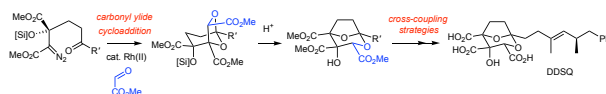


Evolution of a cycloaddition–rearrangement approach to the squalestatins: a quarter-century odyssey

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Abstract The highs, lows and diversions of a journey leading to two syntheses of 6,7-dideoxysqualstatin H5 is described. Both syntheses relied on highly diastereoselective *n*-alkylations of a tartrate acetonide enolate and subsequent oxidation–hydrolysis to provide an asymmetric entry to β-hydroxy-α-ketoester motifs. The latter were differentially elaborated to diazoketones which underwent stereo- and regioselective Rh(II)-catalysed cyclic carbonyl ylide formation–cycloaddition and then acid-catalysed transketalisation to generate the 2,8-dioxabicyclo[3.2.1]octane core of the squalestatin/zaragolic acids at the correct tricarboxylate oxidation level. The unsaturated side-chain was either protected with a bromide substituent during the transketalisation, or introduced afterwards by a stereoretentive Ni-catalyzed Csp³–Csp² cross-electrophile coupling.

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Key words zaragolic acid, squalestatin, tartrate alkylation, squarate, α-ketoester, cross-coupling, alkene protection, ozonolysis

1 Introduction

Following Peter Vollhardt's invitation to contribute an Encore Account to our 2006 essay on lithiated epoxides and aziridines² and his reassurances against the principal author's (DMH's) wariness of stepping in the same river twice, the following provides an overview of our synthetic studies to the

squalestatins. Once again an attempt has been made to keep the tone of this article in line with the original aims of these Accounts.³ Like the lithiated epoxide research programme our squalestatin studies, although only recently completed, can also be traced back to the start of DMH's independent academic career at the University of Reading in 1990. At that time, occasional departmental trips would be arranged to see prominent external speakers visiting the Dyson Perrins Laboratory in nearby Oxford. The first of these DMH attended in October 1990 was given by Al Padwa, whose emerging studies with diazo carbonyl compounds in Rh(II)-catalysed tandem carbonyl ylide formation–1,3-dipolar cycloadditions⁴ left a lasting impression of the potential power of this transformation to rapidly generate molecular complexity.

The triacid **1** (Figure 1) was independently reported in the mainstream literature by Glaxo and Merck groups in 1992 and assigned the names squalestatin S1⁵ and zaragolic acid A (ZA-A),⁶ respectively. It was discovered during screening programmes of fungal metabolites to find inhibitors of specific enzymatic steps in the synthesis of cholesterol. The triacid **1** was the first natural product found to be a potent inhibitor of squalene synthase and it also exhibited broad spectrum antifungal activity. Because of its extraordinary potency, the triacid **1** and structurally related congeners such as 6,7-dideoxysqualstatin H5 (DDSQ) **2**⁷ represented exciting new therapeutic leads in the treatment of hypercholesterolemia and fungal infections. They possess a novel densely functionalised 2,8-dioxabicyclo[3.2.1]octane core and the development of a general synthetic route to this system represented a significant and worthwhile challenge to the synthetic chemist.⁸

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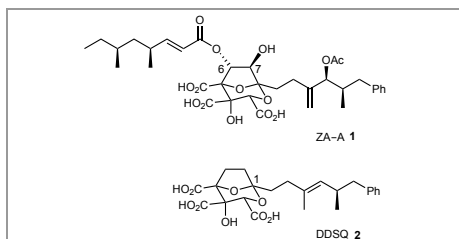
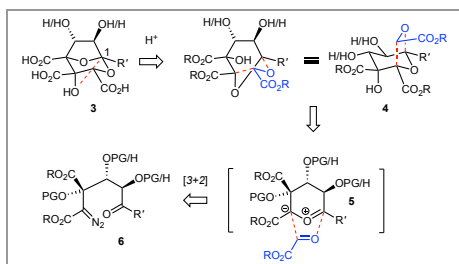


Figure 1 Representative squalestatin/zaragozic acids

Analysis of the 2,8-dioxabicyclo[3.2.1]octane core **3** (Scheme 1) of the squalestatin as the acyclic keto-triol indicated that it might be obtained by rearrangement of a 6,8-dioxabicyclo[3.2.1]octane **4**. In turn, it was considered that the 6,8-dioxabicyclo[3.2.1]octane **4** could be prepared via a carbonyl ylide **5** from the diazoketone diester **6** (PG = protecting group), potentially derived from natural (*R,R*)-tartaric acid, in a significant extension of Padwa's investigations into the generation and utility of carbonyl ylides.



Scheme 1 Retrosynthetic analysis of the squalestatin core **3** (PG = protecting group)

In the summer of 1993, with the support of a Nuffield Foundation undergraduate research bursary award, Vittorio Caprio (now at Manchester Metropolitan University) found that a glyoxylate can function as a dipolarophile with a carbonyl ylide and that it reacted with the desired regiochemistry, but undesired *exo*/*endo*-stereochemistry. Nevertheless, this preliminary result assisted a research grant application to the UK Science and Engineering Research Council (SERC), which was assessed by an organic chemistry subcommittee who could recommend earmarked studentships to the chemistry committee (Figure 2). In the SERC's current successor, the EPSRC, long gone are the possibilities of obtaining earmarked studentships and the separate organic chemistry and chemistry committees.

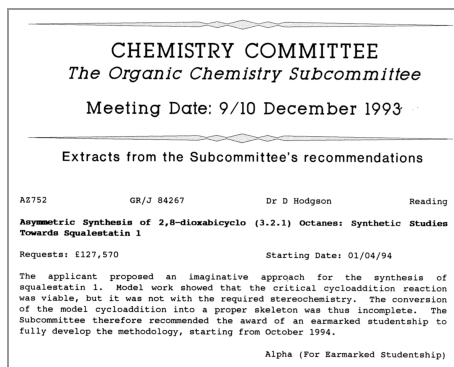
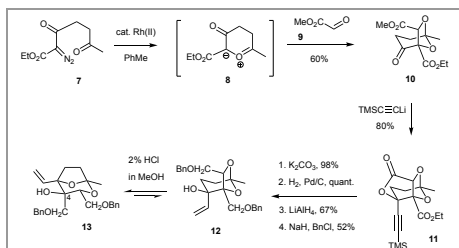


Figure 2 Initial earmarked studentship support from SERC

2 Racemic Model Studies to the Squalestatin/Zaragozic Acid Core

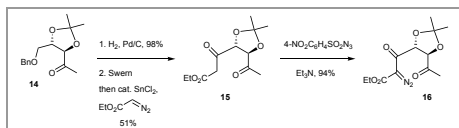
In the autumn of 1994, on the earmarked studentship, James Bailey commenced detailed investigations towards the synthesis of DDSQ **2** using carbonyl ylide cycloaddition and rearrangement chemistry as the key transformations to construct the 2,8-dioxabicyclo[3.2.1]octane skeleton. Initially, a racemic model study (the C1 alkyl side-chain = Me) was investigated, starting with the known and readily prepared α -diazooester **7** (Scheme 2).⁹ When α -diazooester **7** reacted with freshly distilled methyl glyoxylate (**9**) in the presence of catalytic $\text{Rh}_2(\text{OAc})_4$, *endo*-cycloadduct **10** (with respect to the ylide-containing ring) was formed as a single regio- and stereoisomer (Scheme 2). The *endo*-orientation was attributed to the influence of a preferred secondary orbital interaction between the ester carbonyl of the methyl glyoxylate (in the *s-trans* conformation) and the ketone moiety of the ylide **8**. Despite the incorrect stereochemistry, cycloadduct **10** was converted via lactone **11** to 6,8-dioxabicyclo[3.2.1]octane **12** to study the acid-catalysed rearrangement. At the time there were recent reports on the propensity of isomerisation of squalestatin-related 6,8- to 2,8-dioxabicyclo[3.2.1]octanes. Nicolaou and co-workers¹⁰ in their relay squalestatin synthesis observed that a more functionalised system favoured the desired 2,8-dioxygenated structure, while studies by Armstrong and Barsanti showed no preference at equilibrium between 2,8- and 6,8-isomers.¹¹ With our system, rearrangement of alcohol **12** using cat. HCl (from SOCl_2 in MeOH) preferentially gave the desired 2,8-dioxabicyclo[3.2.1]octane core **13** (**12**:**13**, 1:3), albeit still with the incorrect stereochemistry at C4.^{9,12}

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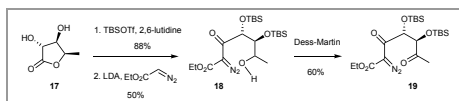
Scheme 2 Model study to the 2,8-dioxabicyclo[3.2.1]octane core **13**

It was considered that the presence of the vicinal protected 6,7-diol functionality (as originally planned, cf ylide **5**, Scheme 1) might provide suitable steric congestion over the *endo* or back-side of the ylide ring, thus making the glyoxylate dipolarophile orient its ester group away from the ring to deliver the desired *exo*-cycloadduct. Dioxxygenated diazo compounds **16** and **19** (Schemes 3 and 4) were prepared to examine the *exo/endo* and facial selectivity in the cycloaddition reaction. α -Diazoester **16** was synthesised in three steps from the known tartrate-derived benzyl ether **14** (Scheme 3). Debenzylation of **14** followed by Swern oxidation gave an aldehyde which was directly homologated to β -ketoester **15**. Diazotransfer using 4-nitrobenzenesulfonyl azide and Et₃N provided α -diazoester **16**.



