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-pyrene (α-pyrene) subunit as a core structure, bearing on position 6 an additional alkenyl chain, are known to display a broad spectrum of pharmacological properties, such as insect growth inhibition, and antimicrobial, cytotoxic, and antitumoral activities. In 2013, Ludere et al 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 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. To date, however, only a single report has appeared on the synthesis of 1. In continuation of our interest in the synthesis of bioactive natural δ-lactones, 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 tetramethysilane (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',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, and treated with p-toluenesulphonyl chloride (3.30 g, 24.7 mmol) in dry THF (40 mL) for 1 hour. It was then diluted with water and extracted with CHCl3 and washed with saturated NaHCO3 solution, water, and brine. The organic layer was washed with brine and dried over anhydrous Na2SO4. Removal of solvent under reduced pressure afforded the unstable crude tosyl compound 7, which was used for further reaction. To a stirred suspension of LiAlH4 (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 Et2O, and quenched by the dropwise addition of saturated aqueous Na2SO4. The solid material was filtered and washed thoroughly with hot EtOAc several times. The combined organic layers were dried over anhydrous Na2SO4 and concentrated under reduced pressure to give 8 (2.0 g, 87%) as a colorless liquid; [α]25°: –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, 9H), 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 C15H25O5, found 261.16963 [M+H]+.

(4S,5R)-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 CH2Cl2 (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 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%) epoxide 5 as a colorless liquid. [α]°D = −42.1 (c 0.8, CHCl₃).

**1H NMR:** (CDCl₃, 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).

**13C NMR:** (CDCl₃, 125 MHz): δ 109.0, 82.6, 73.5, 50.8, 43.5, 27.2, 26.5, 17.7. **IR (neat):** 3019, 2926, 1693, 1517, 1213, 746 cm⁻¹.

**MS (ESI):** m/z: 305 [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)₃NI 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-butylsalicylilide)-1,2-cyclohexanediaminocobalt(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 (dd, 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]+.

(5)-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 CH₂Cl₂ (20 mL) were added Et₃N (0.46 mL, 4.54 mmol) followed 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 CH₂Cl₂ (5 mL). The organic layer was washed with 5% NaHCO₃ solution (2×5 mL), then brine (2×5 mL), and dried over anhydrous Na₂SO₄. 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. [α]°D = +9.0 (c 0.8, CHCl₃). **1H NMR:** (CDCl₃, 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). **13C NMR:** (CDCl₃, 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 [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) was added, and after the reaction mixture 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 mL) was stirred at RT under hydrogen atmosphere to a sphere (1 atm) until partially reduced product appeared on TLC. The reaction mixture was filtered through a pad of Celite® and the crude product was purified by silica gel column chromatography (hexane/EtOAc [7:3]) to afford compound 15 as a colorless oil (0.31 g, 90%). [α]₃⁵D = −20.3 (c=0.06, CHCl₃). 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). ¹C-NMR (CDCl₃, 125 MHz): δ 163.7, 159.3, 144.9, 129.3, 126.9, 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 [M+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 g, 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]₃⁵D = +4.8 (c=0.3, CHCl₃). 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 (s, 2H), 2.40–2.20 (m, 2H). ¹C-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-((4-methoxybenzyl)oxy)methyl)-5,6-dihydro-2H-pyran-2-one (4)
To an ice-cooled solution of 2-iodoacetylbenzoic 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 3 as a colorless oil (0.07 g, 75%). [α]D 25 = +22.1 (c 0.3, CHCl₃).

To a stirred solution of compound 3 (0.1 g, 0.43 mmol) and 4 (0.13 g, 1.27 mmol) in CH₂Cl₂ (3 mL), 10 mol-% Grubbs catalyst II (0.03 g, 0.04 mmol) was added and stirred at RT for 24 hours under N₂. 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 (SiO₂; 6:4% EtOAc/hexane) to give 17 (9 mg, 90%) as a colorless oil. [α]D 25 = +22.1 (c 0.3, CHCl₃).

