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 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 Na2SO4 and concentrated below 40°C in vacuo.

To a stirred solution of D-mannitol (8) (0.30 g, 1.27 mmol) in CH2Cl2 (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, 5% EtOAc in pet. ether) afforded 7 (0.07 g, 0.27 mmol) as a pale yellow syrup;

(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 CH2Cl2 (7.5 mL) at 0°C, Et3N (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 CHCl3 (10 mL) and washed with water (10 mL), brine (10 mL) and dried (Na2SO4). 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; [α]D28+ = +17.5 (c 0.30, CHCl3); IR (neat): 2935, 2858, 2313, 1727, 1644, 1568, 1551, 1516, 1466, 1449, 1406, 1367, 1264, 1047, 925, 846, 807, 772, 669 cm-1; 1H NMR (300 MHz, CDCl3): 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 = 2.0, 10.1 Hz, allylic), 2.48 (td, 1H, J = 3.0, 10.1 Hz, allylic), 1.65-1.53 (m, 8H, allylic), 2.61 (td, 1H, J = 3.0, 10.1 Hz, allylic), 1.40-1.32 (m, 2H, cyclohexyl); 13C NMR (75 MHz, CDCl3): δ 144.9, 140.1, 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 C31H37O8 (M+Na)+ 529.1410, found 529.1408.

(S)-6-((R)-1,4-Dioxaspiro[4.5]decan-2-yl)-5,6-dihydro-2H-pyrano[2,3-b]pyran-2-one (8)

To a stirred solution of 7 (0.07 g, 0.27 mmol) in CH2Cl2 (50 mL), Grubbs-I catalyst (10 mol%) was added and stirred 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, 30% EtOAc in pet. ether) afforded 8 (0.05 g, 81%) as a colorless syrup; [α]D25 = -59.0 (c 0.70, CHCl3); IR (neat): 3020, 2314, 1727, 1711, 1663, 1590, 1553, 1483, 1467, 1289, 742, 668 cm-1; 1H NMR (300 MHz, CDCl3): 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, 1H, -OCH), 3.82 (dd, 1H, J = 5.0, 18.1 Hz, allylic), 2.48 (td, 1H, J = 3.0, 10.1 Hz, allylic), 1.55-1.53 (m, 8H, allylic), 1.48-1.32 (m, 2H, allylic); 13C NMR (75 MHz, CDCl3): δ 165.4, 151.8, 146.6, 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 C15H16O4 (M+) 289.1104, found 289.1107.

(S)-6-Vinyl-5,6-dihydro-2H-pyrano[2,3-b]pyran-2-one (5)

To a stirred solution of 8 (0.30 g, 1.27 mmol) in CH2CN (5 mL) at 0°C, CuCl2·2H2O (0.47 g, 0.35 mmol) was added and stirred at room temperature for 6 h. The reaction mixture was evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, 20% EtOAc in pet. ether) afforded 5 (0.09 g, 33%) as a pale yellow syrup; [α]D28+ = +17.5 (c 0.30, CHCl3); IR (neat): 2935, 2858, 2313, 1727, 1644, 1568, 1551, 1516, 1466, 1449, 1406, 1367, 1264, 1047, 925, 846, 807, 772, 669 cm-1; 1H NMR (300 MHz, CDCl3): 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 = 2.0, 10.1 Hz, allylic), 2.33 (m, 2H, allylic), 1.67-1.50 (m, 2H, cyclohexyl), 1.40-1.32 (m, 2H, cyclohexyl); 13C NMR (75 MHz, CDCl3): δ 165.4, 151.8, 146.6, 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 C15H16O4 (M+) 289.1104, found 289.1107.

Figure 1: Structures of 1 and 2.

