Stereoselective Total Synthesis of 4-Ketoclonostachydiol

by **Singanaboina Rajaram**, **Udugu Ramulu**, **Dasari Ramesh**, **Peddikotla Prabhakar**, and **Yenamandra Venkateswarlu***[†1])

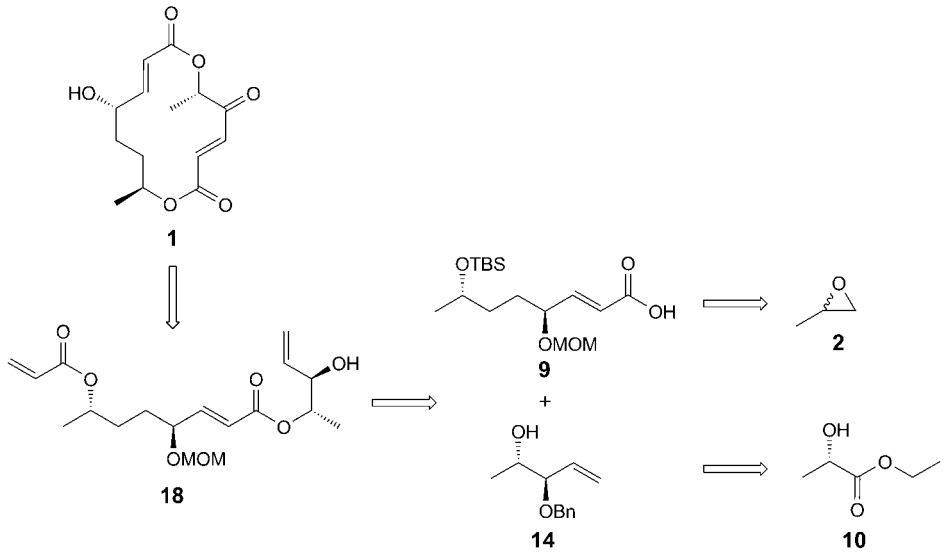
Division of Natural Products Chemistry, Natural Products Laboratory, Indian Institute of Chemical Technology, Hyderabad – 500007, India

An efficient stereoselective total synthesis of the bioactive 14-membered natural macrocyclic bislactone 4-ketoclonostachydiol is described. The strategy involves a *Jacobsen*'s hydrolytic kinetic resolution (HKR), epoxide opening, *MacMillan* α-hydroxylation, *Horner–Wadsworth–Emmons* olefination, a *Grignard* reaction, and *Hoveyda–Grubbs-II*-catalyzed ring-closing metathesis (RCM) as key steps.

Introduction. – Marine fungi are attractive sources for anticancer, antifungal, and antibacterial secondary metabolites [1]. Macrocyclic bislactone-containing natural products are receiving significant attention due to their potent biological activities [2]. 4-Ketoclonostachydiol (**1**), a 14-membered macrocyclic bislactone belongs to the colletol family, was isolated from alga-derived fungus *Gliocladium* sp. [3]. 4-Ketoclonostachydiol (**1**) exhibits various biological properties, such as strong cytotoxicity against P388 cells (IC_{50} 0.55 μM) and significant activities against *Bacillus subtilis*, the fungi *Trichophyton mentagrophytes*, and *Cladosporium resinae*. The synthesis of compounds of colletol family have been carried out by many groups [2]. Previously, we have synthesized clonostachydiol using the strategy of *MacMillan* α-hydroxylation, *Horner–Wadsworth–Emmons* olefination, *Grignard* reaction, and *Hoveyda–Grubbs*-II-catalyzed ring-closing metathesis (RCM). The structure of **1** has recently been patented for its excellent cytotoxic and antibacterial activities [4]. Only one synthesis of **1** has been reported so far, and the absolute configuration was determined by *She* and co-workers [5]. In continuation of our interest in total synthesis of lactone containing molecules [6], 4-ketoclonostachydiol (**1**) with its promising biological properties and interesting structural features prompted us to attempt its synthesis. In the present study, we report a stereoselective synthesis of **1** utilising *MacMillan* α-hydroxylation, *Horner–Wadsworth–Emmons* olefination, *Grignard* reaction, and *Hoveyda–Grubbs*-II-catalyzed ring-closing metathesis (RCM). According to the retrosynthetic analysis outlined in *Scheme 1*, **1** can be synthesized by RCM of compound **18**, which in turn could be obtained from the fragments **9** and **14** *via* esterification. The compounds **9** and **14** could be synthesized starting from (±)-propylene oxide (**2**) and ethyl (*S*)-2-hydroxypropanoate (**10**), respectively.

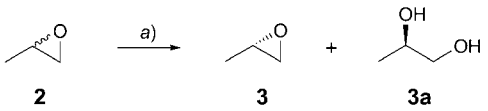
[1]) Deceased, July 17, 2013; correspondence should be addressed to Dr. *K. Suresh Babu* (phone: +91-40-27191881; e-mail: suresh@iict.res.in).

Scheme 1. *Retrosynthetic Analysis*



Results and Discussion. – As outlined in *Scheme 2*, the synthesis of **1** started with the commercially available (±)-propylene oxide (=2-methyloxirane; **2**), which was subjected to *Jacobsen*'s hydrolytic kinetic resolution (HKR) [7] with [((*S*,*S*)-salen)Co(OAc)] as catalyst to afford (*S*)-2-methyloxirane (**3**) as a single isomer ($[\alpha]_D^{25} = +11.6$ ($c = 1$, $CHCl_3$), 43%), which was easily separated from the more polar diol **3a** by distillation.

