Tetrahedron 64 (2008) 5861–5865

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Proline-catalyzed stereoselective synthesis of natural and unnatural nocardiolactone

G. Kumaraswamy *, B. Markondaiah

Organic Division III, Fine Chemicals Laboratory, Indian Institute of Chemical Technology, Hyderabad-500 607, India

ARTICLE INFO

Article history:
Received 14 February 2008
Received in revised form 14 April 2008
Accepted 16 April 2008
Available online 18 April 2008

Keywords:
Nocardiolactone
Unnatural nocardiolactone
trans-β-Lactone
Proline
Glyceraldehyde acetonide
Aldolization

ABSTRACT

A concise diastereo and enantioselective synthesis of natural and unnatural nocardiolactone is accomplished by proline-catalyzed crossed-aldol reaction as the key step.

1. Introduction

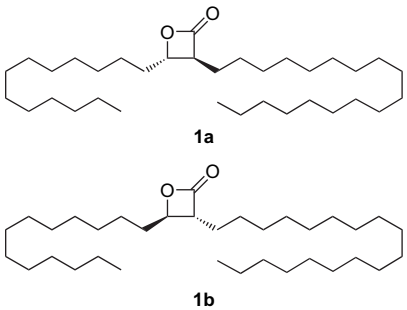
Disubstituted *trans*-β-lactones are considered to be pivotal structural motif for many natural and unnatural molecules such as ebelactones, lipstatin, panclicins, tetrahydrolipstatin, 1233A, belactosins, and nocardiolactone.[1] These molecules display significant biological activity such as antibiotic and antiobesity.[1c,d] Additionally, the simplified disubstituted *trans*-β-lactones potentially act as inhibitors of several enzymes including proteases,[2] HMG Co-A synthase,[3] and esterase.[4] Nocardiolactone **1a**, a trans-disposed disubstituted β-lactone was isolated by Mikami et al. from pathogenic *Nocardia strains* and found to exhibit narrow spectrum activity against Gram-positive bacteria, *Bacillus subtilis* ATCC 6633[5] (Fig. 1). Nocardiolactone **1a** has been synthesized for the first time through an enantioselective route based on Crimmins aldolization followed by DBU-mediated lactonization thereby establishing the absolute configuration of the *trans*-β-lactone as *S*,*S*.[6]

Recently, impressive organocatalytic routes have been developed for the disubstituted *cis*-β-lactones in high enantiopurity.[7] The *cis*-β-lactones were also epimerized to thermodynamically favored *trans*-β-lactones under strong basic conditions.[8]

2. Results and discussion

Our continuing interest in the development of enantioselective synthetic routes[9] for the disubstituted *trans*-β-lactones prompted us to apply *S*-proline-catalyzed crossed-aldol reaction to install the two stereocenters of the *trans*-β-lactone in a highly diastereo and enantioselective manner. Our approach toward the synthesis of nocardiolactone **1a** is shown in Scheme 1.

We have initiated *S*-proline (10 mol %) catalyzed crossed-aldol reaction between eicosanal **2** and glyceraldehyde acetonide **3**, which in turn was prepared from D-mannitol. After considerable experimentation, the reaction was carried out with 10 mol % of *S*-proline and 1 equiv of **2** and 2 equiv of **3** in dry DMF at ambient



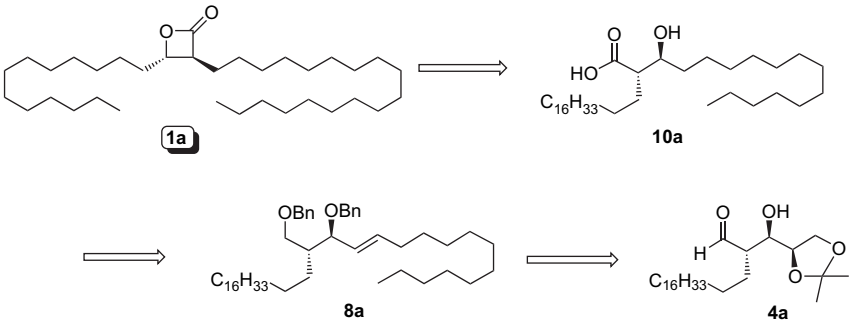
1a

1b

Figure 1.

* Corresponding author. Tel.: +91 40 27193154; fax: +91 40 27193275.
E-mail address: gkswamy_iict@yahoo.co.in (G. Kumaraswamy).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.04.062



Scheme 1.

