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A concise stereoselective formal total synthesis of the cytotoxic macrolide (+)-Neopeltolide via Prins cyclization

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ABSTRACT

A convergent and highly stereoselective formal total synthesis of the naturally occurring, cytotoxic 14-membered macrolide neopeltolide has been achieved via two Prins cyclizations.

1. Introduction

During the past 40–50 years, numerous novel compounds have been isolated from marine organisms and many of these have been reported to have range of biological activities such as cytotoxic, antibiotic, *anti*-inflammatory, antispasmodic, antiviral, cardiotonic, cardiovascular, antioxidant, and enzyme inhibition activities. Interestingly, some of which are of interest from the point of view of potential drug development. These compounds provide an enormous reservoir of structurally diverse secondary metabolites with unique molecular architectures.[1] Their synthetic analogues continue to provide fascinating insights into the mechanisms of many important biological processes, and for this reason, chemical interest in the synthesis of such structures remains high.[2]

In 2007, the search for new bioactive marine natural products resulted in the discovery of neopeltolide **1** (Fig. 1), isolated from a deep-water Caribbean sponge by Wright et al.[3] Initial testing demonstrated cytotoxic activity against several cancer lines, including P388 murine leukemia, A-549 human lung adenocarcinoma, and NCI-ADR-RES human ovarian sarcoma, with their respective IC_{50} values of 0.56, 1.2, and 5.1 nM, respectively. The key structural features of neopeltolide include a 14-membered macrolactone ring **3** (Fig. 1), containing an ether bridge forming a tetrahydropyran subunit. Moreover, there are six stereogenic centers in this structure. The hydroxyl group at C5 is acylated with an oxazol- and a carbamate-containing side chain. This substituent occupies an axial position in the pyran ring. The side chain is identical to another macrolide leucascandrolide A **4** (Fig. 1), which displays a similar biological profile.[4,12d] Other related natural products with a macrolactone part similar to neopeltolide include polycavernoside,[5] lyngbyaloside,[6] lyngbouilloside,[7] aurisides,[8] and callipeltoside.[9]

The Prins cyclization has emerged as a powerful synthetic tool for the construction of multi-substitued tetrahydropyran derivatives and has been utilized in the synthesis of several natural products.[15] Our group has made a significant effort to explore the utility of Prins cyclization for the synthesis of various polyketide intermediates and has subsequently applied to the synthesis of some natural products.[16] As a part of our interest on the synthesis of biologically active molecules, we herein report the synthesis of neopeltolide macrolactone **3**, which directly relates to neopeltolide **2**.[10–14]

The synthesis of Scheidt[11], Lee[12a], and Maier[12b] utilized a Prins cyclization to fashion the pyran ring of neopeltolide by combining a C1–C6 fragment with a C7–C16 part having an aldehyde function at C7. Our plan was to develop a novel synthesis of a C7–C16 aldehyde by starting from a fragment containing the methyl-bearing stereocenter at C9 and to create the C11–C13 diol region by intermolecular Prins–cyclization strategy. This plan led to (*S*)-citronellol as starting material.

2. Results and discussion

Protection of (*S*)-citronellol with benzyl bromide followed by the oxidation with PhSeOH-*t*-BuOOH yielded an allylic alcohol **6**.

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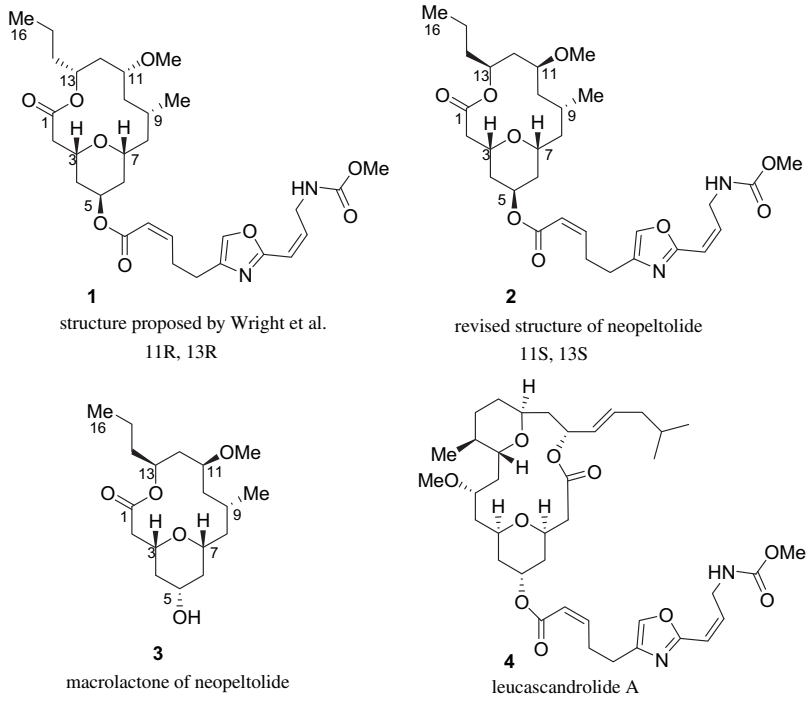
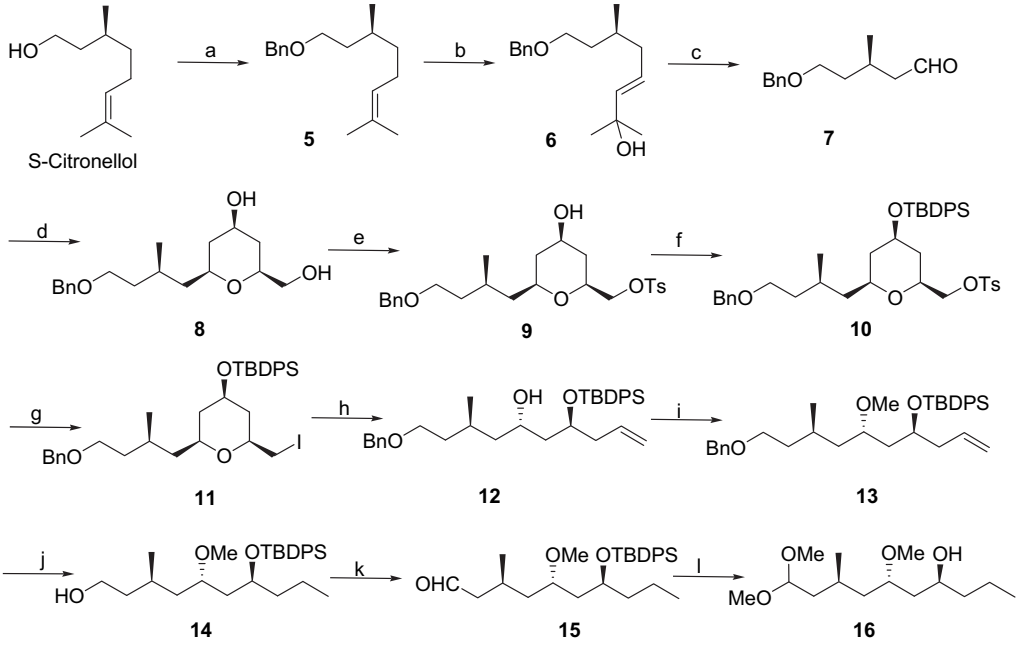


