbon bond formation between two acyl functionalities in the reacting di-ester.

2.2.1.2 Ethylene Glycol as a Linker

With the results of 1,8-octane diol in hand, our attention turned to use of the shorter ethylene glycol as the tether.

Following the same protocol, symmetrical di-esters 2-**12** and 2-**13** were separately prepared by diesterification of ethylene glycol with commercially available 4-phenylbutanoyl chloride

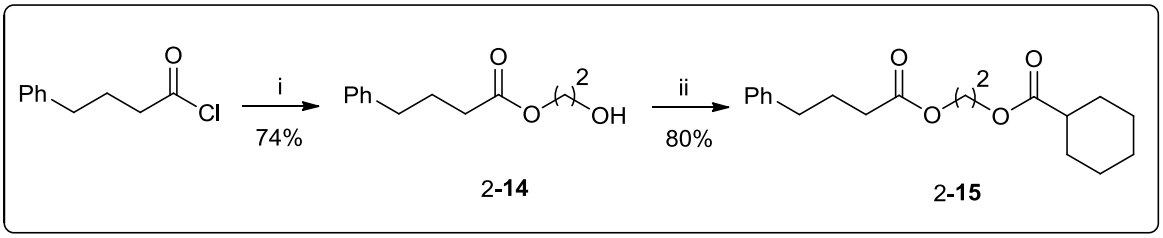
and cyclohexanecarbonyl chloride to deliver the di-esters 2-**12** in 89% yield and 2-**13** in 76% (Scheme 2-**9**). Compound 2-**12** was then exposed to the Li/DBB reduction conditions to furnish acyloin 2-**5** in moderate yield of 45%, while reduction of di-ester 2-**13** yielded 44% of the acyloin 2-**6** (Scheme 2-**9**).[43] Pleasingly, the yield of the reaction was significantly higher than the 22% yield reported by Hutchinson *et al*. under heterogenous conditions (see Table 1-**2**, Entry **3**).



Reagents and conditions: i) Pyridine (2.5 eq.), diol (2.0 eq.), CH_2Cl_2, r.t, 16h, ii) Li (10 eq.), DBB (4.0 eq.), THF, –78 °C, 4.5 h. iii) NH_4Cl (aq.).

Scheme 2-**9** – Reduction of symmetrical di-esters 2-**12** and 2-**13** to the acyloins 2-**5** and 2-**6**.

Having confirmed that the reaction works with the symmetrical di-esters 2-**12** and 2-**13**, the reaction was conducted with non-symmetrical di-ester 2-**15** in order to investigate the potential chemoselectivity of the reaction. Compound 2-**15** was obtained in an overall yield of 60% over two steps, by stepwise esterification of ethylene glycol via mono-ester 2-**14** (Scheme 2-**10**).

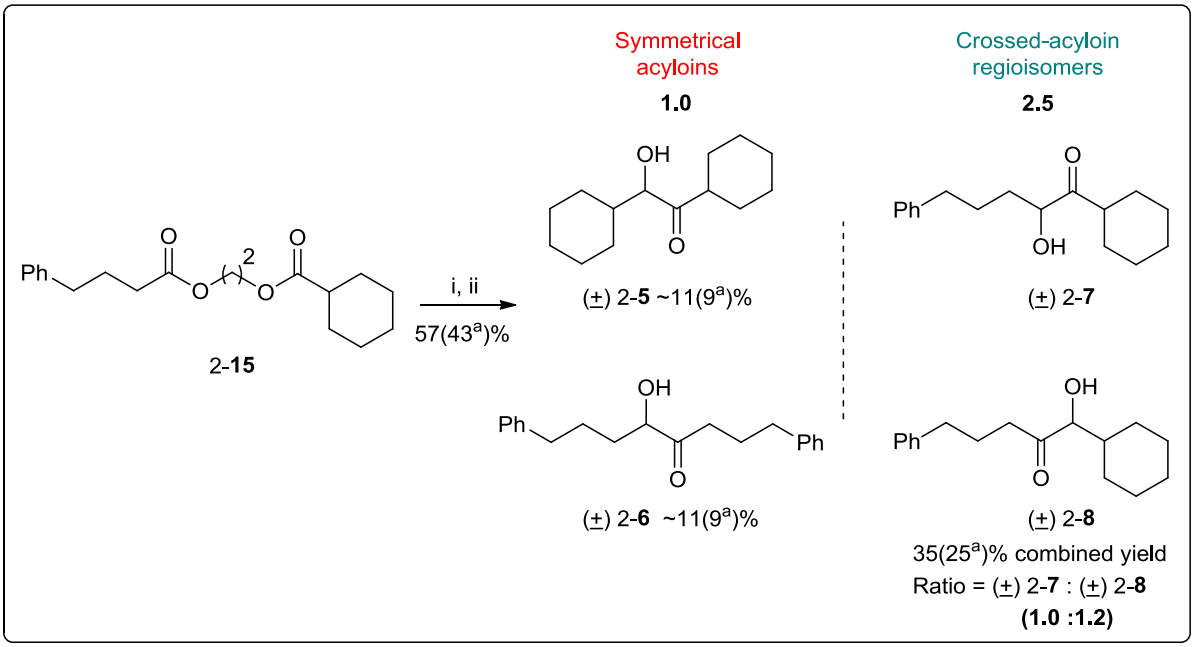


Reagents and conditions: i) Pyridine (1.2 eq.), diol (1.5 eq.), CH_2Cl_2, r.t, 3h.
ii) Acid chloride, pyridine (2.5 eq.), CH_2Cl_2, r.t, 16h.

Scheme 2-**10** – Preparation of the non-symmetrical di-ester 2-**15**.

The appearance of four protons as a singlet at δ 4.28 ppm in the ^{1}H-NMR spectrum and the presence of the characteristic signals of the *O*-alkyl functionalities at δ 62.2 ppm and δ 61.9 ppm in the ^{13}C-NMR spectrum confirmed the formation of product 2-**15**.

Subjecting 2-**15** to the Li/DBB reduction conditions generated symmetrical acyloins 2-**5** and 2-**6**, both in 9% yield, while forming the crossed-acyloins 2-**7** and 2-**8** in a combined yield of 25% (Scheme 2-**11**).



Reagents and conditions: i) Li (10 eq.), DBB (4.0 eq.), THF, –78 °C, 4.5 (3.0) h. ii) NH_4Cl (aq.).

Scheme 2-**11** – Reduction of di-ester 2-**15** to the corresponding acyloins 2-**5**, 2-**6**, 2-**7** and 2-**8**.
a) Addition of the Li/DBB reducing agent to the di-ester 2-**15**.

It was hypothesised that the radical decomposition of the substrate would be minimised in higher dilution/reverse addition of the substrate to the Li/DBB solution, *i.e.* sufficient concentration of electrons in the reaction improves the dimerisation instead radical decomposition of the di-ester. Thus, the reaction conditions were repeated by slow addition of a solution of 2-**15** to a stirring solution of Li/DBB at −78 °C; this change improved the yield of the crossed-acyloin products to 57%, and reduced the reaction time to three hours, but the chemoselectivity of the reaction remained the same. However, the reaction produced a significant amount of the parent carboxylic acids as by-products, which accounted for the rest of the consumed mass. This observation was consistent with previous reports in the literature (see Scheme 1-**18**).[18]

As before, by comparing the integrals of the diagnostic signals of the symmetrical acyloins 2-**5** and 2-**6**, and the crossed acyloins 2-**7** and 2-**8**, and in ^{1}H-NMR spectrum of the crude mixture, the ratio was established in 1.0:2.5 favour of the formation of crossed acyloins 2-**7** and 2-**8** (Figure 2-**5**).

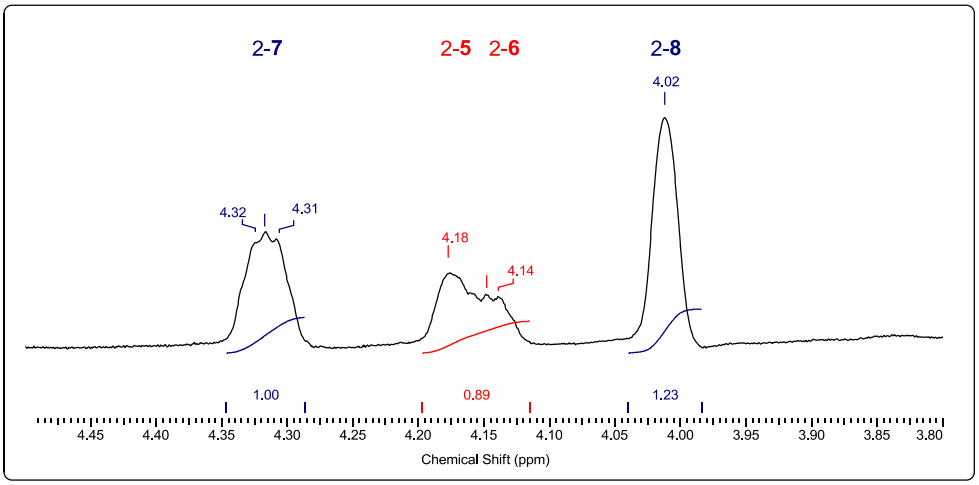
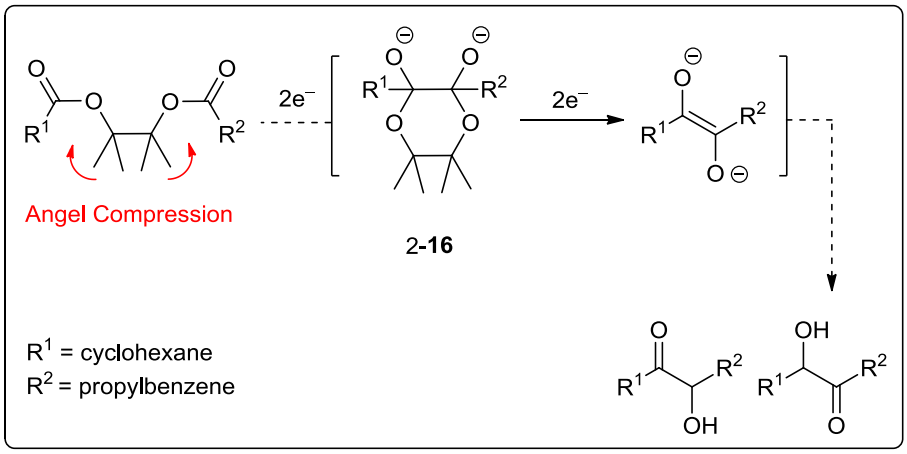


Figure 2-**5:** Depicts the appearance of a multiplet at δ 4.30-4.27 ppm (2-**7**, CHOH), a multiplet at δ 4.18-4.14 ppm (2-**5** and 2-**6**, CHOH) and a broad singlet at δ 4.02 ppm (2-**8**, CHOH) in the 200 MHz ^{1}H-NMR spectrum of the crude mixture.

2.2.2 Substituted Diols

Encouragingly, the results obtained from employing ethylene glycol as a tether demonstrated that close proximity of the ketyl radical anions promoted the intramolecular reaction pathway, thus providing higher selectivity and yield. The use of substituted diols as potential linkers in intramolecular crossed-acyloin condensation mediated by Li/DBB was then investigated (Scheme 2-**12**). It was hypothesised that the application of Thorpe-Ingold effect would accelerate the intramolecular reaction, *i.e.* a higher angle compression in the substituted diols could favour the formation of the six-membered ring di-alkoxy 2-**16** as the key intermediate in the reaction (Scheme 2-**12**).



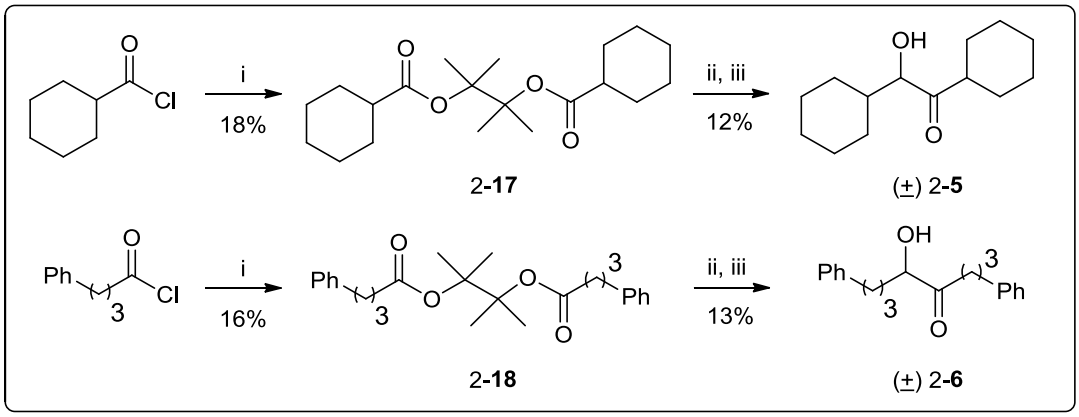
Scheme 2-**12** – Employment of Thorpe-Ingold effect in tethered based crossed-acyloin conditions.

Consequently, pinacol and 2,2-dimethylpropane-1,3-diol were chosen as good candidates due to their bulky characteristics.

2.2.2.1 Pinacol as a Linker

Following the previously described procedure, di-esters 2-**17** and 2-**18** were synthesised, which delivered di-ester 2-**17** in 16% yield, and di-ester 2-**18** in 18% yield (Scheme 2-**13**).

The poor yield of the reaction was most likely due to the imposed steric bulk of the methyl group present in the pinacol, which drastically reduced the nucleophilicity of the diol.



Reagents and conditions: i) Pyridine (2.2 eq.), diol (2.5 eq.), CH_2Cl_2, r.t, 16 h
ii) Li (10 eq.), DBB (4.0 eq.), THF, –78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**13** – Reduction of symmetrical di-esters 2-**17** and 2-**18** to the acyloins 2-**5** and 2-**6**.

Compound 2-**17** and 2-**18** were separately subjected to the Li/DBB reduction conditions, which respectively yielded acyloin 2-**5** in 12% yield and acyloin 2-**6** in 13% (see Scheme 2-**13**). The experimental observation indicated that the poor yield was due to the radical decomposition of the substrates to the parent carboxylic acids.

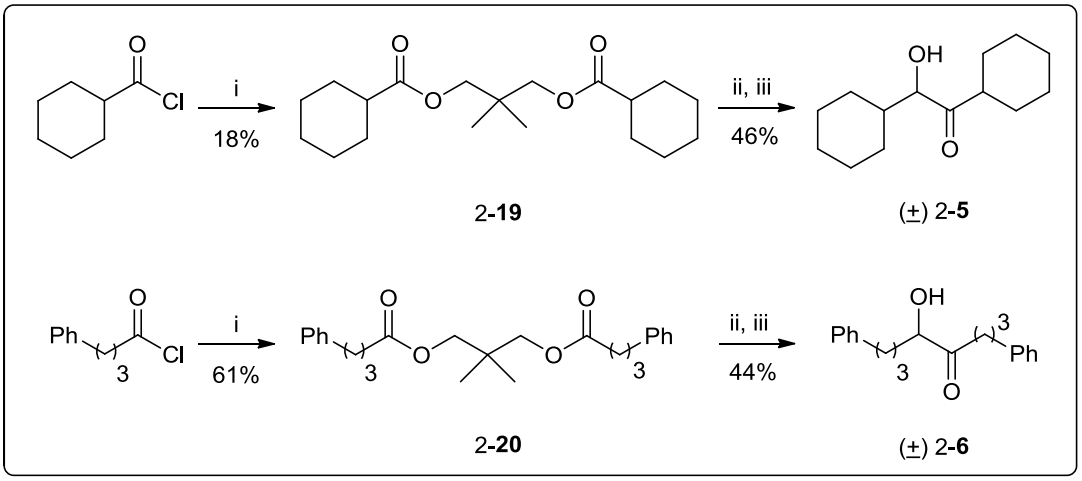
These negative results were consistent with previous observations in the group that the Li/DBB mediated reduction of *t*-butyl esters predominantly formed the parent carboxylic acids, caused by radical cleavage of the *O*-alkyl functionality. Due to the impact of this side reaction, it was decided that the application of this linker would be unproductive in crossed-acyloin condensations.

2.2.2.2 2,2-Dimethyl 1,3-Propane Diol as a Linker

The next hypothesis was to investigate the compatibility of 2,2-dimethyl 1,3-propane diol as a

tether in Li/DBB mediated conditions; it had been demonstrated in the group that esters bearing unsubstituted *O*-alkyl carbon chains minimised radical decomposition of the substrate. It was proposed that by using 2,2-dimethyl 1,3-propane diol as the linker, the risk of decomposition would be avoided, allowing the geminal effect of the dimethyl group to be examined.

As before, symmetrical di-esters 2-**19** and 2-**20** were generated separately by acylation of 2,2-dimethyl-1,3-propane diol with commercially available 4-phenylbutanoyl chloride and cyclohexanecarbonyl chloride, which furnished di-ester 2-**19** in 61% yield, while di-ester 2-**20** was delivered in 18% yield (Scheme 2-**14**).



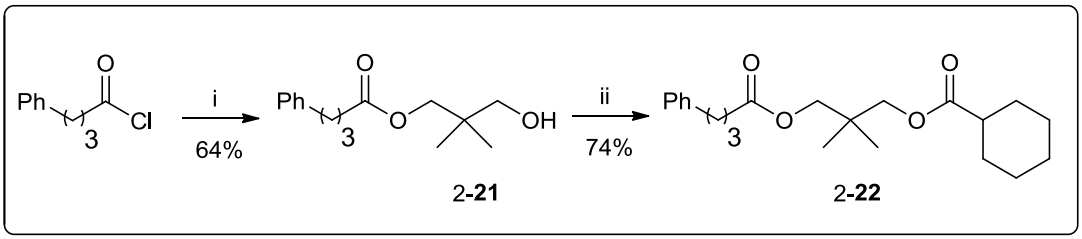
Reagents and conditions: i) Pyridine (2.2 eq.), diol (2.5 eq.), CH_2Cl_2, r.t, 16h.
ii) Li (10 eq.), DBB (4.0 eq.), THF, –78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**14** – Reduction of symmetrical di-esters 2-**19** and 2-**20** to the acyloins 2-**5** and 2-**6**.

With the symmetrical di-esters 2-**19** and 2-**20** in hand, our attention turned to subjecting these esters to Li/DBB reducing conditions. The SET reduction of the di-ester 2-**19** delivered symmetrical acyloin 2-**5** in 44% yield, while reduction of di-ester 2-**20** formed acyloin 2-**6** in 46% yield (see Scheme 2-**13**). As previously observed, radical cleavage generates the parent carboxylic acid, resulting in lower yield of acyloins 2-**5** and 2-**6**. Nevertheless, the yield

of the reaction improved significantly compared to previous attempts with pinacol (see Scheme 2-**13**).

After establishing the potential reactivity of the symmetrical di-esters 2-**19** and 2-**20** in Li/DBB conditions, our attention turned to the employment of 2,2-dimethyl 1,3-propane diol in an intramolecular crossed-acyloin reaction. For that purpose, mono-ester 2-**21** was readily synthesised by mono-esterification of the diol with 4-phenylbutanoic acid to deliver 2-**21** in 64% yield. Further acylation of 2-**21** with an excess of cyclohexanecarbonyl chloride in the presence of pyridine produced di-ester 2-**22** in 74% yield (Scheme 2-**15**).

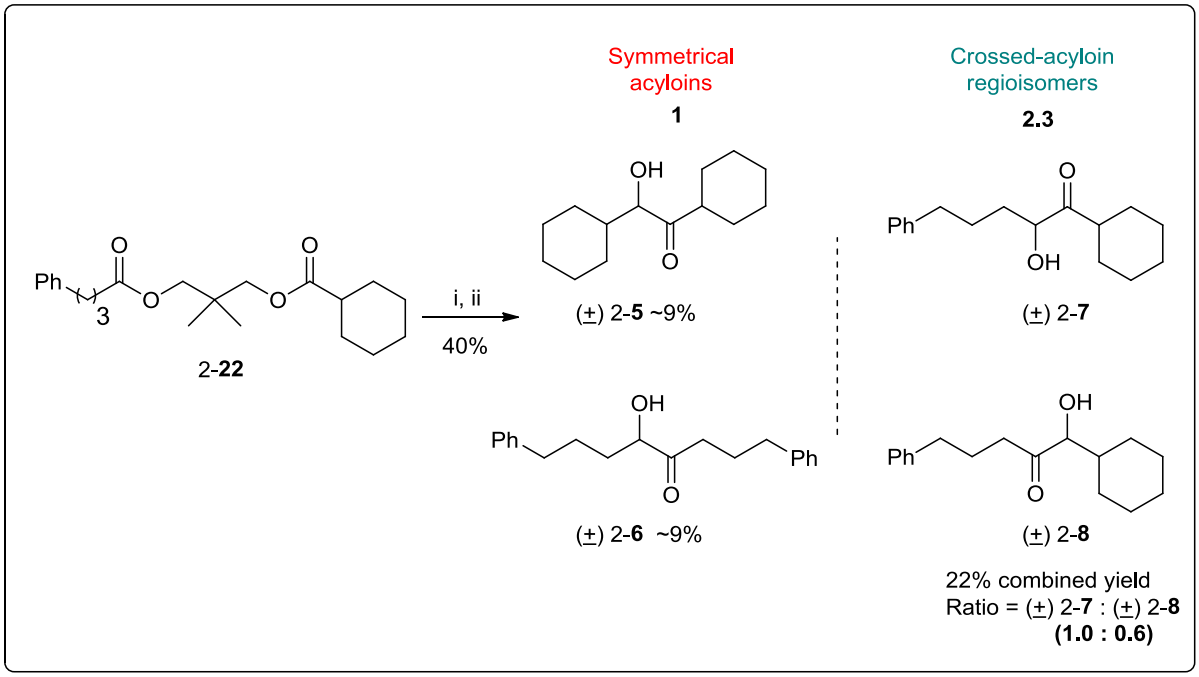


Reagents and conditions: i) Pyridine (1.2 eq.), diol (1.5 eq.), CH_2Cl_2, r.t, 3h.
ii) Acid chloride, pyridine (2.5 eq.), CH_2Cl_2, r.t, 16h.

Scheme 2-15 – Preparation of the non-symmetrical di-ester 2-**22**.

The appearance of four protons as two singlets at δ 3.89 ppm and δ 3.88 ppm in the ^{1}H-NMR spectrum and the presence of two carbonyl peaks at δ 175.4 ppm and δ 173.4 ppm as well as two *O*-alkyl signals at δ 69.2 ppm and δ 68.8 ppm in the ^{13}C-NMR spectrum, confirmed the bis-acylation of the diol.

The investigation was continued by exposing 2-**22** to the Li/DBB reduction conditions to furnish the two crossed-acyloin regioisomers 2-**7** and 2-**8** in a combined yield of 22% (Scheme 2-**16**).



Reagents and conditions: i) Li (10 eq.), DBB (4.0 eq.), THF, –78 °C, 3 h. ii) NH_4Cl (aq.).

Scheme 2-16 – Reduction of di-ester 2-**22** to the corresponding acyloins 2-**5**, 2-**6**, 2-**7** and 2-**8**.

The remaining symmetrical acyloins 2-**5** and 2-**6** were both isolated in 9% yield, which confirmed the formation of symmetrical (2-**5** and 2-**6**): and the crossed-acyloin (2-**7** and 2-**8**) in the ratio of (1:2) (see Scheme 2-**16**).

As before, the ratio of the involved acyloins was confirmed by analysis of the ^{1}H-NMR spectrum of the crude product mixture; appearance of the characteristic acyloin signals for the symmetrical acyloins 2-**5** and 2-**6**: crossed-acyloins 2-**7** and 2-**8**, confirmed the ratio of 1:2 (Figure 2-**7**).

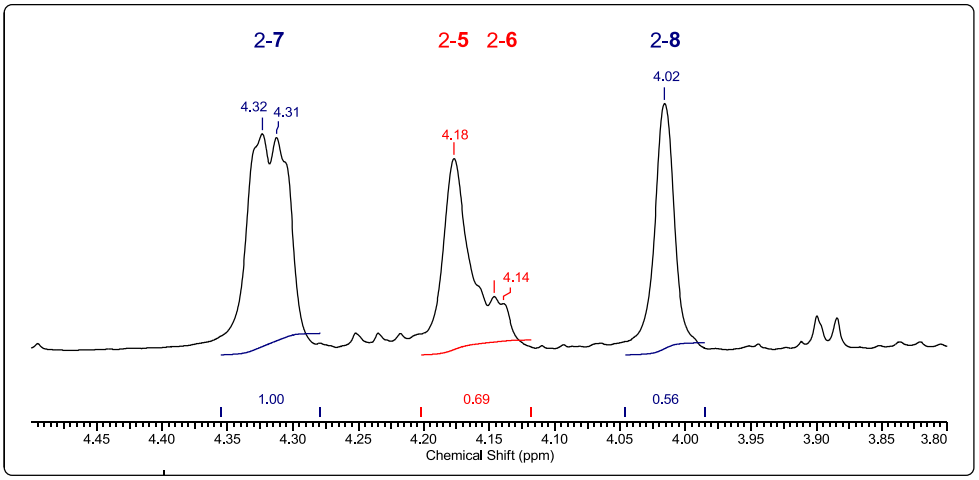


Figure 2-7: Depicts the appearance of a multiplet at δ 4.30-4.27 ppm (2-**7**, CHOH), a multiplet at δ 4.17-4.15 ppm (2-**5** and 2-**6** CHOH) and a broad singlet at δ 4.03 ppm (2-**8**, CHOH) in the 200 MHz ^{1}H-NMR spectrum of the crude mixture.

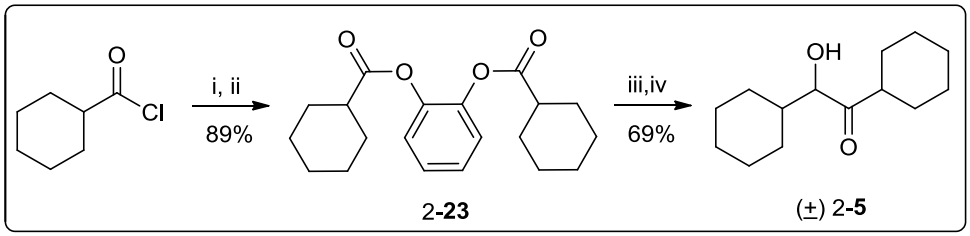
These results from the 2,2-dimethyl 1,3-propane diol indicated that the steric bulk of the geminal methyl groups did not have a significant effect on the chemoselectivity and yield of the reaction, in comparison to ethylene glycol (*symmetrical* acyloins 2-**5** and 2-**6**: *crossed*-acyloins 2-**7** and 2-**8**, 1.0:2.5, see Figure 2-**5**). Therefore, it was decided to improve the selectivity by employing a more rigid aromatic 1,2 diol such as pyrocatechol as a linker. It was suggested that the diol would provide closer proximity between the reacting acyl functionalities at the transition state, which consequently would affect the selectivity.

2.2.3 Pyrocatechol as Linker

As illustrated in the previous section, the close positioning of the ketyl radical anion groups did enhance the chemoselectivity of the crossed-acyloin reaction. Therefore, our attentions turned to investigating pyrocatechol as a potential linker in intramolecular crossed-acyloin condensation mediated by Li/DBB. It was speculated that the rigid aromatic structure of pyrocatechol would provide closer proximity for the acyl groups to react, due to the small

torsion angle (ϕ = 0°) between the hydroxyl groups in the diol.

Thus, symmetrical di-ester 2-**23** was synthesised in 89% yield following the same esterification procedure employing cyclohexanecarbonyl chloride and pyrocatechol as reagents. Compound 2-**23** was then exposed to the Li/DBB reduction conditions to deliver acyloin 2-**5** in 69% yield (Scheme 2-**17**).

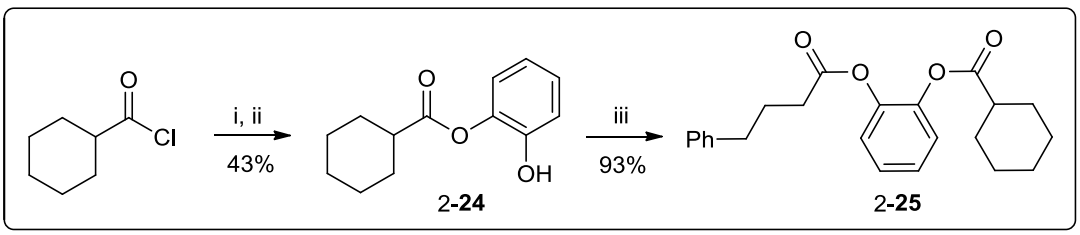


Reagents and conditions: i) Et_3N (2.2 eq.), diol (2.5 eq.), CH_2Cl_2, r.t, 16h.
ii) Li (10 eq.), DBB (4.0 eq.), THF, – 78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**17** – Reduction of symmetrical di-ester 2-**23** to the corresponding acyloin 2-**5**.

To our satisfaction, application of the catechol linker provided higher yields compared to previous attempts.

This positive outcome led us to employ pyrocatechol as the linker in an intramolecular crossed-acyloin condensation. The desired non-symmetrical di-ester 2-**25** was synthesised by esterification of the diol to form mono-ester 2-**24** in 43% yield, which was subsequently reacted with cyclohexanecarbonyl chloride to deliver di-ester 2-**25** in 93% yield (Scheme 2-**18**).

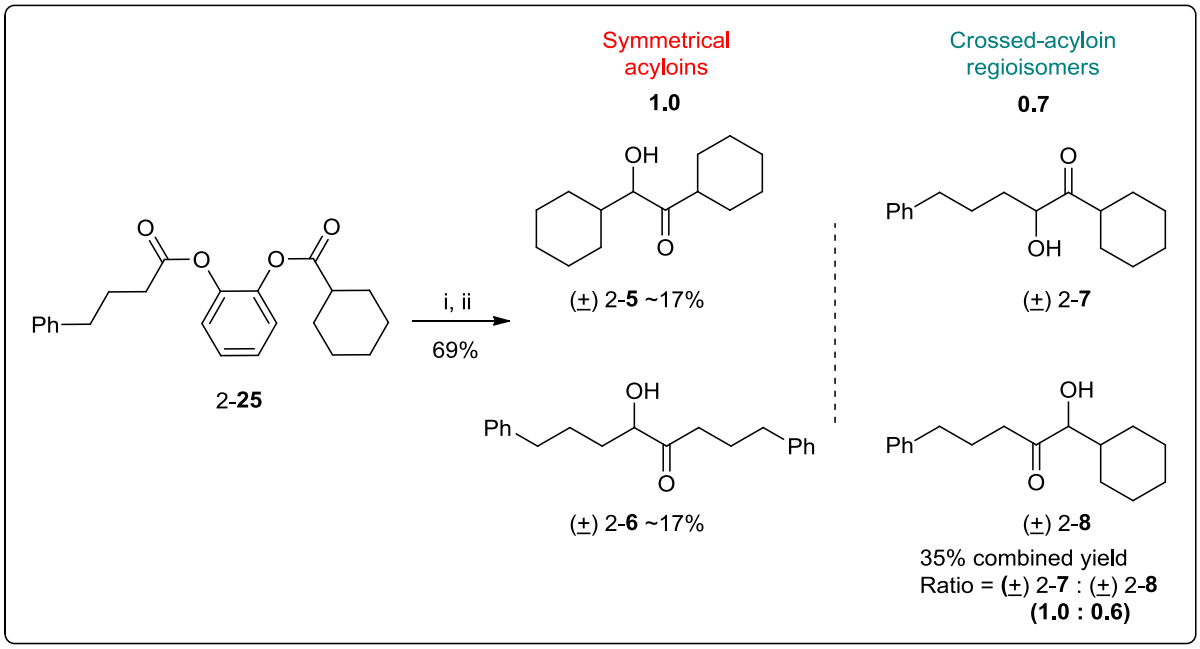


Reagents and conditions: i) Pyridine (1.1 eq.), diol (1.5 eq.), CH_2Cl_2, r.t, 3h.
ii) Acid chloride (2.5 eq.), Et_3N (2.5 eq.), CH_2Cl_2, r.t, 16h.

Scheme 2-**18** – Preparation of the non-symmetrical di-ester 2-**25**.

The appearance of nine protons as a multiplet in the aromatic region at δ 7.32-7.18 ppm in the ^{1}H-NMR spectrum confirmed the presence of two phenyl groups corresponding to the catechol and the phenyl substituent in the di-ester 2-**25**. Furthermore, the distinctive carbonyl signals at δ 175.9 ppm and δ 173.4 ppm in the ^{13}C-NMR spectrum confirmed the formation of di-ester 2-**25**.

Subsequent treatment of di-ester 2-**25** with the Li/DBB reduction conditions delivered a mixture of acyloins 2-**5**, 2-**6**, 2-**7** and 2-**8** in a combined yield of 69% (Scheme 2-**19**).



Reagents and conditions: i) Li (10 eq.), DBB (4.0 eq.), THF, –78 °C, 3 h. ii) NH_4Cl (aq.).

Scheme 2-**19** – Reduction of di-ester 2-**25** to the corresponding acyloins 2-**5**, 2-**6**, 2-**7** and 2-**8**.

Disappointingly, the reaction generated an almost statistical mixture of the acyloin products 2-**5**, 2-**6**, 2-**7** and 2-**8** based on isolated yields by flash column chromatography. As previously, the ratio of the acyloin products was confirmed by analysis of the ^{1}H-NMR spectrum of the crude acyloin mixture, the ratio between the crossed acyloins 2-**7** and 2-**8**, and the symmetrical acyloins 2-**5** and 2-**6** was 1:1 (Figure 2-**8**).

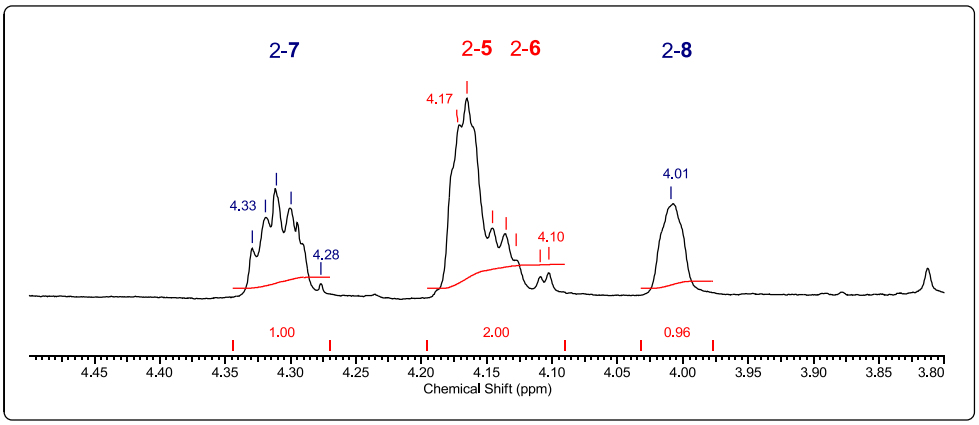
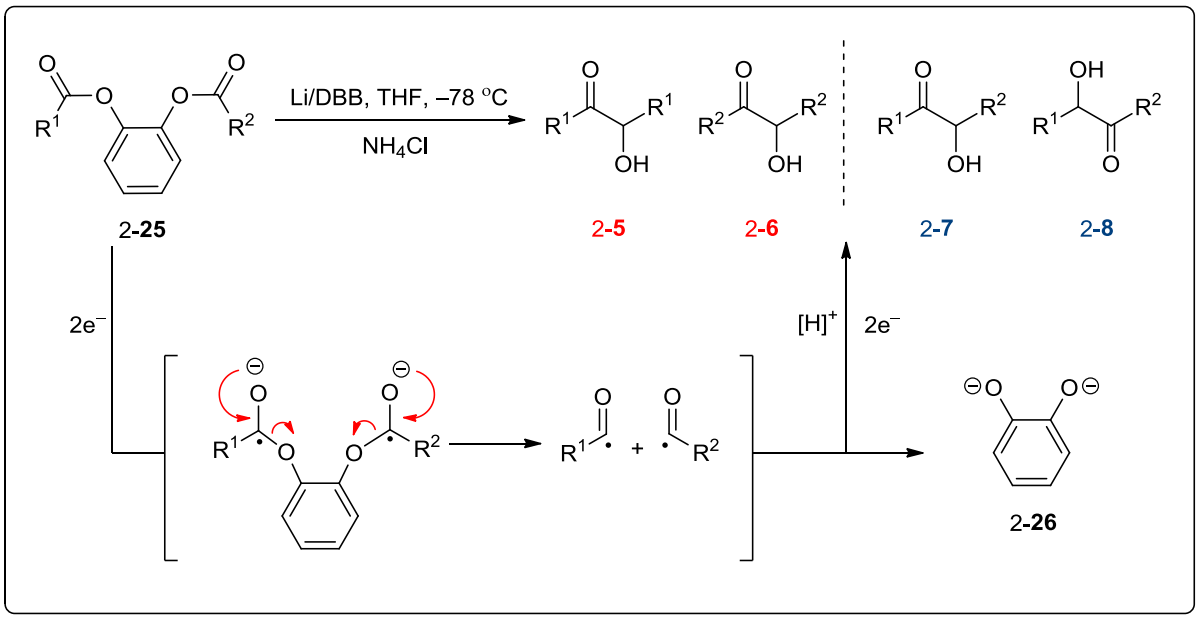


Figure 2-8: Depicts the appearance of a multiplet at δ 4.33-4.28 ppm (2-**7**, CHOH), a multiplet at δ 4.17-4.10 ppm (2-**5** and 2-**6**, CHOH) and a broad singlet at δ 4.03 ppm (2-**8**, CHOH) in the 200 MHz ^{1}H-NMR spectrum of the crude mixture.

It was speculated that the low chemoselectivity was the result of the higher stability of the catechol anion 2-**26** (pK$_a$ = 9.45 and 12.8) compared to alkoxides (pK$_a$ ~ 16.0) as in previous cases. This would promote the rapid decomposition of the ketyl radical to form *untethered* acyl radicals, which then randomly dimerise to form a statistical mixture of acyloin products 2-**5**, 2-**6**, 2-**7** and 2-**8** (Scheme 2-**20**). Similar observations have been previously described in the literature.[18]



Scheme 2-20 – Postulated mechanism for the decomposition of the 2-**25**.

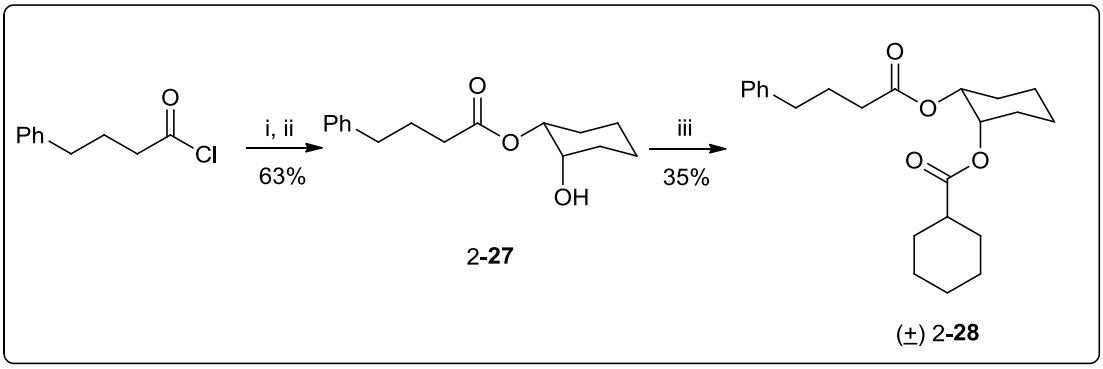
The apparent beneficial effect of the pyrocatechol employed as a linker in these conditions was to subdue the competitive side reaction, which in previous cases caused the radical *β*-scission of the di-ester to form the parent carboxylic acids (see Scheme 1-**18**). These results led us to select cyclic 1,2 *cis*-diols as linkers. It was envisaged that these diols would provide an alignment between the reacting acyl functionalities in the di-ester at the transition state, which consequently would improve the intramolecular selectivity of the reaction.

2.2.4 Cyclic Diols

As it was demonstrated in section (**2.2.1.2**), ethylene glycol as a linker delivered the best chemoselectivty under Li/DBB mediated crossed-acyloin condensation (see Figure 2-**5**). It was suggested that the employment of robust cyclic diols such as non-substituted *cis*-cyclohexane-1,2-diol or bicyclic *exo*-*exo*-norbornenediol 2-**29** as linker, would provide close proximity between the reacting acyl functionally in the di-ester. As result, this could improve the intramolecular radical dimerisation of the involving di-ester, towards formation of crossed-acyloin products.

2.2.4.1 *cis*-Cyclohexane-1,2-Diol as Linker

The desired non-symmetrical di-ester 2-**28** was obtained by subjecting the commercially available *cis*-cyclohexane-1,2-diol to two subsequent esterification *via* mono-ester 2-**27** to deliver di-ester 2-**28** in 22% yield over two steps (Scheme 2-**21**).

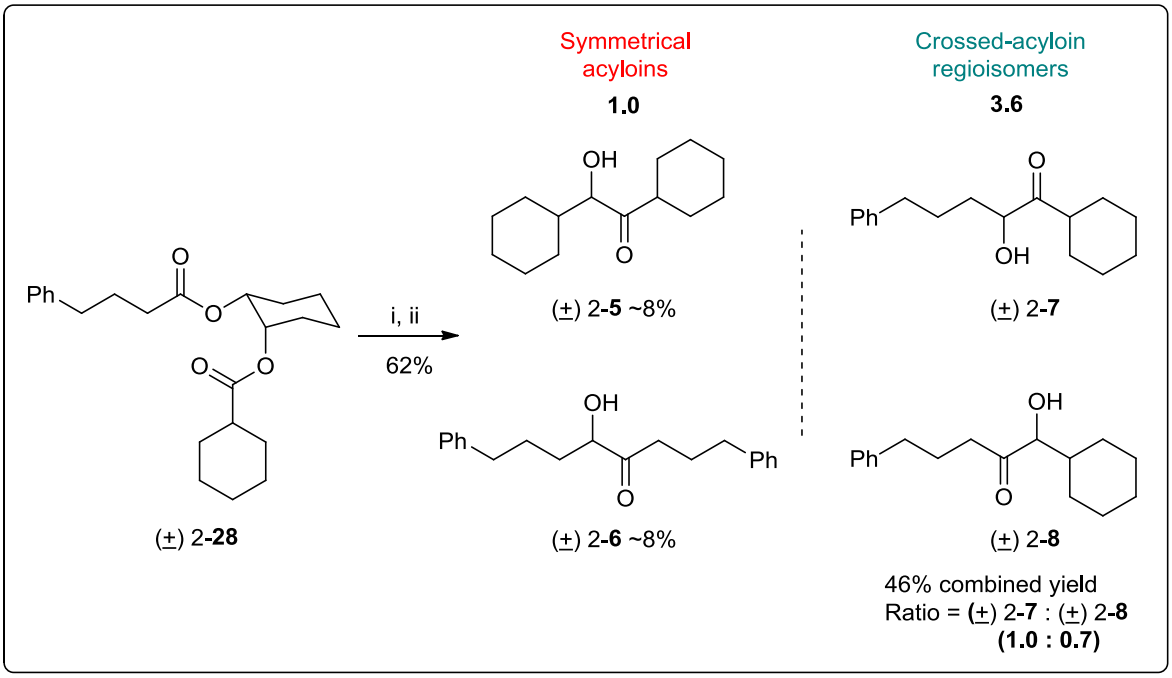


Reagents and conditions: I) Pyridine (1.1 eq.), diol (1.5 eq.), CH_2Cl_2, r.t, 3h.
ii) Acid chloride (2.5 eq.), pyridine (2.5 eq.), CH_2Cl_2, r.t, 16h.

Scheme 2-21 – Preparation of the non-symmetrical di-ester 2-**28**.

The appearance of two protons as a multiplet at δ 5.08-5.00 ppm corresponding to the *O*-alkyl protons in the ^{1}H-NMR spectrum confirmed the formation of di-ester 2-**28**. Furthermore, the appearance of two carbonyl signals at δ 175.3 ppm and δ 172.7 ppm in the ^{13}C-NMR spectrum and the presence of a sharp carbonyl signal at ν 1734 in the IR spectrum confirmed the expected identity of di-ester 2-**28**.

Subsequent exposure of 2-**28** to Li/DBB reduction conditions generated a mixture of acyloins 2-**5**, 2-**6**, 2-**7** and 2-**8** in a combined yield of 62%. To our excitement, the reaction yielded just 8% of each of the symmetrical acyloins 2-**5** and 2-**6**, whilst forming the crossed-acyloins 2-**7** and 2-**8** in a combined yield of 46% (Scheme 2-**22**).



Reagents and conditions: i) Li (10 eq.), DBB (4.0 eq.), THF, –78 °C, 3 h. ii) NH_4Cl (aq.).

Scheme 2-**22** – Reduction of di-ester 2-**28** to the corresponding acyloins 2-**5**, 2-**6**, 2-**7** and 2-**8**.

This positive result was confirmed by the analysis of the crude ^{1}H-NMR spectrum of the crossed acyloins 2-**7** and 2-**8**, symmetrical acyloins 2-**5** and 2-**6** with the ratio of 4:1 (Figure 2-**9**).

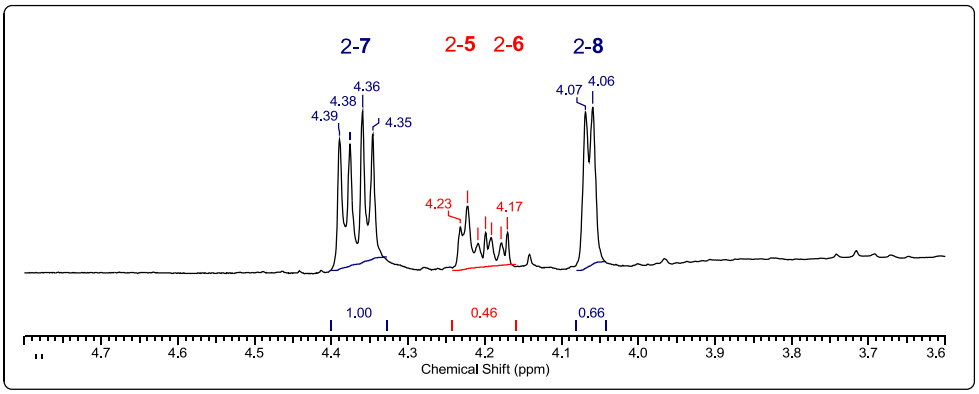


Figure 2-**9:** Depicts the appearance of a double doublet at δ 4.37 ppm (2-**7**, CHOH), a multiplet at δ 4.23-4.17 ppm (2-**5** and 2-**6**, CHOH) and a doublet at δ 4.06 ppm (2-**8**, CHOH) in the 200 MHz ^{1}H-NMR spectrum of the crude mixture.

These encouraging results led us to believe that the increase of chemoselectivity could be explained by the size of torsion angle ϕ between the two alcohols in *cis*-cyclohexane-1,2-diol,

which decreased from ethylene glycol ~ϕ = 180° to ϕ = 60° in the case of *cis*-cyclohexane-1,2-diol (Figure 2-**10**). These experimental observations suggested that smaller angle ϕ between the acyl functionalities in the reacting di-ester promoted an efficient intramolecular reaction.

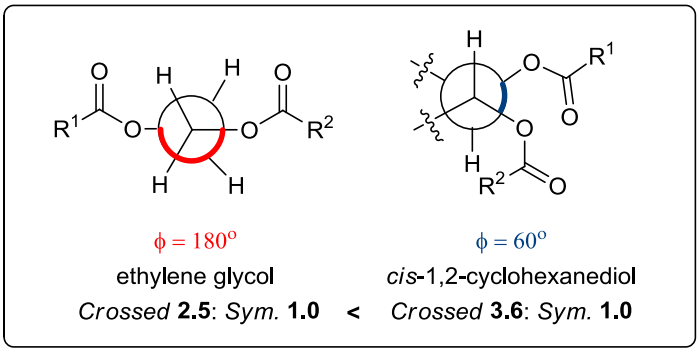


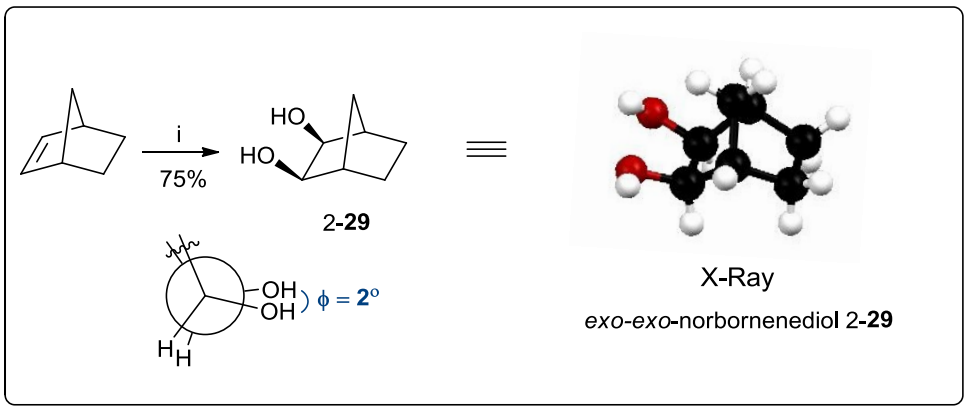
Figure 2-10 – Displays the correlation between ϕ and the chemoselectivity.

As a result, it was suggested that a more rigid bicyclic diol with smaller dihedral angle as a linker would provide the desired proximity between the reacting ketyl radical anions, which could promote the chemoselectivity of the reaction towards the sole formation of crossed-acyloin regioisomers 2-**7** and 2-**8**.

2.2.4.2 *Exo-exo*-Norbornenediol as a Linker

Exo-exo-norbornenediol 2-**29** was selected as a tether due to the small dihedral angle ϕ = 2° between the hydroxyl groups and the strained nature of the linker. Diol 2-**29** was readily prepared following a literature procedure, by subjecting commercially available norbornene to Upjohn dihydroxylation, which delivered 2-**29** as a white crystalline solid in 75% yield (Scheme 2-**23**). The structure of the diol 2-**29** was confirmed by X-ray crystallography

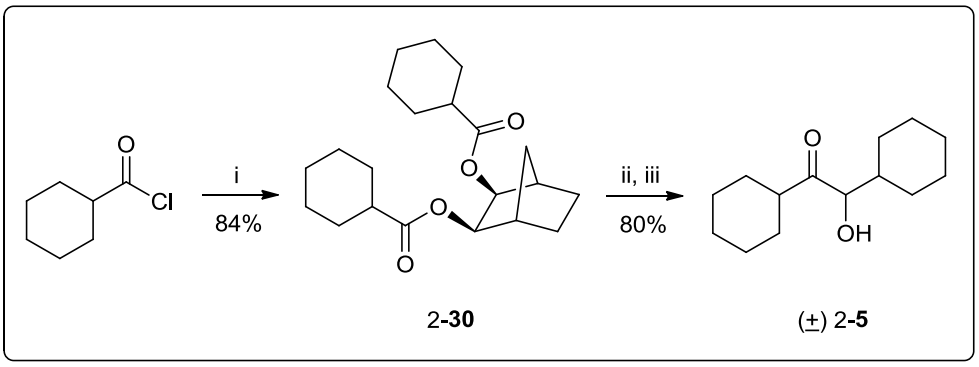
(Appendix 1).†



Reagents and conditions: i) OsO_4 (0.6 mol%), TMO (1.5 eq.), pyridine, *t*-BuOH/H_2O, 80 °C, 24 h.

Scheme 2-23 – Dihydroxylation of norbornene to the corresponding *exo-exo*-norbornenediol 2-**29**.

With 2-**29** in hand, our attention was first focused on examining the impact of the linker on the yield of the acyloin condensation. The diol 2-**29** was thus subjected to the previously described esterification procedure, to furnish symmetrical di-ester 2-**30** in 84% yield. Compound 2-**30** was then exposed to Li/DBB reduction conditions to deliver acyloin 2-**5** in an excellent 80% yield (Scheme 2-**24**).



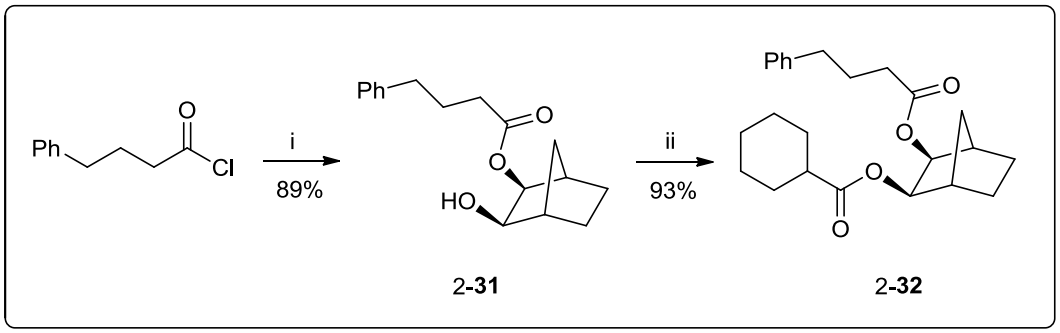
Reagents and conditions: i) Pyridine (2.2 eq.), 2-**9** (2.5 eq.), CH_2Cl_2, r.t, 16h.
ii) Li (10 eq.), DBB (4.0 eq.), THF, – 78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-24 –Reduction of symmetrical di-ester 2-**30** to the corresponding acyloin 2-**5**.

As a result, di-ester 2-**32** was prepared by sequential esterification of 2-**29** with

† X-ray crystallography by Akshat Rathi

cyclohexanecarbonyl chloride and 4-phenylbutanoyl chloride *via* the mono-ester 2-**31**, to furnish 2-**32** in a combined yield of 83% (Scheme 2-**25**).

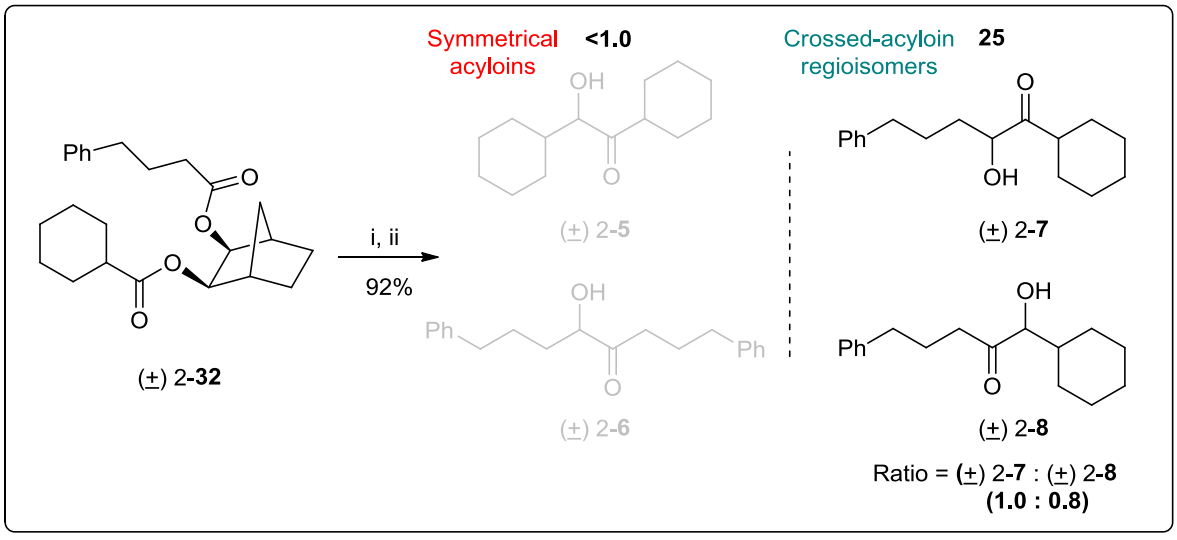


Reagents and conditions: i) Pyridine (1.1 eq.), 1-**28** (1.5 eq.), CH_2Cl_2, r.t, 3 h.
ii) Acid chloride (2.5 eq.), pyridine (2.5 eq.), CH_2Cl_2, r.t, 16 h.

Scheme 2-**25** – Preparation of the non-symmetrical di-ester 2-**32**.

The appearance of two doublets at δ 4.73 ppm and δ 4.69 ppm in the ^{1}H-NMR spectrum indicated the presence of the *O*-alkyl protons in 2-**32**. Furthermore, in the ^{13}C-NMR spectrum the signals at δ 175.0 ppm and δ 172.5 ppm indicated the presence of the di-ester functionality.

The investigation was continued by exposure of 2-**32** to a stoichiometric loading of Li/DBB in THF at –78 °C (Scheme 2-**26**).



Reagents and conditions: i) Li (10 eq.), DBB (4.0 eq.), THF, –78 °C, 3 h. ii) NH_4Cl (aq.).

Scheme 2-**26** – Reduction of di-ester 2-**32** to the corresponding acyloins 2-**7** and 2-**8**.

To our great satisfaction, the reaction exclusively generated the crossed-acyloin regioisomers 2-**7** and 2-**8** in an excellent combined yield of 92%, with quantitative recovery of the diol 2-**29** and DBB 1-**28** (Scheme 2-**26**). The chemoselectivity of the reaction was also observed in the crude ^{1}H-NMR spectrum; with the appearance of a double doublet at δ 4.32 ppm (2-**7**, CHOH) and doublet at δ 4.01 ppm (2-**8**, CHOH) in a ratio of 1:0.8, confirmed the exclusive formation of crossed-acyloins 2-**7** and 2-**8** (Figure 2-**11**).

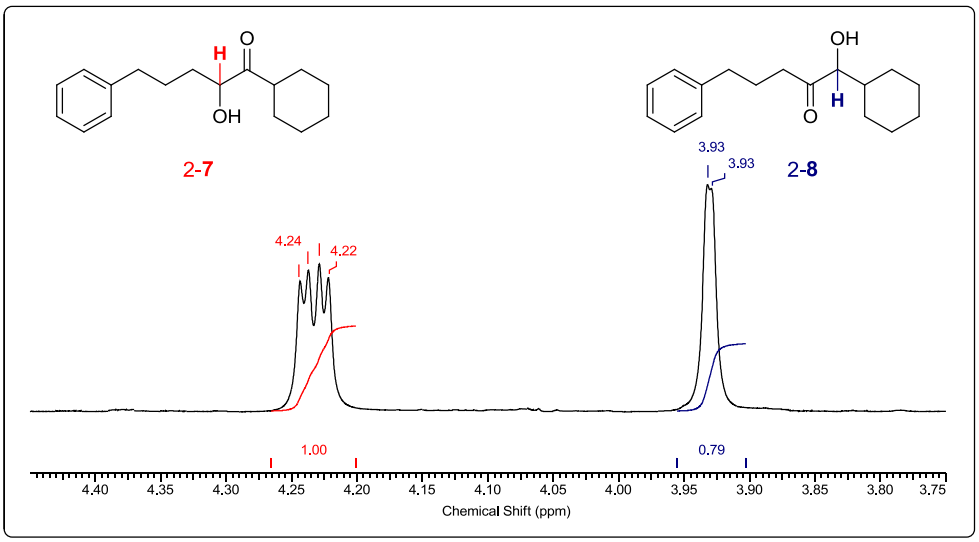


Figure 2-**11**: 500 MHz ^{1}H-NMR spectrum of the crude product mixture derived from the acyloin reaction of 2-**32**. Shows the appearance of a double doublet at δ 4.23 ppm corresponded to the labelled proton of 2-**7**. The double at δ3.93 ppm was assigned to the labelled proton of 2-**8**.

As it was hypothesised the main factor responsible for the much improved chemoselectivity and yield was probably due to closer proximity of the reaction ketyl radical intermediate (Scheme 2-**27**) in the case of diol 2-**29** as a linker. The experimental data confirmed the validity of the hypothesis, by comparing the yield and chemoselectivity in the crossed-acyloin condensation between di-esters linked with 1,2-cis-cyclohaxanediol and *exo-exo*-norbornenediol 2-**29** (Figure 2-**12**).

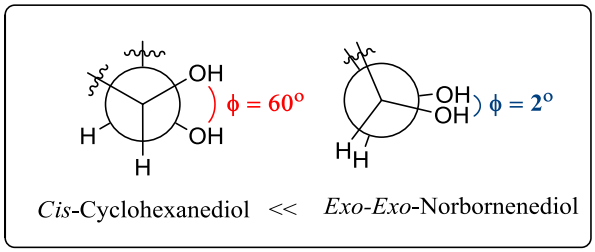
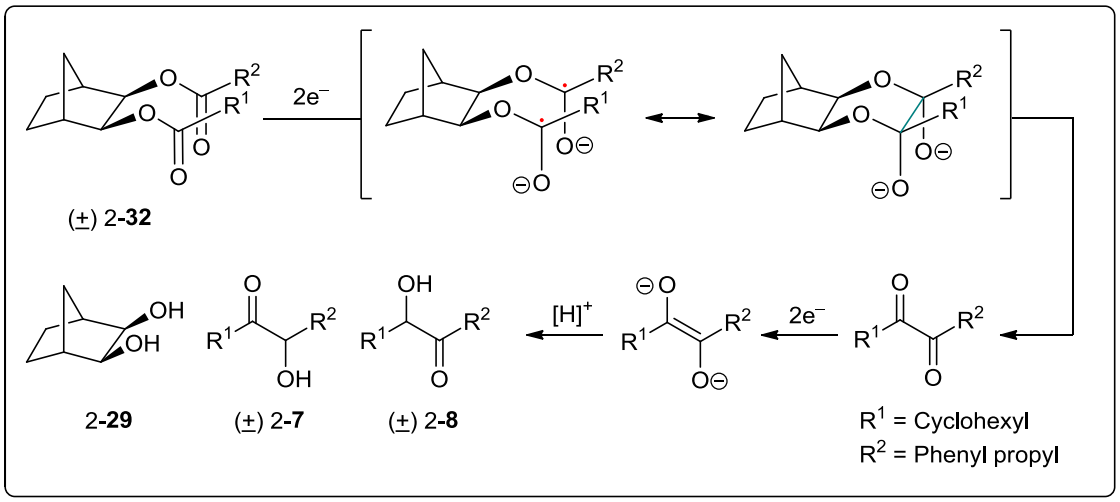


Figure 2-12 – Relation between chemoselectivty and dihedral angle ϕ.

