Organic Chemistry
Current Research
ISSN: 2161-0401

Rajender et al., Organic Chem Curr Res 2016, 5:3
DOI: 10.4172/2161-0401.1000166

Research Article Open Access

Stereoselective Total Synthesis of (-)-Anamarine from D-Mannitol

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Abstract

Stereoselective total synthesis of (-)-anamarine was achieved from D-mannitol through demonstrating the effect of electron withdrawing group in cross-metathesis reaction. The key reactions involved are regioselective ring opening, cross-metathesis and ring closing metathesis reactions.

Keywords: (-)-anamarine; D-mannitol; Cross-metathesis; Ring closing metathesis

Introduction

The δ-lactone moiety is an important structural unit found in various bioactive natural products, which show a wide range of biological activities, [1-13] such as anti-cancer and anti-leukemic activity, anti-HIV (protease), inducing apoptosis. Due to the biological importance of this class of molecules, several syntheses [14-17] were reported for the 5,6-dihydro-2H-pyran-2-one containing (-)-anamarine (**2**), which is a non-natural δ-lactone. Herein, I report the synthesis of (-)-anamarine from D-mannitol (Figure 1).

Experimental

General methods

Solvents were dried over standard drying agents and were freshly distilled prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (Acme's, 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40°C in vacuo. ^{1}H NMR (300 MHz and 500 MHz) and ^{13}C NMR (75 MHz and 125 MHz) spectra were measured with a, Bruker Avance 300 MHz, 600 MHz and Varian Unity Inova-500 MHz with tetramethylsilane as an internal standard for solutions in $CDCl_3$. *J* values are given in Hertz. IR spectra were recorded on at Perkin–Elmer IR-683, JASCO FT/IR-5300 spectrophotometer with NaCl and KBr optics. Optical rotations were measured with JASCO DIP 300 digital polarimeter. Mass spectra were recorded on BRUKER MAXIS and CEC-21–11013 or Fannigan Mat 1210 double focusing mass spectrometers operating at a direct inlet system or LC/MSD Trap SL (Agilent Technologies).

(*S*)-1-((*R*)-1,4-Dioxaspiro[4.5]decan-2-yl)but-3-enyl acrylate (7)

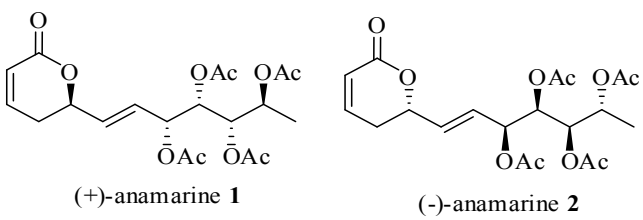
To a stirred solution of **6** (0.74 g, 3.49 mmol) in CH_2Cl_2 (7.5 mL) at 0°C, Et_3N (1.46 mL, 10.46 mmol), DMAP (cat.) and acryloyl chloride (0.31 mL, 3.84 mmol) were added sequentially and stirred at room temperature for 2 h. The reaction mixture was diluted with $CHCl_3$ (10 mL) and washed with water (10 mL), brine (10 mL) and dried (Na_2SO_4). Solvent was evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, 5% EtOAc in pet. ether) afforded **7** (0.76 g, 82%) as a pale yellow syrup; $[\alpha]^{28}_D$ = +17.5 (*c* 0.30, $CHCl_3$); IR (neat): 2935, 2858, 2313, 1727, 1644, 1568, 1551, l516, 1466, 1449, 1406, 1367, 1264, 1047, 925, 846, 807, 772, 669 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.41 (d, 1H, *J* = 17.4 Hz, olefinic), 6.11 (dd, 1H, *J* = 10.2, 17.0 Hz, olefinic), 5.88-5.69 (m, 2H, olefinic), 5.15-5.03 (m, 2H, olefinic), 4.22-3.98 (m, 3H, 3 x -OCH), 3.82 (dd, 1H, *J* = 6.4, 7.9 Hz, -OCH), 2.55-2.33 (m, 2H, allylic), 1.67-1.50 (m, 8H, cyclohexyl), 1.40-1.32 (m, 2H, cyclohexyl); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 133.0, 131.1, 128.3, 118.1, 110.1, 75.8, 72.9, 65.7, 36.0, 34.8, 35.3, 25.1, 23.9, 23.8; HRMS (ESI+): *m/z* calculated for $C_{15}H_{22}O_4$ $(M+Na)^+$ 289.1410, found 289.1408.

(*S*)-6-((*R*)-1,4-Dioxaspiro[4.5]decan-2-yl)-5,6-dihydro-2H-pyran-2-one (8)

To a stirred solution of **7** (0.07 g, 0.27 mmol) in CH_2Cl_2 (50 mL), Grubbs-I catalyst (10 mol %) was added and stirred at reflux for 6 h. Most of the solvent was then distilled off and the concentrated solution was left to stir at room temperature for 2 h under a flow of air to decompose the catalyst. The reaction mixture was evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, (60-120 mesh Silica gel, 30% EtOAc in pet. ether) afforded **8** (0.05 g, 81%) as a colorless syrup; $[\alpha]^{28}_D$ = -59.0 (*c* 0.70, $CHCl_3$); IR (neat): 3020, 2314, 1727, 1711, 1663, 1569, 1551, 1533, 1483, 1467, 1215, 928, 742, 668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.91 (m, 1H, olefinic), 6.02 (dd, 1H, *J* = 2.0, 10.1 Hz, olefinic), 4.30-4.24 (m, 1H, -OCH), 4.18-4.12 (m, 2H, -OCH), 4.06-4.00 (m, 1H, -OCH), 2.61 (td, 1H, *J* = 5.0, 18.1 Hz, allylic), 2.48 (td, 1H, *J* = 3.0, 10.1 Hz, allylic), 1.65-1.53 (m, 8H, allylic), 1.48-1.32 (m, 2H, allylic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 144.9, 121.3, 110.6, 78.1, 75.8, 66.7, 36.6, 34.5, 26.4, 25.0, 23.7; HRMS (ESI+): *m/z* calculated for $C_{13}H_{18}O_4$ $(M+Na)^+$ 261.1097, found 261.1097.

