

Stereoselective total synthesis of lippialactone

Gowravaram Sabitha
Purushotham Reddy Karra
Purushotham Reddy Sudina

Natural Products Chemistry Division,
Council of Scientific & Industrial
Research-Indian Institute of Chemical
Technology, Hyderabad, India

Abstract: The stereoselective synthesis of lippialactone was achieved in high overall yield from commercially available D-mannitol. Key reactions involved in the synthesis are preparation of required epoxide (**5**), its opening with vinyl Grignard reagent, and olefin cross-metathesis. A new route to a vinyl lactone (**4**) was explored.

Keywords: D-mannitol, epoxide, vinyl Grignard, cross-metathesis

Introduction

Natural products possessing the 5,6-dihydro-2-pyrone (α -pyrone) subunit as a core structure, bearing on position 6 an additional alkenyl chain, are known to display a broad spectrum of pharmacological properties,¹⁻⁴ such as insect growth inhibition, and antimicrobial, cytotoxic, and antitumoral activities. In 2013, Ludere et al⁵ isolated a new antimalarial agent, lippialactone (**1**) (Figure 1), from aerial parts of *Lippia javanica*. Lippialactone is active against the chloroquine-sensitive D10 strain of *Plasmodium falciparum*, with a half maximal inhibitory concentration (IC₅₀) value of 9.1 μ g/mL, and is known to show mild cytotoxicity. The relative stereochemistry of lippialactone was determined by molecular modeling based on the determination of the relative configuration, by quantum mechanical gauge including atomic orbitals (GIAO) ¹³C chemical-shift calculations. Lippialactone (**1**) is structurally related to synargentolide A (**2**) (Figure 1), whose structure was revised by our team.⁶ To date, however, only a single report has appeared on the synthesis of **1**.⁷ In continuation of our interest in the synthesis of bioactive natural δ -lactones,⁸⁻¹⁴ we herein describe a stereoselective total synthesis of lippialactone.

Experimental General

Reactions were conducted under N₂, in anhydrous solvents such as CH₂Cl₂, tetrahydrofuran (THF), and ethyl acetate (EtOAc). All reactions were monitored by thin-layer chromatography (TLC) (silica-coated plates and visualization under ultraviolet [UV] light). *n*-Hexane (bp 60°C–80°C) was used. Yields refer to chromatographically and spectroscopically (¹H and ¹³C nuclear magnetic resonance [NMR]) homogeneous material. Air-sensitive reagents were transferred by syringe or double-ended needle. Evaporation of solvents was performed at reduced pressure on a BÜCHI rotary evaporator (BÜCHI Labortechnik AG, Flawil, Switzerland). ¹H and ¹³C NMR spectra of samples in CDCl₃ were recorded on Varian FT-400MHz (Varian Medical Systems Inc.,

Correspondence: Gowravaram Sabitha
Natural Products Chemistry Division,
CSIR-Indian Institute of Chemical
Technology, Hyderabad 500 007, India
Tel +91 40 2719 1629
Fax +91 40 2716 0512
Email sabitha@iict.res.in

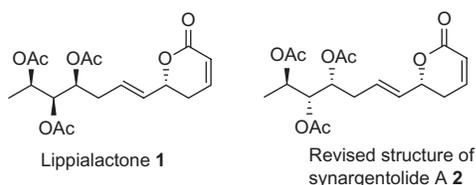


Figure 1 Structures of lippialactone (1) and revised structure of synargentolide A (2).

Palo Alto, CA, USA), Varian FT-500MHz (Varian Medical Systems Inc.), and Bruker UXNMR FT-300MHz (Avance; Bruker Corporation, Billerica, MA, USA) spectrometers. Chemical shift δ is reported relative to tetramethylsilane (TMS) ($\delta=0.0$) as an internal standard. Mass spectra recorded E1 conditions at 70 eV on ES-MSD (Agilent Technologies, Santa Clara, CA, USA) spectrometers. Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co, India. TLC was performed on Merck 60 F-254 silica gel plates (Merck KGaA, Darmstadt, Germany). Optical rotations were measured with a JASCO DIP-370 Polarimeter (JASCO Corp, Tokyo, Japan).

(4*R*,4'*R*,5*S*)-2,2,2',2',5-pentamethyl-4,4'-bi(1,3-dioxolane) (8)

A solution of **6** (2.0 g, 8.65 mmol) in dry CH_2Cl_2 (15 mL), containing triethylamine (2.5 g, 24.7 mmol) and *p*-dimethylaminopyridine (DMAP) (0.04 g), was cooled to 0°C and treated with *p*-toluenesulphonyl chloride (3.30 g, 17.30 mmol). The reaction mixture was stirred at room temperature (RT) for 1 hour. It was then diluted with water and extracted with CH_2Cl_2 . The organic layer was washed with brine and dried over anhydrous Na_2SO_4 . Removal of solvent under reduced pressure afforded the unstable crude tosyl compound **7**, which was used for further reaction. To a stirred suspension of LiAlH_4 (0.49 g, 12.89 mmol), in dry THF (10 mL) at 0°C , was added dropwise a solution of compound **7** (2.5 g, 6.47 mmol) in dry THF (10 mL). The reaction mixture was refluxed for 3 hours. It was then cooled to 0°C , diluted with Et_2O , and quenched by the dropwise addition of saturated aqueous Na_2SO_4 . The solid material was filtered and washed thoroughly with hot EtOAc several times. The combined organic layers were dried over anhydrous Na_2SO_4 . The solvent was removed under vacuo, and the residue was purified by silica gel column chromatography (SiO_2 , EtOAc/hexane [4:6]) to afford the compound **8** (1.20 g, 87%) as a viscous liquid. $[\alpha]_{\text{D}}^{25}$: -39.9 (*c* 0.7, CHCl_3); $^1\text{H NMR}$: (CDCl_3 , 500 MHz): δ 4.14–4.06 (m, 1H), 4.04–3.98 (m, 2H), 3.94 (dd, $J=8.3, 5.0$ Hz, 1H), 3.45 (d, $J=7.9$ Hz, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.37–1.31 (m, 9H); $^{13}\text{C NMR}$: (CDCl_3 , 125 MHz):

δ 109.7, 108.7, 82.8, 77.4, 77.3, 67.9, 27.5, 27.0, 26.9, 25.5, 18.9; **infrared (IR) (neat)**: 2986, 2926, 2875, 1692, 1455, 1217, 1070, 771 cm^{-1} ; MS (ESI) *m/z*: 239 $[\text{M}+\text{Na}]^+$.

