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Total Synthesis of a 6,6-Spiroketal Metabolite, Dinemasone A

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The stereoselective total synthesis of dinemasone A has been accomplished. The key reactions, Sharpless asymmetric epoxidation, lithium-mediated epoxy alcohol opening, and double-intramolecular hetero-Michael addition, gave access to dinemasone A from lactic acid esters. The stereochemistry at the spiro carbon was determined using extensive NMR studies.

Introduction

Spiroketal-containing natural products constitute an important class of bio-active molecules, due to their remarkable and diverse biological activities.[1] The majority of these compounds are non-racemic chiral molecules isolated from various sources, including plants, insects, microbes, fungi, marine organisms etc. As a result of their pharmacological significance, spiroketals have been of substantial interest to synthetic organic chemists as well as medicinal chemists.[2] Dinemasones A–C (**1–3**, Figure 1) are anti-microbial metabolites isolated from the ethyl acetate extracts of a culture of the endophytic fungus, *Dinemasporium strigosum*, which had been isolated from the roots of *Calystegia sepium*.[3] The absolute configurations were established by their carbonyl n–π* CD transitions and the exciton chirality of their respective dibenzoate derivatives. One of these three natural products, dinemasone A (**1**), has a [6,6]-spiroketal skeleton containing five stereogenic centres. The presence of a hydroxy group on the carbon adjacent to the spiroketal carbon (quaternary carbon) is a unique feature of this natural product. Furthermore, **1** has shown considerable activity against the Gram-positive bacterium *Bacillus megaterium*, the fungus *Microbotryum violaceum*, and the alga *Chlorella fusca*. The above features of **1** combined with our interest in the synthesis of tetrahydropyran-containing natural products[4] spurred us to synthesise dinemasone A.[5]

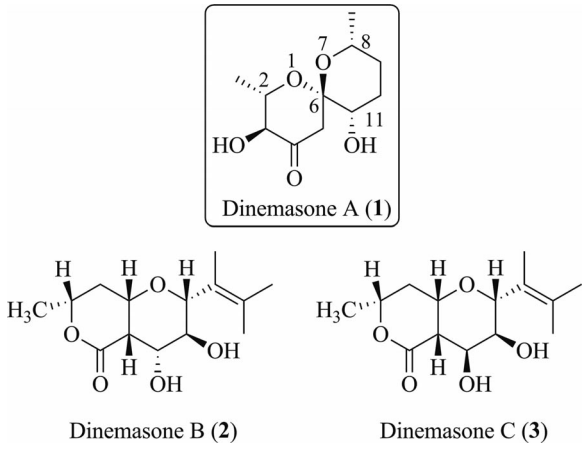

Figure 1. Structure of dinemasones A–C.

In this paper, we report the enantioselective total synthesis of dinemasone A (**1**) using double-intramolecular hetero-Michael addition[6] as the key step.

Results and Discussion

As shown in Scheme 1, dinemasone A (**1**) was envisioned to arise from ynone **4** by double-intramolecular hetero-Michael addition. Enyne **4** was intended to come from aldehyde **5** and alkyne **6**, which in turn could be obtained from ethyl (–)-L-lactate and methyl (+)-D-lactate, respectively. The desired propargylic alcohol functionality in **6** would be obtained using Sharpless asymmetric epoxidation and lithium-mediated opening of the epoxy alcohol as the key steps.

As outlined in Scheme 2, aldehyde fragment **5** was prepared by a sequence of high-yielding steps. Following a literature procedure,[7] we prepared allylic alcohol **10** starting

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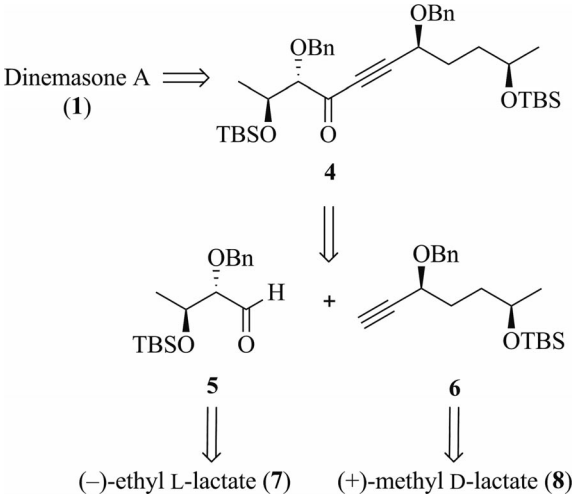
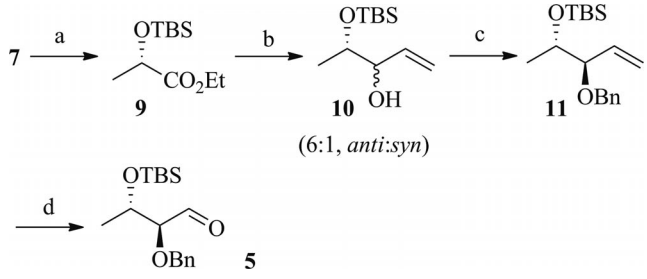


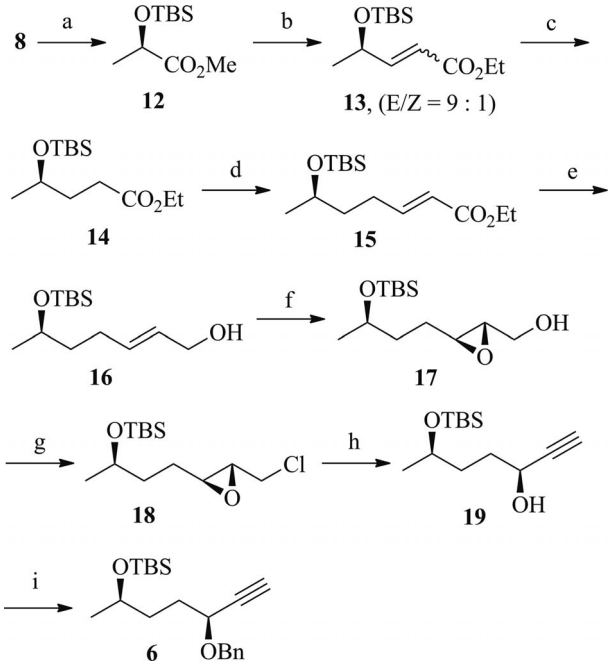
Scheme 1. Retrosynthesis of dinemasone A.

from (–)-ethyl L-lactate (**7**) via ester **9**. Alcohol **10** was obtained with a 6:1 (*anti*/*syn*) diastereomeric ratio (in 72% combined yield), and the diastereomers were separated at the next stage. Benzyl protection of allylic alcohol **10** using BnBr/Ag_2O in dichloromethane at reflux temperature provided the desired benzyl ether (i.e., **11**) in 71% yield. Oxidative cleavage of the terminal double bond in **11** under ozonolysis conditions gave aldehyde **5**, which was used immediately in the next step.



