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Synthesis of the polyketide segment of apratoxin A

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Abstract—Apratoxin A **1** is a potent cytotoxic agent extracted from a marine cyanobacterium. We report the results of our synthetic approaches to the polyketide segment 3-OTBS-7-OPMB-2,5,8,8-tetramethylnonanoic acid **4**, and the scope and limitations of these approaches.

1. Introduction

Marine cyanobacteria, in particular those of the genus *Lyngbya*, have provided abundant bioactive secondary metabolites over the past two decades.[1,2] During the investigation of one particular *Lyngbya* sp. from Finger's Reef, Apra Harbor, Guam, apratoxin A–C (Fig. 1) were isolated by Moore and co-workers.[3,4] Complete structure assignment for apratoxin A **1** has resulted from extensive NMR, molecular modelling, chiral HPLC, and derivatization studies. Apratoxin A **1** displays potent in vitro cytotoxicity against KB and LoVo cancer cell lines with IC_{50} values of 0.52 and 0.36 nM, respectively. In contrast to most known potent anticancer natural products, the cellular and molecular basis of apratoxins' action is unknown at present.[3] Apratoxin A uniquely combines a tetrapeptide and a polyketide portion within a macrolactone ring, which possesses a number of intriguing structural elements, including a *tert*-butyl group as the starter unit of the polyketide segment and a thiazoline ring attached to the beta carbon of an α,β-unsaturated amide.

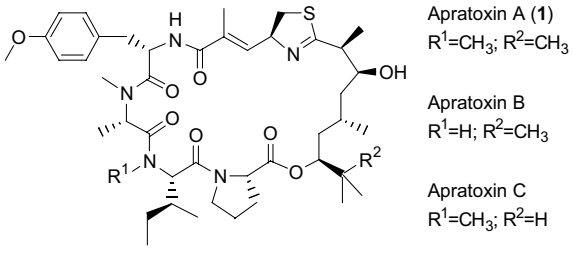

Figure 1.

Intrigued by the unusual molecular architecture, striking biological profile, and limited availability of apratoxin A, we recently undertook its total synthesis.[5] Herein we report the results of synthetic approaches to the polyketide segment **4**.

From a retrosynthetic perspective, the known propensity of the stereogenic centers at, and adjacent to, the thiazoline ring to undergo facile epimerization[6,7] led us to targets **2** and **3** as advanced intermediates. This will make the synthetic strategy more convergent. In both of these two synthetic plans, the targeted molecular **1** was divided into two parts, the peptidic segment and the polyketide segment. We have secured the key polyketide 3,7-dihydroxy-2,5,8,8- tetramethylnonanoic acid (Dtena) as a partially protected intermediate **4** (Fig. 2), in our quest for the synthesis of apratoxin A. The PMB protected alcohol provides a means of attaching to the proline residue in the peptidic portion of the molecule, while the carboxylic acid could be incorporated into the thioamide or thioester, which could then be further converted into the thiazoline motif.[8–17]

2. Results and discussion

The synthesis commenced with commercially available starting materials, with our first generation synthesis of

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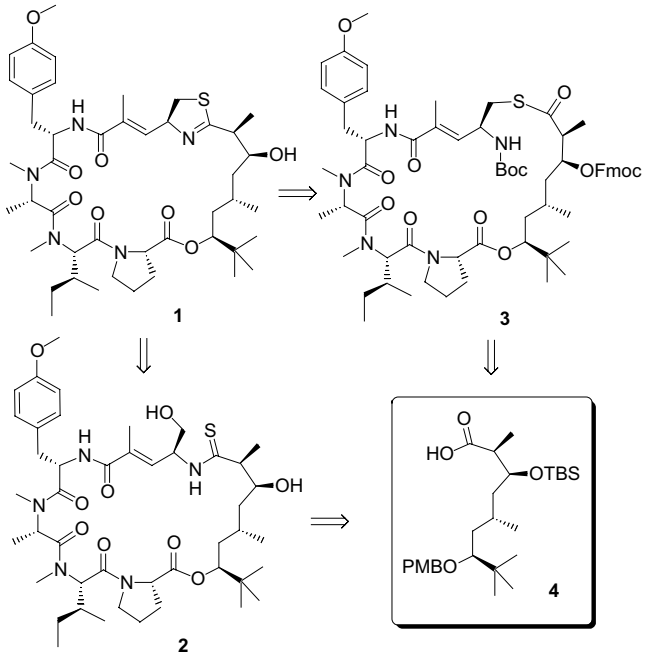
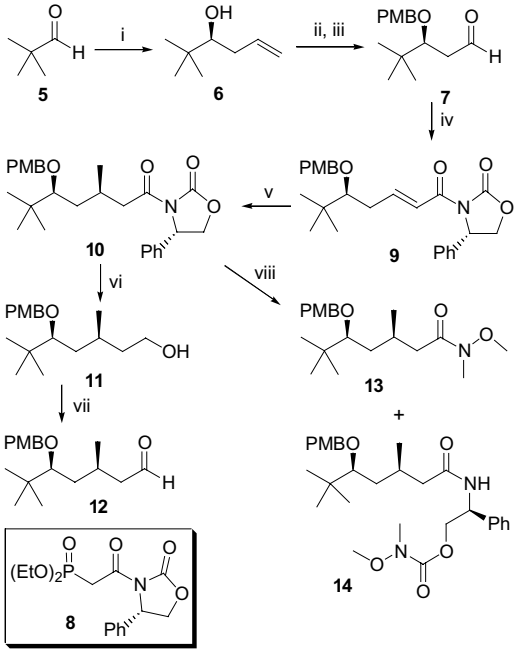


Figure 2. Retrosynthetic analysis of apratoxin A.

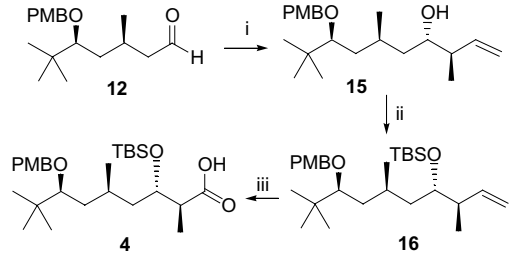


Scheme 1. Reagents and conditions: (i) (−)-IPC_2BOMe, allyl-magnesium bromide, then H_2O_2, Et_3N, 60%; (ii) PMB-Br, NaH, THF, 95%; (iii) (a) NMO, OsO_4 (cat), methanesulfonamide, *t*-BuOH/H_2O; (b) $NaIO_4$–silica gel, CH_2Cl_2, 90%; (iv) **8**, KHMDS, THF/HMPA, then **7**, 69%; (v) CH_3MgBr, CuBr–DMS, DMS–THF, 92%; (vi) $NaBH_4$, THF–H_2O, 67%; (vii) $(COCl)_2$, DMSO, CH_2Cl_2, then DIPEA, 94%; (viii) $HN(CH_3)OCH_3$, $(CH_3)_3Al$, CH_2Cl_2, −50 °C 90% (with a ratio of **13**:**14** = 1:1.7).

