Tetrahedron: *Asymmetry* 20 (2009) 1120–1124

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Total synthesis of phytotoxic herbarumin-I from D-mannitol

Ahmed Kamal *, P. Venkat Reddy, S. Prabhakar

Chemical Biology Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 607, India

ARTICLE INFO

Article history:
Received 12 February 2009
Accepted 10 March 2009
Available online 22 May 2009

ABSTRACT

A simple carbohydrate-based convergent approach towards the total synthesis of herbarumin-**I**, a 10-membered lactone is described. The key features of the synthetic strategy include Grignard reaction and ring-closing metathesis reaction for the formation of the 10-membered ring and *E*-olefinic moiety. D-Mannitol has been used as a chiral pool material for the construction of the key fragment.

1. Introduction

In recent years naturally occurring 10-membered lactones commonly known as decanolides have attracted synthetic as well as bioorganic chemists, due to their interesting structural properties and biological activities.[1] Some examples, such as herbarumin-**I 1**, herbarumin-**II 2**, herbarumin-**III 3**,[2] microcarpalide **4**,[3] lethaloxin **5**,[4] and decarestrictine D **6**[5] belong to this class of molecules as shown in Figure 1. Mata et al. have extracted three phytotoxic lactones namely herbarumin-**I 1**, herbarumin-**II 2** and herbarumin-**III 3**,[2a,b] from the culture broth and mycelium of the fungus *Phoma herbarum.* Amongst these lactones herbarumin-**I 1** shows promising phytotoxic effects with IC_{50} (M) values as low as 5.43×10^{-5}. These lactones exhibit significant phytotoxic effects when tested against the seedlings of *Amaranthus hypochondriacus* at very low concentrations,[6] thus making this class of compounds promising new lead structures in the search for novel herbicidal agents.

2. Results and discussion

Some approaches have been developed in the literature for the synthesis of these 10-membered lactones starting from various sugars as chiral pool templates,[7] such as D-ribose, L-arabinose, D-glucose and L-ascorbic acid. However, the interesting structural properties, especially the presence of oxygen substituents at C7, C8 and C9 positions in the ring and the *trans* relationship between any two oxygens in its scaffold make herbarumin-**I** an attractive and challenging synthetic target. As part of our studies directed towards the synthesis of lactones and other biologically active molecules,[8] we herein report an efficient convergent approach for the total synthesis of herbarumin-**I 1** by employing D-mannitol, a cost-effective and readily available starting material.

Retrosynthetically herbarumin-**I** can be obtained from bis-alkene **11** via the ring-closing metathesis, a key reaction strategy that has been widely used for the synthesis of 10-membered lactones possessing similar carbon skeletons. Moreover, this bis-alkene **11** is accessible by the esterification of **10** with 5-hexenoic acid, whereas **10** in turn can be obtained from the commercially available D-mannitol (Scheme 1).

1,2:3,4:5,6-Tri-*O*-isopropylidene-D-mannitol, a fully protected D-mannitol was treated with H_5IO_6 according to the reported literature procedure[9] to afford the aldehyde, which without further purification was taken up for reduction with $NaBH_4$ to provide the primary alcohol **2**. Then treatment of alcohol **2** with PPh_3 and $NaHCO_3$ in CCl_4 at reflux for 1 h gave the chloride **3** in 89% yield, which on further treatment with Na in dry ether afforded the allylic alcohol **4** in 92% yield. Protection of the resulting secondary alcohol with BnBr and NaH, in THF afforded **5**, which on subsequent acetonide deprotection with TFA (THF/H_2O 9:1) gave the diol **6**. Selective protection of the primary hydroxyl group of **6** as the TBDMS ether provided **7**, which was followed once again by protection of the resulting secondary alcohol with BnBr, NaH and TBAI (cat) in THF to give the dibenzylated compound **8**. Treatment of this dibenzyl ether **8** with TBAF in THF afforded the primary alcohol **9**, which is the key intermediate for the synthesis of herbarumin-**I 1**. Thus, **9** was subjected to Swern oxidation to provide the aldehyde, which then without further purification was taken up for the Grignard addition using propyl magnesium chloride in dry toluene (8.78 mL, 17.56 mmol, 2 M in diethyl ether) at −78 °C to afford the corresponding *anti*- and *syn*-diastereomeric alcohols in 7:3 ratio as separable diastereomers **10** and **10a**. Formation of major diastereomeric alcohol **10** can be explained on the basis of non-chelation-controlled addition of Grignard nucleophile to the aldehyde (see Scheme 2).

