Synthesis of the non-adjacent bis-THF core of *cis*-sylvaticin using a double oxidative cyclisation†

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A short synthesis of the non-adjacent bis-THF core of the *Annonaceous* acetogenin *cis*-sylvaticin (**1**) is described. C_2 Symmetrical (*Z,E,E,Z*)- and (*E,E,E,E*)-tetraenes **5** and **6** were synthesised in six and three steps respectively from (1*E*,5*E*,9*E*)-cyclododeca-1,5,9-triene. Subsequent permanganate promoted asymmetric bi-directional oxidative cyclisation of tetraene **5** was used to create the non-adjacent bis-THF core of **1**, installing seven of the nine stereogenic centres present in the natural product in a single step. Desymmetrisation of the oxidative cyclisation product by mono-tosylation gave access to a C11–C32 fragment of *cis*-sylvaticin.

Introduction

The *Annonaceous* acetogenin family of natural products has attracted considerable interest due to the discovery of potent cytotoxic antitumour activity along with various other biological effects.[1] Recently we described a total synthesis of *cis*-sylvaticin (**1**),[2] a C37 non-adjacent bis-THF acetogenin isolated from leaf extracts of the tropical fruit tree *Rollinia mucosa*.[3] The prominent challenge to be addressed during a total synthesis of **1** is the stereocontrolled assembly of its non-adjacent bis-THF core.[4] In our published approach this was achieved through the coupling of two major THF-containing fragments, where the non-adjacent bis-THF was formed using a tethered metathesis reaction (Fig. 1). Donohoe *et al.* also reported a total synthesis of *cis*-sylvaticin using an osmium-catalysed double oxidative cyclisation of a protected tetrahydroxydiene.[4f]

Prior to our successful total synthesis of *cis*-sylvaticin using the fragment-based approach outlined in Fig. 1, we investigated a bi-directional strategy. Herein we report the results from these earlier studies using double oxidative cyclisation of tetraenes to install the non-adjacent bis-THF core and seven of the nine stereogenic centres present in the natural product.

Results and discussion

Inspection of the non-adjacent bis-THF core of *cis*-sylvaticin reveals that it could be derived from C_2 symmetrical precursors such as the double oxidative cyclisation products **3** or **4** (Fig. 2). Desymmetrisation could be achieved by a selective reaction at either of the homotopic termini present in various intermediates including the bis-epoxide **2**.[5] The bis-THF **3** could be obtained

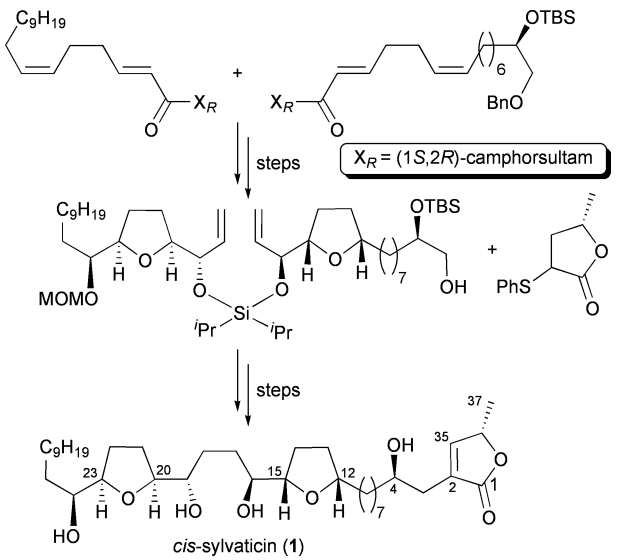

Fig. 1 Our previously reported total synthesis of *cis*-sylvaticin.

by diastereoselective double oxidative cyclisation of (*Z,E,E,Z*)-tetraene **5**, using a sultam chiral auxiliary to direct the facial selectivity. The control of polyene geometry is of key significance due to the stereospecific addition of vicinal oxygen functionalities across the double bond during the oxidative cyclisation, which results in *threo*- or *erythro*-configured products from *E*- and *Z*-alkenes respectively.[6,7] The C23–C24 *erythro* configuration present in the natural product **1** would be most readily accessed from a *Z*-alkene precursor such as **5**. Oxidative cyclisation of the all *E*-tetraene **6** would lead to a *threo* relationship between C23 and C24, which for the total synthesis of **1**, would have to be corrected at a later stage by inversion of the C24 hydroxyl group.

Synthetic work began with the oxidative cleavage of (1*E*,5*E*,9*E*)-cyclododeca-1,5,9-triene (**7**) to give dialdehyde **8** following the protocol reported by Hoye and Ye (Scheme 1).[8] Subsequent *Z*-selective olefination with Ando's phosphonate reagent **11** under modified Still–Gennari conditions afforded diethyl ester **9** in 61% yield.[9] The (2*E*,6*E*,10*E*,14*Z*)-isomer was isolated in 15% yield,

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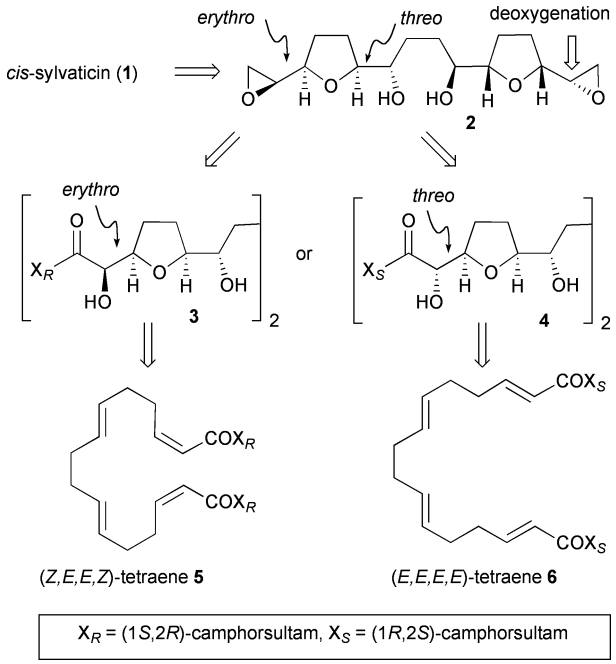
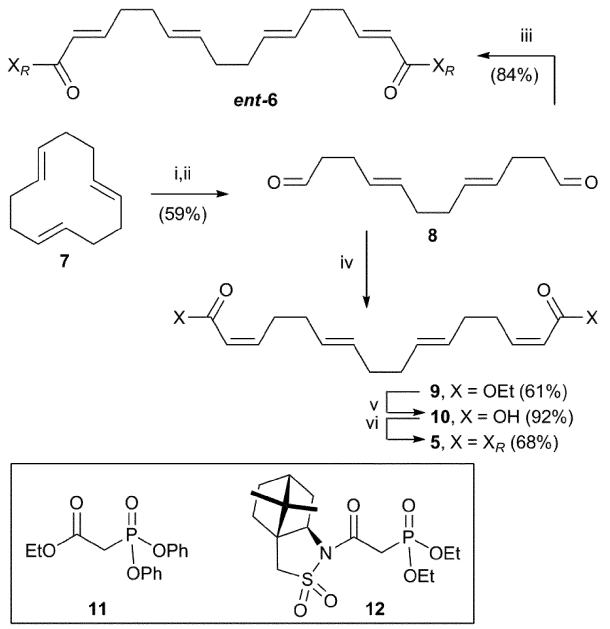


Fig. 2 Two directional synthetic approach to *cis*-sylvaticin.