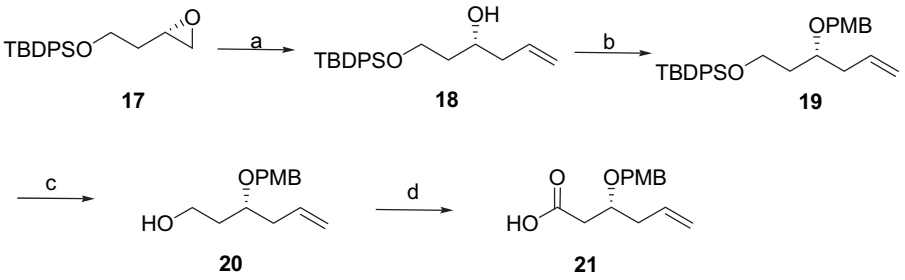
Figure 1. Structure proposed by Wright et al. (**1**), revised structure of neopeltolide (**2**), macrolactone of neopeltolide (**3**), leucascandrolide A (**4**).

This was ozonized in MeOH. The resulting ozonide was reduced with Me_2S to give the desired aldehyde **7**.[17] Intermolecular Prins cyclization of aldehyde **7** with (*S*)-pent-4-ene-1,2-diol[18] in the presence of TFA followed by hydrolysis of the resulting trifluoroacetate gave trisubstituted pyran **8** in 56% yield.[18,19] The stereochemistry of compound **8** was assumed to be in anticipated line as it was well examined and established previously.[15,16] Furthermore, tosylation of **8** with 1.1 equiv of tosyl chloride in the presence of TEA in DCM afforded corresponding primary tosylate **9** in 92% yield.[16a] TBDPS protection of the secondary alcohol **9** with TBDPSCl, DMAP, and imidazole gave corresponding TBDPS ether **10**. Treatment of tosylate **10** with NaI in refluxing acetone gave corresponding iodo compound **11**. Upon exposure of compound **11** to unactivated zinc in refluxing ethanol gave key intermediate **12** in 96% yields. The alcohol functionality in the **12** was protected using Meerwein's salt in the presence of proton sponge.[20] One-pot olefin reduction and benzyl ether deprotection with Raney nickel gave saturated primary alcohol[21] **14**. Oxidation of **14** with Dess–Martin periodinane (DMP) yielded aldehyde **15**. One-pot aldehyde protection and silyl ether deprotection led to seco-alcohol **16** using trimethyl orthoformate with PTSA as catalyst (Scheme 1).



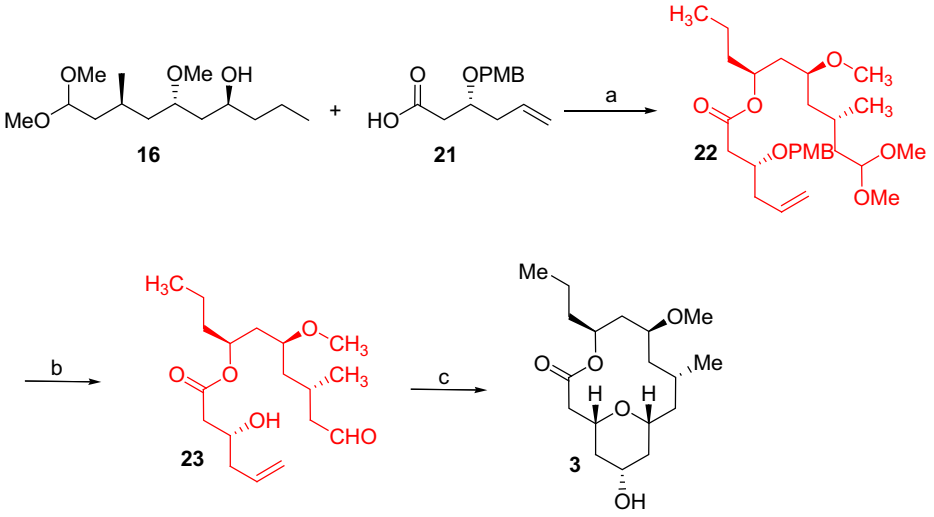
Scheme 1. Reagents and conditions: (a) NaH, BnBr, TBAI, THF, 12 h, 92%; (b) H_2O_2, PhSeSePh, *t*-BuOOH, $MgSO_4$, CH_2Cl_2, 27 h, 80%; (c) O_3, Me_2S, CH_3OH, 88%; (d) (*S*)-pent-4-ene-1,2-diol, TFA, CH_2Cl_2 then K_2CO_3, CH_3OH, 3.5 h, 56%; (e) TsCl, Et_3N, CH_2Cl_2, 5 h, 92%; (f) TBDPSCl, DMAP, imidazole, CH_2Cl_2, 3 h, 97%; (g) NaI, acetone, reflux, 24 h, 94%; (h) Zn, EtOH, reflux, 1 h, 96%; (i) Me_3OBF_4, proton sponge, CH_2Cl_2, 48 h, 86%; (j) H_2, Raney nickel, EtOH, 6 h, 93%; (k) DMP, $NaHCO_3$, CH_2Cl_2,1 h, 93%; (l) PTSA, $CH(OMe)_3$, CH_3OH, 6 h, 76%.

Compound **21** was synthesized starting from known chiral epoxide **17**.[22] Cu- mediated regioselective opening of epoxide **17** provided homoallylic alcohol **18**. Conversion of the alcohol to PMB ether **19** was accomplished by reacting with *p*-methoxybenzyl trichloroacetimidate in the presence of catalytic CSA. Deprotection of the primary TBDPS ether with TBAF and subsequent oxidation of **20** with DMP and $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene in *t*-BuOH/H_2O afforded the acid fragment **21** in 96% yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) CuI, CH_2=CHMgBr, THF, −20 °C, 2 h, 92%; (b) PMBOC(NH)CCl_3, CSA, CH_2Cl_2, 12 h, 76%; (c) TBAF, THF, 12 h, 90%; (d) DMP, CH_2Cl_2; $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, 6 h, 96%.

Esterification of free OH group of **16** with (*R*)-3-(4-methoxybenzyloxy)hex-5-enoic acid **21** in the presence of DCC and a catalytic amount of DMAP gave compound **22**, which on treatment with DDQ yielded the corresponding aldehydic homoallylic alcohol **23** required for intramolecular Prins cyclization. The compound **23** was treated with triethylsilyl trifluoromethanesulfonate (TESOTf) in acetic acid in the presence of trimethylsilyl acetate (TMSOAc) and subsequently treated under basic conditions to yield bicyclic macrolactone **3**[12a] (Scheme 3), whose data was identical in all respects with the data reported in literature.[12]



Scheme 3. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 3 h, 92%; (b) DDQ, pH buffer, CH_2Cl_2, 36 h, 92%; (c) TESOTf, TMSOAc, AcOH then K_2CO_3, CH_3OH, 0.5 h, 66%.

