DOI: 10.1002/ejoc.201100354

Enantioselective Total Synthesis of (+)-Vittatalactone

Jhillu S. Yadav,*[a,b] Nagendra Nath Yadav,[a] T. Srinivasa Rao,[a] B. V. Subba Reddy,[a] and Ahmad Al Khazim Al Ghamdi[c]

Keywords: Natural products / Synthetic methods / Enzyme catalysis / Wittig reactions / Hydroboration / Alkylation / Pheromones / Vittatalactone / Lactones

An enantioselective asymmetric total synthesis of (+)-vittatalactone has been accomplished employing enzymatic desymmetrization approach to create two methyl chiral centres. Other key steps involved are Wittig reaction, Evan's asymmetric alkylation, hydroboration, TEMPO-BAIB-mediated selective oxidation of 1,3-diol and lactonization mediated by *p*-toluenesulfonyl chloride. The total synthesis was achieved by a linear synthetic sequence with an overall yield of 11.8 %.

Introduction

Natural products derived from polydeoxypropionates are known to exhibit various biological activities.[1–3] (+)-Vittatalactone (**1**), a structurally unique pheromone containing five stereogenic centers was first identified by Morris and Francke et al. in 2005 from the pheromone mixture secreted by the feeding male striped cucumber beetles, *Acalymma vittatum*.[4] The structural features of (+)-vittatalactone includes the presence of trideoxypropionate unit and β-lactone units. Recently, Breit et al. have assigned the relative and absolute configuration of natural (+)-**1** and its stereoisomers **2a**, **2b** (see Figure 1).[5a,5b]

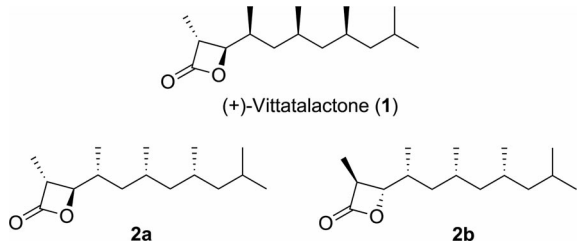
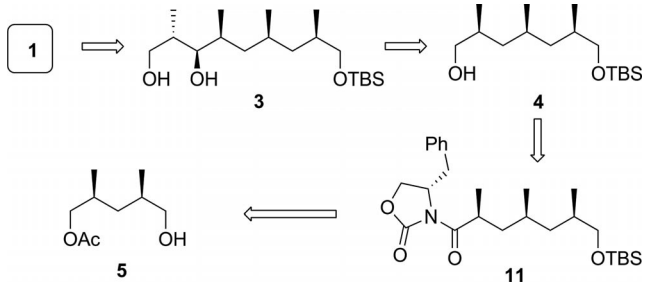


Figure 1. Chemical structures of (+)-vittatalactone (**1**) and its stereoisomers **2a**, **2b**.

Our continuing interest in the total synthesis of various biologically active natural products and the inherent biological activity of (+)-**1** encouraged us to explore the synthesis of this molecule. More recently, enantioselective total synthesis of (+)-**1** has been reported by Breit et al. by the *o*-DPPB-directed allylic substitution and by Schneider et al. by using the [Ir(cod)L]BAr_F catalyst for the hydrogenation reaction.[5b,5c] We herein report an alternative enantioselective total synthesis of (+)-**1** by using Evan's alkylation and hydroborane oxidation of the *E*-enal to generate the three chiral centres out of the five stereogenic centres in good diastereoselectivity.

Results and Discussion

The retrosynthetic approach for (+)-**1** is depicted in Scheme 1 where the target molecule (+)-**1** can easily be envisioned from the diol **3** having all the required five chiral centres. Further, compound **3** could be obtained by a sequence of reactions such as Wittig reaction, DIBAL-H reduction, hydroboration and oxidation with alkaline hydrogen peroxide from compound **4** having the required three chiral centres. Then compound **4** can in turn be obtained from the known compound **5** via **11** by means of Wittig reaction followed by stereoselective Evan's alkylation.



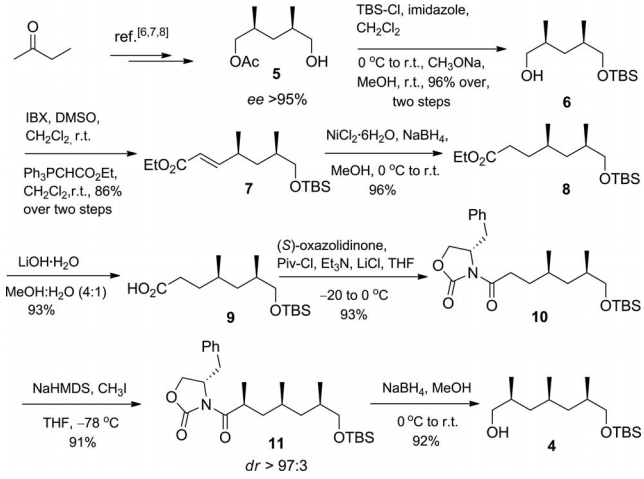
Scheme 1. Retrosynthetic analysis of (+)-vittatalactone (**1**).

Our synthesis began with the known precursor **5** that has two chiral centres already in place. Compound **5** was synthesized in four steps starting from *cis*-4,6-dimethylcy-

[a] Organic Chemistry Division I, Indian Institute of Chemical Technology (CSIR),
Hyderabad 500007, India
Fax: +91-40-27160512
E-mail: yadavpub@iict.res.in
[b] Bee Research Chair – College of Food and Agriculture Science, King Saudi University,
P. O. Box 2455, Riyadh 11451, Saudi Arabia
[c] Engineer Abdullah Baqshan for Bee Research, King Saudi University,
Saudi Arabia