Scheme 3 Synthesis of α -diazoester **16**

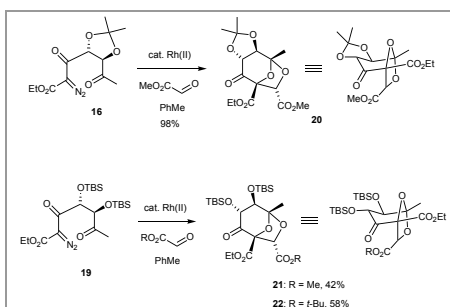
Bis-TBS ether **19** was accessed from known tartrate-derived lactone **17** in three steps (Scheme 4). Diol **17** was bis-silylated with TBSOTf, followed by addition of lithiated ethyl diazoacetate to give alcohol **18**. Subsequent Dess-Martin oxidation gave bis-TBS ether **19**.



Scheme 4 Synthesis of bis-TBS ether **19**

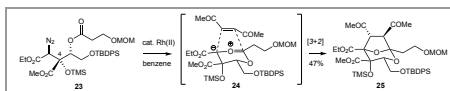
α -Diazoesters **16** and **19** were found to be less reactive under the previously established cycloaddition conditions (Scheme 2), likely due to the steric congestion. After optimisation (higher concentration), cycloaddition of α -diazoesters **16** and **19** with methyl glyoxylate gave single cycloadduct diastereomers (**20** and **21**, Scheme 5). Disappointingly, NMR studies indicated undesired stereochemistry in both cases. Cycloaddition using the more sterically demanding *tert*-butyl glyoxylate with α -diazoester **19** also led to the same outcome (cycloadduct **22**). The stereochemistry observed in the

cycloadditions of α -diazoesters **16** and **19** likely has its origins in that the lower face of the intermediate dipole is less hindered for the approach of the dipolarophile, whilst the glyoxylate ester still experiences secondary orbital overlap with the ylide ketone group.



Scheme 5 Cycloadditions of α -diazoesters **16** and **19**

To control the *endo:exo* selectivity, a modified synthetic strategy needed to be pursued where the presumed secondary orbital overlap was eliminated with a bias to allow the formation of the *exo*-cycloadduct. During the above studies, Hashimoto and co-workers had reported that the configuration at C4 in more substituted diazotriester **23** was crucial to the success of related cycloadditions (Scheme 6).¹³ Cycloaddition of diazotriester **23** with (*E*)-hex-3-ene-2,5-dione occurred stereoselectively from the β -face of the ylide **24**, thereby avoiding non-bonding interactions with the C4 pseudoaxial TMS ether, to generate 2,8-dioxabicyclo[3.2.1]octane **25** as a single diastereomer.

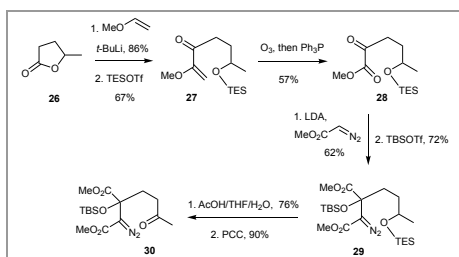


Scheme 6 Hashimoto and co-workers' cycloaddition approach to zaragozic acid C¹³

Encouraged by the above chemistry, it was hypothesised that modification of the β -keto group of the α -diazoester **7** (Scheme 2) to more sterically demanding β -silyloxy functionality would remove the putative secondary orbital overlap effect and lead to the desired *exo*-cycloadduct. To examine facial and *exo-endo* selectivity issues, cycloaddition substrate keto diazodiester **30** was synthesised by Carol Villalonga-Barber in seven steps from γ -valerolactone **26** (Scheme 7).^{14,15} Thus, addition of α -lithio methyl vinyl ether to lactone **26** gave, following secondary alcohol etherification using TESOTf, enone **27**. Ozonolysis of enone **27** gave the α -ketoester **28** which was treated with lithiated methyl diazoacetate to afford TBS ether **29** (1:1 mixture of diastereomers) after tertiary alcohol silylation. Selective TES ether desilylation and oxidation of the resulting secondary alcohol gave keto diazodiester **30**. The lability of the secondary TES ether under mild conditions was crucial, as it, along with mild oxidation of the resulting intermediate secondary alcohol, allowed access to keto diazodiester **30** in

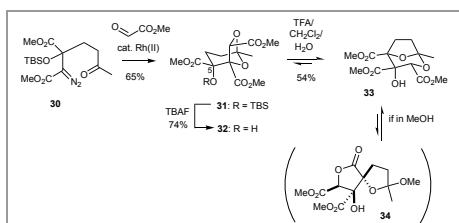
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which both the tertiary silyl ether and the diazo functionality were retained.



Scheme 7 Synthesis of a more sterically demanding β -silyloxy- α -diazoester **30**

Pleasingly, a significant result was obtained when keto diazoester **30** reacted with methyl glyoxylate in the presence of cat. $\text{Rh}_2(\text{OAc})_4$, as it gave the required *exo*-cycloadduct **31** (65%) as the major isomer along with others in a ratio of 12:1:1 (Scheme 8). Interestingly, decreasing the bulkiness of the β -siloxy functionality by using a TMS ether instead of a TBS ether led to a lower proportion of the *exo*-cycloadduct **31** (TMS instead of TBS) (8:1:1) in 63% yield. The cycloaddition preferentially occurs with glyoxylate approaching on the less-hindered face of the intermediate ylide (opposite to the silyloxy group) and *exo* to avoid steric interaction between the ester group of methyl glyoxylate and ester functionality at C5. After TBS-deprotection, acid-catalysed rearrangement with 2% HCl in MeOH (reflux, 15 h) gave a mixture of the cycloadduct **32** with the desired rearranged core **33** and spirolactone **34** (**32**, **33**, **34**, 69:21:10, respectively). After screening of a range of other acidic conditions (2% HCl in CHCl_3 , TfOH in DMSO, CAS in MeOH), rearrangement of cycloadduct **32** using Evans' conditions (TFA/ $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$, 10:20:1)¹⁶ at 40 °C for 68 h gave the 2,8-dioxabicyclo[3.2.1]octane core **33** of the squalastatins/zaragozic acids at the correct tricarboxylate oxidation level in 54% yield (83% based on recovered **32**). That acid-catalysed equilibrium had been reached was established by subjecting **33** to same acidic conditions, which returned the same 66:34 ratio of **33**:**32**, respectively (Scheme 8).

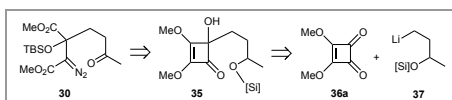


Scheme 8 Successful cycloaddition and rearrangement to squalastatin core **33**

3 Asymmetric Model Studies to a Keto α -Diazoester

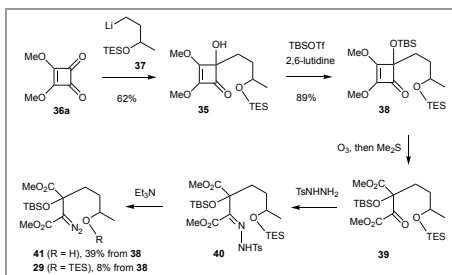
3.1 Dialkyl Squarate Desymmetrisation

Having developed a racemic strategy to the core of the squalastatins/zaragozic acids (Scheme 8), the next step was to control the absolute stereochemistry of α -diazoester **30**. Initially, Herman Sintim (currently at Purdue University) envisaged that dialkyl squarates could be elaborated into the desired ketodiester motif *via* monoaddition of an organolithium to a dialkyl squarate (Scheme 9), followed by an ozonolytic cleavage of the squarate double bond, eventually carrying out the organolithium addition in an asymmetric manner.



Scheme 9 Retrosynthetic analysis of **30** based on a squarate approach

Regioselectivity in the addition of alkylolithiums to squarates is generally the desired 1,2-pathway.¹⁷ To examine if we could access the requisite ε -keto- α -diazoester motif from dialkyl squarates, a TES-substituted butyl side-chain **37** was introduced onto the squarate **36a**, to obtain the 1,2-addition product **35** (Scheme 10).¹⁸ After silylation and ozonolysis of silyl ether **38**, the resulting sensitive α -ketosuccinate **39** was best taken directly to hydrazone **40**. Et_3N was used to carry out the Bamford-Stevens-type sulfinate elimination to give the corresponding α -diazoester **41** (39% over 3 steps). A small amount of the diazodiketoester **29** still retaining the TES group as also isolated (8%). Both diazoesters (**41** and **29**) could be converted to the desired ε -keto- α -diazoester **30** (Scheme 7).

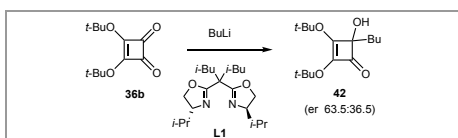


Scheme 10 Synthesis of diazoesters **41** and **29** from squarate **36a**.

