Tetrahedron: *Asymmetry* 21 (2010) 216–221

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

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

Total synthesis of the phytotoxic stagonolides A and B

Peddikotla Prabhakar, Singanaboina Rajaram, Dorigondla Kumar Reddy, Vanam Shekar, Yenamandra Venkateswarlu *

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500 003, India

ARTICLE INFO

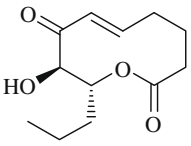
Article history:
Received 30 November 2009
Accepted 20 January 2010

ABSTRACT

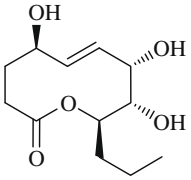
The chemo-enzymatic and covergent synthesis of stagonolide B and the synthesis of stagonolide A, a phytotoxic 10-membered lactone have been achieved starting from D-ribose with overall yields of 25% and 8.7%, respectively. The synthesis contained simple steps in developing three centers' key intermediates, namely the enzymatic (Novozyme-435) resolution of a propargylic alcohol followed by macrolactonization and RCM.

1. Introduction

Stagonospora crisii (a pathogen of *Crisium arvense*) is a perennial noxious weed, which produces six phytotoxic metabolites, all these are usually mentioned as stagonolides. Structurally stagonolides A and B are very similar to those of herbarumins, and are phytotoxins with potential herbicidal activity isolated from *Phoma herbarum*.[1] The initial structural and stereochemical assignment of stagonolide A was established by Berestetskiy et al.[2] Stagonolide B was established by Evidente et al.[3] by spectroscopic studies. Ramana et al.[4] further established the structure by total synthesis and X-ray analysis. Stagonolide A has shown very good phytotoxic activity compared with the other stagonolides. Herein we report the chemo-enzymatic and covergent synthesis of stagonolide B and the synthesis of stagonolide A from D-ribose as a chiral source.



Stagonolide A **1**



Stagonolide B **2**

2. Results and discussion

The retro synthetic analysis of stagonolides A and B is outlined in Scheme 1. Stagonolide A was prepared by the esterification of readily available 5-hexenoic acid with intermediate **7** followed by RCM.[5] The intermediate **7** was prepared from the Vasella fragmentation of the D-ribose derivative. Stagonolide B was prepared by the esterification of acid intermediate **17** with intermediate **7** followed by RCM. Intermediate **17** was prepared from 1,4-butanediol.

As outlined in Scheme 2, intermediate **7** was prepared from D-ribose, following the literature procedure.[6] The D-ribose, protected as an acetonide and methylated at the anomeric hydroxyl group, was prepared in one pot to give compound **4** in 91% yield. The compound **4** was reacted with iodine in the presence of triphenyl phosphine and imidazole at reflux to give iodo compound[7] **5** in 95% yield, which was reacted with Zn in ethanol to give a low-boiling Vasell' intermediate[8] **6** in 89% yield. Compound **6** without purification was reacted with *n*-propyl magnesium bromide to give compound **7** (*anti*/*trans*:*syn*/*cis*: 81:19) in 95% yield. The required *anti*/*trans* isomer was purified chromatographically to yield **7** in 79% yield.

The 1,4-butane diol was protected with benzyl bromide to give benzyl ether **9** in 95% yield; the primary alcohol in the benzyl-protected butanol **9** was oxidized with pyridinium chlorochromate to give compound **10** in 92% yield, which was reacted with ethynyl magnesium bromide in tetrahydrofuran to give racemic propargylic alcohol[9] **11** in 82% yield**.** Following the literature procedure, we carried out the chemo-enzymatic (Novozyme-435) resolution[9] of compound **11** using vinylacetate in diisopropyl ether to give compound (*R*)-**12** (53% yield, 80% ee) and acetylated compound (*S*)-**12** (45% yield, 90%ee). Partial hydrogenation[9] of compound (*R*)-**12** using Lindlar catalyst (palladium on $CaCO_3$, poisoned with Pb) in ethyl acetate gave compound **13** in 86% yield, and the secondary alcohol in compound **13** was protected with methoxy methyl chloride[10] (MOM-Cl) using *N*,*N*-diisopropylethylamine (DIPEA) in dichloromethane to give compound **14** in 94% yield. The debenzylation[11] of compound **14** was carried out with Li–naphthalenide in dry THF at −25 °C to give compound **15** in 82% yield, which was oxidized with IBX acid (2-iodoxy benzoicacid) to afford aldehyde **16** in 94% yield. Oxidation[12] of **16** with $NaClO_2$ and NaH_2PO_4 afforded acid **17** in 98% yield.

Acid compound **17** was esterified with the previously prepared compound **7** in the presence of DCC and DMAP in dry dichlorometh-

* Corresponding author. Tel.: +91 40 27193167; fax: +91 40 27160512.
E-mail address: luchem@iict.res.in (Y. Venkateswarlu).