Esterification of diastereomer **10** with 5-hexenoic acid in the presence of DCC and DMAP at 0 °C to ambient temperature provides the diene **11** in 81%. This has allowed the stage to be set for the macrolactonization via ring-closing metathesis.

* Corresponding author. Tel.: +91 40 27193157; fax: +91 40 27193189.
E-mail address: ahmedkamal@iict.res.in (A. Kamal).

0957-4166/$ - see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2009.03.039

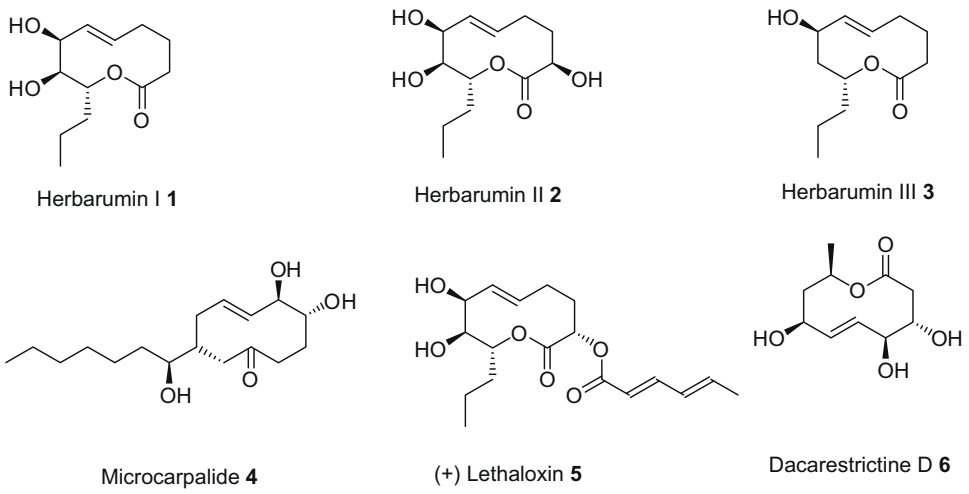
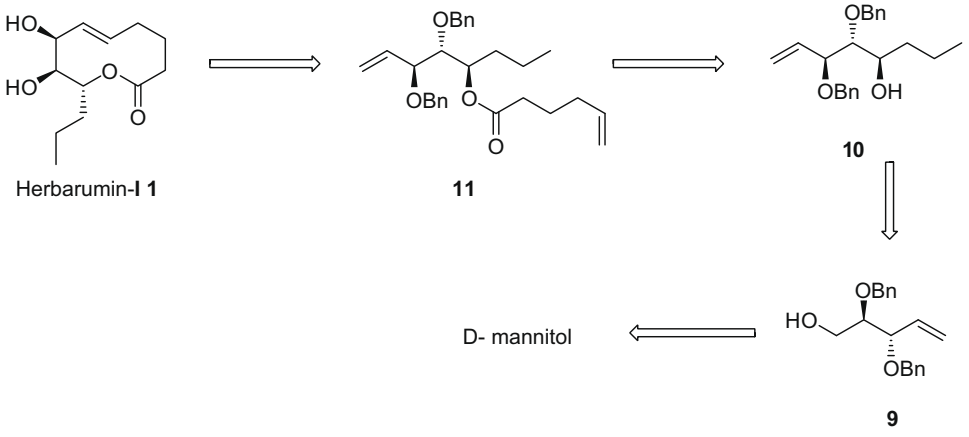
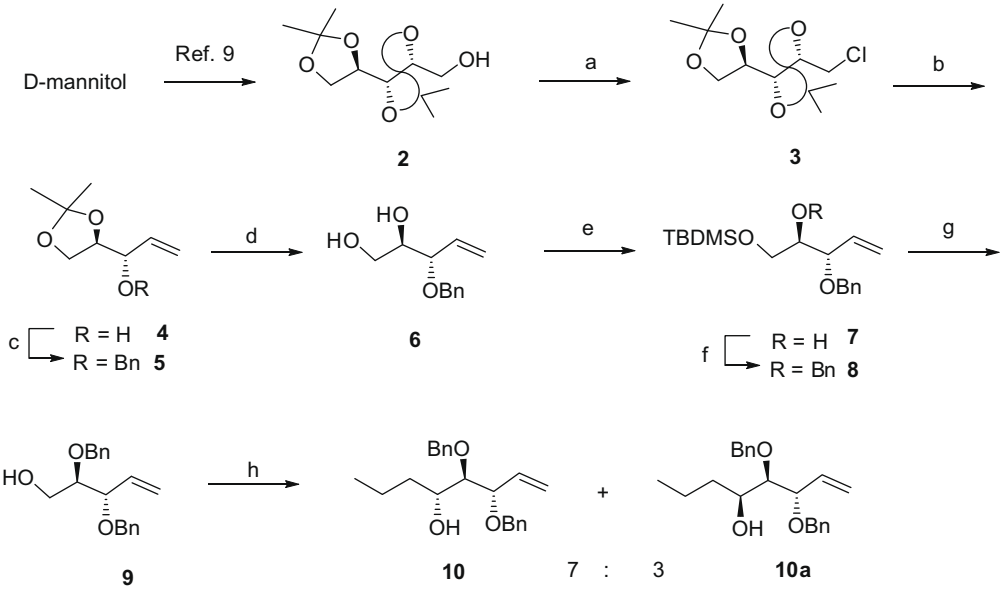