Having established that dimethyl squarate **36a** could be transformed into α -diazoester **30**, we considered squarate addition by an organolithium in the presence of a chiral ligand (L^*) as a potential asymmetric variation towards these systems. The addition of butyllithium to di-*tert*-butyl squarate **36b** (Scheme 11) was studied in the presence of representative chiral ligands.¹⁸ Of the ligands screened, bisoxazoline **L1** displayed the highest (although still modest) enantioselectivity (er 63.5:36.5), however in low conversion (25% yield). Also,

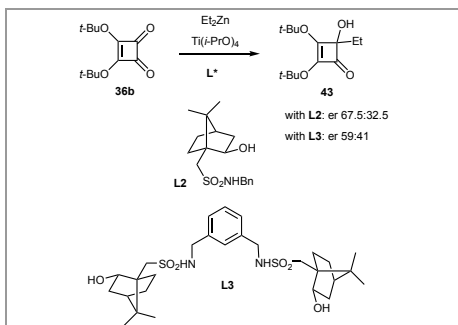
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the latter result was observed with 3 equiv of **L1** relative to BuLi; equimolar quantities gave a lower er (55:45).



Scheme 11 Asymmetric addition of alkyl lithium to squarate **36b**

Given the low asymmetric induction observed using an organolithium with various chiral ligands, we also considered the use of organozincs. Reaction between di-*tert*-butyl squarate **36b** and Et₂Zn (3 equiv) in the presence of Ti(*i*-PrO)₄ (1.7 equiv) and ligands **L2** or **L3** (20 mol %) in toluene at 60 °C gave the best conversion to the desired 1,2-mono-addition product, ethylated squarate **43** (~60%, Scheme 12), with ers of 65.5:34.5 and 59:41, respectively. Variation of the reaction conditions with camphorsulfonamide **L3** at 60 °C and higher (60 mol %) or lower (5 mol %) chiral catalyst loadings gave ers for **43** of 67.5:32.5 and 59:41. It was notable that the reaction of **L3** at 60 °C for 20 h was shown to be scale dependent: at 0.2 mmol scale, ethylated squarate **43** was isolated in only 5% yield (er 65.5:34.5), whereas at 3 mmol scale a 51% yield of **43** (er 58:42) was obtained. Instability of the ethylated squarate **43** on silica likely contributed to the variation in isolated yields.

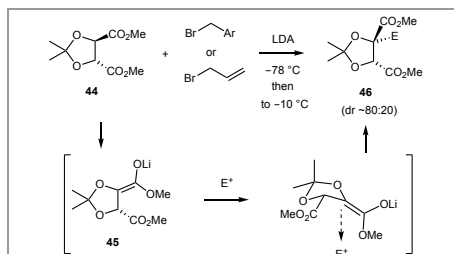


Scheme 12 Asymmetric addition of dialkylzinc to squarate **36b**

As the above route from squarates showed only modest asymmetric induction, an alternative asymmetric approach was investigated to the desired ϵ -keto- α -diazoesters.

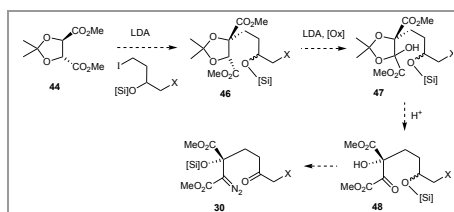
3.2 Tartrate Alkylation

In 1981, Seebach and Naef reported that the lithium enolate of (*R,R*)-tartrate acetonide (**44**→**45**) could be trapped in a stereoselective manner with reactive alkyl halides, such as allylic halides and benzylic halides (but not with *n*-alkyl halides), to give the major alkylated diastereomer **46** (~80:20 dr, Scheme 13).^{19,20}



Scheme 13 Contrasteric alkylation developed by Seebach and co-workers^{19,20}

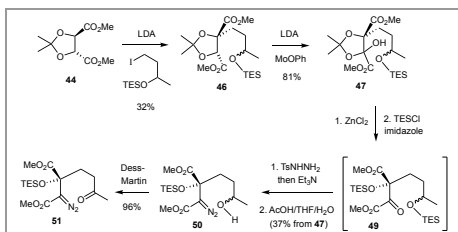
An alternative and asymmetric route to ϵ -keto- α -diazoester **30** was designed involving Seebach's chemistry (Scheme 14). If an alkylated tartrate **46** could be accessed from a silyloxy-substituted alkyl iodide and subsequently oxidised through a second enolate to lactol **47**, then this would give α -ketoester **48** after acetonide removal. This approach was considered more feasible than acetonide deprotection of alkylated tartrate **46** (related systems requiring prolonged heating with acid) followed by selective alcohol oxidation. α -Ketoester **48** should in principle be a progenitor to the desired ϵ -keto- α -diazoester **30** (*cf* Schemes 7 and 10).



Scheme 14 Tartrate alkylation strategy to ϵ -keto- α -diazoester **30**

Although Seebach had originally reported that the alkylation of the lithium enolate of tartrate acetonide **44** was only feasible with reactive halides, we were pleased to find after reaction adjustment (prolonged reaction time at -78 °C before quenching at the same temperature) that (*R,R*)-tartrate and a 3-silyloxy-1-iodobutane did generate alkylated tartrate **46** and the alkylation occurred exclusively *cis* to the unenolised ester group (Scheme 15).²¹ Access to hydroxy diazoester **50** was achieved by oxidation of the lithium enolate of the alkylated tartrate **46** using freshly prepared MoOPh,²² followed by acid-catalysed elimination of acetone from the resulting hydroxy acetonide. The acidic conditions (1% aq HCl) removed both the acetonide and TES groups in hydroxy acetonide **47**. Subsequent silylation using TESOTf gave the bis TES ketone **49**, which was converted to diazo alcohol **50** (17% from **47**). The efficiency of the sequence from hydroxy acetonide **47** to diazo alcohol **50** could be improved (to 37%) using ZnCl₂ for the initial deprotection and TESCl in the silylation; the latter minimises formation of the undesired silylated six-membered lactol form of **49**.

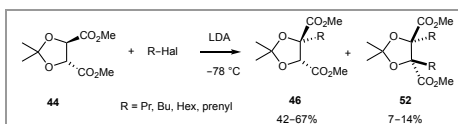
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Scheme 15 Tartrate approach towards enantioenriched α -diazoester **51**

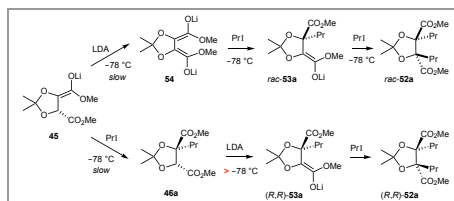
3.2.1 Further Studies on Seebach's Alkylation Chemistry

Alkylation of dimethyl tartrate acetonide **44** with other primary 'non-activated' alkyl iodides was also achieved at -78°C (with work-up at the same temperature) in acceptable yields; small quantities of *trans*-dialkylated products **52** were also isolated (Scheme 16).²¹



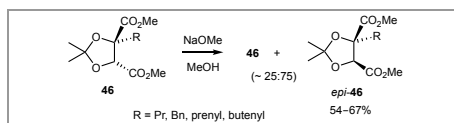
Scheme 16 Tartrate alkylation with n-alkyl halides

Studies were carried out with the aim of rationalising the reaction pathway leading to *trans*-dialkylated by-product **52** during the alkylation process, and whether the dialkylated by-product was racemic or obtained in high enantioenrichment. Chiral HPLC studies showed that the observed *trans*-dipropylated material **52** (**52a**: R = Pr) was racemic (52:48 er), likely forming *via* dienolate **54** (Scheme 17). Further investigation showed that when monopropylated tartrate **46** (**46a**: R = Pr) was subjected to propylation under same monoalkylation conditions (-78°C) this mainly returned starting **46a** (68%). However, propylation of the monopropylated tartrate **46a** was achieved in 98:2 er (34% yield) when the reaction mixture was warmed to -50°C . Thus, the ability to form the dienolate **54** to some extent at -78°C (Scheme 17) led to racemic dialkylated product; and also, once monoalkylation has occurred from the mono-enolate tartrate **45**, then **46a** is not readily deprotonated unless warmed to -50°C . These observations imply that generation of (*R,R*)- (or (*S,S*)-) *C*₂-symmetric dialkylated tartrates is best carried out through two separate reactions.



Scheme 17 Rationalisation of dialkylation observations

To extend the tartrate alkylation scope further, we examined the feasibility of preparing the epimers (*R,S*) of mono-alkylated tartrate products by epimerisation at the C3 position. The *2R,3S* stereochemistry of the monoalkylated tartaric acid motif is also directly present in several other natural products.²³ Alkylated tartrate **46** (R = prenyl) was exposed to NaOMe in MeOH (0.5 M) at room temperature which gave only partial epimerisation (**46:epi-46** 75:25). However, the equilibrium shifted to a 25:75 ratio in favour of *epi-46* in MeOH (0.06 M) at reflux for 30 h (Scheme 18). That true equilibrium had been reached was established by treating *epi-46* to these latter reaction conditions, which returned the same 25:75 ratio of **46:epi-46**. Epimerisation of other monoalkylated tartrates **46** (R = Pr, Bn, butenyl) gave similar equilibrium ratios, providing chromatographically separable *epi-46* in 54–67% yield.



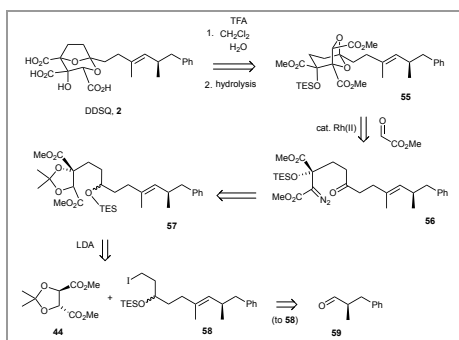
Scheme 18 Epimerisation of monoalkylated tartrates

Base-induced epimerisation of the monoalkylated tartrates favours *cis*-disposition of the ester groups on the five-membered ring, thereby accessing the predominant stereochemistry found in several substituted tartaric acid-containing natural products. These findings on origins of the dialkylated by-products, and on epimerisation conditions of the monoalkylated tartrates, broaden the scope and understanding of Seebach's alkylation chemistry.

