Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: *Asymmetry* 18 (2007) 2473–2478
Tetrahedron: *Asymmetry*

Towards the synthesis of Palmerolide A: asymmetric synthesis of C1–C14 fragment

S. Chandrasekhar,* K. Vijeender, G. Chandrashekar and Ch. Raji Reddy

Organic Division-I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

Received 29 August 2007; accepted 8 October 2007

Dedicated to the memory of Professor Charles Mioskowski, UniVersite' Louis Pasteur, BP 24, 67 401 Illkirch, France, who has passed away recently

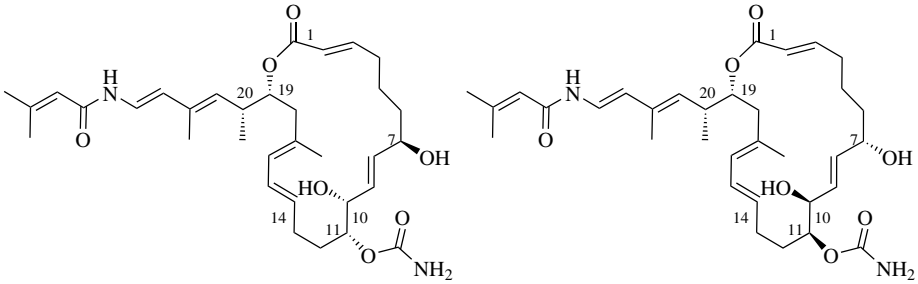
Abstract—The synthesis of a C1–C14 fragment of a marine cytotoxic natural product Palmerolide A is described. The key steps involved in this synthesis are deoxygenative rearrangement of an alkynol followed by an asymmetric dihydroxylation of a diene ester and CBS-reduction.

1. Introduction

A marine natural product Palmerolide A **1** (Fig. 1) was recently isolated from the Antarctic marine tunicate *synoicum adareanum* by Baker et al.[1] It exhibits unusual selectivity against a number of cell lines in the 60 cell panel of the National Cancer Institute (NCI) that correlates to vacuolar ATPase inhibitors. In particular, Palmerolide A was found to exhibit potent activity against the melanoma cell line UACC-62 ($LC50 = 18$ nm), which is of particular importance. Further biological studies confirmed that Palmerolide A is indeed a potent inhibitor of bovine brain V-ATPase ($IC_{50} = 2$ nM).[2]

Palmerolide A is a 20-membered macrolide with a side chain containing an enamide, five stereogenic centres and a 1,3-diene system. The interesting structure and biological profile have attracted the synthetic organic chemists. Recently, the structure of Palmerolide A has been revised **1a** (Fig. 1),[3] while two total syntheses and one partial synthesis have been reported.[3,4] We were interested in developing new structural analogues of potent cytotoxic agents[5] especially related to melonoma. Herein we report a reagent controlled synthesis of the C1–C14 fragment of Palmerolide A.

The C1–C14 fragment of Palmerolide A (from a revised structure) should be accessible from alkynol **5**, through

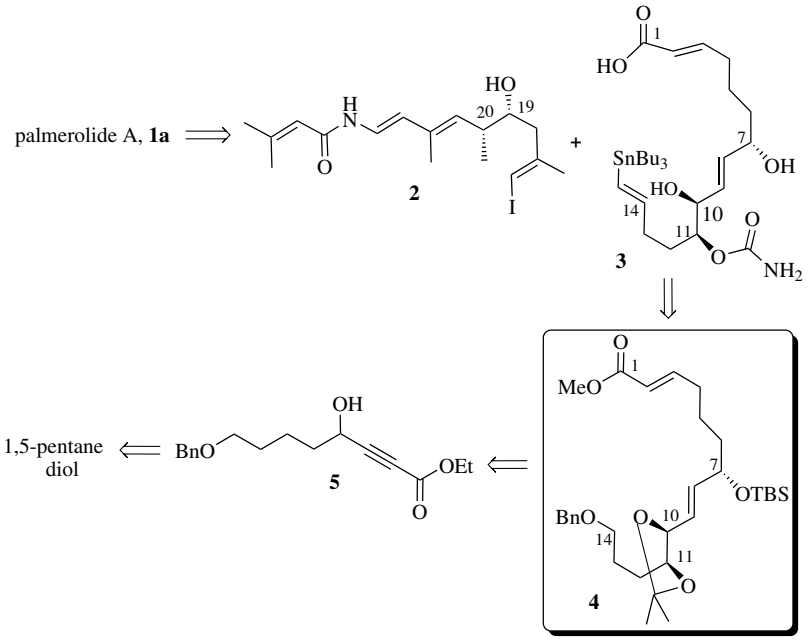


Originally proposed (7*R*,10*R*,11*R*,19*R*,20*R*)-**1** Revised structure (7*S*,10*S*,11*S*,19*R*,20*R*)-**1a**

Figure 1. Structure of Palmerolide A.

