Asymmetric Total Synthesis of Stagonolide G

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A simple asymmetric total synthesis of stagonolide G (**1**) is described. Asymmetric dihydroxylation, regioselective epoxide ring opening, and vinyl *Grignard* reactions are involved in generating the stereogenic centers C(4) and C(8), followed by *Grubbs-II*-catalyzed ring-closing metathesis (RCM).

Introduction. – Naturally occurring macrolides, particularly ten-membered-ring-containing lactones have continued to attract synthetic chemists as well as biologists during recent years [1], due to their interesting structural properties and potent biological activities [2]. Owing to the scarce availability of these macrolides, only few of them were evaluated for biological activity. Some examples, mainly ten-membered macrolides such as putaminoxin and pinolidoxin displayed potent biological activities [3]. The main metabolite, stagonolide A shows phytotoxic property [4], and stagonolide F exhibits antibacterial and antifungal activity [5a,b]. Stagonolides G–I, nonenolides were produced by *Stagonopora crisis* DAVIS, which is a fungal pathogen isolated from *Cirsium arvense* and proposed as a potential mycoherbicide of this perennial noxious weed, and produces phytotoxic metabolites in liquid and solid cultures [5c].

Biological properties and interesting structural features, such as geometrically defined C=C bonds and with established configurations of OH-carrying centers render stagonolides as significant synthetic targets. In continuation of our studies towards total synthesis of lactone-containing molecules [6], we have synthesized ten-membered macrolides, such as stagonolide A [6c], stagonolide B [6c], and herbarumin I [6d], and we were subsequently interested in a concise synthesis of stagonolide G (**1**; *Fig.*). In this article, we report a simple synthesis of stagonolide G (**1**), and while we were working on the synthesis of **1**, the first stereoselective synthesis of **1** has been reported [7].

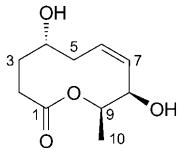
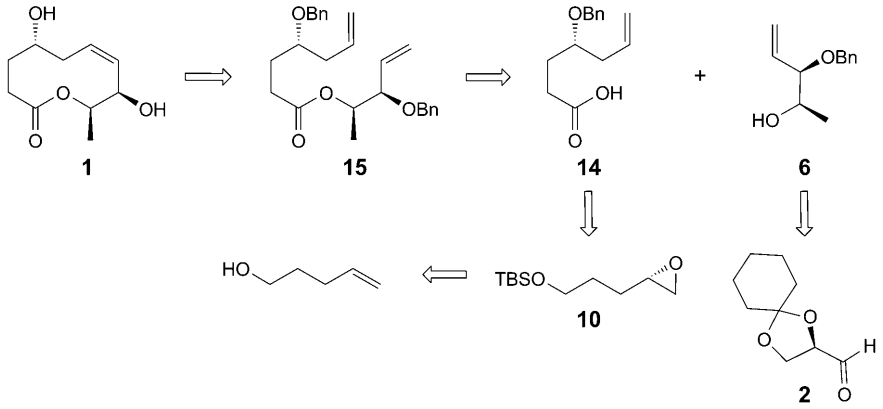


Figure. *Structure of stagonolide G*

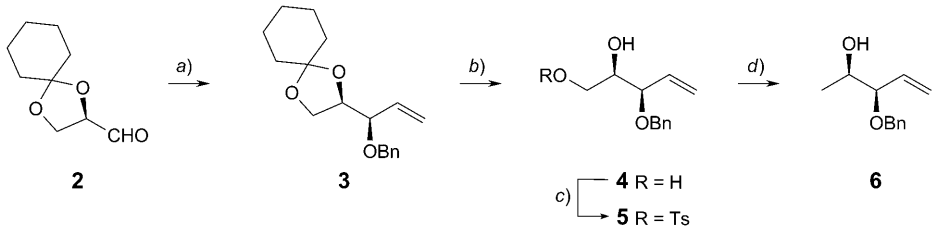
Results and Discussion. – The retrosynthetic analysis of stagonolide G (**1**) is outlined in *Scheme 1*. Compound **1** can be obtained from diene ester **15** by ring-closing methathesis (RCM) protocol, a key reaction strategy that has been widely used for the synthesis of macrolides. Furthermore, compound **15** in turn can be obtained by *Steglich* esterification of acid **14** and alcohol **6**. The intermediate **6** is envisaged from (+)-(*R*)-glyceraldehyde, and intermediate **14** can be easily prepared from commercially available pent-4-en-1-ol. Thus, in the present strategy, the two stereogenic centers C(4) and C(8) (*Fig.*) are constructed: one by dihydroxylation on **7** (*cf. Scheme 3*, below) and the second by vinyl *Grignard* reaction on **2** (*cf. Scheme 2*, below), leading to (4*S*)- and (8*R*)-configurations.

