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Recent synthetic studies on the zaragozic acids (squalestatins)

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1. Introduction

Coronary heart disease is the major cause of death in the Western world,[1] and a prime reason for its onset in man is a high concentration of cholesterol in the bloodstream. Treatment to reduce this high concentration of cholesterol, via change in diet and lifestyle is often used, but is not always successful and medical intervention by the use of drugs is often called for. A number of approaches to treat hypercholesterolemia are used at the moment, including the use of HMG-CoA reductase inhibitors and bile acid sequestrants. These methods can be successful (treatments such as lovastatin are amongst the highest earning drugs currently on the market) but can have unpleasant side effects. HMG-CoA reductase inhibitors work by preventing the biosynthesis of mevalonic acid, an intermediate early in the synthesis of cholesterol. However, mevalonic acid is also important in the biosynthesis of other compounds, such as ubiquinones and dolichols. If cholesterol biosynthesis could be prevented further down the pathway, then these side effects could be avoided. Squalene synthase is the enzyme responsible for the production of squalene, which is

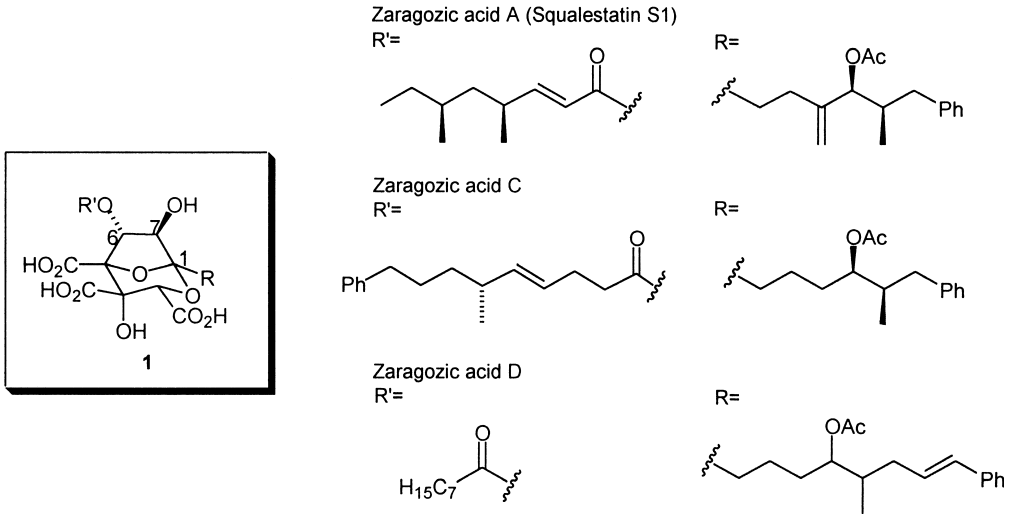

Figure 1. Representative zaragozic acids (squalestatins).

Keywords: regioselectivity; acetonide; zaragozic acids.

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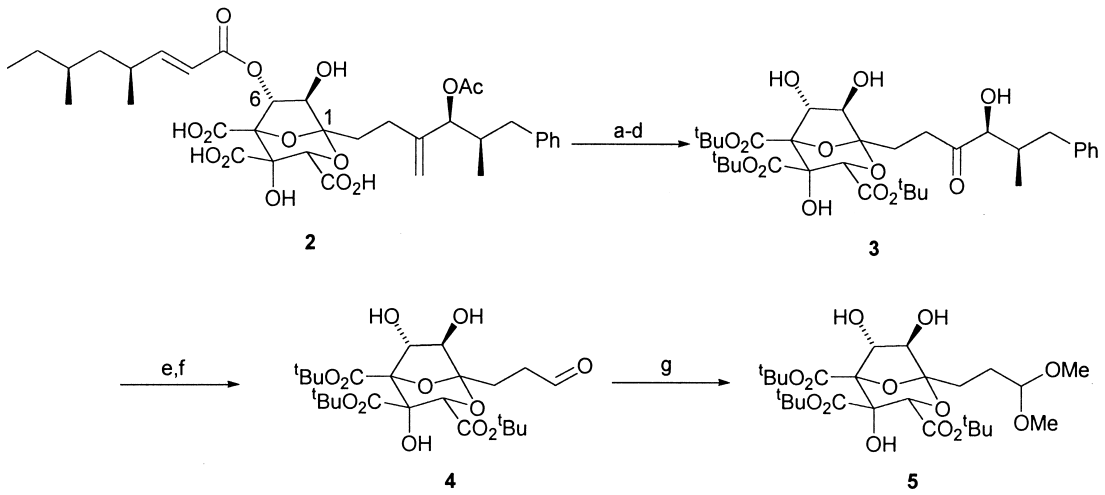


Scheme 1. Degradation of the natural product. *Reagents and conditions*: (a) ^{i}PrN=C(O^{t}Bu)NH^{i}Pr, CH_2Cl_2, reflux, 87%; (b) $HONH_2$·HCl, NaOAc, MeOH; (c) EtMgBr, $CeCl_3$, −78°C, 91% over 2 steps; (d) (i) O_3, CH_2Cl_2, −78°C; (ii) Me_2S, 94%; (e) $NaBH_4$, MeOH, 0°C; (f) $Pb(OAc)_4$, benzene, 100°C, 73% over 2 steps; (g) MeOH, $(MeO)_3CH$, PPTS, rt, 95%.

the first committed step in the production of cholesterol in the body. Inhibition of this step would be ideal from a therapeutic point of view and it was during random screening for lead compounds that three groups[2–4] independently discovered the zaragozic acids or squalestatins **1** (Fig. 1). These compounds, isolated from a series of different fungi, possessed an unusual and intriguing 2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core. The level of complex functionality observed in this highly oxygenated molecule was unprecedented, with six contiguous stereocentres present. The core system is common to all members of the family (although some derivatives lack oxygenation at C6 and C7), with the only differences arising at the C1 alkyl and C6 acyl side chains.

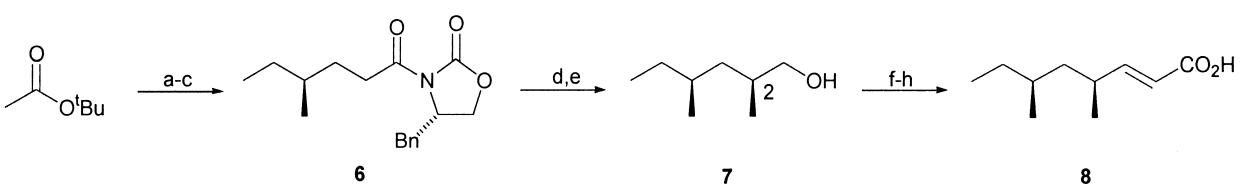
They were shown to be nanomolar inhibitors of squalene synthase, with zaragozic acid D also exhibiting strong inhibition of *ras*-farnesyl protein transferase. Given that the zaragozic acids also possess antifungal properties, they have a wide ranging and potent biological activity. This combination of potent biological activity and their intriguing chemical structure led to the zaragozic acids becoming an area of intense interest. This has provoked a large number of synthetic studies towards the core system and several total syntheses. The chemistry and biology of the zaragozic acids was reviewed by Nicolaou and Nadin in 1996[5a] and the present report seeks to provide an overview of the synthetic work that has taken place since that time. While this manuscript was in preparation, a further review of the field has recently appeared.[5b]

2. Total syntheses

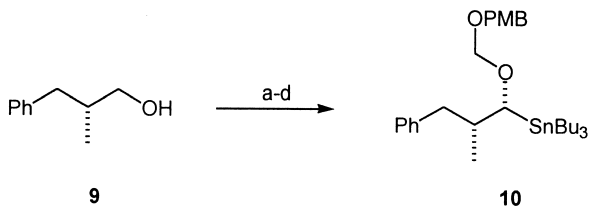
Eight total syntheses of members of the zaragozic acid family have been achieved so far: three of zaragozic acid A,[6–8] four of zaragozic acid C[9–12] and one of the less-oxygenated 6,7-dideoxysqualestatin H5.[13] The work of Nicolaou (zaragozic acid A),[6] Carreira (C)[9] and Evans (C)[10] was described in the previous review;[5a] this section will detail the more recent total syntheses.

Heathcock[7] utilised a relay approach towards zaragozic acid A (ZA-A) **2**. This is a viable approach to the natural product as reasonable quantities are readily available for degradation and synthetic reassembly. Degradation of ZA-A into the relay compound began with protection of the triacid as the tri-*tert*-butyl ester by treatment with an isourea[14] (Scheme 1). The C6 acyl side chain could then be removed with hydroxylamine and the side chain acetate cleaved by treatment with an ethyl Grignard reagent and cerium chloride. Ozonolysis of the side chain alkene furnished **3**. The side chain could be cleaved by reduction of the ketone to furnish the vicinal diol, which upon treatment with $Pb(OAc)_4$ gave **4**. It should be noted that this was achieved with selectivity, leaving the vicinal diol at C6–C7 untouched. Protection of the terminal aldehyde as the dimethyl acetal furnished the relay product **5**. Overall, the relay product was synthesised in seven steps with an overall yield of 52%.

To reassemble the natural product, the C6 acyl and C1 alkyl



Scheme 2. Synthesis of the C6 side chain. *Reagents and conditions*: (a) (i) LDA, THF, −78°C; (ii) (*S*)-1-iodo-2-methylbutane, DMPU, −78 to −45°C to rt; (b) TFA; (c) (i) $COCl_2$, DMF (cat), CH_2Cl_2; (ii) (*S*)-3-lithio-4-benzyl-2-oxazolidinone, THF; (d) (i) NaHMDS, THF, −78°C; (ii) CH_3I, −78°C to rt; (e) $LiBH_4$, MeOH, Et_2O, 0°C to rt; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (g) Ph_3P=$CHCO_2Me$, CH2Cl2, rt; (h) LiOH, H_2O, THF.



9 10

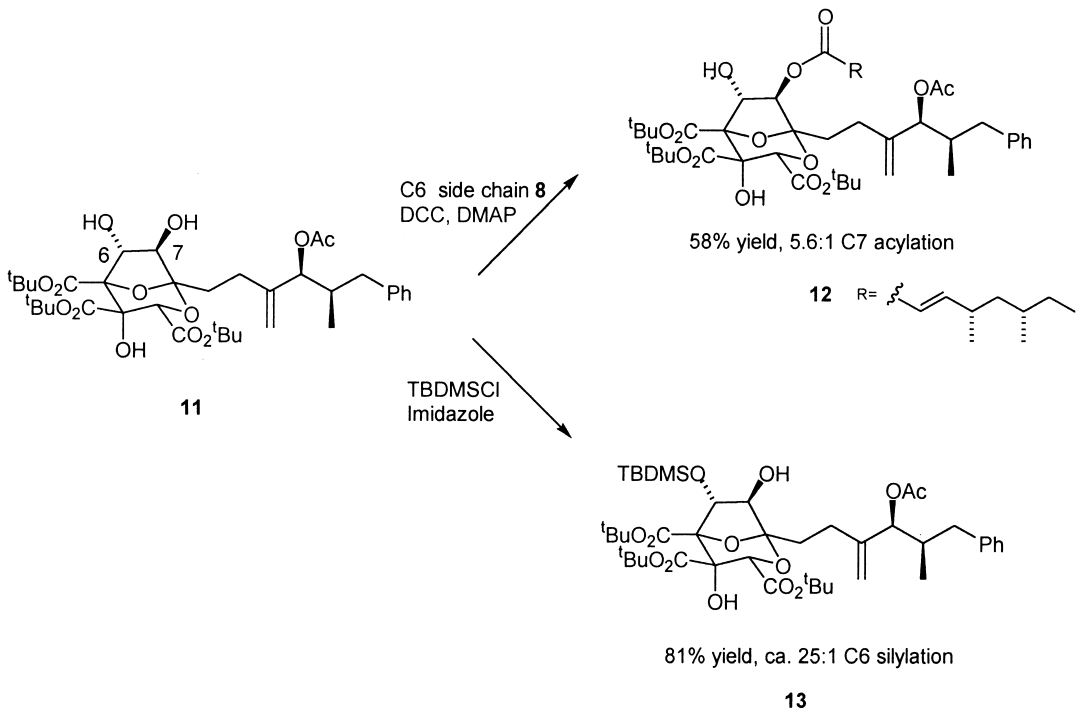
Scheme 3. Synthesis of the C1 side chain. *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) Bu_3SnLi, THF, −78°C; (c) $PMBOCH_2CH_2Cl$, Hunig's base (d) HPLC separation, 32% over 3 steps, 28% of other diastereomer.

side chains had to be synthesised. These compounds were synthesised as shown in Schemes 2 and 3.

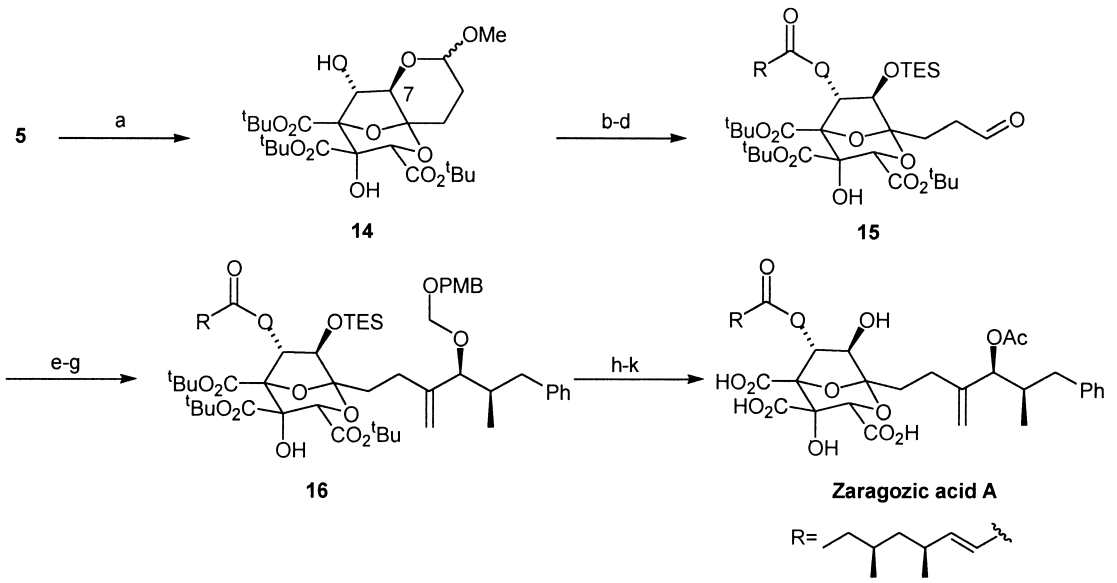
The C6 side chain was established using chiral pool material and Evans methodology[15] to control the stereocentres. The enolate of *tert*-butyl acetate was alkylated with (*S*)-1-iodo-2-methylbutane (prepared from the commercially available (*R*)-3-hydroxy-2-methylpropanoate) and the resulting ester hydrolysed with TFA, to give the free acid in reasonable yield. The acid was then turned into the acid chloride, enabling it to be attached to an Evans oxazolidinone to yield **6**. Formation of the sodium enolate, followed by quenching with methyl iodide gave the required product as 17:1 mixture of diastereomers, which were readily separable by chromatography. Removal of the auxiliary using the standard lithium borohydride furnished **7**. Homologation to the α,β unsaturated acid was required to complete the synthesis of the side chain. This was easily achieved by oxidation of **7** to the aldehyde under standard Swern conditions, followed by Wittig reaction to yield the *E*-isomer as the sole product in good overall yield. Saponification of the ester was achieved with lithium hydroxide to give **8**, in a total of eight steps with a yield of 35%.

With the C6 acyl side chain complete, attention was turned to C1 alkyl side chain (Scheme 3). It was intended to introduce this back into the natural product as a cerium reagent derived from an α-alkoxystannane. Swern oxidation of **9**, followed by immediate introduction of (tributylstannyl)lithium at low temperature gave an approximately 1:1 diastereomeric mixture of alkoxyalkylstannanes. Protection of the free alcohol allowed separation of the diastereomers (e.g. **10**) by HPLC, in a moderate yield over the three steps. With both side chains synthesised the relay compound could be reassembled to the natural product.

In all total syntheses of the zaragozic acids, one question of importance is how to differentiate the C6 and C7 secondary alcohols. Unless this can be achieved early in the synthesis (as was the case in Evans synthesis of ZA-C[10]) it can prove difficult, leading to a mixture of products where both C6 and C7 alcohols are acylated. Whilst attempting to attach the C6 side chain, Heathcock made an important observation (Scheme 4). Treatment of **11** with the C6 side chain **8** under standard acylating conditions gave a 5.6:1 mixture of isomers, with the C7 acylated isomer **12** as the major product. However, when attempting to silylate **11** with TBDMSCl, **13** was found to be the major product, in a ratio of ca. 25:1. These results were explained by differences in the acidity and steric environment of the two hydroxyl groups. The C6 hydroxyl is the less acidic of the two, but because silylation involves attack of neutral hydroxyl,[16] the controlling factor is steric hindrance and the reaction outcome is a reflection of the greater steric accessibility of the C6 hydroxyl. The C7 hydroxyl is more acidic due to the presence of the two electron-withdrawing acetal oxygens. In DMAP-catalysed acylations, the counterions present are associated with general base catalysis,[17] indicating that formation of an alkoxide prior to acylation occurs. This favours reaction at C7 and this is indeed what is observed.



Scheme 4. Differentiating the C6 and C7 hydroxyls.

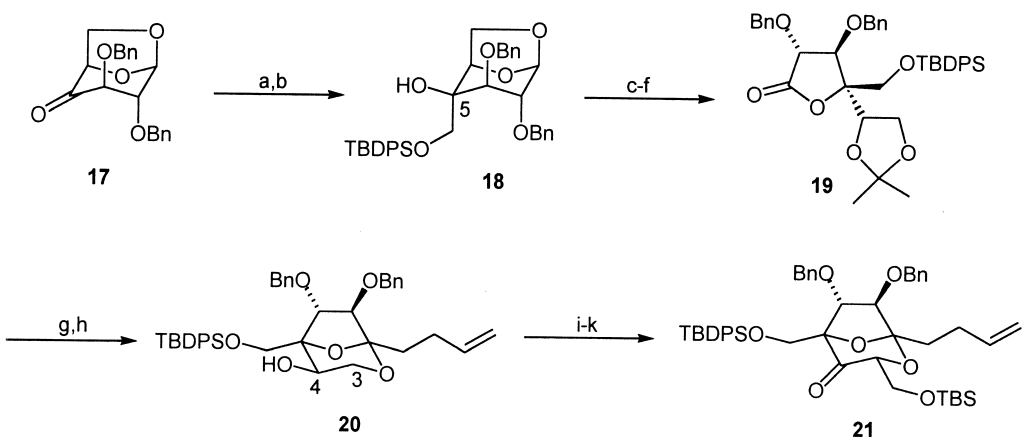


Scheme 5. Reassembly of the natural product. *Reagents and conditions*: (a) PPTS, 4 Å sieves, benzene, reflux, 99%; (b) **8**, DCC, DMAP, CH_2Cl_2, 0°C to rt, 95%; (c) H_2O, acetone, PPTS, 50°C; (d) Et_3SiCl, pyridine, rt, 80% over 2 steps; (e) **10**, ^nBuLi, THF, then, $CeCl_3$, then **15**, 87%; (f) Dess–Martin periodinane, pyridine, CH_2Cl_2, 92%; (g) Tebbe reagent, THF, 0°C, 77%; (h) DDQ, CH_2Cl_2, H_2O, 91%; (i) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0°C, 100%; (j) HF, pyridine, THF, 0°C, 87%; (k) TFA, CH_2Cl_2, rt, 74%.

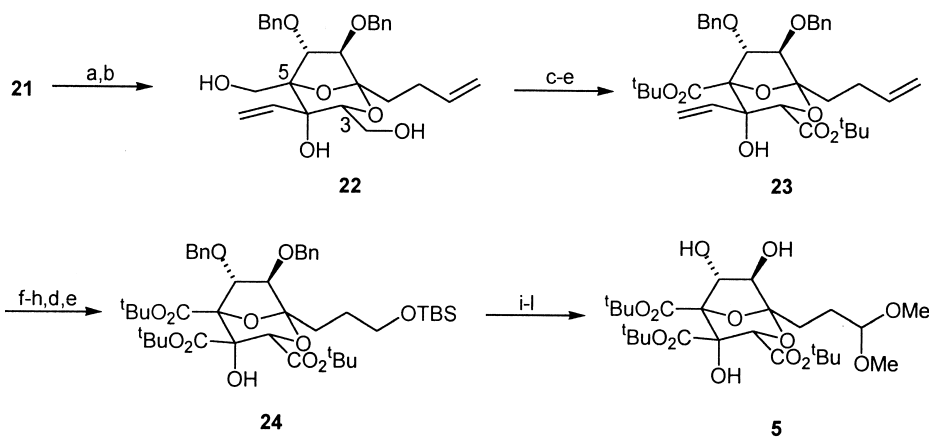
The problem of regioselectivity was neatly solved when it was observed that treatment of the relay compound **5** with PPTS and molecular sieves gave rise to a cyclic methyl acetal **14** via reaction exclusively at C7 (Scheme 5). This allowed attachment of the C6 side chain without the question of regioselectivity arising. Opening of the cyclic acetal **14** to give the free aldehyde and protection of the C6 hydroxyl gave **15**, allowing reattachment of the C1 side chain.