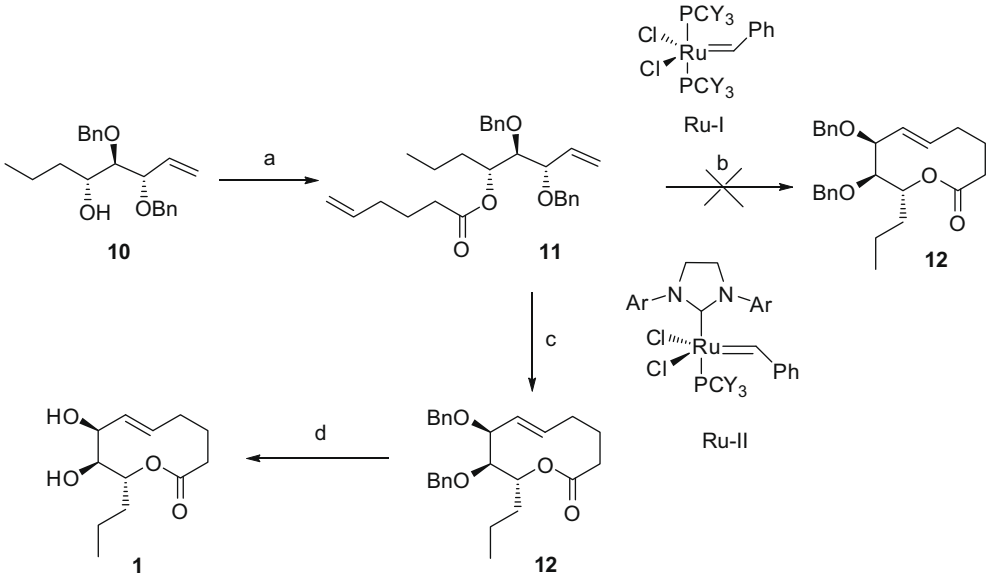
Figure 1.



Scheme 1. Retrosynthetic analysis of **1**.



Scheme 2. Reagents and conditions: (a) Ph_3P, $NaHCO_3$, CCl_4, reflux, 1 h, 89%; (b) Na, dry ether, 0 °C to rt, 15 h, 92%; (c) NaH, BnBr, THF, 0 °C to rt, 6 h, 93%; (d) TFA (THF/H_2O 9:1) 84% (e) TBDMSCl, imidazole, CH_2Cl_2, 0 °C to rt, 6 h, 82%; (f) NaH, BnBr, TBAI (cat), THF, 0 °C to rt, 6 h; (g) TBAF, THF, rt, 2 h, 85%; (h) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 0.5 h; (ii) propylmagnesium chloride, dry toluene, −78 °C, 3 h, 62%.



Scheme 3. Reagents and conditions: (a) 5-hexenoic acid, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 3 h, 81%; (b) 20 mol% Ru-I, benzene, 12 h; (c) 20 mol % Ru-II, benzene, 12 h, 62%; (d) $TiCl_4$, CH_2Cl_2, 0 °C, 0.5 h, 82%.