3. Conclusion

In summary, we have accomplished a convergent and enantioselective total synthesis of (+)-neopeltolide macrolide **3** in 15-step sequence from the known (*S*)-pent-4-ene-1,2-diol, epoxide **17** and the commercially available (*S*)-Citronellol. The present synthesis features an efficient route to **3** using two consequtive Prins cyclizations. Further applications of the Prins cyclization in the synthesis of natural products are in progress.

4. Experimental section

4.1. General

All reactions were carried out under inert atmosphere unless mentioned otherwise. Solvents were dried and purified by conventional methods prior to use. The progress of all the reactions was monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel-60 F_{254} to a thickness of 0.5 mm (Merck). Column chromatography was performed on silica gel (60-mesh) and neutral alumina using diethyl ether, ethyl acetate, and hexane as the eluents. Optical rotation values were measured with a Perkin-Elmer P241 polarimeter and JASCO DIP-360 digital polarimeter at 25 °C and IR spectra were recorded with a Perkin-Elmer FTIR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with Varian Gemini 200 MHz, Bruker Avance 300 MHz, Varian Unity 400 MHz, or Varian Inova 500 MHz spectrometer using trimethylsilane as an internal standard in $CDCl_3$. Mass spectra were recorded on Micro mass VG-7070H for EI and VG Autospec M for FABMS.

*4.1.1. (S)-((3,7-Dimethyloct-6-enyloxy)methyl)benzene (**5**).* To a stirred suspension of NaH (10 g, 416 mmol, 60% W/V dispersion in mineral oil) in dry THF (460 mL) was added dropwise a solution of *S*-citronellol (26 g, 167 mmol) at 0 °C. After stirring for 30 min at 0 °C, TBAI (0.7 g) and benzyl bromide (34.2 g, 200 mmol) were added subsequently and stirred overnight at room temperature. The reaction mixture was quenched with small ice-pieces and extracted with ethyl acetate (2×250 mL). The combined organic layers were washed with water (150 mL), brine (150 mL) and dried

over anhydrous Na_2SO_4. Solvent was removed under *vacuo* and the residue was purified by silica gel column chromatography to afford **5** (37.7 g, 92% yield) as a colorless liquid. R_f=0.8 (SiO_2, 10% EtOAc in hexane). $[\alpha]_D^{20}$ −2.6 (*c* 1.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.13 (5H, m, ArH), 5.10–5.00 (1H, m, Olefin), 4.46 (2H, s, OCH_2Ph), 3.46 (2H, t, *J* 6.0 Hz, OCH_2), 2.05–1.85 (2H, m, CH_2), 1.70–1.50 (2H, m, CH_2), 1.66 (3H, s, CH_3), 1.58 (3H, s, CH_3), 1.48–1.22 (2H, m, CH_2), 1.20–1.08 (1H, m, CHMe), 0.88 (3H, d, *J* 6.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.6, 130.9, 128.2, 127.5, 127.3, 124.7, 72.8, 68.6, 37.1, 36.6, 29.5, 25.6, 25.4, 19.5, 17.5; IR (neat): υ 3398, 3062, 3030, 2960, 2921, 2856, 1453, 1371, 1204, 1102, 1028, 829, 736 cm^{-1}; ESI-MS: *m*/*z* 247 $[M+H]^+$; HRMS (ESI): Calculated for $C_{17}H_{27}O$ $[M+H]^+$: 247.2061. Found: 247.2066.

*4.1.2. (S,E)-8-(Benzyloxy)-2,6-dimethyloct-3-en-2-ol (**6**).* 30% H_2O_2 (6.24 g) was added to a stirred and ice-cooled solution of PhSeSePh (17.12 g, 54.9 mmol) in CH_2Cl_2 (260 ml). After the addition, the mixture was stirred for 30 min at 0 °C. Powdered anhydrous $MgSO_4$, (9.22 g) was added to the mixture and stirring was continued for 30 min. The ice-bath was removed and **5** (9.0 g, 36.6 mmol) was added to the mixture. The stirring was continued for 6 h at room temperature. Subsequently 70% *t*-BuOOH (25.35 g) was added to the stirred and ice-cooled mixture, which was stirred for 20 h at room temperature. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in ether (400 mL). The ether solution was washed with 5% Na_2CO_3 solution and water. Then it was added dropwise to a vigorously stirred aq soln of $FeSO_4$, (10%, 360 mL). The ether layer was separated, washed with water, satd $NaHCO_3$ soln, water and brine, dried over Na_2SO_3, and concentrated under vacuo. The crude alcohol was purified by silica gel column chromatography to afford pure alcohol **6** (7.67 g, 80% yield) as a colorless liquid. R_f=0.3 (SiO_2, 20% EtOAc in hexane). $[\alpha]_D^{25}$ −3.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41–7.17 (5H, m, ArH), 5.65–5.54 (2H, m, Olefin), 4.46 (2H, s, OCH_2Ph), 3.46 (2H, t, *J* 6.0 Hz, OCH_2), 2.09–1.80 (2H, m, CH_2), 1.76–1.58 (2H, m, CH_2), 1.53–1.08 (7H, m, 2×CH_3, 1×CHMe), 0.87 (3H, d, *J* 6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.4, 138.5, 128.2, 127.5, 127.4, 125.2, 72.8, 70.5, 68.4, 39.6, 36.1, 29.9, 29.7, 19.6, 19.4; IR (neat): υ 3422, 3029, 2964, 2924, 2863, 1718, 1455, 1367, 1270, 1101, 1026, 973, 914, 800, 739 cm^{-1}; ESI-MS: *m*/*z* 280 $[M+NH_4]^+$; HRMS (ESI): Calculated for $C_{17}H_{30}NO_2$ $[M+NH_4]^+$: 280.2276. Found: 280.2284.

*4.1.3. (R)-5-(Benzyloxy)-3-methylpentanal (**7**).* O_3 was bubbled into a cooled solution of **6** (10.0 g) in MeOH (70 mL) at −50 °C. When **6** disappeared as checked by TLC, the solution was cooled to −60 °C. N_2 was bubbled into the solution to remove O_3. Then Me_2S (5 mL) was added dropwise to the stirred solution and the temperature was gradually raised to room temperature. After stirring overnight, the mixture was concentrated under vacuo. The residue was diluted with water and extracted with ether. The ether solution was washed with water and brine, dried over Na_2SO_3 and concentrated under vacuo. The crude aldehyde was purified by silica gel column chromatography to afford pure aldehyde **7** (6.92 g, 88% yield) as a colorless liquid. R_f=0.7 (SiO_2, 10% EtOAc in hexane). $[\alpha]_D^{25}$ +4.3 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.71 (1H, s, CHO), 7.31–7.18 (5H, m, ArH), 4.46 (2H, s, OCH_2Ph), 3.42 (2H, t, *J* 6.8 Hz, OCH_2), 2.41–2.35 (1H, m, CH_aCH_bCHO), 2.24–2.19 (1H, m, CH_aCH_bCHO), 2.09–2.02 (1H, m, CHMe), 1.45–1.38 (1H, m, CH_aCH_b), 1.34–1.23 (1H, m, CH_aCH_b), 0.97 (3H, d, *J* 6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.2, 138.2, 127.9, 127.2, 127.1, 72.5, 69.9, 50.5, 32.9, 26.8, 19.5; IR (neat): υ 3032, 2960, 2930, 2873, 1708, 1454, 1408, 1277, 1178, 1096, 1027, 948, 741, 703 cm^{-1}; ESI-MS: *m*/*z* 229 $[M+NH_4]^+$; HRMS (ESI): Calculated for $C_{13}H_{18}NaO_2$ $[M+Na]^+$: 229.1204. Found: 229.1210.

