EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Total Synthesis of Anticancer Marine Natural Product Mycalol

Authors: Kalikinidi Nageswara Rao, Katragunta Kumar, and Subhash Ghosh

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201701562

Link to VoR: http://dx.doi.org/10.1002/ejoc.201701562

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201701562

WILEY-VCH

Total Synthesis of Anticancer Marine Natural Product Mycalol

K. Nageswara Rao,[a] Katragunta Kumar,[b] and Subhash Ghosh*[a]

Abstract: This communication describes the synthetic study of the proposed structure of mycalol (**1**) and the total synthesis of the actual structure of anticancer marine natural product mycalol (**2**). The total synthesis of the proposed structure of mycalol (**1**) was targeted via late stage asymmetric dihydroxylation, which ended up with inseparable mixture of diastereomers. Thus a new strategy has been developed for the total synthesis of the revised structure of mycalol (**2**), where all the stereocenters, except the C2′-OH have been created via asymmetric fashion by utilizing Maruoka allylation, Noyori asymmetric reduction and asymmetric alkynylation.

Introduction

Marine organisms have produced a large number of potent anticancer compounds and many of them are either in clinical development or in 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 the marine sponge by Fontana and co-workers 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 study. In 2015, Reddy et al. developed an elegant strategy for the synthesis of the proposed structure of mycalol (**1**) by utilizing Sharpless asymmetric kinetic resolution, Jacobsen kinetic resolution and cross-metathesis reaction as key steps and found the structure proposed by Fontana et al. is incorrect. Subsequently, they hypothesized the correct structure could be **2** (Figure 1) based on detailed NMR data comparison and confirmed the same via its total synthesis.[3] Subsequently, Goswami et al. reported the synthesis of the proposed structure of mycalol and several of its analogs by using L-arabinose as a chiral pool material and confirmed the structural revision reported by Reddy et al.[4] Very recently Reddy et al. also synthesized several analogs of mycalol (**2**) and tested their anticancer activity against human derived ATC cell lines.[5]

[a] K. Nageswara Rao, Subhash Ghosh*
Organic and Biomolecular Chemistry Division
CSIR-Indian Institute of Chemical Technology
Hyderabad 500007, India
E-mail: subhash@iict.res.in
[b] Katragunta Kumar
Division of Natural Products Chemistry
CSIR-Indian Institute of Chemical Technology
Hyderabad 500007, India

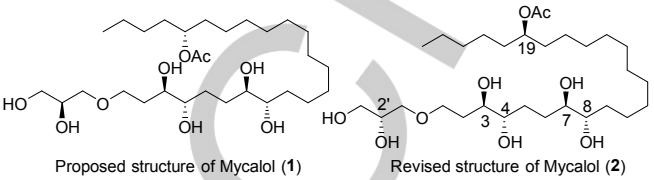
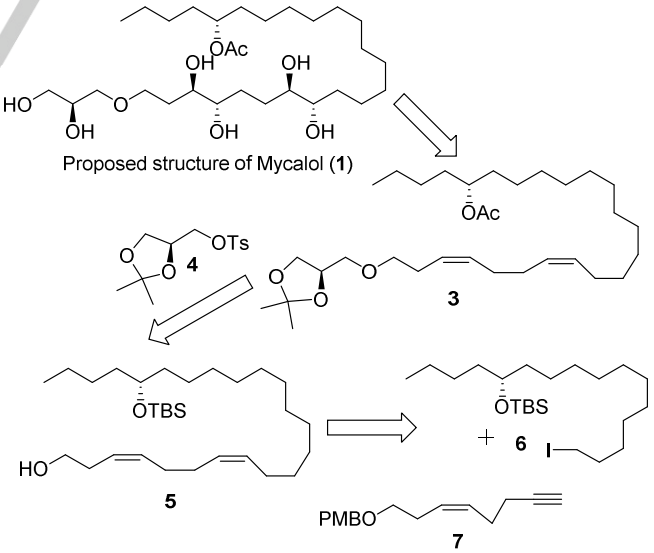


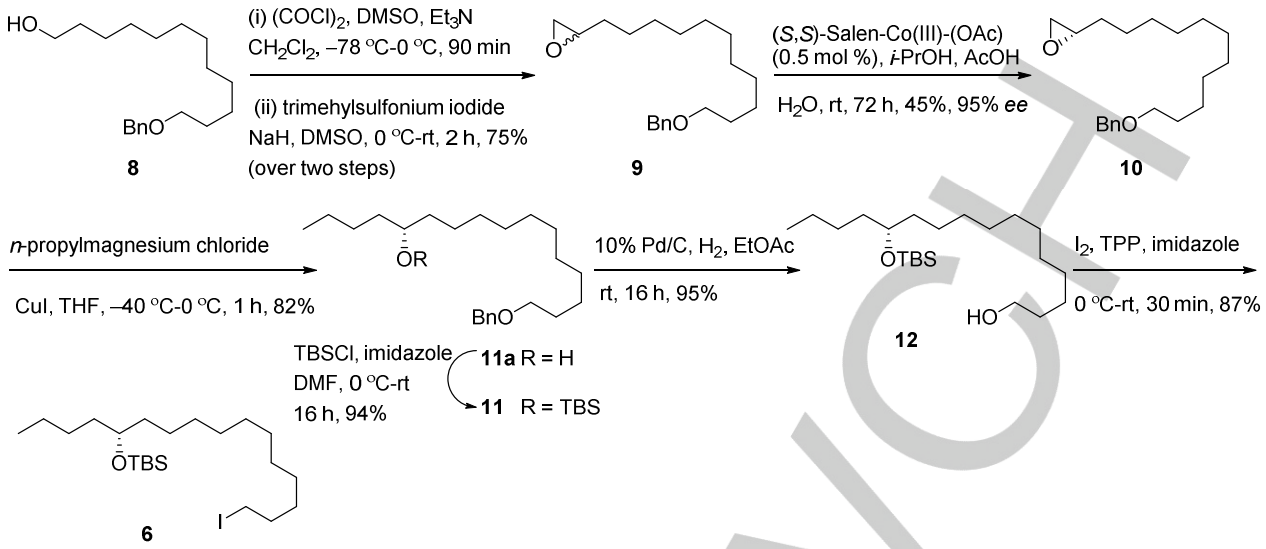
Figure 1: Proposed and revised structures of mycalol

Results and discussion

Because of the interesting structure and biological activity of mycalol, we also became interested to develop a synthetic strategy for the proposed structure of mycalol (**1**) after its immediate isolation, via a late stage asymmetric dihydroxylation as a key step (Scheme 1). The precursor **3** for asymmetric dihydroxylation was planned to obtain from compound **5** by alkylation with **4** followed by protecting group manipulation. We thought the diene compound **5** might be obtained by means of alkylation of alkyne **7** with the iodide **6** followed by *cis* selective reduction of alkyne functionality and oxidative removal of PMB group.



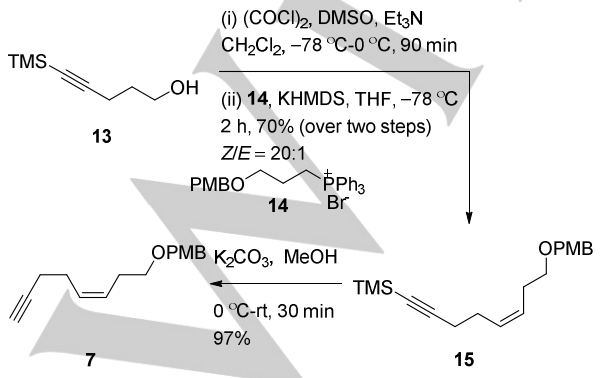
Scheme 1. Retrosynthetic analysis of the proposed structure of mycalol (**1**)



Scheme 2. Synthesis of iodide **6**

Thus as per the plan, the synthesis of iodide **6** commenced from known alcohol **8**[6], which on oxidation under Swern conditions followed by Corey-Chaykovsky reaction[7] furnished racemic epoxide **9** in good overall yield 75% (Scheme 2). Hydrolytic kinetic resolution of the terminal epoxide **9** under Jacobsen conditions[8] provided enantiomerically pure epoxide **10** (95% *ee*) in 45% yield. The epoxide **10** was opened with propylmagnesium chloride in presence of catalytic amount of CuI to afford an alcohol **11a** in 82% yield.[9] Protection of the hydroxyl group of **11a** as its TBS ether followed by debenzylation via hydrogenolysis (H_2, 10% Pd/C) furnished alcohol **12** in 89% over two steps. Finally, alcohol **12** on treatment with TPP and iodine gave the iodo compound **6** in 87% yield.[10]

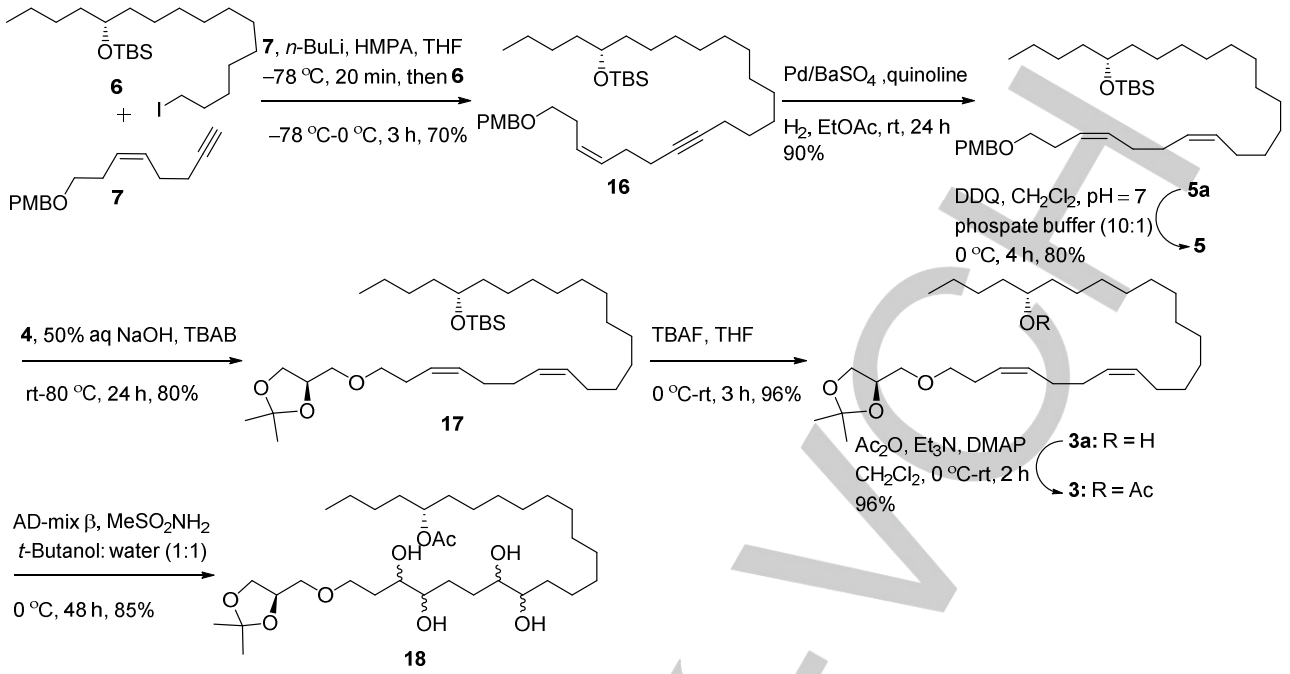
The synthesis of alkyne **7** is depicted in Scheme **3**. Oxidation of the known alcohol **13**[11] under Swern conditions gave an aldehyde, which on reaction with ylide generated from known phosphoniumbromide **14**[12a,b] with KHMDS afforded desired *Z*-olefin **15** in 70% yield over two steps (*Z*/*E*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



