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Full Paper

Natural Product Synthesis

Total Synthesis of the Anticancer Marine Natural Product Mycalol

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Abstract: This communication describes a synthetic study of the originally proposed structure of mycalol (**1**) and the total synthesis of the actual structure of the anticancer marine natural product mycalol (**2**). The total synthesis of the originally proposed structure of mycalol (**1**) was targeted by a late-stage asymmetric dihydroxylation, which resulted in an inseparable mixture of diastereomers. Thus a new strategy was developed for the total synthesis of the revised structure of mycalol (**2**); all the stereocentres except the C-2′-OH were created in an asymmetric fashion by using a Maruoka allylation, a Noyori asymmetric reduction, and an asymmetric alkynylation.

Introduction

Marine organisms have produced a large number of potent anticancer compounds, and many of them are either in clinical development or on the market, used for the treatment of cancer.[1] Mycalol, a polyhydroxylated lipid molecule, is an example of a cytotoxic marine natural product that was isolated from a marine sponge by Fontana and coworkers in 2013.[2] Initial biological studies revealed that mycalol selectively kills human anaplastic thyroid carcinoma (ATC). Initially, the structure of mycalol was proposed to be **1**, based on detailed NMR spectroscopic studies. In 2015, Reddy et al. developed an elegant strategy for the synthesis of the proposed structure of mycalol (**1**) by using Sharpless asymmetric kinetic resolution, Jacobsen kinetic resolution, and cross metathesis as key steps. They found the structure proposed by Fontana et al. to be incorrect. Subsequently, they hypothesized that the correct structure could be **2** (Figure 1), based on a detailed comparison of NMR spectroscopic data, and they confirmed this by total synthesis.[3] Subsequently, Goswami et al. reported the synthesis of the originally proposed structure of mycalol (**1**) and several of its analogues using L-arabinose as a chiral-pool starting material, and they confirmed the structural revision reported by Reddy et al.[4] Very recently, Reddy et al. also synthesized several analogues of mycalol (**2**), and tested their anticancer activity against human-derived ATC cell lines.[5]

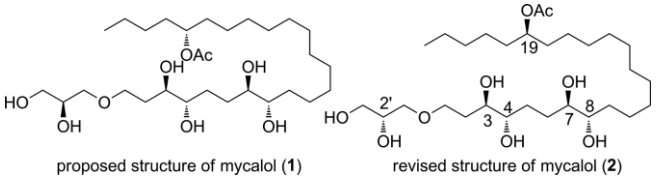
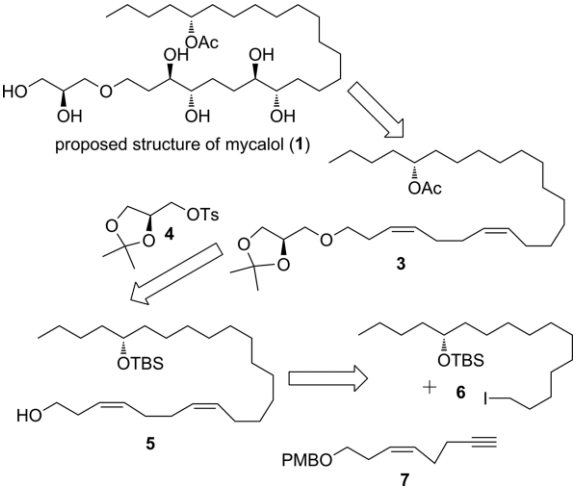


Figure 1. Originally proposed and revised structures of mycalol.

Results and Discussion

Because of the interesting structure and biological activity of mycalol, soon after its isolation we also became interested in developing a synthetic strategy for the originally proposed structure of mycalol (**1**), using a late-stage asymmetric dihydroxylation as a key step (Scheme 1). We planned to obtain the precursor **3** for the asymmetric dihydroxylation from compound **5** by alkylation with **4**, followed by protecting-group manipulation. We thought diene **5** might be obtained through alkylation of alkyne **7** with iodide **6**, followed by *cis*-selective



Scheme 1. Retrosynthetic analysis of the originally proposed structure of mycalol (**1**). TBS = *tert*-butyldimethylsilyl.

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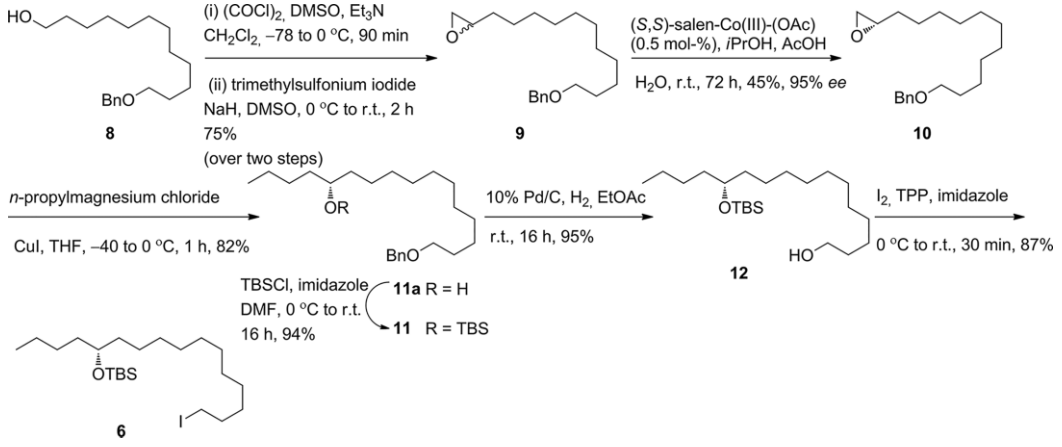
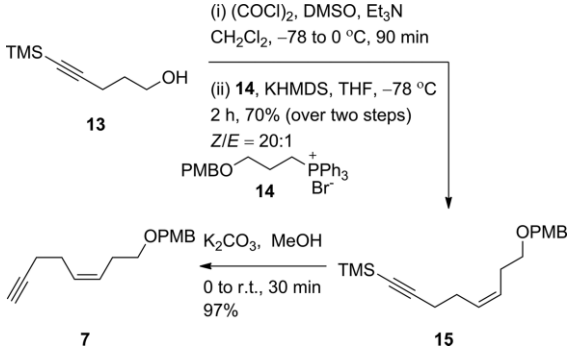


Scheme 2. Synthesis of iodide **6**.

reduction of the alkyne functionality and oxidative removal of the PMB (4-methoxybenzyl) group.

Thus, the synthesis of iodide **6** started from known alcohol **8**.[6] This underwent oxidation under Swern conditions followed by Corey–Chaykovsky reaction[7] to give racemic epoxide **9** in a good overall yield of 75 % (Scheme 2). Hydrolytic kinetic resolution of the terminal epoxide **9** under Jacobsen conditions[8] gave enantiomerically pure epoxide **10** (95 % *ee*) in 45 % yield. Epoxide **10** was opened with propylmagnesium chloride in the presence of a catalytic amount of CuI to give alcohol **11a** in 82 % yield.[9] Protection of the hydroxy group of **11a** as its TBS ether followed by debenzylation by hydrogenolysis (H_2, 10 % Pd/C) gave alcohol **12** in 89 % yield over two steps. Finally, alcohol **12** was treated with TPP (triphenylphosphine) and iodine to give iodo compound **6** in 87 % yield.[10]

The synthesis of alkyne **7** is shown in Scheme 3. Oxidation of known alcohol **13**[11] under Swern conditions gave an aldehyde, which reacted with the ylide generated from known phosphonium bromide **14**[12a,12b] and KHMDS [potassium bis(trimethylsilyl)amide] to give the desired *Z*-olefin **15** in 70 % yield over two steps (*Z*/*E* = 20:1).[13] Deprotection of the TMS (trimethylsilyl) group from compound **15** was carried with K_2CO_3 in MeOH to give alkyne **7** in 97 % yield.



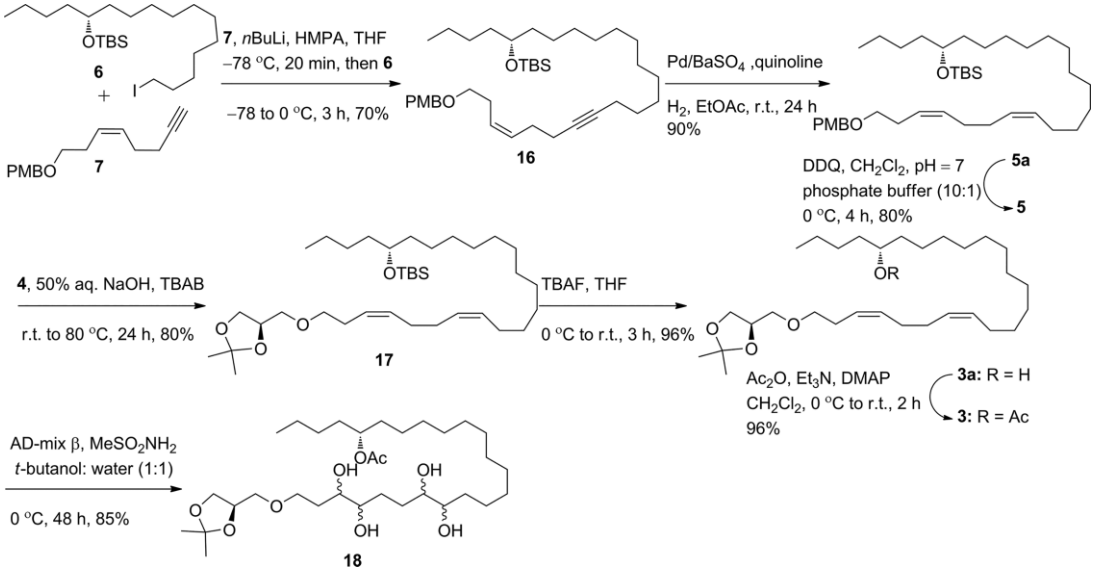
Scheme 3. Synthesis of alkyne **7**.

The final strategy for the completion of the synthesis of the originally proposed structure of mycalol (**1**) is shown in Scheme 4. Alkylation of alkyne **7** with iodide **6** in the presence of *n*BuLi and HMPA (hexamethylphosphoramide) proceeded smoothly to give compound **16** in good yield (70 %).[14] Partial reduction of the alkyne functionality of **16** under Lindlar hydrogenation conditions[15] (Pd/$BaSO_4$, quinoline) followed by oxidative removal of the PMB group with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) gave alcohol **5** in 72 % yield over two steps. Williamson-type etherification[16] between alcohol **5** and the tosyl derivative of (*R*)-solketal **4**[17] was carried out in the presence of NaOH (50 % aq.) and TBAB (tetrabutylammonium bromide) to give compound **17** in 80 % yield. Deprotection of the TBS group from **17** was carried out with TBAF (tetrabutylammonium fluoride) to give an alcohol **3a**, which was acetylated with Ac_2O in the presence of Et_3N and DMAP [4-(dimethylamino)pyridine] to give compound **3** in 92 % yield over two steps. Now the stage was set for the crucial dihydroxylation with AD-mix β to complete the synthesis. However, dihydroxylation of compound **3** with AD-mix β gave an inseparable mixture of diastereomers of compound **18**.[18] At this stage, we wanted to develop a new strategy for the synthesis of the originally proposed structure of mycalol (**1**). However, by this time the structure of mycalol had been revised by Reddy et al. Therefore, we planned to devise a new strategy for the synthesis of the revised structure of mycalol (**2**).

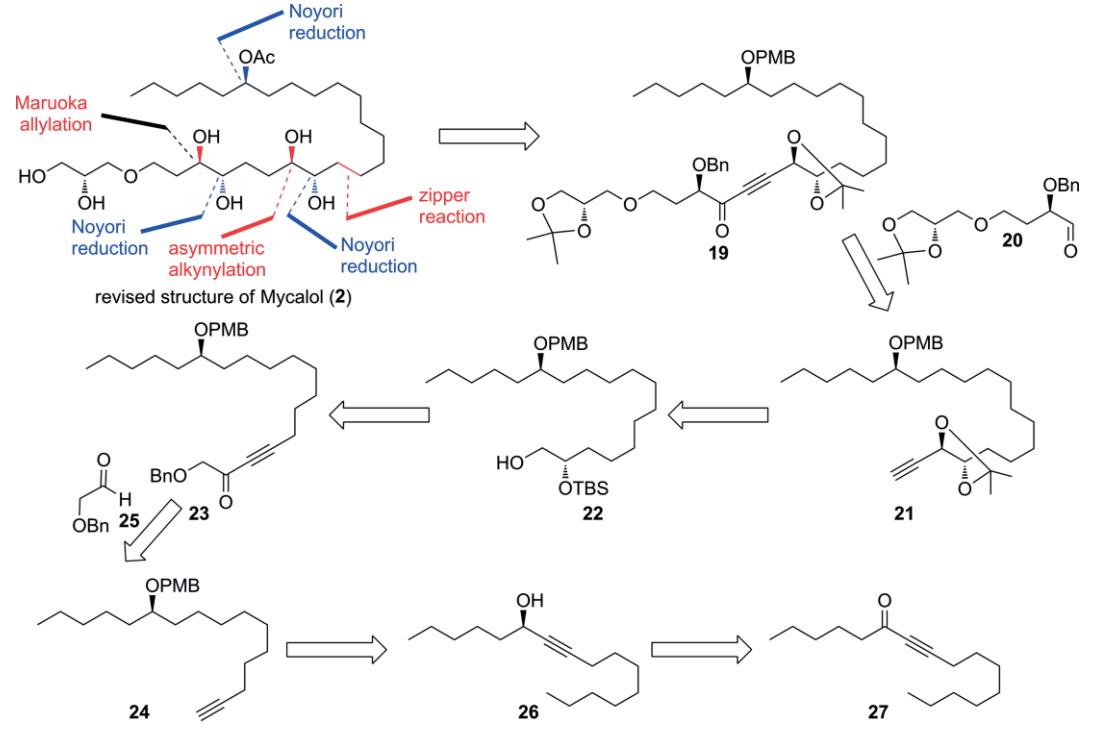
In the new strategy, we planned to generate all the stereogenic centres except for the C-2′ centre in a catalytic way, so that structural and stereochemical analogues of mycalol (**2**) could be generated easily. Retrosynthetically, mycalol (**2**) could be synthesized from ynone **19** by asymmetric reduction followed by functional-group manipulations (Scheme 5). Ynone **19** could be obtained by the addition of alkyne **21** to aldehyde **20**, followed by oxidation. Alkyne **21** would be obtained from alcohol **22** by oxidation followed by asymmetric alkynylation and then protecting-group manipulations. Compound **22** might be obtained by Noyori asymmetric reduction of ynone **23**, followed by functional-group manipulation. Ynone **23** could be accessed by the addition of alkyne **24** to aldehyde **25**, followed by oxidation of the resulting propargylic alcohol. Terminal alkyne **24** would be obtained from propargylic alcohol **26** by the alkyne zipper reaction. Finally, propargylic alcohol **26** could be obtained from ynone **27** by asymmetric reduction.