Initial attempts for the ring-closing metathesis of diene **11** using Grubbs' first generation catalyst (Ru-I) were not successful, but this reaction, under varying conditions such as different solvents and temperatures, showed some traces of dimer formation along with the recovered starting material. However, use of Grubbs' second generation catalyst (Ru-II, 20 mol %) in benzene under argon at 70 °C for 12 h, resulted in the ring-closing metathesis[10] of **11** which led to the exclusive formation of lactone **12** (in *E*-form) bearing the *trans* geometry at the newly formed double bond and interestingly no *cis*-form was detected. The doublet of a doublet at 5.88–5.97 ppm in the ^{1}H NMR spectrum with a coupling constant of $J_{H\text{-}5,\ H\text{-}6}$ = 15.6 Hz allowed us to assign the *E*-stereochemistry for **12**. After the lactone formation, the bis-benzyl-protected diol groups at 7 and 8 positions need to be deprotected. Accordingly, bis-benzyl-protected diol was treated with $TiCl_4$ in dichloromethane[11] at 0 °C to afford the target molecule **1** (see Scheme 3). The spectral and analytical data were comparable to the previously reported data in the literature.[2,7b]

3. Conclusion

In conclusion, we have developed a simple, convenient and efficient approach for the synthesis of naturally occurring herbarumin-**I 1** by employing D-mannitol as a chiral template. This protocol involves the use of a Grignard reaction and ring-closing metathesis as key steps. The synthesis of related compounds of this family is underway in our laboratory.

4. Experimental

4.1. General experimental

Reagents and chemicals were purchased from Aldrich. All solvents and reagents were purified by standard techniques. THF was freshly distilled from $LiAlH_4$. Crude products were purified by column chromatography on 60–120 silica gel. IR spectra were recorded on a Perkin–Elmer 683 spectrometer. Optical rotations were obtained on a Horiba 360 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200, Brucker Avance 300. Chemical shifts are reported in parts per million with respect to the internal TMS. Mass spectra were recorded on VG micromass-7070H (70 Ev).

4.2. 1,2:3,4-Di-*O*-isopropylidine-(2*R*,3*R*,4*S*)-5-chloropentane-1,2,3,4-tetraol 3

To a stirred solution of compound **2** (7 g, 30.17 mmol), in dry CCl_4 (15 mL), Ph_3P (11.8 g, 45.25 mmol) and $NaHCO_3$ (5.06 g, 60.34 mmol) were added and heated at reflux for 1 h. CCl_4 was evaporated under reduced pressure and the residue that was obtained was extracted with $CHCl_3$ (2 × 100 ml), dried over anhydrous Na_2SO_4, evaporated and purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 6:94) to afford **3** (6.72 g, 89%) as a liquid. $[\alpha]_D^{25} = +12.9$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3443, 2987, 2936, 2882, 1215, 1155, 1065, 840 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 1.44 (s, 3H), 3.65 (dd, *J* = 5.35 Hz, 1H), 3.79 (t, *J* = 7.56 Hz, 1H), 3.80–3.85 (m, 1H), 3.90–4.05 (m, 2H), 4.10–4.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.1, 26.5, 26.9, 27.1, 44.6, 67.4, 76.8, 78.1, 79.7, 109.6, 109.9; MS-EIMS: *m/z* 273.5 $(M+Na)^+$.

4.3. (1*S*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-propen-1-ol 4

Compound **3** (6.5 g, 25.94 mmol) was dissolved in dry ether (75 mL) at −10 °C and shining Na pieces (1.79 g, 77.84 mmol) were added under nitrogen atmosphere. After complete addition, the reaction mixture was allowed to stir at room temperature for 12 h. Then the reaction mixture was carefully quenched with MeOH at 0 °C, diluted with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 15:85) to afford **4** (3.77 g, 92%) as a liquid. $[\alpha]_D^{25} = +2.9$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3442, 2925, 2854, 1649, 1022, 754; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.44 (s, 3H), 2.07 (d, *J* = 3.05 Hz, 1H), 3.83–3.95 (m, 2H), 4.05 (q, *J* = 4.53, 6.80 Hz, 1H), 4.25 (m, 1H), 5.22–5.42 (m, 2H), 5.76–5.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.04, 26.33, 64.77, 71.87, 78.05, 109.33, 116.72, 136.23; MS-EIMS: *m/z* 181 $(M+Na)^+$.

4.4. (4*R*)-4-[(1*S*)-1-(Benzyloxy)-2-propenyl]-2,2-dimethyl-1,3-dioxolane 5

To a stirred solution of the compound **4** (3.5 g, 22.15 mmol) in dry THF (40 mL), sodium hydride (1.06 g, 44.30 mmol) and benzyl bromide (2.63 mL, 22.15 mmol) were added at 0 °C and stirred at room temperature for 4 h. After completion of the reaction, THF was evaporated, extracted with $CHCl_3$ (2 × 75 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 5: 95) to afford **5** (5.10 g, 93%) as a yellow oil. $[\alpha]_D^{25} = +49.5$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3405, 2925, 2874, 1719, 1643, 1555, 1394, 1275, 1211, 1066, 933, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.41 (s, 3H), 3.75 (t, *J* = 5.85, 7.30 Hz, 1H), 3.84–3.93 (m, 1H), 4.01–4.17 (m, 2H), 4.36–4.65 (m, 2H), 5.30–5.42 (m, 2H), 5.75–5.92 (m, 1H); 7.24–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.14, 26.38, 65.77, 70.37, 77.65, 80.85, 109.53, 119.42, 127.44, 127.63, 128.18, 135.10, 137.89; MS-EIMS: *m/z* 271.2 $(M+Na)^+$.