*4.1.4. (4R,6S)-2-((R)-4-(Benzyloxy)-2-methylbutyl)-6-(hydroxymethyl)-tetrahydro-2H-pyran-4-ol (**8**).* Trifluoroacetic acid (47.5 mL) was added slowly to a solution of the (*S*)-pent-4-ene-1,2-diol (3 g, 29.37 mmol) and aldehyde **7** (7.87 g, 38.2 mmol) in CH_2Cl_2 (90 mL) at 25 °C under nitrogen atmosphere. The reaction mixture was stirred for 3 h and then saturated sodium hydrogen carbonate solution (200 mL) was added and pH was adjusted to >7 by addition of triethylamine. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4×70 mL). The organic layers were combined and the solvent was removed under reduced pressure. The trifluoroacetate obtained in this reaction was directly used in the next reaction without purification. The residue was dissolved in methanol (40 mL) and stirred with potassium carbonate (8.11 g) for 0.5 h. The methanol was removed under reduced pressure and water (30 mL) was added. The mixture was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification of the crude product by column chromatography on silica yielded **8** (2.44 g, 56%) as a colorless liquid. R_f=0.3 (SiO_2, 70% EtOAc in hexane). $[\alpha]_D^{25}$ −5.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.17 (5H, m, ArH), 4.47 (2H, s, OCH_2Ph), 3.82–3.67 (1H, m, OCH), 3.59–3.31 (6H, m, OCH), 2.33 (1H, br s, OH), 1.90–1.53 (5H, m, aliphatic), 1.50–1.36 (1H, m, CHMe), 1.28–1.05 (3H, m, aliphatic), 0.89 (3H, d, *J* 6.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.3, 128.2, 127.5, 127.4, 75.9, 73.4, 72.7, 68.2, 67.6, 65.7, 43.1, 41.5, 36.9, 36.6, 26.4, 19.5; IR (neat): υ 3400, 2924, 2862, 1453, 1369, 1090, 1027, 740 cm^{-1}; ESI-MS: *m*/*z* 326 $[M+NH_4]^+$; HRMS (ESI): Calculated for $C_{18}H_{32}NO_4$ $[M+NH_4]^+$: 326.2331. Found: 326.2340.

*4.1.5. ((2S,4R)-6-((R)-4-(Benzyloxy)-2-methylbutyl)-4-hydroxy-tetrahydro-2H-pyran-2-yl)methyl4-methylbenzenesulfonate (**9**).* To the solution of diol **8** (2.0 g, 6.49 mmol) in dry CH_2Cl_2 (15.0 mL), triethylamine (1.31 g, 12.97 mmol) was added at 0 °C. Tosyl chloride (1.36 g, 7.14 mmol) was added over 2 h. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was treated with aqueous 1 N HCl (10 mL) and extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with saturated $NaHCO_3$ (15 mL) and water (15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. Silica gel column chromatography of the crude afforded tosylate **9** (2.76 g, 92%) as a gummy liquid. R_f=0.5 (SiO_2, 60% EtOAc in hexane). $[\alpha]_D^{25}$ −10.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74 (2H, d, *J* 8.3 Hz, ArH), 7.36–7.17 (7H, m, ArH), 4.45 (2H, s, OCH_2Ph), 3.99–3.88 (2H, m, OCH), 3.75–3.65 (1H, m, OCH), 3.52–3.14 (3H, m, OCH), 3.35–3.25 (1H, m, OCH), 2.42 (3H, s, $ArCH_3$), 1.90–1.69 (4H, m, aliphatic), 1.65–1.32 (3H, m, aliphatic), 1.16–1.00 (3H, m, aliphatic), 0.85 (3H, d, *J* 7.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.6, 138.4, 132.7, 129.7, 128.2, 127.8, 127.5, 127.3, 73.4, 72.8, 72.7, 71.9, 68.4, 67.3, 43.0, 41.1, 36.9, 36.7, 26.2, 21.5, 19.4; IR (neat): υ 3422, 3030, 2924, 2862, 1598, 1452, 1361, 1176, 1189, 1097, 1029, 977, 814, 743, 698 cm^{-1}; ESI-MS: *m*/*z* 480 $[M+NH_4]^+$; HRMS (ESI): Calculated for $C_{25}H_{38}NO_6S$ $[M+NH_4]^+$: 480.2419. Found: 480.2429.

*4.1.6. ((2S,4R)-6-((R)-4-(Benzyloxy)-2-methylbutyl)-4-(tert-butyldiphenylsilyloxy)-tetrahydro-2H-pyran-2-yl)methyl 4-methylbenzenesulfonate (**10**).* To a solution of alcohol **9** (2.6 g, 5.63 mmol) in anhyd CH_2Cl_2 (16 mL) at 0 °C were added TBDPSCl (1.85 g, 6.75 mmol), DMAP (Cat.) and imidazole (1.15 g, 16.88 mmol) successively and the mixture was stirred for 3 h at 25 °C. The reaction mixture was quenched by adding H_2O (10 mL) and extracted with CH_2Cl_2 (3×20 mL). The organic extracts were washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum and the crude was purified by silica gel column chromatography to afford the pure product **10** (3.82 g, 97%) as a colorless liquid; R_f=0.8 (SiO_2, 10% EtOAc in hexane). $[\alpha]_D^{25}$ −4.1 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74–7.54 (6H, m, ArH), 7.44–7.14 (13H, m, ArH), 4.44 (2H, s, OCH_2Ph), 3.90–3.78 (2H, m, OCH), 3.74–3.61

(1H, m, OCH), 3.40 (2H, t, *J* 6.4 Hz, OCH_2), 3.32–3.22 (1H, m, OCH), 3.12–3.02 (1H, m, OCH), 2.40 (3H, s, $ArCH_3$), 1.72–1.56 (2H, m, aliphatic), 1.54–1.30 (3H, m, aliphatic), 1.25–1.15 (1H, m, aliphatic), 1.06–0.96(3H, m, aliphatic), 1.02 (9H, s, Me_3CSi), 0.76 (3H, d, *J* 6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 144.4, 138.4, 135.5, 133.9, 133.8, 132.8, 129.5, 128.1, 127.7, 127.4, 127.3, 73.2, 72.7, 72.5, 71.9, 68.8, 68.3, 42.9, 41.4, 36.9, 36.8, 26.7, 26.1, 21.4, 19.3, 18.9; IR (neat): υ 3020, 2926, 2855, 1741, 1597, 1451, 1358, 1176, 974 cm^{-1}; ESI-MS: *m*/*z* 718 $[M+NH_4]^+$; HRMS (ESI): Calculated for $C_{41}H_{56}NO_6SSi$ $[M+NH_4]^+$: 718.3597. Found: 718.3594.