Scheme 1. *Retrosynthetic Analysis*



As outlined in *Scheme 2*, intermediate **6** was prepared from (+)-(*R*)-2,3-di-*O*-cyclohexylideneglyceraldehyde **2** [8]. The aldehyde **2** was reacted with CH_2=CHMgBr in THF to give an inseparable mixture of alcohols in a ratio of 1:1 [9]. Benzylation of the secondary alcohol with BnBr in the presence of NaH in THF afforded compound **3**, and the required isomer was separated by column chromatography. The hexylidene protecting group in **3** was removed by using *Dowex* H^+ resin in MeOH to give the diol **4**

Scheme 2

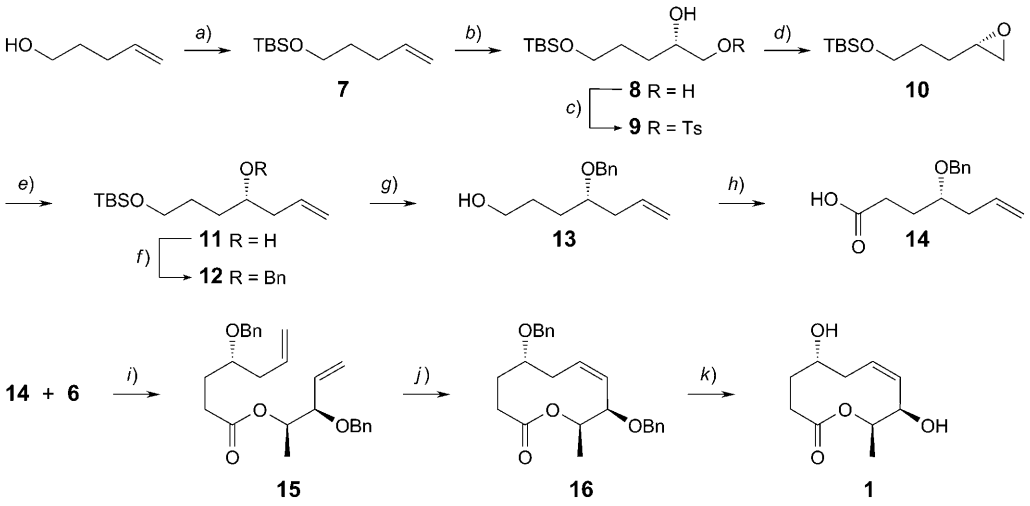


a) 1. CH_2=CHMgBr, THF, −78°, 2 h; 89%; 2. NaH, BnBr, THF, 0° to r.t., 4 h; 41% (separation of isomers). *b*) *Dowex* H^+ resin, MeOH, r.t., 20 h; 91%. *c*) Et_3N, TsCl, Bu_2SnO, CH_2Cl_2, r.t., 4 h; 92%. *d*) $LiAlH_4$, THF, reflux, 1 h; 86%.

[10]. The primary OH group in **4** was selectively protected with $TsCl/Et_3N$ in the presence of Bu_2SnO in dry CH_2Cl_2 to afford the tosyl derivative **5** in 92% yield. The latter was reduced with $LiAlH_4$ in THF to provide the key intermediate **6** for the synthesis of stagonolide G (**1**).

The pent-4-en-1-ol was protected with ^{t}BuMe$_2$SiCl (TBS–Cl) to give compound **7**, and the asymmetric dihydroxylation of the terminal olefine in **7** with *AD-mix-α* ($K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, hydroquinine phthalazine-1,4-diyl diether ($(DHQ)_2PHAL$)) at 0° furnished diol **8** [11], which was further subjected to monotosylation in the presence of a catalytic amount of Bu_2SnO to give **9**; the subsequent exposure to K_2CO_3 afforded epoxide **10** (*Scheme 3*). The regioselective ring opening of **10** with CH_2=CHMgBr in the presence of CuI yielded alcohol **11** [12], which was protected with BnBr using NaH to furnish compound **12**. Deprotection of ^{t}BuMe$_2$Si group in **12** afforded **13**, which was oxidized with [bis(acetoxy)iodo]benzene (BAIB) to give **14** [13].

Scheme 3



a) 1*H*-Imidazole, ^{t}BuMe$_2$SiCl, CH_2Cl_2, r.t., 3 h; 93%. *b*) *AD-mix-α* ($K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, hydroquinine phthalizine-1,4-diyl diether ($(DHQ)_2PHAL$)), ^{t}BuOH/H_2O 1:1, 0°, 24 h; 94%. *c*) Et_3N, TsCl, Bu_2SnO, CH_2Cl_2, r.t., 4 h; 91%. *d*) K_2CO_3, MeOH, r.t., 2 h; 89%. *e*) CH_2=CHMgBr, CuI, THF, –78°, 3 h; 86%. *f*) NaH, BnBr, THF, 0° to r.t., 4 h; 93%. *g*) ^{t}Bu$_4$NF, THF, r.t., 3 h; 92%. *h*) [Bis(acetoxy)iodo]benzene (BAIB), 2,2,6,6-tetramethylpiperidin-1-yl oxide (TEMPO), MeCN/H_2O 2:1, r.t., 3 h; 84%. *i*) Dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0°, 12 h; 83%; see also [7]. *j*) *Grubbs-II* catalyst, CH_2Cl_2, 40°, 3 h; 88%; see also [7]. *k*) $TiCl_4$, CH_2Cl_2, 0°, 3 h; 73%; see also [7].

