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Total synthesis of palmyrolide A and its 5,7-*epi* isomers

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ABSTRACT

Stereoselective total synthesis of palmyrolide A, a 15-membered neuroactive macrolide, was described by adopting a synthetic strategy developed for the proposed structures, and its 5,7-*epi* isomers. The strategy was designed in such a way that the set of stereoisomers, which were needed for establishing the absolute configuration of palmyrolide A, could be obtained from one time operation. The diastereoselective hydrogenation of *exo*-methylene-γ-butyrolactone to α-methyl-γ-butyrolactone, Yamaguchi esterfication, and intramolecular dehydrative cyclization to form *trans*-enamide were the key steps involved in the synthesis.

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1. Introduction

Marine cyanobacteria constitute a rich source of novel bioactive secondary metabolites with unprecedented structural skeletons. A class of macrolides with a rare *N*-methyl enamide, and 1,3-methyl and tertiary butyl containing branch linked through lactone such as laingolide (**1**), laingolide A (**2**) and madangolide (**3**) were isolated from *Lyngbya bouillonii*.[1] Structurally related neuroactive 15-membered macrolide palmyrolide A was isolated from a marine cyanobacterial assemblage composed of *Leptolyngbya* and *Oscillatoria* spp. collected from Palmyra Atoll.[2] It has shown sodium channel blocking activity in neuro-2a cells (IC_{50}=5.2 μM) without appreciable cytotoxicity. Based on the NMR studies, planar structure was established for former molecules (**1**–**3**). While for the palmyrolide A, in addition to the planar structure, the absolute configuration at C(14)[3] was determined as *R* by comparing the data of the degradation product obtained from palmyrolide A and the known 2-methylglutaric acid and its derivatives. As the ester hydrolysis was resistant in palmyrolide A, the absolute configuration at C(5) and C(7) was not established but it was proposed[2] that the methyl at C(5) and the *tert*-butyl at C(7) are in *syn* relation as shown in **4** and **4a** (Fig. 1) based on carbon-proton spin-coupling constants.[4]

Impressive biological activity associated with stereochemical challenges stimulated the synthetic groups. The first total synthesis was reported by Maio and co-workers, which revealed the absolute configuration of palmyrolide A[5] and subsequently the second total synthesis was reported very recently by Brimble and co-workers.[6] In the first total synthesis, the key macrocyclization step was relied on the *trans*-enamide formation catalysed by copper(I) iodide and caesium carbonate where the second synthesis was achieved using a sequential ring closing metathesis/olefin isomerization reaction. We report herein, intramolecular dehydrative cyclization is as a key macrocyclization step and three synthetic routes to the macrolide: one for the proposed structures *syn* **4** & **4a**, one for the *anti* **4b** & **4c**, and a final for the stereoselective synthesis of palmyrolide A (**4b**) in which two fragments are derived from the same starting material.

We envisioned that developing a synthetic strategy for the synthesis of palmyrolide A would also be applicable in the synthesis of other molecules of this class. The synthesis of palmyrolide A could primarily be from assembling of fragments **A** and fragment **B** (Fig. 1) by either first intermolecular condensation to form enamide and late-stage macrolactonization approach or esterfication and intramolecular enamide formation sequence. At the outset of our plan, the absolute configuration of palmyrolide A had not yet been disclosed, thus, it was expected that the assembling of fragment B with four possible stereoisomers of fragment A, independently, would lead finally required number of isomers to establish the absolute configuration of palmyrolide A. We devised a strategy in such a way that the set of stereoisomers **4** & **4a**, proposed structures of palmyrolide A,[2] or **4b** & **4c** could be obtained in one time operation rather than for each isomer following separate steps.

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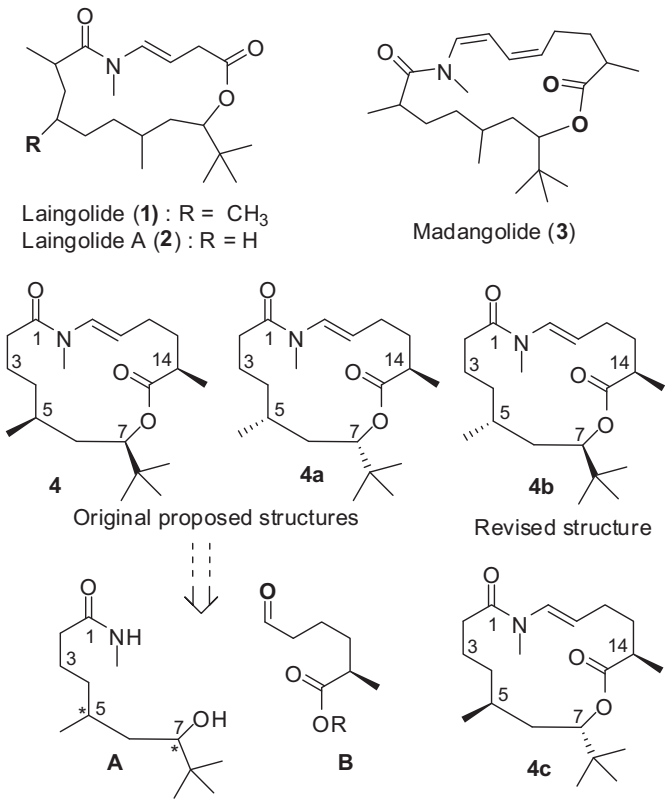


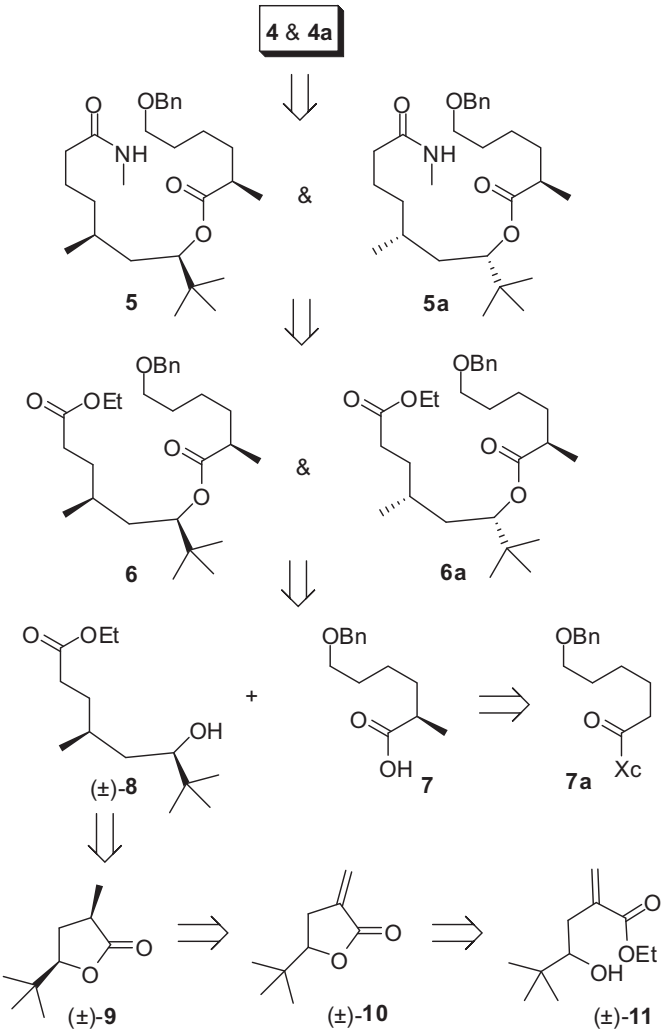
Fig. 1. Structure of laingolides (**1**–**2**), madangolide (**3**), proposed structures (**4** & **4a**),[2] and revised structure (**4b**),[5,6] 5,7-*epi* isomer (**4c**), and fragments A and B of palmyrolide A.

2. Results and discussion

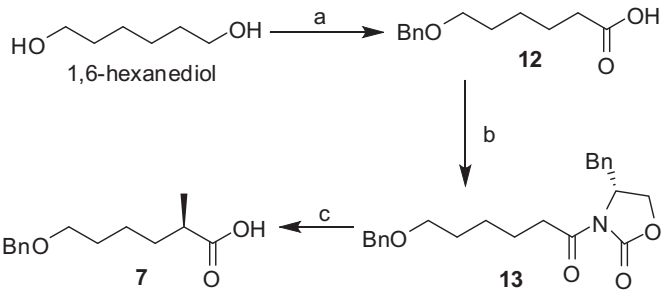
According to our retrosynthetic analysis shown in Scheme 1, **4** and **4a** could be derived from **5** and **5a** by deprotection of *O*-benzyl, oxidation of primary hydroxyl and subsequent dehydrative cyclization. Key intermediates **5** and **5a** could be obtained from ethyl ester hydrolysis of **6** and **6a**, homologation, followed by amide formation. The ester **6** and **6a** could easily be accessible from joining of two fragments **7** and (±)-**8**. Acid **7** could easily be procured from **7a** by the chiral auxiliary based approach while (±)-**8** could be obtained from γ-butyrolactone (±)-**9** by reduction of lactone to lactol, 2C-Wittig reaction, and hydrogenation sequence. The synthesis of γ-butyrolactone (±)-**9**, in turn, was planned from diastereoselective hydrogenation of *exo*-methylene-γ-butyrolactone (±)-**10**, which could be obtained from homo allylic alcohol (±)-**11**.

Synthesis of the first fragment **7** was begun from commercially available 1,6-hexanediol. Controlled benzyl group protection on 1,6-hexanediol gave monobenzyl ether, which was in two-step oxidation sequence furnished acid **12** (Scheme 2). Treatment of **12** with pivaloyl chloride and subsequent treatment with lithiated (*R*)-4-benzyl-2-oxazolidinone afforded **13**. Methylation of **13** at −78 °C followed by basic hydrolysis afforded **7** in 60% yield from **12** (*dr* 97.4:2.6 at methylation step).

The synthesis of fragment (±)-**8** (Scheme 3) was commenced from (±)-**11**, which was synthesized by reacting trimethylacetaldehyde and ethyl α-bromomethylacrylate under Reformatsky-type reaction conditions reported in literature.[7] Homoallylic alcohol (±)-**11** was converted to lactone (±)-**10** under acidic conditions in quantitative yield. Hydrogenation of (±)-**10** provided exclusively one diastereomer (±)-**9** in excellent yield.[7c,8] Here, the racemic (±)-**9** is pivotal in the simultaneous synthesis of **4** & **4a**. The enantioselective synthesis of **4** or **4a** could be achieved from



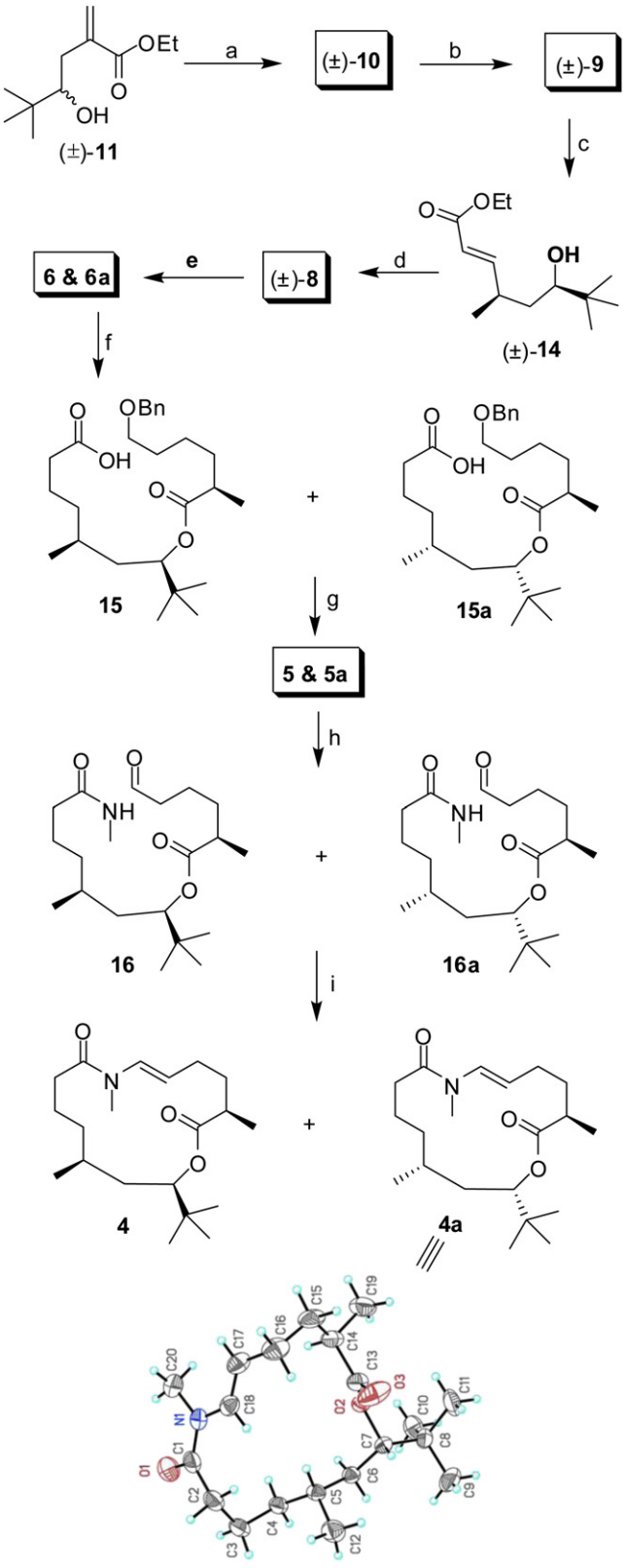
Scheme 1. Retrosynthetic analysis for **4** & **4a**.