4 twice employing Brown's asymmetric synthesis via organoborane chemistry[18–22] to build up the C2, C3, and C7 stereogenic centers, with the C5 stereogenic center being introduced by Hruby's asymmetric conjugate addition protocol (Scheme 1).[23,24]

Thus, treatment of pivalaldehyde **5** at −100 °C with the chiral boron reagent derived from (−)-*B*-(methoxy)-diisopinocampheylborane and allylmagnesium bromide afforded the corresponding allylic alcohol **6** in 60% yield and with excellent enantioselectivity (99% ee).[19] This was protected as its PMB ether by reaction with *p*-methoxybenzyl bromide and sodium hydride. The terminal alkene was then converted into the corresponding aldehyde **7** by first treating the PMB ether of **6** with osmium tetroxide, *N*-methylmorpholine *N*-oxide (NMO) and methanesulfonamide, and the resulting diol was oxidatively cleaved with sodium periodate coated on silica gel.[25] The aldehyde **7** was obtained in 91% yield over three steps.

Wadsworth–Emmons condensation[26] of phosphonate **8**,[27] with aldehyde **7** provided *trans*-α,β-unsaturated enimide as the sole stereoisomer, which simultaneously homologated and introduced the chiral auxiliary required for the asymmetric conjugate addition. The oxazolidinone-derived chiral phosphonate **8** was in turn prepared from L-phenylglycine.[28–31] Treatment of enimide precursor **9** with an excess of methylmagnesium bromide and 1 equiv amount of copper(I) bromide–dimethyl sulfide complex, led to the methylated adduct **10** in 92% yield, with excellent diastereoselectivity (>95% de). The chiral auxiliary in **10** was then reductively cleaved to furnish the alcohol **11** by use of sodium borohydride.[32,33] The usual procedure[34,35] of treating the imide **10** with *N*,*O*-dimethyl hydroxylamine failed to produce the Weinreb amide **13** cleanly, appearing to attack the carbamate carbon to produce **14** instead. The primary alcohol **11** was easily converted into the corresponding aldehyde **12** under Swern conditions,[36] and thus setting the stage for the pivotal asymmetric crotylation (Scheme 2).

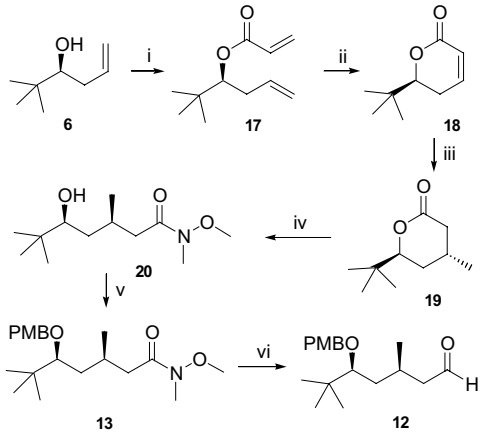


Scheme 2. Reagents and conditions: (i) (+)-IPC_2BOMe, *trans*-2-butene, *t*-BuOK, *n*-BuLi, BF_3–Et_2O, **11**, −100 °C, then H_2O_2, Et_3N, THF, 53%; (ii) TBS-Cl, imid., DMF, 93%; (iii) (a) NMO, OsO_4 (cat), methanesulfonamide, *t*-BuOH/H_2O; (b) $NaIO_4$–silica gel, CH_2Cl_2; (c) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, *t*-BuOH/H_2O, 83% (three steps).

Treatment of aldehyde **12** with the chiral boron reagent derived from (*E*)-2-butene, *n*-butyllithium, potassium *tert*-butoxide, and (+)-*B*-(methoxy)diisopinocampheyl borane in the presence of boron trifluoride etherate gave secondary alcohol **15** in 53% yield and with excellent diastereoselectivity (>95% de).[22] TBS protection of the

secondary alcohol of **15**, oxidative cleavage of the alkene unit and further oxidation of the corresponding aldehyde under mild conditions by use of sodium chlorite[37] furnished the key intermediate **4** (83% yield over three steps).

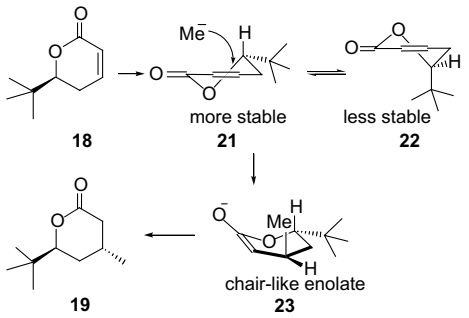
Although successful, this route was not entirely satisfactory, since it employed a chiral auxiliary during the conjugate addition for the C5 stereogenic center, and some of the obtained yields were poor for a multi-step synthesis. An alternative method was sought, which produced the C5 stereogenic center without the need of an auxiliary/stoichiometric amount of reagent, and provided a more viable way of producing **4** in gram quantities. The second approach is outlined in Scheme 3.



Scheme 3. Reagents and conditions: (i) CH_2=CHCOCl, Et_3N, THF, 92%; (ii) Grubbs's cat, CH_2Cl_2, reflux, 88%; (iii) CuCN, MeLi, Et_2O, −78 °C 86%; (iv) $HN(CH_3)OCH_3$, $(CH_3)_3Al$, CH_2Cl_2, −50 °C 91%; (v) NaH, PMBBr, TBAI, THF, 91%; (vi) DIBAL-H, CH_2Cl_2, −78 °C 92%.

Alcohol **6** was reacted with acryloyl chloride to form ester **17**. Treatment of **17** in dichloromethane with Grubbs' catalyst effected the ring-closing metathesis reaction[38–53] to yield unsaturated lactone **18**. This was subjected to a conjugate addition with methyllithium and copper(I) cyanide to provide the methyl-substituted lactone **19** in 83% yield as the only detectable stereoisomer.[54–57] Ring opening of the lactone **19** with *N*,*O*-dimethyl hydroxylamine[34,35] gave the corresponding alcohol **20**, which was converted into its PMB ether **13** in the presence of *p*-methoxybenzyl bromide, sodium hydride, and tetra-*n*-butyl-ammonium iodide.[58] Weinreb amide **13** was readily converted into the corresponding aldehyde **12** under reductive condition. The aldehyde **12** was then transformed into key compound **4** by the previously described procedures.

A simple, yet compelling explanation for the stereochemical outcome resulted from the mixed higher order cyanocuprate-mediated conjugate addition of **18** involves the stereoelectronic effects.[59] The kinetically controlled conjugate addition to a conjugated enone takes place preferentially by way of the chair-like enolate, which resulted from the more stable half-chair conformer. As shown in Scheme 4, attack on the top face of the most stable conformation **21** gives the chair-like enolate ion **23**, which would produce **19**. The sterically hindered *tert*-butyl group enhanced the selectivity via formation of the most stable conformer **21** exclusively.



Scheme 4.

3. Conclusions

In summary, two alternative practical methods have been developed for the synthesis of a fully elaborated fragment related to the polyketide segment of the unique anti-tumor natural product apratoxin A. Key steps involve asymmetric allylation, crotylation, and asymmetric conjugate additions. Both strategies are very efficient and proceed with high levels of stereocontrol throughout. Progress toward the total synthesis continues and will be reported in due course.