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

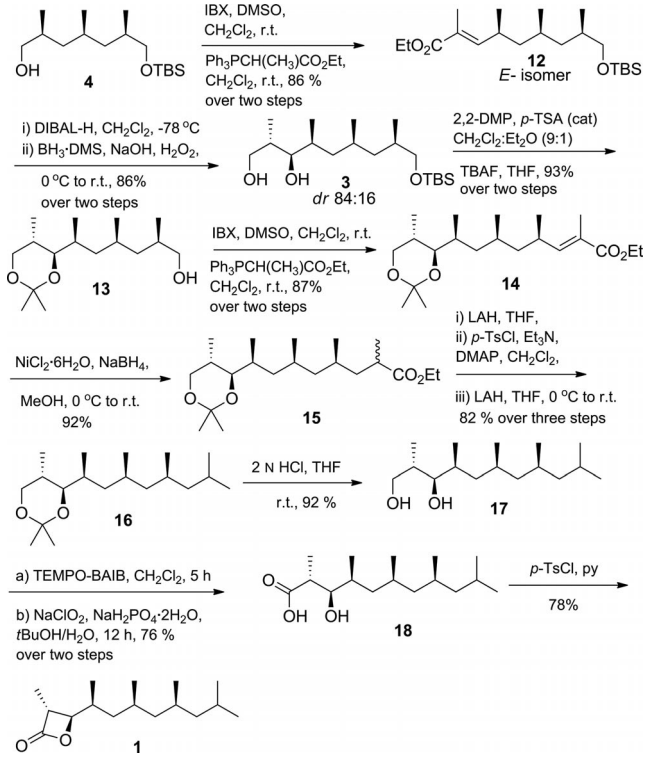
clohexan-1,3-dione following a well-reported protocol.[6] Accordingly, *cis*-diketone was converted into the diacid by periodate oxidation.[7] $LiAlH_4$ reduction of the diacid in THF at room temperature gave the *meso*-diol in 98% yield. Desymmetrization of *meso*-diol by using porcine pancreatic lipase (PPL) and vinyl acetate in THF at ambient conditions furnished the mono acetate **5** in 47% yield and at least 95% *ee* along with the *meso*-diacetate.[8] It is noteworthy to mention that the *meso*-diacetate obtained was again converted back to the *meso*-diol by treatment with CH_3ONa in methanol in quantitative yield for further utililations. Mono acetate **5** in hand was protected as its silyl ether using TBSCl and imidazole in dichloromethane and then treated with CH_3ONa in methanol to furnish the desired terminal alcohol **6**. Subsequently, oxidation of alcohol **6** followed by two-carbon atoms extension by means of Wittig reaction gave the α,β-unsaturated ester **7** in 86% yield in overall two steps. Subsequent reduction of the double bond with $NaBH_4$ in the presence of $NiCl_2{\cdot}6H_2O$ in MeOH afforded the saturated ester **8**,[9] in 96% yield which was then hydrolyzed under basic conditions to furnish the corresponding carboxylic acid **9** in 93% yield. Coupling of acid **9** with the Evan's chiral oxazolidinone using piavloyl chloride in presence of triethylamine and LiCl furnished the required compound **10** in 93% yield.[10] Diastereoselective methylation of the Na-enolate of compound **10** with MeI furnished the desired compound **11** in 91% yield and in > 97:3[5c] which was confirmed by ^1H NMR, and then subjected to $NaBH_4$ in MeOH to obtain the desired primary alcohol **4** having a new additional chiral centre in 92% yield (Scheme 2).



Scheme 2. Synthesis of alcohol **4**.

Next, alcohol **4** was subjected to oxidation using IBX in DMSO followed by C_3-Wittig reaction to afford the α,β-unsaturated ester **12** (*E*-isomer) as a sole product in 86% over two steps.[11]

The ester **12** was then reduced to give the corresponding aldehyde and the latter subjected to hydroboration followed by oxidation to obtain the diol **3** in 72% yield with all the five chiral centres in place along with 14% of the another diastereoisomer (overall yield 86%, *dr*, 84:16 by ^1H NMR and after separation by column chromatography).[12] The analytical data of the diol **3** was found to be identical to the prepared one by an alternative method (by oxidation, C_2-Wittig reaction, DIBAL-H reduction, Sharpless asymmetric epoxidation and Gillman's opening of chiral epoxide).[5b] The di-hydroxy groups of diol **3** were protected as their acetonide followed by the deprotection of silyl ether on the other terminal with TBAF in THF afforded compound **13** in 93% yield in two steps. Oxidation of compound **13** with IBX in DMSO furnished the corresponding aldehyde for the envisioned Wittig reaction. Interestingly, the Wittig olefination using the unstable ylide $Ph_3{=}CMe_2$ provided only poor yield (< 35%) towards the formation of the corresponding olefin as a result olefination of aldehyde with stable ylide was performed, i.e. $Ph_3P{=}C(CH_3)CO_2Et$ to furnish the corresponding α,β-unsaturated ester **14** in > 85% yield from alcohol **13**.[11] Reduction of the double bond using $NiCl_2{\cdot}6H_2O$ and $NaBH_4$ in MeOH gave the saturated ester **15** in 92% yield. Then treatment of compound **15** with $LiAlH_4$ followed by tosylation and further reduction furnished the required compound **16** in 82% yields in overall 3 steps. Deprotection of acetonide **16** under acidic condition furnished the 1,3-diol **17** in 92% yield for which the analytical data was in comparison with the data reported in the literature.[13] Selective oxidation of 1,3-diol **17** using TEMPO-BAIB afforded the β-hydroxy aldehyde, which was used as such in the next step without further purification for the oxidation of β-hydroxy aldehyde under Pinniks conditions ($NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$) and furnished the β-hydroxy acid **18** in 76% yield.[14] The NMR (^1H and ^{13}C) analysis and optical rotation $[\alpha]_D$ = –7.6 of **18**



Scheme 3. Synthesis of (+)-vittatalactone (**1**).

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

were in good agreement with literature value.[13] Eventual lactonization of β-hydroxy acid with *p*-toluenesulfonyl chloride in pyridine finally furnished the target natural product, (+)-vittatalactone in 78% yield (Scheme 3).

Conclusions

In conclusion, we have accomplished the total synthesis of (+)-vittatalactone in enantioselective manner employing enzymatic desymmetrization of *meso*-diol, Wittig reaction, hydroboration/oxidation of *E*-enal, TEMPO-BAIB-mediated selective oxidation and lactonization of β-hydroxy acid as key steps. The synthesis follows linear synthetic sequence with an overall yield of 11.8%.