Thus the synthesis of the actual structure of mycalol (**2**) began with the asymmetric allylation of known aldehyde **28**[19] under Maruoka allylation conditions[20] to give enantiomerically pure alcohol **29** in 80 % yield with 96 % *ee* (Scheme 6). Protection of alcohol **29** as its benzyl ether followed by ozonolysis[21] of the olefin gave an aldehyde, which, upon reduction with $NaBH_4$, produced alcohol **31** in 68 % yield over three steps. Etherification of alcohol **31** with the tosyl derivative of (*S*)-solketal **32**[22] in the presence of NaOH (50 % aq.) and TBAB gave compound **33** in 92 % yield. Oxidative removal of the PMB group from **33** was carried out with DDQ[23] to give alcohol **34** in 72 % yield. Finally, oxidation of alcohol **34** with DMP (Dess–Martin periodinane)[24] gave aldehyde **20** in quantitative yield.

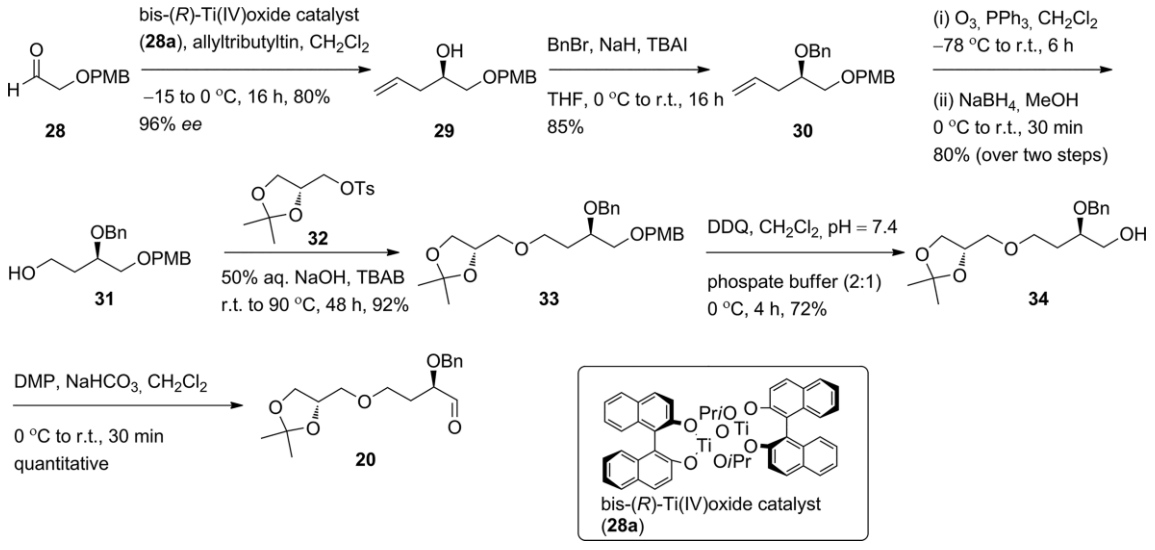
The synthesis of alkyne **21** started from known ynone **27**[25] (Scheme 7). The ketone moiety of **27** was reduced with (*R*,*R*)-Ru catalyst **23a**[26] in the presence of HCOOH/Et_3N to give enantiomerically pure alcohol **26** (94 % *ee* by Mosher ester analysis) in 88 % yield. The configuration of **26** was confirmed by Mosher ester analysis. The internal triple bond of **26** was transferred to the terminal position through the zipper reaction with 1,3-diaminopropane and NaH to give compound **35** in 82 % yield.[27] The hydroxy group of **35** was protected as its PMB



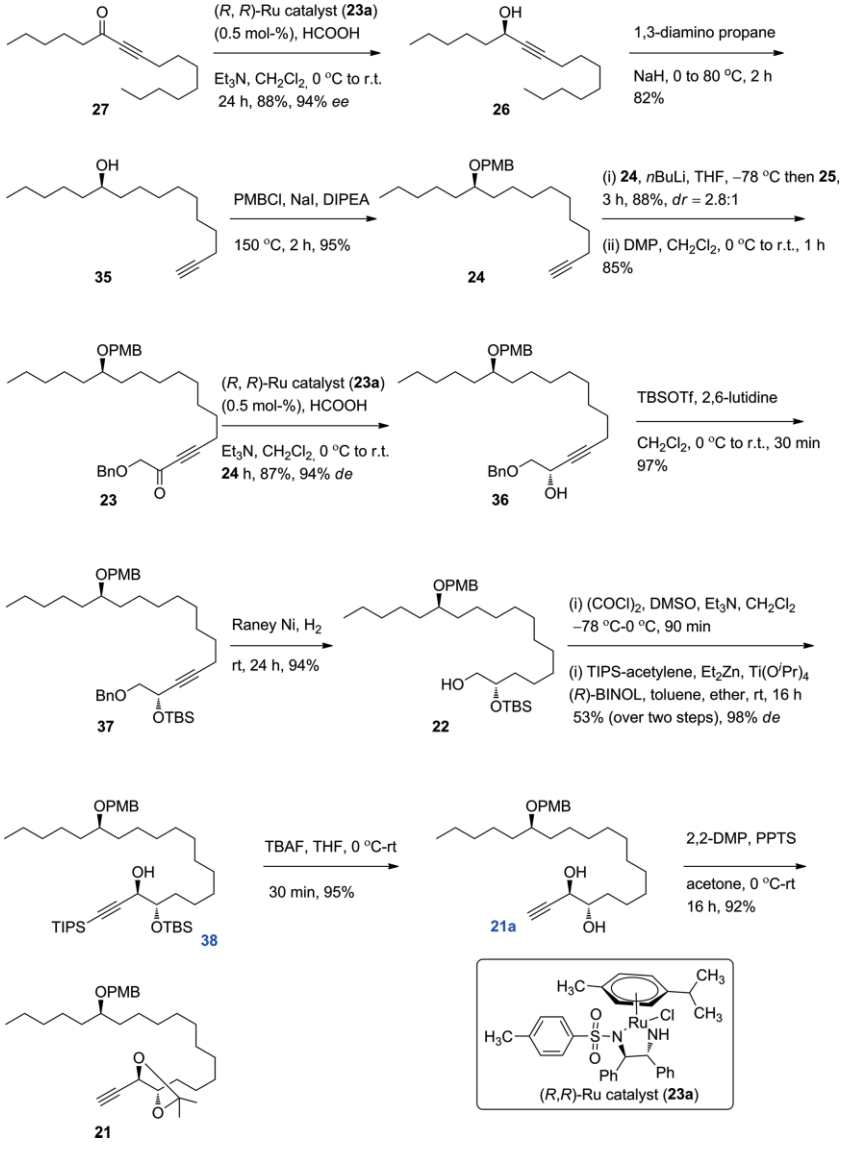
Scheme 4. Final strategy for the synthesis of the originally proposed structure of mycalol (**1**).



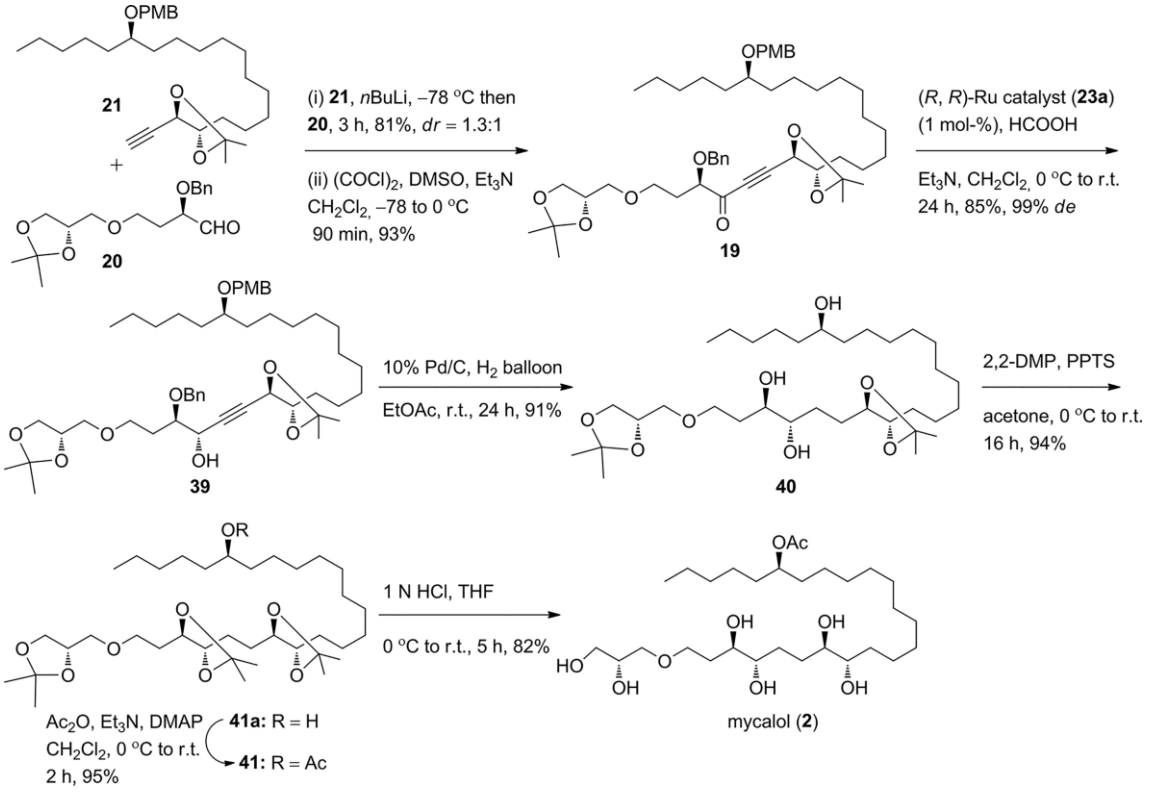
Scheme 5. Retrosynthetic analysis of the revised structure of mycalol (**2**).



Scheme 6. Synthesis of aldehyde **20**. TBAI = tetrabutylammonium iodide.



Scheme 7. Synthesis of alkyne **21**. BINOL = 1,1′-bi-2-naphthol; TIPS = triisopropylsilyl.



Scheme 8. Completion of the synthesis of mycalol (**2**).

ether by treatment with PMBCl/NaI/DIPEA (*N*,*N*-diisopropylethylamine) to give compound **24** in 95 % yield.[28] Compound **24** was treated with *n*BuLi, and the resulting anion underwent an addition reaction with known aldehyde **25**[29] to give an inseparable mixture of diastereomeric alcohols (*dr* = 2.8:1). This was oxidized with DMP to give ynone **23** in 75 % yield over two steps. Ynone **23** was subjected to Noyori reduction with (*R*,*R*)-Ru catalyst **23a** in the presence of HCOOH/Et_3N to give alcohol **36** in 87 % yield (94 % *de*). The free hydroxy group of **36** was protected as its TBS ether by treatment with TBSOTf/2,6-lutidine to give compound **37** in 97 % yield. Selective removal of the benzyl group and reduction of the triple bond of compound **37** was carried out with Raney Ni/H_2 to give alcohol **22** in 94 % yield.[30] Alcohol **22** was oxidized under Swern conditions to give an aldehyde, which, on treatment with TMS-acetylene in the presence of (*R*)-BINOL/Ti(O*i*Pr)$_4$, gave the required product in poor yield (10 %).[31a] However treatment of the aldehyde with TIPS-acetylene in the presence of (*R*)-BINOL/Ti(O*i*Pr)$_4$ gave highly diastereomerically pure compound **38** in 53 % yield over two steps (98 % *de*).[31b] Deprotection of the TIPS and TBS groups from compound **38** was carried out with TBAF to give diol **21a**. This then underwent acetonide protection with 2,2-DMP (2,2-dimethoxypropane) in the presence of PPTS (pyridinium *p*-toluenesulfonate) to give alkyne **21** in 87 % yield over two steps.

The remaining part of the synthesis is shown in Scheme 8. Addition of the anion generated from alkyne **21** to aldehyde **20** gave an inseparable mixture of diastereomers (*dr* = 1.3:1). This was oxidized under Swern conditions to give ynone **19** in 75 % yield over two steps. The ketone functionality of **19** was reduced with (*R*,*R*)-Ru catalyst **23a** in the presence of HCOOH/Et_3N to give diastereomerically pure alcohol **39** in 85 % yield (99 % *de*). Alcohol **39** was subjected to hydrogenation with a hydrogen-filled balloon in the presence of Pd/C (10 %) to give triol **40** in 91 % yield. Acetonide protection of triol **40** with 2,2-DMP in the presence of PPTS followed by acetylation of the C-19-OH with Ac_2O in the presence of DMAP/Et_3N gave triacetonide **41** in 89 % yield over two steps. Finally, global deprotection of triacetonide **41** was carried out with HCl (1 N aq.) to complete the synthesis of mycalol (**2**) in 82 % yield. The spectral and analytical data of this synthetic mycalol (**2**) {$[\alpha]_D^{25}$ = +4.28 (*c* = 0.20, MeOH)} were in good agreement with the data reported in the literature for natural mycalol {$[\alpha]_D^{25}$ = +3.45 (*c* = 0.10, MeOH)}.