4. Experimental

4.1. General experimental

All nonaqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and all reaction vessels were oven-dried. Solvents were distilled prior to use: THF from Na/benzophenone, dichloromethane, DMF, triethylamine, and diisopropylethylamine from CaH. NMR spectra were recorded on Bruker Advance DPX 300 MHz or AV400 MHz spectrometers. Chemical shifts are reported in parts per million (ppm), relative to either a tetramethylsilane internal standard or the signals due to the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad), integration, and coupling constants. Low- and high-resolution EI and FAB mass spectra were obtained using a Finnigan MAT 95 mass spectrometer, while ESI mass spectra were obtained with Micromass Q-Tof-2^{TM} spectrometer. IR spectra were recorded neatly or as KBr disk on a Bio-Red FTS 165 Fourier transform spectrophotometer. Optical rotations were recorded on a Perkin Elmer 343 Polarimeter.

TLC was carried out using pre-coated sheets (Merck silica gel 60-F_{250}, 0.2 mm), which, after development, were visualized at 254 nm, and/or staining in *p*-anisole, ninhydrin, or phosphomolybdic acid solution followed by heating. Flash column chromatography was performed using the indicated solvents (with $R_f = 1.5$–2.0 for the desired component) on E. Merck silica gel 60 (230–400 mesh ASTM). Melting points were measured on Carl Zeiss and were uncorrected.

4.2. (4*S*)-4-(*para*-Methoxy-benzyloxy)-5,5-dimethyl-1-hexene

To the suspension of NaH (703 mg, 17.6 mmol, 60% dispersion in mineral oil) in THF (10 mL) was added homoallyl alcohol **6** (750 mg, 5.86 mmol) in THF (2 mL) at 0 °C. Ten minutes later, freshly prepared PMB-Br (1.5 g, 7.6 mmol) in THF (2 mL) was added. The mixture was then allowed to warm to room temperature and stirred for 12 h. Cold water (5 mL) was carefully added to quench the reaction; ethyl acetate (3 × 50 mL) was used for extraction after volatiles were removed in vacuo. The combined extractive organic layers were washed with saturated aqueous NH_4Cl (50 mL) and brine (50 mL), dried over Na_2SO_4, and evaporated. The residue, after chromatographic purification on silica gel using ethyl acetate–hexane (5:95) as eluant, produced the title compound (1.38 g, 95%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.28 (m, 2H), 6.83–6.87 (m, 2H), 5.90–5.99 (m, 1H), 5.00–5.13 (m, 2H), 4.58 (d, 1H, $J = 10.5$ Hz), 4.40 (d, 1H, $J = 10.7$ Hz), 3.78 (s, 3H), 3.05 (dd, 1H, $J = 3.3$ Hz, 8.4 Hz), 2.19–2.38 (m, 2H), 0.93 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.95, 137.46, 131.33, 129.09, 115.89, 113.58, 87.43, 73.94, 55.17, 36.00, 35.82, 26.39; IR (film): 2954.9, 2868.1, 1513.7, 1247.9, 1081.4, 1038.5, 910.4, 820.9 cm^{-1}; $[\alpha]_D^{20} = -7.45$ (*c* 15.2, $CHCl_3$); EI-HRMS, calcd for $C_{16}H_{24}O_2$ 248.1776, found 248.1770.

4.3. (3*S*)-3-(*para*-Methoxy-benzyloxy)-4,4-dimethyl-pentanal, 7

To a solution of the above alkene (1.29 g, 5.2 mmol) in *t*-BuOH–acetone–H_2O (30 mL, 2:1:2), chilled with an ice-water bath, was added successively NMO (2.82 mL, 10.4 mmol, 50 wt % in H_2O), OsO_4 (1.3 mL, 0.05 mmol, 10 mg/mL in H_2O), and $CH_3SO_2NH_2$ (496 mg, 5.2 mmol) with vigorous stirring. Then the mixture was stirred at room temperature for 24 h. After being diluted with brine (15 mL), the reaction was quenched with an excess of Na_2SO_3. After being stirred for an additional 3 h, volatiles were removed under reduced pressure and the reaction mixture was extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (50 mL) and brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo to provide the corresponding diol. To a solution of the diol in dichloromethane (50 mL), a pre-coated $NaIO_4$–SiO_2 (17.7 g, 10.4 mmol, 1 mmol/1.7 g) was added and the suspension was then stirred at room temperature for 30 min. The reaction mixture was filtered and the inorganic cake was washed with ethyl acetate (150 mL). The combined filtrate was dried over sodium sulfate. Removal of the solvent in vacuo followed by chromatography on silica gel (ethyl acetate–hexane = 1:4) afforded aldehyde **7** (1.17 g, 90%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (t, 1H, $J = 2.0$ Hz), 7.25–7.26 (m, 2H), 7.23–7.24 (m, 2H), 4.52 (d, 1H, $J = 11.3$ Hz), 4.48 (d, 1H, $J = 11.3$ Hz), 3.79 (s, 3H), 3.64 (dd, 1H, $J = 4.6$ Hz, 6.8 Hz), 2.62–2.65 (m, 2H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.07, 159.13, 130.60, 129.21, 113.71, 81.85, 73.48, 55.23, 45.84, 35.73, 26.11; IR (film): 2958.6, 2837.1, 1724.2, 1612.4, 1514.0, 1247.9, 1080.1, 1035.7, 821.6 cm^{-1}; $[\alpha]_D^{20} = -17.3$ (*c* 3.3, $CHCl_3$); ESI-HRMS calcd for $C_{15}H_{22}NaO_3$ (M+23) 273.1467, found 273.1471.

4.4. (4*S*)-3-[(5*S*)-5-(4-Methoxy-benzyloxy)-6,6-dimethyl-hept-2-enoyl]-4-phenyl-oxazolidin-2-one, 9

To a solution of the phosphonate **8** (2.88 g, 8.4 mmol) in THF (65 mL) at −70 °C was successively added KHMDS (18.1 mL, 7.24 mmol, 0.4 M in toluene) and HMPA (2.9 mL, 16.9 mmol). The mixture was brought to room temperature and stirred for 45 min and then cooled to −70 °C again. Aldehyde **7** (1.51 g, 6 mmol) in THF (20 mL) was added via a cannula. The reaction mixture, after being stirred for 16 h, was quenched with pH 7.0 phosphonate buffer (25 mL). Volatiles were removed in vacuo and the residue was then extracted with ethyl acetate (3 × 75 mL). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (50 mL) and brine (50 mL), dried over sodium sulfate. Removal of the solvent in vacuo followed by chromatography on silica gel, using ethyl acetate–hexane (1:4) as eluant, afforded the title compound **9** (1.82 g, 69%) as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17–7.40 (m, 9H), 6.79–6.82 (m, 2H), 5.47 (dd, 1H, $J = 4.0$ Hz, 8.7 Hz), 4.67 (t, 1H, $J = 8.8$ Hz), 4.43 (d, 1H, $J = 10.8$ Hz), 4.37 (d, 1H, $J = 10.7$ Hz), 4.23 (dd, 1H, $J = 4.1$ Hz, 8.9 Hz), 3.77 (s, 3H), 3.12 (dd, 1H, $J = 3.7$ Hz, 8.2 Hz), 2.39–2.57 (m, 2H), 0.93 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.31, 158.96, 153.61, 150.32, 139.06, 130.68, 129.20, 129.09, 128.52, 125.75, 121.45, 113.60, 86.45, 73.90, 69.85, 57.62, 55.17, 36.10, 34.70, 26.26; IR (film): 2958, 2869, 1778, 1698, 1613, 1513, 1248, 1197 cm^{-1}; $[\alpha]_D^{20} = +22.1$ (*c* 7.7, $CHCl_3$); HR-EIMS calcd for $C_{26}H_{31}NO_4$ 437.2202, found 437.2197.

