Stereoselective total synthesis of lippialactone

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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 µg/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 conformation, 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.,...
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) (δ = 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).

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

A solution of 6 (2.0 g, 8.65 mmol) in dry CHCl₃ (15 mL), containing triethylamine (2.5 g, 24.7 mmol) and p-dimethylaminopyridine (DMAP) (0.04 g), was cooled to 0°C under N₂ atmosphere. This was followed by a dropwise addition of pivaloyl chloride (PivCl) (0.49 mL, 20.06 mmol) at 0°C (J = 6.0 Hz, 3H), 1.23 (s, 3H), 1.37–1.31 (m, 9H); 1H NMR: (CDCl₃, 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). 1H NMR: (CDCl₃, 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 [M+Na]⁺.

(R)-1-((4S,5S)-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 CH₂CN (10 mL) was added CuCl₂·2H₂O (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 NaHCO₃ (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; [α]D²⁵ : −38.3 (c 0.3, CHCl₃); 1H NMR: (CDCl₃, 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). 13C NMR: (CDCl₃, 125 MHz): δ 108.4, 82.6, 74.8, 72.1, 63.7, 27.2, 26.8, 18.9. IR (neat): 3243, 1526, 1424, 1214, 743 cm⁻¹; MS (ESI) m/z: 177 [M+H⁺].

(R)-2-hydroxy-2-((4S,5S)-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 CH₂Cl₂ (10 mL) was added Et₃N (2.03 mL, 20.06 mmol) at 0°C under N₂ 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 CH₂Cl₂ and washed with saturated NaHCO₃ solution, water, and brine. The organic layer was dried over anhydrous Na₂SO₄ 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. [α]D²⁵ : −18.9 (c 0.5, CHCl₃); 1H NMR: (CDCl₃, 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, 3H), 1.22 (d, J = 6.0 Hz, 3H); 13C NMR: (CDCl₃, 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 C₁₁H₂₂O₅, found 261.16963 [M-H]-.
(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 CH₂Cl₂ and washed with water and brine. The CH₂Cl₂ layer was dried over anhydrous Na₂SO₄ 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 K₂CO₃ 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 Na₂SO₄ before concentration. The crude product was chromatographed over silica gel to give (0.35 g, 85%) as a colorless liquid. [α]D = +2.0 (c 0.5, CHCl₃).

1H NMR: (CDCl₃, 300 MHz): δ 4.14–3.99 (m, 1H), 3.54 (brs, 1H), 3.50–3.45 (m, 1H), 3.35 (dd, 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). 13C NMR: (CDCl₃, 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, 2934, 1739, 1514, 1373, 1216, 748 cm⁻¹; MS (ESI) m/z: 181 [M+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, (Bu)₃N catalytic amount and (±) epichlorohydrin × (2.0 g, 21.73 mmol) in THF (15 mL) were added as well. The mixture was stirred for 16 hours, quenched with saturated NH₄Cl solution, and extracted into EtOAc (3×10 mL). The combined organic layer was washed with water, then brine, dried over anhydrous Na₂SO₄, 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-butylsalicylidy)-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%). [α]D = +10.3 (c = 0.5, CHCl₃).

1H NMR (CDCl₃, 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).

13C NMR (CDCl₃, 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 [M+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, BF₃·OEt₂ (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) at RT under hydrogen atmosphere (5 wt%), and quinoline (catalytic amount) was stirred for 3 hours at −78°C, it was quenched by adding a saturated aqueous NH₄Cl solution (20 mL). The resulting mixture was extracted with EtOAc (2×20 mL), and the combined organic layers were dried with anhydrous Na₂SO₄. The solvent was removed under reduced pressure, and the crude product was used directly for the next step.

The filtrate was concentrated, and the unsaturated aldehyde product was used directly for the next step without further purification by column chromatography.

(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%). [α]D²⁵ =−3.3 (c=0.2, CHCl₃). 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 [M+Na]⁺.