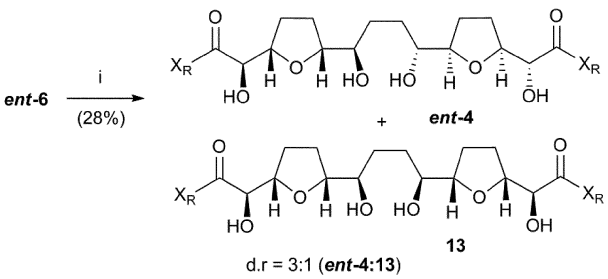


Scheme 1 Synthesis of the tetraenes **5** and *ent*-**6**. *Reagents and conditions*: (i) OsO_4, NMO; (ii) $NaIO_4$–SiO_2; (iii) **12**, toluene, NaH, –10 °C→rt; (iv) **11**, KHMDS, 18-crown-6, THF; (v) NaOH, $NaHCO_3$, MeOH–H_2O, 95 °C; (vi) $(COCl)_2$, CH_2Cl_2, DMF, 0 °C→rt; then (1*S*,2*R*)-camphorsultam, NaH, toluene, –10 °C→rt.

which corresponds to a *Z* : *E* selectivity ratio of ~9 : 1 per olefination. Following hydrolysis of diester **9**, the resultant diacid **10** was coupled to the (1*S*,2*R*)-camphorsultam *via* the bis-acid chloride. The coupling with the sodium salt of the sultam was carried out in toluene, as polar solvents promoted isomerisation of the *Z*-enoyl systems and formation of by-products due to 1,4-addition of the auxiliary. We also attempted to effect *cis*-olefination with sultam derived phosphonates, but these reactions were unselective.

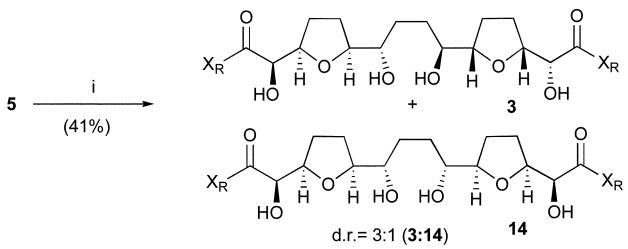
The corresponding all *E*-tetraenedioyl bis-sultam *ent*-**6** was more readily synthesised, requiring just one step from the dialdehyde **8** by direct HWE reaction with phosphonate **12** (Scheme 1).[10] The (1*S*,2*R*)-camphorsultam auxiliary was employed, due to its availability in our laboratory. However, it should be noted that the (1*R*,2*S*)-camphorsultam would be required in order to establish the correct absolute configuration required for the synthesis of *cis*-sylvaticin (**1**).

Oxidative cyclisation of the tetraene *ent*-**6** produced an inseparable mixture of bis-THF-tetrols *ent*-**4** and **13** in a combined yield of 28% (Scheme 2), thus demonstrating the viability of the double oxidative cyclisation. We were not able to determine the diastereoisomeric ratio from the ^{1}H NMR, but an approximate ratio of 3 : 1 (*ent*-**4** : **13**) was estimated from the ^{13}C NMR spectrum of the mixture. No further optimisation of this oxidative cyclisation was carried out, and our attention moved to the (*Z*,*E*,*E*,*Z*)-tetraene **5**, which would give the correctly configured non-adjacent bis-THF directly.



Scheme 2 Oxidative cyclisation of tetraene *ent*-**6**. *Reagents and conditions*: (i) $KMnO_4$ (2.8 equiv), AcOH–acetone (2 : 3), –30 °C.

A variety of conditions were explored in order to improve the efficiency of the double oxidative cyclisation of (2*Z*,6*E*,10*E*,14*Z*)-tetraene **5** (Scheme 3). In previous studies using more lipophilic substrates,[10,11] phase-transfer conditions or AcOH–acetone mixtures had been found to give the best results. In the present study, the most efficient conversion was obtained using $NaMnO_4$ as the oxidant in aqueous acetone. The use of the sodium salt greatly increases the solubility of the permanganate ion in the aqueous mixture. Under these conditions the oxidative cyclisation products **3** and **14** were obtained as an inseparable mixture in a combined yield of 41%. This mixture of stereoisomers was used in the subsequent reactions. A third C_2 symmetrical minor diastereoisomer and a hydroxyketone by-product were isolated



Scheme 3 Oxidative cyclisation of tetraene **5**. *Reagents and conditions*: (i) $NaMnO_4$ (3.0 equiv), AcOH–acetone–buffer, –30 °C→–10 °C.

but repeated purification prevented us from determining accurate yields for these compounds.

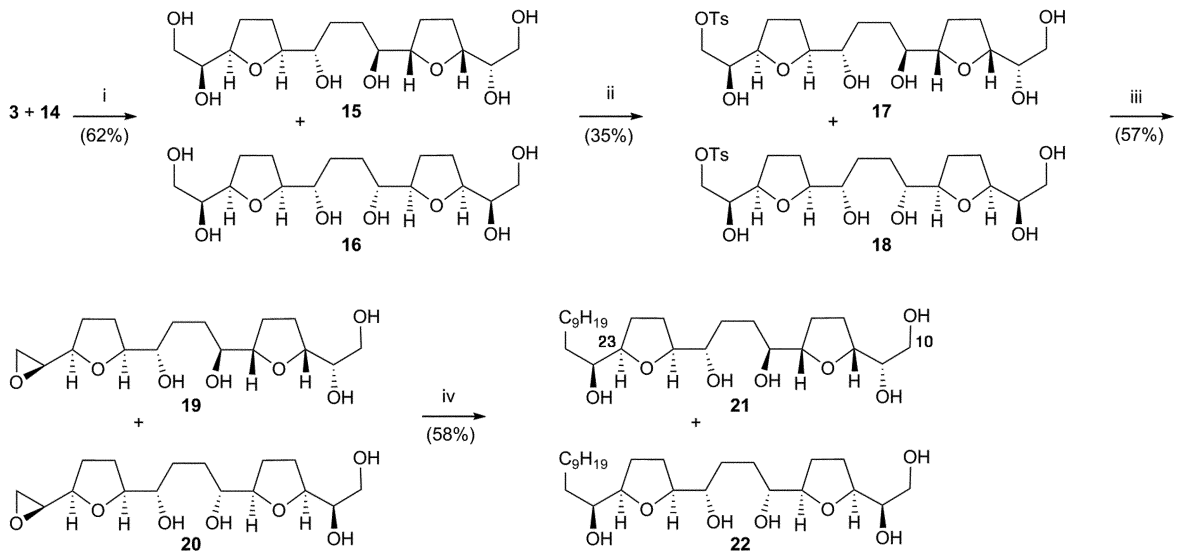
Curiously, this mixture of oxidative cyclisation products displayed a single set of ^{1}H and ^{13}C NMR signals. Based on the diastereoselectivities observed in the oxidative cyclisations of dienoyl sultams (dr = 6 : 1→10 : 1) we would have expected two major diastereoisomers in an approximate ratio of 3 : 1.[2,10–12] It later emerged (after reductive cleavage of the chiral auxiliaries) that we had indeed obtained a mixture of diastereoisomers **3** and **14** (dr ~ 3 : 1) which were indistinguishable on the basis of their spectroscopic data (*vide infra*).

Although the yield of the bis-THF oxidative cyclisation product was modest, the installation of eight new stereogenic centres in a single reaction step was an impressive achievement. Furthermore, structurally complex non-adjacent bis-THF intermediates **3** and *ent*-**4** had been obtained from a commercial triene in four and seven steps respectively. With these valuable intermediates secured, we next needed to address the desymmetrisation and introduce either of the required sidechains present in **1**.[5] Two strategies were explored, the first focussing on formation of a mono-epoxide intermediate (Scheme 4). Reductive cleavage of the chiral auxiliary from the diastereoisomeric mixture of **3** and **14** returned the highly water soluble C_2 symmetrical and *meso*-hexols **15** and **16** in a 62% yield. At this stage the presence of two diastereoisomers, in a ratio of 3 : 1 (**15** : **16**), was clearly evident from inspection of the ^{13}C NMR spectrum. Unfortunately, the stereoisomers were still inseparable by silica gel column chromatography.