(*S*)-6-Vinyl-5,6-dihydro-2H-pyran-2-one (5)

To a stirred solution of **8** (0.30 g, 1.27 mmol) in CH_3CN (5 mL) at 0°C, $CuCl_2.2H_2O$ (0.47 g, 0.35 mmol) was added and stirred at room



(+)-anamarine **1** (-)-anamarine **2**

Figure 1: Structures of **1** and **2**.

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Received: June 24, 2016; **Accepted:** July 14, 2016; **Published:** July 21, 2016

Citation: Rajender K, Venkateshwarlu R, Rao VP (2016) Stereoselective Total Synthesis of (-)-Anamarine from D-Mannitol. Organic Chem Curr Res 5: 166. doi:10.4172/2161-0401.1000166

temperature for 30 min. It was quenched with sat. $NaHCO_3$ (1 mL), filtered through a pad of celite and washed with EtOAc (10 mL). The organic layer was dried (Na_2SO_4), evaporated and used as such for the next reaction. To a stirred solution above diol (0.20 g, 1.27 mmol), Ph_3P (1.33 g, 5.08 mmol) and imidazole (0.35 g, 5.08 mmol) in CH_2Cl_2 (10 mL) at 0°C, I_2 (0.97 g, 3.81 mmol) was added and stirred at room temperature for 4 h. The reaction mixture was quenched with sat. aq. NaOH (1 mL) solution and extracted with $CHCl_3$ (3 × 5 mL). The organic layers were washed with aq. hypo (4 mL), brine (4 mL) and dried (Na_2SO_4). Solvent was evaporated and purification of the residue by column chromatography (60-120 mesh Silica gel, 20% EtOAc in pet. ether) gave olefin **5** (0.11 g, 70%) as a colorless liquid; $[\alpha]^{25}_D$ = -87.5 (*c* 0.10, $CHCl_3$); lit.[6] $[\alpha]^{25}_D$ = -93.4 (*c* 0.10, $CHCl_3$); IR (neat): 3016, 2943, 2882, 1726, 1426, 1382, 1215, 1160, 1108, 971, 819, 748, 703, 667, 609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.89 (ddd, 1H, *J* = 3.8, 5.3, 9.8 Hz, olefinic), 6.10-5.90 (m, 2H, olefinic), 5.42 (d, 1H, *J* = 17.4 Hz, olefinic), 5.31 (d, 1H, *J* = 10.6 Hz, olefinic), 4.94 (m, 1H, -OCH), 2.52-2.41 (m, 2H, allylic); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 144.4, 134.8, 121.6, 117.8, 77.7, 29.3; HRMS (ESI+): *m/z* calculated for $C_7H_8O_2$ $(M+Na)^+$ 147.0422, found 147.0429.

(1*R*)-1-((4*R*,4'*R*)-2,2,2',2'-Tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)ethanol (11)

To a stirred solution of **9** (21.00 g, 80.15 mmol) in CH_2Cl_2 (210 mL) at 0°C, Et_3N (13.94 mL, 100.19 mmol) followed by *n*-Bu_2SnO (0.50 g, 2.00 mmol) and *p*-TsCl (15.28 g, 80.15 mmol) were added. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 (8 mL) and washed with water (2 × 5 mL), brine (2 × 5 mL) and dried (Na_2SO_4). Solvent was evaporated to give **10**, which was used as such for the next step. To a stirred suspension of $LiAlH_4$ (2.92 g, 76.92 mmol) in THF (50 mL) at 0°C, a solution of **10** (32.00 g, 76.92 mmol) in THF (100 mL) was added drop wise under nitrogen atmosphere and stirred at room temperature for 3 h, cooled to 0°C and treated with sat. Na_2SO_4 solution (10 mL) and filtered. Aq. layer was extracted EtOAc (50 mL) and dried (Na_2SO_4). Solvent was evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, 20% EtOAc in pet. ether) furnished **11** (13.9 g, 74%) as a light yellow syrup; $[\alpha]^{28}_D$ = +6.4 (*c* 0.20, $CHCl_3$); IR (neat): 3470, 3434, 2990, 2936, 2890, 1597, 1460, 1373, 1306, 1252, 1217, 1179, 1069, 938, 841, 710, 667, 554, 513, 490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.15 (q, 1H, *J* = 5.7 Hz, -OCH), 4.05-4.00 (m, 2H, -OCH), 3.71 (m, 1H, -OCH), 3.67-3.57 (m, 2H, -OCH), 2.47 (br. s, 1H, -OH), 1.44 (s, 3H, Me), 1.35 (s, 6H, 2 x Me), 1.34 (s, 3H, Me), 1.24 (d, 3H, *J* = 6.0 Hz, Me); ^{13}C NMR (75 MHz $CDCl_3$): δ 110.1, 109.1, 84.4, 80.8, 76.4, 68.5, 26.8, 26.7, 26.5, 25.1, 19.5; HRMS (ESI+): *m/z* calculated for $C_{12}H_{22}O_5$ $(M+Na)^+$ 269.1364, found 269.1353.

tert.-Butyldiphenyl((1*R*)-1-((4*R*,4'*R*)-2,2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl) etho xy)silane (12)

To a stirred solution of alcohol **11** (13.80 g, 56.09 mmol) in CH_2Cl_2 (68 mL), imidazole (11.44 g, 168.29 mmol), TPSCl (17.61 mL, 67.31 mmol) and DMAP (cat.) were added sequentially and stirred at room temperature for 1 h. The reaction mixture was treated with water (25 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with brine (65 mL) and dried (Na_2SO_4). Solvent was evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, 5% EtOAc in pet. ether) to afford **12** (18.20 g, 66%) as a colorless syrup; $[\alpha]^{28}_D$ = +4.4 (*c* 0.10, $CHCl_3$); IR (neat): 2930, 2859, 1659, 1462, 1428, 1379, 1240, 1152, 1111, 1057, 845, 739, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (m, 4H, Ar-H), 7.36 (m, 6H, Ar-H), 4.06-3.92 (m, 3H, -OCH), 3.88-3.75 (m, 3H, -OCH), 1.32 (s, 6H, 2 x Me), 1.24 (s, 6H, 2 × Me), 1.06 (d, 3H, *J* = 6.04 Hz), 1.06 (s, 9H, 3 × Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 134.4, 133.9, 129.6, 129.5, 127.5, 127.4, 109.5, 109.3, 84.4, 78.3, 76.9, 69.8, 66.8, 27.3, 27.2, 27.0, 26.4, 25.3, 19.3, 18.6; HRMS (ESI+): *m/z* calculated for $C_{28}H_{40}O_5Si$ $(M+Na)^+$ 507.2542, found 507.2533.

(1*R*)-1-((4*R*)-5-((*R*)-1-(*tert.*-Butyldiphenylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (13)

To a stirred solution of 12 (18.0 g, 37.11 mmol) in CH_3CN (360 mL) at 0°C, $CuCl_2.2H_2O$ (5.69 g, 33.40 mmol) was added and stirred at 0°C for 30 min. It was quenched with sat. $NaHCO_3$ (4 mL), filtered through a pad of celite and washed with EtOAc (40 mL). The organic layers were dried (Na_2SO_4), evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, 30% EtOAc in pet. ether) afforded **13** (9.0 g, 98%, based on starting material recovery) as a colorless syrup; $[\alpha]^{28}_D$ = -14.6 (*c* 1.0, $CHCl_3$); IR (neat): 3335, 3073, 2934, 2859, 1721, 1590, 1474, 1429, 1381, 1319, 1252, 1159, 1113, 1082, 1024, 949, 912, 872, 822, 743, 702, 612, 500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.74-7.67 (m, 4H, Ar-H), 7.43-7.35 (m, 6H, Ar-H), 3.90-3.78 (m, 3H, 3 x -OCH), 3.71-3.43 (m, 3H, 3 x -OCH), 2.69 (d, 1H, OH, *J* = 4.5 Hz), 1.95 (t, 1H, OH, *J* = 5.3 Hz), 1.34 (s, 3H, Me), 1.28 (s, 3H, Me), 1.08 (d, 3H, *J* = 5.3 Hz, Me), 1.05 (s, 3H, 3 x Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.8, 129. 9, 129.6, 84.1, 78.2, 76.6, 66.7, 63.6, 27.3, 26.4, 19.9, 18.6; HRMS (ESI+): *m/z* calculated for $C_{25}H_{36}O_5Si$ $(M+Na)^+$ 467.2229, found 467.2233.

(2*R*)-2-((4*R*)-5-((*R*)-1-(*tert.*-Butyldiphenylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxol an-4-yl)-2-hydroxyethyl benzoate (14)

To a stirred and cooled (0°C) solution of **13** (2.0 g, 4.50 mmol) in CH_2Cl_2 (20 mL), Et_3N (1.5 mL, 9.01 mmol), *n*-Bu_2SnO (cat.) followed by BzCl (0.52 mL, 4.50 mmol) were added and stirred at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 (8 mL) and washed with water (2 × 5 mL), brine (2 × 5 mL) and dried (Na_2SO_4). Solvent was evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, 15% EtOAc in pet. ether) afforded **14** (2.20 g, 89%) as a colorless syrup; $[\alpha]^{28}_D$ = +51.2 (*c* 0.20, $CHCl_3$); IR (neat): 3478, 3071, 2934, 2859,1723, 1599, 1452, 1428, 1379, 1277, 1157, 1111, 822, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, 2H, *J* = 7.4 Hz, Ar-H), 7.68 (d, 4H, *J* = 6.4, 22.3 Hz, Ar-H), 7.54 (t, 1H, *J* = 7.4 Hz, Ar-H), 7.44-7.35 (m, 8H, Ar-H), 4.53 (dd, 1H, *J* = 2.5, 11.9 Hz, -OCH), 4.30 (dd, 1H, *J* = 6.4, 11.9 Hz, -OCH), 3.94 (m, 3H, -OCH), 3.84 (m, 1H, -OCH), 2.56 (d, 1H, *J* = 4.5 Hz, -OH), 1.36 (s, 3H, Me), 1.31 (s, 3H, Me), 1.09 (d, 3H, *J* = 5.4 Hz, Me), 1.04 (s, 9H, 3 x Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 135.8, 133.9, 133.3, 133.1, 129.8, 129.7, 128.3, 127.7, 127.5, 109.8, 84.0, 78.5, 71.9, 71.2, 66.5, 27.2, 26.9, 19.8, 19.2; HRMS (ESI+): *m/z* calculated for $C_{32}H_{40}O_6Si$ $(M+Na)^+$ 571.2491, found 571.2479.

(2*R*)-2-((4*S*)-5-((*R*)-1-(*tert.*-Butyldiphenylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxola n-4-yl)-2-(tosyloxy)ethyl benzoate (15)

To a stirred and cooled (0°C) solution of **14** (2.13 g, 3.89 mmol) in CH_2Cl_2 (10 mL), Et_3N (0.68 mL, 4.86 mmol), DMAP (cat.) and *p*-TsCl (0.74 g, 3.89 mmol) were added and stirred at room temperature for 5 h. Work up as described for **14** and purification of the residue by column chromatography (60-120 mesh Silica gel, 3% EtOAc in pet. ether) afforded **15** (2.30 g, 84%) as a colorless syrup; $[\alpha]^{25}_D$ = -6.0 (*c* 0.10, $CHCl_3$); IR (neat): 3745, 3684, 3642, 3610, 3020, 2314, 1839, 1785, 1765, 1743, 1727, 1678, 1568, 1551, 1516, 1449, 1115, 929, 742, 668,

625 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.93 (d, 2H, J = 7.2 Hz, Ar-H), 7.80-7.65 (m, 6H, Ar-H), 7.56 (t, 1H, J = 7.4 Hz, Ar-H), 7.49-7.30 (m, 8H, Ar-H), 7.17 (d, 2H, J = 8.1 Hz, Ar-H), 4.85 (dt, 1H, J = 2.5, 6.0 Hz, -OCH), 4.55 (dd, 1H, J = 2.5, 12.7 Hz, -OCH), 4.50-4.36 (m, 2H, -OCH), 4.01-3.87 (m, 3H, 3 x -OCH), 2.32 (s, 3H, Me), 1.38 (s, 3H, Me), 1.29 (s, 3H, Me), 1.03 (s, 9H, 3 x Me), 0.98 (d, 3H, J = 5.9 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 135.8, 133.1, 129.8, 129.7, 129.6, 128.3, 127.7, 127.6, 127.5, 110.6, 82.9, 79.0, 76.1, 69.2, 62.9, 27.9, 27.8, 27.0, 22.7, 21.6, 19.6; HRMS (ESI+): *m/z* calculated for $C_{39}H_{46}O_8SSi$ $(M+Na)^+$ 725.2575, found 725.2580.

tert.-Butyl((1*R*)-1-((5*R*)-2,2-dimethyl-5-((*S*)-oxiran-2-yl)-1,3-dioxolan-4-yl) ethox y) diph enylsilane (16)

To a stirred solution of **15** (2.20 g, 3.14 mmol) in MeOH (4 mL) at 0°C, K_2CO_3 (1.29 g, 9.37 mmol) was added and stirred at room temperature for 1 h. Reaction mixture was treated with aq. NH_4Cl solution (3 mL), MeOH was evaporated below 40°C under reduced pressure and residue extracted with solvent ether (3 × 10 mL). Organic layer was washed with water (10 mL), brine (10 mL) and dried (Na_2SO_4). Solvent was evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, 8% EtOAc in pet. ether) afforded **16** (1.20 g, 90%) as a colorless syrup; $[\alpha]^{28}_D$ = +5.1 (*c* 0.10, $CHCl_3$); IR (neat): 3077, 2984, 2934, 2894, 2861, 1730, 1649, 1590, 1472, 1428, 1379, 1254, 1161, 1109, 928, 876, 822, 741, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.74-7.65 (m, 4H, Ar-H), 7.44-7.32 (m, 6H, Ar-H), 4.04-3.95 (m, 2H, -OCH), 3.90 (m, 1H, -OCH), 2.99 (q, 1H, J = 3.8 Hz, epoxide), 2.66 (dq, 2H, J = 3.8, 5.3 Hz, epoxide), 1.33 (s, 6H, 2 x Me), 1.06 (s, 9H, 3 x Me), 1.04 (d, 3H, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8, 134.1, 133.4, 129.7, 129.6, 127.6, 127.5, 109.6, 82.4, 76.9, 69.5, 52.2, 44.5, 27.2, 27.0, 26.5, 19.8, 19.2; HRMS (ESI+): *m/z* calculated for $C_{25}H_{34}O_4Si$ $(M+Na)^+$ 449.2124, found 449.2074.

(1*S*)-1-((4*R*)-5-((*R*)-1-(*tert.*-Butyldiphenylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxo la n-4-yl)prop-2-en-1-ol (4)

To a stirred solution of Me_3SI (0.95 g, 4.67 mmol) in THF (5 mL) at -20C, *n*-BuLi (2.71 mL, 6.77 mmol, 2.5 molar) was added and stirred for 30 min. A solution of **16** (0.50 g, 1.16 mmol) in THF (5 mL) was added and stirred at -20°C for 30 min. The reaction mixture was quenched with aq. NH_4Cl (2 mL) and extracted with EtOAc (2 × 10 mL). Organic layers were washed with water (10 mL), brine (10 mL) and dried (Na_2SO_4). Solvent was evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, 10% EtOAc in pet. ether) afforded **4** (0.34 g, 67%) as a colorless syrup; $[\alpha]^{28}_D$ = +22.4 (*c* 0.10, $CHCl_3$); IR (neat): 3468, 3073, 2984, 2934, 2892, 2859, 1647, 1590, 1472, 1428, 1373, 1242, 1111, 891, 822, 741, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72-7.64 (m, 4H, Ar-H), 5.76 (m, 1H, olefinic), 5.27 (td, 1H, J = 2.3, 17.4 Hz, olefinic), 5.14 (td, 1H, J = 1.5, 10.6 Hz, olefinic), 4.11 (t, 1H, J = 6.0 Hz, -OCH), 3.94-3.80 (m, 3H, 3 x -OCH), 2.08 (d, 1H, J = 8.3 Hz, OH), 1.39 (s, 3H, Me), 1.28 (s, 3H, Me), 1.06 (d, 3H, J = 5.3Hz, Me), 1.04 (s, 9H, 3 x Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 135.9, 135.8, 134.2, 133.5, 129.8, 129.7, 127.7, 127.5, 116.4, 109.5, 81.6, 81.3, 72.1, 71.1, 27.4, 27.3, 27.0, 20.3, 19.3; HRMS (ESI+): *m/z* calculated for $C_{26}H_{36}O_4Si$ $(M+Na)^+$ 463.2280, found 463.2273.

(2*R*,3*R*,4*R*,5*S*)-Hept-6-ene-2,3,4,5-tetrayl tetraacetate (17)

A solution of **4** (0.20 g, 0.82 mmol) in CH_2Cl_2 (1 mL) at 0°C was treated with CF_3COOH (1 mL) and stirred at room temperature for 15 min. Solvent was evaporated and the crude tetrol **4a** was used as such for the next reaction. A solution of the above tetrol in pyridine (3 mL) was cooled to 0°C and treated with Ac_2O (2 mL), DMAP (cat.) and stirred at room temperature for 20 h. Work up as described for **5** and purification of the residue by column chromatography (60-120 mesh Silica gel, 12% EtOAc in pet. ether) gave tetraacetate **17** (0.12 g, 81%) as a light yellow oil; $[\alpha]^{28}_D$ = -10.6 (*c* 0.20, $CHCl_3$); IR (neat): 2924, 2854, 2314, 1743, 1678, 1645, 1586, 1569, 1551, 1533, 1483, 1450, 1372, 1219, 1033, 722, 687, 671 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.83-5.68 (m, 1H, olefinic), 5.39-5.26 (m, 4H, 2 x olefinic, 2 x -OCH), 5.23 (m, 1H, -OCH), 4.94 (m, 1H, -OCH), 2.13 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.07 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.19 (d, 3H, J = 6.4 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 169.8, 132.4, 119.4, 79.4, 78.6, 74.0, 70.4, 27.2, 26.9, 21.1, 21.0, 15.5; HRMS (ESI+): *m/z* calculated for $C_{15}H_{22}O_8$ $(M+Na)^+$ 353.1207, found 353.1207.

(*S*)-6-((*S*,*E*)-3-((4*R*,5*S*)-5-((*R*)-1-(*tert.*-Butyldiphenylsilyloxy) ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxyprop-1-enyl)-5,6-dihydro-2H-pyran-2-one (3)

To a mixture of olefins **5** (0.02 g, 0.04 mmol) and **4** (0.01 g, 0.08 mmol) in toluene (1 mL) under nitrogen atmosphere, Grubbs-II catalyst (0.01 g, 0.01 mmol) was added and stirred at reflux for 8 h. Work up as described for **8** and purification of the residue by column chromatography (60-120 mesh Silica gel, 35% EtOAc in pet. ether) afforded **3** (0.02 g, 81%) as a light yellow syrup; $[\alpha]^{25}_D$ = -52.0 (*c* 0.20, $CHCl_3$); IR (neat): 3020, 2924, 2054, 2313, 1785, 1727, 1678, 1663, 1630, 1569, 1551, 1516, 1449, 1216, 929, 771, 668, 626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75-7.66 (m, 4H, Ar-H), 7.47-7.36 (m, 6H, Ar-H), 6.87 (ddd, 1H, J = 3.4, 5.1, 8.5 Hz, olefinic), 6.06 (td, 1H, J = 1.5, 9.8 Hz, olefinic), 5.92-5.76 (m, 2H, olefinic), 4.91 (m, 1H, -OCH), 4.22 (t, 1H, J = 3.8 Hz, -OCH), 4.01-3.85 (m, 3H, -OCH), 2.86-2.37 (m, 2H, allylic), 1.40 (s, 3H, Me), 1.27 (s, 3H, Me), 1.09 (d, 3H, J = 5.7 Hz, Me), 1.04 (s, 9H, 3 x Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.8, 144.5, 135.9, 135.8, 133.9, 133.4, 133.3, 129.8, 129.7, 128.4, 127.7, 127.5, 121.5, 109.6, 81.4, 81.0, 77.0, 71.3, 70.6, 29.6, 29.5, 27.2, 27.0, 20.7, 19.3; HRMS (ESI+): *m/z* calculated for $C_{31}H_{40}O_6Si$ $(M+Na)^+$ 559.2486, found 559.2487.

(2*R*,3*R*,4*R*,5*S*,*E*)-7-((*S*)-6-oxo-3,6-dihydro-2H-pyran-2-yl) hept-6-ene-2,3,4,5-tetrayl tetraacetate ((-)-Anamarine) (2)

A solution of **3** (0.05 g, 0.09 mmol) in CH_2Cl_2 (1 mL) at 0°C was treated with CF_3COOH (0.3 mL) and stirred at room temperature for 15 min. Evaporation of the solvent gave tetrol **3a**, which was used as such for the next reaction. To a solution of the above tetrol **3a** in pyridine (2 mL) at 0°C, Ac_2O (0.5 mL) and DMAP (cat.) were added and stirred at room temperature for 20 h. Work up as described for **17** and purification of the residue by column chromatography (60-120 mesh silica gel, 28% EtOAc in pet. ether) gave tetraacetate **2** (0.03 g, 86%) as a gummy liquid; $[\alpha]^{25}_D$ = -17.8 (*c* 0.30, $CHCl_3$); IR (neat): 3751, 3656, 3574, 3019, 2313, 1742, 1727, 1550, 1532, 1215, 1058, 929, 747, 668, 626 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (ddd, 1H, J = 9.6, 4.7, 3.8 Hz, olefinic), 6.06 (td, 1H, J = 1.9, 9.8 Hz, olefinic), 5.86-5.76 (m, 2H, olefinic), 5.37 (dd, 1H, J = 5.3, 7.2 Hz, -OCH), 5.31 (dd, 1H, J = 3.4, 7.2 Hz, -OCH), 5.18 (dd, 1H, J = 3.4, 6.8 Hz, -OCH), 5.04-3.87 (m, 2H, 2 x -OCH), 2.46 (m, 2H, allylic), 2.13 (s, 3H, OAc), 2.08 (s, 6H, 2 x OAc), 2.03 (s, 3H, OAc), 1.18 (d, 3H, J = 6.4 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 169.9, 169.8, 169.7, 163.5, 144.5, 133.0, 125.5, 121.4, 75.8, 71.9, 71.6, 70.4, 67.3, 29.1, 21.0, 20.9, 20.8, 20.6, 15.8; HRMS (ESI+): *m/z* calculated for $C_{20}H_{26}O_{10}$ $(M+Na)^+$ 449.1418, found 449.1420.

(2*R*,3*R*,4*R*,5*S*,*E*)-7-((*S*)-6-oxo-3,6-dihydro-2H-pyran-2-yl) hept-6-ene-2,3,4,5-tetrayl tetraacetate ((-)-Anamarine) (2)

To a solution of **5** (0.02 g, 0.12 mmol) and **17** (0.02 g, 0.06 mmol) in CH_2Cl_2 (2 mL) under nitrogen atmosphere, Grubbs-II catalyst (0.01 g, 0.01 mmol) was added and stirred at reflux for 5 h. Work up as described

for **16** and purification of the residue by column chromatography (60-120 mesh Silica gel, 28% EtOAc in pet. ether) afforded **2** (0.02 g, 68%), whose spectral data was comparable with **2** synthesized from **8**.

Results and Discussion

Retrosynthesis

The retrosynthetic analysis of **2** revealed that **3** (Scheme 1) is the late stage intermediate. Olefin **3** could be realized by a cross-metathesis of olefin **4** and lactone **5**. The requisite lactone **5** and olefin **4** could be prepared from D-mannitol.

Synthesis of vinyl lactone fragment 5

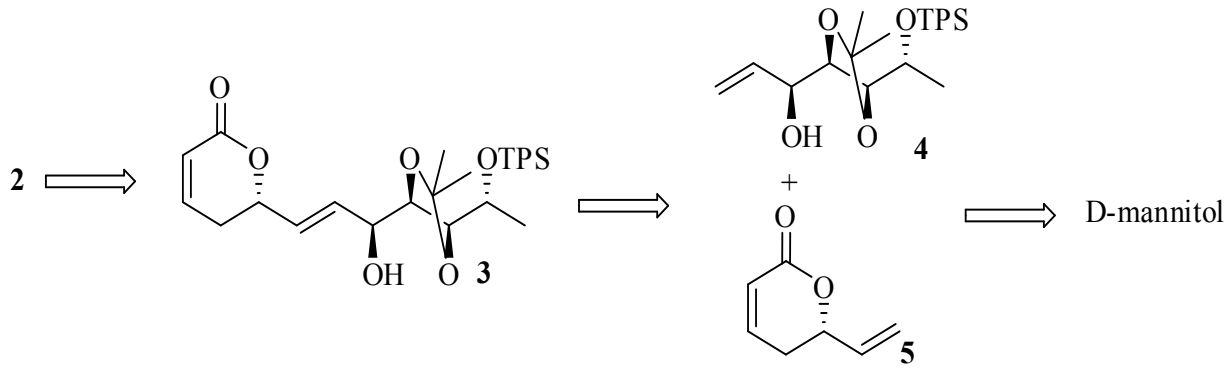
Vinyl lactone **5** was achieved from D-mannitol (Scheme 2). Accordingly, reaction of alcohol **6**[9] (**6** was achieved from D-Mannitol in two steps with overal yield 70%) with acryloyl chloride and Et_3N in CH_2Cl_2 furnished the acrylate **7** in 82% yield, Which on RCM reaction with Grubbs-I[10] catalyst gave α,β-unsaturated lactone **8** in 81% yield (exclusively Z-olefin). Grubbs-I[10] catalyst for RCM is more prior for construction of Z-olefin while compared to Wittig or related strategies for synthesis of olefin. Treatment of **8** with $CuCl_2.2H_2O$ in CH_3CN afforded the diol, which on subsequent treatment with Ph_3P, iodine and imidazole[11] in CH_2Cl_2 furnished **5** in 70% yield, $[\alpha]^{25}_D$ = -87.5 (*c* 0.10, $CHCl_3$); lit. [17] $[\alpha]^{25}_D$ = -93.4 (*c* 0.10, $CHCl_3$).

Synthesis of tetraacetate fragment 4

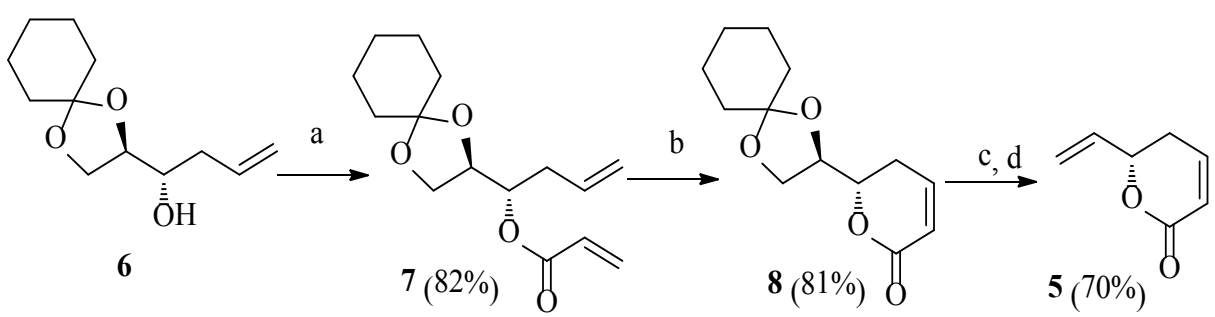
For the synthesis of **4**, diol **9**[12] (**9** was achieved from D-Mannitol in one step with 80% yield) was subjected to reaction with *p*-TsCl in the presence of Et_3N and *n*-Bu_2SnO in CH_2Cl_2[13] to give tosylate **10**, which on further deoxygenation with $LiAlH_4$ in THF furnished **11** in 74% yield (Scheme 3). Treatment of the alcohol **11** with TPSCl and imidazole in CH_2Cl_2 afforded **12** in 66% yield. Selective deprotection of **12** using $CuCl_2.2H_2O$[14] in CH_3CN furnished diol **13**, which on treatment with benzoyl chloride in the presence of Et_3N and *n*-Bu_2SnO in CH_2Cl_2 to give **14** in 89% yield (Scheme 3). Reaction of alcohol **14** with *p*-TsCl, Et_3N and cat. DMAP in CH_2Cl_2 furnished **15** in 84% yield. Treatment of tosylate **15** with K_2CO_3 in MeOH afforded **16** (90%), which on reaction with Me_3SI and *n*-BuLi in THF at -20°C gave **4** in 67% yield. Treatment of **4** with CF_3COOH in CH_2Cl_2 gave tetrol **4a**, which on treatment with Ac_2O and pyridine in CH_2Cl_2 furnished tetraacetate **17**[8] in 81% yield.

Synthesis of 2

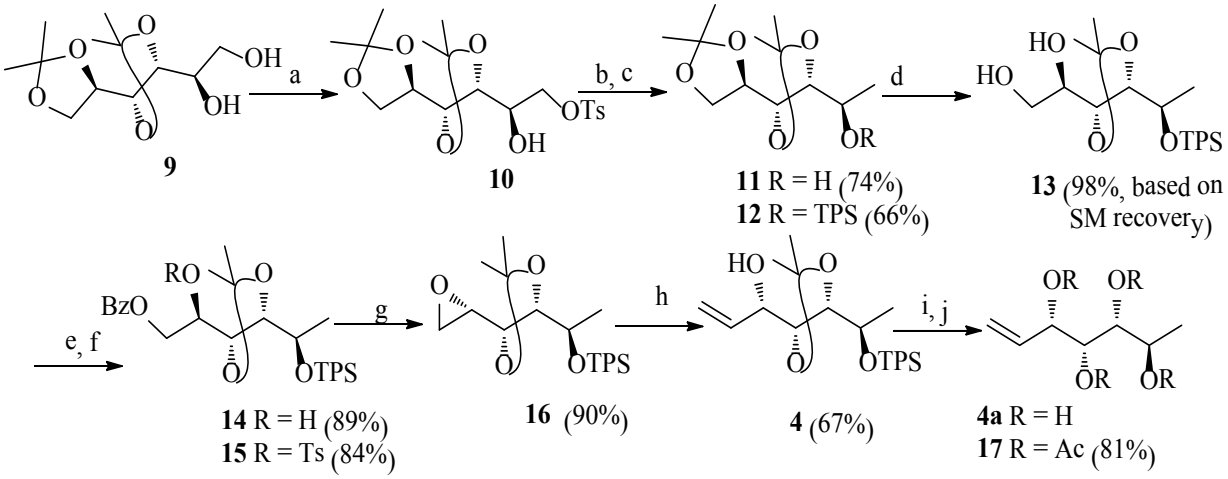
Finally, for the synthesis of (-)-anamarine **2**, olefins **17** and **5** were subjected to olefin cross-metathesis conditions using Grubbs-II catalyst in toluene at reflux to give **3** (81%) yield (Scheme 4). Cross-metathesis conditions using Grubbs-II catalyst favours more percentage of E-olefin while compared to other strategies for synthesis of olefin. Compound **3** was treated with CF_3COOH in CH_2Cl_2 to give tetrol **3a** by the simultaneous deprotection of silyl and acetonide groups. Finally, reaction of **3a** with Ac_2O and pyridine in CH_2Cl_2 furnished (-)-anamarine **2** (86%). The spectral data of **2** was in accordance with the literature values [17-31] (Tables 1 and 2). $[\alpha]^{25}_D$=-17.8 (*c* 0.3, $CHCl_3$); lit.[5] $[\alpha]^{24}_D$ = -16.0 (*c* 0.5, $CHCl_3$). Alternatively, coupling of **5** with **4** under cross-metathesis conditions using Grubbs-II catalyst [26] afforded (-)-anamarine **2** (68%) (Scheme 4). Though **2** could be obtained from the alternative coupling, the yields were albeit less when compared to the earlier experiments. From the above studies, it is evident that, in the absence of acetyl group at allylic position, cross metathesis reaction is facilitated for higher yields.



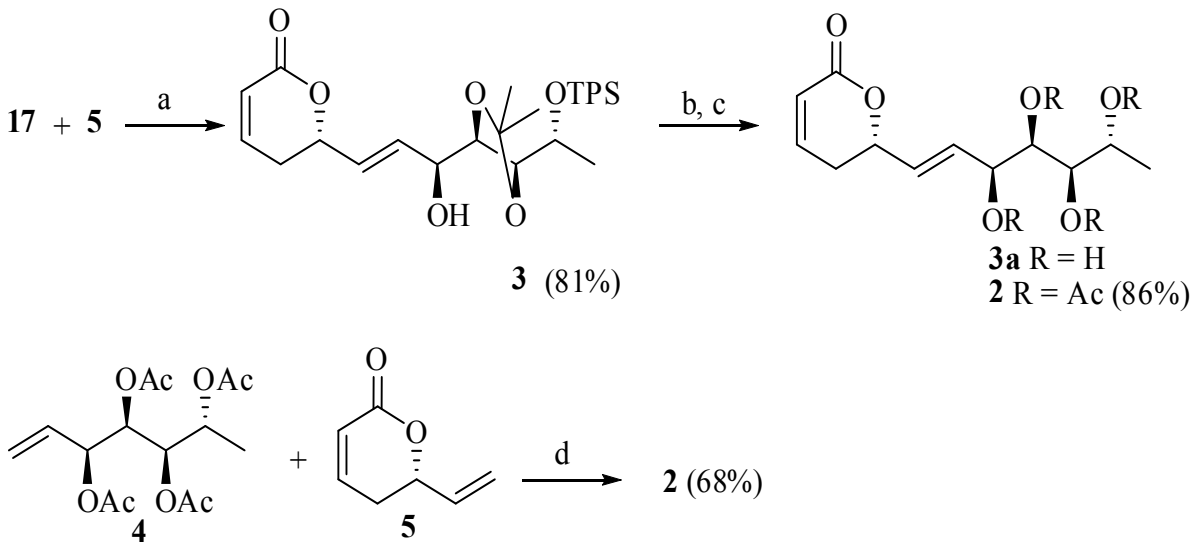
Scheme 1: Retrosynthetic strategy of (-)-anamarine 2.



Scheme 2: Reagents and conditions: a) acryloyl chloride, Et_3N, cat. DMAP, CH_2Cl_2, 0°C-rt, 2 h; b) Grubss-I catalyst, CH_2CL_2, reflux, 6 h; c) $CuCl_2.2H_2O$, CH_3CN, 0°C, 30min; d) Ph3P, I2, imidazole, CH_2CL_2, 0°C-rt, 2 h.



Scheme 3: Reagents and conditions: a) *p*-TsCl, Et_3N, *n*-Bu_2SnO, CH_2Cl_2, 0°C-rt, 1 h; b) $LiAlH_4$, THF, 0°C-rt; c) TPSCL, imidazole, CH_2Cl_2, 0°C-rt 1 h; d) $CuCl_2.2H_2O$, CH_3CN, 0°C, 30 min; e) BzCl, Et_3N, CH_2Cl_2, *n*-Bu_2SnO, 0°C-rt, 1 h; f) *p*-TsCl, Et_3N, cat. DMAP, CH_2Cl_2, rt, 12 h; g) K_2O_3, MeOH, 0°C-rt, 1 h; h) Me_3SI, *n*-BuLi, -20°C, 30 min; i) CF_3COOH, CH_2Cl_2, 0°C-rt, 15 mn; j) Ac_2O, pyridine, cat. DMAP, CH_2Cl_2, rt, 20 h.



Scheme 4: Reagents and conditions: a) Grubbs-II catalyst, toluene reflux, 8 h; b) CF_3COOH, CH_2Cl_2, 0°C-rt, 15 min; c) Ac_2O, pyridine, cat. DMAP, CH_2Cl_2, rt, 20 h; d) Grubbs-II catalyst, CH_2Cl_2, reflux, 5 h.

S. No	Protan	Spectral data for (-)- anamarine from literature (Meshram et al.) [17]	(-) - anamarine
1	olefinic	6.89 (ddd, 1H, *J* = 9.3, 5.0, 3.5 Hz, olefinic),	6.90 (ddd, 1H, *J* = 9.6, 4.7, 3.8 Hz, olefinic),
2	olefinic	6.07 (d, 1H, *J* = 9.5 Hz, olefinic),	6.06 (td, 1H, *J* = 9.8, 1.9 Hz, olefinic),
3	olefinic	5.90-5.75 (m, 2H, olefinic),	5.86-5.76 (m, 2H, olefinic),
4	-OCH	5.36 (dd, 1H, *J* = 7.0, 6.0 Hz, -OCH),	5.37 (dd, 1H, *J* = 7.2, 5.3 Hz, -OCH),
5	-OCH	5.31 (dd, 1H, *J* = 7.3, 3.5 Hz, -OCH),	5.31 (dd, 1H, *J* = 7.2, 3.4 Hz, -OCH),
6	-OCH	5.18 (dd,1H, *J* = 6.9, 3.5 Hz, -OCH),	5.18 (dd, 1H, *J* = 6.8, 3.4 Hz, -OCH)
7	-OCH	4.97 (td, 1H, *J* = 12.6, 7.7 Hz, -OCH), 4.91 (quint, 1H, J = 6.5 Hz, -OCH),	5.04-3.87 (m, 2H, 2 x -OCH),
8	allylic	2.50-2.40(m, 2H, allylic)	2.46 (m, 2H, allylic),
9	OAc	2.13 (s, 3H, OAc),	2.13 (s, 3H, OAc),
10	OAc	2.07 (s, 6H, 2 x OAC), 2.03 (s, 3H, OAc),	2.08 (s, 6H, 2 x OAc), 2.03 (s, 3H, OAc)
11	methyl	1.18 (d, 3H, J = 6.42 Hz, Me),	1.18 (d, 3H, *J* = 6.4 Hz, Me)

Table 1: Comparison table of ^1H NMR.

S. No	^{13}C	Spectral data for (-)- anamarine from literature (Meshram et al.)	(-) - anamarine
1	C-OAc	170.0	170.0
2	C-OAc	169.8	169.9
3	C-OAc	169.83	169.8
4	C-OAc	169.76	169.7
5	C1	163.5	163.5
6	C3	144.5	144.5
7	C7	133.0	133.0
8	C6	125.5	125.5
9	C2	121.5	121.4
10	C5	75.8	75.8
11	C8	71.9	71.9
12	C10	71.6	71.6
13	C9	70.4	70.4
14	C11	67.3	67.3
15	C4	29.1	29.1
16	C-CO	21.0	21.0
17	C-CO	20.91	20.9
18	C-CO	20.86	20.8
19	C-CO	20.6	20.6
20	C12	15.8	15.8

Table 2: Comparison table of ^{13}CNMR.

Conclusion

In conclusion, an efficient convergent synthetic strategy is developed for the synthesis of (-)-anamarine from D-mannitol and explicated the effect of electron withdrawing group in cross-metathesis reaction. Vinyl lactone and olefinic acyclic fragments were synthesized and coupled to give (-)-anamarine. This approach is adoptable for the diversity oriented efficient synthesis of such relevant lactone class of compounds.

Acknowledgments

The author (K. R.) thanks the UGC, New Delhi, India for the financial support in the form of a fellowship.

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