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Synthesis of the C1-side chain of zaragozic acid D and progress towards a total synthesis

Alan Armstrong,[a,b,*] Paul A. Barsanti,[a] Toby J. Blench[a,b] and Ron Ogilvie[c]

[a]*School of Chemistry, University of Nottingham, Nottingham NG7 2RD, UK*
[b]*Department of Chemistry, Imperial College, South Kensington, London SW7 2AY, UK*
[c]*Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK*

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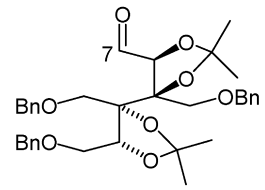
Abstract—A synthesis of a 1,3-dithiane corresponding to the C1-side chain of zaragozic acid D is described. An aldol reaction using an Evans oxazolidinone is the key step in controlling stereochemistry. Metallation of the derived dithiane monosulfoxide and coupling to an aldehyde effected construction of the C1–C7 bond. Subsequent steps are also reported, including acid-mediated ketalization resulting in formation of an advanced synthetic intermediate containing the bicyclic ketal core of the natural product.

1. Introduction

The zaragozic acids (squalestatins) (Fig. 1) are some of the most intensely studied synthetic targets of the last ten years.[1] They are potent inhibitors of squalene synthase, and therefore have potential as cholesterol-lowering drugs. They also inhibit the enzyme *ras*-farnesyl protein transferase, an enzyme of interest in the anti-cancer area. To synthetic chemists, additional interest is imparted by their complex and intriguing structure: in particular, the highly substituted 2,8-dioxabicyclo[3.2.1]octane core has stimulated the development of some highly inventive synthetic strategies.[1] We recently reported[2] a total synthesis of (+)-zaragozic acid C **2** in which a key step was coupling of the monosulfoxide derived from the dithiane **5** with the aldehyde **4**, obtained by double asymmetric dihydroxylation of an appropriately functionalised 1,3-diene. We wished to demonstrate that our strategy could potentially be applied to other members of the natural product series, and selected zaragozic acid D **3** as a suitable target. While total syntheses have been recorded for zaragozic acid A[3] (squalestatin S1) and zaragozic acid C,[4] as well as for zaragozic acid H5,[5] no synthetic studies have been reported to date on zaragozic acid D, which shows the most potent *ras*-farnesyl protein transferase inhibition in this natural product series.[6] The stereochemistry of the C1-side chain has not been unambiguously assigned, although it is reasonable to assume that the configuration will be the same as in the analogous stereocentres in **1** and **2**. Here we report the first synthesis of a C1-side chain **6** corresponding to the assumed configuration of zaragozic acid D, and preliminary studies that demonstrate that this can be advanced towards the natural product using our dithiane monoxide coupling approach.



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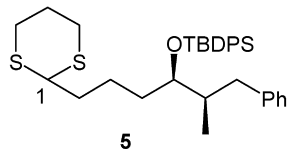

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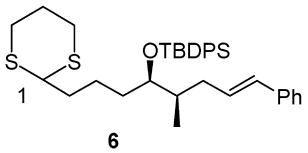

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2. Results and discussion

As in the synthesis of the zaragozic acid C C1-side chain,[2,4a] the key step to establishing the *syn*-stereochemistry in **6** was to be an Evans aldol reaction[7] between aldehyde **7** and an enolate bearing an oxazolidinone auxiliary. This was performed with the valine-derived oxazolidinone **8** in place of the phenylalanine-derived chiral auxiliary used

Keywords: aldol; acetal; 1,3-dithiane.

* Corresponding author. Address: Department of Chemistry, Imperial College, South Kensington, London SW7 2AY, UK. Tel.: +44-20-75945876; fax: +44-20-75945804; e-mail: a.armstrong@ic.ac.uk

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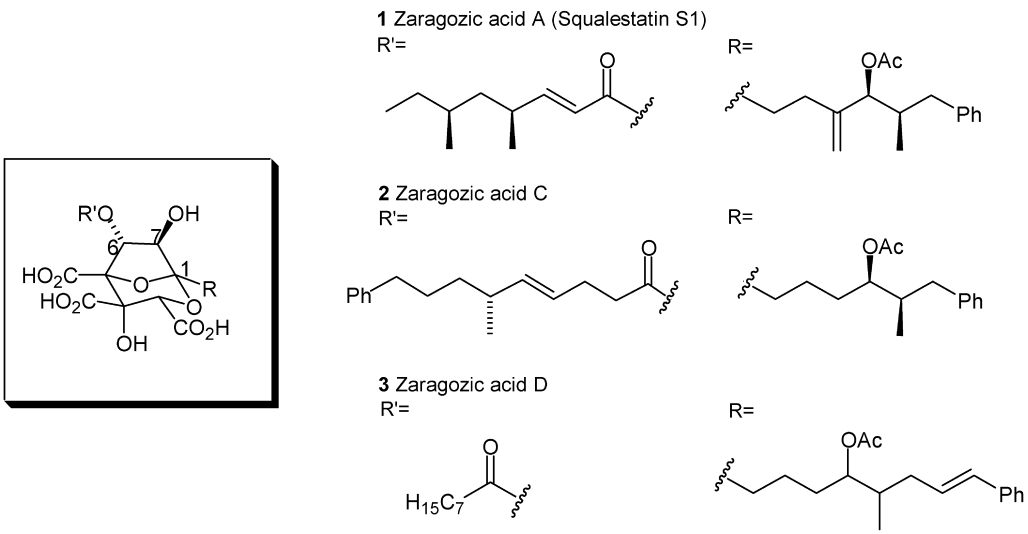
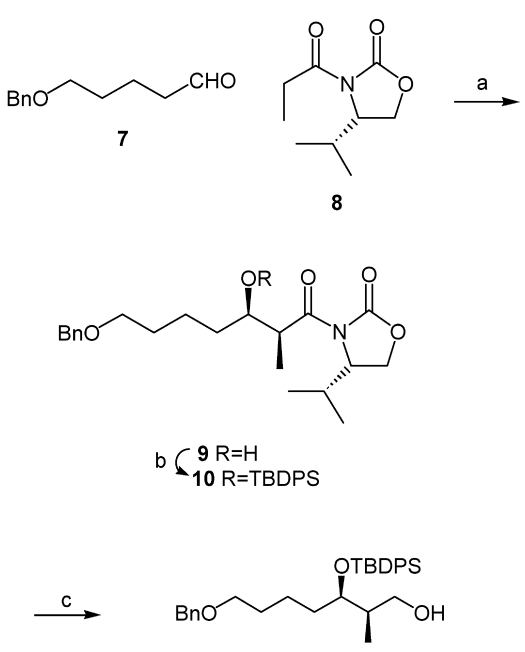


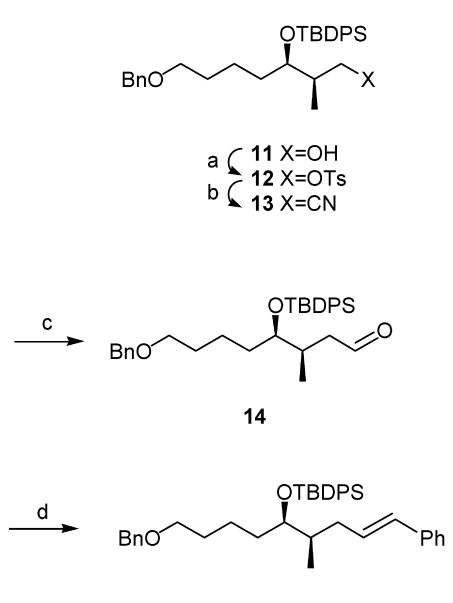
Figure 1. Representative zaragozic acids (squalestatins).

previously in the literature.[2,4a] Thus, treatment of **8** with Bu_2BOTf and Et_3N at −78°C followed by addition of aldehyde **7** gave the desired aldol product **9** in 88% yield and as a single diastereomer. Protection of the free secondary alcohol in **9** as the TBDPS ether **10** followed by reductive removal of the auxiliary led to the primary alcohol **11** (Scheme 1).