The acid **14** was esterified with the alcohol **6** in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) at 0° to provide the diene ester **15** in 83% yield, which was subjected to RCM using *Grubbs-II* catalyst to afford the doubly benzyl-protected macrolide **16**. Deprotection of the Bn groups was achieved with $TiCl_4$ in CH_2Cl_2 at 0° to provide the natural product stagonolide G (**1**; *Scheme 3*) in

73% yield. The spectroscopic data of synthetic stagonolide G (**1**) are identical to those of the natural product reported in [5b].

Conclusions. – We have reported a simple and concise total synthesis of stagonolide G (**1**). This protocol involves an asymmetric dihydroxylation, regioselective epoxide ring opening, *Grignard* reaction and *Grubbs-II*-catalyzed ring-closing metathesis as key steps. The synthesis and biological evaluation of structurally related macrolides are in progress in our laboratory.

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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 (anh. Na_2SO_4) and concentrated *in vacuo* below 40°. Column chromatography (CC): silica gel (SiO_2, *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- (300 MHz) and ^{13}C-NMR (75 MHz) spectra: *Bruker Avance 300* instrument, in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. ESI-MS: *Agilent Technologies 1100 Series* (*Agilent* Chemistation Software); in *m*/*z*.

*(2*R*)-2-[(1*R*)-1-(Benzyloxy)prop-2-enyl]-1,4-dioxaspiro[4.5]decane* (**3**). To a soln. of *(+)-(*R*)-2,3-di*-O*-cyclohexylideneglyceraldehyde* (**2**; 1.5 g, 8.82 mmol) in dry THF was added 1.0M CH_2=CHMgBr soln. (13.2 ml, 13.2 mmol) in THF at −78°. The mixture was stirred at the same temp. for 2 h and allowed to reach r.t. After completion, the reaction was quenched with sat. NH_4Cl soln. (150 ml), and the resulting mixture was extracted with AcOEt (2 × 75 ml). The combined org. phases were washed with brine and dried (anh. Na_2SO_4). The solvent was removed under reduced pressure to give an inseparable mixture of alcohols in a ratio of 1:1 (1.55 g). The crude product was then used for the next step without any purification. To a soln. of the crude alcohol mixture (1.3 g, 6.56 mmol) in dry THF (20 ml) was added NaH (0.52 g, 13.13 mmol) at 0°, and the mixture was stirred for 10 min at the same temp. To this, BnBr (0.78 ml, 6.56 mmol) was added at 0° and stirred at r.t. for 4 h. After completion of the reaction, the mixture was diluted with H_2O (100 ml) and extracted with AcOEt (2 × 75 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by CC (SiO_2; hexane/AcOEt 9.8:0.2) to give pure **3** (0.77 g, 41%). Colorless liquid. R_f (hexane/AcOEt 4:1) 0.8. $[\alpha]_D^{25} = -18.5$ (c = 0.49, $CHCl_3$). IR (neat): 2933, 2859, 1449, 1099, 929. ^{1}H-NMR: 1.39 (br. *s*, 2 H); 1.56 (br. *s*, 8 H); 3.66–3.94 (*m*, 3 H); 4.11–4.19 (*m*, 1 H); 4.55 (*AB*, *J* = 12.8, 2 H); 5.26–5.36 (*m*, 2 H); 5.64–5.80 (*m*, 1 H); 7.20–7.41 (*m*, 5 H). ^{13}C-NMR: 23.68; 23.85; 25.03; 34.75; 36.01; 65.24; 70.15; 76.97; 80.95; 119.82; 127.35; 127.61; 128.14; 134.13; 138.21. ESI-MS: 306 ($[M + NH_4]^+$).

*(2*R*,3*R*)-3-(Benzyloxy)pent-4-ene-1,2-diol* (**4**). To a soln. of **3** (0.6 g, 2.08 mmol) in MeOH (15 ml) was added *Dowex H*$^+$ resin (5 g), and the mixture was stirred at r.t. for 20 h. After completion of reaction, the mixture was filtered, and MeOH was evaporated under reduced pressure to afford a crude product, which was purified by CC (hexane/AcOEt 70:30) to afford pure **4** (390 mg, 91%). Colorless liquid. $[\alpha]_D^{25} = -36.92$ (c = 0.25, $CHCl_3$). IR (neat): 3426, 2924, 2852, 1637, 1067. ^{1}H-NMR: 3.12 (br. *s*, 1 H); 3.43–3.68 (*m*, 3 H); 3.76–3.85 (*m*, 1 H); 4.46 (*AB*, *J* = 11.5, 2 H); 5.30–5.43 (*m*, 2 H); 5.67–5.83 (*m*, 1 H); 7.20–7.37 (*m*, 5 H). ^{13}C-NMR: 62.98; 70.43; 73.68; 81.33; 120.61; 127.85; 127.94; 128.47; 134.57; 137.72. ESI-MS: 226 ($[M + NH_4]^+$).

