A Convergent Synthesis of a Twelve-Membered Macrolide Natural Product, (6*R*,12*S*)-6-Hydroxy-12-methyl-1-oxacyclododecane-2,5-dione

by **Palakodety Radha Krishna*** and **Pendyala Venkata Arun Kumar**

D-211, Discovery Laboratory, Organic & Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500607, India
(phone: +91-40-27193158; fax: +91-40-27160387; e-mail: prkgenius@iict.res.in)

A new polyketide metabolite, the twelve-membered macrolide **1**, isolated from the endophytic fungal strain *Cladosporium tenuissimum* LR 463 of *Maytenus hookeri*, whose structure had been determined as (6*R*,12*S*)-6-hydroxy-12-methyl-1-oxacyclododecane-2,5-dione, was synthesized for the first time by a convergent strategy *via Yamaguchi* esterification of **2** with **3** and ring-closing metathesis (RCM) to afford the cyclic ester **1** that was eventually transformed to the target molecule. However, the total synthesis revealed that the assigned structure of the natural product is not correct.

Introduction. – Endophytic fungi constitute an important source of biologically active chemical compounds with significant pharmacological activity, which can be further employed as lead compounds. *Colletotrichum magna*, a non-pathogenic endophytic fungus, on inoculation of watermelon and cucumber seedlings, rapidly induces systematic defense responses which include the production of peroxidase, phenylalanine ammonia-lyase, lignin, and salicylic acid. A hexaketide lactone **1** was isolated [1] along with the known cladospolides (cladospolides A and B, and isocladospolide B) from the fermented strain *Cladosporium tenuissimum* LR 463 of *Maytenus hookeri*. As part of our interest in the synthesis of bioactive natural products [2], here we report the synthesis of **1** (*Fig.*) by a convergent strategy. Structurally, this natural product bears close resemblance to cladospolides [3]. Our strategy involves the esterification of the respective acid component and alcohol moiety under *Yamaguchi* conditions, followed by the *Grubbs*' catalyst-mediated ring-closing metathesis (RCM) to afford the cyclic ester. The cyclic ester was transformed to the target macrolide.

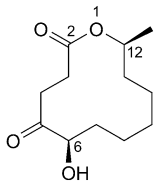
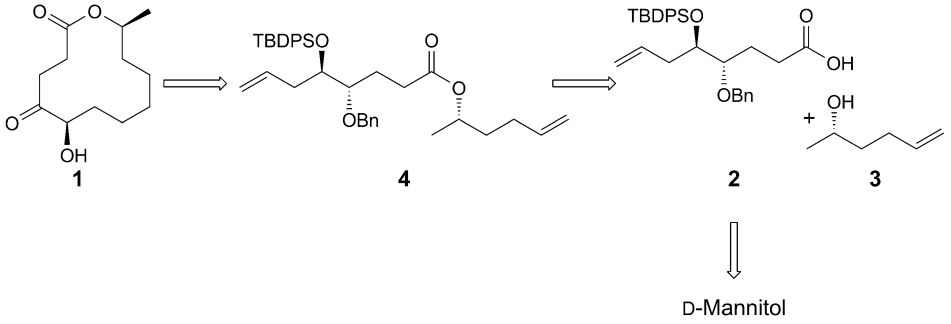


Figure. *Proposed structure of the natural product (6*R*,12*S*)-6-hydroxy-12-methyl-1-oxacyclododecane-2,5-dione*

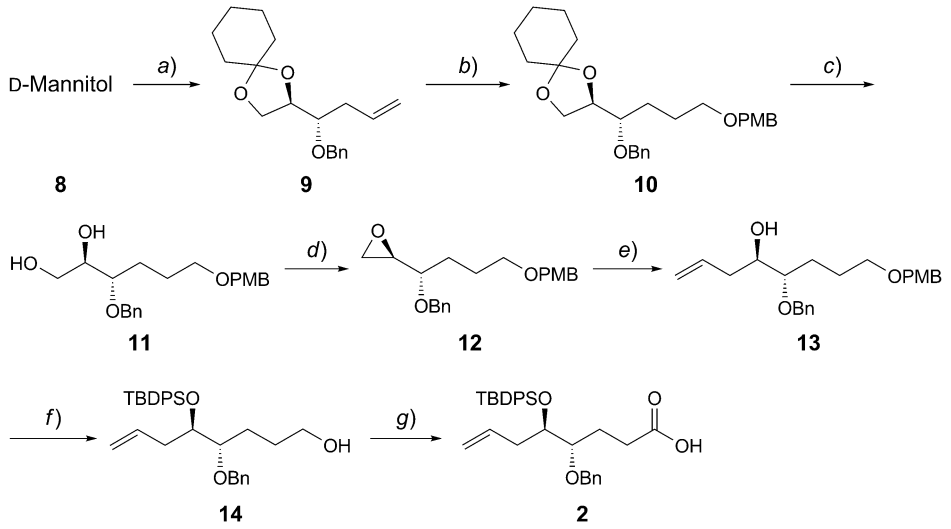
Interesting structural features coupled with the biological activity of the isolated natural product has attracted us to embark on its first total synthesis. Here, we report our synthetic efforts *en route* to **1** achieved through the respective key intermediates **2** and **3** (*Scheme 1*).