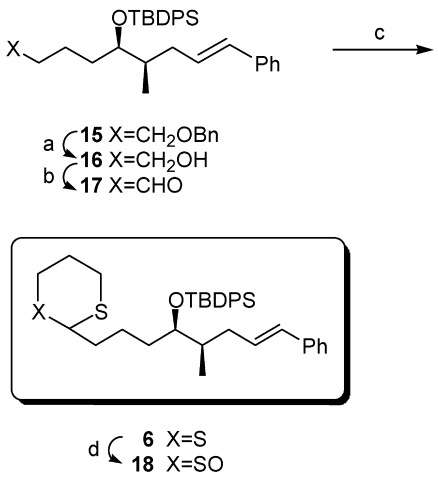
The next challenge in the synthesis was to introduce the *E*-alkene unit that is unique to the side chain of zaragozic acid D. Initial attempts focused on introducing this unit directly. Alcohol **11** was converted to tosylate **12** (Scheme 2). An initial attempt to displace the tosylate with the magnesio cuprate[8] derived from *trans*-β-bromostyrene resulted in no reaction. Another attempt using the higher order cuprate,[9] formed from the bromostyrene by treatment with ^{t}BuLi and CuCN, also resulted in no reaction. Displacement with lithium phenylacetylide was also unsuccessful. As an alternative approach, we envisaged one-carbon homologation to the aldehyde **14** and subsequent olefination as an appropriate route. Tosylate **12** was converted to nitrile **13**, reduction of which (DIBAL-H) and hydrolysis of the intermediate imine gave the desired aldehyde **14**. Several alternatives were investigated for olefination of **14**. Wittig olefination with benzyltriphenylphosphonium bromide/PhLi in ether gave the desired product in good yield (97%) but poor stereoselectivity (1.6:1 *E*/*Z*). Julia olefination with benzylphenyl sulfone also afforded disappointing selectivity (2.6:1 *E*/*Z*). Better results were ultimately achieved using a recently reported[10] modification of the Wadsworth–Emmons olefination. Thus, addition of a mixture of aldehyde **14** and diethyl



Scheme 1. *Reagents and conditions*: (a) **8**, Bu_2BOTf, Et_3N, CH_2Cl_2, −78°C, then **7**, 88%; (b) TBDPSCl, imidazole, DMF, 81%; (c) $LiBH_4$, MeOH, THF, 0°C, 62%.



Scheme 2. *Reagents and conditions*: (a) TsCl, pyridine, CH_2Cl_2, 89%; (b) NaCN, DMSO, 60°C, 98%; (c) DIBAL-H, CH_2Cl_2, −78°C, then H_3O^+, 74%; (d) diethyl benzylphosphonate, NaH, 15-C-5, THF, 0°C to rt, 77%.



Scheme 3. *Reagents and conditions*: (a) $BCl_3{\cdot}SMe_2$, CH_2Cl_2, 95%; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 94%; (c) propane-1,3-dithiol, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 100%; (d) *m*CPBA, CH_2Cl_2, 0°C, 76%, ca. 5:1 *trans*/*cis*.

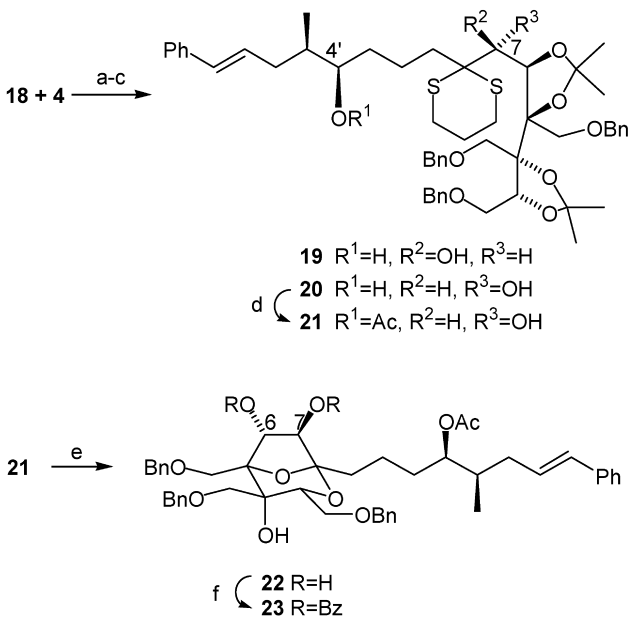
benzylphosphonate to a slurry of NaH in THF containing catalytic amounts of 15-crown-5 afforded *E*-alkene **15** in good yield (77%), in which the *Z*-isomer could not be detected by ^{1}H NMR spectroscopy.

Now that the *E*-alkene had been installed, all that remained was to introduce the dithiane unit at the other end of the molecule. This was done in an efficient four-step process (Scheme 3). Removal of the benzyl protecting group was achieved by exposure of **15** to $BCl_3{\cdot}SMe_2$ in CH_2Cl_2[11] to give the primary alcohol **16**. Dess–Martin oxidation of **16** to aldehyde **17** and subsequent dithiane formation with propane-1,3-dithiol and catalytic $BF_3{\cdot}OEt_2$ gave **6** in quantitative yield (Scheme 3). Overall, then, an efficient and stereocontrolled synthesis of the C1-side chain **6** of zaragozic acid D had been achieved.

2.1. Coupling to the core aldehyde 4

Now that the C1-side chain **6** had been successfully synthesised, its coupling with the core aldehyde **4** could be studied. As with the simpler dithiane **5**, we experienced problems in effecting metallation of **6**, despite examining a range of bases, solvents and additives. In line with our earlier work,[2] we therefore elected to oxidise the dithiane **6** to the monosulfoxide **18** in order to increase the acidity of the protons α- to sulfur. This was achieved by treatment of **6** with *m*CPBA in CH_2Cl_2 at 0°C to give the monosulfoxide **18** (76%) as a mixture of all four possible diastereomers, which appeared as two major separable spots by TLC. In accord with our findings for the zaragozic acid C side chain,[2] we assigned the minor, less polar spot as the two *cis* isomers (sulfoxide oxygen *cis* with respect to the substituent on the 2-position of the 1,3-dithiane ring), and the major spot as the *trans* isomers. The major, *trans* isomers were carried through the synthesis.

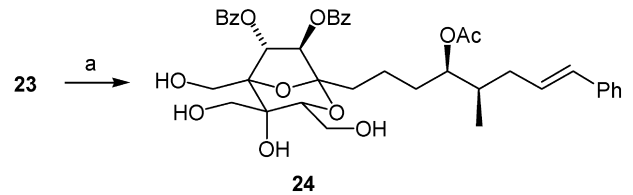
Aldehyde **4** was synthesised as previously reported.[2] The coupling of the two partners and conversion to the bicyclic ketal **22** was performed in a manner analogous to our zaragozic acid C synthesis[2] (Scheme 4). Thus, 3 equiv. of the monosulfoxide **18** in THF were treated with 3.1 equiv. ^{n}BuLi at low temperature to form the corresponding anion, followed by dropwise addition of 1 equiv. of the aldehyde **4**,



Scheme 4. *Reagents and conditions*: (a) 3 equiv. **18**, 3.1 equiv. ^{n}BuLi, THF, −78°C, then 1 equiv. **4**, THF, −78°C; (b) P_2I_4, Et_3N, CH_2Cl_2; (c) TBAF, THF, 80°C, 12% **20** from **4**; (d) Ac_2O, cat. DMAP, pyridine, 65°C, 69%; (e) 20:10:1 CH_2Cl_2/TFA/H_2O, 78%; (f) BzCl, cat. DMAP, pyridine, 98%.

also in THF (Scheme 4). After chromatographic removal of the excess of unreacted side chain, treatment of the complex mixture of diastereomeric adducts with 0.55 equiv. of P_2I_4 in the presence of Et_3N[12] gave the dithiane as an inseparable mixture of the two C7 epimers. Removal of the silyl protecting group on the C4′-alcohol by treatment with TBAF in THF at 80°C allowed chromatographic separation. The more polar of the two diastereomers (12% over **3** steps from **4**) was tentatively assigned as having the desired C7-configuration **20** by analogy to the relative polarity of the two corresponding C7-epimers in our zaragozic acid C work.[2] This assumption proved to be correct (vide infra). The other diastereomer **19** (ca. 17%) could not be isolated pure since it co-ran with an isomeric material tentatively assigned as resulting from acetonide migration. Selective acetylation of the C4′-hydroxyl in **20** was effected by exposure to acetic anhydride and DMAP in pyridine at 65°C, to give **21** in 69% yield, with no evidence of formation of the diacylated product.