4.5. (4*S*)-3-[(3*R*,5*S*)-5-(4-Methoxy-benzyloxy)-3,6,6-trimethyl-heptanoyl]-4-phenyl-oxazolidin-2-one, 10

To a suspension of copper(I) bromide–dimethylsulfide complex (1.62 g, 7.9 mmol) in THF–Me_2S (30 mL, 1:1) at −40 °C was added slowly a solution of methyl magnesium bromide (5.6 mL, 7.9 mmol, 1.4 M in Et_2O). One hour later, the yellow slurry was cooled to −78 °C and **9** (1.38 g, 3.16 mmol) in THF (10 mL) was added dropwise via a cannula. The reaction was maintained at −78 °C for 2 h, and then slowly warmed to room temperature and stirred overnight. A saturated aqueous solution of

NH_4Cl (20 mL) was used to quench the reaction and volatiles were removed in vacuo. The reaction mixture was further extracted with ethyl acetate (3×75 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. After concentration, the residue was subjected to chromatography on silica gel, eluting with ethyl acetate–hexane (1:4), to afford **10** (1.32 g, 92%) as a clear oil. De value (>95%) for this adduct was determined by NMR technicque. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.39 (m, 7H), 6.82–6.86 (m, 2H), 5.41 (dd, 1H, $J = 3.7$ Hz, 8.7 Hz), 4.63 (t, 1H, $J = 8.8$ Hz), 4.49 (dd, 2H, $J = 10.7$ Hz, 18.54 Hz), 4.22 (dd, 1H, $J = 3.7$ Hz, 8.9 Hz), 3.77 (s, 3H), 3.04 (dd, 1H, $J = 2.9$ Hz, 8.5 Hz), 2.95 (dd, 1H, $J = 4.7$ Hz, 10.6 Hz), 2.82 (dd, 1H, $J = 8.7$ Hz, 16.53 Hz), 2.17–2.25 (m, 1H), 1.37–1.52 (m, 2H), 0.92 (d, 3H, $J = 6.7$ Hz), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.93, 158.83, 153.67, 139.12, 131.26, 129.09, 129.05, 128.53, 125.74, 113.56, 85.22, 73.96, 69.74, 57.51, 55.13, 41.53, 38.41, 36.09, 27.27, 26.37, 21.22; IR (film): 2958, 2870, 1781, 1612, 1513 cm^{-1}; $[\alpha]_D^{20} = +17.8$ (c 3.1, $CHCl_3$); EI-HRMS calcd for $C_{27}H_{35}NO_5$ 453.2515, found 453.2512.

4.6. (5*S*,3*S*)-5-(4-Methoxy-benzyloxy)-3,6,6-trimethyl-heptan-1-ol, 11

To a solution of compound **10** (1.1 g, 2.4 mmol) in THF–H_2O (30 mL, 3:1) at 0 °C $NaBH_4$ (737 mg, 19.4 mmol) in cold water (2 mL) was added slowly. The mixture was stirred for 24 h at room temperature before being quenched carefully with 10% solution of citric acid (30 mL) at 0 °C THF was removed in vacuo and the residue was extracted with ethyl acetate (4×30 mL). The combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 and evaporated to leave an oily residue, which was then purified by chromatography on silica gel, using ethyl acetate–hexane (2:3) as eluant, to provide alcohol **11** (479 mg, 67.0%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.29 (m, 2H), 6.86–6.89 (m, 2H), 4.54 (s, 2H), 3.80 (s, 3H), 3.70–3.75 (m, 1H), 3.60–3.66 (m, 1H), 3.12 (dd, 1H, $J = 4.9$ Hz, 7.1 Hz), 1.71–1.83 (m, 2H), 1.39–1.42 (m, 2H), 1.26–1.32 (m, 1H), 1.20–1.22 (br, 1H), 0.96 (d, 3H, $J = 6.7$ Hz), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.92, 131.44, 129.02, 113.64, 85.42, 74.21, 61.03, 55.22, 39.28, 38.89, 36.12, 26.90, 26.46, 21.07; IR (film): 3377.3(br), 2954.7, 2869.9, 1613.2, 1513.9, 1248.9, 1109.7, 1037.9, 820.7, 771.7 cm^{-1}; $[\alpha]_D^{20} = -30.7$ (c 3.0, $CHCl_3$); EI-HRMS calcd for $C_{18}H_{30}O_3$ 294.2195, found 294.2191.

4.7. (3*R*,5*S*)-5-(4-Methoxy-benzyloxy)-3,6,6-trimethyl-heptanoic acid methoxy-methyl-amide 13 and (3*R*,5*S*)-5-(4-Methoxy-benzyloxy)-3,6,6-trimethyl-heptanoic acid [(*S*)-2-methoxymethyl carbamyloxy-1-phenyl-ethyl]-amide, 14

To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (31.2 mg, 0.32 mmol) in DCM (3 mL) at −30 °C was added $(CH_3)_3$)Al (160 μL, 0.32 mmol, 2.0 M in hexane). The reaction mixture was brought to an ice-water bath for 30 min and then cooled to −30 °C again before compound **10** (71.6 mg, 0.16 mmol) in DCM (0.5 mL) was added slowly via a cannula. The reaction mixture was then slowly warmed to room temperature and stirred overnight. Saturated aqueous solution of Rochelle's salt (10 mL) was used to quench the reaction, vigorous stirring was continued until the mixture became clear (ca. 1.5 h). Ethyl acetate (3×25 mL) was then used for extraction and the combined organic layers were washed with saturated aqueous solution of NH_4Cl (30 mL) and brine (30 mL), and dried over Na_2SO_4. Removal of the solvent in vacuo followed by chromatography on silica gel, using ethyl acetate–hexane as eluant, provided compound **13** (3:7 eluant recipe) (20 mg, 36%) as an oil and **14** (1:1 eluant recipe) (44 mg, 54%) as white needle-like crystal.

13 ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.33 (m, 2H), 6.85–6.88 (m, 2H), 4.60 (d, 1H, $J = 10.4$ Hz), 4.50 (d, 1H, $J = 10.2$ Hz), 3.79 (s, 3H), 3.68 (s, 3H), 3.20 (s, 3H), 3.08 (dd, 1H, $J = 3.3$ Hz, 8.0 Hz), 2.49–2.53 (m, 1H), 2.21–2.33 (m, 2H), 1.48 (ddd, 2H, $J = 3.2$ Hz, 8.0 Hz, 11.1 Hz), 1.02 (d, 3H, $J = 6.2$ Hz), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.06, 158.93, 131.39, 129.17, 113.66, 85.63, 74.12, 61.16, 55.25, 39.03, 38.60, 36.16, 32.12, 27.65, 26.47, 21.60; IR (film): 2957.3, 2869.7, 1660.2, 1514.1, 1463.0, 1385.3, 1248.9, 1173.9, 1072.7, 1036.8, 820.3, 749.8 cm^{-1}; $[\alpha]_D^{20} = -29.6$ (c 0.7, $CHCl_3$); EI-HRMS calcd for $C_{20}H_{33}NO_4$ 351.2490, found 351.2408.