Scheme 1. *Retrosynthetic Scheme*



As depicted in *Scheme 2*, the synthesis of fragment **2** was initiated with the preparation of **9** [4] from D-mannitol. Then, the corresponding primary alcohol was generated by hydroboration of **9** with cyclohexene, $BH_3 \cdot Me_2S$, THF at 0° in 87% yield, followed by its conversion into *para*-methoxybenzyl (PMB)-ether with PMB-Br and NaH in THF at 0° to afford **10** in 85% yield. Diol **11** was formed from **10** by the deprotection of the acetal group with 60% aqueous AcOH at room temperature in 70% yield. The primary OH group of the diol **11** was protected with Ts group ($TsCl/Et_3N/CH_2Cl_2$/0°/room temperature, 72%), leading to oxirane **12** (69%) upon treatment with K_2CO_3 in MeOH.

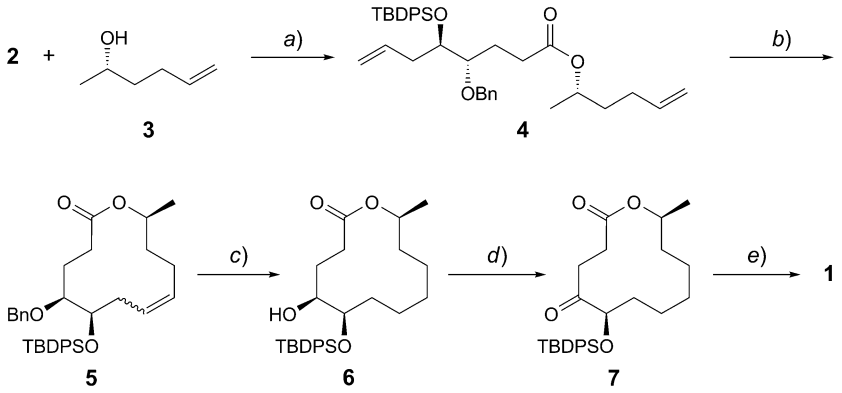
Scheme 2. *Synthesis of Fragment* **2**



a) See [4]. *b*) 1. $BH_3 \cdot Me_2S$, cyclohexene/THF, 0° to r.t., 3 h; 2. NaOH, 30% H_2O_2, 2 h; 87%; 3. PMB-Br (= *para*-methoxybenzyl bromide), NaH, THF, 0°, 6 h; 85%. *c*) 60% AcOH, r.t., 12 h; 70%. *d*) 1. Et_3N, TsCl, CH_2Cl_2, 0° to r.t., 4 h; 72%; 2. K_2CO_3/MeOH, r.t., 1 h; 69%. *e*) CuI, VinylMgBr, THF, −20°, 1 h; 87%. *f*) 1. (^{t}Bu)Ph_2SiCl (TBDPS-Cl), 1*H*-imidazole, CH_2Cl_2, 0° to r.t., 12 h, 92%; 2. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), CH_2Cl_2/H_2O, 19:1; 87%. *g*) 1. $(COCl)_2$/DMSO, Et_3N, CH_2Cl_2, −78°, 1 h; 89%; 2. $NaClO_2$, $NaH_2PO_4 \cdot 2\,H_2O$, ^{t}BuOH, 2-methylbut-2-ene, 0° to r.t., 2 h; 79%.

Ring-opening reaction of oxirane **12** with vinylmagnesium bromide [5] in the presence of CuI in THF at $-20°$ gave homoallylic alcohol **13** (87%). Silyl protection of **13** ((^{t}Bu)Ph_2SiCl (TBDPS-Cl)/1*H*-imidazole/CH_2Cl_2; 92%), followed by the removal of the PMB group under conventional conditions (DDQ in CH_2Cl_2/H_2O, 19:1) furnished **14** in 87% yield. Oxidation of the latter to the corresponding aldehyde (89%) under *Swern* conditions, followed by a second oxidation [6] with $NaClO_2$, $NaH_2PO_4 \cdot 2\,H_2O$ in *t*-BuOH and 2-methylbut-2-ene gave the acid **2** (79%). As outlined in *Scheme 3*, the coupling of the two fragments **2** and (2*S*)-hex-5-en-2-ol (**3**; commercially available) *via Yamaguchi* esterification [7] (Et_3N/2,4,6-trichlorobenzoyl chloride/DMAP/THF/0°) gave **4** (69%). Subsequently, the *Grubbs*' catalyst [8] mediated RCM (G-II/CH_2Cl_2/reflux) of compound **4** afforded the cyclic ester **5** (80%) as (*E*)/(*Z*)-mixture in a ratio of 34:66. However, no efforts were made to separate the geometrical isomers, since the presence of the mixture bears little relevance in the later part of the synthesis.

Scheme 3. *Synthesis of the Target Compound* **1**



a) 1. 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF, 0° to r.t., 4 h; 2. 4-(dimethylamino)pyridine (DMAP), toluene, 0° to r.t., 2 h; 69%. *b*) *Grubbs*-II, CH_2Cl_2, reflux, 5 h; 80%. *c*) H_2, Pd/C, MeOH, r.t., 12 h; 84%. *d*) *Dess–Martin* periodinane, CH_2Cl_2, 0° to r.t., 2 h; 89%. *e*) HF-pyridine/THF, r.t., 12 h; 86%.