Transmetallation of the alkoxystannane **10** to the lithiated reagent, followed by formation of the cerium reagent, allowed addition of the C1 side chain to **15**. The formation of the cerium reagent was necessary to prevent enolisation, which was caused by the much more basic lithiated reagent. A 1:1 mixture of diastereomers was formed, but this was not important as this stereocentre was then oxidised to the ketone, allowing formation of the required side chain alkene by treatment with the Tebbe reagent to give **16**. Removal of the side chain protecting group and acylation of the resulting free hydroxyl put in place all the required functionality. All that remained was removal of the C7 TES group and hydrolysis of the triester to give zaragozic acid A. This completed the reassembly of the relay compound to the natural product in a total of 10 steps and 27% overall yield. All that remained was to synthesise the relay compound.

In common with the majority of synthetic approaches towards the zaragozic acids, Heathcock's synthesis of zaragozic acid A relies on the chiral pool to provide the starting point of his approach and control the absolute stereochemistry. The start of the route was **17**, which can be synthesised from commercially available methyl α-D-glucopyranoside in five steps, with an overall yield of 48%.[18] While this starting material provided the absolute stereochemistry and the relative stereochemistry at C6 and C7, it was still necessary to introduce the three carboxylic acid groups, the side chain and rearrange the skeleton to the



Scheme 6. Towards the synthesis of the relay compound. *Reagents and conditions*: (a) (i) $Me_2(^iPrO)SiCH_2MgCl$, THF, −78°C; (ii) H_2O_2, MeOH, THF, $NaHCO_3$; (b) $^tBuPh_2SiCl$, imidazole, DMF, 92% over 2 steps; (c) TFA, Ac_2O; (d) NaOMe, MeOH; (e) acetone, H^+; (f) PDC, sieves, CH_2Cl_2, 77% over 4 steps; (g) $CH_2{=}CHCH_2CH_2CeCl_2$, THF, −78°C; (h) HCl, H_2O, THF, 74% over 2 steps; (i) DMSO, TFAA, Et_3N, CH_2Cl_2; (j) ^tBuLi, CH_2O, THF; (k) $^tBuMe_2SiCl$, imidazole, DMF, 88% over 3 steps.



Scheme 7. Completion of the relay compound synthesis. *Reagents and conditions*: (a) CH_2=CHMgBr, $CeCl_3$; (b) TBAF, THF, 88% over 2 steps; (c) Dess–Martin, CH_2Cl_2; (d) $NaClO_2$; (e) (^{t}BuO)(^{i}PrNH)C=N(^{i}Pr), 76% over 3 steps; (f) (i) O_3; (ii) $NaBH_4$; (g) O_3; (h) ^{t}BuMe$_2$SiCl, imidazole, DMF; 25% over 5 steps; (i) TBAF, THF; (j) Dess–Martin; (k) $(MeO)_3CH$, MeOH, PPTS; (l) H_2, $Pd(OH)_2$, MeOH, 61% over 4 steps.

required bicyclic core. The C5 group was the first to be introduced, by addition of a Grignard reagent containing a terminal silicon group, followed by Tamao oxidation of the silicon group to the alcohol which could be protected as the TBDPS ether, to give **18**. This protecting group was necessary as it was found that the TBDMS group was unstable to acidic conditions used later in the synthesis. Treatment of the anhydropyranose with TFA in acetic anhydride gave a triacetate, the product of ring opening and esterification. Saponification of the triacetate was achieved with sodium methoxide, allowing acetonide formation under standard conditions. The lactol product was oxidised with PDC to furnish the lactone **19** in good yield over the four steps (Scheme 6).

The C1 side chain could now be attached via the corresponding cerium reagent. It was found that use of the more usual Grignard reagent caused elimination of the benzyloxy group at C7. Treatment with acid gave **20**, which contains the correct core structure of the zaragozic acids, but lacking the carboxylic groups at C3 and C4. It should be noted that **20** was the only product formed upon acid-mediated ketalisation. In other related systems more than one product has been observed and some have been found to convert between the isomers upon re-exposure to cyclisation conditions. The alcohol at C4 was oxidised to the ketone in order to introduce the remaining functionality. Enolisation of the ketone utilising ^{t}BuLi and quenching with paraformaldehyde introduced the required one-carbon unit at C3, but in a moderate 57% yield with 39% unreacted starting material. The reaction could not be optimised further as this led to undesired side products. Protection of the primary alcohol as the silyl ether gave **21**.

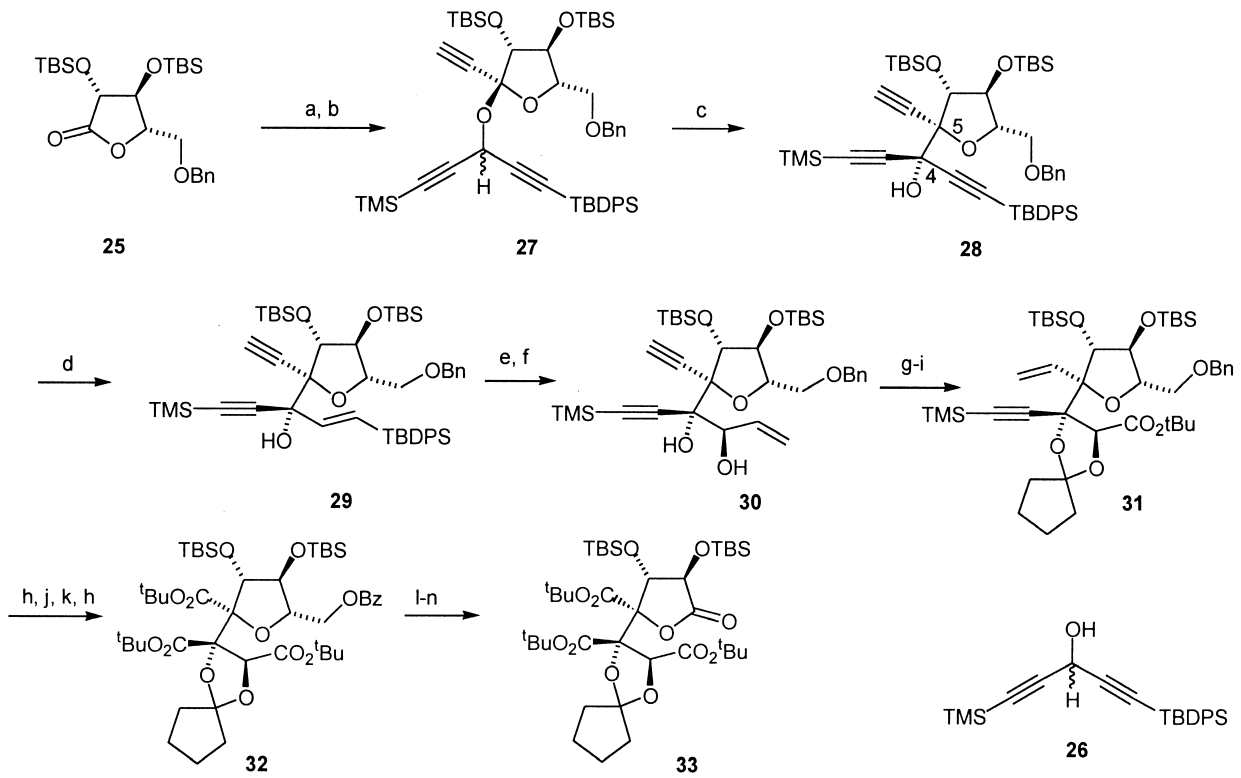
In order to introduce the C4 one-carbon unit, a vinylcerium reagent was used (Scheme 7). Once again the cerium reagent was required to circumvent problems associated with the vinyl Grignard or lithium reagent. The addition gave the required product as a single desired stereoisomer, contrary to the observations of Carreira[9] in similar systems. Removal of the silyl protecting groups gave **22**.

Compound **22** contains the required carbon framework and all that remained was elaboration to the correct oxidation state throughout the molecule. The C3 and C5 substituents were simultaneously oxidised to the acid level by sequential oxidation with Dess–Martin and Pinnick (sodium chlorite) oxidations. Esterification with the isourea reagent as used in the degradation studies gave **23**. Selective cleavage of the C1 side chain was achieved by careful ozonolysis and reduction of the ozonide gave the primary alcohol. Further ozonolysis of the C4 alkene furnished the aldehyde. The primary alcohol of the side chain was protected at this stage, allowing the Pinnick oxidation of the aldehyde and protection as the *tert*-butyl ester, giving **24**. Elaboration of the side chain was achieved in straightforward manner, by deprotection, oxidation to the aldehyde level, acetal formation and final deprotection of the benzyl groups to yield the relay product **5**.

This completed the total synthesis of zaragozic acid A in 35 synthetic steps in the longest linear sequence. The synthesis is marked by formation of a relay compound by degradation of the natural product, and use of a sugar derivative to control the stereochemistry of the relay compound and an acid-mediated ketalisation to form the bicyclic core.

A further synthesis of zaragozic acid A has recently been described by Tomooka.[8a] Central to his work is the development of novel variants of the [1,2]-Wittig rearrangement. Following proof of concept in successful model studies,[8b,c] the total synthesis began with the conversion of L-arabinose into the lactone **25** in eight steps (Scheme 8). Addition of lithium acetylide followed by coupling with the racemic bisalkynylmethanol **26** afforded **27**. Treatment of **27** with ^{n}BuLi effected rearrangement to **28**, installing the C4 and C5-stereocentres of the natural product. The stereocontrol at C4, resulting from the intermediate radical recombination being able to distinguish between the TMS and TBDPS-protected alkynes, is remarkable. Equally noteworthy is the subsequent selective reduction of the TPDPS-alkyne in **28** to **29**, allowing its ozonolytic cleavage and chelation-controlled vinylation leading to **30**. Functional group manipulations, including sequential conversion of the vinyl groups into the carboxylic acids via ozonolysis and chlorite oxidation, led to lactone **33**.

Synthesis of the C1-side chain also used the [1.2]-Wittig

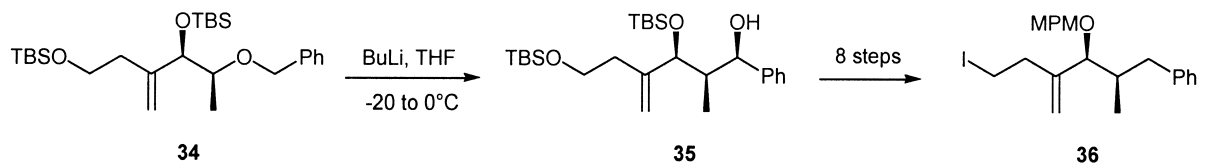


Scheme 8. Tomooka's rearrangement strategy. *Reagents and conditions*: (a) Lithium acetylide, Et_2O, −78°C, 75%; (b) Alkyne **26**, montmorillonite K10, 4 Å MS, CH_2Cl_2, 80%; (c) ^nBuLi, THF, −78°C, 54%, 84:16 at C4. (d) Red-Al, Et_2O, −15°C, 83%; (e) O_3, MeOH, −78°C, then Me_2S; (f) CH_2═$CHMgBr$, toluene, −78°C, 49% for 2 steps; (g) cyclopentanone dimethylacetal, *p*TsOH, PhH, 87%; (h) O_3, MeOH, −78°C, then Me_2S; $NaClO_2$, $NaHPO_4$, Me_2C═CHMe, $^tBuOH/H_2O$; *N,N′*-diisopropyl-*O-tert*-butylisourea, CH_2Cl_2, rt, 73–84% for 3 steps; (i) H_2, Pd/C, MeOH, 88%; (j) TBAF, THF, 94%; (k) H_2, Lindlar cat., MeOH, 93%; (l) KOH, MeOH, 78%; (m) TPAP, NMO, 4 Å MS, 98%; (n) O_2, $Cu(OAc)_2$, 2,2′-bipyridyl, DABCO, DMF, 70°C, 72%.

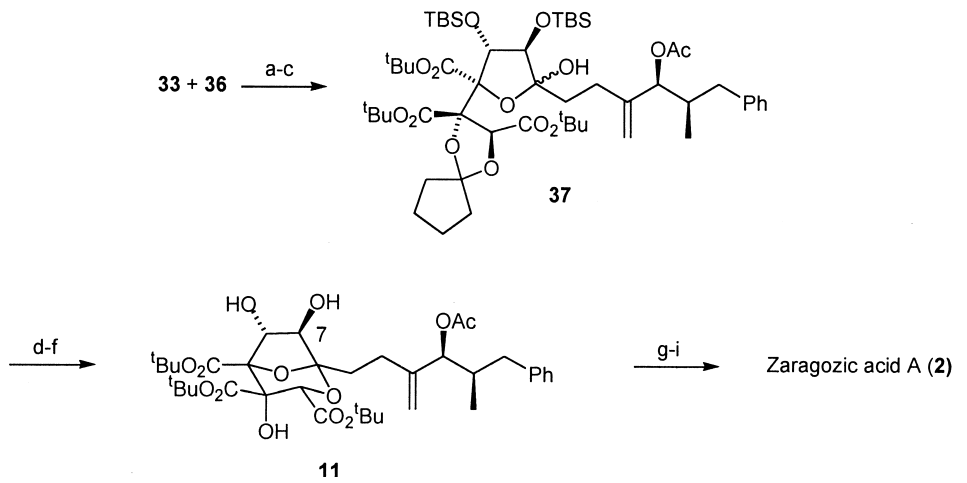
rearrangement as a key step (Scheme 9). Thus, treatment of benzyl ether **34**, prepared in five steps from *S*-methyl lactate, with BuLi, afforded **35** with good diastereoselectivity (88% dr), albeit in moderate yield (32% plus 58% recovered **34**). This was converted into **36** in eight steps (Scheme 9).

Conversion of iodide **36** to the corresponding organolithium and addition to the lactone **33** followed by protecting group interchange provided **37**. Subsequent exposure to TFA in CH_2Cl_2/H_2O effected removal of the cyclopentylidene acetal and formation of the desired bicyclic ketal, with simultaneous deprotection of the *tert*-butyl esters, which needed to be reintroduced. Removal of the TBS ethers then afforded **11**, which was converted to the natural product via selective protection at C7, introduction of the C6 side chain and final deprotection. The synthesis of (+)-zaragozic acid A had thus proceeded with a longest linear sequence of ca. 33 steps from L-arabinose (Scheme 10).

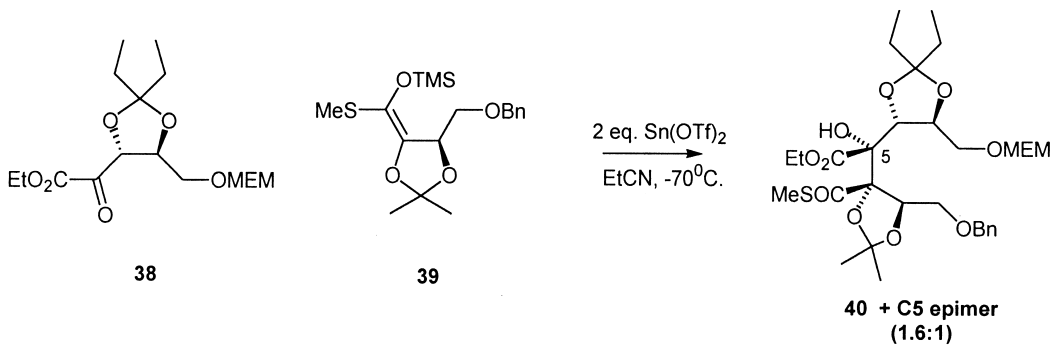
Hashimoto[11] provided the third synthesis of zaragozic acid C. Here, the approach was based on an aldol reaction to assemble the majority of the carbon framework. This method was applicable as two tartaric acid units were identified in the core structure, allowing reaction between an α-ketoester and an enolate. It is a noteworthy approach as the key step forms two contiguous quaternary stereocentres simultaneously. The actual aldol reaction (Scheme 11) involved reaction between a ketoester **38** and 2 equiv. of the silylketene thioacetal **39**. Considerable experimentation was required to find the ideal conditions and reacting partners. It was demonstrated that use of the (*Z*)-silylketene thioacetal was favoured in terms of yield and diastereoselectivity. Throughout there was almost complete selectivity at the C4 carbon to give the desired configuration, indicating that the silylketene thioacetal was reacting with almost complete diastereofacial selectivity at the more accessible *si*-face. However, facial selectivity of the α-ketoester reacting partner was less selective and favoured formation of the undesired epimer at C5. Eventually, after variation of the protecting groups of the α-ketoester partner, it was found that **38** provided the greatest selectivity in favour of the required isomer of **40**, but in only a moderate 1.6:1 selectivity. However, the two epimers could be separated and elaborated towards the natural product (Scheme 12). The first step was methanolysis of the thioester to give the



Scheme 9.

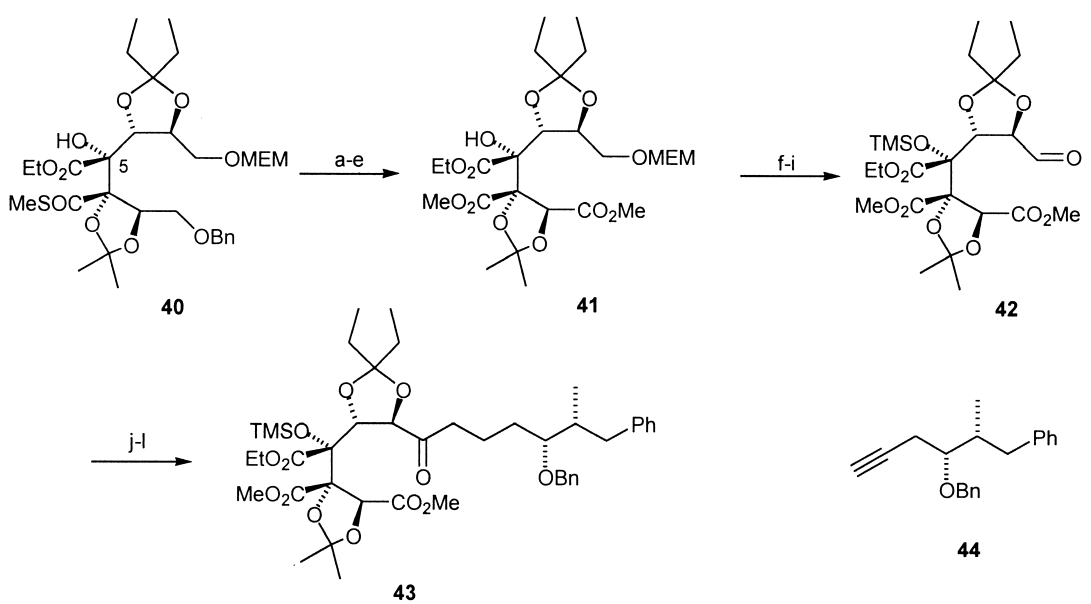


Scheme 10. Final steps in Tomooka's synthesis of zaragozic acid A. *Reagents and conditions*: (a) 3.2 equiv. **36**, 5 equiv. BuLi, 5:1 hexane/ether, −40°C, then **33**, −40°C, 96%; (b) DDQ, CH_2Cl_2, 96%; (c) Ac_2O, DMAP, CH_2Cl_2, 95%; (d) 10:20:1 TFA/CH_2Cl_2/H_2O; (e) *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea, CH_2Cl_2; (f) TBAF, THF, 51% for 3 steps; (g) (^{t}BuOCO)$_2$O, 4-pyrrolidinopyridine, CH_2Cl_2, 0°C, 81%; (h) side chain acid **8**, DCC, DMAP, CH_2Cl_2, 82%; (i) TFA, CH_2Cl_2, 73%.