* Corresponding author. Tel.: +91 40 27193210; fax: +91 40 27160512; e-mail: srivaric@iict.res.in

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.10.011



Scheme 1. Retrosynthesis of Palmerolide A.

deoxygenative rearrangement followed by an asymmetric dihydroxylation. Alkynol **5** was further synthesized from commercially available 1,5-pentane diol (Scheme 1).

2. Results and discussion

5-Benzyloxy-1-pentanal **6** (synthesized from 1,5-pentane diol in two steps)[6] was exposed to lithiated ethylpropiolate to realize the formation of hydroxy alkynoate **5** in 85% yield. The critical diene ester intermediate **7** has been obtained from hydroxy alkynoate **5** by triphenylphosphine mediated deoxygenative rearrangement via an allene[5a,7] as the key step. This key rearrangement allowed us to obtain diene ester **7** ready for the stereoselective incorporation of hydroxyl groups via a Sharpless asymmetric dihydroxylation. The enantio and regioselective Sharpless asymmetric dihydroxylation[8] of diene ester **7** with ADmix-α, in ^{t}BuOH/H_2O (1:1) provided diol **8**, which was masked as its acetonoide **9** using 2,2-dimethoxy propane and catalytic camphorsulfonic acid (CSA) in 85% yield with 96% ee.[9] Compound **9** was converted into the α,β-unsaturated aldehyde **11** in two steps. Initially **9** was treated with 2 equiv of DIBAL-H to furnish alcohol **10**, which was further oxidized with IBX[10] to aldehyde **11**. This aldehyde was exposed to magnesium homoallyl bromide to realize the formation of allyl alcohol **12**, which was formed as an inseparable mixture (1:1) in 80% yield. Allyl alcohol **12** was converted into α,β-unsaturated ketone **13** using IBX. The α,β-unsaturated ketone **13** was treated with (*R*)-(−)-2-methyl-CBS-oxazaborolidine[11] and BH_3·DMS at −40 °C to furnish allyl alcohol **14** with an (*S*)-configuration in 90% yield with 97% de.[12] The newly created alcohol functionality was masked as its TBDMS ether **15** using TBDMSCl, imidazole as a base in 95% yield. The terminal olefin in **15** was selectively hydroborated to a 1°-alcohol using 9-BBN in THF to give compound **16** in 82% yield. The alcohol was oxidized using IBX to furnish the aldehyde, which was immediately exposed to the two carbon Wittig ylide, methoxycarbonylmethylenetriphenylphosphorane, to furnish the target C1–C14 fragment **4** in 93% yield (Scheme 2).