It was clear that the smaller ϕ angle in the diol improved significantly the outcome of the reaction, which in the case of diol 2-**29** delivered exclusively crossed-acyloin regioisomers 2-**7** and 2-**8** in excellent yield. In addition, the increased strain in the boat-shaped six-membered ring might have an impact in reducing the activation energy of the carbon-carbon bond formation for the intramolecular reaction compared to the intermolecular reaction (Scheme 2-**27**).



Scheme 2-27 – Suggested mechanism for crossed-acyloin condensation promoted by 2-**29**.

In an attempt to optimise the Li/DBB reduction conditions, di-ester 2-**32** was subjected to screening, in which the temperature and equivalents of DBB were altered (Table 2-**2**).

Entry	Reagents	Loading/ (eq.)	Temp./ °C	Combined yield/ (%) 2-**7** & 2-**8**	Chemoselectivity[a] 2-**5**,2-**6** : 2-**7**, 2-**8**
1	1-**28**	4.0	0 °C	20	>1:25
	Li	10			
2	1-**28**	4.0	–20 °C	39	>1:25
	Li	10			
3	1-**28**	4.0	–40 °C	59	>1:25
	Li	10			
4	1-**28**	4.0	–78 °C	92	>1:25
	Li	10			
5	1-**28**	2.0	–78 °C	90	>1:25
	Li	20			
6	1-**28**	1.0	–78 °C	89	>1:25
	Li	40			

Table 2-**2** – Optimization of the Li/DBB-mediated acyloin condensation in THF.

a) Determined by ^{1}H-NMR of the crude product.

Reaction temperatures higher than –78 °C caused radical decomposition of the substrate to the corresponding carboxylic acids, resulting in lowered yields (Table 2-**2**, Entries **1**-**3**). The reactions performed with sub-stoichiometric loadings of DBB (Table 2-**2**, Entries **5** and **6**) gave comparable yields and chemoselectivities to those obtained with a stoichiometric amount of DBB (Table 2-**2**, Entry **4**), although they were more time consuming and required an increased loading of lithium metal.

In conclusion, it is the presence of the diol 2-**29** in the intramolecular crossed-acyloin reaction that contributed to the excellent yield and chemoselectivity, which generated exclusively the two regioisomers 2-**7** and 2-**8**. It is worth noting that the reaction employing 2-**29** as tether did not produce any carboxylic acids as by-product, as it has been observed in previous cases.

This would indicate that no radical cleavage of 2-**32** has occurred. Furthermore, the reaction conditions prove to be reliable on a gram scale with quantitative recovery of the linker 2-**29** and DBB 1-**28**.

After identifying the *exo*,*exo*-norbornene-1,2-diol 2-**29** as a suitable tether for a highly chemoselective acyloin cross coupling, our focus was to improve the regioselectivity of protonation of bis-enolate intermediate 1-**10** (see Scheme 1-**6**) in this reaction.

2.3 Investigation into the Regioselective Crossed-Acyloin Condensation

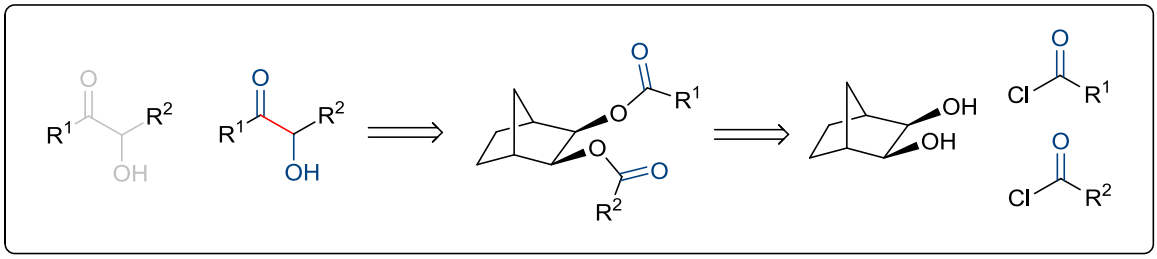
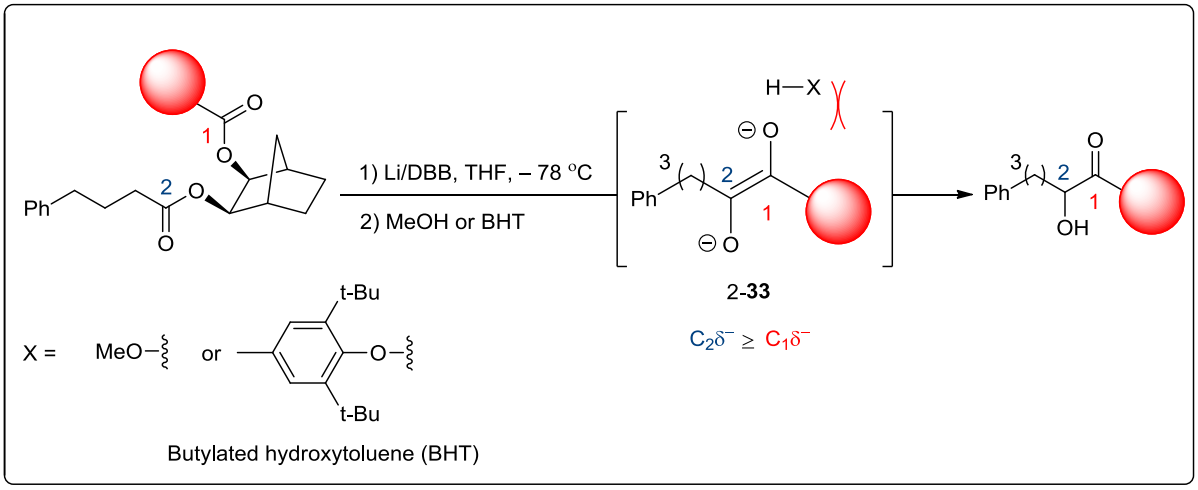


Figure 2-**13 –** Substrate based insertion of regioselective in crossed-acyloin condensation.

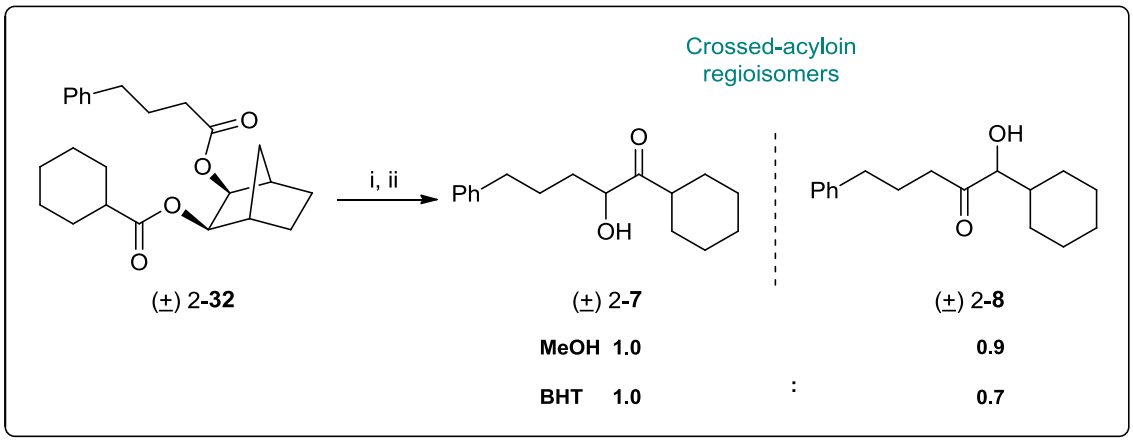
As elaborated in the previous chapter, the exposure of di-ester 2-**32** to Li/DBB mediated conditions generated a mixture of crossed-acyloin regioisomers 2-**7** and 2-**8** in a ratio of 1.0:0.8 in an excellent yield of 92% (see Figure 2-**11**). Following this key achievement, the next task was to investigate the regioselectivity of protonation of the bis-enolate intermediate in the Li/DBB mediated crossed-acyloin conditions.

Initially, the effect of the steric bulk of the proton source used to quench the reaction was investigated. It was thought that ene-diolate 2-**33** containing sterically bulkier substituents such as cyclohexyl or *t*-butyl groups could block the protonation of carbon C_1 (Scheme 2-**28**), which in synergy with a bulkier proton source could lead to a more regioselective protonation.



Scheme 2-**28** – suggestion of a regioselective protonation of the ene-diolate 2-**33**.

Quenching the reaction with methanol gave a regioisomer ratio of acyloins 2-**7**/2-**8** = 1.0:0.9 (Table 2-**3**, Entry **1**), whilst the use of the hindered proton source 2,6-di-*tert*-butyl-4-methylphenol (BHT) gave only a minor improvement in the regioselectivity (2-**7**/2-**8** = 1.0:0.7) (Table 2-**3**, Entry **2**).



Entry	X [H]⁺	Products	Yield %	Regioselectivity (2-7: 2-8)[a]	Chemoselectivity[b]
1	MeOH	2-**7**/2-**8**	92	1: 0.9	> 1:25
2	BHT	2-**7**/2-**8**	88	1: 0.7	> 1:25

Reagents and conditions: i) Li (20 eq.), DBB (2.0 eq.), THF, – 78 °C, 3 h. ii) X.

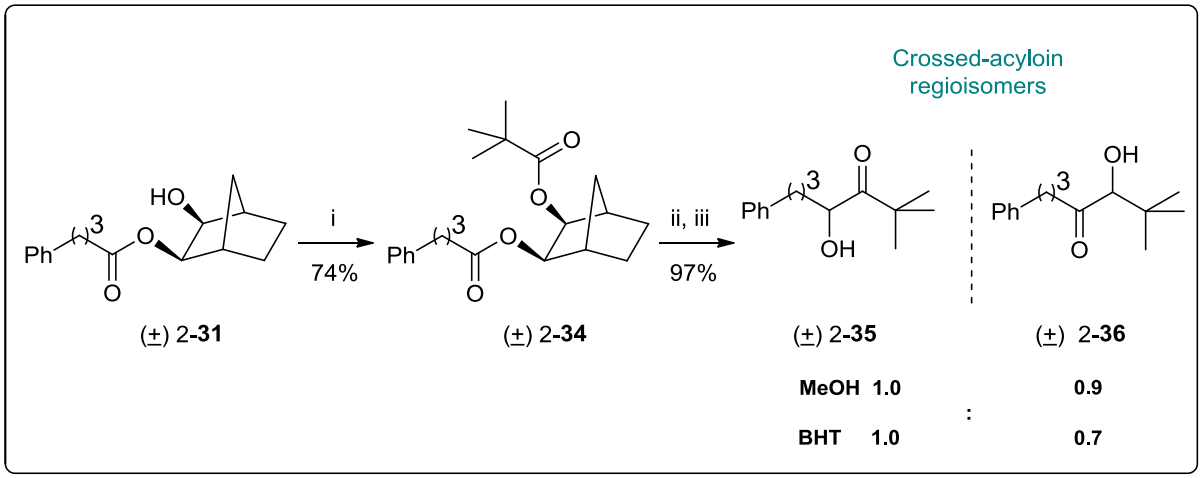
Table 2-**3**: SET reduction of di-ester 2-**32**. a) The ratio of (2-**7**/2-**8**) was determined in ^{1}H-NMR spectroscopy. b) Determined by ^{1}H-NMR of the crude product

Consequently, it was envisaged that replacing the cyclohexyl substituent in the di-ester 2-**32**

with a more sterically hindered group in concert with bulkier proton sources could improve the regioselectivity of the crossed-acyloin reaction.

2.3.1 *t*-Butyl Substituent

In order to test this hypothesis, mono-ester 2-**31** was first subjected to esterification with pivaloyl chloride to deliver the desired di-ester 2-**34** in 74% yield (Scheme 2-**29**). Initially, compound 2-**34** was exposed to the Li/DBB reduction conditions and the reaction was quenched by the addition of methanol to deliver a mixture of crossed-acyloins 2-**35** and 2-**36** in combined yield of 97% as a 1.0:0.9 regioisomeric mixture (Scheme 2-**29**).



Reagents and conditions: i) Pyridine (2.2 eq.), PivCl, CH_2Cl_2, r.t, 16h.
ii) Li (20 eq.), DBB (2.0 eq.), THF, – 78 °C, 3 h. iii) MeOH or BHT.

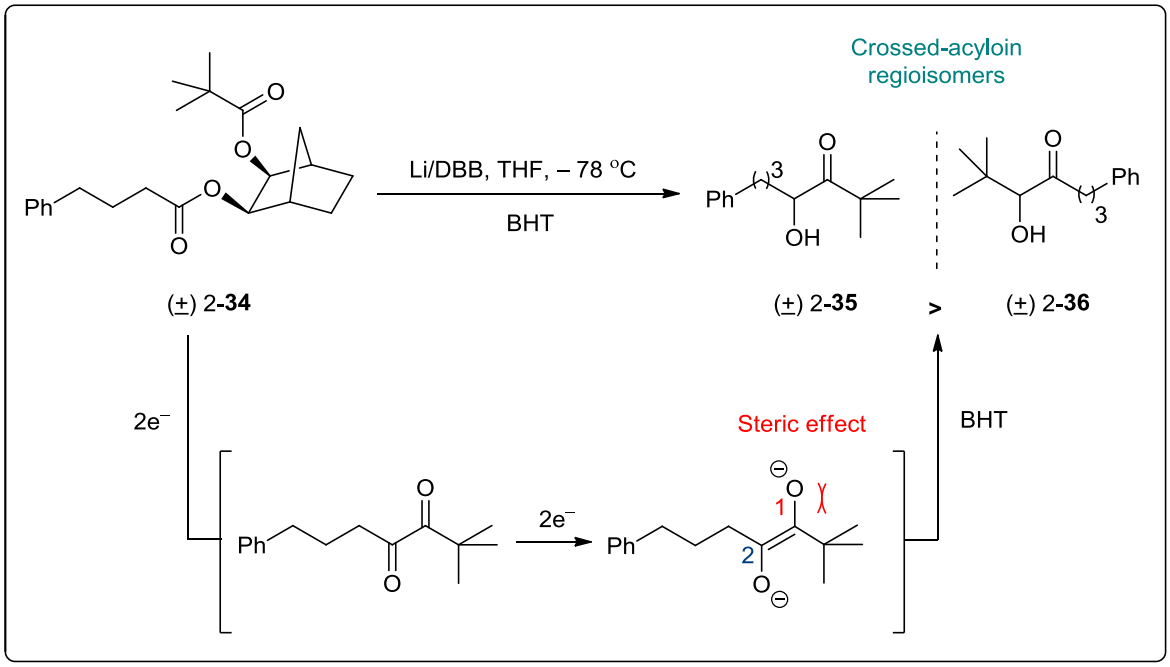
Scheme 2-**29** – Reduction of di-ester 2-**34** to the crossed acyloin regioisomers 2-**35** and 2-**36**.

The reaction was repeated and quenched this time with the more bulky proton source (BHT). The yield of the reaction remained similar as well as the regioselectivity of the reaction, which was slightly improved to 1.0:0.7 in favour of the formation of the acyloin 2-**35** (see Scheme 2-**29**).

The structures of the acyloins 2-**35** and 2-**36** were confirmed by ^{1}H- and ^{13}C-NMR

spectroscopy; the presence of an apparent doublet at δ 4.52 ppm (2-**35**, CHOH) and a singlet at δ 3.84 ppm (2-**36**, CHOH) in the ^{1}H-NMR spectrum with the corresponding signals at δ 81.2 ppm (2-**35**, CHOH) and δ 75.2 ppm (2-**36**, CHOH) in ^{13}C-NMR spectrum indicated the presence of two secondary alcohol functionalities. Furthermore, the appearance of the two carbonyl signals at δ 217.9 and δ 213.3 in the ^{13}C-NMR spectrum were consistent with the observation of a sharp signal at ν 1703 cm^{-1} in the IR spectrum.

Thus, it appeared that the sterically encumbered t-Bu group showed limited effect on the regioselectivity of the crossed-acyloin, leading to a slight improvement for the formation of crossed-acyloin 2-**35** (Scheme 2-**30**).



Scheme 2-**30** – Reduction of di-ester 2-**34** to crossed acyloin regioisomers 2-**35** and 2-**36**.

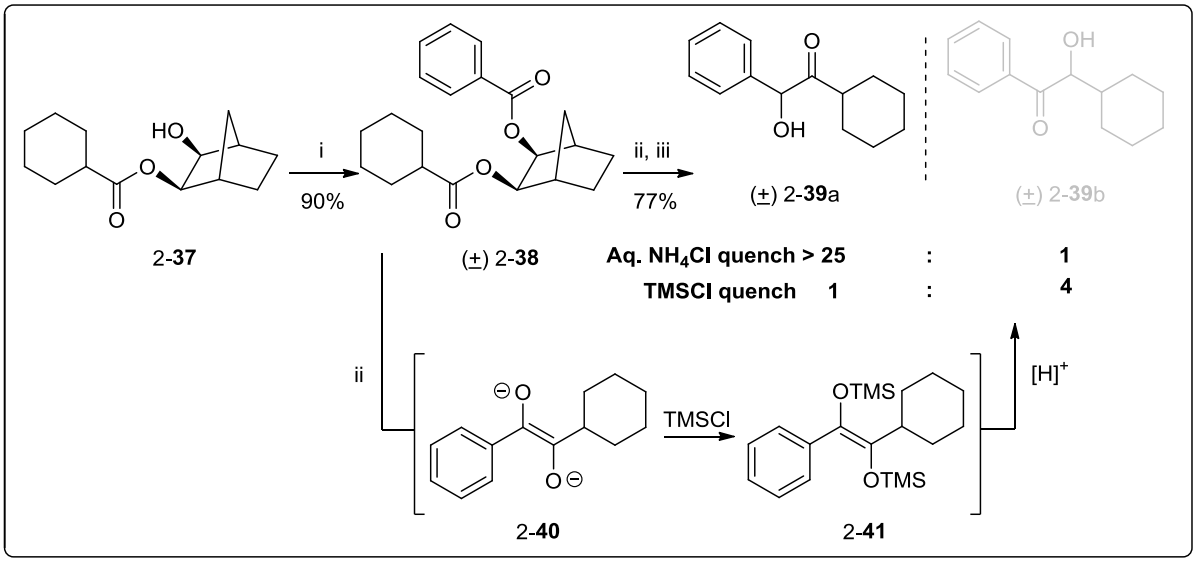
Armed with these results, our investigation into improving the regioselectivity of the reaction continued by employing aromatic substituted di-esters as potential candidates in the crossed- acyloin condensation.

2.3.2 Aromatic Substituents

2.3.2.1 Unsubstituted Phenyl Rings

With the results from the *t*-butyl substituent in hand, our attention moved to aryl substituents, in order to obtain a regioselective crossed-acyloin reaction. It was speculated that the presence of these substituents could affect the selectivity due to their inherent resonance stabilising properties, which could have some impact in the protonation step.

Therefore, mono-ester 2-**37** was acylated with benzoyl chloride to deliver di-ester 2-**38** in 90% yield, which was subsequently reacted under the Li/DBB reduction conditions and quenched with an aqueous solution of ammonium chloride. Pleasingly, these reaction conditions generated exclusively the single crossed-acyloin regioisomer 2-**39a** in an excellent 77% yield (Scheme 2-**31**).



Reagents and conditions: i) Benzoyl chloride, pyridine (2.2 eq.), CH_2Cl_2, r.t, 16h.
ii) Li (20 eq.), DBB (2.0 eq.), THF, –78 °C, 3 h. iii) NH_4Cl (aq.) or TMSCl/HCl.

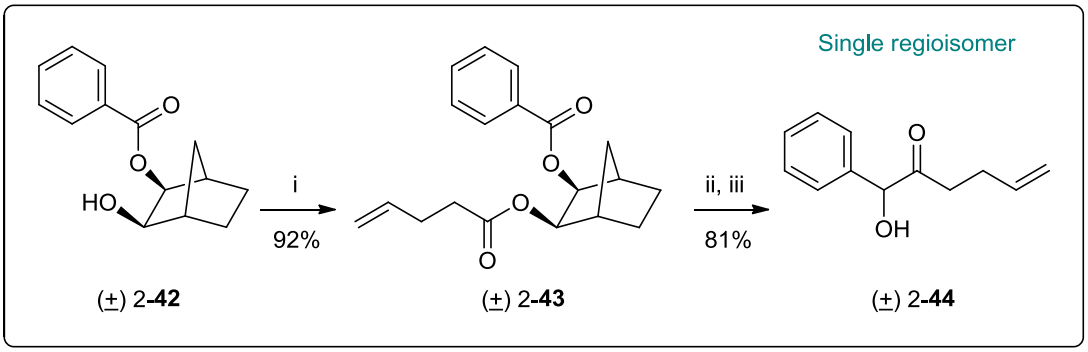
Scheme 2-31 – Reduction of di-ester 2-**38** to the corresponding crossed acyloin regioisomer 2-**39a**.

In order to examine the regioselectivity of the reaction, the same conditions were repeated

but this time the bis-ene-diolate intermediate 2-**40** was trapped as the bis-silyl enol ether 2-**41** with TMSCl at –78 °C, followed by acidic quench at room temperature, to deliver a regioisomeric mixture of 2-**39a** and 2-**39b** in a ratio of 1:4 determined by ^{1}H-NMR spectroscopic analysis (see Scheme 2-**31**).

These results indicated that the reaction condition exclusively formed the kinetically favoured acyloin product 2-**39a** when the reaction mixture was quenched with an aqueous solution of NH_4Cl at lower temperatures. The spectroscopic properties of 2-**39a** were consistent with the data reported in the literature.[44]

To corroborate this previous result, di-ester 2-**43** was synthesised in 92% yield *via* mono-ester 2-**42**. To our satisfaction, the reaction once again exclusively generated the crossed-acyloin 2-**44** as a single regioisomer in 81% yield (Scheme 2-**32**).



Reagents and conditions: i) Pent-4-enoyl chloride, pyridine (2.2 eq.), CH_2Cl_2, r.t, 16h. ii) Li (20 eq.), DBB (2.0 eq.), THF, –78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**32** – Reduction of di-ester 2-**43** to the corresponding crossed-acyloin regioisomer 2-**44**.

The structure of acyloin 2-**44** was deduced from NMR and IR spectroscopy analyses; the appearance of a proton as a doublet at δ 5.08 ppm (2-**44**, CHOH) with a coupling constant J = 3.9 Hz correlated with a doublet at δ 4.40 ppm (2-**44**, CHOH) with a coupling constant J = 3.9 Hz, which confirmed the formation of the secondary alcohol in the acyloin. In addition, the presence of the signals at δ 208.8 ppm (ketone) and δ 79.8 ppm (alcohol) were

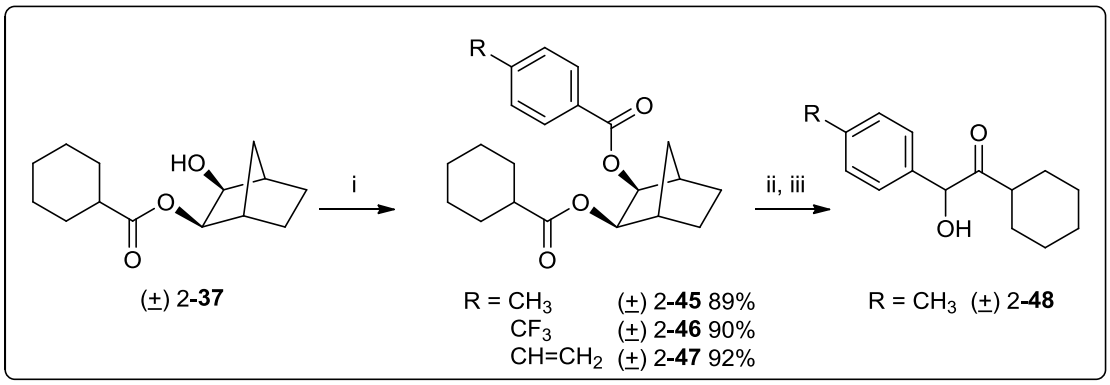
consistent with the presence of a broad OH stretch at ν 3462 cm^{-1} and a sharp carbonyl signal at ν 1716 cm^{-1} in the IR spectrum.

Following these key improvements, the potential regioselectivity of a series of di-esters bearing mono-substituted phenyl rings were investigated in the crossed-acyloin condensation.

2.3.2.2 Substituted Phenyl Rings

Having established effective reaction conditions for this transformation, the investigation was followed by examining the regioselectivity of the Li/DBB mediated crossed-acyloin condensation by employing a series of mono-substituted phenyl esters.

Thus, a series of di-esters 2-**45**, 2-**46** and 2-**47** was synthesised *via* esterification of the mono-ester 2-**37** (Table 2-**4**).



Entry	Substrate	R	Products	Yield/ %	Chemoselectivity (Hetero:Homo)[a]	Regioselectivity (Kin.:Ther.)[b]
1	2-**45**	CH_3	2-**48**	81	>25:1	>25:1
2	2-**46**	CF_3	–	n.d	n.d	n.d
3	2-**47**	$CH{=}CH_2$	–	n.d	n.d	n.d

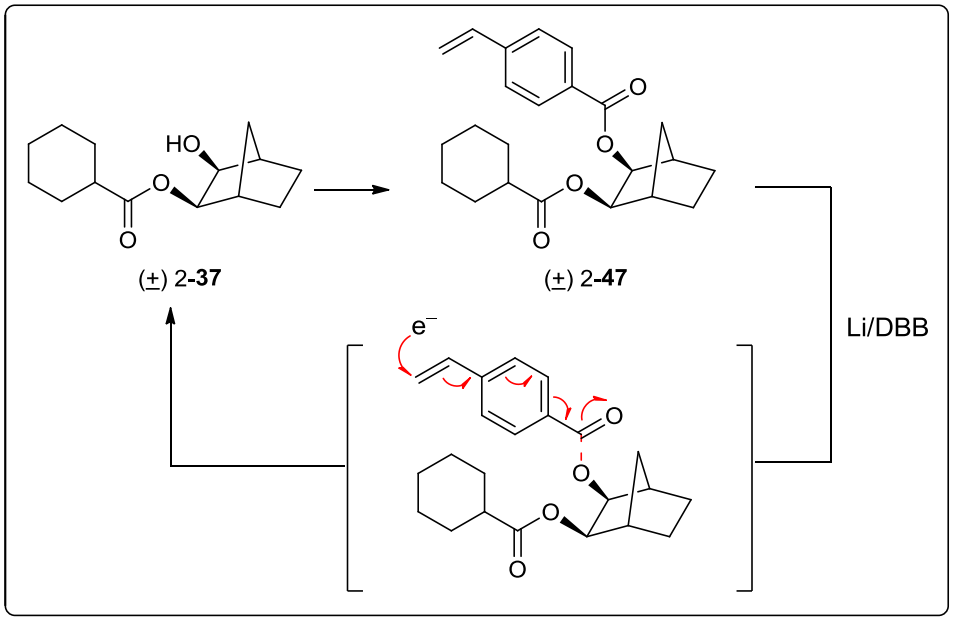
Reagents and conditions: i) Acid chloride (2.5 eq.), pyridine (2.2 eq.), CH_2Cl_2, r.t, 16h.
ii) Li (20 eq.), DBB (2.0 eq.), THF, – 78 °C, 3 h. iii) NH_4Cl (aq.).

Table 2-**4** – Reduction of di-ester 2-**45** to the corresponding crossed-acyloin regioisomer 2-**48**.

The esterification of 2-**37** with *p*-toluoyl chloride yielded 89% of the di-ester 2-**45**, while reacting 2-**37** with the electron deficient *p*-(trifluoromethyl)benzoyl chloride delivering di-ester 2-**46** in 90% yield (see Table 2-**4**). Finally, di-ester 2-**47** was synthesised by subjecting 2-**37** and 4-vinylbenzoyl chloride to basic conditions to furnish 2-**47** in 92% yield (Table 2-**4**). To our satisfaction, SET reduction of compound 2-**45** delivered the acyloin 2-**48** in 81% yield, as a single regioisomer (Table 2-**4**, Entry **1**). The appearance of one proton as a singlet at δ 5.16 ppm and corresponding hydroxyl proton as a broad singlet at δ 4.35 ppm indicated the existence of a secondary alcohol in the ^{1}H-NMR spectrum. Furthermore, the presence of a carbonyl signal at δ 212.7 ppm and an *O*-alkyl signal at δ 78.1 ppm in the ^{13}C-NMR spectrum, and the sharp ketone peak at ν 1707 cm^{-1} and the broad OH stretch at ν 3457 cm^{-1} in the IR spectrum further proved the formation of the acyloin functionality.

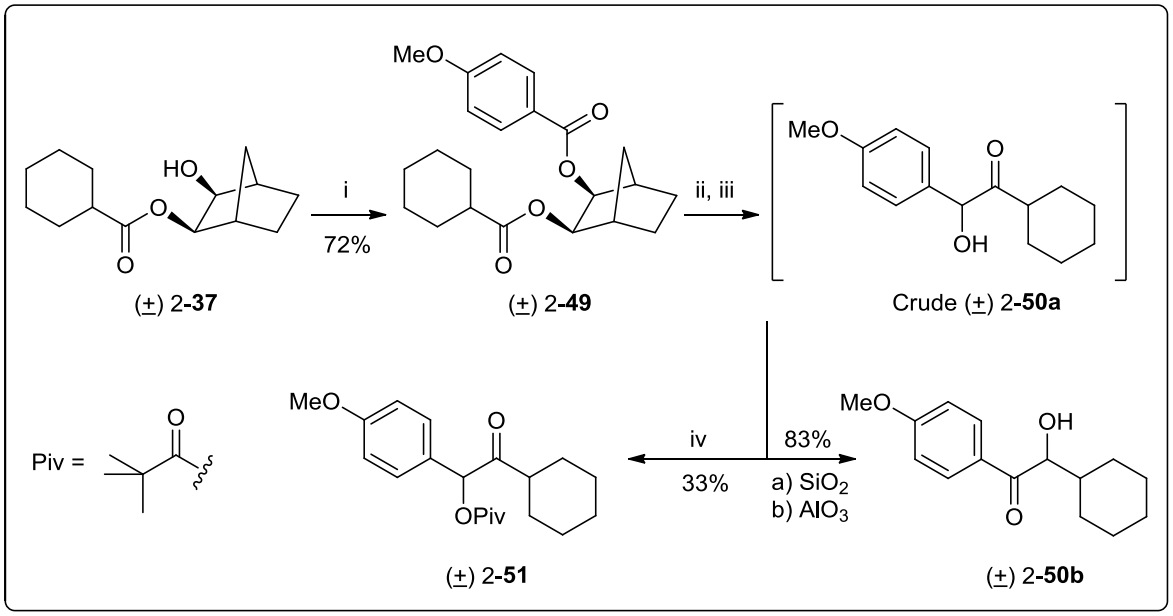
Compound 2-**46** was then submitted to Li/DBB conditions forming an inseparable mixture of products. It is worth noting that 2-**46** was not recovered and the crude ^{1}H-NMR spectrum did not indicate the formation of the corresponding acyloin (see Table 2-**4**, Entry **2**). It was suggested that the radical cleavage of a C-F bond in the SET reduction conditions could cause the polymerisation or decomposition of the di-ester 2-**46**. The apparent change of the colour of the reaction mixture from teal-blue to dark brown during the addition of the substrate to Li/DBB solution is consistent with the consumption of electrons.

The investigation was continued by exposing 2-**47** to Li/DBB reduction conditions to only recover the parent mono-ester 2-**37** in 64% (see Table 2-**4**, Entry **3**), probably due to radical decomposition of di-ester 2-**47** (Scheme 2-**33**).



Scheme 2-**33** – Reduction/degradation of di-ester 2-**47** to the parent mono-ester 2-**37**.

Investigation was continued by esterification of the 2-**37** with electron-donating (Hammett constant: $\sigma_p = -0.27$)[45] *p*-anisoyl chloride to furnish di-ester 2-**49** in 72% yield (Scheme 2-**34**).



Reagents and conditions: i) *p*-Anisoyl chloride, pyridine (2.2 eq.), CH_2Cl_2, r.t, 16h. ii) Li (20 eq.), DBB (2.0 eq.), THF, – 78 °C, 3 h. iii) NH_4Cl (aq.). iv) Hünig's base, pivaloyl chloride, CH_2Cl_2, DMAP, 0 °C, 1 h.

Scheme 2-**34** – Reduction of di-ester 2-**49** to the corresponding crossed-acyloin regioisomer 2-**50b**.

Di-ester 2-**49** was then submitted to Li/DBB conditions to generate crossed-acyloin 2-**50a** as a single regioisomer according to the ^{1}H-NMR spectrum of the crude mixture (see Scheme 2-**34**). But when the crude product, composed predominantly of 2-**50a**, was purified by flash column chromatography over silica gel or basic alumina, 2-**50a** completely isomerised to the other regioisomer acyloin 2-**50b**, (2-**50a**:2-**50b** > 25:1) while was obtained in 83% yield (see Scheme 2-**3**, Figure 2-**14**).

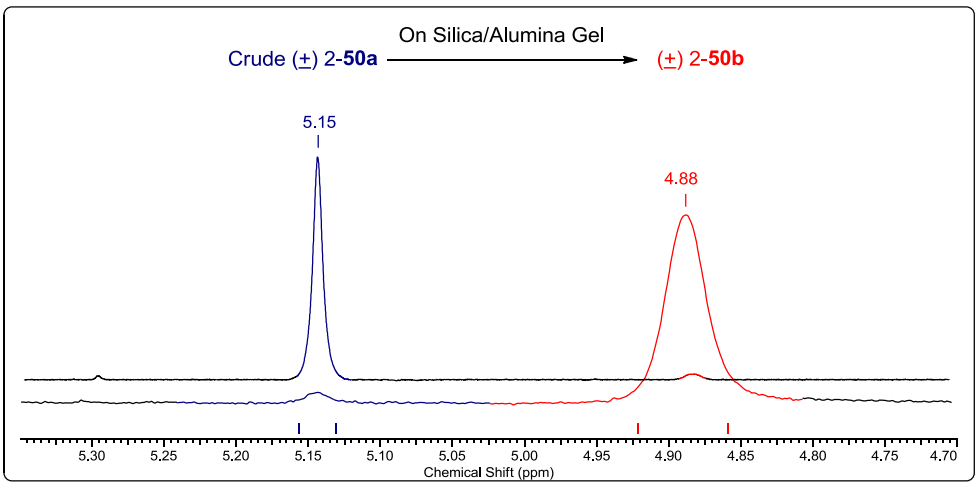
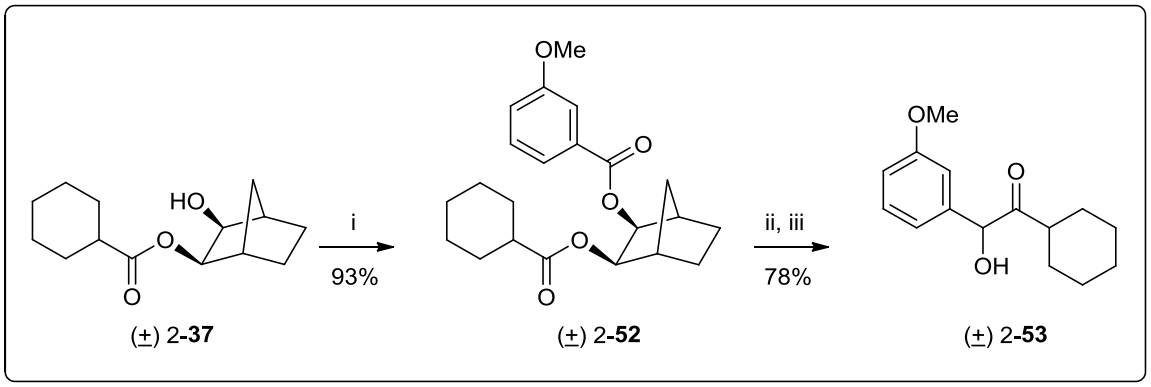


Figure 2-**14**: 200 MHz ^{1}H-NMR spectrum of the crude product mixture derived from the acyloin reaction of 2-**49** to form 2-**50**a at δ 5.16 ppm as a crude product, which readily isomerises to the corresponding 2-**50**b at δ4.88 ppm on silica/alumina gel.

The appearance of the diagnostic signals of acyloin in the ^{1}H-NMR spectrum as a singlet at δ 4.89 ppm and a broad singlet at δ 3.67 ppm indicated the presence of a secondary alcohol in the acyloin 2-**50b**. Furthermore, in the ^{13}C-NMR spectrum, presence of a carbon signal at δ 55.6 ppm and a carbonyl signal at δ 200.3 ppm, in conjunction with the appearance of a sharp ketone peak at ν 1709 cm^{-1} and the broad OH stretch at ν 3455 cm^{-1} in the IR spectrum confirmed the existence of the acyloin functionality.

Although attempts to purify and isolate acyloin 2-**50a** itself using other methods failed, it was found that crude 2-**50a** could be protected as the pivalate 2-**51**, which could then be obtained

in 33% yield after purification by flash column chromatography on silica gel (Scheme 2-**34**). As result, employment of the electron-withdrawing *m*-anisoyl group (Hammett constant: σ_m = +0.12)[45] as substituent was investigated. Thus, di-ester 2-**52** was synthesised *via* esterification of mono-ester 2-**37** with *m*-anisoyl chloride, which delivered the di-ester 2-**52** in 93% yield (Scheme 2-**35**). The crossed-acyloin 2-**53** was obtained in 78% yield as a single regioisomer, by subjecting 2-**52** to Li/DBB reduction conditions (Scheme 2-**35**). It is worth noting that no isomerisation occurred in the purification step on silica gel.



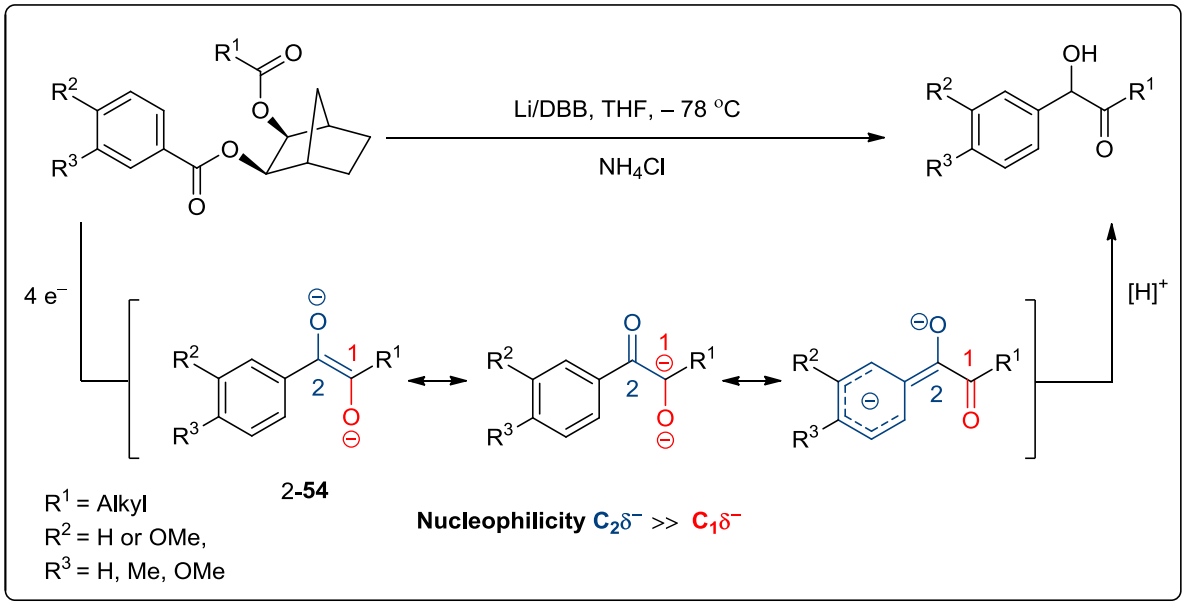
Reagents and conditions: i) *m*-Anisoyl chloride, pyridine (2.2 eq.), CH_2Cl_2, r.t, 16h. ii) Li (20 eq.), DBB (2.0 eq.), THF, –78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**35 –** Reduction of di-ester 2-**52** to the corresponding crossed-acyloin regioisomer 2-**53**.

The structure of the acyloin 2-**53** was confirmed by observation of the distinctive signals of the acyloin in NMR and IR spectrum; the appearance of a proton as a singlet at δ 5.17 ppm and a broad singlet at δ 4.39 ppm confirmed the formation of the secondary alcohol in the 2-**53**. In addition, the appearance of the signals at δ 212.4 ppm and δ 78.2 ppm was consistent with the broad OH signal at ν 3490 cm^{-1} and a sharp carbonyl signal at ν 1734 cm^{-1} in the IR spectrum.

In conclusion, the reaction proved to be high yielding and selective towards the formation of the kinetically stable acyloin products such as 2-**39a**, 2-**44**, 2-**48**, and 2-**53**. It was suggested

that the resonance stabilising effect (delocalisation properties) of the aromatic rings increased the nucleophilicity of the benzylic carbon C_2 in the enediolate 2-**54** at lower temperatures in the protonation step, favouring the formation of the kinetic acyloins (Scheme 2-**36**).



Scheme 2-36 – The resonance stabilising properties of aromatic rings promotes the regioselectivity.

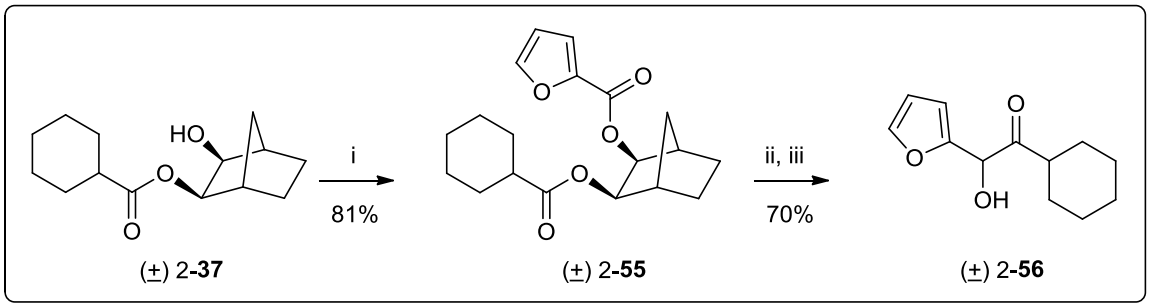
The results indicate that the protonation process favours the formation of the kinetically stable acyloin products at lower temperatures. This is illustrated in the case of the TMSCl quench followed by desilylation in acidic conditions at room temperature (see Scheme 2-**31**), which delivered a regioisomeric mixture of the crossed-acyloins 2-**39a** and 2-**39b** in a 1:4 ratio in favour of the formation of the thermodynamically stable acyloin product 2-**39b** (see Scheme 2-**31**). Furthermore, reduction of 2-**49** substituted with the electron-donating *p*-anisol demonstrated that the crude kinetic acyloin 2-**50a** is readily isomerised to the corresponding thermodynamically stable product 2-**50b** on exposure to silica/alumina gel. This indicates that the protonation of the ene-diolates intermediate at lower temperatures promoted the formation of the kinetic acyloin products.

With the established results from the phenyl substituted ester, our attention turned to expand the scope of the investigation to examine the potential reactivity of aromatic heterocyclic substituted esters in crossed-acyloin condensation mediated by Li/DBB.

2.3.2.3 Aromatic Heterocyclic Substituents

Armed with the results from the previous section, the project was continued by investigating the chemo- and regioselectivity of di-esters bearing heterocyclic aromatic rings such as furanyl, thiophenyl and pyridyl.

Di-ester 2-**55** was readily accessed by esterification of 2-**37** with furan-2-carbonyl chloride under basic conditions to deliver 2-**55** in 81% yield. Compound 2-**55** was then submitted to Li/DBB mediated conditions to deliver crossed-acyloin 2-**56** in 70% yield as a single regioisomer (Scheme 2-**37**).



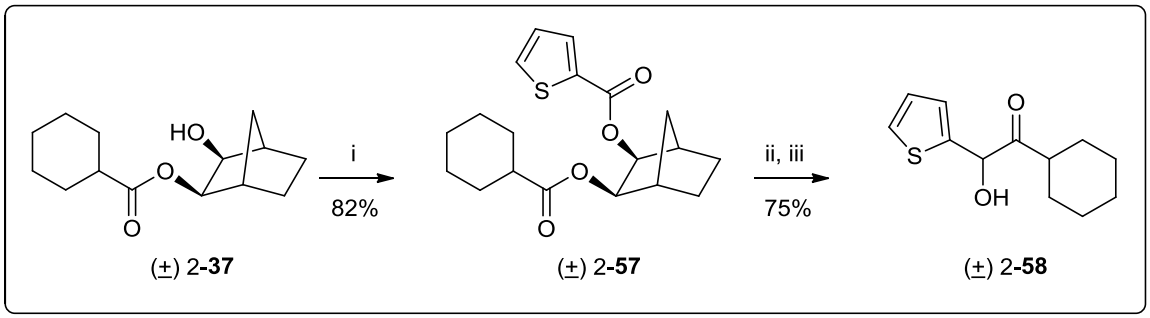
Reagents and conditions: i) Furan-2-carbonyl chloride, pyridine (2.2 eq.), CH_2Cl_2, r.t, 16h. ii) Li (20 eq.), DBB (2.0 eq.), THF, – 78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**37** – Reduction of di-ester 2-**55** to the corresponding crossed-acyloin regioisomer 2-**56**.

The appearance of the diagnostic signals of the acyloin in the ^{1}H-NMR spectrum as a singlet at δ 5.20 ppm and a broad singlet at δ 4.43 ppm indicated the presence of a secondary alcohol. Furthermore, in the ^{13}C-NMR spectrum, the presence of a carbon signal at δ 71.4 ppm and a carbonyl signal at δ 210.0 ppm, in conjunction with the appearance of a sharp

ketone peak at ν 1737 cm^{-1} and the broad OH stretch at ν 3427 cm^{-1} in the IR spectrum confirmed the presence of the acyloin functionality.

The project was continued by synthesis of the di-ester 2-**57** *via* esterification of the mono-ester 2-**38** with thiophene-2-carbonyl chloride to furnish 2-**57** in 82% yield (Scheme 2-**38**). Compound 2-**57** was then submitted to Li/DBB reduction conditions to deliver the crossed-acyloin 2-**58** as a single regioisomer in 75% yield (Scheme 2-**38**).



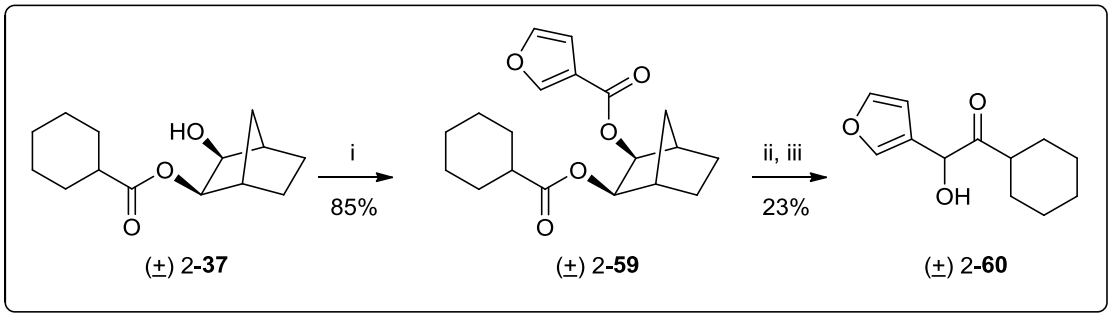
Reagents and conditions: i) Thiophene-2-carbonyl chloride, pyridine (2.2 eq.), CH_2Cl_2, r.t, 16h. ii) Li (20 eq.), DBB (2.0 eq.), THF, –78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**38** – Reduction of di-ester 2-**57** to the corresponding crossed-acyloin regioisomer 2-**58**.

The appearance of one proton as a singlet at δ 5.47 ppm and corresponding hydroxyl proton as a broad singlet at δ 4.37 ppm indicated the existence of a secondary alcohol in the ^{1}H-NMR spectrum. Furthermore, the presence of a carbonyl signal at δ 211.0 ppm and an *O*-alkyl signal at δ 73.3 ppm in the ^{13}C-NMR spectrum, and the sharp ketone peak at ν 1707 cm^{-1} and the broad OH stretch at ν 3458 cm^{-1} in the IR spectrum further provided the evidence for the formation of the acyloin functionality.

With the successful results from the α-substituted five-membered furyl and thiophenyl rings in hand, it was decided to subject mono-ester 2-**38** to the esterification procedure with furan-3-carbonyl chloride to deliver di-ester 2-**59** in 85% yield (Scheme 2-**39**). The reaction sequence was followed by exposure of 2-**59** to Li/DBB reduction conditions to furnish the crossed-

acyloin 2-**60** in a modest yield of 23% (Scheme 2-**39**). The rest of the mass was consumed by radical β-scission forming the corresponding carboxylic acids.

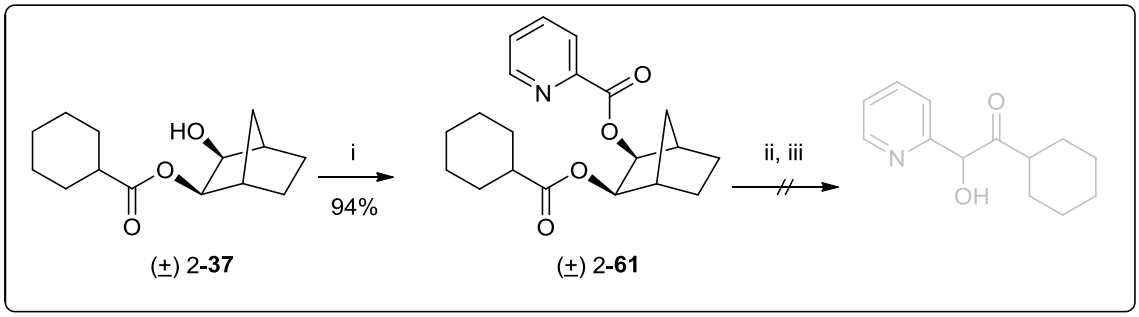


Reagents and conditions: i) Furan-3-carbonyl chloride, pyridine (2.2 eq.), CH_2Cl_2, r.t, 16h. ii) Li (20 eq.), DBB (2.0 eq.), THF, –78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**39 –** Reduction of di-ester 2-**59** to the corresponding crossed-acyloin regioisomer 2-**60**.

The structure of the acyloin 2-**60** was deduced from the observation of the diagnostic signals of the acyloin in NMR and IR spectrum; the appearance of a proton as a singlet at δ 5.20 ppm and a singlet at δ 4.10 ppm confirmed the formation of the secondary alcohol in 2-**60**. In addition, the appearance of the signals at δ 212.2 ppm and δ 70.2 ppm were consistent with the presence of a broad OH stretch at ν 3428 cm^{-1} and a sharp carbonyl signal at ν 1738 cm^{-1} in the IR spectrum.

The scope of the methodology was then expanded to 2-pyridyl substituted di-ester 2-**61**, which was generated by esterification of 2-**38** with picolinoyl chloride to deliver 2-**61** in 94% yield (Scheme 2-**40**). To our disappointment, exposure of 2-**61** to Li/DBB reduction conditions formed an inseparable mixture of products.



Reagents and conditions: i) Picolinoyl chloride, pyridine (2.2 eq.), CH_2Cl_2, r.t, 16h.
ii) Li (20 eq.), DBB (2.0 eq.), THF, – 78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**40** – Reduction of di-ester 2-**61** to form inseparable mixture of products.

These positive results were followed by development of a procedure to isomerise the kinetic acyloins such as 2-**40a**, 2-**56a** and 2-**58a** to the corresponding thermodynamic acyloins 2-**40b**, 2-**56b** and 2-**58b**.

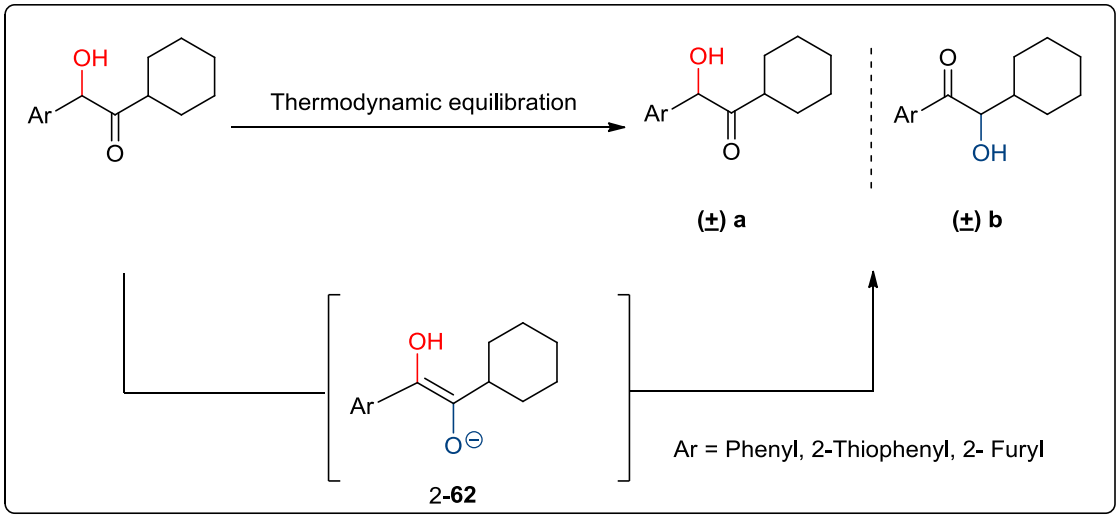
2.3.3 Isomerisation of Aromatic Acyloins

Our previous hypothesis was that the protonation of the ene-diolates 2-**62** (Table 2-**5**) substituted with activating aryl substituents provided the kinetically stable acyloins 2-**40a**, 2-**56a** and 2-**58a** at lower temperatures. The investigation was continued by examining the mesomeric effect of aryl substituents on the ene-diolate intermediate 2-**62** in the isomerisation process. Previous reports in literature have shown that aromatic acyloins undergo isomerisation in both acidic and basic conditions.[46]

As result, acyloin 2-**40a** was subjected to various acidic/basic isomerisation methods (Table 2-**5**, Entries **1**-**5**); experimental observation indicated that the basic conditions promoted the isomerisation of acyloin 2-**40a** to generate the regioisomeric mixture of 2-**40a** and 2-**40b** with ratio of 1.0:2.3 (Table 2-**5**, Entry **5**).

With these results from the acyloin 2-**40a** in hand, acyloin 2-**56a** was subjected to basic

conditions, to deliver a regioisomeric mixture of 2-**58a** and 2-**58b** with the ratio of 1:7 (Table 2-**5**, Entry **6**). After exposure of 2-**56a** to basic conditions the thermodynamically stable acyloin product 2-**56b** was formed in 79% yield (Table 2-**5**, Entry **7**).



Entry	R	Reagent	Solvent	Temp./°C	Time/ h	Yield/ %	Regioselectivity (a:b)
1	Phenyl	NH_4Cl (2.0 eq.)	Et_2O	20	48	90	0.9: 1.0
2	Phenyl	$NaHCO_3$ (2.0 eq.)	Et_2O	20	48	97	>25:1.0
3	Phenyl	NaOAc (1.2 eq.)	Ac_2O	140	5	n.d	n.d
4	Phenyl	$Al(O\text{-}i\text{-}Pr)_3$ (1.2 eq.)	PhMe	110	4	n.d	n.d
5	Phenyl	Et_3N (1.5 eq.),	EtOH	78	48	78	1.0:2.3
6	2-Thiophenyl	Et_3N (1.5 eq.),	EtOH	78	48	70	1.0:7.0
7	2-Furyl	Et_3N (1.5 eq.),	EtOH	78	48	79	>1.0:25

Table 2-5 – Isomerisation of crossed-acyloins 2-**40a**, 2-**56a** and 2-**58a**.

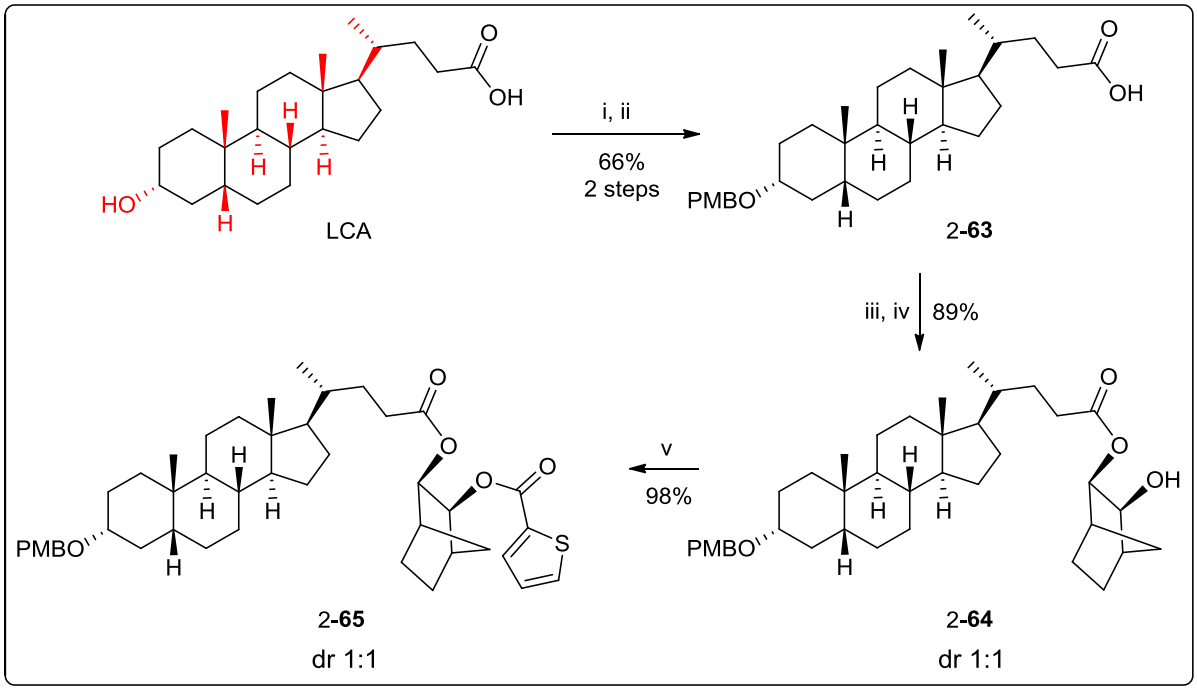
The results displayed in Table 2-**5** demonstrate that the mesomeric effect of aryl substituents on the ene-diolate 2-**62** would facilitate isomerisation of kinetic aryl acyloins 2-**40a**, 2-**56a** and 2-**58a**. In the case of 2-**56a**, the impact of the effect resulted in complete isomerisation towards the thermodynamically stable acyloin 2-**56b** (see Table 2-**5**, Entry **7**).

2.3.4 Aliphatic Substituents

2.3.4.1 Steroid Substituents

With the encouraging results from the regioselective directing effect of the aryl substituents in hand, the methodology was applied in an intramolecular reductive coupling reaction between a lithocholic acyl and a thiophenyl group, linked with 2-**29** (Scheme 2-**41**). The reason lithocholic acid (LCA) was selected as an aliphatic substituent was due to its interesting chemical structure; a steroid motif containing 9 stereogenic centres. In the human body, LCA is formed in a bacterial process in the colon, where it acts as a mediator to solubilise fats in the metabolic process. Previous reports in the literature have highlighted the biological activities of lithocholic acid derivatives.[47,48]

In order to avoid complications in the esterification step, the secondary alcohol of LCA was subjected to PMB protection followed by saponification of the intermediate PMB ester, to deliver PMB-LCA 2-**63** in 66% yield over two steps (Scheme 2-**41**). The resulting 2-**63** was then converted to the corresponding acyl chloride, which was reacted with the linker 2-**29** under basic conditions to yield mono-ester 2-**64** in 89% as a 1:1 diastereoisomeric mixture (Scheme 2-**41**). The desired di-ester 2-**65** was synthesised in 98% yield as a 1:1 mixture of diastereoisomers by treating 2-**64** with thiophene-2-carbonyl chloride in the presence of base (Scheme 2-**41**).



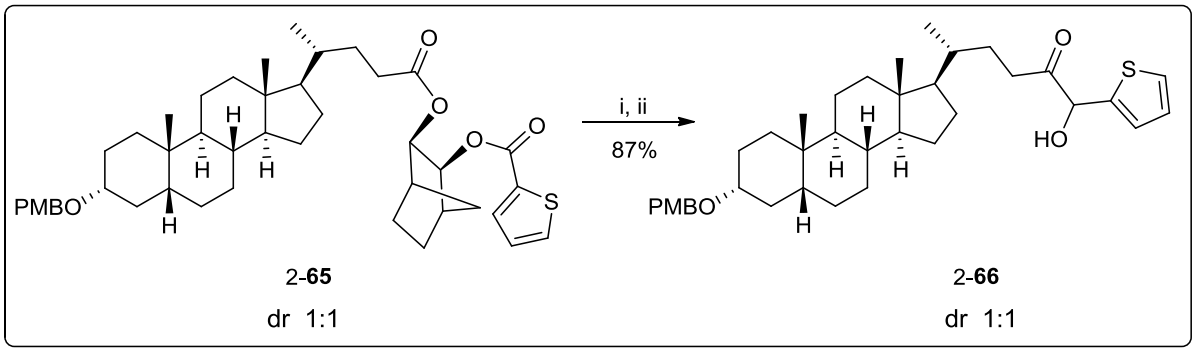
Reagents and conditions: i) NaH, PMBCl, TBAI, THF, 0 - 25 °C , 16 h. ii) 5% NaOH, THF/MeOH/H_2O, 80 °C, 4 h. iii) $(COCl)_2$, DMF, CH_2Cl_2, r.t, 5 h. iv) 2-**29** (1.5 eq.), Pyridine (1.1 eq.), CH_2Cl_2, r.t, 3 h. v) Thiophene-2-carbonyl chloride, pyridine (2.2 eq.), DMAP, CH_2Cl_2, r.t, 16h.