*4.1.7. ((4R,6S)-2-((R)-4-(Benzyloxy)-2-methylbutyl)-6-(iodomethyl)-tetrahydro-2H-pyran-4-yloxy)(tert-butyl)diphenylsilane (**11**).* To a stirred solution of **10** (3.6 g, 5.14 mmol) in dry acetone (66 mL) under nitrogen atmosphere was added NaI (2.45 g, 16.46 mmol) at 0 °C. The reaction mixture was stirred at reflux for 24 h and filtered. Removal of solvent under *vacuo* and purification on silica gel column chromatography afforded **11** (3.17 g, 94%) as a colorless liquid. R_f=0.6 (SiO_2, 20% EtOAc in hexane). $[\alpha]_D^{25}$ +8.1 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.54 (4H, m, ArH), 7.36–7.15 (11H, m, ArH), 4.40 (2H, s, OCH_2Ph), 3.76–3.62 (1H, m, OCH), 3.44–3.55 (2H, m, OCH), 3.16–3.06 (1H, m, OCH), 3.05–3.01 (1H, m, OCH), 3.01–2.96 (2H, m, CH_2I), 1.89–1.73 (2H, m, aliphatic), 1.59–1.45 (2H, m, aliphatic), 1.40–1.30 (1H, m, aliphatic), 1.24–1.11 (2H, m, aliphatic), 1.06–0.96(2H, m, aliphatic), 0.97 (9H, s, Me_3CSi), 0.76 (3H, d, *J* 6.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.7, 135.6, 134.7, 134.1, 129.6, 128.2, 127.5, 127.3, 75.0, 73.4, 72.8, 69.2, 68.6, 43.1, 41.6, 41.0, 37.1, 26.9, 26.4, 19.3, 19.0, 8.94; IR (neat): υ 3067, 2931, 2857, 1460, 1427, 1368, 1188, 1110, 1074, 824, 740, 702 cm^{-1}; ESI-MS: *m*/*z* 679 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{34}H_{45}INaO_3Si$ $[M+Na]^+$: 679.2080. Found: 679.2086.

*4.1.8. (3R,5S,7S)-1-(Benzyloxy)-7-(tert-butyldiphenylsilyloxy)-3-methyldec-9-en-5-ol (**12**).* To a solution of **11** (2.2 g, 3.35 mmol) in ethanol (80 mL), commercial zinc dust (3.27 g, 50.30 mmol) was added. The mixture was refluxed for 1 h and cooled to 25 °C. Addition of solid ammonium chloride (8.17 g) and ether (120 mL) followed by stirring for 5 min gave a gray suspension. The suspension was filtered through Celite and filtrate was concentrated under *vacuo* and purification on silica gel column chromatography afforded **12** (1.70 g, 96%) as a colorless liquid. R_f=0.3 (SiO_2, 10% EtOAc in hexane). $[\alpha]_D^{25}$ +1.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72–7.66 (4H, m, ArH), 7.56–7.19 (11H, m, ArH), 5.64–5.46 (1H, m, Olefin), 4.96–4.78 (2H, m, Olefin), 4.46 (2H, s, OCH_2Ph), 4.03–3.96 (1H, m, OCH), 3.94–3.86 (1H, m, OCH), 3.58–3.40 (2H, m, OCH), 2.42–2.07 (2H, m, allylic CH_2), 1.86–1.70 (1H, m, aliphatic), 1.63–1.37 (5H, m, aliphatic), 0.97 (9H, s, Me_3CSi), 1.04–0.95 (1H, m, aliphatic), 0.84 (3H, d, *J* 6.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.6, 135.8, 134.2, 133.6, 133.3, 129.8, 128.2, 127.5, 127.3, 117.2, 72.8, 71.5, 68.5, 65.5, 45.2, 42.3, 41.0, 37.3, 26.9, 26.3, 19.2, 19.1; IR (neat): υ 3505, 3069, 2930, 2858, 1460, 1427, 1365, 1107, 999, 914, 821, 738, 702 cm^{-1}; ESI-MS: *m*/*z* 553 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{34}H_{46}NaO_3Si$ $[M+Na]^+$: 553.3113. Found: 553.3116.

*4.1.9. ((4S,6S,8R)-10-(Benzyloxy)-6-methoxy-8-methyldec-1-en-4-yloxy)(tert-butyl)diphenylsilane (**13**).* To a solution of alcohol **12** (3.4 g, 6.42 mmol) in CH_2Cl_2 (100 mL) in the dark at room temperature was added Me_3OBF_4 (3.32 g, 22.45 mmol) and proton sponge (6.86 g, 32.07 mmol). The mixture was allowed to stir for 48 h. After complete reaction (monitored by TLC), H_2O was added (50 mL) and the mixture extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under *vacuo*. Purification by silica gel chromatography gave the **13** (3.0 g, 86%) as a colorless liquid. R_f=0.4 (SiO_2, 10% EtOAc in hexane). $[\alpha]_D^{25}$ +8.2 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.71–7.65 (4H, m, ArH), 7.42–7.25 (11H, m, ArH), 5.80–5.69 (1H, m, Olefin), 4.99–4.89 (2H, m, Olefin), 4.48 (2H, s, OCH_2Ph), 3.93–3.88 (1H, m, OCH), 3.49–3.40 (2H, m, OCH), 3.34–3.28 (1H, m, OCH), 3.07 (3H, s, OCH_3), 2.25–2.11 (2H, m, aliphatic), 1.80–1.52 (3H, m, aliphatic), 1.48–1.32 (3H, m, aliphatic), 1.05 (9H, s, Me_3CSi), 0.95–0.89 (1H, m, aliphatic), 0.83 (3H, d, *J* 6.6 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.6, 135.9, 134.5, 134.1, 129.5, 128.2, 127.6, 127.5, 127.4, 117.0, 75.3, 72.8, 70.2, 68.6, 55.6, 41.9, 41.8, 41.7, 37.1, 27.0, 26.6, 19.8, 19.3; IR (neat): υ 3067, 2928, 2856, 2777, 1575, 1456, 1428, 1380, 1184, 1106, 1030, 999, 936, 820, 738, 702 cm^{-1}; ESI-MS: *m*/*z* 567 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{35}H_{48}NaO_3Si$ $[M+Na]^+$: 567.3270. Found: 567.3278.