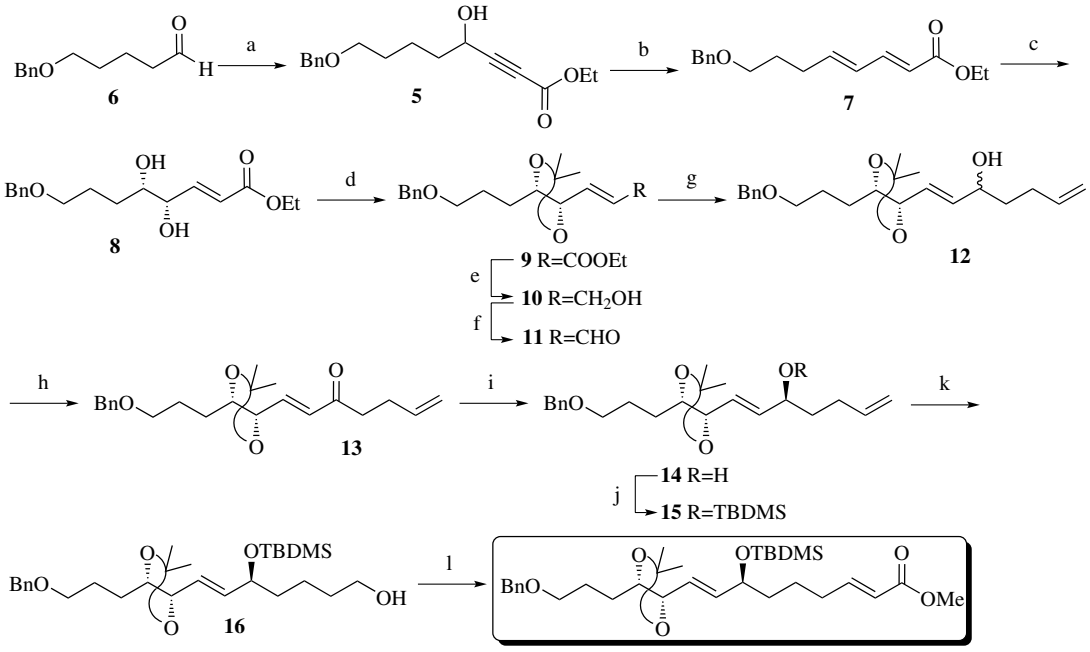
3. Conclusions

In conclusion, we have achieved a highly efficient stereoselective synthesis of a functionalized C1–C14 fragment of a marine metabolite Palmerolide A allowing us to synthesize other structural analogs. The synthetic ease of this approach allows us to prepare multigram of the key fragment, which will enable us to design closely related analogs for SAR studies. The work is presently being pursued.

4. Experimental

4.1. General

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 and Brucker Avance 300. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in Hz. Mass spectra were obtained on an Agilent Technologies LC/MSD Trap SL.



Scheme 2. Reagents and conditions: (a) LHMDS, ethyl propiolate, THF, −78 °C, 3 h, 85%; (b) TPP, Benzene, rt, 2 h, 73%; (c) AD-mix-α, $CH_3SO_2NH_2$, ^{t}BuOH: H_2O (1:1), 0 °C, 24 h, 78%, 96% ee; (d) 2,2-DMP, CSA, DCM, 0 °C, 3 h, 85%; (e) DIBAL-H, CH_2Cl_2, 0 °C, 5 h, 90%; (f) IBX, DMSO, THF, rt, 2 h, 82%; (g) Mg, THF, homoallyl bromide 0 °C, 80%; (h) IBX, DMSO, THF, rt, 1 h, 85%; (i) *R*-CBS catalyst, THF, −40 °C, BH_3·DMS, 3 h, 90%, 97% de; (j) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to rt, 5 h, 94%; (k) 9-BBN, THF, 0 °C, 4 h, then 20% NaOH, 30% H_2O_2, 3 h, 82%; (l) (i) IBX, DMSO, THF, 2 h; (ii) $Ph_3P{=}CHCO_2CH_3$, 3 h, 93%.

4.1.1. Ethyl 8-(benzyloxy)-4-hydroxyoct-2-ynoate 5. To a stirred solution of ethyl propiolate (1.93 mL, 22.91 mmol) in THF (100 mL) at −78 °C was slowly added LiHMDS (1.06 M in hexanes, 28.76 mL, 34.44 mmol) and the whole mixture was stirred at −78 °C for 1 h. Aldehyde **6** (4 g, 20.83 mmol) in THF (30 mL) was then added dropwise to the reaction mixture at −78 °C and the stirring continued for 30 min. The reaction was quenched with aqueous saturated NH_4Cl (20 mL) before warming to room temperature. The reaction mixture was diluted with water (15 mL) and extracted with diethyl ether (2 × 20 mL), the combined organic layers were washed with brine (20 mL), dried on over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on silica gel eluted with hexanes/EtOAc (8:2) to give alkynol **5** (5.13 g, 85% yield) as a colourless oil: IR (neat): ν 3407, 2931, 2861, 2234, 1710, 1246, 1095, 747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.22 (m, 5H), 4.47 (s, 2H), 4.43–4.30 (m, 1H), 4.19 (q, $J = 7.1$ Hz, 2H), 3.45 (t, $J = 6.0$ Hz, 2H), 1.80–1.50 (m, 6H), 1.31 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 153.5, 138.2, 127.0, 127.5, 87.9, 76.3, 72.8, 69.9, 62.0, 61.6, 36.4, 29.0, 21.6, 13.8; ESIMS: m/z 313 $(M+Na)^+$; HRMS calcd for $C_{17}H_{22}O_4Na$: 313.1415 $(M+Na)^+$; found, 313.1410.

