Tetrahedron 68 (2012) 3725–3728

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

First enantioselective total synthesis of (*S*)-(−)-longianone

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ARTICLE INFO

Article history:
Received 8 February 2012
Received in revised form 28 February 2012
Accepted 6 March 2012
Available online 13 March 2012

Keywords:
1,2-Cyclopropanecarboxylate
One-pot reaction
Intramolecular hetero Michael addition
1,7-Dioxaspiro[4,4]nonane
Carbohydrates

ABSTRACT

An efficient stereoselective synthesis of (*S*)-(−)-longianone was achieved from sugar derived 1,2-cyclopropanecarboxylate involving bromonium ion mediated solvolytic ring opening and a one-pot dehydrohalogenation, stereoselective intramolecular hetero Michael addition (IHMA) and ester hydrolysis as key steps.

1. Introduction

1,7-Dioxaspiro[4.4]nonane is one of the significant structural unit present in a number of bioactive natural products.[1] Some of these include bacterial metabolites secosyrins **1**, syringolides **2**[2] isolated from *Pseudomonas syringae* as well as sphydrofuran **3**[3] obtained from a strain of Actinomycetes. Longianone **4**[4] is a structurally related but biosynthetically different natural product containing this spirobicyclic system. Longianone was also proposed to be an intermediate during the biosynthesis of secosyrins **1** and syringolides **2**.[5] Hyperolactone A **5**,[6] also a structurally similar natural product possessing an alternative 1,7-dioxaspiro[4.4]nonane skeleton[7] (Fig. 1). Interestingly, a number of methods for the stereoselective synthesis of all the above-mentioned spirobicyclic natural products were reported except longianone, where the absolute configuration was also unknown.

Longianone is produced along with its isomeric mycotoxin metabolites patulin[8] and isopatulin[9] by the fungus *Xylaria longiana*, an uncommon member of the fungus genus *Xylaria*.[4] All these three metabolites are originated from a single biosynthetic origin derived from oxidative ring opening of the aromatic polyketide metabolide, 6-methylsalicylic acid (6-MSA).[5] In our investigations towards the synthetic application of 1,2-cyclopropanecarboxylated sugar derivatives,[10] we recently reported a stereoselective method for the construction of *C*-spiroglycosides possessing 1,7-dioxaspiro[4.4]nonane systems.[11] Herein, we report the first stereoselective synthesis of longianone and revealed the absolute configuration of the natural product.

The first total synthesis of racemic longianone was reported by Steel,[12] 12 years ago, involving a free radical cyclization of an enyne as a key step to construct the β-disubstituted-γ-butyrolactone. Recently Stratakis et al.,[13] reported a divergent synthesis of racemic longianone along with isopatulin and (*Z*)-ascladiol starting from furan diol. A formal synthesis of (±)-longianone was also reported recently using acyl radical cyclizations with β-alkoxyacrylates.[14]

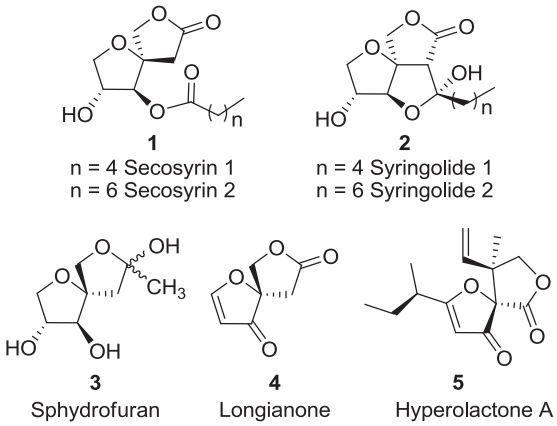

Fig. 1. Natural products possessing 1,7-dioxaspiro[4.4]nonane core.