Scheme 2. Synthesis of fragment **5**; *Reagents and conditions:* (a) TBSCl, imidazole, CH_2Cl_2, 0 °C to room temp., 12 h, 90%; (b) (i) DIBAL-H, CH_2Cl_2, –78 °C, 1 h; (ii) vinylmagnesium bromide, THF, –78 °C, 1 h, 72% (over two steps); (c) BnBr, Ag_2O, CH_2Cl_2, reflux, 24 h, 71% (yield of desired isomer); (d) O_3/DMS, CH_2Cl_2, –78 °C, 15 min, 82% (TBSCl = *tert*-butyldimethylsilyl chloride; DIBAL-H = diisobutylaluminium hydride).

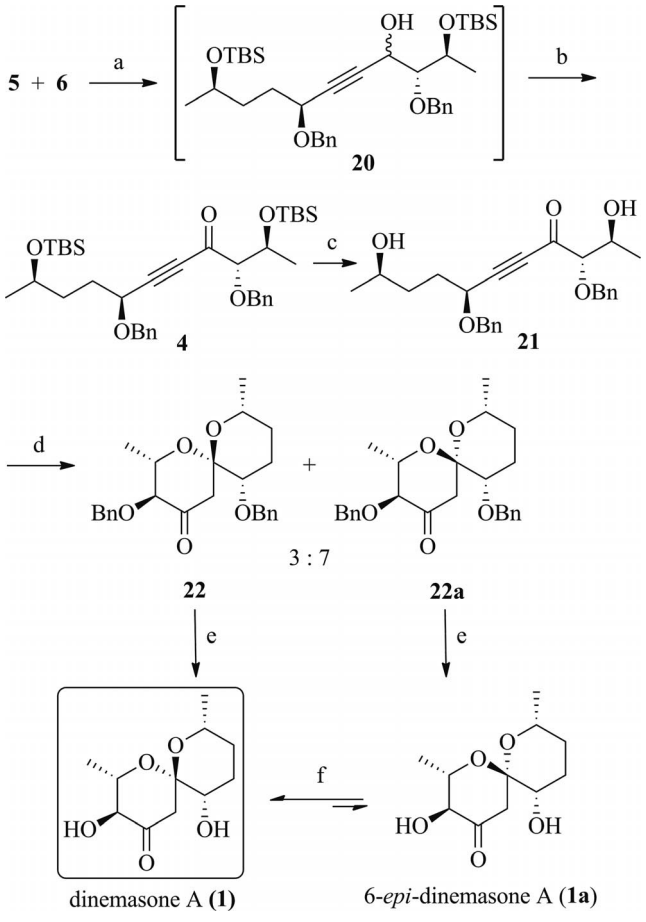
The synthesis of alkyne fragment **6** began with commercially available (+)-methyl D-lactate, which was initially protected as its *tert*-butyldimethylsilyl ether (i.e., **12**) using TBSCl/imidazole in CH_2Cl_2 (91% yield; Scheme 3). The installation of the additional four-carbon chain was accomplished with sequential Wittig reactions. Thus, the reduction of ester **12** to the aldehyde, followed by the treatment with the two-carbon ylide, ethoxycarbonyl methylene triphenylphosphorane (Ph_3P=CHCOOEt), gave α,β-unsaturated ester **13** in 85% yield (*E*/*Z* = 9:1). Reduction of the olefin functionality in **13** by hydrogenation gave ester **14** in 93% yield. Next, ester **14** was again subjected to DIBAL-H reduction and subsequent two-carbon homologation with Ph_3P=CHCOOEt to obtain exclusively (*E*)-α,β-unsaturated ester **15** in 80% yield over two steps. The ester functionality in **15** was selectively reduced to give allylic alcohol **16** using DIBAL-H in dichloromethane (89%). The required chiral epoxide was introduced at this stage by Sharpless catalytic asymmetric epoxidation[8] using (+)-diethylisopropyl tartrate to yield epoxide **17** in 78% yield and with good diastereoselectivity (*dr* > 95:5). The conversion of epoxy alcohol **17** to chloro epoxide **18** was accomplished by treatment with Ph_3P in CCl_4 at refluxing temperature (72%). Treatment of chloro epoxide **18** with *n*BuLi in THF at –78 °C gave the desired propargylic alcohol (i.e., **19**) in 70% yield.[9] Protection of the hydroxy group in **19** as its benzyl ether provided the alkyne fragment (i.e., **6**) in 72% yield.



Scheme 3. Synthesis of fragment **6**; *Reagents and conditions:* (a) TBSCl, imidazole, CH_2Cl_2, 0 °C to room temp., 12 h, 91%; (b) (i) DIBAL-H, CH_2Cl_2, –78 °C, 30 min; (ii) PPh_3=CHCOOEt, CH_2Cl_2, reflux, 1 h, 85% (over two steps); (c) H_2, Pd-C, EtOH, room temp., 4 h, 93%; (d) (i) DIBAL-H, CH_2Cl_2, –78 °C, 30 min; (ii) PPh_3=CHCOOEt, CH_2Cl_2, room temp., 12 h, 80% (over two steps); (e) DIBAL-H, CH_2Cl_2, –78 °C to –20 °C, 1 h, 89%; (f) (+)-DIPT, Ti(O*i*Pr)$_4$, TBHP, –20 °C, 4 h, 78%; (g) PPh_3, CCl_4, $NaHCO_3$, reflux, 3 h, 72%; (h) *n*BuLi, THF, –78 °C, 5 h, 70%; (i) BnBr, NaH, TBAI, DMF, 0 °C to room temp., 12 h, 72% (DIPT = diisopropyl tartrate; TBHP = *tert*-butyl hydroperoxide; TBAI = tetrabutylammonium iodide).

Having achieved the synthesis of both aldehyde **5** and alkyne **6**, the coupling of these two units to give ynone **4** was planned (Scheme 4). Thus, alkyne **6** was lithiated using *n*BuLi, and the resulting anion underwent addition with aldehyde **5** to give propargylic alcohol **20** as a diastereomeric mixture (1:1, 77%). This product was immediately oxidised with Dess–Martin periodinane[10] to give alkynone **4** in 85%

yield. The conversion of compound **4** into spiroketal **22** was initially attempted in one pot under various acidic conditions. However, all of these reactions resulted either in complex mixtures or in no reaction. Therefore, a two-step sequence was considered for this transformation. The reaction of **4** with aqueous HF in acetonitrile promoted the desilylation of both silyl groups to give diol **21** in 88% yield. The crucial spiroketalisation reaction was carried out by treatment of **21** with *p*TSA·H_2O in toluene at room temperature for 24 h, which provided a seperable mixture of two spiroketals **22** and **22a** (3:7 ratio) in 89% combined yield through double-intramolecular hetero-Michael addition.[6] At this juncture, we decided to carry out a debenzylation to reach the target molecule, so that the characterisation data of the synthetic product and the natural product could be compared. Accordingly, spiroketals **22** and **22a** were independently subjected to debenzylation using 10% Pd-C under a hydrogen atmosphere in ethyl acetate to give diols **1** (78%) and **1a** (76%), respectively. The spectroscopic data of **1** (^{1}H and ^{13}C NMR, mass spectrometry, and IR) including 2D NMR spectroscopic techniques, COSY, HSQC, and NOESY (Figure 2),[11] were in full agreement with those reported for natural dinemasone A. The specific rotation observed for synthetic **1**, $[\alpha]_D^{20}$ = –79.3 (*c* = 0.21, $CHCl_3$) was also comparable with the reported value for the natural product[3] {$[\alpha]_D^{25}$ = –80.4 (*c* = 0.68, $CHCl_3$)}.



