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Natural Product Synthesis

Synthesis and Configurations of (–)-Furospongin-1 and (+)-Dihydrofurospongin-2

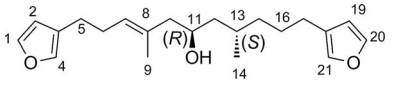
Dong-Xing Tan,[a,b] Ze-Jun Xu,[a] Hui-Jun Chen,[a] Yikang Wu,*[a] and Jun You*[b]

Abstract: The long-known furanoterpenes furospongin-1 and dihydrofurospongin-2 were synthesized for the first time using a chiral-pool-based route in an effort to secure the previous configurational assignments. The key C-11 stereogenic centre was taken from D-mannose, and the C-13 alkyl centre was installed exploiting the chirality of mannose. Due to deprotonation and/or enolization of the building blocks used, introduction of the furan moieties was problematic, and so some reactions had to be avoided. The trisubstituted alkene was most satisfactorily constructed using a Julia–Kocienski olefination in 1,2-dimethoxyethane, with the best (*E*)/(*Z*) ratio achieved using a secondary sulfone. The synthetic samples not only provided the first unequivocal piece of evidence for the C-13 configuration of both natural products, but also confirmed the absolute configuration at C-11 of furospongin-1.

Introduction

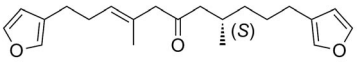
Furospongin-1 (**1**; Figure 1) was initially isolated from the marine sponge *Spongia officinalis* and *Hippospongia communis* by Cimino et al. in 1971.[1] Its gross structure was convincingly established by extensive NMR experiments, with the absolute configuration of the stereogenic centre at C-11 assigned as (*S*) using Horeau's[2a,2b] method, and that of the centre at C-13 assigned as (*R*) through comparison of the optical rotation {$[\alpha]_D$ = +1.30 (*c* = 2, $CHCl_3$)} of its degradation product (2-methyladipic acid) with that {$[\alpha]_D$ = –1.42 (*c* = 4, EtOH)} of an authentic sample.[3] One year later, Cimino et al. revised the C-13 configuration from the previously assigned (*R*) to (*S*) when they reported the isolation of dihydrofurospongin-2 (**2**) from *S. officinalis* and *H. communis*,[4] as a result of the then recently correction[5] of the absolute configuration of (–)-2-methyladipic acid from (*S*) to (*R*).

In 1986, Pietra[6] et al. isolated the same compound (i.e., **1**) from the sponge *Cacospongia scalaris*, along with **2** and several other compounds. They updated the optical rotation of **1** to $[\alpha]_D^{20}$ = +8.9 (*c* = 1.0, $CHCl_3$). The ketone (i.e., **2**) that they isolated was identical to that obtained by oxidation of the concurrently isolated natural **1** in all aspects, but it showed an optical rotation nearly ten times larger than reported[4] earlier {i.e., $[\alpha]_D^{20}$ = –8.1 (*c* = 2.31, $CHCl_3$) vs. $[\alpha]_D$ = –0.91 (unspecified concentration, $CHCl_3$) for the isolated ones, or $[\alpha]_D^{20}$ = –8.6 (*c* = 2.93, $CHCl_3$) vs. $[\alpha]_D$ = –1.04 (unspecified concentration, $CHCl_3$) for those obtained by oxidation of **1**}. The addition of a chiral shift reagent to their **1** did not lead to splitting of signals in the ^1H NMR spectrum, confirming the purity of their sample. Then Pietra et al. concluded that the previously[4] assigned C-13 absolute configuration was wrong, and therefore should be revised to (*S*).[7]



1 (+)-furospongin-1

$[\alpha]_D^{20}$ = +8.9 (*c* = 1.0, $CHCl_3$)



2 dihydrofurospongin-2

$[\alpha]_D^{20}$ =–8.1 (*c* = 2.31, $CHCl_3$)

Figure 1. The structures of natural **1** and **2**, and their optical rotations. The position-numbering system is adopted from ref.[1,8,11] The configurations at C-11 and C-13 for **1** and **2** are depicted according to ref.[8,11] and the optical rotations are taken from ref.[6]

A subsequent structural study on furospongin-1 by Kobayashi[8] et al. appeared in 1992, and doubts about the assignment of C-11 using Horeau's method were presented.[9] The more reliable Mosher's[10] method was then used, and this led to a revision of the C-11 configuration from the initially assigned (*S*) to (*R*). The C-13 configuration of both **1** and **2** was simply depicted in the paper by Kobayashi et al.[8] as (*S*). Reference was simply made to Cimino's[1,4] work without mentioning that the configuration shown in the main text of both papers was wrong; the revision of the C-13 configuration from the originally

[a] *State Key Laboratory of Bioorganic and Natural Products Chemistry, Collective Innovative Center for Chemistry and Life Sciences, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China*
E-mail: yikangwu@sioc.ac.cn;
http://www.sioc.ac.cn

[b] *Key Laboratory of Green Chemical Technology of College of Heilongjiang Province, College of Chemical and Environmental Engineering, Harbin University of Science and Technology, Harbin 150040, P. R. China*

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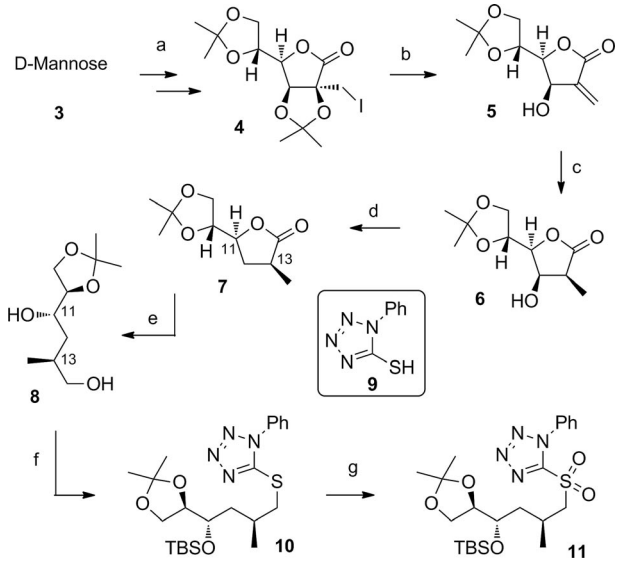
assigned (*R*) to (*S*) could be found only in a footnote of the later[4] reference, and is rather easily overlooked.

In 2011, Manzo[11] et al. reported the isolation of **1** and **2** (along with several other furanoterpenes including epoxide **3**) from *S. officinalis* again. In this most recent paper, the structures and absolute configurations of **1** and **2** were explicitly shown (as depicted in Figure 1). However, neither new experimental proofs nor comments on the configurations were given. Thus, although the absolute configurations of natural **1** and **2** have experienced two revisions over the years, i.e., from the initially determined (11*S*,13*R*) via the partially revised (11*S*,13*S*) to the latest (11*R*,13*S*), and seemingly reconfirmed by the clearly depicted absolute configurations in the very recent paper, the line of reasoning/underlying argument about the C-13 configuration still remains unconvincing, because the critical piece of evidence comes from the optical rotations, which were measured in $CHCl_3$ and EtOH, rather than in the same solvent. Thus, an enantioselective synthesis appears to be necessary to remove the doubt from the literature.

Results and Discussion

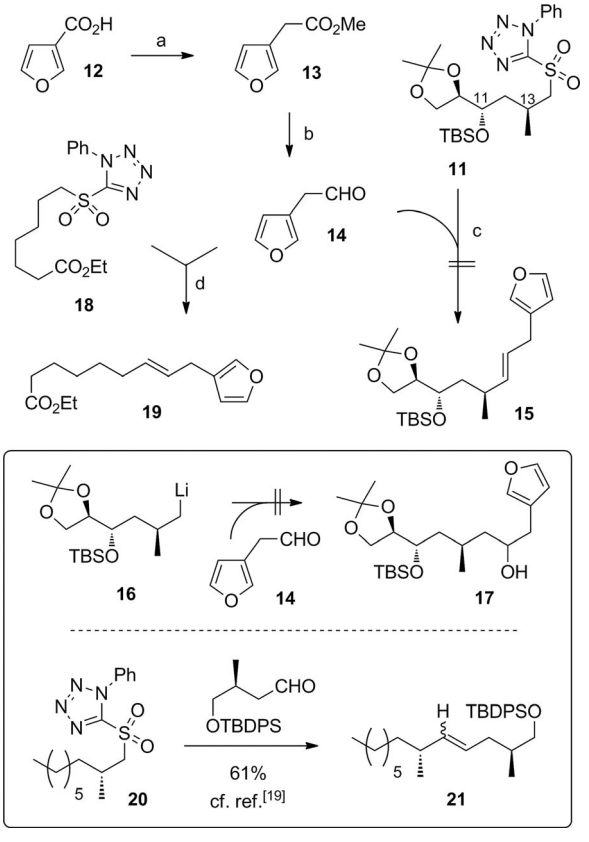
Our synthesis began with the conversion of D-mannose **3** into **4** according to literature procedures (Scheme 1). Thus, treatment of D-mannose with I_2/acetone introduced the two acetonide protecting groups (78 %).[12] Subsequent exposure to K_2CO_3/MeOH/HCHO installed the quaternary centre with high stereoselectivity (81 %).[13] Selective oxidation of the hemiacetal with I_2/K_2CO_3/*t*BuOH gave the intermediate lactone,[14] which, on treatment with I_2/Ph_3P/imidazole/MePh, gave iodide **4** (93 %).[15]



Scheme 1. Reagents and conditions. a) literature procedures; b) Zn dust, THF/H_2O (3:1), 90 %; c) H_2, Pd/C, MeOH, 92 % for **6** along with traces of **7**; d) (i) MsCl, Et_3N, CH_2Cl_2, 83 %, (ii) Pd/C, MeOH, 86 %; e) $LiAlH_4$, THF, 98 %; f) (i) **9**, Ph_3P, DEAD, THF, 90 %, (ii) imidazole, TBSCl, DMF, 88 %; g) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 65 %; DEAD = diethyl azodicarboxylate, *m*-CPBA = *m*-chloroperbenzoic acid, Ms = methylsulfonyl, TBS = *tert*-butyldimethylsilyl.

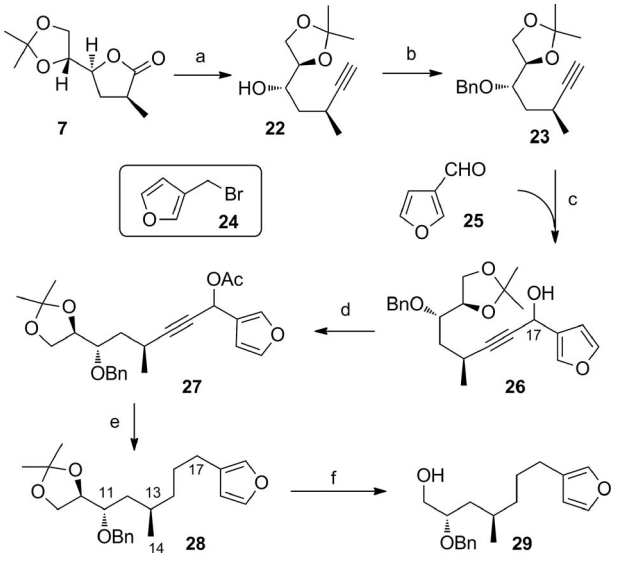
Reductive elimination of the iodide/acetonide from **4** with Zn dust[16] led to exocyclic alkene **5**. Saturation of this double bond by hydrogenation occurred with high facial selectivity to give **6** in 92 % yield. A deoxygenation was then carried out through sequential activation of the hydroxyl group with MsCl, β-elimination, and hydrogenation. Lactone **7** (with the C-13 configuration fully secured by NOESY) thus obtained was reduced with $LiAlH_4$ to give diol **8**, which was further converted into **10** through reaction[15a] with **9**[17b] in the presence of DEAD/Ph_3P, followed by TBS protection of the secondary hydroxyl group. Finally, oxidation with *m*-CPBA provided sulfone **11**.