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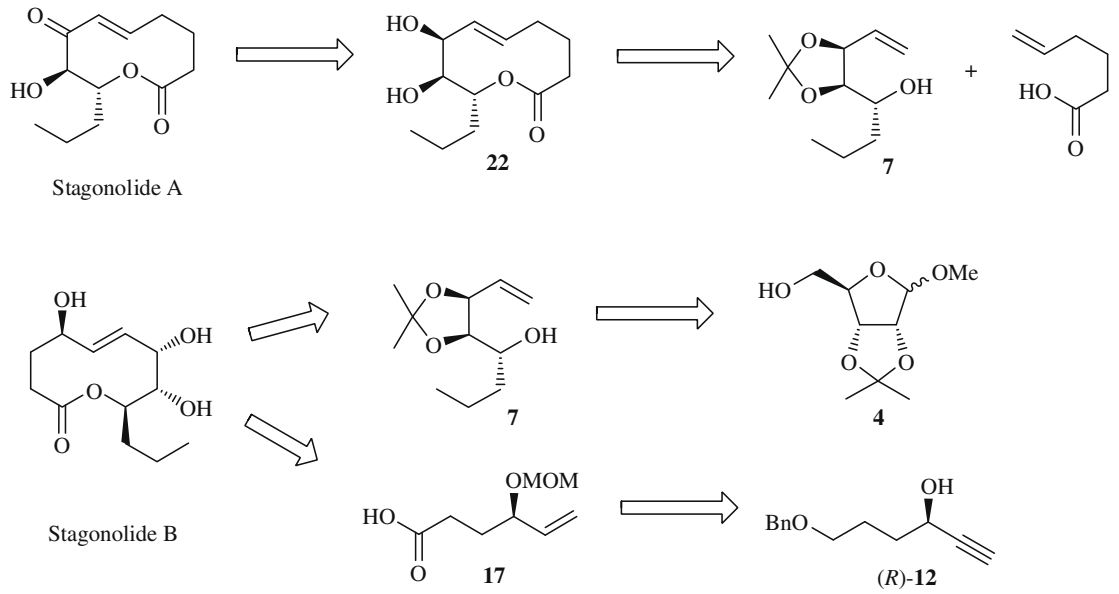
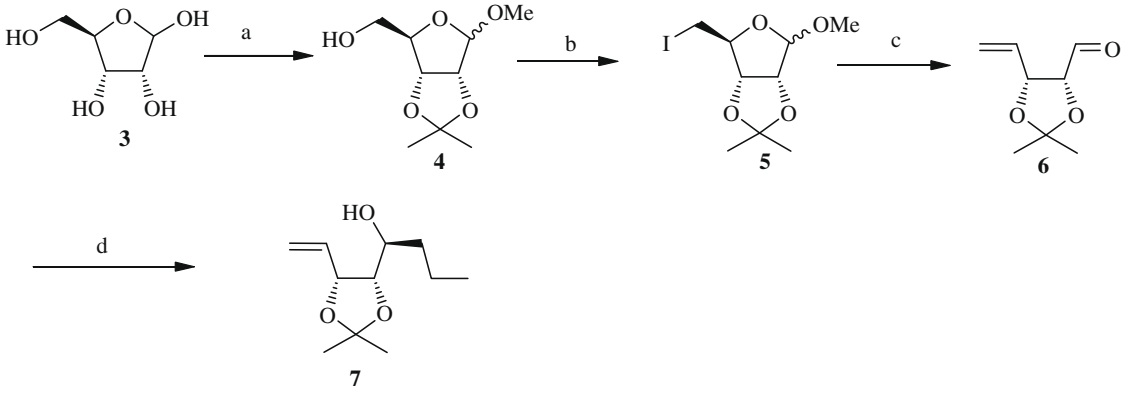
doi:10.1016/j.tetasy.2010.01.010



Scheme 1. Retrosynthesis of stagonolides A and B.



Scheme 2. Reagents and conditions: (a) 2,2-dimethoxy propane, acetone, $HClO_4$, methanol, 4 h, 91%; (b) I_2, PPh_3, imidazole, toluene, 2 h, 72%; (c) Zn, EtOH, 90 °C, 89%; (d) *n*-propyl magnesium bromide, dry THF, 0 °C, 79%.

ane to give ester compound **18** in 65% yield, which was subjected to ring closure metathesis (RCM) using Grubbs' II generation catalyst to give the protected lactone **19** in 65% (required *E*-isomer). The RCM reaction was very smooth and MOM protection did not hinder the formation of RCM product **19**. The removal of the acetonide protection and MOM-protecting groups was carried out using trifluoroacetic acid to give stagonolide B in 90% yield (Scheme 3).

The synthesis of stagonolide A was carried out by esterification[5] of 5-hexenoic acid with the previously prepared compound **7** in the presence of DCC and DMAP to give ester **20** in 95% yield. The ring closure metathesis (RCM) of compound **20** using Grubbs' I generation catalyst led to the protected lactone **21** in 80% yield (as the required *E*-isomer). The acetonide-protecting group in compound **21** was carried out using trifluoro acetic acid (TFA) to give compound **22** in 90% yield, which was oxidized[13] with MnO_2 to afford stagonolide A **1** in 82% yield (Scheme 4). The physical and spectroscopic data of synthetically prepared stagonolides A and B were identical to those of the natural products.

3. Conclusion

In conclusion, we have reported a simple and economic route for the total synthesis of stagonolides A and B from D-ribose with overall yields of 25% and 8.7%, respectively.