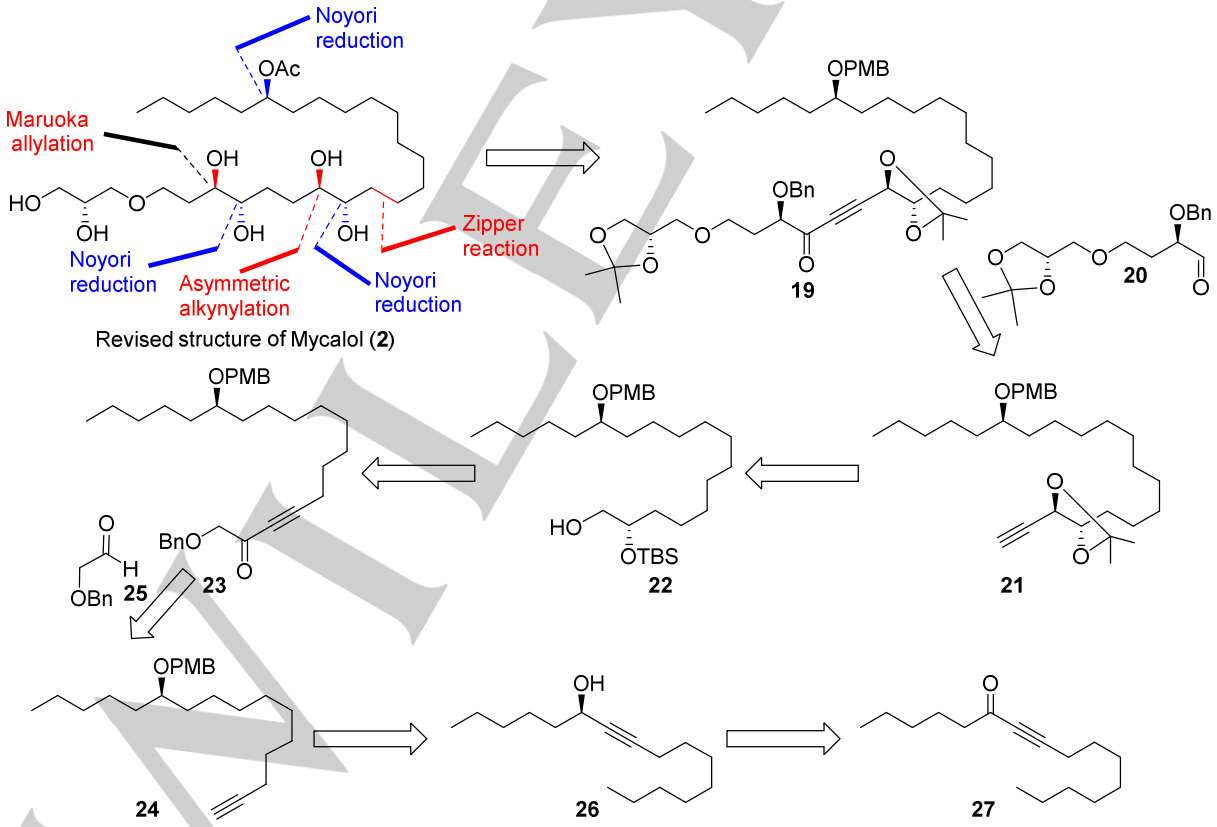
Scheme 3. Synthesis of alkyne **7**

The final strategy for the completion of the synthesis of the proposed structure of mycalol (**1**) is depicted in scheme **4**. Alkylation of the alkyne **7** with the iodide **6** in presence of *n*-BuLi and HMPA went smoothly to furnish compound **16** in good yield (70%).[14] Partial reduction of the alkyne functionality of **16** under Lindlar hydrogenation conditions[15] ($Pd/BaSO_4$, quinoline), subsequently oxidative removal of PMB group with DDQ furnished alcohol **5** in 72% yield over two steps. Williamson type etherification[16] between alcohol **5** and tosyl derivative of (*R*)-Solketal **4**[17] was performed in presence of 50% aqueous NaOH and TBAB to give compound **17** in 80% yield. Deprotection of TBS group from **17** was carried out with TBAF to obtain an alcohol **3a**, which on acetylation with Ac_2O in presence of Et_3N, DMAP afforded compound **3** in 92% yield over two steps. Now the stage was set for crucial dihydroxylation with AD-mix β to complete the synthesis. However, dihydroxylation of the 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 for the synthesis of the proposed structure of mycalol (**1**). However by this time the structure of mycalol was revised by Reddy et al. Therefore we planned to device a new strategy for the revised structure of mycalol (**2**).

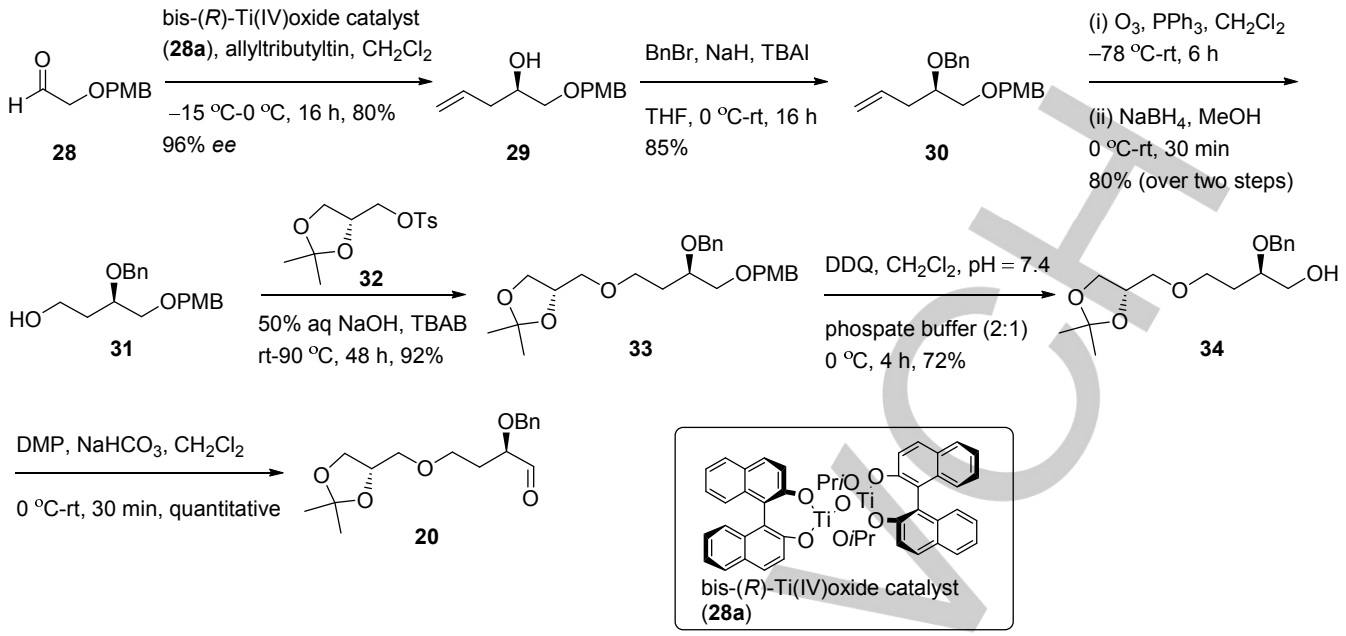
In the new strategy, we planned to generate all the stereo centers except the C2' center via catalytic way so that structural and stereochemical analogs of mycalol (**2**) can be generated easily. Thus retrosynthetically mycalol (**2**) could be synthesized from ynone **19** via asymmetric reduction followed by functional group manipulations (Scheme 5). The ynone **19** could be obtained by the addition of alkyne **21** to the aldehyde **20** followed by oxidation. Alkyne **21** would be obtained from alcohol **22** via oxidation followed by asymmetric alkynylation and then protecting group manipulations. Compound **22** might be obtained through the Noyori asymmetric reduction of ynone **23** followed by functional group manipulation. Ynone **23** could be



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



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



Scheme 6. Synthesis of aldehyde **20**

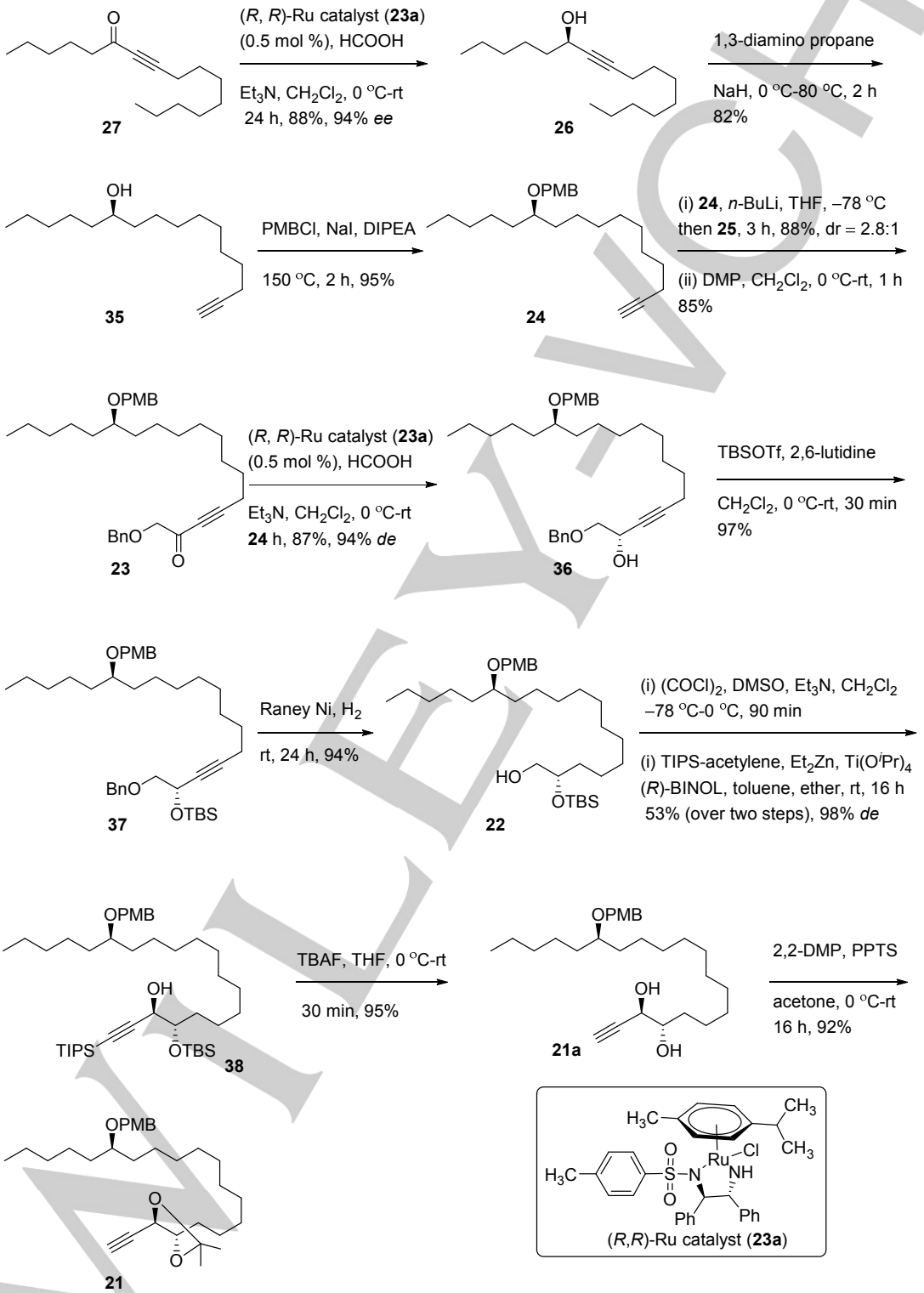
accessed via the addition of the alkyne **24** to the aldehyde **25** followed by oxidation of the resulting propargylic alcohol. The terminal alkyne **24** would be obtained from the propargylic alcohol **26** through alkyne Zipper reaction. Finally, the propargylic alcohol **26** could be obtained from ynone **27** by asymmetric reduction.