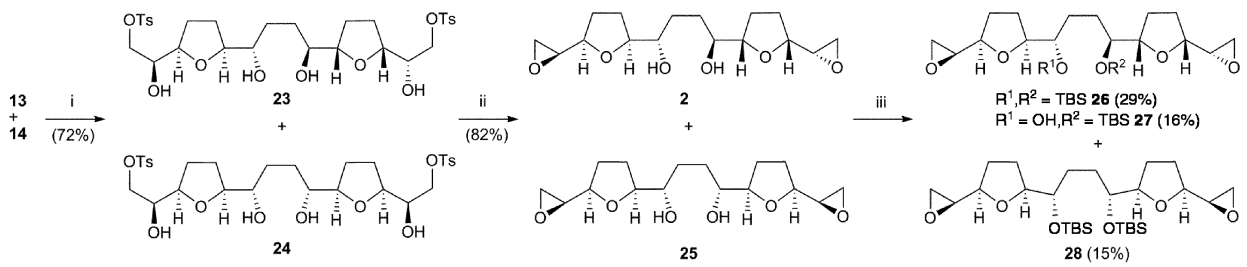
It was observed that when 1,4-dioxane was used as the reaction solvent the mono-tosylates **17** and **18** could be obtained in moderate yield, effecting desymmetrisation at this juncture (Scheme 4). Pleasingly the mono-tosylates afforded the mono-epoxides **19** and **20** respectively in 57% yield, although still as an inseparable mixture of diastereoisomers. Opening the mono-epoxide with nonylmagnesium bromide inserted the C24–C32 alkyl chain, and afforded an intermediate **21** that is suitable for progression to *cis*-sylvaticin.

At this point with only limited yields of desymmetrised materials, combined with difficulties encountered separating the diastereoisomeric mixtures, we decided to investigate desymmetrisation of a bis-epoxide intermediate (Scheme 5). The bis-epoxides **2** and **25** were prepared in high yields from tetraols **23** and **24** (dr = 3 : 1, ^{13}C NMR) *via* the corresponding bis-tosylates. Desymmetrisation at this point through the attempted addition of organocuprate reagents proved problematic generating a mixture of starting material, mono- and bis-ring opened products which could not be separated by chromatography.

However, protection of the 1,4-diols as TBS ethers led to three epoxides (**26–28**),[12] which were separable by column



Scheme 4 Desymmetrisation by mono-tosylation. *Reagents and conditions*: (i) $LiBH_4$, THF, –10 °C; (ii) Bu_2SnO (1.25 equiv.), dioxane, TsCl (1.2 equiv.); (iii) DBU, CH_2Cl_2, 0 °C; (iv) $C_9H_{19}MgBr$, CuI, THF, –70→–40 °C.



Scheme 5 Bi-directional approach towards *cis*-sylvaticin. *Reagents and conditions*: (i) Bu_2SnO, C_6H_6, TsCl; (ii) DBU, CH_2Cl_2, 0 °C; (iii) 2,6-lutidine, TBSOTf, CH_2Cl_2, –10 °C.

chromatography. Significantly, for the first time we were able to separate the desired chiral diastereoisomer **26** from the *meso* compound **28**. Furthermore, the minor diastereoisomer **28** provided a crystal structure that allowed us to confirm its assignment as the *meso* stereoisomer (Fig. 3).[13] The relatively low mass recovery from the silylation was in part due to the low reactivity of the secondary alcohol groups flanking the *cis*-THF rings, and these reactions were complicated by epoxide opening to give chlorohydrins when TBSCl was employed. Rapid silylation of **2**/**25** occurred in the presence of TBSOTf, although decomposition of the epoxide functionalities could not be completely avoided.

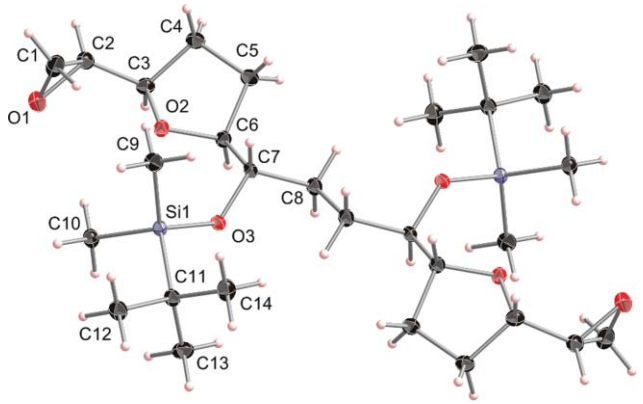


Fig. 3 X-Ray structure of *meso*-bis-epoxide **28**, thermal ellipsoids drawn at the 50% probability level. The molecule lies on a centre of inversion.

Mono-addition of organometallic nucleophiles to C_2 symmetrical bis-epoxides has been demonstrated previously as a desymmetrisation strategy,[8] and this will be the focus of future studies. However, more efficient access to a suitably protected isomerically pure bis-epoxide will first be required. We have recently discovered that epoxyalcohols structurally similar to **3** can be protected using MOM-Cl in high yield without disrupting the epoxide functionality.[2] It is likely that revision of the protecting group strategy will provide the key to completing the total synthesis of **1** following our two-directional approach.

Conclusions

We have described a short synthesis of the non-adjacent bis-THF core of *cis*-sylvaticin (**1**) with the key oxidative cyclisation installing eight stereogenic centres in a single step. Separation of the major diastereoisomers has been realised through silylation of the C16/C19 hydroxyl groups, and we have also shown that desymmetrisation of *C*2 symmetrical intermediates is possible through mono-functionalisation of hexaol **15** to give the C10–C32 portion of the natural product.

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL GX270, Bruker AC300, Bruker AM300 or Bruker DPX400 spectrometers. *J* values are given in Hz. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR instrument, a Bio-Rad FTS 135 instrument using a Golden Gate adaptor or a Nicolet Impact 400 instrument using a Thunderdome adaptor. Absorptions were recorded in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w) or broad (br). Melting points were measured on a Gallenkamp electrothermal melting point apparatus. Low-resolution mass spectra were obtained on a Fisons VG platform single quadrupole mass spectrometer in either chemical ionisation or electron impact ionisation mode or on a Micromass platform mass analyser with an electrospray ion source. All reactions were conducted under nitrogen atmosphere unless otherwise stated.

1,16-(2*R*)-*N*-[(2*E*,6*E*,10*E*,14*E*)-16-Oxo-2,6,10,14-hexadecatetraenoyl]-di-camphor-10,2-sultam (*ent*-6)

To a stirred solution of diethyl-2-oxo-2-((1*S*,2*R*)-*N*-camphor-10,2-sultam)-ethylphosphonate (**12**, 405 mg, 1.04 mmol) in THF (15 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 41 mg, 1.04 mmol). The mixture was warmed to rt over 30 min before cooling to 0 °C. A solution of (4*E*,8*E*)-dodeca-4,8-dienedial (**8**) (100 mg, 0.52 mmol) in THF (5 mL) was added dropwise and the mixture warmed to rt over 14 h. H_2O (30 mL) and EtOAc (50 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (402 mg). Purification on SiO_2 (3 × 15 cm) eluting with EtOAc–hexane (1 : 4→2 : 3) afforded the title compound as a colourless oil (292 mg, 0.44 mmol, 84%). $[\alpha]_D^{25}$ −78.4 (*c* 0.56 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2959 m, 2941 m, 2892 w, 2848 w, 1680 s and 1638 s; δ_H(400 MHz; $CDCl_3$) 7.08 (2H, dt, *J* 15.1, 7.0, 2 × C*H*CHC(O)), 6.56 (2H, d, *J* 15.1, 2 × CHC*H*C(O)), 5.50–5.35 (4H, m, 2 × $CH_2CHCHCH_2$), 3.93 (2H, dd, *J* 7.5, 5.3, 2 × CHN), 3.51 (2H, d, *J* 13.6, 2 × C*H*HSO$_2$), 3.43 (2H, d, *J* 13.6, 2 × CH*H*SO$_2$), 2.31 (4H, q, *J* 7.0, 2 × CH_2CHCHC(O)), 2.20–2.06 (8H, m, 2 × CH_2CH_2CHCHC(O) and 2 × CH_2CHN), 2.05–2.00 (4H, m, CHCH_2CH_2CH), 1.97–1.84 (6H, m, 2 × C*H*CH_2CHN and 2 × CH_2CHCH$_2$CHN), 1.47–1.32 (4H, m, 2 × CH_2CCHN), 1.18 (6H, s, 2 × CH_3), 0.98 (6H, s, 2 × CH_3); δ_C(100 MHz; $CDCl_3$) 164.2 (C), 150.4 (CH), 131.2 (CH), 128.8 (CH), 121.2 (CH), 65.3 (CH), 53.3 (CH_2), 48.6 (C), 47.9 (C), 44.9 (CH), 38.7 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 32.6 (CH_2), 31.0 (CH_2), 26.6 (CH_2), 21.0 (CH_3), 20.0 (CH_3); LRMS (ES$^+$) *m*/*z* 695 [M + Na]$^+$; HRMS (ES$^+$) $C_{36}H_{52}N_2O_6S_2Na^+$ Calcd. 695.3159, found 695.3144.