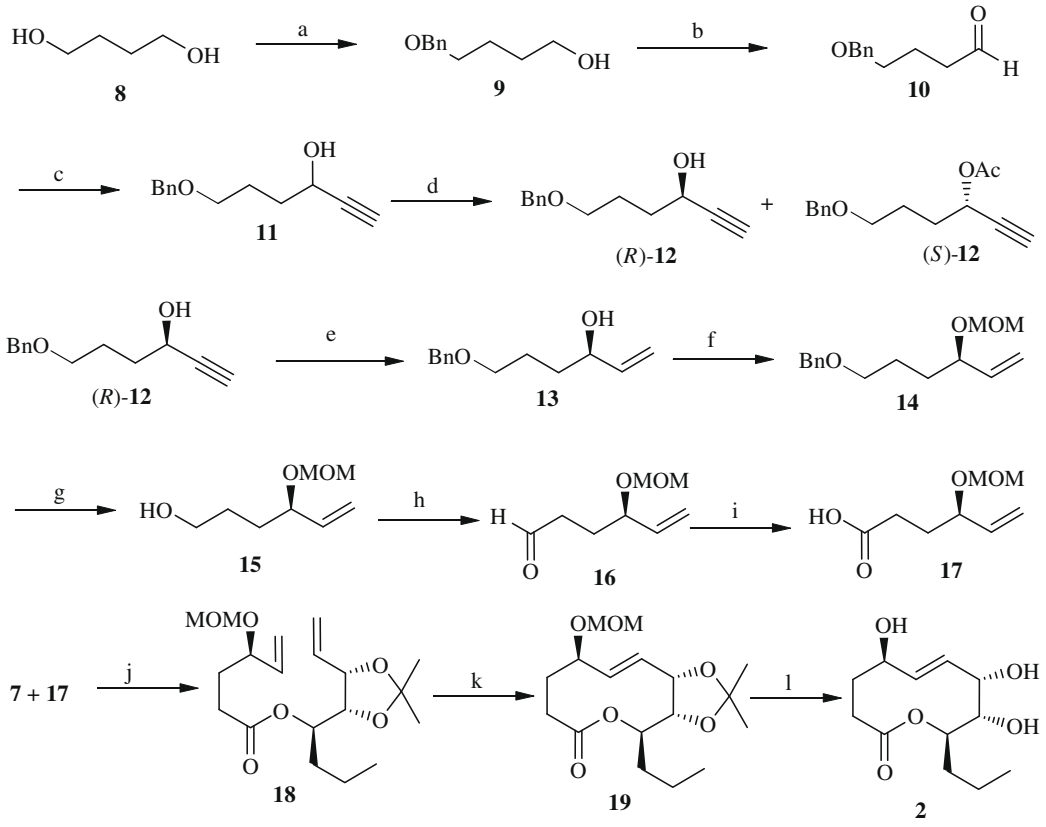
4. Experimental

4.1. General methods

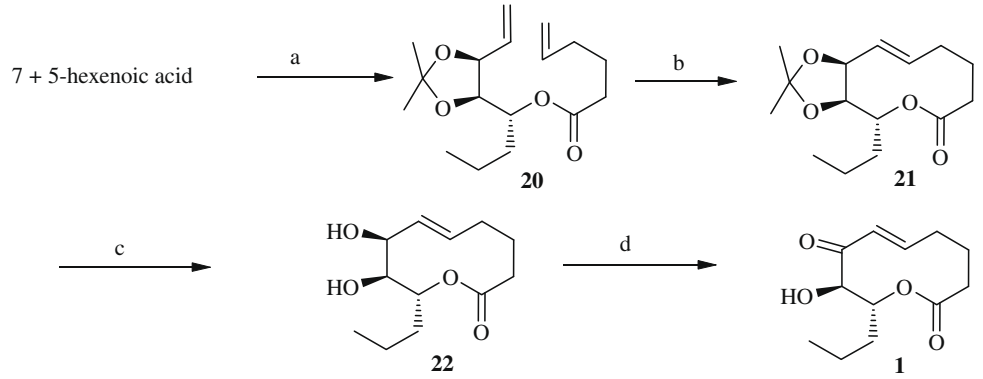
All solvents and reagents were purified by standard techniques. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). The IR spectra were recorded on a Perkin–Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were recorded on a HORIBA SEPA-300 polarimeter, 2 mL cell. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Varian Gemini 200 and a Brucker Avance 300. Chemical shifts are reported in parts per million with respect to internal TMS. Coupling constants (*J*) are quoted in hertz. Mass spectra were recorded on CEC-21-11013 and Fannigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

4.1.1. Methyl 2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside 4

To a stirred solution of D-(−)-ribose (4.0 g, 26.6 mmol) and 2,2-dimethoxypropane (8 mL, 65.2 mmol) in acetone (25 mL) was added perchloric acid (aq 70%, 1.6 mL, 18.4 mmol) dropwise at 0 °C and stirred for 2 h at room temperature. Later methanol (6 mL, 147 mmol) was added and the solution was stirred for 2 h at room temperature. After completion of the reaction as moni-



Scheme 3. Reagents and conditions: (a) BnBr, NaH, dry THF, 0 °C, 5 h, 95%; (b) PCC, DCM, rt, 1 h, 92%; (c) C_2HMgBr, dry THF, 0 °C, 5 h, 82%; (d) vinyl acetate, Novozyme-435, diisopropyl ether, rt, 2 h, 54%; (e) Lindlar's catalyst, quinoline, ethyl acetate 2 h, 86%; (f) MOM-Cl, DIPEA, DCM, rt, 4 h, 94%; (g) Li-metal, naphthalene, dry THF, −25 °C, 4 h, 82%; (h) IBX acid, DMSO, DCM, rt, 4 h, 94%; (i) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, DMSO, H_2O, rt, 1 h, 98%; (j) DCC, DMAP, DCM, rt, 12 h, 65%; (k) Grubbs II, DCM, 45 °C, 12 h, 65%; (l) TFA, 0 °C, 2 h, 90%.



