STUDIES TOWARDS THE STEREOSELECTIVE SYNTHESIS OF C₁₃ TO C₂₁ FRAGMENT OF BRASILINOLIDES FAMILY OF IMMUNOSUPPRESSIVE MACROLIDES

Hajari Ravindranath,* Gangavaram V. M. Sharma

D-206, Discovery Laboratory, Organic & Biomolecular Chemistry Division, CSIR-Indian Institute of Chemical Technology Hyderabad 500 007, India

E-mail: ravindranathiict@gmail.com

SUPPORTING INFORMATION

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GENERAL PROCEDURES

Solvents were dried over standard drying agents and freshly distilled prior to use. All commercially available chemicals were used without further purification. All reactions were performed under Nitrogen. ^1H NMR and ^{13}C NMR spectra were measured with Varian Gemini FT 200 MHz spectrometer, Bruker Avance 300 MHz, Unity 400 MHz and Inova 500 MHz with tetramethylsilane as internal standard for solutions in CDCl_3 . J values are given in Hz. Chemical shifts were reported in ppm relative to solvent signal. 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*. IR spectra were recorded on FT IR (Perkin-Elmer IR-683) spectrophotometer with NaCl optics. JASCO DIP 300 digital polarimeter was used for measurement of optical rotations at 25 °C. Mass spectra were recorded on direct inlet system or LC by MSD trap SL (Agilent Technologies), the HRMS data were obtained using Q-TOF mass spectrometry.

(S)-4-(Benzyloxy)-2-hydroxybutyl benzoate (**18**):

To a stirred solution of **17** (19 g, 96.9 mmol) in CH_2Cl_2 (50 mL), Et_3N (27.1 mL, 193.8 mmol), BzCl (11.2 g, 96.9 mmol) and Bu_2SnO (0.37 g, 1.9 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 2 h and extracted into chloroform (2 × 50 mL). Organic layers were washed with water (2 × 50 mL), brine (50 mL) and dried (Na_2SO_4). Solvent was evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, EtOAc :hexane, 1:4) to furnish **18** (22 g, 75%) as a yellow syrup. $[\alpha]_{\text{D}}^{25} = -51.30$ (c 0.7, CHCl_3); IR (KBr): 3462, 3063, 3031, 2923, 2860, 1715, 1601, 1583, 1493, 1451, 1363, 1314, 1269, 1094, 1070, 1070, 1025, 971, 938, 914, 772, 710, 614 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 8.06 (m, 2H, ArH), 7.57 (m, 1H, ArH), 7.44 (m, 2H, ArH), 7.34 (m, 5H, ArH), 4.55 (s, 2H, PhCH_2), 4.37 (dd, 1H, $J = 4.2, 7.0$ Hz, OCH), 4.31 (dd, 1H, $J = 6.2, 5.0$ Hz, OCH), 4.21 (m, 1H, OCH), 3.70 (m, 1H, OCH), 3.71 (m, 1H, OCH), 3.1 (d, 1H, $J = 2.7$ Hz, -OH), 1.90 (m, 2H, 2 × CH); ^{13}C NMR (CDCl_3 , 75 MHz): δ 166.7, 137.9, 133.2, 130.0, 129.8 (2C), 128.6 (2C), 128.5 (2C), 127.9, 127.8 (2C), 73.5, 69.1, 68.7, 68.2, 33.2; HRMS (ESI): m/z calculated for $\text{C}_{18}\text{H}_{20}\text{O}_4$ $[\text{M}+\text{Na}]^+$: 323.1253; found: 323.1255.

(R)-2-(2-(Benzyloxy) ethyl)oxirane (6):

To a stirred solution of **18** (22 g, 73.4 mmol) in CH₂Cl₂ (50 mL), Et₃N (14.8 mL, 146.6 mmol), *p*-TsCl (16.8 g, 88.0 mmol) and DMAP(cat.) were added. The reaction mixture was stirred at room temperature for 6 h and extracted into chloroform (2 × 50 mL). Organic layers were washed with water (2 × 50 mL), brine (50 mL) and dried (Na₂SO₄). Solvent was evaporated to give **18a**, which was used for the next step as such.