The stage was now set for the key ketalisation step. Treatment of **21** with 20:10:1 CH_2Cl_2/TFA/H_2O, the conditions developed by Evans,[4b] resulted in the formation of the desired bicyclic ketal **22** in a good yield (78%) (Scheme 5). As in our earlier work, this reaction cascade involved remarkably facile removal of the 1,3-dithiane and acetonide protecting groups as well as selective ketalisation. Bis-benzoylation then afforded **23**. The assignment of



Scheme 5. *Reagents and conditions*: (a) $BCl_3{\cdot}SMe_2$, 24 h, CH_2Cl_2, 65%.

structure to the desired ketal **23** was made by comparison with the corresponding zaragozic acid C intermediate. The ^{1}H NMR spectrum was very similar to those obtained previously, and displayed the key coupling between H6 and H7 of 2–3 Hz which is characteristic for the correct C6/C7 stereochemistry and the correct ketal isomer.

Completion of a total synthesis would require conversion of the three benzyloxy groups in **23** to the triacid unit of the natural product. In our zaragozic acid C work,[2] the triple deprotection of the three benzyl ethers was achieved by hydrogenolysis. However, the presence of the alkene in the C1 side chain was likely to preclude this for **23**, so Lewis acid methods were examined. Pleasingly, good results were obtained by reaction with a large excess of $BCl_3{\cdot}SMe_2$ for 24 h, leading to formation of the desired alcohol **24** in 65% yield (Scheme 5). The ^{1}H NMR spectrum clearly showed that the alkene in the C1 side chain remained intact. While **24** has not been progressed any further towards the natural product **1**, we have therefore demonstrated that the side chain alkene will withstand most of the important synthetic transformations that are required for a total synthesis. Triple oxidation of the alcohols to the acid level and, after suitable protecting group manipulation, selective attachment of the C6 acyl side chain has good precedent in our earlier work.[2]

3. Conclusions

We have accomplished a synthesis of the dithiane **6** which corresponds to the C1-side chain of zaragozic acid D. We have also demonstrated that this dithiane is compatible with many of the key synthetic steps needed to complete a total synthesis of the natural product, and have successfully prepared an advanced synthetic intermediate.

4. Experimental

4.1. General procedures

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400, Bruker DRX 400, Bruker DRX 500 or JEOL GX-270 NMR spectrometer using residual protic solvent ($CHCl_3$, δ_H=7.26 ppm), tetramethylsilane (δ_H=0 ppm) or $CDCl_3$ (δ_C=77.0 ppm, t) as internal reference. The multiplicities in ^{13}C spectra were determined by DEPT experiments. Infrared spectra were run on a Perkin–Elmer 1605 FT-IR or a Mattson Satellite FT-IR machine from 4000–600 cm^{-1}. Mass spectra were recorded under the conditions stated on either a VG Autospec or a VG 70E. Microanalyses were performed at the University of Nottingham. Optical rotations were measured on either a JASCO DIP 370 digital or an Optical Activity Polarimeter. Melting points were measured on Laboratory Devices Mel-Temp II and are uncorrected. Column chromatography was performed on Merck Kiselgel 60 (230–400 mesh). Diethyl ether and tetrahydrofuran solvents were distilled from sodium-benzophenone ketyl; dichloromethane from calcium hydride and dimethyl formamide from anhydrous magnesium sulfate. Petrol refers to petroleum ether of boiling range 40–60°C which was distilled prior to use. All other reagents were used as purchased unless stated otherwise. Analytical thin layer chromatography was performed using pre-coated glass-backed plates (Merck Kiselgel 60 F254) and visualised by ultra-violet light and potassium permanganate, acidic ammonium molybdate or anisaldehyde as appropriate.

4.1.1. Preparation of (4*S*,2′*R*,3′*R*)-3-(7-benzyloxy-3′-hydroxy-2′-methylheptanoyl)-4-isopropyl-oxazolidin-2-one 9. To a solution of **8** (18.5 g, 100 mmol) in CH_2Cl_2 (260 mL) at −78°C was added Bu_2BOTf (105 mL, 105 mmol, 1 M in CH_2Cl_2, 1.05 equiv.) and Et_3N (15.9 mL, 115 mmol, 1.15 equiv.) dropwise under nitrogen. The solution was allowed to 0°C and stirred for 50 min. The solution was re-cooled to −78°C and then a solution of aldehyde **7** (21.2 g, 110 mmol, 1.1 equiv.) in CH_2Cl_2 (70 mL) at −78°C was added via cannula over 1 h. The mixture was stirred at −78°C for 1.5 h and then allowed to come to rt and stirred for a total of 16 h. The reaction was quenched at 0°C with pH 7 phosphate buffer (100 mL) and MeOH (270 mL). A mixture of 2:1 MeOH/30% H_2O_2 (270 mL) was added and the solution allowed to come to rt over 1.5 h. The mixture was poured onto water and the organics separated. The aqueous was extracted with CH_2Cl_2 (×2) and the combined organics were dried ($MgSO_4$) and the solvent removed to yield a pale yellow oil. The crude mixture was purified by flash chromatography (35–45% ethyl acetate/petrol) to yield the title compound **9** (33.2 g, 88%) as a colourless oil; $[\alpha]_D^{21}$=+48.9 (*c* 0.96, $CHCl_3$); ν_{max} (film) 3524, 2939, 2866, 1778, 1696, 1454, 1386, 1300, 1204, 1105, 990, 738 and 700 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36–7.24 (5H, m, Ph), 4.49 (2H, s, PhCH_2O), 4.47–4.43 (1H, m, NCH(^{i}Pr)), 4.27 (1H, t, *J*=9.0 Hz, one of CH(^{i}Pr)CH_2O), 4.20 (1H, dd, *J*=3.0, 9.0 Hz, one of CH(^{i}Pr)CH_2O), 3.95–3.91 (1H, m, CH_2CH(OH)), 3.74 (1H, dq, *J*=2.5, 7.0 Hz, CH(CH_3)C=O), 3.47 (2H, t, *J*=6.5 Hz, BnOCH_2), 3.05 (1H, br s, OH), 2.37–2.29 (1H, m, CH_3CHCH_3), 1.68–1.51 (4H, m, $BnOCH_2CH_2CH_2$-CH_2), 1.46–1.35 (2H, m, $BnOCH_2CH_2CH_2CH_2$), 1.23 (3H, d, *J*=7.0 Hz, CH(CH_3)C=O), 0.91 (3H, d, *J*=7.0 Hz, one of CH_3CHCH_3), 0.87 (3H, d, *J*=7.0 Hz, one of CH_3-$CHCH_3$); δ_C (100 MHz, $CDCl_3$) 177.8 (s), 153.3 (s), 138.6 (s), 128.4 (d), 127.6 (d), 127.5 (d), 72.9 (t), 71.1 (d), 70.2 (t), 63.3 (t), 58.2 (d), 42.0 (d), 33.5 (t), 29.6 (t), 28.3 (d), 22.7 (t), 17.9 (q), 14.7 (q), 10.7 (q); *m*/*z* (FAB+) 378 (M+H, 41), 360 (7), 270 (10), 231 (3), 184 (2), 154 (5), 147 (2), 141 (13); observed 378.2288, $C_{21}H_{32}NO_5$ (M+H) requires 378.2280.

4.1.2. Preparation of (4*S*,2′*R*,3′*R*) 3-[7-benzyloxy-3′-(*tert*-butyldiphenylsilanyloxy)-2′-methylheptanoyl]-4-isopropyloxazolidin-2-one 10. To a solution of alcohol **9** (47.1 g, 125 mmol) in DMF (80 mL) was added imidazole (25.5 g, 375 mmol) and TBDPSCl (52 mL, 200 mmol, 1.6 equiv.) under nitrogen. The solution was stirred for 23 h and then poured onto saturated aqueous NH_4Cl. The mixture was extracted with ether (×3) and the combined organics were washed successively with 2 M HCl (×1), water (×1), brine (×1), dried ($MgSO_4$) and the solvent removed to yield a cloudy yellow oil. The crude mixture was purified by flash chromatography (10–20–50% ether/hexane) to yield the title compound (62 g, 81%) as a colourless oil; $[\alpha]_D^{21}$=+27.9 (*c* 0.86, $CHCl_3$); ν_{max} (film) 2933, 1778, 1704, 1589, 1454, 1428, 1384, 1300, 1203, 1105, 822, 739, 702 and 613 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.68–7.64 (4H, m, Ph), 7.45–7.26