Scheme 2

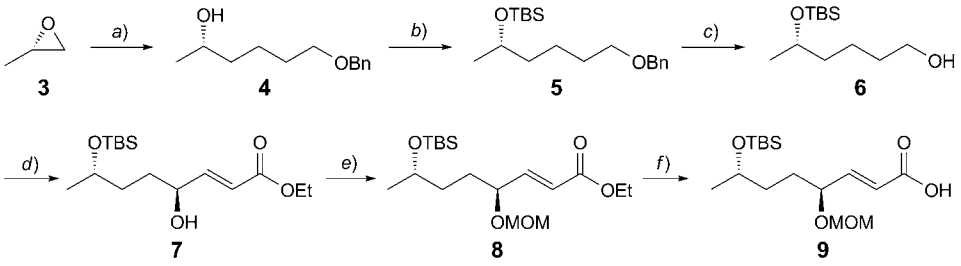


a) [(*S*,*S*)-salen)Co(OAc)] (0.5 mol-%), dist. H_2O (0.55 equiv.), 0°, 16 h (salen = *N*,*N*′-ethylenebis(salicylimine)).

The enantiomerically pure **3** was subjected to regioselective copper-catalyzed (CuI) [8] opening with *Grignard* reagent, derived from benzyl (Bn)-protected bromopropanol, to furnish alcohol **4** in 73% yield (*Scheme 3*). Compound **4** was protected with TBSCl (^{t}Bu(Me_2)SiCl) in the presence of 1*H*-imidazole in dry CH_2Cl_2 to afford the silyl ether **5** in 95% yield. The Bn group in **5** was removed using Li in liquid NH_3 to afford alcohol **6**. The primary alcohol **6** was subjected to *Swern* oxidation [9] to afford the corresponding aldehyde in 81% yield, which was subjected to the crucial *MacMillan* α-hydroxylation [10] using nitrosobenzene (PhNO) and 40% of D-proline in dry DMSO,

followed by rapid *Horner–Wadsworth–Emmons* olefination using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to furnish the unstable anilinoxy compound, which was further treated with 20 mol-% of $CuSO_4 \cdot 5\,H_2O$ in MeOH at room temperature to cleave the O–N bond to give the γ-hydroxy α,β-unsaturated ester **7** [11] in 55% yield with high diastereoselectivity (de 96%). The sequence of the reactions for the preparation of compounds **5** to **7** were already reported earlier by *Yadav* and coworkers [12]. The OH group in **7** was protected as its methoxymethyl (MOM) ether to give **8** in 85% yield, followed by hydrolysis of the ethyl ester with $LiOH \cdot H_2O$ in aqueous THF, leading to the corresponding α,β-unsaturated carboxylic acid **9** in 85% yield (*Scheme 3*).

Scheme 3

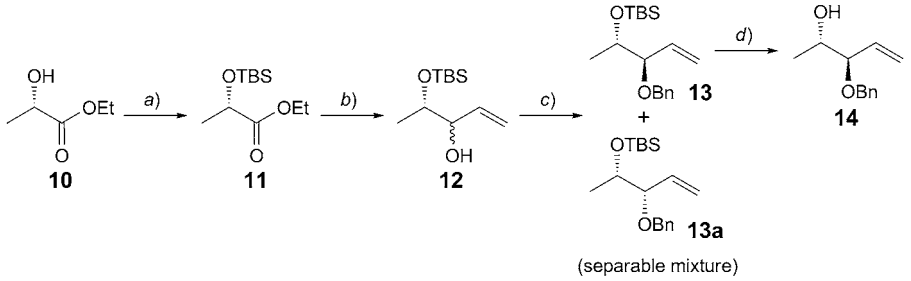


a) $PhCH_2O(CH_2)_3MgBr$, CuI, dry THF, −78°, 5 h; 73%. *b*) 1*H*-Imidazole, (*tert*-butyl)chlorodimethylsilane ($^tBuMe_2SiCl$, TBSCl), dry CH_2Cl_2, 0° to r.t., 6 h; 95%. *c*) Li/liq. NH_3, dry THF, −78°, 10 min; 86%. *d*) 1. $(COCl)_2$, dry DMSO, Et_3N, dry CH_2Cl_2, −78°, 1 h; 81%; 2. PhNO (nitrosobenzene), $C_5H_9NO_2$ (D-proline), dry DMSO, 20°, 25 min; then $(EtO)_2P(O)CH_2CO_2Et$ (triethyl phosphonoacetate), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), LiCl, 0°, 1 h; then MeOH, $CuSO_4 \cdot 5\,H_2O$, r.t., 12 h; 55% (one pot). *e*) Chloromethyl methyl ether (MOMCl), EtN^iPr_2, dry CH_2Cl_2, 0° to r.t., 5 h; 85%. *f*) $LiOH \cdot H_2O$, THF/H_2O 1:1, 8 h; 85%.

The key intermediate **14** was prepared from ethyl (*S*)-2-hydroxypropanoate (**10**, *Scheme 4*). The secondary OH group in **10** was protected as its silyl ether, **11**, in 92% yield, followed by reduction of the ester group using DIBAL-H to give the aldehyde in 88% yield, which, on reaction with CH_2=CHMgBr [13] in Et_2O, led to an inseparable mixture of alcohols **12** in 83% yield (dr 8.5:1.5, determined by HPLC on a chiral solid phase), which were separated by converting them to the benzyl ethers **13** and **13a** in 70% and 13% yields, respectively. The TBS moiety in the major diastereisomer **13** was removed with $^tBu_4NF$ (TBAF) in dry THF to give the secondary alcohol **14** in 89% yield (*Scheme 4*).