To a stirred solution of tosylate **18a** (33.5 g, 73.4 mmol) in methanol (80 mL), K₂CO₃ (20.6 g, 147.5 mmol) was added at 0 °C and stirred at room temperature for 1 h. It was filtered through a pad of celite and washed with ethylacetate. It was dried (Na₂SO₄), evaporated and purified the residue by column chromatography (60-120 mesh Silica gel, 4% EtOAc in pet. ether) to afford **6** (10 g, 76%). $[\alpha]_D^{25} = 51.30$ (*c* 0.7, CHCl₃); IR (CHCl₃): 3018, 2923, 2859, 1721, 1494, 1453, 1361, 1214, 1100, 1026, 909, 832, 748, 667, 623 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ 7.33 (m, 5H, Ar-H), 4.50 (s, 2H, Ph-CH₂), 3.62 (m, 2H, OCH₂), 3.07 (m, 1H, epoxy), 2.78 (dt, 1H, *J* = 4.5, 0.37 Hz, epoxy), 2.52 (dd, 1H, *J* = 2.6, 2.6 Hz, epoxy), 1.97-1.68 (m, 2H, CH₂); ¹³C NMR (75MHz, CDCl₃): 138.1, 128.1 (2C), 127.3 (3C), 72.8, 66.8, 49.7, 46.7, 32.7; HRMS (ESI): *m/z* calculated for C₁₁H₁₄O₂ [M+Na]⁺: 201.0886; found: 201.0889.

(S)-1-(Benzyloxy)-7-(tetrahydro-2H-pyran-2-yloxy)hept-5-yn-3-ol (8) :

A solution of *n*-BuLi in hexane (67.4 mL, 168 mmol, 2.5 M solution in hexane) was added to a solution of THP ether **17** (23.4 g, 168 mmol) in THF (80 mL) at -78 °C under nitrogen atmosphere, and stirred the mixture for 15 min. BF₃·Et₂O (21.3 mL, 168.5 mmol) was added to the solution and the stirring was continued for 15 min. at -78 °C. Finally a solution of epoxide **6** (10 g, 56.1 mmol) in dry THF (30 mL) was added, and stirred the reaction mixture for 1 h at -78 °C. The reaction was quenched with aq. NH₄Cl (40 mL) and extracted with EtOAc (3 x 100 mL). It was dried (Na₂SO₄), evaporated and purified the residue by column chromatography (60-120 mesh, Silica gel, EtOAc:hexane, 1:3) to afford alcohol **8** (13 g, 73%) as a viscous liquid. $[\alpha]_D^{25} = 12.03$ (*c* 0.3, CHCl₃); IR (CHCl₃): 3873, 3844, 3743, 3723, 3423, 3457, 3395, 3031, 2941, 2866, 2311, 1818, 1743, 1693, 1627, 1550, 1497, 1452, 1360, 1264, 1203, 1184, 1115, 1077, 1022, 972, 947, 902, 870, 772, 698, 670 cm⁻¹; ¹H NMR (300 MHz,

CDCl₃): δ 7.33 (m, 5H, ArH), 4.79 (t, 1H, J = 3.0 Hz, O₂CH), 4.50 (s, 2H, ArCH₂), 4.32-4.1 (m, 2H, OCH₂), 3.90 (brs, 1H, OH), 3.87-3.47 (m, 5H, 5 x OCH), 2.43 (dd, 2H, J = 4.15, 1.88 Hz, CH₂), 2.00-1.69 (m, 2H, 2 x CH), 1.61-1.44 (m, 6H, 6 x CH); ¹³C NMR (75 MHz, CDCl₃): δ 137.8, 128.3 (2C), 127.6, 127.5 (2C), 96.7, 82.8, 73.2, 69.4, 68.4, 61.9 (2C), 54.5, 35.3, 30.2, 27.4, 25.2, 19.0; HRMS (ESI): m/z calculated for C₁₉H₂₆O₄ [M+Na]⁺: 341.1723; Found: 341.1727.

