Towards the synthesis of the squalestatins/zaragozic acids: Synthesis of an advanced intermediate and introduction of the C-1 sidechain

Robert K. Mann, Jack G. Parsons and Mark A. Rizzacasa *

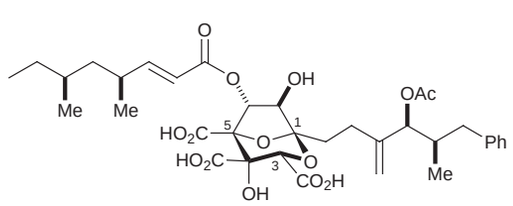
School of Chemistry, The University of Melbourne, Parkville Victoria, 3052, Australia

A highly convergent synthesis of a squalestatin/zaragozic acid A C-4-decarboxydeoxy intermediate has been achieved. The key step involves the construction of the C-1–C-1′ bond by the addition of a fully functionalized C-1 sidechain anion (derived from iodide 34) to a bicyclic core precursor lactone 24 which provides the lactols 35. Mild acid-induced deprotection and ring closure gives the 2,8-dioxabicyclo[3.2.1]octane 36 as a 3 : 1 mixture of C-3 epimers. Two-step oxidation of the C-3 alcohol to the acid followed by esterification then gives the ester 37 as the only diastereoisomer. The C-1 sidechain 34 has been synthesized in 11 steps from butane-1,4-diol while lactone 24 has been synthesized in 13 steps from the D-mannose-derived alcohol 14.

Introduction

The squalestatins[1] and zaragozic acids[2] are a group of related compounds isolated from several fungal species that have been shown to be *in vivo* picomolar inhibitors of mammalian squalene synthetase,[3] the enzyme which catalyses the dimerization of farnesyl pyrophosphate to squalene.[4] Therefore, these compounds show promise for use in the treatment of high serum-cholesterol levels and have attracted the attention of many synthetic research groups.[5] Numerous approaches towards the highly substituted 2,8-dioxabicyclo-[3.2.1]octane core common to all these compounds have been reported,[6] and in 1994 the first total syntheses of zaragozic acid C **2** by Carreira[7] and of squalestatin S1/zaragozic acid A **1** by Nicolaou's group[8] where reported, closely followed by a total synthesis of zaragozic acid C **2** by Evans *et al.*[9] Recently, Heathcock and co-workers have also reported a total synthesis of squalestatin S1/zaragozic acid A **1**,[10] while Hashimoto's group has achieved a synthesis of zaragozic acid C.[11]

Extensive structure–activity relationship studies have been conducted on naturally derived analogues as well as analogues obtained from biosynthetic feeding.[12] One finding of these studies is that the C-5 free acid is essential for activity. Furthermore, either of the C-4 and C-3 acids as well as the C-4 hydroxy group can be protected[13] or removed[14] while the C-1 sidechain should be six atoms in length and terminate in an aromatic ring.[15] However, it should be noted that these changes are not necessarily independent.



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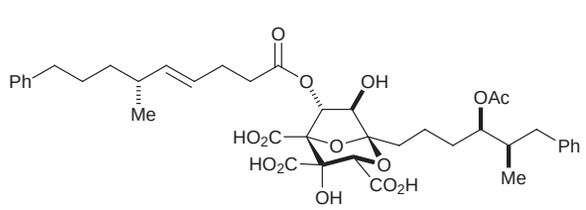

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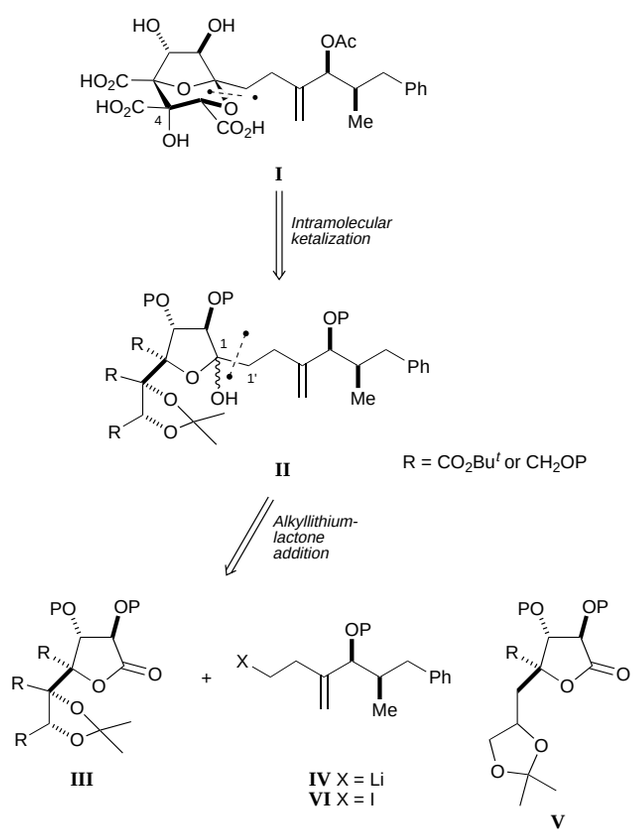
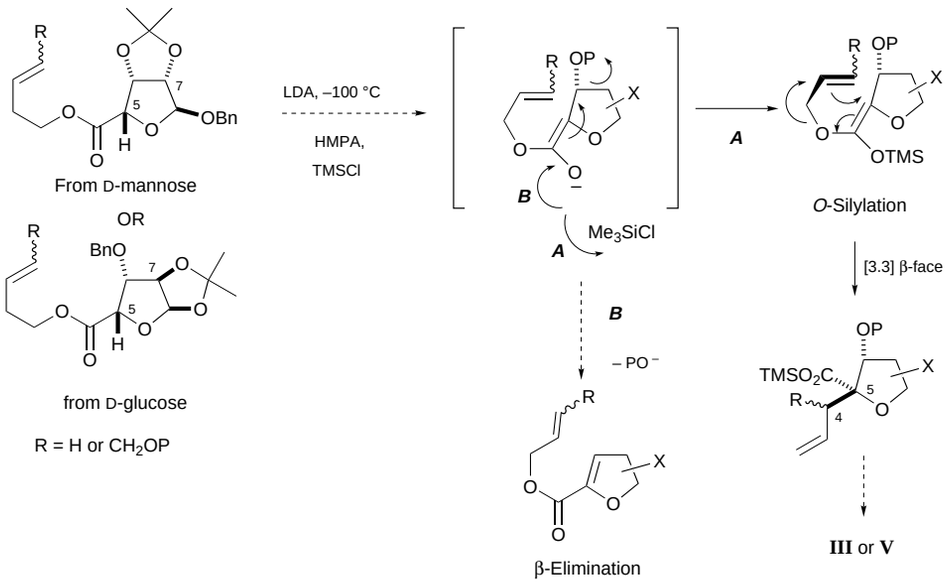
Retrosynthetic analysis

A retrosynthetic approach towards squalestatin H1 **I**, the simplest member of this class of natural products, is depicted in Scheme 1. Along with the synthesis of the naturally occurring



Scheme 1 Retrosynthetic analysis of squalestatin H1 **I**

compounds, another goal was the production of simplified analogues from a common intermediate. It was envisaged that squalestatin H1 **I**, which may also be converted into squalestatin S1/zaragozic acid A **1** by selective C-6 acylation,[7b] could be derived from an intermediate lactol such as **II** by acid-induced deprotection and ring closure. Introduction of the C-1–C-1′ bond could be then achieved in a highly convergent manner by addition of anion **IV** to a lactone **III** and, during the course of our work,[16] this C-1–C-1′ bond-formation approach was successfully utilized in the synthesis of zaragozic acid C **2** by



Scheme 2

Evans[9] as well as the Heathcock synthesis of squalestatin S1/zaragozic acid A **1**.[10] We now report the application of this approach using a simplified protected lactone such as compound **V** for a core precursor and iodide **VI** as a precursor to a sidechain anion.

Results and discussion

Introduction of the C-5 stereocentre

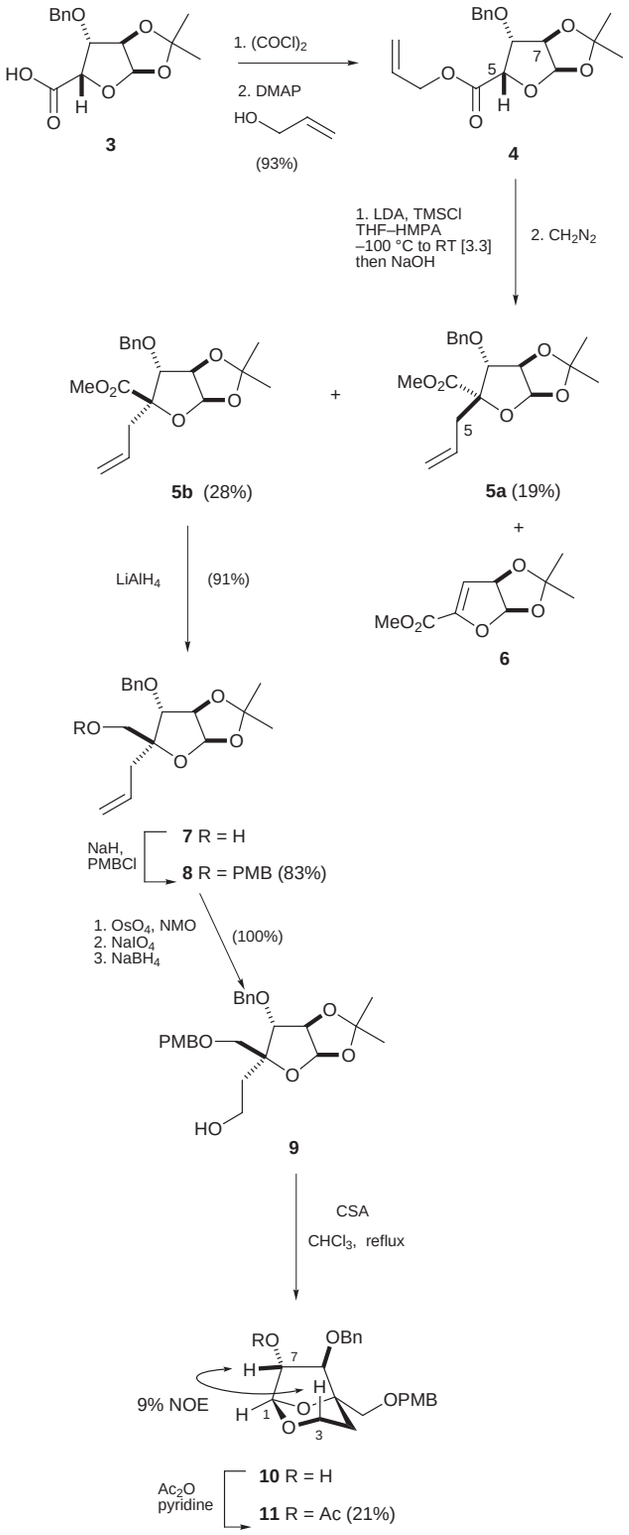
Initially, attention was focussed on the introduction of the C-5 stereocentre owing to the biological importance of the acid functionality at this position. It was envisaged that the C-4–C-5 bond (squalestatin/zaragozic acid numbering) could be constructed in a stereoselective manner by a [3,3]-sigmatropic rearrangement of a silyl ketene ketal (Ireland–Claisen rearrangement)[17] derived from an appropriate carbohydrate precursor. As shown in Scheme 2, enolization and silylation of a D-xylo or D-lyxofuranoside allyl ester (path ***A***), derived from either D-glucose or D-mannose respectively, and subsequent rearrangement from the β-face would introduce the C-5 stereocentre. An attractive aspect of this approach is that both the C-5 centre and the entire carbon skeleton of the bicyclic core can be introduced by the formation of only one carbon–carbon bond. It should also be noted that the possible major problem of β-elimination (path ***B***) has been addressed in similar systems. Under certain conditions (−100 °C; TMSCl–HMPA co-solvent) enolate O-silylation can be achieved in the presence of a β-leaving group.[18,19] Although the D-glucose-derived ester has the required stereochemistry at C-6 and C-7, the selectivity of the rearrangement may not be adequate. A D-lyxofuranoside ester, which possesses a more sterically hindered α-face, is an alternative substrate but an inversion at C-7 would be required at some stage.

