Anodic Cyclization Reactions: The Total Synthesis of Alliacol A.

John Mihelcic and Kevin D. Moeller*

Department of Chemistry, Washington University, St. Louis, MO 63130

Synthesis of 7. A 250 mL round-bottomed flask was charged with 13.5 g (116 mmol) of 4-(hydroxy)-3,3-dimethyl-2-butanone and 77 mL of anhydrous methanol, placed under nitrogen atmosphere, and cooled to -10°C (acetone/ice). After adding 5.9 mL (116 mmol) of Br_2 via syringe in one steady stream, the bath was changed to ice water and stirring was continued for 1 h. The reaction mixture was diluted with 110 mL ethyl acetate, transferred to a separatory funnel, washed with 110 mL water, and extracted with ethyl ether (5x100 mL). The combined organic layers were then washed with 50 mL of 10% aqueous K_2CO_3 and brine, dried over MgSO_4 , and concentrated *in vacuo* to furnish 1-bromo-4-(hydroxy)-3,3-dimethyl-2-butanone (21.7 g, 96% crude yield) as a pale orange oil: IR(neat) 3451 (s, br), 2969 (s), 2944 (s), 2874 (s), 1715 (s), 1465 (m), 1407 (m), 1387(m), 1368 (m), 1259 (m), 1164 (m), 1051 (s), 675 (s) cm^{-1} ; ^1H NMR (300MHz, CDCl_3) δ 4.72 (br s, 1 H), 4.28 (s, 2 H), 3.64 (s, 2 H), 1.25 (s, 6 H); ^{13}C NMR (75MHz, CDCl_3) δ 206.7, 69.5, 49.5, 33.4, 22.0; high resolution mass spectrometry (EI) m/z 195.0016 [(M+H) $^+$]; calc'd for $\text{C}_6\text{H}_{12}^{79}\text{BrO}_2$: 195.0021], 197.0001 [(M+H) $^+$]; calc'd for $\text{C}_6\text{H}_{12}^{81}\text{BrO}_2$: 195.0021]

To 21.3 g (98.1%) of the crude product made above in a 500 mL round bottomed flask were added 110 mL CH_2Cl_2 and 8.91 g (130.8 mmol) imidazole. The solution was placed under nitrogen and cooled to 0°C . TBSCl (18.9 g, 125.4 mmol) was added in two portions, the cooling bath was removed, and the mixture stirred for 2 h and 15 min. The reaction was then diluted with 50 mL of water, transferred to a separatory funnel, and washed first with 60 mL of water and then an additional 200 mL of water. The combined aqueous layers were extracted with ethyl ether (2x150 mL). The organic layers were then dried over MgSO_4 and concentrated *in vacuo* to 35.2 g. Chromatography through silica gel, slurry-packed in 1% triethylamine in hexanes, using 3% ethyl acetate in hexanes as the eluant provided the TBS protected bromoketone (25.3 g, 72% yield) as a colorless oil: IR(neat) 2952 (s), 2930 (s), 2885 (s), 2857 (s), 1726 (s), 1465 (m), 1390-1365 (m, db), 1097 (s), 836 (s), 661 (m) cm^{-1} ; ^1H NMR (300MHz, CDCl_3) δ 4.23 (s, 2 H), 3.54 (s, 2 H), 1.16 (s, 6 H), 0.84 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR (75MHz, CDCl_3) δ 205.4, 70.8, 49.7, 34.6, 26.0, 22.0, 18.3, -5.5; high resolution mass spectrometry (EI) m/z 309.0899 [(M+H) $^+$]; calc'd for $\text{C}_{12}\text{H}_{26}^{79}\text{BrO}_2\text{Si}$: 309.0885], 311.0866 [(M+H) $^+$]; calc'd for $\text{C}_{12}\text{H}_{26}^{81}\text{BrO}_2\text{Si}$: 311.0865]