Conclusions

The total synthesis of the originally proposed structure of mycalol (**1**) was targeted using a late-stage asymmetric dihydroxylation, but this resulted in an inseparable mixture of diastereomers. This result forced us to modify our strategy for the synthesis of the actual structure of the natural product to use a Noyori asymmetric reduction, a zipper reaction, an asymmetric alkynylation, a Maruoka allylation, and a Williamson-type etherification. Using the modified strategy, the total synthesis of natural mycalol (**2**) was achieved in 26 steps (longest linear sequence of 19 steps) from the known compound **27**, with an

overall yield of 8.04 %. The strategy developed here is quite different from the strategies developed by Reddy et al. (longest linear sequence of 12 steps, overall yield of 2.3 %) and Goswami et al. (longest linear sequence of 16 steps, overall yield of 11.1 %). In both of those cases, chiral-pool materials were used extensively to establish the stereocentres in the molecule. In contrast, in our synthesis most of the stereocentres were generated through asymmetric reactions. The strategy is highly convergent, and can be used for the synthesis of structural and stereochemical analogues of the molecule.

Experimental Section

General Information: All air- and moisture-sensitive reactions were carried out under an inert atmosphere (nitrogen or argon) in oven-dried glassware. Yields refer to chromatographically and spectroscopically pure materials, unless otherwise stated. Anhydrous tetrahydrofuran (THF) and diethyl ether (Et_2O) were prepared by distillation from sodium/benzophenone. Toluene was distilled from sodium wire before use. Triethylamine (Et_3N), dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), dichloromethane (CH_2Cl_2), and hexamethylphosphoramide (HMPA) were distilled from CaH_2 before use. Acetic anhydride (Ac_2O) was distilled from P_2O_5 to make it free from acetic acid. Acetone was distilled from $KMnO_4$. Triphenylphosphine (PPh_3) was recrystallized from hexane. Commercially available reagents were used without further purification unless otherwise stated. Compounds were purified by column chromatography on silica gel (100–200 mesh) packed in glass columns. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ and C_5D_5N solvents with 300, 400, 500, and 700 MHz spectrometers (^1H at 300, 400, 500, and 700 MHz and ^{13}C at 75, 100, 125, and 175 MHz), using tetramethylsilane as an internal standard. Chemical shifts were calibrated using internal $CHCl_3$ (δ = 7.26 ppm) or tetramethylsilane (δ = 0.0 ppm) or C_5D_5N (δ = 7.19 ppm) for ^1H NMR spectra, and $CDCl_3$ (δ = 77.0 ppm) or C_5D_5N (δ = 123.50 ppm) for ^{13}C NMR spectra. In ^1H NMR data, multiplicities are defined as: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet, dd = doublet of doublets; ddd = doublet of doublet of doublets; dddd = doublet of doublet of doublet of doublets; dt = doublet of triplets; td = triplet of doublets; qd = quartet of doublets; ddt = doublet of doublet of triplets; dtd = doublet of triplet of doublets; tdd = triplet of doublet of doublets; dtd = doublet of triplet of doublets; m = multiplet; br. s = broad singlet; br. d = broad doublet. Optical rotation values were recorded with a Horiba sepa 300 polarimeter using a 2 mL cell with a 10 mm path length. FTIR spectra were recorded with a Bruker Alpha infrared spectrophotometer. High-resolution mass spectra (HRMS, ESI^+) were obtained using either a TOF or double-focussing spectrometer.

2-[11-(Benzyloxy)undecyl]oxirane (9): Anhydrous DMSO (5.45 mL, 76.58 mmol) was added dropwise over a period of 5 min to a stirred solution of oxalyl chloride (3.14 mL, 35.90 mmol) in anhydrous CH_2Cl_2 (70 mL) at –78 °C. The mixture was stirred for 15 min. A solution of alcohol **8** (7.0 g, 23.93 mmol) in anhydrous CH_2Cl_2 (70 mL) was added at –78 °C, and the reaction mixture was stirred for 45 min. Et_3N (16.65 mL, 119.65 mmol) was then added at –78 °C. The resulting solution was warmed to 0 °C, and stirred for 30 min. After this time, the reaction was quenched with saturated aqueous NH_4Cl (50 mL), and the mixture was diluted with water (50 mL) and CH_2Cl_2 (50 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 20 % EtOAc/hexane) to give the aldehyde (6.65 g, 22.90 mmol) as a colourless oil. This aldehyde was used immediately in the next step without further characterization. R_f = 0.7 (SiO_2, 30 % EtOAc/hexane).

A stirred solution of trimethylsulfonium iodide (7.0 g, 34.35 mmol) in anhydrous DMSO (35 mL) was treated with NaH (1.37 g. 34.35 mmol) at 0 °C. The solution was slowly warmed to room temperature and stirred for 15 min. A solution of the above aldehyde (6.65 g, 22.90 mmol) in anhydrous THF (49 mL) was added by cannula at room temperature, and the mixture was stirred for 2 h. After this time, TLC (10 % EtOAc/hexane) indicated the complete consumption of the aldehyde. The reaction was quenched with saturated aqueous NH_4Cl (40 mL) at 0 °C, and the mixture was diluted with water (40 mL) and ethyl acetate (50 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The crude material was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 3 % EtOAc/hexane) to give racemic epoxide **9** (5.55 g, 18.06 mmol, 75 % over two steps) as a colourless oil. R_f = 0.7 (SiO_2, 30 % EtOAc/hexane). IR (neat): $\tilde{\nu}$ = 3035, 2925, 2853, 1457, 1362, 1266, 1206, 1105, 1028, 912, 837, 737, 698, 610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.25 (m, 5 H), 4.50 (s, 2 H), 3.46 (t, *J* = 6.8 Hz, 2 H), 2.94–2.87 (m, 1 H), 2.77–2.72 (m, 1 H), 2.46 (dd, *J* = 5.3, 3.0 Hz, 1 H), 1.67–1.21 (m, 20 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.62, 128.26, 127.54, 127.39, 72.75, 70.43, 52.37, 47.09, 32.44, 29.70, 29.46, 29.41, 26.12, 25.92 ppm. HRMS (ESI): calcd. for $C_{20}H_{32}O_2Na$ $[M + Na]^+$ 327.2300; found 327.2292.

(*S*)-2-[11-(Benzyloxy)undecyl]oxirane (10): Acetic acid (7.3 µL, 0.128 mmol) was added to a stirred solution of Co^{II}(*S*,*S*)-*N*,*N*-bis-(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino precatalyst (38.7 mg, 0.064 mmol, 0.5 mol-%) in dry toluene (1.0 mL) at room temperature, and the mixture was stirred open to the air for 1 h. During this time, the colour of the solution changed to dark red. After this time, the solvent was evaporated under reduced pressure. The resulting catalyst, (*S*,*S*)-salen-Co^{III}(OAc), was dried under high vacuum for 1 h to make the catalyst free from acetic acid.

The catalyst was treated with racemic epoxide **9** (3.9 g, 12.81 mmol) in 2-propanol (0.5 mL) at 0 °C. Water (231 µL, 12.81 mmol) was added portionwise over a period of 1 h to the resulting solution, and the mixture was stirred at room temperature for 72 h. The mixture was then purified by silica gel column chromatography (SiO_2, 100–200 mesh, 3 % EtOAc/hexane) to give enantiomerically pure epoxide **10** (1.76 g, 5.78 mmol, 45 %, 95 % *ee*) as a colourless oil. R_f = 0.7 (SiO_2, 30 % EtOAc/hexane). $[\alpha]_D^{25}$ = +1.67 (*c* = 0.60, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3035, 2925, 2853, 1457, 1362, 1266, 1206, 1105, 1028, 912, 837, 737, 698, 610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.25 (m, 5 H), 4.50 (s, 2 H), 3.46 (t, *J* = 6.8 Hz, 2 H), 2.94–2.87 (m, 1 H), 2.77–2.72 (m, 1 H), 2.46 (dd, *J* = 5.3, 3.0 Hz, 1 H), 1.67–1.21 (m, 20 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.62, 128.27, 127.54, 127.39, 72.79, 70.46, 52.37, 47.10, 32.44, 29.70, 29.46, 29.41, 26.12, 25.92 ppm. HRMS (ESI): calcd. for $C_{20}H_{32}O_2Na$ $[M + Na]^+$ 327.2300; found 327.2295.

(*R*)-16-(Benzyloxy)hexadecan-5-ol (11a): CuI (108 mg, 0.568 mmol) was added to a stirred solution of epoxide **10** (1.73, 5.68 mmol) in anhydrous THF (17 mL), followed by *n*-propylmagnesium chloride (2 M solution in ether; 7.1 mL, 14.2 mmol) at –40 °C.

The mixture was stirred for 1 h. After this time, the solution was warmed to 0 °C, and quenched with saturated aqueous NH_4Cl (30 mL). The mixture was stirred for 30 min, and then it was diluted with water (30 mL) and ethyl acetate (50 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 10 % EtOAc/hexane) to give alcohol **11a** (1.63 g, 4.68 mmol, 82 %) as a pale yellow oil. R_f = 0.5 (SiO_2, 20 % EtOAc/hexane). $[\alpha]_D^{25}$ = –2.60 (*c* = 1.50, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3388, 2925, 2854, 1459, 1364, 1206, 1104, 1026, 735, 698, 611 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.25 (m, 5 H), 4.50 (s, 2 H), 3.63–3.53 (m, 1 H), 3.46 (t, *J* = 6.7 Hz, 2 H), 1.67–1.55 (m, 3 H), 1.51–1.20 (m, 23 H), 0.91 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.62, 128.30, 127.60, 127.42, 72.78, 71.97, 70.49, 37.44, 37.12, 29.73, 29.67, 29.54, 29.44, 27.81, 26.15, 25.63, 22.75, 14.08 ppm. HRMS (ESI): calcd. for $C_{23}H_{40}O_2Na$ $[M + Na]^+$ 371.2926; found 371.2934.

(*R*)-{[16-(Benzyloxy)hexadecan-5-yl]oxy}(*tert*-butyl) dimethylsilane (11): A stirred solution of alcohol **11a** (1.6 g, 4.59 mmol) in anhydrous DMF (9 mL) was treated with imidazole (624 mg, 9.18 mmol) followed by TBSCl (1.04 g, 6.89 mmol) at 0 °C, and the mixture was stirred at room temperature for 16 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (20 mL) at 0 °C, and the mixture was diluted with diethyl ether (40 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 3 % EtOAc/hexane) to give TBS-protected compound **11** (2.0 g, 4.32 mmol, 94 %) as a colourless oil. R_f = 0.7 (SiO_2, 10 % EtOAc/hexane). $[\alpha]_D^{25}$ = –1.10 (*c* = 2.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2927, 2855, 1462, 1365, 1252, 1099, 1252, 1099, 1007, 939, 835, 773, 734, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 4.50 (s, 2 H), 3.61 (quin, *J* = 5.5 Hz, 1 H), 3.46 (t, *J* = 6.4 Hz, 3 H), 1.68–1.55 (m, 3 H), 1.47–1.18 (m, 22 H), 0.94–0.84 (m, 12 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.69, 128.31, 127.58, 127.43, 72.84, 72.36, 70.52, 37.14, 36.83, 29.87, 29.76, 29.65, 29.60, 29.48, 27.55, 26.19, 25.95, 25.33, 22.91, 18.16, 14.13, –4.42 ppm. HRMS (ESI): calcd. for $C_{29}H_{54}O_2SiNa$ $[M + Na]^+$ 485.3791; found 485.3777.

(*R*)-12-[(*tert*-Butyldimethylsilyl)oxy]hexadecan-1-ol (12): A stirred solution of TBS-protected compound **11** (1.95 g, 4.21 mmol) in anhydrous ethyl acetate (20 mL) was treated with Pd/C (10 %; 390 mg, 20 % w/w), and the mixture was hydrogenated using a hydrogen-filled balloon at room temperature for 16 h. The reaction mixture was filtered through a Celite plug, which was then washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 14 % EtOAc/hexane) to give alcohol **12** (1.49 g, 4.0 mmol, 95 %) as a colourless oil. R_f = 0.5 (SiO_2, 20 % EtOAc/hexane). $[\alpha]_D^{25}$ = –1.42 (*c* = 1.55, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3359, 2927, 2856, 1464, 1370, 1252, 1127, 1055, 938, 835, 773, 717, 665 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.67–3.57 (m, 3 H), 1.57 (quin, *J* = 6.7 Hz, 2 H), 1.49–1.20 (m, 24 H), 0.94–0.85 (m, 12 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 72.32, 63.01, 37.09, 36.77, 32.76, 29.82, 29.55, 29.38, 27.48, 25.89, 25.69, 25.28, 22.86, 14.08, –4.48 ppm. HRMS (ESI): calcd. for $C_{22}H_{48}O_2SiNa$ $[M + Na]^+$ 395.3321; found 395.3304.

(*R*)-*tert*-Butyl[(16-iodohexadecan-5-yl)oxy]dimethylsilane (6): A stirred solution of TPP (1.41 g, 5.37 mmol) and imidazole (365 mg, 5.37 mmol) in anhydrous CH_2Cl_2 (11 mL) was treated with iodine (1.36 g, 5.37 mmol) at 0 °C, and the resulting solution was warmed to room temperature and stirred for 10 min. A solution of alcohol **12** (1.0 g, 2.68 mmol) in anhydrous CH_2Cl_2 (6 mL) was then added by cannula at room temperature, and the resulting mixture was stirred for 30 min. The reaction was quenched with saturated aqueous sodium thiosulfate (20 mL) at 0 °C. The mixture was diluted with water (20 mL) and CH_2Cl_2 (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 2 % EtOAc/hexane) to give iodide **6** (1.13 g, 2.34 mmol, 87 %) as a colourless oil. Compound **6** was used in the next reaction without further characterization. R_f = 0.7 (SiO_2, 5 % EtOAc/hexane).