*(2*R*,3*R*)-3-(Benzyloxy)-2-hydroxypent-4-en-1-yl 4-Methylbenzenesulfonate* (**5**). To a soln. of **4** (350 mg, 1.68 mmol), Bu_2SnO (41 mg, 0.168 mmol), and Et_3N (0.23 ml, 1.68 mmol) in dry CH_2Cl_2 was added TsCl (320 mg, 1.68 mmol) at 0° under N_2, and the mixture was stirred for 4 h at r.t. After completion, the reaction was quenched with $NaHCO_3$ soln. (50 ml), and the mixture was extracted with

CH_2Cl_2 (2 × 25 ml). The org. extract was washed with brine, dried (anh. Na_2SO_4), and the solvent was removed under reduced pressure. The crude residue was purified by CC (hexane/AcOEt 9:1) to yield pure **5** (560 mg, 92%). Colorless liquid. R_f (hexane/AcOEt 7:3) 0.7. $[\alpha]_D^{25} = -16.6$ ($c = 0.32$, $CHCl_3$). IR (neat): 3459, 2924, 2851, 1637, 1360, 1176. ^{1}H-NMR: 2.44 (*s*, 3 H); 3.68–3.77 (*m*, 1 H); 3.82–3.89 (*m*, 1 H); 3.94–4.11 (*m*, 2 H); 4.43 (*AB*, $J = 11.3$, 2 H); 5.31–5.40 (*m*, 2 H); 5.70–5.83 (*m*, 1 H); 7.20–7.34 (*m*, 7 H); 7.73–7.79 (*m*, 2 H). ^{13}C-NMR: 21.58; 69.88; 70.60; 71.44; 79.74; 120.84; 127.88; 127.94; 128.43; 129.80; 133.85; 137.46; 144.84. ESI-MS: 380 ($[M + NH_4]^+$).

*(2*R*,3*R*)-3-(Benzyloxy)pent-4-en-2-ol* (**6**). To a soln. of **5** (500 mg, 1.38 mmol), in dry THF (5 ml) was added $LiAlH_4$ (76 mg, 2.07 mmol), and the mixture was heated to reflux for 1 h. After completion of the reaction (TLC), the mixture was cooled to r.t., diluted with H_2O (100 ml), and extracted with AcOEt (3 × 30 ml). The combined org. layer was dried (anh. Na_2SO_4), and the solvent was removed under reduced pressure to afford a crude compound. The crude residue was purified by CC (hexane/AcOEt 9.4:0.6) to give pure **6** (228 mg, 86%). Colorless liquid. R_f (hexane/AcOEt 9:1) 0.5. $[\alpha]_D^{25} = -48.6$ ($c = 0.14$, $CHCl_3$). IR (neat): 3448, 2977, 2928, 2870, 1453, 1259, 1068. ^{1}H-NMR: 1.12 (*d*, $J = 6.3$, 3 H); 2.66 (br. *s*, 1 H); 3.50 (*t*, $J = 7.9$, 1 H); 3.62–3.73 (*m*, 1 H); 4.47 (*AB*, $J = 11.5$, 2 H); 5.28–5.39 (*m*, 2 H); 5.63–5.76 (*m*, 1 H); 7.22–7.37 (*m*, 5 H). ^{13}C-NMR: 18.12; 69.50; 70.34; 85.99; 120.23; 127.68; 127.86; 128.38; 135.10; 137.95. ESI-MS: 215 ($[M + Na]^+$).

*(*tert*-Butyl)(dimethyl)(pent-4-en-1-yloxy)silane* (**7**). To a soln. of the pent-4-en-1-ol (1 g, 11.62 mmol) in dry CH_2Cl_2 (20 ml) was added 1*H*-imidazole (1.18 g, 17.44 mmol), and the mixture was stirred for 10 min at 0°. To this soln., ^{t}BuMe$_2$SiCl (2.1 g, 13.95 mmol) was added at 0°, and the mixture was stirred at r.t. for 3 h. After completion of the reaction, the mixture was diluted with H_2O, extracted with AcOEt (2 × 50 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by CC (hexane/AcOEt 9.9:0.1) to give pure **7** (2.16 g, 93%). Pale yellow liquid. R_f (hexane/AcOEt 9:1) 0.9. $[\alpha]_D^{25} = -5.43$ ($c = 0.53$, $CHCl_3$). IR (neat): 2930, 2858, 1642, 1472, 1255, 1101. ^{1}H-NMR: 0.03 (*s*, 6 H); 0.89 (*s*, 9 H); 1.53–1.66 (*m*, 2 H); 2.03–2.18 (*m*, 2 H); 3.54–3.66 (*m*, 2 H); 4.89–5.04 (*m*, 2 H); 5.69–5.87 (*m*, 1 H). ^{13}C-NMR: −5.18; 26.09; 30.16; 32.08; 62.31; 114.79; 138.30. ESI-MS: 202 ($[M + H]^+$).