Scheme 2-**41 –** Synthesis of the di-ester 2-**65**.

The appearance of four aromatic protons as two multiplets at δ 7.27 ppm and at δ 6.87 ppm with 8.2 Hz coupling constant and the methoxy peak as a singlet at δ 3.79 ppm in the ^{1}H-NMR spectrum confirmed the PMB protection of the secondary alcohol. Furthermore, the presence of the characteristic signals of the thiophene; a doublet at δ 7.79 ppm, a doublet at δ 7.55 ppm and a triplet at δ 7.10 ppm validates the second acylation reaction. In the ^{13}C-NMR spectrum, the presence of the signals at δ 173.3 ppm and δ 173.2 ppm confirmed the carbonyl functionalities in the di-ester 2-**65**.

To our satisfaction, treatment of compound 2-**65** with Li/DBB reducing conditions delivered the crossed-acyloin 2-**66** as a single regioisomer in 87% yield (Scheme 2-**42**). It is worth noting that the reaction formed an inseparable 1:1 diastereomeric mixture, which was confirmed by ^{13}C-NMR spectrum, which exhibited doubling of the carbon signals,

corresponding to a 1:1 mixture.



Reagents and conditions: i) Li (20 eq.), DBB (2.0 eq.), THF, – 78 °C, 3 h. ii) NH_4Cl (aq.).

Scheme 2-42 – Reduction of di-ester 2-**65** to form crossed-acyloin 2-**66**.

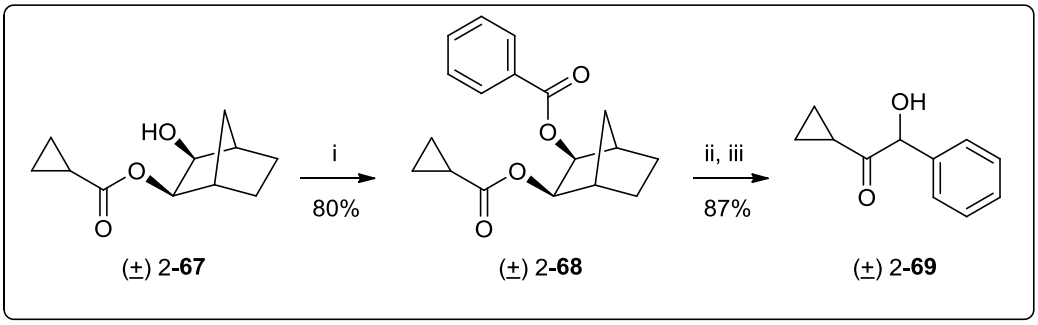
The structure of the crossed-acyloin 2-**66** was characterised by the NMR and IR spectroscopy. The appearance of two protons as a doublet at δ 5.37 ppm and a broad single at δ 4.35 ppm in the ^{1}H-NMR spectrum confirmed the formation of the acyloin functionality in 2-**66** (dr 1:1). This indication was further confirmed by the presence of the carbonyl signal at δ 208.9 ppm and δ 208.7 ppm, and the *O*-alkyl peak at δ 75.1 ppm and δ 74.8 ppm in the ^{13}C-NMR spectrum. Furthermore, in the IR spectrum the appearance of a broad OH stretch at ν 3471 cm^{-1} and a sharp peak at ν 1695 cm^{-1} confirmed the formation of the acyloin functionality.

2.3.4.2 Cyclopropane as a Substituent

The project was continued by investigating the stability of cyclopropane rings under the Li/DBB reductive conditions. Previous reports in the literature have indicated that cyclopropane rings undergo radical cleavage under Birch reaction conditions (Na/NH_3) at –78°C.[49]

Di-ester 2-**68** was generated by subjecting mono-ester 2-**67** and benzoyl chloride to basic

esterification procedure to deliver 2-**68** in 80% yield (Scheme 2-**43**).

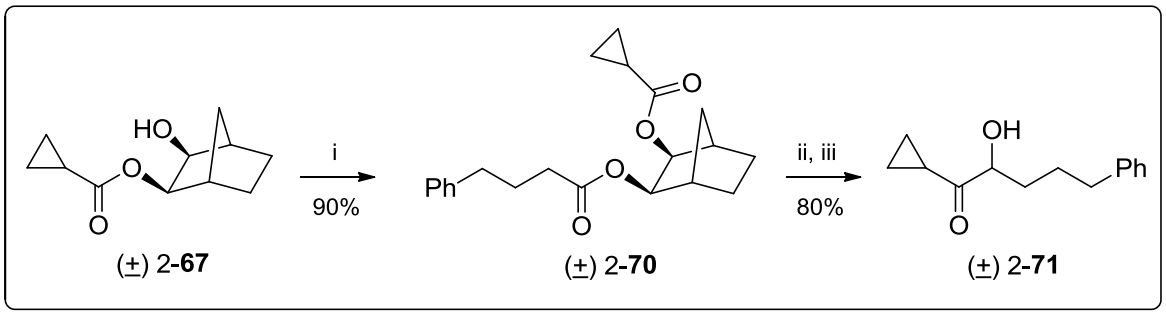


Reagents and conditions: i) Benzoyl chloride, pyridine (2.2 eq.), CH_2Cl_2, r.t, 16h.
ii) Li (20 eq.), DBB (2.0 eq.), THF, – 78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**43 –** Reduction of di-ester 2-**68** to the corresponding crossed-acyloin 2-**69**.

To our surprise, the Li/DBB mediated reduction of 2-**68** did not cause the cleavage of the cyclopropane ring and exclusively formed the known crossed-acyloin 2-**69** as a single regioisomer in 87% yield (see Scheme 2-**43**).[50]

In order to further examine the stability of cyclopropane in the Li/DBB reduction conditions, di-ester 2-**70** was synthesised *via* esterification of mono-ester 2-**31** with 4-phenylbutanoyl chloride to deliver 2-**70** in 90% yield (Scheme 2-**44**). To our excitement, submission of 2-**70** to the reduction conditions formed the crossed-acyloin 2-**71** as a single regioisomer in 80% yield (Scheme 2-**44**).



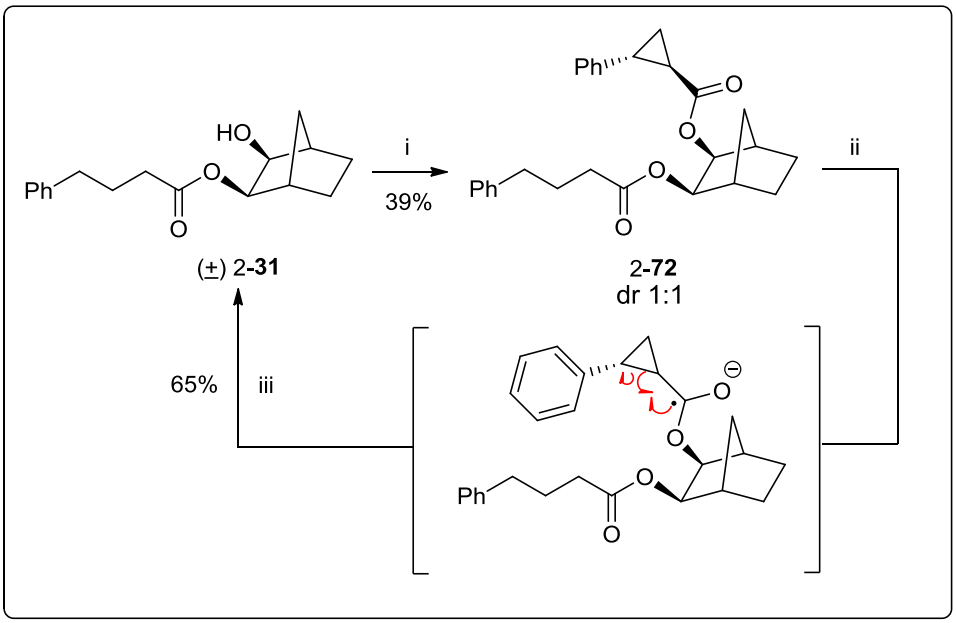
Reagents and conditions: i) 4-phenylbutanoyl chloride, pyridine (2.2 eq.), CH_2Cl_2, r.t, 16h.
ii) Li (20 eq.), DBB (2.0 eq.), THF, – 78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**44 –** Reduction of di-ester 2-**70** to the corresponding crossed-acyloin 2-**71**.

The structure of the acyloin 2-**71** was characterised by NMR and IR spectroscopy; the

appearance of a proton as a double doublet at δ 4.41 ppm and a broad singlet at δ 3.54 ppm in the ^{1}H-NMR spectrum with corresponding signals at δ 76.7 ppm in ^{13}C-NMR spectrum indicated the presence of a secondary alcohol. Furthermore, in the ^{13}C-NMR spectrum the appearance of the carbonyl signals at δ 212.1 ppm was consistent with the observation of a sharp signal at ν 1695 cm^{-1} in the IR spectrum.

In the light of these exciting results from the non-substituted cyclopropane, the investigation was continued by examining the stability of phenylcyclopropane substituted di-ester 2-**72** in the Li/DBB mediated reduction conditions. In order to avoid epimerisation compound 2-**72** was formed *via* DCC coupling reaction between mono-ester 2-**31** and *(2S)*-2-phenylcyclopropanecarboxylic acid to deliver the desired 2-**72** in 39% yield as a 1:1 diastereomeric mixture (Scheme 2-**45**). To our disappointment, reduction of 2-**72** under Li/DBB reductive conditions only recovered the parent mono-ester 2-**31** in 65% yield (Scheme 2-**45**).



Reagents and conditions: i) *(2S)*-2-Phenylcyclopropanecarboxylic acid, DMAP (1.0 eq.), DCC (1.0 eq.), CH_2Cl_2, r.t, 16h. ii) Li (20 eq.), DBB (2.0 eq.), THF, – 78 °C, 3 h. iii) NH_4Cl (aq.).

Scheme 2-**45** – Reduction/degradation of di-ester 2-**72** to the parent mono-ester 2-**31**.

It was suggested that the substrate 2-**72** underwent a radical decomposition *via* a SET reduction of phenyl ring, which probably caused cleavage of the cyclopropane ring followed by elimination of the acyl group to regenerate mono-ester 2-**31** (see Scheme 2-**45**).

Previous reports in the literature have suggested that the cyclopropyl ring can be characterized as a strong π-donor. The stabilisation of the system is maximal when the cyclopropyl ring is able to adopt a bisected conformation with respect to an adjacent π-system (Figure 2-**15**).[51]

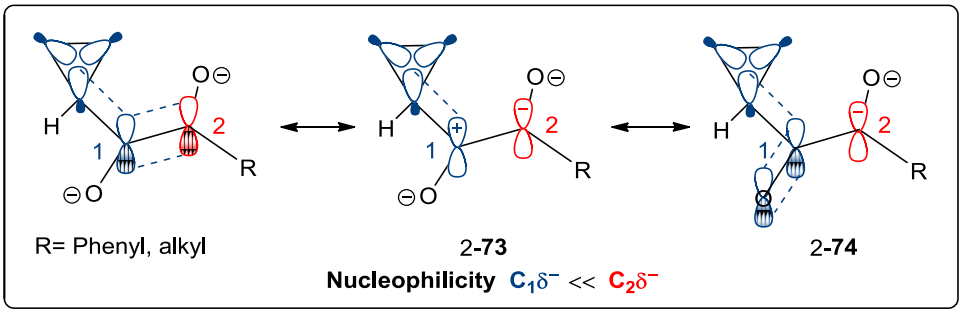


Figure 2-**15** – The electron donating properties of cyclopropane promotes the regioselectivity.

This suggestion could explain the regio directing effect of the cyclopropane in our case. The alignment of the π orbitals of the ene-diolate with the electron donating cyclopropane ring could promote the stabilisation of the intermediate 2-**73**, which consequently increases the nuclophilicity of the C_2 carbon atom, illustrated by the resonance form 2-**74** (see Figure 2-**15**).

The regio directing effect of the cyclopropane in the Li/DBB mediated crossed-acyloin methodology could provide the opportunity to exploit cyclopropane acyloins as useful intermediates to generate non-symmetrical aliphatic acyloins.[52,53] Indeed, there are several methods reported in the literature for the ring cleavage of cyclopropane carbonyls to yield synthetically useful intermediates such as alcohols, ethers or alkyl halides.[54,55,56,57]

2.4 Crossed-acyloins as a Useful Synthetic Tool in the Synthesis of Heterocyclic Aromatic Rings

With the positive results described in the previous chapters on the implementation of Li/DBB mediated conditions in chemo- and regioselective crossed-acyloin condensation reaction, our attentions turned to investigating the potential reactivity of the acyloin adduct in the synthesis of heterocyclic aromatic rings. Due to their inherent reactivity, acyloins could serve as precursors to several interesting heterocyclic aromatic compounds (e.g. imidazoles, oxazoles and indoles).[58,59,60,61]

These compounds are significant because of their biological activity and their applications in the synthesis of pharmaceuticals, herbicides and dyes.[62] Indeed, heterocyclic aromatic moieties are ubiquitous in important classes of natural products such as alkaloids, vitamins, hormones and antibiotics (Figure 2-**16**).

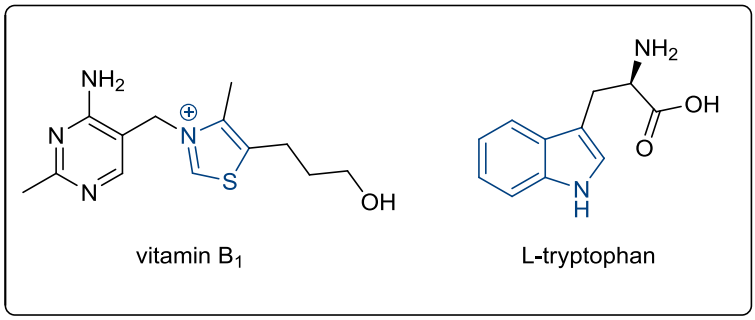
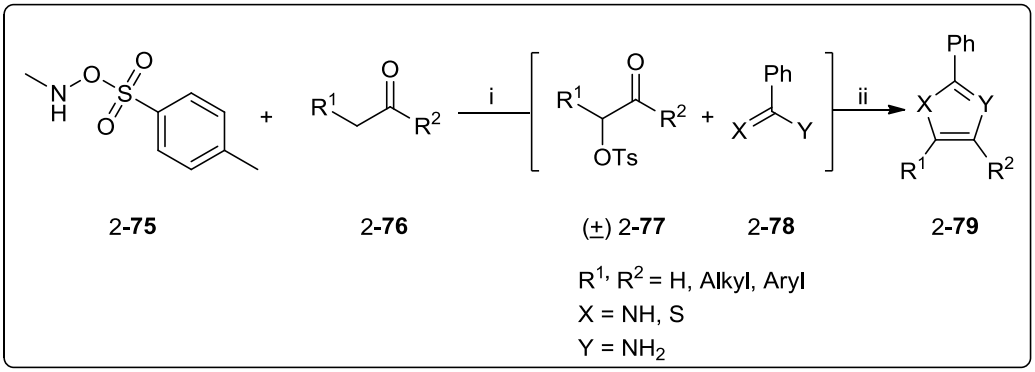


Figure 2-16 – The structure of vitamin B_1 and L-tryptophan.

2.4.1 Synthesis of Tri-Substituted Thiazoles

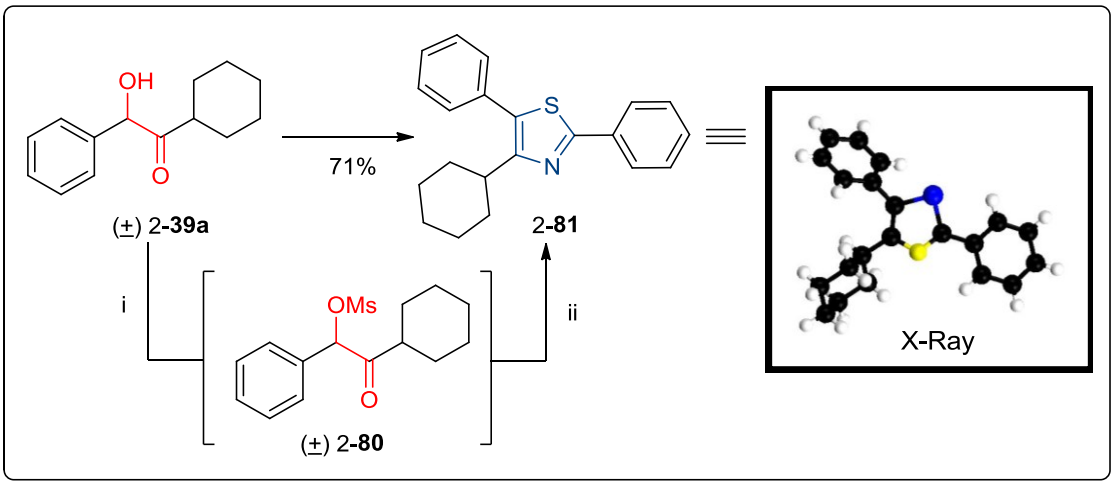
Previous work by Tomkinson *et al.* in 2007 has demonstrated that *N*-methyl-*O*-tosylhydroxylamine 2-**75** is an effective reagent for the direct *α*-oxytosylation of carbonyl compounds 2-**76** (Scheme 2-**46**). [63]



Reagents and conditions: i) TsOH (1.5 eq.), THF/PhMe (1:1), 40 °C, 15 h.
ii) 2-**78** (3 eq.), THF/PhMe (1:1), 80 °C, 18 h.

Scheme 2-**46** – Formation of aromatic hetreocycles 2-**79**.

Addition of a bis-heteronucleophile 2-**78** directly to the crude *α*-tosyloxy ketone 2-**77** in a one-pot process led to the corresponding heterocyclic aromatic products 2-**79** (see Scheme 2-**46**). This methodology was then adapted and employed in our case for the cyclisation of an activated acyloin adduct by converting first crossed-acyloin 2-**40a** to the corresponding *α*-mesyloxy ketone 2-**80**.



Reagents and conditions: i) MsCl (1.1 eq.), Et_3N (1.5 eq.), Et_2O, 40 °C, 2 h.
ii) Thiobenzamide (3 eq.), THF/PhMe (1:1), 80 °C, 16 h.

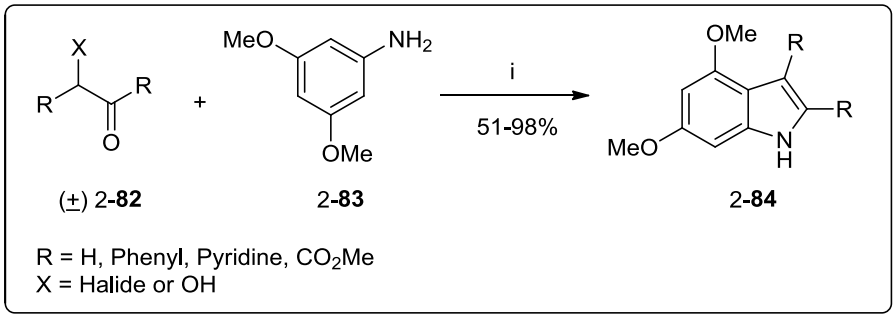
Scheme 2-**47** – Conversion of crossed-acyloin 2-**39a** to the corresponding thiazole 2-**81**.

The crude product 2-**80** was then treated with thiobenzamide to deliver the desired thiazole 2-**81** in 71% yield (Scheme 2-**47**). The structure of 2-**81** was confirmed by X-ray

crystallography (Appendix **2**).‡

2.4.2 Synthesis of Tetra-Substituted Indoles

The indole nucleus is present in a wide range of natural products, and consequently a variety of methods for their synthesis have been developed.[64,65,66] This was especially the case for the construction of activated 3-substituted-4,6-dimethoxyindoles 2-**84** (Scheme 2-**48**). Among these procedures, the Bischler-Möhlau indole synthesis employs *α*-halo/hydroxyketones 2-**82** and aniline 2-**83** as precursors to generate tetra-substituted indoles. Black *et al.* in 1986 reported a modified Bischler-Möhlau indole synthesis procedure, involving symmetrical acyloins 2-**82** and 3,5-dimethoxyaniline 2-**83** to generate a range of tetra-substituted indoles 2-**84** in modest to excellent yields (Scheme 2-**48**).[67]

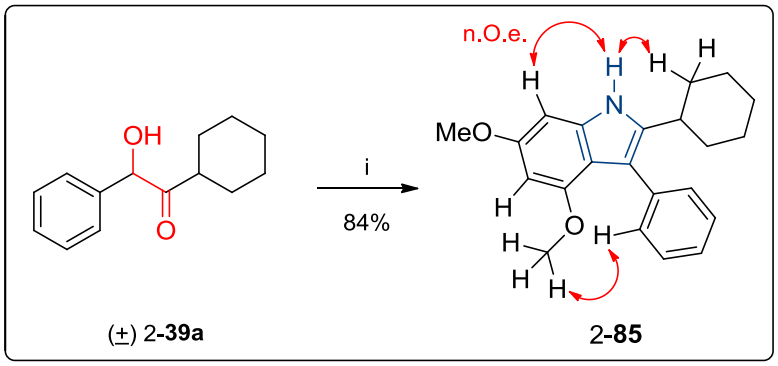


Reagents and conditions: i) HI (cat.), PhMe, 120-140 °C,1 h.

Scheme 2-48 – Conversion of symmetrical *α*-halo/hydroxyketones to the corresponding indoles 2-**84**.

Based on this methodology, crossed-acyloin 2-**39a** and 3,5-dimethoxyaniline 2-**83** were reacted in the presence of catalytic loading of aqueous hydroiodic acid, which delivered the tetra-substituted indole 2-**85** in 84% yield as a single regioisomer (Scheme 2-**49**).

‡ X-ray crystallography by Dr. Cedric Callens



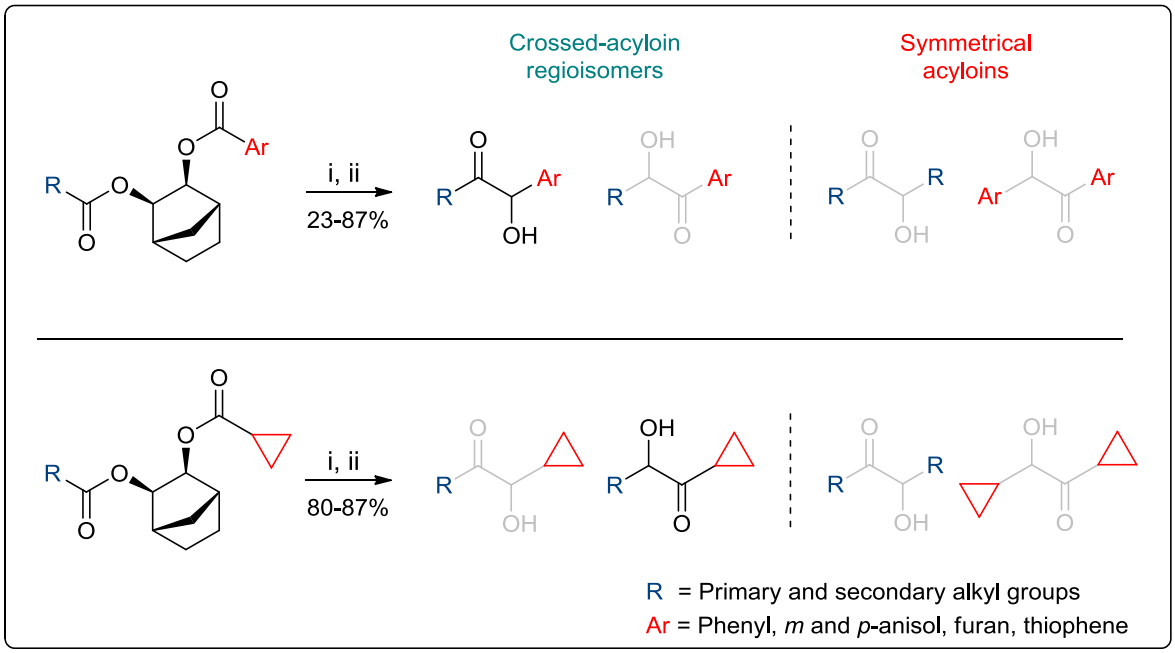
Reagents and conditions: i) HI (cat.), 2-**83** (2 eq.), PhMe, 110 °C, 3 h.

Scheme 2-**49** – Conversion of crossed-acyloin 2-**40a** to the corresponding indole 2-**85**.

The structure of the indole 2-**85** was confirmed by analysis of the NMR and IR spectra. The appearance of a proton as a broad singlet at δ 7.92 (2-**85**, NH) indicated the formation of the pyrrole ring in 2-**85**. Furthermore, the presence of multiple aromatic signals between δ 7.46-6.23 ppm corresponding to seven protons and two singlets at δ 3.85 ppm and δ 3.68 ppm related to two methoxy groups provided further evidence of the formation of 2-**85**. The regioselectivity of the reaction was confirmed by n.O.e. analysis (depicted as red arrows in the Scheme 2-**49**), showing correlation between the NH proton, the aromatic proton ArH and the cyclohexane protons on the γ position. In addition, the n.O.e. spectrum indicated a through space interaction between the aromatic ring ArH and the adjacent methoxy group.

2.5 Conclusion

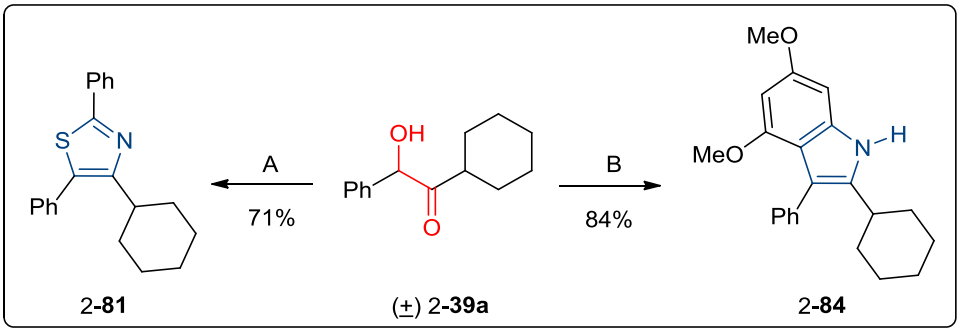
A novel procedure for the formation of crossed-acyloins mediated by Li/DBB has been developed. The rigid bicyclic diol, *exo*,*exo*-norbornene-1,2-diol 2-**29** was identified as an efficient linker for two different acyl groups promoting a highly *chemoselective* crossed acyloin coupling with excellent yields (Scheme 2-**50**).



Reagents and conditions: i) Li (20 eq.), DBB (2.0 eq.), THF, –78 °C, 3 h. ii) NH_4Cl (aq.).

Scheme 2-50 – Regioselective intramolecular acyloin condensation.

As for the *regioselectivities*, these were found to be poor if both of the esters were substituted with aliphatic groups. However, crossed-acyloin reaction between alkyl and aromatic or cyclopropyl di-esters resulted in complete regioselectivity (see Scheme 2-**50**). Furthermore, it has been shown that the regioselectivity of the crossed-acyloin condensation could be exploited as useful synthetic tool in the synthesis of single regioisomer aromatic heterocycles such as thiazole 2-**81** and indole 2-**85** (Scheme 2-**51**).



Reagents and conditions: A i) MsCl (1.1 eq.), Et_3N (1.5 eq.), Et_2O, 40 °C, 2 h. ii) Thiobenzamide (3 eq.), THF/PhMe (1:1), 80 °C, 16 h. B) HI (cat.), 2-**83**, PhMe, 110 °C, 3 h.

Scheme 2-51 – Conversion of crossed-acyloin 2-**39a** to the corresponding thiozole 2-**81** or indole 2-**85**.

Chapter 3: Introduction – Metal Mediated Synthetic Routes to *trans*-2,5-Disubstituted THFs

3.1 Metal Mediated Synthetic Routes to *trans*-2,5-Disubstituted THFs

Trans-2,5-disubstituted-tetrahydrofurans (*trans*-THFs) are widely occurring subunits in natural products such as monensin 3-**1** and pectenotoxin-4 3-**2,** which possess antitumor activity against a wide variety of human cancer cell lines (Figure 3-**1**).[68,69]

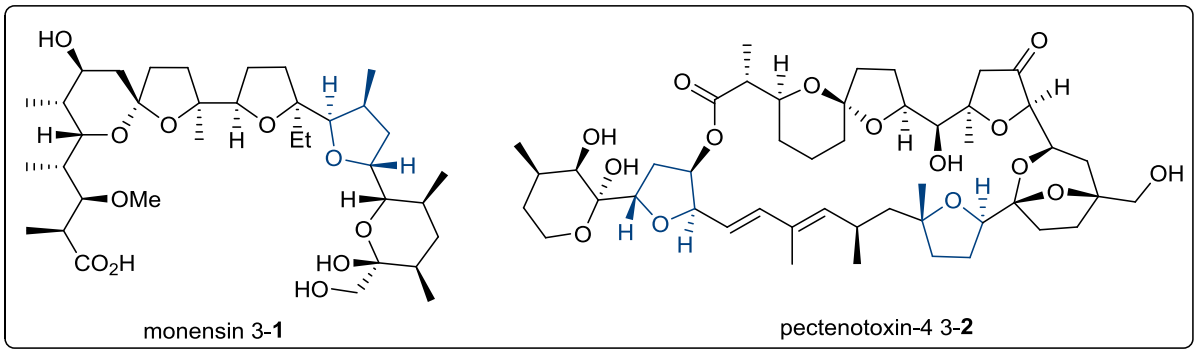
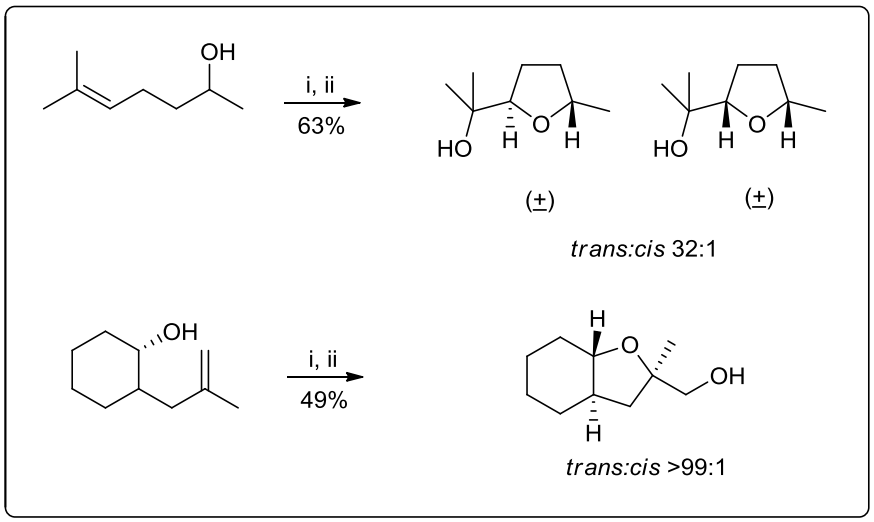


Figure 3-**1** –Structure of monensin 3-**1** and pectenotoxin-4 3-**2**.

One of the most challenging aspects in the preparation of these natural products is the stereocontrolled construction of *trans*-THF units and, as a result, a variety of methodologies have been developed for their synthesis. The following chapter is a summary of metal catalysed oxidative cyclisation methods for the formation of the *trans*-THF unit and their application in the field of natural product synthesis.

3.1.1 Rhenium Mediated Oxidative Cyclisation

In 1992, Kennedy *et al.* developed a rhenium(VII)oxide (Re_2O_7) mediated oxidative cyclisation of unactivated bishomoallylic alcohols to generate THFs with modest to excellent *trans* selectivity (Scheme 3-**1**).[70,71]



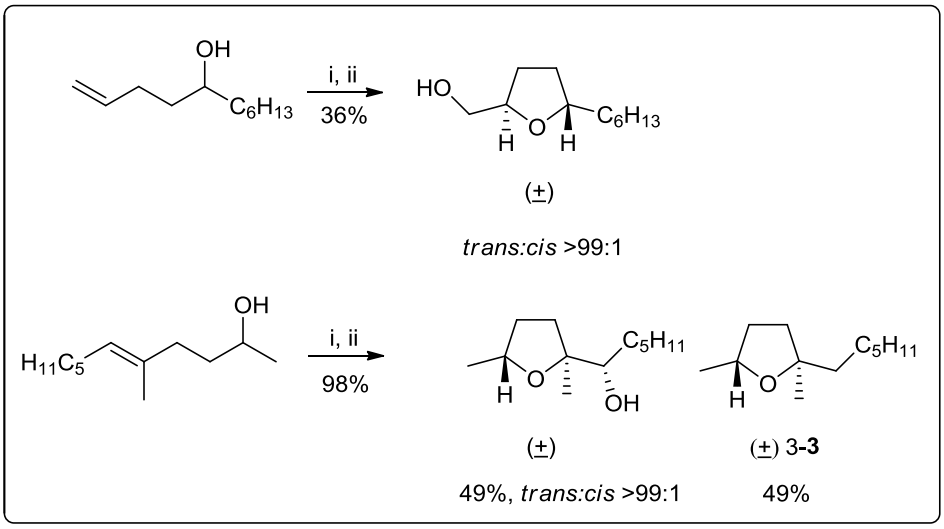
Reagents and Conditions: i) Re_2O_7 (3.0 eq), 2,6-lutidine (3.3 eq), CH_2Cl_2, 0 °C, 10 h. (ii) $NaHSO_3$ (aq.).

Scheme 3-1 – Rhenium(VII) oxide mediated oxidative cyclisation of bishomoallylic alcohol.

In comparison to other more powerful oxidants such as permanganate(VII) ($KMnO_4$) and chromium(VI) (CrO_2Cl_2), rhenium oxide is not capable of oxidising the alcohol functionality present in both the starting material and the final product to the corresponding carbonyl compound.[72]

Preliminary results indicated that stoichiometric quantities of rhenium oxide were required to drive the reaction to completion. Additional ^{1}H-NMR spectroscopic studies provided evidence that rhenium was strongly chelated by the THF products, producing rhenium complex 3-**6** (see Scheme 3-**3**). This necessitated the use of aqueous $NaHSO_3$ in the work-up procedure to cleave the rhenium-THF complexes and liberate the product. Furthermore, it was proposed by Kennedy *et al.* that the presence of a non-nucleophilic solvent and base were essential to avoid competitive coordination to the rhenium(VII) oxide. Later work established that a sub-stoichiometric loading of Re_2O_7 in the presence of periodic acid (H_5IO_6) as co-oxidant also facilitated the reaction. However, these conditions led to a reduction in the yield, and in the case of trisubstituted alkenes, the reaction also provided non-oxidative

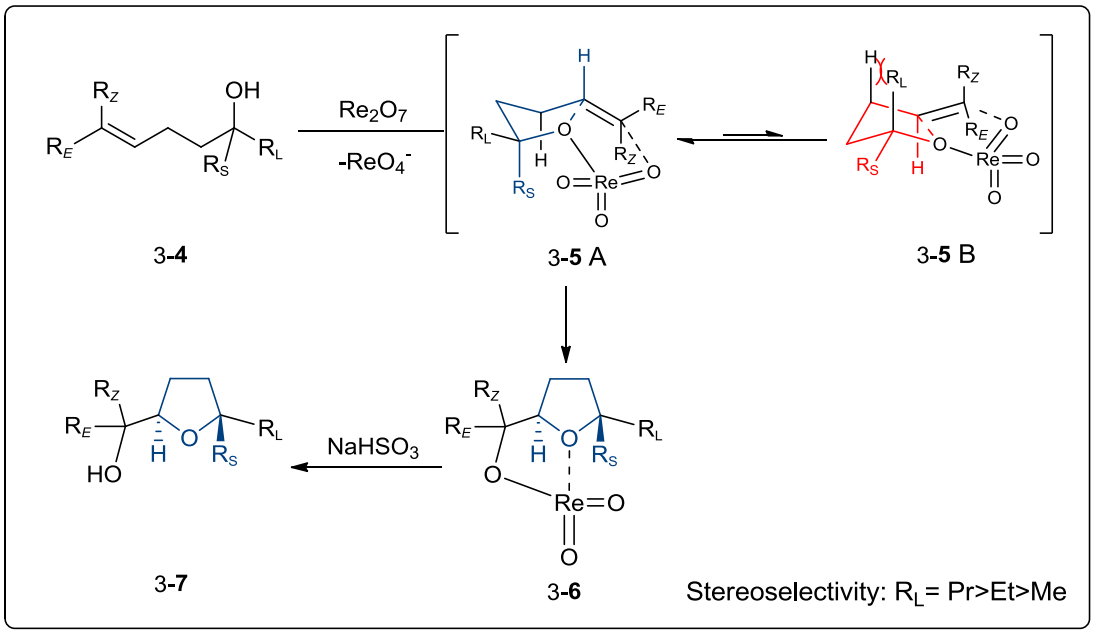
cyclisation side products 3-**3** (Scheme 3-**2**).[73]



Reagents and Conditions: i) Re_2O_7 (0.5 eq.), H_5IO_6 (1.3 eq.), CH_2Cl_2, 0 °C, 16 h. (ii) $NaHSO_3$ (10 eq.).

Scheme 3-**2** – Substoichiometric rhenium(VII)oxide mediated oxidative cyclisation.

The mechanism of this reaction was first formulated by Kennedy *et al*, who suggested that the initial step was a transesterification between rhenium(VII) oxide and bishomoallylic alcohol 3-**4** to deliver the perrhenate ester 3-**5** (Scheme 3-**3**).

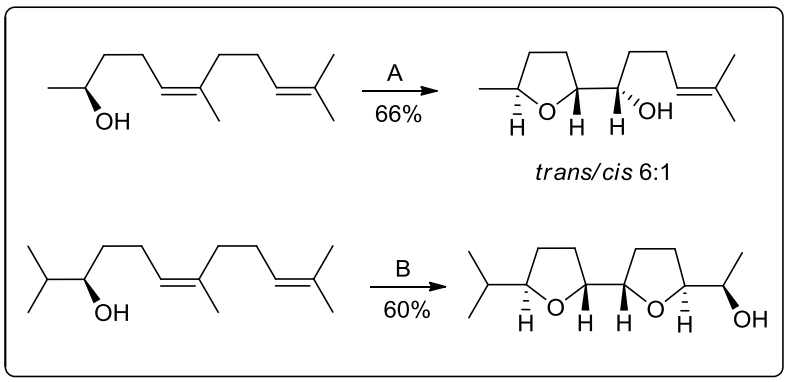


Scheme 3-**3** – Mechanism of rhenium mediated oxidative cyclisation.

The hypothesis formulated was that the transition state structure adopted a chair-like

conformation with the large group R_L being in a pseudoequatorial position relative to the pendant alkene, due to 1,3 diaxial strain: 3-**5**A state would then be favoured over 3-**5**B (see Scheme 3-**3**). The reaction was described as (3+2) intramolecular cycloaddition of 3-**5**A to 3-**6**, which upon subsequent exposure to aqueous $NaHSO_3$ underwent decomplexation to deliver *trans*-THF 3-**7** (see Scheme 3-**3**).[74]

Further work by McDonald *et al*. contributed to the development of new conditions for the rhenium oxide mediated *syn*-oxidative cyclisation. Indeed, the discovery was made that a non-nucleophilic base such as 2,6-lutidine prevented the formation of non-oxidative by-products resulting from acid-catalysed hydration of the olefin (pK_a of perrhenic acid −1.25). It was therefore proposed that by changing the leaving group from perrhenate (O_3ReO^-) to a less acidic trifluoroacetate ($CF_3CO_2^-$), the yield of the reaction would improve. This was indeed the case but the reaction then proceeded only with moderate stereoselectivity. Further modification of the reaction conditions by using (dichloroacetyl)perrhenate in the absence of base resulted in a bis-cyclisation to produce a bis-tetrahydrofuran in moderate yield (Scheme 3-**4**).[75]



Reagent and Conditions: A) $(CF_3CO_2)Re_2O_3$ (1.0 eq.), 2,6-lutidine (3.3 eq), CH_2Cl_2, 20 °C, 16 h. $NaHSO_3$ (10 eq.) B) $(Cl_2CHCO_2)ReO_3$ (2.0 eq.), $(Cl_2CHCO_2)O$, CH_2Cl_2, 20 °C, 16 h. $NaHSO_3$ (10 eq.)

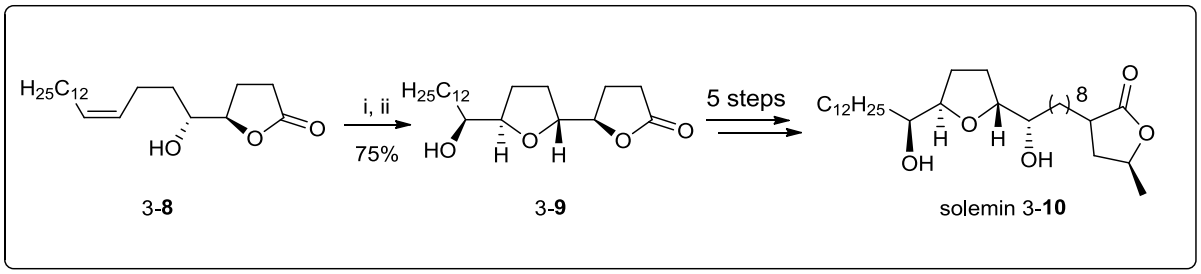
Scheme 3-4 – $(CF_3CO_2)Re_2O_3$ mediated oxidative cyclisation.

It was also discovered that addition of dichloroacetic anhydride or TFAA to the reaction

trapped trace amounts of perrhenic acid produced in the course of the reaction, as well as regenerating the (dichloroacetyl)perrhenate reagent, which then accelerated the rate of oxidative cyclisation; this observation has also been supported by Morimoto *et al*.[76] It is worth noting that the actual loading of the rhenium reagent was still stoichiometric in this modified procedure.

The methodology has been employed in numerous synthesis of annonaceous acetogenins.[77,78,79,80] These natural products typically consist of one to three THF rings attached to a common butenolide core structure by a linear carbon chain.

In the course of the synthesis of solamin 3-**10**, Sinha *et al*. employed the procedure successfully by cyclising bishomoallylic alcohol 3-**8** to the corresponding *trans*-THF 3-**9** as a single diastereomer in 75% yield (Scheme 3-**5**).[81]

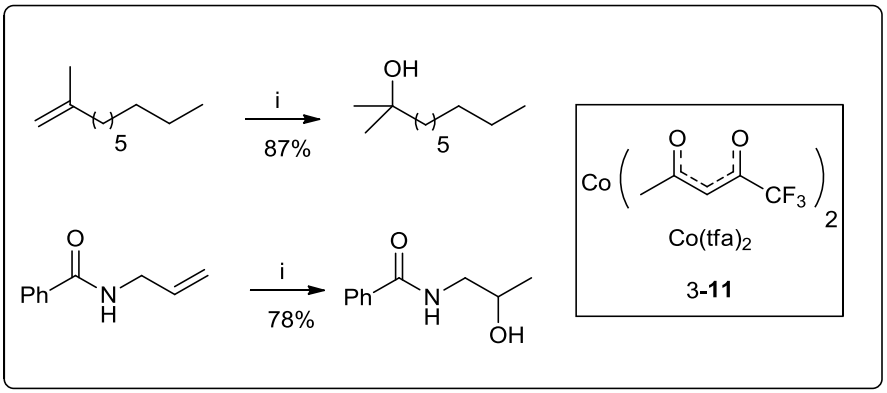


Reagents and Conditions: i) Re_2O_7 (0.5 eq.), H_5IO_6 (1.3 eq.), CH_2Cl_2, 0 °C, 16 h. (ii) $NaHSO_3$ (10 eq.)

Scheme 3-5 – Synthesis of solemin 3-**10** by Sinha *et al*.

3.1.2 Cobalt Catalysed Oxidative Cyclisation

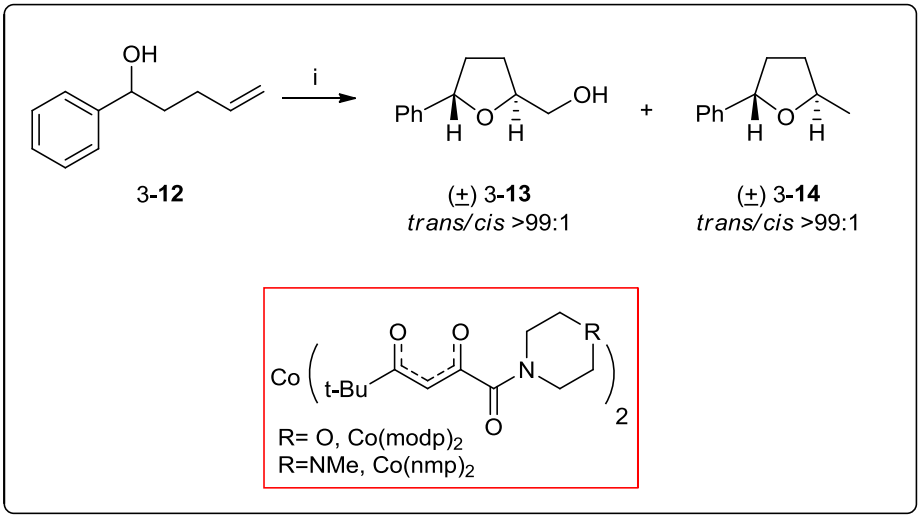
Preparation of *trans*-THFs *via* the Co(II) catalysed oxidative cyclisation of bis-homallylic alcohols was originally reported by Mukaiyama *et al*. in 1990.[82] This method was developed in the course of investigations into the oxidation, reduction, and hydration of terminal olefins catalysed by $Co(tfa)_2$ 3-**11** in 2-propanol under an oxygen atmosphere (Scheme 3-**6**).



Reagents and Conditions: i) O_2 (1 atm.), 3-**11** (0.4 eq.), 2-PrOH, M.S. 4 Å, 75°C. 4-15 h.

Scheme 3-**6 –** Oxidation-reduction and hydration of alkene catalysed by $Co(tfa)_2$.

It was later found that bishomoallylic alcohol 3-**12** could be oxidised with oxygen in the presence of 3-**11** to form *trans*-THF product 3-**13** together with the non-oxidative by-product 3-**14** in poor yield but excellent *trans*-selectivity (>99%) (Table 3-**1**, Entry **1**).[83]



Entry	Co(II)catalyst (X)	Temp./°C (Y)	Additive	Time/h	Yield/ %		*Trans*/ %
					1-**13**	1-**14**	
1	(20 mol%)	75	none	4.0	21	24	>99%
2	$Co(modp)_2$ (20 mol%)	50	TBHP	0.5	73	*	>99%
3	$Co(nmp)_2$ (5 mol%)	55	TBHP	16	91	*	>99%

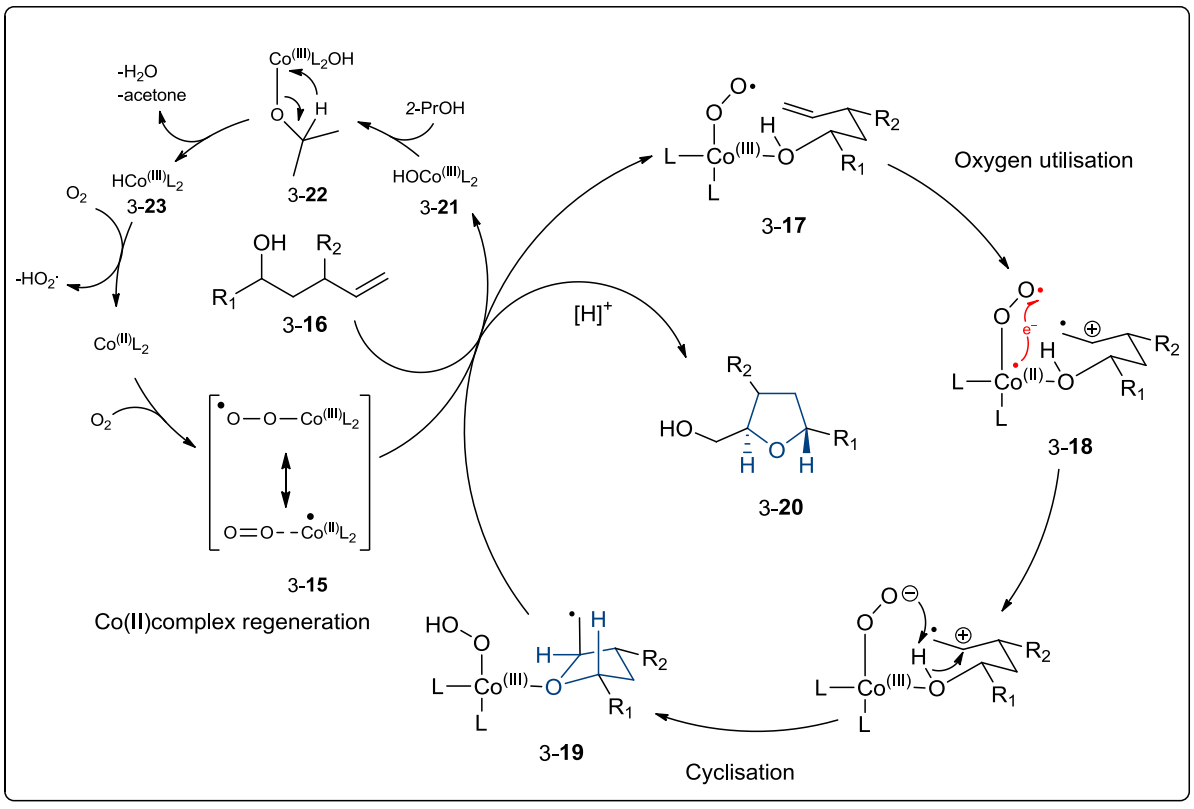
Reagents and Conditions: i) O_2 (1 atm.), X, 2-PrOH, M.S. 4 Å, Y. * Not detected.

Table 3-**1 –** Variation of Co(II)complex catalyst and temperature in the oxidative cyclisation reaction.

In order to optimise the yield of the reaction, several Co(II)complex reagents were screened at different temperatures. The optimal conditions were reached by the application of $Co(modp)_2$ at 50 °C in the presence of stoichiometric *t*-BuOOH (TBHP), employed as re-oxidant (Table 3-**1**, Entry **2**).

Pagenkopf *et al.* further developed this methodology by employing $Co(nmp)_2$ as a catalyst, which required a lower catalytic loading and led to a significantly improved yields without affecting the stereoselectivity (see Table 3-**1**, Entry **3**).[84]

From a mechanistic point of view, it was proposed that the reaction proceeded *via* a radical oxygen activation of the Co(II)complex, yielding to the strong Lewis acid superoxo Co(III)complex 3-**15** (Scheme 3-**7**).

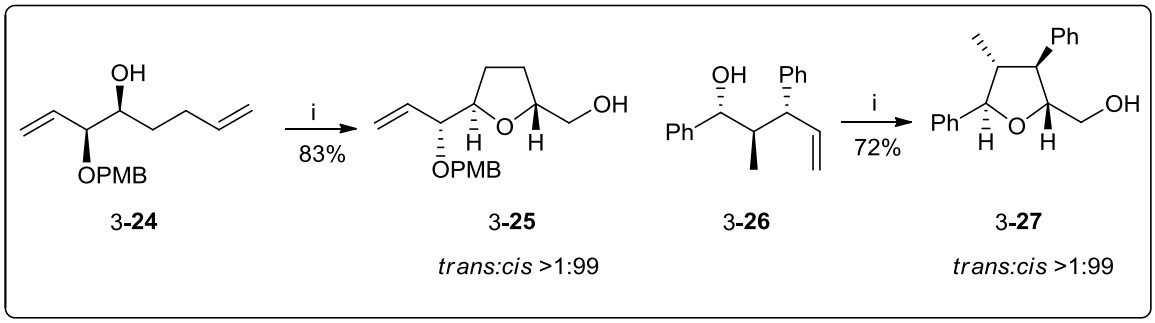


Scheme 3-**7** – Mechanism of cobalt(II) catalysed oxidative cyclisation.

The oxygen of the bishomoallylic alcohol 3-**16** would then react with 3-**15** to yield

intermediate 3-**17**, which would subsequently undergo an intramolecular redox reaction to deliver radical cation 3-**18**. A rapid 5-*exo* ring closure would then occur to yield the radical Cobalt-THF intermediate 3-**19**. It was postulated that the steric interaction imposed by the cobalt(II) complex structure would facilitate the folding of the alkenol chain into a chairlike conformation 3-**19**, in which the substituents R^1 and R^2 would adopt pseudoequatorial positions (see Scheme 3-**7**).[85] The hydroxyl *trans*-THF 3-**20** would then be obtained by final oxidation of the radical intermediate 3-**19** bearing the pendant cobalt peroxide. Collapse of the cobalt-THF complex 3-**19** would also lead to the formation of hydroxyCo(III)complex 3-**21** as a by-product. Catalyst 3-**15** would then be regenerated in the presence of a protic solvent (*e.g.* 2-propanol) under an atmosphere of oxygen as described in Scheme 3-**7**. Indeed, 3-**21** would subsequently react with 2-propanol forming intermediate 3-**22**, followed by a hydride shift resulting in hydridcobalt(III)complex 3-**23**, water and acetone as by-products. Further reduction of 3-**23** by oxygen would generate the required Co(II)complex 3-**15** (see Scheme 3-**7**).

The methodology has been successfully applied in a wide range of cyclisation reactions of enantiopure bishomoallylic alcohols such as 3-**24** and 3-**26** to generate the corresponding *trans*-THF 3-**25** and 3-**27** with high stereoselectivity (Scheme 3-**8**).[85,86,]



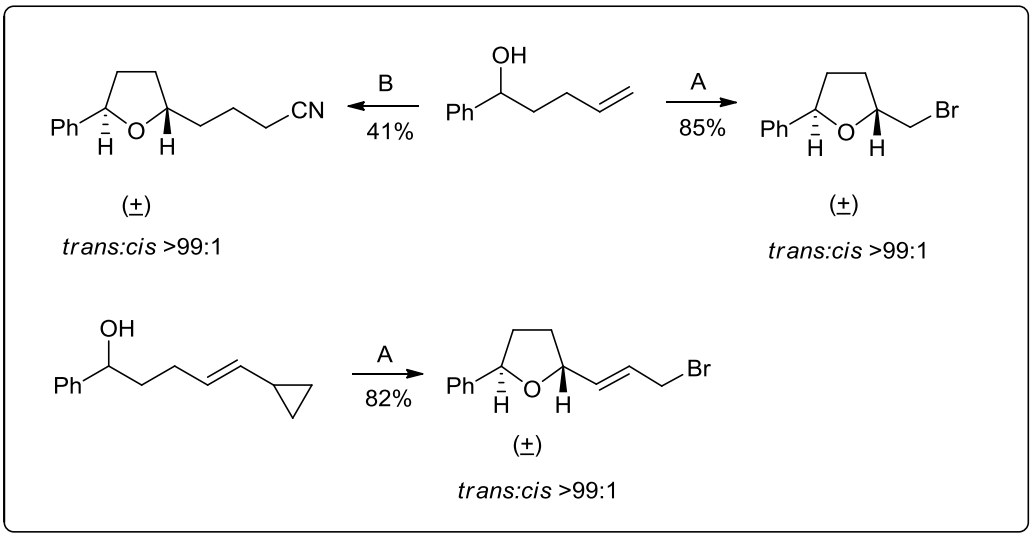
3-**24** 3-**25** 3-**26** 3-**27**

trans:cis >1:99 *trans:cis* >1:99

Reagents and Conditions: i) O_2 (1 atm.), $Co(modp)_2$ (0.1 eq.), TBHP, 2-PrOH, M.S. 4 Å, 60 ºC, 2 h.

Scheme 3-**8** – $Co(modp)_2$ catalysed oxidative cyclisation of chiral bishomoallylic alcohol.

Investigations by Hartung *et al*. on the cobalt-catalysed aerobic oxidative cyclisation of terminally substituted olefins (methyl and iso-propyl) has shown that oxidation of both *(E)*- and *(Z)*-configured substrates are possible. However, these reactions were not stereospecific and the stereochemical information associated with the π-bond was lost through the process. This observation provided further evidence that the reaction proceeded *via* a free carbon radical intermediate (see Scheme 3-**7**), which could be converted into a variety of synthetically valuable functionalities. Hence, these reaction conditions were adopted for the cobalt catalysed bromocyclisation and alkylation reaction (Scheme 3-**9**).[87]



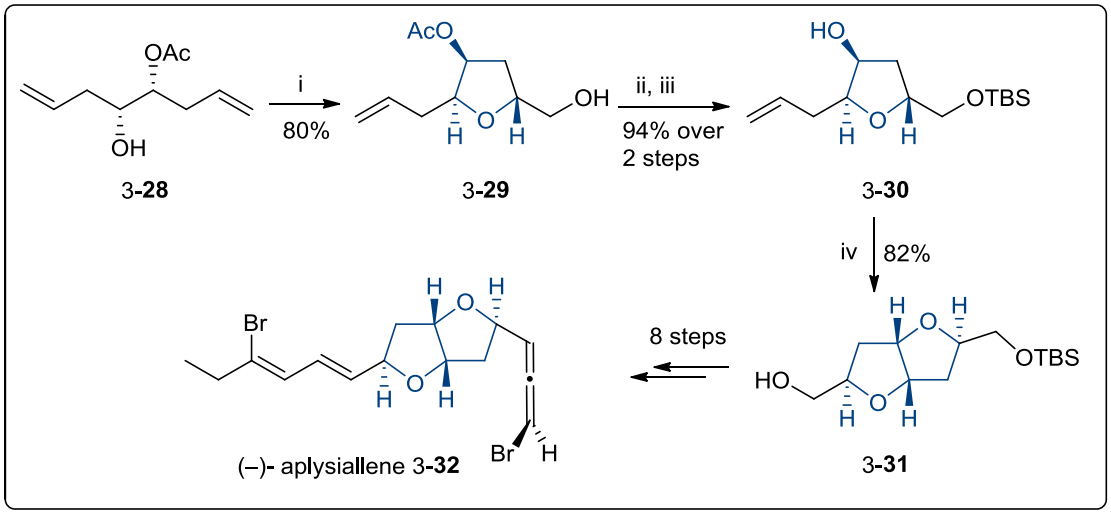
Reagents and Conditions: A) 3-**11** (0.2 eq.), cyclohexadiene (30 eq.), $BrCCl_3$ (10 eq.), benzene, 60°C, 2 h.
B) 3-**11** (0.2 eq.), cyclohexadiene (30 eq.), acrylonitrile (10 eq.), PhMe, 60°C, 3 h.

Scheme 3-9 – Cobalt-catalysed bromocyclisation and alkylation reaction.

It was established that the reaction could be self-promoted in the presence of a catalytic loading of 3-**11** and an excess of cyclohexadiene acting as a radical trapping agent in toluene (see Scheme 3-**9**).

The Mukaiyama aerobic oxidative cyclisation methodology described previously has been applied to the total synthesis of numerous natural products.[88,89,90] Pagenkopf reported its use

in the synthesis of the mono-THF ring enroute to (–) aplysiallene 3-**32** (Scheme 3-**10**).[91]



Reagents and Conditions: i) O_2 (1 atm.), $Co(modp)_2$ (0.1 eq.), TBHP (1.0 eq.), 2-PrOH, 50 °C, 24 h. ii) TBSCl (1.2 eq.), imidazole (1.2 eq.), DMF, r.t, 15 h. iii) EtMgBr (1.1 eq.), Et_2O, 0 °C-r.t, 3 h. iv) O_2 (1 atm.), $Co(modp)_2$ (0.1 eq.), TBHP (10 eq.), 2-PrOH, 50 °C, 16h.

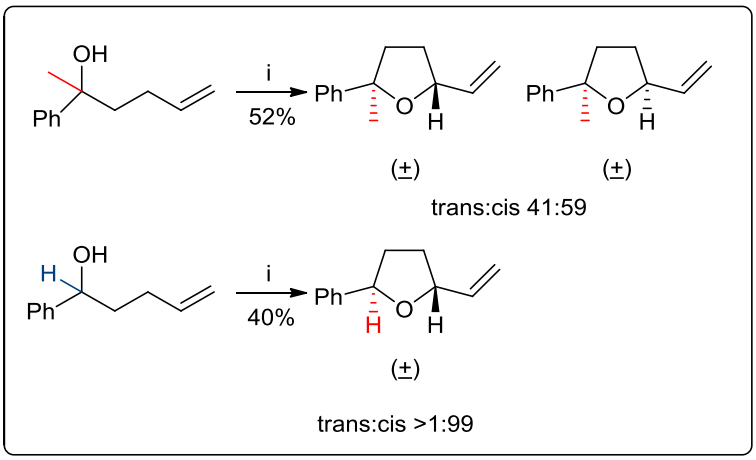
Scheme 3-**10** – Synthesis of (–)-aplysiallene 3-**32** by Pagenkopf *et al*.

By subjecting the enantiopure mono protected diol 3-**28** to the original Mukaiyama cyclisation procedure, they isolated mono *trans*-THF 3-**29** as a single diastereoisomer in excellent yield. In order to construct the two *cis*-fused THF rings, the primary hydroxyl group was protected as a silyl ether and the secondary alcohol was deprotected by ethyl magnesium bromide to furnish intermediate 3-**30**. By repeating the cyclisation reaction, the group was able to generate *cis*-fused *bis*-THF 3-**31** in an excellent 82% yield (see Scheme 3-**10**).