(*Z*)-{8-[(4-Methoxybenzyl)oxy]oct-5-en-1-yn-1-yl}trimethylsilane (15): Alcohol **13** (2.0 g, 12.80 mmol) was oxidized under Swern conditions to give the corresponding aldehyde (1.85 g) as a colourless oil. R_f = 0.7 (SiO_2, 30 % EtOAc/hexane).

A stirred solution of phosphonium bromide **14** (12.5 g, 23.98 mmol) in anhydrous THF (20 mL) was treated with KHMDS (0.5 M solution in toluene; 45.56 mL, 22.78 mmol) at –78 °C, and the mixture was stirred at the same temperature for 20 min. A solution of the above aldehyde (1.85 g, 11.99 mmol) in anhydrous THF (12 mL) was added by cannula at –78 °C, and the mixture was stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (40 mL) at 0 °C, and the mixture was diluted with water (20 mL) and diethyl ether (50 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with water (40 mL) and brine (40 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 3 % EtOAc/hexane) to give compound **15** (2.84 g, 9.00 mmol, 70 % over two steps, *Z*/*E* = 20:1) as a pale yellow oil. R_f = 0.5 (SiO_2, 10 % EtOAc/hexane). IR (neat): $\tilde{\nu}$ = 2956, 2925, 2855, 2174, 1713, 1609, 1513, 1248, 1171, 1095, 1037, 841, 761, 700, 640 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 2 H), 6.90–6.86 (m, 2 H), 5.50 (dt, *J* = 11.0, 6.4 Hz, 1 H), 5.47 (dt, *J* = 11.0, 6.7 Hz, 1 H), 4.45 (s, 2 H), 3.81 (s, 3 H), 3.45 (t, *J* = 7.0 Hz, 2 H), 2.38 (dd, *J* = 12.8, 6.9 Hz, 2 H), 2.30–2.24 (m, 4 H), 0.15 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.10, 130.53, 129.64, 129.20, 127.05, 113.74, 106.89, 84.58, 72.53, 69.58, 55.25, 28.02, 26.68, 20.13, 0.13 ppm. HRMS (ESI): calcd. for $C_{19}H_{28}O_2SiNa$ $[M + Na]^+$ 339.1756; found 339.1739.

(*Z*)-1-Methoxy-4-[(oct-3-en-7-yn-1-yloxy)methyl]benzene (7): A stirred solution of compound **15** (2.8 g, 8.85 mmol) in MeOH (16 mL) was treated with K_2CO_3 (2.45 g, 17.70 mmol) at 0 °C. The resulting solution was warmed to room temperature and stirred for 30 min. The reaction mixture was filtered through a Celite plug, which was then washed with ethyl acetate (30 mL). The filtrate and the washings were concentrated under reduced pressure. The resulting crude compound was diluted with ethyl acetate (30 mL) and saturated aqueous ammonium chloride (30 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concen-

trated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 4 % EtOAc/hexane) to give alkyne **7** (2.10 g, 8.60 mmol, 97 %) as a pale yellow oil. R_f = 0.45 (SiO_2, 10 % EtOAc/hexane). IR (neat): $\tilde{\nu}$ = 3295, 3009, 2856, 1692, 1609, 1512, 1458, 1360, 1302, 1245, 1173, 1091, 1033, 820, 638 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 2 H), 6.90–6.86 (m, 2 H), 5.52 (dt, J = 11.0, 5.9 Hz, 1 H), 5.49 (dt, J = 11.0, 6.1 Hz, 1 H), 4.45 (s, 2 H), 3.80 (s, 3 H), 3.46 (t, J = 7.0 Hz, 2 H), 2.38 (m, 2 H), 2.32–2.26 (m, 2 H), 2.25–2.20 (m, 2 H), 1.94 (t, J = 2.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.08, 130.49, 129.44, 129.21, 127.32, 113.71, 84.05, 72.52, 69.49, 68.38, 55.22, 28.00, 26.39, 18.68 ppm. HRMS (ESI): calcd. for $C_{16}H_{20}O_2Na$ $[M + Na]^+$ 267.1361; found 267.1363.

(*R*,*Z*)-*tert*-Butyl({24-[(4-methoxybenzyl)oxy]tetracos-21-en-17-yn-5-yl}oxy)dimethylsilane (16): A stirred solution of alkyne **7** (762 mg, 3.12 mmol) in anhydrous THF (6 mL) was treated with *n*BuLi (1.6 M solution in hexane; 1.89 mL, 3.02 mmol) at –78 °C, and the mixture was stirred at the same temperature for 20 min. Anhydrous HMPA (1.05 mL, 8.58 mmol) was then added at –78 °C, followed by a solution of iodide **6** (500 mg, 1.04 mmol) in anhydrous THF (3 mL). The mixture was stirred at the same temperature for 2 h. The reaction mixture was slowly warmed to 0 °C over a period of 1 h, and then it was quenched with saturated aqueous NH_4Cl (20 mL) at 0 °C. The mixture was diluted with water (20 mL) and ethyl acetate (30 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 2 % EtOAc/hexane) to give compound **16** (434 mg, 0.725 mmol, 70 %) as a colourless oil. R_f = 0.5 (SiO_2, 10 % EtOAc/hexane). $[\alpha]_D^{25}$ = –2.51 (c = 1.55, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2927, 2855, 1613, 1513, 1462, 1362, 1301, 1248, 1174, 1091, 1042, 938, 833, 773, 719, 665 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.19 (m, 2 H), 6.87–6.82 (m, 2 H), 5.54–5.37 (m, J = 11.3, 6.8 Hz, 2 H), 4.41 (s, 2 H), 3.77 (s, 3 H), 3.61 (quin, J = 5.6 Hz, 1 H), 3.45 (t, J = 7.1 Hz, 2 H), 2.37 (m, 2 H), 2.29–2.08 (m, 6 H), 1.53–1.20 (m, 26 H), 0.95–0.83 (m, 12 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.07, 130.52, 130.12, 129.19, 126.72, 113.70, 80.57, 79.50, 72.51, 72.34, 69.61, 55.22, 37.12, 36.81, 29.86, 29.66, 29.61, 29.55, 29.17, 29.11, 28.89, 28.02, 27.54, 27.14, 25.93, 25.33, 22.89, 19.09, 18.74, 18.15, 14.13, –4.44 ppm. HRMS (ESI): calcd. for $C_{38}H_{66}O_3SiNa$ $[M + Na]^+$ 621.4679; found 621.4703.

***tert*-Butyl({(*R*,17*Z*,21*Z*)-24-[(4-methoxybenzyl)oxy]tetracosa-17,21-dien-5-yl}oxy)dimethylsilane (5a):** A stirred solution of compound **16** (200 mg, 0.33 mmol) in ethyl acetate (3 mL) was treated with quinoline (20 mg, 10 % w/w), followed by $Pd/BaSO_4$ (30 mg, 15 % w/w). The mixture was hydrogenated using a hydrogen-filled balloon at room temperature for 24 h. The reaction mixture was filtered through a Celite plug, which was then washed with ethyl acetate (30 mL). The filtrate and the washings were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 2 % EtOAc/hexane) to give diene compound **5a** (180 mg, 0.30 mmol, 90 %) as a colourless oil. R_f = 0.6 (SiO_2, 3 % EtOAc/hexane). $[\alpha]_D^{25}$ = –1.93 (c = 1.35, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2926, 2854, 1613, 1513, 1463, 1249, 1092, 1042, 833, 733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.23 (m, 2 H), 6.91–6.84 (m, 2 H), 5.51–5.32 (m, 4 H), 4.45 (s, 2 H), 3.80 (s, 3 H), 3.61 (m, 1 H), 3.45 (t, J = 7.0 Hz, 2 H), 2.36 (m, 2 H), 2.14–1.96 (m, 6 H), 1.46–1.20 (m, 26 H), 0.94–0.85 (m, 12 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.08, 131.26, 130.57, 130.47, 129.19, 128.91, 125.88, 113.71, 72.50, 72.36, 69.67, 55.23, 37.13, 36.82, 29.87, 29.73, 29.66, 29.57, 29.32, 27.98, 27.54, 27.49, 27.26, 27.23, 25.93, 25.33, 22.90, 18.15, 14.12, –4.43 ppm. HRMS (ESI): calcd. for $C_{38}H_{68}O_3SiNa$ $[M + Na]^+$ 623.4835; found 623.4849.

(*R*,3*Z*,7*Z*)-20-[(*tert*-Butyldimethylsilyl)oxy]tetracosa-3,7-dien-1-ol (5): A solution of diene **5a** (215 mg, 0.36 mmol) in a mixture of solvents CH_2Cl_2 and pH = 7 phosphate buffer (10:1; 3 mL) was treated with DDQ (204 mg, 0.90 mmol) at 0 °C. The solution was warmed to room temperature and stirred for 4 h. After this time, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) at 0 °C, and the mixture was diluted with water (20 mL) and ethyl acetate (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 5 % EtOAc/hexane) to give alcohol **5** (137 mg, 0.29 mmol, 80 %) as a colourless oil. R_f = 0.25 (SiO_2, 10 % EtOAc/hexane). $[\alpha]_D^{25}$ = +5.62 (c = 1.05, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3335, 2926, 2855, 1462, 1370, 1252, 1126, 1051, 939, 835, 773, 720, 666 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.60–5.53 (m, 1 H), 5.43–5.32 (m, 3 H), 3.64 (t, J = 6.4 Hz, 2 H), 3.60 (dd, J = 11.4, 5.8 Hz, 1 H), 2.36–2.30 (m, 2 H), 2.16–2.06 (m, 4 H), 2.01 (m, 2 H), 1.46–1.20 (m, 26 H), 0.91–0.86 (m, 12 H), 0.03 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.78, 130.68, 128.73, 125.44, 72.34, 62.23, 37.09, 36.80, 30.78, 29.81, 29.67, 29.61, 29.53, 29.29, 27.52, 27.43, 27.23, 27.17, 25.89, 25.31, 22.87, 18.12, 14.11, –4.48 ppm. HRMS (ESI): calcd. for $C_{30}H_{60}O_2SiNa$ $[M + Na]^+$ 503.4260; found 503.4275.

***tert*-Butyl((*R*,17*Z*,21*Z*)-24-{[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}tetracosa-17,21-dien-5-yl)oxydimethylsilane (17):** A solution of alcohol **5** (110 mg, 0.23 mmol) in NaOH (50 % aq.; 1.1 mL, 13.8 mmol) was stirred at 80 °C for 30 min. Then TBAB (14.8 mg, 0.046 mmol) was added at the same temperature, and the mixture was stirred for 30 min. The reaction mixture was cooled to room temperature, and a solution of tosyl compound **4** (263 mg, 0.92 mmol) in the minimum amount of diethyl ether (0.5 mL) was added. The resulting solution was again warmed to 80 °C, and stirred for 24 h. The reaction mixture was cooled to room temperature, and diluted with water (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 2 % EtOAc/hexane) to give compound **17** (110 mg, 0.184 mmol, 80 %) as a colourless oil. R_f = 0.4 (SiO_2, 5 % EtOAc/hexane). $[\alpha]_D^{25}$ = +8.86 (c = 0.35, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2927, 2856, 1695, 1649, 1463, 1374, 1251, 1215, 1118, 1056, 939, 837, 774, 727, 665 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.53–5.31 (m, 4 H), 4.27 (quin, J = 6.0 Hz, 1 H), 4.06 (dd, J = 8.3, 6.8 Hz, 1 H), 3.73 (dd, J = 8.3, 6.8 Hz, 1 H), 3.61 (m, 1 H), 3.54 (dd, J = 9.8, 6.0 Hz, 2 H), 3.48 (dd, J = 6.8, 2.3 Hz, 1 H), 3.44 (m, 1 H), 2.34 (q, J = 6.8 Hz, 2 H), 2.15–1.96 (m, 6 H), 1.43 (s, 3 H), 1.37 (s, 3 H), 1.35–1.22 (m, 26 H), 0.93–0.86 (m, 12 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 131.42, 130.54, 128.88, 125.60, 74.73, 72.38, 71.84, 71.33, 66.90, 37.15, 36.84, 29.88, 29.66, 29.58, 29.35, 27.86, 27.55, 27.49, 27.29, 27.23, 26.77, 25.95, 25.43, 25.34, 22.91, 18.17, 14.13, –4.41 ppm. HRMS (ESI): calcd. for $C_{36}H_{70}O_4SiNa$ $[M + Na]^+$ 617.4941; found 617.4952.

(*R*,17*Z*,21*Z*)-24-{[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methoxy}tetracosa-17,21-dien-5-ol (3a): TBAF (1 M solution in THF; 0.42 mL, 0.42 mmol) was added to a stirred solution of compound

17 (85 mg, 0.14 mmol) in anhydrous THF (1.0 mL) at 0 °C. The solution was warmed to room temperature and stirred for 3 h. After this time, the solution was quenched with saturated aqueous NH_4Cl (5 mL) at 0 °C, and diluted with water (5 mL) and ethyl acetate (15 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 10 % EtOAc/hexane) to give alcohol **3a** (65 mg, 0.135 mmol, 96 %) as a colourless oil. R_f = 0.4 (SiO_2, 20 % EtOAc/hexane). $[\alpha]_D^{25}$ = –5.84 (*c* = 1.25, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3434, 2924, 2855, 1721, 1460, 1374, 1252, 1214, 1114, 1053, 845, 725 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.50–5.32 (m, 4 H), 4.26 (quin, *J* = 6.0 Hz, 1 H), 4.05 (dd, *J* = 8.2, 6.4 Hz, 1 H), 3.73 (dd, *J* = 8.2, 6.4 Hz, 1 H), 3.61–3.55 (m, 1 H), 3.53 (dd, *J* = 9.8, 5.6 Hz, 1 H), 3.51–3.46 (m, 2 H), 3.44 (dd, *J* = 9.9, 5.6 Hz, 1 H), 2.34 (qd, *J* = 7.0, 1.0 Hz, 2 H), 2.12–2.04 (m, 4 H), 2.01 (q, *J* = 6.7 Hz, 2 H), 1.48–1.43 (m, 2 H), 1.42 (s, 3 H), 1.41–1.37 (m, 2 H), 1.36 (s, 3 H), 1.35–1.24 (m, 22 H), 0.91 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 131.40, 130.50, 128.86, 125.59, 109.35, 74.70, 71.97, 71.81, 71.30, 66.88, 37.48, 37.16, 29.70, 29.62, 29.53, 29.30, 27.83, 27.47, 27.25, 27.21, 26.75, 25.64, 25.40, 22.75, 14.06 ppm. HRMS (ESI): calcd. for $C_{30}H_{56}O_4Na$ $[M + Na]^+$ 503.4076; found 503.4077.