Hence, removal of the Bn group as well as the hydrogenation of the C=C bond (10% Pd-C/H_2/r.t.) was carried out in one-pot to produce **6** (84%). Hydroxy compound **6** was then oxidized using *Dess–Martin* periodinane [9] at 0° to give **7** (89%), and subsequent removal of the TBDPS group by HF-pyridine in THF afforded compound **1** (86%; white solid, m.p. 119–121°; $[\alpha]_D^{19} = +37.2$ ($c = 0.3$, MeOH; [1]: $[\alpha]_D^{19} = -39.5$ ($c = 0.57$, MeOH)). However, the spectroscopic data of **1** (^{1}H- and ^{13}C-NMR) differed from the reported data of the natural product, and, in addition, the optical rotation value ($[\alpha]_D^{19}$) of the synthetic sample **1** shows the opposite sign of rotation than the reported value. Therefore, the structure of macrolide **1** was erroneously assigned and hence a structural revision is needed for the natural product.

In summary, the stereoselective total synthesis of the twelve-membered macrolide natural product was attempted by a convergent strategy wherein oxirane ring-opening reaction, *Yamaguchi* esterification, and ring-closing metathesis were the key steps. The

mismatched spectroscopic data revealed that the structure was erroneously assigned, and hence structural revision was necessary.

Experimental Part

General. Reactions were carried out under N_2 in anh. solvents such as CH_2Cl_2 and THF. All reactions were monitored by TLC (silica-coated plates; visualizing with α-napthol charring). Org. solns. were dried (Na_2SO_4) and concentrated below 40° under reduced pressure in a *Büchi* rotary evaporator. All column chromatographic (CC) separations were performed using silica gel (SiO_2; *Acme*'s, 60–120 mesh) with AcOEt and hexane as eluents. TLC was performed on *Merck 60 F_{254}* silica gel plates. Yields refer to chromatographically and spectroscopically (^{1}H- and ^{13}C-NMR) homogeneous material. Air-sensitive reagents were transferred by syringe and double-ended needle. Optical rotations: *JASCO P-1020* instrument; $[\alpha]_D$ values in units of 10^{-1} deg cm^2 g^{-1} at 25°. IR Spectra: *Perkin-Elmer IR-683* spectrophotometer with NaCl optics. ^{1}H- and ^{13}C-NMR: *Varian Gemini 200 MHz*, *Bruker Avance-300 MHz*, *Unity 400 MHz*, and *Inova 500 MHz* for ^{1}H, and *Varian Gemini FT-200 MHz* and *Bruker Avance 300 MHz* spectrometers for ^{13}C at 50 MHz and 75 MHz, resp., with 7–10 mM solns. in $CDCl_3$, TMS as internal standard; *J* values are given in Hz. MS: *Finnigan Mat 1210* double focusing mass spectrometer operating at a direct inlet system; ESI-MS was recorded with ion-trap mass spectrometer.

*4-*O*-Benzyl-5,6-*O*-(cyclohexane-1,1-diyl)-2,3-dideoxy-1-*O*-(4-methoxybenzyl)-*D*-erythro-hexitol* (**10**). To a stirred soln. of cyclohexene (2.65 g, 32.5 mmol) in dry THF (20 ml), $BH_3 \cdot Me_2S$ (1.45 ml, 16.2 mmol) was added at 0°, and the mixture was stirred for 2 h to form a white solid. Then, compound **9** (1.64 g, 5.4 mmol) in dry THF (10 ml) was added at 0°, and then the mixture was stirred for 3 h. Afterwards, MeOH (1.2 ml, 27.08 mmol) was added to the mixture, followed by the addition of 2N NaOH (16.7 ml), 30% H_2O_2 (4.9 ml), and then stirred for 2 h. The mixture was diluted with AcOEt (50 ml). The org. layer was washed with H_2O (2 × 20 ml) and brine (20 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (SiO_2, 60–120 mesh; 22% AcOEt/hexane) to afford a yellow oil (1.51 g, 87%).

This yellow oil (1.48 g, 4.6 mmol) in dry THF (10 ml) was added to a suspension of NaH (0.28 g, 6.9 mmol) in THF (3 ml) under N_2 at 0°, and the mixture was stirred for 30 min. To this, a soln. of PMB-Br (1.10 g, 5.54 mmol) in dry THF (5 ml) was added, and the mixture was stirred for 6 h at r.t. The reaction was quenched with sat. aq. NH_4Cl soln. (5 ml), and the mixture was extracted with AcOEt (2 × 30 ml). The org. layer was washed with H_2O (2 × 30 ml) and brine (30 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (SiO_2, 60–120 mesh; 10% AcOEt/hexane) to afford **10** (1.73 g, 85%). Yellow oil. $[\alpha]_D^{25} = +15.8$ ($c = 1.5$, $CHCl_3$). IR (neat): 3049, 2988, 1634, 1282, 1114, 1062, 739, 702. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.29–7.26 (*m*, 7 arom. H); 6.78 (*d*, *J* = 8.3, 2 arom. H); 4.56 (*AB*, *J* = 11.7, 2 H); 4.37 (br. *s*, 2 H); 4.00 (*quint.*, *J* = 6.0, CH_2O); 3.82 (*t*, *J* = 6.7, CH–O); 3.76 (*s*, MeO); 3.52–3.47 (*m*, CH–O); 3.42–3.30 (*m*, 2 CH–O); 1.73–1.55 (*m*, 6 CH_2); 1.38 (*s*, CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 138.5; 130.5; 129.1; 128.2; 127.7; 127.4; 113.6; 109.4; 78.7; 77.4; 72.7; 72.3; 69.8; 65.8; 55.1; 36.1; 34.8; 27.8; 25.2; 25.1; 23.9; 23.7. ESI-MS: 463 ($[M + Na]^+$). HR-MS: 463.2475 ($[M + Na]^+$, $C_{27}H_{36}NaO_5^+$; calc. 463.2460).