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temperature for 30 min. It was quenched with sat. NaHCO₃ (1 mL), filtered through a pad of celite and washed with EtOAc (10 mL). The organic layer was dried (Na₂SO₄), evaporated and used as such for the next reaction. To a stirred solution above diol (0.20 g, 1.27 mmol), Ph₃P (1.33 g, 5.08 mmol) and imidazole (0.35 g, 5.08 mmol) in CH₂Cl₂ (10 mL) at 0°C, 1.07 (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 CHCl₃ (3 × 5 mL) and dried (Na₂SO₄). 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; [α]D²⁰ = -87.5 (c = 0.10, CHCl₃); lit.[α]D²⁰ = -93.4 (c = 0.10, CHCl₃); IR (neat): 3016, 2943, 2882, 1726, 1426, 1382, 1211, 1150, 1081, 971, 819, 748, 703, 667, 409 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.89 (d, 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), 1.11, 10.8, 293, 1042, 1477, 1344, 1340, 1206, 1171, 179, 77.7, 293; HRMS (ESI+): m/z calculated for C₃H₅O₂ (M+Na⁺) 147.0422, found 147.0429.

(1R)-1-((4R,4'R)-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 CH₂Cl₂ (210 mL) at 0°C, Et₃N (13.94 mL, 100.19 mmol) followed by n-ButSnO₂ (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 mixture was diluted with CH₂Cl₂ (8 mL) and washed with water (2 × 5 mL), brine (2 × 5 mL) and dried (Na₂SO₄). Solvent was evaporated to give 10, which was used as such for the next step. To a stirred suspension of LiAlH₄ (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. Na₂SO₄ solution (10 mL) and filtered. Aq. layer was extracted EtOAc (50 mL) and dried (Na₂SO₄). 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; [α]D⁰ = +6.4 (c = 0.20, CHCl₃); IR (neat): 3470, 3434, 2990, 2936, 2830, 1597, 1460, 1373, 1306, 1252, 1127, 1179, 938, 841, 710, 667, 554, 513, 490 cm⁻¹; ¹H NMR (300 MHz, CDCl₃); 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); ¹³C NMR (75 MHz, CDCl₃); 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 C₁₃H₉O₂ (M+Na⁺) 269.1364, found 269.1353.

tert.-Butyldiphenyl(11R)-1-((4R,4'R)-2,2',2'-tetramethyl-4,4'-bi(1,3-dioxolan)-5-yl)-ethoxy)silane (12)

To a stirred solution of alcohol 11 (13.80 g, 56.99 mmol) in CH₂Cl₂ (68 mL), imidazole (11.44 g, 168.29 mmol), TPSCI (17.61 g, 67.31 mmol) and DMAP (cat.) were added sequentially and stirred at room temperature for 1 h. The reaction mixture was diluted with water (2 × 5 mL), 571.2491, found 571.2479.

(2R)-2-((4S)-5-((R)-1-(tert.-Butyldiphenylsilyloxy)ethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(tosyloxy)ethyl benzolate (15)