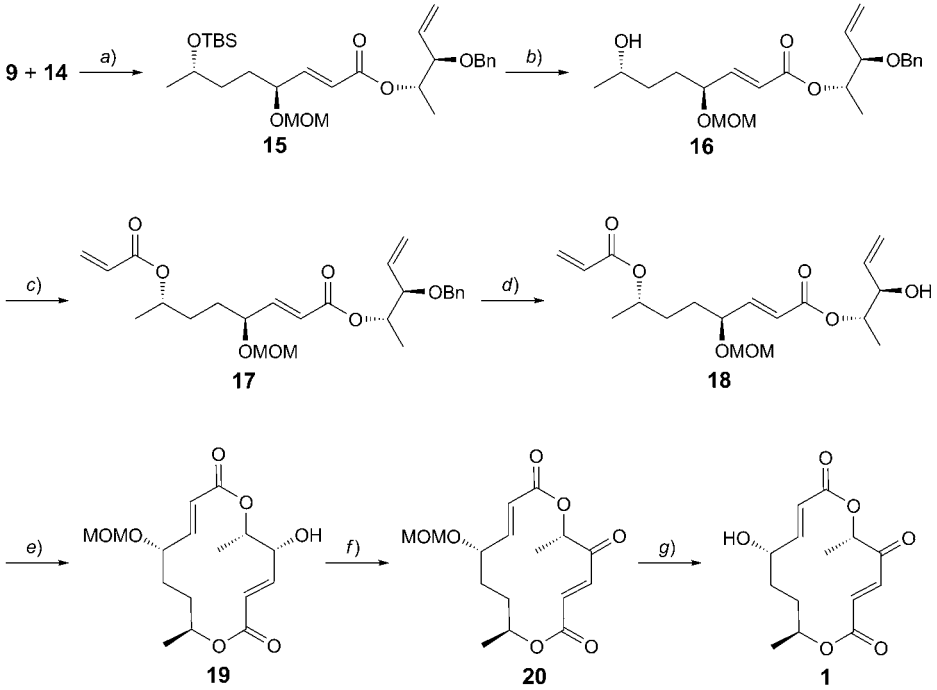
The acid **9** was esterified with alcohol **14** in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in dry CH_2Cl_2 to give the ester **15** in 80% yield (*Scheme 5*). The TBS protecting group in **15** was removed using TsOH in MeOH to give the secondary alcohol **16** in 90% yield. The acrylation of the latter with CH_2=CHCOCl and dry Et_3N in dry CH_2Cl_2 at 0° afforded the acrylate **17** in 86% yield. Compound **17** was subjected to oxidative debenzylation with 4,5-dichloro-3,6-

Scheme 4



a) 1*H*-Imidazole, ^{t}BuMe$_2$SiCl, dry CH_2Cl_2, 0° to r.t., 5 h; 92%. *b*) 1. DIBAL-H (= diisobutylaluminium hydride), dry CH_2Cl_2, −78°, 0.5 h; 88%. 2. CH_2=CHMgBr, dry Et_2O, −78°, 1 h; 83%. *c*) NaH, BnBr, Bu_4NI, dry THF, 0° to r.t., 8 h; 70%. *d*) ^{t}Bu$_4$NF, THF, 0° to r.t., 7 h; 89%.

Scheme 5



a) Dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), dry CH_2Cl_2, 0°, 12 h; 80%. *b*) TsOH, MeOH, 0°, 0.5 h; 90%. *c*) Dry Et_3N, acryloyl chloride (CH_2=CHCOCl), dry CH_2Cl_2, 0°, 1 h; 86%. *d*) 4,5-Dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ), dry CH_2Cl_2, 50°, 4 h; 74%. *e*) *Hoveyda–Grubbs-II* catalyst, dry toluene, 80°, 0.5 h; 78%. *f*) *Dess–Martin* periodinane (DMP), dry CH_2Cl_2, 5 h; 72%. *g*) CF_3COOH, dry CH_2Cl_2, 0° to r.t., 3 h; 82%.

dioxocyclohexa-1,4-diene-1,2-dicarbonitrile (DDQ) [14] in dry CH_2Cl_2 to afford ester **18** in 74% yield. Compound **18** was subjected to *Hoveyda–Grubbs-II*-catalyzed (10 mol-%) [15] RCM in toluene at 80° to afford the MOM-protected 14-membered macrolide **19** (it is enantiomeric derivative in [16]) in 78% yield. The secondary alcohol in compound **19** was subjected to *Dess–Martin* periodinane (DMP) oxidation to afford keto compound **20** in 72% yield, followed by deprotection of MOM moiety with CF_3COOH in dry CH_2Cl_2 to give **1**.

The physical and spectroscopic data of synthetic 4-ketoclonostachydiol (**1**) were identical to those reported in literature [3].

Conclusions. – In conclusion, the total synthesis of 4-ketoclonostachydiol (**1**) has been accomplished by *MacMillan* α-hydroxylation, *Horner–Wadsworth–Emmons* olefination, *Grignard* reaction, and *Hoveyda–Grubbs-II*-catalyzed ring closing metathesis (RCM), starting from commercially available 2-methyloxirane and ethyl (*S*)-2-hydroxypropanoate.

The authors are thankful to *CSIR*, New Delhi India, for financial assistance, and to the Director, Indian Institute of Chemical Technology (IICT), for his encouragement.

Experimental Part

General. Solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from *Aldrich* and *Acros*, and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under N_2. Org. solns. were dried (Na_2SO_4) and concentrated *in vacuo* below 40°. Column chromatography (CC): silica gel (*Acme*'s 60–120 mesh and 100–200 mesh). Optical rotations: *Horiba* high-sensitive polarimeter *SEPA-300* at 25°. IR Spectra: *Perkin-Elmer IR-683* spectrophotometer with NaCl optics; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR (300 and 75 MHz, resp.) spectra: *Bruker Avance 300* instrument; δ in ppm rel. to Me_4Si as internal standard in $CDCl_3$; *J* in Hz. MS: *Agilent Technologies 1100 Series* (*Agilent* Chemstation Software).