Experimental Section

General: All reactions were carried out under inert atmosphere of argon or nitrogen using standard syringe, septa, and cannula techniques unless otherwise mentioned. Commercial reagents were used without further purification. All solvents were purified by standard techniques. Infrared (IR) spectra were recorded on a Perkin–Elmer 683 spectrometer using NaCl optics. Spectra were calibrated against the polystyrene absorption at 1610 cm^{-1}. Samples were scanned neat, in KBr wafers or in chloroform as a thin film. ^1H NMR spectra were recorded in $CDCl_3$ on Bruker 300, Varian Unity 500 NMR spectrometer. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ using tetramethylsilane as a reference standard. Column chromatography was performed using silica gel (60–120 mesh) and the column was usually eluted with a mixture of ethyl acetate/petroleum ether. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light or by dipping the plates to ethanolic anisaldehyde/sulfuric acid/acetic acid or into phosphomolybdic acid/sulfuric acid solution and heating the plates at 120 °C. Mass spectra were obtained on a Finnigan MAT1020B or micromass VG 70-70H spectrometer operating at 70 eV using a direct inlet system. Optical rotations were recorded on Perkin–Elmer 241 polarimeter in 1.0 dm, 1.0 mL cells.

(2*S*,4*R*)-5-Hydroxy-2,4-dimethylpentyl Acetate (5): To a stirred solution of *meso*-diol (4.0 g, 22.9 mmol) in THF (130 mL) and water (170 μL) was added PPL (11.6 g) and vinyl acetate at room temperature. The reaction mixture was stirred for 6 h at room temperature. After complete conversion of the starting material (as indicated by TLC), the reaction mixture was filtered off through a pad of Celite, washed with ethyl acetate, dried with Na_2SO_4, concentrated in vacuo and purified by chromatography on silica gel (1:5, EtOAc/hexane) to afford the monoacetate **5** (2.47 g, 47%) as a colorless liquid. $[\alpha]_D$ = +9.8 (c = 0.6, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 3.97 (dd, J = 10.5, 5.2 Hz, 1 H), 3.85 (dd, J = 10.5, 6.7 Hz, 1 H), 3.49 (dd, J = 10.5, 6.0 Hz, 1 H), 3.42 (dd, J = 10.5, 6.0 Hz, 1 H), 2.05 (s, 3H), 1.82–1.96 (m, 1 H), 1.64–1.78 (m, 1 H), 1.43 (br., 1 H), 1.39–1.49 (m, 1 H), 1.15–1.30 (m, 1 H), 0.96 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.7 Hz, 3H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.3, 69.1, 67.9, 37.2, 32.9, 29.9, 20.9, 17.8, 17.2 ppm.

(2*S*,4*R*)-5-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-2,4-dimethylpentan-1-ol (6): To a cold (0 °C) solution of alcohol **4** (5.0 g, 28.7 mmol) in dry CH_2Cl_2 (80 mL) was added imidazole (3.9 g, 57.4 mmol) and *tert*-butyldimethylsilyl chloride (5.16 g, 34.44 mmol). The resulting mixture was stirred at room temperature for 3 h. After completion of the reaction as indicated by TLC, the mixture was quenched with saturated aqueous NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure to furnish crude acetate. To the above mixture in MeOH (80 mL) was added sodium methoxide (2.3 g, 43.05 mmol) at room temperature. Then the mixture was stirred for 1 h at room temperature and concentrated under reduced pressure. The residue was then quenched by the addition of saturated NH_4Cl and extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water, brine, dried with Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (1:9 EtOAc/hexane) to give the product as a colorless oil **6** in (6.77 g, 96%) yield. $[\alpha]_D$ = +0.9 (c = 1.2, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3348, 2954, 2928, 2857, 1466, 1252, 1097, 837, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.32–3.50 (m, 4 H), 1.60–1.77 (m, 2 H), 1.36–1.50 (m, 2 H), 0.93 (d, J = 6.7 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 68.2, 67.9, 37.2, 33.1, 25.8, 18.2, 17.7, 17.6, –5.4 ppm.

Ethyl (2*E*,4*S*,6*R*)-7-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-4,6-dimethyl-2-heptenoate (7): To a stirred solution of IBX (11.43 g, 40.8 mmol) in DMSO (30 mL) at 25 °C, was added slowly dropwise a solution of alcohol **6** (6.7 g, 27.2 mmol) in CH_2Cl_2 (80 mL). The resulting mixture was stirred at 25 °C for 3 h. The solid was filtered and washed with diethyl ether. The filtrate was washed with saturated aqueous $NaHCO_3$ solution, water, brine and dried with Na_2SO_4. The solvent was removed under reduced pressure to furnish crude aldehyde. To the above crude mixture (4.94 g, 29.07 mmol) in CH_2Cl_2 (150 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (17.03 g, 48.96 mmol) and resulting mixture was stirred for 12 hours at room temperature. The reaction mixture was concentrated under reduced pressure and purified on silica gel chromatography (5% EtOAc/hexane) to afford the unsaturated ester **7** (7.3 g, 86%) as a colourless liquid. $[\alpha]_D$ = +17.9 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2957, 2859, 1722, 1652, 1465, 1367, 1259, 1180, 1094, 1042, 840, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.76 (dd, J = 15.8, 8.3 Hz, 1 H), 5.75 (d, J = 15.8 Hz, 1 H), 4.17 (q, J = 14.3, 6.7 Hz, 2 H), 3.37 (dd, J = 5.2, 1.5 Hz, 2 H), 2.32–2.51 (m, 1 H), 1.44–1.67 (m, 2 H), 1.29 (t, J = 6.7 Hz, 3 H), 1.06–1.15 (m, 1 H), 1.06 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.86 (d, J = 6.7 Hz, 3 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 166.7, 154.3, 119.7, 68.3, 60.0, 39.8, 34.1, 33.3, 25.8, 20.4, 18.2, 16.5, 14.2, –5.4 ppm. MS (ESI): m/z = 337 [M + Na]$^+$. HRMS: calcd. for $C_{17}H_{34}NaO_3Si$ [M + Na]$^+$ 337.2174; found 337.2174.