Scheme 4. Coupling of **5** and **6**. *Reagents and conditions:* (a) *n*BuLi, THF, –78 °C to room temp., 1 h, 77%; (b) Dess–Martin periodinane, CH_2Cl_2, room temp., 30 min, 85%; (c) HF (aq.), CH_3CN, room temp., 5 h, 88%; (d) *p*TSA, toluene, room temp., 24 h, 89% (combined yield); (e) Pd-C (10%), H_2, EtOAc, room temp., 12 h, 95% for **1**; 93% for **1a**; (f) $ZnBr_2$, CH_2Cl_2, room temp., 5 h, (**1**/**1a**, 2:1; 90% combined yield) (*p*TSA = *p*-toluenesulfnic acid).

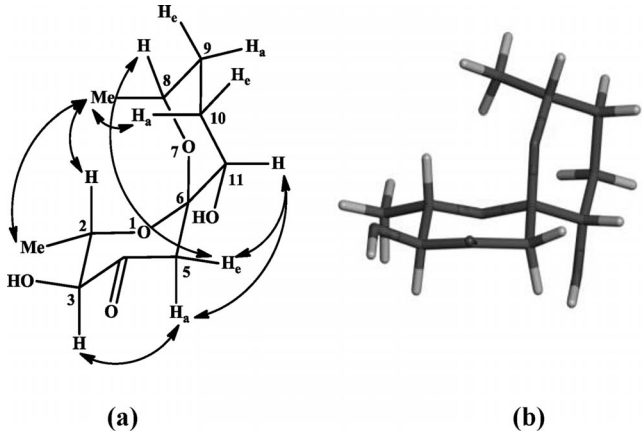


Figure 2. (a) nOes observed for **1**; (b) energy-minimised MD structure of **1**.

Diol **1a** was also analysed using 1D and 2D NMR spectroscopic techniques, COSY, HSQC and NOESY. Restrained MD simulation, with the help of observed NOE cross-peaks between 2-H–10a-H, 2-H−10e-H, 8-H−10a-H, 11-H−5e-H, 3-H−5a-H, and 11-H−5a-H, as well as $^3J_{H,H}$ couplings (Figure 3), suggest that the stereochemistry at C-6 is "*R*". This stereochemistry is "*S*" in the natural compound, and therefore compound **1a** is confirmed to be 6-*epi*-dinemasone A (**1a**).

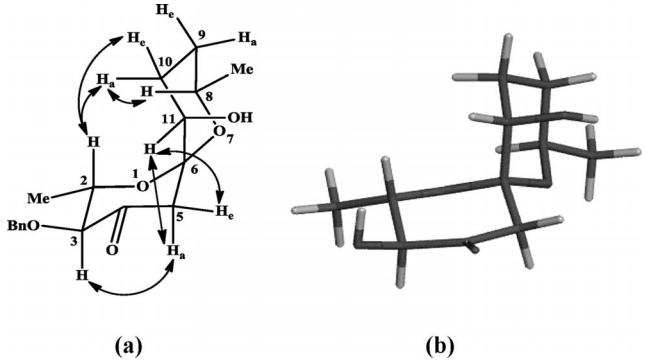


Figure 3. (a) nOes observed for **1a**; (b) energy-minimised MD structure of **1a**.

The above results showed that unnatural 6-*epi*-dinemasone A was obtained as the major isomer, due to the favourable formation of axial–equatorial mono-anomeric spiroketal **22a** over axial–axial doubly anomeric spiroketal **22** (required for dinemasone A). This can be explained by considering the two possible transition states during the acid-catalysed spiroketalisation of **21**.[2f] The minor formation of doubly anomeric spiroketal **22** through axial attack may be due to unfavourable steric interactions between the axial C-8-methyl group and the axial C-2-hydrogen (**22**-TS, Fig-

ure 4). As a result, the favourable mode of attack is equatorial attack (**22a**-TS) to give mono-anomeric spiroketal **22a**, which leads to the undesired 6-*epi*-dinemasone A (i.e., **1a**). However, the conversion of **1a** into the desired natural product, i.e., dinemasone A (**1**), was also accomplished by equilibration using a Lewis acid.[12] After treatment with zinc(II) bromide in dichloromethane for 5 h, a separable mixture of epimers was formed in a 2:1 ratio in favour of the desired dinemasone A (**1**, Scheme 4).[13] Prolonging the reaction time or increasing the amount of the Lewis acid did not improve the formation of **1**, but simply promoted the slow decomposition of the products (as observed in TLC monitoring).

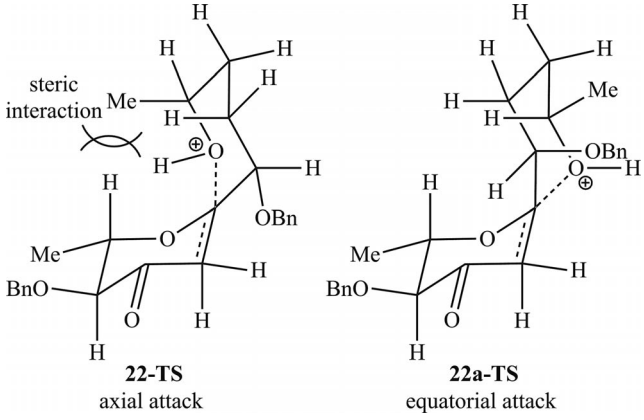


Figure 4. Possible transition states in the spiroketalisation of **21**.