Thus the synthesis of the actual structure of mycalol (**2**) commenced with the asymmetric allylation of the 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 the alcohol **29** as its benzyl ether followed by ozonolysis[21] of the olefin furnished an aldehyde, that on reduction with $NaBH_4$ produced the alcohol **31** in 68% yield over three steps. Etherification of the alcohol **31** with the tosyl derivative of (*S*)-Solketal **32**[22] in presence of 50% aqueous NaOH and TBAB afforded compound **33** in 92% yield. Oxidative removal of PMB group from **33** was carried out with DDQ[23] to afford alcohol **34** in 72% yield. Finally, oxidation of the alcohol **34** with DMP[24] afforded aldehyde **20** in quantitative yield.

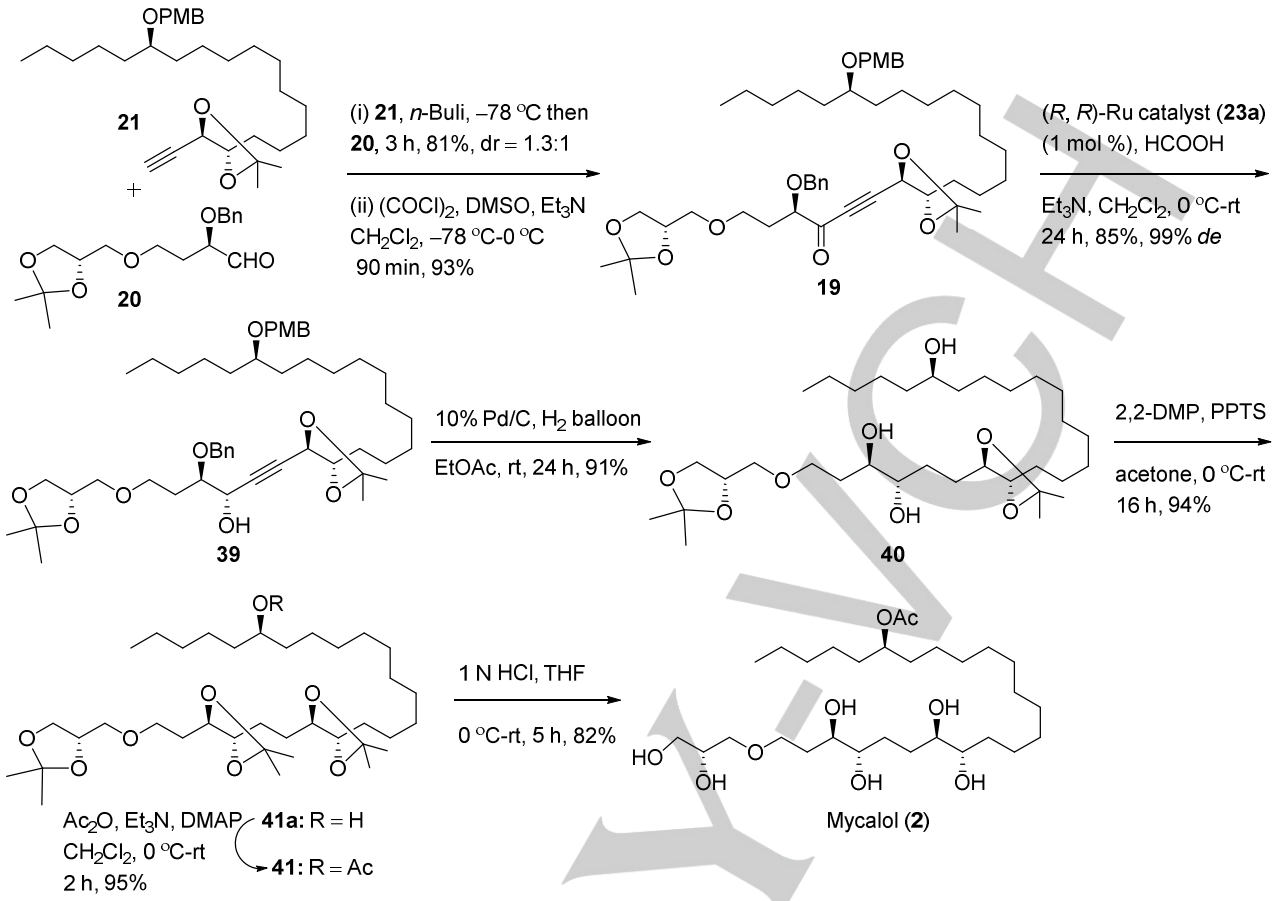
Synthesis of alkyne **21** was eventually begun from known ynone **27**[25] (Scheme 7). The keto moiety of **27** was reduced with (*R*,*R*)-Ru catalyst **23a**[26] in presence of HCOOH/Et_3N to obtain enantiomerically pure alcohol **26** (94% *ee* by Mosher ester analysis) in 88% yield and the configuration of **26** was confirmed by Mosher ester analysis. Internal triple bond of **26** was transferred to the terminal position through Zipper reaction with 1,3-diaminopropane and NaH to get compound **35** in 82% yield.[27] The hydroxyl group of **35** was protected as PMB ether with PMBCl/NaI/DIPEA to afford compound **24** in 95% yield.[28] The addition of the anion generated from compound **24** with *n*-BuLi on known aldehyde **25**[29] afforded an inseparable mixture of diastereomeric alcohols, (*dr* = 2.8:1) that on oxidation with DMP provided ynone **23** in 75% yield over two steps. The ynone **23** was subjected to Noyori reduction with (*R*,*R*)-Ru catalyst (**23a**) in presence of HCOOH/Et_3N to give alcohol **36** in 87% yield (94% *de*). The free hydroxyl group of **36** was protected as TBS ether with TBSOTf/2,6-lutidine to afford compound **37** in 97% yield. Selective removal of benzyl group and reduction of triple bond of compound **37** was carried out with Raney Ni/H_2 to obtain alcohol **22** in 94% yield.[30] Alcohol **22** was oxidized under Swern conditions to give an aldehyde that on treatment with TMS-acetylene in presence of (*R*)-BINOL/Ti(O^iPr)$_4$, provided required compound in poor yield (10%).[31a] However reaction of the aldehyde with TIPS-acetylene in presence of (*R*)-BINOL/Ti(O^iPr)$_4$ afforded highly diastereomerically pure compound **38** in 53% yield over two steps (98% *de*).[31b] Deprotection of both TIPS and TBS groups from compound **38** was carried out with TBAF to obtain a diol compound **21a** which on acetonide protection with 2,2-DMP in presence of PPTS afforded alkyne **21** in 87% yield over two steps.

The remaining part of the synthesis is depicted in Scheme 8. The addition of the anion generated from alkyne **21** on aldehyde **20** afforded an inseparable mixture of diastereomers (*dr* = 1.3:1) which was oxidized under Swern conditions to give ynone **19** in 75% yield over two steps. The keto functionality of **19** was reduced with (*R*,*R*)-Ru catalyst (**23a**) in presence of HCOOH/Et_3N to afford diastereomerically pure alcohol **39** in 85% yield (99% *de*). Alcohol **39** was subjected to hydrogenation with H_2 filled balloon in presence of 10% Pd/C to afford triol **40** in 91% yield. Acetonide protection of triol **40** with 2,2-DMP in presence of PPTS followed by acetylation of the C19-OH with Ac_2O in presence of DMAP/Et_3N afforded triacetonide **41** in 89% yield over two steps. Finally, global deprotection of triacetonide **41** was carried out with 1 N HCl to complete the

synthesis of mycalol (**2**) in 82% yield. Whose spectral and analytical data {$[\alpha]_D^{25}$ = +3.45 (*c* 0.10, MeOH) for Natural mycalol, and $[\alpha]_D^{25}$ = +4.28 (*c* 0.20, MeOH) for synthetic Mycalol (**2**)} were in good agreement with the data reported in the literature



Scheme 7. Synthesis of the alkyne **21**



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

Conclusions

In conclusion, the total synthesis of the proposed structure of mycalol (**1**) was targeted via a late stage asymmetric dihydroxylation, which ended up with an inseparable mixture of diastereomers. That forced us to modify the strategy for the synthesis of the actual structure of the natural product by utilizing Noyori asymmetric reduction, Zipper reaction, asymmetric alkynylation, Maruoka allylation and Williamson type etherification. With the modified strategy the total synthesis of natural mycalol (**2**) was achieved in **26** steps (**19** longest linear sequences) from the known compound **27**, with an overall yield of 8.04%). The strategy developed here is quite different from the strategy developed by Reddy et al (12 longest linear sequences, overall yield 2.3%) and Goswami et al (16 longest linear sequences, overall yield 11.1%). Both the cases chiral pool materials were used extensively for getting the stereo centers present in the molecule. Whereas, in the present case most of the stereo centers has been generated via asymmetric reactions. The strategy is highly convergent, and can be used for the synthesis of structural and stereochemical analogs of the molecule.