Ethyl (4*R*,6*R*)-7-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-4,6-dimethylheptanoate (8): To a cooled (0 °C) solution of **7** (7.2 g, 22.9 mmol) and $NiCl_2{\cdot}6H_2O$ (1.08 g, 4.58 mmol) in MeOH (100 mL), was added $NaBH_4$ (2.0 g, 54.96 mmol) in small portions to the solution. During addition of $NaBH_4$, the reaction temperature was maintained at 0 °C. After complete addition of $NaBH_4$, the reaction mixture was stirred for 1 h at room temperature and the resulting black precipitate was filtered and then washed with MeOH. The solvent was removed under reduced pressure and then diluted with water (100 mL) and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water, brine and dried with anhydrous Na_2SO_4. Removal of solvent under reduced pressure followed by purification on silica gel column chromatography using ethyl acetate/hexane (5% EtOAc/hexane) gave the product **8** (6.9 g, 96% yield) as a colorless oil. $[\alpha]_D$ = +3.8 (c = 1.2, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2956, 1738, 1636, 1253, 1094, 772, 570 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.10 (q, J = 14.3, 6.7 Hz, 2 H), 3.41 (dd, J = 9.8, 6.0 Hz, 1 H), 3.33 (dd, J = 9.8, 6.0 Hz, 1 H), 2.18–

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

2.34 (m, 2 H), 1.28–1.75 (m, 6 H), 1.26 (t, J = 6.7 Hz, 3 H), 0.90 (d, J = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.87 (d, J = 6.0 Hz, 3 H), 0.02 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.0, 68.2, 60.1, 40.7, 33.0, 31.8, 31.5, 29.6, 25.9, 20.0, 18.2, 17.3, 14.2, –5.4 ppm. MS (ESI): m/z = 339 [M + Na]$^+$. HRMS: calcd. for $C_{17}H_{36}NaO_3Si$ [M + Na]$^+$ 339.2331; found 339.2321.

(4*R*,6*R*)-7-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-4,6-dimethylheptanoic Acid (9): LiOH·H_2O (2.7 g, 64.5 mmol) was added portion wise to a cooled solution (0 °C) of ester **8** (6.8 g, 21.5 mmol) in 80 mL of CH_3OH/H_2O (3:1) and the stirring was continued for 2 h at room temperature. The reaction mixture was then concentrated in vacuo and the residue was diluted with EtOAc (80 mL) and washed with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated under reduced pressure. Removal of solvent followed by column chromatography using 20% EtOAc/hexane afforded the acid **9** (5.7 g, 93% yield) as a colorless liquid. $[\alpha]_D$ = +5.0 (c = 0.7, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2956, 2930, 2858, 1711, 1464, 1414, 1253, 1094, 938, 839, 775, 667 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.30–3.45 (m, 2 H), 2.24–2.42 (m, 2 H), 1.06–1.78 (m, 6 H), 0.92 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 180.2, 68.1, 40.6, 33.0, 31.5, 31.2, 29.6, 25.9, 19.9, 18.3, 17.4, –5.3 ppm. MS (ESI): m/z = 311 [M + Na]$^+$. HRMS: calcd. for $C_{15}H_{32}NaO_3Si$ [M + Na]$^+$ 311.2018; found 311.2028.

(4*S*)-4-Benzyl-3-{(4*R*,6*R*)-7-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-4,6-dimethylheptanoyl}-1,3-oxazolan-2-one (10): To a stirred solution of acid **9** (5.6 g, 19.4 mmol) in THF (100 mL) at –20 °C was added Et_3N (6.74 mL, 48.5 mmol) followed by PivCl (2.4 mL, 19.4 mmol). After stirring for 1 h at –20 °C, LiCl (1.23 g, 29.1 mmol) followed by (*S*)-oxazolidinone (3.77 g, 21.34 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 (50 mL) and extracted with ethyl acetate (2 × 80 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:16) to gave **10** (8.0 g, 93%) as a viscous liquid. $[\alpha]_D$ = +38.8 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2954, 2928, 2857, 1784, 1700, 1461, 1386, 1353, 1251, 1208, 1093, 839, 772, 701, 591 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.15–7.38 (m, 5 H), 4.54–4.67 (m, 1 H), 4.09–4.23 (m, 2 H), 3.43 (dd, J = 9.8, 5.2 Hz, 1 H), 3.25–3.40 (m, 2 H), 2.78–3.03 (m, 2 H), 2.69 (dd, J = 13.5, 9.8 Hz, 1 H), 1.08–1.80 (m, 6 H), 0.95 (d, J = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.6, 153.3, 135.3, 129.3, 128.8, 127.2, 68.2, 66.0, 55.1, 40.8, 37.8, 33.1, 33.0, 30.8, 29.7, 25.9, 20.0, 18.3, 17.4, –5.3 ppm. MS (ESI): m/z = 470 [M + Na]$^+$. HRMS: calcd. for $C_{25}H_{41}NNaO_4Si$ [M + Na]$^+$ 470.2702; found 470.2714.

(4*S*)-4-Benzyl-3-{(2*S*,4*S*,6*R*)-7-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-2,4,6-trimethylheptanoyl}-1,3-oxazolan-2-one (11): To a stirred solution of **10** (4.0 g, 8.9 mmol) in dry THF (80 mL) at –78 °C, NaHMDS (1 M solution in THF, 13.35 mL, 13.35 mmol) was added slowly dropwise with stirring under nitrogen atmosphere. After stirring at –78 °C for 30 min, MeI (1.56 mL, 26.7 mmol) was added dropwise to the reaction mixture and then stirring was continued for another 2 h at –78 °C. Then the mixture was quenched with saturated NH_4Cl (50 mL) and warmed to room temperature and then extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine (50 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:19) to afford the product **11** as a colorless liquid (3.73 g, 91%). $[\alpha]_D$ = +41.6 (c = 1.3, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2956, 2928, 2857, 1783, 1699, 1460, 1385, 1351, 1249, 1208, 1096, 839, 774, 700 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.37 (m, 5 H), 4.55–4.68 (m, 1 H), 4.08–4.22 (m, 2 H), 377–3.93 (m, 1 H), 3.22–3.47 (m, 3 H), 2.70 (dd, J = 12.8, 9.8 Hz, 1 H), 1.25–1.98 (m, 5 H), 1.20 (d, J = 6.7 Hz, 3 H), 0.96–1.12 (m, 1 H), 0.89 (s, 9 H), 0.88 (d, J = 6.7 Hz, 6 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 177.2, 152.9, 135.2, 129.4, 128.8, 127.2, 68.3, 65.9, 55.2, 41.2, 40.4, 37.8, 35.2, 33.0, 28.1, 25.9, 20.7, 18.5, 18.3, 17.4, –5.3 ppm. MS (ESI): m/z = 484 [M + Na]$^+$. HRMS: calcd. for $C_{26}H_{43}NaO_4Si$ [M + Na]$^+$ 484.2859; found 484.2875.