*(2*S*)-5-{[(*tert*-Butyl)(dimethyl)silyl]oxy}pentane-1,2-diol* (**8**). To a cooled (0°) soln. of **7** (2.1 g, 10.5 mmol) in ^{t}BuOH/H_2O 1:1 (100 ml) was added *AD-mix-α* ($K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PHAL$; 13 g), and the mixture was stirred at the same temp. for 24 h. To this mixture, Na_2SO_3 (15 g) was added, and the mixture was stirred for 30 min and then filtered. The org. layer was separated, and the aq. layer was extracted with AcOEt (3 × 75 ml). The combined org. layer was dried (anh. Na_2SO_4) and concentrated under reduced pressure. The residue was purified by CC (SiO_2; hexane/AcOEt 7:3) to afford pure **8** (2.3 g, 94%). Colorless liquid. R_f (hexane/AcOEt 7:3) 0.2. $[\alpha]_D^{25} = -5.55$ ($c = 0.45$, MeOH). IR (neat): 3383, 2931, 2859, 1466, 1254, 1096. ^{1}H-NMR: 0.04 (*s*, 6 H); 0.88 (*s*, 9 H); 1.41–1.69 (*m*, 4 H); 2.82 (br. *s*, 1 H); 3.32–3.45 (*m*, 1 H); 3.50–3.71 (*m*, 4 H); 4.01 (br. *s*, 1 H). ^{13}C-NMR: −5.32; 25.98; 29.09; 30.57; 63.44; 66.76; 71.94. ESI-MS: 235 ($[M + H]^+$).

*(2*S*)-5-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-2-hydroxypentyl 4-Methylbenzenesulfonate* (**9**). To a soln. of **8** (2.2 g, 9.40 mmol), Bu_2SnO (234 mg, 0.94 mmol), and Et_3N (1.7 ml, 10.3 mmol) in dry CH_2Cl_2 was added TsCl (1.79 g, 9.4 mmol) at 0° under N_2, and the mixture was stirred for 4 h at r.t. After completion of the reaction, the mixture was diluted with sat. $NaHCO_3$ soln. and extracted with CH_2Cl_2 (2 × 75 ml). The org. extract was washed with H_2O and dried (anh. Na_2SO_4). The solvent was removed under reduced pressure to afford a crude product. The residue was purified by CC (SiO_2; hexane/AcOEt 8.4:1.6) to afford pure **9** (3.31 g, 91%). Colorless liquid. R_f (hexane/AcOEt 7:3) 0.6. $[\alpha]_D^{25} = +2.1$ ($c = 0.48$, $CHCl_3$). IR (neat): 3423, 2924, 1634, 1352, 1175. ^{1}H-NMR: 0.04 (*s*, 6 H); 0.87 (*s*, 9 H); 1.39–1.73 (*m*, 4 H); 2.46 (*s*, 3 H); 3.11 (br. *s*, 1 H); 3.59–3.67 (*m*, 2 H); 3.75–3.87 (*m*, 1 H); 3.88–3.98 (*m*, 2 H); 7.34 (*d*, $J = 8.3$, 2 H); 7.78 (*d*, $J = 8.3$, 2 H). ^{13}C-NMR: −5.41; 21.7; 25.94; 28.66; 30.62; 63.26; 69.14; 73.53; 127.94; 129.80; 132.76; 144.83. ESI-MS: 389 ($[M + H]^+$).

*(*tert*-Butyl)(dimethyl){3-[(2*S*)-oxiran-2-yl]propoxy}silane* (**10**). To a stirred soln. of **9** (3.2 g, 8.24 mmol) in dry MeOH (15 ml) was added K_2CO_3 (2.28 g, 16.49 mmol) under N_2, and the mixture was stirred for 2 h. After completion of the reaction, MeOH was removed under reduced pressure. The residue was diluted with H_2O (100 ml) and extracted with CH_2Cl_2 (2 × 100 ml). The combined org. phases were washed with H_2O and brine, and dried (anh. Na_2SO_4). After evaporation of the solvent, the

crude residue was purified by CC (SiO_2; hexane/AcOEt 9.6:0.4) to give pure **10** (1.58 g, 89%). Colorless liquid. R_f (hexane/AcOEt 4:1) 0.8. $[\alpha]_D^{25} = -4.3$ ($c = 0.19$, $CHCl_3$). IR (neat): 1252, 1098, 835, 773. ^{1}H-NMR: 0.04 (*s*, 6 H); 0.88 (*s*, 9 H); 1.51–1.72 (*m*, 4 H); 2.44–2.48 (*m*, 1 H); 2.73 (*t*, $J = 4.0$, 1 H); 2.88–2.95 (*m*, 1 H); 3.58–3.70 (*m*, 2 H). ^{13}C-NMR: −5.38; 25.89; 28.97; 29.08; 47.01; 52.07; 62.54. ESI-MS: 217 ($[M+H]^+$).