A 100 mL round-bottomed flask was charged with 25.3 g (81.9 mmol) of the bromoketone and 16.9 mL (98.3 mmol) of triethylphosphite and then fitted with a short path condenser under nitrogen atmosphere. The mixture was heated at 131°C for 2.5 h while collecting approx. 6 mL of bromoethane in the distillate flask. The product was then vacuum distilled ($130^{\circ}\text{C}/750$ mmHg) to yield **7** (30.0 g, > 99% yield) as a colorless oil: IR(neat) 2958 (s), 2930 (s), 2902 (s), 2857 (s), 1709 (s), 1465 (m), 1393 (m), 1365 (m), 1256 (s), 1099 (s), 1032 (s), 839(s) cm^{-1} ; ^1H NMR (300MHz, CDCl_3) δ 4.12 (spt, $J = 4.5$ Hz, 2 H), 3.53 (s, 2 H), 3.18 (d, $J = 21$ Hz, 2 H), 1.29 (t, $J = 6$ Hz, 3 H), 1.10 (s, 6 H), 0.83 (s, 9 H), -0.01 (s, 6H); ^{13}C NMR (75MHz, CDCl_3) δ 207.0, 70.3, 62.5, 50.7, 37.5 (d, $J = 135$ Hz), 26.0, 21.4, 18.3, 16.5, -5.5; high resolution mass spectrometry (EI) m/z 367.2077 [(M+H) $^+$]; calc'd for $\text{C}_{16}\text{H}_{36}\text{O}_5\text{PSi}$: 367.2070]

Synthesis of 5. A 100 mL round-bottomed flask was charged with 530 mg of 60% NaH in mineral oil then 9 mL of hexanes was added. The resulting slurry was stirred well for 20 min. After removing most of the hexanes via syringe, the residual solvent was evaporated under a stream of nitrogen in order to obtain approximately 365 mg (15.2 mmol) of the oil free NaH. At this point, 10 mL of THF was added to the flask and the slurry cooled using an acetone/ice bath. A solution of **7** in 7 mL THF was added via cannula and then an additional 2 mL of THF used to ensure complete transfer. After 3 min a solution of **8** in 16 mL of THF was added via cannula, portion wise over 4 min. An additional 3 mL of THF was used to ensure complete transfer in this case. Immediately afterward, the white slurry had become a pale yellow suspension and upon removal of the cold bath gas evolution was seen. The cold bath was then replaced briefly and again removed and the reaction allowed to stir and warm over 3 h. The reaction was then carefully quenched with 50 mL water and extracted with ethyl ether (3x70 mL). The organic layer washed with brine, dried over MgSO₄ and concentrated *in vacuo* to afford 9.4 g of the crude product. Chromatography through silica gel, slurry-packed in 5% ethyl acetate in hexanes, using 14% ethyl acetate in hexanes as eluant provided the enone furan (2735 mg, 83% yield from **8**) as a pale gold oil: IR(neat) 3538 (w), 3371 (w), 3132 (w), 2958 (s), 2930 (s), 2885 (s), 2857 (s), 1689(s), 1625 (s), 1502 (w), 1465 (m), 1393 (m), 1362 (m), 1105 (s), 837 (s) cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 7.34 (s, 1 H), 7.22 (s, 1 H), 6.89 (dt, J = 15 Hz, J = 6 Hz, 1 H), 6.52 (d, J = 15 Hz, 1 H), 3.58 (s, 2 H), 2.58 (t, J = 6 Hz, 2 H), 2.45 (qtr, J = 6 Hz, 2 H), 1.09 (s, 6 h), 0.85 (s, 9 H), 0.01 (s, 6 H); ¹³C NMR (75MHz, CDCl₃) δ 203.5, 145.6, 143.1, 139.2, 126.0, 124.1, 111.0, 69.8, 48.6, 33.1, 26.0, 23.8, 21.5, 18.4, -5.4; high resolution mass spectrometry (EI) *m/z* 337.2199 [(M+H)⁺; calc'd for C₁₉H₃₃O₃Si: 337.219899]

