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Stereo Selective Total Synthesis of Phomonol

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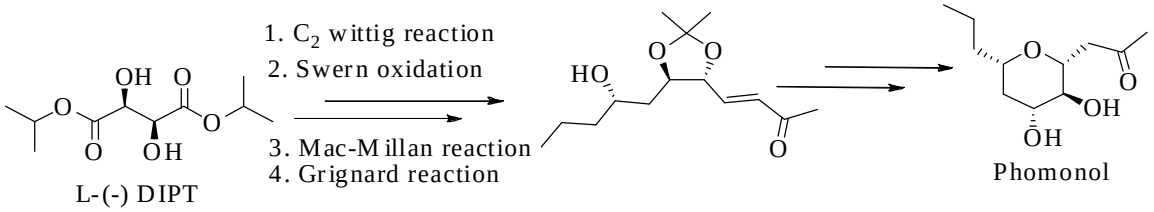
ABSTRACT

A new stereo selective method has been described for the total synthesis of phomonol from optically active L-(-) diisopropyl tartarate (L-(-) DIPT). The sequence of synthesis includes Swern oxidation, Mac-Millan, Grignard and Oxa-Michael addition reactions as key steps in achieving the target molecule.

KEYWORDS: Phomonol, Swern oxidation, Wittig olefination, Mac-Millan reaction, Grignard reaction, Oxa-Michael addition

GRAPHICAL ABSTRACT



A new stereo selective method has been described for the total synthesis of Phomonol from optically active L-(-) diisopropyl tartarate (L-(-) DIPT). The sequence of synthesis includes Swern oxidation, Mac-Millan, Grignard and Oxa-Michael addition reactions as key steps in achieving the target molecule.

1. INTRODUCTION

Substituted tetrahydropyrans are constituents of many biologically important natural products such as aspergilides,[1a] amphidinolides,[1b] decytospolide A[1c] and neopeltolide.[1d] Phomonol a 2,6-disubstituted tetrahydropyran (fig.1) was isolated along with phomonolides D-H by Shen and co- workers from endophytic fungal strain *phomopsis* sp. A123.The specific endophyte fungal strain was obtained from the leaves of mangrove species *kandelia candel* native of china[2a]. The structure of phomonol was elucidated as 1- ((2*R*, 3*S*, 4*R*, 6*S*)-3,4-dihydroxy-6-propyltetrahydro-2H-2yl) propane-2-one. The natural product was found to contain 4 asymmetric centres with $[\alpha]_D^{25}$+2.3 specific rotation[2b].

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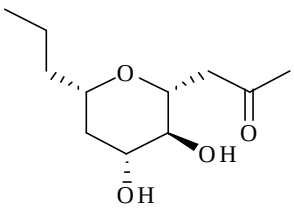
Due to the interesting structure with four chiral centres and substituentes, as well as important biological properties, the synthesis of Phomonol (**1**) has been an attractive target for the organic chemists.[3a,4a] In the pursuit of total synthesis of biologically active natural products, herein, we illustrate the novel synthesis of phomonol along with an alternate route for the total synthesis of target molecule starting from commercially available L-(-) diisopropyl tartarate. While our work was under progress an alternate synthesis of **1** has been disclosed using same starting material[4b].



1

Fig.1. Structure of Phomonol

2. EXPERIMENTAL

2.1. Material and Methods

All reactions were carried out under nitrogen atmosphere using flame dried glassware. Solvents dichloromethane, triethylamine were distilled from CaH_2 and tetrahydrofuran from Na/Benzophenone prior to use. Nuclear Magnetic Resonance (^1H and ^{13}C NMR) spectra were recorded on Varian 300 MHz and 500 MHz spectrometers, using tetramethylsilane (TMS) as the internal standard. Chemical shifts were given in ppm, coupling constants *J* are expressed in Hertz (multiplicity: singlet (s), doublet (d), triplet (t), quadruplet (q) multiplet (m), broad singlet (brs), doublet of doublet (dd), doublet of triplet (dt), quadruplet of triplet (qt) and doublet of doublets of doublets (ddd) ESI MS in m/z.