(11H, m, Ph), 4.42 (2H, s, PhCH_2O), 4.18–4.14 (2H, m, CH_2CH(OSi)CH(CH_3) and NCH(^{i}Pr)), 4.08 (1H, dd, J=2.0, 9.0 Hz, one of CH(^{i}Pr)CH_2O), 3.93 (1H, t, J=9.0 Hz, one of CH(^{i}Pr)CH_2O), 3.87 (1H, m, CH(OSi)CH(CH_3)), 3.28 (2H, t, J=6.5 Hz, BnOCH_2), 2.41–2.37 (1H, m, $CH_3CH$$CH_3$), 1.55–1.46 (2H, m, $BnOCH_2CH_2CH_2CH_2$), 1.39–1.32 (2H, m, $BnOCH_2CH_2CH_2$), 1.28–1.19 (2H, m, $BnOCH_2CH_2CH_2$-CH_2), 1.27 (3H, d, J=70.0 Hz, CH(OSi)CH(CH_3)), 1.07 (9H, s, ^{t}Bu), 0.88 (3H, d, J=7.0 Hz, one of CH_3CHCH_3), 0.83 (3H, d, J=7.0 Hz, one of CH_3CHCH_3); δ_C (100 MHz, $CDCl_3$) 174.8 (s), 153.6 (s), 138.7 (s), 136.1 (d), 136.0 (d), 134.6 (s), 133.8 (s), 129.6 (d), 129.5 (d), 128.3 (d), 127.6 (d), 127.5 (d), 127.4 (d), 127.4 (d), 73.5 (d), 72.8 (t), 70.1 (t), 63.0 (t), 58.8 (d), 42.3 (d), 35.0 (t), 29.6 (t), 28.0 (d), 27.0 (q), 21.4 (t), 19.5 (s), 18.1 (q), 14.5 (q), 11.0 (q); m/z (FAB+) 616 (M+, 6), 558 (28), 538 (17), 390 (7), 360 (18), 346 (7), 323 (7), 289 (3), 261 (6), 252 (3); observed 615.3385, $C_{37}H_{49}NO_5Si$ (M+) requires 615.3380.

4.1.3. Preparation of (2*R*,3*R*)-7-(benzyloxy)-3-(*tert*-butyldiphenylsilyloxy)-2-methylheptanol 11.[4a] To a solution of **10** (32 g, 52 mmol) in THF (220 mL) at 0°C was added MeOH (8.1 mL, 208 mmol, 4 equiv.) then $LiBH_4$ (104 mL, 208 mmol, 2 M in THF, 4 equiv.) dropwise over 40 min. The solution was allowed to come to rt and then stirred for 30 min. A further 8.1 mL of MeOH was added and the solution stirred for 30 min. Another 8.1 mL of MeOH was added, the solution stirred for 10 min and then poured onto saturated aqueous Rochelle's salt (250 mL). Sufficient 2 M HCl was added to dissolve the salts, the mixture was extracted with ether (×3). The combined organics were washed with water (×1), brine (×1), dried ($MgSO_4$) and the solvent removed to yield a colourless oil. The crude mixture was purified by flash chromatography (35% ether/hexane) to yield the alcohol **11** (30.4 g, 62%) as a colourless oil; δ_H (400 MHz, $CDCl_3$) 7.72 (4H, m, Ph), 7.45–7.25 (11H, m, Ph), 4.39 (2H, s, $CH_2OC$$H_2$Ph), 3.85–3.79 (1H, m, CH_2CH(OSi)CH(CH_3)), 3.65 (1H, t, J=9.2 Hz, OH), 3.56–3.43 (1H, m), 3.30–3.17 (2H, m), 1.95–1.82 (2H, m), 1.60–1.07 (15H, m, includes 1.05 (9H, s, ^{t}Bu)). 0.83 (3H, d, J=6.9 Hz, CH(OSi)CH(CH_3)). Data consistent with those reported in the literature.[4a]

4.1.4. Preparation of (2*R*,3*R*)-7-(benzyloxy)-3-(*tert*-butyldiphenylsilyloxy)-2-methylheptanol *p*-toluenesulfonate 12. To a stirred solution of alcohol **11** (68 mg, 0.14 mmol) in CH_2Cl_2 (0.3 mL) was added *p*-toluenesulfonyl chloride (40 mg, 0.21 mmol), followed by pyridine (34 μL, 0.42 mmol). After one day, the mixture was partitioned between 2 M HCl (1 mL) and CH_2C1_2 (5 mL). The organics were separated and the aqueous layer extracted with CH_2Cl_2 (3×5 mL). The organics were combined and washed with 30% aqueous $CuSO_4$ solution (1×10 mL), H_2O (3×10 mL), saturated brine (3×10 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (30% ether/petrol) to give the tosylate **12** (80 mg, 89%) as a clear oil, $[\alpha]_D^{21}$=−5.6 (c 0.93 in $CHCl_3$); ν_{max} (film) 3068, 2931, 2857, 1598, 1495, 1455, 1428, 1363, 1189, 1177, 1110, 1044, 968, 816, 741, 703 and 666 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.66 (2H, d, J=8.3 Hz, Ar), 7.53–7.50 (4H, m, Ar), 7.39–7.17 (13H, m, Ar), 4.30 (2H, s, $CH_2OC$$H_2$Ph), 3.98 (1H, dd, J=9.3, 6.4 Hz), 3.90–3.84 (1H, m), 3.62–3.58 (1H, m, $CH_2C$$H$(OSi)CH($CH_3$)), 3.16–3.08 (2H, m), 2.36 (3H, s, $SO_2ArC$$H_3$), 1.88–1.81 (1H, m, CH_2CH(OSi)CH(CH_3)), 1.40–0.84 (15H, m, includes 0.87 (9H, s, ^{t}Bu), 0.81 (3H, d, J=6.9 Hz, CH(OSi)CH(CH_3)); δ_C (100 MHz, $CDCl_3$) 145.1 (s), 139.1 (s), 136.5 (d), 135.0 (s), 134.0 (s), 133.7 (s), 130.4 (d), 130.3 (d), 130.1 (d), 128.9 (d), 128.5 (d), 128.2 (d), 128.2 (d), 128.1 (d), 128.0 (d), 77.8 (d), 73.9 (d), 13.8 (t), 73.4 (t), 70.5 (t), 34.1 (t), 29.9 (t), 27.6 (q), 22.8 (t), 22.2 (q), 20.0 (s), 10.9 (q); m/z (+FAB) 643 $(M-H)^+$, 473, 443, 419, 389, 353, 333, 293, 273, 217, 197, 183, 135, 121, 109, 91, 71; found: C, 70.8; H, 7.6. $C_{38}H_{48}O_5SSi$ requires C, 70.8; H, 7.5%.

4.1.5. Preparation of (3*R*,4*R*)-8-(benzyloxy)-4-(*tert*-butyldiphenylsilyloxy)-3-methyloctanitrile 13. To a solution of tosylate **12** (51.8 g, 80 mmol) in DMSO (320 mL) was added NaCN (4.72 g, 96 mmol, 1.2 equiv.) under nitrogen. The mixture was stirred at 60°C for 20 h, allowed to come to rt, poured onto water and then extracted with ether (×4). The combined organics were washed with brine (×1), dried ($MgSO_4$) and the solvent removed to yield a colourless oil. The crude mixture was purified by flash chromatography (20–25% ether/petrol) to yield the nitrile **13** (39.3 g, 98%) as a colourless oil; $[\alpha]_D^{22}$=−8.76 (c 1.37, $CHCl_3$); ν_{max} (film) 3070, 2932, 2858, 2246, 1589, 1454, 1428, 1387, 1361, 1189, 1110, 1027, 822, 741, 703 and 614 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.69–7.66 (4H, m, Ph), 7.47–7.26 (11H, m, Ph), 4.41 (2H, s, PhCH_2O), 3.69 (1H, dt, J=2.5, 6.5 Hz, $CH_2C$$H$(OSi)CH($CH_3$)), 3.26 (2H, app. dt, J=1.5, 6.5 Hz, BnOCH_2), 2.43 (1H, dd, J=5.8, 16.6 Hz, one of CH(CH_3)CH_2CN), 2.27 (1H, dd, J=8.9, 16.6 Hz, one of CH(CH_3)CH_2CN), 2.02–1.95 (1H, m, CH(OSi)CH(CH_3)CH_2), 1.50–1.31 (4H, m, $BnOCH_2C$$H_2$-$CH_2CH_2$), 1.18–1.08 (2H, m, $BnOCH_2CH_2C$$H_2CH_2$), 1.06 (9H, s, ^{t}Bu), 1.03 (3H, d, J=7.0 Hz, CH(OSi)CH(CH_3)); δ_C (100 MHz, $CDCl_3$) 138.5 (s), 135.9 (d), 135.8 (d), 134.1 (s), 133.3 (s), 129.9 (d), 129.7 (d), 128.3 (d), 127.8 (d), 127.6 (d), 127.5 (d), 119.6 (s), 75.1 (d), 72.8 (t), 69.9 (t), 35.2 (d), 33.1 (t), 29.4 (t), 27.1 (q), 22.3 (t), 21.1 (t), 19.5 (s), 13.4 (q); m/z (FAB+) 500 (M+H, 10), 442 (4), 364 (5), 274 (46), 254 (7), 244 (5), 199 (14); observed 500.2995, $C_{32}H_{42}NO_2Si$ (M+H) requires 500.2984.