*(2*R*,3*S*)-3-(Benzyloxy)-6-[(4-methoxybenzyl)oxy]hexane-1,2-diol* (=*4-*O*-Benzyl-2,3-dideoxy-1-*O*-(4-methoxybenzyl)-*D*-erythro-hexitol*; **11**). To **10** (1.70 g, 3.8 mmol), 60% aq. AcOH (15 ml) was added at r.t., and the mixture was stirred for 12 h. After completion of reaction, the reaction was quenched with solid $NaHCO_3$, and the mixture was extracted with AcOEt (3 × 50 ml). The solvent was evaporated *in vacuo* and purified by CC (SiO_2, 60–120 mesh; 40% AcOEt/hexane) to afford **11** (0.96 g, 70%). Colorless liquid. $[\alpha]_D^{25} = +27.8$ ($c = 0.9$, $CHCl_3$). IR (neat): 3446, 2924, 1611, 1245, 1174, 1064, 741, 699. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.32–7.14 (*m*, 7 arom. H); 6.77 (*d*, *J* = 8.8, 2 arom. H); 4.48 (br. *s*, 2 H); 4.34 (br. *s*, 2 H); 3.74 (*s*, MeO); 3.66–3.51 (*m*, 3 CH–O); 3.51–3.34 (*m*, 3 CH–O); 3.15 (br. *s*, OH); 1.74–1.55 (*m*, 2 CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 138.1; 130.2; 129.2; 128.3; 127.7; 113.6; 80.3; 72.5; 72.3; 69.8; 63.4; 55.1; 26.6; 25.1. ESI-MS: 383 ($[M + Na]^+$). HR-MS: 383.1816 ($[M + Na]^+$, $C_{21}H_{28}NaO_5^+$; calc. 383.1834).

*5,6-Anhydro-4-*O*-benzyl-2,3-dideoxy-1-*O*-(4-methoxyphenyl)-*D*-erythro-hexitol* (**12**). To a stirred soln. of **11** (0.93 g, 2.58 mmol) in CH_2Cl_2 (20 ml), Et_3N (0.72 ml, 5.18 mmol) was added at 0°, and the

mixture was stirred for 0.5 h. Then, TsCl (0.49 g, 2.16 mmol) was added, and the soln. was stirred for 4 h at r.t. Then, the mixture was diluted with CH_2Cl_2 (20 ml), and washed with H_2O (20 ml) and brine (20 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (SiO_2, 60–120 mesh; 20% AcOEt/hexane) to afford a pale yellow oil (0.96 g, 72%). Then, the yellow oil (0.93 g, 1.81 mmol) was dissolved in MeOH (10 ml), and K_2CO_3 (0.48 g, 0.32 mmol) was added at r.t., and the mixture was stirred for 1 h. After consumption of all the starting material, the reaction was quenched with NH_4Cl soln. (3 ml), MeOH was evaporated under reduced pressure, the residue was extracted with AcOEt (4 × 3 ml), and washed with H_2O (5 ml) and brine (5 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (SiO_2, 60–120 mesh; 18% AcOEt/hexane) to afford **12** (0.43 g, 69%). Colorless liquid. $[\alpha]_D^{25} = -17.3$ ($c = 0.8$, $CHCl_3$). IR (neat): 3049, 2955, 1618, 1250, 1104, 1062, 741, 701. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.26–7.16 (*m*, 7 arom. H); 6.82 (*d*, *J* = 8.4, 2 arom. H); 4.62 (*AB*, *J* = 11.7, 1 H of O–CH_2–Ph); 4.42 (*AB*, *J* = 11.7, 1 H of O–CH_2–Ph); 4.37 (br. *s*, 2 H); 3.78 (*s*, MeO); 3.39 (*t*, *J* = 5.1, 2 CH–O); 3.28–3.23 (*m*, CH–O); 2.88–2.83 (*m*, 1 H, epoxy); 2.73–2.63 (*m*, 2 H, epoxy); 1.84–1.56 (*m*, 2 CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.0; 138.4; 130.5; 129.1; 128.2; 127.6; 113.6; 77.6; 72.4; 72.2; 69.7; 55.2; 53.4; 45.4; 29.4; 25.4. ESI-MS: 365 ($[M + Na]^+$). HR-MS: 365.1742 ($[M + Na]^+$, $C_{21}H_{26}NaO_4^+$; calc. 365.1729).