(*R*,17*Z*,21*Z*)-24-{[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methoxy}tetracosa-17,21-dien-5-yl Acetate (3): Et_3N (52 µL, 0.375 mmol) was added to a stirred solution of alcohol **3a** (60 mg, 0.125 mmol) in anhydrous CH_2Cl_2 (1.0 mL) at 0 °C, then a catalytic amount of DMAP (1.5 mg, 0.0125 mmol) was added. The mixture was stirred for 10 min, then Ac_2O (24 µL, 0.25 mmol) was added at 0 °C. The solution was warmed to room temperature and stirred for 2 h. After this time, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) at 0 °C, and the mixture was diluted with water (10 mL) and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 4 % EtOAc/hexane) to give compound **3** (63 mg, 0.120 mmol, 96 %) as a colourless oil. R_f = 0.6 (SiO_2, 10 % EtOAc/hexane). $[\alpha]_D^{25}$ = –9.58 (*c* = 0.95, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 2856, 1736, 1460, 1373, 1242, 1116, 1053, 847, 729 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.51–5.30 (m, 4 H), 4.86 (quin, *J* = 6.2 Hz, 1 H), 4.26 (quin, *J* = 6.0 Hz, 1 H), 4.05 (dd, *J* = 8.2, 6.2 Hz, 1 H), 3.73 (dd, *J* = 8.2, 6.4 Hz, 1 H), 3.53 (dd, *J* = 9.8, 5.7 Hz, 1 H), 3.51–3.46 (m, 2 H), 3.44 (dd, *J* = 9.8, 5.5 Hz, 1 H), 2.34 (qd, *J* = 7.1, 1.0 Hz, 2 H), 2.12–2.07 (m, 3 H), 2.04 (s, 3 H), 2.03–1.99 (m, 3 H), 1.54–1.47 (m, 4 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 1.35–1.22 (m, 22 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.93, 131.41, 130.51, 128.86, 125.58, 109.36, 74.71, 74.42, 71.82, 71.31, 66.87, 34.12, 33.80, 29.72, 29.62, 29.54, 29.32, 27.83, 27.47, 27.27, 27.21, 26.75, 25.41, 25.30, 22.59, 21.28, 13.98 ppm. HRMS (ESI): calcd. for $C_{32}H_{58}O_5Na$ $[M + Na]^+$ 545.4182; found 545.4187.

(5*R*)-24-{[(*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methoxy}-17,18,21,22-tetrahydroxytetracosan-5-yl Acetate (18): A stirred solution of AD-mix β (214 mg, 2.8 g/mmol) in *t*BuOH/H_2O (1:1; 4 mL) was treated with $MeSO_2NH_2$ (22 mg, 0.23 mmol) at room temperature, and the mixture was stirred until it became a clear solution (5 min). Then the solution was cooled to 0 °C, and a solution of compound **3** (40 mg, 0.077 mmol) in the minimum amount of *t*BuOH (0.5 mL) was added. The mixture was stirred at 0 °C for 48 h. After this time, the reaction was quenched with $Na_2S_2O_5$ (220 mg, 1.16 mmol) at 0 °C, and the solution was warmed to room temperature and stirred for 30 min. The mixture was diluted with water (10 mL), and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 3 % MeOH/$CHCl_3$) to give compound **18** (39 mg, 0.066 mmol, 85 %) as a pale brown semisolid, an inseparable mixture of diastereomers. R_f = 0.3 (SiO_2, 10 % MeOH/$CHCl_3$). IR (neat): $\tilde{\nu}$ = 3620, 3300, 2923, 2854, 1734, 1700, 1522, 1462, 1373, 1242, 1120, 1060, 1026, 848 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.86 (quin, *J* = 6.2 Hz, 1 H), 4.27 (quin, *J* = 5.7 Hz, 1 H), 4.05 (m, 1 H), 3.80–3.59 (m, 7 H), 3.57–3.50 (m, 2 H), 2.04 (s, 3 H), 1.90–1.80 (m, 1 H), 1.79–1.73 (m, 2 H), 1.61–1.48 (m, 4 H), 1.44 (s, 3 H), 1.36 (s, 3 H), 1.34–1.22 (m, 27 H), 0.91–0.86 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.01, 109.60, 109.56, 74.73, 74.55, 74.44, 74.35, 74.32, 74.19, 74.13, 73.99, 72.06, 71.95, 70.25, 70.10, 66.34, 66.24, 34.09, 33.79, 31.61, 30.50, 29.67, 29.56, 29.50, 28.35, 27.52, 27.46, 26.68, 26.65, 26.03, 25.28, 25.24, 25.22, 22.58, 21.29, 13.98 ppm. HRMS (ESI): calcd. for $C_{32}H_{62}O_9Na$ $[M + Na]^+$ 613.4292; found 613.4299.

(*R*)-1-[(4-Methoxybenzyl)oxy]pent-4-en-2-ol (29): A stirred solution of $TiCl_4$ (1 M solution in toluene; 0.42 mL, 0.42 mmol) in anhydrous CH_2Cl_2 (16 mL) was treated with $Ti(OiPr)_4$ (0.37 mL, 1.25 mmol) at 0 °C, and the solution was warmed to room temperature and stirred for 1 h in the absence of light. Freshly prepared Ag_2O (192 mg, 0.83 mmol) was then added at room temperature, and the mixture was stirred for a further 5 h. The solution was diluted with anhydrous CH_2Cl_2 (4 mL), and treated with (*R*)-BINOL (478 mg, 1.67 mmol) at room temperature. The mixture was stirred for 2 h. At this point, the solution had turned brick red in colour.

The in-situ-generated bis[(*R*)-Ti^{IV} oxide] catalyst **28a** was cooled to –15 °C. A solution of aldehyde **28** (1.5 g, 8.33 mmol) in anhydrous CH_2Cl_2 (4 mL) was added, followed by allyltributyltin (2.81 mL, 9.16 mmol). The solution was warmed to 0 °C and stirred for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) at 0 °C. The mixture was stirred for 30 min, then it was filtered through a Celite plug, which was washed with CH_2Cl_2 (3 × 30 mL). The filtrate was diluted with water (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with water (40 mL) and brine (40 mL), dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 15 % EtOAc/hexane) to give alcohol **29** (1.48 g, 6.66 mmol, 80 %, 96 % *ee*) as a pale yellow oil. R_f = 0.25 (SiO_2, 20 % EtOAc/hexane). $[\alpha]_D^{25}$ = –4.0 (*c* = 1.7, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3458, 2915, 2860, 1713, 1609, 1513, 1461, 1300, 1248, 1174, 1095, 1033, 917, 822 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.26 (m, 2 H), 6.89 (m, 2 H), 5.82 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1 H), 5.14–5.07 (m, 2 H), 4.49 (s, 2 H), 3.87 (m, 1 H), 3.81 (s, 3 H), 3.49 (dd, *J* = 9.4, 3.4 Hz, 1 H), 3.35 (dd, *J* = 9.4, 7.5 Hz, 1 H), 2.27–2.23 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.22, 134.19, 129.97, 129.30, 117.52, 113.77, 73.53, 72.95, 69.64, 55.19, 37.84 ppm. HRMS (ESI): calcd. for $C_{13}H_{18}O_3Na$ $[M + Na]^+$ 245.1154; found 245.1154.

(*R*)-1-({[2-(Benzyloxy)pent-4-en-1-yl]oxy}methyl)-4-methoxybenzene (30): A solution of alcohol **29** (500 mg, 2.25 mmol) in anhydrous THF (3.5 mL) was added by cannula to a suspension of NaH (135 mg, 3.38 mmol) in anhydrous THF (3.5 mL) at 0 °C. The resulting solution was warmed to room temperature, and stirred for 30 min. The solution was then recooled to 0 °C, and benzyl bromide

(0.4 mL, 3.38 mmol) was added, followed by TBAI (83 mg, 0.225 mmol). The solution was warmed to room temperature and stirred for 16 h. After this time, TLC (20 % EtOAc/hexane) indicated the complete consumption of alcohol **29**. The reaction was slowly quenched with saturated aqueous ammonium chloride (20 mL) at 0 °C, and the mixture was diluted with water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with water (40 mL) and brine (40 mL), dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 4 % EtOAc/hexane) to give compound **30** (600 mg, 1.92 mmol, 85 %) as a colourless oil. R_f = 0.4 (SiO_2, 10 % EtOAc/hexane). $[\alpha]_D^{25}$ = +4.42 (*c* = 0.95, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2904, 2858, 1610, 1511, 1453, 1351, 1300, 1245, 1175, 1091, 1033, 995, 914, 818, 737, 696, 580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.22 (m, 7 H), 6.90–6.84 (m, 2 H), 5.83 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1 H), 5.13–5.01 (m, 2 H), 4.65 (d, *J* = 11.8 Hz, 1 H), 4.60 (d, *J* = 11.8 Hz, 1 H), 4.48 (s, 2 H), 3.81 (s, 3 H), 3.65 (quin, *J* = 5.6 Hz, 1 H), 3.53 (dd, *J* = 5.2, 0.6 Hz, 2 H), 2.39–2.32 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.12, 138.76, 134.60, 130.41, 129.20, 128.23, 127.66, 127.42, 117.08, 113.71, 77.68, 72.97, 71.87, 71.77, 55.24, 36.29 ppm. HRMS (ESI): [M + Na]$^+$calcd. for $C_{20}H_{24}O_3Na$ [M + Na]$^+$ 335.1623; found 335.1627.

(*R*)-3-(Benzyloxy)-4-[(4-methoxybenzyl)oxy]butan-1-ol (31): Ozone was bubbled into a solution of compound **30** (550 mg, 1.76 mmol) in CH_2Cl_2 (10 mL) at –78 °C until the colour of the solution became sky blue (10 min). After this time, TLC (10 % EtOAc/hexane) indicated the complete consumption of compound **30**, and the formation of the ozonide. The solution was warmed to 0 °C, and oxygen was bubbled into the solution until the sky-blue colour disappeared (5 min). Triphenylphosphine (508 mg, 1.94 mmol) was added to the reaction mixture at 0 °C. The solution was warmed to room temperature and stirred for 6 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 20 % EtOAc/hexane) to give the aldehyde (500 mg) as a colourless oil. This compound was used immediately in the next reaction without further characterization. R_f = 0.7 (SiO_2, 50 % EtOAc/hexane).

$NaBH_4$ (66 mg, 1.75 mmol) was added to a stirred solution of the above aldehyde (500 mg, 1.59 mmol) in methanol (4 mL) at 0 °C. The solution was warmed to room temperature and stirred for 30 min. The reaction was quenched with saturated aqueous ammonium chloride (10 mL) at 0 °C, and the mixture was diluted with water (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 40 % EtOAc/hexane) to give alcohol **31** (450 mg, 1.42 mmol, 80 % over two steps) as a colourless oil. R_f = 0.3 (SiO_2, 50 % EtOAc/hexane). $[\alpha]_D^{25}$ = +30.91 (*c* = 1.1, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3395, 2927, 2857, 1715, 1611, 1513, 1455, 1248, 1174, 1090, 1033, 820, 740, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 7 H), 6.90–6.85 (m, 2 H), 4.71 (d, *J* = 11.7 Hz, 1 H), 4.56 (d, *J* = 11.7 Hz, 1 H), 4.48 (s, 2 H), 3.83–3.77 (m, 4 H), 3.72 (t, *J* = 5.7 Hz, 2 H), 3.59 (dd, *J* = 9.7, 4.8 Hz, 1 H), 3.53 (dd, *J* = 10.1, 5.0 Hz, 1 H), 2.42 (br. s, 1 H), 1.82 (dd, *J* = 11.4, 5.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.21, 138.29, 130.02, 129.27, 128.40, 127.83, 127.70, 113.78, 76.95, 73.06, 72.08, 72.01, 60.19, 55.23, 34.64 ppm. HRMS (ESI): [M + Na]$^+$calcd. for $C_{19}H_{24}O_4Na$ [M + Na]$^+$ 339.1567; found 339.1579.