(R)-6-(5-hexyl)-5,6-dihydro-2H-pyran-2-one (16)
To a cooled (0°C) solution of 15 (0.25 g, 1.00 mmol) in CH₂Cl₂ (4.5 mL) and H₂O (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 NaHCO₃ solution was added, and the aqueous layer was extracted with CH₂Cl₂ (2×10 mL). The combined organic extract was washed over anhydrous Na₂SO₄ 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.

(R)-6-(4-hydroxymethyl)-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 CH₂CN (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 N₂ 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 crude aldehyde in dry THF (10 mL) was added dropwise, and the resulting mixture was stirred at RT for 2 hours, quenched with aqueous NH₄Cl, and extracted with EtOAc (2×10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ 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%), $[\alpha]_D^{25} = +10.2$ (c = 0.2, CHCl₃).

1H NMR: (CDCl₃, 500 MHz): $\delta$ 6.93–6.87 (m, 1H), 6.08–6.04 (m, 1H), 5.41 (dd, $J_{1,2}$ = 17.2, 0.9 Hz, 1H), 5.30 (dd, $J_{1,3}$ = 10.5, 0.7 Hz, 1H), 2.53–2.39 (m, 2H).

13C NMR: (CDCl₃, 125 MHz): $\delta$ 163.7, 144.4, 134.7, 121.5, 117.8, 77.7, 29.3. IR (neat): 2930, 1720, 1520, 1314, 1201, 747 cm⁻¹.


For stereostructure, see Figure 1.

(2R,3S,5S,6E)-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 1 (9 mg, 90%) as a colorless oil. $[\alpha]_D^{25} = +22.1$ (c = 0.3, CHCl₃).

1H NMR: (CDCl₃, 500 MHz): $\delta$ 6.89 (s, 3H), 6.03 (dd, $J_{1,2}$ = 9.6, 5.0, 3.3 Hz, 1H), 5.72 (dd, $J_{1,5}$ = 15.4, 6.8 Hz, 1H), 5.65 (dd, $J_{1,5}$ = 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). IR (neat): 2930, 2925, 1693, 1516, 1417, 1212, 747 cm⁻¹;


Figure 1 Retrosynthetic analysis. Abbreviation: PMBO, para-methoxybenzyl alcohol.
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-methathesis 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 as a new synthetic route.

The synthesis of fragment 3 (Figure 3) commenced from a primary alcohol 6, which was prepared from D-mannitol 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 Cul afforded homoallyl alcohol 11. The resulting free secondary hydroxyl group was acetylated to give a monoacetate compound 3.

The other fragment, vinyl lactone 4, was prepared from a known epoxide 12 as shown in Figure 4. The epoxide was subjected to regioselective ring opening with propargyl alcohol using LiHMDS, then BF3.OEt2 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)iodo]benzene [(PhI(OAc)2)(BAIB)] 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/CH2CN, 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-methathesis 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 3 Synthesis of fragment 3.](image)

**Figure 3 Synthesis of fragment 3.**

**Notes:** Reagents and conditions: a) TsCl, Et3N, DMAP, CH2Cl2, 0°C-rt, 1 hour, b) LiAH, THF, 3 hours, 87% for two steps, c) CuCl2, 2HO, CH2CN, 0°C-rt, 1 hour, 90%, d) PivCl, Et3N, DMAP, CH2Cl2, 0°C-rt, 4 hours, 87%, e) i) MsCl, Et3N, DMAP, CH2Cl2, °C to °20°C, 12 hours, ii) K2CO3, MeOH, rt, 2 hours, 85% for two steps, f) Cul, vinylMgBr, THF, °20°C, 1 hour, 88%, g) Ac2O, Et3N, DMAP, CH2Cl2, 0°C, 1 hour, 92%. *Reported in Wu and Wu and Ghosh and Rao.*

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

![Figure 4 Synthesis of vinyl lactone 4.](image)

**Figure 4 Synthesis of vinyl lactone 4.**

**Notes:** Reagents and conditions: a) LiHMDS, propargyl alcohol, THF, BF3.OEt2, °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/CH2CN, ii) PPh3=CH2, THF, 0°C-rt, 75% over two steps.

**Abbreviations:** BAIB, bis(acetoxy)iodobenzene; 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.
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.

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Disclosure
The authors report no conflicts of interest in this work.

References