2.2. Synthetic Procedure

((4R,5R)-5-(((Tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (6)

^1H NMR (300 MHz, $CDCl_3$): *d* 0.08 (s, 6H), 0.9 (s, 9H), 1.40 (s, 3H), 1.41 (s, 3H), 2.45 (brs, 1H), 3.6 (d, *J*=4.2 Hz, 2H), 3.85-3.91 (dt, *J*=7.5, 3.96 Hz, 2H), 4.2 (dd, *J*=7.3, 1.7Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): *d* -5.5, 18.29, 25.83, 26.87, 26.99, 62.71, 63.67, 78.12, 80.14, 109.07. ESI MS: m/z 277 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{28}O_4Si$: C, 56.48; H, 10.21%. Found: C, 56.44; H, 10.23%.

(*E*)-Ethyl 3-((4*R*,5*R*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (7)

To a solution of oxalyl chloride (3.10 mL, 36.23 mmol) in dry CH_2Cl_2 (25 mL), dry DMSO (5.6 mL, 72.51 mmol) was added drop wise at -78 °C and stirred for 10 min at same temperature. A solution of alcohol **6** (5.0 g, 18.11 mmol) in dry CH_2Cl_2 (10 mL) was added and stirred for 1 h at -78 °C. Next, Et_3N (20.35 mL, 145.10 mmol) was added and the reaction mixture was stirred for an additional 10 minutes. The reaction mixture was washed with water (20 mL), brine (20 mL), dried (Na_2SO_4) and evaporated to furnish the corresponding aldehyde.

The crude aldehyde (4.5 g, 16.42 mmol) was dissolved in dry THF (50 mL) and (ethoxycarbonylmethylene)- triphenylphosphorane (21.59 g, 62.05 mmol) was added portion wise at room temperature. The mixture was stirred overnight, poured in 100 mL water and extracted with ethyl acetate (3x75 mL). After drying over anhydrous Na_2SO_4, the extract was filtered and evaporated under reduced pressure. The resulting residue was purified by flash chromatography using EtOAc/hexane, 1:9 as an eluent, to afford the unsaturated ester **7** (5.2 g, overall yield at the of two steps is 83%). ^1H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.9 (s, 9H),1.29 (t, *J*=7.17 Hz, 3H), 1.40 (s, 3H), 1.41 (s, 3H), 3.71 (m, 2H), 3.85 (m, 1H), 4.2 (q, *J*=7.36 Hz, 2H), 4.51 (d, *J*=11.14 Hz, 1H), 4.52 (d, *J*=11.14 Hz, 1H), 6.2 (d, *J*=15.86 Hz, 1H), 6.91-6.98 (m,1H). ^{13}C NMR (75 MHz, $CDCl_3$): *d* -5.48, 14.14, 18.24, 25.82, 25.89, 26.76, 26.87, 60.46, 62.70, 77.78, 80.71, 109.84, 121.87, 144.66, 166.07. ESI MS: m/z 345 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{32}O_5Si$: C, 59.27; H, 9.36%. Found: C, 59.30; H, 9.35%.

Ethyl 3-((4*R*,5*R*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propanoate (8)

To a stirred solution of unsaturated ester **7** (4.0 g, 11.62 mmol) in MeOH (25 mL) $NiCl_2.6H_2O$ (0.55 g, 1.74 mmol) was added at 0 °C. The resultant mixture was stirred at 0 °C for 10 min and $NaBH_4$ (0.88 g, 23.29 mmol) was added portion wise at same temperature. The reaction mixture was stirred for another 3 h at room temperature and quenched with water. The whole reaction mixture was concentrated to get the residue, which was extracted with EtOAc. The organic extract was washed with brine and dried over anhydrous Na_2SO_4 filtered and evaporated. The crude reaction mixture was purified by silica gel column chromatography using EtOAc/hexane (10%) as an eluent to provide the corresponding saturated ester **8** (3.6 g, 90%).