4 Failure at the Penultimate Step to DDSQ

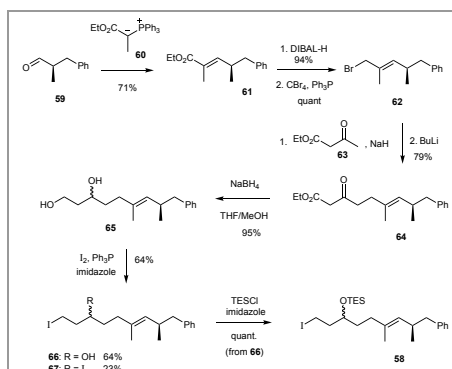
With encouragement from the above model studies (Schemes 8 and 15), Herman Sintim proceeded to address the total synthesis of DDSQ (**2**) by alkylative introduction of the full C1 side-chain **58** to tartrate acetonide **44**, as outlined in Scheme 19.

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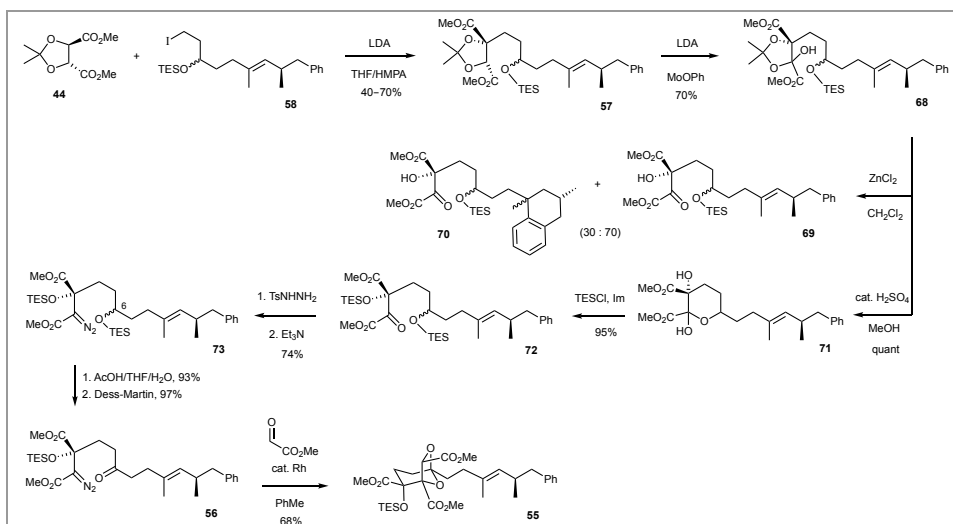
Scheme 19 Retrosynthesis of DDSQ 2

The C1 side-chain iodide **58** was prepared in 7 steps from (*R*)-aldehyde **59** (Scheme 20).²⁴ Wittig olefination of aldehyde **59** with ylide **60**, then 1,2-reduction with DIBAL-H of the resulting unsaturated ester then OH→Br conversion gave allylic bromide **62**. Bromide **62** was then coupled with the dianion of ethyl acetoacetate **63**, to produce β-ketoester **64** in 79% yield. Following Soai and Oyamada's procedure,²⁵ β-ketoester **64** was reduced to 1,3-diol **65** and iodination of the latter gave mono iodide **66**, along with some diiodide **67** (~23%). Finally, TES protection of mono iodide **66** gave the desired side-chain iodide **58** (Scheme 20).

Scheme 20 Synthesis of the side-chain iodide **58**

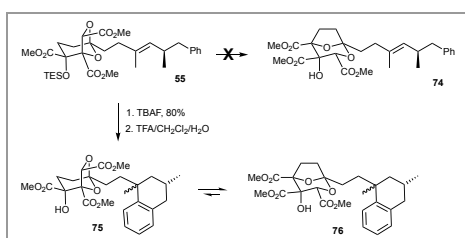
Elaboration of side-chain iodide **58** to the cycloadduct **55** mostly followed the chemistry developed in the earlier model studies (Scheme 15). Alkylation of lithiated dimethyl L-tartrate acetone **44** with iodide **58** gave the alkylated tartrate **57** in 40–70% yield (Scheme 21). Then, the enolate of alkylated tartrate **57** was treated with MoOPH, thereby accessing hydroxylated acetone **68**. In the model study, ZnCl₂ (or AlCl₃) were successfully used to hydrolyse hydroxylated acetone to keto-ester, followed by TES-silylation (**47**→**49**, Scheme 15). Unfortunately, these Lewis acids were unsuitable for the hydrolysis of the more elaborate hydroxylated acetone **68**, leading to a ~ 70:30 mixture of **69** and **70** respectively. However, cleavage of the isopropylidene moiety could be achieved under acidic conditions (0.1 M H₂SO₄ in MeOH) to give lactol **71**. Treatment of lactol **71** with TESCl in the presence of imidazole gave ketone **72**. Hydrazone condensation of ketone **72** with tosylhydrazide gave a hydrazone which on exposure to Et₃N gave a diazodiester **73** with small amount of C6 desilylated material. The diazodiester **73** was completely desilylated at the secondary ether with a 1:2:1 mixture of AcOH:THF:H₂O, and then Dess–Martin oxidation led to the required cycloaddition precursor, diazoketone **56**. Pleasingly, and following earlier conditions (Scheme 8), 1,3-dipolar cycloaddition of diazoketone **56** using cat. Rh₂(OAc)₄ in the presence of methyl glyoxylate gave the desired *exo*-cycloadduct **55**.

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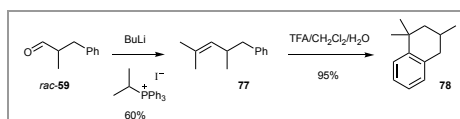
Scheme 21 The first approach towards DDSQ (2)

Following the model study (Scheme 8), deprotection of TES ether **55**, and then acid-catalysed rearrangement was anticipated to give the desired DDSQ triester **74** (Scheme 22). However, when cycloadduct **55** was subjected to the rearrangement conditions (TFA/CH₂Cl₂/H₂O) following TBAF-induced desilylation, a mixture of two compounds with loss of the unsaturation in the side-chain was obtained. Very disappointingly, variation in the reaction conditions (temperature, time, acid and ratio of TFA with CH₂Cl₂/H₂O) all failed to give the desired rearranged material.



Scheme 22 Undesired loss of the alkene moiety

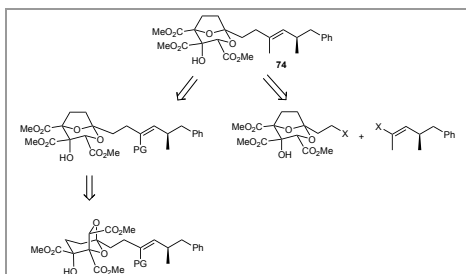
The undesired compound mixture generated under the rearrangement conditions was considered to be tetralins **75** and **76**, arising from TFA-induced generation of a tertiary carbocation at the acid-labile trisubstituted alkene which was subsequently trapped by the aromatic ring. In support of the above analysis, exposing a simpler model system, 2,4-dimethyl-5-phenyl-2-pentene (**77**), to the rearrangement conditions [TFA:CH₂Cl₂:H₂O (10:20:1), 40 °C, 68 h] gave the tetralin **78** in 95% yield (Scheme 23).²⁶



Scheme 23 Preparation and acid-catalysed cyclisation of alkene 77

From the above studies, the alkene moiety is highly reactive to Friedel-Crafts cyclisation: this occurred within 5 min, whereas the desired rearrangement requires 48–62 h. Failure was particularly painful at the penultimate hurdle. At this point in time alternative strategies were considered to overcome the issue: either the use of an alkene protecting-group approach (Scheme 24, PG = 'protecting-group'), or introduction of the alkene bearing side-chain after the acidic rearrangement step (Scheme 24, X = halide). However, 15 years would elapse before Herman Sintim saw elements of the strategy he developed being applied in a successful total synthesis.

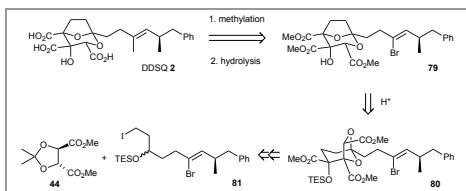
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Scheme 24 Potential modified strategies towards DDSQ

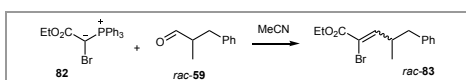
5 Second-Generation Approach to DDSQ: a Bromide Substituent Strategy

We first focused on the issue of how to directly protect an electron-rich C=C under the acid-catalysed rearrangement conditions. It was considered that a temporary halide substituent on the alkene (Scheme 25) could reduce its propensity to protonation. In this strategy, post-rearrangement methylation cross-coupling/esters hydrolysis would allow access the natural product from bromide **79**. Cycloadduct **80** was considered as being accessible through tartrate alkylation with *Z*-alkenyl bromide-bearing side-chain **81**, in a similar manner to the route developed by Sintim (Scheme 21).