4.1.2. (2*E*,4*E*)-Ethyl 8-(benzyloxy) octa-2,4-dienoate 7. A mixture of alkynol **5** (3 g, 10.34 mmol) and TPP (3.52 g, 13.44 mmol) in benzene (30 mL) was stirred at room temperature. After completion of the reaction (2 h, monitored by TLC), the solvent was removed under vacuum and the crude was purified on a silica gel column (eluting with 5% ethyl acetate in hexanes) to give the conjugated diene ester **7** (2.07 g, 73% yield): IR (neat): ν 2926, 2855, 1711, 1641, 1252, 1136, 1104, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30–7.14 (m, 6H), 6.13–6.07 (m, 2H), 5.72 (d, $J = 15.4$ Hz, 1H), 4.46 (s, 2H), 4.17 (q, $J = 7.1$ Hz, 2H), 3.43 (t, $J = 6.0$ Hz, 2H), 2.26 (q, $J = 6.7$ Hz, 2H), 1.77–1.68 (m, 2H), 1.29 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.0, 144.7, 143.5, 138.3, 128.6, 128.2, 127.4, 127.4, 119.3, 72.7, 69.1, 60.0, 29.5, 28.6, 14.1; ESIMS: m/z 275 $(M+1)^+$, 297 $(M+Na)^+$; HRMS calcd for $C_{17}H_{22}O_3Na$: 297.1466 $(M+Na)^+$; found, 297.1459.

4.1.3. (4*S*,5*S*,*E*)-Ethyl 8-(benzyloxy)-4,5-dihydroxyoct-2-enoate 8. Into a 250 mL round-bottomed flask were added 25 mL of ^{t}BuOH, 25 mL of water and ADmix-α (7 g, 1.4 g/mmol) and methanesulfonamide (0.47 g, 5.0 mmol). The mixture was stirred at room temperature for about 5 min., and cooled to 0 °C. To this cooled solution was added compound **7** (1.3 g, 5.0 mmol) and the mixture was stirred for 24 h at 0 °C. The reaction was quenched with solid sodium sulfite (7 g) at room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and after separation of the layers, the aqueous layer was further extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified on silica gel column eluting with hexanes/EtOAc (1:1) to give diol **8** (1.13 g, 78% yield) as a viscous liquid: $[\alpha]_D^{25} = -12.2$ (*c* 5.7, $CHCl_3$): IR (neat): ν 3418, 2923, 2855, 1713, 1273, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34–7.22 (m, 5H), 6.87 (dd, $J = 4.9$, 15.67 Hz, 1H), 6.08 (dd, $J = 1.5$,

15.6 Hz, 1H), 4.49 (s, 2H), 4.16 (q, $J = 7.1$ Hz, 2H), 4.05–4.01 (m, 1H), 3.65 (br s, 1H), 3.52–3.44 (m, 3H), 3.09 (br s, 1H), 1.79–1.47 (m, 4H), 1.29 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 147.0, 137.7, 128.3, 127.6, 122.0, 74.0, 73.6, 72.9, 70.1, 60.4, 30.2, 25.8, 14.0; ESIMS: m/z 331 $(M+Na)^+$; HRMS calcd for $C_{17}H_{24}O_5Na$: 331.1521 $(M+Na)^+$; found, 331.1518.

4.1.4. (*E*)-Ethyl 3-((4*S*,5*S*)-5-(3-(benzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate 9. To a stirred solution of diol **8** (1.5 g, 4.87 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added CSA (0.112 g, 0.487 mmol) followed by 2,2-dimethoxypropane (1.01 mL, 9.74 mmol). The mixture was stirred for 1 h and quenched with saturated aq $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous layer further extracted with dichloromethane (2×30 mL). The combined organic layers were washed with water (25 mL), brine (20 mL), dried over Na_2SO_4 and the solvent was evaporated in vacuo. The residue obtained was purified by column chromatography on silica gel eluted with hexanes/EtOAc (9:1) to give the acetonide compound **9** (1.39 g, 85% yield) as a colourless oil: $[\alpha]_D^{25} = -14.5$ (c 4.6, $CHCl_3$); IR (neat): ν 2985, 2933, 2861, 1721, 1255, 1169, 1040, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.23 (m, 5H), 6.80 (dd, $J = 5.2$ Hz, 15.4 Hz, 1H), 6.05 (dd, $J = 1.5$, 15.4 Hz, 1H), 4.46 (s, 2H), 4.17 (q, $J = 7.1$ Hz, 2H), 4.12–4.07 (m, 1H), 3.72–3.4 (m, 1H), 3.48–3.44 (m, 2H), 1.82–1.57 (m, 4H), 1.39 (s, 3H), 1.36 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.7. 143.8, 138.3, 128.2, 127.4, 122.6, 109.2, 80.1, 80.0, 72.7, 69.6, 60.4, 28.5, 27.1, 26.5, 26.0, 14.0; ESIMS: m/z 371 $(M+Na)^+$; HRMS calcd for $C_{20}H_{28}O_5Na$: 371.1834 $(M+Na)^+$; found, 371.1823.