(*R*)-1-((4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (9)

To a solution of the compound **8** (1.0 g, 4.62 mmol) in CH_3CN (10 mL) was added $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (1.57 g, 9.20 mmol) as a solid. The reaction mixture was stirred at 0°C for 1 hour. The reaction mixture was quenched with solid NaHCO_3 (5.0 g), and the resulting mixture was filtered. The filtrate was concentrated under reduced pressure, and the crude product was purified by column chromatography (1:1% EtOAc/hexane), to afford diol **9** (0.72 g, 90%) as a colorless oil; $[\alpha]_{\text{D}}^{25}$: -38.3 (*c* 0.3, CHCl_3); $^1\text{H NMR}$: (CDCl_3 , 300 MHz): δ 3.96–3.89 (m, 1H), 3.81–3.68 (m, 4H), 3.62–3.44 (m, 1H), 2.46 (brs, 1H), 1.38 (s, 3H), 1.36 (s, 3H), 1.27 (d, $J=6.8$ Hz, 3H). $^{13}\text{C NMR}$: (CDCl_3 , 125 MHz): δ 108.4, 82.6, 74.8, 72.1, 63.7, 27.2, 26.8, 18.9. **IR (neat)**: 3243, 1526, 1426, 1214, 743 cm^{-1} ; MS (ESI) *m/z*: 177 $[\text{M}+\text{H}]^+$.

(*R*)-2-hydroxy-2-((4*S*,5*S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)ethyl pivalate (10)

To a solution of the diol **9** (0.7 g, 4.02 mmol) and DMAP (catalytic) in dry CH_2Cl_2 (10 mL) was added Et_3N (2.03 mL, 20.06 mmol) at 0°C under N_2 atmosphere. This was followed by a dropwise addition of pivaloyl chloride (PivCl) (0.49 mL, 4.06 mmol) with vigorous stirring. The reaction was allowed to proceed for 4 hours with gradual warming to RT. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated NaHCO_3 solution, water, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was chromatographed over silica gel to give (0.87 g, 87%) pure monopivaloate **10** as a colorless liquid. $[\alpha]_{\text{D}}^{25}$: -18.9 (*c* 0.5, CHCl_3); $^1\text{H NMR}$: (CDCl_3 , 500 MHz): δ 4.30 (dd, $J=11.7, 3.5$ Hz, 1H), 4.20–4.08 (m, 2H), 3.92–3.85 (m, 1H), 3.54 (t, $J=7.6$ Hz, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.23 (s, 9H), 1.22 (d, $J=6.0$ Hz, 3H); $^{13}\text{C NMR}$: (CDCl_3 , 125 MHz): δ 179.0, 108.5, 81.6, 75.0, 71.2, 66.1, 38.8, 26.7, 27.2, 27.1, 19.0; **IR (neat)**: 2980, 2935, 1715, 1458, 1215, 1160, 752 cm^{-1} ; **high resolution mass spectroscopy (HRMS) (ESI)**: calc. 261.16965 $\text{C}_{13}\text{H}_{25}\text{O}_5$, found 261.16963 $[\text{M}-\text{H}]^-$.

(4*S*,5*R*)-2,2,4-trimethyl-5-((*S*)-oxiran-2-yl)-1,3-dioxolane (5)

To a cooled (-80°C) solution of the pivaloate compound **10** (0.8 g, 3.05 mmol) and triethylamine (1.32 mL, 13.04 mmol) in dry CH_2Cl_2 (10 mL) was added methanesulfonyl chloride

(0.69 mL, 6.05 mmol), dropwise. The reaction mixture was stirred for 15 minutes at the same temperature and kept in a freezer (-20°C) overnight. The reaction mixture was diluted with more CH_2Cl_2 and washed with water and brine. The CH_2Cl_2 layer was dried over anhydrous Na_2SO_4 and concentrated on a rotary evaporator. The crude yellow solid was dissolved in MeOH, 0.9 g (2.67 mmol, 2.5 equiv based on theoretical yield) of finely powdered K_2CO_3 was added, and the mixture was stirred vigorously at RT for 2 hours. Methanol was evaporated on a rotary evaporator. The residue was taken in water and extracted with diethyl ether, and the combined organic layers were washed with brine and dried over anhydrous Na_2SO_4 before concentration. The crude product was chromatographed over silica gel to give (0.35 g, 85%) epoxide **5** as a colorless liquid. $[\alpha]_{\text{D}}^{25}$: -42.1 (c 0.8, CHCl_3); $^1\text{H NMR}$: (CDCl_3 , 300 MHz): δ 4.14–3.99 (m, 1H), 3.35 (dd, $J=8.3, 5.2$ Hz, 1H), 3.02–2.95 (m, 1H), 2.80 (t, $J=5.2$ Hz, 1H), 2.68 (dd, $J=5.2, 3.0$ Hz, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 1.31 (d, $J=6.0$ Hz, 3H). $^{13}\text{C NMR}$: (CDCl_3 , 125 MHz): δ 109.0, 82.6, 73.5, 50.8, 43.5, 27.2, 26.5, 17.7. **IR (neat)**: 3019, 1550, 1473, 1212, 742 cm^{-1} ; MS (ESI) m/z : 181 $[\text{M}+\text{Na}]^+$.