4.5. (2*R*,3*S*)-3-(Benzyloxy)-4-pentene-1,2-diol 6

Compound **5** (4.8 g, 19.35 mmol) was dissolved in THF/H_2O (9:1; 30 mL) and was treated with trifluoroacetic acid (2.87 mL, 38.70 mmol) at 0 °C and further stirred for 4 h at room temperature. After completion of the reaction, the reaction mixture was quenched with aqueous sodium bicarbonate solution, THF was evaporated, extracted with EtOAc (2 × 60 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 3:7) to afford **6** (3.38 g, 84%) as a syrup. $[\alpha]_D^{25} = +54.5$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3412, 2965, 2931, 2877, 1718, 1274, 1068, 1022, 700; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.13–2.23 (br s, 1H), 2.57–2.62 (br s, 1H), 3.53–3.75 (m, 3H), 3.84–3.95 (m, 1H), 4.31–4.67 (m, 2H), 5.27–5.44 (m, 2H), 5.70–5.92 (m, 1H) 7.24–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.17, 70.47, 73.35, 81.75, 119.73, 127.59, 127.69, 128.28, 134.95, 137.85; MS-EIMS: *m/z* 231.1 $(M+Na)^+$.

4.6. (2*R*,3*S*)-3-(Benzyloxy)-1-[1-methyl-1-(1,1,1-trimethylsilyl)ethoxy]-4-penten-2-ol 7

To a cooled (0 °C) solution of **6** (3.2 g, 15.38 mmol) in CH_2Cl_2 (35 mL), imidazole (1.56 g, 23.07 mmol) was added followed by TBDMSCl (2.32 g, 15.38 mmol) and stirred for 4 h at room temperature. The reaction mixture was treated with 20 mL of saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (2 × 30 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 15:85) to afford **7** (4.06 g, 82%) as a liquid. $[\alpha]_D^{25} = +26.5$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3471, 2954, 2930, 2858, 1466, 1254, 1110, 1069, 838, 776, 698; ^{1}H NMR (300 MHz, $CDCl_3$): 0.10 (s, 6H), 0.92 (s, 9H), 2.30 (br s, 1H), 3.66–3.72 (m, 3H), 3.81–3.85 (m, 1H), 4.37–4.66 (m, 2H), 5.31–5.41 (m, 2H), 5.82–5.94 (m, 1H), 7.26–7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): −5.44, 18.2, 25.82, 63.45, 70.33, 73.32, 80.62, 119.58, 127.53, 127.73, 128.29, 135.25, 138.20; MS-EIMS: *m/z* 345.8 $(M+Na)^+$.

4.7. (2*R*,3*S*)-2,3-Ddi(benzyloxy)-4-penten-1-ol 8

To a stirred solution of the compound **7** (3.8 g, 11.80 mmol) in dry THF (40 mL), sodium hydride (0.56 g, 23.60 mmol), benzyl bromide (1.40 mL, 11.80 mmol) and TBAI (catalytic amount) were added at 0 °C and stirred at room temperature for 6 h. After completion of the reaction, the THF was evaporated, extracted with $CHCl_3$ (2 × 30 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude **8**. This was dissolved in dry THF, cooled to 0 °C and TBAF (19.56 mL, 19.56 mmol, 1 M in THF) was added slowly. The reaction mixture was stirred for 1 h at room temperature. After completion of the reaction, the reaction mixture was quenched with water, THF was evaporated, extracted with $CHCl_3$ (2 × 25 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 1:3) to afford **9** (2.50 g, 85% from two steps) as a liquid. $[\alpha]_D^{25} = +60.4$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3456, 2954, 2930, 2858, 1466, 1254, 1110, 1069, 838, 777, 698; ^{1}H NMR (300 MHz, $CDCl_3$): 2.04 (br s, 1H), 3.51–3.56 (m, 1H), 3.71–3.73 (m, 2H), 3.93–3.98 (m, 1H), 4.41–4.70 (m, 4H), 5.33–5.39 (m, 2H), 5.82–5.94 (m, 1H), 7.25–7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): 61.84, 70.54, 72.61, 73.31, 80.68, 119.25, 127.55, 127.59, 127.64, 127.70, 127.84, 128.33, 134.91, 135.5, 138.06; MS-EIMS: *m/z* 321.0 $(M+Na)^+$.