Scheme 2. Synthesis of **7**. a) (i) NaH, BnBr, TBAI, THF, 12 h; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1.5 h; (iii) $NaClO_2$, NaH_2PO_4, ^tBuOH/2-methyl-2-butene (2:1), 2 h, 61% (3 steps); b) Piv-Cl, Et_3N, (*R*)-4-benzyl-2-oxazolidinone, LiCl, THF, −20 °C, 4 h, 85%; c) (i) NaHMDS, MeI, −78 °C, 3 h, 75%; ii) $LiOH·H_2O$, H_2O_2, THF/H_2O, 3 h, 95%.

enantiomerically pure **9**, which could be derived from enantiomerically pure *exo*-methylene-γ-butyrolactone[9] **10**. The racemic (±)-**9** was converted to (±)-**14** in two steps such as reduction of lactone to lactol followed by 2C-Wittig reaction. Hydrogenation of (±)-**14** produced (±)-**8**, which was coupled with **7** by using Yamaguchi esterfication[10] to yield inseparable diastereomers **6** & **6a** in 87% yield over two steps.

Chemoselective ester hydrolysis of **6** & **6a**, as expected,[11] furnished acid, which was homologated to give **15** & **15a** in 63% yield



Scheme 3. Synthesis of **4** and **4a**. a) PTSA, toluene, 2 h, quantitative yield; b) H_2, Pd/C, EtOH, 2 h, 92%; c) (i) DIBAL-H, toluene, −78 °C, 1.5 h; ii) Ph_3PCHCO_2Et, CH_2Cl_2, reflux, 2 d, 77% (2 steps); d) H_2, Pd/C, EtOH, 2 h, 92%; e) **7**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF, 12 h, 94%; f) (i) $LiOH·H_2O$, THF/MeOH/H_2O (3:1:1), 3 h; (ii) EtOCOCl, Et_3N, THF, CH_2N_2, 3 h; (iii) CH_3CO_2Ag, dioxane/H_2O, ultrasound irradiation, 0.5 h, 63% (3 steps); g) CH_3NH_2.HCl, DCC, HOBt, Et_3N, CH_2Cl_2, 6 h, 94%; h) (i) H_2, Pd/C, MeOH, 2 h, 93%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1.5 h, 92%; i) TFA, benzene, reflux, 3 d, 33% (55%, brsm). Inset: ORTEP representation of the X-ray crystal structure of **4a**: the molecular structure of **4a**, with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius.

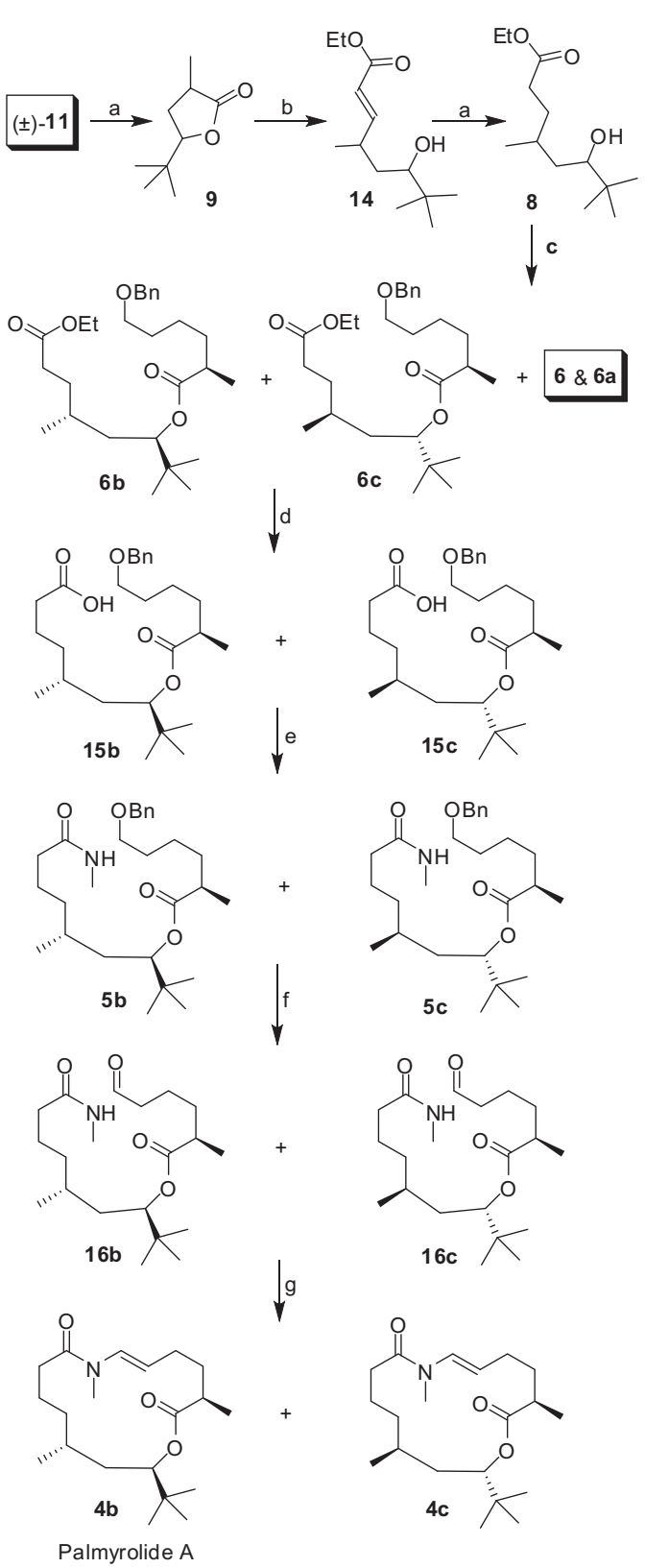
over three steps. Treatment of **15** & **15a** with DCC, HOBt, Et_3N and CH_3NH_2.HCl[12] provided **5** & **5a**, which were subjected for hydrogenolysis followed by Swern oxidation to give expected aldehydes **16** & **16a**. Finally, dehydrative cyclization[13] using TFA in benzene and 4 (Å) MS under reflux conditions afforded the desired column chromatographic separable cyclic products **4** & **4a** (1:1.7 ratio) in 33% combined yield and 55% yield based on recovery of starting material (brsm). Crystal structure of **4a**[14] confirmed the absolute configuration of **4** and **4a**, evident that there was no *syn* relation between the methyl at C(5) and the *tert*-butyl at C(7) as for the proposed structures of palmyrolide A.[2]

The simultaneous synthesis for **4b** & **4c** was planned from (±)-**11** (Scheme 4). Hydrogenation of (±)-**11** furnished **9**, a mixture of *syn* and *anti* (1:1). Subsequently followed the same sequence of reactions such as reduction and 2C-Wittig reaction, **9** gave **14**, which was converted to **8**. Assembling of **8** with **7** delivered column chromatographically separable *syn* **6** & **6a** and *anti* **6b** & **6c** (*syn* and *anti* 1:1) in 94% combined yield. The diastereomeric mixture of *anti* **6b** & **6c** was subjected to ester hydrolysis followed by the Arndt–Eistert synthesis allowed the formation of homologated carboxylic acids **15b** & **15c** in 63% yield (two steps). Treatment of acids **15b** & **15c** with methylamine in the presence of coupling reagents afforded amides **5b** & **5c** in 94% yield. Hydrogenolysis of **5b** & **5c** and subsequent oxidation furnished the aldehydes **16b** & **16c** in a yield of 86%. Intramolecular cyclization afforded column chromatographically separable diastereomers **4b** & **4c** (1:2 ratio) in combined yield of 33% and 55% yield brsm. One of these diastereomers, **4b** is identical in all respects with the palmyrolide A. Unsuccessful in getting the crystal structure of any of these isomers **4b** & **4c**, the absolute stereochemistry was confirmed only after the report by Maio group.[5a]

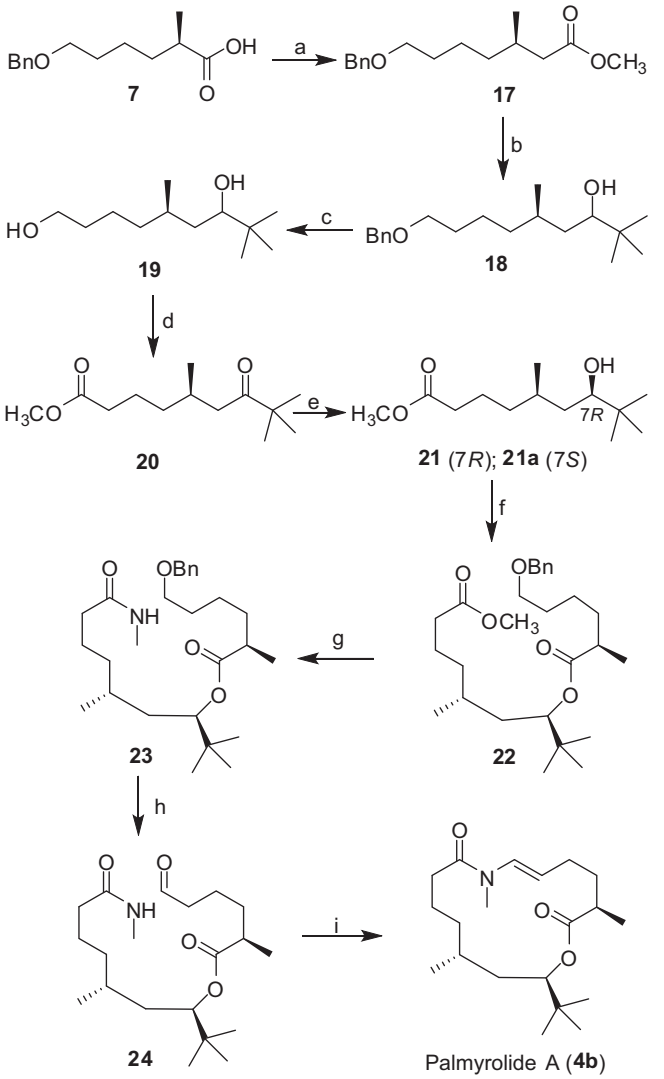
Then we envisioned that the fragment B has the required structural features to provide the fragment A if it is subjected to few transformations such as homologation and introducing hydroxyl stereocenter by the addition of *tert*-butyl lithium. The transformations on the α-methyl acid **7** (fragment B) would lead to the stereoselective synthesis of palmyrolide A from the same strategy and sequence of reactions developed for its 5,7-*epi* isomers. Accordingly, α-methyl acid **7** was homologated to produce methyl ester **17**,[15] which was reduced to aldehyde followed by the addition of ^{t}BuLi[16] yielded **18** (Scheme 5). Hydrogenolysis of benzyl ether in **18** furnished diol **19**. Upon two-step oxidation sequence **19** yielded ketoacid that was treated with excess of diazomethane to afford keto ester **20**. Stereoselective reduction of ketone **20** using (*S*)-CBS catalyst in the presence of $BH_3·DMS$ afforded the desired hydroxyl ester **21** along with the column chromatographically separable *anti* **21a** (*dr* 89:11) in 83% combined yield.[17] Coupling of fragments **21** and **7** using Yamaguchi esterfication[10] afforded diester **22**. Chemoselective methyl ester hydrolysis and subsequent amide formation furnished **23**. Hydrogenolysis of benzyl ether in **23** followed by Swern oxidation yielded aldehyde **24**. Finally, **24** was refluxed with TFA in benzene for 3 days to get the anticipated palmyrolide A (**4b**) in 33% yield and 54% yield brsm.