14 ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23–7.35 (m, 7H), 6.82–6.87 (m, 2H), 6.50 (d, 1H, $J = 7.8$ Hz), 5.28–5.35 (m, 1H), 4.56 (dd, 2H, $J = 10.5$ Hz, 16.2 Hz), 4.43 (dd, 1H, $J = 7.9$ Hz, 11.5 Hz), 4.28 (dd, 1H, $J = 4.6$ Hz, 11.5 Hz), 3.77 (s, 3H), 3.59 (s, 3H), 3.10 (s, 3H), 3.09–3.12 (m, 1H), 2.43 (dd, 1H, $J = 5.4$ Hz, 13.6 Hz), 2.16–2.25 (m, 1H), 1.86–1.93 (m, 1H), 1.46–1.50 (m, 2H), 0.99 (d, 3H, $J = 6.7$ Hz), 0.93 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.00, 158.94, 157.04, 138.32, 131.11, 129.11, 128.63, 127.76, 126.63, 113.68, 85.35, 74.17, 67.62, 61.48, 55.17, 53.00, 43.56, 37.96, 36.18, 35.40, 28.48, 26.45, 21.10; IR (film): 3261.4, 2954.7, 1733.9, 1710.7, 1637.5, 2552.6, 1512.1, 1245.9, 1170.7, 1039.6, 808.1 cm^{-1}; $[\alpha]_D^{20} = +18.0$ (c 0.1, $CHCl_3$); mp: 146.1 °C; FAB HRMS calcd for $C_{29}H_{43}N_2O_6$ (M+1) 515.3121, found 515.3129.

4.8. (3*R*,5*S*)-5-(4-Methoxy-benzyloxy)-3,6,6-trimethyl-heptanal, 12

To a solution of $(COCl)_2$ (314.1 μL, 3.6 mmol) in DCM (7 mL) at −78 °C was added DMSO (514 μL, 5.38 mmol) in DCM (1.5 mL) via a cannula, the cloudy mixture was stirred for 10 min before alcohol **11** (527 mg, 1.79 mmol) in DCM (1.5 mL) was introduced. One hour later, DIPEA (1.5 mL, 10.76 mmol) was added slowly at −78 °C The reaction mixture was warmed to −60 °C within 1 h and quenched with a saturated aqueous solution of NH_4Cl. (10 mL). After that, the mixture was poured into ethyl acetate (150 mL), layers were separated and the organic phase was washed with water (30 mL) and brine (30 mL). This solution, after being dried over

Na_2SO_4, was concentrated in vacuo. The resulting crude product was subjected to chromatography on silica gel, using ethyl acetate–hexane (1:4) as eluant, to give the title aldehyde **12** (492 mg, 94%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 (dd, 1H, $J = 1.8$ Hz, 2.9 Hz), 7.25–7.29 (m, 2H), 6.84–6.89 (m, 2H), 4.57 (d, 1H, $J = 10.8$ Hz), 4.49 (d, 1H, $J = 10.9$ Hz), 3.79 (s, 3H), 3.05 (dd, 1H, $J = 3.7$ Hz, 8.0 Hz), 2.44–2.49 (m, 1H), 2.09–2.19 (m, 2H), 1.42–1.47 (m, 2H), 1.01 (d, 3H, $J = 6.5$ Hz), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.69, 159.06, 131.12, 129.12, 113.71, 85.22, 74.32, 55.20, 50.11, 38.70, 36.18, 26.44, 25.66, 21.52; IR (film): 2959.7, 2870.5, 1724.5, 1613.6, 1513.9, 1248.5, 1110.5, 1075.8, 1036.6, 821.2 cm^{-1}; $[\alpha]_D^{20} = -19.3$ (*c* 8.30, $CHCl_3$); EI-HRMS calcd for $C_{18}H_{28}O_3$ 292.2038, found 292.2046.

4.9. (3*R*,4*S*,6*S*,8*S*)-8-(4-Methoxy-benzyloxy)-3,6,9,9-tetramethyl-dec-1-en-4-ol, 15

To a solution of KOBu^t (301.3 mg, 2.69 mmol) in THF (5 mL) in a three-neck round bottom flask equipped with an argon inlet and a dry ice–acetone condenser was added *trans*-2-butene (ca. 0.4 g) at −78 °C, followed by addition of *n*-BuLi (1.78 mL, 2.69 mmol, 1.51 M in hexane). Upon the end of addition, the mixture was moved to a −45 °C cooling bath and kept there for 45 min. The resulting orange solution was again cooled to −78 °C and (+)-*B*-OMe(Ipc)$_2$ (908 mg, 2.87 mmol) in THF (2.5 mL) was added slowly along the inner sides of the flask. One hour later, $BF_3{\cdot}OEt_2$ (386 μL, 3.05 mmol) was added and the mixture was brought to −100 °C when aldehyde **12** (524 mg, 1.8 mmol) in THF (3 mL) was added to the flask within 30 min. The reaction mixture was stirred at −78 °C for further 12 h and then quenched by addition of Et_3N (2 mL) and H_2O_2 (2 mL, 50% solution). After being stirred at room temperature for 3 h, the solution was diluted with brine (15 mL). The volatiles were removed in vacuo and the residue was then extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over Na_2SO_4 and evaporated under reduced pressure. After concentration, the residue was subjected to chromatography on silica gel, using ethyl acetate–hexane (1:4) as eluant to afford **15** (329 mg, 53%) as an oil. De value (>95%) of the title compound was determined by NMR technique. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.29 (m, 2H), 6.82–6.86 (m, 2H), 5.70–5.79 (m, 1H), 5.08–5.13 (m, 2H), 4.61 (d, 1H, $J = 10.5$ Hz), 4.49 (d, 1H, $J = 10.4$ Hz), 3.77 (s, 3H), 3.71–3.78 (m, 1H), 3.48 (m, 1H), 3.10 (dd, 1H, $J = 2.6$ Hz, 9.1 Hz), 2.11–2.19 (m, 1H), 1.89–2.01 (m, 1H), 1.51–1.57 (m, 1H), 1.40–1.49 (m, 1H), 1.29–1.38 (m, 1H), 1.06–1.16 (m, 1H), 1.02 (d, 3H, $J = 6.8$ Hz), 0.95 (d, 3H, $J = 6.6$ Hz), 0.92 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.89, 140.58, 131.61, 129.11, 116.17, 113.61, 85.19, 74.09, 72.26, 55.19, 45.18, 40.75, 39.75, 36.07, 26.59, 26.48, 20.88, 16.15; IR (film): 3480.4(br), 2961.5, 2868.8, 1612.9, 1513.9, 1248.3, 1086.2, 1037.4, 810.3, 702.3 cm^{-1}; $[\alpha]_D^{20} = -60.4$ (*c* 2.5, $CHCl_3$). EI-HRMS calcd for $C_{22}H_{36}O_3$ 348.2664, found 348.2658.