Scheme 4. Reagents and conditions: (a) DCC, DMAP, DCM, rt, 12 h, 95%; (b) Grubbs I, DCM, 45 °C, 8 h, 80%; (c) TFA, 0 °C, 2 h, 90%; (d) MnO_2, DCM, rt, 12 h, 82%.

tored by TLC, the reaction mixture was neutralized with saturated $NaHCO_3$ solution (20 mL) and the reaction mixture was filtered. The filtrate was evaporated under reduced pressure and extracted with diethylether (3 × 30 mL). The combined organic layer was washed with brine solution (20 mL) and dried over anhydrous Na_2SO_4 after which the solvent was evaporated under reduced pressure to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (9:1) to obtain pure compound **4** (6.0 g, 95%) as a yellow liquid. $[\alpha]_D^{25} = -94$ (*c* 0.1, $CHCl_3$); IR (neat): 3452, 2939, 1373, 1209, 1160, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H), 1.47 (s, 3H), 3.09 (dd, *J* = 3.02, 9.80 Hz, 1H), 3.44 (s, 3H), 3.61 (m, 2H), 4.37 (t, *J* = 3.02, 1H), 4.53 (d, *J* = 6.03, 1H), 4.78 (d, *J* = 6.03, 1H), 4.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 24.6, 26.3, 55.4, 63.9, 81.4, 85.7, 88.3, 109.9 and 112.0; ESI-MS: *m*/*z* 227 $[M+Na]^+$.

4.1.2. Methyl 5-deoxy-5-iodo-2,3-*O*-(1-methylethylidene)-β-D-ribofuranoside 5

To a stirred solution of compound **4** (6.0 g, 28.4 mmol) in toluene (100 mL), imidazole (5.8 g, 85.2 mmol) and triphenylphosphine (11.2 g, 42.7 mmol) was added iodine (10.1 g, 39.8 mmol) and stirred at 80 °C for 2 h. After completion of the reaction as monitored by TLC, the reaction was quenched with a solution of sodium thiosulphate pentahydrate (10 mL) and extracted into ethyl acetate. The organic layer was separated and dried over Na_2SO_4 and the solvent was removed under reduced pressure to give a

crude residue, which was purified by a silica gel (60–120 mesh) column using hexane/ethyl acetate (9:1) to obtain pure compound **5** (6.7 g, 72%) as a colorless oil: $[\alpha]_D^{25} = -68.3$ (*c* 0.1, $CHCl_3$); IR (neat): 2986, 2935, 1372, 1210, 1194, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.49 (s, 3H), 3.16 (t, *J* = 10.0 Hz, 1H), 3.29 (dd, *J* = 9.9, 6.0 Hz, 1H), 3.37 (s, 3H), 4.44 (dd, *J* = 10.1, 6.0 Hz, 1H), 4.63 (d, *J* = 5.9 Hz, 1H), 4.77 (d, *J* = 5.8 Hz, 1H), 5.05 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 6.6, 24.9, 26.3, 55.2, 82.9, 85.3, 87.4, 109.6 and 112.6; ESI-MS: *m*/*z* 337 $[M+Na]^+$.

4.1.3. (4*R*,5*R*)-2,2-Dimethyl-5-vinyl-[1,3]dioxolane-4-carbaldehyde 6

To a stirred solution of compound **5** (2.0 g, 5.6 mmol) in EtOH 95% (25 mL) was added activated Zn dust (3.0 g, 46.5 mmol) and stirred for 1 h at reflux. After completion of the reaction as monitored by TLC, the reaction mixture was filtered and the solvent was evaporated to yield crude aldehyde **6**, which was used in the next step without any further purification.

4.1.4. (*R*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)butan-1-ol 7

To a stirred solution of *n*-propyl magnesium bromide (1 M solution) in THF was added compound **6** (950 mg, 6.0 mmol) in dry THF at 0 °C and stirred for 5 h at the same temperature. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated NH_4Cl (10 mL), extracted into ethyl acetate, evaporated under reduced pressure, and purified by a silica gel column (60–120 mesh) using hexane/ethyl acetate (9:1) to obtain pure compound **7** (962 mg, 79%) as a yellow liquid. $[\alpha]_D^{25} = +4.5$ (*c* 0.012, $CHCl_3$): IR (neat): 3465, 1645, 1375, 1096 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, *J* = 5.66 Hz, 3H), 1.32–1.40 (m, 2H), 1.37 (s, 3H), 1.45–1.57 (m, 2H), 1.50 (s, 3H), 1.99 (d, *J* = 5.28 Hz, 1H), 3.53 (m, 1H), 3.95 (dd, *J* = 5.28, 6.79 Hz, 1H), 4.52 (t, *J* = 6.79 Hz, 1H), 5.22–5.36 (m, 2H), 5.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 14.1, 18.8, 25.2, 27.1, 27.6, 36.1, 69.2, 79.1, 80.8, 118.9 and 134.4; ESI-MS: *m*/*z* 223 $[M+Na]^+$.