*(4*S*)-7-{[(*tert*-Butyl)(dimethyl)silyl]oxy}hept-1-en-4-ol* (**11**). To a cooled (−78°) soln. of CuI (0.12 g, 0.65 mmol) in dry THF (5 ml) was added 1.0M CH_2=CHMgBr soln. (16.2 ml, 16.2 mmol) in THF. To this soln. was added **10** (1.4 g, 6.48 mmol) in dry THF (15 ml), and the mixture was stirred at the same temp. for 3 h and allowed to reach r.t. After completion, the reaction was quenched with sat. NH_4Cl soln. (50 ml), and the mixture was extracted with AcOEt (3 × 50 ml). The combined org. phases were washed with H_2O and brine, and dried (anh. Na_2SO_4). The solvent was removed under reduced pressure, and the crude residue was purified by CC (SiO_2; hexane/AcOEt 9.4:0.6) to give pure **11** (1.36 g, 86%). Pale yellow liquid. R_f (hexane/AcOEt 90:10) 0.5. $[\alpha]_D^{25} = -27.10$ ($c = 0.24$, $CHCl_3$). IR (neat): 3422, 2931, 2858, 1640, 1253, 1098, 835. ^{1}H-NMR: 0.05 (*s*, 6 H); 0.90 (*s*, 9 H); 1.40–1.70 (*m*, 4 H); 2.11–2.30 (*m*, 2 H); 2.40 (br. *s*, 1 H); 3.57–3.69 (*m*, 3 H); 5.03–5.16 (*m*, 2 H); 5.73–5.91 (*m*, 1 H). ^{13}C-NMR: −5.42; 25.88; 29.06; 33.80; 41.85; 63.38; 70.55; 117.43; 135.05. ESI-MS: 245 ($[M+H]^+$).

*{(4*S*)-[4-(Benzyloxy)hept-6-en-1-yl]oxy}(*tert*-butyl)(dimethyl)silane* (**12**). To a cooled (0°) soln. of **11** (1.2 g, 4.91 mmol) in dry THF (20 ml) was added NaH (0.39 g, 9.83 mmol) at 0°, and the mixture was stirred for 10 min. To this mixture, BnBr (0.59 ml, 4.91 mmol) was added and stirred at r.t. for 4 h. After completion of the reaction, the mixture was diluted with H_2O (100 ml), extracted with AcOEt (2 × 75 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by CC (SiO_2; hexane/AcOEt 9.7:0.3) to afford pure **12** (1.52 g, 93%). Colorless liquid. R_f (hexane/AcOEt 9:1) 0.8. $[\alpha]_D^{25} = -9.04$ ($c = 0.31$, $CHCl_3$). IR (neat): 2931, 2858, 1252, 1095. ^{1}H-NMR: 0.03 (*s*, 6 H); 0.89 (*s*, 9 H); 1.48–1.71 (*m*, 4 H); 2.23–2.42 (*m*, 2 H); 3.41–3.52 (*m*, 1 H); 3.55–3.63 (*m*, 2 H); 4.52 (*AB*, $J = 11.3$, 2 H); 5.01–5.15 (*m*, 2 H); 5.74–5.94 (*m*, 1 H); 7.28–7.41 (*m*, 5 H). ^{13}C-NMR: −5.28; 25.96; 28.58; 29.93; 38.30; 63.11; 70.78; 78.27; 116.89; 127.40; 127.63; 128.25; 134.89; 138.84. ESI-MS: 335 ($[M+H]^+$).

*(4*S*)-4-(Benzyloxy)hept-6-en-1-ol* (**13**). To a soln. of **12** (1.4 g, 4.19 mmol) in dry THF (15 ml) was added 1M ^{t}Bu$_4$NF soln. (4.19 ml) in THF, and the mixture was stirred for 3 h at r.t. After completion, the reaction was quenched with sat. $NaHCO_3$ soln. (100 ml), and the mixture was extracted with AcOEt (2 × 50 ml), the org. layer was washed with brine, dried (anh. Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by CC (SiO_2; hexane/AcOEt 4:1) to yield pure **13** (850 mg, 92%). Colorless liquid. R_f (hexane/AcOEt 7:3) 0.3. $[\alpha]_D^{25} = -12.96$ ($c = 0.24$, $CHCl_3$). IR (neat): 3401, 2934, 2865, 1449, 1060. ^{1}H-NMR: 1.51–1.75 (*m*, 4 H); 2.23–2.48 (*m*, 2 H); 3.43–3.52 (*m*, 1 H); 3.54–3.61 (*m*, 2 H); 4.53 (*AB*, $J = 11.5$, 2 H); 5.01–5.13 (*m*, 2 H); 5.72–5.92 (*m*, 1 H); 7.27–7.38 (*m*, 5 H). ^{13}C-NMR: 28.19; 29.87; 37.81; 62.13; 70.57; 78.10; 116.80; 127.24; 127.47; 128.02; 134.39; 138.21. ESI-MS: 221 ($[M+H]^+$).

*(4*S*)-4-(Benzyloxy)hept-6-enoic Acid* (**14**). To a soln. of **13** (750 mg, 3.40 mmol) in MeCN/H_2O 2:1 (10 ml) were added [bis(acetoxy)iodo]benzene (BAIB; 2.41 g, 7.49 mmol) and 2,2,6,6-tetramethylpiperidin-1-yl oxide (TEMPO; 106 mg, 0.68 mmol). The mixture was stirred at r.t. for 3 h. After completion of the reaction (TLC), the mixture was filtered and extracted with AcOEt (2 × 25 ml). The combined org. phases were dried and concentrated under reduced pressure. The crude residue was purified by CC (SiO_2; hexane/AcOEt 7.8:2.2) to give pure **14** (660 mg, 84%). Pale yellow liquid. R_f (hexane/AcOEt 7:3) 0.25. $[\alpha]_D^{25} = -26.7$ ($c = 0.32$, $CHCl_3$). IR (neat): 3428, 2928, 1707, 1447, 1072, 916, 739. ^{1}H-NMR: 1.72–1.96 (*m*, 2 H); 2.21–2.48 (*m*, 4 H); 3.43–3.54 (*m*, 1 H); 4.51 (*AB*, $J = 11.3$, 2 H); 5.03–5.13 (*m*, 2 H); 5.72–5.88 (*m*, 1 H); 7.20–7.34 (*m*, 5 H). ^{13}C-NMR: 28.50; 29.90; 37.95; 70.82; 77.0; 117.34; 127.41; 127.60; 128.17; 134.05; 138.21; 179.83. ESI-MS: 257 ($[M+Na]^+$).