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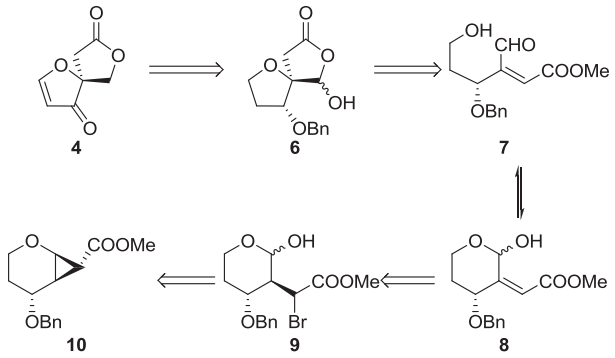
doi:10.1016/j.tet.2012.03.021

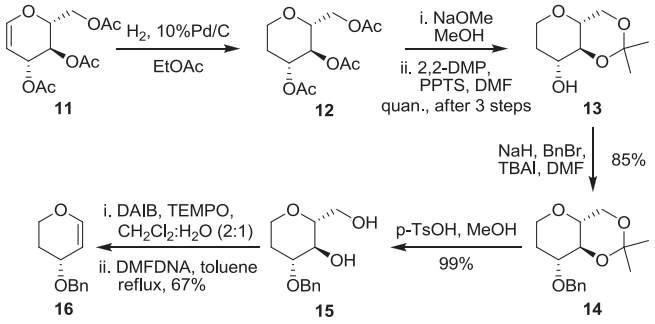
2. Results and discussion

Towards the stereoselective synthesis of longianone, we envisaged that the α,β-unsaturated ketone functionality in **4** could be attained from spirocyclic lactol **6**, which could be obtained from hydroxyaldehyde **7** via a stereoselective intramolecular hetero Michael addition (IHMA) followed by ester hydrolysis. Compound **7** could exist in equilibrium with the more stable hemi-acetal **8**, which could be synthesized from bromohydrin **9** by dehydrohalogenation. Bromohydrin **9** will be easily accessible by an electrophilic ring opening of known 1,2-cyclopropanecarboxylate **10**[15] (Scheme 1).



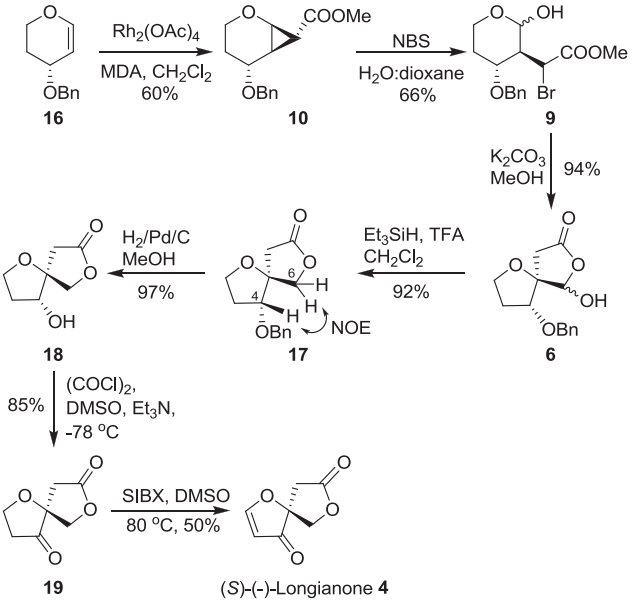
Scheme 1. Retrosynthetic analysis of longianone.