(2*S*,4*R*,6*R*)-7-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-2,4,6-trimethylheptan-1-ol (4): To a stirred solution of **11** (5.0 g, 10.8 mmol) in MeOH (40 mL) at 0 °C was added $NaBH_4$ portion wise (1.23 g, 32.4 mmol). The reaction mixture was allowed to stir for 1 hour at same temperature and then quenched with saturated aqueous NH_4Cl. The solvent was removed under reduced pressure and the resulting residue was diluted with water and extracted with EtOAc (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (10%, EtOAc/hexane) to afford the pure product **4** (2.86 g, 92%) as a viscous liquid. $[\alpha]_D$ = –5.8 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3351, 2956, 2928, 2858, 1465, 1383, 1253, 1098, 1040, 838, 775, 667 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.29–3.55 (m, 4 H), 2.60 (s, 1 H), 0.96–1.88 (m, 7 H), 0.93 (d, J = 7.5 Hz, 3 H), 0.90 (d, J = 6.7 Hz, 3 H), 0.89 (s, 9 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 68.1, 67.9, 41.2, 41.0, 33.0, 27.6, 25.9, 21.0, 18.3, 17.9, 17.5, –5.3 ppm. MS (ESI): m/z = 289 [M + H]$^+$. HRMS: calcd. for $C_{16}H_{36}NaO_2Si$ [M + Na]$^+$ 311.2382; found 311.2398.

Ethyl (2*E*,4*S*,6*R*,8*R*)-9-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-2,4,6,8-tetramethyl-2-nonenoate (12): The procedure was same as to that described for the preparation of **7**. The alcohol **4** (600 mg, 2.08 mmol), was treated with IBX (874 mg, 3.12 mmol) followed by ethyl 2-(triphenylphosphoranylidene)propanoate (1.5 g, 4.16 mmol) to give the product **12** (661 mg, 86%) as a colorless liquid. $[\alpha]_D$ = +23.5 (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2957, 2928, 2858, 1713, 1649, 1462, 1371, 1257, 1098, 839, 775 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.44 (d, J = 10.5 Hz, 1 H), 4.17 (q, J = 14.3, 7.5 Hz, 2 H), 3.29–3.43 (m, 2 H), 2.52–2.70 (m, 1 H), 1.84 (s, 3 H), 1.02–1.75 (m, 9 H), 0.99 (d, J = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.85 (d, J = 6.0 Hz, 3 H), 0.84 (d, J = 6.7 Hz, 3 H), 0.02 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.3, 148.0, 126.2, 68.1, 60.2, 44.2, 41.4, 32.9, 30.7, 28.1, 25.9, 20.6, 20.4, 18.2, 17.3, 14.2, 12.4, –5.4 ppm. MS (ESI): m/z = 393 [M + Na]$^+$. HRMS: calcd. for $C_{21}H_{43}O_3Si$ [M + H]$^+$ 371.2981; found 371.2977.

(2*S*,3*R*,4*S*,6*S*,8*R*)-9-[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy-2,4,6,8-tetramethylnonane-1,3-diol (3): To a cooled (–78 °C) solution of **12** (650 mg, 1.75 mmol) in dry CH_2Cl_2 (10 mL), DIBAL-H (1.3 mL, 1.75 mmol, 20% solution in toluene) was added slowly over 15 min. The resulting mixture was allowed to stir for 30 min at –78 °C, before being quenched with sodium potassium tartarate solution (10 mL). The mixture was then stirred at room temperature until it becomes clear solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were concentrated in vacuo and then purified the residue by flash column chromatography (1:4, EtOAc/hexane) to furnish the crude aldehyde. To a cooled (0 °C) solution of aldehyde in dry THF (15 mL) was added borane–dimethyl sulfide complex (2 M solution in THF, 4.8 mL, 9.6 mmol) dropwise and the resulting mixture was stirred

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

at room temperature for 3 h. After complete conversion of the starting material as indicated by TLC, the mixture was cooled to 0 °C, and then treated with 15% NaOH solution (48 mL) followed by 30% H_2O_2 (24 mL) solution. The resulting mixture was warmed to room temperature and then allowed to stir for 3 h. The mixture was quenched with $NaHCO_3$ solution and extracted with EtOAc (3 × 20 mL). Removal of solvent followed by purification on silica gel column chromatography (15% ethyl acetate/hexane) gave the desired product **3** (435 mg, 72%) along with undesired diastereoisomer (84 mg, 14%) as a viscous liquid. $[\alpha]_D$ = +4.2 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3405, 2958, 2927, 1707, 1461, 1380, 1253, 1092, 1032, 838, 775 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.55–3.74 (m, 2 H), 3.29–3.50 (m, 3 H), 0.94–1.89 (m, 8 H), 0.90 (s, 9 H), 0.88 (d, *J* = 6.7 Hz, 6 H), 0.86 (d, *J* = 6.7 Hz, 3 H), 0.81 (d, *J* = 6.7 Hz, 3 H), 0.03 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 79.5, 68.9, 68.0, 41.4, 41.2, 37.4, 33.0, 31.9, 27.3, 25.9, 20.8, 18.3, 17.9, 13.4, 12.8, –5.3 ppm. MS (ESI): *m*/*z* = 369 $[M + Na]^+$. HRMS: calcd. for $C_{19}H_{43}O_3Si$ $[M + H]^+$ 347.2981; found 347.2971.