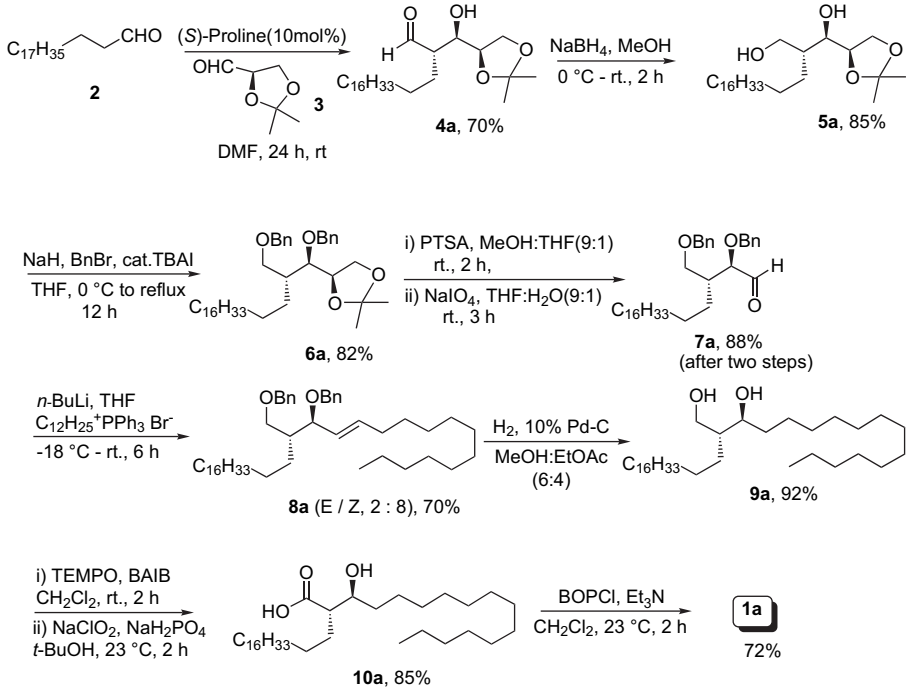
temperature stirring for 24 h, which lead to the *anti*-aldol product **4a** in 70% isolated yield (dr=9:1).[10] Interestingly, we were also able to show that by changing (*S*)- to (*R*)-proline (10 mol %), under otherwise identical conditions, the aldol product **4b** was received in slightly less yields with same diastereoselectivity. The result indicates that there is a negligible matched or mismatched effect on the outcome diastereoselectivity of product **4a** and **4b**. Furthermore, the reagent plays a decisive role on the *anti*-aldol diastereoselectivity, which is also consistent with similar proline-catalyzed reactions.[11]

The subsequent reduction of **4a** using $NaBH_4$/MeOH resulted to the 1,3-diol **5a** in 85% yield. The 1,3-hydroxyl groups were protected as its benzyl ethers using NaH/BnBr in the presence of catalytic amount of TBAI. The acetonide was deprotected with PTSA/(MeOH:THF) (9:1) to give 1,2-diol, followed by oxidative cleavage of the corresponding 1,2-diol using sodium metaperiodate in THF/H_2O (9:1) resulting in aldehyde **7a** in 88% yield. This aldehyde was subjected to Wittig reaction using $C_{12}H_{25}^{+}PPh_3Br^{-}$ and *n*-BuLi in THF to give the olefin (*E*/*Z*, 2:8) **8a** in 70% yield. Hydrogenation of **8a** with 10% Pd–C/H_2 in MeOH/EtOAc (6:4) gave the corresponding 1,3-diol **9a** in 92% yield.

The TEMPO catalyzed chemoselective oxidation[12a] of **9a** with bis(acetoxy)iodobenzene (BAIB) in CH_2Cl_2 followed by further oxidation of the resulting aldehyde employing perchlorite/dihydrogen orthophosphate furnished the β-hydroxy acid[12b] **10a** in 85% yield. The β-hydroxy acid **10a** was lactonized to bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) and Et_3N as base lead to the title compound **1a** in 72% yield (Scheme 2). The spectral and analytical data of **1a** were in full agreement with the reported data ($[\alpha]_D^{25}$ −12.6 (*c* .01, $CHCl_3$); lit.[5] $[\alpha]_D^{25}$ −12.7 (*c* 2.5, $CHCl_3$)).[5] The unnatural nocardiolactone **1b** was synthesized starting from **4b** following the same reaction sequence of **1a**. The optical rotation of **1b** found to be similar in magnitude but opposite in sign to that of **1a**.

3. Conclusion

In conclusion, we have developed the organocatalytic route for the total synthesis of natural and unnatural nocardiolactone molecules. To the best of our knowledge this is the first catalytic route to nocardiolactone **1a**. Significantly, the chirality of the β-lactone moiety was installed with inexpensive naturally occurring amino-acid such as L-proline. Application of this novel methodology to synthesize various disubstituted *trans*-β-lactones in order to study their activity profiles is under progress.



Scheme 2.

4. Experimental section

4.1. General

Solvents were dried over standard drying agents and freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C in vacuo. ^1H NMR (200 and 300 MHz) and ^{13}C NMR (50 and 75 MHz) spectra were measured with a Varian Gemini FT-200 MHz spectrometer and Bruker Avance 300 MHz, with tetramethylsilane as an internal standard for solutions in deuteriochloroform. *J* values are given in hertz. IR spectra were recorded on a Perkin–Elmer IR-683 spectrophotometer. Optical rotations were measured with HORIBA SEPA-300 high sensitive polarimeter at 25 °C. Mass spectra were recorded on CEC-21-11013 or Finnigan Mat 1210 double focusing mass spectrometer operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

4.2. Typical procedure for the aldol reaction: (*S*)-2-((*R*)-hydroxy ((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-icosanal, 4a