*4.1.10. (3R,5S,7S)-7-(tert-Butyldiphenylsilyloxy)-5-methoxy-3-methyldeca-1-ol (**14**).* Raney Nickel 10 g was added in one portion to a stirred solution of **13** (3.0 g, 6.89 mmol) in 20 mL of absolute ethanol. The flask was fitted with a balloon of H_2, and the reaction mixture was stirred at room temperature for 6 h. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under *vacuo* and the residue was purified by silica gel column chromatography to afford **14** (2.33 g, 93% yield) as a colorless liquid. R_f=0.3 (SiO_2, 30% EtOAc in hexane). $[\alpha]_D^{25}$ −10.6 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.76–7.61 (4H, m, ArH), 7.44–7.28 (6H, m, ArH), 3.89–3.78 (1H, m, OCH), 3.65–3.49 (2H, m, OCH), 3.30–3.18 (1H, m, OCH), 3.06 (3H, s, OCH_3), 1.70–1.55 (2H, m, aliphatic), 1.47–1.17 (10H, m, aliphatic), 1.04 (9H, s, Me_3CSi), 0.83 (3H, d, *J* 6.6 Hz, CH_3), 0.73 (3H, t, *J* 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.9, 134.6, 129.4, 127.4, 75.9, 70.5, 60.6, 55.9, 42.0, 41.6, 40.2, 39.4, 27.0, 26.1, 19.9, 19.3, 17.7, 13.9; IR (neat): υ 3395, 3056, 2935, 2867, 1459, 1377, 1260, 1098, 787, 703 cm^{-1}; ESI-MS: *m*/*z* 457 $[M+H]^+$; HRMS (ESI): Calculated for $C_{28}H_{45}O_3Si$ $[M+H]^+$: 457.3137. Found: 457.3140.

*4.1.11. (3R,5S,7S)-7-(tert-Butyldiphenylsilyloxy)-5-methoxy-3-methyldecanal (**15**).* To a solution of alcohol **14** (0.296 g, 0.65 mmol) in CH_2Cl_2 (5 mL) was added $NaHCO_3$ (0. 17 g, 2.0 mmol) and Dess–Martin periodinane (DMP) (0.43 g, 1.0 mmol) at 0 °C. After 0.5 h at this temperature, a saturated aqueous $NaHCO_3$ solution was added and the bilayer system was allowed to stir at 0 °C for an additional 0.5 h. The organic phase separated, the aqueous layer extracted with CH_2Cl_2 (2×5 mL), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and filtered. After concentration under *vacuo*, the crude aldehyde was purified by silica gel column chromatography to afford **15** (0.27 g, 93% yield) as a liquid. R_f=0.6. (SiO_2, 10% EtOAc in hexane). $[\alpha]_D^{25}$ −10.6 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.71 (1H, s, CHO), 7.72–7.68 (4H, m, ArH), 7.43–7.33 (6H, m, ArH), 3.86–3.76 (1H, m, OCH), 3.29–3.21 (1H, m, OCH), 3.06 (3H, s, OCH_3), 2.34–2.24 (1H, m, CH_aH_bCHO), 2.20–2.09 (2H, m, 1×CH_aH_bCHO, 1×$CHCH_3$), 1.74–1.66 (1H, m, aliphatic), 1.52–1.36 (3H, m, aliphatic), 1.36–1.16 (3H, m, aliphatic), 1.04 (9H, s, Me_3CSi), 0.98–1.02 (1H, m, aliphatic), 0.86 (3H, d, *J* 6.6 Hz, CH_3), 0.73 (3H, t, *J* 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.7, 136.0, 134.6, 134.3, 129.6, 127.5, 127.4, 75.6, 70.5, 55.6, 51.4, 42.0, 41.4, 39.6, 27.0, 24.8, 20.0, 19.3, 17.7, 13.9; IR (neat): υ 3032, 2966, 2942, 2876, 1706, 1456, 1408, 1278, 1178, 1096, 1027, 948, 741, 703 cm^{-1}; ESI-MS: *m*/*z* 477 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{28}H_{42}NaO_3Si$ $[M+Na]^+$: 477.2800. Found: 477.2808.

*4.1.12. (4S,6S,8S)-6,10,10-Trimethoxy-8-methyldeca-4-ol (**16**).* A solution of **15** (0.121 g, 0.27 mmol) in 3 mL of dry methanol was treated with trimethyl orthoformate (0.178 g, 1.68 mmol) and PTSA (0.01 g, 0.05 mmol) and the resulting solution was stirred for 2 h at rt, diluted with ether (100 mL), treated with K_2CO_3 (0.129 g, 0.93 mmol) filtered through Celite, and concentrated under *vacuo*. The crude oil was purified by silica gel column chromatography to give the acetal

16 (0.053 g, 76% yield) as a liquid. R_f=0.6. (SiO_2, 10% EtOAc in hexane). $[\alpha]_D^{25}$ +12.6 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 4.43 (1H, dd, *J* 4.8, 8.1 Hz, $CH(OMe)_3$), 3.99–3.86 (1H, m, OCH), 3.66–3.54 (1H, m, OCH), 3.37 (3H, s, OCH_3), 3.32 (3H, s, OCH_3), 3.31 (3H, s, OCH_3), 2.97 (1H, br s, OH), 1.75–1.69 (3H, m, aliphatic), 1.66–1.61 (1H, m, aliphatic), 1.55–1.50 (1H, m, aliphatic), 1.60–1.36 (5H, m, aliphatic), 1.26–1.20 (1H, m, aliphatic), 0.86 (3H, d, *J* 6.6 Hz, CH_3), 0.73 (3H, t, *J* 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 103.1, 77.6, 68.4, 56.6, 52.9, 52.3, 41.3, 40.0, 39.8, 39.3, 26.0, 20.1, 18.6, 13.9; IR (neat): υ 3446, 2930, 2859, 1730, 1460, 1378, 1188, 1111, 1078, 958, 797, 740, 703 cm^{-1}; ESI-MS: *m*/*z* 285 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{14}H_{30}NaO_4$ $[M+Na]^+$: 285.2041. Found: 285.2036.

*4.1.13. (R)-1-(tert-Butyldiphenylsilyloxy)hex-5-en-3-ol (**18**).* 36.8 mL of vinylmagnesiumbromide (1 M solution in THF) was quickly added to a THF solution of epoxide **17** (6 g, 18.4 mmol) and CuI (0.524 g, 2.76 mmol) at −20 °C. The reaction was monitored by TLC and after completion a saturated solution of NH_4Cl was added. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under *vacuum* affording a yellow oil and the crude product was chromatographed on silica gel to afford **18** (5.99 g, 92%) as a colorless liquid. R_f=0.7 (SiO_2, 30% EtOAc in hexane). $[\alpha]_D^{25}$+2.3 (*c* 1.40, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.72–7.69 (4H, m, ArH), 7.48–7.40 (6H, m, ArH), 5.87 (1H, m, Olefin), 5.16–5.10 (2H, m, Olefin), 4.02–3.96 (1H, m, OCH), 3.93–3.84 (2H, m, OCH), 2.34–2.25 (2H, m, allylic CH_2), 1.79–1.68 (2H, m, aliphatic), 1.08 (9H, s, Me_3CSi); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.6, 135.2, 135.0, 134.8, 129.9, 129.7, 127.8, 127.8, 117.5, 70.9, 63.3, 42.0, 37.9, 26.6, 19.1; IR (neat): υ 3449, 3069, 2930, 2858, 1466, 1426, 1251, 1107, 1000, 821, 741, 702 cm^{-1}; ESI-MS: *m*/*z* 377 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{22}H_{30}NaO_2Si$ $[M+Na]^+$: 377.1912. Found: 377.1916.