3. Conclusions

A unique synthetic strategy was developed for the synthesis of all stereoisomers of palmyrolide A, which were needed for comparison of the data and utilized a dehydrative cyclization for macrocyclization, that is, distinct from the earlier two reports. The unreactivity of ester to hydrolysis found in palmyrolide A was exploited to achieve chemoselective ester hydrolysis, which



Scheme 4. Synthesis of palmyrolide A (**4b**) & **4c**. a) H_2, Pd/C, EtOH, rt, 3 h, 92%; b) (i) DIBAL-H, toluene, −78 °C, 1.5 h; (ii) PPh_3CHCO_2Et, CH_2Cl_2, 2 d, 77% (2 steps); c) **7**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF, 12 h, 94%; d) (i) $LiOH·H_2O$, THF/MeOH/H_2O (3:1:1), 3 h; (ii) EtOCOCl, Et_3N, THF, CH_2N_2, 3 h; (iii) CH_3CO_2Ag, dioxane/H_2O, ultrasound irradiation, 0.5 h, 63% (3 steps); e) $CH_3NH_2·HCl$, HOBt, DCC, Et_3N, CH_2Cl_2, 6 h, 94%; f) (i) H_2, Pd/C, MeOH, 2 h, 94%; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1.5 h, 92%; g) TFA, benzene, reflux, 3 d, 55% brsm).



Scheme 5. Synthesis of palmyrolide A (**4b**). a) (i) EtOCOCl, Et_3N, THF, CH_2N_2, 0 °C, 12 h; (ii) CH_3CO_2Ag, Et_3N, MeOH, 2 h, 61% (2 steps); b) (i) DIBAL-H, toluene, −78 °C, 1.5 h; (ii) ^tBuLi, THF, −78 °C, 2 h, 69% (2 steps); c) H_2, Pd/C, MeOH, 2 h, 93%; d) (i) DMP, CH_2Cl_2, 1 h; (ii) $NaClO_2$, NaH_2PO_4, ^tBuOH/2-methyl-2-butene (2:1), 1 h; (iii) CH_2N_2 in ether, 0.5 h, 80%, (3 steps); e) (*S*)-CBS, toluene, 0 °C, 4 h, 83%; f) **7**, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP, THF, 12 h, 94%; g) (i) $LiOH.H_2O$, THF/MeOH/H_2O, (3:1:1), 3 h; (ii) $CH_3NH_2·HCl$, DCC, HOBt, Et_3N, CH_2Cl_2, 6 h, 92% (2 steps); h) (i) H_2, Pd/C, MeOH, 2 h; (ii) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C, 1.5 h, 85% (2 steps); i) TFA, benzene, reflux, 3 d, 33% (54%, brsm).

minimized the protecting groups use in this synthesis. The crystal structure of **4a** provided additional support to the reassignment of stereochemistry confirmed by the previous reports.

4. Experimental section

4.1. General methods

Anhydrous solvents were dried and distilled by standard methods prior to use. Commercially available reagents were used without further purification unless otherwise specified. All the reactions were performed under an atmosphere of nitrogen or argon in oven-dried glassware under magnetic stirring. Column chromatography was carried out using silica gel (60–120 or 100–200 or 230–400 mesh) and the column was eluted with ethyl acetate/petroleum ether or ethyl acetate. Analytical thin layer chromatography (TLC) was performed on precoated silica gel-60 F254

(0.5 mm) glass plates. Visualization of the spots on TLC plates was achieved either by UV light or by staining the plates in methanolic anisaldehyde/sulfuric acid/acetic acid or in methanol/phosphomolybdic acid/sulfuric acid solution and charring on hot plate. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ solvent on 500 MHz, 400 MHz, 300 MHz and 75 MHz, 125 MHz spectrometer, respectively, at ambient temperature. Chemical shifts are reported as δ values relative to internal $CHCl_3$ δ 7.26 or TMS δ 0.0 for ^{1}H NMR and $CHCl_3$ δ 77.0 for ^{13}C NMR. ^{1}H NMR data is recorded as follows: chemical shift [multiplicity, coupling constant(s) J (Hz), relative integral] where multiplicity is defined as: s=singlet; d=doublet; t=triplet; q=quartet; dd=doublet of doublet; ddd=doublet of double of doublet; dt=doublet of triplet; m=multiplet; br s=broad singlet. FTIR spectra were recorded on Bruker (Alpha) spectrometer. Optical rotation values were measured on Horiba high sensitive polarimeter using a 2 mL cell with a 10 mm path length. Mass spectra were recorded on Micro Mass VG-7070H mass spectrometer for ESI and are given in mass units (m/z). High resolution mass spectra (HRMS) [ESI$^+$] were obtained using either a TOF or a double focussing spectrometer.

*4.1.1. 6-(Benzyloxy)hexanoic acid (**12**).* Sodium hydride (8.13 g, 203.38 mmol) was added portion wise to a stirred solution of hexane-1,6-diol (20 g, 169.49 mmol) in THF (507 mL) at 0 °C under nitrogen atmosphere. After the additions were completed, the reaction mixture was stirred at 0 °C for 15 min. Then benzylbromide (20.2 mL, 169.49 mmol) was added slowly to the stirred reaction mixture followed by the addition of TBAI (3.13 g, 8.47 mmol). After stirring for 12 h at room temperature, the reaction mixture was quenched at 0 °C by slow addition of saturated aqueous NH_4Cl solution. THF was removed under reduced pressure and the product was extracted from aqueous layer with EtOAc. The combined organic layer was washed with brine, and dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (28–30% EtOAc/hexane) afforded 6-(benzyloxy)hexan-1-ol (21.6 g, 72%, brsm (3 g)) as colourless oil; R_f (30% EtOAc/hexanes) 0.4; IR (Neat) ν_{max} 3620, 2362, 1693, 1647, 1516, 1463, 1352 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.20 (m, 5H), 4.46 (s, 2H), 3.58 (t, J=6.4 Hz, 2H), 3.43 (t, J=6.4 Hz, 2H), 1.67–1.48 (m, 4H), 1.45–1.30 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.4, 128.2, 127.5, 127.3, 72.7, 70.2, 62.5, 32.5, 29.5, 25.8, 25.4; HRMS (ESI); calcd for $C_{13}H_{20}O_2Na$ [M+Na]$^+$ 231.1360; found 231.1353.

To a solution of oxalyl chloride (18.1 mL, 207.38 mmol) in dry CH_2Cl_2 (460 mL) at −78 °C, DMSO (29.4 mL, 414.76 mmol) was added slowly in drop wise manner, with stirring under nitrogen atmosphere. After 20 min stirring, compound (21.6 g, 103.69 mmol, dissolved in 60 mL of dry CH_2Cl_2) was added into the reaction mixture. After 0.5 h of stirring at −78 °C, Et_3N (72.1 mL, 518.45 mmol) was added and stirred for another 15 min at −78 °C and then for 15 min at 0 °C. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The aldehyde (19.7 g, 92%) thus obtained, was directly used after flash chromatography (5–6% EtOAc/hexane) for the next reaction. R_f (10% EtOAc/hexane) 0.5.

To a solution of aldehyde in t-BuOH/2-methyl-2-butene (265 mL (2:1)) at rt, the mixture of $NaClO_2$ (19.9 g, 219.88 mmol) and NaH_2PO_4 (26.4 g, 219.88 mmol), dissolved in minimum amount of water, was added. After being stirred for 1 h, the solvent was removed in rotatory evaporator and the residue was extracted with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography (15% EtOAc/hexane) afforded pure compound **12** (19.9 g, 94%) as a colourless liquid; R_f (30% EtOAc/hexanes) 0.4; IR (Neat) ν_{max} 2932, 2860, 1705, 1453, 1411, 1363, 1204, 1094, 1027, 940, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.19 (m, 5H), 4.46 (s, 2H), 3.43 (t, J=6.4 Hz, 2H), 2.33 (t, J=7.5 Hz, 2H), 1.71–1.57 (m, 4H), 1.49–1.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 138.2, 128.2, 127.5, 127.4, 72.6, 69.8, 33.8, 29.1, 25.5, 24.3; HRMS (ESI): calcd for $C_{13}H_{18}O_3Na$ [M+Na]$^+$ 245.1153; found 245.1148.

*4.1.2. (R)-4-Benzyl-3-(6-(benzyloxy)hexanoyl) oxazolidin-2-one (**13**).* To a stirred solution of compound **12** (19.9 g, 89.63 mmol) in THF (224 mL) at −20 °C was added Et_3N (31.2 mL, 224.07 mmol) followed by Piv-Cl (11 mL, 89.63 mmol). After stirring for 1 h at −20 °C, LiCl (5.7 g, 134.44 mmol) followed by (*R*)-4-benzyl-2-oxazolidinone (15.9 g, 89.63 mmol) were added to it at the same temperature. The stirring was continued for 1 h at −20 °C and then 2 h at 0 °C. It was then quenched with saturated NH_4Cl solution and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by column chromatography (10–12% EtOAc/hexane) afforded compound **13** (29 g, 85%) as a syrupy liquid; R_f (20% EtOAc/hexanes) 0.5; $[\alpha]_D^{26.3}$ −28.1 (c 0.4, $CHCl_3$); IR (Neat) ν_{max} 2926, 2858, 1779, 1697, 1453, 1385, 1205, 1096, 740 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.15 (m, 10H), 4.60 (m, 1H), 4.47 (s, 2H), 4.19–4.09 (m, 2H), 3.46 (t, J=6.7 Hz, 2H), 3.30 (dd, J=13.5, 3.7 Hz, 1H), 3.01–2.80 (m, 2H), 2.69 (dd, J=9.8, 13.5 Hz, 1H), 1.76–1.61 (m, 4H), 1.54–1.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 153.3, 138.5, 135.2, 129.3, 128.8, 128.2, 127.5, 127.4, 127.2, 72.8, 70.0, 66.0, 55.0, 37.8, 35.3, 29.4, 25.6, 23.9; HRMS (ESI): calcd for $C_{23}H_{27}NO_4Na$ [M+Na]$^+$ 404.1832; found 404.1820.

*4.1.3. (R)-6-(Benzyloxy)-2-methylhexanoic acid (**7**).* To a solution of compound **13** (29 g, 76.1 mmol) in dry THF (190 mL) at −78 °C, NaHMDS (114.2 mL, 1 M solution in THF) was added slowly drop wise with stirring under nitrogen atmosphere. After stirring at −78 °C for 0.5 h, CH_3I (14.2 mL, 228.3 mmol) was added into the reaction mixture and stirred for an additional 3 h at −78 °C. Then the reaction mixture was quenched with saturated NH_4Cl, warmed to rt and extracted with EtOAc. The combined organic extracts were washed with water, brine and dried over Na_2SO_4, filtered and concentrated vacuo. Column chromatography (9–10% EtOAc/hexane) gave pure (*R*)-4-benzyl-3-((*R*)-6-(benzyloxy)-2-methylhexanoyl)oxazolidin-2-one (22.5 g, 75%) as a syrupy liquid; R_f (20% EtOAc/hexanes) 0.5; $[\alpha]_D^{26.5}$ −43.8 (c 0.29, $CHCl_3$); IR (Neat) ν_{max} 2936, 2861, 1704, 1458, 1235, 1098, 698 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.16 (m, 10H), 4.60 (m, 1H), 4.45 (s, 2H), 4.14–4.09 (m, 2H), 3.69 (m, 1H), 3.46–3.40 (dt, J=6.8, 2.9 Hz, 2H), 3.27 (dd, J=12.7, 2.9 Hz, 1H), 2.70 (dd, J=13.7, 9.8 Hz, 1H), 1.75 (m, 1H), 1.65–1.56 (m, 2H), 1.47–1.35 (m, 3H), 1.21 (d, J=6.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 152.8, 138.4, 135.1, 129.2, 128.7, 128.1, 127.4, 127.2, 127.1, 72.6, 69.9, 65.7, 55.1, 37.6, 37.4, 32.9, 29.5, 23.7, 17.2; HRMS (ESI): calcd for $C_{24}H_{29}NO_4Na$ [M+Na]$^+$ 418.1994; found 418.1984.