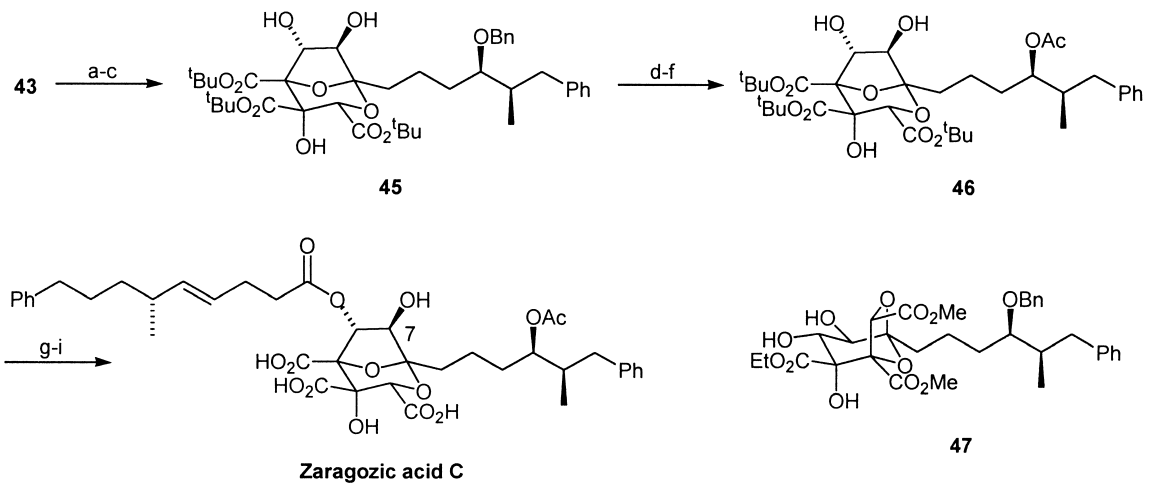


Scheme 11. Tin(II)-mediated aldol reaction.

ester at C4. Debenzylation then allowed oxidation of the C3 position to the acid level by sequential Dess–Martin and Pinnick oxidation, and protection as the methyl ester by treatment with diazomethane gave **41**. Selective removal of the MEM group was achieved with TMSCl/NaI and the C5 tertiary alcohol was protected by a two step bis-silylation/mono-desilylation procedure. Oxidation of the primary alcohol with the Dess–Martin reagent gave **42**, setting the



Scheme 12. Hashimoto's approach to zaragozic acid C. *Reagents and conditions*: (a) $Hg(OCOF_3)_2$, MeOH, reflux, 82%; (b) H_2, Pd/C, MeOH; (c) Dess–Martin, CH_2Cl_2; (d) $NaClO_2$, NaH_2PO_2, 2-methyl-2-butene, ^{t}BuOH, H_2O; (e) CH_2N_2, Et_2O, 0°C, 88% over 4 steps; (f) TMSCl, NaI, MeCN, 0°C, 88%; (g) MeN(TMS)$COCF_3$, 90°C; (h) 10% aq. HCl, Et_2O, 79% over 2 steps. (i) Dess–Martin, CH_2Cl_2, 98%; (j) **44**, ^{n}BuLi, THF, −78°C, then **42**, −78°C; (k) Dess–Martin, CH_2Cl_2, 79% over 2 steps; (l) H_2, 10% Pd/C, AcOEt, 87%.



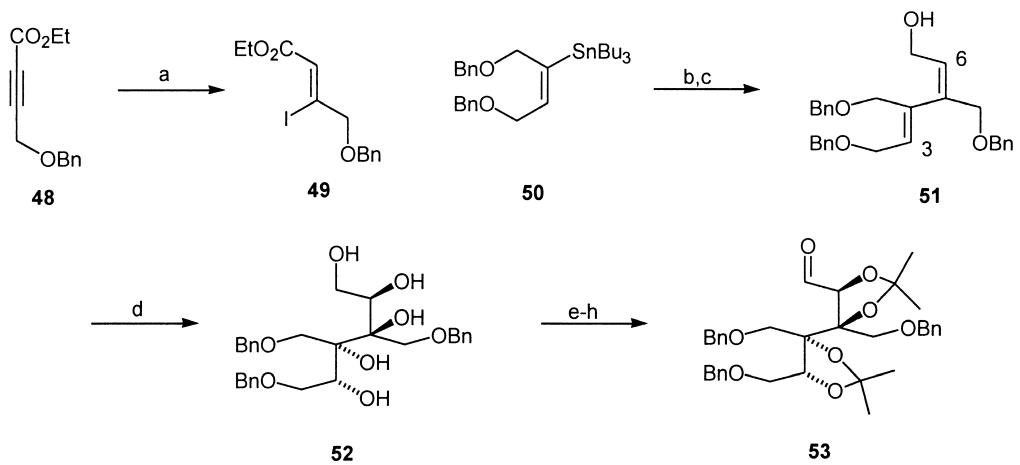
Scheme 13. Completion of Hashimoto's synthesis of zaragozic acid C. *Reagents and conditions*: (a) 90% aq. TFA, 68%, 7% of **47**; (b) 1N KOH, 1,4-dioxane, reflux; (c) *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea, CH_2Cl_2, 40% over 2 steps; (d) H_2, 10% Pd/C, MeOH, 86%; (e) Ac_2O, DMAP, CH_2Cl_2, 85%; (f) K_2CO_3, MeOH, 91%; (g) $(Boc)_2O$, 4-pyrrolidinopyridine, Et_3N, CH_2Cl_2, 0°C, 71%; (h) C6 acyl sidechain, DCC, DMAP, CH_2Cl_2, 85%; (i) TFA, CH_2Cl_2, 100%.

scene for the introduction of the C1 side chain, which was introduced as a lithium acetylide of **44** in good yield. Attempts to introduce the side chain as an alkyllithium or Grignard reagent were marked by formation of complex mixtures. The C1 alcohol (zaragozic acid numbering) was then re-oxidised to the ketone and the alkyne exhaustively hydrogenated to give **43**. This molecule contained all the required carbon framework of the natural product and allowed for cyclisation to the bicyclic core.

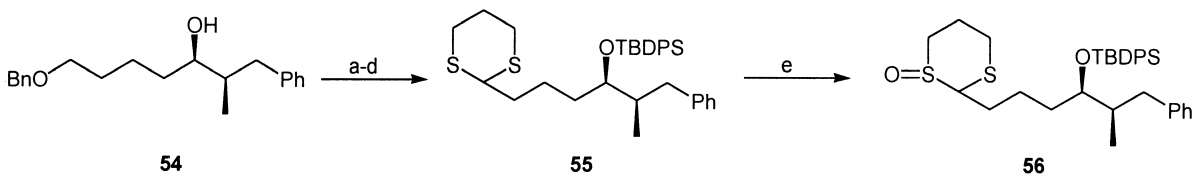
Ketalisation (Scheme 13) was achieved by treatment of **43** with 90% aq. TFA to give the required cyclised core system in a reasonable 68% yield, which after saponification and reprotection as the tris *tert*-butyl ester gave **45**. It is interesting to note that 7% of **47** was also formed upon treatment of **43** with acid. These isomeric ketal products were found not to be in equilibrium with each other and the selectivity in the ketalisation reaction was ascribed to the differential rates of hydrolysis of the two acetal protecting groups in **43**. Removal of the benzyl group in **45** by hydrogenolysis allowed peracetylation. Subsequent selective removal of the C6 and C7 acetyl groups gave **46**, which intersects with a late intermediate in Carreira's synthesis.[9] This completed a formal synthesis and only required attachment of the C6 acyl side chain, which can be achieved by selective protection of the C7 alcohol with a BOC group. This allowed standard coupling of the C6 side chain and final deprotection to give zaragozic acid C.

The total synthesis was achieved in 22 synthetic steps from **38** and **39**, which are available from diethyl tartrate in eight and six steps, respectively.[11] The key steps are a tin-mediated aldol reaction to provide the carbon framework and an acid-mediated cyclisation to the core system.

The most recent synthesis of zaragozic acid C was provided by our own group.[12] Although it employs a conceptually similar route to that of Nicolaou,[6] our approach was rare amongst most efforts as it employed catalytic asymmetric reactions to control the stereochemistry of the final product, rather than using members of the chiral pool as the starting point. The key step for control of the stereochemistry was the double asymmetric dihydroxylation (AD) of a prochiral



Scheme 14. Armstrong's approach to the core system. *Reagents and conditions*: (a) LiI, AcOH, 70°C, 95%; (b) **49** and **50**, CuTC, NMP, 87%; (c) DIBAL-H, CH_2Cl_2, −30°C, 94%; (d) (i) AD-mix β, 1 mol% OsO_4, 5 mol% $(DHQD)_2PHAL$, 2 equiv. $CH_3SO_2NH_2$, 2 equiv. $K_2S_2O_8$, 1:1 $^tBuOH/H_2O$, 0°C to rt, (ii) 1 mol% OsO_4, 5 mol% $(DHQD)_2PHAL$, 2 equiv. NMO, 5:1 acetone/H_2O, 45%; (e) PivCl, pyridine, DMAP, CH_2Cl_2, 77%; (f) 2-methoxypropene, cat. *p*TsOH, DMF, 77%; (g) DIBAL-H, CH_2Cl_2, −78°C, 91%; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 75%.



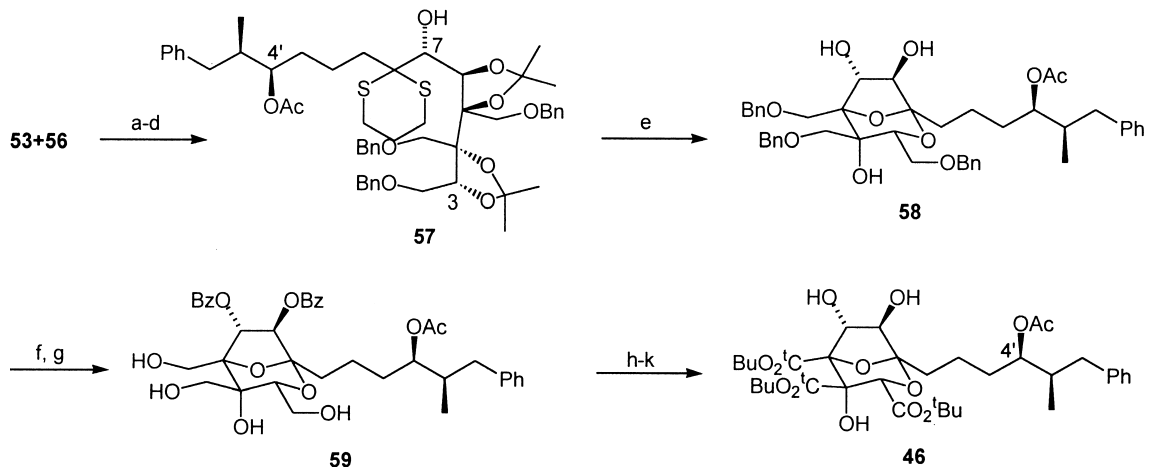
54 55 56

Scheme 15. Synthesis of C1 side chain. *Reagents and conditions*: (a) TBDPSCl, imidazole, DMF, 100°C, 93%; (b) BCl_3.DMS, CH_2Cl_2, 94%; (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 97%; (d) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 92%; (e) *m*CPBA, CH_2Cl_2, 0°C, 78% *trans*/*cis* 5:1.

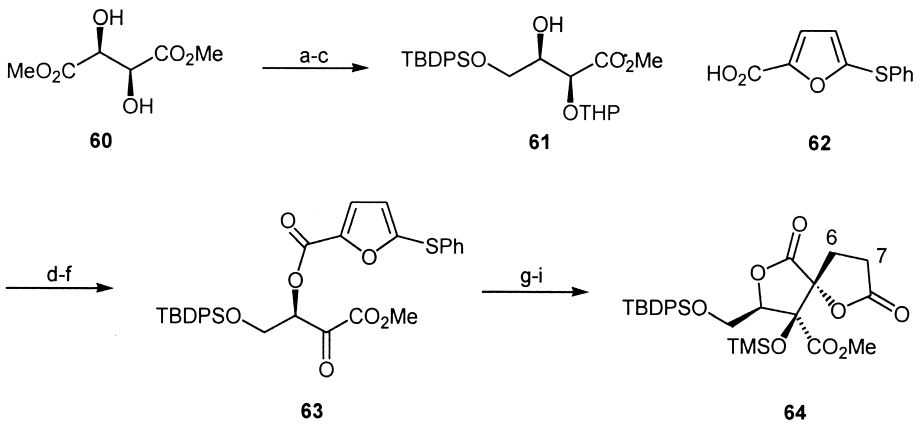
diene, which could be made in a stereocontrolled fashion via a Stille coupling of two alkene units. The synthesis of the required diene and its reaction under AD conditions are shown in Scheme 14.

Starting with the known alkyne **48**, Michael addition of lithium iodide gave **49**, one of the reacting partners required in the Stille coupling, as a single geometrical isomer. The other partner **50** was a known compound also available as a single isomer, from palladium-catalysed addition of Bu_3SnH to the corresponding alkyne. With the two reacting partners in hand, a number of conditions were screened to effect cross coupling. Eventually, the use of stoichiometric copper(I) thiophenecarboxylate[19] was found to be the most effective. Palladium-catalysed cross coupling was also feasible if trifurylphosphine was used as ligand. Reduction of the ester group was cleanly accomplished with DIBAL-H to yield **51**. The scene was now set to attempt the double AD reaction. Conveniently, it was predicted that the required stereochemistry at the four stereocentres from C3–C6 could be controlled by use of the same chiral ligand in the AD reaction,[20a] which meant that they could theoretically be introduced simultaneously. Once again, a good deal of experimentation was required to find the ideal conditions to effect the desired transformation. Treatment of **51** under the standard AD conditions developed by Sharpless[20a] resulted in formation of a regioisomeric mixture of triols that could not be exhaustively dihydroxylated under longer reaction times. Application of the monophasic acetone/water conditions where NMO is used as the co-oxidant[20b] in the presence of chiral ligand did result in the conversion of **51** to the required pentaol **52**, but the product was obtained in low enantiomeric excess. In the end, the problem was solved by use of a two-stage process. Diene **51** was treated under Sharpless AD conditions to give the previously observed triol mixture, which could be exhaustively dihydroxylated by application of the one-phase NMO/acetone/water system to the triol mix to give **52** in reasonable ee (76%) and good diastereoselectivity (9:1). Differential protection of the primary alcohol was achieved by formation of the pivaloate ester. The secondary alcohols were protected as the acetonides, which after removal of the pivaloate group and Swern oxidation of the primary alcohol gave **53**, the core system. Preparation of the C1 side chain was now necessary. This was achieved as shown in Scheme 15.

The starting point for the synthesis was **54**, which Carreira[9] had made in his synthesis of zaragozic acid C. The stereochemistry of **54** was controlled by use of an Evans aldol reaction. Protection of the secondary alcohol as the silyl ether was accomplished under standard conditions and the primary benzyl ether was deprotected under Lewis acid conditions. The primary alcohol was oxidised to the aldehyde under Swern conditions and then transformed into the dithiane to give **55**. It was intended to introduce the side chain to the core utilising the metallated dithiane as an acyl anion equivalent, but it was found that **55** could not be cleanly metalated under a variety of conditions and that conversion to the more acidic monosulfoxide **56** was required. The lack of reactivity of **55** was attributed to the presence of the oxygenated functionality in the δ-position. With the side chain in hand, the coupling of the two fragments and elaboration to the natural compound could now attempted. This is shown in Scheme 16.



Scheme 16. Completion of the synthesis. *Reagents and conditions*: (a) 3 equiv. of **56**, 3.1 equiv. of ^{n}BuLi, THF, −78°C, then 1 equiv. **53**, −78°C; (b) 0.55 equiv. P_2I_4, 1 equiv. Et_3N, CH_2Cl_2, dark, 59% over 2 steps; (c) TBAF, THF, 80°C, 32% and 36% of undesired C7 epimer; (d) Ac_2O, DMAP, pyridine, 80°C, 85%; (e) 20:10:1 CH_2Cl_2/TFA/H_2O, 90%; (f) PhCOCl, DMAP, pyridine, 97%; (g) H_2, 10% Pd/C, 89%; (h) 3.5 equiv. $(COCl)_2$, 7 equiv. DMSO, 10.5 equiv. Et_3N, −78°C, (i) $NaClO_2$, pH, 3.5 aqueous phosphate buffer, 5:1.2 ^{t}BuOH/β-isoamylene; (j) *N*,*N*′ diisopropyl-*O*-*tert*-butylisourea, CH_2Cl_2, 33% over 3 steps; (k) 0.2% K_2CO_3 in MeOH, 75%.



Scheme 17. Martin's approach to squalestatin H5. *Reagents and conditions*: (a) DHP, PPTS, CH_2Cl_2, 69%; (b) $BH_3{\cdot}SMe_2$, $NaBH_4$ (cat.); (c) TBDPSCl, imidazole, CH_2Cl_2, 50% over 2 steps; (d) **61**+**62**, DCC, DMAP, CH_2Cl_2: (e) Me_2AlCl; (f) Dess–Martin, CH_2Cl_2, 94% over 3 steps; (g) $TiCl_4$, CH_2Cl_2, 0°C to rt, 40%; (h) H_2, $Pd(OH)_2/C$, EtOAc; (i) TMSCl, imidazole, 75% over 2 steps.

Metallation of **56** was accomplished with ^{n}BuLi and the core aldehyde **53** was then added to achieve coupling of the two fragments. Reduction of the monosulfoxide gave the two diastereomers that were epimeric at C7, which could be separated by chromatography after removal of the side chain silyl ether protecting group. Selective formation of the acetate at the C4′ position as required in the natural product was achieved to give **57**. The undesired C7 epimer could not be recycled to the required diastereomer by Mitsunobu reaction as the C7 hydroxyl group was found to be extremely sterically hindered (which explains the high selectivity in the acylation of C4′ over the C7 position). Attempts to obtain the desired isomer by oxidation of the incorrect epimer and subsequent reduction were unsuccessful, and only the undesired product was returned on reduction with $NaBH_4$ or $Zn(BH_4)_2$.

The next step was the key cyclisation to form the required bicyclic system. It had been observed in a model system that if the dithiane group was removed to reveal the ketone prior to treatment with TFA/H_2O then a 1:1 ratio of the desired bicyclic system and the isomer derived from ketalisation of the C3 and C4-hydroxyls resulted. The ratio of products, which was found to be under kinetic control, was influenced by the relative rates of hydrolysis of the acetonides, as observed by Hashimoto.[11] It was speculated that if the C5–C6 acetonide were hydrolysed first, then this would lead to formation of the required bicyclic system. Alternatively, if the C3–C4 acetonide were hydrolysed first then the undesired product would be formed. It was proposed that if both acetonides were hydrolysed before the ketone was unmasked then the sole formation of the required isomer might result. This was indeed found to be the case, and in the natural product system, treatment of **57** with TFA/H_2O effected acetal deprotection and remarkably facile removal of the dithiane group, giving **58**, the required bicycle, as the sole product in excellent yield.

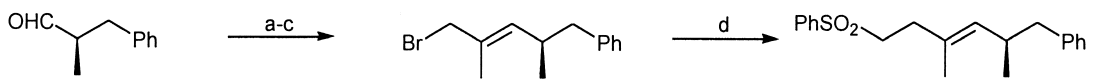
Protection of the C6 and C7 alcohols as benzoate esters allowed hydrogenolysis of the three benzyl groups to give **59**. It was now possible to attempt the final key step of triple oxidation of the three primary alcohols to the acid level. Treatment of **59** with 3.5 equiv. of the Swern reagent gave the tris-aldehyde without formation of lactol or lactone side products. The aldehyde could then be oxidised with sodium chlorite to the acid level and protected as the tris-*tert*-butyl ester. Removal of the benzoate groups gave **46**, which is an intermediate in the Carreira and Hashimoto syntheses, completing a formal synthesis. Selective attachment of the C6 acyl group using the method of Carreira[9] (vide supra) completed the total synthesis.

The total synthesis was completed in a concise 24 steps, with essentially four key stages: the control of stereochemistry via asymmetric dihydroxylation, introduction of the side chain as a monosulfoxide, acid-mediated cyclisation and triple oxidation to the acid level.

The final total synthesis is that reported by the Martin group of 6,7-dideoxysqualestatin H5.[13] This member of the family of natural products is deoxygenated at C6 and C7 and consequently has no C6 acyl side chain. Here, the key step was to be an intramolecular vinylogous aldol reaction to assemble the majority of the framework, followed by an acid-mediated ketalisation to form the desired bicyclic system.