(S)-1-((4S,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol (**11**)

Freshly prepared vinylmagnesium bromide (2.46 mL, 2.4 mmol) in THF (1 M solution) was added dropwise to a solution of CuI (0.036 g, 0.15 mmol) in THF (15 mL) at -20°C . The mixture was stirred for 30 minutes, and chiral epoxide **5** (0.30 g, 1.89 mmol) in THF (5 mL) was added dropwise. After completion of the reaction, a saturated solution of NH_4Cl (10 mL) was added and diluted with Et_2O (5 mL). The two layers were separated, and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine (2×5 mL), dried with anhydrous Na_2SO_4 , and concentrated under reduced pressure, and gave alcohol **11** (0.30 g, 88%) as a colorless oil; $[\alpha]_{\text{D}}^{25}$: $+2.0$ (c 0.5, CHCl_3); $^1\text{H NMR}$: (CDCl_3 , 500 MHz): δ 5.90–5.78 (m, 1H), 5.16–5.07 (m, 2H), 4.09–4.01 (m, 1H), 3.54 (brs, 1H), 3.50–3.45 (m, 1H), 2.28 (brs, 2H), 2.21 (brs, 1H), 1.39 (s, 3H), 1.37 (s, 3H), 1.26 (d, $J=5.9$ Hz, 3H). $^{13}\text{C NMR}$: (CDCl_3 , 125 MHz): δ 134.2, 117.7, 108.4, 84.3, 73.0, 69.2, 39.2, 27.4, 26.8, 17.8. **IR (neat)**: 3019, 2926, 1693, 1517, 1213, 746 cm^{-1} ; **HRMS (ESI)**: calc. 187.13288 $\text{C}_{10}\text{H}_{18}\text{O}_3$, found 186.13290 $[\text{M}-\text{H}]^-$.

(S)-1-((4R,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)but-3-en-1-yl acetate (**3**)

To a solution of the compound **11** (0.2 g, 1.07 mmol) in dry CH_2Cl_2 (20 mL) were added Et_3N (0.46 mL, 4.54 mmol) fol-

lowed by acetic anhydride (0.21 mL, 2.05 mmol) and catalytic amount of DMAP at 0°C . The reaction mixture was continued to stir for 1 hour and then diluted with CH_2Cl_2 (5 mL). The organic layer was washed with 5% NaHCO_3 solution (2×5 mL), then brine (2×5 mL), and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure, and the crude residue was purified on silica gel column chromatography (30% EtOAc/hexane) to provide the compound **3** (0.22 g, 92%) as a colorless oil. $[\alpha]_{\text{D}}^{25}$: $+9.0$ (c 0.8, CHCl_3); $^1\text{H NMR}$: (CDCl_3 , 500 MHz): δ 5.84–5.65 (m, 1H), 5.18–4.95 (m, 2H), 3.93–3.80 (m, 1H), 3.61 (dd, $J=8.3, 3.0$ Hz, 1H), 2.43 (t, $J=6.9$ Hz, 2H), 2.07 (s, 3H), 1.40 (s, 3H), 1.38 (s, 3H), 1.28 (d, $J=6.0$ Hz, 3H). $^{13}\text{C NMR}$: (CDCl_3 , 125 MHz): δ 170.5, 133.2, 118.2, 108.4, 82.4, 72.6, 70.2, 35.7, 27.3, 26.5, 20.9, 17.7. **IR (neat)**: 2934, 1739, 1514, 1373, 1216, 748 cm^{-1} ; MS (ESI) m/z : 305 $[\text{M}+\text{Na}]^+$.

(R)-2-(((4-methoxybenzyl)oxy)methyl)oxirane (**12**)

To a stirred suspension of NaH (1.0 g, 41.66 mmol) in THF (10 mL) at 0°C was added para-methoxybenzyl alcohol (PMBOH) (3.0 g, 21.73 mmol) in THF (5 mL) dropwise. After being stirred under nitrogen for 30 minutes at 0°C , $(\text{Bu})_4\text{NI}$ catalytic amount and (\pm) epichlorohydrin (\times (2.0 g, 21.73 mmol) in THF (15 mL) were added as well. The mixture was stirred for 16 hours, quenched with saturated NH_4Cl solution, and extracted into EtOAc (3×10 mL). The combined organic layer was washed with water, then brine, dried over anhydrous Na_2SO_4 , and the volatiles were evaporated. The crude residue was purified by column chromatography (hexane/EtOAc 8:2) to afford **12** (3.6 g, 87%) as a viscous liquid.

A mixture of (*S,S*)-bis(3,5-di-*tert*-butylsalicylide)-1,2-cyclohexanediamino-Co(II) complex (0.031 g, 0.51 mmol), toluene (2 mL), and acetic acid (0.062 g, 1.02 mmol) were stirred in open air for 1 hour at RT. The solvent was evaporated under reduced pressure, and compound **12** (1.0 g, 5.15 mmol) and water (1.0 mL, 55.55 mmol) were added to the brown residue at bath temperature below 15°C , and the reaction mixture was stirred at RT for 36 hours. The crude reaction mixture was purified by silica gel column chromatography (hexane/EtOAc [8:2]) to afford the chiral epoxide **12** (0.88 g, 42%). $[\alpha]_{\text{D}}^{25}$: -10.3 ($c=0.5$, CHCl_3). $^1\text{H-NMR}$ (CDCl_3 , 500 MHz): δ 7.28 (d, $J=8.3$ Hz, 2H), 6.88 (d, $J=9.0$ Hz, 2H), 4.52 (ABq, $J=18.8, 11.3$ Hz, 2H), 3.81 (s, 3H), 3.74 (dd, $J=11.3, 3.0$ Hz, 1H), 3.41 (dd, $J=11.3, 6.0$ Hz, 1H), 3.22–3.15 (m, 1H), 2.80 (t, $J=4.5$ Hz, 1H), 2.61 (dd, $J=5.2, 3.0$ Hz, 1H). $^{13}\text{C-NMR}$ (CDCl_3 , 125 MHz): δ 159.0, 131.6, 129.7, 129.2, 113.6, 72.7, 70.3, 55.0, 50.7, 44.1. **IR (neat)**: 1609, 1513, 1249, 1093 cm^{-1} ; **ESI-MS**: m/z 217 $[\text{M}+\text{Na}]^+$.