A 250 mL round-bottomed flask was charged with 1935 mg (21.6 mmol) copper(I) cyanide and placed under vacuum for 10 min. The flask was then backfilled with nitrogen. The flask was flushed with argon before adding 48 mL of THF. The slurry was cooled to -78°C and treated, over 8 min, with 28.4 mL (42.6 mmol) of a methyllithium solution (Aldrich, 1.5M solution, complex with lithium bromide). Once the addition was complete, the cold bath was removed and then replaced after 10 min. After allowing the reaction mixture to cool over 12 min, 2646 mg (17.55 mmol) of TBSCl in 4 mL THF was added using a syringe that was subsequently rinsed with 2 mL THF. To this resulting mixture 2735 mg (8.14 mmol) of the enone furan in 5 mL THF was immediately added. An additional 2 mL of THF was used to ensure complete transfer. The reaction was allowed to warm slowly over 12 h then diluted with 90 mL of ethyl ether, transferred to a separatory funnel, carefully quenched with 75 mL of a phosphate buffer solution (Fisher Scientific, 0.05M, pH=7) and washed with brine. The aqueous layer was vacuum filtered through Celite 545 (Fischer), the residue washed with water and ethyl ether and the filtrate extracted with ethyl ether (2x60 mL). The combined organic extracts were dried over MgSO₄, concentrated *in vacuo* to afford 7.5 g of the crude product that was then chromatographed through silica gel, slurry-packed in 1% triethylamine in hexanes, using 5% ethyl ether in hexanes to give **VIII** (3309 mg, 91% yield) as a colorless oil: IR(neat) 3548 (w), 2958 (s), 2930 (s), 2857 (s), 1662 (m), 1502 (w), 1461(m), 1359 (m), 1342(m), 1099 (s), 940 (m), 836 (s) cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 7.32 (s, 1 H), 7.18 (s, 1 H), 6.26 (s, 1 H), 4.28 (d, J = 9.9 Hz, 1 H), 3.42 (d, J = 9 Hz, 1 H), 3.39 (d, J = 9 Hz, 1 H), 2.49 (m, J = 7.7 Hz, 1 H), 2.37 (t, J = 8.1 Hz, 2 H), 1.46 (m, J=7.7 Hz, 2 H), 1.00 (s, 3 H), 0.99 (s, 3 H), 0.95 (s, 9 H), 0.92 (d, J= 6.6 Hz, 3 H), 0.88 (s, 9 h), 0.13 (s, 3 H), 0.12 (s, 3 H)

0.01 (s, 6 H); ^{13}C NMR (75MHz, CDCl_3) δ 153.8, 142.7, 139.0, 125.7, 112.4, 111.4, 69.7, 42.2, 38.6, 29.5, 26.7, 26.1, 24.0, 22.8, 21.6, 19.4, 18.5, -2.7, -3.2, -5.2; high resolution mass spectrometry (EI) m/z 466.3290 $[(\text{M})^+]$; calc'd for $\text{C}_{26}\text{H}_{50}\text{O}_3\text{Si}_2$: 466.3299]

Synthesis of 3. Constant Current Experiment To a 250 mL 3-neck round-bottomed flask under nitrogen was added 1.537 g (3.44 mmol) **5**, 110 mL of CH_2Cl_2 , 28 mL anhydrous MeOH, 2.0 mL (17.2 mmol) 2,6 lutidine and 6.160 g (57.8 mmol) of LiClO_4 . The reaction flask was then fitted with a RVC (ca. 1 cm^3) carbon anode and a carbon rod cathode (6.5 mm diam) and sonicated under nitrogen for 5 min. A constant current of 15.3 mA was then applied to the solution until a total of 736 C (2.2 F/mol) of charge had been passed (about 13.5 h). At this point the oxidation was complete as indicated by thin layer chromatography. *p*-Toluenesulfonic acid monohydrate (4.98 g 26.2 mmol) was then added to the flask and the mixture stirred for an additional 4.5 h. The reaction was diluted with 500 mL of ethyl ether, washed with water (2x130 mL) and brine, and then dried over MgSO_4 . The crude mixture was then concentrated *in vacuo* to afford 1.7 g of crude oil. Chromatography through silica gel using 1:2 ethyl acetate in hexanes provided **3** (716 mg, 88% yield) as a yellow oil: IR(neat) 3473 (s, br), 2963 (s), 2968 (s), 2857 (s), 1768 (w), 1707 (s), 1504 (w), 1463(m), 1379 (m), 1364(m), 1208 (w), 1108(w), 1052 (s), 1032 (s), 726 (w), cm^{-1} ; ^1H NMR (300MHz, CDCl_3) δ 7.21 (s, 1 H), 6.20 (s, 1 H), 3.87 (d, $J = 7$ Hz, 1 H), 3.73 (A of ABX, $J_{\text{AB}} = 11.4$ Hz, $J_{\text{AX}} = 6.6$ Hz, 1 H), 3.56 (B of ABX, $J_{\text{BA}} = 11.7$ Hz, $J_{\text{BX}} = 7.4$ Hz, 1 H), 2.59 (t, $J = 7.1$ Hz, 1 H), 2.47 (m, 2 H), 2.23 (m, 1 H), 1.94 (m, 1 H), 1.49 (m, 1 H), 1.33 (s, 3 H), 1.27 (s, 3 H), 1.03 (d, $J = 7$ Hz, 3 H); ^{13}C NMR (75MHz, CDCl_3) δ 217.0, 148.2, 141.5, 118.9, 110.5, 69.7, 50.4, 48.9, 33.7, 29.5, 21.7, 21.4, 20.4, 20.3; high resolution mass spectrometry (EI) m/z 236.1418 $[(\text{M})^+]$; calc'd for $\text{C}_{14}\text{H}_{20}\text{O}_3$: 236.1412].