(2*R*,4*S*,6*S*)-2,4-Dimethyl-6-[(4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]heptan-1-ol (13): 2,2-Dimethoxypropane (0.5 mL, 3.45 mmol) and CSA (54 mg, 0.23 mmol) were added successively to a solution of diol **3** (400 mg, 1.15 mmol) in a 10 mL mixture of CH_2Cl_2/Et_2O (9:1). The resulting solution was stirred for 1 h at room temperature and then quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with diethyl ether (4 × 100 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and concentrated in vacuo. The crude residue was dissolved in dry THF at 0 °C, and then 2.5 mL of TBAF (1 M in THF) was added. The resulting mixture was allowed to stir at room temperature for 6 h. It was then quenched with saturated NH_4Cl solution (10 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane (1:9) to give the product **13** (292 mg, 93%) as a viscous liquid. $[\alpha]_D$ = +35.5 (*c* = 1.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3420, 2957, 2873, 1630, 1459, 1379, 1265, 1199, 1052, 865, 519 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.69 (dd, *J* = 11.3, 4.9 Hz, 1 H), 3.30–3.52 (m, 4 H), 1.42–1.91 (m, 4 H), 1.38 (s, 3 H), 1.33 (s, 3 H), 1.12–1.32 (m, 2 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.81–1.0 (m, 2 H), 0.87 (d, *J* = 6.7 Hz, 3 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.71 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 97.9, 74.9, 68.5, 66.3, 41.6, 39.8, 32.9, 30.6, 29.8, 29.6, 26.6, 20.5, 18.9, 16.8, 13.7, 12.2 ppm. $C_{16}H_{32}O_3$ (272.43): calcd. C 70.54, H 11.84; found C 70.69, H 12.05.

Ethyl (2*E*,4*R*,6*S*,8*S*)-2,4,6-Trimethyl-8-[(4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]-2-nonenoate (14): The procedure was same as to that used for the preparation of **12**. The alcohol **13** (270 mg, 1.0 mmol), was treated with IBX (420 mg, 1.5 mmol), followed by ethyl 2-(triphenylphosphoranylidene)propanoate (724 mg, 2.0 mmol) to give product **14** (307 mg, 87%) as a colorless liquid. $[\alpha]_D$ = +2.1 (*c* = 1.1, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2960, 2929, 2873, 1711, 1457, 1377, 1268, 1202, 1153, 1100, 1059, 866, 753, 519 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.45 (d, *J* = 9.9 Hz, 1 H), 4.16 (q, *J* = 14.8, 6.9 Hz, 2 H), 3.63 (dd, *J* = 10.9, 4.9 Hz, 1 H), 3.42 (t, *J* = 10.9 Hz, 1 H), 3.34 (d, *J* = 9.9, 1.9 Hz, 1 H), 2.55–2.69 (m, 1 H), 1.85 (s, 3 H), 1.69–1.83 (m, 1 H), 1.24–1.44 (m, 5 H), 1.33 (s, 3 H), 1.31 (s, 3 H), 1.3 (t, *J* = 7.9 Hz, 3 H), 1.09–1.21 (m, 1 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 0.83 (d, *J* = 5.9 Hz, 6 H), 0.70 (d, *J* = 5.9 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.2, 148.0, 126.1, 97.9, 75.1, 66.3, 60.2, 44.9, 40.9, 30.7, 30.6, 29.8, 29.6, 27.3, 20.2, 19.5, 18.8, 14.2, 13.4, 12.4, 12.1 ppm. MS (ESI): *m*/*z* = 377 $[M + Na]^+$. HRMS: calcd. for $C_{21}H_{38}NaO_4$ $[M + Na]^+$ 377.2667; found 377.2653.

Ethyl (4*R*,6*S*,8*S*)-2,4,6-Trimethyl-8-[(4*R*,5*S*)-2,2,5-trimethyl-1,3-dioxan-4-yl]nonanoate (15): The procedure was same as to that used for the preparation of **8**. The unsaturated ester **14** (280 mg, 0.79 mmol) was treated with $NiCl_2{\cdot}6H_2O$ (38 mg, 0.16 mmol) and $NaBH_4$ (72 mg, 1.9 mmol) to give the saturated ester **15** (258 mg, 92%) as a viscous liquid. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.15 (q, *J* = 14.3, 6.7 Hz, 2 H), 3.63 (dd, *J* = 11.3, 5.2 Hz, 1 H), 3.33–3.49 (m, 2 H), 2.38–2.56 (m, 1 H), 1.63–1.87 (m, 3 H), 1.39–1.61 (m, 3 H), 1.19–139 (m, 3 H), 1.37 (s, 3 H), 1.31 (s, 3 H), 1.26 (t, *J* = 6.7 Hz, 3 H), 1.12 (dd, *J* = 6.7, 5.2 Hz, 3 H), 0.89–1.08 (m, 1 H), 0.87 (d, *J* = 6.7 Hz, 3 H), 0.84 (d, *J* = 6.7 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H), 0.70 (d, *J* = 6.7 Hz, 3 H) ppm. MS (ESI): *m*/*z* = 379 $[M + Na]^+$. HRMS: calcd. for $C_{21}H_{40}NaO_4$ $[M + Na]^+$ 379.2824; found 379.2840.