To a stirred solution of compound 17 (0.05 g, 0.15 mmol) in anhydrous CH₂Cl₂ (7 mL), TiCl₄ (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 NaHCO₃ 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. [α]D 25 = +18.9 (c 0.4, CHCl₃).

The residue was purified by column chromatography (hexane/EtOAc 8:2) to give compound 4 as a colorless oil (0.07 g, 75%). [α]D 25 = −10.2 (c=0.2, CHCl₃). ¹H NMR: (CDCl₃, 500 MHz): δ 6.93–6.87 (m, 1H), 6.08–6.04 (m, 1H), 5.72 (dd, J=9.7, 3.5 Hz, 1H), 5.14–5.09 (m, 1H), 3.91–3.84 (m, 1H), 3.61 (dd, J=9.7, 3.5 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), 1.93 (s, 3H), 1.93 (s, 3H). ¹C NMR: (CDCl₃, 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 C₁₄H₂₈O₄N, found 302.15985 [M+Na]⁺.

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

To a stirred solution of the lactone 18 (10 mg, 0.03 mmol) in dry CH₂Cl₂ (5 mL) were added Et,N (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 CH₂Cl₂ (3 mL). The organic layer was washed with 5% NaHCO₃ solution (2×2 mL), then brine (2×2 mL), and dried over anhydrous Na₂SO₄. 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. [α]D 25 = +22.1 (c 0.3, CHCl₃). ¹H NMR: (CDCl₃, 500 MHz): δ 6.89 (dd, 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). ¹C NMR: (CDCl₃, 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 C₁₄H₂₈O₄N, found 302.15985 [M+Na]⁺.

Figure 2 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-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\textsuperscript{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\textsuperscript{16,17} according to the reported procedure. Tosylation of the primary hydroxyl group in compound 6, with TsCl, Et\textsubscript{3}N, and DMAP in CH\textsubscript{2}Cl\textsubscript{2}, gave compound 7, which on treatment with lithium aluminum hydride (LAH) gave a terminal methyl compound 8. Selective deprotection of the terminal acetonide with CuCl\textsubscript{2},2H\textsubscript{2}O in CH\textsubscript{3}CN afforded diol 9. Selective protection of the primary hydroxy group in 9, as the pivaloyl ester, with PivCl, Et\textsubscript{3}N, and DMAP in dichloromethane (DCM) gave compound 10. Mesylation of the secondary hydroxy group in compound 10, with MsCl, Et\textsubscript{3}N, and DMAP in CH\textsubscript{2}Cl\textsubscript{2}, gave secondary mesylate. This was followed by the treatment with anhydrous K\textsubscript{2}CO\textsubscript{3} 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 hydroxy group was acetylated to give a mono-acetate compound 3.

The other fragment, vinyl lactone 4, was prepared from a known epoxide 12\textsuperscript{15} as shown in Figure 4. The epoxide was subjected to regioselective ring opening with propargyl alcohol using LiHMDS, then BF\textsubscript{3}OEt\textsubscript{2} at \( -78^\circ\text{C} \) 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 \([\text{bis(acetoxy)iodo}]\text{benzene} ([\text{Phi(OAc)}\textsubscript{2}]\text{}(\text{BAIB})]\textsuperscript{18} produced the desired \( \delta \)-lactone 15, in 90\% yield.

Oxidative removal of the 4-methoxybenzyl ether (PMB) group (DDQ/CH\textsubscript{2}Cl\textsubscript{2}:H\textsubscript{2}O, 9:1, 0\degree 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/CH\textsubscript{3}CN, b) PPh\textsubscript{3}=CH\textsubscript{2}, THF, 0\degree C-rt, 75\% over two steps).

With the two key fragments in hand, the CM reaction was planned. Olefin cross-metathesis\textsuperscript{19-21} between fragment 3 and vinyl lactone 4 was promoted smoothly by the second-generation Grubb’s catalyst in CH\textsubscript{2}Cl\textsubscript{2} 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
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.

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