(2*Z*,6*E*,10*E*,14*Z*)-Diethyl hexadeca-2,6,10,14-tetraenedioate (9)

To a stirred solution of phosphonate (**11**, 1.98 g, 6.19 mmol) and 18-crown-6 (1.64 g, 6.19 mmol) in THF (50 mL) at −10 °C was added KHMDS (0.5 M in toluene, 12.4 mL, 6.19 mmol) dropwise. After 5 min the yellow mixture was cooled to −65 °C and (4*E*,8*E*)-dodeca-4,8-dienedial (**8**, 0.572 g, 2.95 mmol) in THF (10 mL) was added dropwise. The mixture was allowed to warm to −50 °C for 1 h before H_2O (50 mL) and Et_2O (50 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (2.50 g). Purification on SiO_2 (5 × 15 cm) eluting with Et_2O–hexane (3 : 97→1 : 19) gave (2*Z*,6*E*,10*E*,14*Z*)-diethyl hexadeca-2,6,10,14-tetraenedioate (**9**, 0.601 g, 1.80 mmol, 61%) as a colourless oil. Also isolated was (2*Z*,6*E*,10*E*,14*E*)-diethyl hexadeca-2,6,10,14-tetraenedioate (0.150 g, 0.45 mmol, 15%). **Data for 9:** ν_{max} (neat)/cm^{-1} 3038 w, 2983 w, 2910 w, 2845 w,

1718 s and 1643 m; δ_H(400 MHz; $CDCl_3$) 6.21 (2H, dt, *J* 11.6, 7.3, 2 × C*H*CHCO$_2$Et), 5.76 (2H, dt, *J* 11.6, 1.5, 2 × CHC*H*CO$_2$Et), 5.50–5.36 (4H, m, 2 × CH$_2$C*H*C*H*CH$_2$), 4.17 (4H, q, *J* 7.0, 2 × C*H*$_2$CH$_3$), 2.71 (4H, qd, *J* 7.3, 1.5, 2 × C*H*$_2$CHCHCO$_2$Et), 2.14 (4H, q, *J* 7.3, 2 × C*H*$_2$CH$_2$CH CHCO$_2$Et), 2.06–2.01 (4H, m, 2 × CH$_2$), 1.29 (6H, t, *J* 7.2, 2 × CH$_2$C*H*$_3$); δ_C(100 MHz; $CDCl_3$) 166.6 (C), 149.8 (CH), 131.0 (CH), 129.4 (CH), 120.0 (CH), 59.9 (CH$_2$), 32.7 (CH$_2$), 32.0 (CH$_2$), 28.9 (CH$_2$), 14.4 (CH$_3$); LRMS (ES$^+$) *m*/*z* 357 ([M + Na]$^+$); HRMS (ES$^+$) $C_{20}H_{31}O_4^+$ Calcd. 335.2217, found 335.2212. **Data for (2*Z*,6*E*,10*E*,14*E*)-diethyl hexadeca-2,6,10,14-tetraenedioate:** ν_{max} (neat)/cm^{-1} 3033 w, 2982 w, 2922 w, 2846 w, 1718 s and 1646 m; δ_H(400 MHz; $CDCl_3$) 6.96 (1H, dt, *J* 15.8, 6.8, C*H*CHCO$_2$Et), 6.21 (1H, dt, *J* 11.5, 7.1, EtCO$_2$CHC*H*), 5.82 (1H, dt, *J* 15.6, 1.5, CHC*H*CO$_2$Et), 5.76 (1H, dt, *J* 11.5, 1.5, EtCO$_2$C*H*CH), 5.50–5.36 (4H, m, 2 × C*H*C*H*), 4.19 (2H, q, *J* 6.8, C*H*$_2$CH$_3$), 4.19 (2H, q, *J* 7.1, C*H*$_2$CH$_3$), 2.72 (2H, qd, *J* 7.1, 1.4, C*H*$_2$CHCHCO$_2$Et), 2.26 (2H, br q, *J* 7.0, CHC*H*$_2$), 2.19–2.11 (2H, m, C*H*$_2$CH), 2.06–2.01 (4H, m, C*H*$_2$C*H*$_2$), 1.29 (6H, t, *J* 7.2, 2 × CH$_2$C*H*$_3$); δ_C(100 MHz; $CDCl_3$) 166.8 (C), 166.6 (C), 149.8 (CH), 148.7 (CH), 131.1 (CH), 130.8 (CH), 129.4 (CH), 128.9 (CH), 121.7 (CH), 120.0 (CH), 60.2 (CH$_2$), 59.9 (CH$_2$), 32.7 (CH$_2$), 32.6 (CH$_2$), 32.4 (CH$_2$), 32.0 (CH$_2$), 31.1 (CH$_2$), 29.0 (CH$_2$), 14.4 (CH$_3$); LRMS (ES$^+$) *m*/*z* 357 ([M + Na]$^+$); HRMS (ES$^+$) $C_{20}H_{31}O_4^+$ Calcd. 335.2217, found 335.2212.

(2*Z*,6*E*,10*E*,14*Z*)-Hexadeca-2,6,10,14-tetraenedioic acid (10)

To a stirred solution of (2*Z*,6*E*,10*E*,14*Z*)-dimethyl hexadeca-2,6,10,14-tetraenedioate (**9**, 1.10 g, 3.60 mmol) in MeOH (11 mL) and H_2O (33 mL) were added NaOH (1.53 g, 38.2 mmol) and $NaHCO_3$ (0.300 g, 3.60 mmol) and the mixture heated at 95 °C for 3 h. The mixture was cooled to rt and washed with CH_2Cl_2 (3 × 20 mL). The aqueous phase was separated, cooled to 0 °C and acidified with aqueous citric acid (30 mL) and 2 M HCl (50 mL) to pH 1. The mixture was stirred for 30 min before Et_2O (100 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow oil (0.92 g, 3.31 mmol, 92%). ν_{max} (neat)/cm^{-1} 2980 m, 2915 br, 2846 m, 1692 s and 1639 m; δ_H(400 MHz; $CDCl_3$) 6.35 (2H, dt, *J* 11.6, 7.4, 2 × C*H*CHCO$_2$H), 5.81 (2H, dt, *J* 11.6, 1.8, 2 × CHC*H*CO$_2$H), 5.51–5.37 (4H, m, 2 × C*H*C*H*), 2.73 (4H, qd, *J* 7.4, 1.5, 2 × C*H*$_2$CHCHCO$_2$H), 2.15 (4H, q, *J* 7.3, 2 × CHC*H*$_2$), 2.09–2.03 (4H, m, C*H*$_2$C*H*$_2$); δ_C(100 MHz; $CDCl_3$) 172.2 (C), 152.7 (CH), 131.0 (CH), 129.3 (CH), 119.5 (CH), 32.6 (CH$_2$), 31.9 (CH$_2$), 29.2 (CH$_2$); LRMS (ES$^-$) *m*/*z* 391 [M + (CF$_3$CO$_2$)]$^-$; HRMS (ES$^-$) $C_{16}H_{21}O_4^-$ Calcd. 277.1445, found 277.1439.