To a stirred and cooled (0°C) solution of 14 (21.3 g, 3.89 mmol) in CH₂Cl₂ (20 mL), Et₃N (1.5 mL, 9.01 mmol), n-ButSnO₂ (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 CH₂Cl₂ (8 mL) and washed with water (2 × 5 mL), brine (2 × 5 mL) and dried (Na₂SO₄). 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; [α]D³⁰ = +51.2 (c = 0.25, CHCl₃); IR (neat): 3478, 3071, 2934, 2859, 1723, 1597, 1452, 1428, 1329, 1277, 1157, 1111, 822, 741 cm⁻¹; ¹H NMR (500 MHz, CDCl₃); δ 8.03 (d, 2H, J = 7.4 Hz, Ar-H), 7.68 (d, 4H, J = 6.2, 22.3 Hz, Ar-H), 7.54 (t, 1H, J = 7.4 Hz, Ar-H), 7.47-7.35 (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); ¹³C NMR (75 MHz, CDCl₃); δ 166.8, 135.8, 133.9, 133.3, 131.3, 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 C₁₉H₂₆O₄Si (M+Na⁺) 571.2491, found 571.2479.
To a stirred solution of Me$_2$Si (0.95 g, 4.67 mmol) in THF (5 mL) at -20°C, 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$_4$Cl solution (2 mL) and extracted with EtOAc (2 x 10 mL). Organic layers were washed with water (10 mL), brine (10 mL) and dried (Na$_2$SO$_4$). Solvent was evaporated and purified by column chromatography (60-120 mesh silica gel, 8% EtOAc in pet. ether) afforded 4 (0.34 g, 67%) as a colorless syrup: [α]$^\text{D}_{20}$ = +22.4 (c 0.10, CHCl$_3$); IR (neat): 3480, 3077, 2987, 2860, 1647, 1472, 1248, 1377, 1242, 1111, 891, 741, 704 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$): δ 7.72-7.68 (m, 4H, Ar-H), 7.44-7.32 (m, 6H, Ar-H), 4.04-3.95 (m, 2H, olefinic), 3.90 (m, 1H, -OCH), 2.99 (q, 1H, J = 3.8 Hz, epoxide), 2.66 (dd, 2H, J = 3.8, 5.3 Hz, epoxide), 1.33 (s, 6H, 2 x Me), 1.06 (d, 3H, J = 6.0 Hz); 13C NMR (75 MHz, CDCl$_3$): δ 135.8, 134.1, 133.4, 129.7, 129.6, 127.6, 109.6, 82.4, 76.9, 69.5, 52.2, 44.5, 42.7, 27.2, 26.5, 19.8, 19.2; HRMS (ESI+): m/z calculated for C$_{13}$H$_{18}$O$_4$Si (M+Na$^+$) 449.2124, found 449.2074.

(1S)-1-((4R)-5-((1R)-1-((Butylidene)bis(3-isoxazolyl))ethyl)-2,2-dimethyl-1,3-dioxo la-3-n-4-y1)-prop-2-en-1-ol (4)

To a stirred solution of Me$_2$Si (0.95 g, 4.67 mmol) in THF (5 mL) at -20°C, 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$_4$Cl solution (2 mL) and extracted with EtOAc (2 x 10 mL). Organic layers were washed with water (10 mL), brine (10 mL) and dried (Na$_2$SO$_4$). Solvent was evaporated and purified by column chromatography (60-120 mesh silica gel, 10% EtOAc in pet. ether) afforded 4 (0.34 g, 67%) as a colorless syrup: [α]$^\text{D}_{20}$ = +22.4 (c 0.10, CHCl$_3$); IR (neat): 3468, 3077, 2984, 2934, 2829, 2859, 1647, 1590, 1472, 1248, 1372, 1242, 1111, 891, 741, 704 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$): δ 7.72-7.64 (m, 4H, Ar-H), 7.44-7.32 (m, 6H, Ar-H), 4.04-3.95 (m, 2H, olefinic), 3.90 (m, 1H, -OCH), 2.99 (q, 1H, J = 3.8 Hz, epoxide), 2.66 (dd, 2H, J = 3.8, 5.3 Hz, epoxide), 1.33 (s, 6H, 2 x Me), 1.06 (d, 3H, J = 6.0 Hz); 13C NMR (75 MHz, CDCl$_3$): δ 135.8, 134.1, 133.4, 129.7, 129.6, 127.6, 109.6, 82.4, 76.9, 69.5, 52.2, 44.5, 42.7, 27.2, 26.5, 19.8, 19.2; HRMS (ESI+): m/z calculated for C$_{13}$H$_{18}$O$_4$Si (M+Na$^+$) 449.2124, found 449.2074.