A DMF solution of glyceraldehyde acetonide **3** (4.3 g, 33.72 mmol) was treated with successively L-proline (0.194 g, 1.68 mmol) and 1-eicosanal **2** (5 g, 16.86 mmol). The resulting reaction mixture was stirred at rt for 24 h, and then the reaction mixture was diluted with diethyl ether (1×125 mL). The ether layer was washed successively with water (2×100 mL) and brine (2×100 mL). The combined aqueous layers were extracted with ethyl acetate (4×150 mL). The combined ether and ethyl acetate layers were dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the β-hydroxy aldehyde **4a** (5 g, 70% yield) as a colorless solid. Mp 49–51 °C; TLC, R_f 0.56 (30% EtOAc/hexane); $[\alpha]_D^{25}$ +3.5 (*c* 0.012, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.72 (d, *J*=3.8 Hz, 1H), 4.12 (ddd, *J*=11.3, 6.8, 4.5 Hz, 1H), 4.03 (dd, *J*=8.3, 6.8 Hz, 1H), 3.80 (dd, *J*=7.5, 6.0 Hz, 1H), 3.72–3.65 (m, 1H), 2.42–2.35 (m, 1H), 2.30–2.25 (m, 1H), 1.84–1.74 (m, 1H), 1.65–1.55 (m, 1H), 1.42 (s, 3H), 1.35 (s, 3H), 1.30–1.22 (m, 32H), 0.88 (t, *J*=6.0 Hz, 3H); ^{13}C NMR (75 MHz): δ 204.6, 109.7, 76.6, 72.1, 65.8, 55.0, 31.9, 29.6, 29.5, 29.2, 27.0, 26.4, 26.3, 25.1, 22.6, 14.0; IR (KBr): 3421, 2920, 2851, 1721, 1463, 1211, 849 cm^{-1}; MS (LC): *m*/*z* 449 $[M+Na]^+$; ESI-HRMS: *m*/*z* calcd for $C_{26}H_{50}O_4Na$ $[M+Na]^+$ 449.3606; found 449.3626.

4.3. (*R*)-2-((*S*)-Hydroxy ((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)icosanal, 4b

The aldol product **4b** (4.88 g, 68% yield) as a colorless solid, mp 47–49 °C, was synthesized from **2** (5 g, 16.86 mmol) according to typical procedure **4a**. TLC, R_f 0.55 (30% EtOAc/hexane); $[\alpha]_D^{25}$ +12.3 (*c* 0.038, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 9.73 (d, *J*=2.7 Hz, 1H), 4.11–4.0 (m, 2H), 3.90–3.81 (m, 1H), 3.68–3.64 (m, 1H), 2.62–2.56 (m, 1H), 2.52–2.45 (m, 1H), 1.81–1.70 (m, 1H), 1.64–1.55 (m, 1H), 1.37 (s, 3H), 1.31 (s, 3H), 1.30–1.20 (m, 32H), 0.88 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ 204.5, 108.9, 76.2, 72.0, 66.0, 52.6, 31.3, 29.1, 28.9, 28.7, 26.7, 26.0, 25.4, 24.5, 22.0, 13.5; IR (KBr): 3421, 2920, 2851, 2721, 1708, 1463, 1214, 849 cm^{-1}; MS (LC): *m*/*z* 449 $[M+Na]^+$; ESI-HRMS: *m*/*z* calcd for $C_{26}H_{50}O_4Na$ $[M+Na]^+$ 449.3606; found 449.3612.

4.4. Typical procedure for the reduction: (1*R*,2*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4yl)-2-octadecylpropane-1,3-diol, 5a

Sodium borohydride (0.67 g, 17.6 mmol) was added to the aldol product **3a** (5 g, 11.73 mmol) dissolved in methanol (100 mL). The resulting reaction mixture was stirred at rt, for 1.5 h. Then the MeOH was removed from the reaction mixture and quenched with saturated NH_4Cl solution at 0 °C. The reaction mixture was extracted with ethyl acetate (2×50 mL). The organic extracts were washed with water (1×20 mL), followed by brine (1×20 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography to give the corresponding 1,3-diol **5a** (4.25 g, 85% yield) as a colorless solid. Mp 55–57 °C; TLC, R_f 0.29 (20% EtOAc/hexane); $[\alpha]_D^{25}$ −13.5 (*c* 0.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.21 (dd, *J*=12.0, 6.8 Hz, 1H), 4.0 (dd, *J*=8.3, 6.8 Hz, 1H), 3.76–3.70 (m, 2H), 3.64–3.50 (m, 2H), 2.76–2.70 (m, 1H), 2.59 (d, *J*=5.3 Hz, 1H), 1.68–1.62 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.31–1.21 (m, 34H), 0.88 (t, *J*=6.0 Hz, 3H); ^{13}C NMR (75 MHz): δ 109.5, 77.5, 74.5, 66.4, 62.8, 43.0, 31.9, 29.8, 29.7, 29.5, 29.3, 28.9, 27.2, 26.5, 25.4, 22.6, 14.0; IR (KBr): 3335, 2917, 1052, 849, 753 cm^{-1}; MS (LC): *m*/*z* 451 $[M+Na]^+$; ESI-HRMS: *m*/*z* calcd for $C_{26}H_{52}O_4Na$ $[M+Na]^+$ 451.3763; found 451.3744.