Our study began with the crystalline D-xylofuranuronic acid **3**, which is prepared in 5 steps from diacetone-D-glucose according to the published procedure.[20] Conversion to the ester *via* the acid chloride provided Ireland–Claisen substrate **4** in excellent yield (Scheme 3). When a mixture of allyl ester **4**, TMSCl and HMPA in THF at −100 °C was treated with a cold (−78 °C) solution of LDA in THF and allowed to warm to RT, three major products were isolated after base hydrolysis and esterification. The esters **5a** and **5b** were obtained in a combined yield of 47% along with varying amounts of glycal **6** resulting from β-elimination. This reaction was particularly capricious and great care had to be taken in the rate of addition of the base and the temperature. On some occasions, the glycal **6** was the major product and little or no rearrangement product was isolated. A number of different conditions were also tried but with similar or worse results. Although the diastereoisomers **5a** and **5b** could be separated by flash chromatography, the minor product **5a** was contaminated with silylated by-products and was fully characterized by reduction to the corresponding alcohol. Furthermore, the major product possessed the undesired stereochemistry at C-5 as shown by conversion to the bicycle **11** according to the following sequence: Reduction of the ester **5b** provided alcohol **7**, which was protected as a *p*-methoxybenzyl (PMB) ether. Oxidative cleavage of the alkene **8** followed by reduction gave alcohol **9**, which on acid treatment cyclized to give the acetal **10** along with a number of other products due to migration and removal of the PMB group. Acetylation then gave acetate **11**, which showed a large nuclear Overhauser enhancement (NOE) between the C-3 and C-7, protons while molecular modelling revealed that the dihedral angle between H-1 and H-7 is 90° ($^3J_{1,7}$ 0 Hz) and this is in agreement with fact that H-1 resonates as a singlet in the ^{1}H NMR spectrum of compound **11**. Therefore, the original rearrangement had proceeded mostly from the undesired α-face of the furanose ring.

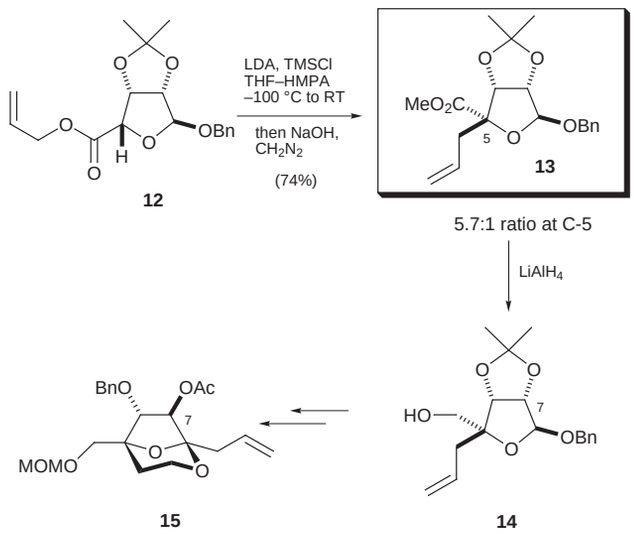
The poor selectivity and low yields obtained in the above study caused us to examine the D-mannose-derived system, which provided far more promising results. As previously reported by this laboratory,[6c,19] the allyl ester **12** synthesized from diacetone-D-mannose, smoothly undergoes enolization, silylation and rearrangement to give the ester **13** as the major product in a 5.7:1 ratio (Scheme 4). Furthermore, the major ester **13** is crystalline and is easily obtained pure and in good yield by simple recrystallization of the crude product from light petroleum. At no time has any elimination product been detected and the reaction can be performed on a multigram scale without loss in yield or selectivity. Ester **13** was then converted into the model core **15** *via* the alcohol **14** by a sequence which addressed the inversion at C-7 and served to confirm the stereochemistry at C-5.[6c] Further confirmation of the C-5 stereochemistry resulted from X-ray analysis of the alcohol derived from the minor ester obtained in the rearrangement.[19]

Synthesis of the lactone fragment 24

The synthesis of the model lactone core precursor **24** was achieved as outlined in Scheme 5. Protection of the alcohol **14** gave the MOM ether **16**[6c] which was subjected to catalytic dihydroxylation and ketalization to give the ketal **17** as a 1:1 mixture of isomers at C-3. Attempts at stereoselective dihydroxylation using the asymmetric catalytic procedures pioneered by Sharpless[21] gave only low selectivity for the desired isomer, however, it was eventually found that the C-3 stereo-



Scheme 3



Scheme 4

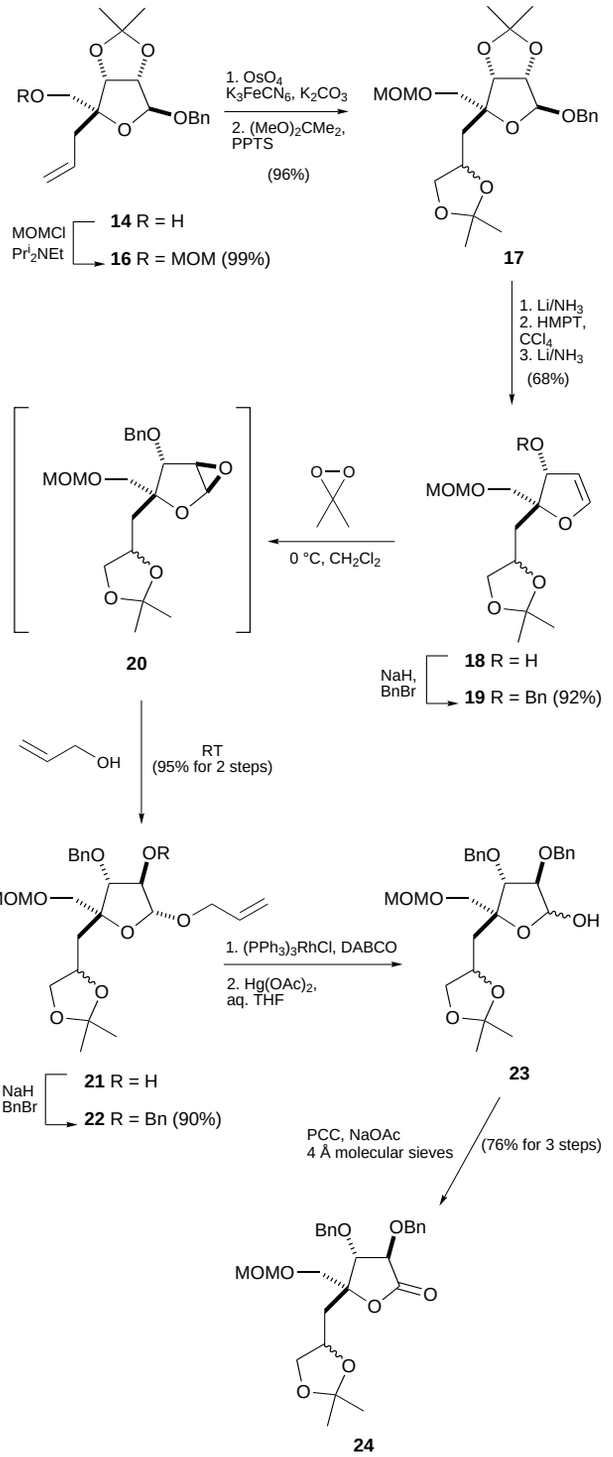
centre could be epimerized at a later stage (*vide infra*). The C-7 stereocentre was then inverted using our previously reported protocol.[6c] Debenzylation with lithium in ammonia and chlorination of the resulting lactols followed by reductive elimination[22] gave the glycal **18**. Benzylation provided the ether **19**, which was epoxidized in a stereoselective manner from the face opposite the benzyloxy group by treatment with cold dimethyldioxirane.[23] Subsequent ring opening of the labile epoxide **20** with neat allyl alcohol gave the acetal **21** and benzylation then afforded ether **22** in excellent yield. Removal of the allyl acetal by isomerization followed by oxymercuration according to the method described by Corey[24] gave the lactol **23**, which was effectively converted into lactone **24** by agency of PCC in the presence of molecular sieves. The addition of simple nucleophiles such as MeLi to the lactone **24** was possible[25] and this mode of reactivity is interesting to note in the light of the fact that Heathcock observed only β-elimination when a related lactone was treated with methyllithium or a Grignard reagent.[6i]

Synthesis of the sidechain anion precursor 34

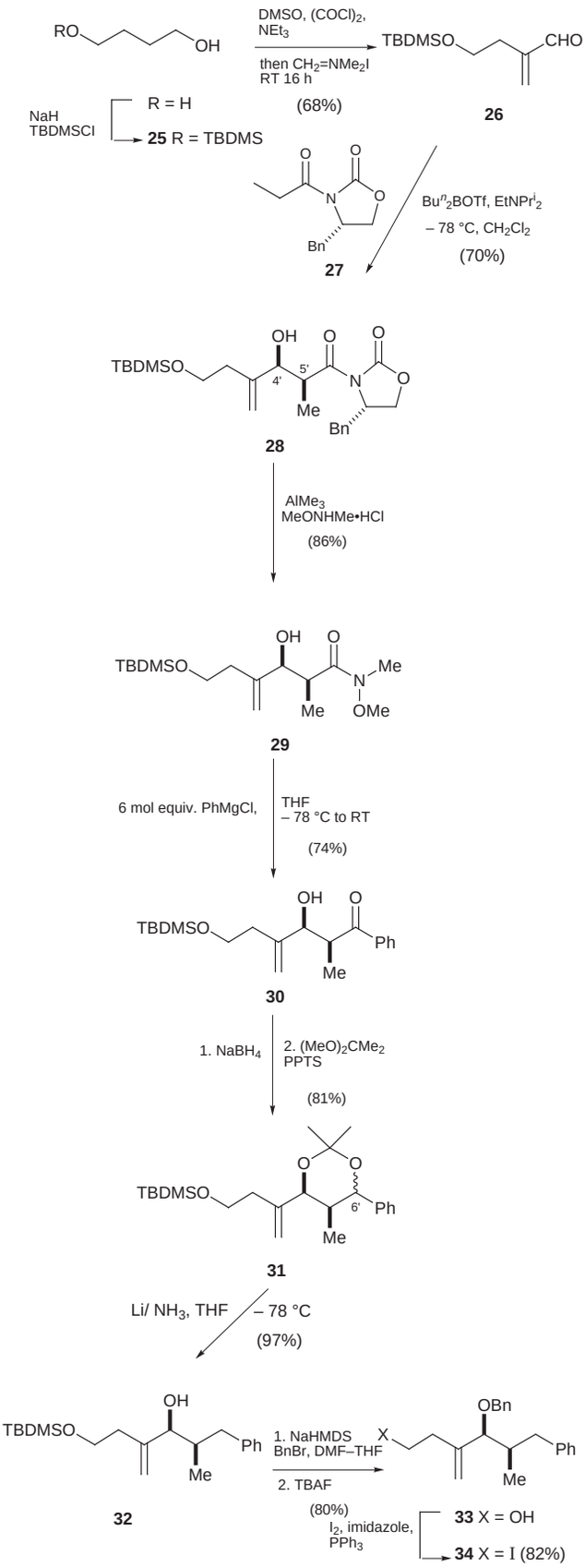
With the desired lactone in hand we then proceeded with the synthesis of the fully functionalized sidechain as depicted in Scheme 6.[16] Monosilylation[26] of butane-1,4-diol gave the *tert*-butyldimethylsilyl (TBDMS) ether **25**, which was subjected to Swern oxidation followed by *in situ* methylenation[27] to give the α,β-unsaturated aldehyde **26** in high yield after distillation. An Evans aldol reaction[28] between the boron enolate derived from the oxazolidinone **27**[29] and aldehyde **26** gave the C-4′–C-5′ *syn*-isomer **28**, which was transformed into the Weinreb amide **29**.[30] Monoaddition of phenylmagnesium chloride then provided adduct **30** in good yield. When the Grignard addition was conducted on a large scale we often observed a considerable amount of what appeared to be epimerization at C-5′. This problem was circumvented by slowly adding the excess Grignard reagent to the amide **29** at −78 °C followed by warming to RT, whereupon the reaction went to completion. Reduction of the ketone **30** followed by protection of the diol gave the acetonides **31** as a 3:1 mixture at C-6′. Originally we had proposed[16] that the iodide derived from compound **31** could serve as an effective sidechain precursor; however, the reactivity of the derived anion was low and the acid lability of the acetonide was also problematic. Dissolving-metal reduction of the mixture of acetonides **31** according to the procedure described by Evans[31] in his analogous sidechain synthesis gave the correctly functionalized sidechain precursor **32**, which was converted into the alcohol **33** by benzylation followed by desilylation. Iodination[32] of alcohol **33** then afforded the sidechain precursor **34**.