The immediate precursor for the preparation of **10** would be the corresponding glycal derivative **16**, which could be synthesized from commercially available 3,4,6-tri-*O*-acetyl-D-glucal **11**. Thus, Pd/C mediated catalytic hydrogenation of **11** provided 1,2-dideoxy-3,4,6-tri-*O*-acetyl-D-glucose **12**,[16] which upon Zemplén deacetylation with NaOMe in MeOH followed by selective isopropylidine protection of 4- and 6-hydroxyls using 2,2-dimethoxypropane/pyridinium *p*-toluene sulfonate in DMF gave the acetonide **13**[17] in quantitative yield after three steps. Benzylation of free hydroxyl in **13** provided **14**, which upon acetonide deprotection using *p*-toluenesulfonic acid in methanol gave the diol **15**[16] in excellent yield. Selective oxidation of the primary alcohol to the corresponding carboxylic acid using diacetoxy iodobenzene (DAIB)/TEMPO in a mixture of dichloromethane/water (2:1) followed by decarboxylative elimination using *N*,*N*-dimethylformamide dineopentyl acetal (DMFDNA) in toluene under reflux conditions lead to the formation of glycal derivative **16**[15] in good yield (67% over two steps) (Scheme 2).



Scheme 2. Synthesis of glycal precursor for cyclopropanation reaction.

Stereoselective cyclopropanation of glycal **16** using methyl diazoacetate (MDA) under catalytic $Rh_2(OAc)_4$ conditions in CH_2Cl_2 provided the 1,2-cyclopropanecarboxylate **10** as a single enantiomer in good yield (Scheme 3). Bromonium ion mediated electrophilic ring opening of **10** with *N*-bromosuccinimide in a mixture of dioxane/water (2:1) gave the bromohydrin **9**. Treatment of **9** with K_2CO_3/MeOH provided a diastereomeric mixture of spirocyclic lactol **6** involving a one-pot dehydrohalogenation, IHMA and ester hydrolysis. Dehydroxylation of **6** using Et_3SiH/TFA in CH_2Cl_2 provided an enantiomerically pure spirolactone **17**. The stereochemistry at spiro centre was assigned based on observing strong NOE between 4-CH and 6-CH_2 (please see Supplementary data). Hydrogenolysis of **17** to give alcohol **18** followed by Swern oxidation provided the (*S*)-(−)-dihydrolongianone **19** (lit. $[\alpha]_D^{20}$ −63 (*c* 1.0, $CHCl_3$))[4] $[\alpha]_D^{25}$ −66 (*c* 0.8, $CHCl_3$). Dehydrogenation of compound **19** using stabilized IBX (SIBX)[13] provided enantiomerically pure (*S*)-(−)-longianone **4** (lit. $[\alpha]_D^{20}$ −85 (*c* 1.0, EtOH))[4] $[\alpha]_D^{25}$ −90 (*c* 0.9, EtOH) in 50% yield based on recovered starting material with a conversion of only ~60% (Scheme 3). The absolute configuration of natural longianone was assigned by comparing the optical rotation of natural and synthetic longianones. To the best of our knowledge, this is the first report on the stereoselective total synthesis of (*S*)-(−)-longianone.



Scheme 3. Stereoselective synthesis of *S*-(−)-longianone.

3. Conclusion

In conclusion, a concise stereoselective synthesis of (*S*)-(−)-longianone was achieved from 3,4,6-tri-*O*-acetyl-D-glucal via 1,2-cyclopropanecarboxylate **10** involving a total of 14 steps with an overall 8% yield. Also, the absolute configuration of the longianone that was isolated from the fungus *X. longiana* (Rehm.)[4] was revealed.

4. Experimental section

4.1. General

All the reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions unless otherwise mentioned. Dichloromethane, dimethyl sulfoxide, methanol and triethyl amine were initially dried and stored over 4 Å molecular sieves. TLC was run on silica gel 60 F_{254} (Merck) and the spots were detected by staining with H_2SO_4 in methanol (5%, v/v) or

phosphomolybdic acid in ethanol (5%, w/v) and heat. Silica gel (100–200 mesh) was used as a stationary phase for column chromatography. NMR spectra were recorded at 25 °C on a Bruker Avance III 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) or 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) instrument with $CDCl_3$ residual $CHCl_3$ (δ_H 7.26 ppm) as internal standard for ^{1}H and $CDCl_3$ (δC 77.0 ppm) as internal standard for ^{13}C. Chemical shifts are given in δ (ppm) and coupling constants (J) in hertz. IR spectra were recorded on JASCO FT/IR-5300. Low-resolution mass spectra were recorded on a Shimadzu-LCMS-2010A mass spectrometer. High-resolution mass spectra were recorded on Bruker maXis ESI-TOF spectrometer.