4.1.6. Preparation of (3*R*,4*R*)-8-(benzyloxy)-4-(*tert*-butyldiphenylsilyloxy)-3-methyloctanal 14. To a solution of **13** (19.7 g, 39 mmol) in CH_2Cl_2 (390 mL) at −78°C was added DIBAL-H (46.8 mL, 46.8 mmol, 1 M in CH_2Cl_2, 1.2 equiv.) dropwise under nitrogen over 35 min. The reaction was stirred for 1 h and then quenched with MeOH (15 mL). The mixture was allowed to come to rt, saturated aqueous NH_4Cl (ca. 100 mL) was added and the mixture stirred vigorously for 20 min. 5% H_2SO_4 (10 mL) and then the mixture was extracted with CH_2Cl_2 (×2). The combined organics were washed with brine (×1), dried ($MgSO_4$) and the solvent removed to yield a yellow oil. The crude mixture was purified by flash chromatography (25% ether/petrol) to yield the aldehyde **14** (14.5 g, 74%) as a colourless oil; $[\alpha]_D^{21}$=−27.6 (c 0.58, $CHCl_3$); ν_{max} 3070, 2933, 2858, 2715, 1961, 1892, 1824, 1725, 1589, 1455, 1427, 1382, 1362, 1110, 1043, 822, 740, 703 and 613 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.58 (1H, s, CHO), 7.68–7.66 (4H, m, Ph), 7.45–7.26 (11H, m, Ph), 4.43 (2H, s, PhCH_2O), 3.65 (1H, dt, J=2.3, 6.0 Hz, $CH_2C$$H$(OSi)CH($CH_3$)), 3.28 (2H,

app. dt, J=2.5, 6.5 Hz, BnOCH_2), 2.60 (1H, d, J=13.0 Hz, one of CH(CH$_3$)CH_2CHO), 2.30–2.18 (2H, m, one of CH(CH$_3$)CH_2CHO and CH(CH$_3$)CH$_2$CHO), 1.48–1.32 (4H, m, BnOCH$_2$CH_2CH$_2$CH_2), 1.29–1.12 (2H, m, BnOCH$_2$CH$_2$CH_2CH$_2$), 1.07 (9H, s, ^{t}Bu), 0.87 (3H, d, J=5.5 Hz, CH(OSi)CH(CH_3); δ_C (100 MHz, CDCl$_3$) 202.8 (d), 138.6 (s), 136.0 (d), 134.8 (s), 134.4 (s), 133.9 (s), 129.7 (d), 129.6 (d), 128.3 (d), 127.6 (d), 127.5 (d), 127.4 (d), 76.3 (d), 72.8 (t), 70.1 (t), 47.2 (t), 33.0 (t), 32.4 (d), 29.6 (t), 27.1 (q), 22.6 (t), 19.5 (s), 14.5 (q); m/z (CI, NH$_4$) 520 (M+NH$_4$, 100), 503 (M+H, 34), 274 (11), 264 (52), 256 (2), 247 (62) 216 (6), 196 (7); observed 503.2985, $C_{32}H_{43}O_3Si$ (M+H) requires 503.2981.

4.1.7. Preparation of (5*R*,6*R*,8*E*)-*O*-benzyl-5-(*tert*-butyldiphenylsilyloxy)-6-methyl-9-phenylnon-8-enol 15. To a cooled (0°C), stirred slurry of NaH (142 mg at 95%, 5.61 mmol) in THF (5 m1) containing 15-crown-5 (0.2 mL, 0.56 mmol) was added a pre-mixed solution of aldehyde **14** (1.41 g, 2.81 mmol) and diethyl benzylphosphonate (0.88 mL, 4.21 mmol) in THF (15 mL). The reaction was allowed to warm to rt and stirred for a further 1 h 20 min. The contents were then poured into 2 M NaOH (10 mL) and extracted with CH_2Cl_2 (4×10 mL). The organics were combined and washed with H_2O (1×10 mL), saturated aqueous brine (3×10 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (20% ether/petrol) to give the alkene **15** (1.69 g, 77%) as a clear oil, $[\alpha]_D^{29}$=+29.0 (c 0.94, CHCl$_3$); ν_{max} (film) 3068, 3026, 2931, 2856, 1589, 1495, 1472, 1454, 1427, 1379, 1361, 1307, 1259, 1189, 1110, 1072, 1028, 966, 939, 821, 740, 702 and 666 cm^{-1}; δ_H (270 MHz, CDCl$_3$) 7.71–7.50 (4H, m, Ph), 7.42–7.18 (16H, m, Ph), 6.27 (1H, d, J=15.8 Hz, CH$_2$CH=CHPh), 6.10–5.95 (1H, m, CH$_2$-CH=CHPh), 4.40 (2H, s, PhCH_2OCH$_2$), 3.70–3.61 (1H, m, CH$_2$CH(OSi)CH(CH$_3$)), 3.26 (2H, t, J=6.5 Hz, PhCH$_2$-OCH_2), 2.50–2.38 (1H, m, CH_2CH=CHPh), 2.12–1.98 (1H, m, CH_2CH=CHPh), 1.80–1.60 (1H, m, CH(OSi)CH(CH$_3$)CH$_2$), 1.53–1.00 (15H, m, includes 1.06 (9H, s, ^{t}Bu)), 0.87 (3H, d, J=6.9 Hz, CH(OSi)CH(CH_3)); δ_C (67.5 MHz, CDCl$_3$) 138.9 (s), 138.1 (s), 136.3 (d), 135.1 (s), 134.6 (s), 131.1 (d), 130.4 (d), 129.7 (d), 129.6 (d), 128.6 (d), 128.5 (d), 127.8 (d), 127.7 (d), 127.6 (d), 127.0 (d), 126.1 (d), 76.5 (d), 73.0 (t), 70.4 (t), 38.0 (d), 36.7 (t), 33.6 (t), 29.8 (t), 27.4 (q), 22.8 (t), 19.8 (s), 14.2 (q); m/z (+FAB) 577 (M+H), 549, 399, 369, 351, 281, 221, 199, 183, 137, 117, 91; found: C, 81.4; H, 8.6. $C_{39}H_{48}O_2Si$ requires C, 81.2; H, 8.4%.