In to a flask was added (*R*)-4-benzyl-3-((*R*)-6-(benzyloxy)-2-methylhexanoyl)oxazolidin-2-one (22.5 g, 57.03 mmol), THF (243 mL), water (41 mL). The homogeneous solution was cooled in an ice bath (0 °C). Hydrogen peroxide (30%, 36.7 mL, 356.43 mmol) and lithium hydroxide (5.98 g, 142.57 mmol) were combined, mixed, and added to the imide solution. The mixture stirred (1.5 h), allowed to warm to ambient temp (over another 1.5 h), returned to the ice bath, quenched with saturated sodium sulfite (giving pH 8 solution), acidified with hydrochloric acid (6 N aqueous, to pH=1), extracted with EtOAc, and washed with water and brine, dried over sodium sulfate. Volatiles were removed under reduced pressure and further purified by column chromatography (16–18% EtOAc/hexane) to afford pure **7** (12.8 g, 95%) as a white solid product; R_f (30% EtOAc/hexanes) 0.4; mp 60–62 °C; $[\alpha]_D^{26.6}$ −8.1 (c 1.0, $CHCl_3$); IR (Neat) ν_{max} 2934, 2860, 2362, 2333, 1778, 1695, 1455, 1385, 1209, 1098, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.19 (m, 5H),

4.46 (s, 2H), 3.43 (t, *J*=6.7 Hz, 2H), 2.43 (m, 1H), 1.76–1.53 (m, 3H), 1.50–1.35 (m, 3H), 1.18 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.0, 138.4, 128.2, 127.5, 127.4, 72.8, 69.9, 39.2, 33.1, 29.5, 23.7, 16.7; HRMS (ESI): calcd for $C_{14}H_{20}O_3Na$ $[M+Na]^+$ 259.1304; found 259.1295.

*4.1.4. Ethyl 4-hydroxy-5,5-dimethyl-2-methylenehexanoate ((±)-**11**).* To a solution of trimethylacetaldehyde (1 g, 11.6 mmol) in a mixture of THF (34 mL) and saturated aqueous NH_4Cl (138 mL) was added zinc dust (4.5 g, 69.6 mmol), followed by the drop wise addition of ethyl 2-bromomethyl acrylate (2.9 g, 15.08 mmol) at 0 °C. The mixture was stirred for 1 h at rt, the solids were filtered by using sintered funnel with Celite, washed with EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried with Na_2SO_4, filtered and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane) to furnish homo allylic alcohol (±)-**11** (2.18 g, 94%) as colourless liquid; R_f (10% EtOAc/hexanes) 0.5; IR (Neat) ν_{max} 2969, 1712, 1197, 1146, 674 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.20 (d, *J*=1.5 Hz, 1H), 5.64 (d, *J*=1.5 Hz, 1H), 4.26–4.16 (q, *J*=6.7 Hz, 2H), 3.27 (dd, *J*=9.8, 1.5, Hz 1H), 2.61 (dd, *J*=13.5, 1.5 Hz, 1H), 2.14 (dd, *J*=13.5, 9.8 Hz, 1H), 1.32 (t, *J*=6.7 Hz, 3H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 138.7, 126.9, 78.4, 60.8, 35.0, 34.9, 25.5, 14.0; HRMS (ESI): calcd for $C_{11}H_{20}O_3Na$ $[M+Na]^+$ 223.1304; found 223.1301.

*4.1.5. tert-Butyl-3-methylenedihydrofuran-2(3H)-one ((±)-**10**).* To a stirred solution of alcohol (±)-**11** (2.18 g, 10.9 mmol) in toluene (22 mL) at rt, was added *p*-toluenesulfonicacid (188 mg, 1.09 mmol) and allowed the reaction mixture to stir at rt for 2 h. The reaction mixture was quenched by the addition of H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (5% EtOAc/hexane) to furnish unsaturated lactone (±)-**10** (1.66 g, 99%) as a colourless liquid; R_f (10% EtOAc/hexanes) 0.5; IR (Neat) ν_{max} 2963, 1759, 1475, 1399, 1338, 1280, 1249, 1131, 995, 813 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.18 (t, *J*=2.9 Hz, 1H), 5.58 (t, *J*=2.9 Hz, 1H), 4.18 (t, *J*=7.3 Hz, 1H), 2.85 (m, 1H), 2.70 (m, 1H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 135.0, 121.4, 84.4, 34.0, 28.6, 24.4; HRMS (ESI): calcd for $C_9H_{15}O_2$ $[M+H]^+$ 155.1066; found 155.1064.

*4.1.6. Synthesis of compound ((±)-**9**).* A solution of lactone (±)-**10** (1.66 g, 10.77 mmol) in EtOH (32 mL) was hydrogenated at 1 atmospheric balloon pressure in the presence of catalytic amount of 10% Pd/C (161 mg) for 2 h. The mixture was then filtered through pad of Celite, washed with EtOAc, evaporated and purified by column chromatography (6% EtOAc/hexane) to afford exclusively *syn* product (±)-**9** (1.54 g, 92%) as a colourless liquid; R_f (10% EtOAc/hexanes) 0.5; IR (Neat) ν_{max} 2964, 2877, 1766, 1459, 1368, 1168, 1048, 994, 931 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (dd, *J*=10.9, 5.4 Hz, 1H), 2.68 (m, 1H), 2.28 (ddd, *J*=12.4, 8.5, 5.4 Hz, 1H), 1.60 (m, 1H), 1.27 (d, *J*=7.1 Hz, 3H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 85.4, 35.7, 32.8, 31.7, 24.6, 14.6; HRMS (ESI): calcd for $C_9H_{17}O_2$ $[M+H]^+$ 157.1223; found 157.1223.

*4.1.7. Synthesis of compound ((±)-**14**).* To a solution of lactone (±)-**9** (1.54 g, 9.87 mmol) in toluene at −78 °C was added DIBAL-H (7.9 mL, 1.5 M solution in toluene). The reaction mixture was stirred for 0.5 h at that temperature and was quenched by the addition of methanol (2 mL). The reaction mixture was then allowed to warm up to rt and diluted with EtOAc added saturated solution of sodium potassium tartrate (15 mL) and stirred for 1 h, filtered. The compound was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography purification (11% EtOAc/hexanes) afforded lactol (1.4 g, 90%) as colourless oil R_f (20% EtOAc/hexanes) 0.5, which was used in the next step without any characterization.

To a solution of lactol (1.4 g, 8.86 mmol) in dry CH_2Cl_2 (27 mL), was added (carbethoxymethylene)triphenylphosphorane (15.5 g, 44.3 mmol). The reaction mixture was then allowed to reflux for 2 days. The reaction mixture was allowed to rt and concentrated in vacuo. The residue was purified by column chromatography (9% EtOAc/hexanes) to furnish unsaturated ester (±)-**14** (1.73 g, 86%) as yellow colour oil; R_f (20% EtOAc/hexanes) 0.5; IR (Neat) ν_{max} 2927, 1707, 1648, 1516, 1464, 1368, 1283, 1180, 1077, 982 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (dd, *J*=15.6, 7.3 Hz, 1H), 5.77 (d, *J*=15.6 Hz 1H), 4.16 (q, *J*=7.1 Hz, 2H), 3.27 (dd, *J*=9.6, 2.0 Hz, 1H), 2.57 (m, 1H), 1.51–1.33 (m, 2H), 1.29 (t, *J*=7.1 Hz, 3H), 1.08 (d, *J*=6.6 Hz, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 155.3, 118.9, 76.9, 60.1, 37.6, 34.9, 33.3, 25.6, 17.9, 14.2; HRMS (ESI): calcd for $C_{13}H_{25}O_3$ $[M+H]^+$ 229.1798; found 229.1789.

*4.1.8. Synthesis of compound ((±)-**8**).* A solution of unsaturated ester (±)-**14** (1.7 g, 7.5 mmol) in EtOH (23 mL) was hydrogenated at 1 atmospheric balloon pressure in the presence of catalytic amount of 10% Pd/C (170 mg) for 2 h. The mixture was then filtered through pad of Celite, washed with EtOAc, evaporated and purified by column chromatography (10% EtOAc/hexane) to furnish the saturated alcoholic ester (±)-**8** (1.6 g, 93%) as colourless liquid; R_f (20% EtOAc/hexanes) 0.6; IR (Neat) ν_{max} 2957, 1736, 1516, 1371, 1258, 1173, 1099, 1032, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (q, *J*=7.1 Hz, 2H), 3.24 (dd, *J*=10.3, 1.7 Hz, 1H), 2.35–2.25 (m, 2H), 1.76–1.43 (m, 4H), 1.39–1.11 (m, 1H), 1.26 (t, *J*=7.1 Hz, 3H), 0.91 (d, *J*=6.2 Hz, 3H), 0.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 77.1, 60.2, 38.4, 34.7, 33.1, 32.1, 29.3, 25.6, 18.6, 14.1; HRMS (ESI): calcd for $C_{13}H_{26}O_3Na$ $[M+Na]^+$ 253.1774; found 253.1771.

*4.1.9. Synthesis of compounds **6** & **6a**.* A solution of acid **7** (600 mg, 2.54 mmol) in dry THF (50 mL) was cooled to 0 °C under N_2. Then, triethylamine (0.9 mL, 6.34 mmol) and 2,4,6-trichlorobenzoyl chloride (0.8 mL, 5.08 mmol) were added drop wise, followed by stirring at rt for 2 h. Subsequently, a solution of alcohol (±)-**8** (584 mg, 2.54 mmol) and DMAP (775 mg, 6.34 mmol) in dry THF (26 mL) was added drop wise at 0 °C. The mixture was then stirred at rt for 12 h. Reaction mixture was quenched with water and extracted with EtOAc, washed with brine, dried over sodium sulfate. Volatiles were removed under reduced pressure and purification by column chromatography (4–5% EtOAc/hexanes) afforded inseparable diastereomeric mixture **6** & **6a** (*dr* 1:1, 1.04 g, 94%) as a colourless liquid; R_f (10% EtOAc/hexanes) 0.5; IR (Neat) ν_{max} 2963, 2866, 1730, 1461, 1370, 1256, 1169, 1031, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H), 4.80 (dd, *J*=10.0, 1.0 Hz, 1H), 4.45 (s, 2H), 4.07 (2q, *J*=7.0 Hz, 2H), 3.42 (t, *J*=6.0 Hz, 2H), 2.40 (m, 1H), 2.27–2.19 (m, 2H), 1.69 (m, 1H), 1.63–1.43 (m, 5H), 1.42–1.33 (m, 3H), 1.28 (m, 1H), 1.24 (2t, *J*=7.0 Hz, 3H), 1.15 (2d, *J*=7.0 Hz, 3H), 0.91 (2d, *J*=6.0 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 173.6, 138.5, 128.2, 127.4, 127.3, 77.6, 72.7, 70.0, 60.1, 39.8, 36.7, 36.6, 34.4, 34.3, 33.3, 32.9, 32.0, 29.5, 29.0, 25.8, 23.9, 18.5, 17.3, 17.2, 14.1; HRMS (ESI): calcd for $C_{27}H_{44}O_5Na$ $[M+Na]^+$ 471.3081; found 471.3075.