(R)-6-((4-methoxybenzyl)oxy)hex-2-yne-1,5-diol (13)

Under nitrogen, lithium bis(trimethylsilyl)amide (1 M solution in hexane, 5.1 mL, 5.14 mmol) was added to a solution of propargylic alcohol (0.2 mL, 3.85 mmol) in THF (10 mL) at -78°C , and the mixture was stirred for 1 hour. Then, $\text{BF}_3 \cdot \text{OEt}_2$ (0.39 mL, 3.08 mmol) was added to the solution, and the stirring was continued for 15 minutes at -78°C . Finally, a solution of chiral epoxide **12** (0.5 g, 2.57 mmol) in dry THF (10 mL) was added, and after the reaction mixture was stirred for 3 hours at -78°C , it was quenched by adding a saturated aqueous NH_4Cl solution (20 mL). The resulting mixture was extracted with EtOAc (2×20 mL), and the combined organic layers were dried with anhydrous Na_2SO_4 . Evaporation of the solvent, followed by column chromatography (50% EtOAc/hexane) afforded pure alcohol **13** (0.547 g, 85%) as a colorless oil; $[\alpha]_D^{25} = -3.3$ ($c=0.2$, CHCl_3). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.25 (d, $J=8.4$ Hz, 2H), 6.88 (d, $J=8.4$ Hz, 2H), 4.48 (s, 2H), 4.19 (brs, 2H), 3.98–3.89 (m, 1H), 3.80 (s, 3H), 3.56–3.41 (m, 2H), 3.32–2.78 (brs, 2H), 2.52–2.36 (m, 2H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 159.2, 129.7, 129.4, 113.7, 81.9, 80.6, 73.0, 72.6, 68.7, 55.2, 50.9, 23.7. **IR (neat):** 3383, 1610, 1512, 1248, 1028 cm^{-1} ; **ESI-MS:** m/z 273 $[\text{M}+\text{Na}]^+$.

(R,Z)-6-((4-methoxybenzyl)oxy)hex-2-ene-1,5-diol (14)

A suspension of compound **13** (0.45 g, 1.80 mmol), Lindlar catalyst (0.026 gr, 5 wt%), and quinoline (catalytic amount) in EtOAc (2 mL) was stirred at RT under hydrogen atmosphere (1 atm) until partially reduced product appeared on TLC. The reaction mixture was filtered through a pad of Celite® with EtOAc (5 mL). The filtrate was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography (50% EtOAc/hexane) to afford compound **14** as a colorless liquid (0.40 g, 90%). $[\alpha]_D^{25} = +4.8$ ($c=0.3$, CHCl_3). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.25 (d, $J=6.0$ Hz, 2H), 6.9 (d, $J=7.9$ Hz, 2H), 5.95–5.75 (m, 1H), 5.68–5.51 (m, 1H), 4.48 (s, 2H), 4.22–3.99 (m, 2H), 3.81 (s, 3H), 3.53–3.29 (m, 2H), 2.40–2.20 (brs, 2H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 159.2, 131.3, 129.7, 129.4, 128.4, 113.8, 73.5, 73.0, 69.2, 57.4, 55.2, 31.0. **IR (neat):** 3394, 1611, 1513, 1248, 1032 cm^{-1} ; **ESI-MS:** m/z 275 $[\text{M}+\text{Na}]^+$.

(R)-6-(((4-methoxybenzyl)oxy)methyl)-5,6-dihydro-2H-pyran-2-one (15)

Bis(acetoxy)iodobenzene (BAIB) (0.53 g, 1.65 mmol) was added to a solution of alcohol **14** (0.35 g, 1.38 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (0.021 g,

0.13 mmol) in 10 mL of CH_2Cl_2 . The reaction mixture was stirred until the alcohol was no longer detectable (TLC), and then it was diluted with CH_2Cl_2 (20 mL). The mixture was washed with a saturated aqueous solution of $\text{Na}_2\text{S}_2\text{O}_3$ (20 mL) and extracted with CH_2Cl_2 (4×20 mL). The combined organic extracts were washed with aqueous NaHCO_3 (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure and purified by silica gel column chromatography (hexane/EtOAc [7:3]) to afford **15** as a colorless oil (0.31 g, 90%). $[\alpha]_D^{25} = -20.3$ ($c=0.06$, CHCl_3). **¹H-NMR (CDCl₃, 500 MHz):** δ 7.26 (d, $J=8.5$ Hz, 2H), 6.92–6.87 (m, 3H), 6.03–6.00 (m, 1H), 4.62–4.55 (m, 1H), 4.53 (d, $J=3.5$ Hz, 2H), 3.81 (s, 3H), 3.66 (d, $J=5.6$ Hz, 2H), 2.59–2.51 (m, 1H), 2.42–2.35 (m, 1H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 163.7, 159.3, 144.9, 129.3, 129.6, 121.1, 113.8, 76.5, 73.2, 70.4, 55.2, 26.1. **IR (neat):** 1722, 1512, 1247 cm^{-1} ; **ESI-MS:** m/z 271 $[\text{M}+\text{Na}]^+$.