4.1.5. (*E*)-4-((4*S*,5*S*)-5-(3-(Benzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl) but-3-en-1-ol 10. To a solution of unsaturated ester **9** (1.5 g, 4.31 mmol) in CH_2Cl_2 (10 mL) at 0 °C was slowly added DIBAL-H (5.43 mL, 20% solution in toluene, 10.34 mmol) and the mixture was stirred for 3 h at 0 °C. The reaction was quenched with saturated aq sodium potassium tartarate (30 mL) and the stirring continued for 1 h. The organic layer was separated and the aqueous layer extracted with dichloromethane (2×30 mL). The combined organic layers were dried over Na_2SO_4 and volatiles were removed under vacuum. The crude product obtained was purified by column chromatography on silica gel eluted with hexanes/EtOAc (8:2) to give allyl alcohol **10** (1.187 g, 90% yield) as colourless oil: $[\alpha]_D^{25} = -6.3$ (c 3.15, $CHCl_3$); IR (neat): ν 3441, 2925, 2855, 1630, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.26–7.21 (m, 5H), 5.94–5.82 (m, 1H), 5.62 (dd, $J = 7.3$, 15.4 Hz, 1H), 4.45 (s, 2H), 4.07 (d, $J = 4.0$ Hz, 2H), 3.95 (t, $J = 8.0$ Hz, 1H); 3.65–3.58 (m, 1H), 3.45–3.42 (m, 2H), 2.17 (br s, 1H), 1.76–1.50 (m, 4H), 1.35 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 134.3, 128.2, 127.5, 127.4, 81.6, 80.3, 75.0, 74.0, 72.7, 69.8, 62.3, 29.9, 28.2, 27.1, 26.8, 26.0; ESIMS: m/z 329 $(M+Na)^+$; HRMS calcd for $C_{18}H_{26}O_4Na$: 329.1728 $(M+Na)^+$; found, 329.1714.

4.1.6. (*E*)-3-((4*S*,5*S*)-5-(3-(Benzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl) acrylaldehyde 11. To a solution of iodoxybenzoic acid (1.38 g, 4.93 mmol) in DMSO (10 mL) was added alcohol **10** (1.0 g, 3.28 mmol) in THF (80 mL) and allowed to stir for 3 h at room temperature. After completion of the reaction, the reaction mixture was filtered through a pad of Celite and washed with ether (200 mL). The filtrate was washed with water (50 mL), brine (50 mL, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluted with hexanes/EtOAc (9:1) to afford α,β-unsaturated aldehyde **11** (0.814 g, 82% yield): $[\alpha]_D^{25} = -13.1$ (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.56 (s, 1H), 7.30–7.25 (m, 5H), 6.6 (dd, $J = 5.3$, 15.6 Hz, 1H), 6.35 (dd, $J = 1.3$, 15.6 Hz, 1H), 4.47 (s, 2H), 4.24–4.19 (m, 1H), 3.76–3.70 (m, 1H), 3.49–3.45 (m, 2H), 1.82–1.63 (m, 4H), 1.41 (s, 3H), 1.37 (s, 3H); ESIMS: m/z 327 $(M+Na)^+$; HRMS calcd for $C_{18}H_{24}O_4Na$: 327.1572 $(M+Na)^+$; found, 327.1561.

4.1.7. (*E*)-1-((4*S*,5*S*)-5-(3-(Benzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl) hepta-1,6-dien-3-ol 12. The homoallyl bromide (0.635 g, 3.97 mmol) in THF (10 mL) was added to a suspension of Mg (0.19 g, 7.94 mmol) in THF at room temperature and stirred for 30 min. To this, aldehyde **11** (0.8 g, 2.64 mmol) was added in THF (10 mL) dropwise at 0 °C and stirring continued for 1 h. After completion of the reaction (monitered by TLC), the mixture was quenched with saturated aq NH_4Cl (10 mL) and extracted with ethylacetate (2×20 mL). The combined organic layers were washed with water (15 mL), brine (15 mL), dried over Na_2SO_4 and evaporated in vacuo. The crude product **12** (0.75 g, 80% yield) was obtained as inseparable mixture and used it in the next step without further purification. IR (neat): ν 3449, 2926, 2857, 1638, 759 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.37–7.28 (m, 5H), 5.87–5.53 (m, 3H), 5.05–4.92 (m, 2H), 4.47 (s, 2H), 4.16–4.05 (m, 1H), 3.94 (t, $J = 8.0$ Hz, 1H), 3.66–3.57 (m, 1H), 3.46–3.43 (m, 2H), 2.18–2.08 (m, 2H), 1.78–1.53 (m, 6H), 1.36 (s, 6H); ESIMS: 383 $(M+Na)^+$; HRMS: calcd for $C_{22}H_{32}O_4Na$: 383.2198; found, 383.2193.