*4.1.14. (R)-tert-Butyl-(3-(4-methoxybenzyloxy)hex-5-enyloxy)-diphenylsilane (**19**).* To a stirring solution of alcohol **18** (1.34 g, 3.94 mmol), freshly prepared 4-methoxybenzyl trichloroacetimidate (1.66 mg, 5.92 mmol), and CH_2Cl_2 (10 mL) in a 15 mL round bottom flask, under an atmosphere of N_2, was added (±)-camphor-10-sulfonic acid (0.092 g, 0.394 mmol) in one portion. The reaction was allowed to proceed for 12 h at rt, after which TLC analysis indicated essentially complete consumption of starting material. The reaction mixture was concentrated under reduced pressure, diluted with 20% EtOAc/hexanes (100 mL), filtered over a pad of Celite, and concentrated under *vacuo* to give red slurry. Purification was accomplished by silica gel column chromatography to give PMB ether **19** (1.42 g, 76% yield) as colorless oil: R_f=0.5 (SiO_2, 20% EtOAc in hexane). $[\alpha]_D^{25}$ −10.6 (*c* 0.40, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 7.63–7.50 (4H, m, ArH), 7.40–7.18 (6H, m, ArH), 7.14–7.03 (2H, m, ArH), 6.79–6.66 (2H, m, ArH), 5.85–5.62 (1H, m, olefin), 5.09–4.88 (2H, m, olefin), 4.47–4.24 (2H, m, OCH), 3.83–3.56 (3H, m, OCH), 3.76 (3H, s, OCH_3), 2.34–2.14 (2H, m, allylic CH_2), 1.74–1.60 (2H, m, aliphatic), 1.03 (9H, s, Me_3CSi); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.9, 135.5, 135.2, 134.7, 133.8, 130.8, 129.5, 129.2, 127.6, 116.9, 113.6, 75.0, 70.7, 60.4, 55.1, 38.4, 36.9, 26.8, 19.1; IR (neat): υ 3069, 3001, 2931, 2857, 1612, 1511, 1464, 1428, 1246, 1107, 1037, 820, 739, 702 cm^{-1}; ESI-MS: *m*/*z* 497 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{30}H_{38}NaO_3Si$ $[M+Na]^+$: 497.2487. Found: 497.2482.

*4.1.15. (R)-3-(4-Methoxybenzyloxy)hex-5-en-1-ol (**20**).* To a stirring solution of PMB ether **19** (4.74 g, 10.0 mmol) and THF (80 mL) in a 250 mL round bottom flask under an atmosphere of N_2, at rt, was added a 1.0 M solution of tetrabutylammonium fluoride (20.0 mL, 20.0 mmol) in THF, dropwise via syringe. The reaction was allowed to proceed for 12 h at rt, after which time TLC analysis indicated complete consumption of starting material. The reaction mixture was concentrated under reduced pressure. Purification was accomplished by silica gel column chromatography and concentrated under reduced pressure to give primary alcohol **20** (2.12 g, 90% yield) as colorless oil. R_f=0.3 (SiO_2, 40% EtOAc in hexane). $[\alpha]_D^{25}$ −31.9 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$ 400 MHz): δ 7.28–7.14 (2H, m, ArH), 6.81 (2H, d, *J* 8.4 Hz, ArH), 5.82–5.71 (1H, m, olefin), 5.12–5.03 (2H, m, olefin), 4.54 (2H, s, OCH_2Ph), 3.80 (3H, s, OCH_3), 3.76–3.61 (3H, m, OCH), 2.50–2.16 (2H, m, allylic CH_2), 1.82–1.68 (2H, m, aliphatic); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.1, 134.7, 134.1, 129.3, 117.3, 113.7, 77.2, 70.5, 60.4, 55.1, 37.9, 35.8; IR (neat): υ 3422, 3072, 2932, 1612, 1512, 1463, 1436, 1346, 1301, 1247, 1175, 1036, 916, 820, 771 cm^{-1}; ESI-MS: *m*/*z* 259 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{14}H_{20}NaO_3$ $[M+Na]^+$: 259.1310. Found: 259.1316.

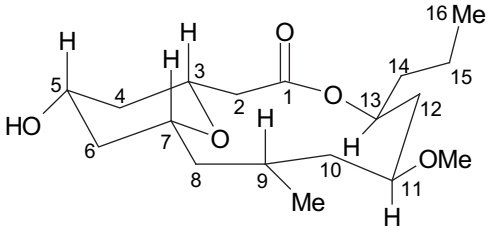
*4.1.16. (R)-3-(4-Methoxybenzyloxy)hex-5-enoic acid (**21**).* Dess–Martin periodinane (4.35 g, 10.3 mmol) was added to a solution of **20** (1.21 g, 5.14 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred at rt for 1 h and the reaction was quenched by addition of satd $Na_2S_2O_3$ solution (45 mL). The reaction mixture was extracted with CH_2Cl_2 (90 mL×3). The organic extracts were dried over Na_2SO_4, filtered, and concentrated under *vacuo*. This crude aldehyde was dissolved in *t*-BuOH (240 mL) and 2-methyl-2-butene (60 mL). After cooling to 0 °C, $NaClO_2$ (1.21 g, 13.34 mmol) and NaH_2PO_4 (2.23 g, 13.38 mmol) in water (40 mL) was added to the solution. The reaction mixture was stirred vigorously for 30 min at rt, diluted with EtOAc (300 mL), and quenched by water (150 mL). The aqueous phase was extracted with EtOAc (300 mL×2) and the combined organic phase was washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under *vacuo*. Purification was accomplished by silica gel column chromatography, which provided **21** (1.25 g, 96%). R_f=0.2 (SiO_2, 30% EtOAc in hexane). $[\alpha]_D^{25}$ −15.6 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.19 (2H, d, *J* 8.0 Hz, ArH), 6.80 (2H, d, *J* 8.0 Hz, ArH), 5.85–5.74 (1H, m, olefin), 5.16–5.06 (2H, m, olefin), 4.53–4.46 (2H, m, OCH_2Ph), 3.96–3.85 (1H, m, OCH), 3.78 (3H, s, OCH_3), 2.60–2.45 (2H, m, CH_2COOH), 2.41–2.30 (2H, m, allylic CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.0, 159.1, 133.6, 130.0, 129.3, 118.0, 113.7, 74.6, 71.1, 55.1, 39.1, 38.2; IR (neat): υ 3074, 2927, 1711, 1642, 1612, 1513, 1437, 1349, 1300, 1247, 1176, 1078, 1034, 919, 821 cm^{-1}; ESI-MS: *m*/*z* 273 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{14}H_{18}NaO_4$ $[M+Na]^+$: 273.1102. Found: 273.1103.