In common with most other routes, the synthesis (Scheme 17) starts with the aid of chiral pool material. In this instance, the starting point is dimethyl tartrate **60**. Protection of one of the secondary alcohols as a THP ether was followed by selective reduction of the ester carbonyl α to the free alcohol with $BH_3{\cdot}Me_2S$ in the presence of a catalytic amount of $NaBH_4$. This resulted in formation of a 4:1 mixture of the 1,2 and 1,3-diols, that could be separated after protection of the primary alcohols as their TBDPS ethers to give **61**. Esterification of **61** with **62** (available in three steps from 5-bromo-2-furancarboxylic acid) was achieved under standard DCC/DMAP coupling conditions, which, after removal of the THP ether and Dess–Martin oxidation, gave **63**, the cyclisation precursor.

The key vinylogous aldol reaction was the next step and a series of Lewis acids was screened to find suitable conditions. It was found that treatment of **63** with 3 equiv. of $TiCl_4$ resulted in formation of the desired product, with only very small amounts of the other possible diastereomeric adducts observed. Other Lewis acids had resulted in either no reaction or formation of complex mixtures. The



65 66 67

Scheme 18. Synthesis of squalestatin H5 side chain. *Reagents and conditions*: (a) Isopropenylmagnesium bromide, 75%; (b) MsCl, Et_3N; (c) NaBr, 81% over 2 steps; (d) $PhSO_2CH_2^-K^+$.

phenylthio substituent of the furan was also found to be important, as the use of a methoxy group in the furan had resulted in a statistical mix of all the possible diastereomers. Reduction of the C6–C7 double bond and protection of the tertiary alcohol as a TMS ether gave **64**, a spiro-fused bis lactone.

It was now necessary to synthesise the C1 side chain and this was achieved as shown in Scheme 18. The starting point was the known aldehyde **65**. Isopropenylmagesium bromide was added to the carbonyl to give a 1:1 mixture of epimers. This mixture was mesylated and the leaving group displaced with sodium bromide, with allylic rearrangement, to give **66**. Allyl bromide **66** was alkylated with the potassium salt of methyl phenyl sulfone to give the fully functionalised side chain **67**. It was now possible to couple the two partners and complete the total synthesis.

The side chain **67** was introduced as the dianion of the sulfone, adding to the less hindered lactone moiety, which, after reductive desulfonylation, gave the hemiketal **68** (Scheme 19). Treatment of the hemiketal with acidic methanol solution resulted in a 2.5:1 equilibrium mixture of **69** and **70**. Lactone **69** represents the product formed by trapping of an intermediate oxonium ion with methanol and removal of the silyl protecting groups, whereas **70** is the desired bicyclic system. This indicates that the key part of the cyclisation is the opening of the lactone moiety, which is slow relative to trapping of the oxonium ion by methanol. The two products could be separated by chromatography and **69** re-equilibrated to furnish greater amounts of **70**. Oxidation of the remaining primary alcohol to the acid level, followed by hydrolysis of the ester groups, gave the natural product 6,7-dideoxysqualestatin H5 **71**. The total synthesis had been achieved in a very concise 14 steps, using an elegant vinylogous aldol reaction to construct the framework, followed by an acid ketalisation to give the bicyclic system.

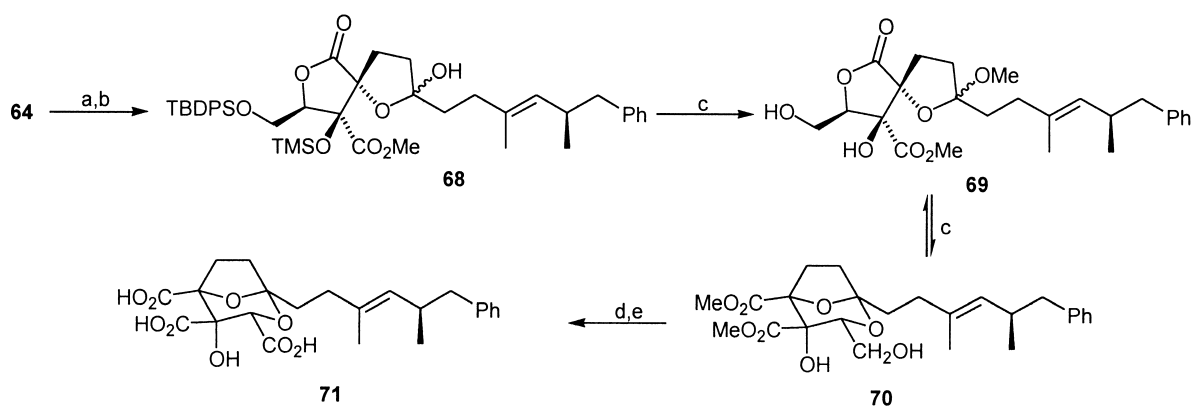
Eight total syntheses of the zaragozic acid/squalestatin family have been achieved, five of which have been described here. They are all marked out by use of disparate methods to construct the complex framework of these important natural products, demonstrating the importance of both chiral pool and catalytic asymmetric approaches to control stereochemistry, and the power and selectivity of modern synthetic methods when applied to sensitive functionality. These natural products have offered a great synthetic challenge, which has been admirably countered by a number of groups.

3. Synthetic approaches to the core system

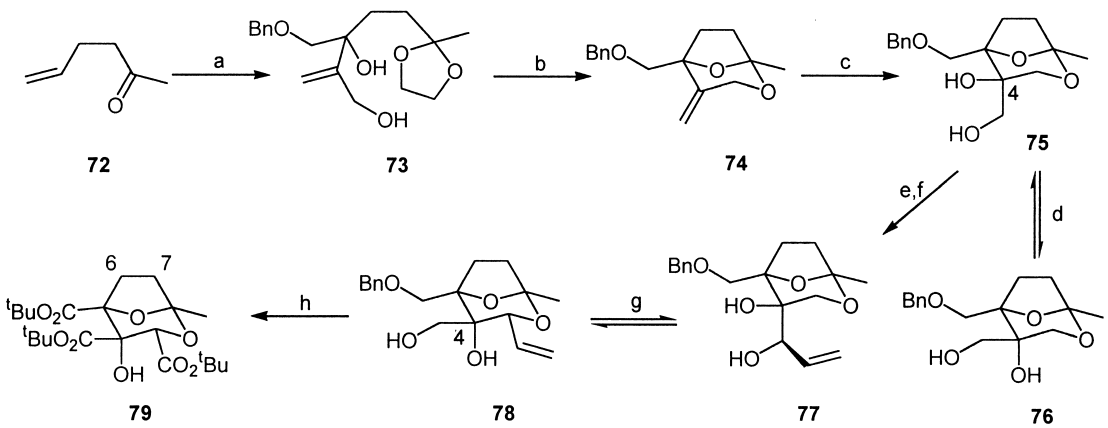
Although a number of total syntheses have now been accomplished in the zaragozic acid/squalestatin family, the bicyclic core remains a popular synthetic target as a showcase for inventive new synthetic methodology. These new approaches fall into essentially two categories: those that use acid-mediated ketalisation as the key step and those that utilise alternative strategies to synthesise the bicyclic system. The excellent review by Nicolaou[5a] has previously described core syntheses up to 1996, and this report therefore concentrates on those that have been published since then.

3.1. Acid-mediated cyclisations

Given that the zaragozic acid core system is essentially a bicyclic ketal, it is perhaps obvious that most retrosyntheses would favour acid-mediated cyclisation of a ketone polyol as the key disconnection. If a suitable hydroxyl protection strategy is not in place, then ketalisation of such ketone polyols can sometimes result in the formation of more than one isomeric bicyclic ketal, depending on which hydroxyl groups participate. As noted in Section 2, ketalisation in several of the natural product syntheses has been reported to



Scheme 19. Completion of the synthesis. *Reagents and conditions*: (a) **69**, ^{n}BuLi, 2 equiv.; (b) Al(Hg), THF/HMPA/H_2O (40:10:1), 73% over 2 steps; (c) 0.1 M H_2SO_4, MeOH, 25% **70**, 65% **69**; (d) TPAP, NMO, aq. CH_3CN; (e) KOH, dioxane, reflux, then H_3O^+, 62% over 2 steps.



Scheme 20. Myles' core synthesis. *Reagents and conditions*: (a) 5 steps, 16%; (b) 10 mol% TFA, CH_2Cl_2, 93%; (c) OsO_4, K_3FeCN, ^{t}BuOH/H_2O, 100%; (d) 10 mol% TFA, CH_2Cl_2, K_{eq}=2; (e) $(COCl)_2$, DMSO, Et_3N; (f) CH_2=CHMgBr, 70% over 2 steps; (g) 10 mol% TFA, CH_2Cl_2, K_{eq}=11, 79%; (h) 10 steps, 29%.

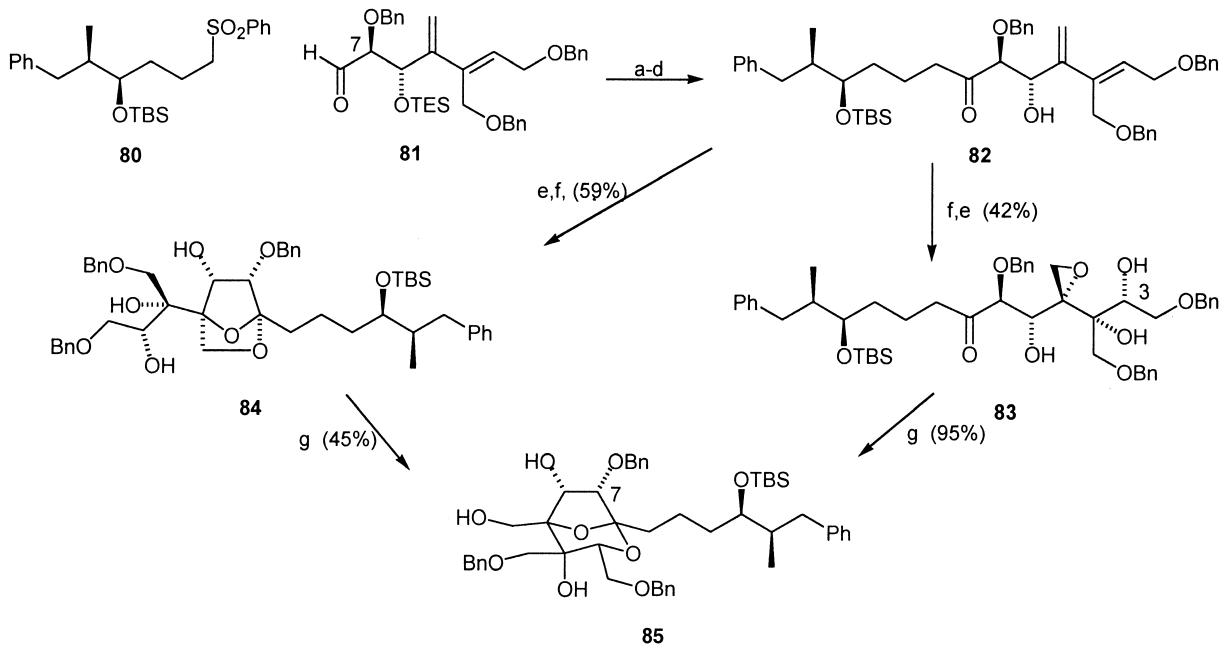
be kinetically controlled. In simple model systems, particularly those lacking C6 and C7-oxygenation and its destabilising inductive effect on a C1-oxonium ion, equilibration between isomeric ketals has commonly been observed (and indeed has played a key role in some synthetic strategies). A computational study of the equilibrium has been reported.[21] If the ketalisation disconnection is adopted, the question then arises of how the acyclic framework can be synthesised and how stereochemistry can be controlled. There are many possibilities and it is instructive to compare the many different solutions to the synthesis of the zaragozic acid core.

Myles[22] avoided the possible problem of formation of ketal isomers by forming the bicyclic ketal early from a ketone diol, where only one isomer is possible, and then using the rigid framework to control the stereochemistry of the incoming functionality. The starting point was allyl acetone **72**, which, after five steps to introduce the remaining framework, gave **73**, a protected ketone diol. Treatment of **73** with TFA gave the required bicyclic framework **74** without the complication of other side products. The exocyclic alkene was then dihydroxylated on the less hindered face to give **75**, which possesses the incorrect stereochemistry at C4. Diol **75** could be equilibrated upon re-exposure to acid to give **76**, which has the correct stereochemistry at C4. This is again in line with the idea that C6/C7-deoxy systems undergo ready equilibration, and this observation was useful later in the synthesis (Scheme 20).

The free primary alcohol of **75** was then oxidised to the aldehyde level and chelation-controlled addition gave **77** as a single diastereomer. The importance of the observation that the synthesised ketal could be equilibrated was now evident when **77** was treated with TFA to give **78**, which possesses all the correct stereochemistry. A series of standard oxidations was then used to provide **79**, a fully functionalised core of a 6,7-dideoxysqualestatin.

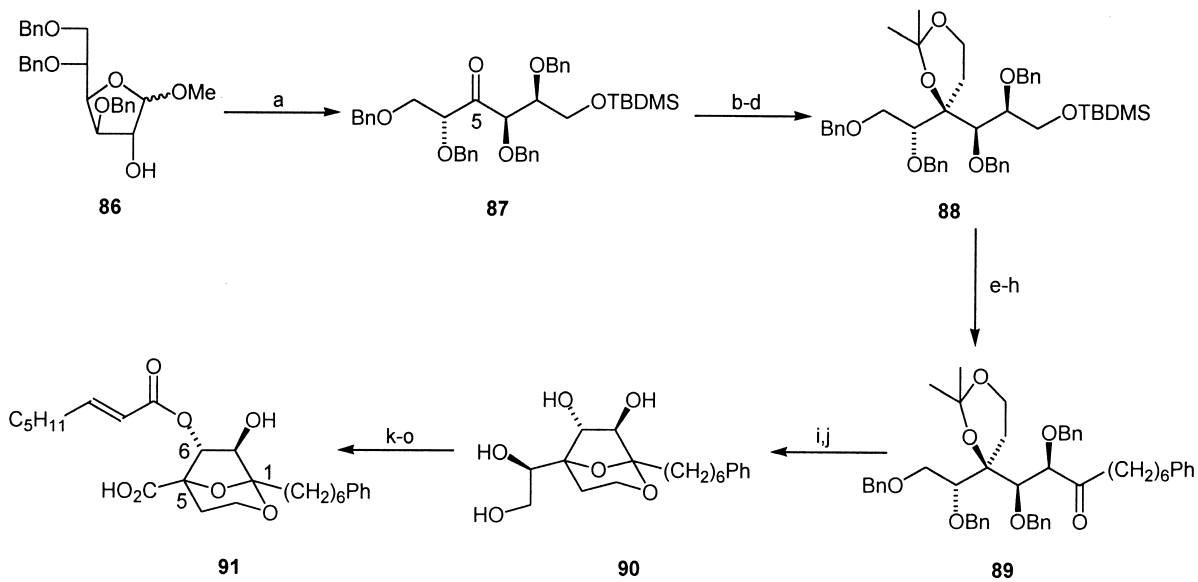
Paterson's approach to the zaragozic acids[23] (Scheme 21) was to employ an acid-mediated epoxide ring opening reaction to form the bicyclic ketal, instead of the more common ketone polyol cyclisation. The starting point was the two fragments **80** and **81**, representing the C1 side chain and core fragments, respectively. The side chain stereochemistry (in **80**) was controlled by alkylation of a psuedoephedrine derivative according to Myers,[24] followed by Brown's allylboration method[25] to set up the *syn* relationship. The core stereochemistry (in **81**) was established using Paterson's own boron mediated *anti*-aldol chemistry.[26] This gives the incorrect stereochemistry at C7, which becomes important later. With the two fragments in hand, the coupling was achieved by addition of the α-lithiated sulfone **80** to the core system **81**, in excellent yield. Oxidation to the ketone level at C1, followed by removal of the sulfone and deprotection of the C6 silyl ether, furnished **82**. At this point, it was necessary to introduce the epoxide functionality and to dihydroxylate the C3–C4 double bond required for cyclisation. If hydroxyl-directed epoxidation was performed before dihydroxylation then compound **84** was formed, due to concomitant nucleophilic attack of the ketone on the epoxide. If, however, the order of reactions was reversed, then the originally intended cyclisation precursor **83** was obtained. If either **83** or **84** were treated under acid conditions then **85**, the correct bicyclic ketal system, was observed. In the case of **83**, this was presumed to proceed via the proposed epoxide cyclisation mode, where, in a cascade reaction, attack of the C3 alcohol on the C1 ketone would provide a hemiacetal which could itself attack the epoxide to supply **85**. Ketal **84**, on the other hand, underwent a more conventional acid-mediated rearrangement process to give **85**. It should be noted that the stereochemistry at C7 is epimeric to that in the natural product, a consequence of the initial anti-aldol used to establish the core system. If, for instance, an Evans aldol reaction[15] had been used to construct the core, then the desired stereochemical relationship at C6 and C7 would have been established, leading to a system matching the natural product. Judicious use of protecting groups and oxidations would then complete the synthesis of the natural product.

Work by Kobayashi[27] (Scheme 22) was directed towards an analogue that was structurally simplified, lacking the carboxylic acid functionality at C3 and C4. This structure was proposed after a study of the structure–activity relationship, which demonstrated that only the C5 carboxylic acid was necessary for inhibitory activity. The

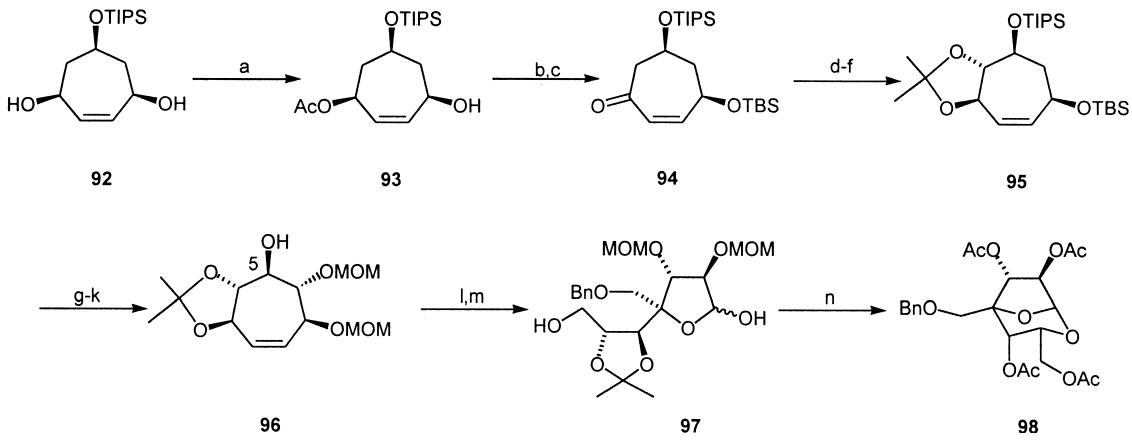


Scheme 21. Paterson's synthesis. *Reagents and conditions*: (a) **80**, ^{n}BuLi, THF/Et_2O, −78°C, then **81**; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78°C, 95% over 2 steps; (c) 6% Na(Hg), Na_2HPO_4, MeOH/THF; (d) HF/py, Py, THF, 64% over 2 steps; (e) 20 mol% $VO(acac)_2$, ^{t}BuOOH; (f) AD-mix β, $MeSO_2NH_2$, ^{t}BuOH/H_2O (1:1); (g) CSA, $CDCl_3$.

activity of the analogue was to be measured and then compared to that of zaragozic acid A. The synthesis of the analogue started once again from chiral pool materials, this time the known furanoside **86**. Furanoside **86** was converted into **87** in a series of standard protection, reduction and oxidation reactions in high yield. The key step was then the stereoselective formation of the C5 (zaragozic acid numbering) quaternary centre. It was found that vinylmagnesium bromide, acting as a masked carboxylic acid equivalent, would add to the ketone with essentially complete diastereoselectivity, to give the desired configuration. Hydroboration of the double bond gave **88** after oxidative work-up and protection as an acetonide. The simple C1 side chain analogue was then attached to the core by Grignard addition to a primary aldehyde (formed by TBAF removal of the silyl ether and oxidation) in the presence of Li_2CuCl_4, which upon re-oxidation to the ketone level gave **89**. The cyclisation to the bicyclic core was achieved upon exposure of **89** to PPTS in refluxing THF/MeOH. In a similar manner to Myles[22] (vide supra), only one product could be formed as only two hydroxyl groups were free to react. Removal of the protecting groups



Scheme 22. Kobayashi's synthetic analogue. *Reagents and conditions*: (a) 5 steps, 80%; (b) CH_2═$CHMgBr$, THF, −78°C, 98%; (c) 9-BBN, THF, reflux, then 3N NaOH, 30% H_2O_2, 88%; (d) $(MeO)_2CMe_2$, PPTS, benzene, reflux, 93%; (e) TBAF, THF; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60°C; (g) $Ph(CH_2)_6MgBr$, Li_2CuCl_4, THF, 0°C, 81% over 3 steps; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60°C; (i) PPTS, THF, MeOH, reflux, 86% over 2 steps; (j) Pd/C, H_2, THF; (k) $NaIO_4$, THF, H_2O; (l) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, ^{t}BuOH, H_2O; (m) CH_2N_2, Et_2O, 63% over 4 steps; (n) K_2CO_3, H_2O, MeOH; (o) 2-octenyl chloride, Et_3N, CH_2Cl_2, 48% over 2 steps.