Coupling of **11** with aldehyde **14** (prepared from the commercially available **12**[18a] via **13**[18b]) failed to give any **15** (Scheme 2); a complex mixture was obtained instead. Starting material **14** was fully consumed, while **11** was almost fully recovered (a similar phenomenon was also observed in the attempted but failed addition of **16** to aldehyde **14**). When a sterically less hindered sulfone (**18**, without a methyl group at the carbon β to the sulfur atom) was used, the condensation with **14** occurred smoothly, providing **19** in 50 % yield. On the other hand, less readily enolizable aldehydes also reacted well with sulfones of similar steric hindrance, as shown by the conversion[19a] of **20** into **21**.[19b] Taken together, all these observations strongly suggested that the difficulties encountered in coupling **11** with **14** were caused by the steric hindrance of **11** and the facile enolisation of **14**.[20]



Scheme 2. Reagents and conditions. a) Me_3SiCHN_2, Ag_2O, Et_3N, MeOH, 48 %; b) DIBAL-H, CH_2Cl_2, –78 °C, 65 %; c) LiHMDS or NaHMDS, THF; d) NaHMDS, THF, –78 °C, 51 % for the (*E*) isomer along with traces of (*Z*) isomer; DIBAL-H = diisobutylaluminum hydride, LiHMDS = lithium hexamethyldisilazide, NaHMDS = sodium hexamethyldisilazide.

Another approach to the installation of the furan moiety was then pursued (Scheme 3). Lactone **7** was partially reduced with DIBAL-H.[21] The resulting lactol was treated with Me_3SiCHN_2/LDA[22] to give alkyne **22**. The use of the Ohira–Bestmann reagent[22c,22d] [$MeCOCH(N_2)P(O)(OEt)_2$] here led to partially epimerized **22** (5:1 ratio of the methyl epimers), although the yield was slightly higher (79 %). After masking the hydroxyl group with BnBr, the terminal alkyne was deprotonated with $CsCO_3$ in the presence of CuI/nBu$_4$NI and bromide **24** in the hope of obtaining the alkylation product. Unfortunately, the main component in the product mixture turned out to be the alkyne self-coupling product, and only a small amount of the expected alkyne–furan compound was observed. Therefore, commercially available aldehyde **25** was next used as the source of the furan moiety, and this did give the expected product (i.e., **26**) in satisfactory yield.

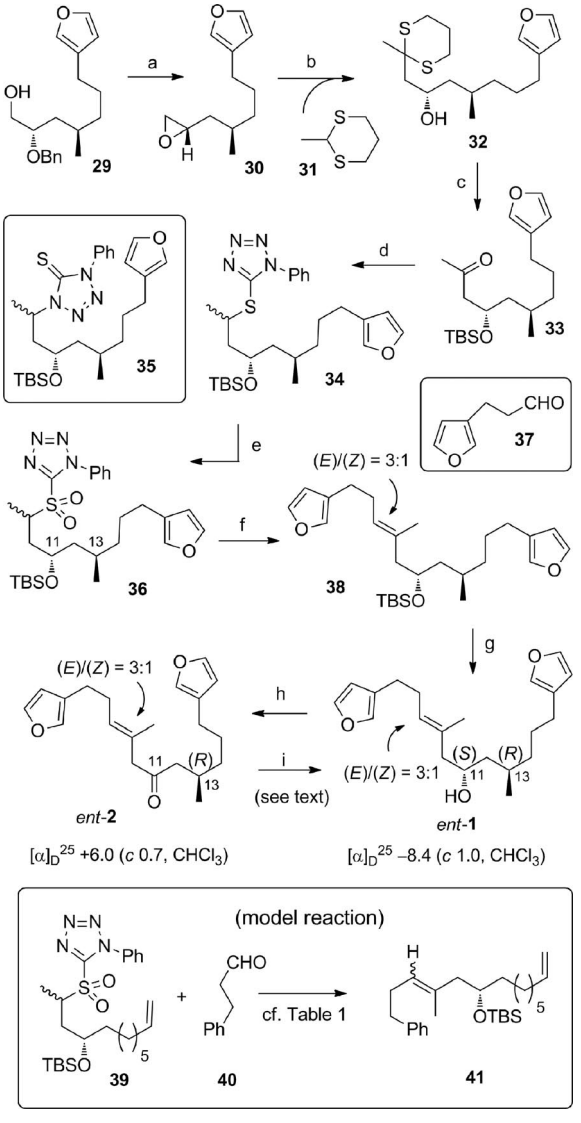


Scheme 3. Reagents and conditions. a) (i) DIBAL-H, CH_2Cl_2, –78 °C, 100 %, (ii) LDA, Me_3SiCHN_2, THF, –78 °C to room temp., 76 %; b) NaH, BnBr, DMF, 88 %; c) nBuLi, THF, –78 °C, 80 %; d) Ac_2O, 100 %; e) H_2, Pd/C, MeCN, 80 %; f) (i) HCl (1 N)/THF (1:1), 100 %, (ii) $NaIO_4$, THF/H_2O (1:1), (iii) $NaBH_4$, MeOH, 92 % from **28**; LDA = lithium diisopropylamide.

Attempted removal of the C-17 OH group in **26** by mesylation[23a] followed by $LiAlH_4$ reduction resulted in a complex mixture, although the desired product could be isolated in low yield. Attempted direct deoxygenation of **26** using Et_3SiH/F_3CCO_2H[23b–23e] also led to a complex mixture. Hydrogenation (under H_2 pressure of 1 or up to 5 atm) of **26** over Pd/C in EtOAc not only saturated the furan ring but also cleaved the benzyl group, while the OH group at C-17 still remained. Acetate **27** behaved similarly. Fortunately, when MeCN was used as the hydrogenation solvent, C-17 deoxygenation and saturation of the triple bond could be achieved satisfactorily without affecting the furan ring.

The acetonide in the resulting compound **28** was then hydrolysed with HCl (1 N). Oxidative cleavage of the terminal vicinal diol with $NaIO_4$ provided the intermediate aldehyde, which, on reduction with $NaBH_4$ in MeOH, gave the corresponding alcohol (i.e., **29**).

The transformation of **29** into *ent*-**1** was carried out as shown in Scheme 4. The benzyl group was removed with Li/naphthalene,[24] and in this way the undesired saturation of the furan ring under hydrogenolysis conditions was avoided. The vicinal diol was converted into an epoxide by regioselective tosylation with nBu$_2$SnO/pTsCl/Et$_3$N/DMAP[25] followed by exposure to K_2CO_3/MeOH. The resulting epoxide (i.e., **30**) was treated with the carbanion derived from dithiane **31** to introduce the methyl ketone moiety. Cleavage of the thioketal protecting group with I_2/$NaHCO_3$[26] in acetone followed by TBS protection gave **33** in 95 % yield (overall from **32**).



$[\alpha]_D^{25}$ +6.0 (*c* 0.7, $CHCl_3$) $[\alpha]_D^{25}$ –8.4 (*c* 1.0, $CHCl_3$)

Scheme 4. Reagents and conditions. a) (i) Li, naphthalene, THF, –78 °C, 100 %, (ii) pTsCl, nBu$_2$SnO, DMAP, Et$_3$N, CH_2Cl_2, (iii) K_2CO_3, MeOH, 80 % from **29**; b) nBuLi, THF, room temp., 90 %; c) (i) I_2, $NaHCO_3$, acetone/H_2O (5:1), 95 %, (ii) TBSCl, imidazole, DMF, 100 %; d) (i) $NaBH_4$, MeOH, 91 %, (ii) **9**, Ph_3P, DEAD, THF, 60 % of **34** along with 16 % of **35**; e) $(NH_4)_6Mo_7O_{24}$·$4H_2O$, 30 % H_2O_2, EtOH, 61 %; f) **37**, NaHMDS, DME, –78 °C, 5 h, 77 %; g) nBu$_4$NF, THF, 65 %; h) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 80 %; i) $NaBH_4$, MeOH, giving an inseparable 1:1 mixture of *ent*-**1** and its C-11 epimer, 90 %; DMAP = 4-(dimethylamino)pyridine, pTs = p-tolylsulfonyl, DME = 1,2-dimethoxyethane.

Construction of the trisubstituted alkene through Wittig[27a] or Julia reaction with methyl ketones appeared normally to pro-

ceed with poor (*E*)/(*Z*) selectivity.[27b] By converting the methyl ketone moiety into a Julia–Kocienski sulfone to react with an aldehyde, (*E*)/(*Z*) selectivity could be achieved. Depending on the reaction conditions, the coupling could be either (*E*)[28a] or (*Z*)[28b] selective. Therefore, we decided to construct the trisubstituted alkene by the reaction of a secondary sulfone with an aldehyde.

To this end, **33** was reduced with $NaBH_4$ and connected with thiol **9** with the aid of Ph_3P/DEAD to give **30**. An unexpected side-product **35**[29] was also formed in 16 % yield. Oxidation of **34** with $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O/H_2O_2$[30] gave sulfone **36**. Subsequent coupling of **36** with aldehyde **37**[31] was achieved using NaHMDS as the base and DME[32] as the solvent (the most satisfactory conditions found using coupling of **39** with **40** as a model reaction, cf. Table 1). Finally, alkene **38** [an inseparable 3:1 mixture of (*E*)/(*Z*) isomers as shown by ^{1}H NMR spectroscopy] was treated with *n*Bu_4NF to give final product *ent*-**1** (the antipode of natural furospongin-1) in 65 % yield along with 23 % of recovered **38**.

Table 1. Condensation of **39** with **40** to give **41** (cf. Scheme 4).[a]

Base/solvent	(*E*)/(*Z*) ratio[b]	Yield [%]
LiHMDS/THF	1:1	90
NaHMDS/THF	4:1	77
KHMDS/THF	1:1	41
NaHMDS/THF/DMF (1:1)	1:1	60
NaHMDS/DMF	3:4	70
NaHMDS/DME	5:1	77

[a] All reactions were carried out at −78 °C for 5 h. KHMDS = $KN(SiMe_3)_2$. [b] As measured from the crude product mixtures by ^{1}H NMR spectroscopy.

The ^{1}H and ^{13}C NMR spectoscopic data for *ent*-**1** agreed very well with those reported for natural **1** [although some extra minor signals from the (*Z*) isomer were also seen]. Oxidation of *ent*-**1** with Dess–Martin periodinane (to give *ent*-**2**) followed by $NaBH_4$ reduction led to a 1:1 mixture of the C-11 epimers. The ^{13}C NMR spectrum of this mixture showed extra signals, for example C-11, C-13, and C-14, from the other diastereomer, which were clearly incompatible with those for natural **1**. It is thus proven beyond all doubt that natural **1** has the same relative configuration as that shown for *ent*-**1**.

It is noteworthy that the above-mentioned oxidation of *ent*-**1** also represents the first synthesis of the long-known dihydrofurospongin-2. The ^{1}H and ^{13}C NMR spectroscopic data showed excellent consistency with those for natural **2**, and its optical rotation was comparable in magnitude but of opposite sign. This unequivocally confirms that *ent*-**2** and natural **2** are antipodes to each other. The hidden yet undeniable doubt about the previously assigned (13*S*) configuration for natural **2** (and consequently, natural **1**) is thus finally eliminated. This unambiguous piece of evidence, together with the results of the comparison of ^{13}C NMR spectroscopic data mentioned above, also unequivocally confirms the (11*R*,13*S*) absolute configuration for natural **1**.

Conclusions

The long-known natural furanoterpenes furospongin-1 and dihydrofurospongin-2 were synthesized for the first time. To secure the reliability of the absolute configurations of the stereogenic centres of the synthetic end products, a chiral-pool-based route was adopted, with both stereognic centres taken from D-mannose. The synthetic samples showed ^{1}H and ^{13}C NMR spectroscopic data with excellent consistency with those of their natural counterparts, confirming that the gross structures assigned were correct. The relative configuration of furospongin-1 was also fully secured with the aid of the ^{13}C NMR spectroscopic data of the other diastereomer. The optical rotation of the synthetic dihydrospongin-2, measured in the same solvent as that for the corresponding natural product, cleared the hidden doubt about the previous assignment of the (13*S*) configuration for natural dihydrofurospongin-2 (and consequently furospongin-1) caused by the comparison of data from different solvents; the configurations of these two natural furoterpenes were thus established beyond all doubt for the first time.