Conclusions

In summary, we have described a stereoselective total synthesis of dinemasone A and its 6-epimer. Key features of the synthesis are: i) formation of both of the the required fragments from lactic acid esters; ii) the use of double intramolecular hetero-Michael addition for spiroketalisation. The major diastereomer obtained in the synthesis, 6-*epi*-dinemasone A, was transformed to dinemasone A by equilibration with $ZnBr_2$. The synthesis required 18 steps with a longest linear sequence of 14 steps. The overall yield of the longest linear sequence for the synthesis of dinemasone A was 5.2%.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with Bruker 300 MHz (Avance), Varian Unity 500 MHz (Innova), Bruker 600 MHz, and Bruker 700 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm relative to TMS as internal standard. FTIR spectra were recorded with a Perkin–Elmer 683 infra-red spectrometer, using neat compounds or as thin films on KBr plates. Optical rotations were measured with an Anton Paar MLP 200 modular circular digital polarimeter using a 2 mL cell with a path length of 1 dm. Low-resolution MS were recorded with an Agilent Technologies LC-MSD trap SL spectrometer. All the reagents and solvents were of reagent grade, and were used without further purification unless otherwise stated. Technical grade EtOAc and hexanes used for column chromatography were distilled before use. THF, when used as solvent for the reactions, was freshly distilled from sodium benzophenone ketyl. Column chromatography was carried on silica gel (60–120 mesh) packed in glass columns. All the reactions were performed under N_2 in flame-dried or oven-dried glassware with magnetic stirring.

Ethyl (*S*)-2-(*tert*-Butyldimethylsilyloxy)propanoate (9): Imidazole (2.0 g, 29.4 mmol) and then *tert*-butyldimethylsilyl chloride (4.2 g, 27.9 mmol) were added to a stirred solution of *S*-ethyl lactate **7** (3 g, 25.4 mmol) in dichloromethane (30 mL) at 0 °C. Then the reaction temperature was raised to 25 °C and the mixture was stirred for 12 h. The reaction was diluted with water (30 mL), and the phases were separated. The organic phase was further washed with brine (20 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5% ethyl acetate in hexanes) to give **9** (5.3 g, 90%) as a colourless liquid. IR (neat): $\tilde{\nu}$ = 2934, 2858, 1724, 1659, 1467, 1261, 1155, 1094, 834, 778 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.5 (q, J = 7.0 Hz, 1 H), 4.15 (q, J = 4.0 Hz, 2 H), 1.36 (d, J = 7.0 Hz, 3 H), 1.27 (t, J = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.07 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 68.2, 60.3, 25.4, 21.0, 18.0, 13.9, –5.1, –5.5 ppm. MS (ESI): m/z = 255 $[M + Na]^+$.

(3*R*,4*S*)-4-(*tert*-Butyldimethylsilyloxy)pent-1-en-3-ol (10): DIBAL-H (25% solution in toluene, 4.9 mL, 8.6 mmol) was added to a stirred solution of silyl ether **9** (2 g, 8.6 mmol) in dry dichloromethane (20 mL) at –78 °C. The reaction mixture was maintained at same temperature for an additional 30 min, and then the reaction was quenched with a saturated aqueous solution of potassium sodium tartrate (10 mL). The mixture was left to stir for 3 h until the organic and aqueous phases had completely separated. The organic phase was washed with brine (20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product. The crude residue was purified by flash chromatography (10% ethyl acetate in hexanes) to give the corresponding aldehyde (1.3 g) as a colourless oil.

Vinylmagnesium bromide (1 M in THF, 9 mL, 9.0 mmol) was added to a stirred solution of the above aldehyde in dry tetrahydrofuran (15 mL) at –78 °C. Stirring was continued for 1 h at the same temperature, and then the reaction was quenched with saturated aqueous NH_4Cl (20 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (5% ethyl acetate in hexanes) to give **10** (1.3 g, 72%; *syn*:*anti* = 1:6) as a colourless oil. IR (neat): $\tilde{\nu}$ = 3454, 2930, 2858, 1463, 1378, 1256, 1094, 1006, 937, 835, 775 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.78 (ddd, J = 6.0, 10.5, 17.3 Hz, 1 H), 5.27 (dd, J = 1.5, 17.3 Hz, 1 H), 5.17 (dd, J = 1.5, 10.5 Hz, 1 H), 4.01–3.95 (m, 1 H), 3.87–3.78 (m, 1 H), 2.09 (d, J = 3.7 Hz, 1 H), 1.07 (d, J = 6.0 Hz, 3 H), 0.90 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.2, 116.1, 76.3, 71.0, 25.4, 17.7, 17.3, –4.7, –5.1 ppm. MS (ESI): m/z = 239 $[M + Na]^+$.

[(2*S*,3*R*)-3-(Benzyloxy)pent-4-en-2-yloxy](*tert*-butyl)dimethylsilane (11): Silver oxide (1.92 g, 8.33 mmol) and benzyl bromide (0.55 mL, 4.58 mmol) were added to a stirred solution of compound **10** (900 mg, 4.16 mmol) in dichloromethane (10 mL) at room temperature. Then, the reaction temperature was raised to reflux, and the mixture was stirred for 24 h. The reaction mixture was filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (2% ethyl acetate in hexanes) to give

pure **11** (0.90 g, 83%) as a colourless liquid. $[\alpha]_D^{20}$ = –14.8 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2929, 2856, 1458, 1255, 1112, 1053, 834, 776 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 4 H), 7.29–7.25 (m, 1 H), 5.80 (ddd, *J* = 7.2, 10.5, 17.7 Hz, 1 H), 5.30 (d, *J* = 10.5 Hz, 1 H), 5.25 (d, *J* = 17.7 Hz, 1 H), 4.62 (d, *J* = 12.1 Hz, 1 H), 4.42 (d, *J* = 12.1 Hz, 1 H), 3.87–3.81 (m, 1 H), 3.57 (t, *J* = 5.6 Hz, 1 H), 1.18 (d, *J* = 6.4 Hz, 3 H), 0.88 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 136.4, 128.2, 127.6, 127.3, 118.5, 85.1, 70.8, 70.4, 25.8, 20.1, 18.1, –4.52, –4.58 ppm. MS (ESI): *m*/*z* = 329 $[M + Na]^+$.

(2*S*,3*S*)-2-(Benzyloxy)-3-[(*tert*-butyldimethylsilyl)oxy]butanal (5): A solution of **11** (120 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) was treated at –78 °C with a stream of ozone until the starting material had been consumed (as monitored by TLC). Then, dimethyl sulfide (DMS, 2.5 mL) was added to the reaction mixture to reduce the ozonide. The reaction mixture was allowed to warm slowly to room temperature and then it was diluted with water (5 mL). The mixture was extracted with CH_2Cl_2 (2× 5 mL). The combined organic extracts were washed with brine (5 mL), dried with Na_2SO_4, and filtered, and the filtrate was concentrated under reduced pressure to give aldehyde **5** (100 mg, 82%), which was used immediately for the preparation of **4**.

Methyl (*R*)-2-(*tert*-Butyldimethylsilyloxy)propanoate (12): Imidazole (3.9 g, 57.6 mmol) and then *tert*-butyldimethylsilyl chloride (7.9 g, 52.8 mmol) were added to a stirred solution of D-methyl lactate **7** (5 g, 48.0 mmol) in dichloromethane (50 mL) at 0 °C. Then the reaction temperature was raised to 25 °C, and the mixture was stirred for 12 h. After complete disappearance of the starting material, the reaction was diluted with water (50 mL), and the layers were separated. The organic layer was washed with brine (50 mL), dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography (5% ethyl acetate in hexanes) to give **12** (9.5 g, 91%) as a colourless liquid. IR (neat): $\tilde{\nu}$ = 2954, 2931, 2858, 1760, 1463, 1257, 1148, 837, 779 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.28 (q, *J* = 6.7 Hz, 1 H), 3.70 (s, 3 H), 1.37 (d, *J* = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.08 (s, 3 H), 0.05 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 68.2, 51.6, 25.6, 21.2, 18.1, –5.0, –5.3 ppm. MS (ESI): *m*/*z* = 241 $[M + Na]^+$.