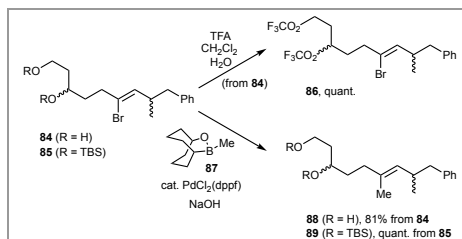
Scheme 25 Alkene protection strategy to DDSQ

Z- α -Bromo- α,β -unsaturated esters are typically prepared directly from aldehydes by Wittig olefination.^{27,28} With aldehydes and brominated ylide **82** (Scheme 26), the reaction normally produces predominantly, but not exclusively, the *Z*-isomer. Preliminary studies by Hamad Al-Mamari to generate *Z*-bromoalkene *rac*-**83** from aldehyde *rac*-**59** led to the use of 2.5 equiv of ylide **82** in benzene or MeCN at reflux for 48 h, ester *rac*-**83** was formed in 30% and 88% yields, respectively (*Z*:*E*, 8:1 and 6:1, respectively), with the geometric isomers being separable by chromatography (75% yield of *Z*-**83** isolated from the reaction in MeCN).²⁹

Scheme 26 Wittig olefination of aldehyde *rac*-**59**

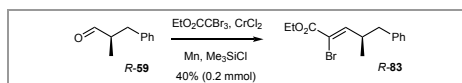
Alkenyl bromides **84** and **85** (prepared from *rac*-**83**) were used in a model study to examine the viability of alkene protection

from an acid (TFA) by the presence of a bromide substituent, and then whether the required methyl group could be installed in a stereoretentive manner (Scheme 27). Pleasingly, reaction of 1,3-diol **84** under the required acidic rearrangement conditions gave the bistrifluoroacetate **86** (quant.), in which the alkenyl bromide was unaffected. Moreover, stereoretentive Suzuki reactions between the 1,3-diol **84** or bis-TBS ethers **85** and the borinate ester **87** gave *E*-alkenes **88** and **89** in 81% and quantitative yields, respectively.



Scheme 27 Stability of alkenyl bromide functionality under the acidic rearrangement conditions and lability to stereoretentive methylation

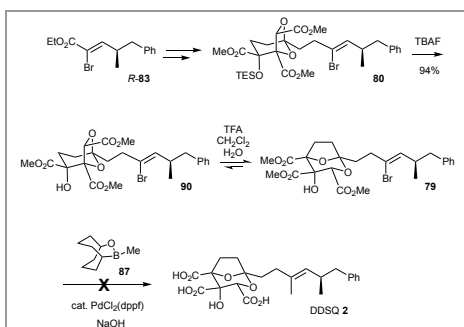
With preservation of alkenyl bromide functionality under the rearrangement reaction conditions demonstrated (Scheme 27), olefination of the *R*-aldehyde **59** was examined. Wittig homologation with ylide **82** and aldehyde *R*-**59** (95% ee) led to erosion of enantiointegrity in the resulting bromo ester *R*-**83** (86% ee). The combination of modest *E/Z*-stereocontrol and reduction in enantiopurity during formation of bromo ester **83** through Wittig chemistry, led us to consider alternative ways of achieving the same transformation that might avoid these issues. Chromium(II)-mediated or -catalysed olefination using trihaloacetates (mainly trichloroacetates, and on 1 mmol scale) has been reported by Falck, Mioskowski and co-workers to produce exclusively *Z*- α -haloacrylates.³⁰ When ethyl tribromoacetate reacted with aldehyde **59** (0.8 mmol scale), the desired *Z*-bromo ester **83** was exclusively formed in 65% yield (Scheme 28), and with no loss of enantiointegrity. However, scale-up of the catalysed reaction (0.2 mole of aldehyde **59**) gave ester **83** in a reduced 40% yield.

Scheme 28 Chromium(II)-catalysed olefination of aldehyde *R*-**59**

Encouraged by the model studies (Scheme 27), bromo ester *R*-**83** was converted to cycloadduct **80** (Scheme 29) in a manner similar to Sintim's work (Schemes 20 and 21). After desilylation, the key rearrangement of the resulting cycloadduct **90** gave a mixture of the desired 2,8-dioxabicyclo[3.2.1]octane **79** and recovered **90** (in 60:40 ratio, respectively), importantly with preservation of the alkenyl bromide. The final steps of the total synthesis were planned to be a one-pot tandem Suzuki–Miyaura methylation and ester hydrolyses. Unfortunately, no evidence of DDSQ (**2**) was observed when the resulting rearrangement

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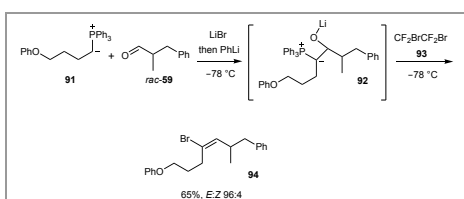
reaction mixture (**79** + **90**) was submitted to Suzuki-Miyaura conditions. Lack of material as well as time constraints did not allow additional investigation of this reaction by Al-Mamari, giving another painful end to the synthesis campaign, now falling at the *final* hurdle.



Scheme 29 The second approach towards DDSQ (**2**)

5.1 Stereoselective Routes to *E*-Alkenyl Halides via β -Oxido Phosphonium Ylides

Tanzeel Arif continued the project, with the initial aim to improve the synthesis of the *Z*-alkenyl bromide side-chain by avoiding the bottle-neck chromium(II)-catalysed olefination (Scheme 28). If successful, it was expected that this should lead to enough material to investigate the problematic cross-coupling methylation step and complete the DDSQ synthesis. An α -substitution plus carbonyl olefination via β -oxido phosphonium ylide (SCOOPY) reaction³¹ was investigated as a convergent and stereoselective route to trisubstituted *Z*-bromoalkenes. However, in a model study, reaction of 1,2-dibromotetrafluoroethane (**93**) with β -lithiooxyphosphonium ylide **92** gave *E*-bromoalkene **94** (96:4) (Scheme 30),³² instead of the *Z*-isomer (alkyl groups mutually *trans*) as anticipated for a Wittig-Schlosser-type reaction.



Scheme 30 Model Wittig-Schlosser-type (SCOOPY) reaction with unexpected stereochemical outcome

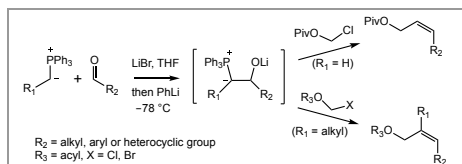
This surprising result diverted our attention towards investigating the reaction of β -lithiooxyphosphonium ylides with a variety of electrophiles. Due to the importance of stereodefined alkenyl bromides and iodides as precursors to a host of organometallic intermediates, we first sought to investigate further the scope of this process towards these

alkenes. A variety of alkylidene(triphenyl)phosphoranes were examined (Table 1) with aromatic (entries 1–3), heteroaromatic (entries 4–6) and aliphatic aldehydes (entries 7–9).³³ The stereochemical outcome of subsequent bromination or iodination (using I_2) of the intermediate β -oxido ylides was acutely sensitive to the size of the alkylidene: increasing the latter beyond ethylidene led predominantly to *E*-alkenyl bromides and iodides (entry 1, compared to entries 2–9).

Table 1 Alkenyl halides from aldehydes

Entry	Ylide	Aldehyde	Alkene	Yield, <i>E:Z</i>
1	P^+Ph_3	$\text{O}=\text{C}(\text{Ph})\text{H}$	$\text{Br}-\text{C}(\text{Ph})=\text{CH}_2$	47%, 1:99
2	$\text{PhO}-\text{CH}_2-\text{CH}_2-\text{P}^+\text{Ph}_3$	$\text{O}=\text{C}(\text{Ph})\text{H}$	$\text{PhO}-\text{CH}_2-\text{CH}_2-\text{C}(\text{Ph})=\text{CH}_2$	X = Br: 57%, 94:6 X = I: 63%, >99:1
3	P^+Ph_3	$\text{O}=\text{C}(\text{Ph})\text{H}$	$\text{X}-\text{C}(\text{Ph})=\text{CH}_2$	X = Br: 72%, 89:11 X = I: 64%, 99:1
4	$\text{PhO}-\text{CH}_2-\text{CH}_2-\text{P}^+\text{Ph}_3$	$\text{O}=\text{C}(\text{Ph})\text{H}$	$\text{PhO}-\text{CH}_2-\text{CH}_2-\text{C}(\text{Ph})=\text{CH}_2$	X = Br: 57%, >99:1 X = I: 66%, >99:1
5	P^+Ph_3	$\text{O}=\text{C}(\text{Ph})\text{H}$	$\text{X}-\text{C}(\text{Ph})=\text{CH}_2$	X = Br: 74%, 96:4 X = I: 59%, 94:6
6	P^+Ph_3	$\text{O}=\text{C}(\text{Ph})\text{H}$	$\text{X}-\text{C}(\text{Ph})=\text{CH}_2$	X = Br, n = 2: 47%, 99:1 X = I, n = 5: 52%, 90:10
7	$\text{PhO}-\text{CH}_2-\text{CH}_2-\text{P}^+\text{Ph}_3$	$\text{O}=\text{C}(\text{Ph})\text{H}$	$\text{PhO}-\text{CH}_2-\text{CH}_2-\text{C}(\text{Ph})=\text{CH}_2$	X = Br: 58%, >99:1 X = I: 57%, >99:1
8	$\text{PhO}-\text{CH}_2-\text{CH}_2-\text{P}^+\text{Ph}_3$	$\text{O}=\text{C}(\text{Ph})\text{H}$	$\text{PhO}-\text{CH}_2-\text{CH}_2-\text{C}(\text{Ph})=\text{CH}_2$	X = Br: 60%, >99:1 X = I: 79%, >99:1
9	P^+Ph_3	$\text{O}=\text{C}(\text{Ph})\text{H}$	$\text{X}-\text{C}(\text{Ph})=\text{CH}_2$	X = Br: 50%, >99:1 X = I: 65%, 87:13