Experimental Section

General Methods: NMR spectroscopic data were recorded with an Agilent 500/54 NMR spectrometer (operating at 500 MHz for ^{1}H), or a Bruker Avance NMR spectrometer (operating at 400 MHz for ^{1}H). IR spectra were measured with a Nicolet 380 Infrared spectrophotometer. ESI-MS data were acquired with a Shimadzu LCMS-2010EV mass spectrometer. ESI-HRMS data were obtained with a Thermo Scientific LTQ FT ULTRA spectrometer. Optical rotations were measured with a Jasco P-1030 polarimeter. Melting points were measured on a hot-stage melting-point apparatus equipped with a microscope. Dry THF was obtained by distillation from Na/Ph_2CO under argon before use. Dry toluene and CH_2Cl_2 were obtained by drying over activated 4 Å molecular sieves. All reagents were reagent grade, and were used as supplied. Column chromatography was carried out on silica gel (300–400 mesh) under slightly positive pressure. Petroleum ether (chromatography eluent) refers to the fraction boiling between 60 and 90 °C.

Conversion of Iodide 4 into Alkene 5: Zn dust (200 mg, 3.06 mmol) was added to a solution of **4** {m.p. 78–80 °C; $[\alpha]_D^{25}$ = +33.2 (*c* = 1.0, $CHCl_3$); 143 mg, 0.36 mmol} in THF/H_2O (3:1, v/v; 6 mL). The mixture was heated with stirring in an 80 °C bath for 1 h. When TLC showed that the reaction was complete, the bath was removed. The mixture was cooled to ambient temperature, then it was filtered through Celite [washing with EtOAc (3 × 20 mL)]. The combined filtrate and washings were transferred to a separatory funnel. The phases were separated. The organic layer was washed with water (5 mL) and brine (5 mL), and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 1.5:1) on silica gel gave alkene **5** (69 mg, 0.32 mmol, 90 %) as a colourless oil, m.p. 36–37 °C. $[\alpha]_D^{25}$ = +81.8 (*c* = 0.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.49 (d, *J* = 1.6 Hz, 1 H), 6.08 (d, *J* = 1.3 Hz, 1 H), 4.98 (d, *J* = 5.4 Hz, 1 H), 4.41 (ddd, *J* = 8.8, 6.1, 4.2 Hz, 1 H), 4.32 (dd, *J* = 8.7, 5.4 Hz, 1 H), 4.20 (dd, *J* = 9.1, 6.1 Hz, 1 H), 4.08 (dd, *J* = 9.1, 4.2 Hz, 1 H), 2.85 (br. s, 1 H), 1.47 (s, 3 H), 1.38 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 137.0, 128.0, 110.2, 80.3, 73.0, 68.5, 67.0, 26.9, 25.0 ppm. FTIR (film): $\tilde{\nu}$ = 3448, 2988, 2936, 1767, 1670, 1409, 1373, 1267, 980, 844 cm^{-1}. MS (ESI) *m*/*z* = 237.1 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{10}H_{15}O_5$ $[M + H]^+$ 215.0914; found 215.0911.

Hydrogenation of Alkene 5 To Give 6 and 7: A mixture of Pd/C (10 %; 12 mg) and **5** (237 mg, 1.11 mmol) in MeOH (24 mL) was stirred at ambient temperature under H_2 (1 atm) for 5 h, after which

time TLC showed the disappearance of starting material **5**. The solids were removed by filtration [washing with EtOAc (3 × 20 mL)]. The combined filtrate and washings were concentrated to dryness on a rotary evaporator. The residue was purified by column chromatography (petroleum ether/EtOAc, 1:1) on silica gel to give **6** (176 mg, 0.81 mmol, 74 %) and **7** (39 mg, 0.20 mmol, 18 %).

Data for **6** (the more polar component), a white solid, m.p. 87–88 °C. $[\alpha]_D^{26}$ = +24.6 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.51–4.50 (m, 1 H), 4.40–4.37 (m, 1 H), 4.20–4.17 (m, 2 H), 4.06 (dd, *J* = 4.0, 9.0 Hz, 1 H), 2.73–2.71 (m, 1 H), 2.58 (d, *J* = 2.9 Hz, 1 H, OH), 1.45 (s, 3 H), 1.38 (s, 3 H), 1.28 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7, 109.7, 81.7, 72.7, 70.4, 67.2, 41.0, 26.9, 25.0, 7.8 ppm. FTIR (film): $\tilde{\nu}$ = 3454, 2987, 2941, 1770, 1640, 1456, 1374, 844, 771 cm^{-1}. MS (ESI): *m/z* = 217.1 $[M + H]^+$. HRMS (ESI): calcd. for $C_{10}H_{16}NaO_5$ $[M + Na]^+$ 239.0890; found 239.0894.

Data for **7** (the less polar component), a white solid, m.p. 66–68 °C. $[\alpha]_D^{25}$ = +1.8 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.29 (ddd, *J* = 3.1, 6.1, 9.8 Hz, 1 H), 4.14 (dd, *J* = 6.3, 11.6 Hz, 1 H), 4.12 (dd, *J* = 6.5, 10.2 Hz, 1 H), 3.90 (ddd, *J* = 4.0, 7.9, 12.0 Hz, 1 H), 2.74–2.66 (m, 1 H), 2.59 (ddd, *J* = 5.9, 8.9, 12.7 Hz, 1 H), 1.75 (ddd, *J* = 9.8, 11.6, 12.5 Hz, 1 H), 1.43 (s, 3 H), 1.36 (s, 3 H), 1.30 (dd, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.8, 109.8, 77.6, 77.0, 66.7, 34.9, 33.4, 26.4, 24.9, 15.1 ppm. FTIR (film): $\tilde{\nu}$ = 2994, 2972, 2936, 2874, 1775, 1455, 1378 cm^{-1}. MS (ESI): *m/z* = 201.1 $[M + H]^+$. HRMS (ESI): calcd. for $C_{10}H_{16}NaO_4$ $[M + Na]^+$ 223.0941; found 223.0941.

Conversion of 6 into 7: MsCl (160 µL, 2.0 mmol) was slowly added to a stirred solution of **6** (289 mg, 1.34 mmol) and Et_3N (2 mL, 13.4 mmol) in dry CH_2Cl_2 (15 mL) at ambient temperature under argon. The mixture was stirred at the same temperature for 5 h, after which time TLC showed that the reaction was complete. Water (2 mL) was added. The mixture was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 1.5:1) on silica gel gave intermediate alkene **6′** (221 mg, 1.12 mmol, 83 %) as a colourless oil, m.p. 34–35 °C. $[\alpha]_D^{22}$ = –127.4 (*c* = 1.0 in $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.22 (br. t, *J* = 1.6 Hz, 1 H), 4.70–4.73 (m, 1 H), 4.12 (dd, *J* = 6.2, 9.7 Hz, 1 H), 4.07 (dd, *J* = 4.0, 9.1 Hz, 1 H), 3.87 (ddd, *J* = 4.0, 6.2, 8.0 Hz, 1 H), 1.94 (br. t, *J* = 1.7 Hz, 3 H), 1.46 (s, 3 H), 1.35 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.6, 147.1, 131.0, 110.2, 80.8, 76.5, 67.0, 26.7, 24.9, 10.7 ppm. FTIR (film): $\tilde{\nu}$ = 2985, 2928, 1766, 1658, 1455, 1373, 956, 888 cm^{-1}. MS (ESI): *m/z* = 199.1 $[M + H]^+$. HRMS (ESI): calcd. for $C_{10}H_{14}NaO_4$ $[M + Na]^+$ 221.0784; found 221.0785.

Intermediate alkene **6′** (221 mg, 1.12 mmol) was dissolved in MeOH (20 mL), and Pd/C (10 %; 11 mg) was added to the resulting solution. The mixture was then stirred at ambient temperature under H_2 (1 atm) for 4 h, after which time TLC showed the disappearance of starting material **6′** (no yellow spot by $KMnO_4$ stain). The solids were removed by filtration [washing with EtOAc (3 × 80 mL)]. The combined filtrate and washings were concentrated to dryness on a rotary evaporator to give **7** (192 mg, 0.96 mmol, 86 % from **6′**, or 72 % over two steps from **6**) as a white solid, which was used directly in the next step.

Reduction of Lactone 7 To Give Diol 8: $LiAlH_4$ (83 mg, 2.18 mmol) was added in small portions to a stirred solution of lactone **7** (218 mg, 1.09 mmol) in dry THF (20 mL) in an ice-water bath. After the addition was complete, the bath was removed. The mixture was stirred at ambient temperature for 1.5 h. When TLC showed that the reduction was complete, water (5 mL) was added carefully, followed by NaOH (10 % aq.; 5 mL) and another portion of water (15 mL). The mixture was stirred for 30 min, then it was filtered through Celite. The filtrate was concentrated on a rotary evaporator to give diol **8** (233 mg, 1.14 mmol, 100 %) as a colourless oil, which was used directly in the next step. $[\alpha]_D^{25}$ = +0.95 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.02 (dd, *J* = 7.2, 5.7 Hz, 1 H), 4.00–3.84 (m, 4 H), 3.72 (ddd, *J* = 10.4, 5.2, 1.7 Hz, 1 H), 3.57 (dd, *J* = 10.7, 4.6 Hz, 1 H), 3.35 (dd, *J* = 10.6, 8.0 Hz, 1 H), 1.89–1.80 (m, 1 H), 1.53 (ddd, *J* = 14.3, 6.2, 1.8 Hz, 1 H), 1.42 (s, 3 H), 1.38–1.32 (m, 1 H), 1.36 (s, 3 H), 0.92 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 109.0, 79.0, 70.4, 68.3, 65.5, 38.3, 33.9, 26.4, 25.2, 17.5 ppm. IR (film): $\tilde{\nu}$ = 3377, 2988, 2985, 2933, 2875, 1457, 1372, 853, 794 cm^{-1}. MS (ESI): *m/z* = 227.9 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{10}H_{20}NaO_4$ $[M + Na]^+$ 227.1254; found 227.1248.

Synthesis of 10 from Diol 8 and Thiol 9: DEAD (0.28 mL, 1.77 mmol) was added dropwise to a stirred solution of diol **8** (241 mg, 1.18 mmol), thiol **9** (315 mg, 1.77 mmol), and Ph_3P (464 mg, 1.77 mmol) in dry THF (12 mL) in an ice-water bath. After the addition was complete, stirring was continued at ambient temperature for 50 min. When TLC showed that the reaction was complete, saturated aq. $NaHCO_3$ (10 mL) was added. The mixture was extracted with EtOAc (50 mL). The organic layer was washed with brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 1:1) on silica gel gave intermediate thioether **9′** (387 mg, 1.06 mmol, 90 % from **8**) as a colourless oil. $[\alpha]_D^{25}$ = –2.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.61–7.52 (m, 5 H), 4.03 (dd, *J* = 7.0, 5.7 Hz, 1 H), 4.00–3.93 (m, 2 H), 3.86–3.83 (m, 1 H), 3.63 (dd, *J* = 13.3, 5.1 Hz, 1 H), 3.23 (dd, *J* = 13.3, 7.6 Hz, 1 H), 2.34–2.15 (m, 1 H), 1.58–1.44 (m, 2 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 1.10 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.9, 133.6, 130.2, 129.8, 123.9, 109.1, 79.0, 70.1, 65.6, 40.7, 38.8, 30.8, 26.6, 25.3, 19.4 ppm. FTIR (film): $\tilde{\nu}$ = 3436, 3065, 2984, 2932, 2872, 1957, 1500, 1459, 762, 694 cm^{-1}. MS (ESI): *m/z* = 365.3 $[M + H]^+$. HRMS (ESI): calcd. for $C_{17}H_{25}N_4O_3S$ $[M + H]^+$ 365.1642; found 365.1644.