4.8. (4*R*,5*R*,6*S*)-5,6-Di(benzyloxy)-7-octen-4-ol 9

To a stirred solution of oxalyl chloride (0.87 mL, 10.06 mmol), in dry CH_2Cl_2 (20 mL), DMSO (1.42 mL, 20.12 mmol), was added at −78 °C and stirred at the same temperature for 30 min. Compound **9** (1.5 g, 5.03 mmol) in dry CH_2Cl_2 (10 mL), was added at −78 °C to the reaction mixture and stirred for 2 h at the same temperature. DIPEA (3.05 mL, 20.08 mmol) was added at −78 °C and the reaction mixture was allowed to warm room temperature for 30 min. The reaction mixture was diluted with water (20 mL) and extracted with $CHCl_3$ (2 × 25 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude aldehyde as a yellow syrup. The crude aldehyde was dissolved in toluene (20 mL) and was cooled to −78 °C. To this *n*-propyl magnesium chloride (8.78 mL, 17.56 mmol, 2 M in di ethyl ether) was added slowly and stirred at the same temperature for 3 h. After completion of the reaction, the reaction mixture was treated with saturated aqueous NH_4Cl solution (20 mL) and extracted with CH_2Cl_2 (2 × 30 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 10:90) to afford **10** (0.92 g, 62%) as a yellow liquid. $[\alpha]_D^{28} = +62.1$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3423, 3015, 2987, 1455, 1378, 1085 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (t, *J* = 6.7 Hz, 3H), 1.36 (m, 2H), 1.52 (m, 2H), 3.39 (t, *J* = 11.5, 5.6 Hz, 1H), 3.69 (br s, 1H), 3.99 (t, *J* = 13.0, 6.6 Hz, 1H), 4.42 (q, *J* = 11.8 Hz, 2H), 4.69 (q, *J* = 11.7 Hz, 2H), 5.34 (m, 2H), 5.92 (m, 1H), 7.26 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): 14.6, 18.7, 34.7, 70.2, 72.3, 74.1, 81.8, 83.7, 119.3, 127.60, 127.62, 127.7, 127.9, 128.2, 128.3, 135.9, 137.9, 138.2; MS-EIMS: *m/z* 363.1 $(M+Na)^+$.

4.9. 2-[(1*R*,2*S*,3*S*)-2,3-Di(benzyloxy)-1-propyl-4-pentenyl]oxy-1,6-heptadiene 10

To a stirred solution of the compound **10** (0.7 g, 2.06 mmol) in dry CH_2Cl_2 (15 mL), DCC (0.84 g, 4.12 mmol), 1-hexenoic acid (0.244 mL, 2.06 mmol) and DMAP (catalytic amount) were added at 0 °C and stirred at room temperature for 3 h. After completion of the reaction, the reaction mixture was filtered through Celite and extracted with CH_2Cl_2 (2 × 20 ml), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 4:96) to afford **11** (0.73 g, 81%) as a liquid. $[\alpha]_D^{28} = +68.2$ (*c* 1.1, $CHCl_3$); IR (neat): γ_{max}: 3067, 2959, 2931, 2871, 1735, 1455, 1170, 1096, 915, 738, 698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.84 (t, *J* = 15.1, 7.5 Hz, 3H), 1.15–1.32 (m, 2H), 1.44–1.71 (m, 4H), 2.05 (m, 2H), 2.19 (m, 2H), 3.58 (t, *J* = 9.8, 4.5 Hz, 1H), 3.75 (t, *J* = 13.5, 6.04 Hz, 1H), 4.46 (m, 4H), 4.98 (m,

2H), 5.09 (m, 1H), 5.30 (m, 2H), 5.79 (m, 2H), 7.26 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): 13.8, 18.6, 23.9, 31.2, 32.9, 33.6, 69.9, 73.5, 73.9, 80.0, 82.0, 115.2, 119.6, 127.4, 127.7, 127.8, 128.0, 128.1, 128.2, 135.2, 137.5, 138.1, 138.3, 172.7; MS-EIMS: *m/z* 459.25 $(M+Na)^+$.