Coupling of lactone 24 and the sidechain anion

After considerable experimentation, halogen–metal exchange[33] of iodide **34** was effected with Bu′Li in freeze–thaw degassed (×3) Et_2O–hexane (3:2), and subsequent addition of a solution of the lactone **24** in degassed Et_2O–hexane followed by warming to 0 °C gave lactols **35** (Scheme 7). Deprotection and ring closure by brief exposure to 10% aq. HCl in methanol yielded the bicycle **36** which consisted of an epimeric mixture at C-3 (~3:1), demonstrating that the undesired acetonide isomer is somewhat reluctant to cyclize under these conditions. Two-step oxidation of the alcohol **36** to the acid by treatment with



Scheme 5



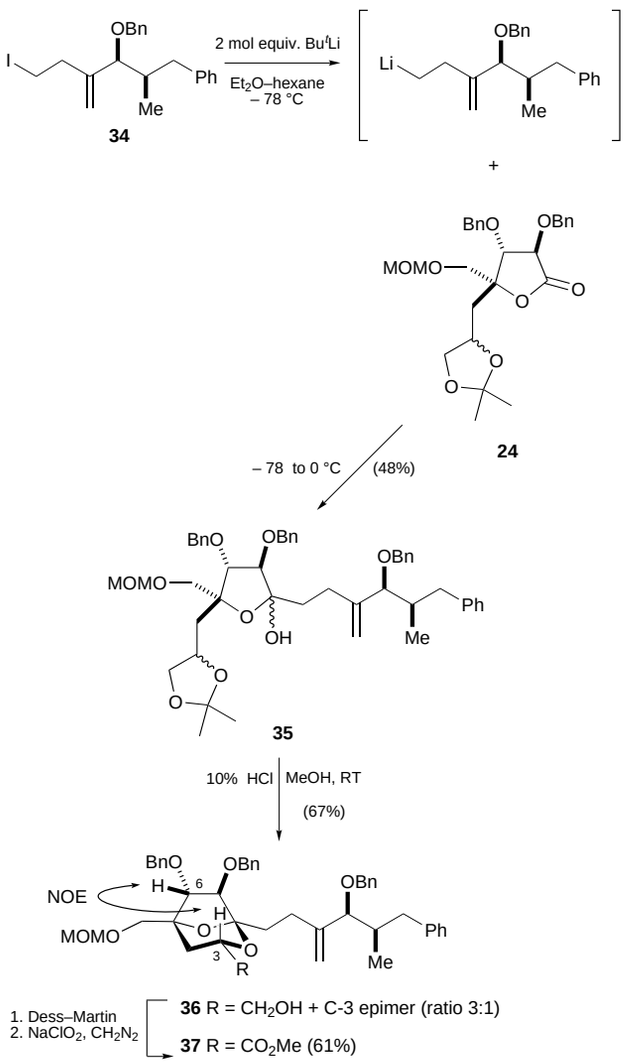
Scheme 6

Dess-Martin reagent[34] followed by $NaClO_2$[35] apparently induces C-3 epimerization and subsequent methylation gave the C4-decarboxydeoxy analogue ester **37** as the only detectable isomer. Thus, stereoselective formation of the C-3 centre by asymmetric dihydroxylation prior to ring closure was not required. The NOESY spectrum of product **37** showed a strong NOE interaction between the H-3 (which resonates as a doublet of doublets at δ 4.89) and H-6 thereby confirming the C-3 stereochemistry, while the ^{13}C NMR spectrum displayed a characteristic resonance at δ_C 104.2 for C-1 of the 2,8-dioxabicyclo[3.2.1]octane ring system.

In conclusion, we have demonstrated that this convergent approach to the squalestatins/zaragozic acids is efficient and could lead to the production of the natural products themselves as well as analogues.

Experimental

^1H NMR (300 MHz or 400 MHz) and proton-decoupled ^{13}C NMR spectra (75.5 MHz or 100 MHz) were recorded for deuteriochloroform solutions with residual chloroform as internal standard, using a Varian Unity 300 or UnityPlus 400 instrument. *J*-Values are given in Hz. Microanalyses were



Scheme 7

carried out at the University of Otago, Dunedin, New Zealand. Optical rotations were recorded in a 10 cm microcell using a JASCO DIP-1000 digital polarimeter; $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were recorded using a Perkin-Elmer 1600 series FTIR spectrophotometer. Low-resolution mass spectra (electronic or chemical ionization) were recorded on a JEOL AX-505H mass spectrometer, and high-resolution mass spectra (electrospray) were measured on a Bruker 4.7T BiOPEX FTMS spectrometer at Monash University, Clayton, Victoria. Flash chromatography was carried out on Merck silica gel 60. Analytical TLC was conducted on aluminium-backed 2 mm thick silica gel 60 GF_{254} plates supplied by Merck, and chromatograms were visualized with solutions of veratraldehyde and conc. H_2SO_4 in ethanol, 20% w/w phosphomolybdic acid in ethanol or vanillin and conc. H_2SO_4 in ethanol. Anhydrous THF was distilled from benzophenone ketyl and potassium metal under nitrogen. All other anhydrous solvents were purified according to standard methods. All organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Light petroleum refers to the fraction with distillation range 60–80 °C.

Prop-2-enyl 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuranuronate 4

To a solution of acid **3**[20] (4.12 g, 14.0 mmol) in anhydrous THF (40 cm^3) at 0 °C was added oxalyl dichloride (2.43 cm^3, 28.0 mmol) and one drop of DMF. After 2 h at RT, the solvent was removed, and the residue was then azeotroped with benzene (3 × 20 cm^3). To a stirred solution of crude acid chloride in anhydrous CH_2Cl_2 (80 cm^3) at 0 °C under were added DMAP (1.62 g, 13.3 mmol) and allyl alcohol (1.13 cm^3, 16.8 mmol). The solution was then stirred at RT for 2 h, water was added and the organic layer was separated. The aqueous layer was then extracted with diethyl ether and the organic layer was washed successively with water and brine, dried ($MgSO_4$), and concentrated. Flash chromatography of the residue on silica gel with 15% EtOAc–light petroleum as eluent afforded the *allyl ester* **4** as a pale yellow oil (4.32 g, 93%); $[\alpha]_D^{23}$ −186.9 (*c* 1.00, $CHCl_3$) (Found: C, 64.4; H, 6.5. $C_{18}H_{22}O_6$ requires C, 64.65; H, 6.7%); ν_{max}(film)/cm^{-1} 2987, 2937, 1769 (CO) and 1455; δ_H(300 MHz) 1.32 (3H, s, Me), 1.47 (3H, s, Me), 4.28 (1H, d, *J* 3.6, OCH), 4.50–4.74 (5H, m, OCH), 4.85 (1H, d, *J* 3.6, OCH), 5.18–5.34 (2H, m, CH=CH_2), 5.86 (1H, m), 6.09 (1H, d, *J* 3.6, C*H*=CH_2) and 7.30 (5H, m, ArH); δ_C(75.5 MHz) 26.3, 26.9, 65.9, 72.3, 79.6, 81.7, 82.9, 105.7, 112.4, 119.0, 127.6, 127.9, 128.4, 131.5, 136.9 and 167.4; *m*/*z* (EI) 276 ($M^+ - Me_2CO$, 8%), 129 (12), 107 (10) and 91 (100).

Methyl 3-*O*-benzyl-1,2-*O*-isopropylidene-4-*C*-(prop-2-enyl)-α-D-xylofuranuronate 5a and methyl 3-*O*-benzyl-1,2-*O*-isopropylidene-4-*C*-(prop-2-enyl)-β-L-arabinofuranuronate 5b

To a solution of Pr^i_2NH (0.92 cm^3, 6.6 mmol) in anhydrous THF at 0 °C was added Bu^{n}Li (2.50 cm^3 of a 2.4 M solution in hexane, 6.0 mmol) dropwise under nitrogen. After 5 min the base solution was cooled to −78 °C and added dropwise *via* cannula to a solution of the allyl ester **4** (1.107 g, 3.31 mmol), TMSCl (1.46 cm^3, 11.5 mmol) and HMPA (2 cm^3) in anhydrous THF (5.2 cm^3) at −100 °C. The resulting mixture was stirred at −100 °C for 10 min, −78 °C for a further 10 min, then allowed to warm to RT over a period of 3 h, and then was cooled to 0 °C. 1 M aq. sodium hydroxide (30 cm^3) was added, the solution was stirred for 20 min, and then was diluted with water and diethyl ether. The ether was discarded and more diethyl ether was added to the aqueous layer, which was then acidified to pH 2 with conc. HCl while being stirred. The organic layer was separated, and the aqueous layer was further extracted with diethyl ether. The combined organic layers were washed successively with water and brine, dried ($MgSO_4$), and concentrated to afford the crude acids as a crystalline material. Treatment of the crude acids with an excess of diazomethane, and chromatography of the crude product on silica with 10% EtOAc–light petroleum as eluent afforded the minor methyl ester **5a**, contaminated with a by-product, as a pale yellow oil, which was characterized as the derived alcohol (see below) (210 mg, 19%); δ_H(300 MHz) 1.35 (3H, s, Me), 1.54 (3H, s, Me), 2.76 (2H, m), 3.71 (3H, s, CO_2Me), 4.01 (1H, s, 3-H), 4.53–4.69 (3H, m, OCH_2Ph, 2-H), 5.07 (2H, m, CH_2CH=CH_2), 5.81 (1H, m, CH_2C*H*=CH_2), 6.16 (1H, d, *J* 4.2, 1-H) and 7.26 (5H, m, ArH). Further elution afforded the major methyl ester **5b** as a pale yellow oil (310 mg, 28%); $[\alpha]_D^{20}$ −74.3 (*c* 3.26, $CHCl_3$) (Found: $M^+ - CH_3$, 333.1339. $C_{18}H_{21}O_6$ requires, *m*/*z*, 333.1338); ν_{max}(film)/cm^{-1} 1736 (CO); δ_H(300 MHz) 1.28 (3H, s, Me), 1.41 (3H, s, Me), 2.57 (1H, dd, *J* 13.8 and 8.1, CH_2C=CH_2), 2.71 (1H, dd, *J* 13.8 and 6.6, CH_2C=CH_2), 3.71 (3H, s, Me), 4.52 (1H, s, 3-H), 4.58 (1H, d, *J* 3.6, 2-H), 4.67 (2H, ABq, *J* 11.4, OCH_2Ph), 5.04 (2H, m, CH_2CH=CH_2), 5.74 (1H, m, CH_2C*H*=CH_2), 5.94 (1H, d, *J* 3.6, 1-H) and 7.35 (5H, m, ArH); δ_C(75.5 MHz) 25.3, 25.7, 38.6, 52.0, 72.9, 82.5, 83.9, 90.5, 105.5, 112.4, 118.4, 127.6, 128.0, 128.5, 132.2, 137.1 and 172.0; *m*/*z* (EI) 348 (M^+, 0.4%), 333 (2) and 91 (100).