4.2. 1,2-Dideoxy-3-*O*-benzyl-4,6-*O*-isopropylidene-D-glucose (14)

To a cooled (0 °C) suspension of sodium hydride (1.27 g, 31.9 mmol) in DMF (10 mL) was added a solution of compound **13** (5.0 g, 26.6 mmol) in DMF (50 mL) for a period of 10 min and the mixture was stirred for another 20 min (until the H_2 evolution ceases). Benzyl bromide (3.48 mL, 29.2 mmol) was added dropwise to the reaction mixture for a period of 10 min and then TBAI (100 mg) was added. The reaction mixture was allowed to stir at room temperature for 6 h. After completion of the reaction, water (20 mL) was added slowly and the reaction mixture was extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with saturated aq NaCl (3×50 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography EtOAc/hexane (1:6) to afford the benzylated isopropylidene derivative **14** (6.3 g, 85%) as a colourless gum. R_f (20% EtOAc/hexane) 0.53; $[\alpha]_D^{25}$ +11 (*c* 1.0, $CHCl_3$). IR (neat): 2873, 1454 cm^{-1}. δ_H NMR (400 MHz, $CDCl_3$): 7.30–7.41 (m, 5H), 4.83 (d, 1H, *J*=12.4 Hz), 4.71 (d, 1H, *J*=12.4 Hz), 3.94 (dd, 1H, *J*=5.2, 11.4 Hz), 3.90 (dd, 1H, *J*=5.6, 10.8 Hz), 3.69–3.78 (m, 2H), 3.54–3.60 (m, 1H), 3.47 (td, 1H, *J*=2.4, 12.8 Hz), 3.19 (dt, 1H, *J*=5.2, 10.0 Hz), 1.98–2.03 (m, 1H), 1.74–1.84 (m, 1H), 1.54 (s, 3H), 1.47 (s, 3H). δ_C NMR (100 MHz, $CDCl_3$): 139.1, 128.3, 127.5, 127.4, 99.4, 76.5, 76.3, 72.6, 72.3, 66.4, 62.4, 32.4, 29.3, 19.2. Low-resolution MS (EI): *m*/*z*: 278 (M^+); HRMS (ESI) calcd for $C_{16}H_{22}O_4$+Na 301.1416, found 301.1416.

4.3. 1,2-Dideoxy-3-*O*-benzyl-D-glucose (15)

To a solution of acetonide **14** (5.5 g, 19.7 mmol) in MeOH (50 mL) was added *p*-toluenesulfonic acid (3.7 g, 19.7 mmol) and the mixture was stirred for 30 min at room temperature. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography EtOAc/hexane (1:2) to afford the product **15** (4.7 g, 99%) as a colourless gum. R_f (50% EtOAc/hexane) 0.21; $[\alpha]_D^{25}$ −32 (*c* 1.0, $CHCl_3$). IR (neat): 3409, 2857, 1454 cm^{-1}. δ_H NMR (400 MHz, $CDCl_3$): 7.29–7.36 (m, 5H), 4.70 (d, 1H, *J*=12.0 Hz), 4.57 (d, 1H, *J*=12.0 Hz), 3.94–3.98 (m, 1H), 3.84 (dd, 1H, *J*=2.8, 11.6 Hz), 3.75 (dd, 1H, *J*=5.2, 12.0 Hz), 3.52 (t, 1H, *J*=8.8 Hz), 3.36–3.45 (m, 2H), 3.18–3.22 (m, 2H), 1.99–2.04 (m, 1H), 1.62 (dq, 1H, *J*=5.2, 12.8 Hz). δ_C NMR (100 MHz, $CDCl_3$): 138.3, 128.4, 127.8, 127.7, 80.3, 79.9, 71.1, 70.9, 65.5, 62.5, 30.6. Low-resolution MS (EI): *m*/*z*: 238 (M^+); HRMS (ESI) calcd for $C_{13}H_{18}O_4$+Na 261.1103, found 261.1103.