4.10. (3*R*,4*S*,6*S*,8*S*)-8-(4-Methoxy-benzyloxy)-3,6,9,9-tetramethyl-4-(*tert*-butyldimethylsilanyloxy)-dec-1-en, 16

To a solution of TBSCl (354 mg, 2.35 mmol) in DMF (0.5 mL) at 0 °C was added alcohol **15** (329 mg, 0.94 mmol) in DMF (0.5 mL), followed by addition of imidazole (320 mg, 4.7 mmol) under argon. The mixture was then stirred at room temperature for 16 h before it was poured into ethyl acetate–benzene (150 mL, 3:1). The mixture was washed sequentially with water (50 mL), saturated aqueous solution of NH_4Cl (50 mL), and brine (50 mL). The organic solution was then dried over sodium sulfate and evaporated in vacuo. The residue was purified by chromatography on silica gel, using ethyl acetate–hexane (1:9) for elution, to produce **16** (406 mg, 93%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.29 (m, 2H), 6.81–6.88 (m, 2H), 5.72–5.79 (m, 1H), 5.00–5.05 (m, 2H), 4.62 (d, 1H, $J = 10.9$ Hz), 4.47 (d, 1H, $J = 10.9$ Hz), 3.81 (s, 3H), 3.82 (td, 1H, $J = 3.0$ Hz, 9.5 Hz), 3.07 (dd, 1H, $J = 4.5$ Hz, 6.4 Hz), 2.37–2.41 (m, 1H), 1.79–1.84 (m, 1H), 1.58–1.65 (m, 1H), 1.40–1.43 (m, 2H), 1.04 (d, 3H, $J = 6.9$ Hz), 0.94 (d, 3H, $J = 6.6$ Hz), 0.92–0.94 (m, 1H), 0.92 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.82, 141.00, 131.70, 128.72, 114.37, 13.56, 85.53, 73.57, 73.00, 55.21, 43.92, 40.37, 38.89, 36.06, 26.62, 26.44, 25.94, 20.65, 18.12, 13.20, −4.27, −4.41; IR (film): 2956.0, 2864.9, 1513.9, 1248.7, 1111.3, 1041.9, 909.6, 835.2, 773.3 cm^{-1}; $[\alpha]_D^{20} = +29.85$ (*c* 2.1, $CHCl_3$); EI-HRMS calcd for $C_{28}H_{50}SiO_3$ 462.3529, found 462.3535.

4.11. (2*S*,3*S*,5*S*,7*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-7-(4-methoxy-benzyloxy)-2,5,8,8-tetramethyl-nonanoic acid, 4

Alkene **16** (270 mg, 0.58 mmol) was dissolved in *t*-BuOH–acetone–H_2O (5 mL, 2:3:3) and chilled with ice-water bath, NMO (315 mg, 1.17 mmol, 50 wt % in H_2O), followed by OsO_4 (0.28 mL, 0.011 mmol, 10 mg/mL in H_2O) and $CH_3SO_2NH_2$ (55.5 mg, 0.58 mmol), was added to the above solution. After being vigorously stirred for 24 h at room temperature, the reaction was quenched with Na_2SO_3 (440.7 mg, 3.498 mmol). The mixture was stirred for further 3 h and then diluted with brine (5 mL). Volatiles were removed in vacuo and the residue was extracted with ethyl acetate (3 × 30 mL). The combined organic layers, were washed with brine (30 mL), dried over Na_2SO_4, and concentrated to provide the corresponding diol (256 mg). To a solution of the diol in dichloromethane (15 mL), a pre-coated $NaIO_4$–SiO_2 (2.2 g, 1.29 mmol, 1 mmol/1.7 g) was added and the resulted suspension was then stirred at room temperature for 20 min. The reaction mixture was filtered and the inorganic cake was washed with ethyl acetate (150 mL). The combined filtrates were dried over Na_2SO_4 and concentrated to provide the crude aldehyde, which was used in next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (d, 1H, $J = 1.5$ Hz), 7.25–7.26 (m, 2H), 6.83–6.86 (m, 2H), 4.56 (d, 1H, $J = 10.9$ Hz), 4.47 (d, 1H, $J = 10.8$ Hz), 4.20 (td, 1H, $J = 3.6$ Hz, 9.0 Hz), 3.79 (s, 3H), 3.04 (dd, 1H, $J = 4.4$ Hz, 6.6 Hz), 2.54–2.58 (m, 1H), 1.74–1.85 (m, 2H), 1.38–1.44 (m, 2H),

1.22–1.30 (m, 1H), 1.15 (d, 3H, $J = 7.0$ Hz), 0.99 (d, 3H, $J = 6.6$ Hz), 0.91 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.21, 158.84, 131.49, 128.66, 113.59, 85.54, 73.63, 70.11, 55.23, 41.13, 40.13, 36.10, 29.67, 26.70, 26.41, 25.81, 20.68, 18.03, 8.99, −4.20, −4.63.

To a solution of the above aldehyde in *t*-BuOH–H_2O (3 mL, 2:1), 2-methyl-2-butene (0.2 mL) was added at 0 °C. A solution of $NaClO_2$ (140 mg, 1.55 mmol) in a pH 4.5 buffer (1.5 mL, prepared from water and 1.0 M NaH_2PO_4) was then added to the above aldehyde solution. After being stirred at 0 °C for 5 min, the reaction mixture was stirred at room temperature for further 15 min and then diluted with brine (5 mL). The volatiles were removed in vacuo and the residue was then extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (40 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo followed by chromatography on silica gel, eluting with ethyl acetate–hexane (3:7), to afford the title acid **4** (250 mg, 89%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50–9.01 (br, 1H), 7.26 (d, 2H, $J = 9.1$ Hz), 6.84–6.87 (m, 2H), 4.59 (d, 1H, $J = 10.9$ Hz), 4.47 (d, 1H, $J = 11.0$ Hz), 4.13–4.17 (m, 1H), 3.80 (s, 3H), 3.05 (dd, 1H, $J = 4.4$ Hz, 6.5 Hz), 2.69–2.76 (m, 1H), 1.72–1.81 (m, 2H), 1.37–1.40 (m, 2H), 1.20 (d, 3H, $J = 7.1$ Hz), 0.95–1.00 (m, 1H), 0.97 (d, 3H, $J = 6.5$ Hz), 0.91 (s, 9H), 0.87 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.57, 158.85, 131.54, 128.69, 113.61, 85.58, 73.63, 71.02, 55.26, 45.87, 40.13, 36.11, 29.68, 26.73, 26.43, 25.81, 20.71, 17.99, 11.00, −4.26, −4.78; IR (film): 3000.0(br), 2954.9, 2929.5, 2856.6, 1709.1, 1514.2, 1463.7, 1249.1, 1111.8, 1041.8, 836.4, 775.1 cm^{-1}; $[\alpha]_D^{20} = -20.5$ (*c* 1.5, $CHCl_3$); EI-HRMS calcd for $C_{27}H_{48}SiO_5$ 480.3271, found 480.3277.