2-((S)-5-(4-Methoxybenzyloxy)-7-(benzyloxy)hept-2-ynyloxy)-tetrahydro-2H-pyran (5):

To a cooled (0 °C) solution of **8** (13 g, 40 mmol) in dry THF (40 mL), NaH (3.9 g, 163.5 mmol) was added, stirred for 30 min and treated with a solution of PMB-Br (9.8 g, 49.0 mmol) in dry THF (40 mL). After stirring at room temperature for 6 h, the reaction mixture was quenched with aq. NH₄Cl solution (8 mL) and extracted with EtOAc (2 x 40 mL). The combined organic layers were washed with water (2 x 10 mL), brine (10 mL) and dried (Na₂SO₄). Solvent was evaporated under reduced pressure and purified the residue by column chromatography (60-120 mesh, Silica gel, EtOAc:hexane, 1:5) to furnish **5** (14.2 g, 79%) as a yellow syrup. [α]_D²⁵ = 41.02 (c 0.4, CHCl₃); IR (CHCl₃): 3744, 3062, 3029, 2939, 2862, 2312, 1738, 1612, 1513, 1454, 1359, 1301, 1246, 1177, 1115, 1077, 1054, 1023, 970, 945, 902, 817, 771, 699, 668 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.31-7.21 (m, 7H, Ar-H), 6.83 (d, 2H, J = 8.6 Hz, Ar-H), 4.80 (t, 1H, J = 3.39, O₂CH), 4.56 (d, 1H, J = 11.33 Hz, Ar-CH), 4.50-4.34 (m, 3H, Ar-CH₂, Ar-CH), 4.33-4.17 (m, 2H, OCH₂), 3.87-3.70 (m, 5H, OMe, 2 x OCH), 3.63-3.44 (m, 3H, 3 x OCH), 2.57-2.41 (m, 2H, CH₂), 2.04-1.61 (m, 2H, 2 x CH), 1.61-1.48 (m, 6H, 6 x CH); ¹³C NMR (75 MHz, CDCl₃): δ 159.0, 138.3, 130.4, 129.3 (2C), 128.2 (2C), 127.5 (2C), 127.4, 113.6 (2C), 96.6, 82.9, 77.6, 74.3, 72.8, 71.1, 66.5, 61.9, 55.1, 54.5, 34.4, 30.1, 25.2, 24.0, 19.0; HRMS (ESI): m/z calculated for C₂₇H₃₄O₅ [M+Na]⁺: 461.2298; Found: 461.2302.

(S)-5-(4-Methoxybenzyloxy)-7-(benzyloxy) hept-2-yn-1-ol (9):

A solution of **5** (14.2 g, 32.4 mmol) in MeOH (80 mL) containing PPTS (~500 mg) for at room temperature for 1 h. The reaction mixture was quenched by the addition of saturated aq. NaHCO₃ solution (20 mL) and evaporated MeOH under reduced pressure. The aqueous phase was extracted with EtOAc (2 x 80 mL) and organic extracts were washed with brine (80 mL). It was dried (Na₂SO₄), evaporated and purified the residue by column chromatography (60-120 mesh, Silica gel,

EtOAc:hexane, 1:4) to afford alcohol **9** (10.3, 89%) as a colourless liquid. $[\alpha]_D^{25} = 33.06$ (*c* 0.2, CHCl₃); IR (CHCl₃): 3418, 3019, 2924, 2862, 1734, 1611, 1513, 1453, 1362, 1301, 1246, 1214, 1176, 1096, 1027, 820, 747, 667 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.37-7.21 (m, 7H, Ar-H), 6.85 (d, 2H, *J* = 8.68 Hz, Ar-H), 4.58-4.37 (m, 4H, 2 x Ar-CH₂), 4.23 (brs, 2H, OCH₂), 3.78-3.69 (br.s, 4H, OMe, OCH), 3.60-3.49 (m, 2H, 2 x OCH), 2.56-2.48 (m, 2H, CH₂), 2.08-1.81 (m, 3H, OH, 2 x CH); ¹³C NMR (75 MHz, CDCl₃): δ 159.1, 138.3, 130.3, 129.4 (2C), 128.3 (2C), 127.8, 127.6, 127.5, 113.7 (2C), 82.5, 80.3, 73.8, 72.9, 71.1, 66.5, 55.2, 51.1, 34.3, 24.2; HRMS (ESI): *m/z* Calculated for C₂₂H₂₆O₄[M+Na]⁺: 377.1723; Found: 377.1729.