*4.1.10. Synthesis of compounds **15** & **15a**.* The ester compounds **6** & **6a** (1.04 g, 2.39 mmol) were taken in THF:MeOH:H_2O (3:1:1, 7.5 mL), $LiOH\cdot H_2O$ (401 mg, 9.56 mmol) was added at 0 °C and the reaction was allowed to stir for 3 h. The reaction mixture was acidified to pH 2 with 1 N HCl and the residue was extracted with EtOAc, washed with H_2O and brine, organic layer dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (16–18% EtOAc/hexane) to afford the acid (984 mg, 98%) as a colourless liquid; R_f (30% EtOAc/hexanes) 0.3; IR (Neat) ν_{max} 3648, 2933, 2866, 1709, 1460, 1370, 1169, 1099, 960, 932 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.37–7.23 (m, 5H), 4.83 (dd, *J*=10.5, 1.5 Hz, 1H), 4.51 (d, *J*=7.5 Hz, 2H), 3.47 (t, *J*=6.8 Hz, 2H), 2.43 (m, 1H), 2.32 (t, *J*=6.7 Hz, 2H), 1.77–1.46 (m, 6H), 1.45–1.19 (m, 5H), 1.15 (d, *J*=6.7 Hz, 3H), 0.92 (m, 3H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 178.7, 176.5, 176.4, 138.4, 138.1, 128.3, 127.7, 127.6, 127.5, 127.4, 77.7, 72.7, 72.6, 70.0, 69.9, 40.0, 39.9, 36.8, 34.5, 34.4, 33.5, 33.4, 32.8, 32.7, 31.7, 29.5, 29.4, 28.9, 28.8, 25.9, 24.0, 18.6, 17.5, 17.4; HRMS (ESI): calcd for $C_{25}H_{40}O_5Na$ $[M+Na]^+$ 443.2768; found 443.2755.

To the acid compound (984 mg, 2.34 mmol) in dry THF (10 mL), triethylamine (0.4 mL, 2.81 mmol) and ethylchloroformate (0.25 mL, 2.57 mmol) were added sequentially at −15 °C, stirring was continued for 15 min at the same temperature, then the solution was warmed up to 0 °C. A solution of diazomethane in diethyl ether was added slowly at 0 °C. Slightly yellow colour solution was allowed to reach rt and was stirred for a further 3 h. Excess diazomethane was decomposed by drop wise addition of CH_3CO_2H. The mixture was washed with aq $NaHCO_3$, aq NH_4Cl and brine solution. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo, to afford diazo ketone (726 mg, 70%) as yellow colour oil. R_f (20% EtOAc/hexanes) 0.4.

The resulted diazo ketone (726 mg, 1.64) was dissolved in dioxane/water (5:1, 16 mL). After addition of silver acetate (27 mg, 0.164 mmol), the mixture was sonicated using an ultrasound cleaning bath for 0.5 h. The reaction progress was monitored by TLC. After completion of the reaction, the solution was acidified to pH 2 with 1 N HCl and extracted with EtOAc, the combined organic layers were washed with water, brine solution and dried over Na_2SO_4, concentrated in vacuo and further purified by column chromatography (20% EtOAc/hexane) to afford acids **15** & **15a** (662 mg, 93%) as a colourless liquid; R_f (30% EtOAc/hexanes) 0.4; IR (Neat) ν_{max} 3620, 2960, 2867, 1707, 1516, 1168, 1103, 956, 692 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.83 (dd, *J*=10.5, 1.5 Hz, 1H), 4.50 (s, 2H), 3.46 (t, *J*=6.6 Hz, 2H), 2.43 (m, 1H), 2.35–2.25 (m, 2H), 1.77–1.47 (m, 6H), 1.48–1.18 (m, 7H), 1.15 (d, *J*=6.9 Hz, 3H), 0.90 (d, *J*=5.8 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.2, 176.4, 138.4, 128.2, 127.5, 127.4, 77.9, 72.7, 70.0, 39.9, 39.8, 37.4, 36.8, 34.5, 34.4, 34.1, 33.4, 29.5, 29.1, 25.9, 23.9, 22.2, 18.8, 17.3; HRMS (ESI): calcd for $C_{26}H_{43}O_5$ $[M+H]^+$ 435.3150; found 435.3146.

*4.1.11. Synthesis of compounds **5** & **5a**.* To a stirred solution of acid compounds **15** & **15a** (662 mg, 1.52 mmol) in dry CH_2Cl_2 (6 mL), HOBt (214 mg, 1.58 mmol) was added followed by DCC (326 mg, 1.58 mmol). After 5 min, to this solution, methylamine hydrochloride (113 mg, 1.67 mmol) and triethylamine (0.3 mL, 2.28 mmol) were added subsequently. The mixture was stirred at rt for 6 h. The precipitated dicyclohexyl urea was removed by subsequent trituration with cold ethyl acetate and filtration. The EtOAc solution was washed with 1 N HCl, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, filtered and concentrated, further purified by column chromatography (30–32% EtOAc/hexane) to afford the amide compounds **5** & **5a** (634 mg, 94%) as yellow colour oil; R_f (50% EtOAc/hexanes) 0.4; IR (Neat) ν_{max} 3302, 2929, 2867, 1724, 1647, 1549, 1461, 1372, 1163, 1070, 957 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 5.62 (br s, 1H), 4.82 (dd, *J*=10.5, 1.5 Hz, 1H), 4.50 (s, 2H), 3.47 (2t, *J*=6.8 Hz, 2H), 2.76 (2d, *J*=5.3 Hz, 3H), 2.43 (m, 1H), 2.14–2.04 (m, 2H), 1.76–1.46 (m, 6H), 1.45–1.19 (m, 7H), 1.16 (d, *J*=7.5 Hz, 3H), 0.91–0.85 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.4, 176.3, 173.7, 173.6, 138.4, 132.9, 132.8, 129.4, 128.2, 127.5, 127.4, 78.1, 78.0, 72.7, 70.1, 64.8, 64.7, 40.0, 39.8, 37.7, 37.6, 36.8, 36.7, 36.6, 34.5, 34.4, 33.4, 33.3, 33.2, 29.6, 29.5, 29.4, 29.3, 29.2, 28.6, 26.1, 25.9, 24.0, 23.9, 23.4, 23.4, 23.3, 23.2, 18.9, 17.4, 17.4; HRMS (ESI): calcd for $C_{27}H_{46}O_4N$ $[M+H]^+$ 448.3421; found 448.3423.

*4.1.12. Synthesis of compounds **16** & **16a**.* The compounds **5** & **5a** (634 mg, 1.43 mmol), in dry methanol (6 mL) were hydrogenated by using 1 atmospheric balloon pressure in the presence of 20% Pd/C (130 mg) for 2 h. The mixture was then filtered through pad of Celite, washed with EtOAc, evaporated and purified by column chromatography (75–80% EtOAc) to afford the alcohol (476 mg, 93%) as colourless liquid; R_f (EtOAc) 0.4; IR (Neat) ν_{max} 3302, 2929, 2867, 1724, 1647, 1549, 1461, 1372, 1163, 1070, 957 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (br, 1H), 4.81 (dd, *J*=10.5, 1.6 Hz, 1H), 3.61 (t, *J*=6.4 Hz, 2H), 2.78 (s, 3H), 2.45 (m, 1H), 2.23 (br s, 1H), 2.12 (t, *J*=7.2 Hz, 2H), 1.71 (m, 1H), 1.66–1.49 (m, 4H), 1.47–1.35 (m, 2H), 1.28 (m, 1H), 1.24–1.13 (m, 7H), 0.89 (d, *J*=6.4 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 176.3, 174.1, 174.0, 78.0, 77.9, 62.3, 62.2, 40.5, 39.7, 37.7, 37.6, 36.9, 36.6, 36.4, 34.4, 33.6, 33.5, 32.6, 32.5, 29.4, 26.1, 25.8, 23.6, 23.4, 18.9, 17.6; HRMS (ESI): calcd for $C_{20}H_{40}O_4N$ $[M+H]^+$ 358.2951; found 358.2953.

To a solution of oxalyl chloride (0.2 mL, 2.66 mmol) in dry CH_2Cl_2 (4 mL) at −78 °C, DMSO (0.4 mL, 5.32 mmol) was added slowly in drop wise manner, with stirring under nitrogen atmosphere. After 20 min stirring, alcoholic compound (476 mg, 1.33 mmol), dissolved in dry CH_2Cl_2 (3 mL) was added in to the reaction mixture. After 0.5 h of stirring at −78 °C, Et_3N (0.7 mL, 6.65 mmol) was added and stirred for another 15 min at −78 °C and then for 15 min at 0 °C. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo, further purified by flash column chromatography (60–65% EtOAc/hexanes) to furnish the aldehydes **16** & **16a** (435 mg, 92%) as colourless liquid; R_f (EtOAc) 0.6; IR (Neat) ν_{max} 2960, 1721, 1641, 1552, 1460, 1407, 1372, 1162, 1067, 958, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (m, 1H), 5.74 (br, 1H), 4.83 (dd, *J*=10.5, 0.7 Hz, 1H), 2.80 (m, 3H), 2.52–2.40 (m, 3H), 2.17–2.09 (m, 2H), 1.79–1.48 (m, 6H), 1.48–1.13 (m, 5H), 1.18 (d, *J*=7.5 Hz, 3H), 0.90 (d, *J*=6.0 Hz, 3H), 0.88 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 201.9, 175.7, 175.6, 173.6, 77.7, 43.2, 39.5, 39.3, 37.4, 37.3, 36.4, 36.3, 34.0, 32.5, 28.9, 25.8, 25.5, 23.0, 22.9, 19.4, 18.5, 17.1; HRMS (ESI): calcd for $C_{20}H_{37}O_4NNa$ $[M+Na]^+$ 378.2614; found 378.2612.

*4.1.13. Synthesis of **4** & **4a**.* A dried 4 (Å) (1.07 g) molecular sieves powder was taken in dry benzene (540 mL) under nitrogen, to this reaction mixture, compounds **16** & **16a** (200 mg, 0.56 mmol) in benzene (20 mL) was cannulated, then trifluoroaceticacid (0.2 mL, 2.59 mmol) was added slowly drop wise to above reaction mixture at rt, and then it was refluxed for 3 days. The solids were filtered out, extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$, brine solution and dried over Na_2SO_4, filtered, and concentrated in vacuo, further purified by column chromatography (11–13% EtOAc/hexanes) to afford the separable cyclic products **4** as a liquid, **4a** as a white gummy solid in 1:1.7 (**4**:**4a**) ratio (62 mg, 55%, brsm (81 mg)). R_f (25% EtOAc/hexanes) 0.4.

*4.1.13.1. Data of compound **4**.* $[\alpha]_D^{26.1}$ +45.5 (*c* 0.56, $CHCl_3$); IR (Neat) ν_{max} 2924, 1726, 1677, 1646, 1516, 1463, 1393, 1175, 1078, 940, 688 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (d, *J*=14.2 Hz, 1H), 5.14 (dt, *J*=14.2, 7.1 Hz, 1H), 4.86 (dd, *J*=10.2, 1.5 Hz, 1H), 3.07 (s, 3H), 2.63–2.53 (m, 2H), 2.46 (m, 1H), 2.22 (m, 1H), 2.12 (m, 1H), 1.89 (m, 1H), 1.82–1.55 (m, 4H), 1.38–1.24 (m, 3H), 1.20 (d, *J*=7.1 Hz, 3H), 1.17 (m, 1H), 0.94 (d, *J*=6.3 Hz, 3H), 0.91 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 172.6, 130.9, 113.0, 78.9, 37.9, 36.5, 36.3, 34.8, 33.8, 32.9, 30.7, 27.6, 27.1, 26.0, 22.6, 20.5, 17.4; HRMS (ESI): calcd for $C_{20}H_{36}O_3N$ $[M+H]^+$ 338.2689; found 338.2689.