4.1.8. Preparation of (5*R*,6*R*,8*E*)-5-(*tert*-butyldiphenylsilyloxy)-6-methyl-9-phenylnon-8-enol 16. To a stirred solution of **15** (56 mg, 0.10 mmol) in CH_2Cl_2 (1.0 mL) was added boron trichloride–dimethyl sulfide complex (315 μL, 2 M solution in CH_2Cl_2, 0.63 mmol) dropwise over 4 min. After 1.5 h the mixture was quenched by addition of saturated aqueous NaHCO$_3$ (5 mL) and diluted with CH_2Cl_2 (5.0 mL). The organics were separated and the aqueous layer extracted with CH_2C1_2 (4×5.0 mL). The organics were combined and washed with H_2O (1×10 mL), saturated aqueous brine (3×10 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (50% ether/petrol) to give the alcohol **16** (45 mg, 95%) as a clear oil, $[\alpha]_D^{31}$=+38.5 (c 1.96 in CHCl$_3$); ν_{max} (film) 3353, 3069, 3024, 2932, 2857, 1472, 1457, 1427, 1388, 1361, 1110, 1049, 965, 821, 740, 702, 665 and 612 cm^{-1}; δ_H (500 MHz, CDCl$_3$) 7.73–7.70 (4H, m, Ph), 7.45–7.41 (2H, m, Ph), 7.38–7.23 (8H, m, Ph), 7.22–7.19 (1H, m, Ph), 6.30 (1H, d, J=15.8 Hz, CH$_2$CH=CHPh), 6.10–6.03 (1H, m, CH$_2$-CH=CHPh), 3.71 (1H, dt, J=6.3, 2.7 Hz, CH$_2$-CH(OSi)CH(CH$_3$), 3.41 (2H, dt, J=1.1, 6.6 Hz, CH$_2$CH_2OH), 2.52–2.46 (1H, m, CH_2CH=CHPh), 2.12–2.05 (1H, m, CH_2CH=CHPh), 1.75–1.70 (1H, m), 1.51–1.36 (2H, m), 1.31–1.22 (2H, m), 1.21–1.08 (11H, m, includes 1.10 (9H, s, ^{t}Bu)), 0.92 (3H, d, J=6.8 Hz, CH(OSi)CH(CH_3); δ_C (125 MHz, CDCl$_3$) 137.8, 136.1, 136.0, 134.8, 134.3, 130.9, 130.1, 129.5, 129.4, 128.4, 127.5, 127.3, 126.8, 125.9, 76.2, 62.7, 37.9, 36.5, 33.3, 32.5, 27.1, 22.1, 19.6, 14.0; m/z (+FAB) 509 (M+Na), 413, 301, 241, 197, 173, 137, 115, 91; found: C, 79.3; H, 8.9. $C_{32}H_{42}O_2Si$ requires C, 79.0; H, 8.7%.

4.1.9. Preparation of (5*R*,6*R*,8*E*)-5-(*tert*-butyldiphenylsilyloxy)-6-methyl-9-phenylnon-8-enal 17. To a stirred solution of alcohol **16** (105 mg, 0.22 mmol) in CH_2Cl_2 (2.1 mL) was added Dess–Martin periodinane reagent (110 mg, 0.26 mmol). After 5 min 'wet' CH_2Cl_2 (0.5 mL) was added and after 15 min the reaction was concentrated in vacuo before the addition of a 1:1 solution of saturated aqueous NaHCO$_3$/1 M $Na_2S_2O_3$ (25 mL) and ether (25 mL), then stirred for 25 min. The organics were separated and the aqueous extracted with ether (3×20 mL). The organics were combined and washed with H_2O (1×25 mL), saturated aqueous brine (3×25 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (50% ether/petrol) to give the aldehyde **17** (98 mg, 94%) as a clear oil, $[\alpha]_D^{27}$=+38.2 (c 0.86 in CHCl$_3$); ν_{max} (film) 3070, 3024, 2931, 2856, 2715, 1725, 1589, 1494, 1472, 1461, 1427, 1388, 1361, 1187, 1110, 1072, 966, 938, 821, 740, 702 and 665 cm^{-1}; δ_H (500 MHz, CDCl$_3$) 9.53 (1H, t, J=1.4 Hz, CHO), 7.70–7.67 (4H, m, SiPh), 7.47–7.04 (11H, m, Ph), 6.28 (1H, d, J=15.8 Hz, CH$_2$CH=CHPh), 6.06–6.00 (1H, m, CH$_2$CH=CHPh), 3.70–3.63 (1H, m, CH$_2$-CH(OSi)CH(CH$_3$), 2.52–2.45 (1H, m), 2.13–2.01 (3H, m), 1.80–1.67 (1H, m), 1.48–1.33 (4H, m), 1.07 (9H, s, ^{t}Bu), 0.88 (3H, d, J=6.8 Hz, CH(OSi)CH(CH_3)); δ_C (125 MHz, CDCl$_3$) 202.3, 137.8, 136.1, 136.0, 131.1, 129.8, 130.0, 129.5, 128.4, 127.5, 127.5, 125.9, 109.6, 75.9, 38.0, 32.9, 27.1, 18.5, 14.1; m/z (+FAB) 485 (M+H), 427 (M−^{t}Bu), 339, 221, 199, 183, 165, 145, 129, 123, 117, 105; observed: M+H, 485.2891. $C_{32}H_{41}O_2Si$ requires M+H, 485.2876.

4.1.10. Preparation of (4′*R*,5′*R*,7′*E*)-2-[4′-(*tert*-butyldiphenylsilyloxy)-5′-methyl-8′-phenyl-oct-7′-en-1′-yl]-1,3-dithiane 6. To a stirred solution of aldehyde **17** (76 mg, 0.16 mmol) in CH_2Cl_2 (2.0 mL) was added 1,3-propanedithiol (16 μL, 0.16 mmol) followed by boron trifluoride etherate (4 μL, 0.03 mmol). After 12 h, the reaction was concentrated in vacuo. The residual yellow oil was purified by flash chromatography (10% ether/petrol) to give the dithiane **6** (90 mg, 100%) as a clear oil, $[\alpha]_D^{25}$=+24.2 (c 1.6 in CHCl$_3$); ν_{max} (film) 3069, 3023, 2931, 2895, 2856, 1588, 1493, 1474, 1461, 1426, 1380, 1360, 1275, 1110, 1072,

1051, 1026, 966, 821, 740, 702 and 612 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.70–7.67 (4H, m, Ph), 7.46–7.40 (2H, m, Ph), 7.39–7.32 (4H, m, Ph), 7.31–7.25 (4H, m, Ph), 7.21–7.16 (1H, m, Ph), 6.27 (1H, d, J=15.8 Hz, CH_2-CH=C*H*Ph), 6.08–5.95 (1H, m, CH_2C*H*=CHPh), 3.79 (1H, t, J=7.0 Hz, CH_2SC*HS*CH_2) 3.70–3.64 (1H, m, CH_2C*H*(OSi)CH(CH_3), 2.83–2.72 (4H, m), 2.47–2.38 (1H, m, C*H*$_2$CH=CHPh), 2.11–2.02 (2H, m), 1.87–1.77 (1H, m), 1.73–1.63 (1H, m), 1.52–1.41 (3H, m), 1.40–1.20 (3H, m), 1.08 (9H, s, ^{t}Bu), 0.89 (3H, d, J=6.8 Hz, CH(OSi)CH(CH_3); δ_C (125 MHz, $CDCl_3$) 137.8 (s), 136.0 (d), 134.8 (s), 130.9 (s), 130.0 (d), 129.5 (s), 129.4 (d), 128.4 (d), 127.5 (d), 127.4 (d), 126.7 (d), 125.9 (d), 76.0 (d), 47.3 (d), 37.6 (d), 36.6 (t), 35.2 (t), 33.2 (t), 30.3 (t), 27.2 (q), 26.0 (t), 22.9 (t), 19.5 (s), 13.8 (q); *m/z* (+FAB) 573 $(M-H)^+$, 517 (M−^{t}Bu), 319, 281, 221, 199, 135, 117, 91, 73; observed: $M^+-{}^t$Bu, 517.2101. $C_{31}H_{37}OSiS_2$ requires $M^+-{}^t$Bu, 517.2055.

4.1.11. Preparation of dithiane monoxide 18. To a solution of dithiane **6** (57 mg, 0.1 mmol) in CH_2Cl_2 (700 μL) at 0°C was added *m*CPBA (217 μL, 0.1 mmol, 0.46 M in CH_2Cl_2, 1 equiv.). The solution was stirred for 5 min, quenched with saturated aqueous Na_2SO_3 and the mixture was extracted with CH_2Cl_2 (×4). The combined organics were dried ($MgSO_4$) and the solvent removed to yield a colourless oil. The crude mixture was purified by flash chromatography (90% ethyl acetate/petrol–ethyl acetate) to yield the dithiane monoxide **18** (45 mg, 76%) as a 5:1 mixture of the *trans* and *cis* pairs of diastereomers. These could be separated by further chromatography (*trans*: 26 mg, 44%; *cis*: 6 mg, 10%), both as white foams, which gave complex ^{1}H NMR spectra indicating the presence of mixtures of diastereomers. Data for **18** *trans*: R_f 0.2 (EtOAc); $[\alpha]_D^{22}$=+24.2 (*c* 0.98, $CHCl_3$); ν_{max} ($CHCl_3$ solution) 2932, 2858, 1599, 1461, 1382, 1110, 1028, 967 and 612 cm^{-1}; *m/z* (ES+) 613 (M+Na, 100); observed 613.2545, $C_{35}H_{46}O_2S_2SiNa$ requires 613.2606. Data for **18** *cis*: R_f 0.29 (EtOAc); $[\alpha]_D^{27.5}$=+15.8 (*c* 0.92, $CHCl_3$); ν_{max} ($CHCl_3$ solution) 2933, 2859, 1599, 1462, 1382, 1362, 1111, 1052, 999, 967, 902 and 612 cm^{-1}; *m/z* (ES+) 613 (M+Na, 100); observed 613.2563, $C_{35}H_{46}O_2S_2SiNa$ requires 613.2606.