1,16-(1*S*,2*R*)-*N*-[(2*Z*,6*E*,10*E*,14*Z*)-16-Oxo-2,6,10,14-hexadecatetraenoyl]-di-camphor-10,2-sultam (5)

To a stirred solution of (2*Z*,6*E*,10*E*,14*Z*)-hexadeca-2,6,10,14-tetraenedioic acid (**10**, 1.29 g, 4.64 mmol) and $(COCl)_2$ (0.81 mL, 9.28 mmol) at 0 °C in CH_2Cl_2 (15 mL) was added DMF (0.05 mL) and the mixture allowed to warm to rt over 3 h. The mixture was concentrated *in vacuo* to give the crude acid chloride (1.40 g) as an orange oil, which was used without further purification. Under an atmosphere of N_2, to a stirred solution of (1*S*,2*R*)-camphorsultam (0.243 g, 1.13 mmol) in toluene (50 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.418 g, 10.4 mmol) [CAUTION: evolution of H_2 gas] and the mixture warmed to rt over 30 min. The mixture was cooled to –10 °C and crude acid chloride (1.40 g) in toluene (40 mL) was added dropwise. The mixture was stirred for 45 min at –10 °C then warmed to rt over 45 min. The mixture was cooled to 0 °C before H_2O (50 mL) and Et_2O (50 mL) were added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (3.00 g). Purification on SiO_2 (5 × 15 cm) eluting with EtOAc–hexane (1 : 4) afforded a white foam (2.12 g, 3.16 mmol, 68%). $[\alpha]_D^{25}$ –72.1 (*c* 0.75 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2959 m, 2915 m, 2844 w, 1680 s and 1630 m; δ_H(400 MHz; $CDCl_3$) 6.45 (2H, dt, *J* 11.5, 1.5, 2 × CHC*H*C(O)), 6.32 (2H, dt, *J* 11.5, 7.1, 2 × C*H*CHC(O)), 5.50–5.36 (4H, m, 2 × C*H*C*H*), 3.93 (2H, dd, *J* 7.3, 5.3, 2 × C*H*N), 3.50 (2H, d, *J* 13.8, 2 × C*H*HSO$_2$), 3.43 (2H, d, *J* 13.8, 2 × CH*H*SO$_2$), 2.68 (4H, qd, *J* 7.3, 1.5, 2 × C*H*$_2$CHCHC(O)), 2.20–2.06 (8H, m, 2 × CHC*H*$_2$ and 2 × C*H*$_2$CHN), 2.05–2.00 (4H, m, C*H*$_2$C*H*$_2$), 1.98–1.84 (6H, m, 2 × C*H*CH$_2$CHN and 2 × C*H*$_2$CHCH$_2$CHN), 1.47–1.32 (4H, m, 2 × C*H*$_2$CCHN), 1.18 (6H, s, 2 × C*H*$_3$C), 0.98 (6H, s, 2 × CC*H*$_3$); δ_C(100 MHz; $CDCl_3$) 164.3 (C), 151.8 (CH), 131.0 (CH), 129.2 (CH), 119.5 (CH), 65.2 (CH), 53.3 (CH$_2$), 48.5 (C), 47.9 (C), 44.9 (CH), 38.8 (CH$_2$), 33.0 (CH$_2$), 32.7 (CH$_2$), 31.9 (CH$_2$), 29.9 (CH$_2$), 26.7 (CH$_2$), 21.0 (CH$_3$), 20.0 (CH$_3$); LRMS (ES$^+$) *m*/*z* 695 [M + Na]$^+$; HRMS (ES$^+$) $C_{36}H_{52}N_2O_6S_2Na^+$ Calcd. 695.3159, found 695.3144.

Oxidative cyclisation products *ent*-4 and 13

To a stirred solution of the tetraene *ent*-**6** (337 mg, 0.50 mmol), AcOH (4 mL) and acetone (6 mL) at –30 °C was added $KMnO_4$ (222 mg, 1.40 mmol) in one portion and the mixture warmed to –20 °C over 25 min, during which time the mixture changed from purple to dark brown. A saturated aqueous solution of $Na_2S_2O_5$ (20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. Brine (10 mL) and EtOAc (20 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL) and CH_2Cl_2 (20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (180 mg). Purification on SiO_2 (2 × 15 cm) eluting with MeOH–CH_2Cl_2 (1 : 49→3 : 47) afforded an inseparable mixture of the title diastereoisomers *ent*-**4/13** (dr ~ 3 : 1) as a white foam (108 mg, 0.140 mmol, 28%). Physical and spectroscopic data were recorded from the mixture of diastereoisomers. $[\alpha]_D^{25}$ –41.0 (*c* 0.75 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3455 w, 2961 m, 2884 m and 1690 m; δ_H(400 MHz; $CDCl_3$) 4.61–4.52 (4H, m, 2 × C(O)C*H*OH and 2 × C(O)CHOHC*H*), 3.97 (2H, dd, *J* 5.2, 7.7, 2 × CHN), 3.88 (2H, td, *J* 6.8, 4.8, 2 × OC*H*CHOHCH$_2$), 3.55–3.41 (6H, m, 2 × CH$_2$SO$_2$ and 2 × C*H*OHCH$_2$), 2.28–2.19 (2H, m, C*H*HCHN), 2.14–2.01 (6H, m, CH*H*CHN and C*H*$_2$ THF), 1.99–1.83 (10H, m, 2 × C*H*CH$_2$CHN, 2 × C*H*$_2$CHCH$_2$CHN and C*H*$_2$ THF), 1.68 (4H, br, C*H*$_2$C*H*$_2$), 1.47–1.31 (4H, m, 2 × C*H*$_2$CCHN), 1.16 (6H, s, 2 × C*H*$_3$), 0.97 (6H, s, 2 × C*H*$_3$); δ_C(100 MHz; $CDCl_3$) 172.0 (C), 83.4 (CH), 78.9 (CH), 74.0 (CH), 73.7 (CH), 66.0 (CH), 53.2 (CH$_2$), 49.1 (C), 48.0 (C), 44.8 (CH), 38.4 (CH$_2$), 33.1 (CH$_2$), 28.3 (CH$_2$), 26.5 (CH$_2$), 21.1 (CH$_3$), 20.0 (CH$_3$); LRMS (ES$^+$) *m*/*z* 795 [M + Na]$^+$; HRMS (ES$^+$) $C_{36}H_{56}N_2O_{12}S_2Na^+$ Calcd. 795.3166, found 795.3147.