*4.1.13.2. Data of compound **4a**.* R_f (20% EtOAc/hexanes) 0.4; mp 40–42 °C: $[\alpha]_D^{25.8}$ −41.2 (*c* 0.16, $CHCl_3$); IR (Neat) ν_{max} 2923, 1727, 1673, 1645, 1516, 1462, 1387, 1334, 1167, 931 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.68 (d, *J*=13.4 Hz, 1H), 4.87 (ddd, *J*=13.4, 10.3, 4.7 Hz, 1H), 4.78 (dd, *J*=9.5, 0.8 Hz, 1H), 3.07 (s, 3H), 2.64 (dt, *J*=13.4, 7.9 Hz, 1H), 2.52 (m, 1H), 2.33–2.21 (m, 2H), 2.16 (m, 1H), 1.92 (m, 1H), 1.76–1.67 (m, 2H), 1.44–1.32 (m, 2H), 1.28–1.20 (m, 3H), 1.23

(d, J=7.1 Hz, 3H), 1.14 (m, 1H), 0.94 (d, J=4.7 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 172.1, 129.8, 110.2, 78.6, 38.4, 36.9, 35.2, 34.8, 31.7, 31.6, 29.7, 29.0, 27.9 25.8, 23.2, 19.5, 19.3; HRMS (ESI): calcd for $C_{20}H_{36}O_3N$ $[M+H]^+$ 338.2689; found 338.2689.

*4.1.14. Synthesis of compound (**9**).* A solution of homo allylic alcohol (±)-**11** (245 mg, 1.225 mmol) in ethanol (4 mL) was hydrogenated at 1 atmospheric balloon pressure in the presence of catalytic amount of 10% Pd/C (50 mg) for 3 h. The mixture was then filtered through pad of Celite, washed with EtOAc, evaporated and purified by column chromatography (6% EtOAc/hexane) to afford **9** (*syn*:*anti* 1:1) product (176 mg, 92%) as a colourless liquid; R_f (10% EtOAc/hexanes) 0.5; IR (Neat) ν_{max} 2864, 1766, 1459, 1368, 1168, 1048, 994 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.22 (dd, J=7.9, 6.6 Hz, 1H), 4.07 (dd, J=10.9, 5.6 Hz, 1H), 2.76–2.60 (m, 2H), 2.34–2.18 (m, 2H), 1.82 (m, 1H), 1.60 (m, 1H), 1.32–1.25 (m, 6H), 0.95 (s, 9H), 0.94 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (180.3, 179.5, 85.7, 85.6, 36.0, 34.8, 34.0, 33.0, 31.9, 30.5, 24.8, 24.8, 16.5, 14.8); HRMS (ESI): calcd for $C_9H_{17}O_2$ $[M+H]^+$ 157.1223; found 157.1222.

*4.1.15. Synthesis of compound (**14**).* Compound **14** was prepared from **9** (176 mg, 1.13 mmol) in a similar manner as compound (±)-**14**. The crude product was purified by column chromatography (9% EtOAc/hexanes) to furnish unsaturated ester **14** (195 mg, 77% over two steps) as yellow colour oil; R_f (20% EtOAc/hexanes) 0.5; IR (Neat) ν_{max} 3489, 2960, 2873, 1709, 1650, 1471, 1369, 1276, 1177, 1037, 985 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (dd, J=15.8, 7.5 Hz, 1H), 6.81 (dd, J=15.8, 9.0 Hz, 1H), 5.83 (dd, J=15.8, 10.5 Hz, 2H), 4.19 (m, 4H), 3.31 (dd, J=9.8, 3.0 Hz, 1H), 3.15 (dd, J=9.8, 3.0 Hz, 1H), 2.73–2.50 (m, 2H), 1.70 (br s, 1H), 1.54–1.35 (m, 4H), 1.33–1.25 (t, J=7.1 Hz, 6H), 1.09 (t, J=6.8 Hz, 6H), 0.89 (s, 9H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 166.7, 155.2, 153.8, 120.4, 118.7, 76.9, 76.8, 60.1, 37.8, 37.4, 34.8, 34.7, 33.6, 33.2, 25.5, 25.4, 20.7, 17.8, 14.1; HRMS (ESI): calcd for $C_{13}H_{24}O_3Na$ $[M+Na]^+$ 251.1617; found 251.1608.

*4.1.16. Synthesis of compound (**8**).* Compound **8** was prepared from **14** (195 mg, 0.855 mmol) in a similar manner as compound (±)-**8**. The crude product was purified by column chromatography (10% EtOAc/hexanes) to furnish saturated alcoholic ester (**8**) (183 mg, 93%) as yellow colour oil; R_f (20% EtOAc/hexanes) 0.6; IR (Neat) ν_{max} 3495, 2957, 2872, 1730, 1469, 1372, 1183, 1099, 664 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (q, J=7.1 Hz, 4H), 3.32 (m, 2H), 2.44–2.22 (m, 4H), 1.94–1.81 (m, 2H), 1.75–1.49 (m, 4H), 1.42–1.15 (m, 4H), 1.26 (t, J=7.1 Hz, 6H), 0.97–0.89 (m, 6H), 0.89 (m, 9H), 0.89 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 173.8, 76.7, 76.5, 60.0, 59.9, 38.6, 38.2, 34.6, 32.9, 31.9, 31.5, 29.8, 29.2, 29.1, 25.5, 20.4, 18.4, 13.9; HRMS (ESI): calcd for $C_{13}H_{26}O_3Na$ $[M+Na]^+$ 253.1774; found 253.1772.

*4.1.17. Synthesis of compounds **6b** & **6c**.* The diastereomers **6b** & **6c** were prepared from **7** (188 mg, 0.795 mmol) & **8** (183 mg, 0.795) in a similar manner as compounds **6** & **6a**. The crude product was purified by column chromatography (4–5% EtOAc/hexanes) to afford inseparable diastereomeric mixture **6b** & **6c** (*dr* 1:1, 335 mg, 94%) as a colourless liquid; R_f (10% EtOAc/hexanes) 0.5; IR (Neat) ν_{max} 2927, 2857, 1731, 1459, 1370, 1250, 1168, 1100, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5H), 4.81 (dd, J=9.0, 3.0 Hz, 1H), 4.49 (s, 2H), 4.11 (q, J=7.1 Hz, 2H), 3.46 (t, J=6.4 Hz, 2H), 2.43 (m, 1H), 2.36–2.12 (m, 2H), 1.83 (m, 1H), 1.77–1.55 (m, 3H), 1.53–1.29 (m, 7H), 1.25 (t, J=7.1 Hz, 3H), 1.16 (d, J=6.9 Hz, 3H), 0.88 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 173.8, 138.5, 128.2, 127.5, 127.4, 78.0, 72.8, 70.1, 60.1, 39.9, 39.8, 37.1, 34.6, 34.5, 33.4, 33.3, 30.4, 29.6, 29.4, 25.9, 2423.9, 20.3, 17.3, 14.1; HRMS (ESI): calcd for $C_{27}H_{44}O_5Na$ $[M+Na]^+$ 471.3081; found 471.3067.

*4.1.18. Synthesis of compounds (**15b** & **15c**).* The diastereomers (**15b** & **15c**) were prepared from (**6b** & **6c**) (335 mg, 0.747 mmol) via acids of **6b** & **6c** in a similar manner as compounds (**15** & **15a**). The crude product was purified by column chromatography (20% EtOAc/hexane) to afford acids (**15b** & **15c**) (207 mg, 65% over two steps) as a colourless liquid.

*4.1.19. Data of acids of **6b** & **6c**.* The acids were prepared from **6b** & **6c** (335 mg, 0.747 mmol) in a similar manner as acids of **6** & **6a**. The crude product was purified by column chromatography (20% EtOAc/hexane) to afford acids **6b** & **6c** (308 mg, 98%) as a colourless liquid; R_f (30% EtOAc/hexanes) 0.4; IR (Neat) ν_{max} 3648, 2961, 2868, 1722, 1458, 1370, 1169, 1100, 935, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.23 (m, 5H), 4.83 (m, 1H), 4.50 (m, 2H), 3.46 (t, J=6.4, 2H), 2.43 (m, 1H), 2.38–2.18 (m, 2H), 1.89 (m, 1H), 1.77–1.55 (m, 3H), 1.49–1.28 (m, 7H), 1.15 (d, J=6.9 Hz, 3H), 0.91–0.86 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 179.3, 176.3, 138.4, 138.3, 128.2, 127.6, 127.5, 127.4, 77.9, 72.7, 70.0, 39.9, 39.8, 37.1, 34.6, 34.5, 33.4, 33.3, 31.6, 30.1, 29.5, 29.2, 29.1, 25.8, 23.9, 20.2, 17.4, 17.2; HRMS (ESI): calcd for $C_{25}H_{40}O_5Na$ $[M+Na]^+$ 443.2768; found 443.2746.

*4.1.20. Data of **15b** & **15c**.* R_f (30% EtOAc/hexanes) 0.4; IR (Neat) ν_{max} 3620, 2959, 1722, 1458, 1369, 1168, 1102, 959, 670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H), 4.81 (m, 1H), 4.49 (s, 2H), 3.46 (t, J=7.0 Hz, 2H), 2.43 (m, 1H), 2.38–2.24 (m, 2H), 1.70 (m, 1H), 1.65–1.58 (m, 3H), 1.55–1.45 (m, 2H), 1.44–1.29 (m, 6H), 1.15 (d, J=7.0 Hz, 3H), 1.07 (m, 1H), 0.90–0.84 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 176.4, 138.5, 128.2, 127.5, 127.4, 78.1, 72.8, 70.1, 40.0, 39.8, 37.2, 34.6, 34.5, 34.1, 33.4, 29.6, 29.2, 25.9, 23.9, 21.8, 20.5, 17.3; HRMS (ESI): calcd for $C_{26}H_{42}O_5Na$ $[M+Na]^+$ 457.2924; found 457.2935.

*4.1.21. Synthesis of compounds **5b** & **5c**.* The diastereomers **5b** & **5c** were prepared from **15b** & **15c** (207 mg, 0.476 mmol) in a similar manner as compounds **5** & **5a**. The crude product was purified by column chromatography (30–32% EtOAc/hexane) to afford the amide compounds **5b** & **5c** (200 mg, 94%) as yellow colour oil; R_f (50% EtOAc/hexanes) 0.4; IR (Neat) ν_{max} 3304, 2941, 2867, 1724, 1647, 1547, 1462, 1368, 1167, 671 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5H), 6.12 (br s, 1H), 4.75 (dd, J=9.0, 3.0 Hz, 1H), 4.49 (s, 2H), 3.46 (t, J=6.4 Hz, 2H), 2.79 (m, 3H), 2.45 (m, 1H), 2.21–1.99 (m, 2H), 1.88 (m, 1H), 1.80–1.56 (m, 4H), 1.53–1.20 (m, 7H), 1.16, (m, 3H), 1.02 (m, 1H), 0.89–0.85 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 174.1, 138.5, 138.4, 128.2, 127.5, 127.4, 78.7, 72.8, 70.0, 40.0, 39.9, 37.6, 36.0, 34.5, 34.4, 33.8, 33.4, 29.6, 28.7, 26.1, 25.8, 23.9, 22.8, 20.7, 17.3; HRMS (ESI): calcd for $C_{27}H_{46}O_4N$ $[M+H]^+$ 448.3421; found 448.3424.

*4.1.22. Synthesis of **16b** & **16c**.* Compounds **16b** & **16c** were prepared from **5b** & **5c** (200 mg, 0.447 mmol) via alcohols of **5b** & **5c** in a similar manner as compounds **16** & **16a**. The crude product was purified by column chromatography (60–65% EtOAc/hexanes) to afford **16b** & **16c** (137 mg, 92%) as colourless liquid.