Experimental section

General information: Under inert atmosphere (nitrogen or argon) all the air and moisture sensitive reactions were carried out in an oven-dried glass apparatus. Yields refer to chromatographically and spectroscopically unless otherwise stated. Anhydrous tetrahydrofuran (THF) and diethyl ether (Et_2O) were prepared via distillation over sodium/benzophenone. Toluene was distilled over sodium wire prior to use. Triethylamine (Et_3N), dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), dichloromethane (CH_2Cl_2) and hexamethylphosphoramide (HMPA) were distilled from CaH_2 prior to use. Acetic anhydride (Ac_2O) was distilled from P_2O_5 to make free from acetic acid and acetone was distilled from $KMnO_4$. Triphenylphosphine (PPh_3) was recrystallized from hexane. Commercially available reagents were used without further purification unless otherwise stated. Purification of compounds was carried out via column chromatography by using silica gel (100-200 mesh) packed in glass columns. ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$, and C_5D_5N solvents on 300 MHz, 400 MHz, 500 MHz, 700 MHz and 75 MHz, 100 MHz, 125 MHz, 175 MHz spectrometer respectively, using TMS as an internal standard. Chemical shifts are measured as ppm values relative to internal $CHCl_3$ δ 7.26 or TMS δ 0.0 or C_5D_5N δ 7.19, for ^1H NMR and $CDCl_3$ δ 77.0, C_5D_5N δ 123.50 for ^{13}C NMR. In ^1H NMR multiplicity defined as: s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet, dd = doublet of doublet; ddd = doublet of doublet of doublet; dddd = doublet of doublet of doublet of doublet; dt = doublet of triplet; td = triplet of doublet; qd = quartet of doublet; ddt = doublet of doublet of triplet; dtd = doublet of triplet of doublet; tdd = triplet of doublet of doublet; dtd = doublet of triplet of doublet; m = multiplet; brs = broad singlet; bd = board doublet. Optical rotation values were recorded on Horiba sepa 300 polarimeter using a 2 mL cell with a 10 mm path length. FTIR spectra were recorded on Alpha (Bruker) infrared spectrophotometer. High resolution mass spectra (HRMS) [ESI+] were

obtained using either a TOF or a double focusing spectrometer. **Abbreviations:** KHMDS = Potassium bis(trimethylsilyl)amide; DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzo quinone; DMP = Dess-Martin periodinane; DMAP = 4-(Dimethylamino) pyridine; TBAI = Tetra butylammonium iodide; TBAB = Tetrabutylammonium bromide; TBAF = Tetrabutylammonium fluoride; DIPEA = *N*,*N*-diisopropylethylamine; PPTS = Pyridinium *p*-toluenesulfonate; PMBCl = 4-Methoxybenzyl chloride; 2,2-DMP = 2,2-dimethoxypropane.

2-(11-(Benzyloxy)undecyl)oxirane (9): To a stirred solution of oxalyl chloride (3.14 mL, 35.90 mmol) in anhydrous CH_2Cl_2 (70 mL) was added anhydrous DMSO (5.45 mL, 76.58 mmol) drop wise over a period of 5 min at –78 °C and stirred for 15 min. To the reaction mixture alcohol **8** (7.0 g, 23.93 mmol) in anhydrous CH_2Cl_2 (70 mL) was added at –78 °C and stirred for 45 min. To the reaction mixture was added Et_3N (16.65 mL, 119.65 mmol) at –78 °C and the solution was warmed to 0 °C and stirred for 30 min. At which time, the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and 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 over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 20% EtOAc/hexane) to afford aldehyde (6.65 g, 22.90 mmol) as a colourless oil. R_f = 0.7 (SiO_2, 30% EtOAc/hexane). The obtained aldehyde was used immediately in the next step without further characterization. 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 and the solution was slowly warmed to room temperature and stirred for 15 min. To this solution aldehyde (6.65 g, 22.90 mmol) in anhydrous THF (49 mL) was cannulated at room temperature and stirred for 2 h. After which time, TLC (10% EtOAc/hexane) indicated the complete consumption of aldehyde. The reaction was quenched with saturated aqueous NH_4Cl (40 mL) at 0 °C and 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) three times. The combined organic extracts were washed with water (50 mL) and brine (50 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 3% EtOAc/hexane) to afford 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): ν_{max} 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, 5H), 4.50 (s, 2H), 3.46 (t, J = 6.8 Hz, 2H), 2.94-2.87 (m, 1H), 2.77-2.72 (m, 1H), 2.46 (dd, J = 5.3, 3.0 Hz, 1H), 1.67-1.21 (m, 20H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{20}H_{32}O_2Na$ 327.2300, found 327.2292.

(*S*)-2-(11-(Benzyloxy)undecyl)oxirane (10): To 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) was added acetic acid (7.3 µL, 0.128 mmol) at room temperature and stirred under open atmosphere for 1 h. During this time the solution colour changed to dark red. After which time, the solvent was evaporated under reduced pressure and the formed catalyst (*S*,*S*)-Salen-Co(III)-(OAc) was dried in high vacuum for 1 h to make catalyst free from acetic acid. The catalyst was treated with racemic epoxide **9** (3.9 g, 12.81 mmol) in isopropanol (0.5 mL) at 0 °C. To the solution water (231 µL, 12.81 mmol) was added portion wise over a period of 1 h and stirred at room temperature for 72 h. The reaction mixture was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 3% EtOAc/hexane) to afford 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): ν_{max} 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, 5H), 4.50 (s, 2H), 3.46 (t, J = 6.8 Hz, 2H), 2.94-2.87 (m, 1H), 2.77-2.72 (m, 1H), 2.46 (dd, J = 5.3, 3.0 Hz, 1H), 1.67-1.21 (m, 20H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{20}H_{32}O_2Na$ 327.2300, found 327.2295.

(*R*)-16-(Benzyloxy)hexadecan-5-ol (11a): To a stirred solution of epoxide **10** (1.73, 5.68 mmol) in anhydrous THF (17 mL) was added CuI (108 mg, 0.568 mmol) followed by *n*-propylmagnesium chloride (2 M ether solution, 7.1 mL, 14.2 mmol) at –40 °C and stirred for 1 h. After which time, the solution was warmed to 0 °C and quenched with saturated aqueous NH_4Cl (30 mL) and stirred for 30 min and 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) three times. The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 10% EtOAc/hexane) to afford 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): ν_{max} 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, 5H), 4.50 (s, 2H), 3.63-3.53 (m, 1H), 3.46 (t, J = 6.7 Hz, 2H), 1.67-1.55 (m, 3H), 1.51-1.20 (m, 23H), 0.91 (t, J = 6.9 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{23}H_{40}O_2Na$ 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 stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) at 0 °C and diluted with ether (40 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 30 mL) two times. The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 3% EtOAc/hexane) to provide 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): ν_{max} 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, 5H), 4.50 (s, 2H), 3.61 (quin, J = 5.5 Hz, 1H), 3.46 (t, J = 6.4 Hz, 3H), 1.68-1.55 (m, 3H), 1.47-1.18 (m, 22H), 0.94-0.84 (m, 12H), 0.04 (s, 6H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{29}H_{54}O_2SiNa$ 485.3791, found 485.3777.

(*R*)-12-((*tert*-Butyldimethylsilyl)oxy)hexadecan-1-ol (12): A stirred solution of above TBS-protected compound **11** (1.95 g, 4.21 mmol) in anhydrous ethyl acetate (20 mL) was treated with 10% Pd/C (390 mg, 20% w/w) and hydrogenated by using hydrogen filled balloon at room temperature for 16 h. The reaction mixture was filtered through celite plug and washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 14% EtOAc/hexane) to afford 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): ν_{max} 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, 3H), 1.57 (quin, 6.7 Hz, 2H), 1.49-1.20 (m, 24H), 0.94-0.85 (m, 12H), 0.04 (s, 6H); ^{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; HRMS (ESI): [M + Na]$^+$ calcd. for $C_{22}H_{48}O_2SiNa$ 395.3321, found 395.3304.

(*R*)-*tert*-Butyl((16-iodohexadecan-5-yl)oxy)dimethyl silane (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 solution was warmed to room temperature and stirred for 10 min. To the solution, alcohol **12** (1.0 g, 2.68 mmol) in anhydrous CH_2Cl_2 (6 mL) was cannulated at room temperature and stirred for 30 min. The reaction was quenched with saturated aqueous hypo (20 mL) at 0 °C and diluted with water (20 mL), CH_2Cl_2 (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) three times. The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 2% EtOAc/hexane) to obtain iodide **6** (1.13 g, 2.34 mmol, 87%) as a colourless oil (R_f = 0.7 (SiO_2, 5% EtOAc/hexane), which was taken for the next reaction without further characterization.

(*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 aldehyde (1.85 g) as a colourless oil. Rf = 0.7 (SiO_2, 30% EtOAc/hexane). A stirred solution of phosphoniumbromide **14** (12.5 g, 23.98 mmol) in anhydrous THF (20 mL) was treated with KHMDS (0.5 M toluene solution, 45.56 mL, 22.78 mmol) at –78 °C and stirred at this temperature for 20 min. To the solution, the above aldehyde (1.85 g, 11.99 mmol) in anhydrous THF (12 mL) was cannulated at –78 °C and stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl (40 mL) at 0 °C and 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) three times. The combined organic extracts were washed with water (40 mL) and brine (40 ml). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 3% EtOAc/hexane) to provide 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): ν_{max} 2956, 2925, 2855, 2174, 1713, 1609, 1513, 1248, 1171, 1095, 1037, 841, 761, 700, 640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 6.90-6.86 (m, 2H), 5.50 (dt, *J* = 11.0, 6.4 Hz, 1H), 5.47 (dt, *J* = 11.0, 6.7 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.45 (t, *J* = 7.0 Hz, 2H), 2.38 (dd, *J* = 12.8, 6.9 Hz, 2H), 2.30-2.24 (m, 4H), 0.15 (s, 9H); ^{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; HRMS (ESI): [M + Na]$^+$ calcd. for $C_{19}H_{28}O_2SiNa$ 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 and the solution was warmed to room temperature and stirred for 30 min. The reaction mixture was filtered through celite plug and the cake was washed with ethyl acetate (30 mL). The filtrate and the washings were concentrated under reduced pressure to give crude compound, which 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) three times. The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 4% EtOAc/hexane) to afford 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): ν_{max} 3295, 3009, 2856, 1692, 1609, 1512, 1458, 1360, 1302, 1245, 1173, 1091, 1033, 820, 638 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.24 (m, 2H), 6.90-6.86 (m, 2H), 5.52 (dt, *J* = 11.0, 5.9 Hz, 1H), 5.49 (dt, *J* = 11.0, 6.1 Hz, 1H), 4.45 (s, 2H), 3.80 (s, 3H), 3.46 (t, *J* = 7.0 Hz, 2H), 2.38 (m, 2H), 2.32-2.26 (m, 2H), 2.25-2.20 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H); ^{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; HRMS (ESI): [M + Na]$^+$ calcd. for $C_{16}H_{20}O_2Na$ 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 hexane solution, 1.89 mL, 3.02 mmol) at –78 °C and stirred at the same temperature for 20 min. To the reaction mixture was added anhydrous HMPA (1.05 mL, 8.58 mmol) followed by iodide **6** (500 mg, 1.04 mmol) in anhydrous THF (3 mL) at –78 °C and stirred at the same temperature for 2 h. The reaction mixture was slowly warmed to 0 °C over a period of 1 h and quenched with saturated aqueous NH_4Cl (20 mL) at 0 °C. It 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) three times. The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 2% EtOAc/hexane) to afford 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): ν_{max} 2927, 2855, 1613, 1513, 1462, 1362, 1301, 1248, 1174, 1091, 1042, 938, 833, 773, 719, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.19 (m, 2H), 6.87-6.82 (m, 2H), 5.54-5.37 (m, *J* = 11.3, 6.8 Hz, 2H), 4.41 (s, 2H), 3.77 (s, 3H), 3.61 (quin, *J* = 5.6 Hz, 1H), 3.45 (t, *J* = 7.1 Hz, 2H), 2.37 (m, 2H), 2.29-2.08 (m, 6H), 1.53-1.20 (m, 26H), 0.95-0.83 (m, 12H), 0.04 (s, 6H); ^{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; HRMS (ESI): [M + Na]$^+$ calcd. for $C_{38}H_{66}O_3SiNa$ 621.4679, found 621.4703.