β-Elimination product 6

Resulting as a by-product from the above reaction: $[\alpha]_D^{20}$ −21.5 (*c* 1.98, $CHCl_3$) (Found: $M^+ + H$, 201.0760. $C_9H_{13}O_5$ requires *m*/*z*, 201.0763); ν_{max}(film)/cm^{-1} 2993, 2956, 1744 (CO), 1632 and 1440; δ_H(300 MHz) 1.45 (6H, s), 3.84 (3H, s, OMe), 5.37 (1H, dd, *J* 5.4 and 2.4, OC*H*CH=C), 6.09 (1H, d, *J* 2.4, CHC*H*=C),

6.17 (1H, d, *J* 5.4, OCHO); δ_C(75.5 MHz) 27.7, 27.9, 52.5, 82.7, 106.7, 110.5, 113.1, 149.9 and 160.0; *m*/*z* (CI) 201 (M^+ + H, 6%), 171 (47) and 83 (100).

3-*O*-Benzyl-5,6,7-trideoxy-4-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-β-D-*xylo*-hept-6-enofuranose 7

To a stirred suspension of $LiAlH_4$ (73 mg, 1.90 mmol) in diethyl ether (3.5 cm^3) at 0 °C was added a solution of the major methyl ester **5b** (334 mg, 1.04 mmol) in diethyl ether (8 cm^3) dropwise. The mixture was stirred at RT for 40 min, cooled to 0 °C, and treated with water (1.5 cm^3) followed by 5 M NaOH (1.5 cm^3). Diethyl ether and $MgSO_4$ were added and the mixture was filtered. Purification of the crude product on silica with 20% EtOAc–light petroleum as eluent afforded the *alcohol* **7** as a clear oil (281 mg, 91%); $[\alpha]_D^{20}$ −20.9 (*c* 3.65, $CHCl_3$) (Found: C, 67.4; H, 7.7. $C_{18}H_{24}O_5$ requires C, 67.5; H, 7.55%); ν_{max}(film)/cm^{-1} 3504 (OH), 2983, 2938, 1455 and 1374; δ_H(300 MHz) 1.34 (3H, s, Me), 1.57 (3H, s, Me), 2.08 (1H, t, *J* 6.6, OH), 2.38 (1H, dd, *J* 13.8 and 8.1, $CH_2CH{=}CH_2$), 2.50 (1H, dd, *J* 13.8 and 6.6, $CH_2CCH{=}CH_2$), 3.61 (2H, d, *J* 6.6, CH_2OH), 4.01 (1H, d, *J* 1.8, 3-H), 4.52–4.76 (3H, m, OCH_2Ph, 2-H), 5.12 (2H, m, $CH_2CH{=}CH_2$), 5.84 (1H, m, CH_2CHCH_2), 5.90 (1H, d, *J* 4.5, 1-H) and 7.34 (5H, m, ArH); δ_C(75.5 MHz) 26.6, 27.1, 36.7, 64.0, 72.2, 84.0, 85.5, 90.1, 104.3, 112.6, 118.6, 127.4, 127.8, 128.4, 133.6 and 137.4; *m*/*z* (EI) 289 (2%), 220 (2) and 91 (100).

3-*O*-Benzyl-5,6,7-trideoxy-4-*C*-(hydroxymethyl)-1,2-*O*-isopropylidene-α-L-*arabino*-hept-6-enofuranose

The minor methyl ester was converted to the *title alcohol* by using a method identical with that described above; $[\alpha]_D^{20}$ −43.7 (*c* 1.51, $CHCl_3$) (Found: C, 67.5; H, 7.55%); ν_{max}(film)/cm^{-1} 3494 (OH), 2985, 2936, 1455 and 1382; δ_H(300 MHz) 1.37 (3H, s, Me), 1.53 (3H, s, Me), 2.21 (1H, dd, *J* 9.0 and 5.1, OH), 2.39 (2H, br d, $CH_2CH{=}CH_2$), 3.54 (1H, dd, *J* 12.0 and 9.0, CH_2OH), 3.77 (1H, dd, *J* 12.0 and 5.1, CH_2OH), 3.99 (1H, d, *J* 2.4, 3-H), 4.50–4.79 (3H, m, OCH_2Ph, 2-H), 5.02 (2H, m, $CH_2CH{=}CH_2$), 5.78 (1H, m, $CH_2CH{=}CH_2$), 6.03 (1H, d, *J* 4.2, 1-H) and 7.32 (5H, m, ArH); δ_C(75.5 MHz) 27.3, 27.6, 66.2, 72.5, 86.6, 87.2, 88.6, 104.8, 113.5, 118.7, 127.9, 128.2, 128.6, 132.9 and 136.9; *m*/*z* (EI) 289 (2%), 91 (100) and 83 (5).

3-*O*-Benzyl-5,6,7-trideoxy-1,2-*O*-isopropylidene-4-*C*-(4-methoxybenzyl)-β-D-*xylo*-hept-6-enofuranose 8

To a suspension of sodium hydride (33 mg, 0.825 mmol; 60% dispersion in mineral oil, washed with anhydrous pentane) in DMF (2 cm^3) was added a solution of alcohol **7** (221 mg, 0.690 mmol) in anhydrous THF (3 cm^3) at 0 °C dropwise under nitrogen. The solution was stirred for 40 min at RT, and 4-methoxybenzyl chloride (0.110 cm^3, 0.81 mmol) was added. After stirring of the mixture at RT for 3 h, water and diethyl ether were added, the organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed successively with water and brine, dried ($MgSO_4$), and concentrated. Purification of the crude product by flash chromatography on silica with 5% EtOAc–light petroleum as eluent afforded the *PMB ether* **8** as a pale yellow oil (252 mg, 83%); $[\alpha]_D^{20}$ −12.8 (*c* 1.15, $CHCl_3$) (Found: C, 70.9; H, 7.5. $C_{26}H_{32}O_6$ requires C, 70.9; H, 7.3%); δ_H(300 MHz) 1.32 (3H, s, Me), 1.44 (3H, s, Me), 2.47 (1H, dd, *J* 14.1 and 8.1, $CH_2CH{=}CH_2$), 2.47 (1H, dd, *J* 14.1 and 6.0, $CH_2CH{=}CH_2$), 3.48 (2H, ABq, *J* 9.6, CH_2OPMB), 3.80 (3H, s, OMe), 4.12 (1H, d, *J* 1.5, 1-H), 4.44 (2H, s), 4.53–4.71 (3H, m, OCH_2Ph, 2-H), 5.09 (2H, m, $CH_2CH{=}CH_2$), 5.86 (1H, m, CH_2CHCH_2), 5.88 (1H, d, *J* 4.8, 1-H), 6.83–7.21 (4H, AA′BB′, ArH) and 7.33 (5H, m, ArH); δ_C(75.5 MHz) 26.5, 26.9, 36.5, 55.2, 71.2, 72.2, 72.9, 84.7, 85.8, 88.8, 104.4, 112.5, 113.6, 118.2, 127.4, 127.6, 128.3, 129.1, 130.4, 133.8, 137.7 and 159.0; *m*/*z* (EI) 440 (M^+, 1%), 137 (14), 91 (100) and 83 (100).

3-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-4-*C*-(4-methoxybenzyl)-β-D-*xylo*-hexofuranose 9

To a solution of the PMB ether **8** (201 mg, 0.456 mmol) in THF (4 cm^3) were added aq. NMO (92 mg, 0.79 mmol in 1 cm^3) and osmium tetraoxide (0.2 M in *tert*-butyl alcohol; 0.057 cm^3, 2.5 mol%). After stirring of the mixture overnight at RT, aq. sodium metaperiodate (205 mg, 0.97 mmol in 4 cm^3) was added, and the mixture was stirred for a further 2 h. Water was added, and the mixture was extracted with diethyl ether. The solvent was removed, and the crude aldehyde was dissolved in ethanol (4 cm^3) and treated with $NaBH_4$ (42 mg, 1.11 mmol). After stirring of the mixture for 40 min at RT, the solvent was removed, and water and diethyl ether were added. The aqueous layer was acidified with 10% HCl at 0 °C, and the mixture was filtered through Celite. The organic layer was separated, washed successively with saturated aq. $NaHCO_3$, water and brine, and dried ($MgSO_4$). Concentration under reduced pressure and purification of the residue on silica with 10% EtOAc–light petroleum as eluent afforded the *alcohol* **9** (202 mg, 100%) as a pale yellow oil; $[\alpha]_D^{20}$ −34.4 (Found: C, 67.8; H, 7.3. $C_{25}H_{32}O_7$ requires C, 67.55; H, 7.3%); ν_{max}(film)/cm^{-1} 3456 (OH), 2937, 1613, 1586, 1513 and 1455; δ_H(300 MHz) 1.31 (3H, s, Me), 1.43 (3H, s, Me), 1.92–2.16 (2H, m), 2.64 (1H, br s, OH), 3.57 (2H, ABq, *J* 9.6, CH_2OPMB), 3.74 (2H, br m, CH_2OH), 3.80 (3H, s, OMe), 4.06 (1H, s, 3-H), 4.46 (2H, ABq, *J* 11.7, OCH_2PMB), 4.52–4.71 (3H, m, OCH_2Ph, 2-H), 5.90 (1H, d, *J* 4.2, 1-H), 6.84–7.20 (4H, AA′BB′, ArH) and 7.32 (5H, m, ArH); δ_C(75.5 MHz), 26.1, 26.6, 34.5, 55.2, 58.7, 71.7, 72.3, 73.1, 84.9, 85.2, 89.6, 112.3, 113.8, 127.5, 127.8, 128.4, 129.3, 129.8, 137.3 and 159.3; *m*/*z* (EI) 386 ($M^+ - Me_2CO$, 2%), 137 (9), 121 (11) 91 (21) and 83 (100).