(*S*)-4-({(*R*)-3-(Benzyloxy)-4-[(4-methoxybenzyl)oxy]butoxy}methyl)-2,2-dimethyl-1,3-dioxolane (33): A stirred solution of alcohol **31** (420 mg, 1.33 mmol) in NaOH solution (50 % aq.; 6.4 mL, 79.8 mmol) was treated with TBAB (87 mg, 0.27 mmol) at room temperature. The solution was warmed to 90 °C and stirred for 30 min. The reaction mixture was cooled to room temperature, and a solution of tosyl derivative **32** (762 mg, 2.66 mmol) in a minimum amount of diethyl ether (1 mL) was added. The solution was again warmed to 90 °C, and stirred for 48 h. The reaction mixture was cooled to room temperature and diluted with water (20 mL) and CH_2Cl_2 (30 mL). The two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with water (40 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 18 % EtOAc/hexane) to give compound **33** (528 mg, 1.23 mmol, 92 %) as a colourless oil. R_f = 0.3 (SiO_2, 20 % EtOAc/hexane). $[\alpha]_D^{25}$ = +22.61 (*c* = 1.15, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2922, 2854, 1715, 1612, 1513, 1456, 1371, 1248, 1093, 844, 823, 740, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 7 H), 6.90–6.85 (m, 2 H), 4.69 (d, *J* = 11.6 Hz, 1 H), 4.54 (d, *J* = 11.6 Hz, 1 H), 4.48 (s, 2 H), 4.20 (quin, *J* = 6.0 Hz, 1 H), 4.0 (dd, *J* = 8.1, 6.4 Hz, 1 H), 3.80 (s, 3 H), 3.77–3.71 (m, 1 H), 3.67 (dd, *J* = 8.1, 6.6 Hz, 1 H), 3.60–3.50 (m, 4 H), 3.44 (dd, *J* = 9.9, 5.6 Hz, 1 H), 3.38 (dd, *J* = 9.9, 5.6 Hz, 1 H), 1.88–1.76 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.11, 138.79, 130.39, 129.19, 128.25, 127.77, 127.45, 113.71, 109.30, 75.19, 74.62, 72.94, 72.46, 72.09, 71.81, 67.97, 66.83, 55.23, 32.16, 26.73, 25.39 ppm. HRMS (ESI): calcd. for $C_{25}H_{34}O_6Na$ [M + Na]$^+$ 453.2248; found 453.2247.

(*R*)-2-(Benzyloxy)-4-{[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}butan-1-ol (34): A stirred solution of compound **33** (500 mg, 1.16 mmol) in a mixture of CH_2Cl_2 and pH = 7.4 phosphate buffer (2:1; 6 mL) was treated with DDQ (395 mg, 1.74 mmol) at 0 °C, and the mixture was stirred at the same temperature for 2 h. After this time, the reaction mixture was again treated with DDQ (132 mg, 0.58 mmol) at 0 °C, and the mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) at 0 °C, and the mixture was diluted with water (20 mL) and ethyl acetate (40 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL), water (30 mL), and brine (30 mL). The combined organic extracts were dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 40 % EtOAc/hexane) to give alcohol **34** (260 mg, 0.84 mmol, 72 %) as a pale yellow oil. R_f = 0.4 (SiO_2, 40 % EtOAc/hexane). $[\alpha]_D^{25}$ = +11.54 (*c* = 0.65, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3501, 2985, 2928, 2871, 1712, 1468, 1454, 1372, 1255, 1213, 1054, 842, 740, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H), 4.60 (d, *J* = 11.7 Hz, 1 H), 4.58 (d, *J* = 11.7 Hz, 1 H), 4.24 (quin, *J* = 6.0 Hz, 1 H), 4.04 (dd, *J* = 8.2, 6.6 Hz, 1 H), 3.73 (dd, *J* = 11.7, 3.8 Hz, 1 H), 3.70 (dd, *J* = 8.2, 6.4 Hz, 1 H), 3.66 (m, 1 H), 3.61–3.54 (m, 3 H), 3.47 (dd, *J* = 9.9, 5.8 Hz, 1 H), 3.46 (dd, *J* = 9.9, 5.2 Hz, 1 H), 2.26 (br. s, 1 H), 1.95–1.88 (m, 1 H), 1.87–1.80 (m, 1 H), 1.42 (s, 3 H), 1.36 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.35, 128.44, 127.75, 109.42, 74.59, 71.93, 71.62, 67.77, 66.66, 64.07, 31.20, 26.71, 25.35 ppm. HRMS (ESI): calcd. for $C_{17}H_{26}O_5Na$ [M + Na]$^+$ 333.1672; found 333.1676.

(*R*)-2-(Benzyloxy)-4-{[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}butanal (20): $NaHCO_3$ (179 mg, 2.13 mmol) was added to a stirred solution of alcohol **34** (220 mg, 0.71 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C. Then DMP (454 mg, 1.07 mmol) was added, and the reaction mixture was then warmed to room temperature

and stirred for 30 min. After this time, TLC (40 % EtOAc/hexane) indicated the complete consumption of alcohol **34**. The reaction was quenched with a mixture of saturated aqueous sodium thiosulfate and saturated aqueous $NaHCO_3$ (30 mL; 1:1) at 0 °C, and the mixture was diluted with CH_2Cl_2 (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 30 % EtOAc/hexane) to give aldehyde **20** (219 mg, 0.71 mmol, quantitative) as a colourless oil, which was used in the next reaction without further characterization. R_f = 0.7 (SiO_2, 40 % EtOAc/hexane).

(*R*)-Hexadec-7-yn-6-ol (26): A stirred solution of ynone **27** (2.5 g, 10.58 mmol) in anhydrous CH_2Cl_2 (50 mL) was treated with a premixed solution of HCOOH (2.99 mL, 79.35 mmol) and Et_3N (11.04 mL, 79.35 mmol) in CH_2Cl_2 (10 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 5 min. The reaction mixture was treated with freshly prepared (*R*,*R*)-Ru catalyst **23a** (35 mg, 0.053 mmol, 0.5 mol-%) at 0 °C, and the solution was warmed to room temperature and stirred for 24 h. The reaction was quenched with saturated aqueous NH_4Cl (30 mL), and the mixture was diluted with water (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 3 % EtOAc/hexane) to give alcohol **26** (2.23 g, 9.35 mmol, 88 %, 94 % *ee*) as a pale yellow oil. R_f = 0.25 (SiO_2, 5 % EtOAc/hexane). $[\alpha]_D^{25}$ = +3.16 (*c* = 0.95, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3394, 2955, 2926, 2856, 1712, 1465, 1022, 772 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.35 (tt, *J* = 6.5, 1.8 Hz, 1 H), 2.20 (td, *J* = 7.0, 1.8 Hz, 2 H), 1.77–1.60 (m, 2 H), 1.53–1.42 (m, 3 H), 1.40–1.22 (m, 15 H), 0.92–0.86 (m, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 85.53, 81.32, 62.77, 38.17, 31.82, 31.47, 29.17, 29.07, 28.83, 28.66, 24.87, 22.64, 22.56, 18.66, 14.07, 13.98 ppm. HRMS (ESI): calcd. for $C_{16}H_{30}ONa$ $[M + Na]^+$ 261.2194; found 261.2188.

(*R*)-Hexadec-15-yn-6-ol (35): NaH (3.93 g, 98.16 mmol) was slowly treated with anhydrous 1,3-diaminopropane (49 mL) at 0 °C under an argon atmosphere. The resulting solution was warmed to 80 °C and stirred for 1 h. The solution was cooled to room temperature, and a solution of alcohol **26** (1.95 g, 8.18 mmol) in 1,3-diaminopropane (10 mL) was added by cannula. The solution was again warmed to 80 °C, and stirred for 2 h. After this time, TLC (10 % EtOAc/hexane) indicated the complete consumption of alcohol **26**. The reaction was slowly quenched with water (30 mL) at 0 °C, and the mixture was diluted with CH_2Cl_2 (40 mL). The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 3 % EtOAc/hexane) to give compound **35** (1.6 g, 6.71 mmol, 82 %) as a pale yellow oil. R_f = 0.45 (SiO_2, 10 % EtOAc/hexane). $[\alpha]_D^{25}$ = +1.0 (*c* = 1.05, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3312, 2926, 2855, 2118, 1463, 1375, 1301, 1248, 1125, 1040, 833, 723, 628 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.58 (m, 1 H), 2.18 (td, *J* = 7.2, 2.6 Hz, 2 H), 1.94 (t, *J* = 2.6 Hz, 1 H), 1.52 (quin, *J* = 7.3 Hz, 2 H), 1.48–1.36 (m, 7 H), 1.36–1.25 (m, 13 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 84.72, 71.96, 68.03, 37.44, 31.90, 29.61, 29.43, 29.01, 28.70, 28.44, 25.60, 25.30, 22.62, 18.36, 14.01 ppm. HRMS (ESI): calcd. for $C_{16}H_{31}O$ $[M + H]^+$ 239.2375; found 239.2375.

(*R*)-1-[(Hexadec-15-yn-6-yloxy)methyl]-4-methoxybenzene (24): A mixture of compound **35** (1.45 g, 6.08 mmol) and DIPEA (2.1 mL, 12.16 mmol) was treated with PMBCl (1.23 mL, 9.12 mmol), followed by sodium iodide (183 mg, 1.22 mmol) at room temperature. The reaction mixture was warmed to 150 °C and stirred for 2 h. After this time, TLC (10 % EtOAc/hexane) indicated the complete consumption of compound **35**. The reaction was quenched with saturated aqueous ammonium chloride (20 mL) at 0 °C, and the mixture was diluted with water (20 mL) and ethyl acetate (30 mL). The two phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 2 % EtOAc/hexane) to give compound **24** (2.08 g, 5.80 mmol, 95 %) as a pale yellow oil. R_f = 0.7 (SiO_2, 10 % EtOAc/hexane). $[\alpha]_D^{25}$ = –1.82 (*c* = 0.83, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2927, 2856, 1704, 1610, 1513, 1461, 1248, 1171, 1075, 1037, 822, 630 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.24 (m, 2 H), 6.89–6.85 (m, 2 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.33 (quin, *J* = 5.9 Hz, 1 H), 2.18 (td, *J* = 7.0, 2.6 Hz, 2 H), 1.94 (t, *J* = 2.6 Hz, 1 H), 1.55–1.42 (m, 4 H), 1.41–1.22 (m, 18 H), 0.89 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.99, 131.31, 129.26, 113.67, 84.77, 78.66, 70.35, 68.02, 55.26, 33.87, 33.83, 32.05, 29.76, 29.47, 29.05, 28.72, 28.47, 25.34, 25.03, 22.66, 18.38, 14.06 ppm. HRMS (ESI): calcd. for $C_{24}H_{38}O_2Na$ $[M + Na]^+$ 381.2770; found 381.2764.

(*R*)-1-(Benzyloxy)-13-[(4-methoxybenzyl)oxy]octadec-3-yn-2-one (23): *n*BuLi (1.6 M solution in hexane; 2.96 mL, 4.74 mmol) was added to a stirred solution of compound **24** (1.70 g, 4.74 mmol) in anhydrous THF (10 mL) at –78 °C. The solution was slowly warmed to 0 °C over a period of 45 min, and then it was recooled to –78 °C. A solution of aldehyde **25** (855 mg, 5.69 mmol) in anhydrous THF (6 mL) was added by cannula, and the mixture was stirred at the same temperature for 2 h. The solution was slowly warmed to room temperature over a period of 1 h. The reaction was quenched with saturated aqueous ammonium chloride (20 mL) at 0 °C, and the mixture was diluted with water (20 mL) and ethyl acetate (30 mL). The two phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 15 % EtOAc/hexane) to give a diastereomeric mixture of alcohols (2.13 g, 4.19 mmol, 88 %, *dr* = 2.8:1) as a colourless oil.

The mixture of alcohols was dissolved in anhydrous CH_2Cl_2 (20 mL), and treated with DMP (3.55 g, 8.38 mmol) at 0 °C. The mixture was stirred at room temperature for 1 h, then the reaction was quenched with a mixture of saturated aqueous sodium thiosulfate and saturated aqueous $NaHCO_3$ (1:1; 30 mL) at 0 °C. The mixture was stirred at room temperature until the solution became clear (2 h). The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The organic extracts were washed with water (30 mL) and brine (30 mL). The combined organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 6 % EtOAc/hexane) to give ynone **23** (1.815 g, 3.58 mmol, 85 %) as a colourless oil. R_f = 0.7 (SiO_2, 20 % EtOAc/hexane). $[\alpha]_D^{25}$ = +2.0 (*c* = 0.75, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2920, 2851,

1711, 1551, 1514, 1460, 1254, 1168, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.23 (m, 7 H), 6.90–6.84 (m, 2 H), 4.64 (s, 2 H), 4.43 (s, 2 H), 4.20 (s, 2 H), 3.80 (s, 3 H), 3.33 (quin, *J* = 5.5 Hz, 1 H), 2.37 (t, *J* = 6.9 Hz, 2 H), 1.63–1.44 (m, 4 H), 1.43–1.18 (m, 18 H), 0.89 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.06, 158.98, 137.09, 131.28, 129.25, 128.46, 127.99, 127.93, 113.67, 97.61, 78.70, 78.64, 75.78, 73.30, 70.35, 55.25, 33.85, 33.81, 32.04, 29.75, 29.39, 28.97, 28.83, 27.56, 25.32, 25.03, 22.65, 19.07, 14.07 ppm. HRMS (ESI): calcd. for $C_{33}H_{46}O_4Na$ $[M + Na]^+$ 529.3294; found 529.3287.

(2*S*,13*R*)-1-(Benzyloxy)-13-[(4-methoxybenzyl)oxy]octadec-3-yn-2-ol (36): Following the same procedure described for the synthesis of compound **26**, the above ynone **23** (1.7 g, 3.36 mmol) was subjected to Noyori reduction conditions. Purification by silica gel column chromatography (SiO_2, 100–200 mesh, 16 % EtOAc/hexane) gave the corresponding alcohol **36** (1.5 g, 2.95 mmol, 87 %, 94 % *de*) as a colourless oil. R_f = 0.45 (SiO_2, 20 % EtOAc/hexane). $[\alpha]_D^{25}$ = +4.74 (*c* = 0.68, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3425, 2927, 2856, 1612, 1512, 1459, 1355, 1303, 1246, 1174, 1111, 1074, 1035, 898, 820, 738, 699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 7 H), 6.89–6.84 (m, 2 H), 4.61 (d, *J* = 12.0 Hz, 1 H), 4.59 (d, *J* = 12.0 Hz, 1 H), 4.43 (s, 2 H), 3.79 (s, 3 H), 3.62 (dd, *J* = 9.8, 3.4 Hz, 1 H), 3.52 (dd, *J* = 9.8, 7.7 Hz, 1 H), 3.33 (quin, *J* = 5.6 Hz, 1 H), 2.49 (br. s, 1 H), 2.19 (td, *J* = 7.2, 2.0 Hz, 2 H), 1.57–1.43 (m, 4 H), 1.42–1.20 (m, 18 H), 0.88 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.96, 137.69, 131.28, 129.25, 128.43, 127.80, 127.73, 113.65, 86.58, 78.65, 77.60, 74.03, 73.32, 70.33, 61.83, 55.24, 33.86, 33.82, 32.03, 29.76, 29.45, 29.05, 28.81, 28.49, 25.33, 25.03, 22.64, 18.68, 14.05 ppm. HRMS (ESI): calcd. for $C_{33}H_{48}O_4Na$ $[M + Na]^+$ 531.3445; found 531.3450.