3-((4*R*,5*R*)-5-(((Tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (9)

To a stirred solution of $LiAlH_4$ (0.65 g, 17.36 mmol) in dry THF (40 mL), a solution of 3-((4*R*,5*R*)-5-(((tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-1-ol (**9**) (3.0 g, 8.67 mmol) in dry THF (15 mL) was added at 0 °C and stirred overnight at room temperature. The reaction was quenched by a drop of saturated Na_2SO_4 solution at 0 °C and The mixture was filtered through celite and washed with ethyl acetate. The solvent was removed to yield pure alcohol **9** (2.6 g, 97%). ^1H NMR (300 MHz, $CDCl_3$): *d* 0.08 (s, 6H), 0.9 (s, 9H), 1.38 (s, 3H), 1.41 (s, 3H), 1.69-1.77 (m, 2H), 1.87-1.96 (m, 1H), 3.50-3.56 (d, *J*=6.8 Hz, 1H), 3.63-3.73 (m, 3H), 3.78-3.85 (m, 3), 3.41 (dt, *J*=7.5 Hz, 3.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): *d* -5.49, 25.83, 26.88, 27.25, 29.49, 30.11, 62.69, 63.42, 78.75, 80.96, 108.54. ESI MS: m/z 327 $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{32}O_4Si$: C, 59.17; H, 10.59%. Found: C, 59.24; H, 10.55%.

(*S*)-3-((4*R*,5*R*)-5-(((Tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propane-1,2-diol (4)

Compound **9** (2.0 g, 6.57 mmol) was converted to corresponding aldehyde following Swern oxidation (as described for **7**).The aldehyde was added drop wise to a solution of nitrosobenzene (0.34 g, 3.26 mmol) and L-Proline (0.036 g, 0.318 mmol) in chloroform (2 mL) at 0 °C, and the solution was vigorously stirred at 0 °C for 2 h. The reaction mixture was a solution of $NaBH_4$ (0.249 g, 6.57 mmol) in ethanol (20 mL) at 0 °C and the solution was stirred for 2 h maintaining same

temperature. The reaction mixture was concentrated and saturated aq. $NaHCO_3$ solution (10 mL) was added. The mixture was extracted with ethyl acetate (3x50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated. The residue was dissolved in 3 : 1 EtOH : AcOH (8 mL) and treated with zinc powder (0.609 g, 9.83 mmol) and the reaction mixture was stirred at room temperature for 12 h, then filtered through celite and concentrated. Purification of the residue by flash column chromatography gave the diol **4** (1.5 g, 71%) as a colorless oil. ^{1}HNMR (300 MHz, $CDCl_3$): *d* 0.08 (s, 6H), 0.9 (s, 9H), 1.38 (s, 3H), 1.41 (s, 3H), 1.69-1.77 (m, 2H), 3.12-3.18 (m, 1H), 3.50-3.56 (d, *J*=6.79 Hz, 1H), 3.63-3.73 (m, 3H), 3.78-3.85 (m, 3), 3.41 (dt, *J*=7.48 Hz, 3.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): *d* -5.49, 25.88, 26.83, 27.23, 29.70, 30.94, 36.18, 63.75, 66.75, 69.69, 80.37, 108.73. ESI MS: m/z 343 $[M+ Na]^+$. Anal. Calcd. for $C_{15}H_{32}O_5Si$: C, 56.21; H, 10.06%. Found: C, 56.15; H, 10.09%.