*(2*S*)-6-(Benzyloxy)hexan-2-ol* (**4**). To a suspension of Mg (0.93 g, 38.79 mmol) in dry THF (25 ml) at r.t. equipped with condenser (cool water circulation) was added $PhCH_2O(CH_2)_3Br$ (8.88 g, 38.79 mmol) dropwise within 15 min, and the mixture was stirred for 0.5 h. After cooling the mixture to −78°, the enantiomerically pure **3** (0.9 g, 15.51 mmol) in dry THF (15 ml) and freshly flame-dried CuI (0.08 g, 0.46 mmol) were added, and the mixture was stirred for 4 h at −78°. After completion, the reaction was quenched with sat. aq. NH_4Cl soln. (20 ml), and the mixture was extracted with AcOEt (3 × 25 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8) to give pure **4** (2.33 g, 73%). Colorless liquid. $[\alpha]_D^{25} = +3.8$ ($c = 6.5$, $CHCl_3$). IR (neat): 3442, 3027, 2927, 2854, 1493, 1451, 1342, 1261, 1163, 1042, 700. ^{1}H-NMR: 7.39–7.24 (*m*, 5 H); 4.50 (*s*, 2 H); 3.85–3.72 (*m*, 1 H); 3.48 (*t*, *J* = 6.8, 2 H); 1.74–1.36 (*m*, 7 H); 1.18 (*d*, *J* = 6.8, 3 H). ^{13}C-NMR: 138.5; 128.3; 127.6; 127.5; 72.9; 70.2; 67.8; 38.9; 29.6; 23.3; 22.3. ESI-MS: 231 ($[M + Na]^+$).

*Ethyl (2*E*,4*S*,7*S*)-7-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-4-(methoxymethoxy)oct-2-enoate* (**8**). To a cooled (0°) soln. of **7** (0.5 g, 15.82 mmol) in dry CH_2Cl_2 was added EtN^iPr_2 (0.82 ml, 4.74 mmol), then MOMCl (0.24 ml, 3.16 mmol) was added dropwise, and the mixture was stirred at r.t. for 5 h. After completion of the reaction, the mixture was diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8) to affor pure **8** (0.48 g, 85%). Yellow liquid. $[\alpha]_D^{25} = -32.2$ ($c = 1.3$, $CHCl_3$). IR (neat): 2934, 2892, 2858, 1723, 1658, 1466, 1369, 1260, 1159, 1039, 834, 775. ^{1}H-NMR: 6.79 (*dd*, *J* = 15.8, 6.8, 1 H); 5.95 (*d*, *J* = 15.8, 1 H); 4.58 (*q*, *J* = 6.8, 2 H); 4.22–4.12 (*m*, 3 H); 3.81–3.71 (*m*, 1 H); 3.35 (*s*, 3 H); 1.77–1.36 (*m*, 4 H); 1.28 (*t*, *J* = 7.6, 3 H); 1.10 (*d*, *J* = 6.2, 3 H); 0.86 (*s*, 9 H); 0.02 (*s*, 6 H). ^{13}C-NMR: 166.1; 147.7; 121.8; 94.5; 75.3; 68.3; 60.3; 55.5; 34.9; 30.9; 25.8; 23.8; 18.0; 14.1; −4.4; −4.8. ESI-MS: 383 ($[M + Na]^+$).

*(2*E*,4*S*,7*S*)-7-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-4-(methoxymethoxy)oct-2-enoic Acid* (**9**). To a cooled (0°) soln. of **8** (0.3 g, 0.83 mmol) in THF (4 ml) and H_2O (4 ml) was added $LiOH \cdot H_2O$ (0.12 g, 4.9 mmol), and the mixture was stirrred for 8 h at r.t. After completion of the reaction, the solvent was removed under reduced pressure, and the residue was diluted with H_2O (5 ml), acidified with $KHSO_4$, and extracted with AcOEt (2×10 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by CC (AcOEt/hexane 3:7) to give pure **9** (0.23 g, 85%). Brown liquid. $[\alpha]_D^{25} = -27.3$ ($c = 0.8$, $CHCl_3$). IR (neat): 3448, 2954, 2931, 2890, 2857, 1700, 1656, 1466, 1253, 1038, 833, 774. ^{1}H-NMR: 6.94 (*dd*, $J = 15.8, 6.2$, 1 H); 5.99 (*d*, $J = 15.8$, 1 H); 4.62 (*q*, $J = 6.8$, 2 H); 4.27–4.17 (*m*, 1 H); 3.84–3.72 (*m*, 1 H); 3.38 (*s*, 3 H); 1.78–1.38 (*m*, 4 H); 1.13 (*d*, $J = 6.2$, 3 H); 0.88 (*s*, 9 H); 0.04 (*s*, 6 H). ^{13}C-NMR: 171.3; 150.7; 120.9; 94.7; 75.3; 68.3; 55.6; 34.9; 30.8; 25.8; 23.8; 18.1; −4.4; −4.7. ESI-MS: 355 ($[M + Na]^+$).

*Ethyl (2*S*)-2-{[(*tert*-Butyl)(dimethyl)silyl]oxy}propanoate* (**11**). To a cooled (0°) soln. of **10** (1.0 g, 8.47 mmol) and 1*H*-imidazole (1.44 g, 21.1 mmol) in dry CH_2Cl_2 (15 ml) was added TBSCl (1.65 g, 11.01 mmol), and the mixture was stirrred for 5 h. After completion of reaction, the mixture was diluted with H_2O (10 ml) and extracted into CH_2Cl_2 (3×20 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 0.5:9.5) to afford pure **11** (1.8 g, 92%). Colorless liquid. $[\alpha]_D^{25} = -24$ ($c = 7.1$, $CHCl_3$). IR (neat): 2943, 2897, 2852, 1759, 1255, 1145, 835, 778. ^{1}H-NMR: 4.16 (*q*, $J = 7.2$, 2 H); 4.29 (*q*, $J = 6.8$, 1 H); 1.38 (*d*, $J = 6.8$, 3 H); 1.26 (*t*, $J = 7.2$, 3 H); 0.89 (*s*, 9 H); 0.05 (*s*, 3 H); 0.08 (*s*, 3 H). ^{13}C-NMR: 173.6; 68.2; 60.3; 25.5; 21.0; 18.0; 13.9; −5.2; −5.5. ESI-MS: 255 ($[M + Na]^+$).