The Use of a 6-Volt Battery as the Power Supply: A 100 mL 3-neck round-bottomed flask under nitrogen was charged with 276 mg (0.618 mmol) **5** in a fashion identical to that described above. In this case, the reaction was attached to a 6-volt battery and current passed for 95 min. At that time, 645 mg (3.39 mmol) of *p*-toluenesulfonic acid monohydrate was added and the mixture was stirred 20 h. The product was isolated as described above to afford 120 mg (82%) of the bicyclic furan **3**.

Synthesis of 2. A 100 mL round-bottomed flask under nitrogen was charged with 3639 mg (13.9 mmol) of PPh_3 and 15 mL of CH_2Cl_2 . The mixture was stirred for 3 min before the addition of 1372 mg (20.2 mmol) of imidazole. After 20 min, 3557 mg (14.0 mmol) of I_2 was added portion wise over 25 min. After an additional 1 h, 1820 mg (7.70 mmol) of **3** in 12 mL of toluene was cannulated into the flask. An additional 7 mL of CH_2Cl_2 was used to ensure complete transfer. The reaction mixture was refluxed at 85°C for 18 h, allowed to cool (3 h), diluted with 110 mL of ethyl ether, transferred to a separatory funnel, and washed with 50 mL saturated aqueous NaHSO_4 . The aqueous layer was extracted with ethyl ether (80 mL) and then the combined organic layers were washed with 25 mL brine, dried over MgSO_4 and concentrated *in vacuo* to yield 20 g of the crude product. Chromatography through silica gel, slurry-packed in 1% triethylamine in hexanes, using 10% ethyl acetate in hexanes as eluant provided the iodo bicyclic furan (2318 mg, 87% yield) as an extremely pale brown oil: IR(neat) 3401 (w), 3148 (w), 3104 (w), 2963 (s), 2924 (s), 2851 (s), 1709 (s), 1631 (w), 1566 (w), 1502 (m), 1463(m), 1384 (m), 1362 (m), 1329 (w), 1306 (w), 1272 (w) 1231 (w), 1208

(m), 1130 (m), 1110 (m), 1049 (m), 951 (w), 884 (m), 730 (m) cm^{-1} ; ^1H NMR (300MHz, CDCl_3) δ 7.21 (s, 1 H), 6.19 (s, 1 H), 3.87 (d, $J = 7$ Hz, 1 H), 3.51 (d, $J = 10.5$ Hz, 1 H), 3.41 (d, $J = 10.5$ Hz, 1 H), 2.46 (m, 2 H), 2.30 (m, 1 H), 1.95 (m, 1 H), 1.51 (m, 1 H), 1.42 (m, 6 H), 1.04 (d, $J = 7$ Hz, 3 H); ^{13}C NMR (75MHz, CDCl_3) δ 211.0, 147.7, 141.5, 118.9, 110.5, 48.8, 48.4, 33.1, 29.0, 25.5, 25.3, 20.2, 20.1, 17.6; high resolution mass spectrometry (EI) m/z 346.0447 $[(\text{M})^+]$; calc'd for $\text{C}_{14}\text{H}_{19}\text{O}_2\text{I}$: 346.0430]