Tert-butyl(((4*R*,5*R*)-2,2-dimethyl-5-((*S*)-oxiran-2-ylmethyl)-1,3-dioxolan-4-yl)methoxy)dimethylsilane (10)

To a solution of the diol **4** (1.5 g, 4.68 mmol) in THF (15 mL) a solution of NaH (60 w/w in mineral oil, 0.136 g, 5.67 mmol) in THF (5 mL) was added at 0 °C. The resulting mixture was then warmed to ambient temperature and stirred for 40 min. The mixture was cooled to 0 °C and tosylimidazole (1.25 g, 5.63 mmol) was added. The temperature of the mixture was allowed to rise up to ambient temperature and stirred for 1 h. The reaction was quenched with water (15 mL) and extracted with EtOAc (3x30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (EtOAc/hexane, 1:9) to give pure epoxide **10** (1.3 g, 91%). ^{1}H NMR (300 MHz, $CDCl_3$): *d* 0.07 (s, 6H), 0.9 (s, 9H), 1.39 (s, 3H), 1.40 (s, 3H), 1.73-1.91 (m, 2H), 2.50-2.52 (dd, *J*=2.26 Hz, 1H), 2.81 (t, *J*=4.72 Hz, 1H), 3.1-3.19 (brs,1H), 3.62-3.82 (m, 3H), 4.15 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): *d* -5.49, 18.6, 25.88, 26.90, 27.29, 29.69, 36.93, 47.48, 49.55, 63.36, 80.90, 84.63, 108.31. ESI MS: m/z 325 $[M+ Na]^+$. Anal. Calcd. for $C_{15}H_{30}O_4Si$: C, 59.56; H, 10.00%. Found: C, 59.48; H, 10.05%.

(*R*)-1-((4*R*,5*R*)-5-(((Tert-butyldimethylsilyl)oxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-ol (11)

A suspension of Grignard reagent in THF (30 mL) was prepared from ethyl bromide (0.88 mL, 11.92 mmol) and Mg (0.38 g, 15.88 mmol). The suspension was cooled (-20 °C) and Cu(I) iodide (1.13 g, 5.94 mmol) was added. The mixture was stirred at -20 °C for 15 min. To this cold organometallic suspension, a solution of epoxide **10** (1.20 g, 3.97 mmol) in THF (20 mL), was added. The mixture was stirred at the same temperature for 1 h and then gradually brought to room temperature. The mixture was then stirred overnight at room temperature. The reaction was quenched by the addition of aqueous saturated NH_4Cl (10 mL) and extracted with EtOAc. The organic layer was washed with 5% aqueous HCl, water, brine and then dried over Na_2SO_4. Solvent was removed under reduced pressure and column chromatography of the residue (silica gel, 10% EtOAc in hexane) afforded pure compound **11** (1.12 g, 84%) as a colorless liquid. ^{1}HNMR (300 MHz, $CDCl_3$): *d* 0.08 (s, 6H), 0.9 (s, 9H), 0.95 (t, *J*=7.0, 3H), 1.37 (s, 3H), 1.41 (s, 3H), 1.42-1.52 (m, 4H), 1.74- 1.82 (m, 2H), 2.69 (brs, 1H), 3.65-3.70 (m, 2H), 3.78-3.86 (m, 2H), 4.13-4.17 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): *d* -5.46, 14.05, 18.88, 26.82, 27.25, 29.67, 39.42, 39.59, 63.74, 68.75, 80.35, 108.57. ESI MS: m/z 333 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{36}O_4Si$: C, 61.40; H, 10.91 %. Found: C, 61.36; H, 10.93%.

((4*R*,5*R*)-5-((*S*)-2-((4-Methoxybenzyl)oxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (3)

Sodium hydride (0.11 g, 4.55 mmol) was added slowly to a solution of compound **11** (1.0 g, 3.01 mmol) in anhydrous THF (40 mL) at 0 °C and stirred for 15 min. Then 4-methoxybenzyl Chloride (0.89 mL, 6.02 mmol) and catalytic amount of TBAI were added at 0 °C and the reaction mixture was stirred at room temperature for 4 h. After completion of the reaction, the reaction was quenched by slow addition of water (5 mL) and extracted with EtOAc (50 mL). The organic layer was separated and washed with water (20 mL) and brine (10 mL). The organic solvent was evaporated and the crude product was purified by silica gel column chromatography using EtOAc/hexane (5:95) as an eluent, to afford PMB-protected compound.