Inspired by the above observations and with consideration of the possible origins of stereoselectivity on trapping β -lithiooxy phosphonium ylides with electrophiles³³ led Arif to spend the majority of his remaining doctoral studies developing procedures for and applications of stereoselective syntheses of disubstituted *Z*-allylic esters³⁴ and trisubstituted *Z*-allylic esters (Scheme 31).³⁵

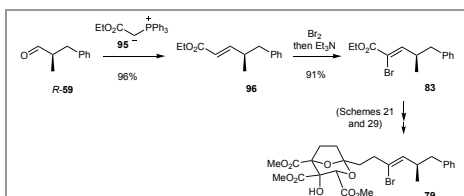


Scheme 31 Stereoselective synthesis of di- and trisubstituted *Z*-allylic esters

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5.2 Back to DDSQ synthesis

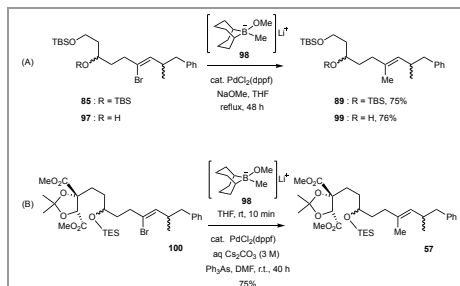
As a main part of his doctoral studies, Hasanain Almohseni began reinvestigating in 2016 the bromination strategy to hopefully reach the natural product target (DDSQ). The bromoalkene route described earlier (Section 5) suffered from a low yield of the *Z*-alkenyl bromide-bearing side-chain **81** and the final problematic methylation/hydrolysis step (**79**→**2**, Scheme 29). To allow greater throughput of the aldehyde **59** to *Z*-bromo ester **83** on scale, and under experimentally more straightforward conditions, a two-step procedure (Scheme 32) involving olefination with the more reactive unbrominated ylide **95**, to give the *E*-enoate **96** followed by bromination-dehydrobromination was developed. This strategy has previously been shown to proceed without erosion of enantiointegrity with such an ester-stabilised ylide on a related α -methyl aldehyde,^{36,37} and was a practical solution to efficiently generating *Z*-bromo ester **83** (94% yield) from aldehyde **59**.



Scheme 32 Olefination and bromination/dehydrobromination of aldehyde **59**, leading to methylation substrate **79**

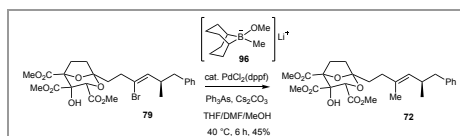
Bromo ester **83** was then advanced to the methylation substrate **79** in a similar manner to Sintim's (Scheme 21) and Al-Mamari's studies (Scheme 29). Unfortunately, again there was no evidence of DDSQ (**2**) with pure **79** under the original one-pot tandem Suzuki–Miyaura methylation and esters hydrolysis conditions of Scheme 29. It was considered that the presence of aq. NaOH (3 M) complicated the reaction by hydrolysis of some of the ester groups, especially the least hindered ester at C3. Softer/weaker bases such as powdered K_2CO_3 or K_3PO_4 were examined (on bromoalkene **97**, as a model); however, methylation did not proceed to completion. Fürstner and Seidel had extended the scope of the Suzuki reaction by using *B*-MeO-9BBN as a vehicle to transfer an alkyl group through formation of a borinate complex (eg **98**, Scheme 33) with the corresponding organometallic reagent, which then underwent transmetalation with an organopalladium complex in the absence of base.³⁸ When freshly prepared borinate complex **98** (from *B*-MeO-9BBN and MeLi) was refluxed with bromoalkene **85** in THF in the presence of 10% $PdCl_2(dppf)$, only a moderate amount of *E*-alkene **89** was detected (37%). However, when anhydrous NaOMe (1.5 equiv) was added to accelerate the reaction, the coupling proceeded smoothly, to give alkene **89** in good yield (75%, Scheme 33 (A)); similarly, alcohol **97** (as a free alcohol is present in the target substrate **79**) gave alcohol **99** (76%). Disappointingly, using this modified methylation cross-coupling on the real system **79**, resulted in only decomposition of the starting material. A new model substrate **100** (Scheme 33 (B)), which shared more functional groups present in the precious real substrate **79**, was then studied. Changing the base from NaOMe to aq. Cs_2CO_3 (3 M) in THF/DMF led to complete

conversion to the desired product **57**, but only in 45% yield. However, the yield was improved to 75% by adding 0.3 equiv of co-ligand Ph_3As .



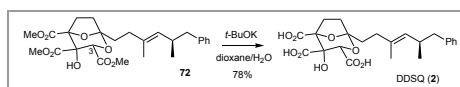
Scheme 33 Further methylation model studies

Unfortunately, application of the methylation cross-coupling conditions used with substrate **100** (Scheme 33 (B)), to 2,8-dioxabicyclic core **79** was not successful. 1H NMR analysis of the obtained mixture indicated the presence of only one ester group (likely at C4, as the ester group at C3 is typically first susceptible to hydrolysis, followed by the more sterically hindered C5 ester). Further investigation showed that modifying the solvent mixture to THF/DMF/MeOH at 40 °C for 8 h resulted in full conversion of model substrate **100** to the alkene **57** (68%), and very pleasingly these conditions also led to successful generation of 6,7-dideoxysqualstatin H5 trimethyl ester **72**, in 45% yield (Scheme 34).



Scheme 34 Synthesis of DDSQ trimethyl ester **72**

With trimethyl ester **72** in hand, TBAF was initially utilised in an attempt to achieve a formal synthesis of DDSQ, by selectively hydrolysing the C3 ester to give the known DDSQ dimethyl ester **142**³⁹ (*vide infra*, Scheme 45). However, under TBAF conditions, trimethyl ester **72** decomposed within 30 min at r.t.; whereas at 0 °C for less than 10 min, 1H NMR analysis of the crude mixture indicated epimerisation at C3.¹⁰ Finally, global hydrolysis using anhydrous KOH from freshly sublimed *t*-BuOK⁴⁰ was attempted. Reaction at –10 °C and then gradual warming to 110 °C, at last gave DDSQ (**2**), following an acidic wash (0.1 N HCl at 0 °C) and MeOH/hexane extraction, in 78% yield (Scheme 35).²⁶

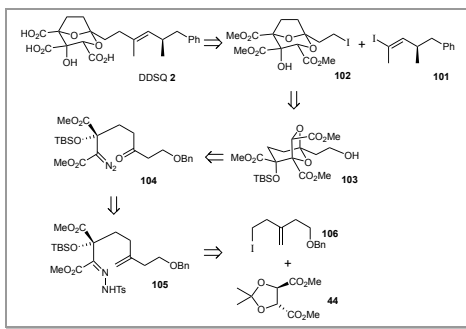


Scheme 35 Synthesis of DDSQ **2**.

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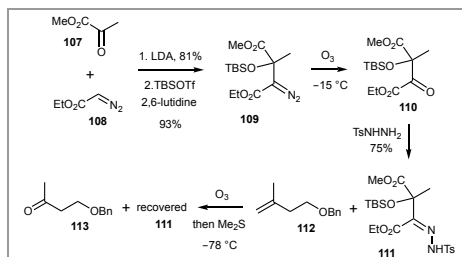
6 An Alternative Strategy to DDSQ: by Cross-Electrophile Coupling

Partly in parallel with the bromide approach above, an alternative strategy for the total synthesis of DDSQ (**2**) was pursued by Tanzeel Arif and subsequently Younes Fegheh-Hassanpour; this involved a different cross-coupling strategy for direct delivery of unsaturated side-chain **101** to the halide-substituted post-rearrangement core **102** (Schemes 24 and 36).⁴¹ The approach aimed to avoid the unwanted reactivity of the alkene moiety in the side-chain during the rearrangement step (**103**→**102**), and also to shorten the synthesis by attaching the side-chain later in the synthesis. In another key step, the carbonyl ylide precursor, diazoketone **104**, was envisaged to be generated from unsaturated hydrazone **105** through sequential chemoselective alkene ozonolysis and hydrazone to diazo transformation. Hydrazone **105** was expected to be accessible by applying our earlier tartrate alkylation approach (Scheme 15), with iodide **106**.



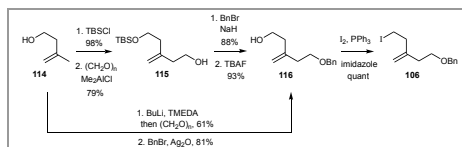
Scheme 36 Retrosynthesis involving side-chain introduction by a cross-coupling strategy

A key feature in this proposed chemistry was selective ozonolysis of an alkene to generate a ketone in the presence of hydrazone functionality. Before committing to this strategy, a model study was designed to establish the stability of a hydrazone moiety towards ozone (Scheme 37). Hydrazone **111**, which structurally resembles hydrazone **105** (Scheme 36), was prepared in four steps from commercially available methyl pyruvate (**107**) and ethyl diazoacetate (**108**). After silylation, α -diazooester **109** was subjected to ozonolysis at -15°C and subsequent hydrazone formation to give hydrazone **111** (75% from **109**). Next, an equimolar solution of hydrazone **111** and alkene **112** (which mimics the alkene portion of unsaturated hydrazone **105**) was exposed to ozone (-78°C) for ~ 5 min, followed by Me_2S as reductant. A mixture of the desired ketone **113** and, importantly, recovered hydrazone **111** was obtained.