3.1.3 Palladium Catalysed Cyclisation

In 1976, Sonoda *et al*. reported the electrophilic cyclisation of bishomoallylic alcohols to form THF rings using a catalytic loading of $Pd(OAc)_2$ in the presence of copper acetate in aqueous methanol.[92] It was discovered that the diastereoselectivity of the reaction was highly dependent on the substrate bulk. Hence, by decreasing the steric hindrance of the substrate,

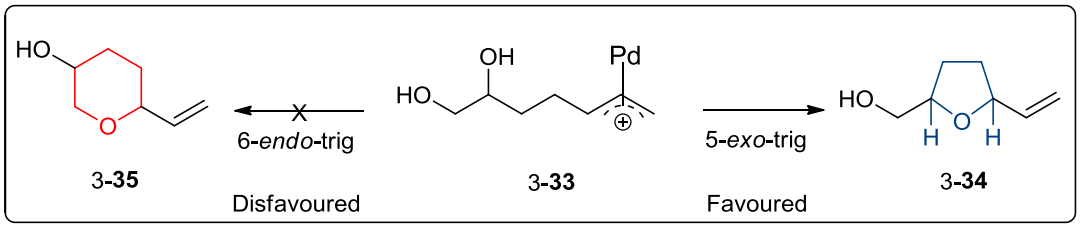
a single *trans* diastereoisomer of THF was produced (Scheme 3-**11**).



Reagents and Conditions: i) $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2{\cdot}H_2O$ (1.0 eq.), $MeOH/H_2O$ (10:1), 24 h, r.t.

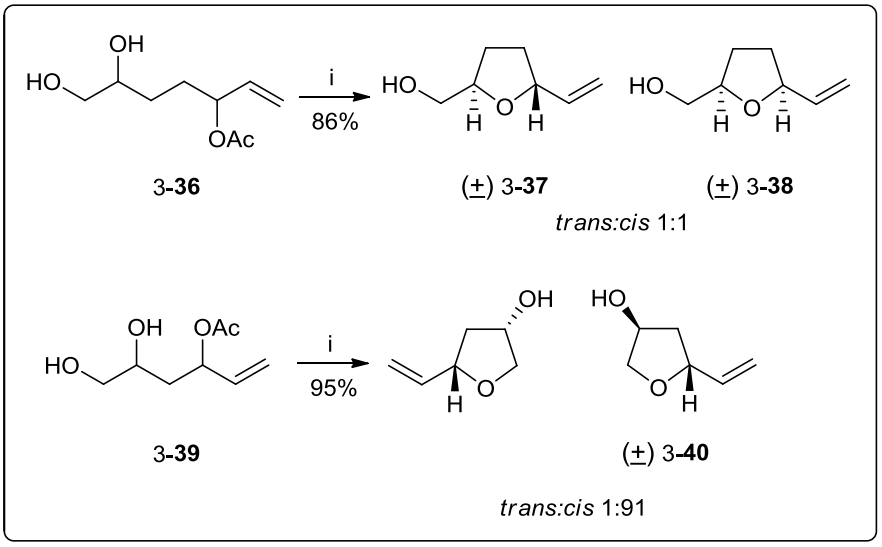
Scheme 3-**11** – $Pd(OAc)_2$ catalysed electrophilic cyclisation of bishomoallylic alcohols.

This method was the subject of further investigations by Trost *et al.* in the chemoselective intramolecular cyclisation of vicinal diol allylic acetates *via* π-allylpalladium cationic intermediates 3-**33**.[93] In this work, the ring closing reaction produced substituted THF rings exclusively, instead of tetrahyropyran (THP) rings. In 1976, Baldwin rationalised the preference for the formation of five-membered THF 3-**34** *via* a 5-*exo*-trig reaction, which proceeded with good orbital overlap rather than the alternative 6-*endo*-trig cyclisation that yield six-membered THP 3-**35** (Scheme 3-**12**).[94]



Scheme 3-**12** – Ring closure of vicinal diol allylic acetates.

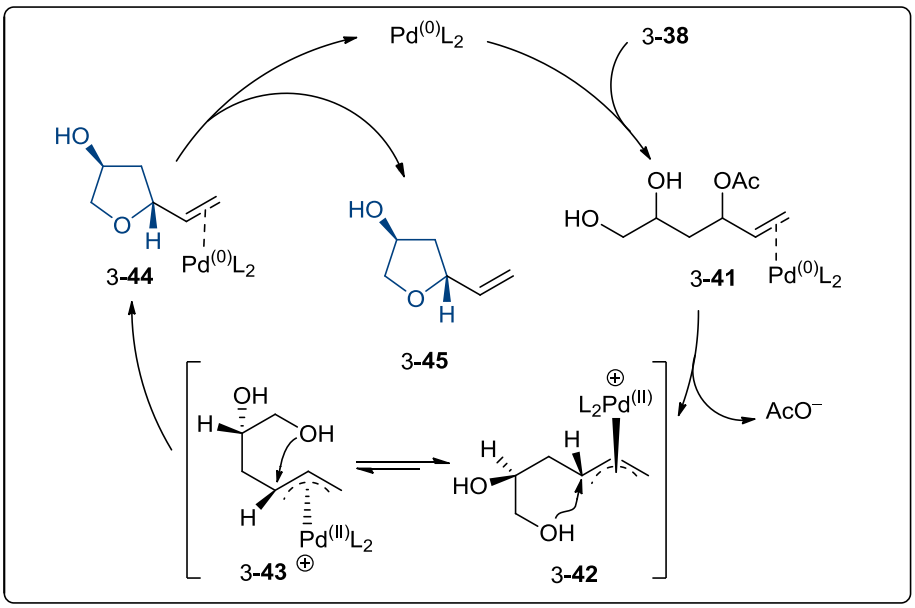
However, the formation of 2,5-disubstituted THF rings was not stereoselective and a 1:1 mixture of the *cis* and *trans* stereoisomers 3-**37** and 3-**38** was obtained (Scheme 3-**13**).



Reagents and Conditions: i) $Pd_2(dba)_3CHCl_3$ (0.4 eq.), Ph_3P (32 eq.), THF, 3.5 h.

Scheme 3-13 – Palladium catalysed electrophilic cyclisation of vicinal diol allylic acetates.

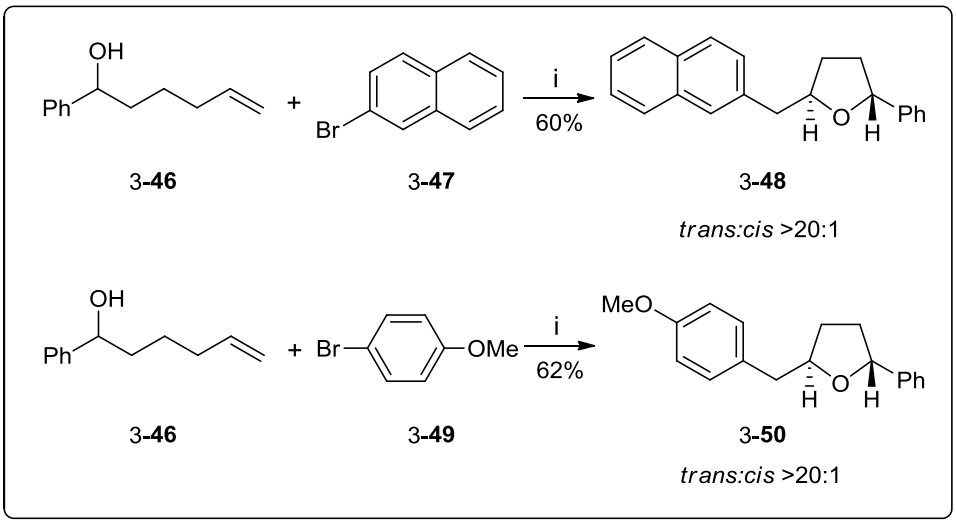
It was later observed that by changing the position of the acyloxy group on the carbon chain in the substrate, from homoallylic 3-**36** to allylic 3-**39**, one could access predominately the 2,3-disubstituted THF 3-**40** in high yield and with *cis* diastereoselectivity (see Scheme 3-**13**). The commonly accepted mechanism of the palladium catalysed cyclisation could be sourced back to the Tsuji-Trost reaction (Scheme 3-**14**).[95]



Scheme 3-14 – Mechanism of intramolecular Tsuji–Trost reaction.

It was suggested that the palladium(0) catalyst would coordinate to the alkene functionality of the bishomoallylic alcohol 3-**39** to form palladium complex 3-**41**, which upon elimination of acetate would produce π-allylpalladium cationic intermediates 3-**42** and 3-**43**. Finally, it is worth noting that the key step in this mechanism would be the swift equilibration of intermediate 3-**42** to 3-**43** before the cyclisation step occurs. Indeed, the stereochemical outcome would confirm that the reaction favours the cyclisation of 3-**42** to deliver palladium-THF complex 3-**44**, which upon decomplexation forms 3-**45** (see Scheme 3-**14**).

Wolf *et al*. subsequently extended the methodology in a tandem palladium-mediated ring closure followed by Heck coupling reaction (Scheme 3-**15**).[96]

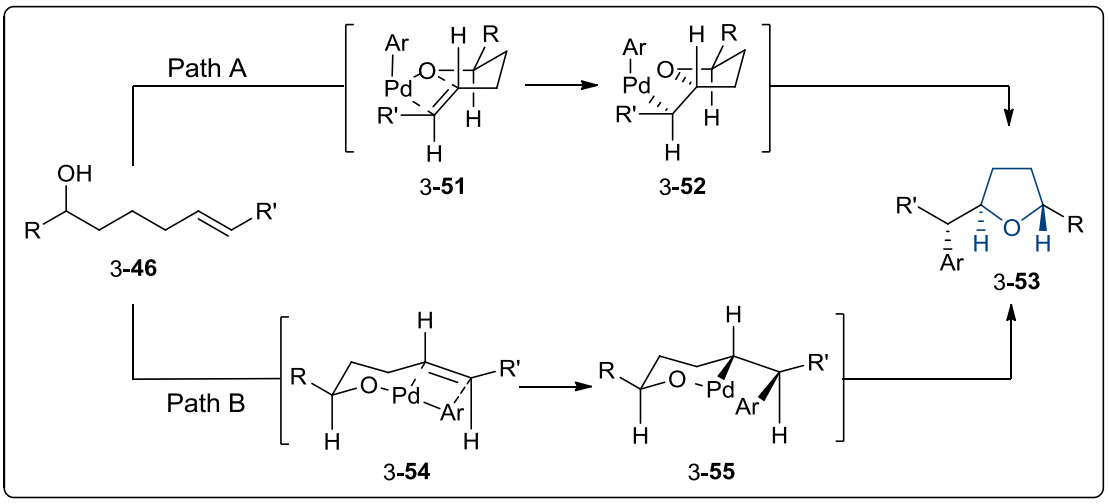


Reagents and Conditions: i) $Pd_2(dba)_3$ (0.1 eq.), DPE-Phos (0.1 eq.), NaO*t*-Bu (2.0 eq.), THF, 65 °C, 2 h.

Scheme 3-15 – Palladium catalysed cyclisation followed by Heck coupling reaction.

By reacting bishomoallylic alcohol 3-**46** with aryl bromide 3-**47** or 3-**49** and a catalytic loading of $Pd(dba)_3$ in the presence of NaO*t*-Bu, the reaction yielded the *trans*-stereoisomers 3-**48** and 3-**50** respectively in moderate yields (see Scheme 3-**15**). The use of 1,1'-[(oxydi-2,1-phenylene)]bis[1,1-diphenylphosphine (DPE-Phos) as the ligand, combined with an excess of aryl bromide and base, accelerated the reaction rate as well as improved the yield.

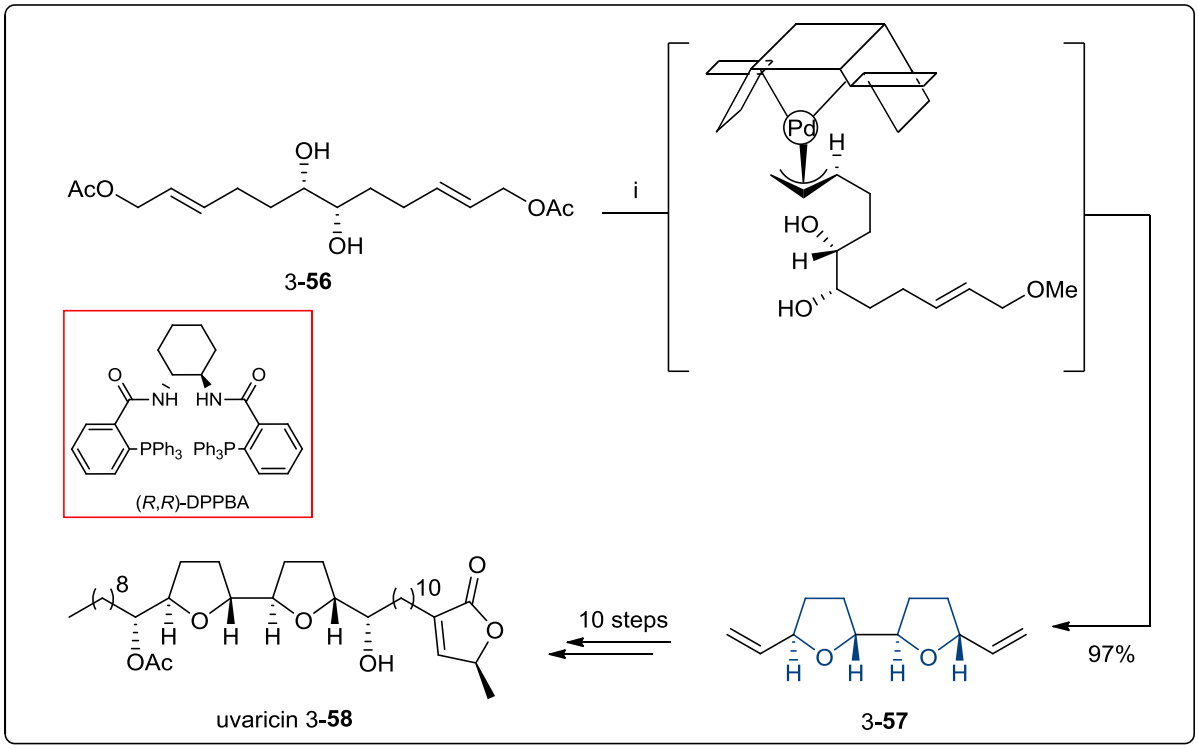
The stereochemical outcome of the reaction was rationalised by proposing two different mechanistic pathways as described in Scheme 3-**16**. It was suggested in both cases that the 1,4-asymmetric induction was achieved by intramolecular chelation between the Pd catalyst and the substrate 3-**46**.



Scheme 3-**16 –** Mechanism of the tandem Heck/cyclisation.

On the one hand, Path A started with coordination of the alkoxide to Pd(Ar)Br, forming the organopalladium intermediate 3-**51**, followed by insertion of the olefin into the Pd-O bond yielding *trans*-THF intermediate 3-**52**, which underwent reductive elimination to generate the *trans*-THF 3-**53**. Similarly, path B started with the coordination of the alkoxide yielding intermediate 3-**54**, which this time underwent insertion of the olefin into the Pd-Ar bond forming intermediate 3-**55**, followed by reductive elimination to generate the *trans*-THF 3-**53** (see Scheme 3-**16**).

In 2001, Burke *et al*. reported the first asymmetric application of the palladium-catalysed ring closure methodology in the synthesis of natural products.[97,98]



Reagents and Conditions: i) $Pd_2(dba)_3$ (0.1 eq.), (*R*,*R*)-DPPBA (0.1 eq.), THF, 0 °C-r.t, 3 h.

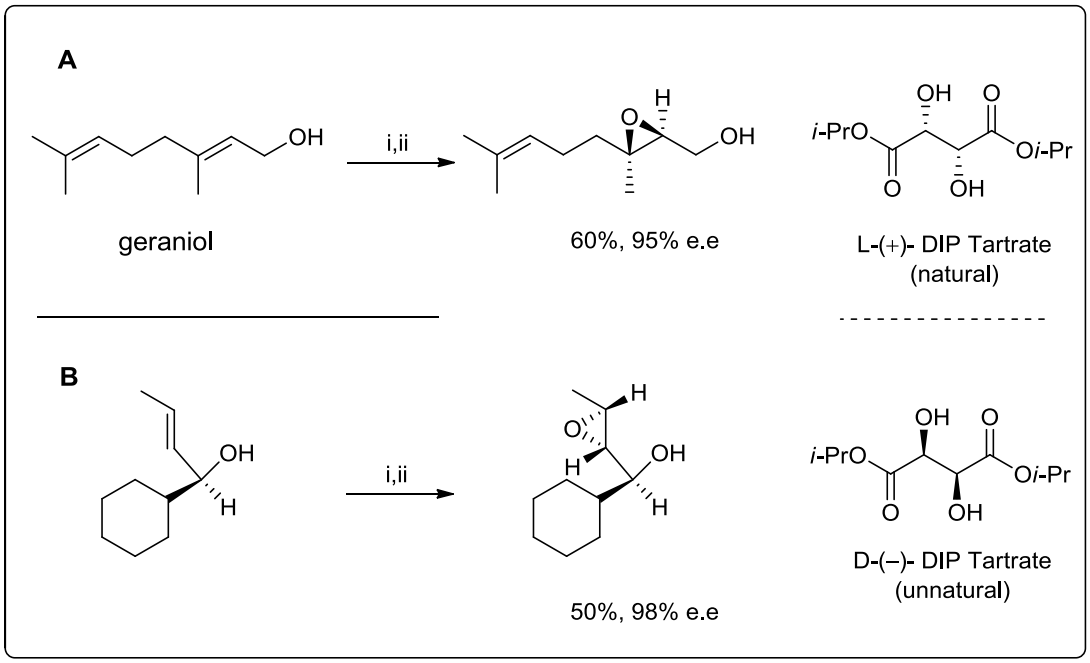
Scheme 3-17 – Application of Pd catalysed cyclisation in the synthesis of uvaricin 3-**58** by Burke *et al.*

In the synthesis of uvaricin 3-**58,** it was shown that the chiral *(R,R)*-DACH-phenyl Trost ligand (DPPBA) promoted the desymmetrisation of the diene 3-**56**, which subsequently underwent tandem cyclisation to form *trans*-bis-THF ring 3-**57** as a single diasteroisomer in 97% yield (see Scheme 3-**17**).

3.2 Aims of this Research Project

The synthetic organic chemistry community has always strived to formulate a strategy to access molecules with both high enantio- and diastereopurity. In 1980, Sharpless *et al.* introduced the titanium(IV) alkoxide catalytic mediated epoxidation of prochiral (A) and chiral (B) allylic alcohols (Scheme 3-**18**) in the presence of optically active tartrate esters (*e.g.* DMT, DET and DIPT) and TBHP to obtain highly enantio enriched epoxy alcohols.[99] Subsequent

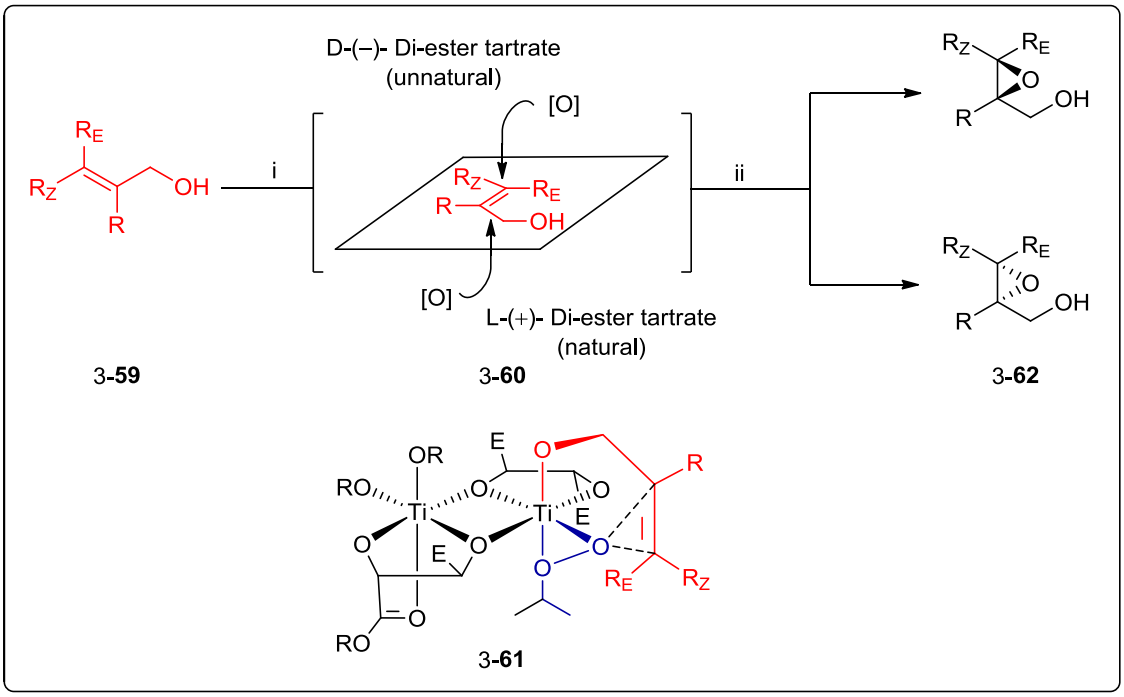
decomplexation of the epoxy titanium complex by the addition of iron(II)sulphate and tartaric acid in a water/brine solution was carried out (Scheme 3-**18**).



Reagents and Conditions: i) L-(+)-DIPT/ D-(–)-DIPT(1.2 eq.), Ti(O-*i*-Pr)$_4$ (1.2 eq.), TBHP (0.6-1.1 eq.), CH_2Cl_2, 4 Å M.S, –20 °C, 12 d. ii) $FeSO_4.7H_2O$ (11 eq.), tartaric acid (11 eq.), H_2O/brine.

Scheme 3-**18** – Sharpless asymmetric epoxidation/kinetic resolution.

The initial step involves the complexation of Ti(O-*i*-Pr)$_4$ to the chiral D(–) or L(+) tartaric esters, followed by a ligand exchange with the allylic alcohol 3-**59** and TBHP to generate the key intermediate titanium-complex 3-**61**. The stereochemistry of the epoxy alcohol 3-**62** resulting from the Sharpless Asymmetric Epoxidation (SAE) can be predicted by employing the mnemonic model 3-**60** depicted in Scheme 3-**19**.



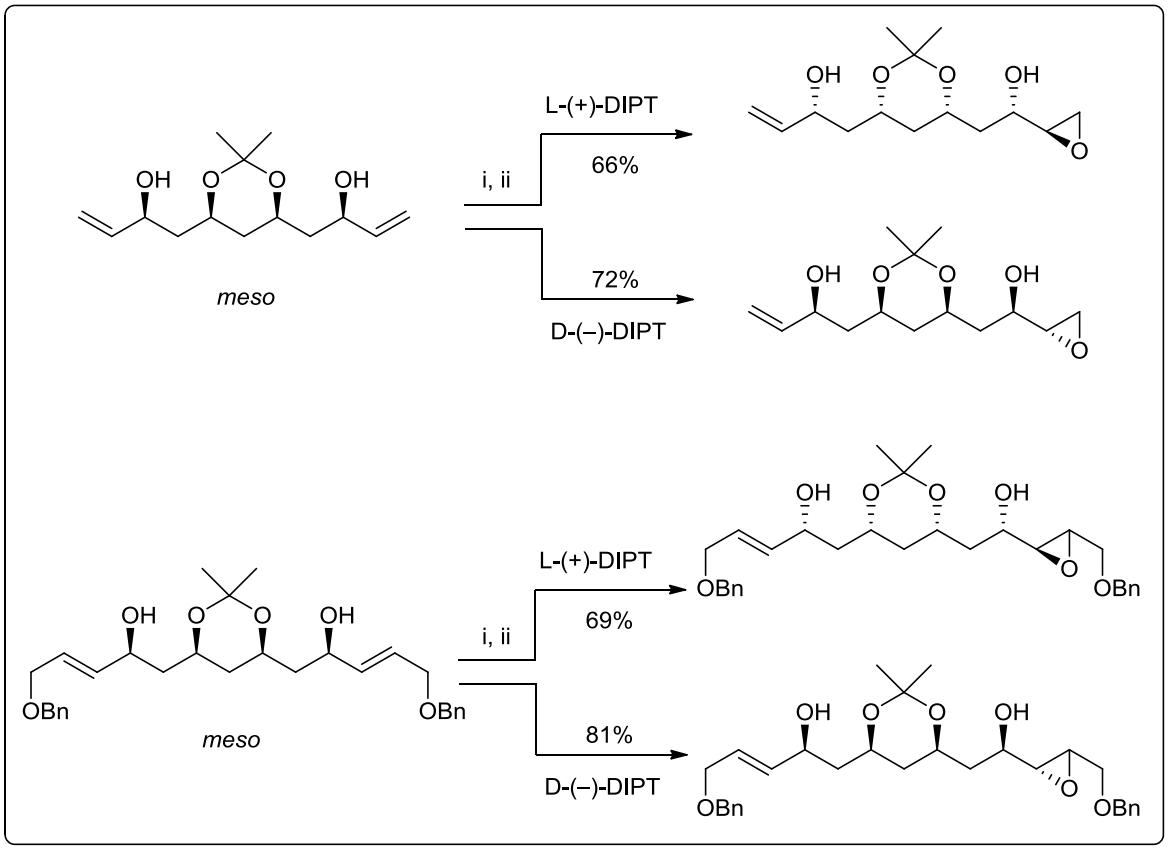
Reagents and Conditions: i) $Ti(O\text{-}i\text{-}Pr)_4$ (1.2 eq.), TBHP (0.6-1.1 eq.), CH_2Cl_2, 4 Å M.S, –20 °C, 15 h-12 d. ii) $FeSO_4.7H_2O$, tartaric acid, H_2O/brine.

Scheme 3-19 – Mechanism of SAE.

As illustrated in Scheme 3-**19**, the unnatural D-(–) dialkyl tartrate favours oxidation of the top face of the alkene, while the L-(+) dialkyl tartrate favours oxidation of the bottom face.

This methodology could also be employed in the kinetic resolution of racemic mixtures of secondary and tertiary allylic alcohols, which consequently results in a maximum yield of 50% of the enantiomericlly enriched epoxy alcohol (see Scheme 3-**18**).

Work by Schreiber *et al.* has demonstrated that the SAE can be exploited in the desymmetrisation of enantiotopic *σ*-symmetric diene diols to furnish epoxy alcohols as single enantiomers (Scheme 3-**20**).[100,101]



Reagents and Conditions: i) Ti(O-*i*-Pr)$_4$ (1.2 eq.), TBHP (1.1 eq.), CH_2Cl_2, 4 Å M.S, –20 °C, 15 h-12 d. ii) $FeSO_4.7H_2O$ (11 eq.), tartaric acid (11 eq.), H_2O/brine.

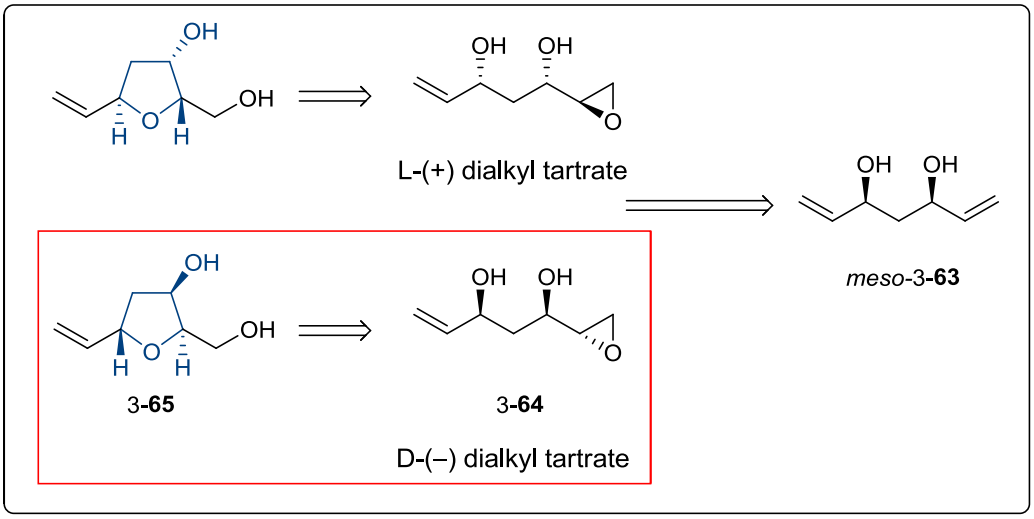
Scheme 3-20 – Enantiotopic SAE.

This method tends to generate slightly higher yields in the case of longer carbon chains and more highly substituted olefinic alcohols, probably due to greater stability of the substituents.

As it was previously described in this chapter, due to the abundant presence of 2,5-*trans*-THF units in nature, various methods have been developed to access these units (see section **3.1**).

The objective of this project was to develop a novel route to synthesise tri-subsituted 2,5-*trans*-THF adducts (Scheme 3-**21**). The idea was to extend Schreiber's methodology, by subjecting *σ*-symmetric diene diol 3-**63** to the D-(–)-DIPT chiral reagent under the SAE

conditions, which would deliver epoxy alcohol 3-**64** as an intermediate. It was speculated that the presence of the Lewis acids Ti(O-*i*-Pr)$_4$ and $FeSO_4$ in the reaction mixture would promote 5-*exo*-tet cyclisation of the intermediate epoxy alcohol 3-**64** to generate the desired *trans*-THF 3-**65** (Scheme 3-**21**).



Scheme 3-**21** – Retrosynthetic analysis of *trans*-THF 3-**65**.

- To accomplish this aim, an investigation was conducted to find an accessible route to synthesise the staring material *meso*-diol 3-**63**, which could provide sufficient quantities for the SAE reaction.

- Upon successful synthesis of 3-**63**, our attention would turn to the SAE/cyclisation to generate *trans*-THF 3-**65**.

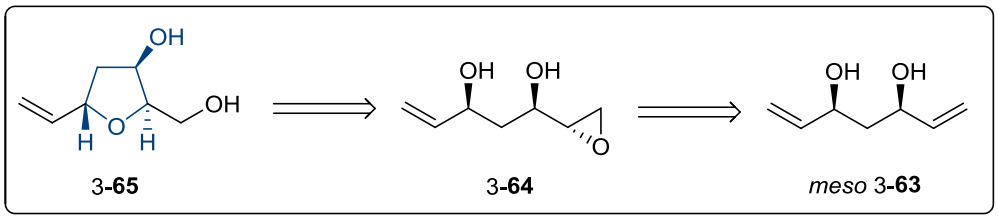
This work is addressed in the following chapter.

Chapter 4: Results & Discussion –

A Novel Route towards *Trans*-THFs

4.0 A Novel Route towards *trans*-THFs

As mentioned previously, the objective of this project was to develop a novel procedure to obtain exclusively *trans*-THF adduct 3-**65**, by employing the methodology developed by Schreiber *et al.*[100,101] This aim could be achieved by the diastereoselective epoxidation of *C*-symmetric diene diol 3-**63** under SAE reaction conditions to generate epoxy alcohol 3-**64**, which could undergo 5-*exo*-tet ring closure to produce the desired THF 3-**65** (Scheme 4-**1**).



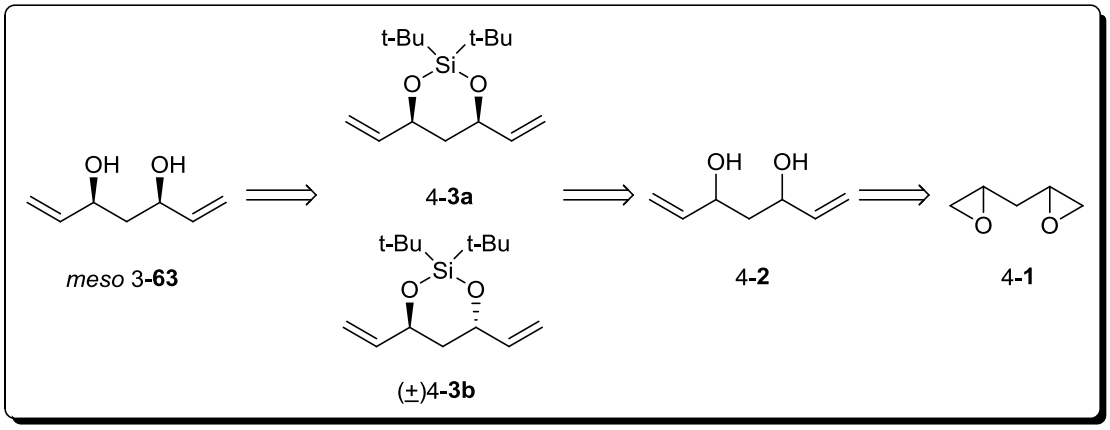
Scheme 4-**1** – Retrosynthetic analysis of *trans*-THF 3-**65** *via* epoxy alcohol 3-**63**.

The primary effort was to develop a feasible route for the synthesise of the *meso*-diol 3-**63**.

4.1 Synthesis of *(3R,5S)*-Hepta-1,6-Diene-3,5-Diol

4.1.1 Separation of the Racemic Mixture on Silica Gel

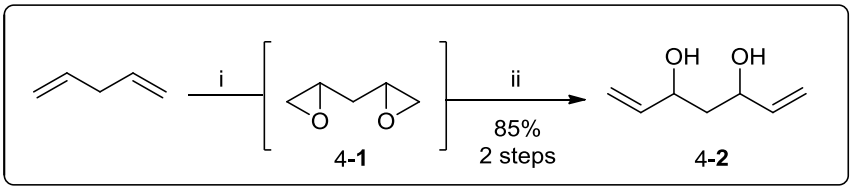
The initial strategy was to follow a literature procedure reported by Mioskowski *et al.*, who had employed a two-directional carbon chain extention of the commercially available 1,5-pentadiene to generate bis-epoxy adduct 4-**1**. Reaction of compound 4-**1** with methylsulfonium iodide (Me_3SI) under basic condition delivered a mixture of *meso* and racemic C_2-symmetric diene diols 4-**2** (Scheme 4-**2**).[102]



Scheme 4-**2 –** Retrosynthetic analysis of the *meso*-diol 3-**63** *via bis*-silyl enol ether 4-**3**.

According to the literature procedure, protection of diol 4-**2** with a bulky silicon protecting group forming *bis*-silyl enol ether 4-**3** would facilitate separation between the racemic mixture of the C_2-symmetric diol 4-**3b** and the σ-symmetric *meso*-diol 4-**3a** on silica gel (see Scheme 4-**2**).[103]

This reaction sequence was initiated in accordance with the literature by addition of 1,5-pentadiene to a slurry of *m*-chloroperoxybenzoic acid in CH_2Cl_2 at 0 °C, which was allowed to warm to ambient temperature overnight to deliver 4-**1** (Scheme 4-**3**).



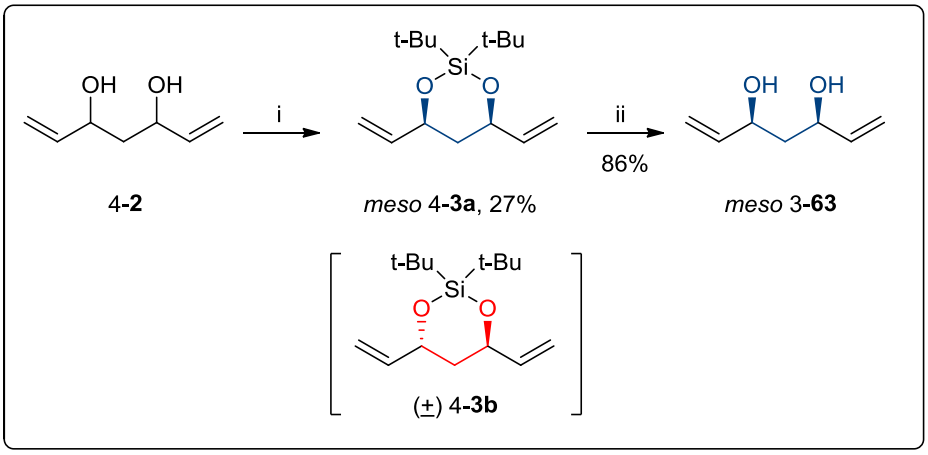
Reagents and Conditions: i) *m*-CPBA, CH_2Cl_2, 0-25 °C, 16 h.
ii) $(CH_3)_3SI$, *n*-BuLi, THF, −40-25 °C, 16h, NH_4Cl (aq.).

Scheme 4-**3 –** Formation of diene diol 4-**2** as a racemic mixture.

A solution of sulfonium ylid formed from reaction of Me_3SI and *n*-BuLi was then added to crude bis-epoxide, delivering diol 4-**2** in 85% yield (over two steps) upon quenching with NH_4Cl (see Scheme 4-**3**).[102]

Diol 4-**2** was protected as the *σ*-symmetric cyclic silyl ether 4-**3a**, and the C_2-symmetric 4-**3b**,

which were separated on silica gel, yielding the desired *meso* 4-**3a** in 27% (Scheme 4-**4**).



Reagents and Conditions: i) (*t*-Bu)$_2$Si(OTf)$_2$, Pyridine, r.t. ii) TBAF, THF, 66 °C, 1 h.

Scheme 4-**4** – Formation of σ-symmetric diene diol 3-**63**.

^{1}H-NMR analysis of *meso* 4-**3a** revealed two singlets at δ 1.06 ppm and δ 1.03 ppm corresponding to diastereotopic *t*-butyl groups, while in the case of racemic 4-**3b**, a singlet at δ 1.05 ppm corresponded to the magnetically equivalent *t*-butyl groups. [102]

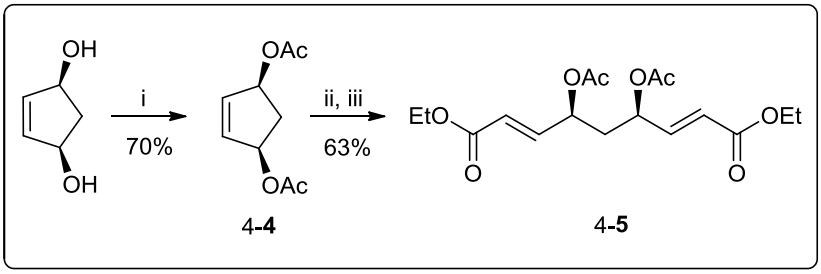
Compound 4-**3a** was then subjected to TBAF deprotection protocol to deliver 3-**63** in 86% yield (see Scheme 4-**4**).

The structure of 3-**63** was analysed by NMR and IR spectroscopy. The appearance of two double doublets at δ 5.88 ppm and δ 5.27 ppm and a double triplet at δ 5.11 ppm corresponding to six protons in the ^{1}H-NMR spectrum indicated the presence of the two terminal alkenes in 3-**63**. In addition the appearance of the *O*-alkyl signal at δ 4.40 ppm with coupling constants of J = 7.0 Hz and 5.9 Hz corresponding to two protons confirmed the formation of 3-**63**. Furthermore, in the ^{13}C-NMR spectrum appearance of the signals at δ 140.5 ppm and δ 114.7 ppm confirmed the presence of the terminal olefin adducts and the signal at δ 73.1 ppm the O-alkyl, which was further proved by the OH broad stretch at ν 3352 cm^{-1} in the IR spectrum.

Despite obtaining the desired *meso*-diol 4-**3a**, due to low yields and difficulties involved in separating the C_2-symmetric diene diol 4-**3b** and σ-symmetric diene diol 4-**3a**, our attention turned to the development of an alternative route to generate the desired diol 4-**3a**.

4.1.2 Ozonolysis/Wittig

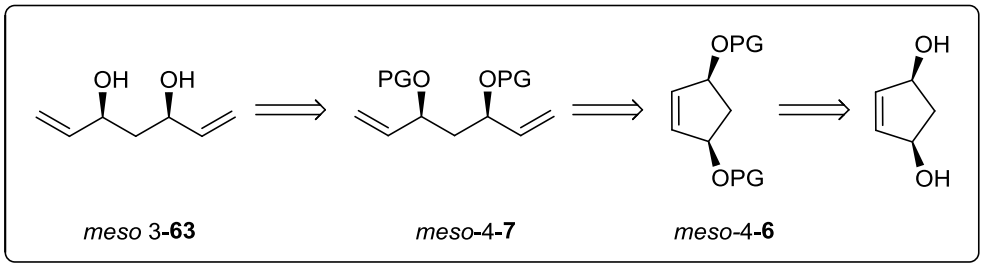
Previous work by Burke *et al.* has demonstrated that commercially available *(1R,3S)*-cyclopent-4-ene-1,3-diol can be converted into diacetate 4-**5** *via* protected diol 4-**4**, which was subjected to ozonolysis (ring cleavage) followed by Wittig olefination to deliver diacetate 4-**5** (Scheme 4-**4**).[104]



Reagents and Conditions: i) Ac_2O, pyridine, DMAP, r.t, 3 h. ii) O_3, PPh_3, MeOH, −78 °C, 3 h. iii) Triethyl phosponoacetate, −78-25°C, 16 h.

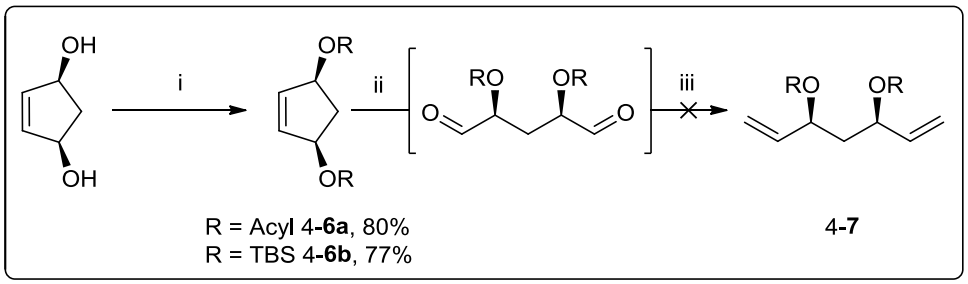
Scheme 4-**4** – Formation of *σ*-symmetric diacetate 4-**5**.

Therefore, it was suggested that a similar protocol could be implemented to generate the desired 3-**63** *via* the protected *σ*-symmetric diene diol 4-**7**, which could be obtained by ozonolysis/Wittig olefination of the protected diol 4-**6** (Scheme 4-**5**).



Scheme 4-**5** – Formation of *σ*-symmetric diene diol 3-**65** *via* a tandem ozonolysis/Wittig procedure.

Following the literature procedure, *(1R,3S)*-cyclopent-4-ene-1,3-diol was submitted to acyl protection to furnish di-acetate 4-**4** in 80% yield (Scheme 4-**6**).[97] Investigations into the ozonolysis/Wittig approach were then carried out with compound 4-**4**.



Entry	Conditions		Yield/ %
	Reagent	Base	
1	PPh_3MeBr	NaH	0
2	PPh_3MeBr	KHMDS	0
3	PPh_3MeBr	n-BuLi	0
4	PPh_3MeCl	NaH	0

Reagents and Conditions: i Ac_2O, pyridine, DMAP, r.t, 3 h (R= Ac). TBSCl, NaH, THF, r.t, 16 h. (R= TBS) ii) O_3, PPh_3, MeOH, −78 °C, 3 h. iii) Methyltriphenylphosphonium bromide/chloride, base, −78-25°C, 16 h.

Table 4-1 – Formation of *σ*-symmetric diene diol 3-**63** *via* a tandem ozonolysis/Wittig procedure.

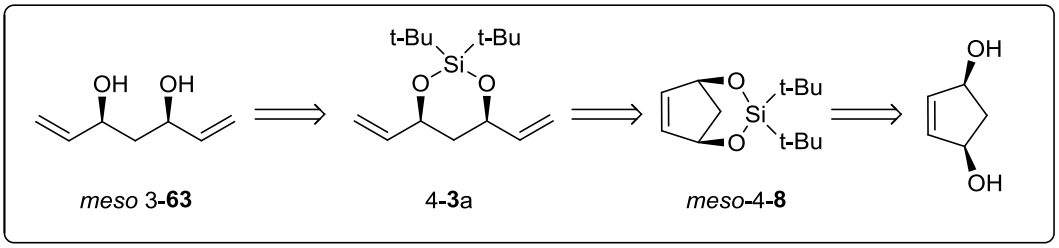
Unfortunately, the reaction produced an inseparable mixture of products (see Table 4-**1**, Entry **1**). Varying the base, as well as phosphonium ylide did not improve the outcome of the reaction, delivering only an inseparable mixture of products (see Table 4-**1**, Entries **2-4**)

Our strategy changed to investigate an alternative route to cleave the cyclopentene ring in the *(1R,3S)*-cyclopent-4-ene-1,3-diol, in order to access *meso*-diol 3-**63**.

4.1.3 Ring Opening/Cross Metathesis Reaction

It was proposed that the silyl enol ether 4-**3a** could be generated by ring opening/cross metathesis (ROM) of the protected *meso*-diol 4-**8** with ethylene (Scheme 4-**6**). It was thought

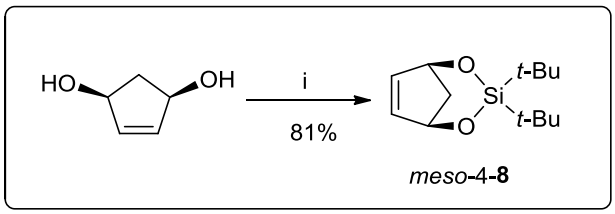
that by tethering the diol in the *(1R,3S)*-cyclopent-4-ene-1,3-diol to a single silicon protecting group, the strain of the molecule would be increased, which would in turn facilitate ring cleavage of the cyclopentene. Furthermore, previous work has shown that protected *meso*-diol 4-**8** could be readily accessed in high yield.[105]



meso 3-**63** 4-**3**a *meso*-4-**8**

Scheme 4-**6** – Formation of 3-**63** *via* ring opening/cross metathesis procedure.

The investigation was continued by following the literature procedure to generate the protected diol 4-**8** in 81% yield (Scheme 4-**7**).[105]

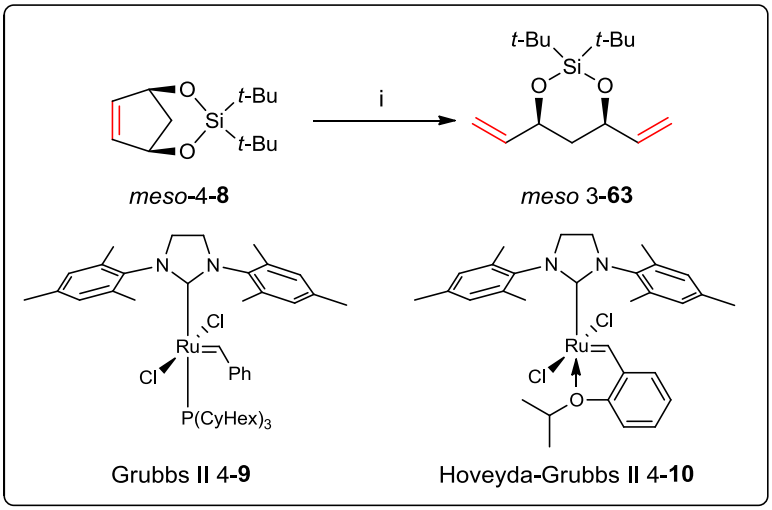


meso-4-**8**

Reagents and Conditions: i) (*t*-Bu)$_2$(OTf)$_2$Si, 2,6-Lutidine, CH_2Cl_2, 0-25 °C, 3 h.

Scheme 4-**7** – Formation protected diol 4-**8**.

The silyl ether 4-**8** was then added slowly to a solution of 6 mol% second generation Grubbs catalyst 4-**9** in toluene under an atmosphere of ethylene gas at 50 °C. The starting material was completely consumed after 40 minutes and the reaction mixture was loaded onto silica gel. To our satisfaction, the reaction formed the desired diene 4-**3a** in 18% yield (Table 4-**2**, Entry **1**). However, Mass spectrometric analysis indicated that polymerisation had also occurred, which could explain the poor yield.



Entry	A/ cata.	Mol%	Time/ min.	B/ Solvent	Temp./ C/ °C	Yield/ %	Scale/ mg
1	4-9	6	40	PhMe	50	18	50
2	4-9	6	40	PhMe	r.t.	25	50
3	4-9	6	40	PhMe	10	34	50
4	4-9	6	40	PhMe	0	43	50
5	4-9	6	40	PhH	0	40	50
6	4-9	6	40	CH_2Cl_2	0	51	50
7	4-9	6	40	PhMe/CH_2Cl_2	0	59	50
8	4-10	6	30	PhMe/CH_2Cl_2	0	75	50
9	4-10	6	30	PhMe/CH_2Cl_2	0	70	100
10	4-10	6	30	PhMe/CH_2Cl_2	0	65	500
11	4-10	6	30	PhMe/CH_2Cl_2	– 10	65	500

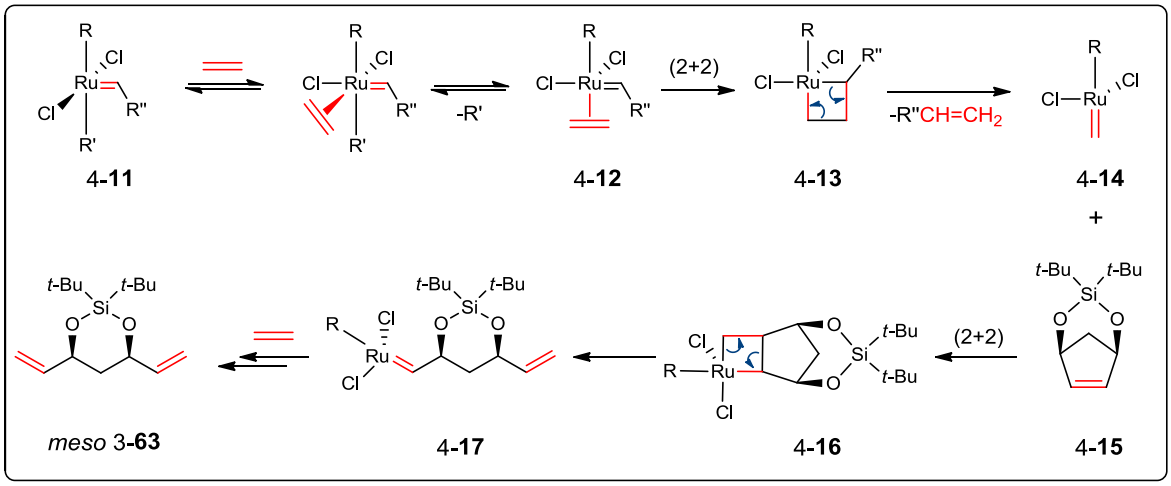
Reagents and Conditions: i) Ethylene (gas), A, B, C.

Table 4-**2** – Optimisation of the ROM reaction.

With this positive result in hand, our attention turned to optimising the reaction, in order to prevent unwanted polymerisation, and improving the yield. Initial effort focussed on the effect of temperature on the reaction. It was suggested that the solubility of the ethene gas (b.p. −103.7 °C) would improve in the solvent at lower temperatures. The modification of the reaction conditions resulted in a significant improvement of the yield to 43% (Table 4-**2**, Entries **2**-**4**). Changing the solvent to benzene did not improve the yield (see Table 4-**2**, Entry

5). Interestingly, the yield of the reaction was further improved to 51% upon use of CH_2Cl_2 as the solvent (see Table 4-**2**, Entry **6**). However, it was realised that due to the volatility of the CH_2Cl_2, the reaction required careful monitoring and addition of solvent, in order to maintain constant concentration, thus avoiding polymerisation of silyl ether 4-**7**. Finally, the reaction was repeated with a 1:1 mixture of PhMe:CH_2Cl_2, which to our satisfaction this improved the yield to 59% (see Table 4-**2**, Entry **7**). The optimisation of the metathesis methodology was further developed by employing second generation Hoveyda-Grubbs catalyst 4-**10**, which improved the yield of the reaction significantly to 75% on a 50 mg scale (see Table 4-**2**, Entry **8**). However, larger reaction scales lowered the yield to some extent (see Table 4-**2**, Entries **9**-**11**).

The mechanism of the reaction initiates with the coordination of the ruthenium catalyst 4-**11** to the π-orbital of the ethylene molecule to form the intermediate 4-**12**, which subsequently undergoes (2+2) cycloaddition to generate ruthenacyclobutane 4-**13** (Scheme 4-**8**).



Scheme 4-**8** – Mechanism of ROM reaction.

The reaction proceeds *via* cycloreversion of the four membered ring to form the ruthenium carbenoid 4-**14**, which undergoes (2+2) cycloaddition with the substrate 4-**15** to form the

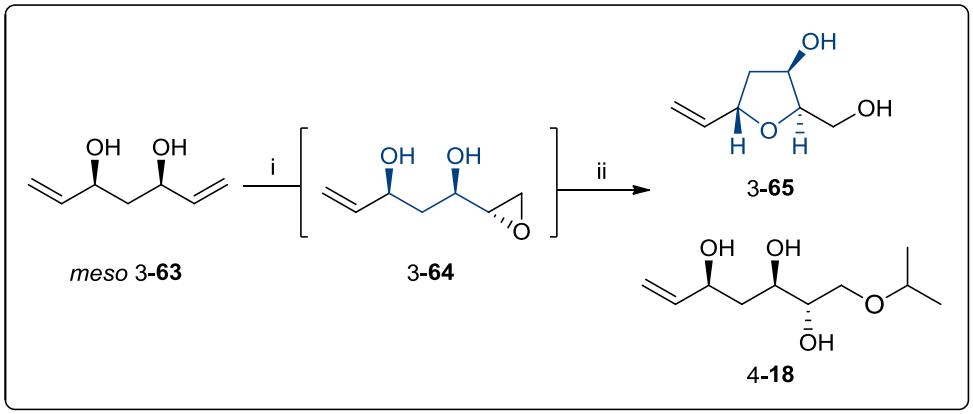
ruthenacyclobutane 4-**16**. The cleavage of the cyclopentane ring occurs upon cycloreversion of the metalobutane to generate the intermediate 4-**17**, which undergoes cross metathesis with the second ethylene molecule to deliver 4-**3a** (see Scheme 4-**8**).

All analytical data for the diol 4-**3a** and 3-**63** were consistent with previous experimental observations and literature (Scheme 4-**4**). [102]

With the *σ*-symmetric diene diol 3-**63** in hand, the feasibility of a subsequent enantioselective SAE followed by a 5-*exo* ring closure to obtain the desired *trans*-THF 3-**65** was investigated (see Scheme 4-**1**).

4.2 Synthesis of *(2R,3R,5S)*-2-(Hydroxymethyl)-5-Vinyltetrahydrofuran-3-ol

Following Schreiber's procedure, 3-**63** was subjected to a stoichiometric loading of Ti(O-*i*-Pr)$_4$, (–)-DIPT and TBHP at –20 °C, formed the desired *trans*-THF 3-**65** in 20% yield, with 45% recovered starting material 3-**63** and 10% of a by-product, which was identified as triol 4-**18** (Table 4-**3**, Entry 1). The reaction was then repeated with 15 mol% catalytic loading over 24 hours, which delivered only 70% recovered starting material 3-**63** and 4% of 4-**18** (Table 4-**3**, Entry **2**). The reaction period was extended to 48 hours, which improved the yield of 3-**65** to 40%, while delivering 27% of *meso*-diol 3-**63** and 12 % of triol 4-**18** (Table 4-**3**, Entry **3**). The optimal yield was obtained once the reaction time was extended to 96 hours, yielding 55% of 3-**65** (Table 4-**3**, Entry **4**).



Entry	hours	Reagents	Loading/ eq.	Yield/%		
				3-63	3-65	4-18
1	24	Ti(O-*i*-Pr)$_4$	1.20	45	20	10
		D-(–)-DIPT	1.20			
2	24	Ti(O-*i*-Pr)$_4$	0.15	70	0	4
		D-(–)-DIPT	0.15			
3	48	Ti(O-*i*-Pr)$_4$	1.20	27	40	12
		D-(–)-DIPT	1.20			
4	96	Ti(O-*i*-Pr)$_4$	1.20	14	55	15
		D-(–)-DIPT	1.20			
5§	76	Ti(O-*t*-Bu)$_4$	1.20	n.d	69	n.d
		D-(–)-DIPT	1.20			
		PPTS	0.05			

Reagents and Conditions: i) Ti(O-*i*-Pr)$_4$, (–)-DIPT, TBHP (1.1 eq.), CH_2Cl_2, –20 °C, X h.
ii) $FeSO_4.7H_2O$ (11 eq.), tartaric acid (11 eq.), brine, 1 h., extraction
CH_2Cl_2 (3 x 20 ml)/ 2M NaOH, 1h., extraction CH_2Cl_2 (3 x 20 ml).

Table 4-3 – Optimisation of the SAE reaction. §) Work carried out by M. J. Tucker

To our satisfaction, recent work in the group§ has demonstrated that the yield of the reaction could be significantly improved by employing a stoichiometric loading of Ti(O-*t*-Bu)$_4$, (–)-DIPT and TBHP, while adding catalytic loading of PPTS after epoxidation to facilitate the cyclisation step (see Table 4-**3**, Entry **5i**). The application of the new conditions improved the

§ Work carried out by M. J. Tucker

yield of 3-**65** to 69 %.

The structure of 3-**65** was analysed by NMR and IR spectroscopy. In the ^{1}H-NMR; a double double doublet at δ 5.86 ppm with coupling constants of J = 17.1 Hz, 10.4 Hz and 6.7 Hz, a double triplet at δ 5.32 ppm with coupling constant *of* J_{trans} = 17.1 Hz and 1.3 Hz and another double triplet at δ 5.18 ppm with J_{cis} = 10.4 Hz and 1.2 Hz confirmed the presence of the olefin bond in 3-**65** in the ^{1}H-NMR spectrum. In addition, the presence of three tertiary *O*-alkyl proton signals at δ 4.62 ppm, δ 4.36 ppm and δ 3.92 ppm provided evidence of the presence of a cyclic system. Furthermore, the ^{13}C-NMR spectrum contained two alkenes signals at δ 137.8 ppm and δ 116.7 ppm, four *O*-alkyl carbon singles at δ 86.9 ppm, δ 79.5 ppm, δ 73.8 ppm and δ 63.3 ppm, and a secondary alkyl peak at δ 42.1 ppm, providing further evidence of the occurrence of the 5-*exo* ring closure transformation. The appearance of the characteristic OH signal at ν 3365 cm^{-1} in the IR spectrum confirmed the presence of hydroxyl functionalities in 3-**65**.

4.2.1 Stereochemistry

Finally, in order to establish the stereochemistry of 3-**65**, n.O.e. NMR spectroscopic experiments were run, as well as, synthesis of both *(R)* and *(S)* Mosher's esters for comparative ^{19}F-NMR studies.

4.2.1.1 n.O.e NMR Analysis

The n.O.e-NMR studies of 3-**65** indicated correlation between H_{α} protons at δ 5.86 ppm, δ 4.36 ppm, δ 3.92 ppm and δ 1.88 ppm, while coupling between $H_{\beta 1}$ at δ 4.62 ppm and $H_{\beta 2}$ at δ

2.06 ppm was detected (Figure 4-**1**).

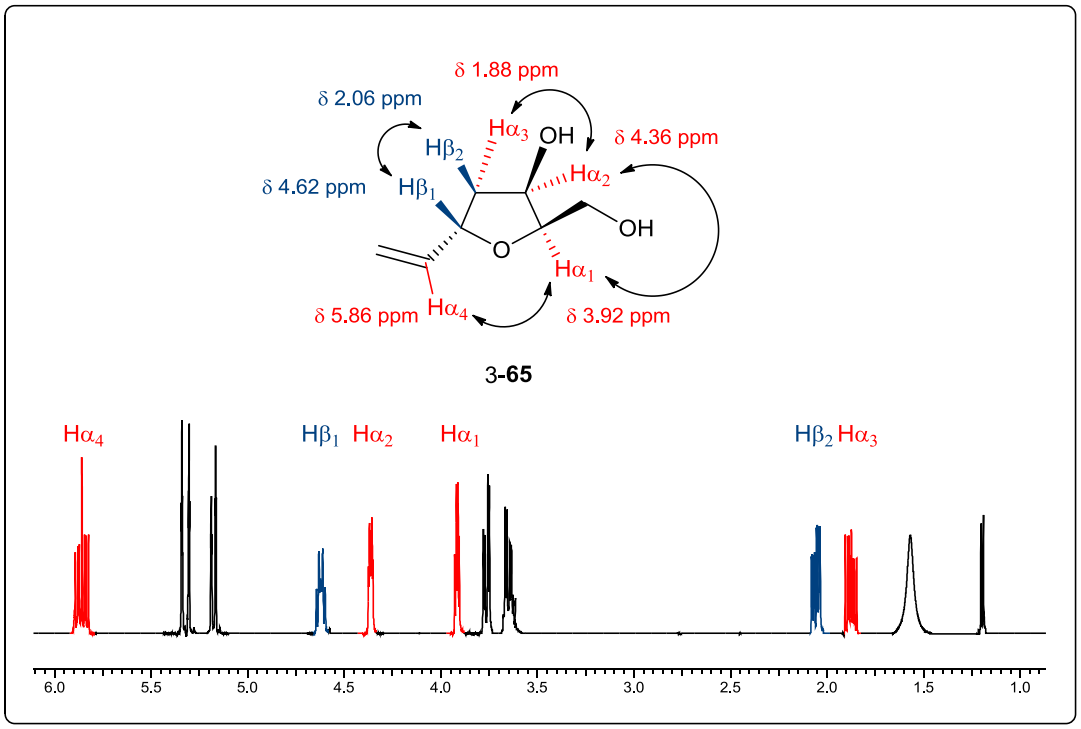


Figure 4-**1** – N.O.e analysis of 3-**65**.