4.1.12. Preparation of (1*S*,3*R*,4*S*,5*R*,6*R*,7*R*,4′*R*,5′*R*,7′*E*)-1-[4′-acetoxy-5′-methyl-8′-phenyl-oct-7′-en-1′-yl]-3,4,5-tris-benzyloxymethyl-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane 22. To a solution of **18** *trans* (3.19 g, 5.4 mmol, 3 equiv.) in THF (15 mL) at −78°C was added ^{n}BuLi (2.48 mL, 5.94 mmol, 2.4 M in hexanes, 3.1 equiv.) dropwise under nitrogen. The solution was stirred for 15 min, then aldehyde **3** (1.0 g, 1.8 mmol) was added via cannula over 10 min. The mixture was stirred for 1 h, quenched with water and then allowed to come to rt. Saturated aqueous NH_4Cl was added and the mixture was extracted with ether (×3). The combined organics were washed with brine (×1), dried ($MgSO_4$) and the solvent removed to yield a yellow oil. The crude mixture was purified by flash chromatography (60% ethyl acetate/petrol–ethyl acetate) to remove unreacted side chain, yielding the adducts (2.95 g) as a yellow oil.

To a solution of P_2I_4 (825 mg, 1.38 mmol, 0.55 equiv.) in CH_2Cl_2 (40 mL), in the dark, was added Et_3N (365 μL, 2.5 mmol, 1 equiv.) under nitrogen, followed by the coupled product (2.95 g, 2.5 mmol) in CH_2Cl_2 (40 mL) via cannula over 10 min. The reaction was stirred at rt for 30 min, quenched with saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2 (×3). The combined organics were washed with brine (×1), dried ($MgSO_4$) and the solvent removed to yield a yellow oil. The crude material was purified by flash chromatography (40% ether/petrol) to yield a pale yellow oil (2.04 g).

To this mixture of alcohols (2.04 g, 1.75 mmol) in THF (44 mL) was added TBAF (8.75 mL, 8.75 mmol, 1 M in THF, 5 equiv.) under nitrogen. The solution was stirred at 80°C for 25 h, allowed to come to rt, quenched with water and then extracted with ether (×3). The combined organics were washed with brine (×1), dried ($MgSO_4$) and the solvent removed to yield a brown oil. The crude mixture was purified by flash chromatography (50% ether/petrol) to yield **20** (194 mg, 12% over three steps) as an orange foam. The other diastereomer **19** could not be isolated pure since it co-ran with an isomeric material tentatively assigned as resulting from acetonide migration. Data for **20**: R_f 0.2 (50% ether/petrol); ν_{max} (film) 3466, 2861, 1599 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.70–7.17 (20H, m, Ph), 6.40 (1H, d, J=15.8 Hz, CH_2CH=C*H*Ph), 6.24–6.17 (1H, m, CH_2-C*H*=CHPh), 4.94 (1H, d, J=6.5 Hz), 4.77 (1H, d, J=7.3 Hz), 4.66 (1H, d, J=12.5 Hz), 4.56–4.41 (5H, m), 4.16 (1H, br d, J=10.9 Hz), 3.90–3.55 (7H, m), 3.05 (1H, m), 2.83 (1H, m), 2.71 (1H, m), 2.57 (1H, m), 2.39–2.30 (2H, m), 2.12 (1H, m), 1.88–1.20 (18H, m), 0.92 (3H, d, J=6.8 Hz); δ_C (125 MHz, $CDCl_3$) 138.6, 138.1, 137.9, 137.6, 131.2, 129.4, 128.5, 128.2, 128.0, 128.0, 127.8, 127.6, 127.5, 127.4, 126.9, 126.0, 110.2, 108.9, 86.4, 81.1, 75.6, 74.2, 73.9 (d), 73.5 (d), 73.0 (d), 71.3 (d), 69.1 (d), 66.1, 59.4, 38.5, 37.3 (d), 35.0 (d), 34.9, 28.3, 27.2, 26.1, 26.0, 25.7 (d), 24.3 (d), 21.3 (d), 13.7.

To a solution of **20** (17 mg, 0.018 mmol) in pyridine (1.3 mL) was added DMAP (1 mg, catalytic amount) followed by Ac_2O (12 μL, 0.126 mmol, 7 equiv.). The reaction was stirred at 60°C for 3 h, allowed to come to rt, quenched with water and then extracted with ether (×3). The combined organics were washed successively with saturated aqueous $CuSO_4$ (×3), brine (×1), dried ($MgSO_4$) and solvent removed to yield a yellow oil. The crude mixture was purified by flash chromatography (50% ether/petrol) to yield **21** (12 mg, 69%) as a yellow oil. R_f 0.36 (50% ether/petrol); δ_H (500 MHz, $CDCl_3$) 7.41–7.19 (20H, m, Ph), 6.41 (1H, d, J=15.8 Hz, CH_2CH=C*H*Ph), 6.25–6.17 (1H, m, CH_2C*H*=CHPh), 4.98–4.94 (2H, m), 4.82 (1H, d, J=8.1 Hz), 4.72–4.17 (7H, m), 4.19 (1H, d, J=10.9 Hz), 3.96–3.79 (4H, m), 3.59 (1H, d, J=10.9 Hz), 3.07 (1H, m), 2.61–2.32 (5H, m), 2.09 (3H, s), 2.07–1.23 (16H, m), 0.97 (3H, d, J=6.8 Hz).

To a solution of **21** (128 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) was added water (150 μL) and TFA (1.5 mL) under nitrogen. The solution was stirred at rt for 2 h, quenched with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2 (×2). The combined organics were dried ($MgSO_4$) and the solvent removed to yield a yellow oil. The crude material was purified by flash chromatography (70%

ether/petrol–ether) to yield bicyclic ketal **22** (79 mg, 78%) as a colourless oil; $[\alpha]_D^{22}=+10.91$ (*c* 0.25, $CHCl_3$); ν_{max} 3436, 3062, 3029, 2925, 2876, 1732, 1495, 1454, 1369, 1244, 1207, 1075, 909, 740 and 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.34–7.24 (17H, m, Ph), 7.21–7.16 (3H, m, Ph), 6.37 (1H, d, *J*=16.0 Hz, CH=C*H*Ph) 6.19–6.13 (1H, m, C*H*=CHPh), 4.91–4.87 (1H, m, H4′), 4.78 (1H, d, *J*=2.5 Hz, H6), 4.54 (1H, d, *J*=12 Hz, one of OCH_2Ph), 4.51 (1H, d, *J*=12 Hz, one of OCH_2Ph), 4.48 (1H, d, *J*=12.0 Hz, one of OCH_2Ph), 4.45 (1H, d, *J*=12.0 Hz, one of OCH_2Ph), 4.41–4.39 (1H, m, H3), 4.31 (2H, s, OCH_2Ph), 4.00 (1H, d, *J*=2.5 Hz, H7), 3.92 (1H, d, *J*=10.0 Hz, one of CH_2OBn), 3.79 (1H, dd, *J*=3.5, 11.0 Hz, one of CH_2OBn), 3.61–3.58 (3H, m, three of CH_2OBn), 3.47 (1H, d, *J*=10 Hz, one of CH_2OBn), 3.47 (1H, br s, OH), 3.34 (1H, br s, OH), 2.32–2.27 (1H, m, one of H6′), 2.03–1.97 (1H, m, one of H6′), 2.03 (3H, s, OCOCH_3), 1.85–1.80 (2H,m, CH_2), 1.74–1.69 (1H, m, C*H*(CH_3)), 1.55–1.48 (2H, m, CH_2), 1.33–1.28 (2H, m, CH_2), 0.92 (3H, d, *J*=7.0 Hz, CH(CH_3)); δ_C (125 MHz, $CDCl_3$) 171.0 (s), 138.1 (s), 137.6 (s), 136.8 (s), 131.5 (d), 128.6 (d), 128.5 (d), 128.3 (d), 128.2 (d), 127.9 (d), 127.7 (d), 127.6 (d), 126.9 (d), 126.0 (d), 105.2 (s), 105.1 (s), 86.8 (s), 83.6 (d), 79.4 (d), 79.3 (d), 73.9 (t), 73.5 (t), 73.2 (t), 73.0 (d), 70.9 (d), 69.5 (t), 69.4 (t), 68.4 (t), 36.7 (t), 36.5 (d), 35.3 (t), 31.2 (t), 21.2 (q), 19.2 (t), 14.2 (q); *m*/*z* (FAB+) 781 (M+H, 5), 721 (1), 531 (2), 461 (1), 391 (2), 355 (2); observed 781.3950, $C_{47}H_{51}O_{10}$ (M+H) requires 781.3952.