({(2*S*,13*R*)-1-(Benzyloxy)-13-[(4-methoxybenzyl)oxy]octadec-3-yn-2-yl}oxy)(*tert*-butyl)dimethylsilane (37): 2,6-Lutidine (1.0 mL, 8.55 mmol) was added to a stirred solution of alcohol **36** (1.45 g, 2.85 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C, followed by TBSOTf (0.73 mL, 3.14 mmol). The solution was warmed to room temperature and stirred for 30 min. After this time, TLC (5 % EtOAc/hexane) indicated the complete consumption of alcohol **36**. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) at 0 °C, and the mixture was diluted with water (20 mL) and CH_2Cl_2 (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 3 % EtOAc/hexane) to give compound **37** (1.72 g, 2.76 mmol, 97 %) as a colourless oil. R_f = 0.5 (SiO_2, 5 % EtOAc/hexane). $[\alpha]_D^{25}$ = +10.47 (*c* = 0.85, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2928, 2855, 2376, 2311, 1713, 1512, 1256, 1170, 1101, 834, 776, 612, 590 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 7 H), 6.88–6.85 (m, 2 H), 4.62 (d, *J* = 12.3 Hz, 1 H), 4.60 (d, *J* = 12.3 Hz, 1 H), 4.55 (m, 1 H), 4.42 (s, 2 H), 3.79 (s, 3 H), 3.55 (dd, *J* = 10.1, 5.0 Hz, 1 H), 3.54 (dd, *J* = 10.1, 6.7 Hz, 1 H), 3.33 (quin, *J* = 5.5 Hz, 1 H), 2.18 (td, *J* = 7.1, 2.0 Hz, 2 H), 1.56–1.43 (m, 4 H), 1.42–1.21 (m, 18 H), 0.92 (s, 9 H), 0.88 (t, *J* = 7.0 Hz, 3 H), 0.13 (s, 3 H), 0.12 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.99, 138.40, 131.31, 129.25, 128.25, 127.51, 127.43, 113.67, 85.70, 79.27, 78.67, 74.92, 73.31, 70.35, 63.19, 55.24, 33.88, 33.83, 32.05, 29.82, 29.53, 29.12, 28.84, 28.55, 25.81, 25.37, 25.04, 22.66, 18.71, 18.31, 14.06, –4.64, –4.86 ppm. HRMS (ESI): calcd. for $C_{39}H_{62}O_4SiK$ $[M + K]^+$ 661.4049; found 661.4076.

(2*S*,13*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-13-[(4-methoxybenzyl)oxy]octadecan-1-ol (22): A stirred solution of compound **37** (1.6 g, 2.57 mmol) in EtOH (30 mL) was treated with freshly activated Raney nickel (800 mg, 50 % w/w), and the mixture was hydrogenated using a hydrogen-filled balloon at room temperature for 24 h. After this time, TLC (20 % EtOAc/hexane) indicated the complete consumption of compound **37**. Then the reaction mixture was filtered carefully through a Celite plug under a nitrogen atmosphere; the plug was then washed with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 6 % EtOAc/hexane) to give alcohol **22** (1.3 g, 2.42 mmol, 94 %) as a colourless oil. R_f = 0.3 (SiO_2, 10 % EtOAc/hexane). $[\alpha]_D^{25}$ = +8.13 (*c* = 0.75, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3409, 2927, 2855, 1613, 1514, 1301, 1249, 1173, 1081, 1040, 1007, 835, 776 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 2 H), 6.88–6.85 (m, 2 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.72 (ddd, *J* = 11.8, 6.1, 3.6 Hz, 1 H), 3.56 (dd, *J* = 10.9, 3.7 Hz, 1 H), 3.44 (dd, *J* = 10.9, 5.3 Hz, 1 H), 3.33 (quin, *J* = 5.9 Hz, 1 H), 1.89 (br. s, 1 H), 1.57–1.42 (m, 6 H), 1.41–1.21 (m, 22 H), 0.90 (s, 9 H), 0.88 (t, *J* = 7.2 Hz, 3 H), 0.09 (s, 6 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.96, 131.29, 129.26, 113.65, 78.67, 72.91, 70.33, 66.26, 55.25, 33.95, 33.87, 33.82, 32.05, 29.84, 29.76, 29.64, 29.6, 29.56, 25.84, 25.37, 25.33, 25.03, 22.67, 18.08, 14.07, –4.44, –4.58 ppm. HRMS (ESI): calcd. for $C_{32}H_{60}O_4SiNa$ $[M + Na]^+$ 559.4159; found 559.4153.

(3*R*,4*S*,15*R*)-4-(*tert*-Butyldimethylsilyl)oxy-15-[(4-methoxybenzyl)oxy]-1-(triisopropylsilyl)icos-1-yn-3-ol (38): Alcohol **22** (1.25 g, 2.33 mmol) was oxidized under Swern conditions. Purification by silica gel column chromatography (SiO_2, 100–200 mesh, 10 % EtOAc/hexane) gave the aldehyde (1.2 g, 2.24 mmol) as a colourless oil, which was used in the next reaction without further characterization. R_f = 0.8 (SiO_2, 10 % EtOAc/hexane).

A stirred solution of TIPS-acetylene (2 mL, 8.96 mmol) in dry toluene (10 mL) was treated with Et_2Zn (1 M solution in hexane; 8.96 mL, 8.96 mmol) carefully at room temperature. The solution was warmed to 120 °C and stirred for 1 h. Then the reaction mixture was cooled to room temperature, and (*R*)-BINOL (257 mg, 0.90 mmol) was added, followed by anhydrous diethyl ether (20 mL) and $Ti(OiPr)_4$ (0.67 mL, 2.24 mmol). The mixture was stirred for 1 h. A solution of the above aldehyde (1.2 g, 2.24 mmol) in anhydrous diethyl ether (20 mL) was then added by cannula at room temperature, and the mixture was stirred for 16 h. The reaction was quenched with tartaric acid (1 M aq.; 20 mL) at 0 °C. The mixture was stirred at room temperature for 30 min, and then it was diluted with water (30 mL) and diethyl ether (50 mL). The two phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 40 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 3 % EtOAc/hexane) to give compound **38** (900 mg, 1.25 mmol, 53 % over two steps, 98 % *de*) as a pale yellow oil. R_f = 0.4 (SiO_2, 10 % EtOAc/hexane). $[\alpha]_D^{25}$ = –1.0 (*c* = 1.10, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3500, 2927, 2857, 1612, 1513, 1463, 1364, 1301, 1249, 1172, 1076, 1039, 883, 836, 777, 677 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.25 (m, 2 H), 6.88–6.85 (m, 2 H), 4.43 (s, 2 H), 4.35–4.32 (m, 1 H), 3.80 (s, 3 H), 3.77–3.73 (m, 1 H), 3.34 (quin, *J* = 5.6 Hz, 1 H), 2.39 (d, *J* = 6.0 Hz, 1 H), 1.75–1.42 (m, 7 H), 1.41–1.20 (m, 21 H), 1.12–1.02 (m, 21 H), 0.9 (s, 9 H), 0.88 (t, *J* = 7.2 Hz, 3 H), 0.10 (s. 3 H), 0.09 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.96, 131.28, 129.26, 113.65, 105.19, 86.79, 78.68, 74.99, 70.34, 66.39, 55.24, 33.88, 33.83, 33.04, 32.05, 29.87, 29.76, 29.66, 29.62, 29.60, 29.49, 25.77, 25.40, 25.37, 25.04, 22.67, 18.57, 18.04, 14.07, 11.12, –4.34, –4.56 ppm. HRMS (ESI): calcd. for $C_{43}H_{80}O_4Si_2Na$ $[M + Na]^+$ 739.5493; found 739.5494.

(3*R*,4*S*,15*R*)-15-[(4-Methoxybenzyl)oxy]icos-1-yne-3,4-diol (21a): A stirred solution of compound **38** (850 mg, 1.18 mmol) in

anhydrous THF (7 mL) was treated with TBAF (1 M solution in THF; 4.72 mL, 4.72 mmol) at 0 °C. The solution was warmed to room temperature and stirred for 30 min. After this time, TLC (10 % EtOAc/hexane) indicated the complete consumption of compound **38**. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was diluted with water (10 mL) and CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 21 % EtOAc/hexane) to give diol **21a** (500 mg, 1.12 mmol, 95 %) as a colourless oil. R_f = 0.3 (SiO_2, 30 % EtOAc/hexane). $[\alpha]_D^{25}$ = +1.52 (c = 1.05, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3392, 3306, 2925, 2854, 1612, 1513, 1461, 1301, 1246, 1175, 1037, 819, 653, 632 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 2 H), 6.89–6.85 (m, 2 H), 4.43 (s, 2 H), 4.32 (dd, J = 3.5, 2.2 Hz, 1 H), 3.8 (s, 3 H), 3.69 (ddd, J = 7.1, 6.4, 3.5 Hz, 1 H), 3.34 (quin, J = 5.6 Hz, 1 H), 2.5 (d, J = 2.0 Hz, 1 H), 2.27 (br. s, 2 H), 1.61–1.42 (m, 7 H), 1.41–1.22 (m, 21 H), 0.88 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.96, 131.26, 129.28, 113.66, 81.31, 78.68, 74.86, 73.97, 70.33, 66.17, 55.25, 33.85, 33.81, 32.72, 32.03, 29.79, 29.67, 29.59, 29.54, 29.50, 25.54, 25.34, 25.03, 22.65, 14.05 ppm. HRMS (ESI): calcd. for $C_{28}H_{46}O_4Na$ $[M + Na]^+$ 469.3294; found 469.3290.

(4*R*,5*S*)-4-Ethynyl-5-{(*R*)-11-[(4-methoxybenzyl)oxy]hexadecyl}-2,2-dimethyl-1,3-dioxolane (21): A stirred solution of diol **21a** (480 mg, 1.07 mmol) in anhydrous acetone (5 mL) was treated with 2,2-DMP (1.32 mL, 10.7 mmol), followed by catalytic amount of PPTS (27 mg, 0.11 mmol) at 0 °C. The mixture was stirred at room temperature for 16 h. After this time, TLC (30 % EtOAc/hexane) indicated the complete consumption of diol **21a**. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL), and the acetone was evaporated under reduced pressure. The crude residue was diluted with water (15 mL) and ethyl acetate (30 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 2 % EtOAc/hexane) to give alkyne **21** (481 mg, 0.99 mmol, 92 %) as a colourless oil. R_f = 0.3 (SiO_2, 5 % EtOAc/hexane). $[\alpha]_D^{25}$ = +20.05 (c = 1.88, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2925, 2855, 1612, 1513, 1460, 1373, 1300, 1243, 1170, 1040, 862, 655 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.24 (m, 2 H), 6.88–6.85 (m, 2 H), 4.71 (dd, J = 5.5, 2.1 Hz, 1 H), 4.43 (s, 2 H), 4.06 (dt, J = 7.1, 6.1 Hz, 1 H), 3.79 (s, 3 H), 3.33 (quin, J = 5.6 Hz, 1 H), 2.51 (d, J = 2.1 Hz, 1 H), 1.85–1.64 (m, 3 H), 1.54 (s, 3 H), 1.53–1.36 (m, 4 H), 1.35 (s, 3 H), 1.34–1.21 (m, 21 H), 0.89 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.94, 131.25, 129.24, 113.63, 109.60, 80.07, 78.62, 77.92, 75.43, 70.31, 69.05, 55.21, 33.85, 33.79, 32.03, 30.54, 29.82, 29.61, 29.56, 29.50, 29.43, 27.79, 26.08, 25.88, 25.34, 25.01, 22.64, 14.05 ppm. HRMS (ESI): calcd. for $C_{31}H_{50}O_4Na$ $[M + Na]^+$ 509.3607; found 509.3604.

(*R*)-4-(Benzyloxy)-6-{[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}-1-((4*R*,5*S*)-5-{(*R*)-11-[(4-methoxybenzyl)oxy]hexadecyl}-2,2-dimethyl-1,3-dioxolan-4-yl)hex-1-yn-3-one (19): A stirred solution of alkyne **21** (477 mg, 0.98 mmol) in anhydrous THF (4 mL) was treated with *n*BuLi (1.6 M solution in hexane; 0.58 mL, 0.93 mmol) dropwise over a period of 3 min at –78 °C. The resulting solution was slowly warmed to 0 °C over a period of 45 min. The reaction mixture was then recooled to –78 °C, and a solution of aldehyde **20** (150 mg, 0.49 mmol) in anhydrous THF (3 mL) was added by cannula. The mixture was stirred at –78 °C for 2 h, then it was slowly warmed to room temperature over a period of 1 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) at 0 °C, and the mixture was diluted with water (20 mL) and ethyl acetate (30 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 19 % EtOAc/hexane) to give an inseparable diastereomeric mixture of alcohols (316 mg, 0.40 mmol, 81 %, *dr* = 1.3:1) as a colourless oil. R_f = 0.35 (SiO_2, 30 % EtOAc/hexane).