A portion of intermediate thioether **9′** (27 mg, 0.074 mmol) was dissolved in DMF (1 mL). Imidazole (20 mg, 0.3 mmol) and TBSCl (34 mg, 0.22 mmol) were added in turn to the resulting solution. The mixture was stirred at ambient temperature for 12 h (TLC showed that the reaction was complete). Water (1 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 5:1) on silica gel gave **10** (31 mg, 0.06 mmol, 87 % from the intermediate thioether-alcohol **9′**, or 78 % over two steps from diol **8**) as a colourless oil. $[\alpha]_D^{24}$ = –6.5 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.58–7.54 (m, 5 H), 3.99–3.94 (m, 2 H), 3.82–3.77 (m, 2 H), 3.44 (dd, *J* = 6.5, 12.8 Hz, 1 H), 3.34 (dd, *J* = 6.6, 12.8 Hz, 1 H), 2.24–2.17 (m, 1 H), 1.69 (ddd, *J* = 4.1, 8.0, 12.2 Hz, 1 H), 1.42 (ddd, *J* = 3.5, 9.7, 13.5 Hz, 1 H), 1.39 (s, 3 H), 1.32 (s, 3 H), 1.08 (d, *J* = 6.7 Hz, 3 H), 0.82 (s, 9 H), 0.07 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.5, 133.7, 130.0, 129.7, 123.8, 109.0, 79.0, 70.6, 66.4, 40.9, 40.8, 29.0, 26.6, 25.8, 25.3, 19.4, 18.0, –4.1, –4.1 ppm. FTIR (film): $\tilde{\nu}$ = 3067, 2956, 2930, 2886, 2856, 1598, 1498, 1471, 1462, 1381, 939, 911 cm^{-1}. MS (ESI): *m/z* = 479.6 $[M + H]^+$. HRMS (ESI): calcd. for $C_{23}H_{39}N_4O_3SSi$ $[M + H]^+$ 479.2507; found 479.2515.

Oxidation of 10 To Give 11: A mixture of **10** (663 mg, 1.4 mmol), $NaHCO_3$ (420 mg, 5.0 mmol), and *m*-CPBA (75 % w/w; 960 mg, 4.2 mmol) in dry CH_2Cl_2 (30 mL) was stirred at reflux temperature for 12 h, after which time TLC showed that the reaction was complete. The heating bath was removed. The mixture was allowed to

cool to ambient temperature, then saturated aq. $Na_2S_2O_3$ (2 mL) was added. The mixture was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 4:1) on silica gel gave sulfone **11** (459 mg, 0.9 mmol, 65 %) as a colourless oil. $[\alpha]_D^{23}$ = +36.1 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.69–7.58 (m, 5 H), 4.00 (dd, *J* = 6.4, 14.0 Hz, 1 H), 3.95 (dd, *J* = 6.3, 12.5 Hz, 1 H), 3.85 (dd, *J* = 4.8, 14.5 Hz, 1 H), 3.80–3.75 (m, 2 H), 3.69 (dd, *J* = 7.9, 14.5 Hz, 1 H), 2.67–2.58 (m, 1 H), 1.78 (ddd, *J* = 4.6, 7.6, 13.5 Hz, 1 H), 1.56 (ddd, *J* = 3.3, 9.2, 13.5 Hz, 1 H), 1.39 (s, 3 H), 1.32 (s, 3 H), 1.20 (d, *J* = 6.7 Hz, 3 H), 0.84 (s, 9 H), 0.08 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.0, 133.1, 131.4, 129.6, 125.1, 109.2, 78.6, 70.5, 66.8, 62.3, 41.4, 26.6, 25.7, 25.2, 24.5, 19.9, 18.0, –4.1, –4.2 ppm. IR (film): $\tilde{\nu}$ = 3066, 2955, 2931, 2887, 2857, 1596, 1498, 1463, 1371, 913, 837 cm^{-1}. MS (ESI): *m/z* = 533.6 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{23}H_{38}N_4NaO_5SSi$ $[M + Na]^+$ 533.2224; found 533.2227.

Synthesis of Sulfone 18: NaH (80 % in mineral oil; 220 mg, 7.17 mmol, washed with petroleum ether to remove mineral oil prior to use) was suspended in dry DMF (3 mL) at ambient temperature under argon (balloon). A solution of thiol **9** (1.12 g, 6.75 mmol) in dry DMF (2 mL) was added slowly (exothermic, with violent gas evolution) to the stirred suspension, followed by a solution of ethyl 7-bromohepanoate (1.00 g, 4.22 mmol) in DMF (1 mL). After the addition was complete, the mixture was stirred at ambient temperature for 1.5 h, after which time TLC showed that the reaction was complete. Water (3 mL) was added. The mixture was then extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 4:1) on silica gel gave the intermediate thioether (1.31 g, 3.92 mmol, 97 %) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.53 (m, 5 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 3.39 (t, *J* = 7.3 Hz, 2 H), 2.29 (t, *J* = 7.4 Hz, 2 H), 1.88–1.80 (m, 2 H), 1.67–1.60 (m, 2 H), 1.51–1.44 (m, 2 H), 1.41–1.33 (m, 2 H), 1.25 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 154.3, 133.6, 130.0, 129.6, 123.7, 60.1, 34.0, 33.1, 28.8, 28.4, 28.1, 24.6, 14.1 ppm. FTIR (film): $\tilde{\nu}$ = 3065, 2977, 2935, 2858, 1731, 1597, 1500, 1463, 1387, 762, 695 cm^{-1}. MS (ESI): *m/z* = 335.4 $[M + H]^+$. HRMS (ESI): calcd. for $C_{16}H_{22}N_4NaO_2S$ $[M + Na]^+$ 357.1356; found 357.1359.

A portion of the intermediate thioether (1.23 g, 3.67 mmol) was dissolved in dry CH_2Cl_2 (60 mL), and the solution was stirred at ambient temperature. $NaHCO_3$ (1.11 g, 13.21 mmol) was added, followed by *m*-CPBA (85 %; 2.24 g, 11.01 mmol). The mixture was then stirred at reflux temperature for 10 h, after which time TLC showed that the reaction was complete. Aaturated aq. $Na_2S_2O_3$ (15 mL) was added. The phases were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 5:1) on silica gel gave sulfone **18** (1.32 g, 3.60 mmol, 98 % from the intermediate thioether, or 95 % over two steps from **9**) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.71–7.57 (m, 5 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 3.73 (t, *J* = 7.9 Hz, 2 H), 2.30 (t, *J* = 7.4 Hz, 2 H), 2.00–1.92 (m, 2 H), 1.68–1.60 (m, 2 H), 1.56–1.49 (m, 2 H), 1.43–1.34 (m, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 153.3, 132.9, 131.3, 129.6, 125.0, 60.2, 55.7, 33.9, 28.2, 27.7, 24.3, 21.7, 14.1 ppm. FTIR (film): $\tilde{\nu}$ = 3069, 2980, 2938, 2863, 1731, 1595, 1498, 1463, 765, 690 cm^{-1}. MS (ESI): *m/z* = 367.4 $[M + H]^+$. HRMS (ESI): calcd. for $C_{16}H_{22}N_4NaO_4S$ $[M + Na]^+$ 389.1254; found 389.1257.

Conversion of 12 into 19 via 13 and 14: $(COCl)_2$ (2 mL, 22.9 mmol) was added dropwise to a solution of acid **12** (1.002 g, 8.92 mmol) in CH_2Cl_2 (25 mL) containing traces of DMF (2 drops from a pipette) stirred in an ice-water bath under argon. After the addition was complete, the mixture was stirred at ambient temperature for 4 h. Solvents were then removed by rotary evaporation.

The yellowish oily residue was dissolved in MeCN/THF (1:1 v/v; 20 mL). The resulting solution was then cooled in an ice-water bath. Me_3SiCHN_2 (2.0 M in hexanes; 11.5 mL, 22.9 mmol) and Et_3N (1.2 mL, 8.92 mmol) were slowly added in sequence. The resulting dark-red solution was stirred at ambient temperature for 4 h. The mixture was then concentrated on a rotary evaporator to give a dark oil.

The oil was directly dissolved in EtOAc (50 mL), and Ag_2O (2.8 g, 12 mmol) was added to the resulting solution. The mixture was stirred at reflux temperature for 5 h, after which time TLC showed that the reaction was essentially complete. Then the mixture was diluted with EtOAc (50 mL), and filtered through a short pad of silica gel. The filtrate was concentrated on a rotary evaporator. The residue was purified by column chromatography (petroleum ether/EtOAc, 2:1) on silica gel to give known ester **13** as a yellowish oil (600 mg, 4.3 mmol, 48 %).

A portion of ester **13** (100 mg, 0.71 mmol) was dissolved in dry CH_2Cl_2 (2 mL), and the resulting solution was stirred in a –72 °C bath (dry ice/EtOH) under argon. DIBAL-H (1.0 M in cyclohexane: 0.85 mL, 0.85 mmol) was added slowly. After the addition was complete, the mixture was stirred at the same temperature for 40 min. MeOH (1 mL) was added carefully, followed by saturated aq. sodium potassium tartrate (1.5 mL). The mixture was stirred at ambient temperature for 1 h, then it was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 4:1) on silica gel gave known aldehyde **14** (50 mg, 0.45 mmol, 65 % from **13**, or 31 % over two steps from **12**) as a colourless oil.

NaHMDS (1.0 M in THF; 0.66 mL, 0.66 mmol) was added to a stirred solution of sulfone **18** (241 mg, 0.66 mmol) in dry THF (9 mL) at –78 °C bath (dry ice/acetone) under argon (balloon). The resulting bright yellow solution was stirred at the same temperature for 1 h, then a solution of aldehyde **14** (60 mg, 0.53 mmol) in dry THF (1 mL) was added. The mixture was then stirred at –78 °C for another 4 h, after which time TLC showed that the reaction was complete. Water (2 mL) was added. The mixture was then extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 3:1) on silica gel gave **19** (73 mg, 0.29 mmol, 51 %) as a colourless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (br. t, *J* = 1.6 Hz, 1 H), 7.18 (br. s, 1 H), 6.24 (br. s, 1 H), 5.55–5.44 (m, 2 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 3.16 (d, *J* = 6.5 Hz, 0.5 H), 3.10 (d, *J* = 4.2 Hz, 1.5 H), 2.28 (t, *J* = 7.5 Hz, 2 H), 2.12–2.07 (m, 0.4 H), 2.03–1.99 (m, 1.6 H), 1.66–1.58 (m, 2 H), 1.41–1.29 (m, 4 H), 1.24 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.8, 142.8, 142.8, 138.9, 138.9, 131.5, 130.7, 128.0, 127.3, 124.0, 111.0, 111.0, 60.2, 34.3, 32.3, 32.2, 29.2, 29.0, 28.7, 28.6, 28.1, 26.9, 24.8, 24.8, 22.9, 14.2 ppm. FTIR (film): $\tilde{\nu}$ = 2980, 2931, 2856, 1736, 1501, 1463, 1373, 874, 778 cm^{-1}. MS (ESI): *m/z* = 251.3 $[M + H]^+$. HRMS (ESI): calcd. for $C_{15}H_{22}NaO_3$ $[M + Na]^+$ 273.1461; found 273.1466.

Conversion of Lactone 7 into Alkyne 22: DIBAL-H (1.0 M in cyclohexane; 0.94 mL, 0.94 mmol) was added dropwise to a stirred solution of lactone **7** (144 mg, 0.72 mmol) in dry CH_2Cl_2 (2 mL) at –72 °C under argon. After the addition was complete, stirring was

continued at the same temperature for 1 h, after which time TLC showed that the reaction was complete. MeOH (1 mL) was carefully added, followed by saturated aq. potassium sodium tartrate (1 mL). The mixture was stirred at ambient temperature for 3 h, then it was filtered through Celite. The filtrate was concentrated on a rotary evaporator to give the crude lactol (154 mg, 0.76 mmol, 100 %), which was used directly in the next step.