Ethyl (*R*,*E*)-4-(*tert*-Butyldimethylsilyloxy)pent-2-enoate (13): DIBAL-H (25% solution in toluene, 13 mL, 22.9 mmol) was added to a stirred solution of silyl ether **12** (5 g, 22.9 mmol) in dry dichloromethane (50 mL) at –78 °C. The reaction mixture was stirred at same temperature for an additional 30 min, and then the reaction was quenched with a saturated aqueous solution of potassium sodium tartrate (20 mL). The mixture was left to stir for 4 h until the organic and aqueous phases had completely separated. The organic phase was washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product.

A mixture of the above crude aldehyde (4.3 g) and (ethoxycarbonylmethylene)triphenylphosphorane (9.5 g, 27.4 mmol) in dichloromethane (60 mL) was heated at reflux for 1 h. The reaction mixture was diluted with hexane and filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the resulting residue was purified by column chromatography (2% ethyl acetate in hexanes) to give α,β-unsaturated esters **13** (5.0 g, 85%; *E*/*Z* = 9:1) which were separable. IR (neat): $\tilde{\nu}$ = 2934, 2858, 1724, 1659, 1467, 1261, 1155, 1094, 834, 778 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.87 (dd, *J* = 4.1, 15.4 Hz, 1 H), 5.92 (dd, *J* = 1.7, 15.4 Hz, 1 H), 4.49–4.38 (m, 1 H), 4.16 (q, *J* = 7.3 Hz, 2 H), 1.37 (d, *J* = 6.7 Hz, 3 H), 1.30 (t, *J* = 6.9 Hz, 3 H), 0.9 (s, 9 H), 0.06 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.7, 151.8, 118.9, 67.6, 60.2, 25.7, 23.4, 21.2, 18.1, 14.2, –4.91, –4.98 ppm. MS (ESI): *m*/*z* = 281 $[M + Na]^+$. HRMS-ESI: calcd. for $C_{13}H_{26}O_3NaSi$ $[M + Na]^+$ 281.1548; found 281.1552.

Ethyl (*R*)-4-(*tert*-Butyldimethylsilyloxy)pentanoate (14): Palladium on carbon (10% by weight, 500 mg) was added to a solution of α,β-unsaturated ester **13** (4 g, 15.5 mmol) in ethanol (20 mL). The reaction mixture was stirred for 4 h under a hydrogen atmosphere. After completion of the reaction, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. Flash chromatography of the residue on silica gel (5% ethyl acetate in hexanes) gave **14** (3.7 g, 93%) as a colourless oil. $[\alpha]_D^{20}$ = –15.2 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2931, 2858, 1739, 1463, 1373, 1256, 1176, 1091, 836, 775 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.1 (q, *J* = 7.5 Hz, 2 H), 3.89–3.78 (m, 1 H), 2.32 (t, *J* = 7.5 Hz, 2 H), 1.80–1.59 (m, 2 H), 1.26 (t, *J* = 7.5 Hz, 3 H), 1.13 (d, *J* = 6.0 Hz, 3 H), 0.88 (s, 9 H), 0.03 (d, *J* = 2.2 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 67.3, 60.0, 34.2, 30.3, 25.7, 23.5, 17.9, 14.1, –4.5, –4.9 ppm. MS (ESI): *m*/*z* = 283 $[M + Na]^+$. HRMS-ESI: calcd. for $C_{13}H_{28}O_3NaSi$ $[M + Na]^+$ 283.1699; found 283.1692.

Ethyl (*R*,*E*)-6-(*tert*-Butyldimethylsilyloxy)hept-2-enoate (15): DIBAL-H (25% solution in toluene, 7.6 mL, 13.4 mmol) was added to a stirred solution of ester **14** (3.5 g, 13.4 mmol) in dry dichloromethane (35 mL) at –78 °C. The reaction mixture was stirred at same temperature for an additional 30 min, and then the reaction was quenched with a saturated aqueous solution of potassium sodium tartrate (20 mL). The mixture was left to stir for 3 h until the organic and aqueous phases were completely separated. The organic layer was washed with brine (15 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product.

A mixture of the above crude aldehyde (3.2 g) and (ethoxycarbonylmethylene)triphenylphosphorane (6.2 g, 17.8 mmol) in dichloromethane (30 mL) was stirred for 12 h. The reaction mixture was diluted with hexane and filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (5% ethyl acetate in hexanes) to give *E* α,β-unsaturated ester **15** (3.1 g, 80% over two steps) as a colourless oil. $[\alpha]_D^{20}$ = –13.2 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2930, 2857, 1722, 1654, 1369, 1258, 1046, 835, 775 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.98–6.88 (m, 1 H), 5.78 (d, *J* = 15.4 Hz, 1 H), 4.16 (q, *J* = 6.7 Hz, 2 H), 3.86–3.78 (m, 1 H), 2.34–2.16 (m, 2 H), 1.62–1.49 (m, 2 H), 1.28 (t, *J* = 6.7 Hz, 3 H), 1.14 (d, *J* = 6.7 Hz, 3 H), 0.88 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 149.0, 121.0, 67.6, 59.8, 37.6, 28.2, 25.6, 23.5, 17.8, 14.1, –4.4, –4.9 ppm. MS (ESI): *m*/*z* = 309 $[M + Na]^+$. HRMS-ESI: calcd. for $C_{15}H_{30}O_3NaSi$ $[M + Na]^+$ 309.1861; found 309.1870.

(*R*,*E*)-6-(*tert*-Butyldimethylsilyloxy)hept-2-en-1-ol (16): DIBAL-H (25% solution in toluene, 13.4 mL, 23.5 mmol) was added to a stirred solution of ester **15** (2.7 g, 9.4 mmol) in dry dichloromethane (30 mL) at –78 °C. The reaction mixture was slowly warmed to –20 °C and stirred for 1 h, then the reaction was quenched with a saturated aqueous solution of potassium sodium tartrate (25 mL). The mixture left to stir for 3 h until the organic and aqueous phases were completely separated. The organic phase was washed with brine (15 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes) to give alcohol **16** (2 g, 89%) as a colourless oil. $[\alpha]_D^{20}$ = –12.6 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3337, 2930, 2857, 1462, 1374, 1255, 1137, 1005, 835, 774 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.73–5.58 (m, 2 H), 4.05 (d, *J* = 3.7 Hz, 2 H), 3.84–3.73 (m, 1 H), 2.19–1.96 (m, 2 H), 1.57–1.39 (m, 2 H), 1.12 (d, *J* = 6.0 Hz, 3 H), 0.88 (s, 9

H), 0.04 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.1, 128.8, 68.0, 63.6, 39.0, 28.4, 25.8, 23.7, 18.0, –4.3, –4.7 ppm. MS (ESI): m/z = 267 $[M + Na]^+$. HRMS-ESI: calcd. for $C_{13}H_{28}O_2NaSi$ $[M + Na]^+$ 267.1756; found 267.1760.