4.10. (8*S*,9*S*,10*R*)-8,9-Di-(benzyloxy)-10-propyl-3,4,5,8,9,10-hexahydro-2*H*-2-oxecinone 12

Second generation Grubbs' catalyst (0.194 g, 0.23 mmol) was added to a solution of diene ester **11** (0.5 g, 1.14 mmol) in degassed anhydrous benzene (1000 mL) and the mixture was heated under an Ar flow for 12 h. After completion of the reaction, most of the solvent was evaporated and then air was bubbled in order to favour catalyst decomposition. The remaining solvent was evaporated under reduced pressure, affording a dark brown oily residue which was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 5:95) to afford **12**(0.29 g, 62%) as a liquid. $[\alpha]_D^{28} = +43.2$ (*c* 1.0) 3069, 2970, 2871, 1738, 1450, 1170, 1080, 925, 730, 695 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.81 (t, *J* = 7.23 Hz, 3H), 1.23–1.27 (m, 4H), 1.61–1.87 (m, 2H), 1.94–2.41(m, 4H), 3.75–3.78 (m, 2H), 4.24–4.64 (dd, 2H) 4.81 (d, 1H), 4.92–4.95 (dd, 1H), 5.06 (d, 1H), 5.46–5.55 (m, 1H), 5.88 – 5.97 (dd, *J* = 15.6 Hz, 1H), 7.27–7.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): 13.85, 18.46, 26.21, 33.61, 33.98, 34.49, 69.10, 73.36, 74.85, 79.70, 84.10, 127.23, 127.31, 127.52, 128.07, 128.21, 128.75, 129.18, 135.14, 138.49, 138.67, 178.46, MS-EIMS: *m/z* 431.2 $(M+Na)^+$.

4.11. (8*S*,9*S*,10*R*)-8,9-Dihydroxy-10-propyl-3,4,5,8,9,10-hexahydro-2*H*-2-oxecinone 1

To a stirred solution of **12** (0.16 g, 0.39 mmol) in dry CH_2Cl_2 (10 mL), $TiCl_4$ (0.086 mL, 0.78 mmol), was added at 0 °C for 15 min. After completion of the reaction, it was taken into dichloromethane, washed with saturated aqueous sodium bicarbonate (10 mL) and water (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 60–120 mesh, EtOAc–hexane 20:80) to afford the desired compound **1** as a colourless low melting solid (0.073 g, 82%). $[\alpha]_D^{28} = +10.6$ (*c* 1.1, EtOH); IR (neat): γ_{max}: 3285, 2927, 2869, 1728, 1455, 1208, 1090 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.5 Hz, 3H), 1.25–1.42 (m, 2H), 1.52–1.63 (m, 2H), 1.83–2.05 (m, 3H), 2.35 (m, 3H), 3.49 (d, *J* = 9.8 Hz, 1H) 4.41 (br s, 1H), 4.93 (td, *J* = 9.8, 2.3 Hz, 1H), 5.45–5.55 (m, 1H), 5.63 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 13.8, 17.9, 24.6, 29.3, 33.3, 33.6, 70.1, 73.2, 73.5, 124.5, 130.7, 176.3; MS-EIMS: *m/z* 251 $(M+Na)^+$.

Acknowledgements

The authors P.V.R. and S.P.R. wish to thank UGC and CSIR, New Delhi for the award of research fellowships.