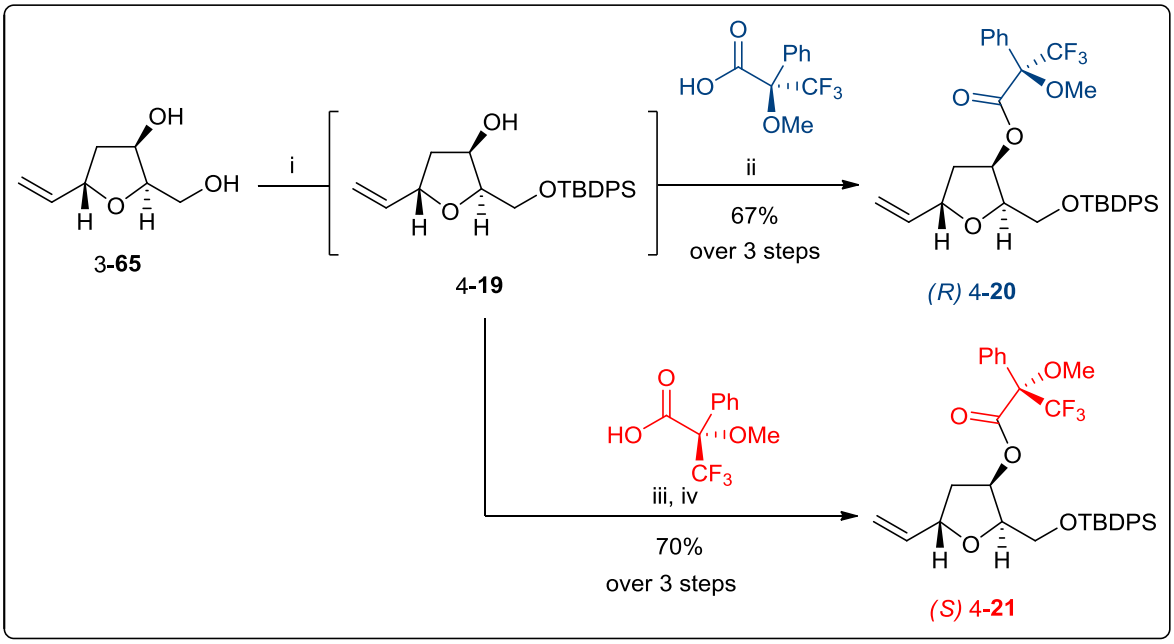
Furthermore, no through space coupling was observed between $H_{\alpha 1}$ and $H_{\beta 2}$ or $H_{\beta 1}$ and $H_{\alpha 2}$, which confirmed the *trans* stereochemistry of 3-**65** (see Figure 4-**1**).

Having established the *trans* selectivity of the methodology by conducting spectroscopic studies of the n.O.e-NMR spectrum of 3-**65**, our attentions turned to the investigation of the enantioselectivity of the reaction.

4.2.1.2 *(R)* and *(S)* Mosher Esters

In order to examine the enantioselectivity of the SAE/cyclisation reaction, the primary alcohol of 3-**65** was subjected to TBDPS protection to furnish the THF 4-**19**. Compound 4-**19** was then separately reacted with the *(R)* and *(S)* Mosher acids, to deliver the two

diastereoisomers, Mosher's esters 4-**20** in 70% and 4-**21** in 67% yield (Scheme 4-**9**).



Reagents and Conditions: i) TBSCl (1.0 eq.), NaH (1.0 eq.), THF, r.t, 3 h. ii) *(R)*-(−)-α-Methoxy-α-(trifluoromethyl) phenylacetyl chloride, pyridine (2.2 eq.), DMAP (0.1 eq.), r.t, 3 h. iii) *(S)*-(+)-α-Methoxy-α-trifluoromethyl-phenylacetic acid, $(COCl)_2$, DMF, CH_2Cl_2, r.t, 4 h. iv) Pyridine (2.2 eq.), DMAP (0.1 eq.), r.t, 3 h.

Scheme 4-**9** – Transformation of 4-**19** to *(R)* and *(S)* Mosher esters 4-**20** and 4-**21**.

Installation of the TBDPS and Mosher ester on 4-**20** and 4-**21** were confirmed by analysis of NMR and IR spectra. Noticeably, the appearance of signals in the aromatic region at δ 7.72-7.66 ppm, δ 7.52 ppm and δ 7.46-7.37 ppm corresponding to 15 protons in the ^{1}H-NMR spectrum. Additionally, in the ^{13}C-NMR spectrum the presence of signals at δ 135.6 ppm, δ 135.5 ppm, δ 133.0 ppm, δ 132.9 ppm, δ 132.2 ppm, δ 129.8 ppm, δ 129.7 ppm, δ 128.5 ppm, δ 127.6 ppm, δ 127.7 ppm and δ 127.2 ppm confirmed the occurrence of the TBDPS mono-protection and esterification steps in both 4-**20** and 4-**21**.

The investigation was continued by subjecting Mosher's esters *(R)*-4-**20** and *(S)*-4-**21** to a comparative ^{19}F-NMR analysis. In the case of *(R)*-4-**20**, the diagnostic CF_3 signal was detected as a singlet at δ –71.8981 ppm, which was comparable with the presence of a singlet at δ –71.9855 ppm for *(S)*-4-**21** (Figure 4-**2**, see Appendix **3** and **4**).

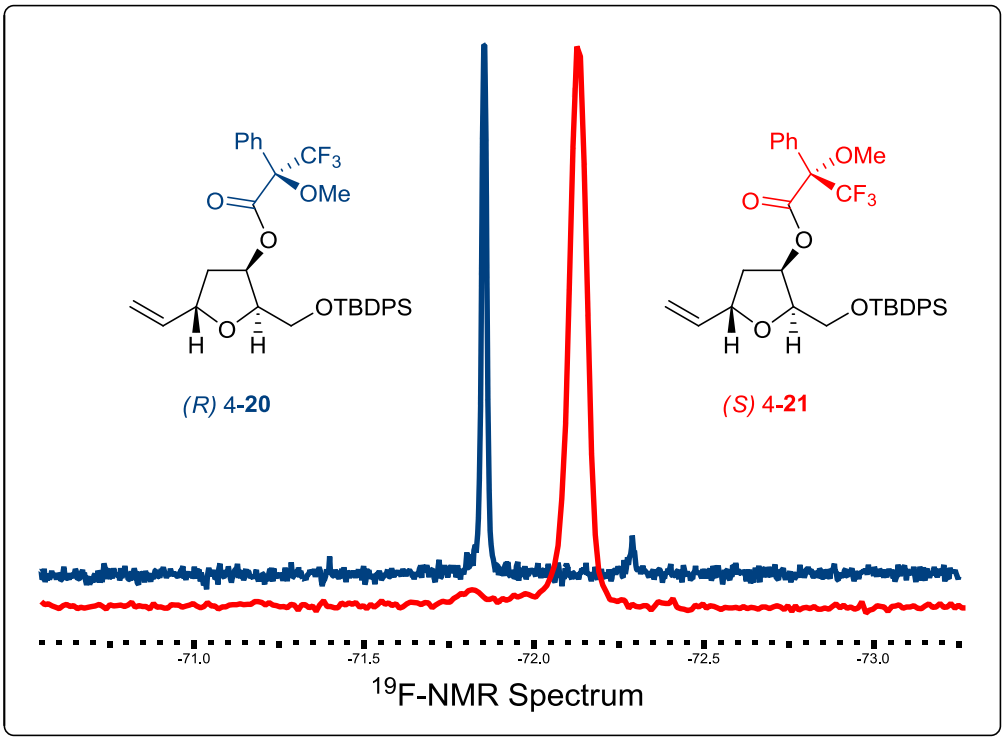
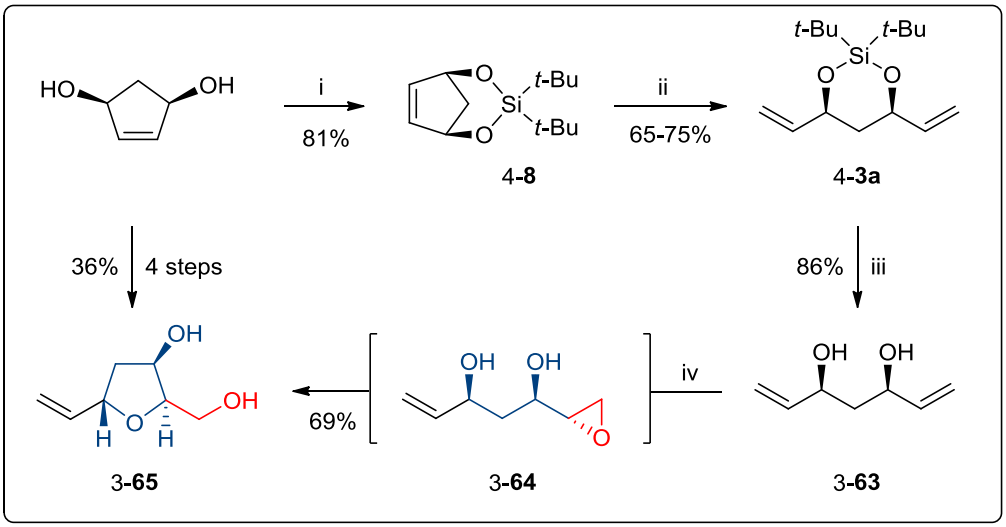


Figure 4-2 – Comparative ^{19}F-NMR spectroscopic studies of Mosher esters 4-**20** and 4-**21**.

This result concludes that the SAE/cyclisation procedure formed *trans*-THF 3-**65** in excellent enantioselectivity >90% e.e.

4.5 Conclusion

In conclusion, we have developed a novel stereoselective route for the formation of *trans*-THF 3-**65** from the commercially available *(1R,3S)*-cyclopent-4-ene-1,3-diol in four steps, with 36% overall yield (Scheme 4-**10**). In the course of the project a novel method was developed to generate the *meso*-diol 3-**63**, which was accessed by a ROM reaction of the strained silyl ether 4-**7** (Scheme 4-**10**).



Reagents and Conditions: i) $(t\text{-Bu})_2(OTf)_2Si$ (1.00 eq.), 2,6-Lutidine (1.10 eq.), CH_2Cl_2, 0-25 °C, 3 h. ii) Ethylene (gas), H-G II (0.06 eq.) , 0 °C, 30 min. iii) TBAF (6.00 eq.), THF, 66 °C, 1 h. iv) $Ti(O\text{-}t\text{-bu})_4$ (1.00 eq.), (–)-DET (1.00 eq.), TBHP (1.10 eq.), PPTS (0.05 eq.), –20 °C, 3 d. $FeSO_4.7H_2O$ (11 eq.), tartaric acid (11 eq.), brine, 1 h.

Scheme 4-**10 –** Formation of *trans*-THF 3-**65** in 4 steps with an overall yield of 36%.

It is hoped that this methodology will be implemented in an ongoing project within the Donohoe group, in the synthesis of the F ring presented in the pectenotoxin 4 3-**2** (Figure 4-**4**).

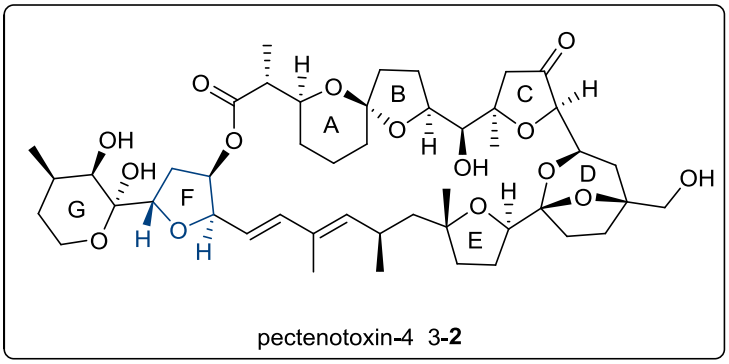


Figure 4-**4** –Structure of pectenotoxin-4 3-**2**.

Chapter 5: Experimental

5.1 Experimental Techniques

NMR Spectroscopy: Hydrogen nuclear magnetic resonance spectra (^{1}H, NMR) were recorded on Varian Gemini (200MHz), Varian Unity Inova 300 (300MHz), Brucker Unity 200 (200MHz), Brucker Unity 400 (400MHz) and Brucker Unity 500 (500MHz). Carbon nuclear magnetic resonance spectra (^{13}C, NMR) were recorded Brucker Unity 400 (100MHz), and Brucker Unity 500 (125MHz), assignments were made in conjunction with APT (attached proton test) correlation (+)/(−). All chemical shifts are quoted in parts per million (ppm) using trimethylsilane as an internal standard. Signal splittings are described as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), multiplet (bm), doublet of doublets (dd), doublet of triplets (dt), doublet of double doublets (ddd), doublet of double triplets (ddt), broad singlet (br. s). Coupling constants (*J*) are measured in Hertz (Hz) and are uncorrected.

IR Spectroscopy: Infra red (IR) spectra were recorded on a Perkin-Elmer 1710 FT Spectrophotometer as evaporated films from dichloromethane Absorption maxima (ν max) are quoted in wavenumber (cm^{-1}) and only the structurally significant peaks are listed.

Mass Spectrometry: Mass Spectra (MS) and High Resolution Mass Spectra (HRMS) were recorded on a Kratos MS25, Kratos concept and VG Trio 2000 mass spectrometer.

Physical properties: Melting points were recorded on a Kofler heated stage microscope and are uncorrected. All temperatures are quoted in °C.

Solvents and Reagents: Ethylene Glycol was dried over $MgSO_4$, distilled (87 ºC, 7 mbar) and stored over 3Å molecular sieves under Argon.

Drying Agents: All organic extracts were dried using anhydrous magnesium sulphate.

Thin Layer Chromatography: Visualisation was achieved by ultraviolet radiation and by developing in a basic solution of potassium permanganate.

5.2 General Procedures

General Procedure A – *Formation of methyl ester*

A solution of carboxylic acid (1.0 eq.) and sulfuric acid (0.1 eq.) in methanol (0.2 M) was stirred at ambient temperature for 4 hours. The reaction mixture was concentrated *in vacuo*. The residue was dissolved in Et_2O, washed with NaOH (2.0 M) and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General Procedure B – *Li/DBB mediated acyloin reaction*

Preparation of Li/DBB solution: A solution of DBB (2.0 eq.) in tetrahydrofuran (THF) (0.1 M) was prepared in a flame-dried Schlenk flask at 0 °C. Lithium wire (20 eq.) was submerged in Petrol and was finely cut into the DBB solution under a fast stream of argon. The resulting teal-blue colour of Li/DBB solution was stirred under an atmosphere of argon at 0 °C for 2 hours and was cooled down to –78 °C.

***Li/DBB mediated acyloin reaction*:** To a solution of methyl ester(s) (1.0 eq.) in THF (0.2 M) at –78 °C was added *via* cannula the Li/DBB solution (2.0 eq.) under an atmosphere of argon. After the addition, the reaction mixture was stirred further for 5 minutes at –78 °C and was quenched by dropwise addition of a saturated aqueous solution of ammonium chloride

(NH_4Cl) (0.2 M). The solution was allowed to warm to ambient temperature and was transferred *via* cannula into brine. The remaining Li was quenched with slow addition of methanol (MeOH). The aqueous layer was extracted with diethyl ether (Et_2O) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General Procedure C – *Formation of symmetrical tethered di-esters*

To a solution of diol (1.0 eq.) in toluene (0.2 M) was added a solution of acid chloride (2.0 eq.) in toluene (0.2 M). The reaction mixture was heated at reflux under an atmosphere of argon for 15 minutes. The reaction mixture was cooled down to ambient temperature, concentrated *in vacuo* and the residue was diluted with EtOAc and washed with NaOH (2.0 M). The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

General Procedure D – *Formation of crossed-tethered di-esters*

1) To a solution of carboxylic acid (1.0 eq.) in dichloromethane (CH_2Cl_2) (0.2 M) at room temperature was added dropwise oxalyl chloride (2.0 eq.) and *N,N*-dimethylformamide (0.1 eq.) under an atmosphere of argon. The reaction mixture was stirred for 3 hours at room temperature and was concentrated *in vacuo* to remove the oxalyl chloride. The residue was dissolved in CH_2Cl_2, passed through a plug of K_2CO_3 and concentrated *in vacuo*. The acid chloride was carried on to next step without further purification.

2) To a solution of diol (1.5 eq.) in CH_2Cl_2 (0.2 M) at 0 °C was added *via* syringe pump (14 mL/hour) a solution of the acyl chloride (1.0 eq.) in CH_2Cl_2 (0.2 M) under an atmosphere of argon. The reaction mixture was stirred overnight and was quenched with a saturated aqueous

solution of sodium bicarbonate ($NaHCO_3$) (0.2 M). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

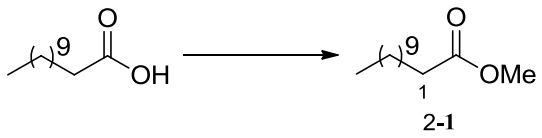
General Procedure E – *Li/DBB mediated acyloin reaction/high dilution*

Preparation of Li/DBB solution: A solution of DBB (2.0 eq.) in THF (0.1 M) was prepared in a flame-dried Schlenk flask at 0 °C. Lithium wire (20 eq.) was submerged in Petrol and was finely cut into the DBB solution under a fast stream of argon. The resulting teal-blue colour of Li/DBB solution was stirred under an atmosphere of argon at 0 °C for 2 hours and was cooled down to –78 °C.

Li/DBB mediated crossed-acyloin reaction: To a stirring solution of the Li/DBB at –78 °C was added *via* syringe pump (5 mL/hour) a solution of the di-ester (1.0 eq.) in THF (0.2 M) under an atmosphere of argon. The teal-blue colour of the Li/DBB solution should remain under the addition of the di-ester. After the addition, the reaction mixture was stirred for 20 minutes and was quenched by dropwise addition of a saturated aqueous solution of NH_4Cl (0.2 M). The reaction mixture was allowed to warm to ambient temperature and was transferred *via* cannula into brine. The remaining Li was quenched with slow addition of MeOH. The aqueous layer was extracted with Et_2O (3 x 50) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

5.3 Experimental Details

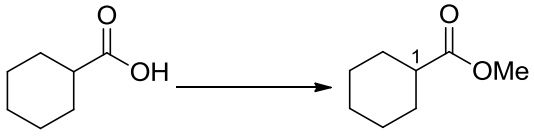
Methyl dodecanoate 2-**1**



2-**1**

Dodecanoic acid (916 mg, 4.58 mmol) was subjected to General Procedure **A**. The crude product was purified by flash column chromatography (SiO_2, 9:1 Petrol-Et_2O) to furnish the ester 2-**1** (941 mg, 96%) as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 3.67 (3 H, s, OMe), 2.31 (2 H, t, J = 7.6 Hz, C(1)H_2), 1.64-1.59 (2 H, m, CH_2), 1.29-1.26 (16 H, m, 8 x CH_2), 0.90-0.87 (3 H, m, CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.4, 51.5, 34.1, 31.9, 29.6, 29.5 (2 Signals), 29.3 (2 Signals), 29.2, 25.0, 22.7, 14.1. *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[106]

Methyl cyclohexanecarboxylate 2-**2**

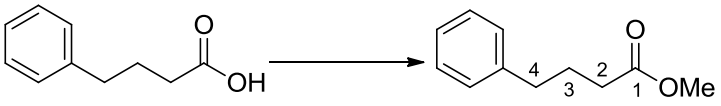


2-**2**

Cyclohexanecarboxylic acid (825 mg, 6.44 mmol) was subjected to General Procedure **A**. The crude product was purified by flash column chromatography (SiO_2, 95:5 Petrol-Et_2O) to furnish the *ester* 2-**2** (870 mg, 95%) as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 3.67 (3 H, s, OC$\underline{H}_3$), 2.32 (1 H, tt, J =11.3 Hz and 3.6 Hz, C(1)$\underline{H}$), 1.92-1.88 (2 H, m, 2 x C(CyH)$\underline{H}$), 1.79-1.74 (2 H, m, 2 x C(CyH)$\underline{H}$), 1.66-1.60 (1 H, m, C(CyH)$\underline{H}$), 1.49-1.39 (2 H, m, 2 x C(CyH)$\underline{H}$), 1.33-1.17 (3 H, m, 3 x C(CyH)$\underline{H}$); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 176.6,

51.5, 43.1, 29.3, 25.8, 25.4. The spectroscopic properties of this compound were consistent with the data reported in the literature.[107]

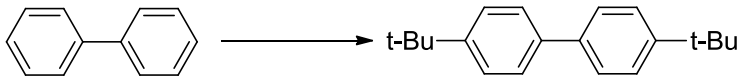
Methyl 4-phenylbutanoate 2-**3**



2-3

4-Phenylbutanoic acid (998 mg, 6.08 mmol) was subjected to General Procedure **A**. The crude product was purified by flash column chromatography (SiO_2, 9:1 Petrol-Et_2O) to furnish the *ester* **2-3** (1.04 g, 96%) as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32-7.18 (5 H, m, Ar<u>H</u>), 3.68 (3 H, s, OMe), 2.66 (2 H, t, J = 7.6 Hz, C(4)<u>H_2</u>), 2.35 (2 H, t, J = 7.5 Hz, C(2)<u>H_2</u>), 1.99 (2 H, quin, J =7.5 Hz, C(3)<u>H_2</u>); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.0, 141.4, 128.5 (2 C), 128.4 (2 C), 126.1, 51.5, 35.1, 33.4, 26.5. *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[42]

4,4-Di-*tert*-butylbiphenyl 1-**28**

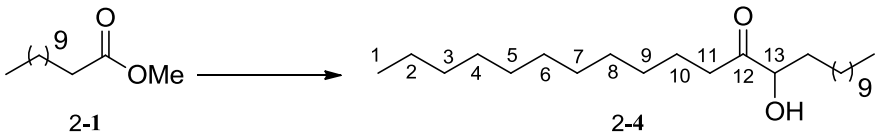


1-28

To a solution of biphenyl (50.0 g, 325 mmol) and anhydrous aluminum chloride (13.0 g, 97.3 mmol) in nitromethane (75 mL), was added under vigorous stirring 2-chloro-2-methylpropane (70.0 mL, 729 mmol) in nitromethane (20 mL) over 30 minutes. The reaction mixture was stirred overnight and poured onto crushed ice in a 500 mL beaker. The solution was warmed to room temperature. The aqueous layer was extracted with petrol (3 × 100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by

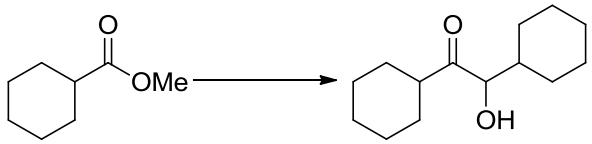
re-crystallisation in EtOH to form the *DBB* 1-**28** (44.1 g, 51%) as a white crystalline solid. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.53-7.44 (8 H, m, ArH), 1.35 (18 H, s, 6 x CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 150.2 (2 C), 137.7 (4 C), 127.1 (4 C), 126.0 (2 C), 34.3 (2 C), 31.6 (6 C); *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[108]

(±)-13-Hydroxytetracosan-12-one 2-**4**



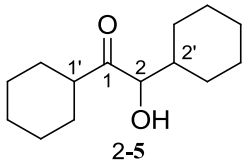
Methyl dodecanoate 2-**1** (200 mg, 934 µmol) was subjected to General Procedure **B**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* 2-**4** (114 mg, 66%) as a white solid.**M.P.** 51 °C; **R_f** (1:1 Petrol-Et_2O) 0.6; **IR** υ_{max} (thin film)/cm^{-1} 3387br, 2916, 2849, 1713,1464, 1102; **^{1}H NMR** (400 MHz, $CDCl_3$): δ_H: 4.19-4.15 (1 H, m, CH), 3.50 (1 H, d, J = 4.8 Hz, OH), 2.53-2.38 (2 H, m, CH_2), 1.62 (2 H, t, J = 6.8 Hz, CH_2), 1.57-1.44 (4 H, m, 2 x CH_2), 1.33-1.24 (32 H, m, 16 x CH_2), 0.88 (6 H, t, J = 6.9 Hz, 2 x CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ_C: 212.6, 76.4, 37.9, 33.8, 31.9, 29.6, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 24.8, 23.7, 22.7, 14.1. **Ms** ***m/z*** (ESI^+) 369 ($M+H^+$, 100%); **HRMS** (ESI^+) Calcd. for $C_{24}H_{48}O_2$ $[M+H]^+$: 369.3727. Found: 369.3731 (1.1 ppm).

(±)-1,2-Dicyclohexyl-2-hydroxyethanone 2-**5**



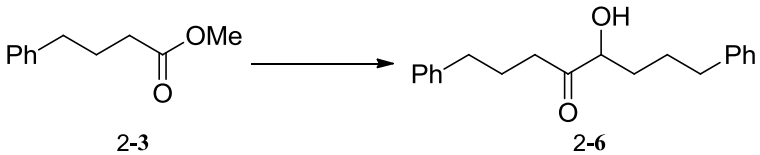
2-**2** 2-**5**

Methyl cyclohexanecarboxylate 2-**2** (50.0 mg, 352 μmol) was subjected to General Procedure **B**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* 2-**5** (28.2 mg, 73%) as a colourless oil (see Scheme 2-**3**, analytical data page **142**).



2-**5**

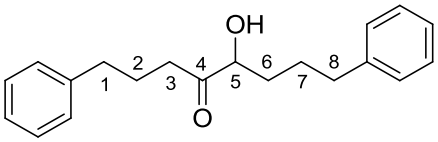
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H: 4.17 (1 H, s, C(2)H), 3.42 (1 H, br. s, OH), 2.58 (1 H, m, C(1')H), 1.83-1.64 (9 H, m, 9 x C(CyH)H), 1.57-1.45 (2 H, m, 2 x C(CyH)H), 1.36-1.09 (10 H, m, 10 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 215.4, 79.3, 46.2, 41.1, 30.3, 30.1, 27.2, 26.6, 25.9, 25.9, 25.8, 25.6, 25.4, 25.1. *Spectroscopic properties of this compound were consistent with the data reported in the literature.*[42]



2-**3** 2-**6**

Methyl 4-phenylbutanoate 2-**3** (50.0 mg, 284 μmol) was subjected to General Procedure **B**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* 2-**6** (28.2 mg, 67%) as a colourless oil (see Scheme 2-**4**, analytical data page **142**).

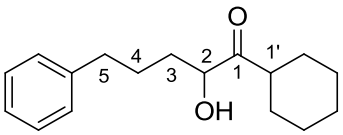
(±)-5-Hydroxy-1,8-diphenyloctan-4-one 2-6



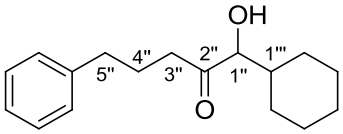
2-6

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H: 7.33-7.16 (10 H, m, ArH), 4.16 (1 H, dt, *J* =7.8 Hz and *J* =3.9 Hz, C(5)H), 3.49 (1 H, br. s, OH), 2.73-2.57 (4 H, m, C(1)H_2 and C(8)H_2), 2.47-2.33 (2 H, m, C(3)H_2), 1.99-1.92 (2 H, m, C(2)H_2), 1.87-1.78 (2 H, m, C(6)H_2), 1.68-1.50 (2 H, m, C(7)H_2); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 212.0, 141.7, 128.4 (4 C), 128.4 (4 C), 126.1, 76.3, 36.9, 35.5, 35.0, 33.1, 26.4, 24.9**.** *Spectroscopic properties of this compound were consistent with the data reported in the literature.*[109]

(±)-1-Cyclohexyl-2-hydroxy-5-phenylpentan-1-one 2-7 **& (±)-1-cyclohexyl-1-hydroxy-5-phenylpentan-2-one** 2-8



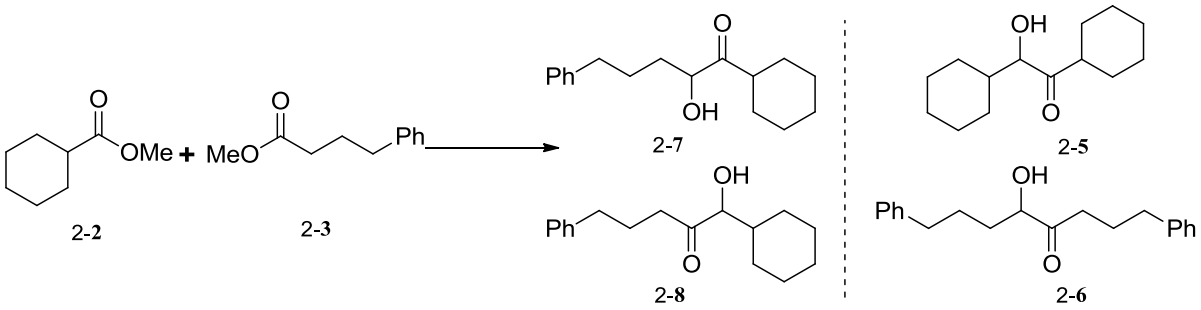
2-7



2-8

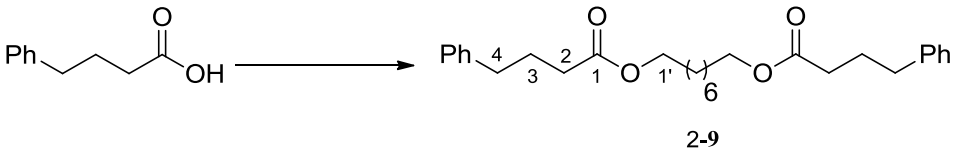
R_f (1:1 Petrol-Et_2O) 0.5; **IR** υ_{max} (thin film)/cm^{-1} 3420, 3028, 2937, 2857, 1706, 1497, 1452, 1255, 1030; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ_H: 7.27-7.19 (2 H, m, ArH), 7.15-7.10 (3 H, m, ArH), 4.23 (0.5 H, dd, *J* = 7.5 and 3.3 Hz, C(2)H), 3.93 (0.5 H, d, *J* = 1.4 Hz, C(1'')H), 3.44 (0.5 H, br. s, OH), 3.32 (0.5 H, br. s, OH), 2.68- 2.51 (2 H, m, C(5)H and C(5'')H), 2.46-2.32 (1.5 H, m, C(3'')H_2 and C(1')H), 1.90 (1 H, quin, *J* = 7.5 Hz, C(4'')H), 1.82-1.54 (5.5 H, m, C(3)H_2 , C(4)H_2, C(1''')H, 3 x C(CyH)H), 1.50-1.34 (2 H, m, 2 x C(CyH)H), 1.27-1.00 (5 H, m, 5 x C(CyH)H). **^{13}C-NMR** (125 MHz, $CDCl_3$): δ_C:215.6, 212.5, 142.2, 141.7, 128.9 (4 signals), 128.8 (2 C), 126.5, 126.3, 81.2, 75.2, 46.4, 41.8, 37.7, 35.9, 35.5 (2 C), 33.4 (2 C),

30.6, 30.3, 27.8, 27.1, 27.0, 26.4, 26.3 (2 C), 26.1, 25.6 (2 C), 25.4; **MS** ***m/z*** (ESI^+) 687 (2M + Na+,100 %); **HRMS** (ESI^+) Calcd. for $C_{17}H_{24}NaO_2$ $[M+Na]^+$: 283.1674. Found: 283.1669 (−1.8 ppm).



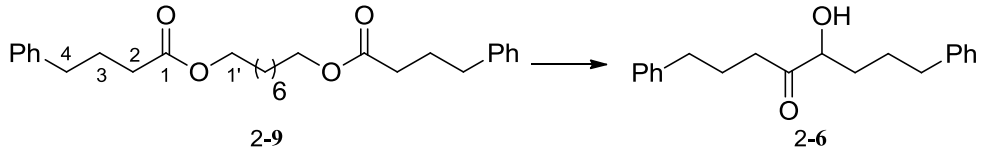
Methyl cyclohexanecarboxylate 2-**2** (125 mg, 880 μmol) and methyl 4-phenylbutanoate 2-**3** (160 mg, 898 μmol) were subjected to General Procedure **B**. The crude product was purified by flash column chromatography (SiO_2, 99:1 Petrol-Et_2O) to furnish an inseparable mixture (1:1) of the *crossed-acyloins* 2-**7** and 2-**8**, and the *acyloins* 2-**5** and 2-**6** (in combined yield of 110 mg, 48%) as a yellow oil (see Scheme 2-**5**, analytical data page **143**).

Octane-1,8-diyl bis(4-phenylbutanoate) 2-**9**



4-Phenylbutanoic acid (5.45 g, 33.3 mmol) was subjected to General Procedure **C**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *di-ester* 2-**9** (1.71 g, 24%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 2932, 2853, 1731; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32-7.18 (10 H, m, Ar$\underline{H}$), 4.06 (4 H, t, *J* = 6.8 Hz, 2 x C(1')$\underline{H_2}$), 2.66 (4 H, t, *J* =7.6 Hz, 2 x C(4)$\underline{H_2}$), 2.33 (4 H, t, *J* = 7.6 Hz, 2 x C(2)$\underline{H_2}$), 1.97 (4 H, quin, *J* = 7.6 Hz, 2 x C(3)$\underline{H_2}$), 1.64-1.59 (4 H, m, 2 x C$\underline{H_2}$), 1.33 (8 H, s, 4

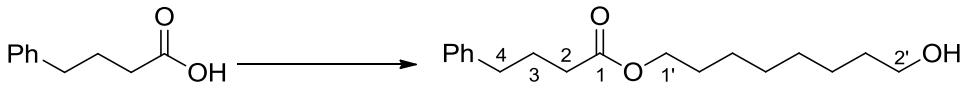
x C$\underline{H}_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 173.6 (2 C), 141.4 (2 C), 128.5 (4 C), 128.4 (4 C), 126.0 (2 C), 64.5 (2 C), 35.2 (2 C), 33.7 (2 C), 29.2 (2 C), 28.6 (2 C), 26.6 (2 C), 25.9 (2 C); **MS** (ESI^+) ***m/z*** 461 ($M + Na^+$, 90 %); **HRMS** (ESI^+) Calcd. for $C_{28}H_{38}O_4$ $[M+H]^+$: 439.2848. Found: 439.2836 (–2.7 ppm).



2-9 **2-6**

Methyl 4-phenylbutanoate **2-9** (100 mg, 228 μmol) was subjected to General Procedure **B**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* **2-6** (20.2 mg, 30%) as a colourless oil (see Scheme 2-**6**, analytical data page **142**).

8-Hydroxyoctyl 4-phenylbutanoate 2-10

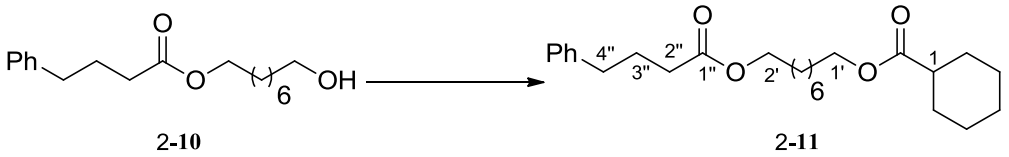


2-10

4-Phenylbutanoic acid (2.75 g, 16.8 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *mono-ester* **2-10** (1.52 g, 31%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.2; **IR** υ_{max} (thin film)/cm^{-1} 3425, 2931, 2857, 1733; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.31-7.18 (5 H, m, Ar$\underline{H}$), 4.07 (2 H, t, J = 6.7 Hz, C(1')$\underline{H}_2$), 3.64 (2 H, t, J = 6.7 Hz, C(2')$\underline{H}_2$), 2.66 (2 H, t, J = 7.6 Hz, C(4)$\underline{H}_2$), 2.33 (2 H, t, J = 7.6 Hz, C(2)$\underline{H}_2$), 1.96 (2 H, quin, J = 7.6 Hz, C(3)$\underline{H}_2$) 1.64-1.54 (4 H, m, 2 x C$\underline{H}_2$), 1.34 (8 H, s, 4 x C$\underline{H}_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 173.7, 141.5, 128.5 (2 C), 128.4 (2 C), 126.0, 62.5, 63.0, 35.2, 33.7, 32.8, 29.3, 29.2, 28.6, 26.6, 25.9, 25.7; **MS**

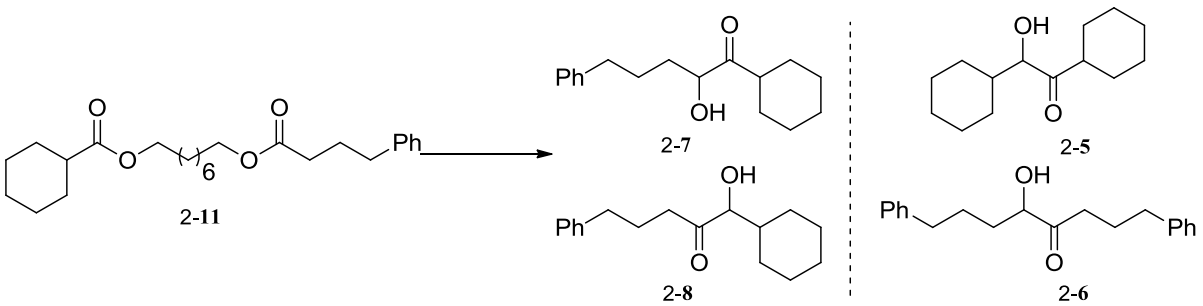
(ESI$^+$) ***m/z*** 607 (2M + Na^+, 100 %); **HRMS** (ESI$^+$) Calcd. for $C_{18}H_{28}NaO_3$ $[M+Na]^+$: 315.1936. Found: 315.1931 (–1.6 ppm).

8-(4-Phenylbutanoyloxy)octyl cyclohexanecarboxylate 2-**11**



2-10 **2-11**

8-Hydroxyoctyl 4-phenylbutanoate 2-**10** (1.45 g, 4.97 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *di-ester* 2-**11** (1.00 g, 50%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.8; **IR** υ_{max} (thin film)/cm^{-1} 2932, 2856, 1733; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32-7.27 (2 H, m, Ar<u>H</u>), 7.17-7.23 (3 H, m, Ar<u>H</u>), 4.09-4.02 (4 H, m, 2 x C(1')<u>H</u>$_2$ and C(2')<u>H</u>$_2$), 2.66 (2 H, t, *J* = 7.6 Hz, C(4'')<u>H</u>$_2$), 2.36-2.25 (3 H, m, C(2'')<u>H</u>$_2$ and C(1)<u>H</u>), 2.01-1.87 (4 H, m, C(3'')<u>H</u>$_2$ and C<u>H</u>$_2$), 1.79-1.72 (2 H, m, 2 x C(CyH)<u>H</u>), 1.68-1.58 (5 H, m, 3 x C(CyH)<u>H</u> C<u>H</u> and C<u>H</u>$_2$), 1.49-1.22 (13 H, m, 5 x C(CyH)<u>H</u> and 4 x C<u>H</u>$_2$); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 176.2, 173.6, 141.4, 128.5 (2 C), 128.4 (2 C), 126.0, 64.5, 64.2, 43.3, 35.2, 33.7, 32.8 (2 C), 29.1 (2 C), 28.6 (2 C), 26.6, 25.9, 25.8 (2 C), 25.5 (2 C); **MS** (ESI$^+$) ***m/z*** 827 (2M + Na^+, 100 %); **HRMS** (ESI$^+$) Calcd. for $NaC_{25}H_{38}O_4$ $[M+Na]^+$: 425.2668. Found: 425.2666 (–0.5 ppm).

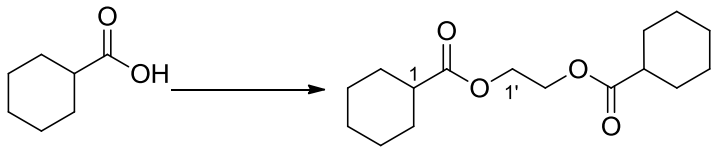


2-11 **2-7** **2-5** **2-8** **2-6**

8-((4-Phenylbutanoyl)oxy)octyl cyclohexanecarboxylate 2-**11** (55.0 mg, 14.0 μmol) was

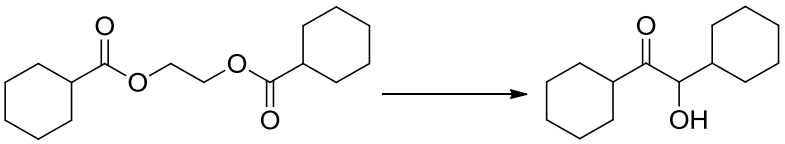
subjected to General Procedure **B**. The crude product was purified by flash column chromatography (SiO2, 99:1 Petrol-Et2O) to furnish an inseparable mixture (1:1) of the crossed-acyloin 2-**7** and 2-**8**, and the acyloins 2-**5** and 2-**6** (in combined yield of 11.0 mg, 31%) as a yellow oil (see Scheme 2-**8**, analytical data page **143**).

Ethane- 1,2 diyl dicyclohexane carboxylate 2-**12**



2-12

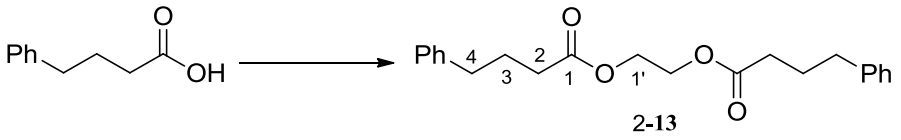
Cyclohexanecarboxylic acid (2.34 g, 18.3 mmol) was subjected to General Procedure **C**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *di-ester* 2-**12** (1.96 g, 76%) as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 4.27 (4 H, s, 2 x C(1')$\underline{H}_2$), 2.31 (2 H, tt, J = 11.3 Hz 3.6 Hz, 2 x C(1)$\underline{H}$), 1.92-1.88 (4 H, m, 2 x C(CyH)$\underline{H}$), 1.79-1.74 (4 H, m, 2 x C(CyH)$\underline{H}$), 1.66-1.60 (2 H, m, 2 x C(CyH)$\underline{H}$), 1.50-1.40 (4 H, m, 4 x C(CyH)$\underline{H}$), 1.33-1.17 (6 H, m, 6 x C(CyH)$\underline{H}$); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 175.8 (2 C), 61.5 (2 C), 43.0 (2 C), 29.0 (4 C), 25.7 (4 C), 25.4 (2 C). *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[18]



2-12 2-5

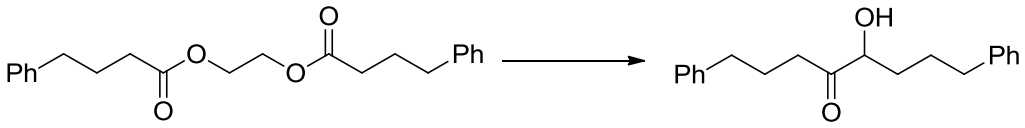
Ethane- 1,2-diyl dicyclohexane carboxylate 2-**12** (100 mg, 354 µmol) was subjected to General Procedure **B**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* 2-**5** (35.0 mg, 44%) as a colourless oil (see Scheme 2-**9**, analytical data page **142**).

Ethane-1,2-diyl bis(4-phenylbutanoate) 2-**13**



2-13

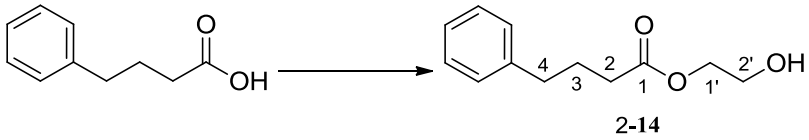
4-Phenylbutanoic acid (2.40 g, 14.7 mmol) was subjected to General Procedure **C**. The crude product was purified by flash column chromatography (SiO_2, 98:02 Petrol-EtOAc) to furnish the *di-ester* 2-**13** (2.31 g, 89%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.3**; IR** υ_{max} (thin film)/cm^{-1} 2948, 2858, 1645; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.33-7.16 (10 H, m, Ar$\underline{H}$), 4.28 (4 H, s, 2 x C(1')$\underline{H_2}$), 2.66 (4 H, t, J = 7.6 Hz, 2 x C(4)$\underline{H_2}$), 2.36 (4 H, t, J = 7.5 Hz, 2 x C(2)$\underline{H_2}$), 2.00-1.93 (4 H, m, 2 x C(3)$\underline{H_2}$); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 173.3 (2 C), 141.7 (2 C), 128.5 (4 C), 128.42 (4 C), 126.0 (2 C), 62.1 (2 C), 35.1 (2 C), 33.4 (2 C), 26.4 (2 C); **Ms** (ESI^+) ***m/z*** 377 ($M + Na^+$, 80 %); **HRMS** (ESI^+) Calcd. for $C_{22}H_{26}NaO_4$ $[M+Na]^+$: 377.1729. Found: 377.1723 (1.6 ppm).



2-13 **2-6**

Ethane-1,2-diyl bis(4-phenylbutanoate) 2-**13** (100 mg, 282 μmol) was subjected to General Procedure **B**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* 2-**6** (37.3 mg, 45%) as a colourless oil (see Scheme 2-**9**, analytical data page **142**).

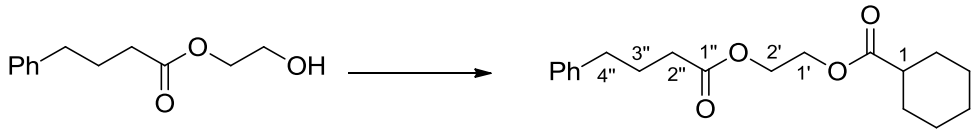
2-Hydroxyethyl 4-phenylbutanoate 2-**14**



2-14

4-Phenylbutanoic acid (895 mg, 5.45 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:02 Petrol-EtOAc) to furnish the *mono-ester* 2-**14** (840 mg, 74%) as a colourless oil**.** **R_f** (1:1 Petrol-Et_2O) 0.2; **IR** υ_{max} (thin film)/cm^{-1}: 3442, 2948, 2858, 1735; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32-7.18 (5 H, m, ArH), 4.23-4.20 (2 H, m, C(1')H_2), 3.84-2.82(2 H, m, C(2')H_2), 2.68 (2 H, t, J = 7.6 Hz, C(4)H_2), 2.39 (2 H, t, J = 7.5 Hz, C(2)H_2), 1.99 (2 H, quin, J = 7.6 Hz, C(3)H_2); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 173.9, 141.3, 128.5 (2 C), 128.4 (2 C), 126.1, 66.0, 61.3, 35.1, 33.5, 26.4; **Ms** (ESI^+) ***m/z*** 231 ($M + H^+$, 70 %); **HRMS** (ESI^+) Calcd. for $C_{12}H_{16}NaO_3$ $[M+Na]^+$: 231.0997. Found: 231.0993 (–1.7 ppm).

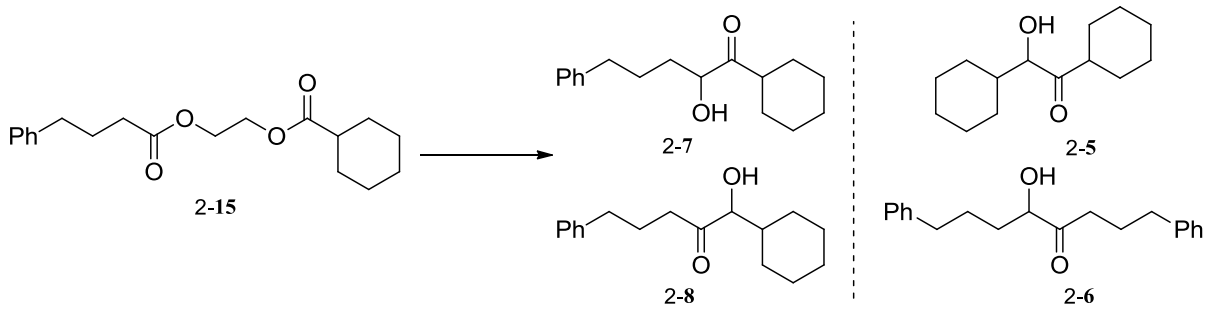
2-(4-Phenylbutanoyloxy)ethyl cyclohexanecarboxylate 2-**15**



2-14 **2-15**

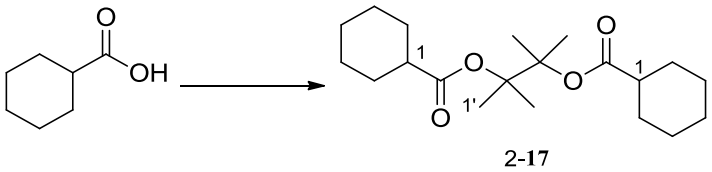
2-Hydroxyethyl 4-phenylbutanoate 2-**14** (900 mg, 4.32 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98: 2 Petrol-EtOAc) to furnish the *di-ester* 2-**15** (1.10 g, 80%) as a colourless oil. **R_f** (1:1 Petrol-Et_2O) 0.5; **IR** υ_{max} (thin film)/cm^{-1} 2934, 2854, 1737; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.31-7.18 (5 H, m, ArH), 4.28 (4 H, s, C(1')H_2, C(2')H_2), 2.67 (2 H, t, J = 7.6 Hz, C(4'')H_2), 2.36 (2 H, t, J = 7.5 Hz, C(2'')H_2), 2.33-2.28 (1 H, m, C(1)H), 2.01-1.93 (2 H, m, C(3'')H_2), 1.93-1.88 (2 H, m, 2 x C(CyH)H), 1.79-1.74 (2 H, m, 2 x C(CyH)H), 1.66-1.62 (1 H, m,

C(CyH)H), 1.48-1.39 (2 H, m, 2 x C(CyH)H), 1.33-1.19 (3 H, m, 3 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 176.6, 173.3, 141.3, 128.5 (2 C), 128.4 (2 C), 126.1, 62.2, 61.9, 43.1, 35.1, 33.5, 29.0 (2 C), 26.5, 25.7 (2 C), 25.4; **Ms** (ESI^+) ***m/z*** 341 ($M + Na^+$,100 %); **HRMS** (ESI^+) Calcd. for $C_{19}H_{26}NaO_4$ $[M+Na]^+$: 341.1729. Found: 341.1737 (2.3 ppm).



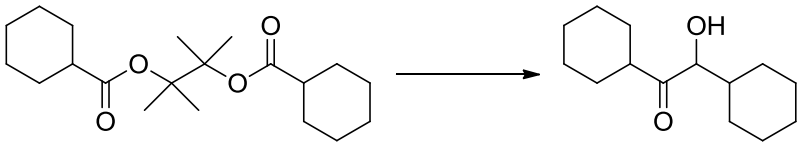
2-((4-phenylbutanoyl)oxy)Ethyl cyclohexanecarboxylate **2-15** (100 mg, 314 µmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 99:1 Petrol-Et_2O) to furnish an inseparable mixture (1:1) of the *crossed-acyloins* 2-**7** and 2-**8**, and the *acyloins* 2-**5** and 2-**6** (in combined yield of 47.1 mg, 57%) as a yellow oil (see Scheme 2-**11**, analytical data page **143**).

2,3-Dimethylbutane-2,3-diyl dicyclohexanecarboxylate 2-**17**



Cyclohexanecarboxylic acid (3.66 g, 28.6 mmol) was subjected to General Procedure **C**. The crude product was purified by flash column chromatography (SiO_2, 98:02 Petrol-EtOAc) to furnish the *di-ester* 2-**17** (870 mg, 18%) as a colourless crystals. **MP** 55.5 ºC; **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (KBr)/cm^{-1} 2933, 2855, 1729**;** **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 2.31 (2 H, tt, J = 11.3 Hz and 3.6 Hz, C(1)H), 1.90-1.87 (4 H, m, 4 x C(CyH)H), 1.76-1.73

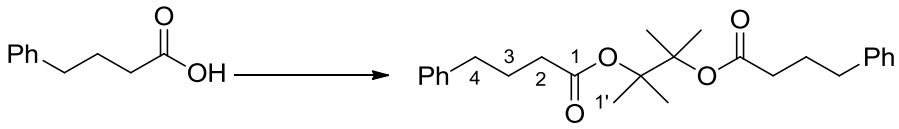
(4 H, m, 4 x C(CyH)H), 1.66-1.61 (2 H, m, 2 x C(CyH)H), 1.56 (12 H, s, 4 x C(1')H_3), 1.45-1.36 (4 H, m, 4 x C(CyH)H), 1.33-1.19 (6 H, m, 6 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.9 (2 C), 84.5 (2 C), 44.4 (2 C), 29.1(4 C), 25.8 (4 C), 25.5 (2 C), 20.4 (4 C); **Ms** (ESI^+) ***m/z*** 361 ($M + Na^+$,100 %); **HRMS** (ESI^+) Calcd. for $C_{20}H_{34}NaO_4$ $[M+Na]^+$: 361,2355. Found: 361.2346 (–2.4 ppm).



2-17 **2-5**

2',3'-dimethylbutane-2',3'-diyl dicyclohexanecarboxylate 2-**17** (200 mg, 591 μmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* 2-**5** (16.0 mg, 12%) as a colourless oil (see Scheme 2-**13**, analytical data page **142**).

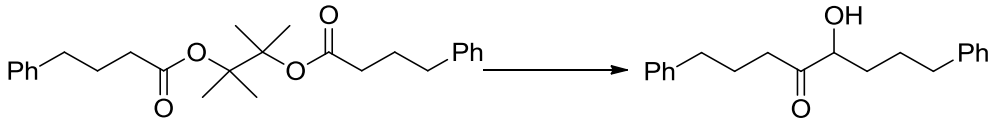
2,3-Dimethylbutane-2,3-diyl bis(4-phenylbutanoate) 2-**18**



2-18

4-Phenylbutanoic acid (2.34 g, 14.3 mmol) was subjected to General Procedure **C**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *di-ester* 2-**18** (468 mg, 16%) as a white crystalline solid. **MP** 70.6 ºC; **R_f** (3:1 Petrol-Et_2O) 0.5; **IR** υ_{max} (KBr)/cm^{-1} 2934, 2854, 1729; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32-7.18 (10 H, m, ArH), 2.65 (4 H, t, J = 7.6 Hz, 2 x C(4)H_2), 2.28 (4 H, t, J = 7.4 Hz, 2 x C(2)H_2), 1.93 (4 H, quin., J = 7.6 Hz, 2 x C(2)H_2), 1.59 (12 H, s, 4 x C(1')H_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 172.3 (2 C), 141.4 (2 C), 128.5 (4 C), 128.4 (4 C), 126.0 (2 C), 85.0 (2 C), 35.1 (2 C), 29.1 (2

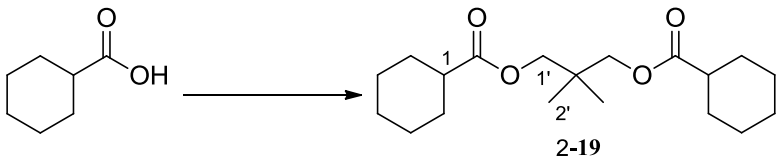
C), 26.7 (2 C), 20.4 (4 C); **Ms** (ESI^+) ***m/z*** 433 ($M + Na^+$, 60 %); **HRMS** (ESI^+) Calcd. for $NaC_{26}H_{34}O_4$ $[M+Na]^+$: 433,2355. Found: 433.2352 (–0.7 ppm).



2-18 **2-6**

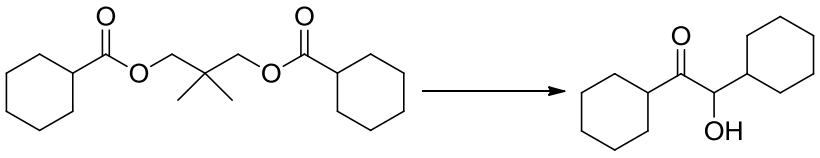
2,3-Dimethylbutane-2,3-diyl bis(4-phenylbutanoate) 2-**18** (200 mg, 488 µmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* 2-**6** (19.1 mg, 13%) as a colourless oil (see Scheme 2-**13**, analytical data page **142**).

2,2-Dimethylpropane-1,3-diyl dicyclohexanecarboxylate 2-**19**



2-19

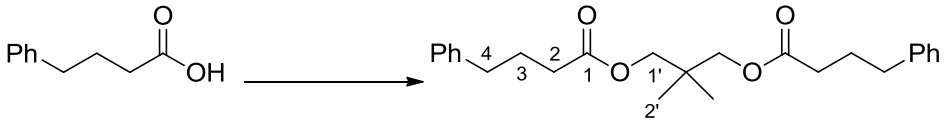
Cyclohexanecarboxylic acid (2.94 g, 13.7 mmol) was subjected to General Procedure **C**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *di-ester* 2-**19** (1.20 g, 27%) as a colourless crystalline solid. **MP** 30.5 ºC; **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (KBr)/cm^{-1} 2933, 2855, 1733; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 3.88 (4 H, s, 2 x C(1')$\underline{H}_2$), 2.32 (2 H, tt, J = 11.3 Hz 3.7 Hz, 2 x C(1)$\underline{H}$), 1.93-1.89 (4 H, m, 4 x C(CyH)$\underline{H}$), 1.77-1.73 (4 H, m, 4 x C(CyH)$\underline{H}$), 1.66-1.60 (2 H, m, 2 x C(CyH)$\underline{H}$), 1.49-1.39 (4 H, m, 4 x C(CyH)$\underline{H}$), 1.33-1.20 (6 H, m, 6 x C(CyH)$\underline{H}$), 0.97 (6 H, s, 2 x C(2')$\underline{H}_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 175.9 (2 C), 68.9 (2 C), 43.0 (2 C), 34.8, 29.0 (4 C), 25.7 (4 C), 25.4 (2 C), 21.8 (2 C); **Ms** (ESI^+) ***m/z*** 671 ($2M + Na^+$,100 %); **HRMS** (ESI^+) Calcd. for $C_{19}H_{32}NaO$ $[M+Na]^+$: 347.2198. Found: 347.2190 (–0.9 ppm).



2-19 **2-5**

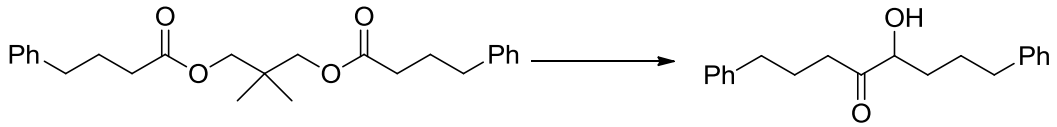
2,2-Dimethylpropane-1,3-diyl dicyclohexanecarboxylate **2-19** (200 mg, 617 μmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* **2-5** (55.1 mg, 40%) as a colourless oil (see Scheme 2-**14**, analytical data page **142**).

2,2-Dimethylpropane-1,3-diyl bis(4-phenylbutanoate) 2-20



2-20

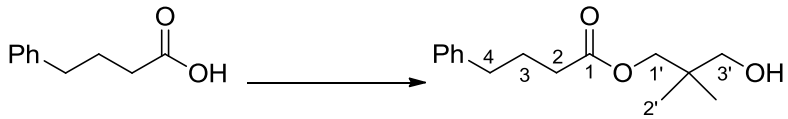
4-Phenylbutanoic acid (3.61 g, 22.0 mmol) was subjected to General Procedure **C**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *di-ester* **2-20** (2.66 g, 61%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.4; **IR** υ_{max} (thin film)/cm^{-1} 2934, 2857, 1705; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32-7.18 (10 H, m, Ar$\underline{H}$), 3.90 (4 H, s, 2 x C(1')$\underline{H}_2$), 2.66 (4 H, t, J = 7.5 Hz, 2 x C(4)$\underline{H}_2$), 2.35 (4 H, t, J = 7.5 Hz, 2 x C(2)$\underline{H}_2$), 1.93 (4 H, quin., J = 7.5 Hz, 2 x C(3)$\underline{H}_2$), 0.98 (6 H, s, 2 x C(2')$\underline{H}_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 173.4 (2 C), 141.3 (2 C), 128.6 (4 C), 128.5 (4 C), 126.0 (2 C), 69.1 (2 C), 35.1 (2 C), 34.2, 33.6 (2 C), 26.6 (2 C), 21.8 (2 C); **Ms** (ESI^+) ***m/z*** 419 ($M + Na^+$,70 %); **HRMS** (ESI^+) Calcd. for $C_{25}H_{32}NaO_4$ $[M+Na]^+$: 419.2198. Found: 419.2190 (−1.9 ppm).



2-20 **2-6**

2,2-Dimethylpropane-1,3-diyl bis(4-phenylbutanoate) 2-**20** (200 mg, 505 μmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* 2-**6** (64.0 mg, 44%) as a colourless oil (see Scheme 2-**14**, analytical data page **142**).

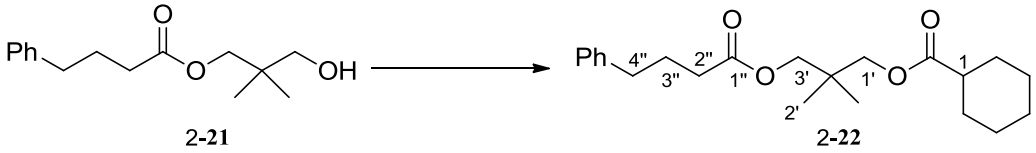
3-Hydroxy-2,2-dimethylpropyl 4-phenylbutanoate 2-**21**



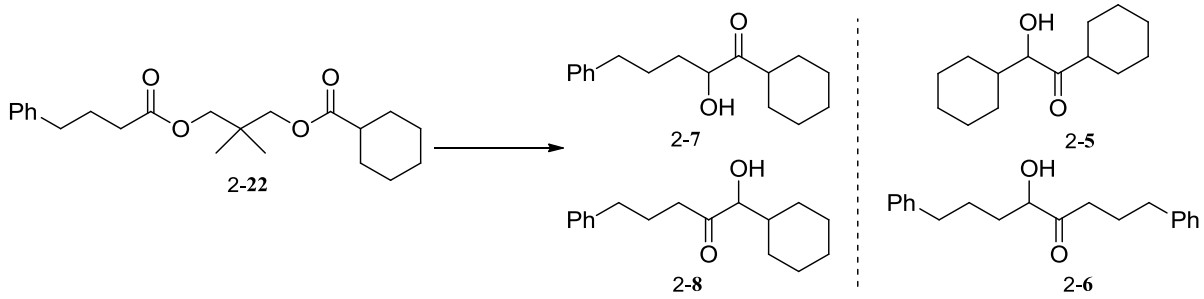
2-21

4-Phenylbutanoic acid (2.70 g, 16.4 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *mono-ester* 2-**21** (2.63 g, 64%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.2; **IR** υ_{max} (thin film)/cm^{-1} 3450, 3027, 2960, 1733; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32-7.18 (5 H, m, Ar$\underline{H}$), 3.95 (2 H, s, C(1')$\underline{H}_2$), 3.30 (2 H, s, C(3')$\underline{H}_2$), 2.67 (2 H, t, J = 7.6 Hz, C(4)$\underline{H}_2$), 2.38 (2 H, t, J = 7.5 Hz, C(2)$\underline{H}_2$), 2.22 (1 H, br. s, O$\underline{H}$), 1.98 (2 H, quin, J = 7.5 Hz, C(3)$\underline{H}_2$), 0.93 (6 H, s, 2 x C(2')$\underline{H}_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.2, 141.2, 128.5 (2 C), 128.4 (2 C), 126.0, 69.3, 68.2, 36.4, 35.1, 33.6, 26.6, 21.5 (2 C); **Ms** (ESI^+) ***m/z*** 273 ($M + Na^+$,100 %); **HRMS** (ESI^+) Calcd. for $C_{15}H_{22}NaO_3$ $[M+Na]^+$: 273.1467. Found: 273.1458 (–3.3 ppm).