{(2*S*,3*S*)-3-[(*R*)-3-(*tert*-Butyldimethylsilyloxy)butyl]oxiran-2-yl}methanol (17): Activated powdered 4 Å molecular sieves (6 g) and dichloromethane (20 mL) were placed in a round-bottomed flask under a nitrogen atmosphere. After cooling the flask to –20 °C, the following reagents were added sequentially with stirring: D-(+)-diisopropyl tartrate (0.43 mL, 2.0 mmol), $Ti(OiPr)_4$ (0.48 mL, 1.6 mmol), and *t*BuOOH (6.5 mL, 32.5 mmol). After stirring the reaction mixture for 1 h at –20 °C, a solution of allylic alcohol **16** (2 g, 8.2 mmol) in dichloromethane (10 mL) was added slowly. After stirring for 4 h at –20 °C, the reaction was quenched with H_2O (9.6 mL) and 10% aq. NaOH saturated with NaCl (4.8 mL). The mixture was stirred at room temperature for 4 h, then it was filtered, and the organic phase was separated. The aqueous phase was extracted with dichloromethane (3× 10 mL). The organic extracts were combined, washed with brine (20 mL), dried with Na_2SO_4, and concentrated. The residual oil was purified by column chromatography (10% ethyl acetate in hexanes) to give **17** (1.6 g, 78%) as a colourless oil. $[\alpha]_D^{20}$ = –26.4 (c = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3444, 2956, 2857, 1746, 1471, 1255, 1104, 1048, 1005, 836, 774 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.98–3.77 (m, 2 H), 3.68–3.54 (m, 1 H), 3.0–2.88 (m, 2 H), 1.74–1.43 (m, 4 H), 1.12 (d, J = 6.0 Hz, 3 H), 0.87 (s, 9 H), 0.04 (d, J = 1.8 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 67.9, 61.7, 58.4, 55.9, 35.4, 27.5, 25.8, 23.5, 18.0, –4.3, –4.7 ppm. MS (ESI): m/z = 283 $[M + Na]^+$. HRMS-ESI: calcd. for $C_{13}H_{28}O_3NaSi$ $[M + Na]^+$ 283.1699; found 283.1698.

***tert*-Butyl{(*R*)-4-[(2*S*,3*R*)-3-(chloromethyl)oxiran-2-yl]butan-2-yloxy}dimethylsilane (18):** $NaHCO_3$ (96 mg, 1.1 mmol) and triphenyl phosphene (1.5 g, 5.7 mmol) were added to a stirred solution of epoxy alcohol **17** (1.5 g, 5.7 mmol) in carbon tetrachloride (15 mL) at room temperature. Then the temperature was raised to reflux temperature, and the mixture was stirred for 3 h at reflux. The reaction mixture was cooled to room temperature, the solvent was evaporated, and the residue was purified by flash chromatography (5% ethyl acetate in hexanes) to give **18** (1.15 g, 72%) as a colourless oil. $[\alpha]_D^{20}$ = –14.4 (c = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2929, 2856, 1462, 1255, 1131, 1042, 835, 774 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.89–3.81 (m, 1 H), 3.60 (dd, J = 5.9, 11.8 Hz, 1 H), 3.39 (dd, J = 5.9, 11.8 Hz, 1 H), 2.94 (td, J = 1.9, 6.9 Hz, 1 H), 2.82 (td, J = 1.9, 6.9 Hz, 1 H), 1.48–1.47 (m, 4 H), 1.13 (d, J = 5.9 Hz, 3 H), 0.88 (s, 9 H), 0.05 (d, J = 1.9 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 67.8, 58.9, 57.1, 44.7, 35.2, 27.4, 25.8, 23.6, 18.0, –4.3, –4.7 ppm. MS (ESI): m/z = 279 $[M + H]^+$. HRMS-ESI: calcd. for $C_{13}H_{27}O_2NaSiCl$ $[M + Na]^+$ 301.1366; found 301.1370.

(3*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)hept-1-yn-3-ol (19): *n*BuLi (2.5 M solution in THF, 5.7 mL, 14.3 mmol) was added to a stirred solution of compound **18** (1.0 g, 3.59 mmol) in tetrahydrofuran (10 mL) at –78 °C. The reaction mixture was stirred at –78 °C for an additional 5 h, and then the reaction was quenched with saturated aqueous NH_4Cl (15 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3× 10 mL). The combined organic extracts were washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (10% ethyl acetate in hexanes) to give **19** (0.61 g, 70%) as a colourless oil. $[\alpha]_D^{20}$ = –21.0 (c = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3448, 2928, 1637, 1463, 1255, 1139, 1040, 835, 774 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.40–4.27 (m, 1 H), 3.97–3.83 (m, 1 H), 2.89 (d, J = 6.0 Hz, 1 H), 2.35 (d, J = 2.2 Hz, 1 H), 1.81–1.66 (m, 2 H), 1.64–1.49 (m, 2 H), 1.15 (d, J = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.06 (d, J = 1.5 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 84.9, 72.7, 67.9, 61.8, 33.9, 32.7, 25.8, 22.8, 18.1, –4.5, –4.8 ppm. MS (ESI): m/z = 243 $[M + H]^+$. HRMS-ESI: calcd. for $C_{13}H_{27}O_2Si$ $[M + H]^+$ 243.1775; found 243.1779.

[(2*R*,5*S*)-5-(Benzyloxy)hept-6-yn-2-yloxy](*tert*-butyl)dimethylsilane (6): Sodium hydride (117 mg, 4.8 mmol) was added to a stirred solution of tetrabutylammonium iodide (180 mg, 0.48 mmol) in dimethylformamide (5 mL) at 0 °C, and then hydroxy compound **19** (600 mg, 2.4 mmol) in dimethylformamide (2 mL) was added. The reaction mixture was stirred for 15 min at room temperature, then it was recooled to 0 °C, and benzyl bromide (0.36 mL, 2.97 mmol) was added. Then, the temperature was raised to room temperature, and the mixture was stirred for 1 h, and then quenched with water (30 mL). The two phases were separated, and the aqueous phase was extracted with diethyl ether (3× 30 mL). The combined organic extracts were washed with brine (30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (5% ethyl acetate in hexanes) to give **6** (0.59 g, 72%) as a colourless oil. $[\alpha]_D^{20}$ = –67.0 (c = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2956, 2857, 2111, 1458, 1734, 1253, 1056, 834, 774 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 5 H), 4.80 (d, J = 11.8 Hz, 1 H), 4.50 (d, J = 11.8 Hz, 1 H), 4.07 (td, J = 1.7, 6.2, 8.1 Hz, 1 H), 3.85–3.73 (m, 1 H), 2.46 (dd, J = 1.7 Hz, 1 H), 1.94–1.67 (m, 2 H), 1.65–1.51 (m, 2 H), 1.12 (d, J = 6.0 Hz, 3 H), 0.88 (s, 9 H), 0.03 (d, J = 1.5 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 128.3, 127.9, 127.6, 82.8, 73.8, 70.4, 68.3, 68.0, 34.8, 31.7, 25.8, 23.7, 18.0, –4.3, –4.7 ppm. MS (ESI): m/z = 355 $[M + Na]^+$. HRMS-ESI: calcd. for $C_{20}H_{33}O_2Si$ $[M + H]^+$ 333.22443; found 333.22398.