A 100 mL round-bottomed flask under nitrogen was charged with 818 mg (2.36 mmol) of the iodo furan, 30 mL of THF, and 16 mL of anhydrous MeOH. The mixture was stirred at ambient temperature and then the solution treated with 820 mg (4.81 mmol) of AgNO_3 , stirred for 8 h, and quenched with ca. 7 mL of saturated aqueous NaHSO_4 . The reaction mixture was filtered and the yellow precipitate was washed with 30 mL of ethyl ether. The filtrate was then washed with 25 mL water. The aqueous layer was extracted with CH_2Cl_2 (2x25 mL) and the combined organic extracts dried over MgSO_4 and concentrated *in vacuo* to yield **2** (594 mg, 99% crude yield, 2.7:1 mixture of acetals) as a clear light brown oil: IR(neat) 3452 (w), 2969 (s), 2930 (s), 2870 (s), 1736 (s), 1672 (w), 1447 (m), 1380 (m), 1363 (m), 1341 (m), 1304 (w), 1254 (w), 1189 (w), 1159 (w), 1100 (m), 1062 (m), 1026 (m), 990 (m), 960 (m), 874 (m), cm^{-1} ; ^1H NMR (300MHz, CDCl_3) δ 5.75 (s, 0.24 H), 5.54 (s, 0.76 H), 5.47 (s, 0.76 H), 5.44 (s, 0.24 H), 3.41 (s, 2.2 H), 3.30 (s, 0.8 H), 2.58 (d, $J = 14.4$ Hz, 1 H), 2.80 (d, $J = 14.1$ Hz, 0.74 Hz), 2.26 (d, $J = 14.1$ Hz, 0.26 H), 2.18 (t, $J = 13.5$ Hz, 1 H), 2.00 – 1.80 (m, 3 H), 1.54 (m, 1 H), 1.30 (s, 2.2H), 1.28 (s, 0.8 H), 1.18 (s, 0.8 H), 1.16 (s, 2.2 H), 1.10 (dd, $J = 12.6$ Hz, $J = 4$ Hz, 1 H), 1.04 (d, $J = 6.6$ Hz, 2.2 H), 1.02 (d, $J = 6.3$ Hz, 0.8 H); ^{13}C NMR (75MHz, CDCl_3) δ 222.1, 148.1, 118.5, 107.8, 90.8, 65.2, 55.5, 48.0, 45.2, 35.9, 32.7, 27.8, 27.0, 25.6, 18.9; high resolution mass spectrometry (EI) m/z 250.1562 $[(\text{M})^+]$; calc'd for $\text{C}_{15}\text{H}_{22}\text{O}_3$: 250.1569]

Synthesis of 10. To 340 mg (1.36 mmol) of the crude **2** was added 4.3 mL of THF. The solution was stirred under argon and cooled to -10°C . Treatment with 5 mmol (5 mL of 1.0 M solution in cyclohexane) of DIBAL-H and stirring for 25 min at the lower temperature was followed by a slow, careful quench with 2.5 mL of 0.5 M HCl and dilution with 4 mL of diethyl ether. The cooling bath was removed and the mixture was stirred for 20 min. The reaction was then filtered through a Celite pad, washed with diethyl ether, and concentrated overnight *in vacuo* to yield a single tricyclic unsaturated alcohol (252 mg, 83% crude yield) as white solid: IR(neat) 3466 (s, br), 3074 (m), 3020 (m), 2962 (s), 2946 (s), 2883 (s), 2683 (m), 1795 (w), 1671 (m), 1578 (m), 1460 (m), 1443 (m), 1359 (m), 1331 (m), 1135 (m), 1103 (s), 1076 (s), 1034 (s), 1009 (m), 827 (m), 685 (w) cm^{-1} ; ^1H NMR (300MHz, CDCl_3) δ 5.37 (d, $J = 1.5$ Hz, 1 H), 4.51 (t, $J = 14.9$ Hz, 2 H), 4.34 (d, $J = 5.4$ Hz, 1 H), 2.41 (dqrt, $J = 13.8$ Hz, $J = 2.1$ Hz, 1 H), 2.03 (tsept, $J = 13.8$ Hz, $J = 1.8$ Hz, 1 H), 1.85 (d, $J = 13.8$ Hz, 1 H), 1.74 (m, 3 H), 1.54 (d, $J = 13.8$ Hz, 1 H), 1.48 (s, b, 1 H), 1.18 (s, 3 H), 1.14 (d, $J = 5.4$ Hz, 3 H), 1.09 (s, 3 H), 1.05 (m, 1 H); ^{13}C NMR (75MHz, CDCl_3) δ 142.3, 116.3, 94.6, 83.8, 73.0, 60.6, 47.2, 39.7, 37.6, 32.3, 31.8, 26.8, 25.3, 22.7; high resolution mass spectrometry (EI) m/z 222.16084 $[(\text{M})^+]$; calc'd for $\text{C}_{14}\text{H}_{22}\text{O}_2$: 222.16198]

A 100 mL round-bottomed flask was charged with 200 mg (ca. 0.90 mmol) of crude unsaturated alcohol, 5 mL benzene, 93 mg (0.35 mmol) of 18-crown-6, 0.7 mL of reagent grade acetone and 2.2 mL of a phosphate buffer solution (Fisher Scientific, 0.05M, pH=7). The reaction was placed in an ice water bath and stirred for 5 min before adding 7.2 mL of an aqueous Oxone[®] solution (0.43 M in 4.0×10^{-4} M $\text{Na}_2[\text{EDTA}]$) via addition funnel over 8 min.