***tert*-Butyl(((*R*,17*Z*,21*Z*)-24-((4-methoxybenzyl)oxy)tetra cosa-17,21-dien-5-yl)oxy) dimethyl silane (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) and hydrogenated by using H_2 filled balloon at room temperature for 24 h. Then the reaction mixture was filtered through celite plug and washed with ethyl acetate (30 mL). The filtrate and the washings were concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 2% EtOAc/hexane) to obtain 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): ν_{max} 2926, 2854, 1613, 1513, 1463, 1249, 1092, 1042, 833, 733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.23 (m, 2H), 6.91-6.84 (m, 2H), 5.51-5.32 (m, 4H), 4.45 (s, 2H), 3.80 (s, 3H), 3.61 (m, 1H), 3.45 (t, *J* = 7.0 Hz, 2H), 2.36 (m, 2H), 2.14-1.96 (m, 6H), 1.46-1.20 (m, 26H), 0.94-0.85 (m, 12H), 0.04 (s, 6H); ^{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; HRMS (ESI): [M + Na]$^+$ calcd. for $C_{38}H_{68}O_3SiNa$ 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 compound **5a** (215 mg, 0.36 mmol) in a mixture of solvents CH_2Cl_2 and pH = 7 phosphate buffer (3 mL, 10:1) was treated with DDQ (204 mg, 0.90 mmol) at 0 °C and the solution was warmed to room temperature and stirred for 4 h. After which time, the reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) at 0 °C and 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) three times. 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 over anhydrous sodium sulphate and filtered. The filtrate

was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 5% EtOAc/hexane) to afford alcohol **5** (137 mg, 0.29 mmol, 80%) as a colourless oil. R_f = 0.25 (SiO2, 10% EtOAc/hexane); $[\alpha]_D^{25}$ = +5.62 (*c* 1.05, $CHCl_3$); IR (Neat): ν_{max} 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, 1H), 5.43-5.32 (m, 3H), 3.64 (t, *J* = 6.4 Hz, 2H), 3.60 (dd, *J* = 11.4, 5.8 Hz, 1H), 2.36-2.30 (m, 2H), 2.16-2.06 (m, 4H), 2.01 (m, 2H), 1.46-1.20 (m, 26H), 0.91-0.86 (m, 12H), 0.03 (s, 6H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{30}H_{60}O_2SiNa$ 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)oxy)dimethyl silane (17):** A solution of alcohol **5** (110 mg, 0.23 mmol) in 50% aqueous NaOH (1.1 mL, 13.8 mmol) was stirred at 80 °C for 30 min then to this solution TBAB (14.8 mg, 0.046 mmol) was added at same temperature and stirred for 30 min. The reaction mixture was cooled to room temperature and tosyl compound **4** (263 mg, 0.92 mmol) in minimum amount of diethyl ether (0.5 mL) was added and 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) and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL) three times. The combined organic extracts were washed with water (15 mL) and brine (15 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 2% EtOAc/hexane) to afford 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): ν_{max} 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, 4H), 4.27 (quin, *J* = 6.0 Hz 1H), 4.06 (dd, *J* = 8.3, 6.8 Hz, 1H), 3.73 (dd, *J* = 8.3, 6.8 Hz, 1H), 3.61 (m, 1H), 3.54 (dd, *J* = 9.8, 6.0 Hz, 2H), 3.48 (dd, *J* = 6.8, 2.3 Hz, 1H), 3.44 (m, 1H), 2.34 (q, *J* = 6.8 Hz, 2H), 2.15-1.96 (m, 6H), 1.43 (s, 3H), 1.37 (s, 3H), 1.35-1.22 (m, 26H), 0.93-0.86 (m, 12H), 0.04 (s, 6H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{36}H_{70}O_4SiNa$ 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): To a stirred solution of compound **17** (85 mg, 0.14 mmol)) in anhydrous THF (1.0 mL) was added TBAF (1 M THF solution, 0.42 mL, 0.42 mmol) at 0 °C and solution was warmed to room temperature and stirred for 3 h. After which 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) three times. The combined organic extracts were washed with water (15 mL) and brine (15 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 10% EtOAc/hexane) to afford 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): ν_{max} 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, 4H), 4.26 (quin, *J* = 6.0 Hz, 1H), 4.05 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.73 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.61-3.55 (m, 1H), 3.53 (dd, *J* = 9.8, 5.6 Hz, 1H), 3.51-3.46 (m, 2H), 3.44 (dd, *J* = 9.9, 5.6 Hz, 1H), 2.34 (qd, *J* = 7.0, 1.0 Hz, 2H), 2.12-2.04 (m, 4H), 2.01 (q, *J* = 6.7 Hz, 2H), 1.48-1.43 (m, 2H), 1.42 (s, 3H), 1.41-1.37 (m, 2H), 1.36 (s, 3H), 1.35-1.24 (m, 22H), 0.91 (t, *J* = 7.1 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{30}H_{56}O_4Na$ 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): To a stirred solution of alcohol **3a** (60 mg, 0.125 mmol) in anhydrous CH_2Cl_2 (1.0 mL) were added Et_3N (52 µL, 0.375 mmol) followed by catalytic amount of DMAP (1.5 mg, 0.0125 mmol) at 0 °C and stirred for 10 min. To the reaction mixture Ac_2O (24 µL, 0.25 mmol) was added at 0 °C and the solution was warmed to room temperature and stirred for 2 h. After which time, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) at 0 °C and diluted with water (10 mL), CH_2Cl_2 (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) three times. The combined organic extracts were washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 4% EtOAc/hexane) to afford 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): ν_{max} 2925, 2856, 1736, 1460, 1373, 1242, 1116, 1053, 847, 729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 5.51-5.30 (m, 4H), 4.86 (quin, *J* = 6.2 Hz, 1H), 4.26 (quin, *J* = 6.0 Hz, 1H), 4.05 (dd, *J* = 8.2, 6.2 Hz, 1H), 3.73 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.53 (dd, *J* = 9.8, 5.7 Hz, 1H), 3.51-3.46 (m, 2H), 3.44 (dd, *J* = 9.8, 5.5 Hz, 1H), 2.34 (qd, *J* = 7.1, 1.0 Hz, 2H), 2.12-2.07 (m, 3H), 2.04 (s, 3H), 2.03-1.99 (m, 3H), 1.54-1.47 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H), 1.35-1.22 (m, 22H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{32}H_{58}O_5Na$ 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 stirred until the solution becomes clear (5 min). Now the solution was cooled to 0 °C and treated with compound **3** (40 mg, 0.077 mmol) in minimum amount of *t*-BuOH (0.5 mL) and stirring continued at 0 °C for 48 h. After which 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 reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 × 15 mL) three times. The combined organic extracts were washed with water (10 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 3% MeOH/$CHCl_3$) to afford an inseparable mixture of diastereomers of compound **18** (39 mg, 0.066 mmol, 85%) as a pale brown semi solid. R_f = 0.3 (SiO_2, 10% MeOH/$CHCl_3$); IR (Neat): ν_{max} 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, 1H), 4.27 (quin, *J* = 5.7 Hz, 1H), 4.05 (m, 1H), 3.80-3.59 (m, 7H), 3.57-3.50 (m, 2H), 2.04 (s, 3H), 1.90-1.80 (m, 1H), 1.79-1.73 (m, 2H), 1.61-1.48 (m, 4H), 1.44 (s, 3H), 1.36 (s, 3H), 1.34-1.22 (m, 27H), 0.91-0.86 (m, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{32}H_{62}O_9Na$ 613.4292, found 613.4299.

(*R*)-1-((4-Methoxybenzyl)oxy)pent-4-en-2-ol (29): A stirred solution of $TiCl_4$ (1 M toluene solution, 0.42 mL, 0.42 mmol) in anhydrous CH_2Cl_2 (16 mL) was treated with $Ti(O^iPr)_4$ (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. To the solution, freshly prepared Ag_2O (192 mg, 0.83 mmol) was added at room temperature and stirred for additional 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 and stirring was continued for 2 h. At this point the solution was turned to brick red colour. The *in situ* generated bis-(*R*)-Ti(IV)oxide catalyst (**28a**) was cooled to –15 °C and treated with aldehyde **28** (1.5 g, 8.33 mmol) in anhydrous CH_2Cl_2 (4 mL) followed by allyltributyltin (2.81 mL, 9.16 mmol) and 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 and stirred for 30 min and filtered through celite plug and washed with CH_2Cl_2 (3 × 30 mL) three times. 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) three times. The combined organic extracts were washed with water (40 mL) and brine (40 mL) and dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 15% EtOAc/hexane) to afford 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): ν_{max} 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, 2H), 6.89 (m, 2H), 5.82 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.14-5.07 (m, 2H), 4.49 (s, 2H), 3.87 (m, 1H), 3.81 (s, 3H), 3.49 (dd, *J* = 9.4, 3.4 Hz, 1H), 3.35 (dd, *J* = 9.4, 7.5 Hz, 1H), 2.27-2.23 (m, 2H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{13}H_{18}O_3Na$ 245.1154, found 245.1154.

(*R*)-1-(((2-(Benzyloxy)pent-4-en-1-yl)oxy)methyl)-4-methoxybenzene (30): To a suspension of NaH (135 mg, 3.38 mmol) in anhydrous THF (3.5 mL) was cannulated alcohol **29** (500 mg, 2.25 mmol) in anhydrous THF (3.5 mL) at 0 °C and the resulting solution was warmed to room temperature and stirred for 30 min. To this solution, benzyl bromide (0.4 mL, 3.38 mmol) followed by TBAI (83 mg, 0.225 mmol) were added at 0 °C and the solution was warmed to room temperature and stirred for 16 h. After which 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 diluted with water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 30 mL) three times. The combined organic phases were washed with water (40 mL) and brine (40 mL) and dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 4% EtOAc/hexane) to afford 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): ν_{max} 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, 7H), 6.90-6.84 (m, 2H), 5.83 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.13-5.01 (m, 2H), 4.65 (d, *J* = 11.8 Hz, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 4.48 (s, 2H), 3.81 (s, 3H), 3.65 (quin, *J* = 5.6 Hz,1H), 3.53 (dd, *J* = 5.2, 0.6 Hz, 2H), 2.39-2.32 (m, 2H); ^{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; HRMS (ESI): $[M + Na]^+$calcd. for $C_{20}H_{24}O_3Na$ 335.1623, found 335.1627.