4.1.5. 4-(Benzyloxy)butan-1-ol 9

To a stirred suspension of NaH (2.66 g, 110 mmol) in dry THF (50 mL) was added compound **8** (5.0 g, 55.5 mmol) in dry THF followed by benzyl bromide (7.9 mL, 66.04 mmol) at 0 °C and stirred at room temperature for 5 h. After completion of the reaction as monitored by TLC, the reaction was quenched with cold water, extracted into ethyl acetate (3 × 20 mL), and evaporated under reduced pressure to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (8:2) to obtain pure compound **9** (8.8 g, 90%) as a yellow liquid. IR (neat): 3625, 3412, 2401, 1953, 1455, 1215, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.64–1.75 (m, 2H), 2.36 (br s, 1H), 3.52 (t, *J* = 5.66 Hz, 2H), 3.64 (t, *J* = 5.85 Hz, 2H), 4.52 (s, 2H), 7.28–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 26.1, 29.2, 61.7, 69.9, 72.5, 127.2, 127.4, 128.1 and 137.9; ESI-MS: *m*/*z* 181 $[M+1]^+$.

4.1.6. 4-(Benzyloxy)butanal 10

To a stirred solution of the compound **9** (5.0 g, 27.7 mmol) in dichloromethane (100 mL) was added PCC (12.0 g, 55.8 mmol) at room temperature and stirred for 1 h. After completion of the reaction as monitored by TLC, the solvent was evaporated under reduced pressure to give a crude residue, which was purified on silica gel (60–120 mesh) column using hexane/ethyl acetate (9:1) to obtain pure compound **10** (4.5 g, 92% yield) as a pale yellow liquid. IR (neat): 3032, 2932, 2865, 1706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.90–1.97 (m, 2H), 2.53 (t, *J* = 6.83 Hz, 2H), 3.50 (t, *J* = 5.85 Hz, 2H), 4.48 (s, 2H), 7.28–7.35 (m, 5H), 9.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 22.5, 40.9, 69.1, 72.9, 127.5, 128.3, 128.4, 138.3 and 202.1; ESI-MS: *m*/*z* 179 $[M+1]^+$.

4.1.7. 6-(Benzyloxy)-hex-1-yn-3-ol 11

To a stirred solution of compound **10** (4.0 g, 22.47 mmol) in dry THF (50 mL) was added C_2HMgBr (3.47 g, 26.89 mmol, 1.6 M solution) at −78 °C and stirred for 5 h. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated NH_4Cl (20 mL) solution and extracted into ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo to give a crude residue, which was purified on a silica gel (60–120 mesh) column using hexane/ethyl acetate (8:2) to afford racemic compound **11** as a pale yellow liquid (3.9 g, 85% yield: IR (neat) 3395, 3282, 2106, 1448, 1365, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.70–1.91 (m, 4H), 2.46 (d, *J* = 2.1 Hz, 1H), 2.90 (br d, *J* = 3.6 Hz, 1H), 3.50–3.60 (m, 2H), 4.2–4.4 (m, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 7.27–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 35.1, 61.6, 70.0, 72.6, 73.1, 85.2, 127.4, 127.8, 128.2, 138.1; ESI-MS: *m*/*z* 205 $[M+1]^+$.

4.1.8. (*R*)-6-(Benzyloxy)-hex-1-yn-3-ol (*R*)-12

To a stirred solution of racemic compound **11** (3.8 g, 18.62 mmol) in diisopropyl ether (50 mL) and vinyl acetate (1.75 mL, 18.97 mmol) was added Novozyme-435 (1.9 g) at room temperature and stirred for 2 h. After completion of the reaction as monitored by TLC, the reaction mixture was filtered through Celite, and the solvent was evaporated under reduced pressure to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (8:2) to obtain pure compounds (*R*)-**12** (2.0 g, 53% yield, 80% ee) as a colorless oil and (*S*)-**12** (1.71 g, 45% yield) as a colorless oil. Data for (*R*)-**12**; $[\alpha]_D^{25} = +10.4$ (*c* 0.1, $CHCl_3$): IR (neat) 3395, 3282, 2106, 1448, 1365, 1092 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.70–1.91 (m, 4H), 2.46 (d, *J* = 2.1 Hz, 1H), 2.90 (br d, *J* = 3.6 Hz, 1H), 3.50–3.60 (m, 2H), 4.2–4.4 (m, 1H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 7.27–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.3, 35.1, 61.6, 70.0, 72.6, 73.1, 85.2, 127.4, 127.8, 128.2, 138.1; ESI-MS: *m*/*z* 205 $[M+1]^+$.

4.1.9. (*R*)-6-(Benzyloxy)-hex-1-en-3-ol 13

To a stirred solution of compound (*R*)-**12** (2.0 g, 9.8 mmol) and quinoline (0.23 mL, 1.9 mmol) in ethylacetate (25 mL) was added Lindlar's catalyst (70w/w%) at room temperature and stirred for 2 h under hydrogen atmosphere. After completion of the reaction as monitored by TLC, the solvent was removed in vacuo to give a crude residue, which was purified on a silica gel (60–120 mesh) column using hexane/ethyl acetate (8:2) to afford compound **13** (1.71 g) in 86% yield as a pale yellow liquid. $[\alpha]_D^{25} = +18.3$ (*c* 0.004, $CHCl_3$): IR (neat) 3417, 1643, 1452, 1362, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.52–1.76 (m, 4H), 2.30 (br s, 1H), 3.48 (t, *J* = 5.28 Hz, 2H), 4.12 (q, *J* = 5.28 Hz, 1H), 5.06 (dt, *J* = 10.57, 1.51 Hz, 1H), 5.20 (dt, *J* = 17.3, 1.5 Hz, 1H), 5.83 (m, 1H), 7.24–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.8, 34.3, 70.3, 72.7, 73.0, 114.4, 127.6, 127.7, 128.3, 138.1 and 140.0; ESI-MS: *m*/*z* 229 $[M+Na]^+$.