*(4*S*)-4-{[(*tert*-Butyl)(dimethyl)silyl]oxy}pent-1-en-3-ol* (**12**). To a cooled (−78°) soln. of **11** (1.7 g, 7.32 mmol) in dry CH_2Cl_2 (20 ml) was added slowly 1M DIBAL-H in toluene (6.58 ml, 6.58 mmol), and the mixture was stirred for 0.5 h. After completion, the reaction was quenched with MeOH (1 ml) and sat. $KNaC_4H_4O_6 \cdot 4\,H_2O$ (sodium potassium tartarate; 10 ml), and the mixture was stirred for 1 h and then extracted with CH_2Cl_2 (2×20 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8) to give a pure aldehyde as a colorless liquid (1.21 g, 88%, which was used in the following reaction). To the aldehyde (1.2 g, 6.38 mmol) in dry Et_2O (20 ml) was added dropwise 1.0M in THF CH_2=CHMgBr (15.13 ml, 12.7 mmol) at −78°, and the mixture was stirred for 1 h. After completion, the reaction was quenched with sat. NH_4Cl soln. (10 ml), and the mixture was extracted with Et_2O (3×20 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8) to furnish an inseparable diastereoisomer mixture **12** (1.14 g, 83%). Colorless liquid. IR (neat): 3445, 3087, 2954, 2932, 2895, 2857, 1635, 1388, 1253, 1095, 934, 836, 772. ^{1}H-NMR: 5.88–5.75 (*m*, 1 H); 5.33–5.13 (*m*, 2 H); 4.06–3.99 (*m*, 1 H); 3.89–3.80 (*m*, 1 H); 1.08 (*d*, $J = 6.4$, 3 H); 0.89 (*s*, 9 H); 0.08 (*s*, 6 H). ^{13}C-NMR: 136.5; 116.4; 76.6; 71.2; 25.7; 18.0; 17.6; −4.5; −4.9. EI-MS: 239 ($[M + Na]^+$).

*{[(2*S*,3*R*)-3-(Benzyloxy)pent-4-en-2-yl]oxy}(*tert*-butyl)dimethylsilane* (**13**). To a cooled (0°) soln. of **12** (0.9 g, 4.16 mmol) in dry THF (15 ml) was added NaH (60%) (0.13 g, 9.16 mmol), and the mixture was stirred for 30 min. To this mixture, BnBr (0.54 ml, 4.58 mmol), and Bu_4NI (cat. amount) were added, and the soln. was stirred at r.t. for 8 h. After completion, the reaction was quenched with cold H_2O (10 ml), and the mixture was extracted with AcOEt (3×15 ml), dried (Na_2SO_4), and concentrated. The crude product was purified by CC (AcOEt/hexane 1:9) to furnish pure **13** (0.89 g, 70%). Colorless liquid. $[\alpha]_D^{25} = -2.8$ ($c = 0.9$, $CHCl_3$). IR (neat): 3075, 3041, 2946, 2930, 2895, 2856, 1635, 1462, 1252, 1073, 926, 745, 669. ^{1}H-NMR: 7.37–7.18 (*m*, 5 H); 5.82–5.73 (*m*, 1 H); 5.29–5.19 (*m*, 2 H); 4.59 (*d*, $J = 12.0$, 1 H); 4.39 (*d*, $J = 12.0$, 1 H); 3.85–3.78 (*m*, 1 H); 3.54 (*dd*, $J = 7.5, 4.5$, 1 H); 1.15 (*d*, $J = 6.0$, 3 H); 0.86 (*s*, 9 H), 0.02 (*d*, $J = 4.5$, 6 H). ^{13}C-NMR: 138.7; 136.4; 128.3; 127.6; 127.3; 118.6; 85.1; 70.9; 70.4; 25.8; 20.2; 18.1; −4.4; −4.6. ESI-MS: 329 ($[M + Na]^+$).

*(2*S*,3*R*)-3-(Benzyloxy)pent-4-en-2-ol* (**14**). To a cooled (0°) soln. of **13** (0.3 g, 0.98 mmol) in dry THF (10 ml) was added 1M ^{t}Bu_4NF in THF (1.96 ml, 1.96 mmol), and the mixture was stirred for 7 h at r.t. After completion of the reaction, the mixture was diluted with H_2O (10 ml) and extracted with AcOEt (3×10 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by CC (AcOEt/hexane 2:8) to give pure **14** (0.16 g, 89%). Colorless liquid. $[\alpha]_D^{25} = -35.2$ ($c = 1.8$, $CHCl_3$). IR (neat): 3446, 3073, 3029, 2977, 2928, 2871, 1637, 1452, 1078, 928, 741,

669. ^{1}H-NMR: 7.39–7.24 (*m*, 5 H); 5.91–5.75 (*m*, 1 H); 5.45–5.26 (*m*, 2 H); 4.65 (*d*, *J* = 12.0, 1 H); 4.39 (*d*, *J* = 12.0, 1 H); 3.96–3.85 (*m*, 1 H); 3.7 (*dd*, *J* = 8.1, 3.9, 1 H); 1.15 (*d*, *J* = 6.4, 3 H). ^{13}C-NMR: 138.2; 134.5; 128.3; 127.6; 127.5; 120.2; 84.2; 70.2; 69.2; 17.9. ESI-MS: 215 ([*M* + Na]$^+$).