4.1.8. (*E*)-1-((4*S*,5*S*)-5-(3-(Benzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl) hepta-1,6-diene-3-one 13. To a solution of iodoxybenzoic acid (0.63 g, 2.08 mmol) in DMSO (10 mL) was added alcohol **12** (0.5 g, 1.38 mmol) in THF (30 mL) and allowed to stir for 3 h at room temperature. After completion of the reaction, the mixture was filtered through a pad of Celite, and washed with ether (30 mL). The filtrate was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel eluted with hexanes/EtOAc (9:1) to afford α,β-unsaturated keto compound **13** (0.422 g, 85% yield): $[\alpha]_D^{25} = -11.9$ (c 5.1, $CHCl_3$); IR (neat): ν 2925, 2857, 1635, 11027, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.29–7.25 (m, 5H), 6.64 (dd, $J = 5.6$, 15.8 Hz, 1H), 6.34 (d, $J = 15.8$ Hz, 1H), 5.85–5.72 (m, 1H), 5.04–4.94 (m, 2H), 4.46 (s, 2H), 4.10 (t, $J = 7.5$ Hz, 1H) 3.94–3.89 (m, 1H), 3.47–3.45 (m, 2H), 2.63 (t, $J = 7.1$ Hz, 2H), 2.34 (q, $J = 6.7$ Hz, 2H), 2.03–1.60 (m, 4H), 1.40 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.6, 141.3, 138.0, 136.5, 129.9, 127.9, 127.1, 127.1, 114.9, 109.0, 79.9, 72.4,

69.3, 39.3, 28.3, 27.3, 26.8, 26.2, 25.7; ESIMS: *m*/*z* 381 $(M+Na)^+$; HRMS calcd for $C_{22}H_{30}O_4Na$: 381.2041 $(M+Na)^+$; found, 381.2031.

4.1.9. (*S*,*E*)-1-((4*S*,5*S*)-5-(3-(Benzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hepta-1,6-dien-3-ol 14. To a stirred solution of α,β-unsaturated keto compound **13** (0.30 g, 1.0 mmol) in THF (3 mL) was added (*R*)-(−)-2-methyl-CBS-oxazaborolidine (1.0 M solution in toluene, 0.55 mL, 0.31 mmol) at −40 °C and stirred for 30 min. To this mixture was added BH_3·DMS (0.08 mL, 1.10 mmol) dropwise and stirred at same temperature for 1 h. After completion of the reaction, the mixture was quenched with MeOH (0.1 mL in 5 mL ether) followed by aq $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were dried and concentrated on rotary evaporator. The crude obtained was purified by flash column chromatography to give product **14** (0.343 g, 90% yield): $[\alpha]_D^{25} = -46.95$ (*c* 1.45, $CHCl_3$); IR (neat): *v* 3449, 2926, 2857, 1638, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.29–7.25 (m, 5H), 5.82–5.71 (m, 2H), 5.58 (dd, *J* = 7.1, 15.4 Hz, 1H), 5.04–4.93 (m, 2H), 4.46 (s, 2H), 4.11 (q, *J* = 6.0 Hz, 1H), 3.94 (t, *J* = 7.5 Hz, 1H), 3.64–3.58 (m, 1H), 3.47–3.44 (m, 2H), 2.14–2.10 (m, 2H), 1.74–1.56 (m, 6H), 1.36 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.0, 137.7, 137.6, 128.3, 127.6, 127.5, 127.4, 114.9, 198.5, 81.6, 80.4, 72.8, 71.2, 69.9, 35.9, 29.5, 28.4, 27.2, 26.9, 26.1; ESIMS: *m*/*z* 383 $(M+Na)^+$; HRMS calcd for $C_{22}H_{32}O_4Na$: 383.2198 $(M+Na)^+$; found, 383.2193.