*n*BuLi (1.6 M in hexanes; 1.2 mL, 1.98 mmol) was added to a stirred solution of *i*Pr$_2$NH (0.3 mL, 1.98 mmol) in dry THF (5 mL) at –75 °C under argon (balloon). After the addition was complete, stirring was continued at the same temperature for 20 min, and at ambient temperature for 1 h. The mixture was then stirred in the cooling bath (–75 °C) again, and TMSCHN$_2$ (2.0 M in hexanes; 0.5 mL, 0.91 mmol) was added dropwise. Stirring was continued at the same temperature for 1.5 h, then a solution of the above-obtained crude lactol (154 mg, 0.76 mmol) in dry THF (3 mL) was added. The bath was removed, and the mixture was stirred at ambient temperature for 12 h. Saturated aq. NH_4Cl (3 mL) was added. The mixture was then extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 1:1) on silica gel gave alkyne **22** (115.3 mg, 0.58 mmol, 76 % overall from **7**) as a colourless oil. $[\alpha]_D^{24}$ = +30.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.02 (dd, *J* = 6.2, 10.2 Hz, 1 H), 4.00 (dd, *J* = 6.1, 9.9 Hz, 1 H), 3.95–3.92 (m, 1 H), 3.90–3.85 (m, 1 H), 2.72–2.62 (m, 1 H), 2.49 (br. s, 1 H, OH), 2.14 (d, *J* = 2.4 Hz, 1 H), 1.68 (ddd, *J* = 3.9, 7.0, 10.9 Hz, 1 H), 1.61 (ddd, *J* = 7.7, 8.8, 13.9 Hz, 1 H), 1.43 (s, 3 H), 1.36 (s, 3 H), 1.24 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.1, 88.7, 78.4, 69.9, 69.2, 65.1, 39.6, 26.4, 25.2, 22.8, 20.6 ppm. FTIR (film): $\tilde{\nu}$ = 3470, 3296, 2985, 2936, 2886, 2111, 1456, 1372 cm^{-1}. MS (ESI): *m*/*z* = 221.2 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{11}H_{19}O_3$ [M + H]$^+$ 199.1329; found 199.1327.

Benzylation of 22 To Give 23: A suspension of **22** (279 mg, 1.41 mmol) and NaH (80 % w/w, washed with petroleum ether to remove the mineral oil before use; 85 mg, 2.82 mmol) in DMF (6 mL) was stirred in an ice-water bath for 80 min. BnBr (0.25 mL, 2.12 mmol) was then added. Stirring was continued at ambient temperature for 28 h, after which time TLC showed that the reaction was complete. Water (8 mL) was added. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 30:1) on silica gel gave **23** (383 mg, 1.33 mmol, 94 %) as a colourless oil. $[\alpha]_D^{27}$ = +31.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 4.68 (d, *J* = 11.5 Hz, 1 H), 4.61 (d, *J* = 11.5 Hz, 1 H), 4.15 (dd, *J* = 6.5, 11.9 Hz, 1 H), 4.04 (dd, *J* = 6.5, 8.1 Hz, 1 H), 3.90 (dd, *J* = 6.7, 8.1 Hz, 1 H), 3.71 (dd, *J* = 5.7, 11.8 Hz, 1 H), 2.73–2.65 (m, 1 H), 2.05 (dd, *J* = 2.4 Hz, 1 H), 1.81 (ddd, *J* = 6.7, 7.6, 14.1 Hz, 1 H), 1.61 (ddd, *J* = 5.8, 6.9, 13.9 Hz, 1 H), 1.43 (s, 3 H), 1.35 (s, 3 H), 1.15 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.4, 128.3, 127.9, 127.6, 109.1, 88.8, 78.6, 76.7, 72.5, 68.5, 66.1, 39.0, 26.4, 25.3, 22.3, 20.7 ppm. FTIR (film): $\tilde{\nu}$ = 3294, 3065, 3031, 2984, 2935, 2876, 2112, 1605, 1497, 1455, 1380, 857, 795 cm^{-1}. MS (ESI): *m*/*z* = 311.3 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{18}H_{24}NaO_3$ [M + H]$^+$ 311.1618; found 311.1618.

Addition of Alkyne 23 to Aldehyde 25 To Give Propargyl Alcohol 26: *n*BuLi (2.0 M in hexanes; 0.2 mL, 0.39 mmol) was added to a stirred solution of **23** (100 mg, 0.35 mmol) in dry THF (1 mL) at –78 °C under argon (balloon). After the addition was complete, stirring was continued at the same temperature for 2 h. A solution of aldehyde **25** (40 mg, 0.39 mmol) in dry THF (1 mL) was added. The cooling bath was removed. The mixture was stirred at ambient temperature for 12 h, after which time TLC showed that the reaction was complete. Saturated aq. NH_4Cl (2 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 4:1) on silica gel gave **26** (*dr* 1:1, 107 mg, 0.28 mmol, 80 % from **22**) as a colourless oil. $[\alpha]_D^{21}$ = +21.6 (*c* = 1.0 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (dd, *J* = 0.8, 1.4 Hz, 1 H), 7.36 (dd, *J* = 1.6, 2.6 Hz, 1 H), 6.47 (d, *J* = 0.6 Hz, 1 H), 6.32 (s, 1 H), 4.65 (d, *J* = 11.6 Hz, 1 H), 4.58 (d, *J* = 11.6 Hz, 0.5 H), 4.58 (d, *J* = 11.6 Hz, 0.5 H), 4.16 (dd, *J* = 7.7, 12.0 Hz, 0.5 H), 4.16 (dd, *J* = 5.1, 11.8 Hz, 0.5 H), 4.03–4.00 (m, 1 H), 3.90 (dd, *J* = 6.7, 8.0 Hz, 1 H), 3.67 (dd, *J* = 5.6, 11.2 Hz, 1 H), 2.78–2.70 (m, 1 H), 2.60 (br. s, 1 H, OH), 1.81 (ddd, *J* = 0.7, 7.5, 14.2 Hz, 1 H), 1.62 (ddd, *J* = 0.7, 6.5, 13.5 Hz, 1 H), 1.42 (s, 3 H), 1.34 (s, 3 H), 1.15 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.4, 139.9, 139.9, 138.2, 128.3, 127.7, 127.6, 126.9, 109.2, 109.1, 89.9, 89.9, 80.0, 80.0, 78.2, 78.2, 76.6, 76.6, 72.4, 72.4, 66.0, 57.1, 38.7, 38.6, 26.4, 25.2, 22.2, 22.2, 20.7, 20.7 ppm. FTIR (film): $\tilde{\nu}$ = 3424, 3030, 2983, 2934, 2876, 2236, 1595, 1501, 1455, 1372, 955, 874, 855 cm^{-1}. MS (ESI): *m*/*z* = 407.3 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{23}H_{28}NaO_5$ [M + Na]$^+$ 407.1829; found 407.1828.

Acetylation of 26 To Give 27: A solution of **26** (*dr* 1:1, 103 mg, 0.27 mmol), Et_3N (0.05 mL, 0.35 mmol), DMAP (3.3 mg, 0.027 mmol), and Ac_2O (0.033 mL, 0.35 mmol) in CH_2Cl_2 (4 mL) was stirred at ambient temperature for 1.5 h, after which time TLC showed that the reaction was complete. The mixture was partitioned between water (2 mL) and EtOAc (20 mL). The phases were separated. The aqueous layer was extracted with EtOAc (10 mL). The combined organic layers were washed with brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave **27** (*dr* 1:1, 109 mg, 0.26 mmol, 96 % crude) as a colourless oil, which was used directly in the next step. $[\alpha]_D^{21}$ = +25.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54 (br. s, 1 H), 7.37 (br. t, *J* = 1.5 Hz, 1 H), 6.47 (br. t, *J* = 1.7 Hz, 1 H), 6.40 (br. s, 1 H), 4.65 (d, *J* = 11.5 Hz, 0.5 H), 4.65 (d, *J* = 11.5 Hz, 0.5 H), 4.59 (d, *J* = 11.5 Hz, 0.5 H), 4.59 (d, *J* = 11.5 Hz, 0.5 H), 4.14 (dd, *J* = 6.5, 12.0 Hz, 0.5 H), 4.14 (dd, *J* = 6.4, 11.9 Hz, 0.5 H), 4.04 (dd, *J* = 6.6, 8.2 Hz, 1 H), 3.90 (dd, *J* = 6.7, 8.1 Hz, 1 H), 3.67 (d, *J* = 5.6, 12.0 Hz, 0.5 H), 3.66 (d, *J* = 5.5, 11.7 Hz, 0.5 H), 2.81–2.75 (m, 1 H), 2.06 (s, 3 H), 1.82 (ddd, *J* = 1.2, 7.7, 14.1 Hz, 1 H), 1.64 (ddd, *J* = 5.7, 7.0, 13.8 Hz, 1 H), 1.43 (s, 3 H), 1.35 (s, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.8, 143.4, 141.6, 141.6, 138.3, 138.3, 128.4, 127.8, 127.7, 123.3, 109.6, 109.1, 90.9, 90.9, 78.5, 78.5, 76.5, 72.5, 72.5, 66.2, 66.2, 58.5, 38.8, 38.8, 26.5, 25.2, 22.5, 22.4, 21.1, 20.5, 20.5 ppm. FTIR (film): $\tilde{\nu}$ = 3030, 2983, 2934, 2875, 2242, 1741, 1598, 1503, 1455, 1370, 944, 874 cm^{-1}. MS (ESI): *m*/*z* = 449.4 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{25}H_{30}NaO_6$ [M + Na]$^+$ 449.1935; found 449.1937.

Conversion of 27 into 28: A mixture of **27** (100 mg, 0.23 mmol) and Pd/C (10 %; 15 mg) in MeCN (7 mL) was stirred at ambient temperature under H_2 (1 atm) for 4 h, after whcih time TLC showed that the reaction was complete. The solids were removed by filtration [washing with EtOAc (3 × 10 mL)]. The combined filtrate and washings were concentrated on a rotary evaporator. The residue was purified by column chromatography (petroleum ether/EtOAc, 5:1) on silica gel to give **28** (70 mg, 0.19 mmol, 80 %) as a colourless oil. $[\alpha]_D^{25}$ = –1.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 6 H), 7.18 (br. s, 1 H), 6.24 (br. s, 1 H), 4.77 (d, *J* = 11.4 Hz, 1 H), 4.58 (d, *J* = 11.4 Hz, 1 H), 4.10 (dt, *J* = 4.3, 6.8 Hz, 1 H), 4.01 (dd, *J* = 6.5, 8.0 Hz, 1 H), 3.92 (br. t, *J* = 7.5 Hz, 1 H), 3.69 (br. dt, *J* = 3.2, 7.4 Hz, 1 H), 2.37 (br. t, *J* = 7.6 Hz, 2 H), 1.73–1.64 (m, 1 H), 1.60–

1.47 (m, 3 H), 1.44 (s, 3 H), 1.36 (s, 3 H), 1.35–1.28 (m, 1 H), 1.23–1.16 (m, 2 H), 0.84 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.6, 138.7, 128.3, 127.8, 127.6, 125.2, 111.0, 108.9, 79.0, 76.6, 73.4, 65.6, 39.3, 37.5, 28.9, 27.4, 26.5, 25.4, 24.9, 19.2 ppm. FTIR (film): $\tilde{\nu}$ = 3064, 3030, 2985, 2931, 2869, 1570, 1499, 1380, 873, 858 cm^{-1}. MS (ESI): m/z = 395.5 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{23}H_{32}NaO_4$ [M + Na]$^+$ 395.2193; found 395.2195.

Conversion of 28 into 29: A solution of **28** (54 mg, 0.15 mmol) in HCl (1 N)/THF (1:1 v/v; 3 mL) was stirred at ambient temperature for 30 h, after which time TLC showed that the reaction was complete. Powdered $NaHCO_3$ was added until gas evolution stopped. The mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave the crude intermediate diol (51 mg, 0.15 mmol).

The crude diol was directly dissolved in THF/H_2O (1:1 v/v; 3 mL), and the solution was stirred in an ice-water bath. $NaIO_4$ (66 mg, 0.31 mmol) was added. Stirring was then continued at ambient temperature for 1 h, after which time TLC showed that the reaction was complete. Water (2 mL) was added. The mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave the crude intermediate aldehyde (50 mg, 0.17 mmol).