*(4*R*,5*S*)-5-(Benzyloxy)-8-[(4-methoxybenzyl)oxy]oct-1-en-4-ol* (**13**). To a stirred soln. of **12** (0.4 g, 1.18 mmol) in dry THF (5 ml), CuI (0.2 g, 1.18 mmol) was added, and the mixture was stirred for 10 min. A 1M soln. of vinylmagnesium bromide (1.77 ml, 1.77 mmol) was added at −20°, and the mixture was stirred for 1 h. The reaction was quenched with sat. aq. NH_4Cl, the mixture was extracted with AcOEt, and the org. layer was washed with H_2O (5 ml), followed by brine (5 ml). The combined org. layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC (SiO_2, 60–120 mesh; 20% AcOEt/hexane) to afford **13** (0.38 g, 87%). Colorless liquid. $[\alpha]_D^{25} = +1.4$ ($c = 0.2$, $CHCl_3$). IR (neat): 3450, 3051, 2934, 1627, 1584, 1263, 1106, 1053, 740, 698. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.35–7.17 (*m*, 7 arom. H); 6.79 (*d*, *J* = 8.4, 2 arom. H); 5.92–5.71 (*m*, CH_2=C*H*); 5.16–5.05 (*m*, CH_2=CH); 4.53 (br. *s*, 2 H); 4.38 (br. *s*, 2 H); 3.78 (*s*, MeO); 3.73 (*t*, *J* = 4.4, CH–O); 3.42–3.38 (*m*, 3 CH–O); 2.23 (*t*, *J* = 7.7, CH_2=CH–CH_2); 1.97 (br. *s*, OH); 1.81–1.57 (*m*, 2 CH_2). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.0; 138.3; 134.9; 130.5; 129.2; 128.3; 127.8; 127.6; 117.6; 113.7; 81.3; 72.5; 72.0; 71.1; 69.9; 55.2; 36.9; 25.6; 25.5. ESI-MS: 393 ($[M + Na]^+$). HR-MS: 393.2036 ($[M + Na]^+$, $C_{23}H_{30}NaO_4^+$; calc. 393.2042).

*(4*S*,5*R*)-4-(Benzyloxy)-5-{[(*tert*-butyl)(diphenyl)silyl]oxy}oct-7-en-1-ol* (**14**). To a stirred soln. of **13** (0.35 g, 0.94 mmol) in CH_2Cl_2 (3.5 ml), 1*H*-imidazole (0.19 g, 2.82 mmol) was added at 0°, and the mixture was stirred for 0.5 h, then TBDPS-Cl (0.29 ml, 1.12 mmol) was added, and the mixture was stirred for 12 h at r.t. The mixture was diluted with CH_2Cl_2 (4 ml), and the org. layer was washed with H_2O (10 ml), followed by brine (10 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (SiO_2, 60–120 mesh; 5% AcOEt/hexane) to afford a colorless liquid (0.53 g, 92%). This liquid was dissolved (0.5 g, 0.82 mmol) in a CH_2Cl_2/H_2O 19:1 (5 ml), DDQ (0.22 g, 0.98 mmol) was added at 0°, and the soln. was stirred for 20 min at r.t. The reaction was quenched with sat. $NaHCO_3$ soln. (5 ml), and the mixture was extracted with CH_2Cl_2 (3 × 15 ml), and washed with H_2O (5 ml) and brine (5 ml). The combined org. layers were dried (Na_2SO_4), evaporated *in vacuo*, and purified by CC (SiO_2, 60–120 mesh; 12% AcOEt/hexane) to afford **14** (0.35 g, 87%). Colorless liquid. $[\alpha]_D^{25} = -11.8$ ($c = 0.3$, $CHCl_3$). IR (neat): 3448, 2951, 2857, 1618, 1595, 1216, 1104, 1064, 699. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.72–7.62 (*m*, 4 arom. H); 7.39–7.16 (*m*, 11 arom. H); 5.68–5.47 (*m*, CH_2=C*H*); 4.96–4.80 (*m*, CH_2=CH); 4.47 (*AB*, *J* = 11.7, 1 H of O–CH_2–Ph); 4.27 (*AB*, *J* = 11.3, 1 H of O–CH_2–Ph); 3.93–3.86 (*m*, CH–O); 3.47 (*t*, *J* = 5.8, CH_2O); 3.29 (*d*, *J* = 5.5, CH–O); 2.22 (*t*, *J* = 6.6, CH_2=CH–CH_2); 1.70–1.42 (*m*, 2 CH_2); 1.06 (br. *s*, 3 Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 138.9; 136.1; 136.0; 135.9; 134.7; 134.3; 133.7; 129.5; 129.1; 128.1; 127.7; 127.4; 127.1; 117.0; 81.5; 74.0; 71.8; 62.8; 38.1; 29.6; 29.2; 27.1; 26.8; 26.1; 19.3. ESI-MS: 511 ($[M + Na]^+$). HR-MS: 511.2623 ($[M + Na]^+$, $C_{31}H_{40}NaO_3Si^+$; calc. 511.2644).