4.1.10. 1-((4-(Methoxymethoxy)-hex-5-enyloxy)methyl) benzene 14

To a stirred solution of compound **13** (1.0 g, 4.85 mmol) and DIPEA (1.9 mL, 14.72 mmol) in dry DCM (20 mL) was added MOM-Cl (0.6 mL, 7.5 mmol) at 0 °C and stirred for 2 h at room temperature. After completion of the reaction as monitored by TLC, water was added, and the reaction mixture was extracted into DCM (3 × 20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed

in vacuo to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (9:1) to afford compound **14** (1.15 g) in 95% yield as a colorless oil. $[\alpha]_D^{25} = +53.65$ (*c* 0.01, $CHCl_3$): IR (neat) 2943, 2856, 1642, 1452, 1361, 1099 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.53–1.74 (m, 4H), 3.32 (s, 3H), 3.45 (t, *J* = 5.28 Hz, 2H), 3.96 (q, *J* = 5.28, 12.08 Hz, 1H), 4.46 (d, *J* = 6.79, 1H), 4.47 (s, 2H), 4.64 (d, *J* = 6.79, 1H) 5.14 (br s, 1H), 5.19 (d, *J* = 6.79 Hz, 1H), 5.64 (m, 1H), 7.27–7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.8, 32.1, 55.3, 70.1, 72.9, 76.9, 93.5, 117.2, 127.4, 127.5, 128.3, 138.5 and 138.6; ESI-MS: *m*/*z* 273 $[M+Na]^+$.

4.1.11. 4-(Methoxymethoxy) hex-5-en-1-ol 15

To a stirred solution of Li-metal (100 mg, 16.6 mmol) was added naphthalene (2.04 g, 15.9 mmol) in dry THF (20 mL) and stirred for 90 min at room temperature. Then compound **14** (1.0 g, 0.00 mmol) in THF was added to the above-mentioned mixture at −25 °C and stirred for 2 h at the same temperature. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated NH_4Cl (5 mL), extracted into ethyl acetate (3 × 20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (7:3) to afford compound **15** (492 mg) in 82% yield as a colorless oil. $[\alpha]_D^{25} = +29.5$ (*c* 0.01, $CHCl_3$): IR (neat) 3415, 2933, 1447, 1643, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.58–1.74 (m, 4H), 1.85 (br s, 1H), 3.36 (s, 3H), 3.64 (t, *J* = 6.04 Hz, 2H), 4.02 (q, *J* = 5.28, 12.8 Hz, 1H), 4.51 (d, *J* = 6.79, 1H), 4.68 (d, *J* = 6.79, 1H) 5.17 (br s, 1H), 5.22 (d, *J* = 7.55 Hz, 1H), 5.67 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.6, 32.0, 55.4, 62.6, 77.05, 93.6, 117.3 and 138.2; ESI-MS: *m*/*z* 161 $[M+1]^+$.

4.1.12. 4-(Methoxymethoxy) hex-5-enal 16

To a suspension of IBX acid (840 mg, 3.0 mmol) in DMSO (2 mL) and DCM (8 mL), a solution of compound **15** (300 mg, 2.0 mmol) in DCM was added at room temperature and stirred for 4 h. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated $NaHCO_3$ solution (5 mL). The reaction mixture was filtered through Celite and extracted into ethyl acetate (3 × 20 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (8:2) to afford compound **16** (281 mg) in 94% yield as a colorless oil. $[\alpha]_D^{25} = +8.0$ (*c* 0.017, $CHCl_3$): IR (neat) 2928, 1705, 1608, 1447, 1097 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.89 (q, *J* = 6.04, 13.5 Hz, 2H), 2.52 (dt, *J* = 1.51, 6.79 Hz, 2H), 3.34 (s, 3H), 4.02 (q, *J* = 6.04, 13.5 Hz, 1H), 4.47 (d, *J* = 6.79, 1H), 4.64 (d, *J* = 6.79, 1H) 5.20 (br s, 1H), 5.24 (d, *J* = 5.28 Hz, 1H), 5.65 (m, 1H), 9.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.8, 39.8, 55.5, 76.1, 93.7, 117.9, 137.7 and 200.9; ESI-MS: *m*/*z* 159 $[M+1]^+$.