*(2*S*,3*R*)-3-(Benzyloxy)pent-4-en-2-yl (2*E*,4*S*,7*S*)-7-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-4-(methoxymethoxy)oct-2-enoate* (**15**). To a cooled (0°) soln. of **9** (0.2 g, 0.6 mmol), DCC (0.15 g, 0.72 mmol), and DMAP (0.014 g, 0.12 mmol) in dry CH_2Cl_2 (10 ml) was added **14** (0.1 g, 0.5 mmol) in 5 ml of dry CH_2Cl_2, and the mixture was stirred at (0°) for 12 h. After completion of the reaction, the mixture was diluted with H_2O (15 ml) and extracted with CH_2Cl_2 (3 × 10 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by CC (AcOEt/hexane 2:8) to yield pure **15** (0.24 g, 80%). Colorless liquid. $[\alpha]_D^{25} = -46.3$ (*c* = 1.0, $CHCl_3$). IR (neat): 2954, 2930, 2889, 2857, 1722, 1657, 1458, 1373, 1256, 1154, 1099, 1044, 834, 775. ^{1}H-NMR: 7.24–7.35 (*m*, 5 H); 6.79 (*dd*, *J* = 15.4, 6.6, 1 H); 5.96 (*d*, *J* = 15.4, 1 H); 5.82–5.73 (*m*, 1 H); 5.35–5.26 (*m*, 2 H); 5.10–5.03 (*m*, 1 H); 4.61 (*q*, *J* = 6.6, 2 H); 4.60 (*d*, *J* = 12.1, 1 H); 4.44 (*d*, *J* = 12.1, 1 H); 4.22–4.14 (*m*, 1 H); 3.87–3.76 (*m*, 2 H); 3.37 (*s*, 3 H); 1.75–1.40 (*m*, 4 H); 1.27 (*t*, *J* = 6.6, 3 H); 1.12 (*d*, *J* = 5.5, 3 H); 0.88 (*s*, 9 H); 0.04 (*s*, 6 H). ^{13}C-NMR: 165.5; 147.9; 138.3; 134.8; 128.2; 127.5; 127.4; 122.1; 119.4; 94.6; 81.8; 75.4; 72.0; 70.4; 68.3; 55.6; 34.5; 31.0; 25.9; 23.8; 18.1; 15.3; −4.7; −4.4. ESI-MS: 529 ([*M* + Na]$^+$).

*(2*S*,3*R*)-3-(Benzyloxy)pent-4-en-2-yl (2*E*,4*S*,7*S*)-7-Hydroxy-4-(methoxymethoxy)oct-2-enoate* (**16**). To a cooled (0°) soln. of **15** (0.23 g, 0.45 mmol) in MeOH (10 ml) was added TsOH (cat.), and the mixture was stirred for 0.5 h. After completion, the reaction was quenched with solid $NaHCO_3$, the mixture was filtered, and the filtrate was concentrated under reduced pressure to afford a crude product, which was purified by CC (AcOEt/hexane 3:6) to furnish pure **16** (0.16 g, 90%). Colorless liquid. $[\alpha]_D^{25} = -68.2$ (*c* = 0.5, $CHCl_3$). IR (neat): 3455, 2930, 1731, 1708, 1657, 1453, 1373, 1262, 1153, 1030, 926, 739, 700. ^{1}H-NMR: 7.37–7.24 (*m*, 5 H); 6.80 (*dd*, *J* = 15.8, 6.8, 1 H); 5.98 (*d*, *J* = 15.8, 1 H); 5.85–5.71 (*m*, 1 H); 5.37–5.26 (*m*, 2 H); 5.12–5.02 (*m*, 1 H); 4.64 (*q*, *J* = 6.8, 2 H); 4.61 (*d*, *J* = 12.1, 1 H); 4.43 (*d*, *J* = 12.1, 1 H); 4.30–4.20 (*m*, 1 H); 3.87–3.76 (*m*, 2 H); 3.39 (*s*, 3 H); 1.84–1.46 (*m*, 4 H); 1.28 (*d*, *J* = 6.8, 3 H); 1.20 (*d*, *J* = 6.1, 3 H). ^{13}C-NMR: 165.5; 147.6; 138.2; 134.7; 128.2; 127.5; 127.4; 122.2; 119.5; 94.7; 81.8; 75.2; 72.1; 70.4; 67.8; 55.7; 34.5; 31.1; 23.5; 15.3. ESI-MS: 415 ([*M* + Na]$^+$).

*(2*S*,3*R*)-3-(Benzyloxy)pent-4-en-2-yl (2*E*,4*S*,7*S*)-4-(Methoxymethoxy)-7-(prop-2-enoyloxy)oct-2-enoate* (**17**). To a cooled (0°) soln. of **16** (0.14 g, 0.35 mmol) in dry CH_2Cl_2 (10 ml) were added dry Et_3N (0.15 ml, 0.53 mmol) and acryloyl chloride (0.038 ml, 0.53 mmol), and the mixture was stirred at (0°) for 1 h. After completion of the reaction, a sat. $NaHCO_3$ soln. (5 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 × 15 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 2:8) to give pure **17** (0.136 g, 86%). Colorless liquid. $[\alpha]_D^{25} = -76.2$ (*c* = 0.8, $CHCl_3$). IR (neat): 2979, 2932, 1721, 1406, 1295, 1274, 1200, 1042, 772. ^{1}H-NMR: 7.36–7.24 (*m*, 5 H); 6.77 (*dd*, *J* = 15.8, 6.2, 1 H); 6.39 (*d*, *J* = 17.2, 1 H); 6.10 (*dd*, *J* = 17.2, 10.4, 1 H); 5.97 (*d*, *J* = 15.8, 1 H); 5.84–5.77 (*m*, 1 H); 5.37–5.26 (*m*, 2 H); 5.11–4.93 (*m*, 2 H); 4.61 (*q*, *J* = 10.3, 1 H); 4.57 (*d*, *J* = 12.2, 1 H); 4.43 (*d*, *J* = 12.2, 1 H); 4.26–4.15 (*m*, 1 H); 3.87–3.80 (*m*, 1 H); 3.37 (*s*, 3 H); 1.73–1.55 (*m*, 4 H); 1.28 (*d*, *J* = 6.0, 3 H); 1.26 (*d*, *J* = 6.7, 3 H). ^{13}C-NMR: 165.7; 165.4; 147.3; 138.3; 134.7; 130.4; 128.8; 128.3; 127.5; 127.4; 122.4; 119.5; 94.5; 81.8; 74.9; 72.1; 70.8; 70.4; 55.6; 31.4; 30.7; 19.9; 15.2. ESI-MS: 469 ([*M* + Na]$^+$).