(*S, E*)-5-(4-Methoxybenzyloxy)-7-(benzyloxy) hept-2-en-1-ol (4):

To a cooled suspension of LAH (1.04 g, 29 mmol) in dry THF (20 mL), a solution of **9** (10.3 mg, 29 mmol) in dry THF (40 mL) was added at 0 °C and stirred at room temperature for 1 h. The reaction mixture was quenched with saturated Na₂SO₄ solution (5 mL) and stirred for 1 h. It was filtered and washed with EtOAc (2 x 50 mL). Combined organic layers were washed with water (2 x 50 mL), brine (2 x 50 mL) and dried (Na₂SO₄). Evaporation of solvent under reduced pressure and purification of the residue by column chromatography (60-120 mesh, Silica gel, EtOAc: hexane, 1:5) furnished **4** (8 g, 77%) as a yellow syrup. $[\alpha]_D^{25} = 31.01$ (*c* 0.2, CHCl₃); IR (CHCl₃): 3744, 3062, 3029, 2939, 2862, 2312, 1738, 1612, 1585, 1513, 1454, 1359, 1301, 1246, 1203, 1177, 1115, 1077, 1054, 1023, 970, 945, 902, 817, 771, 699, 668, 593 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.38-7.17 (m, 7H, Ar-H), 6.86 (d, 2H, *J* = 8.68, ArH), 5.69 (m, 2H, Olefinic), 4.51-4.35 (m, 4H, 2 x Ar-CH₂), 4.00 (brs, 2H, OCH₂), 3.70 (s, 4H, OMe, -OH), 3.60-3.50 (m, 3H, 3 x OCH), 2.31 (t, 2H, *J* = 5.0 Hz, CH₂), 1.79 (q, 2H, 2 x CH); ¹³C NMR (75 MHz, CDCl₃): δ 159.1, 138.4, 131.1, 130.7, 129.4 (2C), 128.6 (2C), 128.3, 127.7 (2C), 127.6, 113.7 (2C), 75.1, 73.0, 70.9, 66.8, 63.6, 55.2, 36.8, 34.3; HRMS (ESI): *m/z* calculated for C₂₂H₂₈O₄ [M+Na]⁺: 379.1879; Found: 379.1883.

(*S, E*)-5-(4-Methoxybenzyloxy)-7-(benzyloxy)hept-2-enyl benzoate (10):

To a stirred solution of **4** (8 g, 22.4 mmol) in CH₂Cl₂ (50 mL), Et₃N (6.3 mL, 44.9 mmol) and Bz-Cl (3.8 g, 26.9 mmol) were added at 0 °C and stirred at room temperature for 2 h. work up as described for **18** and purification of the residue by column chromatography (60-120 mesh, Silica gel,

EtOAc: hexane, 16:84) to furnished **10** (8 g, 77%) as a yellow syrup. $[\alpha]_D^{25} = 119.01$ (*c* 0.2, CHCl₃); IR (CHCl₃): 3745, 3020, 2923, 2854, 2314, 1717, 1645, 1513, 1451, 1271, 1247, 1214, 1109, 1029, 929, 743, 667, 625 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.15-7.99 (m, 3H, Ar-H), 7.64-7.36 (m, 4H, ArH), 7.3 (br.s, 4H, ArH), 7.19 (d, 1H, *J* = 8.30, ArH), 6.80 (d, 2H, *J* = 8.30 Hz, Ar-H), 5.95-5.68 (m, 2H, olefinic), 4.78 (d, 2H, *J* = 5.66 Hz, ArCH₂), 4.51-4.36 (m, 4H, ArCH₂, 2 x OCH), 3.7 (s, 3H, OMe), 3.71-3.48 (m, 3H, 3 x OCH), 2.35 (t, 2H, *J* = 6.04 Hz, allylic CH₂), 1.82 (q, 2H, *J* = 6.4, 12.4 Hz, CH₂); ¹³C NMR (75 MHz, CDCl₃): δ 166.5, 159.3, 138.6, 133.8, 133.0, 132.2, 130.8, 130.3, 129.8 (2C), 129.6 (2C), 128.5 (2C), 128.5 (2C), 127.9, 127.7, 126.7, 113.9 (2C), 75.2, 73.2, 71.2, 66.9, 65.7, 55.4, 37.4, 34.7; HRMS (ESI): *m/z* calculated for C₂₉H₃₂O₅ [M+Na]⁺: 483.2142; Found: 483.2145.