Oxidative cyclisation products 3 and 14

To a stirred solution of 1,16-(1*S*,2*R*)-*N*-[(2*Z*,6*E*,10*E*,14*Z*)-16-oxo-2,6,10,14-hexadecatetraenoyl]-di-camphor-10,2-sultam (**5**, 109 mg, 0.16 mmol), phosphate buffer (0.25 mL) and acetone (4.20 mL) at −30 °C was added a mixture of $NaMnO_4$ (0.4 M aq, 1.22 mL, 0.49 mmol) and AcOH (0.05 mL, 0.88 mmol) dropwise over 10 min. The mixture was allowed to warm to −10 °C over 30 min, during which time the mixture turned from purple to dark brown. A saturated solution of $Na_2S_2O_5$ (20 mL) was added to reduce the precipitated brown MnO_2, and the mixture stirred until clear. Brine (20 mL) and EtOAc (50 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 50 mL) and CH_2Cl_2 (50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give a pale yellow foam (102 mg). Purification on SiO_2 (1.5 × 15 cm) eluting with MeOH–CH_2Cl_2 (1 : 49→3 : 47) afforded a mixture of the title diastereoisomers **3**/**14** (dr ~ 3 : 1) as a white foam (51 mg, 0.07 mmol, 41%). Physical and spectroscopic data were recorded from the mixture of diastereoisomers. $[\alpha]_D^{25}$ −59.9 (*c* 0.52 in MeOH); ν_{max} (neat)/cm^{-1} 3503 w, 2958 m, 2881 m and 1692 m; δ_H(400 MHz; $CDCl_3$) 4.71 (2H, br d, *J* 5.0, 2 × C(O)C*H*OH), 4.37 (2H, appt. q, *J* 5.0, 2 × C(O)CHOHC*H*), 3.96–3.91 (2H, m, 2 × CHN), 3.87 (2H, td, *J* 6.8, 4.8, 2 × C*H*CHOHCH$_2$), 3.65 (2H, br, CHO*H*), 3.55–3.41 (6H, m, 2 × CH_2SO_2 and 2 × C*H*OHCH$_2$), 2.25–2.21 (2H, m, CH*H*CHN), 2.13–1.83 (16H, m, C*H*HCHN, C*H*$_2$ THF, C*H*CH$_2$CHN, C*H*$_2$CHCH$_2$CHN), 1.73–1.60 (4H, m, 2 × CHOHC*H*$_2$), 1.49–1.31 (4H, m, 2 × C*H*$_2$CCHN), 1.16 (6H, s, 2 × C*H*$_3$), 0.98 (6H, s, 2 × C*H*$_3$); δ_C(100 MHz; $CDCl_3$) 171.0 (C), 83.1 (CH), 79.3 (CH), 73.9 (CH), 73.0 (CH), 65.5 (CH), 53.0 (CH_2), 49.2 (C), 48.0 (C), 44.7 (CH), 38.2 (CH_2), 32.9 (CH_2), 31.0 (CH_2), 28.3 (CH_2), 26.7 (CH_2), 26.5 (CH_2), 20.9 (CH_3), 20.0 (CH_3); LRMS (ES$^+$) *m*/*z* 795 [M + Na]$^+$; HRMS (ES$^+$) $C_{36}H_{56}N_2O_{12}S_2Na^+$ Calcd. 795.3167, found 795.3206.

Hexaols 15 and 16

To a stirred solution of a mixture of the tetraols **3** and **14** (323 mg, 0.42 mmol) in THF (5 mL) at −10 °C was added $LiBH_4$ (2 M in THF, 0.84 mL, 1.67 mmol) dropwise. MeOH (3 mL) was added after 30 min at −10 °C, and the mixture was concentrated *in vacuo* to give a white solid (355 mg). Purification on SiO_2 (2 × 10 cm) eluting with MeOH–CH_2Cl_2 (1 : 9→7 : 3) gave a mixture of the title diastereoisomers **15**/**16** (dr ~ 3 : 1) as a pale yellow oil (90 mg, 0.26 mmol, 62%). Physical and spectroscopic data were recorded from the mixture of diastereoisomers. NMR data for the major and minor isomers are indicated where possible. $[\alpha]_D^{25}$ +3.6 (*c* 0.13 in MeOH); ν_{max} (neat)/cm^{-1} 3339 s, 2941 m, 2924 m and 2883 m; δ_H(400 MHz; CD_3OD) 3.75 (2H, td, *J* 6.8, 5.3, 2 × C*H*CHOHCH$_2$OH), 3.66 (2H, td, *J* 6.5, 5.0, 2 × CH$_2$CHOHC*H*), 3.53 (2H, td, *J* 5.3, 5.1, 2 × C*H*OHCH$_2$OH), 3.46 (2H, dd, *J* 11.0, 4.5, 2 × CHOHC*H*HOH), 3.37 (2H, dd, *J* 11.0, 6.3, 2 × CHOHCH*H*OH), 3.33–3.27 (2H, m, 2 × CH$_2$C*H*OHCH), 1.83–1.72 (4H, m, 2 × C*H*$_2$ THF), 1.67–1.58 (4H, m, C*H*$_2$), 1.52–1.44 (4H, m, 2 × C*H*$_2$CHOHCH); δ_C(100 MHz; CD_3OD) for major isomer **15** 83.91 (CH), 81.53 (CH), 74.8 (CH), 74.5 (CH), 65.0 (CH_2), 31.0 (CH_2), 28.6 (CH_2), 27.28 (CH_2); [Additional peaks corresponding to the minor diastereoisomer **16**: 83.87 (CH), 81.51 (CH), 27.30 (CH_2)]; LRMS (ES$^+$) *m*/*z* 373 [M + Na]$^+$; HRMS (ES$^+$) $C_{16}H_{30}O_8Na^+$ Calcd. 373.1833, found 373.1840.

Mono-tosylates 17 and 18

To a stirred solution of the hexaols **15** and **16** (20 mg, 0.06 mmol) in dioxane (1 mL) at rt was added Bu_2SnO (18 mg, 0.07 mmol) and the mixture heated to reflux for 2 h. The mixture was cooled to rt and TsCl (13 mg, 0.07 mmol) was added. After 14 h the mixture was concentrated *in vacuo* to give a yellow solid (45 mg). Purification on SiO_2 (3.5 × 15 cm) eluting with MeOH–CH_2Cl_2 (3 : 47→1 : 9) gave the title diastereoisomers **17**/**18** (dr ~ 3 : 1) as a colourless oil (10 mg, 0.02 mmol, 35%). Physical and spectroscopic data were recorded from the mixture of diastereoisomers. NMR data for the major and minor isomers are indicated where possible. $[\alpha]_D^{25}$ −11.8 (*c* 0.50 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3374 m, 2949 w, 2909 w and 2879 w; δ_H(400 MHz; CD_3OD) 7.81 (2H, d, *J* 8.0, 2 × C Ar*H*), 7.44 (2H, d, *J* 8.0, 2 × C Ar*H*), 4.19 (1H, dd, *J* 3.2, 10.3, TsOC*H*H), 3.99 (1H, dd, *J* 6.3, 10.3, TsOCH*H*), 3.90 (1H, m, C*H*OHCH$_2$OTs), 3.84–3.60 (6H, m, C*H*OH, C*H*HOH and C*H*O), 3.53 (1H, dd, *J* 4.9, 11.1, CH*H*OH), 3.46–3.34 (2H, m, C*H*OHCH$_2$CH$_2$C*H*OH), 2.45 (3H, s, CC*H*$_3$), 2.00–1.35 (12H, m, C*H*$_2$); δ_C(100 MHz; CD_3OD) 146.9 (C), 134.8 (C), 131.4 (CH), 129.5 (CH), 84.7 (CH), 84.3 (CH), 81.9 (CH), 80.7 (CH), 75.1 (CH), 74.9 (CH), 74.7 (CH), 73.7 (CH_2), 72.8 (CH), 65.4 (CH_2), 31.4 (CH_2), 31.3 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 28.6 (CH_2), 27.7 (CH_2), 22.0 (CH_3); [Additional peaks corresponding to the minor diastereoisomer **18**: 75.6 (CH), 75.4 (CH), 31.9 (CH_2), 31.7 (CH_2)]; LRMS (ES$^+$) *m*/*z* 527 [M + Na]$^+$; HRMS (ES$^+$) $C_{23}H_{36}O_{10}SNa^+$ Calcd. 527.1921, found 527.1924.