*(4*S*,5*R*)-4-(Benzyloxy)-5-{[(*tert*-butyl)(diphenyl)silyl]oxy}oct-7-enoic Acid* (**2**). To a stirred soln. of oxalyl chloride (0.09 ml, 0.97 mmol) in dry CH_2Cl_2 (2 ml), DMSO (0.14 ml, 1.95 mmol) was added at −78°, and the mixture was stirred for 30 min at same temp., followed by the addition of **14** (0.32 g, 0.65 mmol) in CH_2Cl_2 (1.5 ml), and the mixture was stirred for 1 h at −78°. The reaction was quenched with Et_3N (0.42 ml, 3.9 mmol) at −78°, and the soln. was stirred for further 15 min. The mixture was extracted with CH_2Cl_2 (2 × 20 ml), and washed with H_2O (5 ml) and brine (5 ml). The combined org.

layers were dried (Na_2SO_4) and concentrated *in vacuo* to give the intermediate aldehyde (0.25 g, 89%) as a pale-yellow syrup, which was used for the next reaction.

The aldehyde (0.25 g, 0.51 mmol) was dissolved in *t*-BuOH/2-methylbut-2-ene 2:1 (2.5 ml). To this soln., $NaClO_2$ (0.09 g, 1.03 mmol) and $NaH_2PO_4 \cdot 2\,H_2O$ (0.16 g, 1.03 mmol), dissolved in minimum amount of H_2O, were added at 0°, and the mixture stirred for 2 h at r.t. The solvent was removed under reduced pressure, and extracted with AcOEt (2 × 3 ml), washed with H_2O (5 ml) and brine (5 ml). The combined org. layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC (SiO_2, 60–120 mesh; 18% AcOEt/hexane) to afford **2** (0.2 g, 79%). Yellow oil. $[\alpha]_D^{25} = -18.1$ ($c = 0.3$, $CHCl_3$). IR (neat): 3445, 2926, 2855, 1709, 1109, 702. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.68–7.63 (*m*, 4 arom. H); 7.40–7.16 (*m*, 11 arom. H); 5.57–5.47 (*m*, CH_2=C*H*); 4.93–4.80 (*m*, CH_2=CH); 4.46 (*AB*, $J = 11.7$, 1 H of O–CH_2–Ph); 4.23 (*AB*, $J = 11.7$, 1 H of O–CH_2–Ph); 3.89 (*t*, $J = 6.2$, CH–O); 3.34 (*d*, $J = 9.2$, CH–O); 2.41–2.26 (*m*, 2 CH–O); 2.20 (*t*, $J = 6.9$, CH_2=CH–CH_2); 2.02–1.93 (*m*, 1 H of CH_2); 1.88–1.80 (*m*, 1 H of CH_2); 1.05 (br. *s*, 3 Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 178.9; 146.9; 138.4; 136.1; 134.4; 133.5; 129.6; 128.2; 127.5; 117.3; 80.4; 73.5; 71.6; 38.2; 29.7; 27.0; 24.3; 19.3. ESI-MS: 525 ([M + Na]$^+$). HR-MS: 525.2434 ([M + Na]$^+$, $C_{31}H_{38}NaO_4Si^+$; calc. 525.2437).

*(2*S*)-Hex-5-en-2-yl (4*S*,5*R*)-4-(Benzyloxy)-5-{[(*tert*-butyl)(diphenyl)silyl]oxy}oct-7-enoate* (**4**). To a soln. of **2** (0.18 g, 0.36 mmol) and Et_3N (0.15 ml, 1.07 mmol) in dry THF (2 ml), 2,4,6-trichlorobenzoyl chloride (0.11 ml, 0.72 mmol) was added dropwise at 0°, and then the mixture was stirred at r.t. for 4 h. The solvent was evaporated, and the residue was diluted in toluene (2 ml), treated with DMAP (0.11 g, 0.89 mmol) and **3** (0.042 g, 0.42 mmol). After 2 h, toluene was evaporated *in vacuo*, and the residue was purified by CC (SiO_2, 60–120 mesh; 0.5% AcOEt/hexane) to afford **4** (0.17 g, 69%). Colorless liquid. $[\alpha]_D^{25} = -13.2$ ($c = 0.4$, $CHCl_3$). IR (neat): 2945, 2875, 1723, 1108, 1062. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.68–7.63 (*m*, 4 arom. H); 7.40–7.18 (*m*, 11 arom. H); 5.81–5.68 (*m*, CH_2=C*H*); 5.58–5.46 (*m*, CH_2=C*H*); 5.05–4.89 (*m*, CH_2=CH); 4.88–4.79 (*m*, CH_2=CH, CH–OCO); 4.44 (*AB*, $J = 11.6$, 1 H of O–CH_2–Ph); 4.24 (*AB*, $J = 11.6$, 1 H of O–CH_2–Ph); 3.88 (*t*, $J = 5.2$, CH–O); 3.33 (*d*, $J = 5.6$, CH–O); 2.39–2.13 (*m*, CH_2–COOH, CH_2=CH–CH_2); 2.10–1.91 (*m*, CH_2=CH–CH_2); 1.90–1.78 (*m*, 1 H of CH_2); 1.70–1.60 (*m*, 1 H of CH_2); 1.56–1.47 (*m*, 1 H of CH_2); 1.39–1.32 (*m*, 1 H of CH_2); 1.14 (*d*, $J = 6.0$, Me); 1.06 (br. *s*, 3 Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 173.4; 138.7; 137.8; 136.0; 135.8; 135.4; 134.5; 129.6; 128.2; 127.5; 117.2; 114.9; 80.6; 73.8; 71.7; 70.1; 38.2; 35.0; 30.9; 29.6; 27.0; 24.9; 19.9; 19.3. ESI-MS: 607 ([M + Na]$^+$). HR-MS: 607.3247 ([M + Na]$^+$, $C_{37}H_{48}NaO_4Si^+$; calc. 607.3220).