4.1.13. Preparation of (1*S*,3*R*,4*S*,5*R*,6*R*,7*R*,4′*R*,5′*R*,7′*E*)-1-[4′-acetoxy-5′-methyl-8′-phenyl-oct-7′-en-1′-yl]-6,7-bisbenzoyloxy-3,4,5-tris-benzyloxymethyl-4-hydroxy-2,8-dioxabicyclo[3.2.1]octane 23. To a solution of **22** (25 mg, 0.032 mmol) in pyridine (640 μL) was added DMAP (ca. 1 mg, catalytic amount) and benzoyl chloride (15 μL, 0.128 mmol, 4 equiv.) under nitrogen. The solution was stirred at rt for 30 h, quenched with water and then extracted with CH_2Cl_2 (×2). The combined organics were washed with saturated aqueous $CuSO_4$ (×2), 2 M H_2SO_4 (×1), water (×1), dried ($MgSO_4$) and the solvent removed to yield a white solid. The crude material was purified by flash chromatography (50% ether/petrol) to yield bisbenzoate **23** (31 mg, 98%) as a white foam; $[\alpha]_D^{23}=+22.6$ (*c* 0.62, $CHCl_3$); ν_{max} 3451, 3063, 3029, 2962, 2928, 2877, 1702, 1693, 1602, 1452, 1370, 1302, 1113, 1026, 967, 752 and 712 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.10–8.04 (4H, m, Ph), 7.62–7.58 (1H, m, Ph), 7.55–7.50 (1H, m, Ph), 7.48–7.45 (2H, m, Ph), 7.33–7.12 (20H, m, Ph), 7.10–7.07 (2H, m, Ph), 6.44 (1H, d, *J*=2.5 Hz, H6), 6.34 (1H, d, *J*=16.0 Hz, CH=C*H*Ph), 6.16–6.08 (1H, m, C*H*=CHPh), 5.52 (1H, d, *J*=2.5 Hz, H7), 4.90–4.87 (1H, m, H4′), 4.78–4.75 (1H, m, H3), 4.63 (1H, d, *J*=12.0 Hz, one of OCH_2Ph), 4.54 (1H, d, *J*=12.0 Hz, one of OCH_2Ph), 4.47 (1H, d, *J*=12.0 Hz, one of OCH_2Ph), 4.34 (2H, app t, *J*=12.0 Hz, OCH_2Ph), 4.21 (1H, d, *J*=12.0 Hz, one of OCH_2Ph), 4.10 (1H, d, *J*=6.0 Hz), 3.95–3.91 (2H, m), 3.78–3.70 (3H, m), 3.61 (1H, d, *J*=10.0 Hz), 2.31–2.25 (1H, m, one of H6′), 2.00–1.92 (4H, m, inc. OCOCH_3 and one of H6′), 1.84–1.77 (1H, m, C*H*(CH_3)), 1.69–1.55 (4H, m, 2×CH_2), 1.35–1.30 (2H, m, CH_2), 0.89 (3H, d, *J*=7.0 Hz, CH(CH_3)); δ_C (100 MHz, $CDCl_3$) 170.9 (s), 165.3 (s), 164.9 (s), 138.4 (s) 137.6 (s), 136.8 (s), 133.3 (d), 133.2 (d), 131.4 (d), 130.1 (d), 129.9 (d), 129.6 (s), 129.3 (s), 128.8 (d), 128.5 (d), 128.3 (d), 128.2 (d), 127.9 (d), 127.8 (d), 127.6 (d), 127.4 (d), 126.9 (d), 126.0 (d), 105.1 (s), 105.0 (s), 85.7 (s), 80.9 (d), 78.2 (d), 76.8 (d), 74.2 (d), 74.1 (t), 73.4 (t), 73.2 (t), 71.9 (s), 69.9 (t), 69.7 (t), 69.3 (t), 36.6 (t), 36.5 (d), 35.9 (s), 35.7 (t), 31.0 (t), 21.1 (q), 19.1 (t), 14.2 (q); *m*/*z* (FAB+) 989 (M+, 1.5), 971 (0.1), 929 (0.1), 911 (0.1), 531 (0.1), 399 (3), 307 (2); observed 989.4428, $C_{61}H_{65}O_{12}$ (M^+) requires 989.4476.

4.1.14. Preparation of (1*S*,3*R*,4*S*,5*R*,6*R*,7*R*,4′*R*,5′*R*,7′*E*)-1-[4′-acetoxy-5′-methyl-8′-phenyl-oct-7′-en-1′-yl]-6,7-bis-benzoyloxy-4-hydroxy-3,4,5-trihydroxymethyl-2,8-dioxabicyclo[3.2.1]octane 24. To a solution of **23** (32 mg, 0.03 mmol) in CH_2Cl_2 (1 mL) was added $BCl_3{\cdot}SMe_2$ (250 μL, 0.5 mmol, 2 M in CH_2Cl_2, 17 equiv.) under nitrogen. The solution was stirred at rt for 21 h, quenched with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2 (×2). The combined organics were washed with brine (×1), dried ($MgSO_4$) and the solvent removed to yield a brown oil. The crude material was purified by flash chromatography (ethyl acetate) to yield the tetraol **24** (14 mg, 65%) as a colourless oil, $[\alpha]_D^{23}=+35.7$ (*c* 0.28, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.09 (2H, dd, *J*=1.0, 8.0 Hz, Ph), 8.03 (2H, dd, *J*=1.0, 8.0 Hz), 7.62–7.57 (2H, m, Ph), 7.49–7.44 (4H, m, Ph), 7.34–7.27 (4H, m, Ph), 7.23–7.17 (1H, m, Ph), 6.35 (1H, d, *J*=16.0 Hz, CH=C*H*Ph), 6.17–6.09 (1H, m, C*H*=CHPh), 5.95 (1H, d, *J*=3.0 Hz, H6), 5.60 (1H, d, *J*=3.0 Hz, H7), 4.93–4.89 (1H, m, H4′), 4.27–4.22 (1H, m, H3), 4.01–3.86 (6H, m, 3×CH_2OH), 3.36 (1H, br s, 1° OH), 3.26 (1H, br s, 1° OH), 3.17 (1H, br s, 1° OH), 2.71 (1H, br s, 3° OH), 2.30–2.22 (1H, m, one of H6′), 2.03 (3H, s, OCOCH_3), 1.99–1.93 (1H, m, one of H6′), 1.83–1.74 (1H, m, C*H*(CH_3)), 1.71–1.45 (4H, m, 2×CH_2), 1.33–1.19 (2H, m, CH_2), 0.92 (3H, d, *J*=7.0 Hz, CH(CH_3)); δ_C (100 MHz, $CDCl_3$) 171.2 (s), 166.2 (s), 165.2 (s), 137.5 (s), 133.7 (d), 133.6 (d), 131.5 (d), 130.3 (d), 129.9 (d), 129.4 (d), 129.0 (s), 128.8 (s), 128.7 (d), 128.6 (d), 128.5 (d), 128.3 (d), 127.4 (d), 127.3 (d), 127.0 (d), 126.6 (d), 126.0 (d), 104.8 (s), 104.7 (s), 86.2 (s), 80.7 (d), 77.8 (d), 77.6 (d), 77.2 (d), 77.0 (d), 76.6 (d), 74.2 (d), 73.9 (d), 72.5 (s), 72.4 (s), 61.8 (t), 61.5 (t), 60.2 (t), 36.7 (t), 36.6 (d), 35.2 (t), 31.0 (t), 29.7 (t), 22.7 (q), 18.9 (t), 14.1 (q); *m*/*z* (FAB+) 741 (M+Na, 1), 719 (M+H, 1.5), 663 (1), 647 (1), 558 (1.5), 538 (1.5), 399 (2.5), 366 (2).

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