7-Acetoxy-6-benzyloxy-5-(4-methoxybenzyl)-2,8-dioxabicyclo[3.2.1]octane 11

To a solution of the alcohol **9** (89.2 mg, 0.201 mmol) in $CHCl_3$ (2 cm^3) was added a crystal of CSA. The solution was heated under reflux for 24 h, water was added, and the mixture was extracted twice with diethyl ether. The combined organic extracts were washed successively with saturated aq. $NaHCO_3$, water and brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded a mixture of compounds as a pale yellow oil. The crude alcohols were dissolved in a mixture of pyridine (1 cm^3) and acetic anhydride (1 cm^3) and the solution was stirred overnight at RT. Water and diethyl ether were added, and the organic layer was washed successively with 10% aq. HCl, saturated aq. $NaHCO_3$, water, and brine. Drying of the organic fraction ($MgSO_4$) followed by concentration under reduced pressure and purification by preparative TLC using 20% EtOAc–light petroleum as eluent afforded the bicyclic compound **11** as a pale yellow oil (18.3 mg, 21%); δ_H(300 MHz) 1.60 (1H, dd, *J* 15.0 and 3.9, 4-H^{eq}), 2.04 (1H, m, 4-H^{ax}), 2.10 (3H, s, Ac), 3.35–3.54 (2H, ABq, *J* 10.8, CH_2OPMB), 3.79 (3H, s, OMe), 3.96 (1H, dd, *J* 11.7 and 6.6, 3-H^{eq}), 4.05 (1H, br s, 6-H), 4.17 (1H, dt, *J* 11.7 and 3.9, 3-H^{ax}), 4.44–4.70 (4H, m, OCH_2Ar), 5.11 (1H, s, 1-H), 5.35 (1H, d, *J* 2.4, 7-H), 6.85–7.25 (4H, AA′BB′, ArH) and 7.26 (5H, m, ArH).

(+)-Benzyl 5,6,7-trideoxy-2,3-*O*-isopropylidene-4-*C*-(methoxymethoxymethyl)-β-L-*ribo*-hept-6-enofuranoside 16

To a stirred solution of the alcohol **14**[19] (2.55 g, 7.98 mmol) in dry CH_2Cl_2 (30 cm^3) under nitrogen was added Pr^i_2NEt (2.66 cm^3, 15.3 mmol). The reaction mixture was then cooled to 0 °C and MOMCl (0.877 cm^3, 11.5 mmol) was added dropwise. After being stirred overnight, the reaction mixture was diluted successively with 10% aq. HCl and water and extracted with diethyl ether. The organic layer was washed successively with 10% aq. HCl and saturated aq. $NaHCO_3$. Purification of the crude product by flash chromatography with 10% EtOAc–light petroleum as eluent afforded the *ether* **16** (2.74 g, 99%) as a pale yellow oil; $[\alpha]_D^{20}$ +44.7 (*c* 1.75, $CHCl_3$) (Found: C, 66.0; H, 7.9.

$C_{20}H_{28}O_6$ requires C, 65.9; H, 7.7%); δ_H(300 MHz) 1.31 (3H, s, Me), 1.48 (3H, s, Me), 2.51 (1H, dd, *J* 13.8 and 8.4, CH_2CH=CH$_2$), 2.65 (1H, dd, *J* 14.0 and 6.3, CH_2CH=CH$_2$), 3.40 (3H, s, OMe), 3.61 and 3.74 (2H, ABq, *J* 9.9, CH_2O-MOM), 4.47 (1H, d, *J* 11.7, OCH_2Ph) 4.58 (1H, d, *J* 6.6, OCH), 4.69 (2H, s, CH$_2$OCH_2OCH$_3$), 4.78 (1H, d, *J* 6.6, OCH), 4.79 (1H, d, *J* 12.3, CH_2OBn), 5.11–5.16 (3H, m, CH=CH_2 and 1-H) 5.68–5.99 (1H, m, CH$_2$C*H*=CH$_2$) and 7.28–7.34 (5H, m, ArH); δ_C(75.5 MHz) 24.7, 26.0, 40.0, 55.3, 67.4, 69.6, 83.7, 86.3, 88.5, 96.9, 107.4, 112.5, 118.5, 127.7, 127.8, 128.4, 133.4 and 137.4; *m*/*z* (CI) 365 (M^+ + H, 7%), 232 (48), 303 (55) and 185 (100).

Benzyl 5-deoxy-2,3 : 6,7-di-*O*-isopropylidene-4-*C*-(methoxymethoxymethyl)-α-L-*allo*/β-D-*talo*-heptofuranoside 17

To an aq. solution of the MOM ether **16** (1.59 g, 4.36 mmol in 22 cm^3) and Bu^{t}OH (22 cm^3) at 0 °C were added K_2CO_3 (1.83 g, 13.2 mmol), K_3FeCN_6 (3.96 g, 12.0 mmol) and OsO_4 (0.219 cm^3; 2 mol% solution in Bu^{t}OH). The resulting orange suspension was allowed to warm to RT and was stirred for 12 h. Sodium sulfite was added until the suspension turned brown, and the mixture was stirred for a further 1 h and then was diluted with diethyl ether and water. The organic layer was washed successively with water and brine, dried, and concentrated to provide the crude diol as a 1 : 1 mixture of diastereoisomers (1.73 g, 100%). To a solution of the diol (1.24 g, 3.12 mmol) in acetone (20 cm^3) and 2,2-dimethoxypropane (9 cm^3 was added PPTS (69 mg, 0.275 mmol) and the reaction mixture was stirred for 16 h at RT. Most of the solvent was removed under reduced pressure and the residue was dissolved in diethyl ether and washed successively with water and brine. Purification of the crude product by flash chromatography using 10% EtOAc–light petroleum as eluent provided the *acetonide* **17** (1.32 g, 96%) as a 1 : 1 mixture of diastereoisomers (Found: C, 63.0; H, 8.1. $C_{23}H_{34}O_8$ requires C, 63.0; H, 7.8%); δ_H(300 MHz) 1.25 (3H, s, Me), 1.31 (3H, s, Me), 1.33 (3H, s, Me), 1.35 (3H, s, Me), 1.36 (3H, s, Me), 1.37 (3H, s, Me), 1.47 (6H, s, 2 × Me), 1.88–2.24 (m, 4H, 2 × CH$_2$), 3.395 (3H, s, OMe), 3.398 (3H, s, OMe), 3.42–3.58 (2H, m), 3.71–3.86 (2H, m), 3.91–3.96 (1H, m), 4.06–4.16 (1H, m), 4.25–4.42 (2H, m), 4.44–4.85 (14H, m), 5.14 (s, 1H, 1-H), 5.16 (1H, s, 1-H) and 7.26–7.36 (10H, m, ArH); δ_C(75.5 MHz) 14.2, 24.8, 24.9, 25.7, 25.9, 26.2, 26.9, 38.8, 39.2, 55.3, 55.5, 60.4, 67.8, 68.2, 69.7, 69.8, 70.0, 70.4, 72.3, 72.4, 84.4, 86.4, 87.5, 88.2, 96.9, 107.6, 107.8, 108.2, 109.0, 112.5, 112.7, 127.6, 127.7, 127.8, 128.0, 128.3, 128.4 and 137.4.

4,7-Anhydro-3,6-dideoxy-1,2-*O*-(isopropylidene)-4-*C*-(methoxymethoxymethyl)-D-*arabino*/D-*ribo*-hept-6-enitol 18

To a blue solution of Li metal (158 mg, 22.8 mmol) in liquid NH_3 (~25 cm^3) at −78 °C was added a solution of the acetonide **17** (500 mg, 1.14 mmol) in THF (12 cm^3). The reaction mixture was stirred for 10 min at −78 °C, then was treated with NH_4Cl until the blue colour had dissipated. The resulting white suspension was diluted with diethyl ether (20 cm^3) and $MgSO_4$ was added. After being stirred for 2 h at RT the reaction mixture was filtered and concentrated to give the crude lactols as an oil. The lactols were dissolved in THF (10 cm^3) and treated with CCl_4 (0.283 cm^3, 2.93 mmol) and HMPT (0.620 cm^3, 3.41 mmol) at −78 °C. The resulting yellow suspension was stirred for 1 h at −78 °C, then was allowed to warm to RT over a period of 1.5 h. The reaction mixture was diluted with diethyl ether and saturated aq. $NaHCO_3$, and the organic layer was washed successively with water and brine. Removal of the solvent furnished the chlorides as an orange oil. The chlorides, in THF, were subjected to Li/NH_3 reduction as described above. Purification by flash chromatography using 20–40% EtOAc–light petroleum as gradient eluent gave the *glycal* **18** (212 mg, 68%) as an oily mixture of diasteroisomers (Found: C, 56.6; H, 8.0. $C_{13}H_{22}O_6$ requires C, 56.9; H, 8.0%); ν_{max}(film)/cm^{-1} 3442 (OH), 2982, 2931, 1611, 1377, 1243, 1152, 1046 and 835; δ_H(300 MHz) 1.30 (3H, s, Me), 1.33 (3H, s, Me), 1.34 (3H, s, Me), 1.36 (3H, s, Me), 1.74–2.05 (4H, m, 2 × CH$_2$), 2.72–2.76 (2H, br m, OH), 3.36 (3H, s, OMe), 3.37 (3H, s, OMe), 3.44 (1H, t, *J* 8.1, 2-H), 3.50 (1H, t, *J* 7.8, 2-H), 3.73 and 3.84 (2H, ABq, *J* 10.5, CH_2OMOM), 3.89 (1H, s), 3.99–4.17 (4H, m), 4.22–4.33 (2H, m), 4.67 (2H, s, CH$_2$OCH_2OCH$_3$), 4.68 (2H, s, CH$_2$O-CH_2OCH$_3$), 4.86 (1H, br d, *J* 9.0, C*H*OH), 5.08–5.13 (2H, m, 2 × C*H*=CHO), 6.47 (1H, d, *J* 2.7, C=CHO) and 6.51 (1H, d, *J* 2.7, C=CHO); δ_C(75.5 MHz) 14.1, 25.7, 25.8, 26.8, 38.2, 39.6, 55.57, 55.61, 60.3, 67.2, 69.3, 70.1, 70.2, 71.4, 72.1, 78.8, 80.0, 87.8, 97.0, 97.1, 103.4, 104.2, 108.5, 108.6, 148.4 and 148.7.

4,7-Anhydro-5-*O*-benzyl-3,6-dideoxy-1,2-*O*-isopropylidene-4-*C*-(methoxymethoxymethyl)-D-*arabino*/D-*ribo*-hept-6-enitol 19

To a suspension of NaH (230 mg, 5.75 mmol; 60% dispersion in oil, hexane washed) in THF (12 cm^3) at 0 °C was added a solution of glycal **18** (650 mg, 2.37 mmol) in DMF (12 cm^3). After stirring of the mixture for 45 min at 0 °C, BnBr (0.395 cm^3, 3.32 mmol) was added and the reaction mixture was stirred for 12 h at RT. Water was added cautiously and the crude product was extracted with diethyl ether. Purification by flash chromatography with 20% EtOAc–light petroleum as eluent provided the *benzyl ether* **19** (790 mg, 92%) as an oily mixture of diastereoisomers (Found: C, 65.7; H, 7.7. $C_{20}H_{28}O_6$ requires C, 65.9; H, 7.7%); δ_H(300 MHz), 1.31 (3H, s, Me), 1.34 (3H, s, Me), 1.35 (3H, s, Me), 1.37 (3H, s, Me), 1.93–2.16 (4H, m, 2 × CH$_2$), 3.36 (3H, s, OMe), 3.37 (3H, s, OMe), 3.46 (1H, t, *J* 7.5, 2-H), 3.53 (1H, t, *J* 7.8, 2-H), 3.80 (2H, s, OCH$_2$), 3.85 and 3.95 (2H, ABq, *J* 9.3, CH_2OMOM), 3.84–4.17 (4H, m, 2 × OCH$_2$), 4.27–4.35 (1H, m), 4.48–4.59 (4H, m), 4.67 (2H, s, CH$_2$OCH_2OCH$_3$), 4.69 (2H, s, CH$_2$OCH_2OCH$_3$), 4.73 (1H, d, *J* 2.4, OCH), 5.11 (1H, t, *J* 3.0, C*H*=CHO), 5.16 (1H, t, *J* 3.0, C*H*=CHO), 6.49 (1H, d, *J* 3.0, CH=C*H*O), 6.51 (1H, d, *J* 3.0, CH=C*H*O) and 7.26–7.38 (10H, m, ArH); δ_C(75.5 MHz) 25.7, 25.9, 26.8, 37.2, 39.1, 55.4, 55.5, 66.4, 68.1, 70.3, 71.45, 71.50, 71.8, 72.5, 84.7, 85.0, 87.9, 88.2, 96.9, 97.0, 100.8, 101.2, 108.4, 108.6, 127.45, 127.49, 127.6, 128.28, 128.32, 138.3, 138.4, 148.7 and 148.9.