The stirring was continued and after 1h, the cooling bath was removed ($T_{\text{bath}} = 15^{\circ}\text{C}$) and the reaction monitored by thin layer chromatography. After 22 h, the pH was adjusted to ca. 7 by addition of 10 mL of 0.5 M KOH. After another 24.5 h, the clear, colorless reaction mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried over MgSO_4 , concentrated *in vacuo* to afford 280 mg of a crude product that was then chromatographed through silica gel using 25% diethyl ether in hexanes as eluant in order to provide **10** (158 mg, 64% yield from the iodo furan) as a white solid: IR(neat) 3479 (s, br), 2952 (s), 2866 (s), 1382 (m), 1364 (m), 1094 (s), 1069 (s), 1056 (s), 1031 (s) cm^{-1} ; ^1H NMR (600MHz, CDCl_3) δ 4.25 (t, $J = 4.8$ Hz, 1 H), 3.94 (d, $J = 10.8$ Hz, 1 H), 3.68 (d, $J = 10.8$ Hz, 1 H), 3.52 (s, 1 H), 2.04 (d, $J = 14.4$ Hz, 1 H), 2.02 (td, $J = 13.5$ Hz, $J = 4.2$ Hz, 1 H), 1.83 (dqrt, $J = 13.5$ Hz, $J = 3.3$ Hz, 1 H), 1.72 (m, 2 H), 1.63 (d, $J = 13.8$ Hz, 1 H), 1.62 (m, 1 H), 1.52 (d, b, $J = 6$ Hz, 1 H), 1.25 (dqrt, $J = 14.4$ Hz, $J = 3.5$ Hz, 1 H), 1.18 (d, $J = 6$ Hz, 3 H), 1.13 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (75MHz, CDCl_3) δ 86.4, 82.9, 68.1, 65.8, 61.7, 56.4, 44.1, 39.0, 3.5, 31.8, 31.5, 26.5, 25.5, 22.2; high resolution mass spectrometry (EI) m/z 238.1562 $[(\text{M})^+]$; calc'd for $\text{C}_{14}\text{H}_{22}\text{O}_3$: 238.1569]

Synthesis of 11 A solution of **10** (125 mg, 0.524 mmol) in 0.9 mL of THF at ambient temperature was treated with 1.4 mL LiBEt_3H (1.0 M in THF) over 4 min and then stirred for 2 h. At that point, an additional 0.3 mL of the LiBEt_3H solution was added. After an additional 1 h, the reaction was cooled in an ice water bath and treated with 0.15 mL of water. The mixture was stirred for 35 min. The ice bath was then refreshed and then 0.65 mL of 30% hydrogen peroxide added to the reaction in a dropwise fashion. The mixture was allowed to warm over 80 min, diluted with 10 mL of ethyl acetate, treated with 8.5 mL of saturated aqueous NaHCO_3 and after 15 min transferred to a separatory funnel. The mixture was extracted with ethyl acetate (2 x 15 mL) and CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over MgSO_4 , concentrated *in vacuo* to afford 155 mg of a crude product that was chromatographed through silica gel using 25% ethyl ether in hexanes as eluant in order to provide the diol (104 mg, 83% yield) as a pale yellow solid: IR(neat) 3317 (s, br), 2958 (s), 2924 (s), 2877 (s), 1464 (m), 1455 (m), 1370 (m), 1351 (m), 1283 (w), 1219 (w), 1161 (m), 1100 (s), 1072 (s), 1023 (s), 995 (m) cm^{-1} ; ^1H NMR (300MHz, CDCl_3) δ 4.36 (s, b, 1 H), 3.85 (td, $J = 8.1$ Hz, $J = 7.2$ Hz, 1 H), 3.76 (tt, $J = 8.6$ Hz, 1 H), 3.65 (d, $J = 4.2$ Hz, 1 H), 3.10 (s, b, 1 H), 2.25 (qtr, $J = 1.9$ Hz, 1 H), 2.18 (d, $J = 14.1$ Hz, 1 H), 2.10 – 1.77 (m, 5 H), 1.25 (m, 1 H), 1.09 (s, 3 H), 1.09 (d, $J = 6.3$ Hz, 3 H), 1.00 (s, 3H); ^{13}C NMR (75MHz, CDCl_3) δ 90.2, 85.5, 74.8, 63.6, 49.7, 45.5, 40.2, 37.9, 30.6, 30.3, 26.8, 26.2, 24.5, 22.7; high resolution mass spectrometry (EI) m/z 240.1732 $[(\text{M})^+]$; calc'd for $\text{C}_{14}\text{H}_{24}\text{O}_3$: 240.1725]