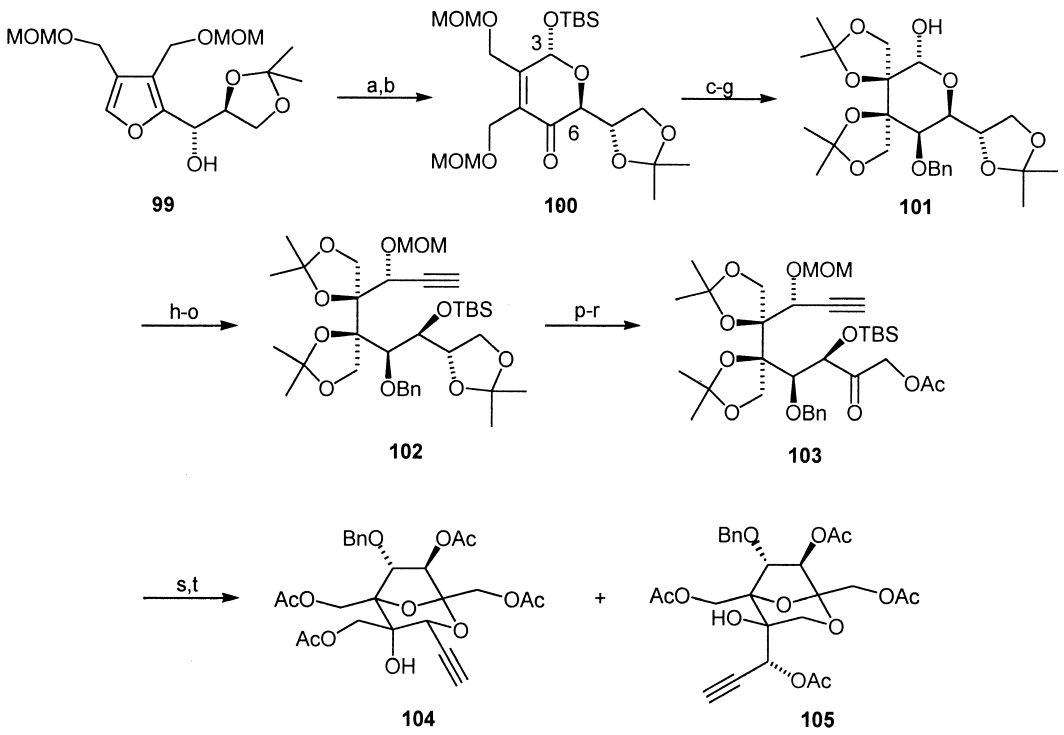
Scheme 23. Johnson's approach to the core. *Reagents and conditions*: (a) *Candida antarctica* lipase B, isopropenyl acetate; (b) TBSCl, imidzole, DMF, 100%; (c) KCN, MeOH, then PDC, 98%; (d) TMSOTf, Et_3N, CH_2Cl_2; (e) *m*CPBA, pentane, then $NaBH_4$, $CeCl_3$, MeOH, 59% over 2 steps; (f) 2,2-dimethoxypropene, CSA, 100%; (g) H_2SiF_6, Et_3N, CH_3CN, then PDC, CH_2Cl_2, 78%; (h) TMSOTf, Et_3N, CH_2Cl_2; (i) *m*CPBA, pentane, then $NaBH_4$, $CeCl_3$, MeOH, 54% over 2 steps; (j) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 100%; (k) TBAF, THF; (l) PCC, CH_2Cl_2, followed immediately by Bu_3SnCH_2OBn, ^{n}BuLi, THF, 88%; (m) O_3, MeOH, CH_2Cl_2, then $NaBH_4$, MeOH; (n) TFA, then Ac_2O, DMAP, 31% over 3 steps.

by hydrogenation gave **90**. Selective cleavage of the C5 vicinal diol was possible due to the fixed *anti*-orientation of the vicinal C6 and C7 diol. The aldehyde resulting from this cleavage process was oxidised to the acid level and protected as the methyl ether to aid isolation and purification. All that remained was selective introduction of the C6 acyl side chain. Hydrolysis of the methyl ester was followed by treatment with 2-octenyl chloride to give the proposed analogue **91** in moderate yield. Interestingly, the only other product observed was a diacylated product formed by reaction at the C5 acid, to give a mixed anhydride, as well as the desired C6 acylation. No acylation at C7 was observed, suggesting to the authors that formation of the mixed anhydride occurs first, followed by intramolecular acyl migration to provide the desired product.

With the analogue **91** synthesised, its biological activity was assessed. It was found that activity was, in fact, much reduced (IC_{50}=1.1 μM versus 0.5 nM for zaragozic acid A), indicating that the presence of acid groups at C4, and possibly C3, is important for the potent inhibitory activity of the zaragozic acids.

Johnson[28] (Scheme 23) provided yet another novel entry into the zaragozic acids where stereochemistry could be controlled by the use of a seven-membered ring, which would also provide the majority of the framework. In this case, the stereochemistry was defined in enantiopure form by a chemoenzymatic method, where *meso*-**92** was desymmetrised with *Candida antarctica* lipase to produce **93**. The stereochemistry present was then able to control all the incoming functionality. Protection of the remaining free alcohol as the TBS ether, removal of the acetate and oxidation gave **94**, a key stage for the introduction of the necessary oxygenated functionality. This was achieved by an iterative Rubottom oxidation/Luche reduction process. Thus, **94** was converted to its silyl enol ether and then treated with *m*CPBA, to give the α-hydroxyketone. This α-hydroxy ketone was then stereoselectively reduced under Luche conditions and protected as the acetonide to give the trans vicinal diol system present in **95**. Selective removal of the TBS ether in the presence of the TIPS ether was accomplished by the use of H_2SiF_6. Oxidation of the revealed alcohol to the ketone level allowed re-application of the Rubottom/Luche protocol to introduce the other *trans* vicinal diol system, which was protected as the bis-MOM ether. TBAF removal of the TIPS group gave **96**. The next key stage was installation of the C5 quaternary stereocentre. This was achieved by oxidation of the C5 alcohol to the ketone level, and then addition of lithium benzyloxymethide to the newly-formed ketone. This nucleophilic addition occurred from the β-face, approaching opposite the two α-substituents, installing the desired stereochemistry. In practice, it was found that **96** decomposed readily and the addition process was carried out directly after oxidation. Ozonolysis of the double bond and reductive work-up produced the lactol **97**, which on exposure to TFA gave **98**, after peracetylation. Bicyclic ketal **98** was formed as the sole product with no evidence of other isomers, although this would have been possible with substrate **97**.

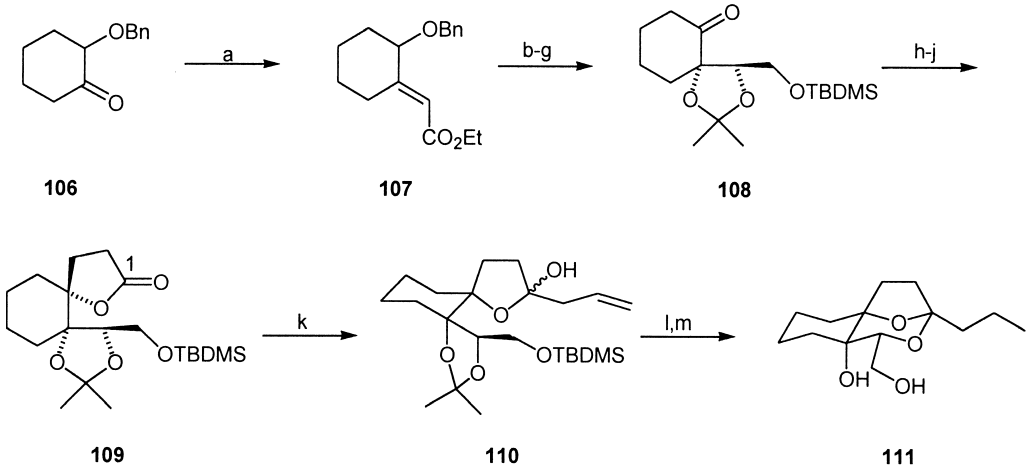
Honda[29] (Scheme 24) approached the core by applying chiral furyl carbinols as a tool to achieve synthesis. The starting point was **99**, formed by chelation-controlled addition of a lithiated furan derivative to (*S*)-2,3-*O*-isopropylideneglyceraldehyde in 83% de. Ring enlargement gave the lactol **100**, after protection of the C3 alcohol as the TBS ether and separation of the minor diastereomer. Stoichiometric osmylation of the alkene occurred *anti* to the TBS ether, which, after a series of protecting group manipulations, was followed by reduction of the C6 (zaragozic acid numbering) ketone and subsequent protection to give a 10:1 mixture of diastereomers in favour of the desired isomer of **101** (as shown in Scheme 24). The key step now was to introduce a C3 carboxylic acid synthon. An acetylide was chosen as the necessary unit. To introduce it, the lactol was reduced to the open-chain bis-alcohol. Protection of the secondary alcohol allowed oxidation of the primary alcohol to the aldehyde, setting up the introduction of the acetylide unit. Addition of the acetylide occurred in high diastereoselectivity and in the desired sense. The outcome was presumed to be due to the formation of an α-chelate. Removal of the terminal TMS group on the acetylene and protection of the newly-formed



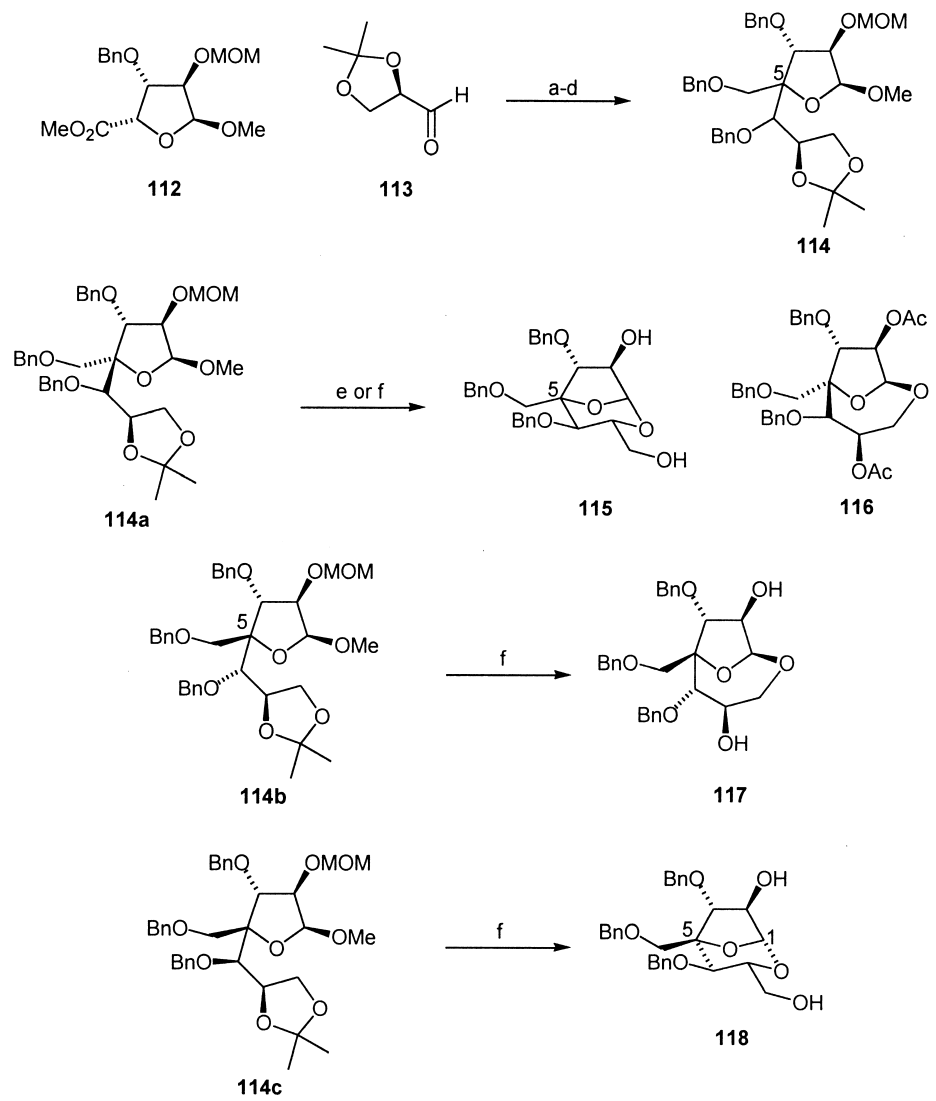
Scheme 24. Honda's core synthesis. *Reagents and conditions*: (a) NBS, THF, H_2O, 90%; (b) TBSCl, Ag_2O, DMF, 72%; (c) OsO_4, pyridine, Et_2O, 100%; (d) *p*TsOH, acetone, 64%; (e) $NaBH_4$, MeOH, 100%; (f) NaH, BnBr, DMF, 94%; (g) TBAF, THF, 95%; (h) $LiAlH_4$, THF, 94%; (i) Ac_2O, DMAP, pyridine, CH_2Cl_2, 96%; (j) TBSOTf, Et_3N, CH_2Cl_2, 93%; (k) 1 M LiOH, MeOH, 91%; (l) Dess–Martin reagent, 100%; (m) Lithium trimethylsilylacetylide, THF, 94%; (n) K_2CO_3, MeOH, 100%; (o) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 97%; (p) $FeCl_3$–SiO_2, $CHCl_3$, 68%; (q) Ac_2O, DMAP, pyridine, CH_2Cl_2, 97%; (r) Dess–Martin reagent, 75%; (s) HCl, MeOH; (t) Ac_2O, DMAP, pyridine, CH_2Cl_2, 32% over 2 steps.

secondary alcohol as a MOM ether provided **102**. Selective removal of the terminal acetonide group, followed by selective acylation of the free primary hydroxyl group and oxidation of the secondary alcohol furnished **103**. This set up the key acid cyclisation step to form the bicyclic ketal system. Treatment of **103** with acid and peracetylation gave **104** and **105** in a 3:2 ratio. This result is somewhat unusual compared to other systems, as both products possess the correct bicyclic framework, but the minor isomer has the incorrect substitution pattern. Elaboration of **104** to the natural product would be possible by oxidation of the core substituents and introduction of a side chain.

One of the keys to success in the synthesis of the zaragozic acids is the ability to control the formation of the bicyclic core to possess the desired structure. Steel[30] (Scheme 25) sought to achieve this by use of a tethered system to control ketal formation. As a model, a simple fused cyclohexane ring was to be used as the tether. Ideally, it was hoped that a tether containing a functional handle, such as an alkene unit, could be used to introduce the carboxylic acids later in the synthesis. The starting point was chosen as the protected α-hydroxyketone **106**. Formation of the (*E*)-α,β unsaturated ester was accomplished by a Wittig reaction, to give **107** as a single geometric isomer. Dihydroxylation of the resulting



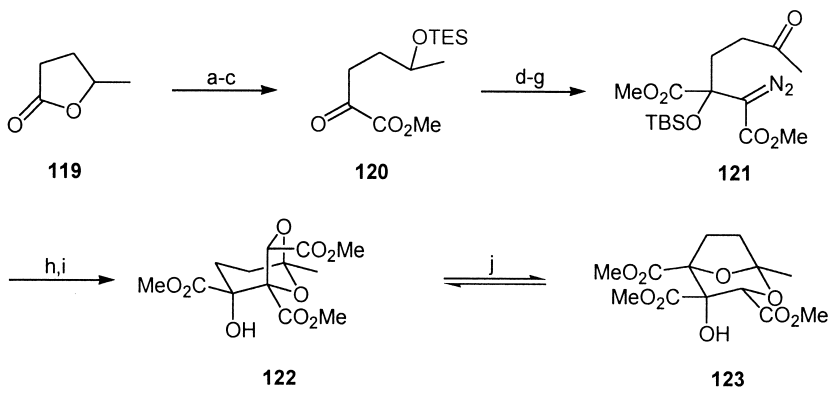
Scheme 25. Steel's model tether system. *Reagents and conditions*: (a) $Ph_3P{=}CHCO_2Et$, benzene, 80°C, 94%; (b) OsO_4, NMO, ^tBuOH, 100%; (c) 2,2-dimethoxypropane, TFA, $CHCl_3$, 70°C, 97%; (d) DIBAL-H, THF, −70°C; (e) H_2, $Pd(OH)_2$, MeOH; (f) TBDMSCl, imidazole, DMF, 66% over 3 steps; (g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (h) AllylMgBr, THF; (i) BH_3·THF then H_2O_2, NaOH; (j) PCC, 49% over 4 steps; (k) AllylMgBr, Et_2O, −78°C, 95%; (l) $Pd(OH)_2$, MeOH, H_2, 94%; (m) 2% HCl, MeOH, 40°C, 37%.



Scheme 26. Hanna's model synthesis. *Reagents and conditions*: (a) KHMDS, THF, $CeCl_3$, −100°C, 60–80%; (b) Dess–Martin oxidation, 88%; (c) $LiAlH_4$, Et_2O, 68%; (d) NaH, BnBr, DMF, 89%; (e) Dowex 50W, MeCN, reflux, **115**: 57%, **116**: 19%; (f) HCl (aq), MeOH/THF, **115**: 53%, **117**: 48%, **118**: 58%.

double bond was performed with catalytic OsO_4 and the vicinal diol protected as the acetonide. The ester was then reduced to the primary alcohol. Initially, the alcohol was protected as its TBDMS ether, but it was found that this protecting group was unstable to the hydrogenolysis conditions that were used later to remove the benzyl group. Consequently, the primary alcohol was left free during the deprotection step, which furnished a diol. Conveniently, the primary alcohol could then be selectively protected as a TBDMS ether, leaving the secondary alcohol free to be oxidised to the ketone level, furnishing **108**. It was now necessary to introduce a γ-lactone unit that would form the basis of the five-membered ring in the zaragozic acid core unit. This was accomplished by a three-step process, starting with addition of an allyl Grignard reagent to the ketone of **108**. The diastereoselectivity in this step was a disappointing 1.3:1, but the two isomers could be separated and the isomer shown could be taken on to the required product. Hydroboration of the alkene unit gave the corresponding primary alcohol after oxidative work-up, which upon treatment with PCC gave the lactone **109**. All that remained was introduction of a C1 side chain analogue and cyclisation to the bicycle. The C1 side chain was introduced by addition of an allyl Grignard to the lactone to furnish **110**. Initial attempts to cyclise **110** gave only a complex mixture of products that could not be identified, but did not show the presence of any olefinic signals. Therefore, to prevent this occurrence, the side chain alkene was hydrogenated to give the simple alkane, accompanied by the formation of a methyl glycoside. This was of no importance, as treatment of the methyl glycoside with acid gave **111** as the sole product in a moderate yield. This demonstrated that tethering could control the formation of the bicycle, directing the ketalisation to give the desired product. The importance of tethering was demonstrated by the fact that the other diastereomer formed during the lactone synthesis could not be cyclised to form a bicyclic ketal system.