The crude aldehyde was directly dissolved in MeOH (2 mL), and the solution was stirred in an ice-water bath. $NaBH_4$ (13 mg, 0.34 mmol) was added. Stirring was then continued at the same temperature for 2 h, after which time TLC showed that the reaction was complete. Water (3 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 2:1) on silica gel gave alcohol **29** (41 mg, 0.14 mmol, 92 % overall from **28**) as a colourless oil. $[\alpha]_D^{27}$ = +7.4 (c = 3.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 6 H), 7.19 (br. s, 1 H), 6.25 (br. s, 1 H), 4.57 (s, 2 H), 3.71 (dd, J = 3.4, 11.4 Hz, 1 H), 3.60–3.55 (m, 1 H), 3.50 (dd, J = 5.6, 11.4 Hz, 1 H), 2.42–2.33 (m, 2 H), 2.03 (br. s, 1 H, OH), 1.71–1.41 (m, 4 H), 1.37–1.30 (m, 1 H), 1.22–1.15 (m, 2 H), 0.87 (dd, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.6, 138.7, 138.4, 128.4, 127.8, 127.7, 125.1, 110.9, 77.8, 71.6, 64.6, 38.7, 37.0, 29.1, 27.3, 24.9, 19.7 ppm. FTIR (film): $\tilde{\nu}$ = 3419, 3030, 2929, 2866, 1498, 1454, 1379, 873 cm^{-1}. MS (ESI): m/z = 325.3 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{19}H_{27}O_3$ [M + H]$^+$ 303.1955; found 303.1950.

Conversion of 29 into Epoxide 30: Li (11 mg, 1.53 mmol) was added to a solution of naphthalene (255 mg, 2.04 mmol) in dry THF (2 mL). The mixture was stirred at ambient temperature for 1 h. The stirring was then continued in a –25 °C bath (dry ice/EtOH). A solution of **29** (153 mg, 0.51 mmol) in dry THF (2 mL) was introduced slowly. The mixture was stirred at the same temperature for 30 min, after which time TLC showed that the reaction was complete. Saturated aq. NH_4Cl (2 mL) was added. Stirring was continued while the bath warmed to ambient temperature. The mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 1:1) on silica gel gave intermediate diol **29′** (96 mg, 0.45 mmol, 89 % from **29**) as a colourless oil. $[\alpha]_D^{27}$ = –3.0 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (br. s, 1 H), 7.20 (br. s, 1 H), 6.25 (br. s, 1 H), 3.81–3.76 (m, 1 H), 3.60 (dd, J = 2.2, 11.1 Hz, 1 H), 3.39 (dd, J = 7.8, 11.1 Hz, 1 H), 2.89 (br. s, 2 H, OH), 2.39 (br. t, J = 7.6 Hz, 2 H), 1.72–1.65 (m, 1 H), 1.62–1.50 (m, 2 H), 1.45 (ddd, J = 4.4, 9.6, 13.9 Hz, 1 H), 1.37–1.30 (m, 1 H), 1.26–1.18 (m, 1 H), 1.08 (ddd, J = 3.4, 9.7, 13.5 Hz, 1 H), 0.89 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.6, 138.7, 125.1, 110.9, 70.1, 67.4, 40.1, 37.3, 28.8, 27.3, 24.9, 19.1 ppm. FTIR (film): $\tilde{\nu}$ = 3355, 2930, 2861, 1501, 1456, 1379, 874, 773 cm^{-1}. MS (ESI): m/z = 235.1 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{12}H_{21}O_3$ [M + H]$^+$ 213.1485; found 213.1482.

A mixture of intermediate diol **29′** (96 mg, 0.45 mmol), Et_3N (0.075 mL, 0.54 mmol), DMAP (5.5 mg, 0.045 mmol), nBu$_2$SnO (11 mg, 0.045 mmol), and pTsCl (95 mg, 0.5 mmol) was stirred at ambient temperature for 3 h, after which time TLC showed that the reaction was complete. The mixture was filtered through Celite [washing with EtOAc (3 × 10 mL)]. The filtrate and washings were combined, and the phases were separated. The organic layer was washed with brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave the crude tosylate.

The crude tosylate was directly dissolved in MeOH (9 mL), and the solution was stirred at ambient temperature. Powdered K_2CO_3 (93 mg, 0.6 mmol) was added. The mixture was stirred at the same temperature for 3 h, after which time TLC showed that the reaction was complete. Then the mixture was diluted with EtOAc (15 mL), and filtered through a short pad of silica gel. Rotary evaporation and purification by column chromatography (petroleum ether/EtOAc, 8:1) on silica gel gave epoxide **30** (72 mg, 0.37 mmol, 82 % overall from **29**) as a colourless oil. $[\alpha]_D^{23}$ = –6.2 (c = 1.98, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (br. t, J = 1.6 Hz, 1 H), 7.19 (br. dd, J = 0.8, 1.3 Hz, 1 H), 6.25 (d, J = 0.8 Hz, 1 H), 2.93–2.89 (m, 1 H), 2.75 (dd, J = 4.3, 4.8 Hz, 1 H), 2.43 (dd, J = 2.7, 5.1 Hz, 1 H), 2.39 (br. t, J = 7.8 Hz, 2 H), 1.75–1.66 (m, 1 H), 1.63–1.56 (m, 1 H), 1.55–1.48 (m, 2 H), 1.44–1.37 (m, 1 H), 1.31 (ddd, J = 5.2, 8.5, 13.8 Hz, 1 H), 1.27–1.21 (m, 1 H), 0.97 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.5, 138.6, 125.0, 110.8, 50.9, 47.3, 39.7, 36.7, 30.8, 27.3, 24.8, 19.5 ppm. FTIR (film): $\tilde{\nu}$ = 3044, 2929, 2859, 1501, 1461, 1380, 874, 781 cm^{-1}. MS (ESI): m/z = 195.2 [M + H]$^+$. HRMS (ESI): calcd. for $C_{12}H_{18}NaO_2$ [M + Na]$^+$ 217.1199; found 217.1199.

Ring Opening of Epoxide 30 with Dithiane 31 To Give 32: nBuLi (2.0 M in hexanes; 0.4 mL, 0.81 mmol) was added to a stirred solution of dithiane **31** (0.098 mL, 0.81 mmol) in dry THF (4 mL) at ambient temperature under argon (balloon). The mixture was stirred at the same temperature for 30 min, then a solution of epoxide **30** (72 mg, 0.37 mmol) in dry THF (1 mL) was added. Stirring was continued at the same temperature for 3 h, after which time TLC showed that the reaction was complete. Saturated aq. NH_4Cl (3 mL) was added, followed by water (2 mL). The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 5:1) on silica gel gave **32** (109 mg, 0.33 mmol, 90 % from **30**) as a colourless oil. $[\alpha]_D^{23}$ = +21.1 (c = 1.06, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (br. t, J = 1.4 Hz, 1 H), 7.20 (br. s, 1 H), 6.26 (br. s, 1 H), 4.13 (dt, J = 3.8, 9.2 Hz, 1 H), 3.36 (br. s, 1 H, OH), 3.14–2.95 (m, 2 H), 2.81–2.76 (m, 2 H), 2.39 (br. t, J = 7.1 Hz, 2 H), 2.37 (dd, J = 9.3, 15.3 Hz, 1 H), 2.08–2.01 (m, 1 H), 1.93–1.84 (m, 1 H), 1.81 (dd, J = 1.0, 15.0 Hz, 1 H), 1.74–1.68 (m, 1 H), 1.64 (s, 3 H), 1.62–1.50 (m, 3 H), 1.37–1.30 (m, 1 H), 1.25–1.17 (m, 1 H), 1.07 (ddd, J = 3.9, 9.4, 13.5 Hz, 1 H), 0.93 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 142.5, 138.6, 125.1, 110.9, 66.3, 48.1, 47.7, 45.2, 37.2, 28.7, 28.5, 27.2, 26.7, 26.5, 24.9, 24.6, 19.2 ppm. FTIR (film): $\tilde{\nu}$ = 3453, 3130, 2929, 2858, 1569, 1500, 1447, 1375, 873, 780 cm^{-1}. MS (ESI): m/z = 351.2 [M + Na]$^+$. HRMS (ESI): calcd. for $C_{17}H_{28}NaO_2S_2$ [M + Na]$^+$ 351.1423; found 351.1426.

Conversion of Thioketal 32 into Methyl Ketone 33: $NaHCO_3$ (236 mg, 2.81 mmol) and solid I_2 (284 mg, 1.12 mmol) were added in turn to a stirred solution of **32** (109 mg, 0.33 mmol) in acetone/H_2O (5:1 v/v; 6 mL) in an ice-water bath. After the addition was complete, the mixture was stirred at ambient temperature for 1 h, after which time TLC showed that the reaction was complete. Saturated aq. $Na_2S_2O_3$ (6 mL) was added to destroy the excess I_2. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 2:1) on silica gel gave intermediate ketone alcohol **32′** (75 mg, 0.31 mmol, 95 % from **32**) as a colourless oil. $[\alpha]_D^{24}$ = +20.7 (*c* = 2.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33 (br. t, *J* = 1.5 Hz, 1 H), 7.20 (br. s, 1 H), 6.26 (br. s, 1 H), 4.16–4.11 (m, 1 H), 2.63–2.51 (m, 2 H), 2.39 (br. t, *J* = 7.6 Hz, 2 H), 2.17 (s, 3 H), 1.76–1.66 (m, 1 H), 1.61–1.51 (m, 3 H), 1.35–1.28 (m, 1 H), 1.24–1.17 (m, 1 H), 1.05 (ddd, *J* = 3.5, 9.6, 13.5 Hz, 1 H), 0.89 (dd, *J* = 6.6 Hz, 3 H), 0.88–0.84 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 210.1, 142.6, 138.7, 125.2, 111.0, 65.3, 50.7, 43.7, 37.3, 30.8, 28.8, 27.3, 25.0, 19.1 ppm. FTIR (film): $\tilde{\nu}$ = 3445, 3142, 3104, 2928, 2858, 1707, 1501, 1460, 1363, 874, 780 cm^{-1}. MS (ESI): *m*/*z* = 239.9 $[M + H]^+$. HRMS (ESI): calcd. for $C_{14}H_{22}NaO_3$ $[M + Na]^+$ 261.1461; found 261.1462.

Intermediate ketone alcohol **32′** (75 mg, 0.31 mmol) was dissolved in DMF (2 mL). To the resulting solution were added in turn imidazole (84 mg, 1.24 mmol) and TBSCl (140 mg, 0.93 mmol). The mixture was then stirred at ambient temperature for 4 h, after which time TLC showed that the reaction was complete. Water (2 mL) was then added to stop the reaction. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 20:1) on silica gel gave **33** (111 mg, 0.31 mmol, 95 % overall from **29**) as a colourless oil. $[\alpha]_D^{22}$ = +5.2 (*c* = 5.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.32 (br. t, *J* = 1.6 Hz, 1 H), 7.19 (br. s, 1 H), 6.25 (br. d, *J* = 0.74 Hz, 1 H), 4.22–4.17 (m, 1 H), 2.59 (dd, *J* = 6.2, 15.3 Hz, 1 H), 2.48 (dd, *J* = 5.8, 15.3 Hz, 1 H), 2.37 (br. t, *J* = 7.8 Hz, 2 H), 2.14 (s, 3 H), 1.60–1.51 (m, 3 H), 1.50–1.43 (m, 1 H), 1.34–1.25 (m, 1 H), 1.20–1.13 (m, 2 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 207.7, 142.5, 138.7, 125.1, 110.9, 67.1, 51.9, 45.2, 36.9, 31.6, 28.8, 27.3, 25.8, 24.8, 19.7, 17.9, –4.5, –4.6 ppm. FTIR (film): $\tilde{\nu}$ = 2956, 2930, 2857, 1719, 1566, 1501, 1472, 1360, 874, 836 cm^{-1}. MS (ESI): *m*/*z* = 375.5 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{20}H_{36}NaO_3Si$ $[M + Na]^+$ 375.2326; found 375.2326.

Reduction of Ketone 33 To Give 34 along with Side-Product 35: $NaBH_4$ (11 mg, 0.28 mmol) was added to a stirred solution of **33** (49 mg, 0.14 mmol) in MeOH (1 mL) in an ice-water bath. After the addition was complete, the cooling bath was removed. Stirring was continued at ambient temperature for 30 min, after which time TLC showed that the reaction was complete. Water (2 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation gave intermediate alcohol **33′** (48 mg, 0.14 mmol, 97 %) as a colourless oil.