(*R*)-3-(Benzyloxy)-4-((4-methoxybenzyl)oxy)butan-1-ol (31): Ozone was purged to a solution of compound **30** (550 mg, 1.76 mmol) in CH_2Cl_2 (10 mL) at –78 °C until the solution colour becomes sky blue (10 min). After which time, TLC (10% EtOAc/hexane) indicated the complete consumption of compound **30** and formation of ozonide. The solution was warmed to 0 °C and oxygen was bubbled to the solution until disappearance of sky blue colour (5 min). To the reaction mixture, triphenylphosphine (508 mg, 1.94 mmol) was added at 0 °C and the solution was warmed to room temperature and stirred for 6 h. The reaction mixture was concentrated under reduced pressure to obtain crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 20% EtOAc/hexane) to afford aldehyde (500 mg) as a colourless oil, which was immediately taken for the next reaction without further characterization. R_f = 0.7 (SiO_2, 50% EtOAc/hexane); To a stirred solution of above obtained aldehyde (500 mg, 1.59 mmol) in methanol (4 mL) was added $NaBH_4$ (66 mg, 1.75 mmol) at 0 °C and the solution was warmed to room temperature and stirred for 30 min. The reaction mixture was quenched with saturated aqueous ammonium chloride (10 mL) at 0 °C and diluted with water (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) three times. The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 40% EtOAc/hexane) to afford 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): ν_{max} 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, 7H), 6.90-6.85 (m, 2H), 4.71 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.48 (s, 2H), 3.83-3.77 (m, 4H), 3.72 (t, *J* = 5.7 Hz, 2H), 3.59 (dd, *J* = 9.7, 4.8 Hz, 1H), 3.53 (dd, *J* = 10.1, 5.0 Hz, 1H), 2.42 (brs, 1H), 1.82 (dd, *J* = 11.4, 5.9 Hz, 2H); ^{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; HRMS (ESI): $[M + Na]^+$calcd. for $C_{19}H_{24}O_4Na$ 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 50% aqueous NaOH (6.4 mL, 79.8 mmol) was treated with TBAB (87 mg, 0.27 mmol) at room temperature and the solution was warmed to 90 °C and stirred for 30 min. The reaction mixture was cooled to room temperature and treated with tosyl compound **32** (762 mg, 2.66 mmol) in a minimum amount of diethyl ether (1 mL) and 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) two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL) three times. The combined organic phases were washed with water (40 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 18% EtOAc/hexane) to obtain 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): ν_{max} 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, 7H), 6.90-6.85 (m, 2H), 4.69 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.48 (s, 2H), 4.20 (quin, *J* = 6.0 Hz, 1H), 4.0 (dd, *J* = 8.1, 6.4 Hz, 1H), 3.80 (s, 3H), 3.77-3.71 (m, 1H), 3.67 (dd, *J* = 8.1, 6.6 Hz, 1H), 3.60-3.50 (m, 4H). 3.44 (dd, *J* = 9.9, 5.6 Hz, 1H), 3.38 (dd, *J* = 9.9, 5.6 Hz, 1H), 1.88-1.76 (m, 2H), 1.40 (s, 3H), 1.35 (s, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{25}H_{34}O_6Na$ 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 CH_2Cl_2 and pH = 7.4 phosphate buffer (6 mL, 2:1) was treated with DDQ (395 mg, 1.74 mmol) at 0 °C and stirring was continued at the same temperature for 2 h. After which time, the reaction mixture was again treated with DDQ (132 mg, 0.58 mmol) at 0 °C and stirring was continued at the same temperature for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ (20 mL) at 0 °C and diluted with water (20 mL), ethyl acetate (40 mL) the layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 30 mL) three times. 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 over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 40% EtOAc/hexane) to provide 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): ν_{max} 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, 5H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.58 (d, *J* = 11.7 Hz, 1H) 4.24 (quin, *J* = 6.0 Hz, 1H), 4.04 (dd, *J* = 8.2, 6.6 Hz, 1H), 3.73 (dd, *J* = 11.7, 3.8 Hz, 1H), 3.70 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.66 (m, 1H), 3.61-3.54 (m, 3H), 3.47 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.46 (dd, *J* = 9.9, 5.2 Hz, 1H), 2.26 (brs, 1H), 1.95-1.88 (m, 1H), 1.87-1.80 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{17}H_{26}O_5Na$ 333.1672, found 333.1676.

(*R*)-2-(Benzyloxy)-4-(((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl) methoxy] butanal (20): To a stirred solution of alcohol **34** (220 mg, 0.71 mmol) in anhydrous CH_2Cl_2 (3 mL) at 0 °C was added $NaHCO_3$ (179 mg, 2.13 mmol) followed by DMP (454 mg, 1.07 mmol) and the reaction mixture was warmed to room temperature and stirred for 30 min. After which time, TLC (40% EtOAc/hexane) indicated the complete consumption of alcohol **34**. The reaction was quenched with (1:1) mixture of saturated aqueous hypo and saturated aqueous $NaHCO_3$ (30 mL) at 0 °C and diluted with CH_2Cl_2 (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) three times. The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 30% EtOAc/hexane) to afford aldehyde **20** (219 mg, 0.71 mmol, quantitative) as a colourless oil, which was taken for 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 pre-mixed 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 argon atmosphere and 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 diluted with water (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) three times. The combined organic extracts were washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 3% EtOAc/hexane) to afford 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): ν_{max} 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, 1H), 2.20 (td, *J* = 7.0, 1.8 Hz, 2H), 1.77-1.60 (m, 2H), 1.53-1.42 (m, 3H), 1.40-1.22 (m, 15H), 0.92-0.86 (m, 6H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{16}H_{30}ONa$ 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-diamino propane (49 mL) at 0 °C under argon atmosphere and the solution was warmed to 80 °C and stirred for 1 h. The solution was cooled to room temperature and alcohol **26** (1.95 g, 8.18 mmol) in 1,3-diamino propane (10 mL) was cannulated and the solution was again warmed to 80 °C and stirred for 2 h. After which 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 diluted with CH_2Cl_2 (40 mL) two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL) three times. The combined organic phases were washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 3% EtOAc/hexane) to afford 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): ν_{max} 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, 1H). 2.18 (td, *J* = 7.2, 2.6 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.52 (quin, *J* = 7.3 Hz, 2H), 1.48-1.36 (m, 7H), 1.36-1.25 (m, 13H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{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; HRMS (ESI): $[M + H]^+$ calcd. for $C_{16}H_{31}O$ 239.2375, found 239.2375.

(*R*)-1-((Hexadec-15-yn-6-yloxy)methyl)-4-methoxy benzene (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 and the reaction mixture was warmed to 150 °C and stirred for 2 h. After which 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 diluted with water (20 mL) and ethyl acetate (30 mL) two phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 30 mL) three times. The combined organic phases were washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 2% EtOAc/hexane) to afford 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): ν_{max} 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, 2H), 6.89-6.85 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.33 (quin, *J* = 5.9 Hz, 1H), 2.18 (td, *J* = 7.0, 2.6 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.55-1.42 (m, 4H), 1.41-1.22 (m, 18H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{24}H_{38}O_2Na$ 381.2770, found 381.2764.

(*R*)-1-(Benzyloxy)-13-((4-methoxybenzyl)oxy)octadec-3-yn-2-one (23): To a stirred solution of compound **24** (1.70 g, 4.74 mmol) in anhydrous THF (10 mL) was added *n*-Buli (1.6 M hexane solution, 2.96 mL, 4.74 mmol) at –78 °C and the solution was slowly warmed to 0 °C over a period of 45 min and again cooled to –78 °C. To this solution aldehyde **25** (855 mg, 5.69 mmol) in anhydrous THF (6 mL) was cannulated and stirring was continued at 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 diluted with water (20 mL) and ethyl acetate (30 mL) two phases were separated and the aqueous phase was extracted with ethyl acetate (3 × 30 mL) three times. The combined organic phases were washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give crude compound which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 15% EtOAc/hexane) to afford diastereomeric mixture of alcohols (2.13 g, 4.19 mmol, 88%, dr = 2.8:1) as a colourless oil that was dissolved in anhydrous CH_2Cl_2 (20 mL) and treated with DMP (3.55 g, 8.38 mmol) at 0 °C. After stirring at room temperature for 1 h, the reaction mixture was quenched with (1:1) mixture of saturated aqueous hypo and saturated aqueous $NaHCO_3$ (30 mL) at 0 °C and stirred at room temperature until the solution becomes clear (2 h). The aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL) three times. The organic extracts were washed with water (30 mL) and brine (30 mL). The combined organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 6% EtOAc/hexane) to afford 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): ν_{max} 2920, 2851, 1711, 1551, 1514, 1460, 1254, 1168,

772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.23 (m, 7H), 6.90-6.84 (m, 2H), 4.64 (s, 2H), 4.43 (s, 2H), 4.20 (s, 2H), 3.80 (s, 3H), 3.33 (quin, *J* = 5.5 Hz, 1H), 2.37 (t, *J* = 6.9 Hz, 2H), 1.63-1.44 (m, 4H), 1.43-1.18 (m, 18H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{33}H_{46}O_4Na$ 529.3294, found 529.3287.

(2*S*,13*R*)-1-(Benzyloxy)-13-((4-methoxybenzyl)oxy) octadec-3-yn-2-ol (36): Following the same Noyori reduction conditions as described in the synthesis of compound **26**, the above ynone **23** (1.7 g, 3.36 mmol) was converted to the corresponding alcohol **36** (1.5 g, 2.95 mmol, 87%, 94% *de*; purification by silica gel column chromatography, SiO_2, 100-200 mesh, 16% EtOAc/hexane) 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): ν_{max} 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, 7H), 6.89-6.84(m, 2H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.59 (d, *J* = 12.0, 1H), 4.43 (s, 2H), 3.79 (s, 3H), 3.62 (dd, *J* = 9.8, 3.4 Hz, 1H), 3.52 (dd, *J* = 9.8, 7.7 Hz, 1H), 3.33 (quin, *J* = 5.6 Hz, 1H), 2.49 (brs, 1H), 2.19 (td, *J* = 7.2, 2.0 Hz, 2H), 1.57-1.43 (m, 4H), 1.42-1.20 (m, 18H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{33}H_{48}O_4Na$ 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): To a stirred solution of alcohol **36** (1.45 g, 2.85 mmol) in anhydrous CH_2Cl_2 (15 mL) was added 2,6-lutidine (1.0 mL, 8.55 mmol) followed by TBSOTf (0.73 mL, 3.14 mmol) at 0 °C and the solution was warmed to room temperature and stirred for 30 min. After which 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 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) three times. The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 3% EtOAc/hexane) to afford 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): ν_{max} 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, 7H), 6.88-6.85 (m, 2H), 4.62 (d, *J* = 12.3 Hz, 1H), 4.60 (d, *J* = 12.3 Hz, 1H), 4.55 (m, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.55 (dd, *J* = 10.1, 5.0 Hz, 1H), 3.54 (dd, *J* = 10.1, 6.7 Hz, 1H), 3.33 (quin, *J* = 5.5 Hz, 1H), 2.18 (td, *J* = 7.1, 2.0 Hz, 2H), 1.56-1.43 (m, 4H), 1.42-1.21 (m, 18H), 0.92 (s, 9H), 0.88 (t, *J* = 7.0 Hz, 3H), 0.13 (s, 3H), 0.12 (s, 3H); ^{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; HRMS (ESI): $[M + K]^+$ calcd. for $C_{39}H_{62}O_4SiK$ 661.4049, found 661.4076.