(2S, 3S, 5R)-5-(4-Methoxybenzyloxy)-7-(benzyloxy)-2, 3-dihydroxyheptyl benzoate (11):

AD mix- α (27 g, 34.7mmol) was dissolved in ^tBuOH (40 mL) and H₂O (40 mL). Methanesulfonamide (3.3 g, 34.7 mmol) and alkene **10** (8 g, 17.3 mmol) were then added at 0 °C and stirred the reaction vigorously for at same temperature 3 days. Na₂SO₃ (36 g) was then added to the reaction mixture and the solution was stirred for 1 h. It was filtered through a pad of celite and the resulting mixture was evaporated and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (60 mL), and dried (Na₂SO₄). Solvent was evaporated under reduced pressure and purified the residue by column chromatography (60-120 mesh, Silica gel, EtOAc/hexanes 1:1.5) to give diol **11** (4.5 g, 52%) as colourless oil. $[\alpha]_D^{25} = 101.30$ (*c* 0.2, CHCl₃); IR (CHCl₃): 3743, 3521, 3439, 3795, 3019, 2948, 2865, 1715, 1610, 1584, 1513, 1452, 1362, 1274, 1248, 1214, 1176, 1112, 1095, 1071, 1029, 929, 820, 743, 667, 626 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 295 K): δ 8.10-8.01 (m, 3H, Ar-H), 7.57 (m, 1H, Ar-H), 7.49-7.39 (m, 3H, Ar-H), 7.37-7.27 (m, 4H, Ar-H), 7.16 (d, 1H, *J* = 8.68 Hz, Ar-H), 6.82 (m, 2H, Ar-H), 4.49-4.31 (m, 7H, 2 x Ar-CH₂, 3 x OCH), 4.0-3.86 (m, 2H, OH), 3.78-3.72 (m, 5H, OMe, 2 x OCH), 2.06-1.94 (m, 2H, 2 x CH), 1.91-1.77 (m, 1H, CH), 1.62 (m, 1H, CH); ¹³C NMR (75 MHz, CDCl₃): δ 166.6, 159.1, 138.0, 132.9, 130.0, 129.8, 129.7, 129.5 (2C), 129.4 (2C), 128.2 (3C), 127.6 (2C), 127.4, 113.7 (2C), 73.6, 72.8, 72.4, 71.2, 68.2, 66.4, 65.9, 55.0, 37.0, 33.9; HRMS (ESI): *m/z* calculated for C₂₉H₃₄O₇ [M+Na]⁺: 517.2196; Found: 517.2203.

((4*R*,5*R*)-5-((*R*)-3-(Benzyloxy)-1-(4-methoxybenzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl benzoate (3**)**

To a stirred solution of **11** (4.5 g, 9.1 mmol) in dry CH₂Cl₂ (20 mL), 2,2 dimethoxypropane (1.3 mL, 10.9 mmol) and PTSA (cat.) were added and stirred at room temperature for 4 h. Et₃N (1 mL) was added to the reaction mixture and stirred for 10 min. The reaction mixture was diluted with CH₂Cl₂ (30 mL), and washed with water (2 x 10 mL) and brine (2 x 10 mL). It was dried (Na₂SO₄), evaporated under reduced pressure. and purified the residue by column chromatography (60-120 mesh, Silica gel, EtOAc:hexane 1:9) to give **3** (4.1 g, 84 %) as a colorless syrup [α]_D²⁵ = 82.10 (*c* 0.2, CHCl₃); IR (CHCl₃): 3064, 3031, 2985, 2923, 2853, 1718, 1605, 1584, 1512, 1452, 1372, 1314, 1271, 1169, 1095, 1070, 1027, 933, 848, 822, 771, 712, 611 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.04 (m, 2H, Ar-H), 7.56 (tt, 1H, *J* = 7.4, 1.2 Hz, Ar-H), 7.46-7.40 (m, 2H, Ar-H), 7.35-7.24 (m, 5H, Ar-H), 7.18 (m, 2H, Ar-H), 6.80-6.70 (m, 2H, Ar-H), 4.52-4.43 (m, 4H, Ar-CH₂, 2 x OCH), 4.32 (m, 1H, OCH), 4.10 (td, 1H, *J* = 8.5, 2.7 Hz, OCH), 4.02-3.91 (m, 1H, OCH), 3.80-3.70 (m, 5H, OMe, 2 x OCH), 3.62-3.52 (m, 2H, OCH), 1.96-1.81 (m, 4H, 2 x CH₂), 1.58 (s, 3H, CH₃), 1.39 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 166.2, 159.0, 138.4, 133.0, 130.7, 129.6 (3C), 129.3 (2C), 128.3 (4C), 127.7 (2C), 127.5 (2C), 113.7 (2C), 79.1, 74.6, 73.4, 73.0, 71.6, 66.6, 64.1, 55.2, 38.9, 35.1, 27.4, 26.9; HRMS (ESI): *m/z* calculated for C₃₂H₃₉O₇ [M+H]⁺: 536.2768; Found: 536.2772.