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

A solution of 4 (0.20 g, 0.82 mmol) in CH$_2$Cl$_2$ (1 mL) at 0°C was treated with CF$_3$COOH (1 mL) and stirred at room temperature for 15 min. Solvent was evaporated and the crude tetro 4a was used as such for the next reaction. A solution of the above tetro in pyridine (3 mL) was cooled to 0°C and treated with Ac$_2$O (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 tetaacetate 17 (0.02 g, 81%) as a light yellow oil; [α]$^\text{D}_{20}$ = -10.6 (c 0.20, CHCl$_3$); IR (neat): 2942, 2854, 2314, 1743, 1678, 1645, 1586, 1569, 1531, 1483, 1450, 1372, 1319, 1033, 722, 687, 671 cm$^{-1}$; 1H NMR (300 MHz, CDCl$_3$): δ 6.83-5.68 (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), 2.07 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.19 (d, 3H, J = 6.4 Hz, Me); 13C NMR (75 MHz, CDCl$_3$): δ 170.0, 169.8, 132.4, 119.4, 79.7, 74.6, 70.4, 70.2, 27.4, 26.5, 77.7, 21.0, 15.5; HRMS (ESI+): m/z calculated for C$_{16}$H$_{24}$O$_8$ (M+Na$^+$) 353.1207, found 353.1207.
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' (6 was achieved from D-mannitol in two steps with overall yield 70%) with acryloyl chloride and Et$_3$N in CH$_2$Cl$_2$ furnished the acrylate 7 in 82% yield, Which on RCM reaction with Grubbs-I$^*$ catalyst gave a,b-unsaturated lactone 8 in 81% yield (exclusively Z-olefin). Grubbs-II 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$_2$H$_2$O in CH$_3$CN afforded the diol, which on subsequent treatment with Ph$_3$P, iodine and imidazole in CH$_2$Cl$_2$ furnished 5 in 70% yield, [α]$^2_D$ = -87.5 (c 0.10, CHCl$_3$); lit. [17] [α]$^2_D$ = -93.4 (c 0.10, CHCl$_3$).

Synthesis of tetraacetate fragment 4

For the synthesis of 4, diol 9 (9 was achieved from D-mannitol in one step with 80% yield) was subjected to reaction with p-TsCl in the presence of Et$_3$N and n-Bu$_3$SnO in CH$_2$Cl$_2$ 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 TPSCI and imidazole in CH$_2$Cl$_2$ afforded 12 in 66% yield. Selective deprotection of 12 using CuCl$_2$2H$_2$O in CH$_3$CN furnished diol 13, which on treatment with benzoyl chloride in the presence of Et$_3$N and n-Bu$_3$SnO in CH$_2$Cl$_2$ to give 14 in 89% yield (Scheme 3). Reaction of alcohol 14 with p-TsCl, Et$_3$N and cat. DMAP in CH$_2$Cl$_2$ furnished 15 in 84% yield. Treatment of tosylate 15 with K$_2$CO$_3$ in MeOH afforded 16 (90%), which on reaction with Me$_3$Si and n-BuLi in THF at -20°C gave 4 in 67% yield. Treatment of 4 with CF$_3$COOH in CH$_2$Cl$_2$ gave tetro 4a, which on treatment with Ac$_2$O and pyridine in CH$_3$CN furnished tetraacetate 17 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$_3$COOH in CH$_2$Cl$_2$ to give tetro 3a by the simultaneous deprotection of silyl and acetone groups. Finally, reaction of 3a with Ac$_2$O and pyridine in CH$_2$Cl$_2$ furnished (-)-anamarine 2 (86%). The spectral data of 2 was in accordance with the literature values [17-31] (Tables 1 and 2). [α]$^2_D$ = -17.8 (c 0.3, CHCl$_3$); lit.$^*$ [α]$^2_D$ = -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.