To a solution of PMB-protected compound (1.22 g, 2.69 mmol) in dry THF (15 mL) 1 M solution (2.9 mL) of Bu_4NF in THF at 0 °C was added and the resulting solution was stirred at room temperature for 3 h. Saturated NH_4Cl solution (15 mL) was added, and the reaction mixture was stirred for 5 min and then diluted with water (50 mL) and extracted with EtOAc (100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by flash chromatography (elution with EtOAc/hexane) to yield corresponding alcohol **3** (0.94 g, all yield at the of end of overall two steps 92%) as a colorless oil. ^{1}HNMR (500 MHz, $CDCl_3$): *d* 0.9 (t, *J*=7.0 Hz, 3H), 1.38 (brs, 3H), 1.4 (brs, 3H), 1.62-1.70 (m, 4H), 1.63-1.75 (m, 2H), 2.09-2.15 (m, 1H), 3.52-3.75 (m, 4H), 3.80 (brs, 3H), 4.0 (m, 1H), 4.4 (d, *J*=10.8 Hz, 1H), 4.5 (d, *J*=10.8 Hz, 1H), 6.85 (d, *J*=8.5 Hz, 2H), 7.27 (d, *J*=8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): *d* 14.23, 18.15, 26.89, 27.32, 36.68, 38.44, 55.24, 62.01, 71.22, 74.62, 76.01, 81.79, 108.43, 113.69, 129.43, 130.84, 159.10. ESI MS: m/z 361 $[M+ Na]^+$. Anal. Calcd. for $C_{19}H_{30}O_5$: C, 67.43; H, 8.93%. Found: C, 67.50; H, 8.89%.

(*E*)-4-((4*R*,5*R*)-5-((*S*)-2-(4-Methoxybenzyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-one (12)

To an icecooled solution of 2-iodoxybenzoic acid (0.34 g, 1.40 mmol) in DMSO (0.82 mL, 11.60 mmol) a solution of alcohol **3** (0.4 g, 1.17

mmol) in dry CH_2Cl_2 (10 mL) was added. The mixture was stirred at room temperature for 1.5 h and then filtered through a Celite pad and washed with ether. The combined organic filtrates were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in *vacuo*. The crude aldehyde was used immediately for the next reaction and was added to a solution of Wittig ylide 1-(triphenyl phosphoranylidene)-2-propanone (0.05 g, 0.16 mmol) in dry THF. The reaction mixture was refluxed for 8 h, solvent was evaporated and the residue was purified by column chromatography (EtOAc/hexane, 5:95) as an eluent, to afford α, ß-unsaturated ketone **12** (0.425 g, 91%, over two steps) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): *d* 0.9 (t, *J* = 7.2 Hz, 3H), 1.36-1.41 (m, 2H), 1.42 (brs, 3H), 1.43 (brs, 3H), 1.47-1.56 (m, 1H), 1.57-1.63 (m, 1H), 1.63-1.77 (m, 2H), 2.26 (brs, 3H), 3.63-3.69 (m, 1H), 3.81 (brs, 3H), 3.98 (dt, *J* = 9.3, 3.1 Hz, 1H), 4.18 (t, *J* = 7.4 Hz, 1H), 4.42 (d, *J* = 11.0 Hz, 1H), 4.53 (d, *J* = 11 Hz, 1H), 6.3 (d, *J* = 16.4 Hz, 1H), 6.65 (dd, *J* = 15.5, 5.6 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): *d* 14.24, 18.12, 26.61, 27.24, 29.66, 36.7, 55.23, 71.34, 75.56, 77.45, 80.65, 109.33, 113.76, 129.34, 130.75, 131.59, 142.43, 159.13, 197.98. ESI MS: m/z 399 $[M+ Na]^+$. Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57%. Found: C, 70.28; H, 8.52%.