Prop-2-enyl 2,3-di-*O*-benzyl-5-deoxy-6,7-*O*-isopropylidene-4-*C*-(methoxymethoxymethyl)-β-L-*altro*/α-D-*galacto*-heptofuranoside 22

To a solution of benzyl ether **19** (240 mg, 0.66 mmol) in CH_2Cl_2 (12 cm^3) at 0 °C was added a solution of dimethyldioxirane in acetone (6.35 cm^3; 0.104 M). After 45 min the solvents were removed under reduced pressure in the absence of water (5 mmHg) and the flask was charged with dry allyl alcohol (3 cm^3). The reaction mixture was stirred at RT for 2 h and the solvent was removed under reduced pressure to afford acetal **21** (275 mg, 95%). A solution of this acetal (275 mg, 0.64 mmol) in DMF (4 cm^3) was added to a suspension of NaH (78 mg, 1.95 mmol; 60% dispersion in oil, hexane washed) in THF (4 cm^3) at 0 °C. After 45 min, BnBr (0.155 cm^3, 1.30 mmol) was added and the reaction mixture was stirred overnight at RT. The reaction was quenched with water and the aqueous layer was extracted with diethyl ether. The organic layer was washed successively with water and brine and concentrated. Purification of the crude product by flash chromatography using 5–20% EtOAc–light petroleum as gradient eluent afforded the *allyl acetal* **22** (300 mg, 90%) as an oily mixture of diastereoisomers (Found: C, 68.4; H, 7.5. $C_{30}H_{40}O_8$ requires C, 68.2; H, 7.6%); δ_H(300 MHz) 1.31 (3H, s, Me), 1.32 (3H, s, Me), 1.36 (3H, s, Me), 1.37 (3H, s, Me), 1.94–2.17 (4H, m, 2 × CH$_2$), 3.340 (3H, s, OMe), 3.345 (3H, s, OMe), 3.47 and 3.53 (2H, ABq, *J* 7.8, OCH$_2$), 3.64 (2H, d, *J* 10.5, 2 × CH_2OMOM), 3.72–3.83 (2H, m), 3.94 (1H, br d, *J* 6.0, OCH), 3.98 (1H, br d, *J* 6.0, OCH), 4.01–4.18 (5H, m), 4.20–4.31 (4H, m), 4.30 (1H, d, *J* 6.0), 4.47–4.66 (12H, m), 5.02 (1H, d, *J* 2.4), 5.18 (1H, d, *J* 9.0), 5.26 (2H, t, *J* 1.0, 2 × CH=CH_2), 5.32 (2H, t, *J* 1.0, 2 × CH=CH_2), 5.83–5.97 (2H, m, 2 × OC*H*=CH$_2$) and 7.22–7.39 (20H, m, ArH); δ_C(75.5 MHz) 14.1, 21.0, 25.9, 26.9, 38.1, 40.3, 55.2, 55.4, 60.3, 68.3, 68.5, 69.2, 70.3, 70.4, 70.8, 71.9, 72.0, 72.2, 72.6, 72.7, 84.3,

85.3, 85.5, 87.3, 88.6, 88.8, 97.0, 105.2, 105.3, 108.3, 108.4, 117.0, 127.58, 127.60, 127.64, 127.78, 127.83, 128.3, 128.4, 134.1 and 138.1.

2,3-Di-*O*-benzyl-5-deoxy-6,7-*O*-isopropylidene-4-*C*-(methoxymethoxymethyl)-L-*altro*/D-*galacto*-heptono-1,4-lactone 24

A solution of the allyl acetal **22** (360 mg, 0.681 mmol), $(Ph_3P)_3RhCl$ (32 mg, 5 mol%) and DABCO (16.3 mg, 0.145 mmol) in EtOH (9 cm^3) was heated to reflux for 2 h. The solvent was removed *in vacuo* and the resulting brown oil was filtered through a plug of silica gel with 20% EtOAc–light petroleum as eluent to afford a yellow oil. The crude enol ether was dissolved in a mixture of THF (10 cm^3) and water (4 cm^3) and treated with aq. $Hg(OAc)_2$ (273 mg, 0.857 mmol in 3 cm^3). After stirring of the mixture for 30 min, THF was removed *in vacuo* and the residue was taken up in diethyl ether–water. The organic layer was washed successively with saturated aq. $NaHCO_3$ and brine, dried and concentrated to give the crude lactol **23** (332 mg, 100%). To a solution of the lactol **23** (107 mg, 0.219 mmol) in CH_2Cl_2 (3 cm^3) were added NaOAc (179 mg, 2.18 mmol), powdered 4 Å molecular sieves (35.6 mg) and PCC (71 mg, 0.329 mmol). The resulting brown suspension was stirred for 30 min at RT, then was filtered through Florisil and the filter cake was washed with EtOAc. The crude product was purified by flash chromatography using 10–20% EtOAc–light petroleum as gradient eluent to afford the *lactone* **24** (81 mg, 76%) as an oily mixture of diastereoisomers (Found: C, 66.6; H, 7.2. $C_{27}H_{34}O_8$ requires C, 66.7; H, 7.0%); ν_{max}(film)/cm^{-1} 2980, 2931, 1782 (CO), 1733 (CO), 1451 and 1046; δ_H(300 MHz) 1.29 (3H, s, Me), 1.31 (3H, s, Me), 1.36 (6H, s, 2 × Me), 1.79 (1H, t, *J* 4.2, 5-H), 1.83 (1H, t, *J* 4.2, 5-H), 1.92–2.06 (2H, m, 2 × 5-H), 3.25 (3H, s, OMe), 3.26 (3H, s, OMe), 3.33–3.49 (4H, m), 3.71 and 3.88 (2H, d, *J* 9.0, C*H*$_2$OMOM), 3.93 (2H, d, *J* 10.0, 2 × OCH), 4.00–4.29 (6H, m), 4.51–4.76 (10H, m), 5.11 (1H, d, *J* 9.6, OCH), 5.15 (1H, d, *J* 9.6, OCH) and 7.21–7.42 (20H, m, ArH); δ_C(100 MHz), 25.7, 25.8, 26.8, 38.2, 40.5, 55.5, 67.5, 69.0, 69.8, 69.9, 70.7, 71.4, 72.6, 72.8, 73.0, 78.9, 82.5, 83.3, 83.8, 85.2, 96.3, 96.4, 109.3, 109.4, 127.6, 127.7, 127.9, 128.04, 128.07, 128.35, 128.39, 128.44, 128.5, 137.1, 137.2, 137.3, 137.5 and 173.0.

2-[2-(*tert*-Butyldimethylsiloxy)ethyl]propenal 26

To a stirred solution of oxalyl dichloride (14.7 cm^3, 169 mmol) in CH_2Cl_2 (250 cm^3) at −70 °C was added dropwise DMSO (16.3 cm^3, 230 mmol) with the evolution of gas. After 15 min, a solution of 4-(*tert*-butyldimethylsiloxy)butan-1-ol **25** (11.4 g, 56.2 mmol) in CH_2Cl_2 (50 cm^3) was added dropwise *via* cannula to the solution with the formation of a precipitate. Triethylamine (118 cm^3, 847 mmol) was then added and the reaction mixture was allowed to warm to RT and was stirred for a further 15 min. *N*,*N*-Dimethyl(methylene)ammonium iodide (24.0 g, 130 mmol) was added to the mixture and the resulting orange suspension was stirred overnight at RT. The reaction mixture was taken up into CH_2Cl_2 and was washed successively with 5% aq. $NaHCO_3$ and brine, and dried. Removal of the solvent gave an orange oil, which was purified by flash filtration through silica gel, using 5% EtOAc–light petroleum as eluent followed by distillation at reduced pressure (95–97 °C at 0.4 mmHg) to give the aldehyde **26** (8.2 g, 68%) as an oil; ν_{max}(film)/cm^{-1} 2956, 2929, 2857, 2360, 1693 (CO), 1256, 1102 and 835; δ_H(400 MHz) 0.04 (6H, s, $SiMe_2$), 0.86 (9H, s, CMe_3), 2.47 (2H, t, *J* 5.5, C*H*$_2$C=CH_2), 3.69 (2H, t, *J* 6.3, C*H*$_2$OTBS), 6.05 (1H, s, C=CH_2), 6.36 (1H, s, C=CH_2) and 9.52 (1H, s, CHO); δ_C(100 MHz) −5.4, 18.2, 25.8, 25.9, 31.4, 61.0, 135.9, 147.1 and 194.5. The aldehyde was characterized as the *semicarbazone derivative*: mp 167–168 °C (Found: C, 53.0; H, 9.3; N, 15.1. $C_{12}H_{25}N_3O_2Si$ requires C, 53.1; H, 9.3; N, 15.5%); δ_H(300 MHz) 0.04 (6H, s, $SiMe_2$), 0.88 (9H, s, $SiCMe_3$), 2.57 (2H, t, *J* 7.2, C*H*$_2$CH$_2$), 3.76 (2H, t, *J* 6.9, C*H*$_2$OTBS), 5.34 (1H, s, C=CH_2), 5.46 (1H, s, C=CH_2), 7.38 (1H, s, C=NH) and 8.90 (1H, s, NH); δ_C(75.5 MHz) −5.2, 18.3, 25.9, 34.3, 61.9, 123.0, 141.2, 144.3 and 157.2.

(+)-[4*S*(2′*S*,3′*S*)]-4-Benzyl-3-{4′-[2-(*tert*-butyldimethylsiloxy)ethyl]-3′-hydroxy-2′-methylpent-4′-enoyl}oxazolidin-2-one 28

To a solution of the oxazolidinone **27**[29] (1.80 mg, 7.72 mmol) in CH_2Cl_2 (26 cm^3) at 0 °C were added dropwise freshly distilled dibutylboryl triflate (2.24 cm^3, 8.91 mmol) and diisopropylethylamine (1.69 cm^3, 9.70 mmol) at a rate such that the internal temperature remained below 3 °C. The nearly colourless solution was cooled to −78 °C and a solution of aldehyde **26** (2.46 g, 12.2 mmol) in CH_2Cl_2 (8 cm^3) was added dropwise at −78 °C *via* cannula to the reaction mixture, which was stirred for 30 min. The mixture was then allowed to warm to 0 °C and was stirred for a further 1 h before being quenched by the addition of pH 7 phosphate buffer (11 cm^3), methanol (38 cm^3) and 2:1 methanol–30% aq. H_2O_2 (38 cm^3). The mixture was stirred at 0 °C for 1 h and extracted with diethyl ether (3 × 30 cm^3). The combined organic layers were washed successively with saturated aq. NH_4Cl and saturated aq. $NaHCO_3$, dried, concentrated, and purified by flash chromatography using 20% EtOAc–light petroleum as eluent to yield *oxazolidinone* **28** (2.42 g, 70%) as a viscous oil; $[\alpha]_D^{20}$ +114.6 (*c* 0.048, $CHCl_3$) (Found: C, 64.5; H, 8.1; N, 3.45. $C_{24}H_{37}NO_5Si$ requires C, 64.4; H, 8.3; N, 3.1%); ν_{max}(film)/cm^{-1} 3515 (OH), 2927, 2854, 1779 (CO), 1700 (CO), 1383, 1209 and 836; δ_H(300 MHz) 0.06 (6H, s, $SiMe_2$), 0.88 (9H, s, $SiCMe_3$), 1.28 (3H, d, *J* 6.9, Me), 2.16–2.28 (1H, m, C*H*$_2$C=CH$_2$), 2.32–2.42 (1H, m, C*H*$_2$C=CH$_2$), 2.74 (1H, d, *J* 9.6, C*H*$_2$Ph), 2.79 (1H, d, *J* 9.6, C*H*$_2$Ph), 2.91–3.01 (1H, m), 3.28 (1H, dt, *J* 12.9, 3.3, C*H*OH), 3.72–3.82 (2H, m, C*H*$_2$OTBS), 3.97–4.06 (1H, m), 4.17 (1H, d, *J* 5.1, OCH), 4.41 (1H, d, *J* 5.7, OCH), 4.61–4.71 (1H, m, NC*H*CH$_2$), 4.99 (1H, s, C=CH$_2$), 5.16 (1H, s, C=CH$_2$) and 7.18–7.39 (5H, m, ArH); δ_C(75.5 MHz) −5.5, −5.4, 8.2, 11.2, 25.9, 29.2, 30.7, 35.9, 41.9, 55.6, 63.4, 113.0, 127.5, 129.8, 129.9, 135.1, 146.3, 173.8 and 176.6; *m*/*z* (EI) 390 (M^+ − Bu′, 10%), 190 (16), 157 (51) and 75 (100).