4.12. (*S*)-Acrylic acid 1-*tert*-butyl-but-3-enyl ester, 17

To a solution of homoallylic alcohol **6** (0.8 g, 6.25 mmol) dissolved in Et_2O (30 mL) at 0 °C acryloyl chloride (0.73 mL, 8.12 mmol) in Et_2O (5 mL), followed by Et_3N (2.6 mL, 18.8 mmol) in Et_2O (8 mL), were added successively. The reaction mixture was then stirred at room temperature for 12 h before it was poured into cold water (30 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (30 mL), NH_4Cl (30 mL) and brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel, using diethyl ether–pentane (1:4) as eluant, to produce the title ester **17** (1.05 g, 92%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.39 (dd, 1H, $J = 1.6$ Hz, 15.3 Hz), 6.11 (dd, 1H, $J = 10.5$ Hz, 17.49 Hz), 5.81 (dd, 1H, $J = 1.7$ Hz, 10.4 Hz), 5.66–5.78 (m, 1H), 4.96–5.07 (m, 2H), 4.87 (dd, 1H, $J = 2.7$ Hz, 1.0 Hz), 2.36–2.45 (m, 1H), 2.16–2.27 (m, 1H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.99, 135.08, 130.25, 128.79, 117.03, 79.84, 34.64, 34.59, 26.90; IR (film): 2967.8, 2920.9, 2880.4, 1726.8, 1642.8, 1480.6, 1405.1, 1367.1, 1295.5, 1270.6, 1191.1, 1045.3, 985.1, 914.9, 807.2 cm^{-1}; $[\alpha]_D^{20} = +18.7$ (*c* 7.0, *n*-pentane) EI-HRMS calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1299.

4.13. (6*S*)-6-*tert*-Butyl-5,6-dihydro-pyran-2-one, 18

To a solution of compound **17** (400 mg, 2.2 mmol) in DCM (60 mL, degassed) was introduced $(PCy_3)_2Cl_2Ru{=}CHPh$ (179 mg, 0.22 mmol) dissolved in DCM (10 mL, degassed) at room temperature. The total volume of the reaction was then made up to 110 mL with degassed DCM and the mixture was brought to reflux for 6 h. The solvent was removed by fractional distillation. The residue was purified by chromatography on silica gel, using ether–pentane (2:3) as eluant to give the title lactone **18** (298 mg, 88%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88–6.94 (m, 1H), 5.32–5.97 (m, 1H), 4.05 (dd, 1H, $J = 5.5$ Hz, 10.8 Hz), 2.28–2.33 (m, 2H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.41, 145.65, 120.87, 85.18, 36.64, 25.18, 24.57; IR (film): 2961.9, 2920.9, 2880.4, 1726.7, 1391.0, 1251.2, 1084.5, 1044.9, 1028.9, 816.9 cm^{-1}; $[\alpha]_D^{20} = -115.2$ (*c* 3.5, *n*-pentane); EI-HRMS calcd for $C_9H_{14}O_2$ 154.2063, found 154.2061.

4.14. (4*R*,6*S*)-6-*tert*-Butyl-4-methyl-tetrahydro-pyran-2-one, 19

CuCN (183.5 mg, 2.16 mmol, dried under high vacuum at 70 °C for 12 h), was suspended in Et_2O (6 mL) at −78 °C. To this suspension MeLi (3.3 mL, 4.32 mmol, 1.3 M in Et_2O) was added. Five minutes later, the reaction mixture was brought to an ice-water bath and stirred for additional 20 min and was then re-cooled to 78 °C again before unsaturated lactone **18** (280 mg, 1.8 mmol) in Et_2O (4 mL) was added via a cannula. The reaction was kept at −78 °C or 20 min and warmed up to −45 °C within 30 min, then to −20 °C within another 30 min. The reaction mixture was diluted with Et_2O (25 mL), followed by addition of 20% aqueous acetic acid (20 mL). The above mixture was further stirred at 0 °C for 2 h and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$ (30 mL), brine (30 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo followed by chromatography on silica gel, using Et_2O–pentane (2:3) as eluant, to give the title compound **19** (263 mg, 86%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (dd, 1H, $J = 3.8$ Hz, 11.8 Hz), 2.42–2.51 (m, 1H), 2.13–2.22 (m, 2H), 1.81 (ddd, 1H, $J = 10.4$ Hz, 11.8 Hz, 14.0 Hz), 1.51 (dddd, 1H, $J = 0.6$ Hz, 4.1 Hz, 4.1 Hz, 13.9 Hz), 1.10 (d, 3H, $J = 6.6$ Hz), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.84, 83.49, 36.89, 33.72, 29.68, 25.11, 24.07, 20.99; IR (film): 2960.3, 2880.4, 1743.1, 1367.2, 1285.1, 1241.5, 1073.5, 1002.6 cm^{-1}; $[\alpha]_D^{20} = +28.3$ (*c* 3.2, Et_2O); EI-HRMS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1313.

4.15. (3*R*,5*S*)-5-Hydroxy-3,6,6-trimethyl-heptanoic acid methoxy-methyl-amide, 20

To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (88 mg, 0.9 mmol) in DCM (2 mL) at −78 °C $Al(CH_3)_3$ (450 μL, 0.9 mmol, 2.0 M in hexane) was

added slowly. The solution was allowed to warm to room temperature and stirred overnight. The reaction vessel was chilled in ice-water bath and lactone **19** (51 mg, 0.3 mmol) in DCM (2 mL) was then added. The reaction mixture was stirred for another 6 h at room temperature before it was quenched at 0 °C with Rochelle's salt (1.0 g, 3.6 mmol) in water (5 mL). After the solution became clear (ca. 2 h), it was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by chromatography on silica gel, using ethyl acetate–hexane (2:3) as eluant, to afford Weinreb amide **20** (58 mg, 91%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.20 (s, 3H), 3.15 (dd, 1H, $J = 2.8$ Hz, 9.8 Hz), 2.80–3.00 (br, 1H), 2.25–2.51 (m, 3H), 1.38 (ddd, 2H, $J = 4.1$ Hz, 9.7 Hz, 9.7 Hz), 1.04 (d, 3H, $J = 6.6$ Hz), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.74, 76.36, 61.13, 39.41, 38.15, 34.66, 32.27, 26.29, 25.85, 22.23; IR (film): 3440.4(br), 2956.2, 2870.3, 1650.8, 1463.0, 1387.8, 1179.9, 1093.9, 1006.1, 987.5 cm^{-1}; $[\alpha]_D^{20} = -22.9$ (c 2.6, $CHCl_3$); EI-HRMS calcd for $C_{12}H_{25}NO_3$: 213.1729, found 213.1727.

4.16. (3*R*,5*S*)-5-(4-Methoxy-benzyloxy)-3,6,6-trimethyl-heptanoic acid methoxy-methyl-amide, 13

To a suspension of NaH (8.8 mg, 0.22 mmol, 60% dispersion) in THF (1 mL) at −10 °C were added solutions of amide **20** (26 mg, 0.11 mmol), TBAI (7.42 mg, 0.02 mmol) dissolving in THF (1.5 mL) PMB-Br (44.00 mg, 0.22 mmol) in THF (0.5 mL) via a cannula. The reaction mixture was stirred at room temperature for 16 h and then quenched with cold water (5 mL). Volatiles were removed under reduced pressure and the residue was extracted with ethyl acetate (3×30 mL). The combined organic layers were washed with saturated aqueous solution of NH_4Cl (30 mL), brine (30 mL), and dried over Na_2SO_4. Purification by chromatography on silica gel gave the title compound **13** (35 mg, 91%). Spectra and other characteristic data were identical with the same product obtained previously.