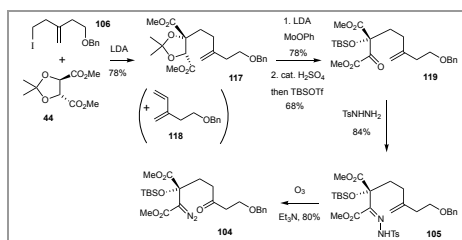
Scheme 37 Synthesis and tolerance to ozonolysis of hydrazone **111**

For the preparation of the halide-substituted core **102** (cf. Scheme 36), unsaturated iodide **106** for tartrate alkylation was first prepared starting with hydroxymethylene homologation of the dianion from readily available alcohol **114** (Scheme 38), to produce symmetrical diol (61%, **115**: TBS = H). Utilising Ag_2O , mono-benzyl protection of the diol (**115**; TBS = H) took place to give benzyl ether **116**. Alternatively, for economic and practical reasons, benzyl ether **116** was prepared starting with TBS-etherification to yield the corresponding silyl ether (98%). Refluxing silyl ether with paraformaldehyde and stoichiometric Me_2AlCl gave the ene-derived homoallylic alcohol **115**. Benzoylation of the latter with BnBr in the presence of NaH gave benzyl ether **116**, after desilylation. Iodination of benzyl ether **116** with I_2 in the presence of imidazole and PPh_3 gave iodide **106** in quantitative yield (Scheme 38).



Scheme 38 Synthesis of unsaturated iodide **106**

Alkylation of tartrate acetonide **44** with iodide **106** gave the desired alkylated tartrate **117** along with minor quantities of the elimination-derived diene **118** (Scheme 39). Hydroxylation using MoOPh followed by hydrolysis/silyl protection gave α -ketoester **119**.



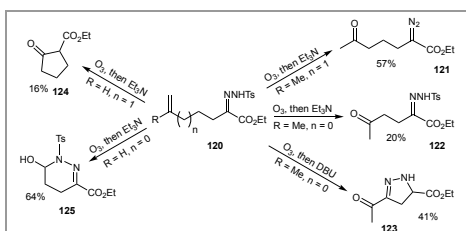
Scheme 39 Synthesis of diazo ketone **104**.

Unfortunately, application of the -78°C ozonolysis conditions from Scheme 37 to hydrazone **105** derived from α -ketoester

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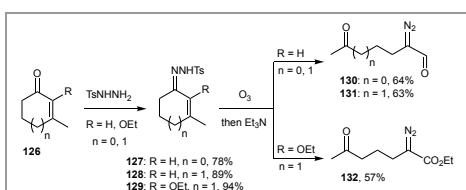
119 did not lead to successful isolation of the expected keto hydrazone. Replacement of Me₂S by Et₃N did, however conveniently generate diazoketone **104** (Scheme 39)! The Et₃N plays a dual role, as both base in anionic cycloreversion of the intermediate ozonide⁴² and in the elimination of sulfinate in the Bamford-Stevens step (the latter seen previously in Schemes 10, 15 and 21).

In order to further explore the ozonolysis of unsaturated tosylhydrazones as a direct approach to diazocarbonyl compounds, several other unsaturated tosylhydrazones **120** were designed to examine their reactivity with O₃ (at -78 °C), followed by hydrazone decomposition with Et₃N (Scheme 40).⁴³ We found that this chemistry is viable to α -diazo- ϵ -ketoester **121**, while an α -diazo- δ -ketoester was not observed under the same conditions and instead only keto hydrazone **122** was isolated; switching from Et₃N to DBU as a stronger base led to the 2-pyrazoline **123** (41%). Interestingly, terminal alkene hydrazones **120** (R = H) provide a route to cyclic systems (**124** and **125**) rather than to diazoaldehydes; the latter being presumed unstable intermediates.



Scheme 40 Ozonolysis followed by base treatment of various unsaturated tosylhydrazones **120**

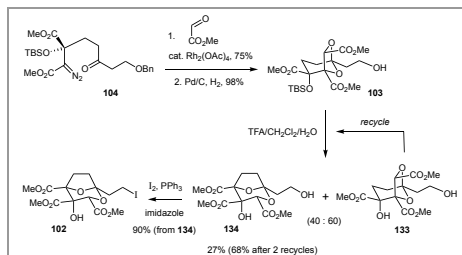
Cyclic α,β -unsaturated hydrazones **127–129**, derived from ketones **126**, underwent ozonolytic ring-cleavage and Bamford-Stevens reaction to give 2,5- and 2,6-diazoketones (**130–132**, Scheme 41).



Scheme 41 Synthesis of 2,5- and 2,6-diazoketones **130–132**

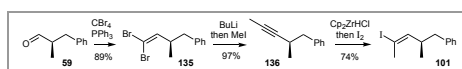
Returning to the DDSQ synthesis, Rh-catalysed cycloaddition of diazoketone **104**, debenzoylation and acid-catalysed rearrangement of alcohol **103** gave a 40:60 ratio of the rearranged core **134** and cycloadduct **133** (Scheme 42). In this case the rearranged core was unfavoured, but in the model system (Scheme 8), and the bromide route (Scheme 29), the rearranged core was favoured (66:34, **33:32**) and (60:40, **79:90**), respectively. These results indicate the equilibrium position is sensitive to variation in the C-1 chain. Nevertheless,

the unrearranged diol **133** could be recycled (68% of rearranged core **134** after 2 recycles). Iodination of the rearranged core **134** gave the iodo-substituted core **102**.



Scheme 42 Synthesis of iodo-substituted core **102**

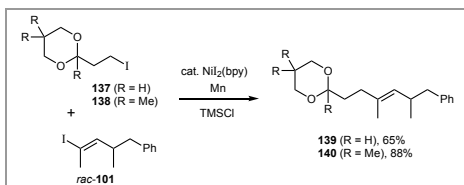
The synthesis of enantiopure alkenyl iodide partner **101** for the iodo-substituted core **102** started with Corey-Fuchs olefination of (*R*)-aldehyde **59** to give dibromoalkene **135** in 89% yield (Scheme 43). Subsequent internal alkyne **136** formation (97%) was followed by hydrozirconation using excess Schwartz's reagent (Cp₂ZrHCl). Subsequent trapping of the intermediate alkenylzirconium with I₂ gave the *E*-alkenyl iodide **101** in good overall yield (74%) from alkyne **136** and with complete control of regio and stereoselectivity.



Scheme 43 Synthesis of alkenyl iodide **101**

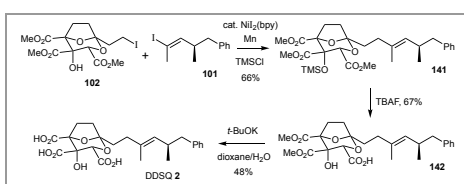
With the key intermediates **101** and **102** in hand, we were now in a position to address their union. Considerable experimentation was carried out on the Csp³–Csp² cross-coupling of alkenyl iodide **101** and iodide core **102** (or their corresponding bromides), but with no or limited success. Unexpected thermal instability (decomposing above ambient) of iodide core **102** was encountered. At the same time as we were studying this issue, Weix and co-workers reported an improved method for cross-coupling of alkyl halides with alkenyl bromides under Ni catalysis in DMPU with Mn and TMSCl at room temperature.⁴⁴ On applying this method with iodide **137** and *rac*-**101** (as a model study, Scheme 44, bpy = 2,2'-bipyridine), we were pleased to find after reaction optimisation (concentration, ratio of reactants) that entirely *E*-alkene **139** was obtained in 65% yield. However, a significant erosion in stereochemical integrity was observed when the same conditions were used with the real coupling partners **101** and **102** (*vide infra* **141**: 3:1, *E/Z*, Scheme 45). A slightly more hindered model alkyl iodide **138**, as a closer mimic of the oxygenated core **102**, was used for further optimisation (Scheme 44). Changing the reaction solvent to DMF instead of DMPU gave alkene **140** in 86% yield with excellent *E/Z* selectivity (~17:1). When 2 equiv of alkyl iodide **138** was used, the selectivity ratio improved to ~20:1 *E/Z*, in 88% yield.

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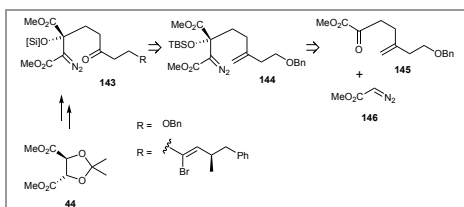
Scheme 44 Model cross-electrophile couplings

Following the optimised conditions (using DMF as a solvent), stereoretentive Ni-catalysed $\text{Csp}^3\text{-Csp}^2$ cross-electrophile coupling between iodide core **102** and iodide side-chain **101** proceeded smoothly to give the TMS triesters DDSQ **141** with exclusive *E*-stereochemistry in 66% yield (Scheme 45). Pleasingly, in this case (*cf.* trimethyl ester **72** discussion before Scheme 35) desilylation of **141** with TBAF was accompanied by hydrolysis of the less hindered C-3 ester to afford the known diester DDSQ **142**.³⁹ Subsequent saponification of the more hindered methyl esters at C4 and C5 gave DDSQ (**2**), with this synthesis being completed before the bromide approach (Section 5.2).