*4.1.23. Data of alcohols of **5b** & **5c**.* Alcohols were prepared from **5b** & **5c** (200 mg, 0.447 mmol). The crude product was purified by column chromatography (75–80% EtOAc/hexanes) to afford alcohols (150 mg, 94%) of **5b** & **5c** as colourless liquid; R_f (EtOAc) 0.4; IR (Neat) ν_{max} 3620, 3304, 2941, 2863, 1724, 1648, 1548, 1462, 1371, 1165, 1070, 961, 673 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.32–6.11 (br s, 1H), 4.78 (m, 1H), 3.64 (t, J=6.2 Hz, 2H), 2.83–2.78 (m, 3H), 2.47 (m, 1H), 2.23–1.88 (m, 3H), 1.82–1.66 (m, 2H), 1.64–1.22 (m, 10H), 1.18 (d, J=7.0 Hz, 3H), 1.0 (m, 1H), 0.91–0.84 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 176.7, 174.0, 173.8, 78.4, 78.3, 62.1, 62.0, 40.0, 39.8, 37.5, 37.4, 36.1, 36.0, 34.5, 34.4, 33.2, 33.1, 32.4, 32.3, 28.7, 26.0, 25.8, 23.4, 23.0, 22.8, 20.6, 17.6, 17.5, 17.3; HRMS (ESI): calcd for $C_{20}H_{40}O_4N$ $[M+H]^+$ 358.2951; found 358.2954.

*4.1.24. Data of **16b** & **16c**.* R_f (EtOAc) 0.6; IR (Neat) ν_{max} 3414, 2956, 2923, 1727, 1647, 1559, 1462, 1367, 1259, 1165, 1076, 960 cm^{-1}; ^{1}H

NMR (300 MHz, $CDCl_3$) δ 9.77 (m, 1H), 6.06 (br s, 1H), 4.77 (m, 1H), 2.81 (d, J=4.5 Hz, 3H), 2.51–2.43 (m, 3H), 2.23–2.02 (m, 2H), 1.83–1.59 (m, 4H), 1.54–1.35 (m, 6H), 1.21–1.17 (m, 3H), 1.02 (m, 1H), 0.92–0.86 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 176.4, 173.9, 78.7, 43.6, 39.9, 37.5, 36.0, 34.4, 32.8, 28.8, 26.1, 25.8, 22.8, 20.7, 19.7, 17.4, 17.3; HRMS (ESI): calcd for $C_{20}H_{38}O_4N$ $[M+H]^+$ 356.2795; found 356.2797.

*4.1.25. Synthesis of **4b** (palmyrolide A) & **4c**.* Compound **4b** (palmyrolide A) & **4c** were prepared from **16b** & **16c** (120 mg, 0.337) in a similar manner as compounds **4** & **4a**. The crude product was purified by column chromatography (13–15% EtOAc/hexanes) to afford the separable cyclic products **4b** & **4c** as a colourless liquid in 1:2 ratio (38 mg, 55% combined yield, brsm (48 mg)); R_f (20% EtOAc/hexanes) 0.4.

*4.1.25.1. Data of palmyrolide A (**4b**).* R_f (25% EtOAc/hexanes) 0.4; $[\alpha]_D^{26.5}$ −28.6 (*c* 0.52, $CHCl_3$); IR (Neat) ν_{max} 2924, 2855, 1725, 1674, 1644, 1462, 1374, 1246, 1177, 1124, 1073, 940 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.47 (d, J=14.1 Hz, 1H), 5.27 (dt, J=14.1, 7.5 Hz, 1H), 4.88 (dd, J=11.3, 1.8 Hz, 1H), 3.04 (s, 3H), 2.48 (m, 1H), 2.43–2.33 (m, 2H), 2.33–2.23 (m, 2H), 1.86–1.71 (m, 3H), 1.71–1.53 (m, 2H), 1.48 (m, 1H), 1.42–1.31 (m, 2H), 1.21 (d, J=7.5 Hz, 3H), 1.06 (m, 1H), 0.90 (d, J=6.6 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 172.9, 130.6, 117.3, 76.9, 38.8, 35.6, 35.2, 34.5, 34.4, 32.8, 31.7, 29.3, 26.9, 26.0, 24.3, 20.6, 16.8; HRMS (ESI): calcd for $C_{20}H_{36}O_3N$ $[M+H]^+$ 338.2689; found 338.2690.

*4.1.25.2. Data of **4c**.* $[\alpha]_D^{26.2}$ +4.3 (*c* 0.46, $CHCl_3$); IR (Neat) ν_{max} 2959, 2928, 1726, 1672, 1645, 1463, 1386, 1336, 1171, 1123, 934 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (d, J=14.1 Hz, 1H), 4.91 (ddd, J=14.1, 9.4, 5.6 Hz, 1H), 4.83 (dd, J=9.4, 1.9 Hz, 1H), 3.04 (s, 3H), 2.59–2.41 (m, 3H), 2.31 (m, 1H), 2.19 (m, 1H), 1.98 (m, 1H), 1.78 (m, 1H), 1.65–1.53 (m, 2H), 1.48–1.38 (m, 3H), 1.34 (m, 1H), 1.25 (d, J=7.5 Hz, 3H), 0.98 (m, 1H), 0.87 (d, J=6.6 Hz, 3H), 0.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 172.7, 129.7, 110.0, 76.3, 37.1, 36.4, 35.3, 34.1, 33.4, 30.9, 29.6, 29.4, 27.3, 25.8, 24.8, 19.9, 19.1; HRMS (ESI): calcd for $C_{20}H_{36}O_3N$ $[M+H]^+$ 338.2689; found 338.2692.

*4.1.26. (R)-Methyl 7-(benzyloxy)-3-methylheptanoate (**17**).* The compound **7** (12.8 g, 54.1 mmol) was dissolved in dry THF (216 mL), triethylamine (9 mL, 64.92 mmol) and ethylchloroformate (7.8 mL, 59.5 mmol) were added sequentially at −15 °C. Stirring was continued for 15 min at the same temp, and then the solution was warmed up to 0 °C. A solution of diazomethane in diethyl ether was added slowly at 0 °C, slightly yellow colour solution was stirred for a further 12 h at 0 °C. Excess of diazomethane was decomposed by drop wise addition of CH_3CO_2H. The mixture was washed with satd $NaHCO_3$, satd NH_4Cl and brine solution. The organic layer was dried over Na_2SO_4, filtered, and evaporated in vacuo.

To a solution of α-diazo ketone (9.6 g, 36.9 mmol) in anhydrous CH_3OH (520 mL) was added drop wise a solution of silver acetate (1.85 g, 11.07 mmol) in triethylamine (41.1 mL, 0.29 mmol) under nitrogen. The mixture was stirred at rt for 2 h. The solvent was evaporated, and the residue was purified by column chromatography (5% EtOAc/hexane). R_f (10% EtOAc/hexane) 0.5; $[\alpha]_D^{26.5}$ +8.1 (*c* 0.58, $CHCl_3$); IR (Neat) ν_{max} 2932, 2856, 1739, 1516, 1460, 1365, 1201, 1164, 696 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5H), 4.50 (s, 2H), 3.65 (s, 3H), 3.46 (t, J=6.6 Hz, 2H), 2.30 (dd, J=14.3, 6.6 Hz, 1H), 2.11 (dd, J=14.3, 8.8 Hz, 1H), 1.95 (m, 1H), 1.65–1.54 (m, 2H), 1.47–1.28 (m, 3H), 1.21 (m, 1H), 0.93 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 138.5, 128.3, 127.5, 127.4, 72.8. 70.2, 51.3, 41.5, 36.4, 30.2, 29.8, 23.5 19.6; HRMS (ESI): calcd for $C_{16}H_{24}O_3$ $[M+Na]^+$ 287.1627 found 287.1648.

*4.1.27. (5R)-9-(Benzyloxy)-2,2,5-trimethylnonan-3-ol (**18**).* To a solution of ester **17** (8.8 g, 33.3 mmol) in toluene at −78 °C was added DIBAL-H (22.2 mL, 1.5 M solution in toluene), the reaction mixture was stirred for 10 min at that temp and was quenched by the addition of methanol (6.7 mL). The reaction mixture was then allowed to warm up to rt and diluted with EtOAc, added saturated solution of sodium potassium tartrate (80 mL) and stirred for 1 h, filtered. The compound was extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash column chromatography purification (5% EtOAc/hexanes) afforded aldehyde (7 g, 90%) as colourless oil; R_f (10% EtOAc/hexanes) 0.5.

To a solution of aldehyde (7 g, 29.89 mmol) in dry THF (75 mL) was added *tert*-BuLi (30 mL, 1.5 M solution in pentane) at −78 °C, and the mixture was stirred for 2 h under argon. The reaction mixture was poured into aqueous solution of NH_4Cl at 0 °C, extracted with EtOAc. The combined organic layers were washed with water, brine solution and dried over Na_2SO_4, filtered, and concentrated in vacuo. Purified by column chromatography (8–9% EtOAc/hexanes) to furnish the required alcohol **18** (6.7 g) as yellow colour oil; R_f (15% EtOAc/hexanes) 0.5; $[\alpha]_D^{26}$ +20.0 (*c* 0.1, $CHCl_3$); IR (Neat) ν_{max} 3436, 2929, 2860, 1631, 1454, 1363, 1104, 733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5H), 4.51 (s, 2H), 3.48 (t, J=6.4 Hz, 2H), 3.28 (m, 1H), 1.73–1.52 (m, 5H), 1.50–0.99 (m, 4H), 0.94 (d, J=6.8 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 127.4, 77.5, 77.2, 72.8, 70.4, 39.2, 38.8, 38.1, 35.3, 34.8, 34.7, 30.0, 29.9, 29.5, 25.7, 25.6, 23.6, 23.4, 20.9, 18.8; HRMS (ESI): calcd for $C_{19}H_{32}O_2Na$ $[M+Na]^+$ 315.2294; found 315.2282.

*4.1.28. (5R)-5,8,8-Trimethylnonane-1,7-diol (**19**).* The compound **18** (6.7 g, 22.9 mmol), in dry methanol (69 mL) was debenzylated by using 1 atmospheric H_2 balloon pressure in the presence of 20% Pd/C (1.34 g) for 2 h. The mixture was then filtered through pad of Celite, washed with EtOAc, evaporated and purified by column chromatography (25–28% EtOAc/hexanes) to afford diol product **19** (4.3 g, 93%) as colourless liquid; R_f (40% EtOAc/hexanes) 0.4; $[\alpha]_D^{26.2}$ +8.8 (*c* 0.48, $CHCl_3$); IR (Neat) ν_{max} 3361, 2935, 1693, 1626, 1516, 1465, 1112, 983 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.65 (t, J=6.5 Hz, 2H), 3.29 (m, 1H), 1.71–1.53 (m, 2H), 1.52–1.15 (m, 6H), 1.07 (m, 1H), 0.95 (d, J=7.0 Hz, 3H), 0.89 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.4, 62.8, 39.1, 38.7, 38.0, 35.1, 34.8, 34.7, 32.9, 29.8, 29.5, 25.6, 23.1, 22.9, 20.9, 18.9; HRMS (ESI): calcd for $C_{12}H_{26}O_2Na$ $[M+Na]^+$ 225.1825; found 225.1821.

*4.1.29. (R)-Methyl 5,8,8-trimethyl-7-oxononanoate (**20**).* To a stirred solution of diol **19** (4.3 g, 21.25 mmol) in CH_2Cl_2 (65 mL) was added DMP (Dess-Martin periodinane, 19.8 g, 46.75 mmol) at 0 °C and the resulted solution was stirred at rt for 1 h. Then the reaction mixture was quenched with 1:1 mixture of saturated $NaHCO_3$ solution and saturated $Na_2S_2O_3$ solution and stirred for 15 min to get clear solution, and then aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and purified by flash column chromatography (5% EtOAc/hexanes) to furnish the aldehyde (3.7 g) as colourless liquid; R_f (10% EtOAc/hexanes) 0.5.

To a solution of aldehyde (3.7 g, 18.65 mmol) in *t*-BuOH/2-methyl-2-butene (2:1, 52 mL) at rt, $NaClO_2$ (3.9 g, 42.89 mmol) and NaH_2PO_4 (5.1 g, 42.89 mmol), were dissolved in minimum amount of water, were added. After being stirred for 1 h, the solvent was removed in rotatory evaporator and the residue was extracted with EtOAc. The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (18–20% EtOAc/hexane) afforded pure acid compound (3.75 g, 94%) as a colourless liquid; R_f (30% EtOAc/hexanes) 0.4.

To a stirred solution of acid (3.7 g, 17.26 mmol) in dry ether (42 mL), was added CH_2N_2 in ether solution at 0 °C, stirring was continued for 0.5 h at the same temp. Excess of diazomethane was decomposed by drop wise addition of CH_3CO_2H, extracted with EtOAc. The combined organic layers were washed with water, brine solution and dried over Na_2SO_4, filtered, and concentrated in vacuo.

Purified by column chromatography (5% EtOAc/hexanes) to furnish the required ester **20** (3.8 g, 97%) as yellow colour oil; R_f (10% EtOAc/hexanes) 0.5; $[\alpha]_D^{25.8}$ −7.1 (*c* 0.6, $CHCl_3$); IR (Neat) ν_{max} 2958, 1739, 1704, 1464, 1365, 1249, 1198, 1167, 1060, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 2.43–2.35 (m, 2H), 2.35–2.24 (m, 2H), 2.06 (m, 1H), 1.71–1.54 (m, 2H), 1.29 (m, 1H), 1.17 (m, 1H), 1.12 (s, 9H), 0.87 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.3, 174.0, 51.4, 44.1, 43.6, 36.1, 34.0, 28.1, 26.2, 22.4, 19.6; HRMS (ESI): calcd for $C_{13}H_{24}O_3Na$ $[M+Na]^+$ 251.1623; found 251.1618.

*4.1.30. (5R,7R)-Methyl 7-hydroxy-5,8,8-trimethylnonanoate (**21**).* To a stirred solution of (*S*)-CBS catalyst (1 M solution in toluene, 5 mL, 4.98 mmol) in dry toluene (34 mL), was added $BH_3.Me_2S$ (1.6 mL, 16.6 mmol) at 0 °C drop wise under nitrogen. After stirring for 10 min at 0 °C, a solution of ketone **20** (3.8 g, 16.6 mmol) in 8 mL of toluene was cannulated and stirring was continued for 4 h at the same temperature. After completion, the reaction mixture was quenched by careful drop wise addition of MeOH (60 mL), diluted with saturated NH_4Cl, stirred for 1 h and then extracted with EtOAc. The combined organic layers were washed with water, brine and dried over Na_2SO_4, and filtered. Purified by column chromatography (12–14% EtOAc/hexanes) to furnish alcohol **21** and **21a** (3.2 g) (*dr* 89:11) as colourless liquid.

*4.1.30.1. Data of **21**.* R_f (20% EtOAc/hexanes) 0.4; $[\alpha]_D^{25.9}$ +45.2 (*c* 0.21, $CHCl_3$); IR (Neat) ν_{max} 3619, 2954, 1739, 1516, 1463, 1366, 1257, 1201, 1169, 1071, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.27 (dd, *J*=10.0, 1.5 Hz, 1H) 2.40–2.22 (m, 2H), 1.80–1.32 (m, 6H), 1.24–1.0 (m, 2H), 0.95 (d, *J*=6.6 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 77.4, 51.4, 39.0, 34.9, 34.8, 34.2, 29.6, 25.6, 22.2, 20.8; HRMS (ESI): calcd for $C_{13}H_{26}O_3Na$ $[M+Na]^+$ 253.1774; found 253.1765.

*4.1.31. (5R,7S)-Methyl 7-hydroxy-5,8,8-trimethylnonanoate (**21a**).* R_f (20% EtOAc/hexanes) 0.4; $[\alpha]_D^{26.3}$ +53.6 (*c* 0.13, $CHCl_3$); IR (Neat) ν_{max} 3613, 2947, 1737, 1510, 1473, 1352, 1257, 1169, 1071, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.29 (dd, *J*=10.4, 2.1 Hz, 1H) 2.31 (t, *J*=7.5 Hz, 2H), 1.76–1.56 (m, 3H), 1.39–1.13 (m, 4H), 0.91–0.87 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.3, 77.2, 51.4, 38.6, 37.7, 34.8, 34.3, 29.3, 25.6, 22.4, 18.8; HRMS (ESI): calcd for $C_{13}H_{26}O_3Na$ $[M+Na]^+$ 253.1774; found 253.1770.

*4.1.32. (5R,7R)-Methyl 7-(((R)-6-(benzyloxy)-2-methylhexanoyl) oxy)-5,8,8-trimethylnonanoate (**22**).* The compound **22** was prepared from **7** (500 mg, 2.115 mmol) & **21** (487 mg, 2.115) in a similar manner as compounds **6** & **6a**. The crude product was purified by column chromatography (4–5% EtOAc/hexanes) to afford **22** (888 mg, 94%) as a colourless liquid; R_f (10% EtOAc/hexanes) 0.5; $[\alpha]_D^{26.5}$ +43.9 (*c* 0.37, $CHCl_3$); IR (Neat) ν_{max} 2963, 2866, 1739, 1727, 1516, 1462, 1167, 1104, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 4.81 (dd, *J*=6.7, 4.9 Hz, 1H), 4.49 (s, 2H), 3.66 (s, 3H), 3.46 (t, *J*=6.6 Hz, 2H), 2.43 (m, 1H), 2.35–2.19 (m, 2H), 1.76–1.56 (m, 4H), 1.56–1.26 (m, 8H), 1.15 (d, *J*=7.0 Hz, 3H), 1.05 (m, 1H), 0.91–0.85 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 174.1, 138.6, 128.2, 127.5, 127.4, 78.0, 72.8, 70.1, 51.3, 40.0, 37.2, 34.7, 34.5, 34.2, 33.4, 29.6, 29.2, 25.9, 24.0, 22.0, 20.5, 17.3; HRMS (ESI): calcd for $C_{27}H_{44}O_5Na$ $[M+Na]^+$ 471.3081; found 471.3056.

*4.1.33. (R)-(3R,5R)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-6-(benzyloxy)-2-methylhexanoate (**23**).* The compound **23** (842 mg, 1.94 mmol) was prepared from acid of **22** in a similar manner as **5** & **5a**. The crude product was purified by column chromatography (30–32% EtOAc/hexanes) to afford **23** (809 mg, 94%) as a yellow colour oil; R_f (50% EtOAc/hexanes) 0.4; $[\alpha]_D^{26.1}$ +43.3 (*c* 0.41, $CHCl_3$); IR (Neat) ν_{max} 3302, 2940, 2865, 1725, 1648, 1547, 1460, 1368, 1168, 1103, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5H), 6.09 (br s, 1H), 4.75 (dd, *J*=9.8, 2.2 Hz, 1H), 4.50 (s, 2H), 3.46 (t, *J*=6.4 Hz, 2H), 2.80 (d, *J*=4.5 Hz, 3H), 2.45 (m, 1H), 2.21–2.01 (m, 2H), 1.83–1.57 (m, 6H), 1.53–1.33 (m, 5H), 1.26 (m, 1H), 1.16 (d, *J*=7.5 Hz, 3H), 1.01 (m, 1H), 0.91–0.84 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9, 173.9, 138.4, 128.2, 127.5, 127.4, 78.6, 72.8, 70.0, 40.0, 37.6, 36.0, 34.4, 33.4, 33.0, 29.6, 28.7, 26.1, 25.9, 24.0, 22.8, 20.8, 17.4; HRMS (ESI): calcd for $C_{27}H_{45}O_4NNa$ $[M+Na]^+$ 470.3240; found 470.3223.

*4.1.34. Data of acid of **22**.* Acid of **22** was prepared from **22** (888 mg, 1.98 mmol) in a similar manner as **15** & **15a**. The crude product was purified by column chromatography (16–18% EtOAc/hexanes) to afford (5*R*,7*R*)-7-(((*R*)-6-(benzyloxy)-2-methylhexanoyl)oxy)-5,8,8-trimethylnonanoic acid (842 mg, 98%) as colourless oil; R_f (30% EtOAc/hexanes) 0.3; $[\alpha]_D^{26.2}$ +36.4 (*c* 0.53, $CHCl_3$); IR (Neat) ν_{max} 3437, 2961, 2938, 1727, 1709, 1631, 1459, 1366, 1262, 1198, 1167, 960, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5H), 4.81 (dd, *J*=7.0, 4.3 Hz, 1H), 4.50 (s, 2H), 3.46 (t, *J*=6.6 Hz, 2H), 2.43 (m, 1H), 2.37–2.26 (m, 2H), 1.78–1.24 (m, 12H), 1.15 (d, *J*=7.0 Hz, 3H), 1.06 (1H), 0.94–0.83 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 176.4, 138.5, 128.3, 127.5, 127.4, 78.1, 72.8, 70.1, 40.0, 37.2, 34.6, 34.5, 34.1, 33.4, 29.6, 29.2, 25.9, 24.0, 21.8, 20.5, 17.3; HRMS (ESI): calcd for $C_{26}H_{42}O_5Na$ $[M+Na]^+$ 457.2929; found 457.2927.

*4.1.35. Data of alcohol of **23**.* The alcohol of **23** was prepared from **23** (809 mg, 1.82 mmol) in a similar manner as alcohol of **5** & **5a**. The crude product was purified by column chromatography (75–80% EtOAc) to furnish the (*R*)-(3*R*,5*R*)-2,2,5-trimethyl-9-(methylamino)-9-oxononan-3-yl-6-hydroxy-2-methylhexanoate (553 mg, 92%) as colourless liquid; R_f (EtOAc) 0.4; $[\alpha]_D^{27}$ +40.0 (*c* 0.58, $CHCl_3$); IR (Neat) ν_{max} 3620, 3301, 2934, 1707, 1647, 1516, 1463, 1372, 1164, 1070, 959, 669 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (br s, 1H), 4.78 (dd, *J*=9.9, 2.2 Hz, 1H), 3.64 (t, *J*=6.6 Hz, 2H), 2.81 (d, *J*=5.5 Hz, 3H), 2.47 (m, 1H), 2.20–2.05 (m, 2H), 1.80–1.64 (m, 4H), 1.62–1.54 (m, 2H), 1.52–1.33 (m, 5H), 1.28 (m, 1H), 1.18 (d, *J*=6.6 Hz, 3H), 1.01 (m, 1H), 0.91–0.85 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 174.0, 78.5, 62.3, 40.1, 37.5, 36.1, 34.4, 33.3, 32.4, 28.7, 26.1, 25.9, 23.5, 22.9, 20.7, 17.3; HRMS (ESI): calcd for $C_{20}H_{40}O_4N$ $[M+H]^+$ 358.2951; found 358.2939.

*4.1.36. (R)-(3R,5R)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl 2-methyl-6-oxohexanoate (**24**).* The compound **24** was prepared from alcohol of **23** (605 mg, 1.69 mmol) in a similar manner as **16** & **16a**. The crude product was purified by flash column chromatography (60–65% EtOAc/hexanes) to afford **24** (553 mg, 92%) as colourless liquid; R_f (EtOAc) 0.6; $[\alpha]_D^{26}$ +39.1 (*c* 0.23, $CHCl_3$); IR (Neat) ν_{max} 3414, 2956, 2923, 1727, 1647, 1559, 1462, 1367, 1259, 1165, 1076, 960 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 6.01 (br s, 1H), 4.78 (dd, *J*=8.8, 3.3 Hz, 1H), 2.81 (d, *J*=4.4 Hz, 3H), 2.50–2.43 (m, 3H), 2.15 (m, 1H), 2.09 (m, 1H), 1.80–1.59 (m, 4H), 1.52–1.36 (m, 5H), 1.26 (m, 1H), 1.19 (d, *J*=7.7 Hz, 3H), 1.02 (m, 1H), 0.91–0.84 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 176.4, 173.9, 78.7, 43.6, 39.9, 37.5, 36.0, 34.4, 32.8, 28.8, 26.1, 25.8, 22.8, 20.7, 19.7, 17.3; HRMS (ESI): calcd for $C_{20}H_{38}O_4N$ $[M+H]^+$ 356.2795; found 356.2781.

*4.1.37. Palmyrolide A (**4b**).* Palmyrolide A (**4b**) was prepared from **24** (100 mg, 0.28 mmol) in a similar manner as **4** & **4a**. The crude product was purified by column chromatography (14–15% EtOAc/hexanes) to afford Palmyrolide A (**4b**) (27 mg, 54%, brsm (47 mg)) as colourless oil.

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Supplementary data

A supplementary data file (^{1}H and ^{13}C NMR) of the synthesized compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.01.048.

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