Hanna[31] (Scheme 26) provided another route to the zaragozic acids, this time providing the core expeditiously. The stereochemistry was, once again, provided by the chiral pool. This time the starting point was **112**, readily available from diacetone-D-glucose in six steps. The rest of the framework was then to be provided by glyceraldehyde **113**,

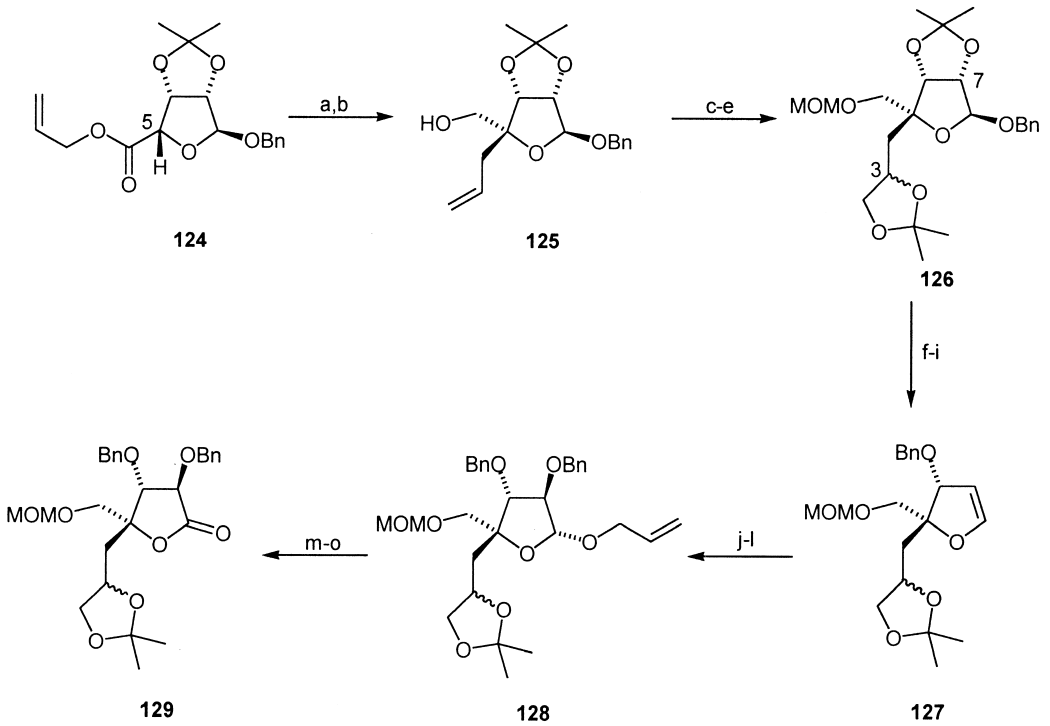


Scheme 27. Hodgson's approach to the core. *Reagents and conditions*: (a) Methyl vinyl ether, ^{t}BuLi, THF, −78°C, 86%; (b) TESOTf, 2,6 lutidine, CH_2Cl_2, −78°C, 67%; (c) O_3, CH_2Cl_2/py 100:1, −78°C, then PPh_3, 57%; (d) methyldiazoacetate, LDA, THF, −78°C, 62%; (e) TBSOTf, 2,6 lutidine, CH_2Cl_2, 72%; (f) AcOH/THF/H_2O 2:4:1, 76%; (g) PCC, NaOAc, CH_2Cl_2, 90%; (h) methyl glyoxylate, cat. $Rh_2(OAc)_4$, toluene, reflux, 65%; (i) TBAF, THF, 74%; (j) CH_2Cl_2/TFA/H_2O 20:10:1, 54%, 83% on recovered starting material.

introduced via an aldol reaction, before acid cyclisation to the core. Considerable experimentation was required to find the correct conditions to provide sufficient quantities of the desired aldol product. Use of standard potassium or lithium enolates gave only small amounts of product and higher temperatures resulted in β-elimination and degradation of the unsaturated ester. Zinc enolates gave moderate yields, but the reaction was capricious. Eventually, it was found that addition of stoichiometric $CeCl_3$ and aldehyde **113** to the potassium enolate at −100°C gave reproducibly good yields of the aldol product, as a mixture of three diastereomers. Oxidation of the resulting free alcohol to the ketone level gave a 4:1 mixture of epimers about the C5 ester, indicating that the aldol reaction had occurred with similar stereoselectivity. However, at this stage it was not possible to ascertain the stereochemistry of the three products and the crude mixture was taken forward. The ester was reduced to the alcohol with $LiAlH_4$ and the two free alcohols were subsequently benzylated under standard conditions to give **114**, as a separable mixture of diastereomers. Each of the diastereomers was then subjected to acid cyclisation conditions separately. The importance of the stereochemistry of the initial compounds on the outcome of the cyclisation reaction was clearly shown. Acetal **114a** possesses the correct stereochemistry at C5 and exposure of it to methanolic HCl resulted in formation of the desired bicyclic core **115** as the only product in moderate yield. Interestingly, exposure of **114a** to Dowex resin resulted in formation of **115**, but also resulted in the formation of **116** (after acetylation to aid isolation) in low yield. Ketal **116** is the product derived from attack of the free primary alcohol at an intermediate oxonium ion to form a seven-membered ring. Exposure of **114b**, which possesses the incorrect stereochemistry at C5, to acid conditions, this time resulted in sole formation of **117**, containing an undesired bicyclic ketal system. This may have been a result of the stereochemistry constraining the secondary alcohol at C3, preventing it from reacting with the intermediate oxonium ion, leaving the more flexible primary alcohol to form the bicyclic system. Ketal **114c** also has incorrect stereochemistry at C5, but is epimeric at C4 relative to **114b**. When treated with acid, the sole product was found to be **118**, which possesses the desired bicyclic system, but is epimeric at C5 and C1 relative to the natural product. This suggests that the C4 configuration has a strong influence on the outcome, controlling which alcohol can favourably attack the intermediate oxonium ion.

Judicious control of the protecting groups would allow introduction of a one-carbon unit; oxidation to the acid level and introduction of a side chain would then complete a synthesis of the natural product. Thus a rapid route has been found to access the core system, using a key aldol reaction, and the importance of stereochemistry in the outcome of the cyclisations has been demonstrated.

Hodgson[32] (Scheme 27) attempted to access the core system in the racemic series via a two-step cycloaddition/acid-mediated rearrangement strategy. The starting point was chosen as γ-valerolactone **119**. Addition of lithiated methyl vinyl ether gave the expected enone, which upon TES protection of the free secondary alcohol and ozonolysis of the alkene gave α-ketoester **120**. Addition of lithiated methyl diazoacetate to the ketone moiety resulted in a 1:1 mixture of diastereomers, which were not separated. The tertiary alcohol was then protected as the TBS ether. Selective removal of the TES ether protecting the secondary alcohol was followed by PCC oxidation to the ketone level, to give the cyclisation precursor **121**. The key cyclisation step was then to be examined. The intention was to form an intermediate carbonyl ylide via a rhodium-catalysed cycloaddition and then trap this ylide in a 1,3-dipolar cycloaddition with methyl glyoxylate. It was hoped this addition would occur to give the *exo* product, as earlier work with an analogue[32a] had shown that an *endo* product carried the incorrect stereochemistry through the rearrangement stage to have the undesired configuration at C4 (zaragozic acid numbering). Treatment of **121** with catalytic $Rh_2(OAc)_4$ in the presence of methyl glyoxylate resulted in the formation of three cycloadducts in a ratio of 12:1:1, with the major adduct shown, after removal of the TBS group, to be **122**, the desired *exo* product. The formation of the *exo* product was proposed to be due to preferential approach of the glyoxylate opposite to the bulky silyloxy group and oriented to avoid steric interactions between the ester of the glyoxylate and the ester of the ylide. With the desired *exo* product in hand, the acid mediated rearrangement was studied. It was found, after some experimentation,



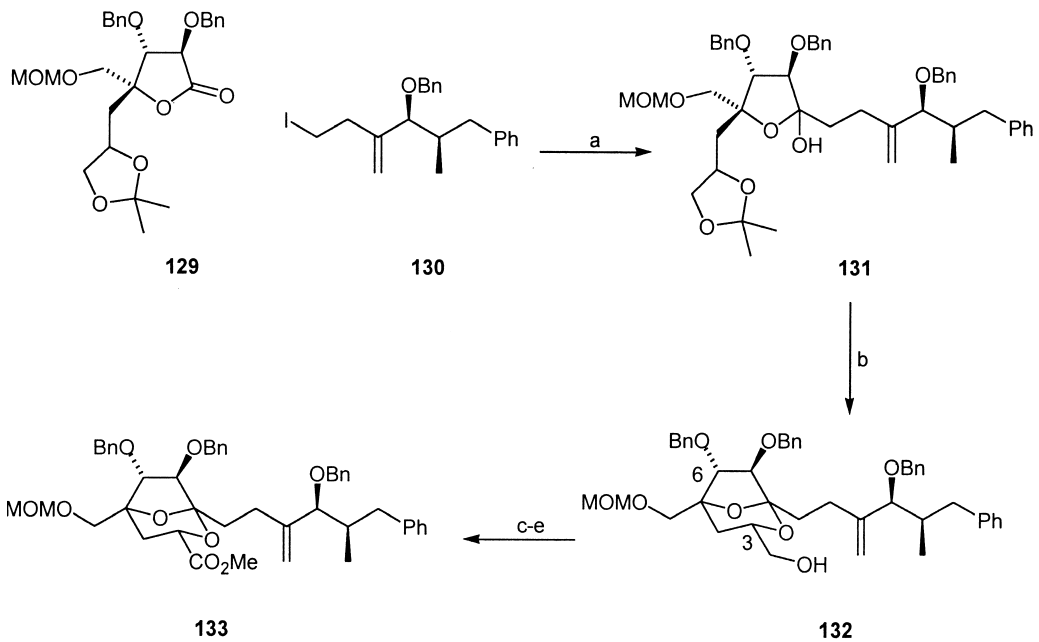
Scheme 28. Rizzacasa's synthesis (part 1). *Reagents and conditions*: (a) LDA, TMSCl, THF/HMPA, −100°C to rt, then NaOH, CH_2N_2, 74%; (b) $LiAlH_4$; (c) MOMCl, $^iPr_2NEt$, 99%; (d) OsO_4, $K_3Fe(CN)_6$, K_2CO_3; (e) $(MeO)_2CMe_2$, PPTS, 96% over 2 steps; (f) Li/NH_3; (g) HMPT, CCl_4; (h) Li/NH_3, 68% over 3 steps; (i) NaH, BnBr, 92%; (j) DMDO, CH_2Cl_2; (k) allyl alcohol, 95% over 2 steps; (l) NaH, BnBr, 90%; (m) $(PPh_3)_3RhCl$, DABCO; (n) $Hg(OAc)_2$, THF (aq); (o) PCC, NaOAc, 4 Å sieves, 76% over 3 steps.

that use of the Evans' cyclisation conditions (CH_2Cl_2, TFA, H_2O)[10] resulted in an equilibrium between the starting bicycle **122** and the desired 6,7-dideoxysqualestatin core system **123** in a ratio of 33:64, with a total of 54% of **123** isolated. It is important to note that, once again the in the 6,7-dideoxy series, the acid rearrangement is under thermodynamic control, whereas cyclisations in the fully substituted systems are more often under kinetic control. Introduction of the required side chain would complete a total synthesis of racemic squalestatin H5. Overall, it has been shown that the use of 1,3-dipolar cycloaddition is effective in the rapid construction of a bicyclic system that can be equilibrated under acidic conditions to the required core.

Rizzacasa[33] has described a further approach employing an acid-mediated ketalisation, again from chiral pool materials (Scheme 28). The starting point was **124**, a derivative of diacetone-D-mannose. The key step in the introduction of the rest of the framework was based around an Ireland–Claisen rearrangement, which establishes the C5 stereocentre. Treatment of the allyl ester **124** under standard Ireland–Claisen conditions resulted in the expected rearrangement, which, after reduction of the ester, resulted in **125**, with a 5.7:1 diastereomeric ratio at C5 in favour of the isomer shown in Scheme 28. Elaboration towards the core started with protection of the free primary alcohol as the MOM ether, a non-selective dihydroxylation of the alkene, followed by protection of the vicinal diol as the acetonide to give **126**. Although there had been no control in establishing the C3 centre, it was found that it could be epimerised later in the synthesis. With the framework in place, the next question was the epimerisation of the C7 stereocentre, which is incorrect relative to the natural product. The need to epimerise this centre would be avoided if, for instance, a glucose derivative had been initially used, but it was found that the Ireland–Claisen rearrangement of such a substrate was low-yielding and non-selective. Inversion of the C7 centre was achieved starting with a four-stage process of debenzylation, chlorination of the lactol, reductive elimination to yield a glycal, with final protection of the free secondary alcohol at C6 to yield **127**. Treatment of the glycal **127** with DMDO resulted in stereoselective epoxidation on the face opposite the secondary benzylated alcohol, and the labile epoxide ring-opened with allyl alcohol. The alcohol at C7 was then protected to give **128**. All that remained to complete the synthesis of the core was removal of the allyl ether to give the free lactol, which was oxidised to the lactone **129** under PCC conditions.

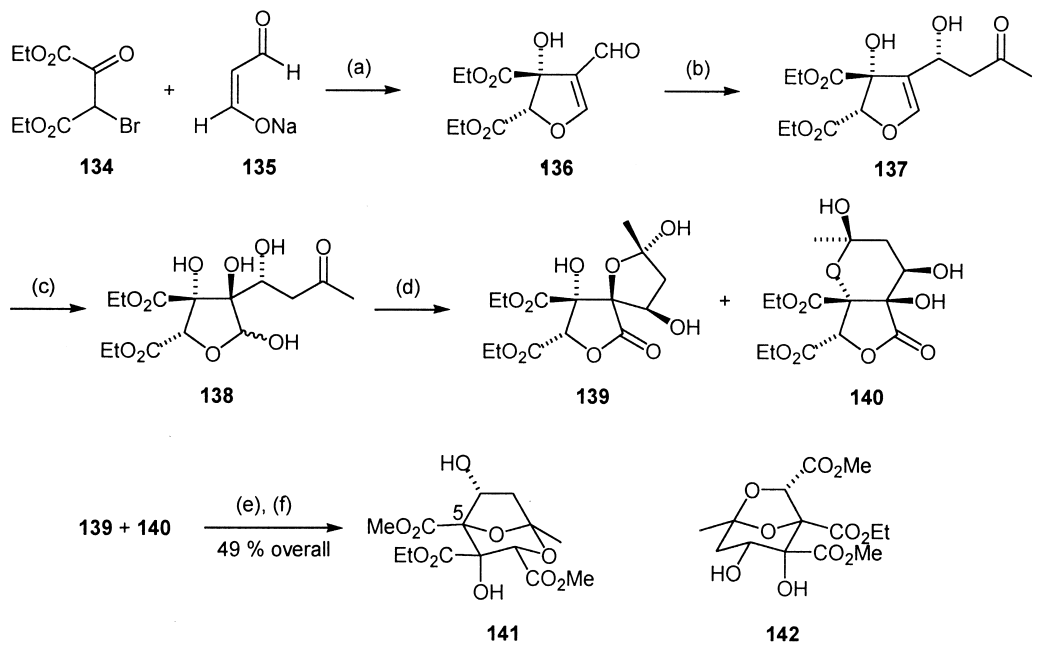
Coupling (Scheme 29) of the core **129** with the zaragozic acid A side chain equivalent **130** (which was synthesised using an Evans aldol reaction as the key step) was accomplished by addition of **129** to the lithiated derivative of **130** at low temperature to afford **131** in moderate yield. Acid-mediated cyclisation of **131** furnished the desired core system **132** as the sole product, but as a 3:1 mixture of epimers at C3, favouring the required equatorial configuration. Interestingly, oxidation of the mixture of C3 epimers with sequential Dess–Martin and Pinnick oxidations, followed by ester protection, resulted in epimerisation of the C3 centre to give only the equatorial product. Introduction of a one-carbon unit at C4 would complete a fully functionalised zaragozic acid A intermediate.

Very recently, an interesting and highly concise synthesis of

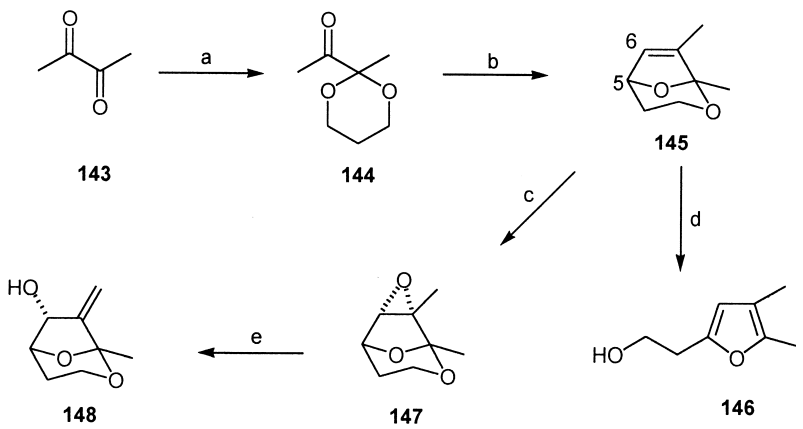


Scheme 29. Rizzacasa's synthesis (part 2). *Reagents and conditions*: (a) **130**, ^{t}BuLi, Et_2O/hexane, −78°C, followed by **129**, 48%; (b) 10% HCl, MeOH, 67%; (c) Dess–Martin; (d) $NaClO_2$; (e) CH_2N_2, 61% over 3 steps.

the 7-deoxy-zaragozic acid core has been reported by Calter and co-workers.[34] A key feature of their approach is the 'interrupted' Fiest–Benary reaction (Scheme 30). Condensation of the bromoester **134** with the sodium salt **135** of malonaldehyde provided the highly functionalised dihydrofuran **136**, albeit in moderate yield. Boron-mediated aldol reaction proceeded in high diastereoselectivity, affording **137**. Dihydroxylation and oxidation of the resulting lactol **138** using *N*-iodosuccinimide/Bu_4NI gave the mixture of lactones **139** and **140**, both possessing the carbon skeleton of the zaragozic acid core. Treatment of this mixture with 2% HCl in MeOH at 70°C afforded a mixture of a furan and an undesired ketal isomer. However, use of 2% HCl in MeOH at room temperature was found to effect transformation to a mixture of the desired **141** and undesired **142** bicyclic ketals in a 1:5 ratio and 76% overall yield, where the C5-carboxylate had also undergone transesterification under the methanolic conditions. At lower reaction temperature (0°C for 5 days), **139** and **140** were converted into **141** almost exclusively (30% yield). Attempts to improve the overall yield by resubmission of recovered starting materials were complicated by incomplete transesterification, so the product mixture was treated with K_2CO_3/MeOH to provide **141** in 49% overall yield.



Scheme 30. Calter's synthesis *Reagents and conditions*: (a) Benzene, rt, 29%; (b) Acetone, $^{n}Bu_2BOTf$, $^{i}Pr_2NEt$, CH_2Cl_2, −78°C, 77%; (c) 5 mol% OsO_4, NMO, acetone/H_2O; (d) NIS, Bu_4NI, CH_2Cl_2, rt, 60% from 137; (e) 2% HCl, MeOH, rt, 5 days, then one resubmission of starting materials; (f) K_2CO_3, MeOH, 0°C.



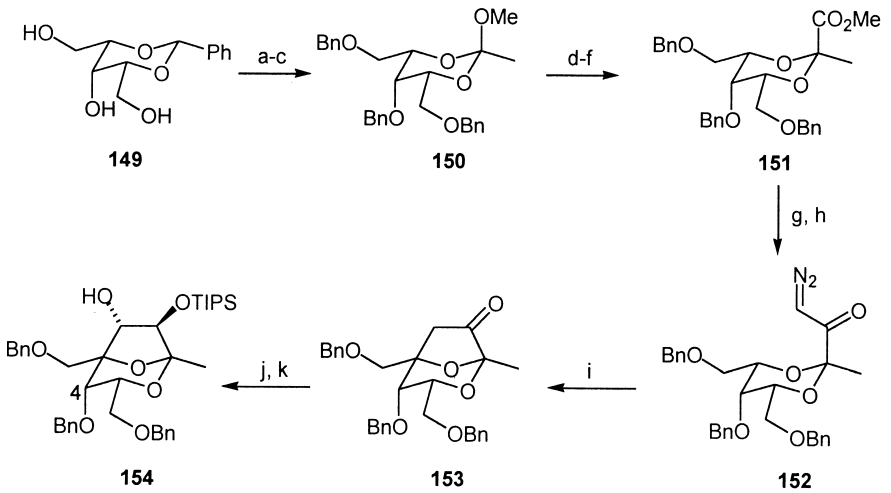
Scheme 31. Wills' core synthesis. *Reagents and conditions*: (a) $HO(CH_2)_3OH$, *p*TsOH, toluene, hexane, 73%; (b) $TMSC(H)N_2$, ^{n}BuLi, DME/hexanes; (c) DMDO, acetone, 28% over 2 steps; (d) silica gel, 64% over 2 steps; (e) (1*R*,2*S*)-norephedrine, ^{n}BuLi, THF, benzene, 62%.

Interestingly, exposure of **141** to 2% MeOH/HCl at room temperature resulted in conversion to **142**, indicating that the latter is thermodynamically preferred. Overall, despite the low yield in the first synthetic step, this approach offers a highly concise access to the 7-deoxyzaragozic acid core, with the tricarboxylic acid unit at the correct oxidation level.