*(5*S*,6*R*,12*S*)-5-(Benzyloxy)-6-{[(*tert*-butyl)(diphenyl)silyl]oxy}-12-methyl-1-oxacyclododec-8-en-2-one* (**5**). To a soln. of **4** (0.15 g, 0.25 mmol) in CH_2Cl_2 (150 ml), *Grubbs*' second-generation catalyst (0.03 g, 0.04 mmol, 10 mol-%) was added, and the mixture was stirred at reflux for 5 h under N_2. The solvent was evaporated *in vacuo*, and the residue was purified by CC (SiO_2, 60–120 mesh; 0.6% AcOEt/hexane) to afford **5** (0.12 g, 80%). Thick syrup. IR (neat): 2940, 2884, 1718, 1116, 1040. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.68–7.60 (*m*, 4 arom. H); 7.38–7.19 (*m*, 11 arom. H); 5.39 (*t*, $J = 14.6$, 0.34 olef. H); 5.17 (*t*, $J = 10.5$, 0.66 olef. H); 4.91–4.82 (*m*, 0.66 olef. H); 4.81–4.70 (*m*, 0.34 olef. H); 4.63–4.54 (*m*, CH–OCO); 4.32–4.18 (*m*, 2 H); 4.01–3.94 (*m*, CH–O); 3.06–3.01 (*m*, CH–O); 2.61–2.48 (*m*, CH_2); 2.47–2.38 (*m*, 1 allylic H); 2.30–2.13 (*m*, 1 allylic H); 2.12–1.99 (*m*, 2 allylic H); 1.98–1.80 (*m*, 1 H of CH_2); 1.79–1.69 (*m*, CH_2); 1.67–1.55 (*m*, 1 H of CH_2); 1.24 (*d*, $J = 5.6$, 1.98 H of Me); 1.20 (*d*, $J = 6.0$, 1.02 H of Me); 1.06 (br. *s*, 3 Me). ESI-MS: 579 ([M + Na]$^+$). HR-MS: 579.2896 ([M + Na]$^+$, $C_{35}H_{44}NaO_4Si^+$; calc. 579.2901).

*(5*S*,6*R*,12*S*)-6-{[(*tert*-Butyl)(diphenyl)silyl]oxy}-5-hydroxy-12-methyl-1-oxacyclo-dodecan-2-one* (**6**). To a stirred soln. of **5** (0.11 g, 0.19 mmol) in MeOH (1 ml) 10% Pd/C (cat.) was added under H_2 for 12 h. The mixture was filtered through a pad of *Celite*, washed with MeOH (3 ml), concentrated *in vacuo*, and purified by CC (SiO_2, 60–120 mesh, 3% AcOEt/hexane) to afford **6** (0.075 g, 84%). Colorless liquid. $[\alpha]_D^{25} = -11.9$ ($c = 0.1$, $CHCl_3$). IR (neat): 3493, 2914, 1718, 1486, 1240. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.68–7.65 (*m*, 4 arom. H); 7.40–7.30 (*m*, 6 arom. H); 4.97–4.94 (*m*, CH–OCO); 3.77–3.73 (*m*, CH–O); 3.52 (br. *s*, CH–O); 2.54–2.43 (*m*, CH_2); 2.15 (*t*, $J = 14.7$, 1 H of CH_2); 1.63–1.43 (*m*, 2 CH_2); 1.42–1.33 (*m*, CH_2); 1.31–1.25 (*m*, 5 H of CH_2); 1.19 (*d*, $J = 6.0$, Me); 1.06 (br. *s*, 3 Me). ^{13}C-NMR (75 MHz, $CDCl_3$): 172.4; 135.8; 129.6; 127.7; 79.7; 75.8; 69.5; 32.4; 31.9; 29.7; 27.0; 22.7; 21.1, 19.5; 18.9. ESI-MS: 491 ([M + Na]$^+$). HR-MS: 491.2603 ([M + Na]$^+$, $C_{28}H_{40}NaO_4Si^+$; calc. 491.2594).