(R)-6-(hydroxymethyl)-5,6-dihydro-2H-pyran-2-one (16)

To a cooled (0°C) solution of **15** (0.25 g, 1.00 mmol) in CH_2Cl_2 (4.5 mL) and H_2O (0.5 mL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.34 g, 1.50 mmol) and stirred at RT for 2 hours. After completion of the reaction, saturated NaHCO_3 solution was added, and the aqueous layer was extracted with CH_2Cl_2 (2×10 mL). The combined organic extract was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography using hexanes/EtOAc (7:3) as an eluent to give alcohol **16** (0.11 g, 92%) as a colorless liquid. $[\alpha]_D^{25} = -29.6$ ($c=0.2$, CHCl_3). **¹H-NMR (CDCl₃, 300 MHz):** δ 7.00–6.91 (m, 1H), 6.04 (dd, $J=9.8$, 3.0 Hz, 1H), 4.62–4.52 (m, 1H), 3.89 (dd, $J=12.0$, 3.0 Hz, 1H), 3.76 (dd, $J=12.8$, 5.2 Hz, 1H), 2.69–2.55 (m, 1H), 2.39–2.28 (m, 1H). **¹³C-NMR (CDCl₃, 125 MHz):** δ 163.9, 145.3, 120.8, 78.3, 63.7, 25.2. **IR (neat):** 3401, 2923, 1712, 1514, 1373, 1216, 748 cm^{-1} ; **ESI-MS:** m/z 151 $[\text{M}+\text{Na}]^+$.

(R)-6-vinyl-5,6-dihydro-2H-pyran-2-one (4)

To an ice-cooled solution of 2-(iodooxy) benzoic acid (0.32 g, 1.17 mmol) in anhydrous CH_3CN (7 mL) was added a solution of alcohol **16** (0.100 g, 0.78 mmol). The mixture was refluxed for 1 hour and then allowed to cool to RT. The solvent was removed under reduced pressure, and the unstable crude aldehyde product was used directly for the next step without further purification by column chromatography.

In a reaction flask, a 2.5 M solution of *n*-BuLi in hexane (0.9 mL, 2.28 mmol) was added under N_2 atmosphere to a

stirred suspension of methyltriphenylphosphonium iodide (0.54 g, 1.51 mmol) in dry THF (15 mL) at -78°C . The mixture was allowed to warm to RT, stirred for 1 hour, and cooled to -78°C again. To this mixture, a solution of above crude aldehyde in dry THF (10 mL) was added dropwise, and the resulting mixture was stirred at RT for 2 hours, quenched with aqueous NH_4Cl , and extracted with EtOAc (2×10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (hexane/EtOAc 8:2) to give compound **4** as a colorless oil (0.07 g, 75%). $[\alpha]_{\text{D}}^{25} = -10.2$ ($c=0.2$, CHCl_3). $^1\text{H NMR}$: (CDCl_3 , 500 MHz): δ 6.93–6.87 (m, 1H), 6.08–6.04 (m, 1H), 6.0–5.92 (m, 1H), 5.41 (dd, $J=17.2$, 0.9 Hz, 1H), 5.30 (dd, $J=10.5$, 0.7 Hz, 1H), 2.53–2.39 (m, 2H). $^{13}\text{C NMR}$: (CDCl_3 , 125 MHz): δ 163.7, 144.4, 134.7, 121.5, 117.8, 77.7, 29.3. **IR (neat)**: 2930, 1720, 1520, 1314, 1201, 752 cm^{-1} ; **ESI-MS**: m/z 147 $[\text{M}+\text{Na}]^+$.

(S,E)-4-((R)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-1-((4R,5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl)but-3-en-1-yl acetate (17)

To a solution of the compound **3** (0.1 g, 0.43 mmol) and **4** (0.13 g, 1.27 mmol) in CH_2Cl_2 (3 mL), 10 mol-% Grubbs catalyst II (0.03 g, 0.04 mmol) was added and stirred at RT for 24 hours under N_2 . Most of the solvent was then distilled off, and the concentrated solution was left to be stirred at RT for 2 hours. The mixture was evaporated to dryness to give a brown residue, which was purified by column chromatography (SiO_2 ; 6:4% EtOAc/hexane) to give **17** (0.11 g, 82%) as a colorless liquid. $[\alpha]_{\text{D}}^{25} = +13.4$ (c 0.2, CHCl_3); $^1\text{H NMR}$: (CDCl_3 , 500 MHz): δ 6.90–6.85 (m, 1H), 6.05 (tt, $J=9.7$, 2.1, 1.5 Hz, 1H), 5.81–5.68 (m, 2H), 5.04–4.98 (m, 1H), 4.91–4.85 (m, 1H), 3.91–3.84 (m, 1H), 3.61 (dd, $J=8.2$, 3.0 Hz, 1H), 2.50–2.45 (m, 2H), 2.44–2.37 (m, 2H), 2.10 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.29 (d, $J=6.1$ Hz, 3H). $^{13}\text{C NMR}$: (CDCl_3 , 75 MHz): δ 170.5, 163.8, 144.4, 130.4, 129.4, 121.5, 108.5, 82.3, 77.5, 72.5, 69.9, 34.1, 29.5, 20.8, 17.7. **IR (neat)**: 1734, 1514, 1378, 1213, 745 cm^{-1} ; **HRMS (ESI)**: calc. 342.19111 $\text{C}_{17}\text{H}_{28}\text{O}_6\text{N}$, found 342.19097 $[\text{M}+\text{NH}_4]^+$.