(2*S*,13*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-13-((4-methoxy benzyl) 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 hydrogenated by using hydrogen filled balloon at room temperature for 24 h. After which time, TLC (20% EtOAc/hexane) indicated the complete consumption of compound **37**. Then the reaction mixture was filtered through celite plug carefully under nitrogen atmosphere and washed with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 6% EtOAc/hexane) to afford 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): ν_{max} 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, 2H), 6.88-6.85 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.72 (ddd, *J* = 11.8, 6.1, 3.6 Hz, 1H), 3.56 (dd, *J* = 10.9, 3.7 Hz, 1H), 3.44 (dd, *J* = 10.9, 5.3 Hz, 1H), 3.33 (quin, *J* = 5.9 Hz, 1H), 1.89 (brs, 1H), 1.57-1.42 (m, 6H), 1.41-1.21 (m, 22H), 0.90 (s, 9H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.09 (s, 6H)); ^{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. HRMS (ESI): $[M + Na]^+$ calcd. for $C_{32}H_{60}O_4SiNa$ 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 to afford aldehyde (1.2 g, 2.24 mmol, purification by silica gel column chromatography, SiO_2, 100-200 mesh, 10% EtOAc/hexane) as a colourless oil, which was taken for 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 hexane solution, 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 was cooled to room temperature and (*R*)-BINOL (257 mg, 0.90 mmol) followed by anhydrous diethyl ether (20 mL) and $Ti(O^iPr)_4$ (0.67 mL, 2.24 mmol) were added at room temperature and stirred for 1 h. To this solution above obtained aldehyde (1.2 g, 2.24 mmol) in anhydrous diethyl ether (20 mL) was cannulated at room temperature and stirred for 16 h. The reaction mixture was quenched with 1 M aqueous tartaric acid (20 mL) at 0 °C and stirred at room temperature for 30 min and diluted with water (30 mL) and diethyl ether (50 mL). Two phases were separated and the aqueous phase was extracted with diethyl ether (3 × 40 mL) three times. The combined organic phases were washed with water (30 mL) and brine (30 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 3% EtOAc/hexane) to afford 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): ν_{max} 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, 2H), 6.88-6.85 (m, 2H), 4.43 (s, 2H), 4.35-4.32 (m, 1H), 3.80 (s, 3H), 3.77-3.73 (m, 1H), 3.34 (quin, *J* = 5.6 Hz, 1H), 2.39 (d, *J* = 6.0 Hz, 1H), 1.75-1.42 (m, 7H), 1.41-1.20 (m, 21H), 1.12-1.02 (m, 21H), 0.9 (s, 9H), 0.88 (t, *J* = 7.2 Hz, 3H), 0.10 (s. 3H), 0.09 (s, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{43}H_{80}O_4Si_2Na$ 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 THF solution, 4.72 mL, 4.72 mmol) at 0 °C and the solution was warmed to room temperature and stirred for 30 min. After which time, TLC (10% EtOAc/hexane) indicated the complete consumption of compound **38**. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and 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) three times. The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 21% EtOAc/hexane) to provide diol compound **21a** (500 mg, 1.12 mmol, 95%) as a colorless oil. R_f = 0.3 (SiO_2, 30% EtOAc/hexane); $[\alpha]_D^{25}$ = +1.52 (*c* 1.05, $CHCl_3$); IR (Neat): ν_{max} 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, 2H), 6.89-6.85 (m, 2H), 4.43 (s, 2H), 4.32 (dd, *J* = 3.5, 2.2 Hz, 1H), 3.8 (s, 3H), 3.69 (ddd, *J* = 7.1, 6.4, 3.5 Hz, 1H), 3.34 (quin. 5.6 Hz, 1H), 2.5 (d, *J* = 2.0 Hz, 1H), 2.27 (brs, 2H), 1.61-1.42 (m, 7H), 1.41-1.22 (m, 21H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{28}H_{46}O_4Na$ 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 and stirred at room temperature for 16 h. After which time, TLC (30% EtOAc/hexane) indicated the complete consumption of diol **21a**. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and 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) three times. The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 2% EtOAc/hexane) to afford 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): ν_{max} 2925, 2855, 1612, 1513, 1460, 1373, 1300, 1243, 1170, 1040, 862, 655 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.24 (m, 2H), 6.88-6.85 (m, 2H), 4.71 (dd, *J* = 5.5, 2.1 Hz, 1H), 4.43 (s, 2H), 4.06 (dt, *J* = 7.1, 6.1 Hz, 1H), 3.79 (s, 3H), 3.33 (quin, *J* = 5.6 Hz, 1H), 2.51 (d, *J* = 2.1 Hz, 1H), 1.85-1.64 (m, 3H), 1.54 (s, 3H), 1.53-1.36 (m, 4H), 1.35 (s, 3H), 1.34-1.21 (m, 21H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{31}H_{50}O_4Na$ 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) hexa decyl)-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 hexane solution, 0.58 mL, 0.93 mmol) drop wise over a period of 3 min at –78 °C and the solution was slowly warmed to 0 °C over a period of 45 min. The reaction mixture was again cooled to –78 °C and the aldehyde **20** (150 mg, 0.49 mmol) in anhydrous THF (3 mL) was cannulated. After stirring at –78 °C for 2 h, the reaction mixture 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 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) three times. The combined organic extracts were washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 19% EtOAc/hexane) to afford an inseparable diastereomeric mixture of alcohols (316 mg, 0.40 mmol, 81%, dr = 1.3:1) as a colorless oil. R_f = 0.35 (SiO_2, 30% EtOAc/hexane). Following the same Swern conditions, experimental procedure as described for the preparation of compound **9**, the above obtained diastereomeric mixture of alcohols (100 mg, 0.126 mmol) was oxidized to corresponding ynone **19** (93 mg, 0.117 mmol, 93%; purification by silica gel column chromatography, SiO_2, 100-200 mesh, 14% EtOAc/hexane) 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): ν_{max} 2927, 2857, 1693, 1612, 1513, 1459, 1374, 1245, 1047, 851, 741, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.24 (m. 7H), 6.89-6.84 (m, 2H), 4.85 (d, *J* = 5.5 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.43 (s, 2H), 4.41-4.38 (m, 1H), 4.17 (quin, *J* = 6.0 Hz, 1H), 4.12 (dt, *J* = 6.5, 5.8 Hz, 1H), 4.08 (dd, *J* = 8.2, 4.4 Hz, 1H), 4.00 (dd, *J* = 7.8, 1.2 Hz, 1H), 3.79 (s, 3H), 3.67 (dd, *J* = 7.9, 6.4 Hz, 1H), 3.65-3.53 (m, 2H), 3.41 (qd, *J* = 9.8, 5.8 Hz, 2H), 3.36-3.28 (m, 1H), 2.10 (m, 1H), 1.97 (m, 1H), 1.79 (m, 1H), 1.66 (m, 1H), 1.51 (s, 3H), 1.50-1.42 (m, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.34-1.22 (m, 23H), 0.89 (t, *J* = 7.2 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{48}H_{72}O_9Na$ 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 pre-mixed 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 argon atmosphere and stirred for 5 min. The reaction mixture was treated with (*R*,*R*)-Ru catalyst **23a** (0.01 M CH_2Cl_2 solution, 63 µL, 0.63 µmol, 1 mol %) at 0 °C and the solution was warmed to room temperature and stirred for 24 h. After which time, TLC (30% EtOAc/hexane) indicated the complete consumption of ynone **19**. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and 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) three times. The combined organic extracts were washed with water (15 mL) and brine (15 mL). The organic layer was dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 18% EtOAc/hexane) to afford 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): ν_{max} 3450, 2927, 2857, 1691, 1608, 1513, 1459, 1374, 1246, 1219, 1163, 1039, 847, 740, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.24 (m, 7H), 6.88-6.85 (m, 2H), 4.75 (dd, *J* = 5.5, 1.4 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.56 (m, 1H) 4.43 (s, 2H), 4.22 (quin, *J* = 5.9 Hz, 1H), 4.07-4.01 (m, 2H), 3.80 (s, 3H), 3.73 (dd, *J* = 5.9, 4.2 Hz, 1H), 3.70 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.65-3.56 (m, 2H), 3.46 (qd, *J* = 9.9, 5.6 Hz, 2H), 3.33 (quin, *J* = 5.8 Hz, 1H), 2.78 (brs, 1H), 1.97 (q, *J* = 6.0 Hz, 2H), 1.82-1.58 (m, 4H), 1.51 (s, 3H), 1.50-1.43 (m, 2H), 1.41 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.33-1.22 (m, 22H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{48}H_{74}O_9Na$ 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 10% Pd/C (7.6 mg, 20% w/w) and hydrogenated by using hydrogen filled balloon at room temperature for 24 h. After which time, TLC (30% EtOAc/hexane) indicated the complete consumption of alcohol **39**. The reaction mixture was filtered through the celite plug and washed with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure to give a crude material which was purified by silica gel column chromatography (SiO_2, 100–200 mesh, 4% MeOH/$CHCl_3$) to afford triol compound **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): ν_{max} 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, 1H), 4.08-4.01 (m, 3H), 3.81-3.74 (m, 2H), 3.73-3.67 (m, 2H), 3.67-3.61 (m, 1H), 3.60-3.56 (m, 1H), 3.53 (d, *J* = 4.9 Hz, 1H), 3.53 (d, *J* = 5.5 Hz, 1H), 3.30 (brs, 1H), 2.67 (brs, 1H), 1.92-1.64 (m, 6H), 1.55-1.39 (m, 14H), 1.36 (s, 3H), 1.33 (s, 3H), 1.32-1.23 (m, 20H), 0.89 (t, *J* = 7 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{33}H_{64}O_8Na$ 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 in the synthesis of compound **21**, the above triol compound **40** (20 mg, 0.034 mmol) was transformed to the corresponding compound **41a** (20 mg, 0.032 mmol, 94%; silica gel column chromatography, SiO_2, 100-200 mesh, 18% EtOAc/hexane) 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): ν_{max} 3506, 2985, 2927, 2857, 1712, 1460, 1374, 1247, 1216, 1164, 1085, 1045, 873, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.26 (quin, *J* = 6.0 Hz, 1H), 4.19 (dt, *J* =10.3, 5.5 Hz, 1H), 4.11-3.98 (m, 4H), 3.74 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.67-3.56 (m, 3H), 3.54 (dd, *J* = 9.9, 5.5 Hz, 1H), 3.45 (dd, *J* = 9.9, 5.6 Hz, 1H), 1.79-1.56 (m, 5H), 1.48 (m, 1H), 1.42 (s, 12H), 1.36 (s, 3H), 1.35-1.24 (m, 31H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{36}H_{68}O_8Na$ 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-ylacetate (41): Following the same acetylation experimental procedure as reported in the synthesis of compound **3**, compound **41a** (15 mg, 0.024 mmol) was converted to the corresponding acetylated triacetonide compound **41** (15.2 mg, 0.023 mmol, 95%; purification by silica gel column chromatography, SiO_2, 100-200 mesh, 16% EtOAc/hexane) 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): ν_{max} 2928, 2858, 1737, 1460, 1374, 1245, 1086, 1032, 871 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.86 (quin, *J* = 6.3 Hz, 1H), 4.26 (quin, *J* = 6.0 Hz, 1H), 4.19 (ddd, *J* = 9.7, 5.5, 4.7 Hz, 1H), 4.10-3.99 (m, 4H), 3.74 (dd, *J* = 8.2, 6.4 Hz, 1H), 3.67-3.57 (m, 2H), 3.54 (dd, *J* = 9.9, 5.6 Hz, 1H), 3.46 (dd, *J* = 9.9, 5.6 Hz, 1H), 2.04 (s, 3H), 1.79-1.60 (m, 5H), 1.56-1.44 (m, 6H), 1.42 (s, 9H), 1.39 (m, 1H), 1.36 (s, 3H), 1.33 (s, 6H), 1.32-1.21 (m, 22H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{38}H_{70}O_9Na$ 693.4918, found 693.4913.