References

1. For a review on synthetic, biosynthetic, and pharmacological aspects of decanolides, see: Dräger, G.; Kirschning, A.; Thiericke, R.; Zerlin, M. *Nat. Prod. Rep.* **1996**, *13*, 365–375.
2. (a) Rivero-Cruz, J. F.; Macias, M.; Gerda-Garcia-Rojas, C. M.; Mata, R. *J. Nat. Prod.* **2003**, *66*, 511–514; (b) Rivero-Cruz, J. F.; Macias, M.; Gerda-Garcia-Rojas, C. M.; Mata, R. *Tetrahedron* **2000**, *56*, 5337–5344.
3. Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. *Org. Lett.* **2001**, *3*, 3479–3481.
4. Arnone, A.; Assante, G.; Montorsi, M.; Nasini, G.; Ragg, E. *Gazz. Chim. Ital.* **1993**, *123*, 71–73.
5. (a) Grabley, S.; Granzer, E.; Hütter, K.; Ludwig, D.; Mayer, M.; Thiericke, R.; Till, G.; Wink, J.; Phillips, S.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 56–60; (b) Hütter, K.; Thiericke, R.; Kirsch, R.; Kluge, H.; Göhrt, A.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 66–73; (c) Hütter, K.; Thiericke, R.; Kirsch, R.; Kluge, H.; Grabley, S.; Hammann, P.; Mayer, M.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 1176–1181; (d) Ayer, W. A.; Sun, M.; Browne, L. M.; Brinen, L. S.; Clardy, J. *J. Nat. Prod.* **1992**, *55*, 649–653.
6. Mata, R.; Macias, M. L.; Rojas, I. S.; Lotina-Hennsen, B.; Toscano, R. A.; Anaya, L. A. *Phytochemistry* **1998**, *49*, 441–449.
7. (a) Fürstner, A.; Radkowski, K. *Chem. Commun.* **2001**, 671–672; (b) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, W. C.; Mynott, R. *J. Am. Chem. Soc.* **2002**, *124*, 7061–7069; (c) Sabino, A. A.; Pilli, R. A. *Tetrahedron Lett.* **2002**, *43*, 2819–2821; (d) Diez, E.; Dixon, D. J.; Ley, S. V.; Polara, A.; Rodriguez, F. *Helv. Chim. Acta* **2003**, *86*, 3717–3729; (e) Gurjar, M. K.; Karmakar, S.; Mohapatra, D. K. *Tetrahedron Lett.* **2004**, *45*, 4525–4526; (f) Nanda, S. *Tetrahedron Lett.* **2005**, *46*, 3661–3663; (g) Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V.; Mohapatra, D. K. *Arkivoc* **2005**, *3*, 237–257; (h) Salaskar, A.; Sharma, A.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2006**, *17*, 325–329; (i) Boruwa, J.; Gogoi, N.; Barua, N. C. *Org. Biomol. Chem.* **2006**, *4*, 3521–3525; (j) Gupta, P.; Kumar, P. *Tetrahedron: Asymmetry* **2007**, *18*, 1688–1692; (k) Nagaiah, K.; Sreenu, D.; Rao, S. S.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 7173–7176; (l) Yadav, J. S.; Kumar, V. N.; Rao, R. S.; Srihari, P. *Synthesis* **2008**, 1938–1942; (m) Yadav, J. S.; Ather, H.; Gayathri, K. U.; Rao, N. V.; Prasad, A. R. *Synthesis* **2008**, 3945–3950.
8. (a) Kamal, A.; Krishnaji, T.; Reddy, P. V. *Tetrahedron: Asymmetry* **2007**, *18*, 1775–1779; (b) Kamal, A.; Krishnaji, T.; Reddy, P. V. *Tetrahedron Lett.* **2007**, *48*, 7232–7235; (c) Kamal, A.; Krishnaji, T.; Khanna, G. B. R. *Tetrahedron Lett.* **2006**, *47*, 8657–8660; (d) Kamal, A.; Shaik, A. A.; Sandbhor, M.; Malik, M. S.; Kaga, H. *Tetrahedron Lett.* **2004**, *43*, 8057–8059; (e) Kamal, A.; Khanna, G. B. R.; Ramu, R.; Krishnaji, T. *Tetrahedron Lett.* **2003**, *44*, 4783–4787.
9. (a) Wu, W.; Wu, Y. *J. Org. Chem.* **1993**, *58*, 3586–3588; (b) Reddy, J. S.; Kumar, A. R.; Rao, V. B. *Tetrahedron: Asymmetry* **2005**, *16*, 3154–3159.
10. (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2002**, *39*, 3012–3043; (b) Liu, D.; Kozmin, S. S. *Org. Lett.* **2002**, *4*, 3005–3007; (c) Murga, J.; Falomir, E.; Garica-Fortanet, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2002**, *4*, 3447; (d) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826–2830; (e) Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V. *Tetrahedron Lett.* **2003**, *44*, 2873–2875; (f) Davoli, P.; Spaggiari, A.; Castagnetti, L.; Prati, F. *Org. Biomol. Chem.* **2004**, *2*, 38–47; (g) Dieters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238; (h) Chavan, S. P.; Praveen, C. *Tetrahedron Lett.* **2005**, *46*, 1939–1941; (i) Davoli, P.; Fava, R.; Morandi, S.; Spaggiari, A.; Prati, F. *Tetrahedron* **2005**, *61*, 4427–4436; (j) Garica-Fortanet, J.; Murga, J.; Falomir, E.; Carda, M.; Marco, J. A. *J. Org. Chem.* **2005**, *70*, 9822–9827; (k) Sharma, G. V. M.; Cherukupalli, G. R. *Tetrahedron: Asymmetry* **2006**, *17*, 1081–1088; (l) Gradillas, A.; Perez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086–6101; (m) Ghosh, S.; Rao, R. V. *Tetrahedron Lett.* **2007**, *48*, 6937–6940.
11. Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346–1353.