(4S,5S,6R,E)-5,6-dihydroxy-1-((R)-6-oxo-3,6-dihydro-2H-pyran-2-yl)hept-1-en-4-yl acetate (18)

To a stirred solution of compound **17** (0.05 g, 0.15 mmol) in anhydrous CH_2Cl_2 (7 mL), TiCl_4 (0.008 mL, 0.05 mmol) was added at 0°C , and the reaction mixture was stirred at the same temperature for 1 hour. The reaction mixture was quenched with solid NaHCO_3 and filtered. The solvent was removed under reduced pressure. The residue was purified by silica gel

column chromatography (1:1% EtOAc/hexane) to afford **18** (0.03 g, 85%) as a colorless oil. $[\alpha]_{\text{D}}^{25} = +18.9$ (c 0.4, CHCl_3); $^1\text{H NMR}$: (CDCl_3 , 500 MHz): δ 6.89 (ddd, $J=9.7$, 4.8, 3.3 Hz, 1H), 6.08–6.03 (m, 1H), 5.93–5.84 (m, 1H), 5.76–5.67 (m, 1H), 5.10–5.00 (m, 1H), 4.96–4.85 (m, 1H), 3.77–3.64 (m, 1H), 3.41 (t, $J=5.0$ Hz, 1H), 2.48–2.29 (m, 4H), 2.09 (s, 3H), 1.30 (d, $J=6.4$ Hz, 3H). $^{13}\text{C NMR}$: (CDCl_3 , 125 MHz): δ 170.1, 164.3, 145.0, 133.5, 129.3, 123.0, 80.0, 78.4, 73.7, 70.2, 67.2, 64.5, 31.9, 29.6, 21.0, 18.9. **IR (neat)**: 3018, 2925, 1693, 1516, 1417, 1212, 747 cm^{-1} ; **HRMS (ESI)**: calc. 302.15981 $\text{C}_{14}\text{H}_{24}\text{O}_6\text{N}$, found 302.15985 $[\text{M}+\text{NH}_4]^+$.

(2R,3S,4S,E)-7-((R)-6-oxo-3,6-dihydro-2H-pyran-2-yl)hept-6-ene-2,3,4-triyl triacetate (lippialactone (1))

To a stirred solution of the lactone **18** (10 mg, 0.03 mmol) in dry CH_2Cl_2 (5 mL) were added Et_3N (0.03 mL, 0.29 mmol), followed by acetic anhydride (0.01 mL, 0.09 mmol) and a catalytic amount of DMAP, at 0°C . The reaction mixture was continuously stirred for 1 hour and then diluted with CH_2Cl_2 (3 mL). The organic layer was washed with 5% NaHCO_3 solution (2×2 mL), then brine (2×2 mL), and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure, and the crude residue was purified on silica gel column chromatography (30% EtOAc/hexane) to provide the lactone **1** (9 mg, 90%) as a colorless oil. $[\alpha]_{\text{D}}^{25} = +22.1$ (c 0.3, CHCl_3); $^1\text{H NMR}$: (CDCl_3 , 500 MHz): δ 6.86 (ddd, $J=9.6$, 5.0, 3.3 Hz, 1H), 6.03 (dt, $J=9.7$, 3.5 Hz, 1H), 5.72 (dd, $J=15.4$, 6.8 Hz, 1H), 5.65 (dd, $J=15.4$, 5.9 Hz, 1H), 5.14–5.09 (m, 1H), 5.08–5.03 (m, 2H), 4.88–4.82 (m, 1H), 2.45–2.37 (m, 2H), 2.36–2.26 (m, 2H), 2.11 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 1.19 (d, $J=5.7$ Hz, 3H). $^{13}\text{C NMR}$: (CDCl_3 , 125 MHz): δ 170.1, 163.7, 144.4, 131.1, 128.3, 121.5, 77.5, 74.1, 70.4, 68.7, 33.9, 29.5, 21.0, 20.8, 20.6, 16.4. **IR (neat)**: 3018, 2924, 1747, 1709, 1645, 1550, 1531, 1213, 746 cm^{-1} ; **ESI-MS**: m/z 386 $[\text{M}+\text{NH}_4]^+$. **HRMS (ESI)**: calc. 386.18094 $\text{C}_{18}\text{H}_{28}\text{O}_8\text{N}$, found 386.18098 $[\text{M}+\text{NH}_4]^+$.

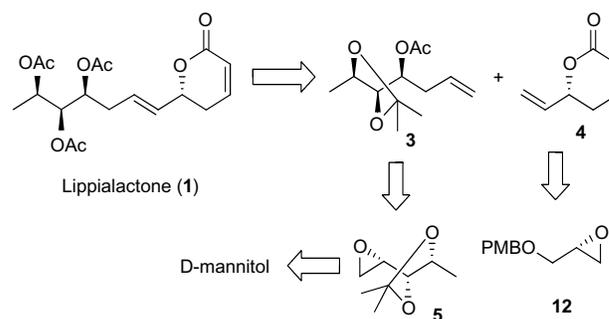


Figure 2 Retrosynthetic analysis.

Abbreviation: PMBO, para-methoxybenzyl alcohol.

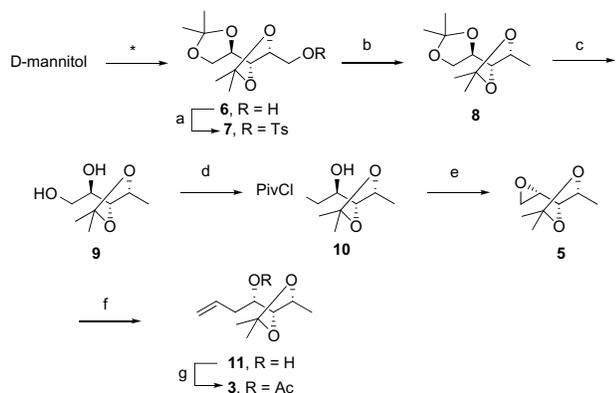


Figure 3 Synthesis of fragment 3.

Notes: Reagents and conditions: a) TsCl, Et₃N, DMAP, CH₂Cl₂, 0°C-rt, 1 hour, b) LiAlH₄, THF, 3 hours, 87% for two steps, c) CuCl₂·2H₂O, CH₃CN, 0°C-rt, 1 hour, 90%, d) PivCl, Et₃N, DMAP, CH₂Cl₂, 0°C-rt, 4 hours, 87%, e) i) MsCl, Et₃N, DMAP, CH₂Cl₂, 0°C-rt, 12 hours, ii) K₂CO₃, MeOH, rt, 2 hours, 85% for two steps, f) CuI, vinylMgBr, THF, 0°C, 1 hour, 88%, g) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 0°C, 1 hour, 92%. *Reported in Wu and Wu¹⁶ and Ghosh and Rao.¹⁷

Abbreviations: DMAP, p-dimethylaminopyridine; PivCl, pivaloyl chloride; rt, room temperature; THF, tetrahydrofuran.