4.4. (*R*)-4-(Benzyloxy)-3,4-dihydro-2*H*-pyran (16)

To a vigorously stirred solution of compound **15** (4.7 g, 19.7 mmol) in dichloromethane and water (2:1, 90 mL) were added TEMPO (0.6 g, 3.94 mmol) and DAIB (15.9 g, 49.3 mmol). Stirring was allowed until TLC indicated complete conversion of the starting material to a lower running spot (~45 min). The reaction mixture was quenched by the addition of 10% $Na_2S_2O_3$ (100 mL) solution. The mixture was then extracted with EtOAc (2×150 mL), dried over anhydrous Na_2SO_4 and concentrated. The resulting yellow oil was evaporated three times with toluene (50 mL) under reduced pressure and was kept under high vacuum for 2 h prior to use. The crude oil was dissolved in toluene (100 mL) and *N*,*N*-dimethylformamide dineopentyl acetal (20.7 mL, 90.0 mmol) was added. The resulting mixture was stirred at 120 °C under argon for 1 h, cooled to 40 °C and the solvent was evaporated to obtain a brown oil containing the crude product, which upon column chromatography using EtOAc/hexane (1:19) provided compound **16** (2.5 g, 67% over two steps) as a yellow oil. R_f (10% EtOAc/hexane) 0.72; $[\alpha]_D^{25}$ +148 (*c* 1.0, $CHCl_3$). IR (neat): 2957, 2868, 1637, 1454 cm^{-1}. δ_H NMR (400 MHz, $CDCl_3$): 7.28–7.39 (m, 5H), 6.54 (d, 1H, *J*=6.0 Hz), 5.00 (td, 1H, *J*=1.2, 4.8 Hz), 4.61 (d, 1H, *J*=11.6 Hz), 4.55 (d, 1H, *J*=12.0 Hz), 4.05–4.10 (m, 2H), 3.90–3.92 (m, 1H), 1.98–2.02 (m, 1H), 1.90–1.93 (m, 1H). δ_C NMR (100 MHz, $CDCl_3$): 147.0, 138.8, 128.4, 127.6, 127.5, 100.9, 69.4, 65.6, 62.3, 28.7. Low-resolution MS (EI): *m*/*z*: 190 (M^+); HRMS (ESI) calcd for $C_{12}H_{14}O_2$+Na 213.0892, found 213.0892.

4.5. (1*R*,5*R*,6*S*)-Methyl 5-(benzyloxy)-2-oxabicyclo[4.1.0] heptane-(7*R*)-carboxylate (10)

To a solution of compound **16** (2.0 g, 10.5 mmol) in dry dichloromethane (40 mL) was added $Rh_2(OAc)_4$ (92.8 mg, 0.21 mmol) at room temperature and stirred for 5 min then methyl diazoacetate (3.0 ml, 31.5 mmol) in 50 ml of dry dichloromethane was added dropwise over a period of 90 min. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure and purified by column chromatography using EtOAc in hexane (1:6) to afford the product **10** (1.65 g, 60 %) as a colourless gum. R_f (20% EtOAc/hexane) 0.56; $[\alpha]_D^{25}$ −26 (*c* 1.0, $CHCl_3$). IR (neat): 2924, 1720, 1441 cm^{-1}. δ_H NMR (400 MHz, $CDCl_3$): 7.28–7.37 (m, 5H), 4.65 (d, 1H, *J*=11.6 Hz), 4.59 (d, 1H, *J*=12.0 Hz), 3.99–4.03 (m, 2H), 3.80 (m, 1H), 3.67 (s, 3H), 3.44–3.49 (m, 1H), 2.00 (dd, 1H, *J*=2.4, 5.6 Hz), 1.77–1.81 (m, 1H), 1.63–1.68 (m, 2H). δ_C NMR (100 MHz, $CDCl_3$): 172.1, 138.1, 128.4, 127.7, 127.5, 70.7, 68.1, 59.8, 59.2, 51.8, 28.4, 25.9, 25.3. Low-resolution MS (EI): *m*/*z*: 262 (M^+); HRMS (ESI) calcd for $C_{15}H_{18}O_4$+Na 285.1103, found 285.1104.