4.1.13. 4-(Methoxymethoxy) hex-5-enoic acid 17

To a stirred solution of compound **16** (200 mg, 1.35 mmol) in DMSO and water (8:2, 10 mL) were added sodium chlorite (145 mg, 1.61 mmol) and NaH_2PO_4 (251 mg, 1.61 mmol) and stirred at room temperature for 1 h. After completion of the reaction as monitored by TLC, the reaction mixture was extracted into ethyl acetate (3 × 20 mL), and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (6:4) to afford compound **17** (182 mg) in 95% yield as a pale yellow liquid. $[\alpha]_D^{25} = +17.75$ (*c* 0.02, $CHCl_3$): IR (neat) 3435, 2924, 1712, 1418, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.88 (q, *J* = 6.79, 13.59 Hz, 2H), 2.45 (t, *J* = 6.79 Hz, 2H), 3.35 (s, 3H), 4.04 (q, *J* = 6.04, 13.5 Hz, 1H), 4.49 (d, *J* = 6.79, 1H), 4.65 (d, *J* = 6.79, 1H) 5.20 (d, *J* = 7.55 Hz, 1H), 5.25 (d, *J* = 7.55 Hz, 1H), 5.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.9, 30.1, 55.5, 75.9, 93.6, 117.9, 137.7 and 179.3; ESI-MS: *m*/*z* 175 $[M+1]^+$.

4.1.14. (4*R*)-(*R*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl) butyl 4-(methoxymethoxy)hex-5-enoate 18

To a stirred solution of compound **7** (100 mg, 0.50 mmol), DCC (123 mg, 0.6 mmol), and DMAP (catalytic) in dry DCM (10 mL) was added compound **17** (78.1 mg, 0.55 mmol) in dry DCM (5 mL) and stirred for 12 h at room temperature. After completion of the reaction as monitored by TLC, the solvent was removed under vacuum to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (9:1) to afford pure compound **18** (104 mg) in 65% yield as a pale yellow liquid. $[\alpha]_D^{25} = +26.1$ (*c* 0.02, $CHCl_3$): IR (neat) 3456, 2931, 1738, 1646, 1458, 1375 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.28 Hz, 3H), 1.30–1.38(m, 2H), 1.58 (m, 1H), 1.66 (m, 1H), 1.83 (q, *J* = 7.28, 14.5 Hz, 2H) 2.30 (dt, *J* = 4.16, 7.28 Hz, 2H), 3.34 (s, 3H), 4.00 (q, *J* = 7.28, 13.5 Hz, 1H), 4.12 (t, *J* = 7.28 Hz, 1H), 4.47 (d, *J* = 7.28, 1H), 4.55 (t, *J* = 6.24, 1H), 4.64 (d, *J* = 6.24 Hz, 1H), 4.86 (dt, *J* = 3.12, 7.28 Hz, 1H), 5.17–5.33 (m, 4H), 5.62–5.68 (m, 1H), 5.71–5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 17.9, 25.3, 27.7, 30.3, 33.5, 55.4, 71.6, 76.0, 78.4, 78.8,, 93.6, 108.7, 117.8, 118.2, 133.4, 137.7 and 172.9; ESI-MS: *m*/*z* 379 $[M+Na]^+$.

4.1.15. (6*E*,5*R*,8*S*,9*S*,10*R*)-4,5,9,10-Tetrahydro-5,8,9-trihydroxy-10-propyl-3*H*-oxecin-2(8*H*)-one 2

To a solution of compound **18** (60 mg, 0.18 mmol) in dry dichloromethane (50 mL) was added Grubbs' II generation catalyst (30.6 mg, 0.036 mmol) and the mixture was degassed thoroughly under a nitrogen atmosphere, after which the reaction mixture was refluxed for 12 h. After completion of the reaction as monitored by TLC, the solvent was removed under reduced pressure to give a crude residue, which was purified by a silica gel (60–120 mesh) column using hexane/ethyl acetate (9:1) to afford compound **19** (38.5 mg, 65% yield) as a colorless liquid. Thus obtained compound **19** (35 mg) was reacted with TFA (5 mL) at 0 °C and stirred for 2 h. After completion of the reaction, water was added (5 mL), extracted into ethyl acetate (3 × 10 mL), and the solvent was evaporated under reduced pressure to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (7:3) to afford pure compound **2** (20.5 mg, 92% yield) as a viscous liquid. $[\alpha]_D^{25} = +24.5$ (*c* 0.01, $CHCl_3$); IR (neat): 3409, 2927, 1729, 1560 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (t, *J* = 7.3 Hz, 3H), 1.21–1.30 (m, 1H), 1.30–1.40 (m, 1H), 1.54 (dd, *J* = 4.9, 9.8 Hz, 1H), 1.60 (br s, 1H), 1.82–1.90 (m, 2H), 2.05–2.12 (m, 2H), 2.24 (d, *J* = 8.4 Hz, 1H), 2.42 (br s, 1H), 2.45 (m, 2H), 3.55 (t, *J* = 8.5 Hz, 1H), 4.45 (s, 1H), 4.60 (s, 1H), 4.95 (dt, *J* = 2.5, 9.6 Hz, 1H), 5.62 (d, *J* = 8.4 Hz, 1H), 5.95 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 18.1, 27.9, 31.6, 33.8, 68.7, 70.1, 73.4, 73.5, 127.3, 127.4, 176.6. ESI-MS *m*/*z*: 267 $[M+Na]^+$.