*(6*R*,12*S*)-6-{[(*tert*-Butyl)(diphenyl)silyl]oxy}-12-methyl-1-oxacyclododecane-2,5-dione* (**7**). To a stirred soln. of **6** (0.05 g, 0.11 mmol) in dry CH_2Cl_2 (2 ml), *Dess–Martin* periodinane (0.05 g, 0.13 mmol) was added at 0°, and was the mixture was stirred for 2 h at r.t. The reaction was quenched with aq. soln. of $NaHCO_3$/Hypo 1:1 (1 ml), and the mixture was extracted with CH_2Cl_2 (2 × 5 ml), and washed with H_2O (5 ml) and brine (5 ml). The combined org. layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC (SiO_2, 60–120 mesh; 1% AcOEt/hexane) to afford **7** (0.043 g, 89%). White syrup. $[\alpha]_D^{25} = +46.3$ ($c = 0.1$, $CHCl_3$). IR (neat): 2948, 1747, 1706, 1248. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.60 (*dd*, $J = 17.9$, 6.5, 4 arom. H); 7.44–7.41 (*m*, 2 arom. H); 7.38 (*t*, $J = 6.5$, 4 arom. H); 4.93–4.81 (*m*, CH–OCO); 4.18 (*t*, $J = 5.9$, CH–O); 3.49–3.35 (*m*, CH–O); 2.65 (*t*, $J = 15.7$, 1 H of CH_2); 2.56–2.38 (*m*, CH_2); 1.66 (*q*, $J = 6.5$, 1 H of CH_2); 1.63–1.54 (*m*, CH_2); 1.45–1.37 (*m*, 1 H of CH_2); 1.32–1.23 (*m*, 3 CH_2); 1.17 (*d*, $J = 6.5$, 3 H CH_2); 1.13 (br. *s*, 3 Me). ^{13}C-NMR (50 MHz, $CDCl_3$): 212.3; 171.1; 135.6; 129.9; 127.8; 78.9; 71.9; 33.6; 32.5; 32.0; 29.6; 28.7; 26.9; 20.0; 19.6. ESI-MS: 489 ($[M + Na]^+$). HR-MS: 489.2430 ($[M + Na]^+$, $C_{28}H_{38}NaO_4Si^+$; calc. 489.2437).

*(6*R*,12*S*)-6-Hydroxy-12-methyl-1-oxacyclododecane-2,5-dione* (**1**). To a stirred soln. of **7** (0.028 g, 0.06 mmol) in dry THF, HF-pyridine (0.28 ml, 0.28 mmol) was added, and the mixture was stirred for 12 h at r.t. The reaction was quenched with $CuSO_4$ soln. (10 ml), and the mixture was extracted with AcOEt (2 × 5 ml), and washed with H_2O (5 ml) and brine (5 ml). The combined org. layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by CC (SiO_2, 60–120 mesh; 6.5% AcOEt/hexane) to afford **1** (0.012 g, 86%). White solid. M.p.: 119–121°. $[\alpha]_D^{25} = +37.2$ ($c = 0.3$, MeOH). IR (neat): 3452, 2919, 1718, 1702, 1470, 1256. ^{1}H-NMR (500 MHz, (D_6)acetone): 4.76 (*sext.*, $J = 6.3$, CH–OCO); 4.24–4.22 (*m*, CH–O); 3.13–3.06 (*m*, 1 H of CH_2); 2.60–2.47 (*m*, CH_2); 2.44–2.40 (*m*, 1 H of CH_2); 1.84–1.79 (*m*, 1 H of CH_2); 1.71 (*quint.*, $J = 6.8$, 1 H of CH_2); 1.46–1.37 (*m*, CH_2); 1.23–1.13 (*m*, 3 CH_2); 1.03 (*d*, $J = 6.3$, Me). ^{13}C-NMR (75 MHz, (D_6)acetone): 212.6; 171.5; 77.3; 71.9; 35.0; 33.7; 32.3; 30.1; 28.2; 21.7; 20.9; 20.1. ESI-MS: 251 ($[M + Na]^+$). HR-MS: 251.1266 ($[M + Na]^+$, $C_{12}H_{20}NaO_4^+$; calc. 251.1259).

One of the authors (*P. V. A.*) thanks the *CSIR*, New Delhi, for financial support in the form of a fellowship.

REFERENCES

[1] H.-Q. Dai, Q.-J. Kang, G.-H. Li, Y.-M. Shen, *Helv. Chim. Acta* **2006**, *89*, 527.
[2] P. Radha Krishna, R. Srinivas, *Tetrahedron: Asymmetry* **2008**, *19*, 1153; P. Radha Krishna, A. Sreeshailam, *Synlett* **2008**, 2795; P. Radha Krishna, P. Srinivas Reddy, *Synlett* **2009**, 209.
[3] Y. Xing, G. A. O'Doherty, *Org. Lett.* **2009**, *11*, 1107.
[4] A. Sharma, S. Gamre, S. Chattopadhyay, *Tetrahedron Lett.* **2007**, *48*, 3705.
[5] C. Bonini, L. Chiummiento, M. T. Lopardo, M. Pullez, F. Colobert, G. Solladié, *Tetrahedron Lett.* **2003**, *44*, 2695.
[6] B. S. Bal, W. E. Childers Jr., H. W. Pinnick, *Tetrahedron* **1981**, *37*, 2091.
[7] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
[8] C. W. Lee, R. H. Grubbs, *J. Org. Chem.* **2001**, *66*, 7155; A. K. Chatterjee, R. H. Grubbs, *Angew. Chem., Int. Ed.* **2002**, *41*, 3171; A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199.
[9] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155; R. J. Linderman, D. M. Graves, *J. Org. Chem.* **1989**, *54*, 661.

Received February 10, 2012