4.6. (*R*)-Methyl 2-((3*S*,4*R*)-4-(benzyloxy)-2-hydroxytetrahydro-2*H*-pyran-3-yl)-2-bromoacetate (9)

To a stirred solution of 1,2-cyclopropanecarboxylate **10** (0.80 g, 3.04 mmol) in 1,4-dioxane/water (15 mL (2:1)) was added *N*-bromosuccinimide (0.65 g, 3.64 mmol) and stirring was continued until the reaction mixture showed the absence of starting material on TLC (~8 h). The reaction mixture was then concentrated to half its volume in vacuo and extracted with CH_2Cl_2 (2×30 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography over silica gel using EtOAc/hexane (1:3) to give bromohydrin **9** (0.72 g, 66%) as a colourless gum. For major diastereomer: R_f (20% EtOAc/hexane) 0.32. IR (neat): 2924, 1719, 1454 cm^{-1}. δ_H NMR (500 MHz, $CDCl_3$): 7.28–7.37 (m, 5H), 4.89 (d, 1H, *J*=4.0 Hz), 4.69 (br d, 1H, *J*=6.0 Hz), 4.56 (d, 1H, *J*=11.0 Hz), 4.48–4.51 (m, 1H), 4.47 (d, 1H, *J*=11.0 Hz), 4.05 (dt, 1H, *J*=4.0, 11.0 Hz), 3.92 (td, 1H, *J*=4.5, 9.0 Hz), 3.50 (s, 3H), 2.38 (ddd, 1H, *J*=4.0, 7.0, 11.0 Hz), 2.01–2.06 (m, 1H), 1.70–1.75 (m, 1H). δ_C NMR (125 MHz, $CDCl_3$): 168.6, 137.5, 128.5, 128.4, 127.9, 95.5, 74.5, 71.5, 60.2, 53.1, 50.6, 48.2, 29.5. Low-resolution MS (EI): *m*/*z*: 358 (M^+); HRMS (ESI) calcd for $C_{15}H_{19}BrO_5$+Na 381.0314, found 381.0318.

4.7. (4*R*,5*R*)-4-(Benzyloxy)-6-hydroxy-1,7-dioxaspiro[4.4] nonan-8-one (6)

To a stirred solution of bromohydrin **9** (0.65 g, 1.81 mmol) in MeOH (8 mL) under nitrogen was added K_2CO_3 (0.50 g, 3.62 mmol) at 25 °C. The reaction mixture was stirred for a period of 6 h. MeOH

was removed under reduced pressure, and the reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with 1% HCl (10 mL) and water (10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. Column chromatography of the crude product with EtOAc/hexane (1:2) afforded the pure spirocyclic lactol **6** (0.45 g, 94%) as a colourless gum. For major diastereomer: R_f (30% EtOAc/hexane) 0.39. IR (neat): 3384, 2925, 1782, 1454 cm^{-1}. δ_H NMR (400 MHz, $CDCl_3$): δ 7.30–7.39 (m, 5H), 5.45 (br s, 1H), 4.66 (d, 1H, J=11.6 Hz), 4.52–4.59 (m, 1H), 4.48 (d, 1H, J=11.6 Hz), 3.96–4.11 (m, 2H), 3.66–3.77 (m, 1H), 3.07 (d, 1H, J=18.0 Hz), 2.61 (d, 1H, J=18.0 Hz), 2.01–2.17 (m, 2H). δ_C NMR (100 MHz, $CDCl_3$): 172.9, 137.1, 128.6, 128.2, 127.8, 100.4, 87.5, 79.3, 72.0, 67.3, 36.1, 31.0. Low-resolution MS (EI): m/z: 264 (M^+); HRMS (ESI) calcd for $C_{14}H_{16}O_5$+Na 287.0896, found 287.0916.