4.1.10. (*S*,*E*)-1-(4*S*,5*S*)-5-(3-(Benzyloxy)propyl)-2-2-dimethyl-1,3-dioxolan-4-yl)hepta-1,6-dien-3-yloxy)(*tert*-butyl)dimethylsilane 15. To a solution of alcohol **14** (0.20 g, 0.55 mmol) in dry CH_2Cl_2 (10 mL), imidazole (0.094 g, 1.38 mmol) and *tert*-butyldimethylsilyl chloride (0.21 g, 1.38 mmol) were added at 0 °C and stirred for 6 h at room temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using hexanes/EtOAc (9:1) as eluent to afford compound **15** (0.247 g, 94% yield): $[\alpha]_D^{25} = -6.5$ (*c* 1.3, $CHCl_3$); IR (neat): *v* 2925, 1632, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.22 (m, 5H), 5.83–5.68 (m, 2H), 5.56–5.47 (m, 1H), 5.01–4.91 (m, 2H), 4.47 (s, 2H), 4.16–4.10 (m, 1H), 3.94 (t, *J* = 7.9 Hz, 1H), 3.64–3.58 (m, 1H), 3.46–3.45 (m, 2H), 2.11–2.04 (m, 2H), 1.79–1.52 (m, 6H), 1.38 (s, 3H), 1.36 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H), 0,03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.4, 138.1, 137.6, 128.3, 127.5, 127.4, 126.8, 126.5, 114.4, 81.8, 81.6, 80.5, 72.7, 72.1, 70.0, 37.2, 29.3, 28.5, 27.2, 26.9, 26.2, 25.8, 25.6, −3.5, −4.2, −4.7; ESIMS: *m*/*z* 497 $(M+Na)^+$; HRMS calcd for $C_{28}H_{46}O_4NaSi$: 497.3063; found: 497.3044.

4.1.11. (*S*,*E*)-7-((4*S*,5*S*)-5-(3-(Benzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-5-(*tert*-butyldimethylsilyoxy)hept-6-en-1-ol 16. To a solution of compound **15** (0.20 g, 0.42 mmol) in dry THF, was added 9-BBN (0.077 g, 0.63 mmol) in THF (10 mL) slowly over a period of 15 min, at 0 °C. The reaction mixture was stirred for 8 h at room temperature. The mixture was treated with 20% aq NaOH (slow addition) at 0 °C until the mixture was basic. To this, was added H_2O_2 (0.095 mL, 30% aq solution, 0.84 mmol) and the stirring continued for 3 h. The reaction mixture was extracted with ethyl acetate (6 × 10 mL), the combined organic layers were washed with brine (25 mL), dried over Na_2SO_4, concentrated on rotary evaporator and the residue was purified by column chromatography to yield alcohol **16** (0.170 g, 82% yield): colourless liquid; $[\alpha]_D^{25} = -79.7$ (*c* 0.9, $CHCl_3$); IR (neat): *v* 3447, 2925, 2856, 763 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.28–7.26 (m, 5H), 5.77–5.41 (m, 2H), 4.47 (s, 2H), 4.20–4.10 (m, 1H), 3.94 (t, *J* = 8.1 Hz, 1H), 3.65–3.44 (m, 5H), 1.74–1.33 (m, 16H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.3, 137.9, 128.3, 127.6, 127.5, 126.5, 81.8, 80.5, 72.8, 72.4, 70.0, 62.7, 37.8, 37.6, 32.6, 28.5, 28.4, 27.2, 26.9, 26.2, 25.8, 21.2, 21.0, −4.3, −4.7; ESIMS: *m*/*z* 515 $(M+Na)^+$; HRMS calcd for $C_{28}H_{48}O_5NaSi$: 515.3168 $(M+Na)^+$; found, 515.3158.