(5*S*,6*S*,10*S*,13*R*)-6,10-Bis(benzyloxy)-2,2,3,3,5,13,15,15,16,16-decamethyl-4,14-dioxa-3,15-disilaheptadec-8-yn-7-one (4): *n*BuLi (1.6 M in hexane, 0.2 mL, 0.35 mmol) was added dropwise to a stirred solution of compound **6** (129 mg, 0.38 mmol) in THF (2 mL) at –78 °C. After stirring for 45 min at –78 °C, aldehyde **5** (100 mg, 0.32 mmol) in THF (1 mL) was added. The temperature was slowly raised to room temperature, the mixture was stirred for 1 h, and then the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The two phases were separated. The aqueous phase was extracted with ethyl acetate (3× 5 mL), and the combined organic extracts were washed with brine (5 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (10% ethyl acetate in hexanes) to give the alcohol (160 mg, 77%) as a mixture of diastereomers.

Dess–Martin periodinane (148 mg, 0.35 mmol) was added in one portion to a stirred solution of the above diastereomeric mixture of alcohols (150 mg, 0.23 mmol) in dry dichloromethane (5 mL). The mixture was stirred for 30 min at room temperature, and then the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (4 mL). The phases were separated, and the aqueous phase was extracted with dichloromethane (3× 5 mL). The combined organic extracts were washed with brine (5 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (5% ethyl acetate in hexanes) to give compound **4** (127 mg, 85%) as a colourless liquid. $[\alpha]_D^{20}$ = –75.4 (c = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2956, 2930, 2209, 1683, 1455, 1373, 1255, 1219, 1119, 1094, 834, 774 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 10 H), 4.76 (d, J = 12.0 Hz, 1 H), 4.73 (d, J = 12.0 Hz, 1 H), 4.53 (d, J = 12.0 Hz, 1 H), 4.48 (d, J = 12.0 Hz, 1 H), 4.27–4.18 (m, 2 H), 3.81–3.72 (m, 2 H), 1.97–

1.89 (m, 1 H), 1.83–1.74 (m, 1 H), 1.60–1.54 (m, 2 H), 1.27 (d, *J* = 6.0 Hz, 3 H), 1.10 (d, *J* = 6.0 Hz, 3 H), 0.87 (s, 18 H), 0.06 (d, *J* = 2.0 Hz, 6 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 188.1, 137.3, 128.3, 128.0, 127.9, 93.6, 89.1, 83.9, 72.8, 70.9, 69.4, 68.4, 67.9, 34.8, 31.2, 25.8, 25.7, 23.7, 20.1, 18.0, 17.9, –4.31, –4.36, –4.7, –4.8 ppm. MS (ESI): *m*/*z* = 661 [M + Na]$^+$. HRMS-ESI: calcd. for $C_{37}H_{59}O_5Si_2$ [M + H]$^+$ 639.3896; found 639.3892.

(2*S*,3*S*,7*S*,10*R*)-3,7-Bis(benzyloxy)-2,10-dihydroxyundec-5-yn-4-one (21): Aqueous HF (25%, 1 mL) was added to a stirred solution of compound **4** (120 mg, 0.18 mmol) in acetonitrile (20 mL) at room temperature, and the mixture was stirred for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3× 10 mL). The combined organic extracts were washed with brine (10 mL), dried with Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (30% ethyl acetate in hexanes) to give compound **21** (68 mg, 88%) as a colourless liquid. $[\alpha]_D^{20}$ = –117.6 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3410, 2967, 2921, 2871, 2208, 1671, 1453, 1261, 1218, 1084, 772, 699 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.25 (m, 10 H), 4.81 (d, *J* = 12.0 Hz, 1 H), 4.77 (d, *J* = 12.0 Hz, 1 H), 4.49 (dd, *J* = 4.1, 11.5 Hz, 2 H), 4.30 (t, *J* = 6.2 Hz, 1 H), 4.23–4.15 (m, 1 H), 3.92 (d, *J* = 4.7 Hz, 1 H), 3.82–3.70 (m, 1 H), 2.03–1.77 (m, 2 H), 1.71–1.48 (m, 2 H), 1.26 (d, *J* = 6.2 Hz, 3 H), 1.15 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 187.6, 136.9, 136.8, 128.5, 128.1, 128.0, 94.4, 83.3, 84.0, 73.1, 71.2, 68.3, 67.3, 60.3, 34.4, 31.1, 23.4, 18.3 ppm. MS (ESI): *m*/*z* = 433 [M + Na]$^+$. HRMS-ESI: calcd. for $C_{25}H_{31}O_5$ [M + H]$^+$ 411.2166; found 411.2162.

(2*S*,3*S*,6*S*,8*R*,11*S*)-3,11-Bis(benzyloxy)-2,8-dimethyl-1,7-dioxaspiro-[5.5]undecan-4-one (22) and (2*S*,3*S*,6*R*,8*R*,11*S*)-3,11-Bis(benzyloxy)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-one (22a): *p*-Toluenesulfonic acid monohydrate (48 mg, 0.25 mmol) was added to a stirred solution of ynone **21** (70 mg, 0.17 mmol) in toluene (2 mL). The mixture was stirred for 12 h. Then the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL), and the phases were separated. The aqueous phase was extracted with ethyl acetate (2× 5 mL). The combined organic extracts were washed with brine (5 mL), dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (5% ethyl acetate in hexanes) to give compound **22** (19 mg) as a colourless solid, and **22a** (43 mg) as a colourless syrup (combined yield 89%).