Mycalol (2): A stirred solution of triacetonide compound **41** (6 mg, 0.0089 mmol) in THF (1.8 mL) was treated with 1 N HCl (0.6 mL) at 0 °C and the solution was warmed to room temperature and stirred for 5 h. After which time, THF from the reaction mixture was evaporated under reduced pressure and water was evaporated by lyophilization to afford crude material which was purified by silica gel column chromatography (SiO_2, 100-200 mesh, 12% MeOH/$CHCl_3$) to afford 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): ν_{max} 3392, 3286, 2921, 2854, 1737, 1516, 1464, 1244, 1056 cm^{-1}; ^1H NMR (700 MHz, C_5D_5N): δ 5.07 (m, 1H), 4.36 (m, 1H), 4.19 (m, 1H), 4.14-4.10 (m, 1H), 4.10-4.03 (m, 3H), 4.03-3.95 (m, 3H), 3.91 (dd, *J* = 9.6, 4.9 Hz, 1H), 3.85 (dd, *J* = 9.6, 6.1 Hz, 1H), 2.59 (bd, *J* = 7.5 Hz, 2H), 2.40 (m, 1H), 2.18-2.10 (m, 3H), 2.08 (s, 3H), 1.99 (m, 1H), 1.91-1.82 (m, 2H), 1.63-1.48 (m, 5H), 1.42-1.26 (m, 8H), 1.26-1.16 (m, 12H), 0.82 (t, *J* = 7.0 Hz, 3H); ^{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; HRMS (ESI): $[M + Na]^+$ calcd. for $C_{29}H_{58}O_9Na$ 573.3979, found 573.3987.

Acknowledgements

K.N.R thanks UGC, New Delhi for the research fellowship. S.G is thankful to CSIR for funding through ORIGIN and CSIR-Young Scientist Research Grant.

Keywords: Marine natural product• mycalol• cytotoxic• Total synthesis• Noyori reduction•

[1] Martins, H. Vieira, H. Gaspar, S. Santos, *Mar. Drugs* **2014**, *12*, 1066-1101.

[2] A. Cutignano, G. Nuzzo, D. D' Angelo, E. Borbone, A. Fusco, A. Fontana, *Angew. Chem. Int. Ed.* **2013**, *52*, 9256-9260.

[3] B. Seetharamsingh, P. R. Rajamohanan, D. S. Reddy, *Org. Lett.* **2015**, *17*, 1652-1655.

[4] S. Das, T. K. Kuilya, R. K. Goswami, *J. Org. Chem.* **2015**, *80*, 6467-6489.

[5] A. Cutignano, B. Seetharamsingh, D. D' Angelo, G. Nuzzo, P. V. Khairnar, A. Fusco, D. S. Reddy, A. Fontana, *J. Nat. Prod.* **2017**, *80*, 1125-1133.

[6] R. A. Fernandes, P. H. Patil, A. K. Chowdhury, *Eur. J. Org. Chem.* **2014**, 237-243.

[7] a) A. B. Pulipaka, S. C. Bergmeier, *J. Org. Chem.* **2008**, *73*, 1462-1467; b) E. E. van Tamelen, T. M. Leiden, *J. Am. Chem. Soc.* **1982**, *104*, 2061-2062.

[8] (a) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315; (b) M. J. Cryle, N. J. Matovic, J. J. De Voss, *Org. Lett.* **2003**, *5*, 3341-3344.

[9] A. Habel, W. Boland, *Org. Biomol. Chem.* **2008**, *6*, 1601-1604.

[10] D. Crich, Md. Y. Rahaman, *J. Org. Chem.* **2009**, *44*, 6792-6796.

[11] M. T. Holmes, R. Britton, *Chem. Eur. J.* **2013**, *19*, 12649-12652.

[12] (a) A. Dahan, M. Portnoy, *J. Org. Chem.* **2001**, *66*, 6480-6482; b) S. R. Schow, T. C. McMorris, *J. Org. Chem.* **1979**, *44*, 3760-3765.

[13] S. A. Snyder, D. S. Treitler, A. P. Brucks, W. Sattler, *J. Am. Chem. Soc.* **2011**, *133*, 15898-15901.

[14] K. Nishikawa, S. Kikuchi, S. Ezaki, T. Koyama, H. Nokubo, T. Kodama, Y. Tachi, Y. Morimoto, *Org. Lett.* **2015**, *17*, 5772-5775.

[15] (a) B. D. Williams, A. B. Smith III, *J. Org. Chem.* **2014**, *79*, 9284-9296; b) F. Messik, M. Oberthür, *Angew. Chem., Int. Ed.* **2013**, *52*, 5871-5875.

[16] F. Dumoulin, D. Lafont, P. Boullanger, G. Mackenzie, G. H. Mehl, J. W. Goodby, *J. Am. Chem. Soc.* **2002**, *124*, 13737-13748.

[17] K. Danielmeier, E. Steckhan, *Tetrahedron: Asymmetry* **1995**, *6*, 1181-1190.

[18] a) R. S. Narayan, B. Borhan, *J. Org. Chem.* **2006**, *71*, 1416-1429; b) T. Das, R. Bhuniya, S. Nanda, *Tetrahedron: Asymmetry* **2010**, *21*, 2206-2211; c) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483-2547.

[19] J. P. Brand, J. Charpentier, J. Waser, *Angew. Chem. Int. Ed.* **2009**, *48*, 9346-9349.

[20] (a) H. Hanawa, T. Hashimoto, K. Maruoka, *J. Am. Chem. Soc.* **2003**, *125*, 1708-1709; (b) J. S. Yadav, B. Suresh, P. Srihari, *Eur. J. Org. Chem.* **2015**, 5856-5863; c) Â. de Fátima, L. K. Kohn, M. A. Antônio, J. E. de Carvalho, R. A. Pilli, *Bioorg. Med. Chem.* **2005**, *13*, 2927-2933.

[21] S. Roldán, A. Cardona, L. Conesa, J. Murga, E. Falomir, M. Carda, J. A. Marco, *Org. Biomol. Chem.* **2017**, *15*, 220-232.

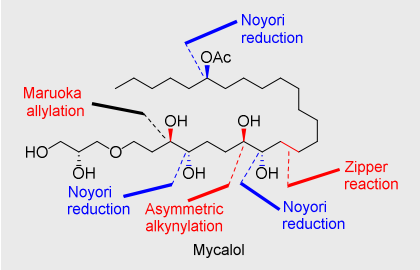
[22] I. Dams, M. Chodyński, M. Krupa, A. Pietraszek, M. Zezula, P. Cmoch, M. Kosińska, A. Kutner, *Tetrahedron*, **2013**, *69*, 1634-1648.

[23] (a) Y. Oikawa, T. Yoshioka, O. Yonemitsu, *Tetrahedron Lett.* **1982**, *23*, 885-888; b) G. Sabitha, A. Sandeep, A. S. Rao, J. S. Yadav, *Eur. J. Org. Chem.* **2013**, 6702-6709.

[24] (a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155-4156; b) K. M. Reddy, J. Shashidhar, S. Ghosh, *Org. Biomol. Chem.* **2014**, 12, 4002-4012.

[25] D. P. Larson, C. H. Heathcock, *J. Org. Chem.* **1997**, *62*, 8406-8418.
[26] (a) K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738-8739; b) K. N. Rao, M. Kanakaraju, A. C. Kunwar, S. Ghosh, *Org. Lett.* **2016**, *18*, 4092-4095.
[27] (a) C. A. Brown, A. Yamashita, *J. Am. Chem. Soc.* **1975**, *97*, 891-892; b) F. Liu, J. Zhong, S. Li, M. Li, L. Wu, Q. Wang, J. Mao, S. Liu, B. Zheng, M. Wang, Q. Bian, *J. Nat. Prod.* **2016**, *79*, 244-247.
[28] J. W. Gathirwa, T. Maki, *Tetrahedron,* **2012**, *68*, 370-375.
[29] L.-S. Li, Y. Wu, Y.-J. Hu, L.-J. Xia, Y.-L. Wu, *Tetrahedron: Asymmetry* **1998**, *9*, 2271-2277.
[30] K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa, O. Yonemitsu, *Tetrahedron*, **1986**, *42*, 3021-3028.
[31] (a) J. A. Marshall, M. P. Bourbeau, *Org. Lett.* **2003**, *5*, 3197-3199; b) D. Moore, L. Pu, *Org. Lett.* **2002**, *4*, 1855-857.
[32] I. Ohtani, T. Kusumi, Y. Kashman, H. Kakisawa, *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.

FULL PAPER



Natural Product Synthesis

*K. N. Rao, K. Kumar, S. Ghosh**

Page No.1 –16

Total Synthesis of Anticancer Marine Natural Product Mycalol

Total synthesis of anticancer marine natural product mycalol has been achieved by the use of Maruoka asymmetric allylation, Noyori asymmetric reduction, asymmetric alkynylation and Zipper reaction as key steps.