(4*R*,5*S*)-2,2,5-Trimethyl-4-[(1*S*,3*S*,5*S*)-1,3,5,7-tetramethyloctyl]-1,3-dioxane (16): To a stirred suspension of $LiAlH_4$ (51 mg, 1.3 mmol) in dry THF (10 mL) at –10 °C was added a solution of **15** (240 mg, 0.67 mmol) in dry THF (10 mL) in dropwise manner. The resulting mixture was allowed to stir for 10 min at same temperature and then quenched with saturated aqueous Na_2SO_4 solution. The precipitate formed was filtered and washed with ethyl acetate. The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure and the crude product was used for next step without any further purification. To this crude alcohol in dry CH_2Cl_2 were added triethylamine (203 mg, 0.28 mL, 2.0 mmol), *p*-toluenesulfonyl chloride (254 mg, 1.34 mmol), and DMAP (16 mg, 134 μmol). The resulting solution was stirred for 3.0 h. After complete conversion as confirmed by TLC, the mixture was quenched with NH_4Cl solution and extracted with EtOAc (3 × 20 mL). Removal of solvent followed by purification on silica gel column chromatography (10% ethyl acetate/hexane) gave the pure tosyl derivative. To a stirred suspension of $LiAlH_4$ (51 mg, 1.3 mmol) in dry THF (10 mL) at –10 °C was added a solution of tosyl derivative in dry THF (10 mL). The resulting mixture was allowed to stir for overnight at room temperature. It was then quenched with dropwise addition of saturated aqueous Na_2SO_4. The precipitate formed was filtered and washed with ethyl acetate. The combined organic extracts were dried with Na_2SO_4 and concentrated under reduced pressure and the residue was purified by silica gel column chromatography (5% ethyl acetate/hexane) to afford compound **16** (163 mg, 82% over three steps) as a viscous liquid. $[\alpha]_D$ = +23.8 (*c* = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2955, 1460, 1377, 1197, 1062, 1010, 866, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.58–3.73 (m, 1 H), 3.34–3.52 (m, 2 H), 1.72–1.90 (m, 2 H), 1.44–1.71 (m, 4 H), 1.38 (s, 3 H), 1.34 (s, 3 H), 0.90–1.34 (m, 5 H), 0.79–0.90 (m, 15 H), 0.72 (d, *J* = 6.6 Hz,3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 97.9, 75.0, 66.4, 47.0, 46.1, 40.1, 30.7, 29.9, 29.7, 27.4, 26.7, 25.1, 23.5, 22.2, 20.5, 20.1, 18.9, 13.8, 12.2 ppm.

(2*S*,3*R*,4*S*,6*S*,8*S*)-2,4,6,8,10-Pentamethylundecane-1,3-diol (17): To a stirred solution of **16** (150 mg, 0.50 mmol) in THF (10 mL) was added aqueous 2 N HCl (1.3 mL, 2.5 mmol) and the resulting mixture was stirred for 5 h at 25 °C. It was then diluted with ethyl acetate and extracted the aqueous layer twice with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and evaporated the solvent under reduced pressure. The resulting crude product was purified by column chromatography (1:4, EtOAc/hexane) to afford the diol **17** (118 mg, 92%) as a viscous liquid. $[\alpha]_D$ = –4.6 (*c* = 0.9, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3367, 2957, 2917, 1461, 1378, 1151, 1070, 1026, 979, 624 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.56–3.75 (m, 2 H), 3.43 (dd, *J*

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

= 9.0, 2.2 Hz, 1 H), 2.68–2.83 (br., 1 H), 2.22–2.50 (br., 1 H), 0.91–1.98 (m, 11 H), 0.88 (d, J = 6.0 Hz, 3 H), 0.85 (d, J = 6.7 Hz, 3 H), 0.84 (d, J = 6.0 Hz, 6 H), 0.84 (d, J = 6.7 Hz, 3 H), 0.81 (d, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 79.4, 68.9, 46.4, 45.8, 41.3, 37.5, 31.9, 27.5, 27.0, 25.1, 23.8, 21.9, 20.5, 13.4, 12.8 ppm. MS (ESI): m/z = 281 $[M + Na]^+$.

(2*R*,3*R*,4*S*,6*S*,8*S*)-3-Hydroxy-2,4,6,8,10-pentamethylundecanoic Acid (18): To a stirred solution of diol **17** (100 mg, 0.38 mmol) in CH_2Cl_2 (5 mL) at room temperature were added bis(acetoxy)iodobenzene (BAIB, 137 mg, 0.42 mmol), and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 6 mg, 0.038 mmol) sequentially. After completion of the reaction, a solution of saturated aqueous $Na_2S_2O_3$ followed by Et_2O (25 mL) was added. The separated organic phase was washed with saturated aqueous $NaHCO_3$ solution followed by brine and then dried with anhydrous Na_2SO_4. Removal of solvent gave the crude product which was used in the next step without purification. To a stirred solution of the above hydroxy aldehyde in a mixture of *tert*-butanol and water in 3:1 ratio at 0 °C were added NaH_2PO_4 (55 mg, 0.45 mmol) followed by 2-methyl-2-butene (66 μL, 0.57 mmol) and the resulting mixture was allowed it to stir for 5 min. Then $NaClO_2$ (42 mg, 0.45 mmol) was added and the stirring was continued at 0 °C. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc. The organic layer was washed once with brine and dried with Na_2SO_4 and concentrated to give the crude residue which was purified by column chromatography (petroleum ether/EtOAc, 1:1) to afford the pure β-hydroxy acid **18** in good yield (78 mg, 76% yield). $[\alpha]_D$ = –8.4 (c = 0.8, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3423, 2956, 1716, 1460, 1378, 1203, 979, 618 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.64 (dd, J = 8.6, 3.0 Hz, 1 H), 2.65 (dq, J = 8.4, 7.1 Hz, 1 H), 1.38–1.79 (m, 6 H), 0.91–1.35 (m, 4 H), 1.18 (d, J = 6.9 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 6.5 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 6 H), 0.83 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 181.4, 74.9, 46.3, 45.6, 43.5, 41.3, 31.2, 27.4, 26.9, 25.1, 23.7, 21.9, 20.5, 20.4, 14.0, 12.9 ppm. MS (ESI): m/z = 295 $[M + Na]^+$.

(+)-Vittatalactone (1b): To a stirred solution of β-hydroxy acid **18** (50 mg, 0.18 mmol) in dry pyridine (1 mL) at 0 °C was added *p*-toluenesulfonyl chloride (102 mg, 0.54 mmol) and the resulting mixture was stirred at 0 °C for 10 h and then placed in the freezer (–20 °C) for 24 h. After complete conversion as indicated by TLC, the mixture was partitioned between water and ether (3 × 8 mL), and the combined organic extracts were washed with brine (15 mL), dried with Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by flash chromatography (pentane/diethyl ether, 9:1) to the target β-lactone **1** (35 mg, 78%) as a colorless liquid. $[\alpha]_D$ = +1.1 (c = 1.3, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ = 2957, 2922, 1827, 1643, 1461, 1381, 1124, 983, 867 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.82 (dd, J = 8.1, 4.1 Hz, 1 H), 3.22 (qd, J = 7.5, 4.1 Hz, 1 H), 1.76–1.95 (m, 1 H), 1.49–1.72 (m, 3 H), 1.39 (d, J = 7.5 Hz, 3 H), 0.93–1.31 (m, 6 H), 1.02 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H), 0.84 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.9, 83.6, 48.7, 45.8, 45.0, 39.6, 34.6, 27.5, 27.1, 25.0, 23.8, 21.6, 20.6, 15.6, 12.7 ppm. MS (ESI): m/z = 526 $[2M + NH_4]^+$. HRMS: calcd. for $C_{16}H_{31}O_2$ $[M + H]^+$ 255.2324; found 255.2330.