4.1.16. (*R*)-1-((4*R*,5*S*)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)butyl hex-5-enoate 20

To a stirred solution of compound **7** (100 mg, 0.50 mmol), DCC (123 mg, 0.6 mmol), and DMAP (catalytic) in dry DCM (10 mL) was added 5-hexenoic acid (0.071 mL, 0.6 mmol) and stirred for 12 h at room temperature. After completion of the reaction as monitored by TLC, the solvent was removed under vacuum to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (9:1) to afford compound **20** (133 mg) in 91% yield as a pale yellow liquid. $[\alpha]_D^{25} = +28.2$ (*c* 0.1, $CHCl_3$): IR (neat) 2928, 1739, 1641, 1458, 1375, 1167 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.92 (t, *J* = 7.28 Hz, 3H), 1.30–1.38 (m, 2H), 1.58 (m, 1H), 1.66 (m, 1H), 1.83 (q, *J* = 7.28, 14.5 Hz, 2H) 2.30 (dt, *J* = 4.16, 7.28 Hz, 2H), 3.34 (s, 3H), 4.00 (q, *J* = 7.28, 13.5 Hz, 1H), 4.12 (t, *J* = 7.28 Hz, 1H), 4.47 (d, *J* = 7.28, 1H), 4.55

(t, J = 6.24, 1H), 4.64 (d, J = 6.24 Hz, 1H), 4.86 (dt, J = 3.12, 7.28 Hz, 1H), 5.17–5.33 (m, 4H), 5.62–5.68 (m, 1H), 5.71–5.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 17.9, 24.0, 25.4, 27.8, 33.2, 33.6, 71.4, 78.4, 78.9, 108.6, 115.6, 118.1, 133.5, 137.5 and 171.8; ESI-MS: m/z 319 $[M+Na]^+$.

4.1.17. (6*E*,8*S*,9*S*,10*R*)-4,5,9,10-Tetrahydro-8,9-dihydroxy-10-propyl-3*H*-oxecin-2(8*H*)-one 22

To a stirred solution of compound **20** (100 mg, 0.33 mmol) in dry dichloromethane (50 mL) was added Grubbs' I generation catalyst (55.6 mg, 0.067 mmol) and the mixture was degassed thoroughly under a nitrogen atmosphere. The reaction mixture was refluxed for 8 h. After completion of the reaction as monitored by TLC, the solvent was removed under reduced pressure to give a crude residue. The residue was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (9:1) to afford pure compound **21** (72.4 mg, 80% yield) as a colorless liquid. The above-mentioned compound **21** (70 mg) was reacted with TFA (5 mL) at 0 °C and stirred for 2 h. After completion of the reaction as monitored by TLC, water was added (5 mL), extracted into ethyl acetate (3 × 10 mL), and the solvent was evaporated under reduced pressure to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (7:3) to afford pure compound **22** (40.4 mg, 90% yield) as a colorless low-melting solid; $[\alpha]_D^{25} = +12.4$ (c 0.5, EtOH); IR (KBr): 3435, 2928, 2852, 1635, 1456, 1210, 1089 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J = 7.3 Hz, 3H), 1.30–1.22 (m, 3H), 1.45– 1.71 (m, 3H), 2.05–1.78 (m, 3H), 2.21–2.35 (m, 2H), 2.65 (br s, 1H), 3.42 (d, J = 9.4 Hz, 1H), 4.42 (br s, 1H), 4.94 (td, J = 9.4, 2.4 Hz, 1H), 5.49 (m, 1H), 5.58 (d, J = 15.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 18.1, 24.6, 33.4, 33.6, 34.5, 70.1, 73.2, 73.5, 124.8, 130.5, 176.1; ESI-MS: m/z 251 $[M+Na]^+$.

4.1.18. (6*E*,9*R*,10*R*)-4,5–9,10-Tetrahydro-9-hydroxy-10-propyl-3*H*-oxecin-2,8-dione 1

To a stirred solution of compound **22** (30 mg, 0.13 mmol) in dry dichloromethane (10 mL) was added activated MnO_2 (22.8 mg, 0.26 mmol) and stirred for 12 h at room temperature. After completion of the reaction as monitored by TLC, the reaction was filtered through Celite and then the total solvent was evaporated under reduced pressure to give a crude residue, which was purified by silica gel (60–120 mesh) column using hexane/ethyl acetate (8:2) to afford compound **1** (staganolide A) (24 mg, 82% yield) as a white solid. $[\alpha]_D^{25} = -41.2$ (c 0.01, EtOH); IR (KBr): 3409, 2927, 1742, 1705, 1634, 1183 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J = 7.3 Hz, 3H), 1.26–1.34 (m, 1H), 1.38–1.44 (m, 1H), 1.65 (m, 1H), 1.91 (m, 1H), 1.95 (m, 1H), 2.02 (m, 1H), 2.06 (m, 1H), 2.12 (dd, J = 2.5, 14.3 Hz, 1H), 2.42 (dd, J = 2.5, 14.3 Hz, 1H), 2.50 (m, 1H), 3.56 (d, J = 6.3 Hz, 1H), 4.01 (dd, J = 2.5, 14.3 Hz, 1H), 4.62 (t, J = 6.3 Hz, 1H), 6.20 (m, 1H), 6.40 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9, 18.0, 25.2, 33.6, 34.1, 34.3, 74.6, 76.6, 131.8, 142.9, 174.1 and 199.5. ESI-MS m/z: 249 $[M+Na]^+$.

Acknowledgments

The authors P.P., D.K.R., and V.S. are thankful to CSIR, New Delhi, India, respectively, for the financial support and Dr. J. S. Yadav Director, Indian Institute of Chemical Technology (IICT), for his encouragement.

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