2,2-Dimethyl-3-(4-phenylbutanoyloxy)propyl cyclohexanecarboxylate 2-22

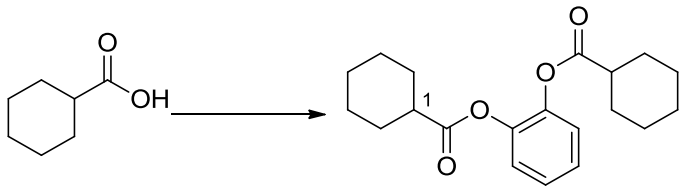


3-Hydroxy-2,2-dimethylpropyl 4-phenylbutanoate 2-**21** (2.20 g, 8.78 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *di-ester* 2-**22** (2.34 g, 74%) as a colourless oil. **R_f** (SiO_2, 3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 2934, 2839, 1734; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32-7.18 (5 H, m, ArH), 3.89 (2 H, s, C(1')H_2), 3.88 (2 H, s, C(3')H_2), 2.66 (2 H, t, J = 7.5 Hz, C(4'')H_2), 2.37-2.29 (3 H, m, C(2'')H_2) and C(1)H), 2.00-1.89 (4 H, m, C(3'')H_2 and 2 x C(CyH)H), 1.76-1.73 (2 H, m, 2 x C(CyH)H), 1.66-1.61 (1 H, m, C(CyH)H), 1.48-1.39 (2 H, m, 2x C(CyH)H), 1.33-1.20 (3 H, m, 3 x C(CyH)H), 0.97 (6 H, m, 2 x C(2')H_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 175.4, 173.4, 141.3, 128.5 (2 C), 128.4 (2 C), 126.0, 69.2, 68.8, 43.3, 35.2, 34.8, 33.6, 29.1 26.5, 25.8, 25.5, 21.8 (2 C); **Ms** (ESI^+) ***m/z*** 383 (M + Na^+, 90 %); **HRMS** (ESI^+) Calcd. for $C_{22}H_{32}NaO_4$ $[M+Na]^+$: 383.2198. Found: 383.2193 (−1.3 ppm).



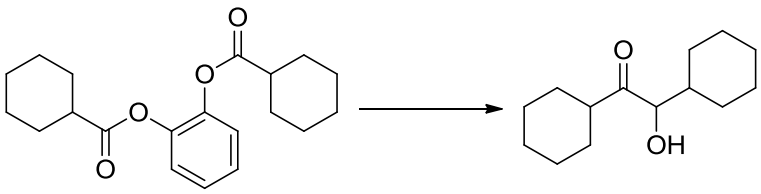
2,2-Dimethyl-3-((4-phenylbutanoyl)oxy)propyl cyclohexanecarboxylate 2-**22** (56 mg, 16 μmol) was subjected to General Procedure E. The crude product was purified by flash column chromatography (SiO2, 99:1 Petrol-Et2O) to furnish an inseparable mixture (1:1) of the crossed-acyloins 2-**7** and 2-**8**, and the acyloins 2-**5** and 2-**6** (in combined yield of 22.3 mg, 55%) as a yellow oil (see Scheme 2-**16**, analytical data page **143**).

1,2-Phenylene dicyclohexanecarboxylate 2-**23**



2-**23**

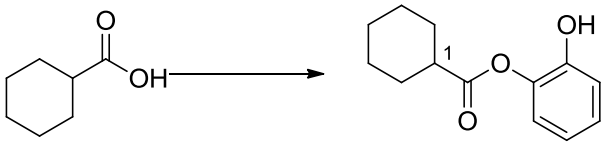
Cyclohexanecarboxylic acid (1.73 g, 13.5 mmol) was subjected to General Procedure **C**. The crude product was purified by flash column chromatography (SiO_2, 98:02 Petrol-EtOAc) to furnish the *di-ester* 2-**23** (1.98 g, 89%) as a colourless oil. **R_f** (9:1 Petrol- EtOAc) 0.4; **IR** υ_{max} (thin film)/cm^{-1} 2933, 2845, 1762; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.27-7.13 (4 H, m, ArH), 2.60-2.51 (2 H, m, 2 x C(1)H), 2.07-2.03 (4 H, m, 4 x C(CyH)H), 1.85-1.81 (4 H, m, 4 x C(CyH)H), 1.71-1.69 (2 H, m, 2 x C(CyH)H), 1.63-1.1.53 (4 H, m, 4 x C(CyH)H), 1.41-1.23 (6 H, m, 2 x CH_2, 6 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 173.4 (2 C), 142.4 (2 C), 126.4 (2 C), 123.5 (2 C), 43.1 (2 C), 29.0 (4 C), 25.7 (4 C), 25.4 (2 C); **Ms** (ESI^+) ***m/z*** 330 (M + Na^+,100 %); **HRMS** (ESI^+) Calcd. for $C_{20}H_{26}NaO_4$ $[M+Na]^+$: 330.1831. Found: 330.1832 (0.3 ppm).



2-**23** 2-**5**

1,2-Phenylene dicyclohexanecarboxylate 2-**23** (100 mg, 303 µmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* 2-**5** (46.5 mg, 69%) as a colourless oil (see Scheme 2-**17**, analytical data page **142**).

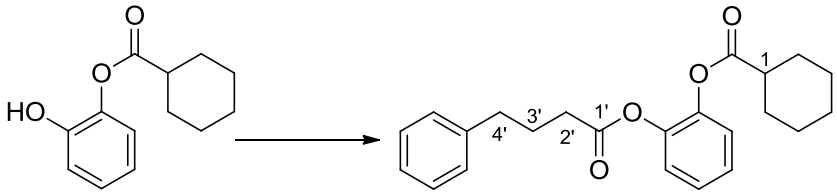
2-Hydroxyphenyl cyclohexanecarboxylate 2-**24**



2-24

Cyclohexanecarboxylic acid (1.00 g, 781 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:02 Petrol-EtOAc) to furnish the *mono-ester* 2-**24** (791 mg, 43%) as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.15-7.05 (2 H, m, ArH), 7.02-6.98 (1 H, m, ArH), 6.95-6.90 (1 H, m, ArH), 5.38 (1H, br. s, OH), 2.64 (1 H, tt, *J* = 11.2 Hz and 3.6 Hz, C(1)H), 2.14-2.05 (2 H, m, 2 x C(CyH)H), 1.88-1.80 (2 H, m, 2 x C(CyH)H), 1.74-1.57 (3 H, m, 3 x C(CyH)H), 1.44-1.25 (3 H, m, 3 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.5, 147.0, 138.8, 126.9, 122.3, 121.0, 117.9, 43.2, 29.3, 25.6, 25.3. *The spectroscopic properties of this compound were consistent with the data reported in the literature.* [110]

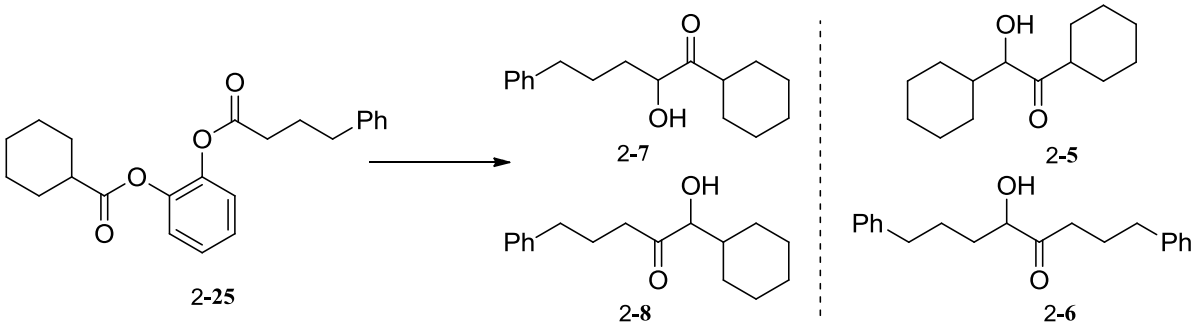
2-(4-Phenylbutanoyloxy)phenyl cyclohexanecarboxylate 2-**25**



2-24 **2-25**

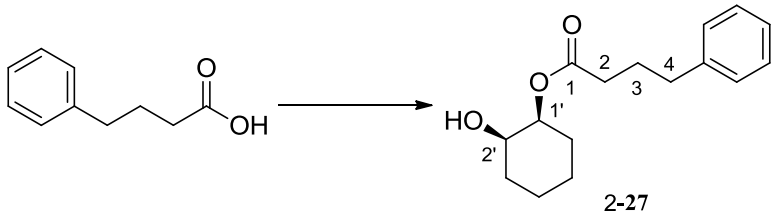
2-Hydroxyphenyl cyclohexanecarboxylate 2-**24** (1.60 g, 7.27 mmol) was obtained by using General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:02 Petrol-EtOAc) to furnish the *di-ester* 2-**25** (2.00 g, 75%) as a colourless oil. **R_f** (9:1 Petrol- EtOAc) 0.6; **IR** ν_{max} (thin film)/cm^{-1} 2935, 2860, 1764; 2935, 2860, 1764; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.34-7.25 (9 H, m, ArH), 2.77-2.73 (2 H, m, C(4')H_2), 2.56 (2 H, t, *J*

= 7.5 Hz, C(2')$\underline{H}_2$), 2.52 (1 H, tt, *J* = 11.3 Hz and 3.6 Hz, C(1)$\underline{H}$), 2.08 (2 H, quin, *J* = 7.5 Hz, C(3')$\underline{H}_2$), 2.03-1.97 (2 H, m, 2 x C(CyH)$\underline{H}$), 1.82-1.76 (2 H, m, 2 x C(CyH)$\underline{H}$), 1.70-1.66 (1 H, m, C(CyH)$\underline{H}$), 1.59-1.49 (2 H, m, C$\underline{H}_2$), 1.37-1.22 (3 H, m, 3 x C(CyH)$\underline{H}$); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 173.4, 170.8, 142.3, 142.2, 141.1, 128.5 (2 C), 126.6 (2 C), 126.4 (2 C), 126.2, 123.5 (2 Signals), 43.0, 35.0, 33.3, 29.0, 26.4 (2 C), 25.6 (2 C), 25.3; **MS** (ESI^+) ***m/z*** 389 ($M + Na^+$, 80%); **HRMS** (ESI^+) Calcd. for $C_{23}H_{26}NaO_4$ $[M+Na]^+$: 389.1729. Found 389.1716 (–3.3 ppm).



2-((4-phenylbutanoyl)oxy)Phenyl cyclohexanecarboxylate 2-**25** (100 mg, 273 µmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 99:1 Petrol-Et_2O) to furnish an inseparable mixture (1:1) the *crossed-acyloins* 2-**7** and 2-**8**, and the *acyloins* 2-**5** and 2-**6** (in combined yield of 49.0 mg, 69%) as a yellow oil (see Scheme 2-**19**, analytical data page **143**).

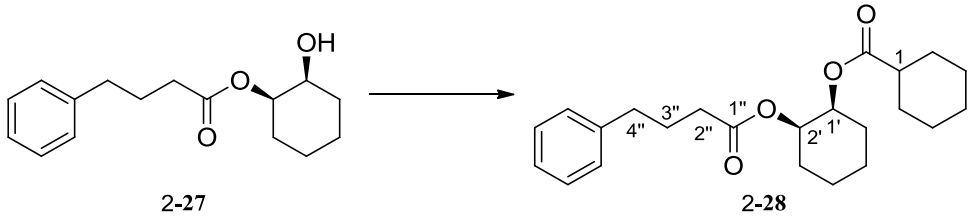
(±) -*(1R,2S)*-2-Hydroxycyclohexyl 4-phenylbutanoate 2-**27**



2-**27**

4-Phenylbutanoic acid (709 mg, 4.32 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *mono-ester* 2-**27** (714 mg, 63%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.2.; **IR** υ_{max} (thin film)/cm^{-1} 3434, 2931, 1720; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32-7.19 (5 H, m, ArH), 4.96-4.94 (1 H, m, C(1')H), 3.89-3.86 (1 H, m, C(2')H), 2.70-2.65 (2 H, m, C(4)H_2), 2.40-2.35 (2 H, m, C(2)H_2), 2.03-1.94 (2 H, m, C(3)H_2), 1.88-1.76 (2 H, m, 2 x C(CyH)H), 1.69-1.59 (4 H, m, 4 x C(CyH)H),1.42-1.36 (2 H, m, 2 x C(CyH)H), **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 176.3, 141.5, 128.5 (2 C), 128.4 (2 C), 126.0, 71.2, 70.2, 43.3, 35.1, 33.9, 29.1, 28.0, 26.6, 25.4; **MS** (ESI^+) ***m/z*** 285 (M + Na^+100%); **HRMS** (ESI^+) Calcd. for $C_{16}H_{22}NaO_3$ $[M+Na]^+$: 285.1467. Found: 285.1461 (–2.1 ppm).

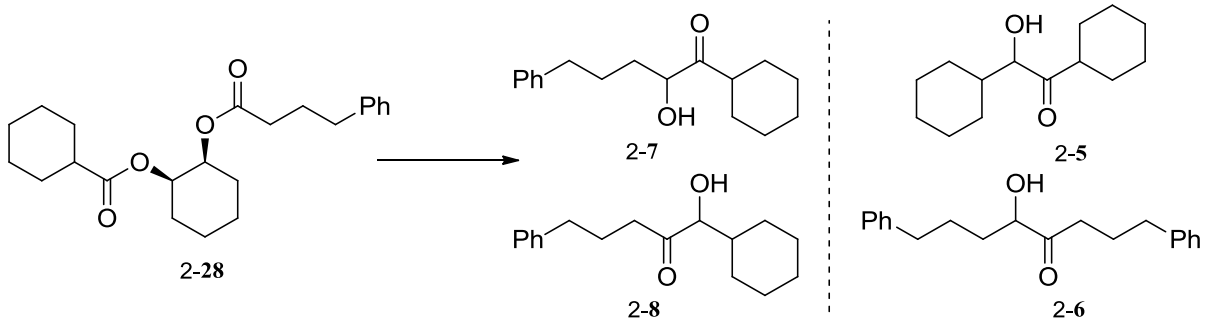
(±) -(*1S,2R*)-2-((4-Phenylbutanoyl)oxy)cyclohexyl cyclohexanecarboxylate 2-**28**



2-**27** 2-**28**

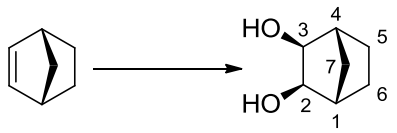
(*1S,2R*)-2-Hydroxycyclohexyl cyclohexanecarboxylate 2-**27** (614 mg, 2.71 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *di-ester* 2-**28** (354 mg, 35%) as colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 3027, 2936, 2857, 2734;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H: 7.32-7.27 (2 H, m, ArH), 7.23-7.17 (3 H, m, ArH), 5.09-5.05 (1 H, m, C(1')H), 5.04-4.99 (1 H, m, C(2')H), 2.69-2.63 (2 H, m, C(4'')H_2), 2.35-2.25 (3 H, m, C(1)H and C(2'')H_2), 1.95 (2 H, quin, J = 7.6 Hz, C(3'')H_2), 1.91-1.78 (4 H, m, 4 x C(CyH)H), 1.75-1.58 (6 H, m, 6 x C(CyH)H), 1.48-1.36 (4 H, m, 4 x C(CyH)H), 1.32-1.18 (4 H, m, 4 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 175.3, 172.7, 141.5, 128.5 (2 C), 128.4 (2 C), 126.0, 71.2, 70.2, 43.3, 35.1, 33.9, 29.1, 29.0, 28.0, 27.9, 26.6, 25.8 (2 C), 25.4, 22.0, 21.4 ; **MS** (ESI^+) ***m/z*** 395 ($M + Na^+$, 80%); **HRMS** (ESI^+) Calcd. for $C_{23}H_{32}NaO_4$ $[M+Na]^+$: 395.2193. Found: 395.2198 (1.3 ppm).



(*1R,2S*)-2-((4-phenylbutanoyl)oxy)Cyclohexyl cyclohexanecarboxylate 2-**28** (100 mg, 269 µmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 99:1 Petrol-Et_2O) to furnish an inseparable mixture (1:1) of the *crossed-acyloins* 2-**7** and 2-**8**, and the *acyloins* 2-**5** and 2-**6** (in combined yield of 42.2 mg, 60%) as a yellow oil (see Scheme 2-**22**, analytical data page **143**).

***(1R,2S,3R,4S)*-Bicyclo[2.2.1]heptane-2,3-diol 2-29**



2-29

MP 90 °C; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 3.69 (2 H, d, J = 1.6 Hz, C(2)H and C(3)H), 2.69 (2 H, br. s, 2 x OH), 2.15-2.13 (2 H, m, C(1)H and C(4)H), 1.79-1.74 (1 H, m, C(7)H), 1.50-1.44 (2 H, m, C(5)H and C(6)H), 1.13-1.03 (3 H, m, C(5)H – C(7)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 74.9 (2 C), 43.1, 31.6 (2 C), 24.5 (2 C). *Spectroscopic properties of this compound were consistent with the data reported in the literature.*[111]

Procedure A:

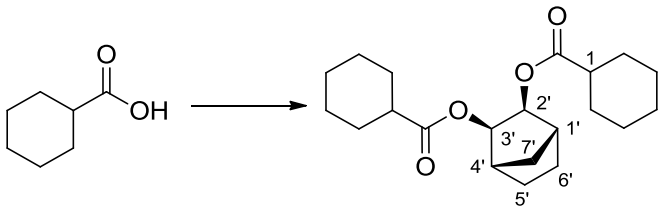
To a solution of (*1R,4S*)-bicyclo[2.2.1]hept-2-ene (10.0 g, 0.11 mol), trimethylamine *N*- oxide dihydrate (TMO) (15.0 g, 0.14 mmol) and pyridine (5 mL) in H_2O/*tert*-butanol (*t*-BuOH) (1:1, 100 mL) was added OsO_4 (60.0 mg, 5.05 mmol). The reaction mixture was stirred in 24 hours at reflux under an atmosphere of argon and was quenched with a saturated aqueous solution of $Na_2S_2O_5$ (10 mL). The *t*-butanol was removed *in vacuo* and the aqueous solution was diluted with brine and extracted with Et_2O (4 x 50 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by re-crystallisation from hot toluene (PhMe) to furnish the *diol* 2-**29** (10.2 g, 75%) as a white crystalline solid.

Procedure B:

To a solution of (*1R,4S*)-bicyclo[2.2.1]hept-2-ene (5.00 g, 53.1 mmol) in H_2O/*t*-BuOH (1:1, 200 mL) at 0°C was added dropwise a solution of $KMnO_4$ (12.0 g, 76.0 mmol) and NaOH (2.61 g, 65.3 mmol) in H_2O (250 mL). The reaction mixture was stirred in 30 minutes and was

quenched with a saturated aqueous solution of $Na_2S_2O_5$ (20 mL) until the solution turned colourless. The mixture was filtered and the *t*-BuOH was removed from the filtrate *in vacuo*. The solution was extracted with EtOAc (4 × 300 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by re-crystallisation from hot toluene (PhMe) to furnish the *diol* 2-**29** (4.97 g, 73 %) as a white crystalline solid.

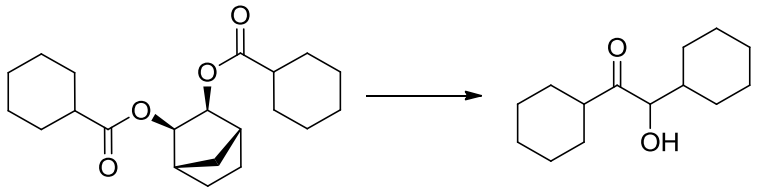
***(1S,2R,3S,4S)*-Bicyclo[2.2.1]heptane-2,3-diyl dicyclohexanecarboxylate 2-30**



2-30

To a solution of diol 2-**29** (1.00 g, 7.81 mmol), pyridine (2.52 mL, 31.2 mmol) and DMAP (190 mg, 1.5 mmol) in CH_2Cl_2 (10 mL) was added a solution of cyclohexanecarbonyl chloride (4.2 mL, 26.3 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred overnight at room temperature and was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with 1M HCl (10 mL) and dried over $MgSO_4$, filtered and concentration *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 99:1, Petrol-Et_2O) to furnish the di-ester 2-**30** (2.29 g, 84%) as a colourless solid crystalline. **MP** 87 °C; **R_f** (9:1 Petrol- EtOAc) 0.6; **IR** υ_{max} (KBr disc)/cm^{-1} 2929, 2856, 1741, 1451, 1381, 1313, 1251, 1163, 1131, 1043; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 4.68 (2 H, s, C(2')H), 2.28-2.20 (4 H, m, C(1')H, C(4')H and 2 x C(1)H), 1.91-1.74 (7 H, m, C(7')H and 6 x C(CyH)H), 1.65-1.64 (2 H, m, 2 x C(CyH)H), 1.54-1.51 (2 H, m, C(5')H and C(6')H),

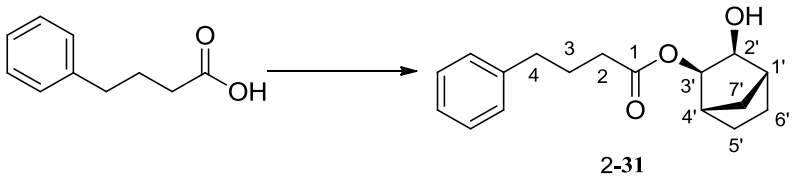
1.46-1.37 (4 H, m, 4 x C(CyH)H), 1.31-1.17 (11 H, m, 8 x C(CyH)H, C(5')H – C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 175.1, 76.3, 43.2, 41.2, 33.5, 29.1, 28.9, 25.8, 25.5, 25.4, 24.3; **Ms** (ESI^+) ***m/z*** 371 ($M + Na^+$,80 %); **HRMS** (ESI^+) Calcd. for $C_{21}H_{32}NaO_4$ $[M+Na]^+$: 371.2193. Found: 371.2187 (0.1 ppm).



2-30 **2-5**

(1*S*,2*R*,3*S*,4*S*)-Bicyclo[2.2.1]heptane-2,3-diyl dicyclohexanecarboxylate **2-30** (100 mg, 287 μmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-Et_2O) to furnish the *acyloin* **2-5** (51.5 mg, 80%) as a colourless oil (see Scheme 2-**24**, analytical data page **142**).

(±)-*(1S,2R,3S,4R)*-3-Hydroxybicyclo[2.2.1]heptan-2-yl 4-phenylbutanoate 2-**31**

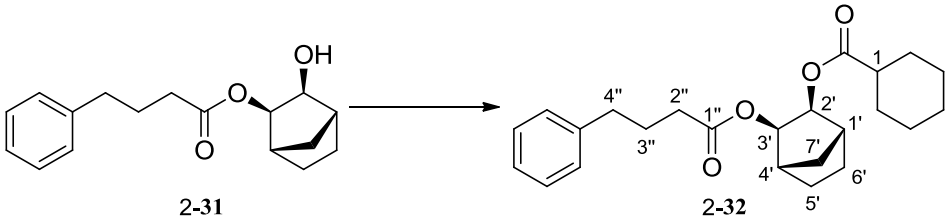


2-31

4-Phenylbutanoic acid (1.00 g, 609 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:02 Petrol-EtOAc) to furnish the *mono-ester* **2-31** (1.49 g, 89%) as a colourless oil. **R_f** (9:1 Petrol- EtOAc) 0.2; **IR** υ_{max} (KBr disc)/cm^{-1} 3468, 3062, 3026, 2962, 1730, 1603, 1497, 1147, 1084; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32-7.26 (2 H, m, ArH), 7.23-7.17 (3 H, m, ArH), 4.56 (1 H, dd, *J* = 5.9 Hz and 1.6 Hz, C(3')H), 3.87 (1 H, dd, *J* = 5.9 Hz and 1.5 Hz, C(2')H), 2.71 (2 H, t, *J* = 7.5 Hz,

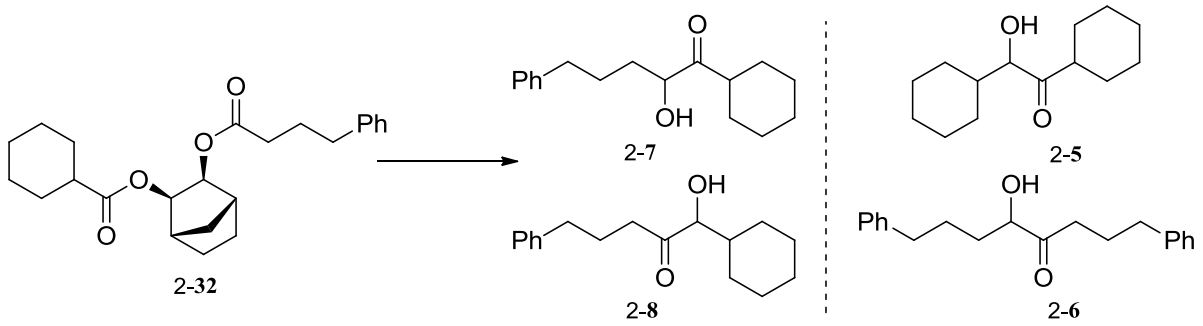
C(4)H$_2$), 2.41 (2 H, t, *J* = 7.5 Hz, C(2)H$_2$), 2.26-2.24 (2 H, m, C(1')H and C(4')H), 2.02-1.99 (3 H, m, C(3)H$_2$ and OH), 1.83-1.78 (1 H, m, 5 x C(7')H), 1.57-1.46 (2 H, m, C(5')H and C(6')H), 1.20-1.08 (3 H, m, C(5')H – C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 173.5, 141.3, 128.5 (2 C), 128.4 (2 C), 126.0, 78.2, 75.6, 43.3, 40.8, 35.1, 33.1, 33.6, 32.7, 26.6, 24.4; **Ms** (ESI$^+$) ***m/z*** 297 (M + Na$^+$, 80 %); **HRMS** (ESI$^+$) Calcd. for $C_{17}H_{22}NaO_4$ [M+Na]$^+$: 297.1467. Found: 297.1462 (–0.2 ppm).

(±)-(*1S,2R,3S,4R*)-3-(4-Phenylbutanoyloxy)bicyclo[2.2.1]heptan-2-yl cyclohexane carboxylate 2-32



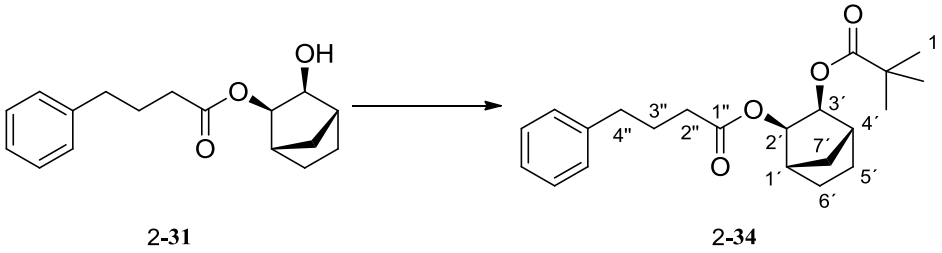
(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylate 2-**31** (980 mg, 4.11 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *di-ester* 2-**32** (1.47 g, 93%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.7 ; **IR** υ_{max} (thin film)/cm^{-1} 3027, 2936, 2857, 1734, 1497, 1452, 1313, 1247, 1170, 1045; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.31-7.27 (2 H, m, ArH), 7.22-7.17 (3 H, m, ArH), 4.73 (1 H, d, *J* = 5.2 Hz, C(3')H), 4.69 (1 H, d, *J* = 5.9 Hz, C(2')H), 2.65 (2 H, t, *J* = 7.6 Hz, C(4'')H$_2$), 2.36-2.18 (5 H, m, C(2'')H$_2$, C(1)H, C(1')H and C(4')H), 1.98-1.91 (2 H, m, C(3'')H$_2$), 1.87-1.82 (3 H, m, C(7')H and 2 x C(CyH)H), 1.73-1.70 (2 H, m, 2 x C(CyH)H), 1.63-1.51 (3 H, m, C(5)H, C(6)H and C(CyH)H), 1.43-1.32 (2 H, m, 2 x C(CyH)H), 1.29-1.16 (6 H, m, 3 x C(CyH)H, C(5')H C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 175.0, 172.5, 141.4, 128.5 (2 C), 128.4 (2 C), 126.0, 76.6, 76.2, 43.2, 41.1 (2 C), 35.2, 33.5 (2 signals), 29.0 (2 signals), 26.5, 25.7, 25.4 (2 C), 24.4, 24.3; **MS** (ESI$^+$)

m/z 407 (M + Na^+,60%); **HRMS** (ESI^+) Calcd. for $C_{24}H_{32}NaO_4$ $[M+Na]^+$: 407.2198. Found: 407.2193 (−1.2 ppm).



(*1S,2R,3S,4R*)-3-((4-phenylbutanoyl)oxy)Bicyclo[2.2.1]heptan-2-yl cyclohexane carboxylate 2-**32** (400 mg, 1.04 mmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 9:1 Petrol-Et_2O) to furnish an inseparable mixture (1:1) of the *crossed-acyloins* 2-**7** and 2-**8** (in combined yield of 249 mg, 92%) as a yellow oil (see Scheme 2-**26**, analytical data page **143**).

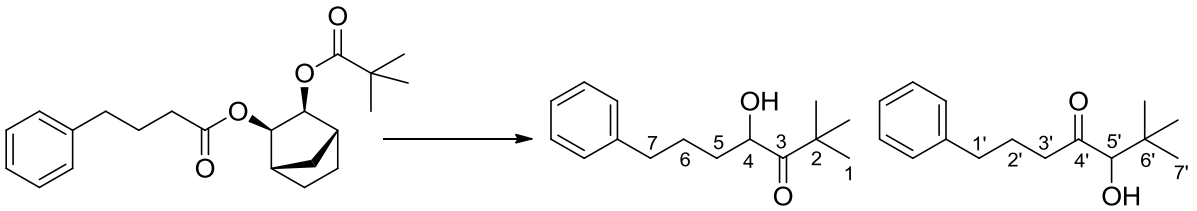
(±)-(*1S,2R,3S,4R*)-3-(Pivaloyloxy)bicyclo[2.2.1]Heptan-2-yl 4-phenyl-butanoate 2-**34**



(1R,2S,3R,4S)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylate2-31 (427 mg, 2.01 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the di-ester 2-**34** (533 mg, 74%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 3063, 3027, 2970, 2877, 1739, 1497, 1479, 14.55, 1418, 1396, 1367, 1284, 1157, 1074, 1043, 1008; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.29-7.26 (2 H, m, ArH), 7.20-7.16 (3 H, m, ArH), 4.72 (1 H, dd, *J* =

4.4 and 1.3 Hz, C(2')H), 4.67 (1 H, d, *J* = 4.8 and 1.3 Hz, C(3')H), 2.65 (2 H, t, *J* = 7.4 Hz, C(4'')H), 2.36-2.23 (4 H, m, C(2'')H_2, C(1')H and C(4')H)), 2.00-1.90 (2 H, m, C(3'')H_2), 1.85 (1 H, dt, *J* = 10.2and 2.0 Hz, C(7')H), 1.56-1.52 (2 H, m, C(5')H and C(6')H), 1.29-1.19 (3 H, m, C(5')H and C(7')H), 1.15 (9 H, s, 3 x C(1)H_3); **^{13}C-NMR** (100 MHz, CDCl3): δ_C: 177.3, 172.4, 141.3, 128.5 (2 C), 128.4, 128.3, 126.0, 76.6, 76.4, 41.2 (2 signals), 38.6, 35.1, 33.5, 33.4, 27.2, 26.4 (2 C), 24.4, 24.2, 24.0; **MS** (ESI^+) m/z 381 (M + Na+, 60%); **HRMS** (ESI^+) Calcd. for $C_{22}H_{30}NaO_4$ $[M+Na]^+$: 381.2042. Found: 381.2037 (–1.3ppm).

(±)-4-Hydroxy-2,2-dimethyl-7-phenylheptan-3-one 2-**35** **& 5-hydroxy-6,6-dimethyl-1-phenylheptan-4-one** 2-**36**

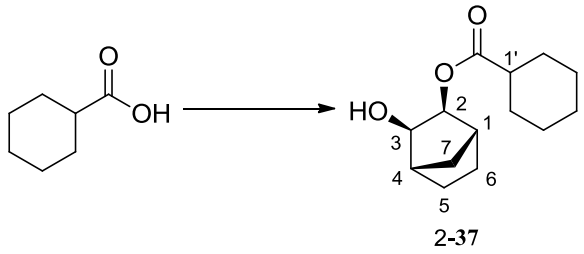


2-34 **2-35** **2-36**

(*1S,2R,3S,4R*)-3-(pivaloyloxy)bicyclo[2.2.1]Heptan-2-yl 4-phenylbutanoate 2-**34** (106 mg, 295 μmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish an inseparable mixture (1:1) of the *crossed-acyloins* 2-**35** and 2-**36** (in combined yield of 67 mg, 97%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 3475, 3063, 3027, 2956, 1703, 1604, 1497, 1479, 1454, 1397, 1367, 1260, 1052, 1017; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.34-7.26 (2 H, m, Ar<u>H</u>), 7.24-7.15 (3 H, m, Ar<u>H</u>), 4.52 (1.0 H, d, *J* = 6.9 Hz, C(4)<u>H</u>), 3.84 (0.7 H, s C(5')<u>H</u>), 3.20 (1 H, br. s, O<u>H</u>), 2.75-2.44 (4 H, m, C(7)<u>H_2</u>, C(1')<u>H_2</u>, C(3')<u>H_2</u> and C(5)<u>H_2</u>), 2.05-1.91 (1 H, m, C(6)<u>H_2</u>), 1.86- 1.72 (1 H, m, C(2')<u>H_2</u>), 1.17 (3.6 H, s, 3 x C(1)<u>H_2</u>), 0.96 (5.4 H, s, 3 x C(7')<u>H_3</u>); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 217.9, 213.3, 141.8, 141.3, 128.9 (4 Signals),

128.8 (2 C), 126.5, 126.3, 81.2, 75.2, 46.4, 41.8, 37.7, 35.9, 35.5, 33.4, 30.6, 27.8, 27.1, 26.8, 26.4, 26.3, 26.1, 25.6 (3 C); **MS** (ESI^+) ***m/z*** 257 ($M + Na^+$, 100%); **HRMS** (ESI^+) Calcd. for $C_{15}H_{22}NaO_2$ $[M+Na]^+$: 257.1517. Found: 257.1512 (–1.9 ppm).

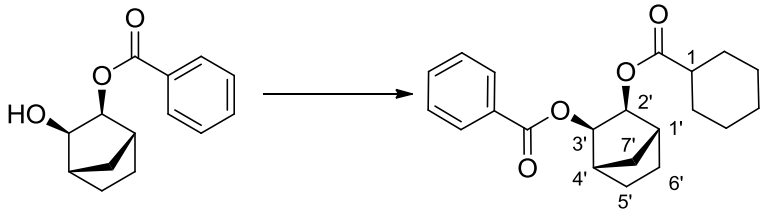
(±)-(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylate 2-**37**



2-**37**

Cyclohexanecarboxylic acid (2.28 g, 17.8 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 9:1 Petrol-EtOAc) to furnish the *mono-ester* 2-**37** (3.85 g, 91%) as a colourless crystalline solid. **MP** 45 °C; **R_f** (3:1 Petrol-Et_2O) 0.2 ; **IR** υ_{max} (KBr)/cm^{-1} 3484, 2933, 2855, 1731, 1450, 1382, 1316, 1249, 1174, 1147, 1.189, 1048; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:4.55 (1 H, dd, *J* = 5.9 and 1.2 Hz, C(2)H), 3.85 (1 H, dt, *J* = 6.0 and 0.8 Hz, C(3)H), 2.36 (1 H, tt, *J* = 11.3 and 3.7 Hz, C(1')H), 2.21 (2 H, appr. t, *J* = 4.0 Hz, C(1)H and C(4)H), 1.92 (2 H, dd, *J* = 13.4 Hz and 2.8 Hz, 2 x C(CyH)H), 1.84-1.71 (3 H, m, C(7)H and 2 x C(CyH)H), 1.69-1.62 (1 H, m, C(CyH)H), 1.57-1.39 (4 H, m, C(5)H, C(6)H and 2 x C(CyH)H), 1.35-1.21 (3 H, m, 3 x C(CyH)H), 1.19-1.07 (3 H, m, C(5)H̃ C(7)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 176.1, 77.8, 75.7, 43.3, 43.2, 40.8, 32.7, 29.2, 29.1, 25.7, 25.4 (2 C), 24.4 (2 signals); **MS** (ESI^+) ***m/z*** 261 ($M + Na^+$,90%); **HRMS** (ESI^+) Found [$M + Na^+$]; **HRMS** (ESI^+) Calcd. for $C_{14}H_{22}NaO_4$ $[M+Na]^+$: 261.1467. Found: 261.1461 (–2.3 ppm).

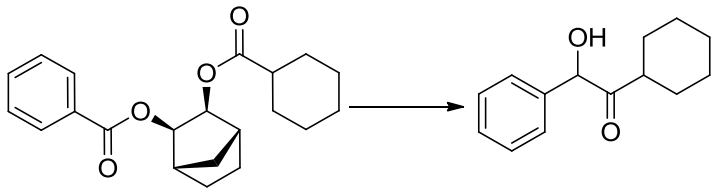
(±)-(*1R,2S,3R,4S*)-2-(Cyclohexanecarbonyloxy)bicyclo[2.2.1]heptan-3-yl benzoate 2-**38**



2-**37** 2-**38**

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl benzoater 2-**37** (1.00 g, 4.20 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 9:1, Petrol-Et_2O) to furnish the *di-ester* 2-**38** (1.29 g, 90%) as a white solid. **MP** 68 °C; **R_f** (3:1 Petrol-Et_2O) 0.6; **IR** υ_{max} (KBr)/cm^{-1} 2933, 2835, 1727; **^{1}H-NMR** (400 MHz, $CDCl_3$) : δ_H: 8.04 (2 H, d, *J* = 7.3 Hz, ArH), 7.56 (1 H, t, *J* = 7.4 Hz, ArH), 7.43 (2 H, t, *J* = 7.7 Hz, ArH), 5.00 (1 H, d, *J* = 5.9 Hz, C(3')H), 4.84 (1 H, d, *J* = 5.9 Hz, C(2')H), 2.43 (1 H, br. s, C(1')H), 2.30 (1 H, br. s, C(4')H), 2.08 (1 H, tt, *J* = 11.2 and 3.6 Hz, C(1)H), 2.00 (1 H, d, *J* = 10.2 Hz, C(7')H), 1.74 (1 H, dd, *J* = 12.8 and 1.5 Hz , C(CyH)H), 1.66-1.45 (6 H, m, C(5')H, C(6')H and 4 x C(CyH)H), 1.34-0.95 (8 H, m, C(5')H C(7')H and 5 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.9, 165.7, 132.9, 130.3, 129.6 (2 C), 128.2 (2 C), 77.1, 76.2, 43.2, 41.3, 41.1, 33.7, 28.9, 28.7, 25.6, 25.3, 25.2, 24.4, 24.3; **MS** (ESI^+) ***m/z*** 265 ($M + Na^+$,40%); **HRMS** (ESI^+) Found [$M + Na^+$]; **HRMS** (ESI^+) Calcd. for $C_{21}H_{26}NaO_4$ $[M+Na]^+$: 365.1729. Found: 365.1726 (–0.8 ppm).

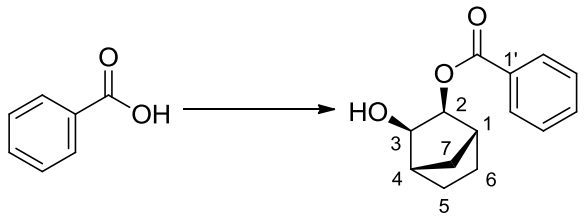
(±) -2-Cyclohexyl-1-hydroxy-1-phenylethanone 2-**39a**



2-38 **2-39a**

(*1S,2R,3S,4R*)-3-((cyclohexanecarbonyl)oxy)Bicyclo[2.2.1]heptan-2-yl benzoate 2-**38** (100 mg, 0.28 mmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *crossed-acyloin* 2-**39a** (63.2 mg, 77%) as a white solid. **MP** 66 ºC; **^{1}H-NMR** (400 MHz, $CDCl_3$) : δ_H: 7.46-7.23 (5 H, m, ArH), 5.20 (1 H, d, *J* = 3.8 Hz, C(1)H), 4.41 (1 H, d, *J* = 4.3 Hz, OH), 2.44 (1 H, tt, *J* = 11.3 and 3.3 Hz, C(3)H), 1.98-1.51 (4 H, m, 4 x C(CyH)H), 1.45-0.93 (6 H, m, 6 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 212.4, 137.9, 128.9 (2 C), 128.7 (2 C), 127.6, 78.3, 46.0, 29.6, 27.9, 25.6, 25.5, 25.0;. *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[112]

(±)-*(1R,2S,3R,4S)*-7-Hydroxybicyclo[2.2.1]heptan-2-yl benzoate 2-**42**

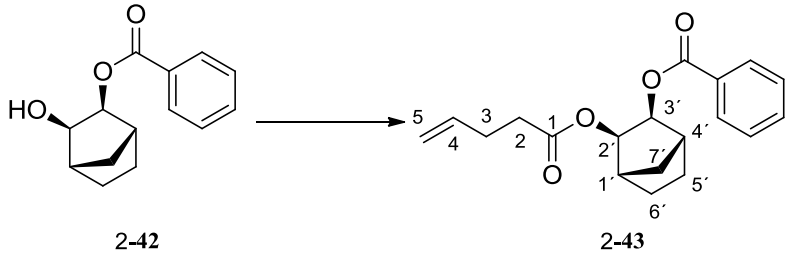


2-42

Benzoyl chloride (3.07 g, 21.9mmol) were subjected to General Procedure **D**. The crude product was purified by FCC (SiO_2, 9:1, Petrol-EtOAc) to furnish the mono-ester 2-**42** as a white solid (6.95 g, 91%). **MP** 64 °C; **IR** υ_{max} (KBr disc)/cm^{-1} 3489, 2963, 2876, 1717; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 8.02 (2H, d, *J* = 7.8 Hz, ArH), 7.58-7.48 (1H, m, C(6)H),

7.46-7.34 (2H, m, ArH), 4.75 (1H, d, *J* = 5.6 Hz, C(2')H), 3.93 (1H, d, *J* = 5.6 Hz, C(3')H), 2.51 (1H, br. s, OH), 2.37 (1H, s, C(1')H), 2.23 (1H, s, C(4')H), 1.97 (1H, d, *J* = 10.4 Hz, C(7')H), 1.62-1.42 (2H, m, C(5')H and C(6')H), 1.24-1.08 (3H, m, C(5')H-C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 166.7, 133.0, 130.0, 129.6, 128.4, 78.9, 75.8, 43.3, 40.8 , 33.0, 24.5 (2 signals); **HRMS** (ESI^+) Calcd. for $C_{14}H_{16}NaO_3$ $[M+Na]^+$: 255.0992. Found: 255.0988 (–0.6 ppm).

(±)-*(1R,2S,3R,4S)*-3-(Pent-4-enoyloxy)bicyclo[2.2.1]heptan-2-yl benzoate 2-**43**

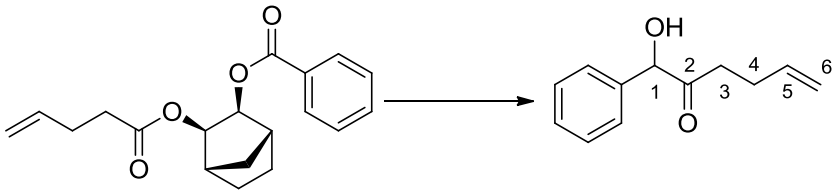


2-**42** 2-**43**

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl benzoate 2-**42** (200 mg, 0.86 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *di-ester* 2-**43** (248 mg, 92%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 3073, 2971, 2878, 1722, 1642, 1602, 1585, 1491, 1451, 1350, 1275, 1176, 1115, 1071, 1029, 1000; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 8.02 (2 H, dd, *J* = 7.0 and 1.4 Hz, ArH), 7.56 (1 H, tt, *J* = 7.5 and 1.4 Hz, ArH), 7.44 (2 H, t, *J* = 7.8 Hz, ArH), 5.70-5.59 (1 H, m, C(4)H), 5.14 (1 H, dd, *J* = 4.7 and 1.2 Hz, C(5)H), 4.92-4.86 (3 H, m, C(5)H, C(2')H and C(3')H), 2.43 (1 H, br. s, C(1')H), 2.32 (1 H, br. s, C(4')H), 2.32-2.12 (4 H, m, C(2)H_2, C(3)H_2), 2.01 (1 H, dt, *J* = 10.3 and 2.0 Hz, C(7')H), 1.66-1.56 (2 H, m, C(5')H and C(6')H), 1.34-1.26 (3 H, m, C(5')H C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 172.0, 165.6, 136.6, 132.9, 130.3, 129.5(2C), 128.3 (2 C),

115.3, 77.0, 76.6, 41.2, 41.1, 33.7, 33.4, 28.6, 24.4, 24.2; **MS** (ESI^+) ***m/z*** 337 ($M + Na^+$, 20%); **HRMS** (ESI^+) Calcd. for $C_{19}H_{22}NaO_4$ $[M+Na]^+$: 337.1416. Found: 337.1409 (–2.1 ppm).

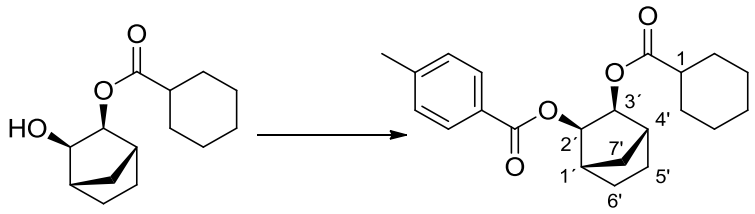
(±)-1-Hydroxy-1-phenylhex-5-en-2-one 2-**44**



2-**43** 2-**44**

(*1R,2S,3R,4S*)-3-(pent-4-enoyloxy)Bicyclo[2.2.1]heptan-2-yl benzoate 2-**43** (484 mg, 1.54 mmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *crossed-acyloin* 2-**44** (237 mg, 81%) as a white solid. **MP** 97.2 °C; $\mathbf{R_f}$ (3:1 Petrol-Et_2O) 0.5; **IR** υ_{max} (KBr)/cm^{-1} 3462, 3065, 3031, 2920, 1716, 1641, 1599, 1494, 1453, 1360, 1277, 1192, 1059, 1001; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.41-7.28 (5 H, m, ArH), 5.71-5.60 (1 H, m, C(5)H), 5.08 (1 H, d, J = 3.9 Hz, C(1)H), 4.94-4.92 (1 H, m, C(6)H), 4.91-4.89 (1 H, m, C(6)H), 4.40 (1 H, d, J = 4.2 Hz, OH), 2.52-2.35 (2 H, m, C(3)H_2), 2.34-2.16 (2 H, m, C(4)H_2); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C : 208.8, 138.0, 136.3, 129.0 (2 C), 128.7, 127.5 (2 C), 115.6, 79.8, 37.0, 27.5; **MS** (ESI^+) ***m/z*** 213 ($M + Na^+$, 60%); **HRMS** (ESI^+) Calcd. for $C_{12}H_{14}NaO_2$ $[M+Na]^+$: 213.0891. Found: 213.0886 (–2.3 ppm).

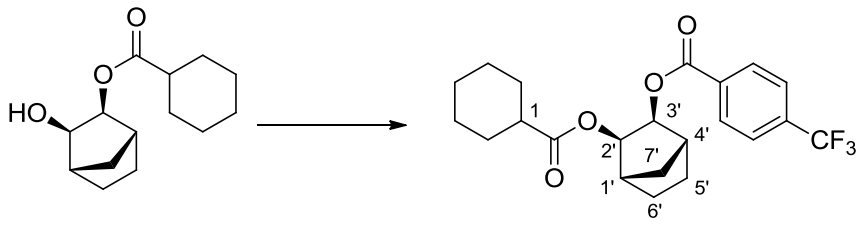
(±)-(*1S,2R,3S,4R*)-3-((Cyclohexanecarbonyl)oxy)bicyclo[2.2.1]heptan-2-yl *p*-methyl benzoate 2-**45**



2-37 2-45

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylate 2-**37** (500 mg, 2.10 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 95:5 Petrol-Et_2O) to furnish the *di-ester* 2-**45** (665 mg, 89%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 2932, 2856, 1733, 1612, 1452, 1408, 1379, 1274, 1171, 1146, 1108, 1071, 1047; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.90 (2 H, d, *J* = 8.1 Hz, ArH), 7.21 (2 H, d, *J* = 8.1 Hz, ArH), 4.96 (1 H, d, *J* = 6.1 Hz, C(2')H), 4.82 (1 H, d, *J* = 6.1 Hz, C(3')H), 2.40 (4 H, s, C(1')H and CH_3), 2.28 (1 H, br. s, C(4')H), 2.07 (1 H, tt, *J* = 11.2 Hz and 3.6 Hz, C(1)H), 1.99 (1 H, d, *J* = 10.1 Hz, C(7')H), 1.78-1.70 (1 H, m, C(CyH)H), 1.63-1.51 (5 H, m, C(5')H, C(6')H and 3 x C(CyH)H), 1.30-1.18 (6 H, m, 6 x C(CyH)H), 1.12-0.97 (3 H, m, C(5')H C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 175.0, 165.8, 143.5, 129.6, 128.9, 127.6, 77.0, 76.2, 43.2, 41.3, 41.1, 33.7, 28.9, 28.7, 25.6 (2 C), 25.4 (2 C), 25.2, 24.4, 24.3, 21.7; **MS** (ESI^+) ***m/z*** 379 ($M + Na^+$, 100%); **HRMS** (ESI^+) Calcd. for $C_{22}H_{28}NaO_4$ $[M+Na]^+$: 379.1885. Found: 379.1882 (–0.8 ppm).

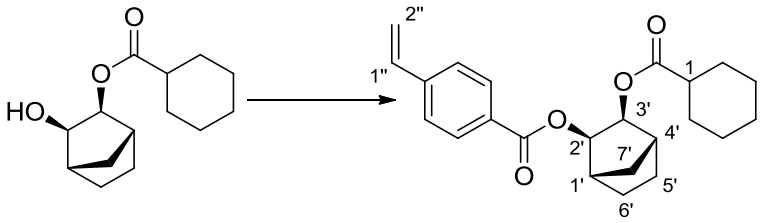
(±)-(*1S,2R,3S,4R*)-2-(Cyclohexanecarbonyloxy)bicyclo[2.2.1]heptan-3-yl *p*-(trifluoro-methyl) benzoate 2-46



2-37 2-46

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylate 2-**37** (477 mg, 2.00 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *di-ester* 2-**46** (739 mg, 90%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.6.; **IR** υ_{max} (thin film)/cm^{-1} 2935, 2820, 1732, 1644; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 8.15 (2 H, d, *J* = 8.0 Hz, ArH), 7.71 (2 H, d, *J* = 7.5 Hz, ArH), 5.02 (1 H, d, *J* = 6.1 Hz, C(2')H), 5.02 (1 H, d, *J*=5.9 Hz, C(3')H), 2.45 (1 H, s, C(1')H), 2.32 (1 H, s, C(4')H), 2.10-2.03 (1 H, m, C(1)H), 1.99 (1 H, dd, *J* = 10.4 Hz and 1.5 Hz, C(7')H), 1.74-1.71 (1 H, m, C(CyH)H), 1.66-1.52 (6 H, m, C(5')H, C(6')H and 4 x C(CyH)H), 1.33-1.17 (5 H, m, 5 x C(CyH)H), 1.14-1.00 (3 H, m, C(5')H-C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.9, 164.5, 135.1, 133.6, 130.0 (2 C), 125.3 (2 signals), 124.2, 77.8, 76.2, 43.2, 41.3, 41.1, 33.8, 28.9, 28.8, 25.6, 25.3, 25.2, 24.4, 24.3; **MS** (ESI^+) ***m/z*** 433 ($M + Na^+$,30%); **HRMS** (ESI^+) Calcd. for $C_{22}H_{25}NaO_4F_3$ $[M+Na]^+$: 433.1603. Found: 433.1601 (0.5 ppm).

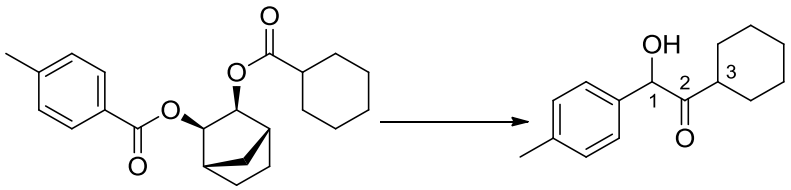
(±)-*(1S,2R,3S,4R)*-3-((Cyclohexanecarbonyl)oxy)bicyclo[2.2.1]heptan-2-yl *p*-vinyl-benzoate 2-**47**



2-**37** 2-**46**

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylate 2-**37** (500 mg, 2.10 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 9:1 Petrol-EtOAc) to furnish the *di-ester* 2-**47** (711 mg, 92%) as a colourless oil. **R_f** (1:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 2930, 1718, 1608, 1451, 1404, 1177, 1146; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.97 (2H, d, *J* = 8.1 Hz, ArH), 7.44 (2H, d, *J* = 8.1 Hz, ArH), 6.74 (1H, dd, *J* = 17.7 Hz and 10.9 Hz, C(1'')H), 5.85 (1H, d, *J* = 17.7 Hz, C(2'')H), 5.37 (1H, d, *J* = 10.9 Hz, C(2'')H), 4.97 (1H, d, *J* = 5.8 Hz, C(2')H), 4.83 (1H, d, *J* = 5.8 Hz, C(3')H), 2.42 (1H, br. s, C(1')H), 2.29 (1H, br. s, C(4')H), 2.07 (1H, tt, *J* = 11.1 Hz and 3.5 Hz, C(1)H), 1.99 (1H, d, *J* = 10.4 Hz, C(7')H), 1.73 (1H, d, *J* = 10.9 Hz, C(CyH)H), 1.66-1.44 (6H, m, C(5')H, C(6')H and 4 x C(CyH)H), 1.32-1.17 (5H, m, 5 x C(CyH)H), 1.13-0.96 (3H, m, C(5')H C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.9, 165.5, 141.9, 136.0, 129.9, 129.5 (2C), 126.0, 116.4, 77.1, 76.2, 43.1, 41.3, 41.1, 33.7, 29.9, 28.7, 25.6, 25.3, 25.2, 24.4, 24.3; **MS** (ESI^+) ***m/z*** 759 ($2M + Na^+$, 100%); **HRMS** (ESI^+) Calcd. for $C_{23}H_{28}NaO_4$ $[M+Na]^+$: 391.1885. Found: 391.1880 (−1.3 ppm).

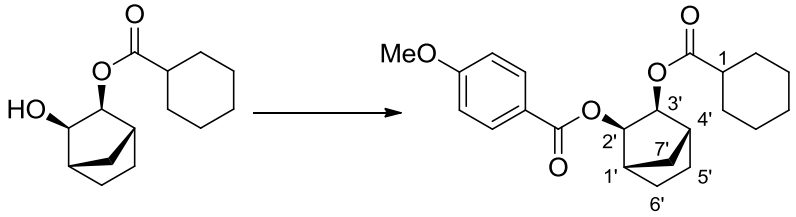
(±)-2-Cyclohexyl-1-hydroxy-1-(*p*-tolyl)ethanone 2-**48**



2-45 **2-48**

(*1S,2R,3S,4R*)-3-((cyclohexanecarbonyl)oxy)Bicyclo[2.2.1]heptan-2-yl 4-methyl-benzoate 2-**45** (96.0 mg, 0.27 mmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *crossed-acyloin* 2-**48** (51.2 mg, 81%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O)0.6; **IR** υ_{max} (thin film)/cm^{-1} 3457, 3031, 2932, 2832, 2856, 1707, 1602, 1493, 1451, 1369, 1316, 1192, 1147, 1116, 1055; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.18 (4 H, s, ArH), 5.16 (1 H, s, C(1)H), 4.35 (1 H, br. s, OH), 2.43 (1 H, tt, *J* = 11.3 and 3.5 Hz, C(3)H), 2.36 (3 H, s, Me), 1.87 (1 H, d, *J*= 13.1 Hz, C(CyH)H), 1.77 (1 H, d, *J* = 11.1 Hz, C(CyH)H), 1.67-1.57 (2 H, m, 2 x C(CyH)H), 1.43-1.30 (2 H, m, 2 x C(CyH)H), 1.29- 1.11 (3 H, m, 3 x C(CyH)H), 1.09-0.96 (1 H, m, C(CyH)H; **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C:212.7, 138.5, 134.9 (2 C), 129.6 (2 C), 127.6, 78.1, 46.0, 29.7, 27.9, 25.7, 25.6, 25.0, 21.2. **MS** (ESI^+) ***m/z*** 255 ($M + Na^+$, 65%); **HRMS** (ESI^+) Calcd. for $C_{15}H_{20}NaO_2$ $[M+Na]^+$: 255.1361. Found: 255.1356 (–2.0 ppm).

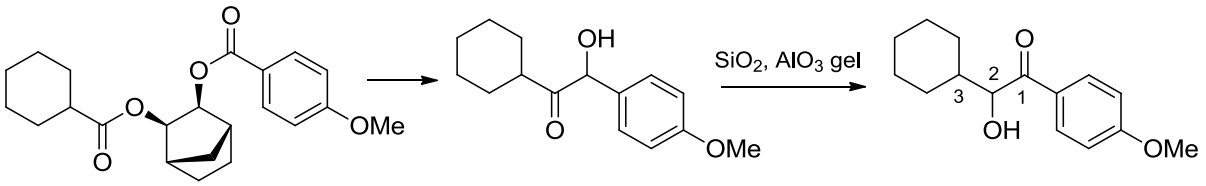
(±)-(*1R,2S,3R,4S*)-3-(Cyclohexanecarbonyloxy)bicyclo[2.2.1]heptan-2-yl *para*-methoxy benzoate 2-**49**



2-37 **2-49**

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylate 2-**37** (506 mg, 2.12 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *di-ester* 2-**49** (569 mg, 72%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.6.; **IR** υ_{max} (thin film)/cm^{-1} 2934, 2855, 1734, 1607; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 8.00-7.96 (2 H, m, ArH) 6.92-6.89 (2 H, m, ArH), 4.96 (1 H, apr. ddd, *J* = 3.7 Hz, 2.2 Hz and 2.0 Hz, C(2'), 4.82 (1 H, apr. ddd, *J* =3.7 Hz, 2.2 Hz and 2.0 Hz, C(3')H), 3.03 (3 H, d, *J* = 4.2 Hz, OMe), 2.40 (1 H, br. s, C(1')H), 2.28 (1 H, br. s, C(4')H), 2.08 (1 H, tt, *J* = 11.3 Hz and 3.6 Hz, C(1)H), 2.00-1.97 (1 H, m, C(7')H), 1.76-1.73 (1 H, m, C(CyH)H), 1.63-1.51 (6 H, m, C(5')H, C(6')H and 4 x C(CyH)H), 1.29-1.02 (8 H, m, C(5')H C(7')H and 5 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 175.0, 165.5, 163.3, 131.6 (2 C), 122.8 (2 C), 113.5, 76.9, 76.2, 55.4, 43.2, 41.3, 41.1, 33.8, 28.9, 28.7, 25.6, 25.4, 25.2, 24.4, 24.3; **MS** (ESI^+) ***m/z*** 395 ($M + H^+$, 60%); **HRMS** (ESI^+) Calcd. for $C_{22}H_{28}NaO_5$ $[M+Na]^+$: 395.1834. Found: 395.1829 (–1.3 ppm).

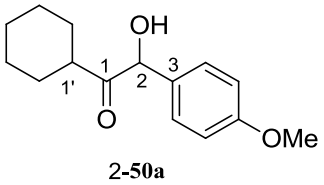
(±)-2-Cyclohexyl-2-hydroxy-1-(*para*-methoxyphenyl)ethanone 2-50b



2-49 2-50a 2-50b

(*1S,2R,3S,4R*)-3-((cyclohexanecarbonyl)oxy)Bicyclo[2.2.1]heptan-2-yl4-methoxy- benzoate 2-**49** (100 mg, 267 µmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *crossed-acyloin* 2-**50b** (55.0 mg, 83%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.4; **IR** υ_{max} (thin film)/cm^{-1} 3455, 2932, 2855, 1709; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.91 (2 H, d, J = 8.9 Hz, ArH), 6.98 (2 H, d, J = 8.9 Hz, ArH), 4.89 (1H, s, C(2)H), 3.90 (3H, s, OMe), 3.66 (1H, d, J = 4.7 Hz, OH), , 1.82-1.71 (3 H, m, C(3)H, 2 x C(CyH)H), 1.67-1.49 (3 H, m, 3 x C(CyH)H), 1.37-1.19 (5 H, m, 5 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 200.3, 164.1, 130.9, 126.9 (2 C), 114.1 (2 C), 76.8, 55.6, 43.0, 30.3, 26.6, 25.9 (2 Signals), 24.8; **MS** (ESI^+) ***m/z*** 271 ($M + Na^+$, 100%); **HRMS** (ESI^+) Calcd. for $C_{15}H_{20}NaO_3$ $[M+Na]^+$: 271.1310. Found: 271.1305 (−1.8 ppm).