(*E*)-4-((4*R*,5*R*)-5-((*S*)-2-Hydroxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-one (2)

The compound **12** (0.2 g, 0.63 mmol) was dissolved in CH_2Cl_2:H_2O (19:1, 3 mL) at 0 °C, DDQ (0.14 g, 0.63 mmol) was added and stirred for 1 h. The reaction was quenched with saturated aq. $NaHCO_3$ (3 mL) and filtered through celite pad with CH_2Cl_2 (2 x 10 mL) and washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude residue was purified by column chromatography (EtOAc/hexane, 5:95) to furnish compound **2** (0.15 g, 92%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *d* 0.95 (t, *J* = 7.0 Hz, 3H), 1.43 (brs, 3H), 1.47 (br. s, 3H), 1.33-1.56 (m, 5H), 1.73 (t, *J* = 5.98 Hz, 2H), 2.21 (brs, 3H), 3.86-3.93 (m, 1H), 4.01-4.08 (m, 1H), 4.22-4.27 (m, 1H), 6.35 (d, *J* = 16.1 Hz, 1H), 6.72 (dd, *J* = 16.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): *d* 13.98, 18.76, 26.62, 27.12, 29.62, 38.32, 39.88, 68.32, 77.87, 80.12, 109.59, 131.49, 142.21, 198.01. ESI MS: m/z 257 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44%. Found: C, 65.55; H, 9.47%.

1-((3a*R*,4*R*,6*S*,7a*R*)-2,2-Dimethyl-6-propyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)propan-2-one (13)

Sodium hydride (0.013 g, 0.54 mmol, 60% w/w dispersion in mineral oil) was dissolved in dry THF (2 mL) at 0 °C. To this cooled solution a, ß-unsaturated ketone **2** (0.07 g, 0.27 mmol) in THF (2 mL) was added drop wise and allowed to stirr for further 1 h at 0°C. The reaction was quenched with saturated aq. NH_4Cl solution (2 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by column chromatography (EtOAc/hexane, 5:95) to afford compound **13** (0.06 g, 88%) as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): *d* 0.9 (t, *J* = 7.2 Hz, 3H), 1.42 (brs, 6H), 1.22-1.64 (m, 5H), 2.14 (qd, *J* = 6.1, 4.0, 2.0 Hz, 1H), 2.19 (brs, 3H), 2.62-2.76 (m, 2H), 3.09 (t, *J* = 8.9 Hz, 1H), 3.38-3.45 (m, 1H), 3.54-3.64 (m, 1H), 3.93 (dt, *J* = 8.9, 3.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): *d* 13.89, 18.78, 26.79, 30.89, 37.57, 39.02, 46.56, 73.14, 75.42, 76.24, 78.04, 79.98, 109.89, 208.42. ESI MS: m/z 279 $[M+ Na]^+$. Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44%. Found: C, 65.69; H, 9.40%.

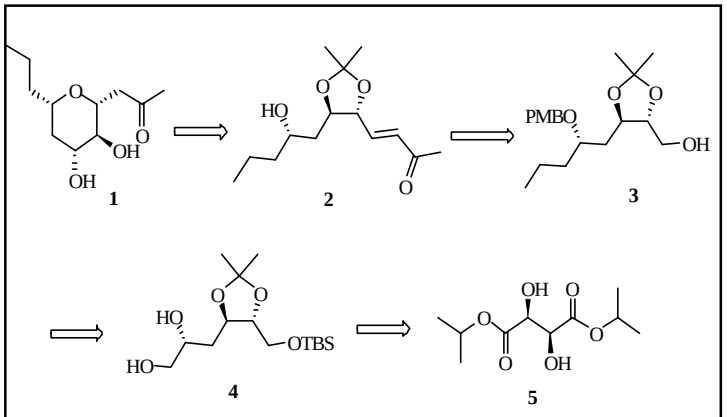
Phomonol (1)