Scheme 45 Cross-coupling and hydrolysis to DDSQ **2**

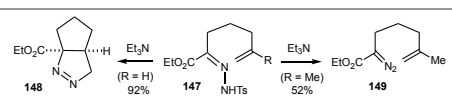
7 Alkene Ozonolysis in the Presence of Diazo Functionality: Accessing α -Ketoester Intermediates

One of the key features of our DDSQ syntheses was the stereoselective alkylation of dimethyl tartrate acetonide (**44**) with alkyl iodides to access the α -diazoesters **143** (Scheme 46). In principle, a more concise approach to such cycloaddition precursors **143** could proceed by aldol reaction between a diazoacetate anion **146** and a suitable α -ketoester **145** (Scheme 46), eventually in an asymmetric manner. In such a strategy to DDSQ, the alkene moiety (in **144**) would be required to be subsequently converted to a ketone by chemoselective ozonolysis in the presence of *diazo* functionality.

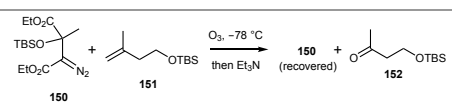
Scheme 46 An alternative strategy to diazoketone **143**

One potential issue with the above alternative route (Scheme 46) was that the α -diazoester functionality could engage in

intramolecular cycloaddition with the electron-rich alkene to form a bicyclic pyrazoline. Indeed, the simpler unsaturated hydrazone **147** ($R = H$) underwent Et_3N -induced diazo formation in CH_2Cl_2 at room temperature to form 1-pyrazoline **148**, in 92% yield (Scheme 47). However, intramolecular cycloaddition was minimised with the 2,2-dialkyl-substituted terminal alkene **147** ($R = \text{Me}$), to give diazo alkene **149** as the major product (52%), along with only small amounts of the corresponding bicyclic pyrazoline (91:9, respectively).

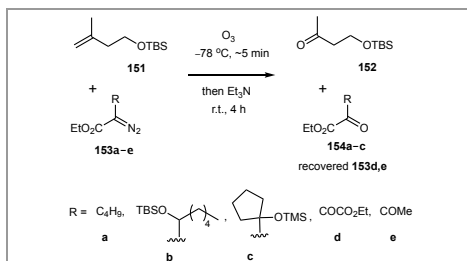
Scheme 47 Reactivity of unsaturated hydrazones **147** with Et_3N

Another concern was the stability of the diazo group under ozonolysis conditions (*cf.* α -diazo to α -keto ester transformation at -15°C , **109**→**110** Scheme 37). While it was considered that electron-rich alkenes should react faster than diazo functionality α - to an electron-withdrawing group (eg. ester), a model study was carried out to check the robustness of the α -diazo ester moiety towards ozone at -78°C (Scheme 48). An equimolar solution of model diazoester **150** (that resembles the diazo pattern in **144** (Scheme 46)) and alkene **151** (which mimics the alkene portion of **144**) was subjected to ozone treatment (-78°C in CH_2Cl_2 for ~5 min then, following N_2 sparging, addition of Et_3N); a clean crude mixture of the desired ketone **152** and recovered diazoester **150** was obtained.

Scheme 48 Stability of α -diazoester **150** towards ozone at -78°C

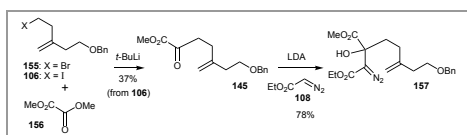
In order to test the generality of this chemistry, more readily accessible β -substituted (or keto) α -diazocarbonyl compounds **153a-e** (Scheme 49) were prepared to determine if steric and/or electronic factors bias the stability of the diazo moiety to ozonolysis. β -Substituted α -diazoesters **153a-c** were reactive at -78°C being converted to the corresponding ketones **154a-c** after addition of Et_3N . In contrast, β -keto- α -diazoesters **153d,e** were found to be stable to ozone. The presence of electron-withdrawing functionality at the β -position of the α -diazoester clearly further reduces the reactivity of the diazo group towards ozone; β -keto- α -diazoester **153d** was stable to ozone even under warming the reaction mixture to -15°C for 1 h (alkene **151** converts to ketone **152** within 5 min at -78°C).

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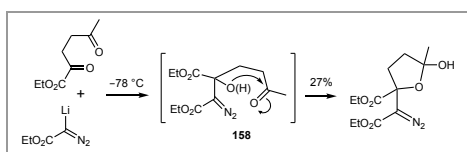
Scheme 49 Tolerance of various β -substituted (β -keto) α -diazoesters towards ozone

Encouraged by the above observations, we examined the aldol/ozonolysis strategy (Scheme 46). Initially, α -ketoester (**145**, Scheme 50) was synthesised through Grignard reaction of bromide **155** with oxalate (**156**), but in only 11% yield. Alternatively, halogen–lithium exchange of iodide **106** using *t*-BuLi improved the yield to 37%. Next, α -ketoester **145** was reacted with lithiated ethyl diazoacetate **108** to give diazo-alcohol **157** (78%), and notably with no undesired intramolecular cycloaddition.



Scheme 50 Synthesis of diazo-alcohol **157**

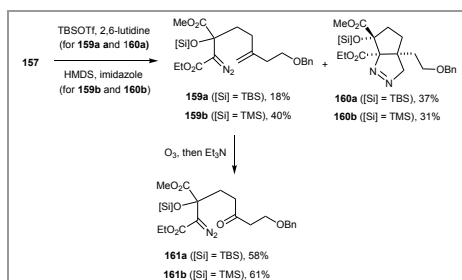
At this stage, we proceeded to protect the OH group, since otherwise it would likely undergo problematic γ -lactolisation with the ketone subsequently generated on ozonolysis. On a similar motif, γ -lactolisation of diazo-alcohol **158** was observed by Carol Villalonga-Barber in one of our very early model studies (Scheme 51).⁴⁵



Scheme 51 γ -Lactolisation of diazo-alcohol **158**

Interestingly, when diazo-alcohol **157** was treated with TBSOTf in the presence of 2,6-lutidine, a mixture of desired TBS ether **159a** along with cycloadduct **160a** (as a single diastereomer) was obtained (**159a**:**160a**, 1:2; Scheme 52). The partial formation of cycloadduct **160a** on silylation was attributed to a Thorpe–Ingold effect, from the bulky silyl group. Indeed, on minimising the steric effect by using a less-hindered trimethylsilyl group, the ratio of silyl ether **159b** to cycloadduct **160b** became 4:3 in favour of the desired non-cyclic product. Lastly, the silyl ethers **159a** and **159b** were subjected to ozonolysis at -78 °C in CH_2Cl_2 for ~ 5 min; subsequent addition

of Et_3N led to the desired diazo-ketones **161a** and **161b** (58% and 61% yields, respectively).⁴⁶



Scheme 52 Synthesis of diazo-ketones **161**

The above chemistry shows that the aldol/ozonolysis strategy, which hinges on chemoselective ozonolysis of unsaturated α -diazoesters, is a viable route to α -diazo- ε -ketoesters. Further adaptation of this strategy towards DDSQ will require development of a challenging asymmetric aldol addition between an alkyl diazoacetate and ketoesters.⁴⁷

8 Summary

"The toughest question to ask in synthetic organic chemistry after the work is done is: what have you learned?"⁴⁸ For the research described in this Account, three learning highlights are: (i) new ways to assemble diazo ketones from direct ozonolytic conversion of unsaturated hydrazones and diazo compounds, (ii) prevention of electrophilic attack (protonation/Friedel–Crafts cyclisation) of an alkene by using a temporary vinylic bromine substituent; (iii) highly stereoselective Wittig–Schlosser-type access to *E*- (rather than the originally anticipated *Z*-) alkenyl bromides and iodides. Our interest in diazocarbonyl-derived carbonyl ylide cycloadditions initiated in this project also led to the development of catalytic asymmetric variants, but that is another story.^{49,50}

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Acknowledgment

The brevity with which the work detailed in this Account is described cannot do justice to the amount of effort that actually went into developing the chemistry. For that reason, D.M.H. would like to thank all the dedicated co-workers who have been involved with him in this area over the past years, especially for their intellectual and practical contributions.

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Biosketches

	Hasanain A. A. Almohseni was born in Najaf Province, Iraq in 1989. He studied chemistry at the University of Kufa from 2006 to 2012, first as undergraduate and subsequently as a masters student in organic chemistry (supervised by Prof Hasan Ghanem). During 2012-15 he worked as an Assistant Lecturer at the College Al Safwa University and then the Sheikh Tusi University College. In 2016-19 he pursued doctoral studies at the University of Oxford, supervised by Prof D. M. Hodgson. His research focused on strategies to the squalastatins, including completion of a total synthesis of 6,7-dideoxysqualastatin H5 via an alkene-protection strategy.
	David M. Hodgson (BSc, University of Bath, and PhD, University of Southampton, with Prof P. J. Parsons) was a lecturer at the University of Reading for five years before moving in 1995 to the University of Oxford, where he is currently a Professor of Chemistry, with interests broadly in the development of synthetic methods and their application in natural product synthesis.

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