Acknowledgments

N. N. Y. and T. S. R. thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for the award of fellowships. The authors acknowledge the partial support by the King Saud University for Global Research Network for Organic Synthesis (GRNOS).

[1] a) M. C. Liu, T. E. Hermann, *J. Biol. Chem.* **1978**, *253*, 5892; b) W. C. Liu, D. S. Slusarchyk, G. Astle, W. H. Trejo, W. E. Brown, E. Meyers, *J. Antibiot.* **1978**, *31*, 815; c) J. S. Hanessian, N. G. Cooke, B. DeHoff, Y. Saikito, *J. Am. Chem. Soc.* **1990**, *112*, 5276; d) D. A. Evans, R. L. Dow, T. L. Shih, J. M. Takacs, R. Zahler, *J. Am. Chem. Soc.* **1990**, *112*, 5290; e) M. Lautens, J. T. Colucci, S. Hiebert, N. D. Smith, G. Bouchain, *Org. Lett.* **2002**, *4*, 1879.

[2] a) J. Berger, L. M. Jampolsky, M. W. Goldberg, *Arch. Biochem.* **1949**, *22*, 476; b) W. Keller-Schierlein, *Helv. Chim. Acta* **1967**, *50*, 731; c) M. O. Duffey, A. LeTiran, J. P. Morken, *J. Am. Chem. Soc.* **2003**, *125*, 1458; d) S. Hanessian, Y. Yang, S. Giroux, V. Mascitti, J. Ma, F. Raeppel, *J. Am. Chem. Soc.* **2003**, *125*, 13784; e) T. Nagamitsu, D. Takano, K. Marumoto, T. Fukuda, K. Furuya, K. Otoguro, K. Takeda, I. Kuwajima, Y. Harigaya, S. Omura, *J. Org. Chem.* **2007**, *72*, 2744; f) T. Nagamitsu, D. Takano, T. Fukuda, K. Otoguro, I. Kuwajima, Y. Harigaya, S. Omura, *Org. Lett.* **2004**, *6*, 1865; g) B. G. Vong, S. H. Kim, S. Abraham, E. A. Theodorakis, *Angew. Chem.* **2004**, *116*, 4037; *Angew. Chem. Int. Ed.* **2004**, *43*, 3947.

[3] a) M. T. Fletcher, S. Chow, L. K. Lambert, O. P. Gallagher, B. W. Cribb, P. G. Allsopp, C. J. Moore, W. Kitching, *Org. Lett.* **2003**, *5*, 5083; b) R. Des Mazery, M. Pullez, F. Lopez, S. R. Harutyunyan, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2005**, *127*, 9966.

[4] B. D. Morris, R. R. Smyth, S. P. Foster, M. P. Hoffmann, W. L. Roelofs, S. Franke, W. Francke, *J. Nat. Prod.* **2005**, *68*, 26.

[5] a) Y. Schmidt, B. Breit, *Org. Lett.* **2009**, *11*, 4767; b) Y. Schmidt, K. Lehr, U. Breuninger, G. Brand, T. Reiss, B. Breit, *J. Org. Chem.* **2010**, *75*, 4424; c) C. F. Weise, M. Pischl, A. Pfaltz, C. Schneider, *Chem. Commun.* **2011**, *47*, 3248.

[6] a) J. J. Miller, P. L. De Benneville, *J. Org. Chem.* **1957**, *22*, 1268; b) G. Stork, V. Nair, *J. Am. Chem. Soc.* **1979**, *101*, 1315.

[7] a) M. L. Wolfrom, J. M. Bobbitt, *J. Am. Chem. Soc.* **1956**, *78*, 2489.

[8] a) K. Tsuji, Y. Terao, K. Achiwa, *Tetrahedron Lett.* **1989**, *30*, 6189; b) G. Lin, W. Xu, *Tetrahedron* **1996**, *52*, 5907; c) J. C. Anderson, S. V. Ley, S. P. Marsden, *Tetrahedron Lett.* **1994**, *35*, 2087; d) K. Fujita, K. Mori, *Eur. J. Org. Chem.* **2001**, 493; e) G. D. McAllister, R. J. K. Taylor, *Tetrahedron Lett.* **2004**, *45*, 2551; f) the enantiomeric excess has been determined by the comparison of $[\alpha]_D$ rotation with the value reported in the literature, see ref.[8d,8e]

[9] T. Satoh, K. Nanba, S. Suzuki, *Chem. Pharm. Bull.* **1971**, *19*, 817.

[10] a) D. A. Evans, M. D. Ennis, D. J. Mathre, *J. Am. Chem. Soc.* **1982**, *104*, 1737; b) T. K. Chakraborty, V. R. Suresh, *Tetrahedron Lett.* **1998**, *39*, 7775.

[11] R. W. Lang, H. J. Hansen, *Helv. Chim. Acta* **1980**, *63*, 438–455.

[12] a) T. Matsumoto, Y. Hosoda, K. Mori, K. Fukui, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3516; b) G. Schmid, T. Fukuyama, K. Akasaka, Y. Kishi, *J. Am. Chem. Soc.* **1979**, *101*, 259; c) D. C. Myles, S. J. Danishefsky, G. Schulte, *J. Org. Chem.* **1990**, *55*, 1636.

[13] Y. Schmidt, K. Lehr, U. Breuninger, G. Brand, T. Reiss, B. Breit, *J. Org. Chem.* **2010**, *75*, 4424.

[14] A. D. Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974.

Received: March 13, 2011
Published Online: June 21, 2011

 © 2011 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim