Towards the total synthesis of Schisandrene: Stereoselective synthesis of Dibenzocyclooctadiene lignans core.

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EXPERIMENTAL SECTION

Methyl 7-hydroxybenzo[d][1,3]dioxole-5-carboxylate (9):

![Chemical Structure of Methyl 7-hydroxybenzo[d][1,3]dioxole-5-carboxylate (9)]

To a mixture of potassium carbonate (4.002 g, 29 mmol), methyl gallate (6 g, 29.7 mmol), in dry DCM and diiodomethane (2.8 mL, 34.8 mmol) was added at room temperature under nitrogen condition, allowed to stir for 5h at 120°C. The resulting mixture was poured into ice cooled water (500 mL) and was extracted with ethyl acetate. The combined organic extracts were washed with brine, then dried over Na₂SO₄, filtered and evaporated under reduced pressure. The residue was purified by column chromatography with 15% EtOAc/hexane to afford compound 9 (3.6 g, 58%) as white amorphous powder. ¹H NMR (300 MHz, CDCl₃) δH 7.35 (1H, s), 7.12 (1H, s), 6.08 (2H, s), 3.04 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δC 166.9, 148.5, 140.1, 138.5, 123.6, 113.7, 101.9, 101.7, 51.8 ppm; MS (ESI): m/z 197 [M + H]^+.

Methyl 6-bromo-7-methoxybenzo [d] [1, 3] dioxole-5-carboxylate (11):

![Chemical Structure of Methyl 6-bromo-7-methoxybenzo [d] [1, 3] dioxole-5-carboxylate (11)]

To a solution of 9 (3.5 g, 16.3 mmol) in THF, solution of NBS (2.9 g, 16.3 mmol) in 25 mL THF was added drop wise at ambient temperature. The resulting mixture stirred for 1h at 0°C, after completion of reaction, reaction mixture was quenched with hypo and extracted with ethyl acetate and washed with brine. The organic layer was dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography with 20% EtOAc/hexane to give compound 10 (3.7 g, 85%) as light yellow liquid. ¹H NMR (300 MHz, CDCl₃): δH 7.02 (1H, s), 6.05 (2H, s), 4.02 (3H, s); 3.89 (3H, s); ¹³C
NMR (75 MHz, CDCl$_3$) $\delta$C 166.1, 148.2, 140.9, 140.4, 126.2, 109.0, 105.4, 102.3, 60.2, 52.3 ppm; MS (ESI): $m/z$ 310 [M + Na]$^+$. 

To a stirred solution of 10 (3.6 g, 13.09mmol) in anhydrous acetone Potassium carbonate (4.48 g, 32.5 mmol) followed by methyl iodide (3.39 mL, 35.8 mmol) was added under Nitrogen atmosphere. The reaction mixture was stirred for 5 h. After completion of reaction by monitoring the TLC, the solid was removed by filtration. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography with 10 % EtOAc/hexane to give compound 11 (3.3 g, 90%) as colorless liquid. $^1$H NMR (300 MHz, CDCl$_3$)$\delta$H 7.00 (1H, s), 6.03 (2H, s), 4.05 (3H, s); 3.91 (3H, s),$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 184.5, 166.6, 159.3, 158.8, 144.6, 127.4, 123.8, 120.7, 78.6, 70.7 ppm. MS (ESI): $m/z$ 298 [M + Na]$^+$. 

6- bromo-7-methoxybenzo [d][1,3] dioxole-5-carbaldehyde (7): 

![Chemical structure](image)

To a stirred solution of 11 (3.3 g, 11.3 mmol) in DCM (35 mL) diisobutylaluminum hydride (DIBAL-H), (16.1mL 28.4mmol 1.6 M in Toluene) at -78°C was added. The reaction mixture was stirred for 20 min at same temperature. After completion of reaction, the reaction mixture was quenched with saturated sodium potassium tartrate solution at 0°C, then extracted with extracted DCM (3 x 50 mL), the organic layer was dried over anhydrous Na$_2$SO$_4$. The solvent was removed under reduced pressure, and the crude product was subjected to flash column chromatography with 10% ethyl acetate-hexane) to give compound 7 (3.04 g, 95%) as white solid. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 10.2 (1H, s) 7.16 (1H, s), 6.09 (2H, s), 4.06 (3H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 190.6, 149.1, 142.8, 140.2, 128.4, 115.6, 102.9, 102.6, 60.3 ppm; MS (ESI): $m/z$ 282 [M + Na]$^+$. 
(6- bromo-7-methoxybenzo [d][1,3] dioxol-5-yl-)methanol (12):

To a solution of aldehyde 7 (1.7 g, 6.538 mmol), in MeOH, sodium borohydride was added portion wise at 0°C under Argon condition. The reaction mixture was stirred for 1 h. After completion of reaction the reaction mixture was filtered through celite, filtrate was evaporated under reduced pressure. The residue was purified by using column chromatography with 20% EtOAc/hexane to afford compound 12 (1.66 g, 98%) as colourless liquid. 1H NMR (300 MHz, CDCl3) δH 6.74 (1H, s), 5.97 (2H, s), 4.94 (2H, J = 5.8 Hz, d), 4.06 (2H, J = 4.5 Hz, d), 4.03 (3H, s); 13C NMR (75 MHz, CDCl3) δC 148.6, 140.2, 136.5, 134.0, 106.8, 103.2, 101.6, 65.0, 60.0 MS (ESI): m/z 260 [M + H]+.

6-(benzyloxy) methyl-5-bromo-4-methoxybenzo [d][1,3] dioxole (13):

To a solution of sodium hydride in dry DMF (0.165 g, 6.8 mmol) at 0°C, compound 12 (1.2 g, 4.58 mmol) in dry DMF (5 mL) was added drop wise and resulting mixture was stirred for 30 min at 0°C then allowed to room temperature, string was continued for 1 hr. The reaction mixture was again taken to 0°C then Benzyl bromide (0.7 mL, 5.9 mmol) was added drop wise (0.7 mL, 5.9 mmol), the reaction mixture was allowed to stir for overnight. The reaction mixture was quenched with ice at 0°C then extracted with ethyl acetate. The organic layer was washed with brine and dried over Na2SO4, filtered and solvent was evaporated under reduced pressure. Resulted residue was purified by column chromatography with 12% EtOAc/hexane to give compound 13 (1.52 g, 95%) as brown liquid. 1H NMR (300 MHz, CDCl3) δH 7.42-7.32 (3H, m),
6.31-7.26 (2H, m), 6.80 (1H, s), 5.94 (2H, s), 4.59 (2H, s) 4.53 (2H, s), 4.01 (3H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) δc 148.6, 140.2, 137.9, 136.5, 131.8, 128.3 (2 C), 127.6 (3 C), 107.2, 103.4, 101.5, 72.8, 71.5, 59.9 ppm; MS (ESI): m/z 374 [M + Na$^+$].

(6-((benzyloxy) methyl)-4-methoxybenzo [d][1,3] dioxol-5-yl)boronic acid (6):

![Structure 1]

To a solution aryl bromide 13 (1.47 g, 4.14mmol), in dry THF n-BuLi was added (4.6mL, 4.62mmol, 1.6M solution) drop wise at -78°C under nitrogen condition. The resulting mixture was stirred for 30 min. to reaction mixture freshly distilled Triisopropyl borate (1.6 mL, 6.8 mmol) was added slowly and the reaction allowed to room temperature. Reaction mixture allowed to stir for overnight, some amount of solvent was removed under reduce pressure and quenched with 1N HCl at 0°C (20 mL). The reaction mixture was stirred for 3h, then extracted with ether. The combined organic layer was neutralized with 1 N NaOH. The aqueous layer was extracted with ethyl acetate and dried over Na$_2$SO$_4$ and solvent removed under reduce pressure at 20°C to dive corresponding boric acid (6) (0.95 g, 75%) as white solid.$^1$H NMR (300 MHz, CDCl$_3$) δH 7.61-7.48 (6H, m) 6.78 (2H, s), 6.19 (2H, s), 4.74 (1H, s), 4.72 (1H, s), 4.23 (3H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) δc 150.7, 148.0, 137.2, 136.7, 136.6, 128.6 (4 C), 128.0 (2 C), 107.1, 101.4, 73.4, 71.7, 60.4 ppm; MS (ESI): m/z 339 [M + Na$^+$].

6’-((benzyloxy) ethyl)-4, 4’-dimethoxy-[5, 5’-bibenzo [d] [1, 3] dioxole]-6-carbaldehyde (5):

![Structure 2]
The sealed tube was charged with required amounts of Pd$_2$(dba)$_3$ (0.45 g, 0.51 mmol), S-Phos ligand (0.25 g, 0.6 mmol), anhydrous K$_3$PO$_4$ (3.98 g, 18.8 mmol), and aryl halide 7 (1.62 g, 6.25 mmol), followed by boronic acid 6 (2.37 g 7.50). The sealed tube was capped with a septum and then evacuated and back filled with nitrogen. Dry toluene (10 mL) (degassed) was added and the resulting mixture stirred for 10 min at room temperature. The septum was replaced with a Teflon screwcap and the mixture was stirred at 100-120°C for 12 h, after completion of aryl halide monitored by TLC, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with ether (50 mL) and filtered through celite. Filtrate was concentrated and purified by column chromatography with 15% EtOAc/hexane to give compound 5 (2.17 g, 82%) as colorless liquid. IR (KBr): $\nu_{\text{max}}$ = 2968, 2936, 2865, 1705, 1463, 1209, 722 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 9.47 (1H, s), 7.32 – 7.22 (4H, m), 7.20 – 7.17 (2H, m), 6.80 (1H, s), 6.08 (2H, $J = 1.4$ Hz, q), 6.00 (2H, $J = 4.9$, 1.4 Hz, dd), 4.31 (2H, $J = 11.8$ Hz, q), 4.11 (1H, $J = 11.6$ Hz, d), 4.01 (1H, $J = 11.6$ Hz, d), 3.84 (3H, s), 3.81 (3H, s); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$C 190.4, 149.5, 149.2, 141.8, 141.3, 140.8, 137.7, 135.8, 132.2, 129.9, 128.9, 128.2 (2 C), 127.6 (2 C), 127.4, 117.9, 103.3, 101.8, 101.1, 100.7, 72.2, 69.7, 59.7, 59.5 ppm; HRMS: 473.1202 ([$\text{M+Na}$]$^+$, C$_{25}$H$_{22}$NaO$_8$; calcd. 473.1207).

6'-(hydroxymethyl)-4, 4'-dimethoxy-[5,5'-bibenzo[d][1,3]dioxole]-6-carbaldehyde (14):

To a solution of 5 in ethyl acetate Pd/C was added at room temperature and stirred for 1 h. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered through celite pad. The filtrate was concentrated under reduced pressure, and purified by flash column chromatography with 20% EtOAc/hexane (1.25 g, 80%) as to give compound 14 (1.25 g, 80%) as white solid. IR (KBr): $\nu_{\text{max}}$ = 3545, 2927, 2917, 2853, 1705, 1463, 1440 1209, 702 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$H 9.46 (1H, s), 7.23 (1H, s), 6.79 (1H, s), 6.11 (2H, $J$...
= 1.7 Hz, d), 6.02 (2H, J = 1.7 Hz, d), 4.18 (2H, J = 2.4 Hz, d), 3.85 (3H, s), 3.84 (3H, s); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \delta 190.8, 149.6, 149.3, 142.3, 141.0, 140.6, 136.6, 135.3, 134.8, 116.5 (2 C), 102.4, 102.1, 101.1, 100.9, 62.2, 59.7, 59.2 ppm; HRMS: 383.0732 ([M+Na]+, C\textsubscript{18}H\textsubscript{16}NaO\textsubscript{8}; calcd. 383.0737).

\textit{6'-}-(bromomethyl)-4,4'-dimethoxy-[5,5'-bibenzo[d][1,3]dioxole]-6-carbaldehyde (15):

![Chemical structure of 6'-bromomethyl-4,4'-dimethoxy-[5,5'-bibenzo[d][1,3]dioxole]-6-carbaldehyde](image)

Tri phenyl phosphate (1.36 g, 5.204 mmol), CBr\textsubscript{4} (1.72 g, 5.2 mmol), were added to a stirred solution of compound 14 (0.125 g, 3.4 mmol) in DCM at 0°C under nitrogen condition. The reaction mixture slowly allowed to room temperature and stirred for 1 h. The resulting mixture was diluted with DCM and the organic layer was washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4}. The solvent was evaporated under reduced pressure to give corresponding bromo compound (15). This compound was used without further column purification.

\textit{6'-allyl-4,4'-dimethoxy-[5,5'-bibenzo[d][1,3]dioxole]-6-carbaldehyde (16)}:

![Chemical structure of 6'-allyl-4,4'-dimethoxy-[5,5'-bibenzo[d][1,3]dioxole]-6-carbaldehyde](image)

To a stirred solution of bromo compound 15 (0.98 g, 2.3 mmol) in degassed Toluene Pd\textsubscript{2}(dba\textsubscript{3}) (0.107 g,0.1mmol), tris-2-furylphosphine (0.10 g, 0.5 mmol) was added at room temperature. The reaction mixture allowed to stir for 15 min, tributylvinyltin (0.9 mL, 3.1 mmol)
was added to reaction mixture slowly. Then reaction mixture was stirred at 80°C for 8 h. After completion of reaction, the reaction mixture was diluted with DCM and washed with water followed by brine. The organic layer was dried over Na₂SO₄. The organic layer was evaporated under reduced pressure obtained residue, which was purified by column chromatography with 18% EtOAc/hexane to give 16 (0.68 g, 78%) as colourless liquid. IR (KBr): vmax = 2934, 2960, 2876, 1704, 1512, 1466, 1440, 1209, 722 cm⁻¹; 1H NMR (300 MHz, CDCl₃) δH 9.44 (1H, s), 7.21 (1H, s), 6.54 (1H, s), 6.09 (2H, s), 5.97 (2H, J = 0.5 Hz, d), 5.76-5.59 (1H, m), 4.94 (½H, J = 1.4 Hz, d), 4.91 (½H, J = 1.5 Hz, d), 4.85 (½ H, J = 1.6 Hz, d), 4.79 (½ H, J = 1.6 Hz, d), 3.86 (3H, 3), 3.84 (3H, s), 3.05-2.86 (2H, m); 13C NMR (75 MHz, CDCl₃) δC 190.7, 149.4, 149.2, 143.3, 141.0, 136.1, 134.5, 133.8, 129.8, 117.5, 116.1 (2 C), 103.5 (2 C), 101.9, 101.0, 100.7, 97.7, 59.7, 59.4, 37.7 ppm; HRMS: 371.1045 ([M+H]^+), C₂₀H₁₈O₇; calcd. 371.371.1039).

1-(6'-allyl-4, 4'-dimethoxy-[5, 5'-bibenzo[d] [1, 3] dioxole]-6-yl) prop-2-en-1-ol (4):

Vinyl magnesium bromide (3.1 mL, 2.6 mmol) was added drop wise to compound 16 in dry THF at 0°C and allowed to stir at 0°C for 1h. The reaction was quenched by the saturated solution of NH₄Cl. The reaction mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over anhydrous Na₂SO₄ and solvent was removed under reduced pressure. Resulted residue was purified by column chromatography with 20% EtOAc/hexane to afford compound 4 (0.48 g, 85%) as colour less liquid. IR (KBr): vmax = 3564, 2932, 2914, 2868, 1463, 1452, 1440 1209, 720 cm⁻¹; 1H NMR (500 MHz, CDCl₃) δH 6.73 (1H, s), 6.56 (1H, s), 5.98 (3H, J = 2.9, 1.6 Hz, dd), 5.96 (1H, J = 1.5 Hz, d), 5.88 – 5.78 (1H, m), 5.74-5.65 (1H, m), 5.29 (½ H, J = 1.8 Hz, t), 5.25 (½ H, J = 1.8 Hz, t), 5.17 (½H, J = 1.7 Hz, t), 5.14 (½H, J = 1.7 Hz, t), 4.96 – 4.91 (1H, m), 4.88 (½H, J = 3.3, 1.6 Hz, dd), 4.84 (½H, J = 3.3, 1.6 Hz, dd), 4.74 (1H, J =
4.5, 1.7 Hz, dt), 3.85 (3H, s), 3.82 (3H, s), 3.01-2.84 (2H, m). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_{C}$ 149.2 (2 C), 148.9 (2 C), 140.8, 140.6, 138.5, 136.7, 136.53, 136.5, 134.1, 115.8 (2 C), 114.5, 105.1, 104.2, 101.1 (2 C), 71.2, 59.9, 59.6, 37.6 ppm; HRMS: 399.1362 ([M+H]$^+$, C$_{22}$H$_{23}$O$_7$; calcd. 399.1368).

**Compound 17:**

Grubbs second generation catalyst (0.076 g, 0.0903 mmol) was dissolved in dry deoxygenated DCM (500 mL), the solution was refluxed. Compound 4 (0.45 g, 1.1 mmol) was dissolved in dry deoxygenated DCM (50 mL) and added drop wise to the above solution over 1 h, using syringe pump. The mixture was reflux for 12 h. After cooling to room temperature, all volatiles were removed under reduced pressure. The residue was purified by flash column chromatography with 40% EtOAc/hexane afforded 17 (0.33 g, 70%) as colourless liquid. IR (KBr): $\nu_{\text{max}}$ = 3740, 2914, 2844, 2356, 1532, 1478, 1216, 1105, 772 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta_{H}$ 6.80 (1H, s), 6.40 (1H, s), 5.96 (4H, $J$ = 4.1, 2.6 Hz, dd), 5.67 (2H, $J$ = 4.3 Hz, d), 5.00 (1H, $J$ = 2.6 Hz, d), 3.93 (3H, s), 3.90 (3H, s), 3.07 – 2.92 (1H, m), 2.80 (1H, $J$ = 15.7, 3.3 Hz, dd); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta_{C}$ 149.6, 149.3, 139.9, 139.5, 135.4, 135.3, 134.7, 134.6, 131.5, 127.4, 121.1, 119.8, 103.5, 100.9, 100.8, 98.7, 68.8, 59.4 (2 C), 33.1 ppm; HRMS: 393.0959([M+Na]$^+$, C$_{20}$H$_{18}$NaO$_7$; calcd. 393.0945).

**Compound (3):**
To a solution of compound 17 (0.3 g, 0.8 mmol), in dry DCM (5 mL) manganese dioxide (0.28 g, 3.2 mmol) was added portion wise and reaction mixture was stirred for 4 h. After completion of reaction, the reaction mixture was filtered through celite, filtrate was evaporated under reduced pressure. The residue was purified using flash column chromatography with 12 % EtOAc/hexane to give compound 3 (0.26 g, 90%) as colourless liquid. IR (KBr): \( \nu_{\text{max}} = 2924, 2845, 2354, 1718, 1516, 1474, 1233, 1152, 722 \text{ cm}^{-1} \); \( ^1\text{H NMR (300 MHz, CDCl}_3\text{)} \delta \text{H} 7.02-6.88 (1H, m), 6.60 (1H, s), 6.42 (1H, s), 6.16 (1H, \text{J} = 11.6, 2.6 \text{ Hz, dd}), 6.03 (2H, \text{J} = 4.1 \text{ Hz, d}), 5.94 (2H, \text{J} = 7.3 \text{ Hz, d}), 3.90 (3H, s), 3.78 (3H, s), 3.45-3.32 (1H, m), 3.11 (1H, \text{J} = 13.7, 9.9 \text{ Hz, dd}); ^{13}\text{C NMR (75 MHz, CDCl}_3\text{)} \delta \text{C} 196.2, 149.2, 149.1, 147.4, 142.7, 139.9, 137.8, 137.5, 136.1, 135.1, 133.5, 120.8, 119.0, 102.2, 102.0, 101.5, 101.0, 59.7, 59.6, 32.9 \text{ ppm}; \text{HRMS: 391.0799 ([M+Na]}^+\text{, C}_{20}\text{H}_{16}\text{Na O}_7\text{; calcd. 391.0788}).

**Compound (18):**

A solution of S-(-)-2-methyl-CBS-oxazaborolidine (1M solution in toluene, 4.9 mmol) in THF (5 mL) was treated with BH3-DMS (2.0 M solution in THF) (0.2 mL, 0.41 mmol) at 0°C for 15 min. A solution of enone 3 (0.150 g, 4.1 mmol) in THF (8 mL) was added slowly at -78°C.
The reaction mixture was stirred for 1 h maintaining the temperature. After completion of reaction, saturated NH₄Cl solution was added. The aqueous layer was extracted with ethyl acetate, the combined organic layer was washed with brine and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash chromatography with 10% EtOAc/hexane gave compound 18 (0.128 g, 85%, ee 98%) as colourless liquid. Specific rotation: [α]D₂₅ -2.53 (c 4.8, CHCl₃); IR (KBr): ν max = 3562, 2972, 2947, 1586, 1448, 1227, 1107, 720 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δH 6.73 (s, 1H), 6.33 (s, 1H), 5.93 – 5.84 (m, 5H), 5.77-5.70 (m, 1H), 4.88 – 4.82 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.93 – 2.86 (m, 1H), 2.76 – 2.70 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δC 149.7, 149.4, 140.0, 139.6, 135.5, 135.4, 134.8, 134.7, 130.0, 129.2, 121.1, 119.9, 103.5, 101.1, 100.9, 98.8, 68.9, 59.4 (2 C), 31.9 ppm; HRMS: 371.1048 ([M+H]+, C₂₀H₂₀O₇ ; calcd. 371.1052).