4.8. (4*R*,5*S*)-4-(Benzyloxy)-1,7-dioxaspiro[4.4]nonan-8-one (17)

To a stirred solution of spiro lactol **6** (0.40 g, 1.51 mmol) in CH_2Cl_2 (10 mL) at 0 °C were added triethyl silane (0.98 mL, 6.05 mmol) and trifluoroacetic acid (0.22 mL, 0.4 mmol) dropwise, respectively, and continued stirring while allowing the reaction mixture to warm to 25 °C. After completion of reaction (2–3 h), CH_2Cl_2 (50 mL) and water (20 mL) were added and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2×25 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, concentrated. The crude product was purified by column chromatography over silica gel using EtOAc/hexane (1:3) to afford pure spirolactone **17** (0.34 g, 92%) as a colourless gum. R_f (20% EtOAc/hexane) 0.33; $[\alpha]_D^{25}$ −30 (*c* 1.0, $CHCl_3$). IR (neat): 2890, 1776, 1454 cm^{-1}. δ_H NMR (500 MHz, $CDCl_3$): 7.29–7.37 (m, 5H), 4.66 (d, 1H, J=12.0 Hz), 4.47 (d, 1H, J=12.0 Hz), 4.19 (d, 1H, J=9.5 Hz), 4.11 (d, 1H, J=9.5 Hz), 3.94–3.97 (m, 1H), 3.85–3.89 (m, 2H), 3.05 (d, 1H, J=18.0 Hz), 2.50 (d, 1H, J=18.0 Hz), 2.16–2.18 (m, 1H), 1.97–2.01 (m, 1H). δ_C NMR (125 MHz, $CDCl_3$): 175.3, 137.3, 128.6, 128.0, 127.6, 86.6, 79.8, 75.5, 72.0, 65.3, 34.9, 30.7. Low-resolution MS (EI): m/z: 248 (M^+); HRMS (ESI) calcd for $C_{14}H_{16}O_4$+Na 271.0947, found 271.0960.

4.9. (4*R*,5*S*)-4-Hydroxy-1,7-dioxaspiro[4.4]nonan-8-one (18)

A solution of compound **17** (250 mg, 1 mmol) in EtOAc (14 mL) and MeOH (1 mL) in presence of one drop of hydrochloric acid (1 N) was hydrogenated over 10% Pd/C (30 mg) under hydrogen atmosphere for 2 h at 25 °C. The catalyst was filtered off and the filtrate was concentrated. The crude product was purified by flash column chromatography over silica gel using EtOAc/hexane (2:3) to afford alcohol **18** (0.15 g, 97%) as a colourless gum. R_f (30% EtOAc/hexane) 0.20; $[\alpha]_D^{25}$ −36 (*c* 1.0, $CHCl_3$). IR (neat): 3386, 1775, 1454 cm^{-1}. δ_H NMR (500 MHz, $CDCl_3$): 4.17 (br s, 3H), 3.94–3.97 (m, 1H), 3.85–3.87 (m, 1H), 3.49 (br s, 1H), 3.00 (d, 1H, J=18.0 Hz), 2.49 (d, 1H, J=18.0 Hz), 2.17–2.20 (m, 1H), 1.94–1.96 (m, 1H). δ_C NMR (125 MHz, $CDCl_3$): 176.3, 87.5, 75.6, 73.2, 65.1, 34.5, 33.8. Low-resolution MS (EI): m/z: 158 (M^+); HRMS (ESI) calcd for $C_7H_{10}O_4$+Na 181.0477, found 181.0487.