Following the same experimental procedure as described for the preparation of compound **9**, the above diastereomeric mixture of alcohols (100 mg, 0.126 mmol) was oxidized under Swern conditions. Purification by silica gel column chromatography (SiO_2, 100–200 mesh, 14 % EtOAc/hexane) gave the corresponding ynone **19** (93 mg, 0.117 mmol, 93 %) as a colourless oil. R_f = 0.5 (SiO_2, 20 % EtOAc/hexane). $[\alpha]_D^{25}$ = +41.20 (c = 2.50, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2927, 2857, 1693, 1612, 1513, 1459, 1374, 1245, 1047, 851, 741, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.24 (m. 7 H), 6.89–6.84 (m, 2 H), 4.85 (d, J = 5.5 Hz, 1 H), 4.76 (d, J = 11.6 Hz, 1 H), 4.43 (s, 2 H), 4.41–4.38 (m, 1 H), 4.17 (quin, J = 6.0 Hz, 1 H), 4.12 (dt, J = 6.5, 5.8 Hz, 1 H), 4.08 (dd, J = 8.2, 4.4 Hz, 1 H), 4.00 (dd, J = 7.8, 1.2 Hz, 1 H), 3.79 (s, 3 H), 3.67 (dd, J = 7.9, 6.4 Hz, 1 H), 3.65–3.53 (m, 2 H), 3.41 (qd, J = 9.8, 5.8 Hz, 2 H), 3.36–3.28 (m, 1 H), 2.10 (m, 1 H), 1.97 (m, 1 H), 1.79 (m, 1 H), 1.66 (m, 1 H), 1.51 (s, 3 H), 1.50–1.42 (m, 3 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.34–1.22 (m, 23 H), 0.89 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 188.36, 158.95, 137.26, 131.28, 129.20, 128.34, 127.98, 127.87, 113.63, 110.25, 109.25, 91.00, 84.01, 81.66, 78.63, 78.13, 74.49, 72.52, 71.86, 70.31, 69.17, 66.83, 55.20, 33.85, 33.80, 32.20, 32.01, 30.47, 29.82, 29.62, 29.58, 29.51, 29.47, 27.79, 26.71, 26.03, 25.97, 25.37, 25.00, 22.62, 14.03 ppm. HRMS (ESI): calcd. for $C_{48}H_{72}O_9Na$ $[M + Na]^+$ 815.5074; found 815.5078.

(3*S*,4*R*)-4-(Benzyloxy)-6-{[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}-1-((4*R*,5*S*)-5-{(*R*)-11-[(4-methoxybenzyl)oxy]hexadecyl}-2,2-dimethyl-1,3-dioxolan-4-yl)hex-1-yn-3-ol (39): A stirred solution of ynone **19** (50 mg, 0.063 mmol) in anhydrous CH_2Cl_2 (3 mL) was treated with a premixed solution of HCOOH (18 µL, 0.47 mmol) and Et_3N (74 µL, 0.54 mmol) in CH_2Cl_2 (1 mL) at 0 °C under an argon atmosphere. The mixture was stirred for 5 min, then it was treated with (*R*,*R*)-Ru catalyst **23a** (0.01 M solution in CH_2Cl_2; 63 µL, 0.63 µmol, 1 mol-%) at 0 °C. The solution was warmed to room temperature and stirred for 24 h. After this time, TLC (30 % EtOAc/hexane) indicated the complete consumption of ynone **19**. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), and the mixture was diluted with water (5 mL) and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water (15 mL) and brine (15 mL). The organic layer was dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 18 % EtOAc/hexane) to give diastereomerically pure alcohol **39** (43 mg, 0.054 mmol, 85 %, 99 % *de*) as a colourless oil. R_f = 0.35 (SiO_2, 30 % EtOAc/hexane). $[\alpha]_D^{25}$ = +22.42 (c = 1.90, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3450, 2927, 2857, 1691, 1608, 1513, 1459, 1374, 1246, 1219, 1163, 1039, 847, 740, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 7 H), 6.88–6.85 (m, 2 H), 4.75 (dd, J = 5.5, 1.4 Hz, 1 H), 4.66 (d, J = 11.6 Hz, 1 H), 4.61 (d, J = 11.6 Hz, 1 H), 4.56 (m, 1 H), 4.43 (s, 2 H), 4.22 (quin, J = 5.9 Hz, 1 H), 4.07–4.01 (m, 2 H), 3.80

(s, 3 H), 3.73 (dd, *J* = 5.9, 4.2 Hz, 1 H), 3.70 (dd, *J* = 8.2, 6.4 Hz, 1 H), 3.65–3.56 (m, 2 H), 3.46 (qd, *J* = 9.9, 5.6 Hz, 2 H), 3.33 (quin, *J* = 5.8 Hz, 1 H), 2.78 (br. s, 1 H), 1.97 (q, *J* = 6.0 Hz, 2 H), 1.82–1.58 (m, 4 H), 1.51 (s, 3 H), 1.50–1.43 (m, 2 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.33–1.22 (m, 22 H), 0.88 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.96, 138.09, 131.29, 129.23, 128.39, 127.76, 113.65, 109.40, 85.62, 82.36, 78.66, 78.09, 74.57, 72.46, 71.81, 70.32, 69.29, 67.41, 66.72, 63.97, 55.23, 33.87, 33.81, 32.03, 30.71, 30.02, 29.85, 29.62, 29.56, 27.93, 26.72, 26.10, 25.99, 25.37, 25.02, 22.63, 14.05 ppm. HRMS (ESI): calcd. for $C_{48}H_{74}O_9Na$ $[M + Na]^+$ 817.5231; found 817.5229.

(3*R*,4*S*)-1-{[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methoxy}-6-{(4*R*,5*S*)-5-[(*R*)-11-hydroxyhexadecyl]-2,2-dimethyl-1,3-dioxolan-4-yl}hexane-3,4-diol (40): A stirred solution of alcohol **39** (38 mg, 0.048 mmol) in anhydrous ethyl acetate (2 mL) was treated with Pd/C (10 %; 7.6 mg, 20 % w/w), and the mixture was hydrogenated using a hydrogen-filled balloon at room temperature for 24 h. After this time, TLC (30 % EtOAc/hexane) indicated the complete consumption of alcohol **39**. The reaction mixture was filtered through a Celite plug, which was then washed with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 4 % MeOH/$CHCl_3$) to give triol **40** (26 mg, 0.044 mmol, 91 %) as a colourless oil. R_f = 0.35 (SiO_2, 8 % MeOH/$CHCl_3$). $[\alpha]_D^{25}$ = +2.0 (*c* = 0.95, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3404, 2926, 2856, 1695, 1515, 1460, 1373, 1247, 1215, 1057, 850 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.30–4.23 (m, 1 H), 4.08–4.01 (m, 3 H), 3.81–3.74 (m, 2 H), 3.73–3.67 (m, 2 H), 3.67–3.61 (m, 1 H), 3.60–3.56 (m, 1 H), 3.53 (d, *J* = 4.9 Hz, 1 H), 3.53 (d, *J* = 5.5 Hz, 1 H), 3.30 (br. s, 1 H), 2.67 (br. s, 1 H), 1.92–1.64 (m, 6 H), 1.55–1.39 (m, 14 H), 1.36 (s, 3 H), 1.33 (s, 3 H), 1.32–1.23 (m, 20 H), 0.89 (t, *J* = 7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.52, 107.37, 78.37, 78.11, 74.55, 74.09, 74.03, 71.98, 71.98, 70.44, 66.32, 37.44, 37.41, 31.88, 30.33, 29.66, 29.61, 29.56, 29.50, 29.43, 29.05, 28.55, 26.66, 26.42, 26.22, 25.90, 25.62, 25.30, 25.25, 22.62, 14.03 ppm. HRMS (ESI): calcd. for $C_{33}H_{64}O_8Na$ $[M + Na]^+$ 611.4499; found 611.4501.

(*R*)-16-((4*R*,5*R*)-5-{2-[(4*R*,5*R*)-5-(2-{[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methoxy}ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}-2,2-dimethyl-1,3-dioxolan-4-yl)hexadecan-6-ol (41a): Following the same synthetic procedure as reported for the synthesis of compound **21**, the above triol **40** (20 mg, 0.034 mmol) was transformed to the corresponding compound **41a**. Purification by silica gel column chromatography (SiO_2, 100–200 mesh, 18 % EtOAc/hexane) gave **41a** (20 mg, 0.032 mmol, 94 %) as a colourless oil. R_f = 0.3 (SiO_2, 30 % EtOAc/hexane). $[\alpha]_D^{25}$ = +14.90 (*c* = 1.0, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3506, 2985, 2927, 2857, 1712, 1460, 1374, 1247, 1216, 1164, 1085, 1045, 873, 848 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.26 (quin, *J* = 6.0 Hz, 1 H), 4.19 (dt, *J* = 10.3, 5.5 Hz, 1 H), 4.11–3.98 (m, 4 H), 3.74 (dd, *J* = 8.2, 6.4 Hz, 1 H), 3.67–3.56 (m, 3 H), 3.54 (dd, *J* = 9.9, 5.5 Hz, 1 H), 3.45 (dd, *J* = 9.9, 5.6 Hz, 1 H), 1.79–1.56 (m, 5 H), 1.48 (m, 1 H), 1.42 (s, 12 H), 1.36 (s, 3 H), 1.35–1.24 (m, 31 H), 0.89 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 109.35, 107.60, 107.37, 78.29, 78.18, 78.07, 74.81, 74.60, 72.01, 71.91, 68.67, 66.83, 37.46, 37.42, 36.61, 31.90, 30.15, 29.68, 29.59, 29.55, 29.51, 28.63, 28.57, 27.14, 27.05, 26.74, 26.32, 25.93, 25.90, 25.63, 25.39, 25.31, 24.67, 22.63, 14.03 ppm. HRMS (ESI): calcd. for $C_{36}H_{68}O_8Na$ $[M + Na]^+$ 651.4812; found 651.4810.

(*R*)-16-((4*R*,5*R*)-5-{2-[(4*R*,5*R*)-5-(2-{[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methoxy}ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]ethyl}-2,2-dimethyl-1,3-dioxolan-4-yl)hexadecan-6-yl Acetate (41): Following the same experimental procedure for acetylation as reported for the synthesis of compound **3**, compound **41a** (15 mg, 0.024 mmol) was converted into the corresponding acetylated triacetonide. Purification by silica gel column chromatography (SiO_2, 100–200 mesh, 16 % EtOAc/hexane) gave compound **41** (15.2 mg, 0.023 mmol, 95 %) as a colourless oil. R_f = 0.35 (SiO_2, 30 % EtOAc/hexane). $[\alpha]_D^{25}$ = +7.21 (*c* = 0.69, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 2928, 2858, 1737, 1460, 1374, 1245, 1086, 1032, 871 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.86 (quin, *J* = 6.3 Hz, 1 H), 4.26 (quin, *J* = 6.0 Hz, 1 H), 4.19 (ddd, *J* = 9.7, 5.5, 4.7 Hz, 1 H), 4.10–3.99 (m, 4 H), 3.74 (dd, *J* = 8.2, 6.4 Hz, 1 H), 3.67–3.57 (m, 2 H), 3.54 (dd, *J* = 9.9, 5.6 Hz, 1 H), 3.46 (dd, *J* = 9.9, 5.6 Hz, 1 H), 2.04 (s, 3 H), 1.79–1.60 (m, 5 H), 1.56–1.44 (m, 6 H), 1.42 (s, 9 H), 1.39 (m, 1 H), 1.36 (s, 3 H), 1.33 (s, 6 H), 1.32–1.21 (m, 22 H), 0.88 (t, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 170.99, 109.42, 107.67, 107.44, 78.38, 78.27, 78.14, 74.89, 74.69, 74.51, 72.00, 68.76, 66.93, 34.18, 34.13, 31.78, 30.24, 29.80, 29.76, 29.61, 28.71, 28.66, 27.24, 27.14, 26.83, 26.42, 26.00, 25.98, 25.48, 25.38, 25.03, 22.60, 21.36, 14.06 ppm. HRMS (ESI): calcd. for $C_{38}H_{70}O_9Na$ $[M + Na]^+$ 693.4918; found 693.4913.

Mycalol (2): A stirred solution of triacetonide **41** (6 mg, 0.0089 mmol) in THF (1.8 mL) was treated with HCl (1 N aq.; 0.6 mL) at 0 °C. The solution was warmed to room temperature and stirred for 5 h. After this time, the THF was evaporated from the reaction mixture under reduced pressure, and the water was evaporated by lyophilization. The crude material was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 12 % MeOH/$CHCl_3$) to give mycalol (**2**; 4.0 mg, 0.0073 mmol, 82 %) as a colourless semisolid. R_f = 0.35 (SiO_2, 20 % MeOH/$CHCl_3$). $[\alpha]_D^{25}$ = +4.28 (*c* = 0.20, MeOH). IR (neat): $\tilde{\nu}$ = 3392, 3286, 2921, 2854, 1737, 1516, 1464, 1244, 1056 cm^{-1}. ^{1}H NMR (700 MHz, C_5D_5N): δ = 5.07 (m, 1 H), 4.36 (m, 1 H), 4.19 (m, 1 H), 4.14–4.10 (m, 1 H), 4.10–4.03 (m, 3 H), 4.03–3.95 (m, 3 H), 3.91 (dd, *J* = 9.6, 4.9 Hz, 1 H), 3.85 (dd, *J* = 9.6, 6.1 Hz, 1 H), 2.59 (br. d, *J* = 7.5 Hz, 2 H), 2.40 (m, 1 H), 2.18–2.10 (m, 3 H), 2.08 (s, 3 H), 1.99 (m, 1 H), 1.91–1.82 (m, 2 H), 1.63–1.48 (m, 5 H), 1.42–1.26 (m, 8 H), 1.26–1.16 (m, 12 H), 0.82 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (175 MHz, C_5D_5N): δ = 170.70, 75.98, 76.96, 75.26, 74.27, 73.77, 72.97, 72.02, 69.68, 64.76, 34.54, 34.47, 33.67, 33.63, 31.92, 30.72, 30.45, 30.35, 30.11, 29.97, 29.86, 29.84, 26.79, 25.75, 25.35, 22.80, 21.16, 14.16 ppm. HRMS (ESI): calcd. for $C_{29}H_{58}O_9Na$ $[M + Na]^+$ 573.3979; found 573.3987.

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