A portion of intermediate alcohol **33′** (42 mg, 0.12 mmol) was dissolved in dry THF (2 mL), and the solution was stirred in an ice-water bath. To this solution were added in turn thiol **9** (64 mg, 0.36 mmol) and Ph_3P (47 mg, 0.18 mmol), followed by DIAD (0.036 mL, 0.18 mmol). After the addition was complete, the mixture was stirred at ambient temperature for 12 h. After this time, TLC showed that the reaction was complete. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 15:1) on silica gel gave **34** (*dr* = 3:2, 42 mg, 0.082 mmol, 69 % from the intermediate alcohol **33′**, or 67 % over two steps from **33**) as a colourless oil, and **35** (*dr* = 3:1, 9.8 mg, 0.019 mmol, 16 % from **33′**) as a colourless oil.

Data for **34** (more polar than **35**): $[\alpha]_D^{22}$ = +8.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.51 (m, 5 H), 7.33 (br. t, *J* = 1.6 Hz, 0.4 H), 7.31 (br. t, *J* = 1.6 Hz, 0.6 H), 7.20 (br. s, 0.4 H), 7.19 (br. s, 0.6 H), 6.26 (br. s, 0.4 H), 6.25 (br. s, 0.6 H), 4.10–4.01 (m, 1 H), 3.93–3.83 (m, 1 H), 2.42–2.30 (m, 2 H), 1.98–1.89 (m, 1 H), 1.82–1.70 (m, 1 H), 1.64–1.43 (m, 7 H), 1.35–1.22 (m, 2 H), 1.17–1.10 (m, 1 H), 0.87 and 0.86 (2 s in a 2:3 ratio, 9 H altogether), 0.865 and 0.83 (2 d in a 3:2 ratio, *J* = 6.5 Hz, 3 H altogether), 0.05 0.034, 0.032, 0.01, and 0.00 (4 s in a 2:2:3:3 ratio, 6 H altogether) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7, 153.7, 142.6, 138.7, 138.7, 133.7, 130.0, 129.7, 125.1, 124.0, 110.9, 110.9, 68.2, 68.2, 44.9, 44.5, 44.5, 44.2, 41.7, 41.6, 36.9, 36.6, 28.8, 28.7, 27.2, 27.2, 25.9, 24.9, 22.4, 22.2, 20.1, 19.7, 18.0, –4.2, –4.4, –4.4 ppm. FTIR (film): $\tilde{\nu}$ = 3062, 2954, 2928, 2856, 1597, 1450, 1471, 1386, 836, 775 cm^{-1}. MS (ESI): *m*/*z* = 537.7 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{27}H_{43}N_4O_2SSi$ $[M + H]^+$ 515.2871; found 515.2874.

Data for **35** (*dr* 3:1, less polar than **34**): $[\alpha]_D^{23}$ = –8.2 (*c* = 0.95 in $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.97–7.95 (m, 2 H), 7.56–7.47 (m, 3 H), 7.34 (br. t, *J* = 1.6 Hz, 0.25 H), 7.32 (br. t, *J* = 1.5 Hz, 0.75 H), 7.20 (br. s, 0.25 H), 7.19 (br. s, 0.75 H), 6.26 (br. s, 0.25 H), 6.25 (br. s, 0.75 H), 5.20–5.15 (m, 0.25 H), 5.13–5.08 (m, 0.75 H), 3.81–3.76 (m, 0.75 H), 3.72–3.67 (m, 0.25 H), 2.47–2.36 (m, 3 H), 2.33–2.26 (m, 0.25 H), 2.04–1.99 (m, 0.25 H), 1.96–1.91 (m, 0.75 H), 1.62–1.46 (m, 3 H), 1.55 (d, *J* = 6.6 Hz, 3 H), 1.37–1.25 (m, 3 H), 1.22–1.12 (m, 1 H), 0.90 and 0.88 (2 s in a 1:3 ratio, 9 H altogether), 0.885 and 0.83 (2 d in a 3:1 ratio, *J* = 5.8 Hz, 3 H altogether), 0.09, 0.04, 0.03 and 0.00 (4 s in a 1:3:3:1 ratio, 6 H altogether) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.8, 142.6, 142.6, 138.7, 138.7, 134.8, 129.5, 129.5, 129.2, 129.2, 125.2, 125.2, 123.9, 123.9, 111.0, 111.0, 67.8, 67.2, 52.5, 52.1, 45.0, 44.2, 43.3, 42.6, 37.0, 36.7, 29.0, 28.7, 27.3, 27.2, 26.0, 25.9, 24.9, 24.9, 20.2, 20.1, 19.9, 19.7, 18.0, –4.2, –4.3, –4.3, –4.4 ppm. FTIR (film): $\tilde{\nu}$ = 3079, 2929, 2856, 1597, 1499, 1462, 1416, 1373, 837, 775 cm^{-1}. MS (ESI): *m*/*z* = 515.6 $[M + H]^+$. HRMS (ESI): calcd. for $C_{27}H_{42}N_4NaO_2SSi$ $[M + Na]^+$ 537.2690; found 537.2690.

Oxidation of 34 To Give Sulfone 36: Commercially sourced $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (22 mg, 0.018 mmol) was added to a stirred solution of **34** (28 mg, 0.05 mmol) in commercially sourced EtOH (95 %; 1 mL) at ambient temperature, and then H_2O_2 (30 % aq.; 0.1 mL) was added. The mixture was then stirred at the same temperature for 12 h, after which time TLC showed that the reaction was complete. Water (1 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aq. Na_2SO_3 and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 5:1) on silica gel gave sulfone **36** (*dr* 1.5:1, 20 mg, 0.04 mmol, 67 %) as a colourless oil. $[\alpha]_D^{22}$ = +6.8 (*c* = 1.98, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.67–7.58 (m, 5 H), 7.35 (br. t, *J* = 1.8 Hz, 0.4 H), 7.34 (br. t, *J* = 1.7 Hz, 0.6 H), 7.22 (br. s, 1 H), 6.28 (br. s, 0.6 H), 6.27 (br. s, 0.4 H), 4.04–3.96 (m, 2 H), 3.92–3.88 (m, 0.5 H), 2.35–2.35 (m, 2 H), 2.35–2.30 (m, 1 H), 2.19 (ddd, *J* = 2.8, 8.0, 13.7 Hz, 0.5 H), 1.76 (ddd, *J* = 3.4, 10.4, 13.8 Hz, 0.5 H), 1.71–1.66 (m, 1 H), 1.63–1.48 (m, 9 H), 1.39–1.26 (m, 2 H), 1.24–1.13 (m, 2 H), 0.90 (s, 9 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.10 (s, 2 H), 0.09 (s, 3 H), 0.08 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.6, 152.6, 142.6, 142.6, 138.7, 138.7, 133.1, 133.1, 131.4, 131.4, 129.5, 129.5, 125.4, 125.3, 125.1, 124.9, 110.9, 110.9, 68.5, 67.2, 58.7, 58.7, 45.0, 45.0, 36.6, 36.5, 36.1, 35.4, 28.9, 28.8, 27.2, 27.0, 25.8, 25.8,

24.8, 24.8, 20.1, 19.9, 17.9, 17.9, 15.1, 13.5, –4.1, –4.3, –4.4, –4.4 ppm. FTIR (film): $\tilde{\nu}$ = 3069, 2956, 2930, 2857, 1728, 1596, 1498, 1380, 837, 776 cm^{-1}. MS (ESI): *m/z* = 569.6 $[M + Na]^+$. HRMS (ESI): calcd. for $C_{27}H_{43}N_4O_4SSi$ $[M + H]^+$ 547.2769; found 547.2767.

Condensation of 36 with Aldehyde 37 To Give 38: NaHMDS (1.0 M in THF; 0.13 mL, 0.13 mmol) was added to a stirred solution of **36** (68 mg, 0.12 mmol) in dry THF (1 mL) at –75 °C under argon (balloon). Stirring was continued at the same temperature for 1 h, then a solution of aldehyde **37** (18 mg, 0.14 mmol) in dry THF (1 mL) was added. After the addition was complete, the mixture was stirred at –75 °C for another 5 h. After this time, TLC showed that the reaction was complete. Water (3 mL) was added. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with saturated aq. Na_2SO_3 and brine, and dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 50:1) on silica gel gave **38** [(*E*)/(*Z*) = 3:1, 39 mg, 0.09 mmol, 71 %] as a colourless oil. $[\alpha]_D^{22}$ = –21.2 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.33 (m, 2 H), 7.21 (br. s, 2 H), 6.27 (br. s, 1.5 H), 6.26 (br. s, 0.5 H), 5.22 (br. t, *J* = 7.0 Hz, 0.25 H), 5.16 (br. t, *J* = 6.9 Hz, 0.75 H), 3.90–3.78 (m, 1 H), 2.47–2.37 (m, 4 H), 2.29–2.17 (m, 3 H), 2.05 (dd, *J* = 7.6, 13.1 Hz, 1 H), 1.69 (d, *J* = 1.1 Hz, 0.7 H), 1.63–1.60 (m, 1 H), 1.58 (br. s, 2.3 H), 1.57–1.51 (m, 1 H), 1.38–1.24 (m, 2 H), 1.23–1.15 (m, 1 H), 1.13–1.07 (m, 1 H), 0.89 (s, 2.4 H), 0.88 (s, 6.6 H), 0.84 (d, *J* = 6.5 Hz, 0.75 H), 0.83 (d, *J* = 6.6 Hz, 2.25 H), 0.06–0.04 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.6, 142.6, 138.8, 138.7, 132.9, 132.9, 126.6, 126.6, 125.3, 125.3, 124.9, 124.8, 111.0, 111.0, 68.9, 68.8, 48.9, 44.3, 44.2, 41.1, 37.4, 37.4, 28.6, 28.6, 28.4, 27.4, 25.9, 25.1, 24.9, 24.9, 24.3, 19.5, 19.4, 18.1, 18.1, 16.6, –4.0, –4.1, –4.5, –4.6 ppm. FTIR (film): $\tilde{\nu}$ = 3137, 3107, 2950, 2929, 2856, 1563, 1501, 1462, 1379, 874, 774 cm^{-1}. MS (ESI): *m/z* = 445.5 $[M + H]^+$. HRMS (ESI): calcd. for $C_{27}H_{44}NaO_3Si$ $[M + Na]^+$ 467.2952; found 467.2956.