(−)-(2*S*,3*S*)-4-[2-(*tert*-Butyldimethylsiloxy)ethyl]-3-hydroxy-*N*-methoxy-*N*,2-dimethylpent-4-enamide 29

A suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (1.37 g, 14.0 mmol) in CH_2Cl_2 (50 cm^3) was treated with $AlMe_3$ (7.14 cm^3, 14.3 mmol; 2.0 M solution in toluene) at 0 °C which resulted in the evolution of CH_4 gas. The clear solution was stirred at RT for 30 min and a solution of oxazolidinone **28** (2.10 g, 4.69 mmol) in CH_2Cl_2 (50 cm^3) was then cannulated into the reaction vessel at 0 °C. The resulting yellow solution was stirred at this temperature for 3.5 h and was then quenched with 100 cm^3 of 0.5 M aq. dipotassium tartrate. The mixture was stirred at RT for 2 h until the aqueous layer became clear. The aqueous layer was then extracted with CH_2Cl_2, the organic layer was washed successively with saturated aq. $NaHCO_3$ and brine, and the crude product was purified by flash chromatography using 30% EtOAc–light petroleum to give the *amide* **29** (1.33 g, 86%) as a gum; $[\alpha]_D^{20}$ −20.3 (*c* 0.19, $CHCl_3$) (Found: C, 57.7; H, 10.2, N, 4.2. $C_{16}H_{33}NO_4Si$ requires C, 58.0; H, 10.0; N, 4.2%); ν_{max}(film)/cm^{-1} 3515 (OH), 2927, 2854, 1779 (CO), 1770 (CO), 1468, 1383, 1288, 1248, 1209, 1081 and 836; δ_H(300 MHz) 0.06 (6H, s, $SiMe_2$) 0.88 (9H, s, CMe_3), 1.15 (3H, d, *J* 6.9, Me), 2.12–2.36 (2H, m, C*H*$_2$C=CH$_2$), 3.05 (1H, m, C*H*Me), 3.18 (3H, s, NMe), 3.68–3.80 (2H, m), 3.70 (3H, s, NOMe), 4.22 (1H, br s, OH), 4.32 (1H, d, *J* 5.4, OCH), 4.97 (1H, s, C=CH$_2$) and 5.20 (1H, s, C=CH$_2$); δ_C(75.5 MHz) −5.4, 11.2, 18.3, 25.9, 29.7, 35.9, 37.8, 61.5, 63.4, 74.2, 113.0, 145.6 and 177.4; *m*/*z* (EI) 331 (M^+, 1%), 274 (57) and 157 (33).

(−)-(2*S*,3*S*)-4-[2-(*tert*-Butyldimethylsiloxy)ethyl]-3-hydroxy-2-methyl-1-phenylpent-4-en-1-one 30

To a solution of amide **29** (244 mg, 0.736 mmol) in THF (8 cm^3) was added PhMgCl (2.21 cm^3, 4.42 mmol; 2.0 M solution in THF) dropwise at −78 °C. The reaction mixture was allowed to

warm to RT and was stirred for 16 h. The solution was diluted with diethyl ether (30 cm^3), and ice-cold 5% aq. HCl (15 cm^3) was added. The organic layer was washed successively with saturated aq. $NaHCO_3$ and brine, dried, concentrated, and purified by flash chromatography using 10% EtOAc–light petroleum as eluent to give *phenyl ketone* **30** (190 mg, 74%) as a clear oil; $[\alpha]_D^{20}$ −9.6 (*c* 0.44 in $CHCl_3$) (Found: C, 68.8; H, 9.3. $C_{20}H_{32}O_3Si$ requires C, 68.9; H, 9.25%); ν_{max}(film)/cm^{-1} 3403 (OH), 2923, 2855, 1679 (CO), 1603, 1469, 1254, 1093 and 835; δ_H(300 MHz) 0.06 (6H, s, $SiMe_2$), 0.88 (9H, s, $SiCMe_3$), 1.27 (3H, d, *J* 7.0, Me), 2.14–2.36 (2H, m, $CH_2C{=}CH_2$), 3.65–3.79 (3H, m, CH_2OTBS and 2-H), 3.90 (1H, d, *J* 3.2, OH), 4.48 (1H, br t, *J* 3.9, CHOH), 4.94 (1H, s, $C{=}CH_2$), 5.17 (1H, s, $C{=}CH_2$) and 7.41–7.95 (5H, m, ArH); δ_C(75.5 MHz) −5.4, 12.5, 18.2, 25.9, 35.9, 43.9, 63.7, 74.6, 113.9, 115.3, 128.4, 128.7, 129.6, 135.4, 146.6 and 204.8.

(4*S*,5*S*,6*RS*)-4-{1-[2-(*tert*-Butyldimethylsiloxy)ethyl]vinyl}-2,2,5-trimethyl-6-phenyl-1,3-dioxane 31

To a solution of ketone **30** (186 mg, 0.534 mmol) in ethanol (7 cm^3) was added $NaBH_4$ (40.4 mg, 1.07 mmol) at 0 °C and the solution was stirred for 30 min. The reaction mixture was concentrated, and diluted with diethyl ether (40 cm^3). Water (10 cm^3) was added at 0 °C, followed by the addition of ice-cold 2% HCl until the aqueous layer was acidic. The organic layer was washed successively with saturated aq. $NaHCO_3$ and brine, and dried to afford the corresponding diol (187 mg, 100%) as a clear oil which ^1H NMR analysis showed to be a 3:1 mixture of diastereoisomers. To a solution of this diol (143 mg, 0.40 mmol) in acetone (5 cm^3) were added 2,2-dimethoxypropane (2.25 cm^3, 29.8 mmol) and PPTS (10 mg, 0.04 mmol). The reaction mixture was stirred overnight at RT then was taken up in diethyl ether (20 cm^3)–water (10 cm^3). The organic layer was washed in turn with saturated aq. $NaHCO_3$ and brine. Purification of the crude product by flash chromatography using 3% EtOAc–light petroleum as eluent afforded *acetonide* **31** (127 mg, 81%) as a viscous oil (Found: C, 71.0; H, 10.0. $C_{23}H_{38}O_3Si$ requires C, 70.7; H, 9.8%); ν_{max}(film)/cm^{-1} 2952, 2855, 1377, 1251, 1098 and 835; δ_H(300 MHz) 0.10 (6H, s, $SiMe_2$), 0.54 (3H, *J* 7.1, Me), 0.95 (9H, s, $SiCMe_3$), 1.57 (3H, s, Me), 1.60 (3H, s, Me), 1.80–2.00 (1H, m, 5-H), 2.20–2.67 (2H, m, CH_2), 3.73–3.85 (2H, m, CH_2OTBS), 4.65 (1H, s, OCH), 4.98 (1H, s, $C{=}CH_2$), 5.19 (1H, d, *J* 0.9, OCH), 5.20 (1H, s, $CH{=}CH_2$) and 7.23–7.34 (5H, m, ArH). The minor isomer showed peaks at δ_H 0.09 (6H, s, $SiMe_2$), 0.81 (3H, d, *J* 6.8, Me), 0.94 (9H, s, $SiCMe_3$), 1.46 (3H, s, Me) and 1.50 (3H, s, Me); δ_C(75.5 MHz) −5.3, 5.4, 19.5, 26.0, 30.0, 35.8, 35.9, 62.8, 74.3, 74.5, 99.2, 110.7, 125.5, 126.8, 126.9, 128.0, 128.4 and 144.5; *m*/*z* (EI) 275 (M^+ − OTBDMS, 1%), 169 (24), 157 (34) and 129 (38).

(−)-(3*S*,4*R*)-2-[2-(*tert*-Butyldimethylsiloxy)ethyl]-4-methyl-5-phenylpent-1-en-3-ol 32

Li metal (40 mg, 5.76 mmol) was dissolved in liquid ammonia at −78 °C. To the blue solution was added a solution of the acetonide **31** (177 mg, 0.453 mmol) in THF (5 cm^3). After stirring of the mixture at −78 °C for 10 min, the reaction was quenched carefully with NH_4Cl until the blue colour had been discharged. The mixture was diluted with diethyl ether (20 cm^3) and stirred at R for 2.5 h. The suspension was filtered off through a filter aid, dried and concentrated. Purification by flash chromatography using 5% EtOAc–light petroleum as eluent afforded the *alcohol* **32** (147 mg, 97%) as a clear oil; $[\alpha]_D^{20}$ −18.0 (*c* 1.70, $CHCl_3$) (Found: C, 71.84; H, 10.23. $C_{20}H_{34}O_2Si$ requires C, 71.8; H, 10.2%); ν_{max}(film)/cm^{-1} 3440 (OH), 2949, 1453, 1251, 1188 and 836; δ_H(300 MHz) 0.07 (6H, s, $SiMe_2$), 0.88 (3H, d, *J* 6.6, Me), 0.90 (9H, s, $SiCMe_3$), 1.87–1.97 (1H, m, 4-H), 2.16–2.43 (2H, m, $CH_2C{=}CH_2$), 2.78 (1H, dd, *J* 13.4 and 5.6, CH_2Ph), 2.95 (1H, d, *J* 4.4, CH_2Ph), 3.63–3.83 (2H, m, CH_2OTBS), 3.88 (1H, br t, *J* 5.4, CHOH), 4.99 (1H, s, $C{=}CH_2$), 5.07 (1H, s, $C{=}CH_2$) and 7.14–7.31 (5H, m, ArH); δ_C(75.5 MHz) −5.5, −5.4, 14.0, 18.3, 25.9, 35.1, 39.2, 40.0, 64.0, 77.9, 112.9, 125.7, 128.2, 129.1, 141.2 and 148.9.