4.1.12. (*S*,2*E*,8*E*)-Methyl 9-((4*S*,5*S*)-5-(3-(benzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-7-(*tert*-butyldimethylsilyloxy)nona-2,8-dienoate 4. To a stirred solution of 2-iodoxybenzoic acid (0.085 g, 0.30 mmol) in DMSO (1 mL) was added alcohol **16** (0.1 g, 0.20 mmol) in THF (10 mL) at room temperature and the mixture was stirred for 3 h. The solid materials were filtered through a sintered funnel and the resulting filtrate was extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to yield the aldehyde (0.089 g), which was used without further purification. This aldehyde (0.089 g, 0.18 mmol) was dissolved in benzene (15 mL), was added carbomethoxy methylenetriphenyl phosphorane (0.095 g, 0.27 mmol) and the resulting solution was stirred for 12 h at room temperature. The solvent was removed under vaccum, and the residue obtained was diluted with dichloromethane (20 mL), washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated on rotary evaporator. The crude product was purified by column chromatography to yield α,β-unsaturated ester **4** (0.103 g, 93% yield): colourless oil; $[\alpha]_D^{25} = -29.6$ (*c* 2.85, $CHCl_3$); IR (neat): *v* 2928, 2856, 1724, 1653, 1253, 1094, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.28–7.26 (m, 5H), 6.98–6.8 (m, 1H), 5.8–5.45 (m, 3H), 4.47 (s, 2H), 4.12–4.10 (m, 1H), 3.9 (t, *J* = 7.7 Hz, 1H), 3.71 (s, 3H), 3.66–344 (m, 3H), 2.21–2.18 (m, 2H), 1.79–1.26 (m, 14H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.1, 149.2, 138.0, 137.4, 128.2, 127.5, 127.8, 126.8, 126.5, 121.0, 81.7, 80.5, 72.7, 72.3, 71.9, 70.0, 51.3, 37.4, 32.0, 29.6, 28.5, 27.2, 26.8, 26.2, 25.7, 23.5, −4.3, −4.8; ESIMS: *m*/*z* 569 $(M+Na)^+$; HRMS calcd for $C_{31}H_{50}O_6NaSi$: 569.3274 $(M+Na)^+$; found, 569.3260.

Acknowledgement

K.V. and G.C.S. thank the CSIR, New Delhi, for financial assistance.

References

1. Diyabalanage, T.; Amsler, C. D.; McClintock, J. B.; Baker, B. J. *J. Am. Chem. Soc.* **2006**, *128*, 5630–5631.
2. Xie, X. S.; Padron, D.; Liao, X.; Wang, J.; Roth, M. G.; De Brabander, J. K. *J. Biol. Chem.* **2004**, *279*, 19755–19763.
3. Jiang, X.; Liu, B.; Lebreton, S.; Brabander, J. K. D. *J. Am. Chem. Soc.* **2007**, *129*, 6386–6387.
4. (a) Kaliappan, K. P.; Gowrisankar, P. *Synlett* **2007**, 1537–1540; (b) Nicolaou, K. C.; Guduru, R.; Sun, Y. P.; Banerji, B.; Chen, D. Y. K. *Angew. Chem., Int. Ed.* **2007**, *46*, 5896–5900.
5. (a) Chandrasekhar, S.; Sultana, S. S. *Tetrahedron Lett.* **2006**, *47*, 7255–7258; (b) Chandrasekhar, S.; Tiwari, B.; Prakash, J. *Arkivoc* **2006**, 155–161; (c) Chandrasekhar, S.; Narsihmulu, Ch.; Jagadeshwar, V.; Sultana, S. S. *Arkivoc* **2005**, 92–98; (d) Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S. S.; Reddy, M. S. *Tetrahedron Lett.* **2004**, *45*, 9299–9301; (e) Chandrasekhar, S.; Jagadeshwar, V.; Narsihmulu, Ch.; Sarangapani, M.; Krishna, D. R.; Vidyasagar, J.; Vijay, D.; Sastry, G. N. *BOMCL* **2004**, *14*, 3687–3689; (f) Tietze, L. F.; Bell, H. P.; Chandrasekhar, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3996–4028; (g) Chandrasekhar, S.; Raji Reddy, Ch. *Tetrahedron: Asymmetry* **2002**, *13*, 261–268.
6. Osterkamp, F. B.; Ziemer, B. U.; Wiesner, K. M.; Raddatz, P.; Goodman, S. L. *Chem. Eur. J.* **2000**, *6*, 666–683.
7. (a) Chandrasekhar, S.; Sultana, S. S. *Tetrahedron Lett.* **2006**, *47*, 7255–7258; (b) Guo, C.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1993**, 394–395.
8. Xu, D.; Crispino, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570–7571.
9. The enantiomeric excess was confirmed by chiral HPLC, Eurocel VE110-column, flow rate: 1.0 mL/min, 254 nm, eluent: hexanes/isopropanol (9:1), retention time: 5.23 min.
10. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
11. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019–8022.
12. The diastereoselectivity was determined by HPLC, Waters C18-column (reverse phase), flow rate: 1.0 mL/min, 225 nm, eluent: acetonitrile/water (7:3), retention time: 5.81 min.