4.5. (1*S*,2*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4yl)-2-octadecylpropane-1,3-diol, 5b

The compound **5b** (4.2 g, 84% yield) as a colorless solid, mp 54–56 °C, was synthesized from **4b** (5 g, 11.73 mmol) according to typical procedure **5a**. TLC, R_f 0.29 (20% EtOAc/hexane); $[\alpha]_D^{25}$ +14.0 (*c* 0.018, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 4.13 (dd, *J*=12.8, 6.0 Hz, 1H), 4.03 (dd, *J*=8.3, 6.0 Hz, 1H), 3.94–3.86 (m, 2H), 3.70–3.64 (m, 2H), 1.63–1.56 (m, 1H), 1.39 (s, 3H), 1.34 (s, 3H), 1.32–1.24 (m, 34H), 0.88 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz): δ 109.1, 76.3, 75.2, 66.0, 64.0, 41.1, 31.9, 29.8, 29.7, 29.5, 29.3, 28.0, 27.1, 26.6, 25.2, 22.6, 14.1; IR (KBr): 3335, 2917, 2849, 1461, 1029, 789 cm^{-1}; MS (LC): *m*/*z* 451 $[M+Na]^+$; ESI-HRMS: *m*/*z* calcd for $C_{26}H_{52}O_4Na$ $[M+Na]^+$ 451.3763; found 451.3773.

4.6. Typical procedure for the benzylation: (*R*)-4-((1*R*,2*R*)-1-(benzyloxy)-2-((benzyloxy)methyl)icosyl)-2,2-dimethyl-1,3-dioxolane, 6a

To a suspension of NaH (60%, 0.82 g, 20.44 mmol) in dry THF (20 mL) was added dropwise a solution of 1,3-diol **5a** (3.5 g, 8.18 mmol) in THF (25 mL) at 0 °C. To this reaction mixture TBAI (0.15 g) and benzyl bromide (2.43 mL, 20.44 mmol) were added subsequently and stirring was continued for 2 h at the same temperature and 12 h at reflux temperature. The reaction mixture was quenched by saturated NH_4Cl solution at 0 °C. The reaction mixture was extracted with ethyl acetate (2×50 mL). The organic extracts were washed with water (1×20 mL), followed by brine (1×20 mL), dried, and concentrated under reduced pressure. The residue was purified by column chromatography to give the benzylated product **6a** (4 g, 82% yield) as a colorless oily liquid. TLC, R_f 0.59 (10% EtOAc/hexane). $[\alpha]_D^{25}$ +5.9 (*c* 0.0135, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.25 (m, 10H), 4.87 (d, *J*=11.3 Hz, 1H), 4.57 (d, *J*=11.3 Hz, 1H), 4.54 (s, 2H), 4.48–4.39 (m, 1H), 4.01–3.96 (dd, *J*=7.5, 6.0 Hz, 1H), 3.66–3.60 (dd, *J*=9.0, 7.5 Hz, 1H), 3.50–3.40 (m, 2H), 3.32–3.27 (dd, *J*=9.8, 5.3 Hz, 1H), 1.55–1.50 (m, 1H), 1.43 (s, 3H), 1.34 (s, 3H), 1.30–1.17 (m, 34H), 0.88 (t, *J*=6.0 Hz, 3H); ^{13}C NMR (75 MHz): δ 139.2, 138.5, 128.7, 128.1, 127.7, 127.4, 127.2, 109.0, 81.0, 79.3, 73.9, 73.1, 70.2, 66.6, 41.8, 32.9, 29.7, 29.6, 29.5, 29.4, 29.3, 27.5, 26.8, 25.7, 22.6, 14.1; IR (KBr): 2924, 2853, 1457, 1372, 1211, 1092, 753 cm^{-1}; MS (LC): *m*/*z* 631 $[M+Na]^+$; ESI-HRMS: *m*/*z* calcd for $C_{40}H_{64}O_4Na$ $[M+Na]^+$ 631.4702; found 631.4705.

4.7. (*R*)-4-((1*S*,2*S*)-1-(Benzyloxy)-2-((benzyloxy)methyl)-icosyl)-2,2-dimethyl-1,3-dioxolane, 6b

The compound **6b** (4.1 g, 84% yield) as a colorless oily liquid was synthesized from **5b** (3.5 g, 8.18 mmol) according to typical procedure **6a**. TLC, R_f 0.58 (10% EtOAc/hexane). $[\alpha]_D^{25}$ +10.2 (*c* 0.014, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30–7.24 (m, 10H), 4.66 (d, *J*=11.7 Hz, 1H), 4.53 (d, *J*=11.7 Hz, 1H), 4.43 (s, 2H), 4.25–4.16 (m, 1H), 3.96 (dd, *J*=8.0, 6.6 Hz, 1H), 3.85 (dd, *J*=8.0, 7.3 Hz, 1H), 3.68–3.59 (m, 1H), 3.57–3.34 (m, 2H), 1.92–1.84 (m, 1H), 1.37 (s, 3H), 1.30 (s, 3H), 1.29–1.19 (m, 34H), 0.88 (t, *J*=5.9 Hz, 3H); ^{13}C NMR (75 MHz): δ 138.5, 138.4, 128.0, 127.5, 127.3, 127.2, 127.0, 108.5, 79.6, 77.2, 73.8, 72.9, 70.1, 66.3, 41.2, 31.9, 29.8, 29.6, 29.5, 29.3, 28.3, 27.5, 26.5, 25.2, 22.7, 14.1; IR (KBr): 2928, 2853, 1494, 1371, 1251, 1082, 852 cm^{-1}; MS (LC): *m*/*z* 631 $[M+Na]^+$; ESI-HRMS: *m*/*z* calcd for $C_{40}H_{64}O_4Na$ $[M+Na]^+$ 631.4702; found 631.4717.

4.8. Typical procedure for the oxidation reaction: (2*R*,3*R*)-2-(benzyloxy)-3-((benzyloxy)methyl)henicosanal, 7a

A solution of benzylproduct **6a** (4 g, 6.57 mmol) in 50 mL MeOH/THF (9:1) was treated with catalytic amount of PTSA. After 2 h, the resulting reaction mixture was concentrated under reduced pressure. Then the resulting residue was dissolved in EtOAc (20 mL) then washed with saturated sodium bicarbonate solution (2×15 mL). The organic phase was dried and concentrated under reduced pressure to give the crude 1,2-diol, it was used directly for further reaction. $NaIO_4$ (2.63 g, 12.32 mmol) was added to the 1,2-diol dissolved in 50 mL THF/H_2O (9:1). The resulting reaction mixture was stirred at rt, for 1.5 h. Then the THF was removed from the reaction mixture and the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic phases were dried and concentrated under reduced pressure. The residue was purified by column chromatography to give the aldehyde **7a** (2.87 g, 88% yield) as a colorless liquid. TLC, R_f 0.50 (10% EtOAc/hexane). $[\alpha]_D^{25}$ +11.2 (*c* 0.026, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.7 (br s, 1H), 7.30–7.23 (m, 10H), 4.77 (d, *J*=11.3 Hz, 1H), 4.46 (d, *J*=11.3 Hz, 1H), 4.4 (s, 2H), 3.70–3.68 (m, 1H), 3.56–3.50 (m, 1H), 3.40–3.31 (m, 1H), 2.2–2.1 (m, 1H), 1.33–1.20 (m, 34H), 0.88 (t, *J*=6.0 Hz, 3H); ^{13}C NMR (75 MHz): δ 203.6, 138.1, 137.6, 128.4, 128.5, 128.1, 127.7, 127.5, 84.0, 73.0, 72.8, 69.0, 41.7, 31.8, 29.6, 29.4, 29.0, 27.6, 26.8, 22.7, 14.1; IR (KBr): 3030, 2924, 2853, 1731, 1459, 1096, 738 cm^{-1}; MS (LC): *m*/*z* 559 $[M+Na]^+$; ESI-HRMS: *m*/*z* calcd for $C_{36}H_{56}O_3Na$ $[M+Na]^+$ 559.4127; found 559.4153.

4.9. (2*S*,3*S*)-2-(Benzyloxy)-3-((benzyloxy)methyl)henicosanal, 7b

The compound **7b** (2.8 g, 86% yield) as a colorless liquid was synthesized from **6b** (4 g, 6.57 mmol) according to typical procedure **7a**. TLC, R_f 0.50 (10% EtOAc/hexane); $[\alpha]_D^{25}$ −7.8 (*c* 0.038, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.7 (d, *J*=1.8 Hz, 1H), 7.31–7.27 (m, 10H), 4.79 (d, *J*=12.4 Hz, 1H), 4.48 (d, *J*=12.4 Hz, 1H), 4.42 (s, 2H), 3.74–3.71 (m, 1H), 3.60–3.51 (m, 1H), 3.42–3.33 (m, 1H), 2.24–2.17 (m, 1H), 1.34–1.20 (m, 34H), 0.89 (t, *J*=6.5 Hz, 3H); ^{13}C NMR (75 MHz): δ 204.4, 138.2, 137.5, 128.4, 128.3, 128.0, 127.9, 127.5, 83.4, 73.0, 72.9, 69.3, 42.7, 31.9, 29.7, 29.6, 29.4, 29.3, 27.8, 27.3, 22.7, 14.1; IR (KBr): 3021, 2927, 2853, 1732, 1495, 1376, 1209, 697 cm^{-1}; MS (LC): *m*/*z* 559 $[M+Na]^+$.

4.10. Typical procedure for the Wittig reaction: 1-(((*R*)-2-((*S*, *E*/*Z*)-1-(benzyloxy)tetradec-2-enyl)icosyloxy)methyl)-benzene, 8a

To a solution of *n*-dodecyl-triphenylphosphonium bromide (3.81 g, 7.46 mmol) in anhydrous THF (10 mL) at −18 °C was added *n*-butyl lithium (4.24 mL, 6.71 mmol, 1.6 M, color change from yellow to orange red was observed). Reaction mixture was stirred at this temperature for 45 min. A solution of aldehyde **7a** (2 g, 3.73 mmol) in anhydrous THF (30 mL) was added dropwise at the same temperature then the reaction mixture was allowed to warm up to rt. After 12 h, the reaction mixture was quenched with saturated solution of NH_4Cl (10 mL). The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (20 mL), washed with water (10 mL) and then with saturated brine solution (5 mL). The organic phase was dried and concentrated under reduced pressure. The residue was purified by column chromatography to give the olefin (*E*/*Z*, 2:8) **8a** (1.8 g, 70% yield) as a colorless liquid. TLC, R_f 0.51 (5% EtOAc/hexane). $[\alpha]_D^{25}$ +8.5 (*c* 0.001, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.18 (m, 10H), 5.67–5.60 (m, 1H), 5.31–5.24 (m, 1H), 4.52 (d, *J*=12.0 Hz, 1H), 4.43 (s, 2H), 4.26–4.19 (m, 2H), 3.59–3.54 (m, 1H), 3.44–3.40 (m, 1H), 2.12–1.93 (m, 2H), 1.70–1.67 (m, 1H), 1.53–1.13 (m, 52H), 0.88 (t, *J*=6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.8, 133.6, 128.7, 128.4, 128.1, 127.5, 127.3, 127.2, 79.7, 74.4, 72.9, 69.5, 43.8, 31.9, 29.9, 29.7, 29.5, 29.3, 27.9, 27.4, 27.2, 22.6, 14.1; IR (KBr): 2925, 2854, 1465, 1149, 1036, 920 cm^{-1}; MS (LC): *m*/*z* 711 $[M+Na]^+$; ESI-HRMS: *m*/*z* calcd for $C_{48}H_{80}O_2Na$ $[M+Na]^+$ 711.6056; found 711.6044.

4.11. 1-(((*R*)-2-((*S*, *E*/*Z*)-1-(Benzyloxy)tetradec-2-enyl)icosyloxy)methyl)benzene, 8b

The olefin (*E*/*Z*, 2:8) **8b** (1.8 g, 70% yield) as a colorless liquid was prepared from **7b** (2 g, 3.73 mmol) according to typical procedure **8a**. TLC, R_f 0.51 (5% EtOAc/hexane); $[\alpha]_D^{25}$ −2.27 (*c* 0.011, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.18 (m, 10H), 5.7–5.6 (m, 1H), 5.4–5.27 (m, 1H), 4.55 (d, *J*=12.1 Hz, 1H), 4.46 (s, 2H), 4.30–4.22 (m, 2H), 3.62–3.55 (m, 1H), 3.47–3.40 (m, 1H), 2.12–1.97 (m, 2H), 1.80–1.72 (m, 1H), 1.45–1.22 (m, 52H), 0.91 (t, *J*=6.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2, 132.1, 131.9, 128.7, 128.3, 128.2, 127.8, 127.4, 127.2, 79.5, 74.4, 72.9, 69.9, 44.1, 32.3, 30.3, 29.4, 27.8, 27.5, 27.3, 22.6, 14.1; IR (KBr): 2927, 2824, 1439, 1152, 1029, 788 cm^{-1}; MS (LC): *m*/*z* 711 $[M+Na]^+$.

4.12. Typical procedure for the hydrogenation reaction: (2*R*,3*S*)-2-octadecylhexadecane-1,3-diol, 9a

Palladium (10%) on carbon (0.1 g) was added to the compound **8a** (1.5 g, 2.18 mmol) dissolved in 30 mL EtOAc/MeOH (4:6), and the mixture was stirred under the balloon pressure of H_2 for 12 h. The catalyst was filtered off, and washed with ethyl acetate (3×5 mL). The combined organic layers were dried and concentrated under reduced pressure. The residue was purified by column chromatography to give the corresponding 1,3-diol **9a** (0.99 g, 92% yield) as a white solid. Mp 59–61 °C; TLC, R_f 0.53 (30% EtOAc/hexane); $[\alpha]_D^{25}$ −5.0 (*c* 0.004, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.92–3.86 (m, 1H), 3.71–3.55 (m, 2H), 2.5 (br s, 2H), 1.64–1.20 (m, 59H), 0.89 (t, *J*=6.2 Hz, 6H); ^{13}C NMR (75 MHz): δ 70.4, 63.9, 39.4, 33.2, 31.9, 29.8, 29.5, 28.5, 27.3, 24.5, 22.6, 14.1; IR (KBr): 3335, 2917, 2849, 1461, 1029, 718 cm^{-1}; MS (LC): *m*/*z* 533 $[M+Na]^+$; ESI-HRMS: *m*/*z* calcd for $C_{34}H_{70}O_2Na$ $[M+Na]^+$ 533.5273; found 533.5290.

4.13. (2*R*,3*S*)-2-Octadecylhexadecane-1,3-diol, 9b

The compound **9b** (0.95 g, 88% yield) as a white solid, mp 58–60 °C, was synthesized from **8b** (1.5 g, 2.18 mmol) according to typical procedure **9a**. TLC, R_f 0.53 (30% EtOAc/hexane); $[\alpha]_D^{25}$ +2.6 (*c* 0.0075, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93–3.89 (m, 1H), 3.65–3.61 (m, 2H), 1.59–1.55 (m, 1H), 1.40–1.25 (m, 58H), 0.89 (t, *J*=6.2 Hz, 6H); ^{13}C NMR (75 MHz): δ 70.5, 63.9, 39.3, 33.2, 31.9, 31.7, 29.8, 29.5, 28.6, 27.3, 24.4, 22.5, 14.1; IR (KBr): 3452, 2927, 2820, 1252, 1034, 778 cm^{-1}; MS (LC): *m*/*z* 533 $[M+Na]^+$.

4.14. Typical procedure for the oxidation reaction: (*S*)-2-((*S*)-1-hydroxytetradecyl)icosanoic acid, 10a

To a stirred solution of the 1,3-diol **9a** (0.50 g, 0.98 mmol) in CH_2Cl_2 (20 mL) was added TEMPO (0.05 mg, 0.29 mmol) followed by iodobenzene diacetate (0.95 g, 2.94 mmol). After 2 h, the reaction mixture was treated with 5% aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). After 15 min, the organic phase was separated and the aqueous phase extracted with Et_2O. The combined organic extracts were dried and concentrated under reduced pressure. The crude product was purified by column chromatography to give the respective aldehyde, which was subjected to further oxidation.

The above β-hydroxy aldehyde was dissolved in *t*-BuOH (10 mL) and treated with a freshly prepared solution of $NaClO_2$ (0.88 g, 9.70 mmol) in 20% aq NaH_2PO_4 (10 mL) at 0 °C. After 4 h of vigorous stirring at 0 °C to rt, the reaction mixture was poured into EtOAc (30 mL) and the aq layer was extracted with EtOAc (4×10 mL). The combined organic layers were concentrated under reduced pressure. The residue was purified by column chromatography to give the β-hydroxy acid **10a** (0.39 g, 85% yield) as a white solid. Mp 62–64 °C; TLC, R_f 0.31 (30% EtOAc/hexane); $[\alpha]_D^{25}$ −4.2 (*c* 0.001, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70–3.63 (m, 1H), 2.45–2.33 (m, 1H), 1.76–1.58 (m, 1H), 1.38–1.20 (m, 57H), 0.89 (t, *J*=6.8 Hz, 6H); ^{13}C NMR (75 MHz): δ 177.0, 70.7, 51.7, 33.2, 32.0, 31.5, 29.8, 29.6, 29.3, 29.2, 24.4, 22.5, 14.1; IR (KBr): 3421, 2920, 2851, 1721, 1463, 1214, 849 cm^{-1}; MS (LC): *m*/*z* 547 $[M+Na]^+$; ESI-HRMS: *m*/*z* calcd for $C_{34}H_{68}O_3Na$ $[M+Na]^+$ 547.5066; found 547.5092.

4.15. (*R*)-2-((*R*)-1-Hydroxytetradecyl)icosanoic acid, 10b

The compound **10b** (0.37 g, 82% yield) as a white solid, mp 61–63 °C, was synthesized from **9b** (0.50 g, 0.98 mmol) according to typical procedure **10a**. TLC, R_f 0.31 (30% EtOAc/hexane); $[\alpha]_D^{25}$ +2.3 (*c* 0.006, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.68–3.55 (m, 1H), 2.48–2.30 (m, 1H), 1.74–1.57 (m, 1H), 1.35–1.21 (m, 57H), 0.89 (t, *J*=6.8 Hz, 6H); ^{13}C NMR (75 MHz): δ 177.0, 70.6, 51.7, 33.1, 31.9, 31.5, 29.8, 29.6, 29.3, 29.2, 27.2, 22.5, 14.1; IR (KBr): 3454, 3027, 2922, 1709, 1247, 993, 747 cm^{-1}; MS (LC): *m*/*z* 547 $[M+Na]^+$.

4.16. Typical procedure for the β-lactone formation: (3*S*,4*S*)-3-octadecyl-4-tridecyloxetan-2-one, 1a

A solution of β-hydroxy acid **10a** (0.15 g, 0.29 mmol) in CH_2Cl_2 (10 mL) was treated with Et_3N (0.122 mL, 0.875 mmol) and BOPCl (0.11 g, 0.44 mmol) at 23 °C. After 1 h, the resulting reaction mixture was diluted with water (1×0.5 mL) and extracted with EtOAc (3×15 mL). The combined organic phases were dried and concentrated under reduced pressure. The crude residue was purified by column chromatography to give the title compound **1a** (0.106 g, 72% yield) as a white solid. Mp 65–66 °C (lit.[5] 66–68 °C); TLC, R_f 0.71(10% EtOAc/hexane); $[\alpha]_D^{25}$ −12.66 (*c* 0.01, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.17 (ddd, *J*=7.4, 6.0, 3.8 Hz, 1H), 3.13 (ddd, *J*=8.7, 6.4, 3.8 Hz, 1H), 1.9–1.6 (m, 4H), 1.40–1.18 (m, 54H), 0.88 (t, *J*=6.8 Hz, 6H); ^{13}C NMR (75 MHz): δ 171.6, 78.1, 56.1, 34.4, 31.9, 29.7, 29.6, 29.4, 29.3, 29.2, 27.9, 27.0, 25.0, 22.7, 14.1; IR (KBr): 2918, 2851, 1803, 1471, 1143, 863, 716 cm^{-1}; MS (LC): *m*/*z* 507 $[M+H]^+$; ESI-HRMS: *m*/*z* calcd for $C_{34}H_{66}O_2Na$ $[M+Na]^+$ 529.4960; found 529.4962.

4.17. (3*R*,4*R*)-3-Octadecyl-4-tridecyloxetan-2-one, 1b

The compound **1b** (0.106 g, 72% yield) as a white solid, mp 63–64 °C, was synthesized from **10b** (0.15 g, 0.29 mmol) according to typical procedure **1a**. TLC, R_f 0.71 (10% EtOAc/hexane); $[\alpha]_D^{25}$ +13.5 (*c* 0.01, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.19 (ddd, *J*=7.2, 6.2, 3.9 Hz, 1H), 3.15 (ddd, *J*=8.5, 6.6, 3.9 Hz, 1H), 1.84–1.62 (m, 4H), 1.41–1.20 (m, 54H), 0.88 (t, *J*=6.4 Hz, 6H); ^{13}C NMR (75 MHz): δ 171.6, 78.1, 56.1, 34.4, 31.9, 29.7, 29.2, 27.8, 25.0, 22.6, 14.0; IR (KBr): 2927, 2852, 1810, 1449, 1381, 1143, 833, 759 cm^{-1}; MS (LC): *m*/*z* 507 $[M+H]^+$; ESI-HRMS: *m*/*z* calcd for $C_{34}H_{66}O_2Na$ $[M+Na]^+$ 529.4960; found 529.4957.

Acknowledgements

We are grateful to Dr. J. S. Yadav, Director, IICT, for his constant encouragement. The DST, New Delhi (Grant No: SR/SI/OC-12/2007) is also gratefully acknowledged for its financial assistance. Thanks are also due to Dr. T. K. Chakraborty for his support. B.M. is thankful to UGC (New Delhi) for awarding the fellowship.

Supplementary data

Copies of spectra of **4a**, **5a**, **1a**, **4b**, **5b**, and **1b** can be found in the Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.062.

References and notes

1. (a) Umezawa, H.; Aoyagi, T.; Uotani, K.; Hamada, M.; Takeuchi, T.; Takahashi, S. *J. Antibiot.* **1980**, *33*, 1594; (b) Uotani, K.; Naganawa, H.; Kondo, S.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1982**, *35*, 1495; (c) Weibel, E. K.; Hadvary, P.; Hochuli, E.; Kupfer, E.; Lengsfeld, H. *J. Antibiot.* **1987**, *40*, 1081; (d) Hochuli, E.; Kupfer, E.; Maurer, R.; Meister, W.; Mercadal, Y.; Schmidt, K. *J. Antibiot.* **1987**, *40*, 1086; (e) Mutoh, M.; Nakada, N.; Matsukuma, S.; Ohshima, S.; Yoshinari, K.; Watanabe, J.; Arisawa, M. *J. Antibiot.* **1994**, *47*, 1369; (f) Asai, A.; Hasegawa, A.; Ochiai, K.; Yamashita, Y.; Mizukami, T. *J. Antibiot.* **2000**, *53*, 81; (g) Aldridge, D. C.; Gile, D.; Turner, W. B. *J. Chem. Soc. C* **1971**, 3888; (h) Pommier, A.; Pons, J.-M.; Kocienski, P. J. *J. Org. Chem.* **1995**, *60*, 7334; (i) Pommier, A.; Pons, J.-M.; Kocienski, P. J.; Wong, L. *Synthesis* **1994**, 1294.
2. Lall, M. S.; Ramtohul, Y. K.; James, M. N. G.; Vederas, J. C. *J. Org. Chem.* **2002**, *67*, 1536.
3. (a) Romo, D.; Harrison, P. H. M.; Jenkins, S. I.; Riddoch, R. W.; Park, K.; Yang, H. W.; Zhao, C.; Wright, G. D. *Bioorg. Med. Chem.* **1998**, *6*, 1255 and references cited therein; (b) Tomoda, H.; Ohbayashi, N.; Kumagai, H.; Hashizume, H.; Sunazuka, T.; Omura, S. *Biochem. Biophys. Res. Commun.* **1999**, *265*, 536.
4. (a) Tomoda, H.; Omura, S. *Yakugaku Zasshi-J. Pharm. Soc. Jpn.* **2000**, *120*, 935; (b) Masse, C. E.; Morgan, A. J.; Adams, J.; Panek, J. S. *Eur. J. Org. Chem.* **2000**, *14*, 2513.
5. Mikami, Y.; Yazawa, Y.; Tanaka, Y.; Ritzau, M.; Grafe, U. *Nat. Prod. Lett.* **1999**, *13*, 277.
6. Sun, Y.-P.; Wu, Y. *Synlett* **2005**, 1477.
7. (a) Calter, M. A.; Tretyak, O. A.; Flaschenriem, C. *Org. Lett.* **2005**, *7*, 1809; (b) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, *126*, 5352; (c) Wedler, C.; Kunath, A.; Schick, H. *J. Org. Chem.* **1995**, *60*, 758; (d) Wedler, C.; Kleiner, K.; Kunath, A.; Schick, H. *Liebigs Ann.* **1996**, 881.
8. Purohit, V. C.; Richardson, R. D.; Smith, J. W.; Romo, D. *J. Org. Chem.* **2006**, *71*, 4549.
9. (a) Kumaraswamy, G.; Padmaja, M.; Markondaiah, B.; Jena, N.; Sridhar, B.; Udaykiran, M. *J. Org. Chem.* **2006**, *71*, 337; (b) Kumaraswamy, G.; Markondaiah, B. *Tetrahedron Lett.* **2007**, *48*, 1707; (c) Kumaraswamy, G.; Markondaiah, B. *Tetrahedron Lett.* **2008**, *49*, 327; (d) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, *37*, 580; (e) List, B. *Tetrahedron* **2002**, *58*, 5573.
10. The *anti*/*syn* diastereomers were separated through silica gel column chromatography eluting with hexane/EtOAc as solvent. The enantioselectivity and absolute configuration of the major compound **4a** were determined on the basis of $[\alpha]_D^{25}$ value of the final product **1a**.
11. (a) Enders, D.; Grondal, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1210; (b) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475; (c) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16; (d) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911.
12. (a) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974; (b) Vatele, J.-M. *Tetrahedron Lett.* **2006**, *47*, 715.