(−)-(1′*S*,2′*R*)-3-(1′-Benzyloxy-2′-methyl-3′-phenylpropyl)but-3-en-1-ol 33

To a solution of the alcohol **32** (475 mg, 1.42 mmol) in THF (6 cm^3) and DMF (3 cm^3) at 0 °C was added sodium hexamethyldisilazide (NaHMDS) (1.85 cm^3, 1.85 mmol; 1.0 M solution in THF). BnBr (0.253 cm^3, 2.13 mmol) was added and the solution was stirred overnight at RT. Diethyl ether and water were added and the organic fraction was washed successively with saturated aq. $NaHCO_3$ and brine, and dried. Removal of the solvent left a pale yellow oil, which was dissolved in THF (15 cm^3) and treated with TBAF (742 mg, 2.84 mmol) at 0 °C. After being stirred for 2 h at RT the reaction mixture was quenched with water and EtOAc. The organic fraction was washed in turn with saturated aq. $NaHCO_3$ and brine, dried, and concentrated. The crude product was purified by flash chromatography using 20% EtOAc–light petroleum as eluent to provide the *benzyl ether* **33** (351 mg, 80%) as an oil; $[\alpha]_D^{20}$ −123.9 (*c* 0.218, $CHCl_3$) (Found: C, 81.00; H, 8.7. $C_{21}H_{26}O_2$ requires C, 81.25; H, 8.4%); ν_{max}(film)/cm^{-1} 3379 (OH), 2925, 2866, 1599, 1492, 1450, 1203, 1027 and 745; δ_H(300 MHz) 0.91 (3H, d, *J* 6.6, Me), 1.96–2.08 (1H, m, 2′-H), 2.16–2.47 (4H, m), 2.70 (1H, dd, *J* 12.0 and 3.0, OH), 3.50 (1H, d, *J* 7.5, 1′-H), 3.65–3.85 (2H, CH_2OH), 4.28 and 4.59 (2H, ABq, *J* 12.0, 2-H), 5.15 (1H, s, $C{=}CH_2$), 5.17 (1H, d, *J* 1.2, $C{=}CH_2$) and 7.01–7.98 (10H, m, ArH); δ_C(75.5 MHz) 15.0, 35.1, 39.7, 61.5, 70.6, 86.5, 115.8, 125.7, 126.9, 127.8, 128.1, 128.3, 128.4, 129.0, 138.3, 140.7 and 144.1; *m*/*z* (CI) 311 (M^+ + H, 100%), 293 (61), 203 (61) and 111 (73).

(−)-(3*S*,4*R*)-3-Benzyloxy-2-(2-iodoethyl)-4-methyl-5-phenylpent-1-ene 34

To a solution of the alcohol **33** (244 mg, 0.786 mmol) in diethyl ether (5 cm^3)–acetonitrile (3.7 cm^3) were added imidazole (83 mg, 1.22 mmol), PPh_3 (231 mg, 0.88 mmol) and I_2 (224 mg, 0.88 mmol) in 3 portions over a period of 3 min. The resulting orange–brown solution was stirred at RT for 2 h. Diethyl ether and 1.5 M aq. $Na_2S_2O_3$ were added and the aqueous phase was extracted with diethyl ether. The organic fraction was washed in turn with saturated aq. $NaHCO_3$ and brine. Purification of the crude product by flash chromatography using 1.5% EtOAc–light petroleum as eluent afforded *iodide* **34** (274 mg, 82%) as a clear oil; $[\alpha]_D^{20}$ −40.8 (*c* 2.45, $CHCl_3$) (Found: C, 60.3; H, 6.1. $C_{21}H_{25}IO$ requires C, 60.0; H, 6.0%); δ_H(300 MHz) 0.93 (3H, d, *J* 6.6, Me), 1.88–2.02 (1H, m, 4-H), 2.29 (1H, d, *J* 9.3, $CH_2C{=}CH_2$), 2.34 (1H, d, *J* 9.3, $CH_2CH{=}CH_2$), 2.49–2.78 (2H, m, CH_2Ph), 3.29 (2H, t, *J* 7.5, CH_2I), 3.54 (1H, d, *J* 6.3, 3-H), 4.28 and 4.61 (2H, ABq, *J* 11.7, OCH_2Ph), 5.16 (1H, d, *J* 0.9, $C{=}CH_2$), 5.23 (1H, s, $C{=}CH_2$) and 7.00–7.41 (10H, m, ArH); δ_C(75.5 MHz) 2.9, 14.9, 35.7, 37.9, 39.9, 70.6, 85.5, 114.5, 125.8, 127.4, 127.7, 128.3, 128.7, 129.0, 138.6, 140.8 and 145.6; *m*/*z* (CI) 421 (M^+ + H, 5%), 313 (100), 293 (56) and 185 (55).

[1*S*(1α,3αβ,5α,7β)]-6,7-Dibenzyloxy-1-{3′-[(1″*S*,2″*R*)-1″-benzyloxy-2″-methyl-3″-phenylpropyl]but-3′-enyl}-3-hydroxymethyl-5-(methoxymethoxymethyl)-2,8-dioxabicyclo[3.2.1]octane 36

To a freeze–thaw-degassed (×3) solution of the iodide **34** (164 mg, 0.390 mmol) in diethyl ether (2.3 cm^3)–hexane (1.6 cm^3) under argon was added Bu′Li (0.505 cm^3, 0.858 mmol; 1.7 M solution in pentane) at −78 °C. After stirring of the mixture for 5 min, a solution of the lactone **24** (106 mg, 0.218 mmol) in freeze–thaw-degassed (×3) diethyl ether (2 cm^3)–hexane (1 cm^3) was added to the reaction vessel *via* cannula. The reaction mixture was stirred at −78 °C for 15 min after which time a precipitate had formed. After being stirred for 30 min at 0 °C the

reaction mixture was quenched with saturated aq. NH_4Cl and diluted with diethyl ether and the organic layer was washed in turn with saturated aq. $NaHCO_3$ and brine, and dried. Removal of the solvent left a yellow oil, which was purified by flash chromatography using 10–20% EtOAc–light petroleum as gradient eluent to give the addition product **35** (82 mg, 48%). The diastereoisomeric lactols **35** (44 mg, 56 μmol) were dissolved in methanol (2.0 cm^3) and treated with 0.6 cm^3 of 10% HCl. The resulting clear solution was stirred for 2 h at RT and the reaction was quenched by the dropwise addition of saturated aq. $NaHCO_3$ (10 cm^3) and extracted with diethyl ether. The organic layer was washed successively with saturated aq. $NaHCO_3$ and brine, dried, and concentrated to give an oil. The crude product was purified on silica gel with 20–40–60% EtOAc–light petroleum as gradient eluent to give the *bicycle* **36** (27 mg, 67%) as an oil (Found: C, 74.6; H, 7.6. $C_{45}H_{54}O_8$ requires C, 74.8; H, 7.5%); δ_H(400 MHz) (3:1 mixture of C-3 epimers) 0.86 (3H, d, *J* 4.8, Me), 1.54 (1H, dd, *J* 13.2 and 4.0, CH), 1.65 (1H, br s, OH), 1.82–2.04 (6H, m), 2.21–2.47 (3H, m), 2.63–2.69 (1H, m), 3.32 (3H, s, OMe), 3.45–3.54 (1H, m), 3.62–3.82 (3H, m), 3.89 (1H, d, *J* 1.6, C*H*OBn), 3.94 (1H, d, *J* 1.6, C*H*OBn), 4.18 (1H, d, *J* 12.0, OCH_2Ph), 4.33–4.39 (1H, m), 4.44–4.67 (6H, m), 5.00 (1H, s, C=CH_2), 5.03 (1H, s, C=CH_2 and 7.03–7.36 (20H, m, ArH). The minor isomer showed peaks at δ_H 0.87 (1H, d, *J* 4.8, Me), 3.35 (3H, s, OMe) and 4.19 (1H, d, *J* 12.0, OCH_2Ph); δ_C(100 MHz) 14.8, 14.9, 24.1, 24.5, 29.7, 31.2, 32.2, 35.5, 36.5, 37.7, 40.0, 55.4, 55.5, 64.2, 65.8, 68.4, 68.4, 69.5, 69.5, 70.3, 71.8, 72.2, 72.7, 77.3, 82.1, 82.2, 86.2, 86.4, 86.9, 88.3, 88.4, 90.0, 96.8, 96.9, 103.8, 104.2, 112.3, 125.7, 127.3, 127.6, 127.7, 127.8, 127.9, 127.9, 128.0, 128.1, 128.2, 128.4, 128.6, 129.1, 137.6, 137.8, 139.0, 144.1 and 146.72.

(−)-[1*S*(1α,3α,5α,6α,7β)]-6,7-Dibenzyloxy-1-{3′-[(1″*S*,2″*R*)-1″-benzyloxy-2″-methyl-3″-phenylpropyl]but-3′-enyl}-5-(methoxymethoxymethyl)-2,8-dioxabicyclo[3.2.1]octane-3-carboxylic acid methyl ester 37

To a stirred solution of the bicyclic alcohol **36** (27 mg, 37.3 μmol) in dry CH_2Cl_2 (2 cm^3) were added pyridine (0.016 cm^3, 187 μmol) and Dess–Martin periodinane (46 mg, 122 μmol) and the resulting suspension was stirred at RT for 4 h. Diethyl ether and water were added and the organic layer was stirred successively with 1.5 M aq. $Na_2S_2O_3$ and saturated aq. $NaHCO_3$ until two clear layers had formed. The organic layer was then washed with brine, dried, and concentrated to give the crude aldehyde. A solution of this crude aldehyde (25 mg, 34.7 μmol) in Bu′OH (3 cm^3) and 2-methylbut-2-ene (0.9 cm^3) was treated with $NaClO_2$ (232 mg, 2.56 mmol) and sodium dihydrogen orthophosphate (178 mg, 1.14 mmol) as a solution in 1.7 cm^3 of water and the reaction mixture was stirred overnight at RT. Diethyl ether and water were added and the organic layer was washed with brine, dried, and concentrated. Treatment of the crude acid with an excess of diazomethane followed by purification by preparative TLC using 20% EtOAc–light petroleum as the eluent afforded *methyl ester* **37** (17 mg, 61%) as an oil; $[a]_D^{20}$ −2.2 (*c* 0.59, $CHCl_3$) (Found: M^+, 750.3735. $C_{46}H_{54}O_9$ requires M, 750.3762); ν_{max}(film)/cm^{-1} 2922, 2851, 1733 (CO), 1451, 1178, 1045, 1026 and 737; δ_H(400 MHz) 0.86 (3H, d, *J* 6.8, Me), 1.93–2.38 (8H, m), 2.66 (1H, dd, *J* 13.4 and 5.6, CH_2Ph), 3.31 (3H, s, OMe), 3.47 (1H, d, *J* 3.6, 1″-H), 3.64 and 3.75 (2H, ABq, *J* 10.4, CH_2OCH_2OCH_3), 3.73 (3H, s, CO_2Me), 3.89 (1H, d, *J* 2.0, C*H*OBn), 3.93 (1H, d, *J* 2.0, C*H*OBn), 4.17 and 4.51 (2H, ABq, *J* 12.0, OCH_2Ph), 4.44 and 4.59 (2H, ABq, *J* 11.6, OCH_2Ph), 4.47–4.64 (4H, m), 4.89 (1H, dd, *J* 8.6 and 3.6, C*H*CO_2Me), 5.01 (1H, s, C=CH_2), 5.03 (1H, s, C=CH_2) and 7.02–7.37 (20H, m, ArH); δ_C(100 MHz) 14.4, 24.2, 33.2, 34.8, 37.2, 39.7, 51.9, 55.1, 67.9, 68.0, 70.0, 71.8, 72.5, 82.0, 85.8, 86.1, 89.2, 96.5, 104.2, 111.9, 125.3, 126.9, 127.3, 127.4, 127.5, 127.6, 127.8, 127.9, 128.1, 128.8, 137.0, 137.3, 138.7, 140.8, 146.2 and 171.1; *m*/*z* (EI) 675 (M^+ − CH_2OMOM, 4%), 303 (3), 247 (8), 181 (9), 141 (8) and 91 (100).

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