Mono-epoxides 19 and 20

To an ice-cooled solution of the tosylates **17**/**18** (106 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) was added DBU (50 µL, 0.32 mmol). The ice bath was removed and the solution was stirred at ambient temperature for 1.5 h. Removal of the solvent *in vacuo* gave a pale yellow oil (148 mg), which was purified on SiO_2 (1.5 × 15 cm) eluting with MeOH–CH_2Cl_2 (3 : 47→1 : 9) to return a mixture of diastereoisomeric mono-epoxides **19**/**20** (dr ~ 3 : 1, 40 mg, 0.12 mmol, 57%) as a colourless oil. Physical and spectroscopic data were recorded from the mixture of diastereoisomers. NMR data for the major and minor isomers are indicated where possible. $[\alpha]_D^{25}$ +6.9 (*c* 0.44 in MeOH); ν_{max} (neat)/cm^{-1} 3361 m, 2952 w, 2921 w and 2880 w; δ_H(400 MHz; CD_3OD) 3.92 (1H, appt. q, *J* 7.0, OC*H*), 3.89–3.77 (3H, m, CH$_2$OCHC*H*O and 2 × C*H*CHOH), 3.72–3.60 (2H, m, C*H*OHC*H*HOH), 3.53 (1H, dd, *J* 4.3, 11.1, CHOHCH*H*OH), 3.52–3.41 (2H, m, C*H*OHCH$_2$CH$_2$C*H*OH), 3.09 (1H, td, *J* 4.0, 2.8, CH$_2$OC*H*CHO), 2.79 (1H, dd, *J* 4.0, 5.0, CH*H*OCHCHO), 2.66 (2H, dd, *J* 5.0, 2.8, C*H*HOCHCHO), 2.02–1.58 (12H, m, C*H*$_2$); δ_C(100 MHz; CD_3OD) 84.7 (CH), 83.9 (CH), 81.5 (CH), 80.3 (CH), 74.7 (CH), 74.6 (CH), 74.5 (CH), 65.0 (CH_2), 54.2 (CH), 46.2 (CH_2), 30.9 (CH_2), 30.5 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 28.3 (CH_2), 27.3 (CH_2); [Additional peaks corresponding to the minor diastereoisomer **20**: 84.6 (CH), 83.9 (CH), 75.3 (CH), 75.2 (CH), 74.8 (CH), 28.5 (CH_2)]; LRMS (ES$^+$) *m*/*z* 355 ([M + Na]$^+$); HRMS (ES$^+$) $C_{16}H_{28}O_7Na^+$ Calcd. 355.1727, found 355.1719.

Compounds 21 and 22

To a stirred solution of CuI (86 mg, 0.45 mmol) in THF (3 mL) at −70 °C was added nonylmagnesium bromide (1 M in Et_2O, 0.90 mL, 0.90 mmol) dropwise. The mixture was warmed to −20 °C over 20 min (mixture white→grey), then cooled to −70 °C. A solution of the epoxides **19** and **20** in THF (3 mL) was added dropwise and the mixture warmed to −40 °C over 1 h. Aqueous NH_4Cl–NH_4OH (4 : 1, 10 mL) and EtOAc (10 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow foam (25 mg). Purification on SiO_2 (1 × 15 cm) eluting with MeOH–CH_2Cl_2 (3 : 47→1 : 9) afforded the title diastereoisomers **21/22** (dr ~ 3 : 1) as a colourless oil (20 mg, 0.04 mmol, 58%). Physical and spectroscopic data were recorded from the mixture of diastereoisomers. NMR data for the major and minor isomers are indicated where possible. $[\alpha]_D^{25}$ +4.2 (*c* 0.56 in MeOH); ν_{max} (neat)/cm^{-1} 3351 m, 2924 w and 2854 w; δ_H(400 MHz; CD_3OD) 3.92 (1H, td, *J* 6.5, 5.3, C*H*CHOHCH$_2$OH), 3.87–3.78 (3H, m, 3 × OC*H*), 3.73–3.67 (2H, m, $C_{10}H_{21}$C*H*OH and C*H*OHCH$_2$OH), 3.64 (1H, dd, *J* 11.3, 4.6, C*H*HOH), 3.54 (1H, dd, *J* 11.3, 6.3, CH*H*OH), 3.50–3.41 (2H, m, C*H*OHCH$_2$CH$_2$C*H*OH), 2.00–1.71 (8H, m, CH_2 THF), 1.69–1.60 (4H, m, CHOHCH_2CH_2CHOH), 1.57–1.45 (2H, m, C_9H_{19}CH_2CHOH), 1.40–1.30 (16H, m, CH_3(CH_2)$_8$), 0.92 (3H, t, *J* 6.8, CH_3); δ_C(100 MHz; CD_3OD) 84.5 (CH), 84.3 (CH), 84.1 (CH), 81.9 (CH), 75.1 (CH), 74.9 (CH), 74.0 (CH), 65.4 (CH_2), 34.9 (CH_2), 33.4 (CH_2), 31.2 (CH_2), 31.1 (CH_2), 30.8 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 27.7 (CH_2), 27.4 (CH_2), 26.4 (CH_2), 24.1 (CH_2), 14.8 (CH_3); [Additional peaks corresponding to the minor diastereoisomer **22**: 84.0 (CH)]; LRMS (ES$^+$) *m*/*z* 483 [M + Na]$^+$; HRMS (ES$^+$) $C_{25}H_{48}O_7Na^+$ Calcd. 483.3292, found 483.3284.

Bis-tosylates 23 and 24

To a stirred solution of the hexaols **13** and **14** (31 mg, 0.09 mmol) in benzene (5 mL) at rt was added Bu_2SnO (55 mg, 0.22 mmol) and the mixture heated to reflux for 3 h. The mixture was cooled to rt and TsCl (37 mg, 0.19 mmol) was added. After 14 h the mixture was concentrated *in vacuo* to give a yellow solid. Purification on SiO_2 (1.5 × 15 cm) eluting with MeOH–CH_2Cl_2 (1 : 49→1 : 24) gave the title diastereoisomers **23/24** (dr ~ 3 : 1) as a colourless oil (41 mg, 0.06 mmol, 72%). Physical and spectroscopic data were recorded from the mixture of diastereoisomers. NMR data for the major and minor isomers are indicated where possible. $[\alpha]_D^{25}$ −5.5 (*c* 0.50 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3347 m, 2949 m, 2920 m and 2884 m; δ_H(400 MHz; $CDCl_3$) 7.80 (4H, d, *J* 8.3, Ar*H*), 7.35 (4H, d, *J* 8.3, Ar*H*), 4.09 (2H, td, *J* 6.6, 6.0, 2 × TsOCH$_2$C*H*OH), 4.03–3.88 (6H, m, 2 × TsOCH_2CHOHC*H*), 3.85–3.75 (2H, m, 2 × C*H*CHOHCH$_2$), 3.61 (1H, br s, O*H*), 3.48–3.38 (2H, m, C*H*OHCH$_2$CH$_2$C*H*OH), 2.45 (6H, s, 2 × CH_3), 1.99–1.54 (12H, m, CH_2); δ_C(100 MHz; $CDCl_3$) 145.2 (C), 132.8 (C), 130.1 (CH), 128.1 (CH), 82.8 (CH), 79.5 (CH), 74.6 (CH), 71.4 (CH_2), 71.1 (CH), 31.2 (CH_2), 28.2 (CH_2), 26.0 (CH_2), 21.8 (CH_3); [Additional peaks corresponding to the minor diastereoisomer **24**: 82.7 (CH), 79.4 (CH), 74.3 (CH)]; LRMS (ES$^+$) *m*/*z* 681 [M + Na]$^+$; HRMS (ES$^+$) $C_{30}H_{42}O_{12}S_2Na^+$ Calcd. 681.2010, found 681.2003.