4.17. (3*R*,5*S*)-5-(4-Methoxy-benzyloxy)-3,6,6-trimethyl-heptanal, 12

To a solution of substrate **13** (170 mg, 0.46 mmol) in DCM (15 mL), DIBAL-H (120 μL, 0.12 mmol, 1.0 M in hexane) was added at −78 °C. The reaction mixture was stirred for 30 min at −78 °C and then quenched with a saturated solution of Rochelle's salt (30 mL) and Et_2O (20 mL). The resulting two-phase mixture was then vigorously stirred at room temperature for 2 h. Layers were separated, and the aqueous phase was further extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4. Removal of the solvent in vacuo followed by chromatography on silica gel, using ethyl acetate–hexane (1:4) as eluant, to afford aldehyde **12** (130 mg, 92%).

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References and notes

1. Burja, A. M.; Banaigs, B.; Abou-Mansour, E.; Burgess, J. G.; Wright, P. C. *Tetrahedron* **2001**, *57*, 9347–9377.
2. Gerwick, W. H.; Tan, L. T.; Sitachitta, N. Nitrogen-containing Metabolites from Marine Cyanobacteria. In *Alkaloids*. 2001, p 184.
3. Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J.; Corbett, T. H. *J. Am. Chem. Soc.* **2001**, *123*, 5418–5423.
4. Luesch, H.; Yoshida, Y.; Moore, R. E.; Paul, V. J. *Bioorg. Med. Chem.* **2002**, *10*, 1973–1978.
5. Xu, Z. S.; Chen, Z. Y.; Ye, T. *Abstracts of Papers*, 225th ACS National Meeting, New Orleans, LA, United States, March 23–27, 2003; American Chemical Society: Washington, DC, 2003; ORGN-415.
6. Boden, C. D. J.; Pattenden, G.; Ye, T. *Synlett* **1995**, 417–419.
7. Muir, J. C.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2243–2250.
8. Chen, J.; Forsyth, C. J. *Org. Lett.* **2003**, *5*, 1281–1283, and references cited therein.
9. Kedrowski, B. L.; Heathcock, C. H. *Heterocycles* **2002**, *58*, 601–634.
10. Fukuyama, T.; Xu, L. H. *J. Am. Chem. Soc.* **1993**, *115*, 8449–8450.
11. Raman, P.; Razavi, H.; Kelly, J. W. *Org. Lett.* **2000**, *2*, 3289–3292.
12. Wipf, P.; Venkatraman, S. *Synlett* **1997**, 1–10.
13. Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267–6270.
14. Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *35*, 5397–5400.
15. Ino, A.; Murabayashi, A. *Tetrahedron* **1999**, *55*, 10271–10282.
16. Charette, A. B.; Chua, P. *J. Org. Chem.* **1998**, *63*, 908–909.
17. North, M.; Pattenden, G. *Tetrahedron* **1990**, *46*, 8267–8290.
18. Brown, H. C.; Ramachandran, P. V. *J. Organomet. Chem.* **1995**, *500*, 1–19.
19. Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401–404.
20. Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093.
21. Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293–294.
22. Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919–5923.
23. Nicolas, E.; Russell, K. C.; Hruby, B. J. *J. Org. Chem.* **1993**, *58*, 766–770.
24. Li, G.; Patel, D.; Hruby, V. J. *Tetrahedron: Asymmetry* **1993**, *4*, 2315–2318.
25. Zhong, Y.-L.; Shing, T. K. M. S. *J. Org. Chem.* **1997**, *62*, 2622–2624.
26. Wadsworth, W. S., Jr. *Org. React.* **1977**, *25*, 73–253.
27. Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761.

28. Sugiyama, H.; Shioiri, T.; Yokokawa, F. *Tetrahedron Lett.* **2002**, *43*, 3489–3492.
29. Wu, M.; Okino, T.; Nogle, L. M.; Marquez, B. L.; Williamson, R. T.; Sitachitta, N.; Berman, F. W.; Murray, T. F.; McGough, K.; Jocobs, R.; Colsen, K.; Asano, T.; Yokokawa, F.; Shioiri, T.; Gerwick, W. H. *J. Am. Chem. Soc.* **2000**, *122*, 12041–12042.
30. Ishizaki, M.; Hara, Y.; Kojima, S.; Hoshino, O. *Heterocycles* **1999**, *50*, 779–790.
31. Romo, D.; Rzasa, R. M.; Shea, H. A.; Park, M.; Langenham, J. M.; Sun, L.; Akhizer, A.; Liu, J. O. *J. Am. Chem. Soc.* **1998**, *120*, 12237–12254.
32. Prashad, M.; Har, D.; Kim, H. Y.; Repic, O. *Tetrahedron. Lett.* **1998**, *39*, 7067–7070.
33. Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307–312.
34. Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171–4174.
35. Smith, A. B., III; Beauchamp, T. J.; LaMarche, M. J.; Kaufman, M. D.; Qiu, Y.; Arimoto, H.; Jones, D. R.; Kobayashi, K. *J. Am. Chem. Soc.* **2000**, *122*, 8654–8664.
36. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
37. Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.
38. Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *32*, 18–29.
39. Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1988**, *39*, 4651–4654.
40. Ghosh, A. K.; Liu, C. *Chem. Commun.* **1999**, 1743–1744.
41. Ramachandran, P. V.; Reddy, M. V. R.; Brown, H. C. *Tetrahedron Lett.* **2000**, *41*, 583–586.
42. Morgan, J. P.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 3153–3155.
43. Nicolaou, K. C.; Pihko, P. M.; Diedrichs, N.; Zou, N.; Bernal, F. *Angew. Chem., Int. Ed.* **2001**, *40*, 1262–1265.
44. Held, C.; Frohlich, R.; Metz, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1058–1060.
45. Cossy, J.; Pradaux, F.; BouzBouz, S. *Org. Lett.* **2001**, *3*, 2233–2235.
46. Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 2777–2780.
47. Bhattacharjee, A.; Soltani, O.; DeBrabander, J. K. *Org. Lett.* **2002**, *4*, 481–484.
48. Reddy, Y. K.; Falck, J. R. *Org. Lett.* **2002**, *4*, 969–971.
49. Du, Y.; Wiemer, D. F. *J. Org. Chem.* **2002**, *67*, 5701–5708.
50. Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513–3516.
51. Wang, Y. G.; Kobayashi, Y. *Org. Lett.* **2002**, *4*, 4615–4618.
52. Esumi, T.; Okamoto, N.; Hatakeyama, S. *Chem. Commun.* **2002**, 3042–3043.
53. Wildemann, H.; Duenkelmann, P.; Mueller, M.; Schmidt, B. *J. Org. Chem.* **2003**, *68*, 799–804.
54. For a CuI mediated conjugate additions of Methyl Lithium to an α,β-unsaturated lactone, see: Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980**, *45*, 4117–4121.
55. For mixed higher order cyanocuprate-mediated conjugate additions, see: Lipshutz, B. H. *Tetrahedron Lett.* **1983**, *24*, 127–130, and Refs. 56, 57.
56. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowskl, J. A. *Tetrahedron* **1984**, *40*, 5005–5038.
57. Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135–631.
58. Czernecki, S.; Georgoulis, C.; Provelenghiou, C.; Fusey, G. *Tetrahedron Lett.* **1976**, *17*, 3535–3536.
59. Czernecki, S.; Georgoulis, C.; Provelenghiou, C.; Fusey, G. *Tetrahedron Lett.* **1976**, *17*, 3535–3536.