1-Cyclohexyl-2-hydroxy-2-(4-methoxyphenyl)ethanone 2-50a (the crude product)



2-50a

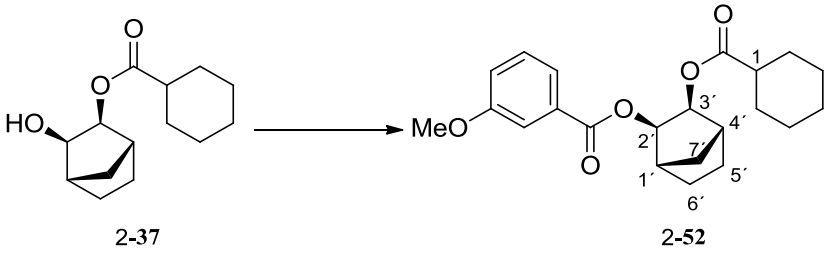
^{1}H-NMR (400 MHz, $CDCl_3$): δ_H: 7.21 (2 H, d, J = 8.7 Hz, ArH), 6.91 (2 H, d, J = 8.7 Hz, ArH), 5.15 (1 H, s, C(3)H), 3.82 (3 H, s, OMe), 3.86 (1 H, be. s, OH), 2.41 (2 H, tt, J = 11.4 Hz and 3.5 Hz, C(1')H), 1.89-1.75 (2 H, m, 2 x C(CyH)H), 1.67-1.58 (3 H, m, 3 x C(CyH)H),

1.39-1.17 (5 H, m, 5 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 210.1, 159.4, 131.4, 130.1 (2 C), 114.4 (2 C), 77.7, 55.3, 46.0, 29.6, 27.9, 25.7, 25.5, 25.0.

(±)-1-Cyclohexyl-2-(*para*-methoxyphenyl)-2-oxoethyl pivalate 2-51

To a solution of crude 1-cyclohexyl-2-hydroxy-2-(4-methoxyphenyl)ethanone 2-**50a**, Hünig´s base (0.40 mL, 2.29 mmol) and DMAP (5.00 mg, 40.9 μmol) in CH_2Cl_2 (5 mL) was added pivaloyl chloride (0.30 mL, 2.77 mmol) under an atmosphere of argon at 0 °C. The reaction mixture was stirred for 2 hours at room temperature and was concentrated *in vacuo* .The residue was re-dissolved in EtOAc/H_2O (30 mL). The aqueous layer was extracted with EtOAc (3 x 30 mL) and the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 98:2 Petrol-EtOAc) to furnish the *ester* 2-**51** (59.1 mg, 33%) as a yellow oil. **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 2932, 2856, 1719; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.33-7.27 (2 H, m, ArH), 6.94-6.90 (2 H, m, ArH), 5.99 (1 H, s, C(2)H), 3.82 (3 H, s, OMe), 2.48-2.43 (1 H, m, C(1')H), 2.02-1.76 (2 H, m, C(CyH)H), 1.67-1.60 (3 H, m, 3 x C(CyH)H), 1.43-1.16 (14 H, m, 3 x C(*t*-Bu)H_3, 5 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 207.2, 178.0, 160.2, 129.8 (2 C), 125.8 (2 C), 114.3, 78.9, 55.3, 47.2, 38.7, 29.5, 27.8, 27.3, 27.1 (2 C), 25.8, 25.7, 25.2; **MS** (ESI$^+$) ***m/z*** 355 (M + Na$^+$, 100%); **HRMS** (ESI$^+$) Calcd. for $C_{20}H_{28}NaO_4$ $[M+Na]^+$: 355.1885. Found: 355.1880 (–1.4 ppm).

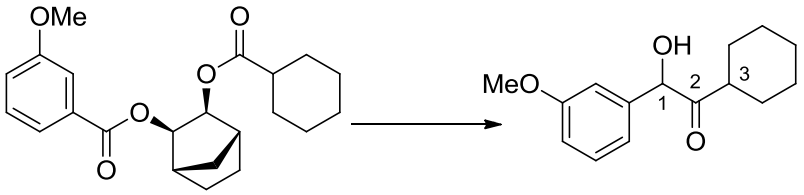
(±)-(*1S,2R,3S,4R*)-3-((Cyclohexanecarbonyl)oxy)bicyclo[2.2.1]heptan-2-yl *m*-methoxy benzoate 2-52



2-37 2-52

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylate 2-**37** (500 mg, 2.10 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 95:5 Petrol-Et_2O) to furnish the *di-ester* 2-**52** (727 mg, 93%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.5; **IR** υ_{max} (thin film)/cm^{-1} 2934, 2856, 1734, 1587, 1488, 1453, 1364, 1279, 1104, 1076, 1047; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.63 (1 H, d, *J* = 7.6 Hz, ArH), 7.55 (1 H, d, *J* = 2.2 Hz, ArH), 7.34 (1 H, t, *J* = 7.9 Hz, ArH), 7.10 (1 H, dd, *J* = 8.1 and 2.2 Hz, ArH), 4.99 (1 H, dd, *J* = 5.9 and 0.7 Hz, C(2')H), 4.83 (1 H, dd, *J* = 5.9 and 0.9 Hz, C(3')H), 3.85 (3 H, s, OMe), 2.43 (1 H, br. s, C(1')H), 2.30 (1 H, br. s, C(4')H), 2.10 (1 H, tt, *J* = 11.2 and 3.6 Hz, C(1)H), 2.00 (1 H, d, *J* = 10.2 Hz, C(7')H), 1.80-1.72 (1 H, m, C(CyH)H), 1.68-1.48 (6 H, m, C(5')H, C(6')H and 4 x C(CyH)H), 1.33-1.19 (5 H, m, 5 x C(CyH)H), 1.18-0.98 (3 H, m, C(5')H C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.9, 165.6, 159.5, 131.7, 129.2, 122.0, 119.1, 114.3, 77.3, 76.2, 55.4, 43.2, 41.3, 41.1, 33.7, 28.9, 28.7, 25.6, 25.4, 25.2, 24.4, 24.3; **MS** (ESI^+) ***m/z*** 395 ($M + Na^+$, 80%); **HRMS** (ESI^+) Calcd. for $C_{22}H_{28}NaO_5$ $[M+Na]^+$: 395.1834. Found: 395.1829 (–1.2 ppm).

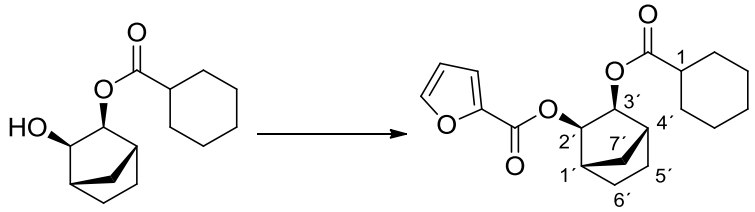
(±)-2-Cyclohexyl-1-hydroxy-1-(*m*-methoxyphenyl)ethanone 2-53



2-52 2-53

(*1S,2R,3S,4R*)-3-((cyclohexanecarbonyl)oxy)Bicyclo[2.2.1]heptan-2-yl 3-methoxy-benzoate 2-**52** (100 mg, 0.27 mmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *crossed-acyloin* 2-**53** (52.3 mg, 78%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.4; **IR** υ_{max} (thin film)/cm^{-1} 3490, 2934, 2856, 1734, 1587, 1488, 1453, 1364, 1279, 1104, 1078, 1047; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.29 (1 H, t, *J* = 7.9 Hz, ArH), 6.86-6.93 (2 H, m, ArH), 6.82 (1 H, s, ArH), 5.17 (1 H, s, C(1)H), 4.39 (1 H, br. s, OH), 3.81 (3 H, s, OMe), 2.46 (1 H, tt, *J* = 11.3 and 3.5 Hz, C(3)H), 1.88 (1 H, d, *J* = 12.6 Hz, C(CyH)H), 1.77 (1 H, d, *J* = 11.5 Hz, C(CyH)H), 1.69-1.58 (2 H, m, 2 x C(CyH)H), 1.42-0.98 (6 H, m, 6 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C:212.4, 160.0, 139.4, 130.0, 120.0, 114.3, 112.8, 78.2, 55.3, 45.9, 29.7, 27.9, 25.7, 25.5, 25.0; **MS** (ESI^+) ***m/z*** 271 ($M + Na^+$, 80%); **HRMS** (ESI^+) Calcd. for $C_{15}H_{20}NaO_3$ $[M+Na]^+$: 271.1310. Found: 271.1305 (–1.8 ppm).

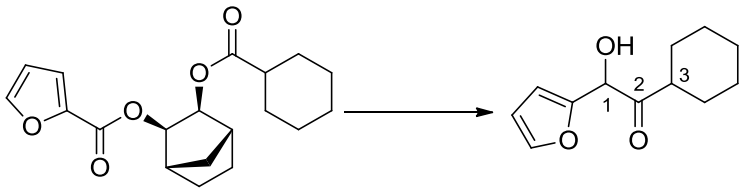
(±)-*(1S,2R,3S,4R)*-3-((Cyclohexanecarbonyl)oxy)bicyclo[2.2.1]heptan-2-yl furan-*o*-carboxylate 2-55



2-37 2-55

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylate 2-**37** (916 mg, 3.85 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *di-ester* 2-**55** (1.04 g, 81%) as a white solid. **MP** 66.4 °C; **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (KBr)/cm^{-1} 3123, 2936, 2854, 1726, 1573, 1474, 1452, 1400, 1308, 1183, 1123, 1066, 1044, 1016; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.56 (1 H, d, *J* = 0.6 Hz, ArH), 7.15 (1 H, d, *J* = 3.4 Hz, ArH), 6.50-6.49 (1 H, m, ArH), 4.95 (1 H, d, *J* = 5.8 Hz, C(2')H), 4.79 (1 H, d, *J* = 5.9 Hz, C(3')H), 2.40 (1 H, br. s, C(1')H), 2.27 (1 H, br. s, C(4')H), 2.13 (1 H, tt, *J* = 11.2 and 3.6 Hz, C(1)H), 1.95 (1 H, d, *J* =10.2 Hz, C(7')H), 1.78 (1 H, d, *J* =13.9 Hz, C(CyH)H), 1.70 (1 H, d, *J* = 13.2 Hz, C(CyH)H)), 1.63-1.52 (5 H, m, C(5')H, C(6')H and 3 x C(CyH)H), 1.31-1.23 (5 H, m, 5 x C(CyH)H), 1.20-1.04 (3 H, m, C(5')H C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C:174.9, 158.0, 146.1, 144.8, 117.8, 111.7, 77.3, 76.1, 43.2, 41.2, 41.0, 33.7, 28.8, 28.7, 25.7, 25.4, 24.3 (3 signals); **MS** (ESI^+) ***m/z*** 355 ($M + Na^+$, 60%); **HRMS** (ESI^+) Calcd. for $C_{19}H_{24}NaO_5$ $[M+Na]^+$: 355.1521. Found: 355.1513 (–2.3 ppm).

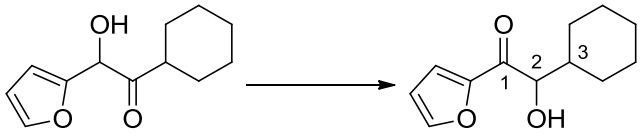
(±)-2-Cyclohexyl-1-(furan-*o*-yl)-1-hydroxyethanone 2-56a



2-55 **2-56a**

(*1S,2R,3S,4R*)-3-((cyclohexanecarbonyl)oxy)bicyclo[2.2.1]heptan-2-yl furan-2-carboxylate 2-**55** (300 mg, 0.90 mmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *crossed-acyloin* 2-**56a** (132 mg, 70%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.5; **IR** υ_{max} (thin film)/cm^{-1} 3427, 2956, 1737, 1497, 1454, 1146, 1081; **^{1}H-NMR** (400 MHz, C_6D_6): δ_H:7.07 (1 H, d, *J* = 0.7 Hz, ArH), 6.21 (1 H, d, *J* = 3.1 Hz, ArH), 6.08 (1 H, dd, *J* = 3.1 and 1.7 Hz, ArH), 5.20 (1 H, s, C(1)H), 4.43 (1H, br. s, OH), 2.45 (1 H, tt, *J* = 11.1 and 3.5 Hz, C(3)H), 1.65-1.40 (6 H, m, 6 x C(CyH)H), 1.26 (1 H, qd, *J* = 12.1 and 3.4 Hz, C(CyH)H), 1.07-0.90 (3 H, m, 3 x C(CyH)H); **^{13}C-NMR** (100 MHz, C_6D_6): δ_C: 210.0, 150.6, 143.1, 110.8, 109.5, 71.4, 46.3, 29.4, 27.5, 25.6, 25.5, 25.1. **MS** (ESI^+) ***m/z*** 231 ($M + Na^+$, 100%); **HRMS** (ESI^+) Calcd. for $C_{12}H_{16}NaO_2$ $[M+Na]^+$: 231.0997. Found: 231.0992 (–2.2 ppm).

(±)-2-Cyclohexyl-1-(furan-2-yl)-2-hydroxyethanone 2-56b

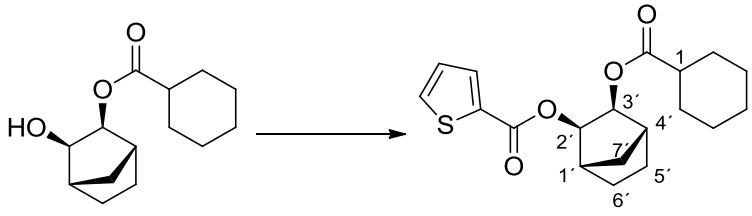


2-56a **2-56b**

To a solution of the (±)-3-cyclohexyl-1-(furan-*o*-yl)-1-hydroxyethanone 2-**56a** (39.0 mg, 0.19 mmol) in ethanol (5 mL) was added Et_3N (0.04 mL, 0.28 mmol) under an atmosphere of argon. The reaction mixture was heated at reflux for 16 hours and was concentrated *in vacuo*.

The residue was re-dissolved in Et_2O and water. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *crossed-acyloin* 2-**56b** (31.1 mg, 79%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.4; **IR** υ_{max} (thin film)/cm^{-1} 3427, 3125, 2926, 2854, 1669, 1567, 1567, 1466, 1386, 1284, 1148, 1117, 1083, 1031; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.65 (1 H, s, ArH), 7.31 (1 H, d, *J* = 3.5 Hz, ArH), 6.60 (1 H, dd, *J* = 3.5 Hz and 1.6 Hz, ArH), 4.70 (1 H, d, *J* = 2.8 Hz, C(2)H), 3.35 (1 H, br. s, OH), 1.87 (1 H, tt, *J* = 11.7 Hz and 3.2 Hz, C(3)H), 1.79 (2 H, t, *J* = 12.9 Hz, 2 x C(CyH)H), 1.71 (1 H, d, *J* = 5.4 Hz, C(CyH)H), 1.63 (1 H, d, *J* = 6.3 Hz, C(CyH)H), 1.51 (1 H, qd, *J*=12.8, 3.9 Hz, C(CyH)H), 1.35-1.24 (2 H, m, 2 x C(CyH)H), 1.20-1.10 (3 H, m, 3 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 190.5, 151.7, 147.0, 118.8, 112.5, 77.6, 42.7, 30.1, 26.5, 25.9 (2 Signals), 25.3; **MS** (ESI^+) ***m/z*** 231 ($M + Na^+$, 80%); **HRMS** (ESI^+) Calcd. for $C_{12}H_{16}NaO_2$ $[M+Na]^+$: 231.0997. Found: 231.0993 (–1.7 ppm).

(±)-(*1S,2R,3S,4R*)-3-(Cyclohexanecarbonyloxy)bicyclo[2.2.1]heptan-2-yl thiophene-2-carboxylate 2-**57**

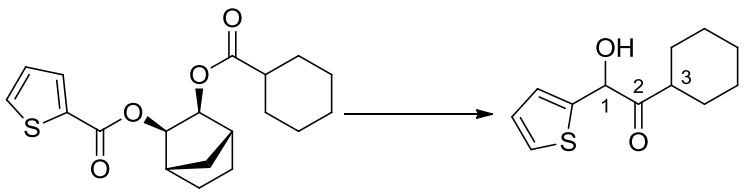


2-**37** 2-**57**

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylate 2-**37** (500 mg, 2.10 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *di-ester* 2-**57** (600 mg, 82%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 2933, 2855, 1732, 1587,

1488, 1452, 1279, 1168, 1104, 1077, 1047; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.80 (1 H, dd, *J* = 3.7 and 0.8 Hz, ArH), 7.56 (1 H, dd, *J* = 5.0 and 0.8 Hz, ArH), 7.10 (1 H, dd, *J* = 4.7 and 4.0 Hz, ArH), 4.95 (1 H, dd, *J* = 5.9 and 1.2 Hz, C(2')H), 4.81 (1 H, dd, *J* = 5.9 and 1.3 Hz, C(3')H), 2.42 (1 H, br. s, C(1')H), 2.29 (1 H, br. s, C(4')H), 2.13 (1 H, tt, *J* = 11.2 and 3.6 Hz, C(1)H), 1.97 (1 H, d, *J* = 10.2 Hz, C(7')H), 1.81-1.78 (1 H, m, C(CyH)H), 1.70-1.51 (6 H, m, 6 x C(CyH)H), 1.33-1.23 (5 H, m, C(5')H, C(6')H and 3 x C(CyH)H), 1.19-1.03 (3 H, m, C(5')H C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C:175.0, 161.4, 133.8, 133.4, 132.3, 127.6, 77.4, 76.1, 43.2, 41.3, 41.1, 33.7, 28.9, 28.6, 25.7, 25.4, 25.3, 24.4, 24.2; **MS** (ESI^+) ***m/z*** 349 ($M + H^+$, 50%); **HRMS** (ESI^+) Calcd. for $C_{19}H_{24}NaO_4S$ $[M+Na]^+$: 371.1293. Found: 371.1288 (–1.3 ppm).

(±)-2-Cyclohexyl-1-hydroxy-1-(thiophen-2-yl)ethanone 2-**58**

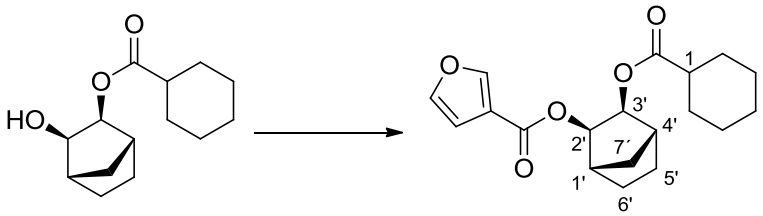


2-57 **2-58**

(*1S,2R,3S,4R*)-3-((cyclohexanecarbonyl)oxy)Bicyclo[2.2.1]heptan-2-yl thiophene-2-carboxylate 2-**57** (100 mg, 0.29 mmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *crossed-acyloin* 2-**58** (48.2 mg, 75%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.5; **IR** υ_{max} (thin film)/cm^{-1} 3458, 3063, 3030, 2933, 2855, 1707, 1493, 1450, 1369, 1316, 1245, 1192, 1147, 1116, 1055; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.32 (1 H, d, *J* = 5.1 Hz, ArH), 7.08 (1 H, d, *J* = 3.4 Hz, ArH), 7.01 (1 H, dd, *J* = 4.6 and 4.0 Hz, ArH), 5.47 (1 H, s, C(1)H), 4.37 (1 H, br. s, OH), 2.57 (1 H, tt, *J* = 11.1 and 3.8 Hz, C(3)H), 1.88 (1 H, d, *J* = 13.0 Hz, C(CyH)H),

1.78 (1 H, dd, *J* = 10.6 and 2.1 Hz, C(CyH)H), 1.73-1.60 (2 H, m, 2 x C(CyH)H), 1.42-1.10 (6 H, m, 6 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 211.0, 141.0, 127.2, 126.6, 126.4, 73.3, 45.8, 29.6, 27.9, 25.7, 25.5, 25.0; **MS** (ESI^+) ***m/z*** 247 ($M + Na^+$, 90%); **HRMS** (ESI^+) Calcd. for $C_{12}H_{16}NaO_2S$ $[M+Na]^+$: 247.0769. Found: 247.0764 (–2.0 ppm).

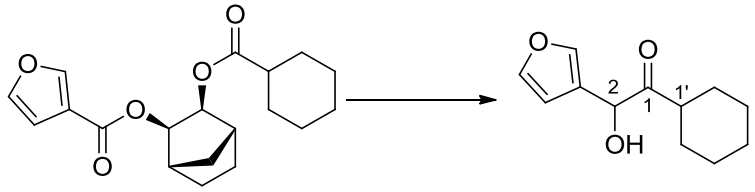
(±)-(*1S,2R,3S,4R*)-3-((Cyclohexanecarbonyl)oxy)bicyclo[2.2.1]heptan-2-yl furan-3-carboxylate 2-59



2-37 2-59

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylate 2-**37** (200 mg, 0.84 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 95:5 Petrol-Et_2O) to furnish the *di-ester* 2-**59** (223 mg, 80%) as a colourless oil. **R_f** (1:1 Petrol-Et_2O) 0.6; **IR** υ_{max} (thin film)/cm^{-1} 2930, 1713, 1638, 1450, 1310, 1247, 1202, 1164; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.99 (1H, s, ArH), 7.42 (1 H, t, *J* = 1.8 Hz, ArH), 6.72 (1 H, d, *J* = 1.3 Hz, ArH), 4.91 (1 H, d, *J* = 6.1 Hz, C(2')H), 4.79 (1 H, d, *J* = 6.1 Hz, C(3')H), 2.36 (1 H, br. s, C(1')H), 2.26 (1 H, br. s, C(4')H), 2.12 (1 H, tt, *J* = 11.1 Hz and 3.7 Hz, C(1)H), 1.91 (1 H, d, *J* = 10.1 Hz, C(7')H), 1.81-1.50 (7 H, m, C(5')H, C(6')H and 5 x C(CyH)H), 1.35-1.19 (5 H, m, 5 x C(CyH)H), 1.19-1.02 (3 H, m, C(5')H – C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.9, 162.3, 147.6, 143.7, 119.4, 109.8, 76.1 (2 C), 43.3, 41.3, 41.1, 33.7, 28.9 (2 signals), 25.7, 25.4, 25.3, 24.4, 24.3; **MS** (ESI^+) ***m/z*** 687 ($2M + Na^+$, 100%); **HRMS** (ESI^+) Calcd. for $C_{19}H_{24}NaO_5$ $[M+Na]^+$: 355.1521, Found: 355.1516 (–1.4 ppm).

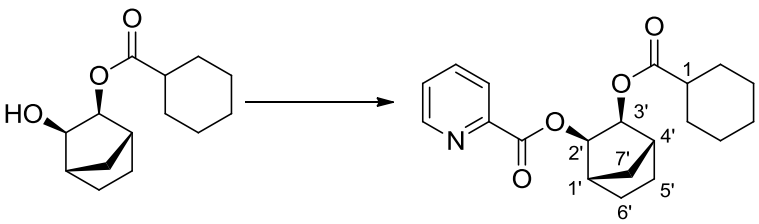
(±)-1-Cyclohexyl-2-(furan-3-yl)-2-hydroxyethanone 2-**60**



2-**59** 2-**60**

(*1S,2R,3S,4R*)-3-((cyclohexanecarbonyl)oxy)Bicyclo[2.2.1]heptan-2-yl furan-3-carboxylate 2-**59** (200 mg, 0.60 mmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 95:5 Petrol-Et_2O) to furnish the *crossed-acyloin* 2-**60** (29.2 mg, 23%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.4; **IR** υ_{max} (thin film)/cm^{-1} 3028, 2968, 1738, 1499, 1461, 1153; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.52 (1 H, s, ArH), 7.42 (1 H, s, ArH), 6.28 (1 H, s, ArH), 5.20 (1 H, s, C(2)H), 4.10 (1 H, br. s, OH), 2.51 (1 H, tt, J = 14.7 Hz and 3.6 Hz, C(1')H), 1.89-1.75 (3 H, m, 3 x C(CyH)H), 1.74-1.61 (3 H, m, 3 x C(CyH)H), 1.33-1.20 (4 H, m, 4 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 212.2, 144.0, 141.2, 122.9, 108.7, 70.2. 46.8, 29.6, 27.8, 25.7, 25.5, 25.0; **MS** (ESI^+) ***m/z*** 231 ($M + Na^+$, 70%); **HRMS** (ESI^+) Calcd. for $C_{12}H_{16}NaO_3$ $[M+Na]^+$: 231,0997. Found: 231.0994 (−1.3 ppm).

(±)-(*1S,2R,3S,4R*)-3-((cyclohexanecarbonyl)oxy)bicyclo[2.2.1]heptan-2-yl picolinate 2-**61**

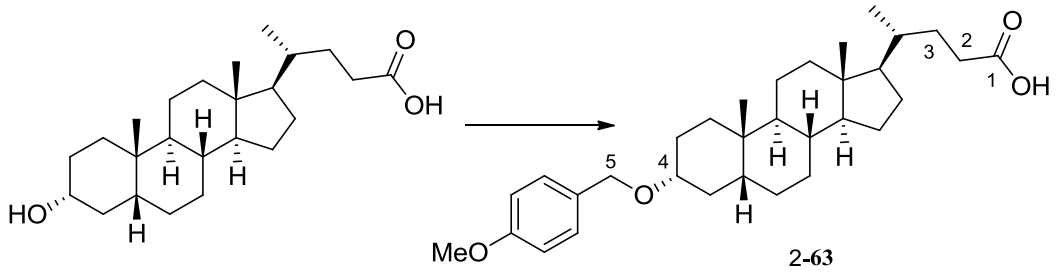


2-**37** 2-**61**

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclohexanecarboxylat 2-**37** (500 mg, 2.10 mmol) was subjected to General Procedure **D**. The crude product was purified by flash

column chromatography (SiO_2, 9:1 Petrol-EtOAc) to furnish the *di-ester* 2-**61** (677 mg, 94%) as a yellow oil. **R_f** (1:1 Petrol-Et_2O) 0.6; **IR** υ_{max} (thin film)/cm^{-1} 2905, 2888, 1715, 1534, 1236, 1045; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 8.74 (1 H, d, *J* = 4.3 Hz, ArH), 8.06 (1 H, d, *J* = 7.8 Hz, ArH), 7.80 (1 H, t, *J* = 7.7 Hz, ArH), 7.44 (1 H, dd, *J* = 7.6 Hz and 4.8 Hz, ArH), 4.99 (1 H, d, *J* = 6.1 Hz, C(2')H), 4.83 (1 H, d, *J* = 6.1 Hz, C(3')H), 2.48 (1 H, br. s, C(1')H), 2.27 (1 H, br. s, C(4')H), 2.11-1.97 (1 H, m, C(1)H), 1.70 (1 H, d, *J* = 11.6 Hz, C(7')H), 1.64-1.41 (6 H, m, C(5')H, C(6')H and 4 x C(CyH)H), 1.30-1.22 (3 H, m, 3 x C(CyH)H), 1.17 (2 H, td, *J* = 12.1 Hz and 3.2 Hz, 2 x C(CyH)H), 1.10-0.92 (3 H, m, C(5')H C(7')H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.9, 164.4, 149.9, 148.2, 136.7, 126.7, 125.1, 78.1, 76.1, 43.1, 41.3, 40.9, 33.8, 28.8, 28.7, 25.6, 25.3, 25.2, 24.4, 24.2; **MS** (ESI^+) ***m/z*** 366 ($M + Na^+$, 40%); **HRMS** (ESI^+) Calcd. for $C_{20}H_{25}NaNO_4$ $[M+Na]^+$: 366.1681. Found: 366.1678 (–0.8 ppm).

(*R*)-4-((*3R,5R,8R,9S,10S,12R,13R,14S*)-3-((4-methoxybenzyl)oxy)-10,12-dimethyl hexadecahydro-1H-cyclopenta[a]phenanthren-13-yl)pentanoic acid 2-**63**



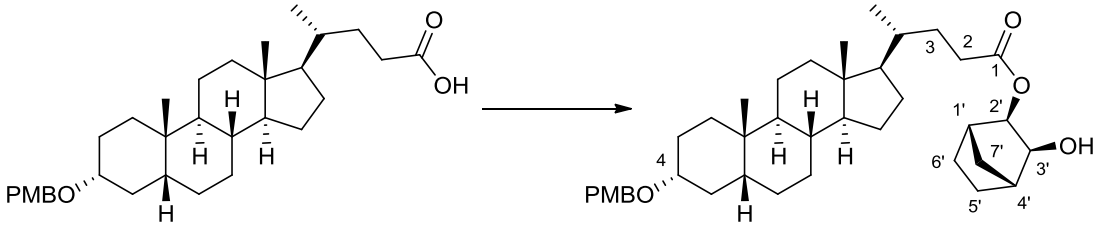
2-**63**

To a slurry of NaH (425 mg, 10.66 mmol, 60% dispersion in mineral oil) and Bu_4NI (432 mg, 1.17 mmol) in THF (50 mL) under an atmosphere of argon at 0 °C was added a solution of lithocholic acid (2.04 g, 5.33 mmol) in THF (10 mL) and a solution of 4-methoxybenzyl chloride (1.58 mL, 11.69 mmol) in THF (5 mL). The reaction mixture was heated at reflux overnight and was allowed to cool to room temperature and was quenched with saturated

aqueous solution of NH_4Cl (20 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was used in the next step without prior purification.

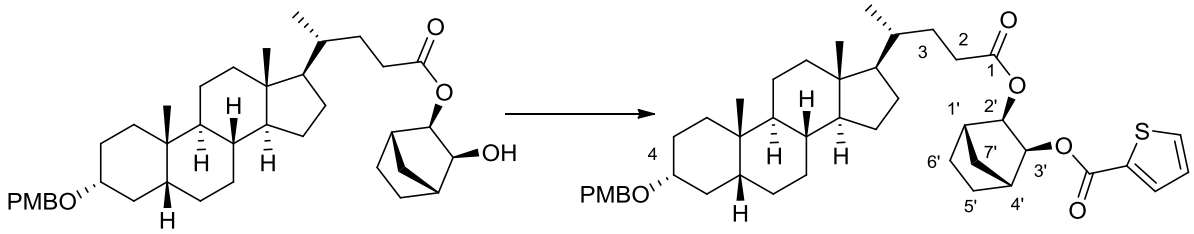
To a solution of the crude *PMB-ester* in THF/MeOH/H_2O (2:1:1, 20 mL) was added NaOH (698 mg, 17.4 mmol). The reaction mixture was heated at reflux for 4 hours and the solvent was removed *in vacuo*. The residue was acidified with 10% aqueous solution of HCl to pH 3 and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 8:2, Petrol-Et_2O) to furnish the *carboxylic acid* 2-**63** (1.78 g, 66%) as a white solid. **MP** 139 °C; **R_f** (3:1 Petrol-EtOAc) 0.2; **IR** υ_{max} (KBr)/cm^{-1} 2936, 2864, 1708, 1613, 1587, 1514, 1451, 1361, 1302, 1247, 1173, 1091, 1038; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.28 (2 H, d, *J* = 8.2 Hz, ArH), 6.88 (2 H, d, *J* = 8.2 Hz, ArH), 4.50 (2 H, s, C(5)H_2), 3.81 (3 H, s, OMe), 3.42-3.31 (1 H, m, C(4)H), 2.45-2.35 (1 H, m, C(PolyCy)H), 2.26 (1 H, ddd, *J* = 15.8, 9.5 and 6.5 Hz, C(PolyCy)H), 1.95 (1 H, app. d, *J* = 12.0 Hz, C(PolyCy)H), 1.91-1.75 (6 H, m, C(2)H_2, C(3)H_2 and 2 x C(PolyCy)H), 1.67-1.54 (2 H, m, 2 x C(PolyCy)H), 1.49-1.01 (16 H, m, 16 x C(PolyCy)H), 0.97-0.87 (8 H, m, 2 x C(PolyCy)H, 2 x C(PolyCy)H_3), 0.65 (3 H, s, C(PolyCy)H_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 180.0, 159.0, 131.2, 129.2 (2 C), 113.8 (2 C), 78.3, 69.5, 56.4, 55.9, 55.3, 42.7, 42.1, 40.3, 40.2, 35.8, 35.3, 34.9, 33.2, 31.0, 30.8, 28.2, 27.3, 27.2, 26.4, 24.2, 23.4, 21.4, 20.8, 18.2, 12.0; **MS** (ESI^+) ***m/z*** 519 ($M + Na^+$, 100%); **HRMS** (ESI^+) Calcd. for $C_{32}H_{48}NaO_4$ $[M+ Na]^+$: 519.3450. Found: 519.3445 (–0.9 ppm).

***(R)-(1R,2S,3R,4S)*-3-hydroxybicyclo[2.2.1]heptan-2-yl 4-(*(3R,5R,8S,9S,10R, 12R, 13R,14S)*-3-((4-methoxybenzyl)oxy)-5,10,12-trimethylhexadecahydro-1H-cyclopenta [a]phenanthren-13-yl)pentanoate 2-64**



(R)-4-*((3R,5R,8R,9S,10S,12R,13R,14S)*-3-((4-methoxybenzyl)oxy)-10,12-Dimethyl hexadecahydro-1H-cyclopenta[a]phenanthren-13-yl)pentanoic acid 2-**63** (500 mg, 1.01 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *mono-ester* 2-**64** (545 mg, 89%) as a colourless oil. **R_f** (1:1 Petrol-EtOAc) 0.5; **IR** υ_{max} (thin film)/cm^{-1} film 3384, 2958, 2830, 1733, 1613, 1587, 1451, 1381, 1248, 1173. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.27 (2 H, d, J = 8.6 Hz, ArH), 6.87 (2 H, d, J = 8.5 Hz, ArH), 4.56 (1 H, d, J = 6.0 Hz, C(2')H), 4.49 (2 H, s, C(PMB)H_2), 3.85 (1 H, d, J = 6.0 Hz, C(3')H), 3.80 (3 H, s, OMe), 3.40-3.31 (1 H, m, C(4)H), 2.45-2.36 (1 H, m, C(PolyCy)H), 2.31-2.19 (3 H, m, C(1')H, C(4')H and C(PolyCy)H), 1.95 (1 H, d, J = 12.1 Hz, C(PolyCy)H), 1.90-1.74 (7 H, m, C(2)H_2, C(3)H_2, C(7')H, 2 x C(PolyCy)H), 1.66-0.98 (25 H, m, C(5')H_2, C(6')H_2, C(7')H and 20 x C(PolyCy)H), 0.97-0.87 (6 H, m, 2 x C(PolyCy)H_3), 0.64 (3 H, s, C(PolyCy)H_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.3 (2 signals), 159.0, 131.3, 129.1 (2 C), 113.8 (2 C), 78.3, 78.2, 75.7, 69.5, 56.4, 55.9, 55.3, 43.3, 42.7, 42.1, 40.8, 40.3, 40.2, 35.8, 35.4, 35.3, 34.9, 33.2, 32.7, 31.2, 31.0, 31.0, 28.2, 27.3, 27.2, 26.4, 24.5, 24.4, 24.2, 23.4, 20.8, 18.3, 12.0, (two diastereoisomers); **MS** (ESI^+) ***m/z*** 629 ($M + Na^+$, 100%); **HRMS** (ESI^+) Calcd. for $C_{39}H_{58}NaO_5$ $[M+Na]^+$: 629.4182. Found: 629.4176 (–0.1 ppm).

***(1R,2S,3R,4S)*-3-((*(R)*-4-((*3R,5R,8R,9S,10S,13R,14S,17R)*-3-((4-Methoxy benzyl) oxy)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoyl) oxy)bicyclo[2.2.1]heptan-2-yl thiophene-*o*-carboxylate 2-65**

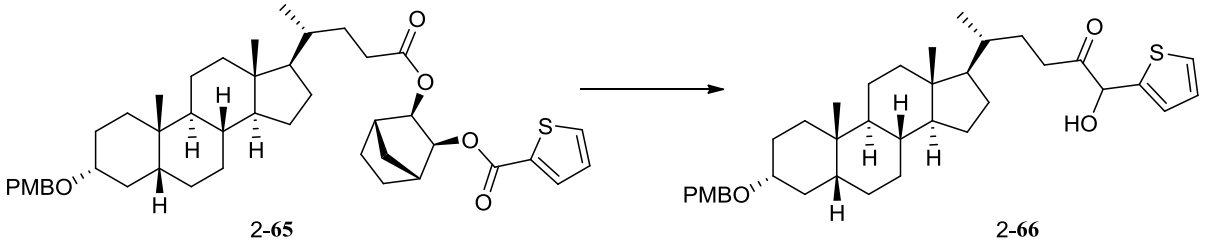


2-64 dr 1:1 **2-65** dr 1:1

(R)-(1R,2S,3R,4S)-3'-Hydroxybicyclo[2.2.1]heptan-2'-yl 4-((*3R,5R,8S,9S,10R, 12R, 13R,14S)*-3-((4-methoxybenzyl)oxy)-5,10,12-trimethylhexadecahydro-1H-cyclopenta [a]phenanthren-13-yl)pentanoate 2-**64** (120 mg, 0.20 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *di-ester* 2-**65** (140 mg, 98%) as a colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.6; **IR** υ_{max} (thin film)/cm^{-1} 2934, 2865, 1716, 1612, 1513, 1451, 1361, 1248, 1172, 1080, 1037; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.79 (1 H, d, *J* = 2.8 Hz, ArH), 7.55 (1 H, d, *J* = 4.3 Hz, ArH), 7.27 (2 H, d, *J* = 8.2 Hz, ArH), 7.10 (1 H, t, *J* = 4.0 Hz, ArH), 6.87 (2 H, d, *J* = 8.2 Hz, ArH), 4.95 (1 H, d, *J* = 5.4 Hz, C(2')H), 4.81 (1 H, d, *J* = 5.7 Hz, C(3')H), 4.49 (2 H, s, C(PMB)H), 3.79 (3 H, s, OMe), 3.36 (1 H, t, *J* = 10.4 Hz, C(4)H), 2.41 (1 H, br. s, C(1')H), 2.31 (1 H, br. s, C(4')H), 2.27-2.17 (1 H, m, C(PolyCy)H), 2.15-2.04 (1 H, m, C(PolyCy)H), 1.98 (1 H, d, *J* = 10.1 Hz, C(PolyCy)H), 1.92-1.74 (6 H, m, C(2)H_2, C(3)H_2, C(7')H and C(PolyCy)H), 1.66-0.93 (25 H, m, C(5')H_2, C(6')H_2, C(7')H and 20 x C(PolyCy)H), 0.90 (3 H, s, C(PolyCy)H_3), 0.77 (3 H, t, *J* = 7.2 Hz, C(PolyCy)H_3), 0.58 (3 H, s, C(PolyCy)H_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 173.3, 173.2, 161.3, 159.0, 133.7, 133.4, 132.2, 131.2, 129.2, 127.7, 113.8, 78.3, 77.2, 77.1, 76.4 (2 signals), 69.6, 69.5, 56.5, 55.8, 55.7, 55.3, 42.7, 42.1, 41.1, 40.3, 40.2, 40.1, 35.8, 35.4, 35.2, 34.9, 33.7, 33.3, 31.1 (2 signals), 30.8, 30.7, 28.1

(2 signals), 27.3, 27.2, 26.4, 24.5, 24.2, 23.4, 20.8, 18.2, 12.0 (49 Signals, due to the presents of two inseparable diastereoisomers); **MS** (ESI^+) ***m/z*** 739 ($M + Na^+$, 100%); **HRMS** (ESI^+) Calcd. for $C_{44}H_{60}NaO_6S$ $[M+Na]^+$: 739.4008. Found: 739.4003 (–0.7 ppm).

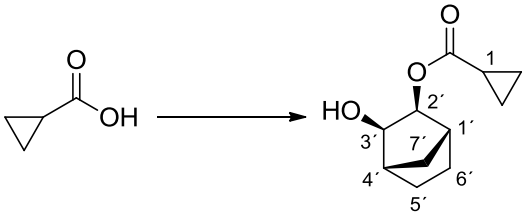
***(5R)*-1-Hydroxy-5-(*(3R,5R,8R,9S,10S,12R,13R,14S)*-3-((4-methoxybenzyl)oxy)-10,12-dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-13-yl)-1-(thiophen-2-yl)hexan-2-one 2-66**



(*1R,2S,3R,4S*)-3-(((*R*)-4-((*3R,5R,8R,9S,10S,13R,14S,17R*)-3-((4-methoxy benzyl) oxy)-10,13-Dimethylhexadecahydro-1H-cyclopenta[a]phenanthren-17-yl)pentanoyl) oxy)bicyclo[2.2.1]-heptan-2-yl thiophene-*o*-carboxylate 2-**65** (140 mg, 0.20 mmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *crossed-acyloin* 2-**66** (101 mg, 87%) as a colourless oil. **R_f** (1:1 Petrol-Et_2O) 0.4; **IR** υ_{max} (thin film)/cm^{-1} 3471, 3026, 2920, 2852, 1695, 1603, 1496, 1454, 1376, 1260, 1195, 1059, 1021; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32 (1 H, d, J = 4.6 Hz, ArH), 7.27 (2 H, d, J = 8.6 Hz, ArH), 7.10 (1 H, d, J = 3.1 Hz, ArH), 7.02 (1 H, t, J = 4.0 Hz, ArH), 6.88 (2 H, d, J = 8.5 Hz, ArH), 5.37 (1 H, d, J = 7.2 Hz, C(1)H), 4.49 (2 H, s, C(PMB)H_2), 4.35 (1 H, br. s, OH), 3.80 (3 H, s, OMe), 3.40-3.32 (1 H, m, C(5)H), 2.53-2.30 (2 H, m, C(3)H_2), 2.17 (1 H, s, C(PolyCy)H), 1.92-1.81 (7 H, m, C(3)H_2 and 5 x C(PolyCy)H), 1.45-0.95 (18 H, m, 18 x C(PolyCy)H), 0.90 (3 H, s, C(PolyCy)H_3), 0.81 (1.5 H, t, J = 6.5 Hz, 0.5 x C(PolyCy)H_3), 0.74 (1.5 H, t, J = 7.2 Hz, 0.5 x C(PolyCy)H_3), 0.60 (3 H, d, J = 7.2

Hz, C(PolyCy)H$_3$); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 208.9, 208.7, 159.0, 141.2, 131.2, 129.1 (2C), 127.2, 126.5, 126.5, 113.8 (2C), 78.3, 75.1, 74.8, 69.5, 56.4 (2 Signals), 55.9, 55.8, 55.3, 42.7, 42.1, 40.3, 40.1, 35.8, 35.4, 34.9, 34.5, 33.2, 30.9, 30.0, 29.9, 28.2, 28.1, 27.3, 27.2, 26.4, 24.2, 23.4, 20.8, 18.3, 18.2, 12.0, (44 peaks due to presence of two diastereoisomers); **MS** (ESI^+) ***m/z*** 615 ($M + Na^+$, 80%); **HRMS** (ESI^+) Calcd. for $C_{37}H_{52}NaO_4S$ $[M+Na]^+$: 615.3484. Found: 615.3479 (–0.8 ppm).

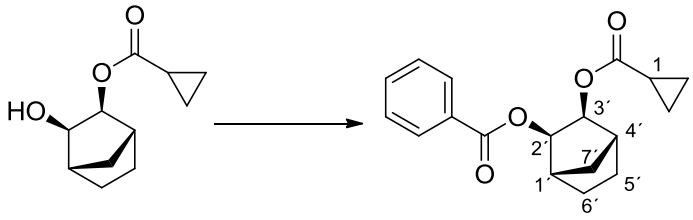
(±)-(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclopropane-carboxylate 2-**67**



2-**67**

(*1R,2S,3R,4S*)-Bicyclo[2.2.1]heptane-2,3-diol 1-**28** (1.00 g, 7.81 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *mono-ester* 2-**67** (909 mg, 90%) as a colourless oil. $\mathbf{R_f}$ (3:1 Petrol-Et_2O) 0.2; **IR** υ_{max} (thin film)/cm^{-1} 3484, 2933, 2854, 1731, 1451, 1382, 1316, 1249, 1174, 1147, 1089, 1048; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:4.56 (1 H, d, J = 5.8 Hz, C(2')H), 3.85 (1 H, d, J = 5.8 Hz, C(3')H), 2.26 (1 H, br. s, C(1')H), 2.22 (1 H, br. s, C(4')H), 2.04 (1 H, br. s, OH), 1.84 (1 H, d, J = 10.4 Hz, C(7')H), 1.66 (1 H, tt, J = 7.6 and 4.6 Hz, C(1)H), 1.57-1.45 (2 H, m, C(5')H and C(6')H), 1.20-1.08 (3 H, m, C(5')H C(7')H), 1.04-0.96 (2 H, m, 2 x C(CyP)H), 0.92-0.87 (2 H, m, 2 x C(CyP)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 175.0, 78.3, 75.7, 43.2, 40.8, 32.8, 24.4 (2 signals), 12.9, 8.9, 8.7; **MS** (ESI^+) ***m/z*** 219 ($M + Na^+$, 30%); **HRMS** (ESI^+) Calcd. for $C_{11}H_{16}NaO_3$ $[M+Na]^+$: 219.0997. Found: 219.0992 (–2.3 ppm).

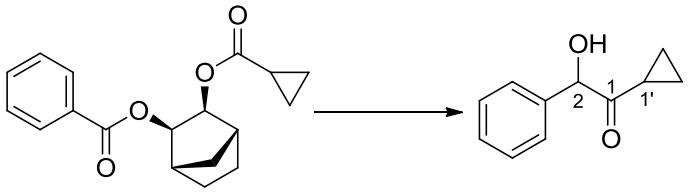
(±)-*(1S,2R,3S,4R)*-3-((Cyclopropanecarbonyl)oxy)bicyclo[2.2.1]heptan-2-yl benzoate 2-68



2-**67** 2-**68**

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclopropanecarboxylate 2-**67** (610 mg, 3.31 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 95:5, Petrol-Et_2O) to furnish the *di-ester* 2-**68** (794 mg, 80%) as a white solid. **MP** 58.3 °C; **R_f** (3:1 Petrol-Et_2O) 0.6; **IR** υ_{max} (KBr)/cm^{-1} 2970, 2878, 1726, 1603, 1585, 1452, 1396, 1356, 1317, 1274, 1176, 1115, 1071, 1024; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 8.04 (2 H, d, *J* = 7.3 Hz, ArH), 7.54 (1 H, t, *J* = 7.6 Hz, ArH), 7.45-7.39 (2 H, t, *J* = 7.8 Hz, ArH), 4.99 (1 H, d, *J* = 6.1 Hz, C(2')H), 4.81 (1 H, d, *J* = 5.8 Hz, C(3')H), 2.41 (1 H, br. s, C(1')H), 2.34 (1 H, br. s, C(4')H), 2.01 (1 H, d, *J* = 10.1 Hz, C(7')H), 1.52-1.64 (2 H, m, C(5')H and C(6')H), 1.46 (1 H, tt, *J* =7.6 and 5.3 Hz, C(1)H), 1.33-1.22 (3 H, m, C(5')H C(7')H), 0.90-0.82 (1 H, m, C(CyP)H), 0.75-0.57 (3 H, m, 3 x C(CyP)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 174.0, 165.6, 132.9, 130.3, 129.6 (2 signals), 128.2 (2 C), 76.8 (2 signals), 41.2, 41.0, 33.7, 24.4, 24.2, 12.7, 8.6, 8.2; **MS** (ESI^+) ***m/z*** 323 ($M + Na^+$, 30%); **HRMS** (ESI^+) Calcd. for $C_{18}H_{20}NaO_4$ $[M+Na]^+$: 323.1259. Found: 323.1254 (–1.5 ppm).

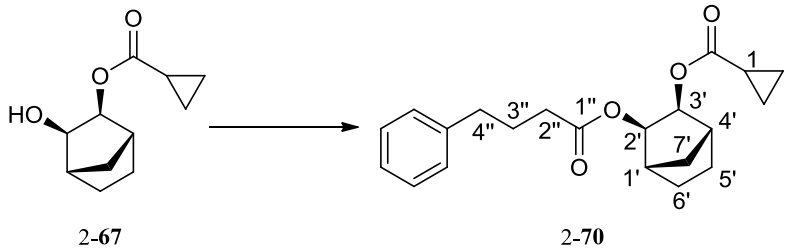
(±)-1-Cyclopropyl-2-hydroxy-2-phenylethanone 2-**69**



2-**68** 2-**69**

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclopropanecarboxylate 2-**68** (100 mg, 0.33 mmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 95:5 Petrol-Et_2O) to furnish the *crossed-acyloin* 2-**69** (51.0 mg, 87%) as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.45-7.32 (5 H, m, ArH), 5.27 (1 H, s, C(2)H), 4.39 (1 H, br. s, OH), 1.88 (1 H, tt, J = 7.7 Hz and 4.6 Hz, C(1')H), 1.20-1.12 (1 H, m, C(CyP)H), 1.10- 0.94 (2 H, m, 2 x C(CyP)H), 0.82 (1 H, qd, J = 7.9 and 3.1 Hz, C(CyP)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 209.6, 138.2, 129.0 (2 C), 128.6, 127.8 (2 C), 80.2, 17.7, 12.8, 12.2. *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[50]

(±)-(*1S,2R,3S,4R*)-2-((4-Phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-3-yl cyclopropane carboxylate 2-**70**

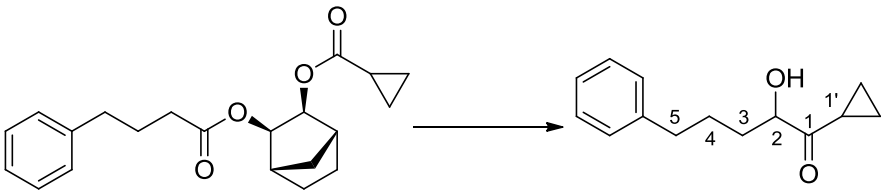


2-**67** 2-**70**

(*1R,2S,3R,4S*)-3-Hydroxybicyclo[2.2.1]heptan-2-yl cyclopropanecarboxylate 2-**67** (500 mg, 2.55 mmol) was subjected to General Procedure **D**. The crude product was purified by flash column chromatography (SiO_2, 95:5 Petrol-Et_2O) to furnish the *di-ester* 2-**70** (785 mg, 90%)

as colourless oil. **R_f** (3:1 Petrol-Et_2O) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 3062, 3025, 2969, 2878, 1734, 1603, 1497, 1454, 1396, 1356, 1177, 1082, 1036; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.32-7.26 (2 H, m, ArH), 7.23-7.16 (3 H, m, ArH), 4.78-4.70 (2 H, m, C(2')H and C(3')H), 2.67 (2 H, t, *J* = 7.6 Hz, C(4'')H), 2.32 (2 H, t, *J* = 7.6 Hz, C(2'')H), 2.27 (2 H, br. s, C(1')H and C(4')H), 1.96 (2 H, quin, *J* = 7.5 Hz, C(3'')H), 1.87 (1 H, d, *J* = 10.1 Hz, C(7')H), 1.63-1.47 (3 H, m, C(5')H, C(6')H and C(1)H), 1.28-1.17 (3 H, m, C(5')H C(7')H), 0.99-0.86 (2 H, m, 2 x C(CyP)H), 0.82-0.71 (2 H, m, 2 x C(CyP)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 173.9, 172.4, 141.5, 128.5 (2 C), 128.4 (2 C), 126.0, 76.6, 76.4, 41.1 (2 signals), 35.2, 33.6, 33.5, 26.6, 25.0, 24.3, 12.8, 8.4, 8.3; **MS** (ESI^+) ***m/z*** 365 ($M + Na^+$, 80%); **HRMS** (ESI^+) Calcd. for $C_{21}H_{26}NaO_4$ $[M+Na]^+$: 365.1729 Found: 365.1723 (–1.6 ppm).

(±)-1-Cyclopropyl-2-hydroxy-5-phenylpentan-1-one 2-**71**

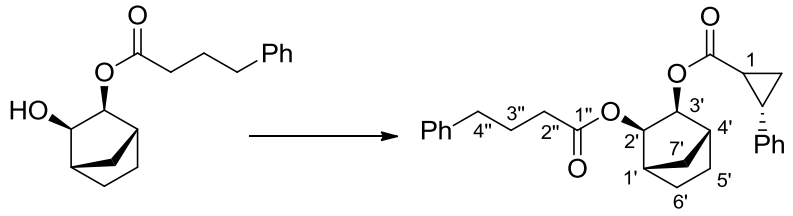


2-**70** 2-**71**

(*1R,2S,3R,4S*)-3-((4-phenylbutanoyl)oxy)Bicyclo[2.2.1]heptan-2-yl cyclopropane-carboxylate 2-**70** (249 mg, 0.73 mmol) was subjected to General Procedure **E**. The crude product was purified by flash column chromatography (SiO_2, 95:5 Petrol-Et_2O) to furnish the *crossed-acyloin* 2-**71** (127 mg, 80%) as a colourless oil. **R_f** (1:1 Petrol-Et_2O) 0.4; **IR** υ_{max} (thin film)/cm^{-1} 3472, 3026, 2926, 2858, 1695, 1603, 1496, 1454, 1376, 1260, 1194, 1059, 1021; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H:7.32-7.16 (2 H, m, ArH), 7.11-7.04 (3 H, m, ArH), 4.41 (1 H, dd, *J* = 6.9 Hz and 3.8 Hz, C(2)H), 2.78-2.60 (2 H, m, C(5)H), 2.05-1.95 (1 H, m, C(1')H), 1.95-1.80 (2 H, m, C(3)H), 1.77-1.62 (2 H, m, C(4)H), 1.20-1.14 (1 H, m, C(CyP)H), 1.08 (1

H, dt, *J* = 9.3 Hz and 4.5 Hz, C(CyP)H), 0.98 (2 H, dd, *J* = 7.7 Hz and 4.1 Hz, 2 x C(CyP)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 212.1, 141.9, 128.4 (2 C), 128.3 (2 C), 125.9, 76.7, 35.6, 33.2, 26.4, 17.0, 12.0, 11.7; **MS** (ESI^+) ***m/z*** 241 ($M + Na^+$, 80%); **HRMS** (ESI^+) Calcd. for $C_{14}H_{18}NaO_2$ $[M+Na]^+$: 241.1204, Found: 241.1199 (–2.1 ppm).

(*2S*)-(*1R,2S,3R,4S*)-2-((4-Phenylbutanoyl)oxy)bicyclo[2.2.1]heptan-3-yl 2-phenylcyclopropanecarboxylate 2-**72**

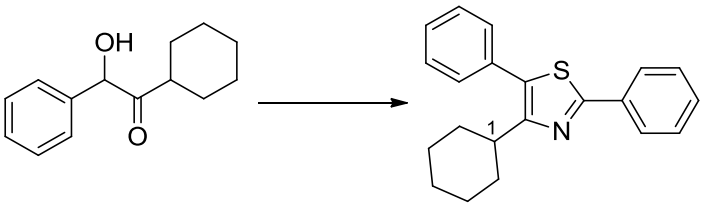


2-**31** 2-**72**

To a solution of (*1R,2S,3R,4S*)-3-hydroxybicyclo[2.2.1]heptan-2-yl 4-phenylbutanoate 2-**31** (500 mg, 1.82 mmol) and DMAP (689 mg, 5.65 mmol) in CH_2Cl_2 (30 mL) was added *N,N*-dicyclohexylcarbodiimide (1.16 g, 5.65 mmol) and (*2S*)-2-phenylcyclopropanecarboxylic acid (916 mg, 5.65 mmol). The reaction mixture was stirred under an atmosphere of at room temperature overnight and was purged through a pad of ciliate and the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 9:1 Petrol-EtOAc) to furnish the *di-ester* 2-**72** (297 mg, 39%) as a colourless oil. **R_f** (1:1 Petrol-Et_2O) 0.8; **IR** υ_{max} (thin film)/cm^{-1} 2967, 1732, 1497, 1454, 1406, 1338, 1174; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.36-7.15 (7 H, m, ArH), 7.14-7.00 (3 H, m, ArH), 4.84-4.75 (2 H, m, C(2')H), 2.70-2.61 (1 H, m, C(3')H), 2.54-2.46 (2 H, m, C(1)H), 2.39-2.20 (4 H, m, C(2'')H, C(4')H and C(1')H), 1.99 (1 H, quin, *J* = 7.7 Hz, C(3'')H), 1.93-1.80 (3 H, m, C(4)H, C(5')H and C(CyP)H), 1.64-1.49 (3 H, m, C(5')H, C(6')H and C(CyH)H), 1.32-1.21 (4 H, m, C(5')H – C(7')H and C(CyP)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 172.5, 172.4, 141.5, 141.4, 140.1, 128.5, 128.4, 126.6, 126.1, 126.0, 76.9, 76.8, 76.6, 41.1 (2 signals),

35.3, 35.1, 33.7, 33.6, 26.7, 26.5, 26.4, 26.2, 24.4, 24.2, 24.1, 17.3; **MS** (ESI^+) ***m/z*** 441 ($M + Na^+$, 50%); **HRMS** (ESI^+) Calcd. for $C_{27}H_{30}NaO_4$ $[M+Na]^+$: 441.2042. Found: 441.2036 (−1.4 ppm).

4-Cyclohexyl-2,5-diphenylthiazole 2-**81**



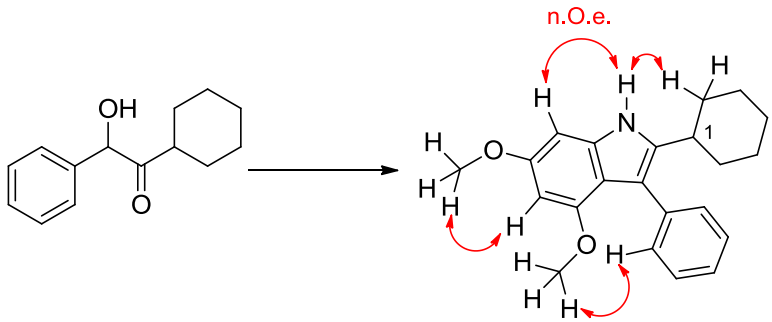
2-**39a** 2-**81**

To a solution of 1-cyclohexyl-2-hydroxy-2-phenylethanone 2-**39** (100 mg, 0.46 mmol) and Et_3N (0.09 mL, 0.69 mL) in Et_2O (5 mL) was added a solution of methanesulfonyl chloride (MsCl) (0.04 mL, 0.51 mmol) in Et_2O (2 mL) and the reaction mixture was stirred under an atmosphere of argon for 2 h at reflux. The reaction mixture was cooled to r. t. and filtered through a plug of celite. The filtrate was poured into water (20 mL) and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was used in the next step without further purification.

To a solution of crude *α-mesyloxy-ketone* in THF/PhMe (1:1, 10 mL) was added a solution of thiobenzamide (181 mg, 1.32 mmol) in THF/PhMe (1:1, 5 mL) and the reaction mixture was stirred under an atmosphere of argon for 16 hours at reflux. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (SiO_2, 96:4, Petrol-CH_2Cl_2) to furnish the *thiozole* 2-**81** (95.4 mg, 71%) as a white crystalline solid. **MP** 120 °C; $\mathbf{R_f}$ (3:1 Petrol- CH_2Cl_2) 0.4; **IR** $\boldsymbol{\upsilon_{max}}$ (KBr disc)/cm^{-1} 3424, 3055, 3021. 3026, 2851, 1524, 1503, 1484, 1457, 1444, 1348, 1324, 1312, 1280, 1261, 1244, 1203, 1177, 1152;

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H: 7.98 (2 H, dd, J = 8.0 and 1.5 Hz, ArH), 7.48-7.37 (8 H, m, ArH), 2.85 (1 H, tt, J = 11.2 and 3.5 Hz, C(1)H), 1.94-1.80 (6 H, m, 6 x C(CyH)H), 1.72 (1 H, s, C(CyH)H), 1.39-1.29 (3 H, 3 x C(CyH)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 165.2, 158.2, 134.2, 132.3, 131.0, 129.7 (2 C), 129.6, 128.8 (2 C), 128.7 (2 C), 127.8, 126.4 (2 C), 38.4, 33.0 (2 C), 26.5 (2 C), 25.9; **MS** (ESI^+) ***m/z*** 320 ($M + H^+$, 80%); **HRMS** (ESI^+) Calcd. for $C_{21}H_{21}NS$ $[M+H]^+$: 320.1473. Found: 320.1468 (–1.6 ppm). *The regioselectivity of the reaction was confirmed by crystal structure.*

2-Cyclohexyl-4,6-dimethoxy-3-phenyl-1H-indole 2-**85**

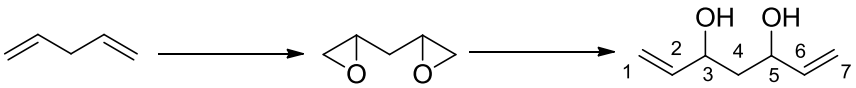


2-**39a** 2-**85**

To a solution of 1-cyclohexyl-2-hydroxy-2-phenylethanone 2-**39** (65.0 mg, 0.30 mmol) and 3,5-dimethoxyaniline (137 mg, 0.89 mmol) in PhMe (5 mL) was added two drops of concentrated HI. The reaction mixture was fitted with a Dean- Stark trap and was stirred at reflux under an atmosphere of argon for 3 hours. The reaction mixture was allowed to cool to the room temperature and the solvent was removed *in vacuo*. The residue was re-dissolved in $CHCl_3$, washed with distilled water and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 99:1, Petrol-Et_2O) to furnish the *indole* 2-**85** (84.0 mg, 84%) as a white crystalline solid. **MP**

175 °C; **R_f** (3:1 Petrol-Et_2O) 0.4; **IR** υ_{max} (KBr disc)/cm^{-1} 3349, 3052, 2995, 2919, 2846, 1631, 1584, 1450, 1346, 1275, 1218, 1191, 1177, 1153, 1127, 1046; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 7.92 (1 H, br. s, ArH), 7.46-7.36 (4 H, m, ArH), 7.33-7.26 (1 H, m, ArH), 6.49 (1 H, d, *J* = 1.6 Hz, ArH), 6.23 (1 H, d, *J* = 1.9 Hz, ArH), 3.85 (3 H, s, OMe), 3.68 (3 H, s, OMe), 2.82 (1 H, tt, *J* = 12.0 and 3.2 Hz, C(1)H), 1.92 (2 H, d, *J* = 12.7 Hz, 2 x C(CyH)H), 1.81 (2 H, d, *J* = 12.6 Hz, 2 x C(CyH)H), 1.74 (1 H, d, *J* = 11.1 Hz, C(CyH)H), 1.46 (2 H, qd, *J* = 12.3 and 2.0 Hz, 2 x C(CyH)H), 1.38-1.21 (3 H, m, 3 x C(CyH)H). *The regioselectivity of the reaction was confirmed by diagnostic NOESY enhancements of the structure (represented by red arrows on the compound structure).* **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 156.9, 154.5, 138.4, 136.4, 136.3, 131.0 (2 C), 127.1 (2 C), 125.5, 112.7, 111.9, 92.0, 86.8, 55.7, 55.2, 35.1, 33.8 (2 C), 26.5 (2 C), 26.1; **MS** (ESI^+) ***m/z*** 334 ($M-H^+$, 100%); **HRMS** (ESI^+) Calcd. for $C_{22}H_{26}NO_2$ $[M+H]^+$: 336.1964. Found: 336.1958 (–1.8 ppm).