*(2*S*,3*R*)-3-Hydroxypent-4-en-2-yl (2*E*,4*S*,7*S*)-4-(Methoxymethoxy)-7-(prop-2-enoyloxy)oct-2-enoate* (**18**). To a soln. of **17** (0.12 g, 0.26 mmol) in dry CH_2Cl_2 (10 ml) was added DDQ (0.73 g, 3.2 mmol), and the mixture was stirred at 50° for 4 h. After completion of the reaction, the mixture was diluted with CH_2Cl_2, and sat. $NaHCO_3$ (10 ml) was added. The mixture was stirred for 30 min and extracted with CH_2Cl_2 (2 × 15 ml). The combined org. extract was washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 4:6) to give pure **18** (0.064 g, 74%). Liquid. $[\alpha]_D^{25} = -57.1$ (*c* = 0.5, $CHCl_3$). IR (neat): 3405, 2940, 2871, 1716, 1448, 1349, 1117, 1022, 941, 812. ^{1}H-NMR: 6.83 (*dd*, *J* = 15.9, 6.1, 1 H); 6.38 (*d*, *J* = 17.4, 1 H); 6.10 (*dd*, *J* = 17.4, 10.6, 1 H); 6.01 (*d*, *J* = 15.9, 1 H); 5.92–5.84 (*m*, 1 H); 5.81 (*d*, *J* = 9.8, 1 H); 5.37 (*dd*, *J* = 17.4, 10.6, 1 H); 5.07–4.95 (*m*, 2 H); 4.61 (*d*, *J* = 12.3, 1 H); 4.29–4.25 (*m*, 1 H); 4.24–4.19 (*m*, 1 H); 3.38 (*s*, 3 H); 1.72–1.60 (*m*, 4 H); 1.27 (*d*, *J* = 6.0, 3 H); 1.25 (*d*, *J* = 6.8, 3 H). ^{13}C-NMR: 166.1; 165.0; 149.6; 145.5; 131.8; 128.7; 124.1; 121.4; 94.5; 74.8; 74.0; 72.8; 69.9; 55.5; 28.1; 27.0; 18.1; 17.8. ESI-MS: 379 ([*M* + Na]$^+$).

*(3*E*,5*R*,6*S*,9*E*,11*S*,14*S*)-5-Hydroxy-11-(methoxymethoxy)-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione* (**19**). To a soln. of **18** (0.025 g, 0.07 mmol) in degassed dry toluene (110 ml) was added *Hoveyda–Grubbs-II* catalyst (0.004 g, 0.007 mmol), and the resulting mixture was heated under N_2 at 80° for 0.5 h. After completion of the reaction, the mixture cooled to r.t., and the solvent was concentrated under reduced pressure. The crude residue was purified by CC (AcOEt/hexane 4:6) to afford pure **19** (0.017 g, 78%). Colorless liquid. $[\alpha]_D^{25} = -13$ ($c = 0.3$, $CHCl_3$). IR (neat): 3502, 2931, 1722, 1645, 1442, 1365, 1223, 1099, 915. ^{1}H-NMR: 6.82 (*dd*, *J* = 15.8, 4.5, 1 H); 6.72 (*dd*, *J* = 15.8, 6.8, 1 H); 5.98–5.87 (*m*, 2 H); 5.21–5.10 (*m*, 1 H); 5.07–4.96 (*m*, 1 H); 4.61 (*q*, *J* = 6.8, 1 H); 4.45–4.37 (*m*, 1 H); 4.16–4.06 (*m*, 1 H); 3.35 (*s*, 3 H); 1.96–1.69 (*m*, 4 H); 1.47 (*d*, *J* = 6.0, 3 H); 1.21 (*d*, *J* = 6.8, 3 H). ^{13}C-NMR: 166.1; 164.9; 149.6; 145.5; 124.1; 121.4; 94.5; 76.6; 74.0; 72.1; 69.9; 55.5; 28.1; 27.1; 18.2; 17.9. ESI-MS: 351 ($[M + Na]^+$).

*(3*E*,6*S*,9*E*,11*S*,14*S*)-11-(Methoxymethoxy)-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,5,8-trione* (**20**). To a cooled (0°) soln. of **19** (0.015 g, 0.045 mmol) in dry CH_2Cl_2 (10 ml) was added *Dess–Martin* periodinane (0.077 g, 0.18 mmol), and the mixture was stirred for 5 h at r.t. The mixture was diluted with CH_2Cl_2, the reaction was quenched with sat. $Na_2S_2O_3$ soln. (5 ml), and the mixture was washed with sat. $NaHCO_3$ soln. The org. extract washed with brine, dried (Na_2SO_4), and concentrated. The crude residue was purified by CC (AcOEt/hexane 3:6) to give pure **20** (0.01 g, 72%). Colorless liquid. $[\alpha]_D^{20} = +29.5$ ($c = 0.2$, $CHCl_3$). IR (neat): 3445, 2932, 1724, 1262, 1047, 917. ^{1}H-NMR: 7.30 (*d*, *J* = 15.6, 1 H); 7.01 (*dd*, *J* = 15.6, 4.3, 1 H); 6.48 (*d*, *J* = 15.6, 1 H); 6.13 (*dd*, *J* = 15.6, 1.2, 1 H); 5.32 (*q*, *J* = 6.9, 1 H); 5.08–5.02 (*m*, 1 H); 4.46–4.41 (*m*, 2 H); 4.16–4.08 (*m*, 1 H); 3.38 (*s*, 3 H); 1.96–1.81 (*m*, 3 H); 1.56–1.62 (*m*, 1 H); 1.54 (*d*, *J* = 6.4, 3 H); 1.28 (*d*, *J* = 6.4, 3 H). ^{13}C-NMR: 199.4; 165.7; 164.1; 150.0; 135.3; 131.1; 120.5; 94.7; 75.5; 73.9; 71.9; 55.6; 28.2; 28.1; 18.5; 16.4. ESI-MS: 349 ($[M + Na]^+$).