*4.1.17. (S)-((4S,6S,8S)-6,10,10-Trimethoxy-8-methyldecan-4-yl)3-(4-methoxybenzyloxy)hex-5-enoate (**22**).* Acid **21** (0.077 g, 0.31 mmol), DCC (0.124 g, 0.60 mmol), DMAP (0.007 g, 0.06 mmol) were added to a solution of alcohol **16** (0.053 g, 0.2 mmol) in CH_2Cl_2 (2 mL) at rt. This mixture was stirred at rt for 3 h, the reaction mixture was concentrated under *vacuo*. Purification of the residue by silica gel column chromatography provided ester **22** (0.091 g, 92%). R_f=0.40 (SiO_2, 20% EtOAc in hexane). $[\alpha]_D^{25}$ −5.5 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.20 (2H, d, *J* 8.1 Hz, ArH), 6.81 (2H, d, *J* 8.1 Hz, ArH), 5.84–5.74 (1H, m, olefin), 5.13–5.06 (1H, m, OCH), 5.13–5.07 (2H, m, olefin), 4.50–4.46 (2H, m, OCH_2Ph), 4.42 (1H, dd, *J* 5.2, 7.9 Hz, $CH(OMe)_3$), 3.96–3.90 (1H, m, OCH), 3.76 (3H, s, OCH_3), 3.30 (3H, s, OCH_3), 3.28 (3H, s, OCH_3), 3.26 (3H, s, OCH_3), 3.24–3.20 (1H, m, OCH), 2.53–2.46 (2H, m, CH_2COOH), 2.36–2.33 (2H, m, allylic CH_2), 1.74–1.66 (1H, m, aliphatic), 1.64–1.44 (5H, m, aliphatic), 1.39–1.34 (2H, m, aliphatic), 1.33–1.23 (2H, m, aliphatic), 1.18–1.14 (1H, m, aliphatic), 0.93 (3H, d, *J* 6.6 Hz, CH_3), 0.83 (3H, t, *J* 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.4, 159.3, 134.3, 130.6, 129.4, 117.9, 113.6, 103.1, 75.6, 75.3, 71.6, 71.4, 57.0, 55.4, 53.1, 52.1, 42.4, 40.1, 40.0, 39.9, 38.6, 37.3, 26.0, 20.4, 18.6, 13.9; IR (neat): υ 2930, 2830, 1728, 1614, 1514, 1663, 1383, 1320, 1174, 1091, 915, 820, 797, 740, 703 cm^{-1}; ESI-MS: *m*/*z* 517 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{28}H_{46}NaO_7$ $[M+Na]^+$: 517.3141. Found: 517.3146.

*4.1.18. (S)-((4S,6S,8S)-6,10,10-Trimethoxy-8-methyldecan-4-yl)3-(4-methoxybenzyloxy)hex-5-enoate (**23**).* DDQ (0.4 g, 1.76 mmol) was added to a solution of ester **22** (0.087 g, 0.18 mmol) in CH_2Cl_2

(20 mL) and pH 7 buffer solution (4 mL) at rt. After 36 h, the reaction was quenched by the addition of saturated $NaHCO_3$ (13 mL). The reaction mixture was extracted with CH_2Cl_2 (3×25 mL), dried over Na_2SO_4, filtered, and concentrated under *vacuo*. Purification of the residue by silica gel column chromatography (hexanes–EtOAc, 10:1) provided aldehyde **23** (54 mg, 92%). R_f=0.6 (SiO_2, 20% EtOAc in hexane). $[\alpha]_D^{25}$ −12.6 (*c* 0.30, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.71 (1H, s, CHO), 5.84–5.76 (1H, m, olefin), 5.16–5.06 (1H, m, OCH), 5.16–5.10 (2H, m, olefin), 4.10–4.06 (1H, m, OCH), 3.31–3.26 (1H, m, OCH), 3.29 (3H, s, OCH_3), 3.16 (1H, d, *J* 4.1 Hz, aliphatic), 2.51–2.40 (3H, m, aliphatic), 2.30–2.16 (4H, m, aliphatic), 1.74–1.51 (4H, m, aliphatic), 1.49–1.21 (4H, m, aliphatic), 0.97 (3H, d, *J* 6.4 Hz, CH_3), 0.89 (3H, t, *J* 7.3 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.5, 172.0, 134.1, 118.2, 76.0, 71.7, 67.8, 56.7, 51.1, 41.5, 41.4, 41.0, 38.9, 37.1, 25.1, 20.6, 18.6, 14.0; IR (neat): υ 3480, 3076, 2960, 2717, 2350, 2310, 1730, 1642, 1564, 1383, 1173, 837, 822, 797, 702 cm^{-1}; ESI-MS: *m*/*z* 351 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{18}H_{32}NaO_5$ $[M+Na]^+$: 351.2147 Found: 351.2146.

*4.1.19. Macrolactone of neopeltolide (**3**).*



TMSOAc (0.6 mL, 3.82 mmol) was added to a solution of aldehyde **23** (0.042 g, 0.127 mmol) in AcOH (12.6 mL) at rt. TESOTf (0.56 mL, 2.55 mmol) was added dropwise to the resulting solution at the same temperature. After 30 min, the reaction mixture was poured into ether (30 mL), and saturated $NaHCO_3$ (30 mL). The layers were separated, and the aqueous layer was extracted with ether (3×30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under *vacuo*. This crude product was dissolved in MeOH (3 mL) and then K_2CO_3 (175 mg, 1.27 mmol) was added. This reaction mixture was stirred for 3 h at rt and concentrated. The residue was dissolved in water (6 mL), and ether (6 mL). The layers were separated, and the aqueous layer was extracted with ether (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under *vacuo*. The residue as purified by silica gel column chromatography to afford neopeltolide macrolactone **3** (0.028 g, 66%) as a colorless oil. R_f=0.3 (SiO_2, 50% EtOAc in hexane). $[\alpha]_D^{25}$ +20.6 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.06–5.16 (1H, m, 13-H), 3.85–3.66 (2H, m, 3-H, 5-H), 3.62–3.53 (1H, m, 7-H), 3.29 (3H, s, 11-$CHOCH_3$), 3.20–3.15 (1H, m, 11-H), 2.59 (1H, dd, *J* 14.5, 4.0 Hz, 2-H), 2.43 (1H, dd, *J* 14.5, 11.0 Hz, 2-H), 1.98–1.92 (1H, m, 4-Ha), 1.89–1.81 (2H, m, 14-H, 4-He), 1.74–1.63 (m, 1H, 9-H), 1.63–1.25 (9H, m, 2×10-H, 2×12-H, 2×15-H, 8-H, 14-H, OH), 1.26–1.07 (3H, m, 6-Ha, 6-He, 8-H), 0.97 (3H, d, *J* 6.8 Hz, 9-CH_3), 0.89 (3H, t, *J* 7.3 Hz, 16-CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8 (C-1), 78.6 (C-7), 75.7 (C-11), 73.2 (C-3), 72.3 (C-13), 68.0 (C-5), 56.0 (11-$CHOCH_3$), 44.0 (C-8), 42.2 (C-10), 42.1 (C-2), 41.9 (C-12), 40.7 (C-6), 40.0 (C-14), 37.1 (C-4), 31.1 (C-9), 25.4 (9-CH_3), 18.9 (C-15), 13.9 (C-16); IR (neat): υ 3414, 2916, 2870, 1732, 1646, 1270, 1456, 1087, 1386, 1246, 1156, 1087, 794 cm^{-1}; ESI-MS: *m*/*z* 351 $[M+Na]^+$; HRMS (ESI): Calculated for $C_{18}H_{32}O_5$ $[M+Na]^+$: 351.2147. Found: 351.2146.

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