To the compound **13** (0.05 g, 0.19 mmol) in MeOH (3 mL) at 0°C catalytic amount of PTSA was added and stirred at room temperature. After 1 h Et_3N (0.5 mL) was added to the reaction mixture at 0 °C. Solvent was evaporated and the residue was purified by column chromatography (EtOAc/hexane, 1:9) to afford phomonol **1** (0.038 g, 90%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): *d* 0.9 (t, *J* = 7.0 Hz, 3H), 1.29-1.42 (m, 4H), 1.44-1.56 (m, 1H), 2.01 (ddd, *J* = 12.98, 5.1, 1.29 Hz, 1H), 2.23 (brs, 3H), 2.88 (dd, *J* = 15.6, 4.8 Hz, 1H), 2.99 (dd, *J* = 15.6, 3.9 Hz, 1H), 3.39-3.44 (m, 1H), 3.09 (t, *J* = 8.98 Hz, 1H), 3.56-3.66 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): *d* 13.88, 18.89, 31.01, 37.52, 39.03, 46.22, 73.15, 75.39, 76.29, 208.65. ESI MS: m/z 239 $[M+ Na]^+$. Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32%. Found: C, 61.00; H, 9.35%.

3. RESULTS AND DISCUSSIONS

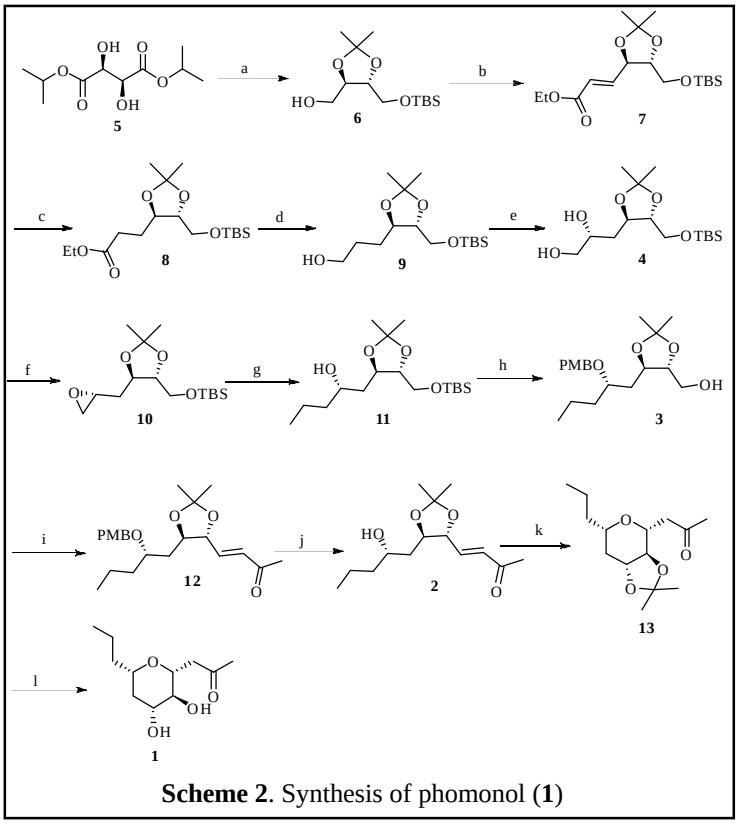
3.1 *Synthesis and characterization*

The retrosynthetic analysis of Phomonol (1) (**Scheme 1**) indicated that the compound (**1**) can be synthesized by intramolecular Oxa-Michael addition of compound **2**, which can be prepared from the primary alcohol **3.** The latter can be achieved from the L-(-) DIPT following a sequence of reactions viz., Swern oxidation, Mac-Millan reaction and Wittig reaction.