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

**Scheme 2:** Reagents and conditions: a) acryloyl chloride, Et$_3$N, cat. DMAP, CH$_2$Cl$_2$, 0°C-rt, 2 h; b) Grubbs-I catalyst, CH$_2$Cl$_2$, reflux, 6 h; c) CuCl$_2$2H$_2$O, CH$_3$CN, 0°C, 30min; d) Ph$_3$P, I$_2$, imidazole, CH$_2$Cl$_2$, 0°C-rt, 2 h.
Scheme 3: Reagents and conditions: a) p-TsCl, Et$_3$N, n-Bu$_2$SnO, CH$_2$Cl$_2$, 0°C-rt, 1 h; b) LiAlH$_4$, THF, 0°C-rt; c) TPSCl, imidazole, CH$_2$Cl$_2$, 0°C-rt 1 h; d) CuCl$_2$.2H$_2$O, CH$_3$CN, 0°C, 30 min; e) BzCl, Et$_3$N, CH$_2$Cl$_2$, n-Bu$_2$SnO, 0°C-rt, 1 h; f) p-TsCl, Et$_3$N, cat. DMAP, CH$_2$Cl$_2$, rt, 12 h; g) KO$_2$, MeOH, 0°C-rt, 1 h; h) Me$_3$Si, n-BuLi, -20°C, 30 min; i) CF$_3$COOH, CH$_2$Cl$_2$, 0°C-rt, 15 mn; j) Ac$_2$O, pyridine, cat. DMAP, CH$_2$Cl$_2$, rt, 20 h.

Scheme 4: Reagents and conditions: a) Grubbs-II catalyst, toluene reflux, 8 h; b) CF$_3$COOH, CH$_2$Cl$_2$, 0°C-rt, 15 min; c) Ac$_2$O, pyridine, cat. DMAP, CH$_2$Cl$_2$, rt, 20 h; d) Grubbs-II catalyst, CH$_2$Cl$_2$, reflux, 5 h.

Table 1: Comparison table of $^1$H NMR.

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<td>2</td>
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<td>6.06 (td, 1H, $J = 9.8, 1.9$ Hz, olefinic),</td>
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<td>5.86-5.76 (m, 2H, olefinic),</td>
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<td>-OCH</td>
<td>5.36 (dd, 1H, $J = 7.0, 6.0$ Hz, -OCH),</td>
<td>5.37 (dd, 1H, $J = 7.2, 5.3$ Hz, -OCH),</td>
</tr>
<tr>
<td>5</td>
<td>-OCH</td>
<td>5.31 (dd, 1H, $J = 7.3, 3.5$ Hz, -OCH),</td>
<td>5.31 (dd, 1H, $J = 7.2, 3.4$ Hz, -OCH),</td>
</tr>
<tr>
<td>6</td>
<td>-OCH</td>
<td>5.18 (dd,1H, $J = 6.9, 3.5$ Hz, -OCH),</td>
<td>5.18 (dd,1H, $J = 6.8, 3.4$ Hz, -OCH),</td>
</tr>
<tr>
<td>7</td>
<td>-OCH</td>
<td>4.97 (td, 1H, $J = 12.6, 7.7$ Hz, -OCH), 4.91 (quint, 1H, $J = 6.5$ Hz, -OCH),</td>
<td>5.04-3.87 (m, 2H, 2 x -OCH),</td>
</tr>
<tr>
<td>8</td>
<td>allylic</td>
<td>2.50-2.40(m, 2H, allylic)</td>
<td>2.46 (m, 2H, allylic),</td>
</tr>
<tr>
<td>9</td>
<td>OAc</td>
<td>2.13 (s, 3H, OAc),</td>
<td>2.13 (s, 3H, OAc),</td>
</tr>
<tr>
<td>10</td>
<td>OAc</td>
<td>2.07 (s, 6H, 2 x OAc), 2.03 (s, 3H, OAc),</td>
<td>2.08 (s, 6H, 2 x OAc), 2.03 (s, 3H, OAc),</td>
</tr>
<tr>
<td>11</td>
<td>methyl</td>
<td>1.18 (d, 3H, $J = 6.4$ Hz, Me),</td>
<td>1.18 (d, 3H, $J = 6.4$ Hz, Me),</td>
</tr>
</tbody>
</table>
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.

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References