Results and discussion

The retrosynthetic analysis of lippialactone (**1**) is summarized in Figure 2. Lippialactone (**1**) could be accomplished from homoallyl alcohol **3** and vinyl lactone **4** via an olefin cross-metathesis reaction. In turn, the construction of three contiguous stereogenic hydroxyl groups in compound **3** could be achieved from commercially available D-mannitol, and vinyl lactone **4** could be prepared from a known chiral epoxide **12**¹⁵ by a new synthetic route.

The synthesis of fragment **3** (Figure 3) commenced from a primary alcohol **6**, which was prepared from D-mannitol^{16,17} according to the reported procedure. Tosylation of the primary hydroxyl group in compound **6**, with TsCl, Et₃N, and DMAP in CH₂Cl₂, gave compound **7**, which on treatment with lithium aluminum hydride (LAH) gave a terminal methyl compound **8**. Selective deprotection of the terminal acetonide with

CuCl₂·2H₂O in CH₃CN afforded diol **9**. Selective protection of the primary hydroxy group in **9**, as the pivaloyl ester, with PivCl, Et₃N, and DMAP in dichloromethane (DCM) gave compound **10**. Mesylation of the secondary hydroxyl group in compound **10**, with MsCl, Et₃N, and DMAP in CH₂Cl₂, gave secondary mesylate. This was followed by the treatment with anhydrous K₂CO₃ in anhydrous MeOH, at RT, which afforded epoxide **5** with the required stereocenter. Opening of epoxide **5** with vinylmagnesium bromide in the presence of CuI afforded homoallyl alcohol **11**. The resulting free secondary hydroxyl group was acetylated to give a mono-acetate compound **3**.

The other fragment, vinyl lactone **4**, was prepared from a known epoxide **12**¹⁵ as shown in Figure 4. The epoxide was subjected to regioselective ring opening with propargyl alcohol using LiHMDS, then BF₃OEt₂ at -78°C to furnish alcohol **13**, in 85% yield. The triple bond in **13** was reduced to a Z-double bond using Lindlar catalyst to afford **14**, in 90% yield. Oxidative cyclization of 1,5-diol **14** with TEMPO and [bis(acetoxy)iiodo]benzene [(PhI(OAc)₂] (BAIB)]¹⁸ produced the desired δ-lactone **15**, in 90% yield.

Oxidative removal of the 4-methoxybenzyl ether (PMB) group (DDQ/CH₂Cl₂·H₂O, 9:1, 0°C-rt, 92%) and oxidation of the resulting alcohol **16** to the corresponding aldehyde, and subsequent treatment with one carbon Wittig reagent furnished vinyl lactone **4** ((a) IBX/CH₃CN, b) PPh₃=CH₂, THF, 0°C-rt, 75% over two steps).

With the two key fragments in hand, the CM reaction was planned. Olefin cross-metathesis¹⁹⁻²¹ between fragment **3** and vinyl lactone **4** was promoted smoothly by the second-generation Grubb's catalyst in CH₂Cl₂ under reflux, to yield the desired lactone **17** (82%) exclusively (Figure 5).

Finally deprotection of acetonide group in compound **17**, followed by acetylation of the resulting diol **18** produced the target molecule, lippialactone (**1**). The spectroscopic and

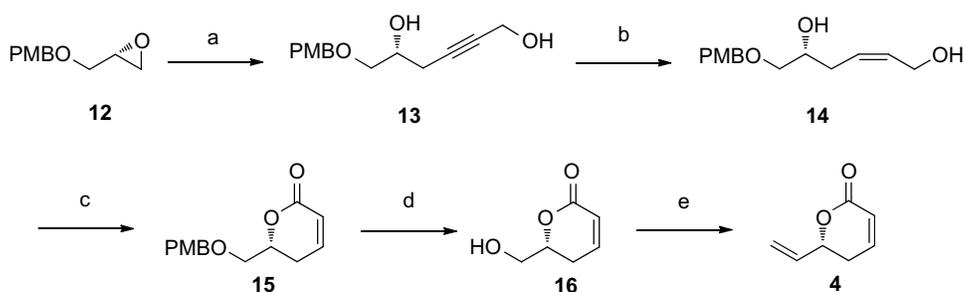


Figure 4 Synthesis of vinyl lactone 4.

Notes: Reagents and conditions: a) LiHMDS, propargyl alcohol, THF, BF₃OEt₂, -78°C, 4 hours, 85%, b) Pd/CaCO₃, H₂, quinoline, EtOAc, rt, 15 minutes, 90%, c) TEMPO/BAIB, CH₂Cl₂, rt, 1 hour, 90%, d) DDQ, CH₂Cl₂·H₂O (9:1), 0°C-rt, 2 hours, 92%, e) i) IBX/CH₃CN, ii) PPh₃=CH₂, THF, 0°C-rt, 75% over two steps.

Abbreviations: BAIB, bis(acetoxy)iiodobenzene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; PMBO, para-methoxybenzyl alcohol; rt, room temperature; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; THF, tetrahydrofuran.

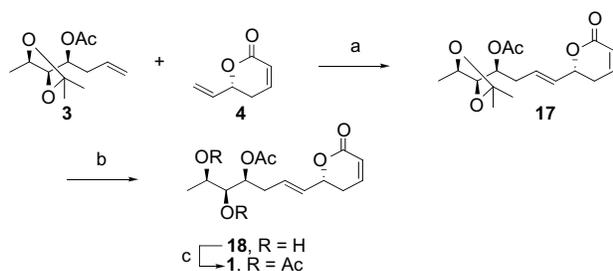


Figure 5 Synthesis of lippialactone (1).