*(2*R*,3*R*)-3-(Benzyloxy)pent-4-en-2-yl (4*S*)-4-(Benzyloxy)hept-6-enoate* (**15**). To a cooled (0°) soln. of **6** (180 mg, 0.937 mmol), DCC (386 mg, 1.874 mmol), and DMAP (11 mg, 0.093 mmol) in dry CH_2Cl_2 (5 ml) was added **14** (219 mg, 0.937 mmol), and the mixture was stirred at same temp. for 12 h. After completion of the reaction (TLC), the mixture was diluted with H_2O (25 ml) and extracted with CH_2Cl_2 (2 × 15 ml). The combined org. phases were dried and concentrated under reduced pressure. The crude residue was purified by CC (SiO_2; hexane/AcOEt 9.6:0.4) to afford pure **15** (317 mg, 83%). Liquid. R_f

(hexane/AcOEt 9:1) 0.6. $[\alpha]_D^{25} = -26.94$ ($c = 0.28$, $CHCl_3$). IR (neat): 2923, 2853, 1731, 1636, 1457, 1070, 697. ^{1}H-NMR: 1.15 (*d*, *J* = 6.8, 3 H); 1.69–1.92 (*m*, 2 H); 2.19–2.41 (*m*, 4 H); 3.40–3.51 (*m*, 1 H); 3.71–3.77 (*m*, 1 H); 4.30–4.64 (*m*, 4 H); 4.93–5.12 (*m*, 3 H); 5.24–5.35 (*m*, 2 H); 5.65–5.87 (*m*, 2 H); 7.16–7.35 (*m*, 10 H). ^{13}C-NMR: 15.97; 28.97; 30.37; 38.22; 70.36; 71.01; 71.27; 77.40; 81.39; 117.41; 119.50; 127.53; 127.71; 128.32; 134.40; 134.57; 172.88. ESI-MS: 431 ($[M + Na]^+$).

*(5*S*,7*Z*,9*R*,10*R*)-5,9-Bis(benzyloxy)-10-methyl-3,4,5,6,9,10-hexahydro-2*H*-oxecin-2-one* (**16**). To a soln. of **15** (100 mg, 0.245 mmol) in degassed anh. CH_2Cl_2 (250 ml) was added *Grubbs-II* catalyst (42 mg, 0.049 mmol), and the mixture was stirred at 40° for 3 h. After completion, the reaction was quenched with CH_2=CHOEt, and the mixture was concentrated under reduced pressure to afford a dark brown residue. The crude residue was purified by CC (SiO_2; hexane/AcOEt 9.6:0.4) to give pure **16** (82 mg, 88%). Liquid. R_f (hexane/AcOEt 9:1) 0.5. $[\alpha]_D^{25} = -1.70$ ($c = 0.32$, $CHCl_3$). IR (neat): 2931, 2861, 1729, 1451, 1251, 1073. ^{1}H-NMR: 1.17 (*d*, *J* = 6.8, 3 H); 1.76–1.92 (*m*, 1 H); 1.97–2.13 (*m*, 1 H); 2.14–2.36 (*m*, 3 H); 2.39–2.56 (*m*, 1 H); 3.53–3.64 (*m*, 1 H); 4.30–4.55 (*m*, 5 H); 5.01–5.13 (*m*, 1 H); 5.36–5.47 (*m*, 1 H); 5.50 (*td*, *J* = 11.3, 4.3, 1 H); 7.13–7.32 (*m*, 10 H). ^{13}C-NMR: 13.0; 26.34; 28.50; 32.40; 69.64; 70.28; 71.11; 76.74; 127.30; 127.50; 128.29; 128.90; 131.14; 138.15; 138.53; 173.18. ESI-MS: 403 ($[M + Na]^+$).