((4*R*,5*R*)-5-((*R*)-3-(benzyloxy)-1-(4-methoxybenzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (12**)**

To a solution of **3** (4.1 g, 7.6 mmol) in methanol (20 mL) K₂CO₃ (2.1 g, 15.3 mmol) was added at 0 °C and stirred for 1 h. It was filtered through a pad of celite and the resulting mixture was evaporated. The residue was diluted with CH₂Cl₂ and washed with 1M HCl(30 mL), aq. NaHCO₃ (30 mL) and brine (30 mL). The organic layers were dried (Na₂SO₄), evaporated and purified the residue by column chromatography (60-120 mesh, Silica gel, EtOAc: hexane, 7:3) to afford **12** (2.5 g, 75%) as a yellow liquid. [α]_D²⁵ = 61.10 (*c* 0.2, CHCl₃); IR (CHCl₃): 3439, 2921, 2852, 1715, 1607, 1549, 1512, 1455, 1372, 1250, 1216, 1167, 1098, 1072, 1031, 905, 849, 823, 745, 714, 698, 635, 608 cm⁻¹; ¹H NMR (300 MHz, CDCl₃, 295 K): δ 7.40-7.15 (m, 7H, Ar-H), 2.05 (d, 2H, *J* = 8.6 Hz, Ar-H), 4.54 (m, 4H, 2x

Ar-CH₂), 4.03 (m, 1H, OCH), 3.85-3.65 (m, 6H, 3 x OCH, OMe), 3.63-3.51 (m, 3H, OCH), 1.93-1.69 (m, 4H, 2 x CH₂), 1.59 (s, 3H, CH₃), 1.38 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 159.1, 138.3, 130.6, 129.5 (2C), 129.4, 128.3 (2C), 127.7 (2C), 127.5, 113.7 (2C), 81.6, 74.2, 73.7, 73.0, 71.6, 66.6, 61.4, 55.2, 38.8, 35.0, 27.3, 26.9; HRMS (ESI): *m/z* Calculated for C₂₅H₃₅O₆ [M+H]⁺: 431.2428; Found: 431.2436.

1-((4*R*,5*R*)-5-((*R*)-3-(benzyloxy)-1-(4-methoxybenzyloxy)propyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-ol (14**)**

To a stirred solution of diastereomeric mixture of alcohol **12** (2.5 g, 5.8 mmol) in CH₂Cl₂ (1.5 mL) under N₂ atmosphere at 0 °C, Dess-Martin periodinane (2.9 g, 6.9 mmol) was added and stirred at room temperature for 2 h. the reaction mixture was quenched with 1:1 mixture of saturated solutions of hypo and NaHCO₃ (3 mL), and extracted with CH₂Cl₂ (2 x 15 mL). The combined organic layers were washed with water (15 mL), brine (10 mL), dried (Na₂SO₄), and evaporated to give **13** which was directly used for the next reaction.