*(3*E*,6*S*,9*E*,11*S*,14*S*)-11-Hydroxy-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,5,8-trione* (**1**). To a cooled (0°) soln. of **20** (0.01g, 0.03mmol) in dry CH_2Cl_2 (5 ml) was added CF_3COOH (1.0 ml), and the mixture was stirred for 3 h at r.t. After completion of the reaction, the mixture was diluted with CH_2Cl_2 (10 ml), and the reaction quenched by addition of solid $NaHCO_3$. Then, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude residue was purified by CC (AcOEt/hexanes 1:1) to give compound **1**. (0.007g, 82%). Colorless liquid $[\alpha]_D^{20} = +70.3$ ($c = 0.2$, MeOH). IR (neat): 3375, 2990, 1764, 1243, 1058, 970. ^{1}H-NMR: 7.35 (*d*, *J* = 16.9, 1 H); 7.12 (*dd*, *J* = 16.0, 4, 1 H); 6.4 (*d*, *J* = 16.0, 1 H); 6.14 (*dd*, *J* = 16.0, 2, 1 H); 5.33 (*q*, *J* = 6.9, 1 H); 5.05–5.0 (*m*, 1 H); 4.55–4.51 (*m*, 1 H) 2.07–1.97 (*m*, 1 H); 1.89–1.82 (*m*, 1 H); 1.78–1.70 (*m*, 2 H); 1.54 (*d*, *J* = 6.9, 3 H); 1.29 (*d*, *J* = 6.2, 3 H). ^{13}C-NMR: 199.5; 165.6; 164.1; 151.3; 135.7; 130.9; 119.6; 75.6; 72.2; 70.3; 31.1; 28.2; 18.9; 16.5. ESI-MS: 283 ($[M + H]^+$).

REFERENCES

[1] J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote, M. R. Prinsep, *Nat. Prod. Rep.* **2006**, *23*, 26; D. J. Faulkner, *Nat. Prod. Rep.* **2002**, *19*, 1; J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote, M. R. Prinsep. *Nat. Prod. Rep.* **2005**, *22*, 15.

[2] G. V. M. Sharma, S. Mallesham, C. Chandra Mouli, *Tetrahedron: Asymmetry* **2009**, *20*, 2513; A. V. R. Rao, V. S. Murthy, G. V. M. Sharma, *Tetrahedron Lett.* **1995**, *36*, 139; U. Ramulu, D. Ramesh, S. Rajaram, S. P. Reddy, K. Venkatesham, Y. Venkateswarlu, *Tetrahedron: Asymmetry* **2012**, *23*, 117; S. Bouz, J. Cossy, *Tetrahedron Lett.* **2006**, *47*, 901.

[3] G. Lang, M. I. Mitova, G. Ellis, S. Sar, R. K. Phipps, J. W. Blunt, N. J. Cummings, A. L. J. Cole, M. H. Munro, *J. Nat. Prod.* **2006**, *69*, 621.

[4] C. Kano, K. Adachi, Y. Shizusato, Jpn. Pat. 5247737, 2005.

[5] J. Han, Y. Su, T. Jiang, Y. Xu, X. Huo, X. She, X. Pan. *J. Org. Chem.* **2009**, *74*, 3930.

[6] P. Prabhakar, S. Rajaram, D. K. Reddy, V. Shekar, Y. Venkateswarlu, *Tetrahedron: Asymmetry* **2010**, *21*, 216; J. J. Selvam, K. Rajesh, V. Suresh, D. Chanti Babu, Y. Venkateswarlu, *Tetrahedron: Asymmetry* **2009**, *20*, 1115; V. Shekhar, D. K. Reddy, S. P. Reddy, P. Prabhakar, Y. Venkateswarlu, *Eur. J. Org. Chem.* **2011**, 4460; D. Ramesh, V. Shekhar, D. Chantibabu, S. Rajaram, U. Ramulu, Y.

Venkateswarlu, *Tetrahedron Lett.* **2012**, *53*, 1258; P. Prabhakar, D. Ramesh, S. Rajaram, D. K. Reddy, Y. Venkateswarlu, *Helv. Chim. Acta* **2011**, *94*, 1481.
[7] S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307.
[8] S. K. Pandey, P. Kumar, *Tetrahedron Lett.* **2005**, *46*, 6625.
[9] S. L. Huang, K. Omura, D. Swern, *J. Org. Chem.* **1978**, *43*, 4537.
[10] S. P. Brown, M. P. Brochu, C. J. Sinz, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 10808; V. Jha, N. B. Kondekar, P. Kumar, *Org. Lett.* **2010**, *12*, 2762; J. S. Yadav, U. V. Subba Reddy, B. Anusha, B. V. Subba Reddy, *Tetrahedron Lett.* **2010**, *51*, 5529.
[11] I. K. Mangion, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 3967; G. N. Varseev, M. E. Maier, *Org. Lett.* **2007**, *9*, 1461.
[12] J. S. Yadav, U. V. Subba Reddy, B. V. Subba Reddy, *Tetrahedron Lett.* **2009**, *50*, 5984; V. Rawat, P. V. Chouthaiwale, G. Suryavanshi, A. Sudalai, *Tetrahedron: Asymmetry* **2009**, *20*, 2173.
[13] B. Schmidt, A. Biernat, *Chem. – Eur. J.* **2008**, *14*, 6135.
[14] J. S. Yadav, S. Chandrashekar, G. Sumitra, K. Rajashekar, *Tetrahedron Lett.* **1996**, *37*, 6603.
[15] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168; Z. Yang, B. Zang, G. Zao, J. Yang, X. Xie, X. She, *Org. Lett.* **2011**, *13*, 5916; T. Ohyoshi, Y. Miyazawa, K. Aoki, S. Ohmura, Y. Asuma, I. Hayakawa, H. Kigoshi, *Org. Lett.* **2011**, *13*, 2160.
[16] J. S. Yadav, T. Swamy, B. V. Subba Reddy, *Synlett* **2008**, *18*, 2773.

Received December 3, 2012