(±)-Hepta-1,6-diene-3,5-diol 4-**2**

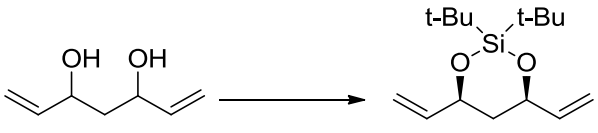


4-**1** 4-**2**

To a solution of 1,4 pentadiene (3.78 mL, 36.7 mmol) in CH_2Cl_2 (30 mL) was added portionwise *m*-chloroperoxybenzoic acid (22.6 g, 91.8 mmol, 70% by wt.) at 0°C. The reaction mixture was stirred at room temperature overnight and was quenched with aqueous saturated solution of $NaHCO_3$. The organic layer was separated and was washed with KOH (10 mL, 1 M), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product 4-**1** was used without further purification.

To a solution of trimethylsulfonium iodide (59.8 g, 0.29 mol) in THF (50 mL) at -40 °C was added dropwise *n*-butyllithium (183 mL, 1.6 M in hexane) over 40 minutes under an atmosphere of argon. The reaction mixture was stirred further for 10 minutes and the crude solution of *diepoxide* 4-**1** in THF (15 mL) was added dropwise. The reaction mixture was stirred for a further 30 minutes and was allowed to slowly warm up to room temperature overnight. The reaction mixture was treated with saturated aqueous solution of NH_4Cl (20 mL) and was extracted with CH_2Cl_2 (4 x 30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2,7:3 Petrol-EtOAc) to furnish the *diol* 4-**2** (4.00 g, 85%) as a yellow oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 5.81-5.96 (2 H, m, C(2)H and C(6)H), 5.27 (2 H, ddd, J = 17.2 Hz, 9.6 Hz and 1.2 Hz, C(1)H and C(7)H), 5.11 (2 H, ddd, J = 11.7 Hz, 10.5 Hz and 1.2 Hz, C(1)H and C(7)H), 4.35-4.48 (2 H, m, C(3)H and C(5)H), 3.19 (2 H, br. s, OH), 1.66 - 1.78 (2 H, m, C(4)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 140.5 (2 C), 114.7 (2 C), 73.1 (2 C), 42.9. *The spectroscopic properties of this compound were consistent with the data reported in the literature* [102]

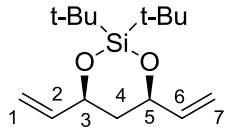
(*4R,6S*)-2,2-Di-*tert*-butyl-4,6-divinyl-1,3,2-dioxasilyane 4-**3a**



4-**2** 4-**3a**

To a solution of hepta-1,6-diene-3,5-diol 4-**2** (2.00 g, 15.6 mmol) in pyridine (10 mL) was added a solution of di-*tert*-butylsilanediyl bis(trifluoromethanesulfonate) (5.50 mL, 17.0 mmol) in pyridine (10 mL) under an atmosphere of argon at 0 °C. The reaction mixture was stirred at room temperature overnight and was concentrated in vacuo. The residue was

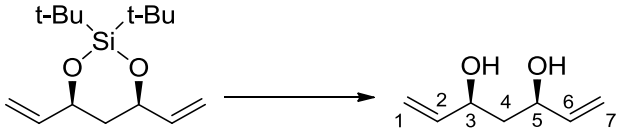
re-disolved in Et_2O (20 mL) and was washed with saturated aqueous solution of NH_4Cl (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 99:1 Petrol-PhMe) to furnish the *silyl-ether* 4-**3a** (1.13 g, 27%) as a colourless oil. (analytical data see page **201**)



4-**3a**

^{1}H-NMR (400 MHz, $CDCl_3$): δ_H: 5.85 (2 H, ddd, J = 17.0 Hz, 10.4 Hz and 4.6 Hz, C(2)H and C(6)H), 5.30 - 5.36 (2 H, dtt, J = 17.0 Hz, 1.7 Hz and 0.6 Hz, C(1)H and C(7)H), 5.06-5.10 (2 H, dtt, J = 10.4 Hz, 1.7 Hz, 0.6 Hz, C(1)H and C(7)H), 4.59-4.65 (2 H, m, C(3)H and C(5)H), 1.79-1.73 (1 H, dtt, J = 14.2 Hz, 2.3 Hz and 0.5 Hz, C(4)H), 1.53 (1 H, dt, J = 14.2 Hz and 11.5 Hz, C(4)H), 1.06 (9 H, s, 3 x C(*t*-Bu)H_3), 1.03 (9 H, s, 3 x C(*t*-Bu)H_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 140.6 (2 C), 113.2 (2 C), 74.0 (2 C), 42.2, 27.4, 27.2, 22.7 (3 C), 19.9 (3 C). *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[103]

(*3R,5S*)-Hepta-1,6-diene-3,5-diol 3-**63**

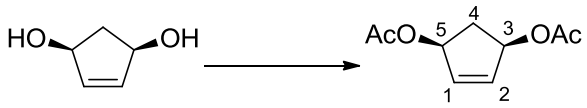


4-**3a** 3-**63**

To a solution of silyl ether 4-**3b** (1.30 g, 4.85 mmol) in THF (5 mL) was added dropwise tetrabutylammonium fluoride (14.6 mL, 14.6 mmol, 1 M in THF) over a period of 2 minutes and the reaction mixture was heated at reflux under an atmosphere of argon for 1 hour. The reaction mixture was quenched with saturated solution of NH_4Cl (2 mL). The aqueous layer

was extracted with EtOAc (3 x 30 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 95:05 Petrol-EtOAc) to furnish the *diol* 3-**63** (528 mg, 86%) as a colourless oil. **R_f** (Petrol-EtOAc) 0.1; **IR** υ_{max} (thin film)/cm^{-1} 3352, 2922, 1645, 1424, 1067; **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 5.88 (2 H, ddd, *J* = 17.0 Hz, 10.6 Hz and 5.9 Hz, C(2)H and C(6)H), 5.27 (2 H, dt, *J* = 17.0 Hz and 1.3 Hz, C(1)H and C(7)H), 5.11 (2 H, dt, *J* = 10.6 Hz and 1.1 Hz, C(1)H and C(7)H), 4.40 (2 H, dt, *J* = 7.0 Hz and 5.9 Hz, C(3)H and C(5)H), 3.16 (2 H, br. s, OH), 1.68 - 1.73 (2 H, m, C(4)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 140.5 (2 C), 114.7 (2 C), 73.1 (2 C), 42.9; **MS** (ESI^+) ***m/z*** 151 ($M + Na^+$, 40%); **HRMS** (ESI^+) Calcd. for $C_7H_{12}NaO_2$ $[M+Na]^+$: 151.0735. Found: 151.0724 (3.3 ppm).

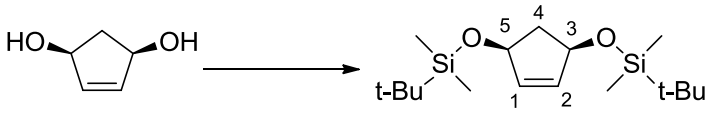
(*1R,3S*)-Cyclopent-4-ene-1,3-diyl diacetate 4-**6a**



4-**6a**

((*1R,3S*)-Cyclopent-4-ene-1,3-diol (200 mg, 2.00 μmol) was subjected to General Procedure **C**. The crude product was purified by flash column chromatography (SiO_2, 9:1 Petrol-EtOAc) to furnish the *di-acetyl* 4-**6a** (283 mg, 80%) as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 6.01 (2 H, d, *J* = 0.8 Hz, C(1)H and C(2)H), 5.46 (2 H, ddd, *J* = 7.6 Hz and 3.9 Hz and 0.8 Hz, C(3)H and C(5)H), 2.80 (1 H, dt, *J* = 15.0 Hz and 7.6 Hz, C(4)H), 1.97 (6 H, s, 2 x CH_3), 1.65 (1 H, dt, *J* = 15.0 Hz and 3.9 Hz, C(4)H); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 170.5 (2 C), 134.5 (2 C), 76.5 (2 C), 37.1, 21.0 (2 C). *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[97]

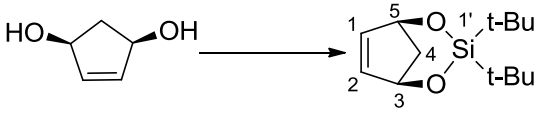
(*3R,5S*)-3,5-Bis((tert-butyldimethylsilyl)oxy)cyclopent-1-ene 4-**6b**



4-**6b**

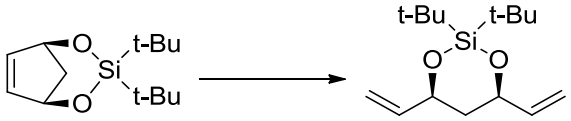
To a suspension of solution of NaH (160 mg, 4.20 mmol, 60% in oil) in THF (10 mL) was added (*1R,3S*)-cyclopent-4-ene-1,3-diol (200 mg, 2.00 mmol) under an atmosphere of argon. The reaction the mixture was stirred for 30 minutes and a solution of *tert*-butyl-dimethylsilylchloride (630 mg, 4.20 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred for a further 30 minutes and was quenched with aqueous saturated solution of NH_4Cl (10 mL). The aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 9:1 Petrol-PhMe) to furnish the *silyl-ether* 4-**6b** (505 mg, 77%) as a colorless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 5.80 (2 H, s, C(1)H and C(2)H), 4.63 (2 H, t, J = 6.6 Hz, C(3)H and C(5)H), 2.67 (1 H, dt, J = 12.9 Hz and 7.1 Hz, C(4)H), 1.54 (1 H, dt, J = 12.7 Hz and 6.2 Hz, C(4)H), 0.91 (18 H, s, 6 x C(*t*-Bu)H_3), 0.09 (12 H, d, J = 2.3 Hz, 4 x CH_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 131.9 (2 C), 77.9 (2 C), 45.3, 25.9, 18.2 (6 C), ~4.5 (4 C). *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[113]

(*1R,3S*)-1,1-Di-*tert*-butyl-1,3-dioxa-1-silabicyclo[3.2.1]oct-4-ene 4-**8**



4-**8**

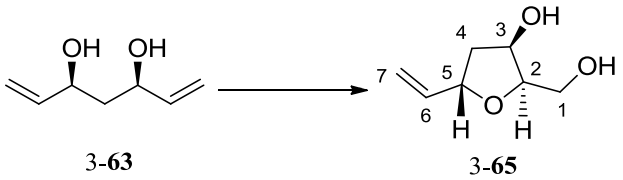
To a suspended solution of hepta-1,6-diene-3,5-diol (500 mg, 5.00 mmol) and 2,6-lutidine (1.50 mL, 15.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise di-*tert*-butylsilanediyl bis(trifluoromethanesulfonate) (5.45 mL, 17.0 mmol) at 0 °C under an atmosphere of argon. The reaction mixture was stirred at 0°C for 10 minutes and was allowed to warm up to room temperature and concentrated *in vacuo*. The residue was re-disolved in Petrol and the suspended solution was filtered, the filtrate was concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 95:05 Petrol-PhMe) to furnish the *silyl-ether* 4-**8** (960 mg, 80%) as a colourless oil. **^{1}H-NMR** (400 MHz, $CDCl_3$): δ_H: 6.47 (2 H, s, C(1)H and C(2)H), 4.80 (2 H, dt, *J* = 1.5 Hz and 0.7 Hz, C(3)H and C(5)H), 2.50 (1 H, dd, *J* = 12.4 Hz and 0.6 Hz, C(4)H), 1.81 (1 H, dt, *J* = 12.4 Hz and 3.1 Hz, C(4)H), 1.04 (9 H, s, 3 x C(*t*-Bu)H_3), 0.96 (9 H, s, 3 x C(*t*-Bu)H_3); **^{13}C-NMR** (100 MHz, $CDCl_3$): δ_C: 140.0 (2 C), 76.1 (2 C), 44.5, 28.8, 28.0, 21.3 (3 C), 20.7 (3 C) *The spectroscopic properties of this compound were consistent with the data reported in the literature.*[103]



4-**8** 4-**3a**

A flame dry Schlenk flask containing PhMe/CH_2Cl_2 (1:1, 5 mL) was purged with ethylene gas at 0 °C for 10 minutes. 3% G-H II catalyst (100 mg, 416 µmol) was added to the solution and the reaction mixture was stirred under continuous pressure of ethylene gas for 10 minutes. To the reaction mixture was added dropwise *via* syringe pump (10 mL/ 1h.) *silyl ether* 4-**8** (300 mg, 1.25 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred further for 10 minutes and was diluted with petrol (10 mL). The solution was loaded on silica and was purified by flash column chromatography (SiO_2, 95:5 Petrol-PhMe) to furnish the *silyl-ether* 4-**3b** (80.4 mg, 72%) as a colourless oil. (analytical data see page **200**)

(*2S,3R,5R*)-2-(Hydroxymethyl)-5-vinyltetrahydrofuran-3-ol 3-**65**

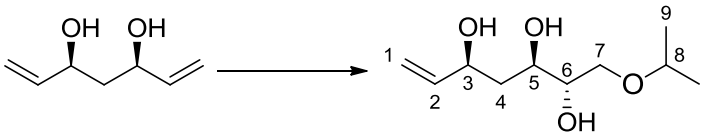


3-**63** 3-**65**

To a solution of Ti(*i*-PrO)$_4$ (267 mg, 0.94 mmol) in CH_2Cl_2 (2 mL) was added D-(−)-Diisopropyl tartrate (220 mg, 0.94 mmol) under an atmosphere of argon at – 30 °C. The reaction mixture was stirred in 30 minutes and a solution of (*3R,5S*)-hepta-1,6-diene-3,5-diol 3-**63** (100 mg, 0.78 mmol) in CH_2Cl_2 (0.2 mL) was added. The reaction mixture was stirred in 30 minutes and TBHP (77.4 mg, 0.86 mmol) was added dropwise. The reaction mixture was left in the freezer at ~20 °C overnight. The reaction mixture was quenched with tartaric acid (1.29 g, 1.62 mmol) and $FeSO_4.7H_2O$ (2.39 g, 8.58 mmol) in H_2O (5 mL/mmol) at 0 °C. The mixture was stirred in 30 minutes and the aqueous layer was extracted with CH_2Cl_2 (4 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was re-dissolved in NaOH/NaCl (0.75 M in brine) solution at 0 °C and was stirred in 30 minutes. The aqueous layer was extracted with EtOAc (3x 15 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 9:1 Petrol-EtOAc) to furnish the *trans-THF* 3-**65** (61.9 mg, 55%) as a colourless oil. **R_f** (1:1 Petrol-EtOAc) 0.2; **IR** υ_{max} (thin film)/cm^{-1} 3365, 2930, 2361, 2341, 1427, 1261; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ_H: 5.86 (1 H, ddd, *J* = 17.1 Hz, 10.4 Hz and 6.7 Hz, C(6)H), 5.32 (1 H, dt, *J* = 17.1 Hz and 1.3 Hz, C(7)H), 5.18 (1 H, dt, *J* = 10.4 Hz and 1.2 Hz, C(7)H), 4.62 (1 H, dt, *J* = 10.9 Hz and 6.7 Hz, C(5)H), 4.36 (1 H, tt, *J* = 5.8 Hz and 2.5 Hz, C(3)H), 3.92 (1 H, td, *J* = 4.3 Hz and 3.1 Hz, C(2)H), 3.76 (1 H, dd, *J* = 11.6 Hz and 4.1

Hz, C(1)H), 3.65 (1 H, dd, *J* = 11.6 Hz and 4.7 Hz, C(1)H), 2.06 (1 H, ddd, *J* = 13.3 Hz, *J* = 5.7 Hz and 2.2 Hz, C(4)H), 1.88 (1 H, ddd, *J* = 13.3 Hz, *J* = 9.8 Hz and 6.3 Hz, C(4)H), 1.26 (1 H, s, OH), 1.19 (1 H, d, *J* = 6.1 Hz, OH); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ_C: 137.8, 116.7, 86.9, 79.5, 73.8, 63.3, 42.1; **MS** (ESI^+) 167 ***m/z*** ($M + Na^+$, 30%); **HRMS** (ESI^+) Calcd. for $C_7H_{12}NaO_3$ $[M+Na]^+$: 167.0684. Found: 167.0679 (–3.0 ppm).

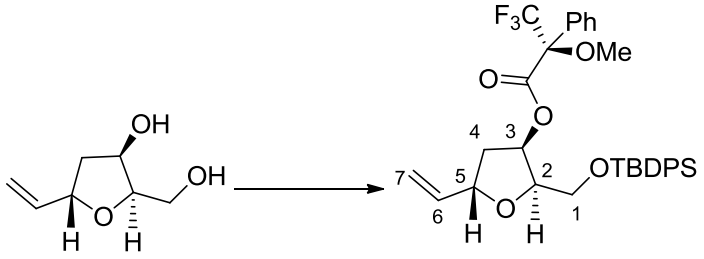
***(2S,3R,5S)*-1-Isopropoxyhept-6-ene-2,3,5-triol** 4-**18**



3-**63** 4-**18**

R$_f$ (1:1 Petrol-EtOAc) 0.1; **IR** ***υ*$_{max}$** (thin film)/cm^{-1} 3356, 2915, 1620, 1420; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ_H: 5.91 (1 H, ddd, *J* = 17.1 Hz, 10.4 Hz and 5.6 Hz, C(2)H), 5.42 (1 H, dt, *J* = 17.2 Hz 1.5 Hz, C(1)H), 5.10 (1 H, dt, *J* = 10.4 Hz 1.5 Hz, C(1)H), 4.42-4.36 (1 H, m, C(3)H), 3.90 (1 H, dt, *J* = 9.6 Hz and 3.0 Hz, C(5)H), 3.57-3.52 (1 H, m, C(6)H), 3.44 (1 H, dd, *J* = 9.3 Hz and 4.5 Hz, C(7)H), 3.37-3.28 (2 H, m, C(7)H and C(8)H), 3.14 (1 H, br. s, OH), 2.81 (1H, br. s, OH), 1.91 (1 H, dt, *J* = 14.3 Hz and 9.6 Hz, C(4)H), 1.61 (1 H, dt, *J* = 14.4 Hz and 3.0 Hz, C(4)H), 1.46 (1 H, br. s, OH), 1.07- 1.00 (6 H, m, 2 x C(9)H_3); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ_C: 141.9, 113.7, 72.8, 72.5, 72.4, 72.3, 70.4, 40.4, 22.0, 21.9; **MS** (ESI^+) 227 ***m/z*** ($M + Na^+$, 80%); **HRMS** (ESI^+) Calcd. for $C_{10}H_{20}NaO_4$ $[M+Na]^+$: 227.1259. Found: 227.1254 (–0.6 ppm).

(*R*)-(2*S*,3*R*,5*R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-5-vinyltetrahydrofuran-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 4-**20**



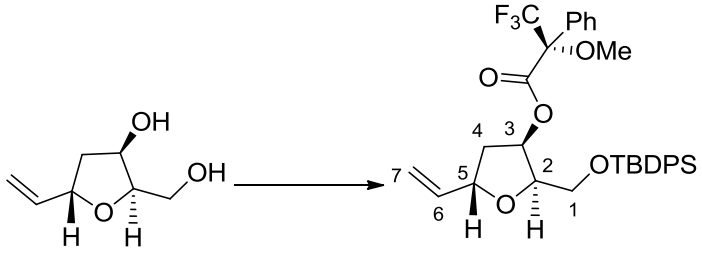
3-**65** 4-**20**

To a solution of THF 3-**65** (10.0 mg, 69.0 μmol) in CH_2Cl_2 (1 mL) was added imidazole (6.00 mg, 83.0 μmol) and was stirred for 10 minutes at 0 °C. To the reaction mixture was added Chloro(methyl)diphenylsilane (20.0 μL, 76.0 μmol) in CH_2Cl_2 (0.5 mL) and was allowed to warm up to ambient temperature. The reaction mixture was stirred overnight and was concentrated *in vacuo*. The crude product 4-**19** was used in the next step without prior purification.

To a solution of the crude mono-protected trans-THF 4-**19** in CH_2Cl_2 (1 mL) was added DMAP (13.0 mg, 0.10 mmol) and was stirred for 10 minutes at 0 °C. (*R*)-(+)-α-Methoxy-α-trifluoromethylphenylacetic acid (25.0 mg, 0.1 mmol) was subjected to General Procedure **C** and was added to the reaction mixture. The reaction mixture was allowed to warm up to ambient temperature and was stirred further for 36 hours and was concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 9:1 Petrol-EtOAc) to furnish the *THF* 4-**20** (27.1 mg, 67%) as a colourless oil. **R_f** (3:1 Petrol-EtOAc) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 2916, 2850, 1744, 1470, 1260, 1171, 1112; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ_H: 7.72-7.66 (4 H, m, ArH), 7.52 (2 H, d, *J* = 7.9 Hz, ArH), 7.46-7.37 (9 H, m, ArH), 5.86 (1 H, ddd, *J* = 17.2 Hz, 10.4 Hz and 6.8 Hz, C(6)H), 5.63 (1 H, d, *J* = 5.4 Hz, C(3)H), 5.32 (1 H, d,

J = 17.0 Hz, C(7)H), 5.18 (1 H, d, *J* = 10.4 Hz, C(7)H), 4.45 (1 H, dt, *J* = 11.0 Hz and 5.7 Hz, C(5)H), 4.00-3.98 (1 H, m, C(2)H), 3.85 (1 H, dd, *J* = 10.9 and 3.3 Hz, C(1)H), 3.71 (1 H, dd, *J* = 11.0 Hz and 4.4 Hz, C(1)H), 3.56 (3 H, s, OMe), 2.18 (1 H, dd, *J* = 13.9 Hz and 4.7 Hz, C(4)H), 2.04 (1 H, ddd, *J* = 13.6 Hz, 11.0 Hz and 5.7 Hz, C(4)H), 1.06 (9 H, s, 3x C(*t*-Bu)H_3); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ_C: 166.1, 137.1, 135.7 (2 C), 135.6 (2 C), 133.1, 132.9, 131.9, 129.8 (2 C), 129.7 (CF_3, 3 signals), 128.5, 127.8, 127.7, 127.3, 117.3, 84.7, 80.0, 79.3, 64.0, 55.4, 39.9, 31.9, 29.7, 29.3, 26.8 (3 C), 22.7, 19.2, 14.1; **MS** (ESI^+) 167 ***m/z*** 621 ($M + Na^+$, 60%); **HRMS** (ESI^+) Calcd. for $C_{33}H_{37}NaF_3O_5$ $[M+Na]^+$: 621.2260. Found: 621.2255 (–0.8 ppm).

(*S*)-(*2S*,*3R*,*5R*)-2-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-5-vinyltetrahydrofuran-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 4-**21**



3-**65** 4-**21**

To a solution of trans-THF 3-**65** (5.00 mg, 35.0 µmol) in CH_2Cl_2 (1 mL) was added imidazole (3.00 mg, 42.0 µmol) and was stirred for 10 minutes at 0 °C. To the reaction mixture was added Chloro(methyl)diphenylsilane (10 µL, 38 µmol) in CH_2Cl_2 (0.5 mL) and was allowed to warm up to ambient temperature. The reaction mixture was stirred overnight and was concentrated *in vacuo*. The crude product 4-**19** was used in the next step without prior purification.

To a solution of the crude mono-protected trans-THF 4-**19** in CH_2Cl_2 (1 mL) was added DMAP (9.00 mg, 78.0 µmol) and the reaction mixture was stirred for 10 minutes at 0 °C. To

the reaction mixture was added (*S*)-(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride (18.0 mg, 78.0 μmol) and the reaction mixture was allowed to warm up to ambient temperature and was stirred for 36 hours and was concentrated *in vacuo*. The crude product was purified by flash column chromatography (SiO_2, 9:1 Petrol-EtOAc) to furnish the di-protected *THF* 4-**21** (15.1 mg, 70%) as a colourless oil. **R_f** (3:1 Petrol-EtOAc) 0.7; **IR** υ_{max} (thin film)/cm^{-1} 2921, 2849, 1744, 1470, 1172; **^{1}H-NMR** (500 MHz, $CDCl_3$): δ_H: 7.72-7.67 (4 H, m, ArH), 7.53 (2 H, d, *J* = 7.9 Hz, ArH), 7.46-7.37 (9 H, m, ArH), 5.84 (1 H, ddd, *J* = 17.1 Hz, 10.3 Hz and 6.9 Hz, C(6)H), 5.60 (1 H, d, *J* = 5.4 Hz, C(3)H), 5.30 (1 H, d, *J* = 17.3 Hz, C(7)H), 5.17 (1 H, d, *J* = 10.4 Hz, C(7)H), 4.40 (1 H, dt, *J* = 11.0 Hz and 5.7 Hz, C(5)H), 4.11-4.09 (1 H, m, C(2)H), 3.85 (1 H, dd, *J* = 10.9 Hz and 3.3 Hz, C(1)H), 3.70 (1 H, dd, *J* = 11.0 Hz and 4.7 Hz, C(1)H), 3.55 (3 H, s, OMe), 2.12-2.05 (1 H, m, C(4)H), 2.04-1.97 (1 H, m, C(4)H), 1.07 (9 H, s, 3 x C(*t*-Bu)H_3); **^{13}C-NMR** (125 MHz, $CDCl_3$): δ_C: 166.1, 137.1, 135.6 (2 C), 135.5 (2 C), 133.0, 132.9, 132.2, 129.8 (CF_3, 3 signals), 129.7, 128.5, 127.6, 127.7, 127.2, 117.3, 84.6, 80.0, 79.4, 64.1, 55.4, 38.7, 34.1, 31.9, 29.7, 29.3, 26.8 (3 C), 22.3, 19.2, 14.0; **MS** (ESI^+) 167 ***m/z*** 621 ($M + Na^+$, 70%); **HRMS** (ESI^+) Calcd. for $C_{33}H_{37}NaF_3O_5$ $[M+Na]^+$: 621.2260. Found: 621.2255 (–0.8 ppm).

Appendix

Appendix 1

structure report

Abstract

Computing details

Data collection: *COLLECT* (Nonius, 1997-2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

References

Altomare, A., Cascarano, G., Giacovazzo, C., Guagliardi, A., Burla, M. C., Polidori, G. & Camalli, M. (1994). J. Appl. Cryst. 27, 435.

Betteridge, P. W., Carruthers, J. R., Cooper, R. I., Prout, K. & Watkin, D. J. (2003). J. Appl. Cryst. 36, 1487.

Nonius (1997–2001). *COLLECT*. Nonius BV, Delft, The Netherlands.

Otwinowski, Z. & Minor, W. (1997). Methods in Enzymology, Vol. 276, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.

Watkin, D. J., Prout, C. K. & Pearce, L. J. (1996). *CAMERON*, Chemical Crystallography Laboratory, Oxford, UK.

(1)

Crystal data

$C_7H_{12}O_2$	$F(000) = 560$
$M_r = 128.17$	$D_x = 1.283$ Mg m^{-3}
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation, $\lambda = 0.71073$ Å
$a = 6.4079$ (2) Å	Cell parameters from 2943 reflections
$b = 21.1852$ (7) Å	$\theta = 5$–$27°$
$c = 9.7921$ (3) Å	$\mu = 0.09$ mm^{-1}
$\beta = 93.1968$ (16)°	$T = 150$ K
$V = 1327.23$ (7) Å^3	Plate, Colourless
$Z = 8$	0.24 × 0.06 × 0.06 mm

structure report

Data collection

Area diffractometer	1614 reflections with $I > 2.0\sigma(I)$
graphite	$R_{int} = 0.045$
ω scans	$\theta_{max} = 27.4°$, $\theta_{min} = 5.1°$
Absorption correction: Multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)	$h = -8 \rightarrow 8$
$T_{min} = 0.99$, $T_{max} = 0.99$	$k = -27 \rightarrow 26$
5396 measured reflections	$l = -12 \rightarrow 12$
3004 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Hydrogen site location: Inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.045$	H-atom parameters constrained
$wR(F^2) = 0.093$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.0P)^2 + 1.11P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$S = 0.90$	$(\Delta/\sigma)_{max} = 0.0004$
2295 reflections	$\Delta\rho_{max} = 0.40$ e Å^{-3}
163 parameters	$\Delta\rho_{min} = -0.35$ e Å^{-3}
0 restraints	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.1997 (2)	0.52967 (7)	0.66352 (13)	0.0335
C2	0.3073 (3)	0.57715 (10)	0.59129 (19)	0.0262
C3	0.3326 (3)	0.56144 (9)	0.43756 (18)	0.0241
O4	0.21059 (19)	0.50661 (6)	0.40222 (14)	0.0300
C5	0.2452 (3)	0.62041 (9)	0.36564 (19)	0.0265
C6	0.3945 (3)	0.67584 (10)	0.3993 (2)	0.0328
C7	0.3522 (3)	0.69150 (10)	0.5504 (2)	0.0336
C8	0.1938 (3)	0.64080 (10)	0.5857 (2)	0.0308
C9	0.0591 (3)	0.63565 (10)	0.4516 (2)	0.0323
O10	−0.2269 (2)	0.51274 (6)	0.87182 (14)	0.0329
C11	−0.1440 (3)	0.56943 (9)	0.93294 (19)	0.0265
C12	−0.2226 (3)	0.62832 (9)	0.85623 (19)	0.0263
C13	−0.0900 (3)	0.68446 (10)	0.9079 (2)	0.0348
C14	−0.1651 (3)	0.69509 (10)	1.0543 (2)	0.0340
C15	−0.3318 (3)	0.64387 (10)	1.06718 (19)	0.0301
C16	−0.4308 (3)	0.64060 (10)	0.92123 (19)	0.0308
C17	−0.2209 (3)	0.58023 (10)	1.08032 (19)	0.0272
O18	−0.3640 (2)	0.53174 (7)	1.11406 (14)	0.0357
H21	0.4459	0.5823	0.6382	0.0325*
H31	0.4810	0.5556	0.4193	0.0324*
H51	0.2112	0.6141	0.2664	0.0348*
H62	0.3625	0.7119	0.3382	0.0422*
H61	0.5403	0.6637	0.3900	0.0427*
H71	0.2907	0.7343	0.5543	0.0435*

H72	0.4805	0.6895	0.6110	0.0428*
H81	0.1163	0.6496	0.6669	0.0399*
H91	−0.0101	0.6760	0.4263	0.0414*
H92	−0.0435	0.6001	0.4544	0.0414*
H111	0.0092	0.5667	0.9364	0.0325*
H121	−0.2307	0.6220	0.7556	0.0343*
H132	−0.1170	0.7221	0.8507	0.0438*
H131	0.0595	0.6752	0.9108	0.0424*
H141	−0.2282	0.7375	1.0598	0.0445*
H142	−0.0507	0.6910	1.1245	0.0436*
H151	−0.4307	0.6511	1.1402	0.0383*
H161	−0.4966	0.6813	0.8917	0.0392*
H162	−0.5295	0.6050	0.9065	0.0387*
H171	−0.0984	0.5823	1.1492	0.0347*
H41	0.2205	0.5022	0.3171	0.0479*
H11	0.0927	0.5176	0.6102	0.0540*
H101	−0.3410	0.5027	0.9112	0.0539*
H181	−0.3153	0.5141	1.1888	0.0577*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0326 (7)	0.0408 (9)	0.0268 (7)	−0.0099 (7)	−0.0021 (6)	0.0108 (7)
C2	0.0232 (10)	0.0306 (12)	0.0247 (10)	−0.0060 (9)	0.0001 (8)	0.0044 (9)
C3	0.0215 (9)	0.0236 (11)	0.0272 (10)	−0.0032 (8)	0.0027 (8)	−0.0020 (8)
O4	0.0322 (7)	0.0272 (8)	0.0304 (7)	−0.0050 (6)	0.0007 (6)	−0.0017 (6)
C5	0.0307 (11)	0.0269 (11)	0.0215 (10)	−0.0031 (9)	−0.0007 (8)	0.0023 (8)
C6	0.0419 (12)	0.0287 (12)	0.0279 (11)	−0.0069 (10)	0.0039 (9)	0.0014 (9)
C7	0.0422 (12)	0.0296 (12)	0.0293 (11)	−0.0040 (10)	0.0045 (9)	−0.0042 (9)
C8	0.0329 (11)	0.0312 (12)	0.0294 (11)	0.0003 (9)	0.0101 (9)	−0.0031 (9)
C9	0.0264 (10)	0.0293 (12)	0.0410 (12)	0.0049 (9)	0.0005 (9)	0.0052 (10)
O10	0.0332 (8)	0.0287 (8)	0.0371 (8)	−0.0032 (6)	0.0038 (6)	−0.0073 (6)
C11	0.0224 (10)	0.0266 (11)	0.0304 (11)	−0.0009 (8)	−0.0004 (8)	−0.0035 (9)
C12	0.0303 (10)	0.0293 (11)	0.0193 (9)	0.0005 (9)	0.0020 (8)	−0.0011 (8)
C13	0.0434 (12)	0.0289 (12)	0.0327 (11)	−0.0060 (10)	0.0074 (10)	−0.0022 (9)
C14	0.0454 (13)	0.0275 (12)	0.0291 (11)	−0.0014 (10)	0.0026 (9)	−0.0049 (9)
C15	0.0309 (11)	0.0340 (12)	0.0262 (10)	0.0012 (9)	0.0077 (8)	−0.0034 (9)
C16	0.0305 (11)	0.0313 (12)	0.0303 (11)	0.0060 (9)	−0.0004 (9)	0.0015 (9)
C17	0.0251 (10)	0.0326 (12)	0.0235 (10)	−0.0068 (9)	−0.0033 (8)	0.0030 (9)
O18	0.0367 (8)	0.0409 (9)	0.0285 (7)	−0.0151 (7)	−0.0065 (6)	0.0117 (7)

Geometric parameters (Å, º)

O1—C2	1.429 (2)	O10—C11	1.431 (2)
O1—H11	0.876	O10—H101	0.872
C2—C3	1.559 (3)	C11—C12	1.527 (3)
C2—C8	1.532 (3)	C11—C17	1.567 (3)
C2—H21	0.983	C11—H111	0.982
C3—O4	1.432 (2)	C12—C13	1.531 (3)
C3—C5	1.525 (3)	C12—C16	1.532 (3)
C3—H31	0.985	C12—H121	0.993

O4—H41	0.845	C13—C14	1.554 (3)
C5—C6	1.539 (3)	C13—H132	0.984
C5—C9	1.532 (3)	C13—H131	0.976
C5—H51	0.994	C14—C15	1.533 (3)
C6—C7	1.555 (3)	C14—H141	0.987
C6—H62	0.985	C14—H142	0.980
C6—H61	0.978	C15—C16	1.533 (3)
C7—C8	1.531 (3)	C15—C17	1.526 (3)
C7—H71	0.990	C15—H151	0.993
C7—H72	0.988	C16—H161	0.996
C8—C9	1.534 (3)	C16—H162	0.990
C8—H81	0.978	C17—O18	1.428 (2)
C9—H91	0.989	C17—H171	1.007
C9—H92	1.001	O18—H181	0.864

C2—O1—H11	107.0	C11—O10—H101	108.7
O1—C2—C3	114.00 (15)	O10—C11—C12	112.06 (15)
O1—C2—C8	113.35 (16)	O10—C11—C17	112.30 (15)
C3—C2—C8	103.20 (15)	C12—C11—C17	102.81 (15)
O1—C2—H21	107.2	O10—C11—H111	108.1
C3—C2—H21	109.6	C12—C11—H111	111.5
C8—C2—H21	109.5	C17—C11—H111	110.0
C2—C3—O4	108.77 (14)	C11—C12—C13	108.08 (15)
C2—C3—C5	102.45 (15)	C11—C12—C16	101.84 (15)
O4—C3—C5	111.80 (14)	C13—C12—C16	102.17 (16)
C2—C3—H31	110.8	C11—C12—H121	112.1
O4—C3—H31	111.9	C13—C12—H121	115.5
C5—C3—H31	110.7	C16—C12—H121	115.9
C3—O4—H41	104.9	C12—C13—C14	102.87 (16)
C3—C5—C6	108.56 (15)	C12—C13—H132	111.3
C3—C5—C9	101.30 (15)	C14—C13—H132	110.7
C6—C5—C9	102.42 (16)	C12—C13—H131	112.2
C3—C5—H51	113.3	C14—C13—H131	110.9
C6—C5—H51	114.4	H132—C13—H131	108.7
C9—C5—H51	115.6	C13—C14—C15	103.09 (16)
C5—C6—C7	103.13 (15)	C13—C14—H141	109.3
C5—C6—H62	110.9	C15—C14—H141	110.5
C7—C6—H62	111.8	C13—C14—H142	112.1
C5—C6—H61	111.4	C15—C14—H142	112.2
C7—C6—H61	111.3	H141—C14—H142	109.5
H62—C6—H61	108.3	C14—C15—C16	102.10 (16)
C6—C7—C8	102.62 (15)	C14—C15—C17	108.00 (16)
C6—C7—H71	108.9	C16—C15—C17	101.85 (16)
C8—C7—H71	111.3	C14—C15—H151	115.2
C6—C7—H72	112.3	C16—C15—H151	115.5
C8—C7—H72	112.0	C17—C15—H151	112.9
H71—C7—H72	109.5	C15—C16—C12	94.03 (14)
C2—C8—C7	107.84 (16)	C15—C16—H161	112.2
C2—C8—C9	102.18 (16)	C12—C16—H161	113.0
C7—C8—C9	101.82 (16)	C15—C16—H162	113.5
C2—C8—H81	113.5	C12—C16—H162	112.0
C7—C8—H81	115.1	H161—C16—H162	111.1

C9—C8—H81	115.0	C15—C17—C11	102.71 (15)
C8—C9—C5	93.88 (14)	C15—C17—O18	110.68 (16)
C8—C9—H91	112.1	C11—C17—O18	110.30 (15)
C5—C9—H91	113.4	C15—C17—H171	111.1
C8—C9—H92	111.7	C11—C17—H171	110.5
C5—C9—H92	112.9	O18—C17—H171	111.3
H91—C9—H92	111.8	C17—O18—H181	107.5

Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H41···O10^{i}	0.84	1.88	2.722 (3)	175
O1—H11···O4^{i}	0.88	2.01	2.780 (3)	146
O10—H101···O18^{ii}	0.87	2.03	2.797 (3)	146
O18—H181···O1^{iii}	0.86	1.84	2.700 (3)	174

Symmetry codes: (i) −*x*, −*y*+1, −*z*+1; (ii) −*x*−1, −*y*+1, −*z*+2; (iii) −*x*, −*y*+1, −*z*+2.

Appendix 2

structure report

Abstract

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al.*, 2003); molecular graphics: *CAMERON* (Watkin *et al.*, 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al.*, 2003).

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(1)

Crystal data

$C_{21}H_{21}NS$	$F(000) = 680$
$M_r = 319.47$	$D_x = 1.258$ Mg m^{-3}
Monoclinic, *Cc*	Mo *K*α radiation, λ = 0.71073 Å
Hall symbol: C -2yc	Cell parameters from 2062 reflections
$a = 19.0971$ (4) Å	θ = 5–27°
$b = 5.7961$ (1) Å	μ = 0.19 mm^{-1}
$c = 17.7767$ (4) Å	$T = 150$ K
β = 120.9931 (10)°	Prism, Colourless
$V = 1686.75$ (6) Å^3	0.50 × 0.20 × 0.20 mm
$Z = 4$	

structure report

Data collection

Area diffractometer	3029 reflections with $I > 2.0\sigma(I)$
graphite	$R_{int} = 0.000$
ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 5.1°$
Absorption correction: Multi-scan *DENZO/SCALEPACK* (Otwinowski & Minor, 1997)	$h = -23 \rightarrow 24$
$T_{min} = 0.96$, $T_{max} = 0.96$	$k = -6 \rightarrow 7$
3222 measured reflections	$l = -23 \rightarrow 22$
3222 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Structure-invariant direct methods
Least-squares matrix: Full	Hydrogen site location: Inferred from neighbouring sites
$R[F^2 > 2\sigma(F^2)] = 0.034$	No H atoms present
$wR(F^2) = 0.074$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.02P)^2 + 1.25P]$, where $P = (\max(F_o^2,0) + 2F_c^2)/3$
$S = 1.01$	$(\Delta/\sigma)_{max} = 0.0003$
3222 reflections	$\Delta\rho_{max} = 0.18$ e Å^{-3}
208 parameters	$\Delta\rho_{min} = -0.22$ e Å^{-3}
2 restraints	

Special details

Experimental. The crystal was placed in the cold stream of an Oxford Cryosystems open-flow nitrogen cryostat (Cosier & Glazer, 1986) with a nominal stability of 0.1K.

Cosier, J. & Glazer, A.M., 1986. J. Appl. Cryst. 105 107.

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²)

	x	*y*	*z*	U_{iso}*/U_{eq}
S1	0.53675 (7)	0.89461 (8)	0.46082 (7)	0.0242
C2	0.63132 (12)	1.0263 (3)	0.51411 (12)	0.0202
C3	0.67814 (12)	0.9412 (3)	0.48190 (12)	0.0197
N4	0.64054 (11)	0.7759 (3)	0.41737 (11)	0.0209
C5	0.56592 (12)	0.7330 (3)	0.39960 (13)	0.0223
C6	0.51313 (12)	0.5521 (3)	0.33887 (12)	0.0223
C7	0.54734 (13)	0.3795 (3)	0.31320 (13)	0.0256
C8	0.49934 (13)	0.1978 (4)	0.26094 (13)	0.0303
C9	0.41737 (14)	0.1876 (4)	0.23442 (14)	0.0315
C10	0.38244 (14)	0.3592 (4)	0.25839 (14)	0.0321
C11	0.42997 (13)	0.5422 (4)	0.31007 (13)	0.0276
C12	0.76614 (12)	0.9993 (3)	0.51398 (13)	0.0202
C13	0.81873 (12)	0.7807 (3)	0.53975 (14)	0.0258
C14	0.90818 (12)	0.8340 (3)	0.57284 (14)	0.0273
C15	0.91650 (14)	0.9696 (4)	0.50463 (16)	0.0335
C16	0.86522 (13)	1.1902 (4)	0.47968 (16)	0.0317
C17	0.77533 (12)	1.1372 (4)	0.44617 (13)	0.0243

C18	0.65188 (12)	1.1907 (3)	0.58640 (13)	0.0209
C19	0.68895 (12)	1.4007 (3)	0.59085 (13)	0.0220
C20	0.70968 (13)	1.5511 (4)	0.65999 (14)	0.0275
C21	0.69270 (14)	1.4944 (4)	0.72461 (14)	0.0309
C22	0.65422 (14)	1.2881 (4)	0.72005 (14)	0.0316
C23	0.63347 (13)	1.1356 (4)	0.65100 (14)	0.0259
H71	0.6036	0.3861	0.3318	0.0305*
H81	0.5233	0.0828	0.2444	0.0366*
H91	0.3830	0.0608	0.1987	0.0386*
H101	0.3241	0.3482	0.2387	0.0380*
H111	0.4060	0.6633	0.3286	0.0333*
H121	0.7873	1.0965	0.5670	0.0247*
H132	0.8131	0.6949	0.5846	0.0311*
H131	0.7966	0.6826	0.4870	0.0316*
H142	0.9311	0.9252	0.6281	0.0325*
H141	0.9383	0.6849	0.5836	0.0322*
H151	0.9741	1.0121	0.5267	0.0400*
H152	0.8963	0.8765	0.4501	0.0405*
H161	0.8855	1.2905	0.5325	0.0384*
H162	0.8702	1.2758	0.4341	0.0388*
H171	0.7431	1.2808	0.4330	0.0290*
H172	0.7532	1.0427	0.3920	0.0288*
H191	0.7005	1.4446	0.5458	0.0256*
H201	0.7353	1.6964	0.6626	0.0347*
H211	0.7053	1.5995	0.7720	0.0372*
H221	0.6421	1.2500	0.7651	0.0380*
H231	0.6081	0.9893	0.6469	0.0313*

Atomic displacement parameters (Å²)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
S1	0.0188 (2)	0.0297 (2)	0.0263 (2)	−0.0041 (2)	0.01315 (17)	−0.0034 (2)
C2	0.0173 (9)	0.0232 (10)	0.0200 (9)	−0.0009 (7)	0.0096 (7)	0.0025 (7)
C3	0.0181 (8)	0.0234 (9)	0.0170 (8)	−0.0023 (7)	0.0087 (7)	0.0024 (7)
N4	0.0196 (8)	0.0230 (8)	0.0194 (7)	−0.0030 (6)	0.0095 (6)	0.0001 (6)
C5	0.0201 (9)	0.0250 (10)	0.0213 (9)	−0.0007 (7)	0.0103 (7)	0.0028 (7)
C6	0.0199 (9)	0.0263 (10)	0.0182 (8)	−0.0031 (7)	0.0079 (7)	0.0019 (7)
C7	0.0224 (9)	0.0276 (11)	0.0228 (9)	0.0005 (8)	0.0087 (8)	0.0022 (8)
C8	0.0324 (11)	0.0275 (11)	0.0251 (10)	0.0012 (8)	0.0107 (9)	0.0009 (8)
C9	0.0302 (11)	0.0303 (12)	0.0246 (10)	−0.0087 (9)	0.0076 (9)	−0.0034 (9)
C10	0.0227 (10)	0.0416 (13)	0.0269 (10)	−0.0101 (9)	0.0091 (9)	−0.0046 (9)
C11	0.0231 (10)	0.0346 (12)	0.0224 (9)	−0.0049 (8)	0.0098 (8)	−0.0047 (8)
C12	0.0179 (8)	0.0228 (10)	0.0204 (8)	−0.0036 (7)	0.0102 (7)	−0.0014 (7)
C13	0.0219 (10)	0.0231 (10)	0.0334 (10)	−0.0004 (8)	0.0150 (8)	0.0049 (8)
C14	0.0205 (9)	0.0263 (11)	0.0350 (11)	0.0011 (8)	0.0143 (8)	0.0015 (8)
C15	0.0292 (11)	0.0309 (12)	0.0504 (13)	0.0015 (9)	0.0277 (10)	0.0042 (9)
C16	0.0263 (10)	0.0278 (11)	0.0489 (12)	−0.0014 (8)	0.0251 (10)	0.0070 (9)
C17	0.0226 (9)	0.0249 (10)	0.0285 (9)	−0.0014 (7)	0.0154 (8)	0.0027 (8)
C18	0.0184 (8)	0.0242 (10)	0.0210 (8)	0.0019 (7)	0.0107 (7)	0.0012 (7)
C19	0.0204 (9)	0.0236 (10)	0.0220 (9)	0.0014 (7)	0.0108 (7)	0.0019 (7)
C20	0.0298 (10)	0.0236 (10)	0.0286 (10)	0.0015 (8)	0.0146 (8)	−0.0016 (8)

C21	0.0379 (11)	0.0291 (12)	0.0287 (10)	0.0021 (9)	0.0192 (9)	−0.0045 (8)
C22	0.0392 (11)	0.0333 (12)	0.0317 (11)	0.0040 (9)	0.0248 (10)	0.0002 (9)
C23	0.0285 (10)	0.0265 (10)	0.0301 (10)	−0.0007 (8)	0.0204 (9)	0.0011 (8)

Geometric parameters (Å, º)

S1—C2	1.7261 (18)	C13—H131	0.986
S1—C5	1.7311 (19)	C14—C15	1.520 (3)
C2—C3	1.378 (2)	C14—H142	0.996
C2—C18	1.481 (3)	C14—H141	1.000
C3—N4	1.379 (2)	C15—C16	1.531 (3)
C3—C12	1.509 (2)	C15—H151	0.990
N4—C5	1.315 (2)	C15—H152	0.997
C5—C6	1.470 (3)	C16—C17	1.531 (3)
C6—C7	1.394 (3)	C16—H161	0.997
C6—C11	1.397 (3)	C16—H162	0.996
C7—C8	1.391 (3)	C17—H171	0.988
C7—H71	0.948	C17—H172	0.993
C8—C9	1.384 (3)	C18—C19	1.390 (3)
C8—H81	0.938	C18—C23	1.400 (2)
C9—C10	1.382 (3)	C19—C20	1.388 (3)
C9—H91	0.972	C19—H191	0.966
C10—C11	1.391 (3)	C20—C21	1.384 (3)
C10—H101	0.983	C20—H201	0.963
C11—H111	0.983	C21—C22	1.384 (3)
C12—C13	1.533 (3)	C21—H211	0.965
C12—C17	1.530 (2)	C22—C23	1.394 (3)
C12—H121	0.989	C22—H221	0.967
C13—C14	1.525 (3)	C23—H231	0.961
C13—H132	0.991		

C2—S1—C5	89.99 (9)	C13—C14—H142	108.9
S1—C2—C3	109.45 (14)	C15—C14—H142	109.8
S1—C2—C18	119.71 (13)	C13—C14—H141	108.5
C3—C2—C18	130.71 (16)	C15—C14—H141	108.2
C2—C3—N4	115.04 (15)	H142—C14—H141	110.7
C2—C3—C12	126.72 (17)	C14—C15—C16	110.42 (16)
N4—C3—C12	118.11 (16)	C14—C15—H151	111.3
C3—N4—C5	111.53 (15)	C16—C15—H151	108.8
S1—C5—N4	113.99 (14)	C14—C15—H152	110.4
S1—C5—C6	121.78 (13)	C16—C15—H152	107.5
N4—C5—C6	124.06 (16)	H151—C15—H152	108.3
C5—C6—C7	119.50 (16)	C15—C16—C17	111.55 (17)
C5—C6—C11	121.27 (17)	C15—C16—H161	109.5
C7—C6—C11	119.13 (17)	C17—C16—H161	107.3
C6—C7—C8	120.21 (18)	C15—C16—H162	109.7
C6—C7—H71	119.6	C17—C16—H162	109.9
C8—C7—H71	120.1	H161—C16—H162	108.8
C7—C8—C9	120.0 (2)	C16—C17—C12	111.03 (15)
C7—C8—H81	119.2	C16—C17—H171	111.1
C9—C8—H81	120.8	C12—C17—H171	108.5

C8—C9—C10	120.34 (19)	C16—C17—H172	108.6
C8—C9—H91	121.3	C12—C17—H172	108.1
C10—C9—H91	118.3	H171—C17—H172	109.4
C9—C10—C11	119.89 (19)	C2—C18—C19	120.83 (16)
C9—C10—H101	118.8	C2—C18—C23	119.89 (17)
C11—C10—H101	121.3	C19—C18—C23	119.28 (17)
C6—C11—C10	120.4 (2)	C18—C19—C20	120.33 (18)
C6—C11—H111	119.0	C18—C19—H191	120.7
C10—C11—H111	120.6	C20—C19—H191	119.0
C3—C12—C13	111.06 (15)	C19—C20—C21	120.27 (19)
C3—C12—C17	112.11 (15)	C19—C20—H201	119.8
C13—C12—C17	110.12 (15)	C21—C20—H201	119.9
C3—C12—H121	108.4	C20—C21—C22	120.05 (19)
C13—C12—H121	107.6	C20—C21—H211	121.0
C17—C12—H121	107.3	C22—C21—H211	118.9
C12—C13—C14	112.29 (16)	C21—C22—C23	120.07 (18)
C12—C13—H132	109.2	C21—C22—H221	119.7
C14—C13—H132	110.8	C23—C22—H221	120.2
C12—C13—H131	107.4	C18—C23—C22	119.98 (19)
C14—C13—H131	109.3	C18—C23—H231	118.0
H132—C13—H131	107.7	C22—C23—H231	122.0
C13—C14—C15	110.70 (16)		

Appendix 3

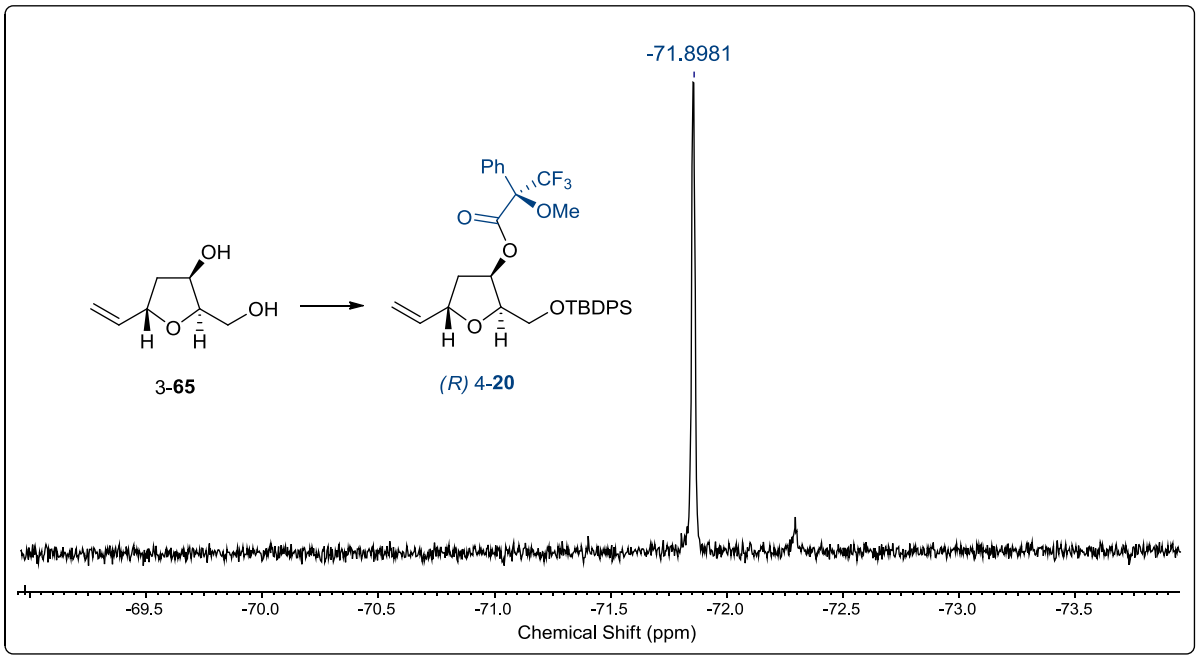

Figure A1 – The 250 MHz ^{19}F-NMR spectrum of the Mosher's ester *(R)*-4-**20** indicated presence of a single stereoisomer, with the diognistic ^{19}F chemical shift at δ–71.8981 ppm.

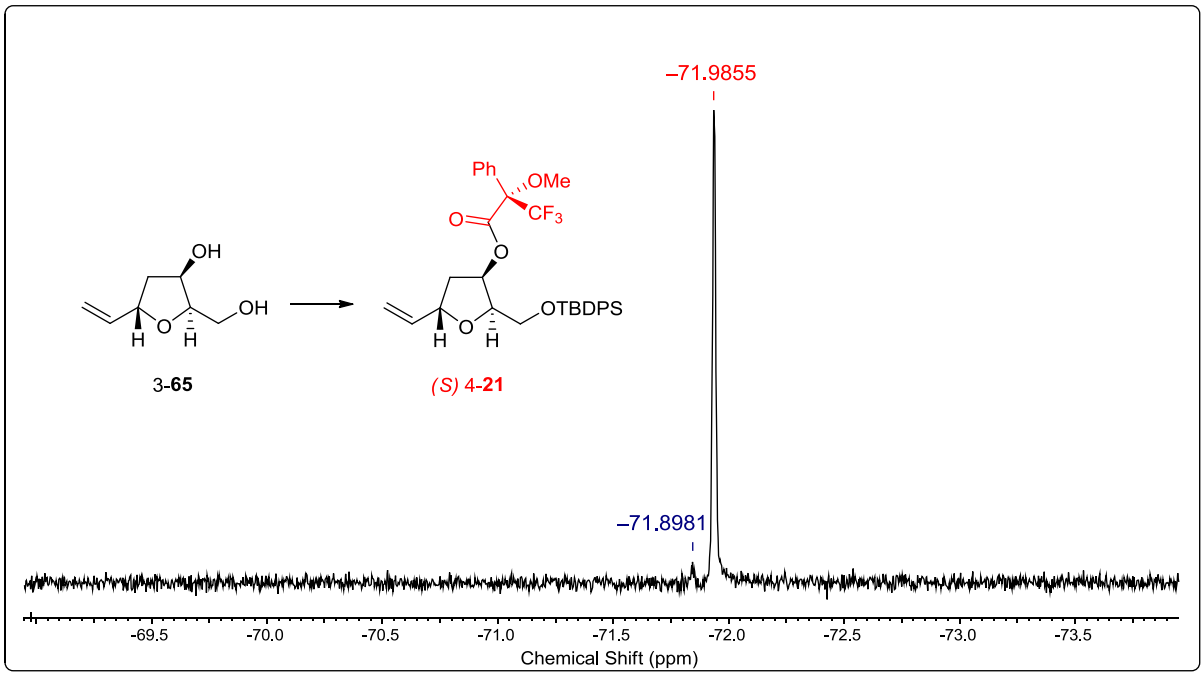

Figure A2 – The 250 MHz ^{19}F-NMR spectrum of the Mosher's ester *(S)*-4-**21** indicated presence of a single stereoisomer, with the diagnostic ^{19}F chemical shift at δ–71.9855 ppm.

Appendix 4

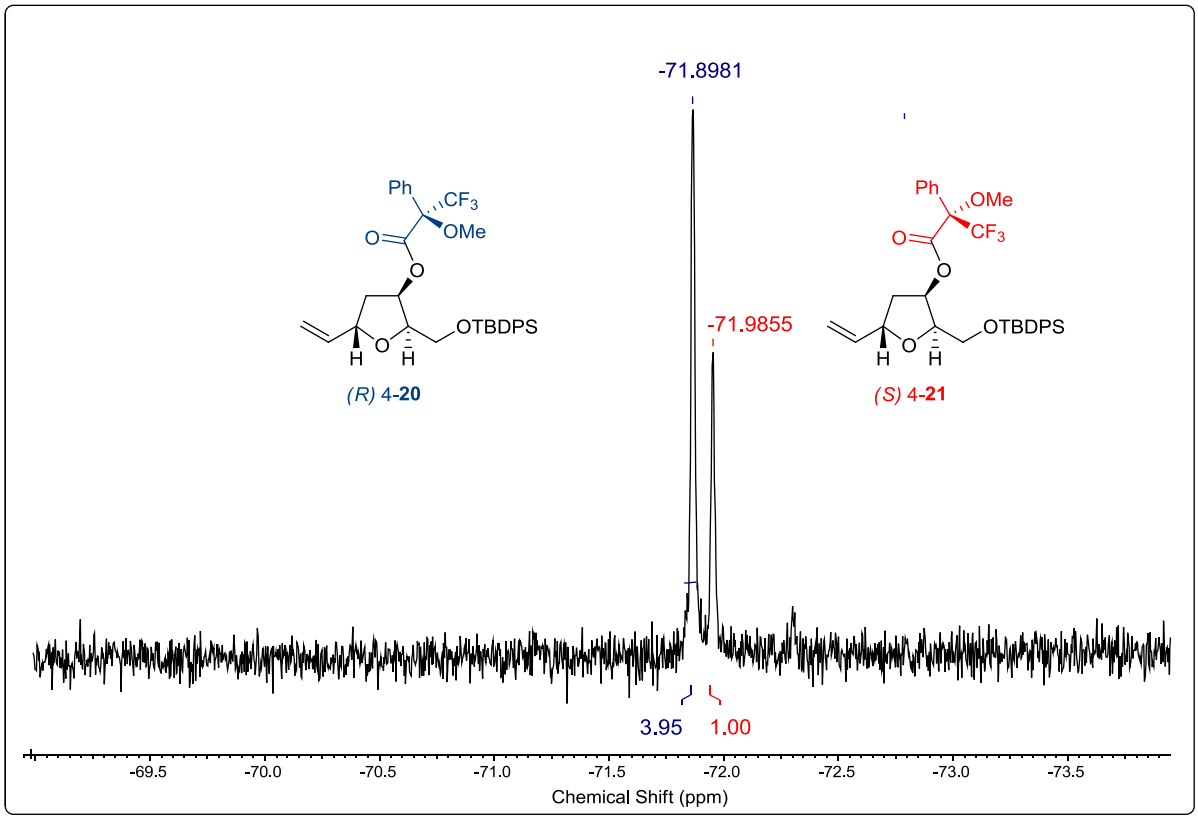

Figure A3 – The 250 MHz ^{19}F-NMR spectrum of a ~4:1 racemic mixture of Mosher's esters *(R)*- 4-**20** and *(S)*- 4-**21**, provided further evidence that the signal at δ –71.8981 ppm corresponds to *(R)*- 4-**20** and the signal at δ –71.9855 corresponds to *(S)*- 4-**21**.

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