Data for 22: $[\alpha]_D^{20}$ = –140.2 (*c* = 0.8, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 1731, 1451, 1218, 1118, 1075, 1012, 772, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.27 (m, 10 H), 4.94 (d, *J* = 11.9 Hz, 1 H), 4.73 (d, *J* = 11.9 Hz, 1 H), 4.61 (d, *J* = 11.9 Hz, 1 H), 4.50 (d, *J* = 10.9 Hz, 1 H), 4.28 (qd, *J* = 6.0, 9.0 Hz, 1 H), 3.91 (sext, *J* = 6.0 Hz, 1 H), 3.66 (dd, *J* = 1.0, 9.0 Hz, 1 H), 3.26 (dd, *J* = 4.0, 8.0 Hz, 1 H), 2.82 (dd, *J* = 1.0, 13.0 Hz, 1 H), 2.52 (d, *J* = 14.0 Hz, 1 H), 1.96 (m, 1 H), 1.77 (m, 1 H), 1.68 (m, 2 H), 1.41 (d, *J* = 6.0 Hz, 3 H), 1.25 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.8, 138.1, 137.5, 128.4, 128.2, 128.0, 127.9, 127.8, 101.5, 84.0, 76.1, 73.1, 71.6, 70.4, 69.5, 47.8, 29.6, 28.4, 21.4, 20.7, 18.6 ppm. MS (ESI): *m*/*z* = 411 [M + H]$^+$.

Data for 22a: $[\alpha]_D^{20}$ = –23.0 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2927, 1732, 1452, 1216, 1118, 1076, 1013, 771, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 10 H), 4.91 (d, *J* = 11.3 Hz, 1 H), 4.59 (d, *J* = 11.7 Hz, 1 H), 4.51 (d, *J* = 11.3 Hz, 1 H), 4.42 (d, *J* = 11.7 Hz, 1 H), 4.12–4.03 (m, 1 H), 3.93–3.85 (m, 2 H), 3.34 (t, *J* = 3.0 Hz, 1 H), 2.88 (d, *J* = 15.6 Hz, 1 H), 2.76 (d, *J* = 15.6 Hz, 1 H), 1.90–1.80 (m, 2 H), 1.70–1.52 (m, 2 H), 1.34 (d, *J* = 5.6 Hz, 3 H), 1.12 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.0, 137.9, 137.2, 128.3, 127.9, 127.6, 100.2, 82.4, 73.3, 72.1, 71.0, 67.1, 60.3, 47.3, 26.1, 21.6, 21.4, 19.6 ppm. MS (ESI): *m*/*z* = 411 [M + H]$^+$. HRMS-ESI: calcd. for $C_{25}H_{31}O_5$ [M + H]$^+$ 411.2166; found 411.2160.

(2*S*,3*S*,6*S*,8*R*,11*S*)-3,11-Dihydroxy-2,8-dimethyl-1,7-dioxaspiro-[5.5]undecan-4-one (1)

Method A, Hydrogenation of 22: Palladium on carbon (10% by weight, 12 mg) was added to a solution of compound **22** (16 mg, 0.04 mmol) in EtOAc (3 mL). The reaction mixture was stirred overnight under a hydrogen atmosphere. After completion of the reaction, the mixture was filtered through Celite, and the filtrate was concentrated in vacuo. Column chromatography of the residue on silica gel (40% ethyl acetate in hexanes) gave compound **1** (8.5 mg, 95%) as a white solid. M.p. 147–149 °C (ref.[3] 149 °C). $[\alpha]_D^{20}$ = –79.3 (*c* = 0.21, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3485, 3422, 3380, 2920, 2853, 1722, 1381, 1334, 1278, 1220, 1165, 1134, 1073, 993, 929, 772 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ = 4.06 (dq, *J* = 9.5, 6.1 Hz, 1 H), 3.89 (sext, *J* = 6.1 Hz, 1 H), 3.83 (dd, *J* = 9.5, 1.0 Hz, 1 H) 3.55 (m, 1 H), 3.52 (d, *J* = 4.0 Hz, 1 H), 2.90 (d, *J* = 13.8 Hz, 1 H), 2.83 (dd, *J* = 13.8, 1.0 Hz, 1 H), 2.50 (d, *J* = 6.3 Hz, 1 H), 1.98 (m, 1 H), 1.75 (m, 1 H), 1.66 (m, 2 H), 1.46 (d, *J* = 6.1 Hz, 3 H), 1.26 (d, *J* = 6.1 Hz, 3 H) ppm. ^{13}C NMR (175 MHz, $CDCl_3$): δ = 205.9, 101.3, 77.9, 72.5, 69.9, 69.6, 44.9, 27.5, 24.7, 20.7, 18.7 ppm. MS (ESI): *m*/*z* = 253 [M + Na]$^+$. HRMS-ESI: calcd. for $C_{11}H_{18}O_5Na$ [M + Na]$^+$ 253.1046; found 253.1045.

Method B, Spiroepimerisation of 1a: Anhydrous $ZnBr_2$ (14.6 mg, 0.06 mmol) was added to a stirred solution of **1a** (15.0 mg, 0.06 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (3 mL), and the mixture was extracted with EtOAc. The organic extract was washed with brine (3 mL), dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography over silica gel (30% EtOAc in hexanes) to give dinemasone A (**1**, 9.5 mg, 63%) as a white solid, together with recovered **1a** (4.0 mg, 27%). These isolated products were fully characterised and gave data comparable with that obtained above.

(2*S*,3*S*,6*R*,8*R*,11*S*)-3,11-Dihydroxy-2,8-dimethyl-1,7-dioxaspiro-[5.5]undecan-4-one (6-*epi*-dinemasone A, 1a): By the same protocol as that described for the preparation of **1**, **22a** (40 mg, 0.1 mmol) was converted into **1a** (21 mg, 93%) as a colourless liquid. $[\alpha]_D^{20}$ = +64.4 (*c* = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3434, 2931, 1727, 1448, 1071, 1010, 968, 757 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.28–4.18 (m, 1 H), 4.15 (dd, *J* = 1.5, 9.8 Hz, 1 H), 3.67–3.56 (m, 2 H), 3.47 (d, *J* = 3.7 Hz, 1 H), 3.05 (d, *J* = 15.8 Hz, 1 H), 2.74 (dd, *J* = 1.5, 15.8 Hz, 1 H), 2.17–2.00 (m, 2 H), 1.80–1.68 (m, 2 H), 1.47 (d, *J* = 6.0 Hz, 3 H), 1.18 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 207.1, 100.1, 76.7, 73.1, 66.9, 65.3, 45.8, 25.7, 25.4, 21.5, 19.7 ppm. MS (ESI): *m*/*z* = 253 [M + Na]$^+$. HRMS-ESI: calcd. for $C_{11}H_{18}O_5Na$ [M + Na]$^+$ 253.1046; found 253.1045.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR of all compounds, and NOESY, COSY, and HSQC analysis of the target molecule.

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[11] Restrained MD simulation, with the help of observed NOE cross-peaks between 3-H–5a-H, 11-H–5a-H, 11-H–5e-H, 8-H–5e-H, 8-Me–10a-H, 8-Me–2-H, and 2-Me–8-Me, as well as $^3J_{H,H}$ couplings, suggest the structure shown in Figure 2 for Dinemasone A.

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[13] The use of zinc(II) chloride in dichloromethane resulted in the equilibration of **1** and **1a** to give a 1:1 mixture.

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