Bis-epoxides 2 and 25

To a stirred solution of tosylates **23** and **24** (102 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added DBU (70 μL, 0.47 mmol) and the mixture stirred for 3 h. The mixture was concentrated *in vacuo* to give a pale yellow oil (108 mg). Purification on SiO_2 (1.5 × 15 cm) eluting with MeOH–CH_2Cl_2 (1 : 49→1 : 24) afforded the title diastereoisomers **2/25** (dr ~ 3 : 1) as a colourless oil (40 mg, 0.13 mmol, 82%). Physical and spectroscopic data were recorded from the mixture of diastereoisomers. NMR data for the major and minor isomers are indicated where possible. $[\alpha]_D^{25}$ +5.6 (*c* 0.69 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3440 m, 2947 m, 2919 m and 2875 m; δ_H(400 MHz; $CDCl_3$) 3.92–3.85 (2H, m, 2 × CH$_2$(O)CHC*H*), 3.84–3.77 (2H, m, 2 × CH$_2$C*H*CHOH), 3.54–3.43 (2H, m, C*H*OHCH$_2$CH$_2$C*H*OH), 3.06–3.00 (2H, m, 2 × CH$_2$(O)C*H*CH), 2.81 (2H, appt. t, *J* 5.0, 2 × C*H*H(O)CH), 2.72 (1H, br, O*H*), 2.65 (1H, br, O*H*), 2.62 (2H, dd, *J* 5.0, 2.6, 2 × CH*H*(O)CH), 2.01–1.89 (4H, m, 2 × CH*H* THF), 1.88–1.72 (4H, m, 2 × C*H*H THF), 1.71–1.58 (4H, m, CHOHCH_2CH_2CHOH); δ_C(100 MHz; $CDCl_3$) 83.3 (CH), 79.5 (CH), 74.2 (CH), 53.2 (CH), 45.9 (CH_2), 29.7 (CH_2), 27.7 (CH_2), 27.6 (CH_2); [Additional peaks corresponding to the minor diastereoisomer **25**: 83.4 (CH), 79.4 (CH), 53.5 (CH), 45.8 (CH_2), 30.2 (CH_2), 27.8 (CH_2), 27.7 (CH_2)]; LRMS (ES$^+$) *m*/*z* 337 [M + Na]$^+$; HRMS (ES$^+$) $C_{16}H_{26}O_6Na^+$ Calcd. 337.1621, found 337.1621.

Silyl ethers 26, 27 and 28

To a stirred solution of the bis-epoxides **2** and **25** (28 mg, 0.089 mmol) in CH_2Cl_2 (1.5 mL) at rt was added 2,6-lutidine (20 μL, 0.18 mmol) dropwise. The mixture was cooled to −10 °C and TBSOTf (40 μL, 0.18 mmol) was added dropwise. After 30 min H_2O (2 mL) and EtOAc (4 mL) were added, the organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 4 mL). The combined organic phases were washed successively with 3 M $KHSO_4$ (5 mL), H_2O (5 mL) and brine (5 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil (65 mg). Purification on SiO_2 (3.5 × 15 cm) eluting with EtOAc–hexane (2 : 23) gave **26** as a colourless oil (14 mg, 0.026 mmol, 29%), **28** as a crystalline solid (7 mg, 0.013 mmol, 15%), and **27** as a colourless oil (6 mg, 0.014 mmol, 16%). **Data for 26:** $[\alpha]_D^{25}$ −6.3 (*c* 0.44 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 2954 m, 2930 m, 2883 m and 2856 m; δ_H(400 MHz; $CDCl_3$) 3.85 (2H, td, *J* 6.9, 6.0, 2 × C*H*CHOTBS), 3.73 (2H, dt, *J* 6.5, 5.8, 2 × CH$_2$(O)CHC*H*), 3.66–3.59 (2H, m, 2 × C*H*OTBS), 2.99–2.94 (2H, m, 2 × CH$_2$(O)C*H*CH), 2.79 (2H, appt. t, *J* 5.0, 2 × C*H*H(O)CH), 2.64 (2H, dd, *J* 5.0, 2.5, 2 × CH*H*(O)CH), 2.02–1.93 (2H, m, CH_2 THF), 1.90–1.75 (4H, m, CH_2 THF), 1.74–1.67 (2H, m, CH_2 THF), 1.55–1.50 (4H, m, CHOHCH_2CH_2CHOH), 0.90 (18 H, s, 2 × C(CH_3)$_3$), 0.08 (6H, s, 2 × SiCH_3), 0.07 (6H, s, 2 × SiCH_3); δ_C(100 MHz; $CDCl_3$) 82.7 (CH), 79.5 (CH), 75.1 (CH), 53.4 (CH), 45.9 (CH_2), 29.2 (CH_2), 28.5 (CH_2), 26.8 (CH_2), 26.1 (CH_3), 18.4 (C), −4.0 (CH_3), −4.5 (CH_3); LRMS (ES$^+$) *m*/*z* 565 [M + Na]$^+$; HRMS (ES$^+$) $C_{28}H_{54}O_6Si_2Na^+$ Calcd. 565.3351, found 565.3357. **Data for 27:** $[\alpha]_D^{25}$ −5.9 (*c* 0.31 in $CHCl_3$); ν_{max} (neat)/cm^{-1} 3453 w, 2951 m, 2928 m, 2881 m and 2857 m; δ_H(400 MHz; $CDCl_3$) 3.92–3.84 (2H, m, C*H*CHOH and CH(OTBS)C*H*), 3.83–3.73 (2H, m, CH$_2$(O)CHC*H* and C*H*CH(O)CH$_2$), 3.67 (1H, m, C*H*OTBS), 3.44 (1H, m, C*H*OH), 3.05–2.97 (2H, m, CH$_2$(O)C*H*CH and

CHC*H*(O)CH_2), 2.82 (1H, dd, *J* 5.0, 4.0, C*H*H(O)CH), 2.79 (1H, dd, *J* 5.0, 4.0, CH(O)CH*H*), 2.65 (1H, dd, *J* 5.0, 2.7, CH*H*(O)CH), 2.61 (1H, dd, *J* 5.0, 2.7, CH(O)C*H*H), 2.05–1.50 (12H, m, CH_2), 0.90 (9H, s, C(CH_3)$_3$), 0.09 (3H, s, SiCH_3), 0.08 (3H, s, SiCH_3); δ_C(100 MHz; $CDCl_3$) 83.2 (CH), 82.5 (CH), 79.3 (CH), 79.2 (CH), 74.54 (CH), 74.47 (CH), 53.3 (CH), 53.0 (CH), 45.70 (CH_2), 45.66 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 28.3 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 26.9 (CH_2), 26.1 (CH_3), 18.2 (C), –4.1 (CH_3), –4.4 (CH_3); LRMS (ES^+) *m*/*z* 451 $[M + Na]^+$; HRMS (ES^+) $C_{22}H_{40}O_6$ $SiNa^+$ Calcd. 451.2486, found 451.2487. **Data for 28:** mp 51–52 °C; δ_H(400 MHz; $CDCl_3$) 3.85 (2H, td, *J* 6.9, 6.0, 2 × C*H*CHOTBS), 3.73 (2H, dt, *J* 6.5, 5.8, 2 × CH_2(O)CHC*H*), 3.64–3.58 (2H, m, 2 × C*H*OTBS), 2.98–2.94 (2H, m, 2 × CH_2(O)C*H*CH), 2.79 (2H, appt. t, *J* 5.0, 2 × C*H*H(O)CH), 2.63 (2H, dd, *J* 5.0, 2.5, 2 × CH*H*(O)CH), 2.02–1.93 (2H, m, CH_2 THF), 1.90–1.76 (4H, m, CH_2 THF), 1.75–1.67 (4H, m, CH_2 THF and CH_2CHOH), 1.35–1.30 (2H, m, CH_2CHOH), 0.90 (18H, s, 2 × C(CH_3)$_3$), 0.08 (6H, s, 2 × SiCH_3), 0.07 (6 H, s, 2 × SiCH_3); δ_C(100 MHz; $CDCl_3$) 82.9 (CH), 79.5 (CH), 75.3 (CH), 53.4 (CH), 45.9 (CH_2), 29.4 (CH_2), 28.5 (CH_2), 26.9 (CH_2), 26.1 (CH_3), 18.4 (C), –4.1 (CH_3), –4.4 (CH_3).

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Notes and references

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13 Crystal data for **28** $C_{28}H_{54}O_6Si_2$, M_r = 542.89, *T* = 120(2) K, triclinic, space group $P\bar{1}$, *a* = 7.417(5), *b* = 10.385(5), *c* = 10.651(5) Å, α = 68.383(5), β = 83.788(5), γ = 82.900(5)°, *V* = 755.1(7) Å^3, ρ_{calc} = 1.194 g cm^{-3}, μ = 0.155 mm^{-1}, *Z* = 1, reflections collected: 12517, independent reflections: 3491 (*R*int = 0.0547), final *R* indices [$I > 2\sigma I$]: *R*1 = 0.0455, w*R*2 = 0.0981, *R* indices (all data): *R*1 = 0.0665. w*R*2 = 0.1072†.