Stagonolide G (=*(5*S*,7*Z*,9*R*,10*R*)-3,4,5,6,9,10-Hexahydro-5,9-dihydroxy-10-methyl-2*H*-oxecin-2-one*; **1**). To a soln. of **16** (60 mg, 0.15 mmol) in dry CH_2Cl_2 (5 ml) was added a soln. of $TiCl_4$ (0.05 ml, 0.47 mmol) in dry CH_2Cl_2 (2 ml) under N_2 at 0°, the mixture was stirred at same temp. for 2 h. After completion of the reaction (TLC), the mixture was diluted with H_2O (50 ml) and extracted with CH_2Cl_2 (2 × 20 ml). The combined org. phases were washed with $NaHCO_3$ soln., dried, and solvent was removed under reduced pressure. The crude compound was purified by CC (SiO_2; hexane/AcOEt 7:3) to afford pure **1** (23 mg, 73%). Viscous liquid. R_f (hexane/AcOEt 7:3) 0.1. $[\alpha]_D^{25} = +9.8$ ($c = 0.18$, $CHCl_3$). IR (neat): 3428, 2921, 2852, 1762, 1459, 1370, 760. ^{1}H-NMR: 1.14 (*d*, *J* = 6.4, 3 H); 1.90–2.09 (*m*, 1 H); 2.29–2.71 (*m*, 5 H); 3.65–3.72 (*m*, 1 H); 4.07–4.15 (*m*, 1 H); 4.50–4.62 (*m*, 1 H); 5.55–5.73 (*m*, 2 H). ^{13}C-NMR: 18.64; 27.43; 28.75; 33.72; 70.82; 72.22; 79.58; 127.79; 132.51; 176.69. ESI-MS: 201 ($[M + H]^+$).

REFERENCES

[1] I. Shiina, *Chem. Rev.* **2007**, *107*, 239.

[2] J. Piel, *Nat. Prod. Rep.* **2009**, *26*, 338; K. C. Nicolaou, J. S. Chen, S. M. Dalby, *Bioorg. Med. Chem.* **2009**, *17*, 2290; T. Arif, J. D. Bhosale, N. Kumar, T. K. Mandal, R. S. Bendre, G. S. Lavekar, R. Dabur, *J. Asian Nat. Prod. Res.* **2009**, *11*, 621; H. Itokawa, S. L. Morris-Natschke, T. Akiyama, K.-H. Lee, *J. Nat. Med.* **2008**, *62*, 263; F. Pietra, *Nat. Prod. Rep.* **1997**, 453.

[3] A. Evidente, R. Capasso, A. Andolfi, M. Vurro, M. Chiara Zonno, *Nat. Toxins* **1999**, *6*, 183.

[4] O. Yuzikhin, G. Mitina, A. Berestetskiy, *J. Agric. Food Chem.* **2007**, *55*, 7707.

[5] a) A. Evidente, A. Cimmino, A. Berestetskiy, G. Mitina, A. Andolfi, A. Motta, *J. Nat. Prod*. **2008**, *71*, 31; b) A. K. Perepogu, D. Raman, U. S. N. Murthy, V. J. Rao, *Bioorg. Chem.* **2009**, *37*, 46; c) A. Evidente, A. Cimmino, A. Berestetskiy, A. Andolfi, A. Motta, *J. Nat. Prod.* **2008**, *71*, 1897.

[6] a) K. Rajesh, V. Suresh, J. J. P. Selvam, C. B. Rao, Y. Venkateswarlu, *Synthesis* **2010**, 1381; b) V. Shekhar, D. K. Reddy, V. Suresh, D. Chanti Babu, Y. Venkateswarlu, *Tetrahedron Lett.* **2010**, *51*, 946; c) P. Prabhakar, S. Rajaram, D. K. Reddy, V. Shekar, Y. Venkateswarlu, *Tetrahedron: Asymmetry* **2010**, *21*, 216; d) J. J. P. Selvam, K. Rajesh, V. Suresh, D. Chanti Babu, Y. Venkateswarlu, *Tetrahedron: Asymmetry* **2009**, *20*, 1115; e) D. K. Reddy, V. Shekhar, T. S. Reddy, S. P. Reddy, Y. Venkateswarlu, *Tetrahedron: Asymmetry* **2009**, *20*, 2315; f) K. Rajesh, V. Suresh, J. J. P. Selvam, C. B. Rao, Y. Venkateswarlu, *Helv. Chim. Acta* **2009**, *92*, 1866; g) M. Narasimhulu, A. Sai Krishna, J. V. Rao, Y. Venkateswarlu, *Tetrahedron* **2009**, *65*, 2989.

[7] P. Srihari, B. Kumaraswamy, D. C. Bhunia, J. S. Yadav, *Tetrahedron Lett.* **2010**, *51*, 2903.

[8] A. Chatopadhyay, B. Dhotare, S. Hassarajani, *J. Org. Chem.* **1999**, *64*, 6874; J. Jurczak, S. Pikul, T. Bauer, *Tetrahedron* **1986**, *42*, 447.

[9] F. Bravo, M. Kassou, S. Castillón, *Tetrahedron Lett.* **1999**, *40*, 1187; N. Sarkar, A. Nayek, S. Ghosh, *Org. Lett.* **2004**, *6*, 1903; J. Nokami, H. Ogawa, S. Miyamoto, T. Mandai, S. Wakabayashi, J. Tsuji, *Tetrahedron Lett.* **1999**, *29*, 5181.

[10] S. C. Bergmeier, D. M. Stanchina, *J. Org. Chem.* **1999**, *64*, 2852.
[11] H. Takahata, M. Kubota, T. Momose, *Tetrahedron: Asymmetry* **1997**, *8*, 2801.
[12] A. Vincent, J. Prunet, *Synlett* **2006**, 2269.
[13] J. B. Epp, T. S. Widlanski, *J. Org. Chem.* **1999**, *64*, 293.

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