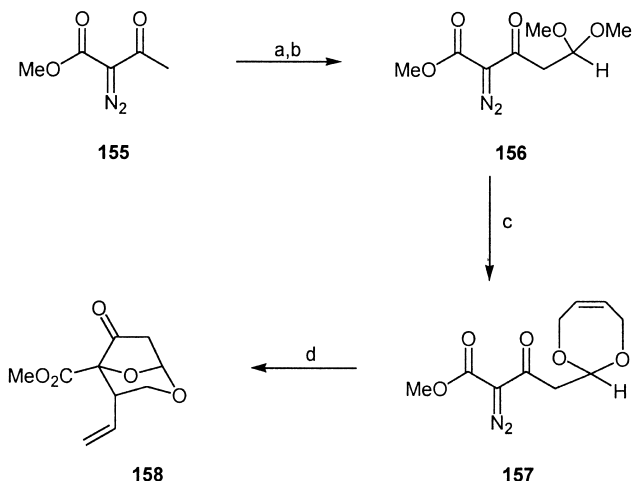
3.2. Other cyclisation methods

Although ketalisation is perhaps the most obvious way to construct the zaragozic acid core, there are, of course, other approaches to the bicyclic system, which would involve disconnections at other bonds. These other disconnections have led to a variety of novel approaches that construct the bicyclic system directly. These are to be discussed in this section.

One interesting departure from the use of ketalisation as the key strategy was seen in the work of Wills[35] (Scheme 31). Here, the key point of the synthesis is the construction of the C5–C6 bond by C–H insertion of an alkylidene carbene. This disconnection allows very rapid access into the basic bicyclooctane framework of the core. Starting with the diketone **143**, monoketal formation with propanediol gives **144**, the cyclisation precursor. Treatment of **144** with lithiated TMS-diazomethane results in formation of the alkylidene carbene in place of the ketone. C–H insertion of the newly formed carbene to the proximal bond furnishes the unstable compound **145**, which possesses the complete carbon framework of the core, in a remarkable two steps. However, it was found that **145** could not be isolated and very rapidly isomerised on exposure to silica gel during chromatography, to give furan derivative **146**. If, on the other hand, the crude cyclisation product was treated with DMDO, then epoxidation of the alkene occurred to give **147** in low yield. These low yields were attributed to the volatility of the product, rather than any inherent reactivity problem. Reacting **147** with the norephedrine dianion gave rise to epoxide rearrangement to yield the allylic alcohol **148**, completing the synthesis of the model system in an extremely rapid four steps. Although the framework lacks much functionality, it would not greatly affect the length of the synthesis to introduce functionality, as some handle could be introduced on the bis-alcohol used in the ketalisation step to allow further derivatisation to the natural product system. Another important bonus for this



Scheme 32. Wardrop's core synthesis. *Reagents and conditions*: (a) NaH, BnBr, Bu_4NI, DMF, rt, 20 h; (b) EtSH, *p*TsOH, CH_2Cl_2, rt, 48 h, 40% for 2 steps; (c) (i) $MeC(OMe)_3$, *p*TsOH, 4 Å MS, CH_2Cl_2, rt; (ii) Na_2CO_3; (d) Me_3SiCN, $SnCl_2$, 4 Å MS, CH_2Cl_2, reflux; (e) NaOH, H_2O_2, EtOH, reflux, 73% for 3 steps; (f) DMF/dimethylacetal (3.5 equiv.), MeOH, 100°C, 73%; (g) LiOH, THF, reflux; (h) (i) Et_3N, rt; (ii) ^{t}BuOCOCl, CH_2Cl_2, −30°C; (iii) CH_2N_2, 0°C, 88%; (i) $Rh_2(OAc)_4$, CH_2Cl_2, rt; 48%; (j) (i) KHMDS, THF, −78°C; (ii) TIPSCl, −30°C, 80%; (k) (i) $BH_3{\cdot}Me_2S$, THF, reflux; (ii) H_2O_2, 0.6 M NaOH, rt, 81%.



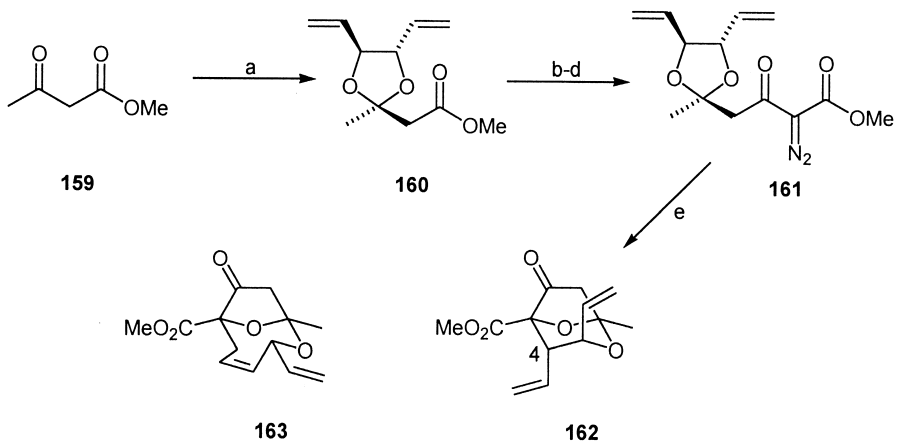
Scheme 33. Calter's assembly of the core. *Reagents and conditions*: (a) TMSOTf, Et_3N; (b) Trimethyl orthoformate, $BF_3{\cdot}OEt_2$, 88% over 2 steps; (c) $TMSOCH_2CH{=}CHCH_2OTMS$, 1 mol% TMSOTf, 83%; (d) 1 mol% $Rh_2(OAc)_4$, benzene, reflux, 72%.

approach is that there is no question of undesired isomer formation that had often been present in ketalisation strategies.

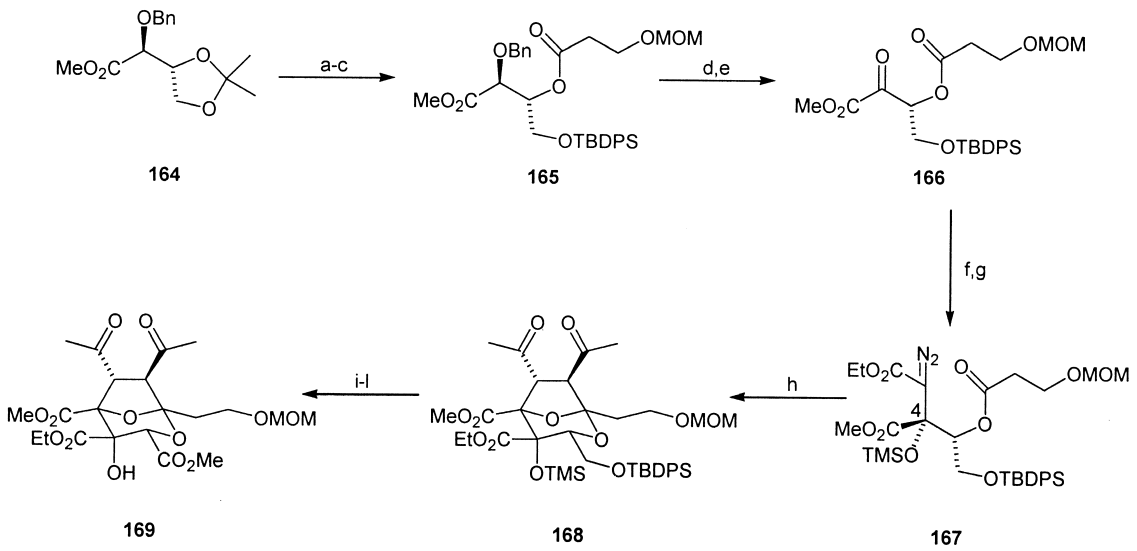
A similar C–H insertion disconnection leading to a more highly functionalised model system was recently described by Wardrop and co-workers (Scheme 32).[36] 3,5-*O*-Benzylidine xylitol **149** was converted into the *meso*-orthoester **150**. Treatment with TMSCN and $SnCl_2$ led to the corresponding anomeric cyanide which was hydrolysed to the amide which, in turn, was converted into the corresponding methyl ester **151** upon reaction with dimethyl formamide dimethyl acetal. Subsequent manipulations provided the key diazoketone **152**. Slow addition of $Rh_2(OAc)_4$ (2 mol%) in CH_2Cl_2 at room temperature led to **153** in 49% yield. Clearly, future studies will examine the use of chiral metal salts to effect desymmetrisation of the *meso*-substrate in this step. The ketone functionality was then converted to its triisopropylsilyl enol ether which underwent hydroboration to install the required *anti*-C6/C7 diol unit in **154**. Thus, the bicyclic core with much of the functionality present in the natural product was prepared in 11 steps from **149**, with addition of the C4-carbon and oxidation to the triacid level being required to complete the full core synthesis.

The work of Calter[37] (Scheme 33) provided another novel approach to construction of the bicycle. This time, the key strategy was based around a C–O insertion sequence. Starting with the α-diazo-β-ketoester **155**, the ketone was converted to the silyl enol ether and then condensed with trimethyl orthoformate to supply **156**. Transketalisation yielded the cyclic acetal **157**, the cyclisation precursor. Once again, the key step could be accessed very rapidly. Exposure of **157** to $Rh_2(OAc)_4$ in refluxing benzene led initially to formation of the metal carbenoid, presumably followed by formation of an oxonium ylide intermediate which then undergoes rearrangement to form the bicyclo-octane framework, **158**, present in the natural product. Thus this approach is also a very fast and effective method for construction of the core. The product also provides a reasonable level of functionality with which to elaborate the core, making this approach powerful. Entry into the non-racemic series is also possible; use of a chiral rhodium catalyst, $Rh_2(S\text{-}TBSP)_4$,[38] in the cyclisation of **157** led to non-racemic **158**, in 47% yield with 34% ee. Although levels of enantioselectivity are low, the principle had at least been demonstrated. The problem of formation of isomers in the cyclisation step has also been avoided.

Zercher[39] (Scheme 34) had earlier provided a similar entry route to the zaragozic acids through oxonium ylide formation and consequent rearrangement. A similar cyclisation substrate to Calter had been proposed, but with a different ketal. Starting with methyl acetoacetate, ketal formation was achieved by exposure of **159** to a mixture of *meso* and *d,l*-1,5-hexadien-3,4-diol under acidic catalysis. The *d,l*-isomer **160** was separated by chromatography and the ester subjected to basic hydrolysis to give the free acid. Homologation to the β-ketoester was achieved following Masamune's procedure.[40] Final diazotisation of the β-ketoester was accomplished with *p*-carboxybenzenesulfonyl azide to give the cyclisation precursor **161** in a concise four steps. The initial cyclisation attempt was performed using $Cu(hfacac)_2$ in refluxing benzene as the catalyst. Two compounds were isolated, one being the necessary bicycle **162** in 42% yield. This would be formed through degradation of the diazo compound to the metal



Scheme 34. Zercher's core synthesis. *Reagents and conditions*: (a) 1,5-hexadien-3,4-diol, *p*TsOH; (b) KOH, MeOH; (c) (i) carbonyl dimidazole, (ii) $Mg(O_2CCH_2CO_2CH_3)_2$; (d) *p*-carboxybenzenesulfonylazide, Et_3N; (e) cat. $Cu(hfacac)_2$, benzene, 80°C or $Rh_2(OAc)_4$, benzene.

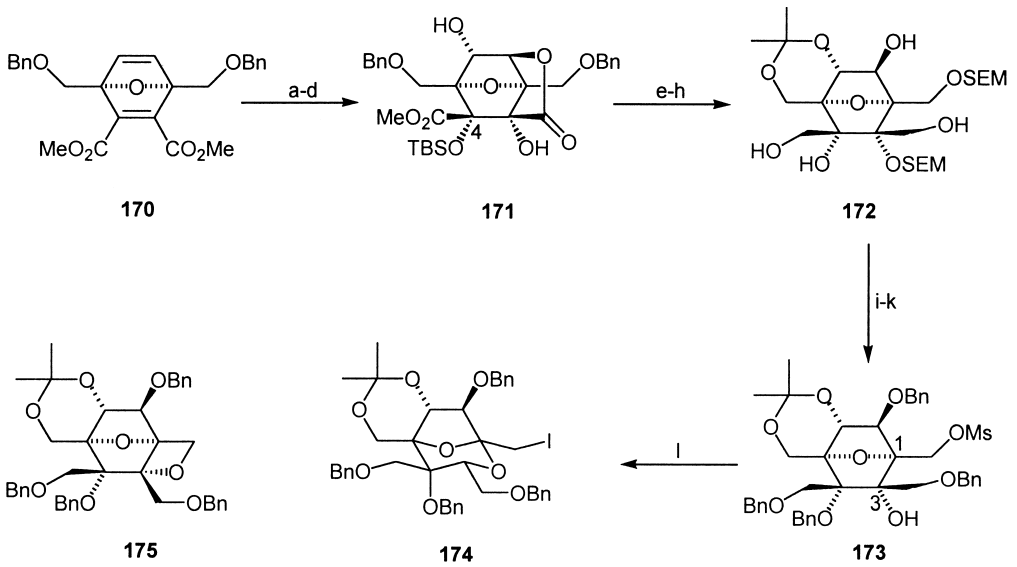


Scheme 35. Hashimoto's second generation approach. *Reagents and conditions*: (a) 10% HCl (aq)/THF 1:1, 0°C, 78%; (b) TBDPSCl, pyridine, DMAP, CH_2Cl_2, 96%; (c) $MOMO(CH_2)_2CO_2H$, EDCI, DMAP, CH_2Cl_2, 89%; (d) H_2, 20% $Pd(OH)_2$/C, MeOH, reflux, 85%; (e) Dess–Martin reagent, 94%; (f) N_2CHCO_2Et, LiHMDS, THF, −78°C; (g) HMDS, imidazole, THF, 40% over 2 steps; (h) (*E*)-3-hexene-2,5-dione, 5 mol% $Rh_2(OAc)_4$, benzene, 80°C, 47%; (i) TBAF, AcOH, THF; (j) Dess–Martin reagent; (k) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $^tBuOH/H_2O$; (l) CH_2N_2, 69% over 4 steps.

carbenoid, which undergoes intermediate formation of the oxonium ylide, rapidly followed by 1,2-shift to give **162**. The other compound, although unstable to purification, was shown to be **163**, formed in 20% yield, which would be created by a 2,3-shift pathway of the same oxonium ylide intermediate. Use of $Rh_2(OAc)_4$ as the catalyst resulted in sole formation of **162** in 64% yield. If the *meso*-variant of **163** was used, then, surprisingly, no products were formed when $Rh_2(OAc)_4$ was employed as catalyst. However, $Cu(hfacac)_2$ resulted in the formation of four products. Two were shown to be **162** and **163** and two other products were a second 1,2-shift product, epimeric at C4 to **162**, and a 2,3-shift product with unidentified stereochemistry. The isolation of **162** from the *meso* starting material meant that the 1,2-shift had occurred with inversion of configuration, not witnessed in the *d*,*l* series. Overall, a highly functionalised core system had been generated in five steps from methyl acetoactetate, although the formation of cyclic isomers was observed, in a similar fashion to the acidic methods.

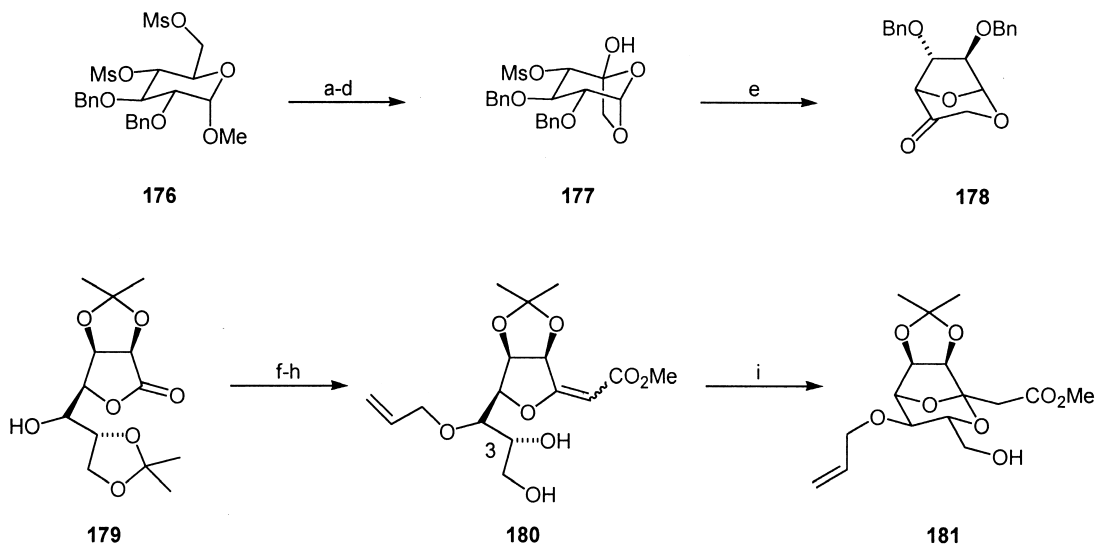
Hashimoto[41] (Scheme 35), who had earlier completed a total synthesis of zaragozic acid C,[11] developed a second generation approach based on a 1,3-dipolar cycloaddition strategy. This is similar in concept to that of Hodgson[32] (vide supra), but forms the core system directly, without the need for further rearrangement. The key intermediate would be diazoester **167**, which would be subjected to catalytic degradation to form a metal carbenoid, then cyclise to an intermediate ylide and be trapped in situ by a dipolarophile. The synthesis of **167** commenced with the known acetonide **164**. Hydrolysis of the acetonide was followed by selective silylation of the primary alcohol and the secondary alcohol was acylated with 3-(methoxymethoxy)propionic acid to form the ester **165**. Hydrogenolysis of the benzyl protecting group allowed oxidation of the resulting free alcohol to the ketone level to afford **166**. To complete the synthesis of **167**, lithiated ethyl diazoacetate was added to **166** and the mixture silylated on the newly formed tertiary alcohol. The addition of the diazoacetate gave a 1.5:1 mixture of adducts that were epimeric at C4. These were separable by chromatography; the major isomer (shown in Scheme 35) possessed the desired stereochemistry for the natural product and was taken on to the cyclisation studies. The tandem cyclisation–addition reaction was performed in the presence of (*E*)-3-hexene-2,5-dione as the dipolarophile and gave the cyclised adduct **168** as a single diastereomer possessing the stereochemistry witnessed in the natural product. This outcome was attributed to attack of the dipolarophile at the β-face to avoid the protected tertiary alcohol on the opposite face. Surprisingly, when the minor isomer of **167**, epimeric at the C4 centre, was subjected to the same conditions, no products were observed. This indicates that the configuration at this site has a strong controlling influence, although it is not known why. Deprotection of the silyl protecting groups present in **168** was followed by oxidation of the primary alcohol to the acid level by sequential Dess–Martin and Pinnick oxidations and, finally, protection as the ester to give **169**. Bicyclic ketal **169** represents a fully functionalised core system and requires only Bayer–Villiger oxidation of the carbonyl groups and attachment of the requisite side chains to complete a total synthesis. This has been shown to be a highly efficient method for the construction of the zaragozic acids with complete stereocontrol.