Scheme 1. Retrosynthetic analysis of phomonol (**1**)

The monoprotected alchol **6** was synthesised from commercially available L-(-) diisopropyl tartarate (**5**) following reported protocol[5] **scheme 2**. The free primary hydroxyl group of **6** was converted to aldehyde by Swern oxidation with $(COCl)_2$, DMSO and Et_3N. The resulting aldehyde underwent Wittig homologation with $Ph_3PCHCOOEt$ to furnish the a,ß-unsaturated ester **7**.[3b] Reduction of **7** with $NiCl_2.6H_2O$/ $NaBH_4$ in MeOH afforded the saturated ester **8** in 90% yield.[6] Compound **8** upon reduction with LAH in dry THF resulted in the primary alcohol **9** in 97% yield[12]. The primary alcohol **9** was subjected to Swern oxidation to form aldehyde, which is subsequently subjected to asymmetric a-hydroxylation by following Mac- Millan reaction condition using L-proline and nitrosobenzene in $CHCl_3$ at 0 °C followed by *in situ* reduction of the resulting anilinoxy aldehyde with $NaBH_4$ in ethanol at 0 °C and treatment with Zn to obtain the diol **4** in 71% yield.[7] The diol **4** was treated with tosylimidazole in the presence of NaH in THF to furnish the epoxide **10** in 91% yield. The epoxide ring of **10** underwent ring opening in the presence of Grignard reagent with catalytic amount of CuI to afford the alcohol **11** in 84% yield[8a,8b]. The hydroxyl group in **11** was protected using PMBCl,[9] which is then treated with TBAF in THF to give primary alcohol **3** in 92% yield[10](over two steps). The primary alcohol **3** was oxidized with IBX in DMSO followed by Wittig olefination with commercially available 1-(triphenyl phosphoranylidene)-2-propane ylide in THF under reflux furnished a,ß-unsaturated ketone **12** in 91% yield (over two steps)[11].



Scheme 2. Synthesis of phomonol (**1**)

Reagents and conditions: (a) ref. 5 (b) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C, 1 h; (ii) $Ph_3P=CH_2CO_2Et$, THF, rt, 8 h, 83% (over two steps); (c) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 0 °C to rt, 3 h, 90%; (d) LAH, dry THF, 0 °C to rt, 97%; (e) (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78°C to rt, 1 h; (ii) PhNO, L-proline, $CHCl_3$, 0 °C, 2 h then $NaBH_4$, EtOH, 0 °C, 2 h then AcOH, Zn, 12 h, 71%; (f) tosylimidazole, NaH, THF, 0 °C to rt, 2 h, 91%; (g) EtBr, Mg, CuI, THF, -20 °C to rt, 12 h, 84%; (h) (i) PMBCl, NaH, THF0 °C to rt, 4 h ; (ii) TBAF, THF, 0 °C to rt, 3 h, 92% (over two steps) (i) (i) IBX, DMSO, CH_2Cl_2, 0 °C to rt, 1.5 h; (ii) 1-(tri phenyl phosphoranylidene)-2-propanone, dry THF, reflux, 8 h, 91% (over two steps); (j) DDQ, CH_2Cl_2:H_2O (19:1), 0 °C to rt, 1 h, 92%; (k) NaH, dry THF, 0°C, 1 h, 88%; (l) PTSA, MeOH, 0 °C to rt, 1 h, 90%.

The α,ß-unsaturated ketone **12** upon treatment with DDQ in CH_2Cl_2/ H_2O resulted in the alcohol **2** in 92% yield. Further, we attempted the intramolecular oxa-Michael addition of a, ß-unsaturated ketone **2** by using NaH in THF which is reported earlier to afford the 2,6-cis-tetrasubstituted tetrahydropyran **13** an exclusive diastereomer (88%)[3]. Finally, the deprotection of acetonide from compound **13** by using PTSA in MeOH furnished phomonol (**1)** in (90%) yield, which is characterized by ^1H NMR, ^{13}C NMR and Mass spectrum (experimental).

4. CONCLUSION

In conclusion, we have developed a new total synthesis of phomonol in a highly stereoselective manner. Our approach involves Swern oxidation, Mac-Millan reaction, Grignard reaction and Oxa-Michael addition reactions as key steps. This novel approach provides an easy access to produce Phomonol with good yield.

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Conflict of interest

The authors confirm that this article content has no conflict of interest

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