Desilylation of 38 To Give *ent*-1: A solution of **38** (35 mg, 0.08 mmol) and nBu_4NF (1.0 M in THF; 0.6 mL, 0.6 mmol) was stirred at ambient temperature for 12 h. The mixture was then diluted with EtOAc (20 mL), and washed with water (3 × 2 mL) and brine, then it was dried with anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (petroleum ether/EtOAc, 50:1 to 10:1) on silica gel gave *ent*-**1** [a 3:1 inseparable mixture of (*E*) and (*Z*) isomers, 17 mg, 0.05 mmol, 65 %] as a colourless oil, along with recovered **38** (8 mg, 0.018 mmol, 23 %). Data for *ent*-**1**: $[\alpha]_D^{25}$ = –8.4 (*c* = 1.0, $CHCl_3$) {ref.[6] $[\alpha]_D^{20}$ = +8.9 (*c* = 1.0, $CHCl_3$) for natural **1**}. ^1H NMR (500 MHz, C_6D_6): δ = 7.15 (br. s, 1 H), 7.13 (br. s, 1 H), 7.09 (br. s, 0.75 H), 7.08 (br. s, 0.25 H), 7.06 (br. s, 1 H), 6.11 (br. s, 0.75 H), 6.10 (br. s, 0.25 H), 6.09 (br. s, 0.25 H), 6.07 (br. s, 0.75 H), 5.26 (br. t, *J* = 7.0 Hz, 0.25 H), 5.17 (br. t, *J* = 6.9 Hz, 0.75 H), 3.75–3.69 (m, 1 H), 2.34–2.20 (m, 4 H), 2.11 (q, *J* = 7.2 Hz, 2 H), 2.03–1.95 (m, 1.5 H), 1.90 (dd, *J* = 4.5, 13.3 Hz, 0.5 H), 1.87–1.82 (m, 0.75 H), 1.81–1.75 (m, 0.25 H), 1.63 (br. s, 0.75 H), 1.58–1.46 (m, 3 H), 1.45 (br. s, 2.25 H), 1.36–1.26 (m, 1 H), 1.21–1.14 (m, 1 H), 1.09–1.03 (m, 1 H), 0.93 (d, *J* = 6.6 Hz, 2.25 H), 0.89 (d, *J* = 6.6 Hz, 0.75 H) ppm. ^{13}C NMR [125 MHz, C_6D_6, with resolved signals for the minor (*Z*) isomer indicated with an asterisk when different from those for the major (*E*) isomer]: δ = 143.08 (C-20), 143.03 (C-20)*, 142.97 (C-1)*, 142.96 (C-1), 139.33 (C-21)*, 139.32 (C-21), 139.21 (C-4), 133.19 (C-8), 132.92 (C-8)*, 127.80 (C-7), 125.52 (C-18), 125.49 (C-18)*, 124.94 (C-4)*, 124.92, 111.31 (C-2), 111.28 (C-2)*, 111.19 (C-19), 67.19 (C-11)*, 66.30 (C-11), 49.50 (C-10), 45.01 (C-12), 41.48 (C-10)*, 37.88 (C-14), 37.85 (C-14)*, 29.46 (C-13), 29.44 (C-13)*, 28.99 (C-6)*, 28.73 (C-6), 27.87 (C-16), 27.86 (C-16)*, 25.45 (C-5)*, 25.31 (C-5), 25.11 (C-17), 24.01 (C-9)*, 19.55 (C-14), 19.44 (C-14)*, 16.22 (C-9) ppm. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.34 (br. s, 2 H), 7.21 (br. s, 2 H), 6.26 (br. s, 2 H), 5.37 (br. t, *J* = 6.9 Hz, 0.25 H), 5.25 (br. t, *J* = 6.8 Hz, 0.75 H), 3.84–3.79 (m, 0.22 H), 3.75–3.70 (m, 0.78 H), 2.48 (br. t, *J* = 7.5 Hz, 2 H), 2.40 (br. t, *J* = 7.5 Hz, 2 H), 2.30 (q, *J* = 7.0 Hz, 2 H), 2.13 (dd, *J* = 2.1, 13.2 Hz, 1 H), 1.99 (dd, *J* = 9.6, 13.2 Hz, 1 H), 1.72 (br. s, 0.8 H), 1.71–1.66 (m, 1 H), 1.61 (br. s, 2.2 H), 1.59–1.51 (m, 2 H), 1.45 (ddd, *J* = 4.4, 9.5, 14.0 Hz, 1 H), 1.36–1.30 (m, 1 H), 1.22–1.17 (m, 1 H), 1.12 (ddd, *J* = 3.2, 9.7, 13.3 Hz, 1 H), 0.90 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR [125 MHz, $CDCl_3$, with resolved signals for the minor (*Z*) isomer indicated with an asterisk when different from those for the major (*E*) isomer]: δ = 142.77 (C-20), 142.67 (C-20)*, 142.60 (C-1)*, 142.59 (C-1), 138.90 (C-21)*, 138.87 (C-21), 138.74 (C-4), 132.82 (C-8), 132.53 (C-8)*, 128.08 (C-7)*, 127.79 (C-7), 125.25 (C-18), 125.22 (C-18)*, 124.63 (C-4), 124.62 (C-4)*, 111.01 (C-2), 111.00 (C-2)*, 110.91 (C-19), 67.10 (C-11)*, 66.03 (C-11), 48.85 (C-10), 44.63 (C-12)*, 44.51 (C-12), 40.92 (C-10)*, 37.43 (C-14)*, 37.39 (C-14), 29.43 (C-13)*, 29.20 (C-13), 28.50 (C-6)*, 28.41 (C-6), 27.37 (C-16)*, 27.34 (C-16), 25.12 (C-5)*, 24.99 (C-5), 24.84 (C-17), 23.76 (C-9)*, 19.29 (C-14), 19.19 (C-14)*, 16.17 (C-9) ppm. IR (film): $\tilde{\nu}$ = 3440, 3133, 3104, 2928, 2855, 1567, 1501, 1459, 1380, 874, 778 cm^{-1}. MS (ESI): *m/z* = 331.4 $[M + H]^+$. HRMS (ESI): calcd. for $C_{21}H_{30}O_3Na$ $[M + Na]^+$ 353.2087; found 353.2093.

Oxidation of *ent*-1 To Give *ent*-2: A mixture of *ent*-**1** (11 mg, 0.033 mmol), $NaHCO_3$ (4.1 mg, 0.05 mmol), and Dess–Martin periodinane (15 wt.-% in CH_2Cl_2; 0.1 mL, 0.05 mmol) in dry CH_2Cl_2 (2 mL) was stirred at ambient temperature for 15 min. After this time, TLC showed that the reaction was complete. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (petroleum ether/EtOAc, 15:1) on silica gel to give *ent*-**2** (9 mg, 0.03 mmol, 82 %) as a colourless oil. $[\alpha]_D^{25}$ = +6.0 (*c* = 0.7, $CHCl_3$) {ref.[6] $[\alpha]_D^{22}$ = –8.1 (*c* = 2.31, $CHCl_3$) for natural **2**}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.34 (br. s, 2 H), 7.21 (br. s, 1 H), 7.20 (br. s, 1 H), 6.27 (br. s, 1 H), 6.26 (br. s, 1 H), 5.40 (br. t, *J* = 6.9 Hz, 0.25 H), 5.28 (br. t, *J* = 6.7 Hz, 0.75 H), 3.07 (br. s, 0.5 H), 3.01 (br. s, 1.5 H), 2.50–2.45 (m, 2 H), 2.41–2.37 (m, 2 H), 2.32 (dd, *J* = 5.7, 14.8 Hz, 2 H), 2.21 (dd, *J* = 7.9, 16.4 Hz, 2 H), 2.05–1.97 (m, 1 H), 1.70 (br. s, 0.8 H), 1.59 (br. s, 2.2 H), 1.58–1.48 (m, 2 H), 1.33–1.26 (m, 1 H), 1.22–1.14 (m, 1 H), 0.89 (d, *J* = 5.8 Hz, 0.75 H), 0.87 (d, *J* = 6.5 Hz, 2.25 H) ppm. ^{13}C NMR [125 MHz, $CDCl_3$, with resolved signals for the minor (*Z*) isomer indicated with an asterisk when different from those for the major (*E*) isomer]: δ = 209.40 (C-11), 208.38 (C-11)*, 142.71 (C-20)*, 142.68 (C-1), 142.66 (C-20), 138.89 (C-4)*, 138.88 (C-4), 138.76 (C-21), 129.74 (C-8), 129.24 (C-8)*, 128.96 (C-7), 128.11 (C-1)*, 125.04 (C-18), 125.02 (C-18)*, 124.60 (C-3), 124.54 (C-3)*, 110.96 (C-2), 110.95 (C-19), 110.93 (C-19)*, 54.48 (C-10), 49.40 (C-12)*, 49.00 (C-12), 47.11 (C-10)*, 36.42 (C-15), 28.91 (C-6)*, 28.88 (C-13)*, 28.83 (C-13), 28.48 (C-6), 27.41 (C-16), 24.83 (C-17), 24.69 (C-5), 24.20 (C-9)*, 19.79 (C-14), 16.48 (C-9) ppm. ^1H NMR (500 MHz, C_6D_6): δ = 7.15 (br. s, 1 H), 7.14–7.12 (m, 1 H), 7.07 (br. s, 2 H), 6.09 (br. s, 2 H), 5.28 (br. t, *J* = 7.2 Hz, 0.25 H), 5.15 (dt, *J* = 1.1, 7.0 Hz, 0.75 H), 2.83 (br. s, 0.5 H), 2.78 (br. s, 1.5 H), 2.33–2.29 (m, 2 H), 2.24–2.20 (m, 2 H), 2.16–2.09 (m, 2 H), 2.07–2.00 (m, 2 H), 1.96–1.90 (m, 1 H), 1.67 (br. d, *J* = 1.2 Hz, 0.75 H), 1.54 (br. s, 2.25 H), 1.46–1.32 (m, 2 H), 1.23–1.16 (m, 1 H), 1.06–0.98 (m, 1 H), 0.83 (d, *J* = 6.6 Hz, 2.25 H), 0.82 (d, *J* = 6.6 Hz, 0.75 H) ppm. ^{13}C NMR [125 MHz, C_6D_6, with resolved signals for the minor (*Z*) isomer indicated with an asterisk when different from those for the major (*E*) isomer]: δ = 206.97 (C-11), 206.11 (C-11)*, 143.05 (C-20)*, 143.02 (C-20), 143.01 (C-1), 139.34 (C-4), 139.32 (C-4)*, 139.23 (C-21), 130.36 (C-8), 129.78 (C-8)*, 128.83 (C-7), 125.34 (C-18), 125.30 (C-18)*, 124.88 (C-3)*, 124.86 (C-3), 111.25 (C-2), 111.24 (C-19), 111.22 (C-19)*, 54.47 (C-10), 49.39 (C-12)*, 48.97 (C-12), 47.09 (C-10)*, 36.68 (C-15), 36.66 (C-15)*, 29.31 (C-6)*, 28.92 (C-13)*, 28.89 (C-13), 28.77 (C-6), 27.81 (C-16), 25.16 (C-5)*, 25.13 (C-17), 25.12 (C-17)*, 24.99 (C-5), 24.40 (C-9)*, 19.99 (C-14), 19.96 (C-14)*, 16.56 (C-9) ppm. IR (film): $\tilde{\nu}$ = 3134, 2926, 2855,

1712, 1501, 1460, 1380, 874, 778 cm^{-1}. MS (ESI): *m/z* = 329.4 $[M + H]^+$. HRMS (ESI): calcd. for $C_{21}H_{28}O_3Na$ $[M + Na]^+$ 351.1931; found 351.1930.

$NaBH_4$ Reduction of *ent*-2 To Give C-11-Epimerized *ent*-1: $NaBH_4$ (1 mg, 0.024 mmol) was added to a stirred solution of *ent*-**2** (4 mg, 0.012 mmol) in MeOH (1 mL) at ambient temperature. The mixture was stirred for 10 min, after which time TLC showed that the reaction was complete. The MeOH was removed by rotary evaporation. The residue was purified by column chromatography (petroleum ether/EtOAc, 8:1) on silica gel to give C-11-epimerized *ent*-**1** (3 mg, 0.009 mmol, 75 %) as a colourless oil. $[\alpha]_D^{24} = -0.5$ (*c* = 0.6, $CHCl_3$). ^1H NMR (500 MHz, C_6D_6): δ = 7.13 (br. s, 2 H), 7.10–7.06 (m, 2 H), 6.11–6.07 (m, 2 H), 5.26 (br. t, *J* = 6.6 Hz, 0.25 H), 5.17 (br. t, *J* = 6.8 Hz, 0.75 H), 3.75–3.68 (m, 1 H), 2.32–2.23 (m, 4 H), 2.11 (q, *J* = 7.1 Hz, 2 H), 2.06–1.95 (m, 1.5 H), 1.93–1.89 (m, 0.5 H), 1.88–1.84 (m, 0.24 H), 1.79–1.68 (m, 0.76 H), 1.63 (br. s, 0.89 H), 1.55–1.47 (m, 2 H), 1.45 (br. s, 2.29 H), 1.42–1.36 (m, 1 H), 1.33–1.25 (m, 1 H), 1.21–1.12 (m, 1 H), 1.10–1.03 (m, 1 H), 0.95–0.89 (m, 3 H) ppm. ^{13}C NMR (125 MHz, C_6D_6): δ = 143.09, 143.08, 143.03, 143.01, 142.98, 142.97, 142.96, 139.32, 139.23, 139.21, 133.20, 133.18, 132.92, 127.80, 125.52, 125.50, 125.49, 125.47, 124.94, 124.92, 111.31, 111.29, 111.27, 111.19, 67.60, 67.18, 66.70, 66.30, 49.50, 49.09, 45.29, 45.21, 45.02, 41.49, 41.12, 37.88, 37.85, 36.44, 36.35, 29.87, 29.46, 28.99, 28.75, 28.74, 27.87, 27.86, 27.79, 27.74, 25.46, 25.32, 25.31, 25.11, 24.01, 23.99, 20.71, 20.67, 19.56, 19.44, 16.22 ppm.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H and ^{13}C NMR spectra and FTIR spectra for all new compounds. Tabular comparison of the ^1H and ^{13}C NMR spectroscopic data.

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