4.10. (*S*)-1,7-Dioxaspiro[4.4]nonane-4,8-dione or (dihydro-(*S*)-(−)-longianone) (19)

To a solution of oxalyl chloride (30 μL, 0.35 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added DMSO (50 μL, 0.70 mmol). After 10 min alcohol **18** (50 mg, 0.32 mmol) in dry CH_2Cl_2 (1 mL) was added dropwise for a period of 10 min and the stirring was continued further 45 min. Then, Et_3N (217 μL, 1.56 mmol) was added and the solution was allowed to warm upto 0 °C. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and extracted with water (3×5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography over silica gel using EtOAc/hexane (1:3) to afford ketone **19** (42 mg, 85%). R_f (30% EtOAc/hexane) 0.40; $[\alpha]_D^{25}$ −66 (*c* 0.8, $CHCl_3$) (lit. $[\alpha]_D^{20}$ −63 (*c* 1.0, $CHCl_3$)). IR (neat): 2923, 2853, 1728 (br), 1456 cm^{-1}. δ_H NMR (500 MHz, $CDCl_3$): 4.33 (d, 1H, J=10.0 Hz), 4.30 (d, 1H, J=10.0 Hz), 4.18–4.28 (m, 2H), 2.78 (d, 1H, J=18.0 Hz), 2.64 (d, 1H, J=7.5 Hz), 2.62 (d, 1H, J=18.0 Hz), 2.61 (d, 1H, J=7.5 Hz). δ_C NMR (125 MHz, $CDCl_3$): 211.9, 173.1, 84.3, 74.3, 63.3, 37.7, 35.9. Low-resolution MS (EI): m/z: 156 (M^+); HRMS (ESI) calcd for $C_7H_8O_4$+Na 179.0321, found 179.0328.

4.11. (*S*)-1,7-Dioxaspiro[4.4]non-2-ene-4,8-dione or ((*S*)-(−)-longianone) (4)

To a 0.5 M solution of dihydro-(−)-longianone **19** (30 mg, 0.19 mmol) in dry DMSO (0.2 mL) was added 2 equiv of stabilized IBX (0.38 mmol) and the mixture was heated to 80 °C and stirred at this temperature for a period of 2 h. After cooling the reaction mixture to 25 °C, EtOAc (25 mL) was added and the reaction mixture was extracted with a saturated $NaHCO_3$ solution. The organic residue was carefully purified by column chromatography (EtOAc/hexane gradually from 1:9 to 1:4), affording 9 mg of (*S*)-(−)-longianone **4** and 12 mg of **19** (50% yield of **4** based on recovered **19**). R_f (30% EtOAc/hexane) 0.39; $[\alpha]_D^{25}$ −90 (*c* 0.9, EtOH) (lit. $[\alpha]_D^{20}$ −85 (*c* 1.0, EtOH)). IR (neat): 2924, 2855, 1728 (br), 1465 cm^{-1}. δ_H NMR (400 MHz, $CDCl_3$): 8.31 (d, 1H, J=2.5 Hz), 5.82 (d, 1H, J=2.5 Hz), 4.40–4.43 (m, 2H), 3.04 (d, 1H, J=18.0 Hz), 2.72 (d, 1H, J=18.0 Hz). δ_C NMR (100 MHz, $CDCl_3$): 199.3, 177.6, 172.3, 106.7, 89.4, 73.9, 37.6. Low-resolution MS (EI): m/z: 154.

Acknowledgements

P.R.S. thank Council of Scientific and Industrial Research (CSIR), New Delhi, India for grant No. 01(2408)/10/EMR-II. K.S. thank CSIR for a senior research fellowship.

Supplementary data

Supplementary data related to this article can be found in the online version, at doi:10.1016/j.tet.2012.03.021.

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