Nagaoka[42] (Scheme 36) provided an entirely novel approach that did not rely on acid-mediated cyclisation or carbene/carbenoid chemistry. Instead, the key step was based on an innovative three-step cascade Grob fragmentation–reduction–iodoacetalisation process. The process commenced from a functionalised [2.2.1]-bicycloheptane **173**, derived from **170** which was synthesised by a Diels–Alder reaction between benzyl-protected 2,5-furandimethanol and dimethyl acetylenedicarboxylate. This manipulation formed the basic framework for the cyclisation precursor and now required insertion of the oxygenated functionality present in the natural product, which started

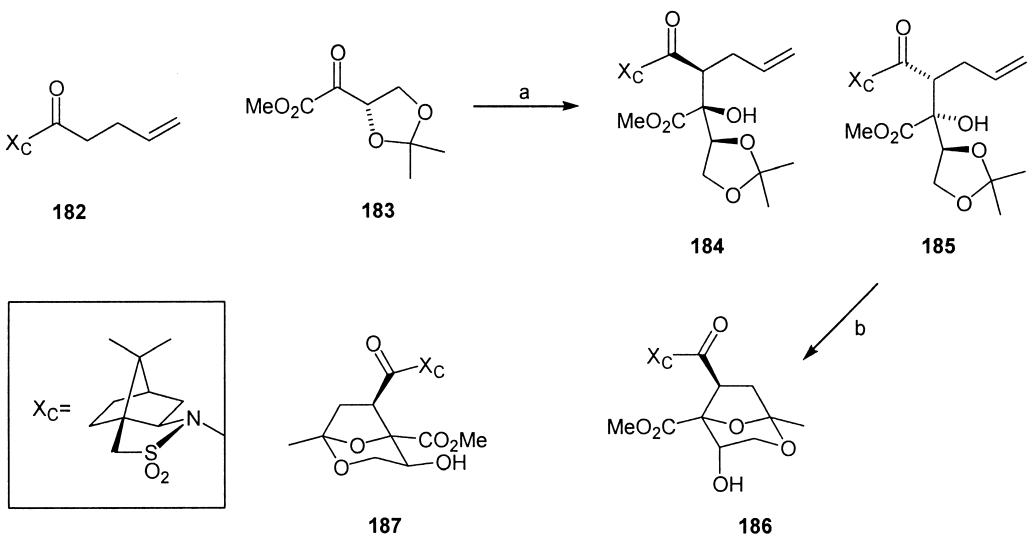


Scheme 36. Nagaoka's core synthesis. *Reagents and conditions*: (a) *m*CPBA, 4,4′-thio-bis-(2-*tert*-butyl-5-methylphenol), $ClCH_2CH_2Cl$, 80°C, 76%; (b) OsO_4, NMO, $MeCN/H_2O$, 98%; (c) *p*TsOH, $MeOH/H_2O$, 65°C, 95%; (d) TBSCl, Et_3N, CH_2Cl_2, 94%; (e) H_2, 10% Pd/C, MeOH; (f) acetone, $Me_2C(OMe)_2$, CSA, 96% over 2 steps; (g) SEMCl, $^iPrNEt_2$, CH_2Cl_2, rt to 40°C, 84%; (h) $LiAlH_4$, THF, 67°C, 63%; (i) BnBr, NaH, Bu4NI, THF, 90%; (j) TBAF, DMPU, 120°C, 94%; (k) MsCl, Et_3N, CH_2Cl_2, 85%; (l) KHMDS, dioxane, 100°C, then $NaBH_4$, MeOH then I_2, 5% $NaHCO_3$, **174**: 43%, **174** C3 epimer: 10%, **175**: 18%.

with epoxidation of the isolated, more electron rich, double bond. The conjugated alkene was then dihydroxylated with OsO_4, with all stereochemistry being controlled by attack at the convex face. The potential for asymmetric synthesis exists at this stage by use of a symmetry-breaking enzymatic reaction. However, the synthesis was continued in the racemic series. Hydrolysis of only one of the esters was followed by lactonisation and ring opening of the epoxide, installing the desired *trans* stereochemistry at C6 and C7. Protection of the more reactive hydroxyl at C4 resulted in production of **171**. Hydrogenolysis of the benzyl groups preceded acetonide formation. The two remaining free hydroxyls were protected as their respective SEM ethers and the lactone and ester functionalities were reduced to the alcohol level, which also resulted in the deprotection of the TBS ether, furnishing **172**. The free alcohols in **172** were exhaustively benzylated and the SEM protecting groups removed. Final selective mesylation of the primary alcohol led to **173**, the cascade sequence precursor. The cascade was performed in a one-pot method, starting with deprotonation of the tertiary alcohol initiating fragmentation. This resulted in the breaking of the C1–C3 bond and elimination of the mesylate group to form a ketone and an exocyclic alkene. The ketone was then reduced to the alcohol and the system exposed to iodine. This resulted in the formation of an intermediate iodonium species through reaction with the exocyclic alkene, which would be rapidly attacked by the free alcohol, completing the iodoacetalisation process of the cascade. The major product was observed to be the desired compound **174**, but also contained a small amount of the C3 epimer of **174** and also **175**. The C3 epimer of **174** was formed in the reduction step, the ratio of products being



Scheme 37. The two methods of Chapleur. *Reagents and conditions*: (a) NaI, butanone, reflux, 90%; (b) NaH, DMF, 73%; (c) $RuCl_3$, $NaIO_4$, $AcOEt/CH_3CN/H_2O$; (d) SiO_2, CH_2Cl_2, 71% over 2 steps; (e) DBU, THF, 74%. (f) $(Bu_2Sn)_2O$, toluene, then allyl bromide, Bu_4NBr, 80°C, 48%; (g) $Ph_3PCH_2CO_2Me$, toluene, 62%; (h) $AcOH/H_2O$ 7:3, THF, 50°C, 90%; (i) DBU, THF, reflux, 76%.



Scheme 38. Perlmutter's construction of the core. *Reagents and conditions*: (a) **182**, Et_2BOTf. $^{i}Pr_2NEt$, CH_2Cl_2, −50°C, then **183**, −78°C, 82%; (b) $PdCl_2$, $CuCl_2$, dimethoxyethane, O_2, 65°C, 75%.

indicative of the stereoselectivity of that reaction. On the other hand, **175** was formed by attack of the alkoxide formed in the initial deprotonation on the mesylate **173** to form the oxetane system and consequently plays no further part in the cascade sequence. Bicyclic ketal **174** represents a highly functionalised system that only requires introduction of the necessary side chains and oxidation to the correct level to complete a total synthesis of the racemic natural product.

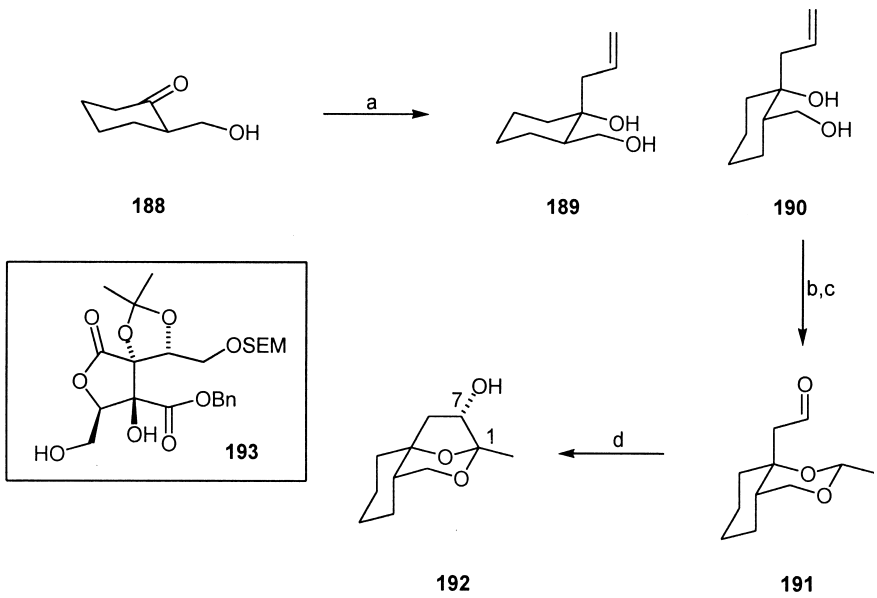
Vogel has also recently described the manipulation of furan–acetylene cycloadducts for the asymmetric preparation of polyhydroxylated compounds as analogues of the zaragozic acid core.[43]

Chapleur[44] (Scheme 37) conceived two approaches to the zaragozic acids based on the concept of basic nucleophilic construction of the zaragozic acids. The first method was based around an attempt to form a large ring under nucleophilic conditions and then effect a transannulation reaction by displacement of a suitably placed leaving group. The starting point for this approach was the glucose derivative **176**, readily available in four steps. Conversion of the primary mesylate to the iodide was followed by elimination to furnish an exocyclic alkene, which was flash dihydroxylated by exposure to RuO_4 for a short time. Exposure of the diol to silica resulted in the formation of the 1,6-anhydro derivative **177**. This set the stage for the nucleophilic rearrangement/cyclisation process to obtain the core. Exposure of **177** to DBU, acting as the base, gave **178**, the required core skeleton of the zaragozic acids. Deprotonation of the tertiary alcohol would result in the opening of the pyranose ring and the newly formed hemiacetal alkoxide would be ideally situated to displace the mesylate group and hence give rise to **178**.

The second method (Scheme 37) is also based about a nucleophilic ring closure, but involves formation of a different bond in the key step and produces a more functionalised derivative. Here, attack of the C3 secondary alcohol at an exocyclic, α,β-unsaturated ester to form the C1–O2 bond was the main disconnection. The starting point was the known D-glucoheptono derivative **179**. The free secondary alcohol was blocked as the allyl ether and the carbonyl of the lactone was then converted to the α,β-unsaturated ester by reaction under Wittig conditions to give the product as a mixture of *E* and *Z* isomers. Hydrolysis of the acetonide gave the cyclisation precursor **180**. Exposure of **180** to basic conditions resulted in a favourable 6-*exo*-trig ring-closing process to give **181**, the model core, in good yield. Basic conditions have therefore been shown to be ideal as a ring-closing application in the zaragozic acids.

Perlmutter[45] (Scheme 38) proposed a two-step sequence for the construction of the zaragozic acids based on a general principle of nucleophilic addition/ring closing as the key method. In this case, the two parts of the sequence were to be made up of an aldol reaction to synthesise the framework and then a Wacker oxidation to complete the formation of the core through ring closing. Realisation of this method was achieved by first application of an asymmetric aldol reaction between **182** and **183**, available from ascorbic acid in three steps. The aldol reaction is somewhat unusual as it features an α-ketoester as the electrophile, but the outcome was successful, producing the adducts **184** and **185**, as a 3:1 mixture. The major isomer **184**, along with 10% of **185**, was exposed to standard Wacker oxidation conditions, forming a ketone at C1 and, in situ, deprotecting the acetonide and completing cyclisation to give the desired product, **186**, and side product **187** (in ca. 10% yield, suggesting it is a result of **185** cyclisation) in a rapid two steps. Overall, a tandem sequence has been developed that can be used to synthesise the core of the zaragozic acids in a concise fashion.

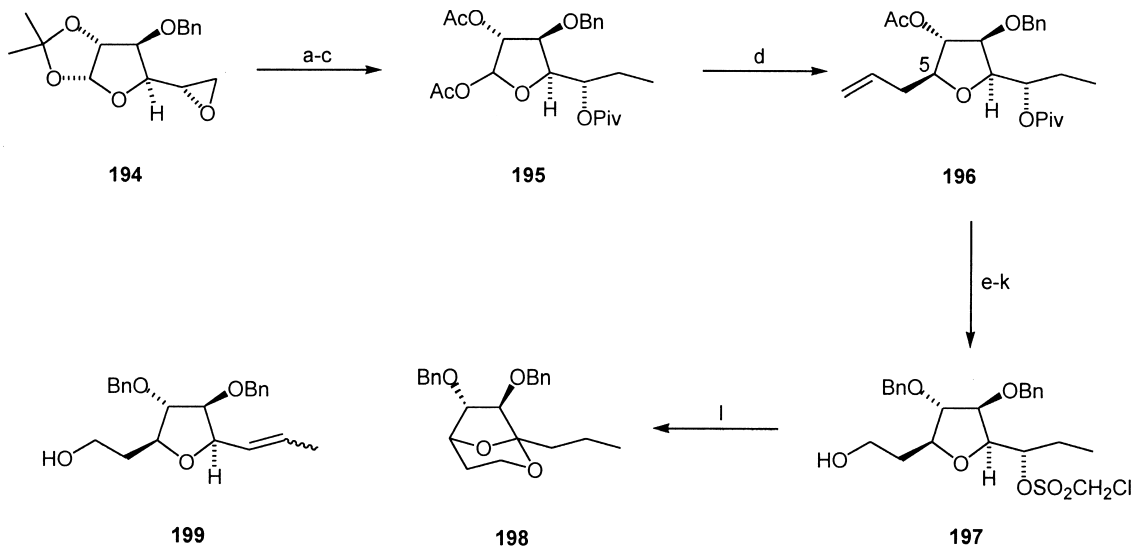
Halcomb[46] (Scheme 39) provided another insight into possible approaches to the zaragozic acids. This time, the key bond construction was to be C1–C7, by application of radical methodology. The key radical would be carbon-based, bearing two oxygen substituents, combining with a radical acceptor to form the bicyclic system. It was intended that formation of this radical system would be achieved by



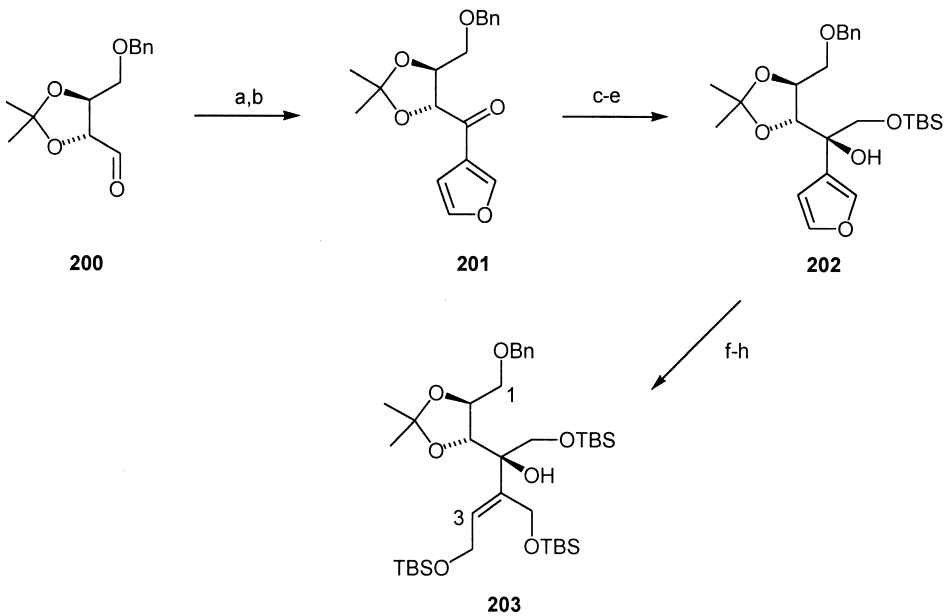
Scheme 39. Halcomb's approach to the core. *Reagents and conditions*: (a) AllylMgBr, THF, 0°C to rt, 65%; (b) $CH_3CH(OCH_3)_2$, *p*TsOH, 80°C, 41%; (c) O_3, MeOH/CH_2Cl_2, −78°C, then Me_2S, 61%; (d) hv, benzene, 59%.

use of a Norrish Type II photochemical reaction. The key intermediate for cyclisation studies was chosen as **191**. β-Hydroxyketone **188** commenced the synthesis of **191**. Addition of allyl Grignard reagent to the ketone resulted in a 1:1 mixture of diastereomers **189** and **190**. Since it was only a model system, it was arbitrarily chosen that **190** would be taken on and used as the cyclisation precursor. Acetal formation was followed by ozonolysis to set up the model studies on the efficacy of a radical method for bond construction. Irradiation of **191** gave rise to an intramolecular 1,6-hydrogen abstraction, intermediate biradical formation and combination to form the desired bicyclooctane skeleton **192** in good yield. The regioselectivity is remarkable as the 1,5-abstraction process is usually much faster than the 1,6-process but, although there are possible 1,5-abstraction sites, it is presumed that the acetal C–H bond is relatively weak compared to a standard C–H bond, promoting the observed cyclisation. This novel approach to the zaragozic acids is being developed into a total synthesis and has resulted in the synthesis of **193**, which represents a formal synthesis of zaragozic acid A, as it intersects with a late Nicolaou intermediate.[6] However, this more functionalised compound has not been sufficiently developed to study the radical cyclisation in complex systems.

The final successful synthesis of the core framework was that provided by Nakata[47] (Scheme 40), and was based around a Lewis acid-mediated intramolecular rearrangement/cyclisation process. The route commenced from the glucose derivative **194**. The epoxide was ring opened at the less hindered site by reaction with methyl cuprate. The resulting secondary alcohol was protected as the pivaloate



Scheme 40. Nakata's core synthesis. *Reagents and conditions*: (a) Me_2CuLi, ether, −78°C, 88%; (b) PivCl, DMAP, pyridine/CH_2Cl_2; (c) Ac_2O/AcOH/H_2SO_4, 15:15:1, 0°C, 78% over 2 steps; (d) AllylTMS, TMSOTf, CH_2Cl_2, −15 to 0°C, 19:1 β-anomer, 93%; (e) K_2CO_3, MeOH, 96%; (f) BnBr, NaH, Bu_4NI, DMF, 0°C; (g) O_3, MeOH, CH_2Cl_2, then $NaBH_4$, 75% over 2 steps; (h) TrCl, 2,6-lutidine, CH_2Cl_2; (i) $LiAlH_4$, ether, 0°C; (j) $ClCH_2SO_2Cl$, 2,6-lutidine, CH_2Cl_2; (k) 5% HCl/MeOH/CH_2Cl_2, 79% over 4 steps; (l) $Zn(OAc)_2$, DMF, 100°C, **198**: 32%, **199**: 17%.

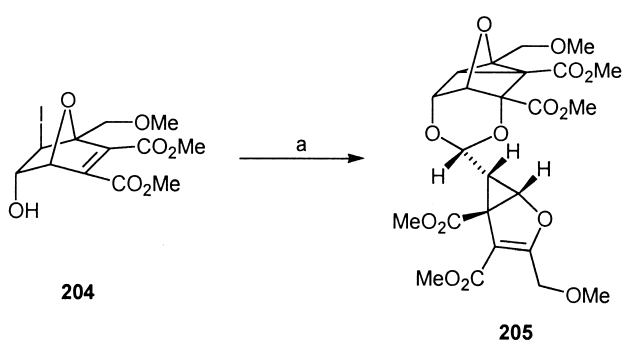


Scheme 41. Paquette's synthetic work. *Reagents and conditions*: (a) 3-Lithiofuran, 72%; (b) Swern oxidation, 91%; (c) $Ph_3P{=}CH_2$, THF, 97%; (d) AD-mix β, $^tBuOH/H_2O$, 95% (21:1); (e) TBSCl, DMF, imidazole, 98%; (f) hv, O_2, Rose Bengal; (g) $NaBH_4$; (h) TBSCl, DMF, imidazole, 60% over 3 steps.

ester and the acetonide removed and converted, in situ, to the bis-acetate **195**. C-allylation at C5 introduced the allyl group in a highly stereocontrolled fashion, with the desired configuration, to give **196**. After protecting group manipulation, ozonolysis of the allyl group followed by reductive work-up gave a primary alcohol that would become the nucleophile in the cyclisation step. All that remained was to convert the pivaloate ester into a suitable leaving group to enable the rearrangement process. This was achieved in a four-step process: the primary alcohol was blocked as the trityl ether, the pivaloate ester removed by reduction and the derived free secondary alcohol converted to the monochlate leaving group (OSO_2CH_2Cl) before removal of the trityl group to provide **197**. Exposure of **197** to $Zn(OAc)_2$, acting as a Lewis acid, resulted in the rearrangement/cyclisation event to give the core skeleton **198** in low yield, as well as **199**, the product of direct elimination of the leaving group. Variation of the cyclisation conditions did not result in improved yields or suppression of side product formation.

3.3. Miscellaneous approaches

Some groups have published work en route to the zaragozic acids, but have yet to form the bicyclic ketal present in the natural product. The key points of their work are discussed in this section.



Scheme 42. Parsons' novel cascade sequence. *Reagents and conditions*: (a) NaH, THF, 0°C, 82%.

Paquette[48] (Scheme 41) based his work on the use of a furan photooxygenation to assemble the framework of the zaragozic acids in a concise fashion. The synthesis started with the aldehyde **200**; addition of 3-lithiofuran resulted in a 1:1 diastereomeric mixture, which upon oxidation afforded ketone **201**. Wittig olefination and Sharpless dihydroxylation then installed the C5-stereocentre. The furan **202** was then subjected to photooxygenation by irradiation in the presence of oxygen, using Rose Bengal as sensitiser. Direct reduction with sodium borohydride was followed by protection of the primary alcohols as the corresponding TBS ethers, to give **203**. The next key step was to be dihydroxylation of the alkene to introduce the C3 and C4 alcohols, which, after oxidation of the C1 alcohol to the aldehyde level and cyclisation, would result in a synthesis of the core system. However, it was found that the alkene proved unreactive and attempts to complete the synthesis have not been forthcoming.

Parsons[49] (Scheme 42) had envisaged a similar approach to Nagaoka,[42] but, whilst attempting to construct an epoxide by 1,3-elimination of iodohydrin **204**, an unusual by-product, **205**, was observed. It was postulated that formation of this dimer occurred by rearrangement of the desired epoxide that results from the 1,3-elimination, to give the cyclopropane portion of the dimer. This cyclopropane aldehyde couples with unreacted iodohydrin to complete formation of the observed dimer. The novel rearrangement of the epoxide is now under development to access a different route into the zaragozic acids.

4. Conclusions

The structural complexity and biological importance of the

zaragozic acids has provided an immense challenge to the ingenuity of the synthetic community to complete total syntheses of the natural product family. A number of groups have risen to the challenge and have demonstrated clearly the ability of modern day synthetic chemistry to approach a complex natural product from many different angles. Much interesting, important and novel chemistry has arisen from attempts to synthesise the zaragozic acids and, after 10 years of effort, continues to do so.

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