Notes: Reagents and conditions: a) Grubbs' II (10 mol%), CH_2Cl_2 , reflux, 24 hours, 82%, b) TiCl_4 , CH_2Cl_2 , 0°C , 1 hour, 85%, c) Ac_2O , Et_3N , DMAP, CH_2Cl_2 , 0°C , 1 hour, 90%.

Abbreviation: DMAP, p-dimethylaminopyridine.

analytical data of the synthetic compound are in good agreement with those reported for the natural product.

Conclusion

In conclusion, the stereoselective synthesis of lippialactone from D-mannitol has been achieved. Vinyl lactone used in the present synthesis was prepared by a new synthetic route. LAH reduction, epoxide opening, and olefin cross-metathesis reactions were used as key steps.

Acknowledgments

KPR thanks Council of Scientific & Industrial Research and SPR thanks the University Grants Commission, New Delhi, India for the financial support in the form of fellowships.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Yasui K, Tamura Y, Nakatani T, Kawada K, Ohtani M. Total synthesis of (-)-PA-48153C, a novel immunosuppressive 2-pyranone derivative. *J Org Chem*. 1995;60(23):7567–7574.
2. Fang XP, Anderson JE, Chang CJ, McLaughlin JL, Fanwick PE. Two new styryl lactones, 9-deoxygoniopyrone and 7-epi-goniopufurone, from *Goniiothalamus giganteus*. *J Nat Prod*. 1991;54(4):1034–1043.
3. Argoudelis AD, Zieserl JF. The structure of U-13,933, a new antibiotic. *Tetrahedron Lett*. 1966;7(18):1969–1973.

4. Davies-Coleman MT, Rivett DE. Naturally occurring 6-substituted 5,6-dihydro- α -pyrones. *Fortschr Chem Org Naturst*. 1989;55:1–35.
5. Ludere MT, van Ree T, Vleggaar R. Isolation and relative stereochemistry of lippialactone, a new antimalarial compound from *Lippia javanica*. *Fitoterapia*. 2013;86:188–192.
6. Sabitha G, Gopal P, Reddy CN, Yadav JS. First stereoselective synthesis of synargentolide A and revision of absolute stereochemistry. *Tetrahedron Lett*. 2009;50(46):6298–6302.
7. Radha Krishna P, Nomula R, Kunde R. First total synthesis of lippialactone and its C9 epime. *Synthesis*. 2014;46(03):307–312.
8. Sabitha G, Bhaskar V, Reddy SSS, Yadav JS. Stereoselective total synthesis of (+)-(6R,2'S)-cryptocaryalactone and (-)-(6S,2'S)-epi cryptocaryalactone. *Tetrahedron*. 2008;64(44):10207–10213.
9. Sabitha G, Gopal P, Reddy CN, Yadav JS. A concise and efficient synthesis of (5R, 7S)-kurzilactone and its (5S, 7R)-enantiomer by the Mukaiyama aldol reaction. *Synthesis*. 2009;2009(19):3301–3304.
10. Sabitha G, Prasad MN, Shankaraiah K, Jhillu S. Stereoselective total synthesis of obolactone via prins cyclization. *Synthesis*. 2010;2010(7):1171–1175.
11. Sabitha G, Reddy SSS, Yadav JS. Total synthesis of cryptopyranmoscatone B1 from 3,4,6-tri-*O*-acetyl-d-glucal. *Tetrahedron Lett*. 2010;51(48):6259–6261.
12. Sabitha G, Reddy CN, Raju A, Yadav JS. Stereoselective total synthesis of the cytotoxic lactone (-)-spicigerolide. *Tetrahedron: Asymmetry*. 2011;22(4):493–498.
13. Sabitha G, Rao AS, Yadav JS. Stereoselective synthesis of (-)-synparvolide B. *Tetrahedron: Asymmetry*. 2011;22(8):866–871.
14. Sabitha G, Reddy DV, Reddy SSS, Yadav JS, Ganesh Kumar C, Sujitha P. Total synthesis of desacetylmuravumbolide, umuravumbolide and their biological evaluation. *RSC Advances*. 2012;2(18):7241–7247.
15. Tsuboi S, Takeda S, Yamasaki Y, et al. A convenient synthesis of platelet-activating factors and their analogues from chiral epichlorohydrin. *Chemistry Lett*. 1992;21(8):1417–1420.
16. Wu W, Wu Y. Chemoselective hydrolysis of terminal isopropylidene acetals and subsequent glycol cleavage by periodic acid in one pot. *J Org Chem*. 1993;58(13):3586–3588.
17. Ghosh S, Rao RV. Total synthesis of aspinolide B: a ring-closing metathesis approach. *Tetrahedron Lett*. 2007;48(39):6937–6940.
18. Hansen TM, Florence GJ, Lugo-Mas P, Chen J, Abrams JN, Forsyth CJ. Highly chemoselective oxidation of 1,5-diols to δ -lactones with TEMPO/BAIB. *Tetrahedron Lett*. 2003;44(1):57–59.
19. Torszell S, Somfai P. A practical synthesis of D-erythro-sphingosine using a cross-metathesis approach. *Org Biomol Chem*. 2004;2(11):1643–1646.
20. Dwyer CL. Metathesis of olefins. In: Chiusoli GP, Maitlis. *Metal-Catalysis in Industrial Organic Processes*. Cambridge: RSC Publishing; 2006:201–217.
21. Chiusoli GP. In: Weissmerl K, Arpe HJ. *Industrial Organic Chemistry*. 4th ed. Wiley-VCH Verlag GmbH & Co. 2008;3:59–89.

Reports in Organic Chemistry

Publish your work in this journal

Reports in Organic Chemistry is an international, peer-reviewed, open access journal publishing original research, reports, reviews and commentaries on all areas of organic chemistry. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use.

Submit your manuscript here: <http://www.dovepress.com/reports-in-organic-chemistry-journal>

Dovepress

Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.