To a stirred solution of the aldehyde **13** (2.4 g, 5.6 mmol) in THF (1.5 mL) at 0 °C, zinc (0.73 g, 11.2 mmol) and allyl bromide (0.58 mL, 6.7 mmol) were added and stirred at room temperature for 2 h. The reaction mixture was quenched with saturated NH₄Cl solution (8 mL) and extracted with EtOAc (2 x 40 mL). The organic layers were washed with water (2 x 10 mL), brine (10 mL), and dried (Na₂SO₄). Solvent was evaporated under reduced pressure and purified the residue by column chromatography (60-120 mesh, Silica gel, EtOAc:hexane, 1.5:8.5) to furnish **14** (2.1 g, 80%) as a yellow syrup. [α]_D²⁵ = 49.03 (*c* 0.3, CHCl₃); IR (CHCl₃): 3438, 3066, 3029, 2922, 2853, 1720, 1661, 1611, 1585, 1513, 1455, 1370, 1300, 1247, 1213, 1168, 1093, 915, 875, 847, 822, 739, 698, 668 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.41-7.12 (m, 16H, Ar-H), 6.83 (m, 2H, Ar-H), 5.80 (m, 2H, olefinic), 5.20-4.90 (m, 4H, olefinic), 4.56-4.37 (m, 8H, 4 x ArCH₂), 4.20-3.97 (m, 2H, 2 x OCH), 3.88-3.41 (m, 16H, 2 x OMe, 10 x OCH), 2.53-1.95 (m, 8H, 2 x Allylic CH₂, 2 x CH₂), 1.95-1.67 (m, 4H, 2 x CH₂), 1.38 (m, 6H, 2 x CH₃), 1.25 (s, 6H, 2 x CH₃); ¹³C NMR (75 MHz, CDCl₃): δ 159.1, 138.4, 138.3, 134.3, 134.2, 130.6, 129.5, 129.4, 128.3, 127.6, 127.5, 118.2, 118.2, 118.1, 117.7, 113.7, 108.5, 108.3, 83.2, 83.0, 82.8, 75.6, 75.5, 73.9, 73.6, 73.5, 73.0, 71.5, 71.5, 71.1, 70.4, 66.7, 66.7, 55.2, 39.8, 39.2, 39.1, 38.2, 38.2, 37.8,

35.0, 33.9, 27.4, 27.3, 27.0, 26.9; HRMS (ESI): m/z Calculated for $C_{28}H_{39}O_6 [M+H]^+$: 471.2734; Found: 471.2738 .

^1H and ^{13}C Spectra for selected compounds

Spectrum 1: ^1H NMR Spectrum of compound **18** (CDCl_3 , 300 MHz).
 ^{13}C NMR Spectrum of compound **18** (CDCl_3 , 75 MHz).

Spectrum 2: ^1H NMR Spectrum of compound **6** (CDCl_3 , 300 MHz).
 ^{13}C NMR Spectrum of compound **6** (CDCl_3 , 75 MHz)

Spectrum 3: ^1H NMR Spectrum of compound **8** (CDCl_3 , 300 MHz).
 ^{13}C NMR Spectrum of compound **8** (CDCl_3 , 75 MHz)

Spectrum 4: ^1H NMR Spectrum of compound **5** (CDCl_3 , 300 MHz).
 ^{13}C NMR Spectrum of compound **5** (CDCl_3 , 75 MHz)

Spectrum 5: ^1H NMR Spectrum of compound **9** (CDCl_3 , 300 MHz).

^{13}C NMR Spectrum of compound **9** (CDCl_3 , 75 MHz)

Spectrum 6: ^1H NMR Spectrum of compound **4** (CDCl_3 , 300 MHz).

^{13}C NMR Spectrum of compound **4** (CDCl_3 , 75 MHz)

Spectrum 7: ^1H NMR Spectrum of compound **10** (CDCl_3 , 300 MHz).

^{13}C NMR Spectrum of compound **10** (CDCl_3 , 75 MHz)

Spectrum 8: ^1H NMR Spectrum of compound **11** (CDCl_3 , 300 MHz).

^{13}C NMR Spectrum of compound **11** (CDCl_3 , 75 MHz)

Spectrum 9: ^1H NMR Spectrum of compound **3** (CDCl_3 , 300 MHz).

^{13}C NMR Spectrum of compound **3** (CDCl_3 , 75 MHz)

Spectrum 10: ^1H NMR Spectrum of compound **12** (CDCl_3 , 300 MHz).

^{13}C NMR Spectrum of compound **12** (CDCl_3 , 75 MHz)

Spectrum 11: ^1H NMR Spectrum of compound **2** (CDCl_3 , 300 MHz).

^{13}C NMR Spectrum of compound **2** (CDCl_3 , 75 MHz)

Spectrum 12: ^1H NMR Spectrum of compound **15** (CDCl_3 , 300 MHz).

^{13}C NMR Spectrum of compound **15** (CDCl_3 , 75 MHz)