A solution of the diol (63.0 mg, 0.26 mmol) in 0.75 mL of CHCl_3 under argon atmosphere was cooled to 5°C and treated with 63 μL (0.78 mmol) of freshly distilled pyridine. After stirring for ca. 5 min, 159 mg (0.832 mmol) of recrystallized tosyl chloride was added at once and the mixture stirred at 5°C for 18 h. The mixture was then loaded directly onto silica gel column that had been slurry-packed using a 25% diethyl ether in pentane solution. The reaction flask was rinsed with CHCl_3 and gradient elution (30% to 80% ethyl ether in pentane to 100% ethyl ether) was used to provide the mono tosylate (41 mg, 38 % yield) as a white solid along with the diol (37 mg, 59% recovery). After 4 cycles in this manner the combined yield was 85.2 mg (83 %) along with 6.7 mg (11%) unreacted diol. IR(neat) 3538 (m, br), 2964 (s), 2928 (s), 2874 (s), 2863 (s), 1599 (w), 1456 (m), 1358 (m), 1256 (w), 1189 (m), 1176 (s), 1098 (w), 977 (m), 964 (m), 876 (s), 833 (m), 666 (s) cm^{-1} ; ^1H

NMR (300MHz, CDCl₃) δ 7.82 (d, J = 8.4 Hz, 2 H), 7.34 (d, J = 7.8 Hz, 2 H), 4.83, (d, J = 6.3 Hz, 1 H), 3.95 (qrt, J = 8.2 Hz, 1 H), 3.82 (td, J = 9.9 Hz, J = 8.2 Hz, 1 H), 2.45 (s, 3 H), 2.21 (m, 1 H), 1.99 – 1.77 (m, 5 H), 1.70 – 1.43 (m, 4 H), 1.25 (s, b, 1 H), 1.09 (d, J = 6.3 Hz, 3 H), 1.01 (s, 3 H), 0.78 (s, 3 H); ¹³C NMR (75MHz, CDCl₃) δ 144.9, 133.9, 129.9, 128.3, 91.2, 90.9, 79.2, 63.4, 53.7, 43.9, 38.1, 37.0, 32.4, 32.0, 31.7, 30.7, 26.9, 21.9, 21.8; high resolution mass spectrometry (EI) m/z 222.1622 [(M)⁺ - HOSO₂C₇H₈; calc'd for C₁₄H₂₂O₂: 222.1620]

A solution of the tosylate (42.0 mg, 0.106 mmol) in 1.2 mL DMF was treated with 120 μ L (0.80 mmol) DBU and heated at 130°C for 1 h. Chromatography through a silica gel column that was slurry-packed in 10% ethyl ether in hexanes and gradient eluted (10% to 30% ethyl ether in hexanes) provided **11** (17.2 mg, 73% yield) as a white solid: IR(neat) 3871 (w), 3742 (w), 3421 (s, br), 2974 (s), 2950 (s), 2930 (s), 2882 (s), 2855 (s), 2680 (w), 1659 (w), 1556 (w), 1488 (m), 1455 (m), 1394 (m), 1357 (m), 1346 (m), 1288 (m), 1189 (m), 1112 (m), 1085 (m), 1044 (m), 894 (m), 843 (w), 780 (w), 697 (m), 657 (m) cm⁻¹; ¹H NMR (300MHz, CDCl₃) δ 5.50 (s, 1 H), 3.85 (d, 2H), 2.61 (pent, J = 6 Hz, 2 H), 2.08 (td, J = 13.5 Hz, J = 2.7 Hz, 1 H), 2.03 (m, 1H), 2.00 (d, J = 13.5 Hz, 1 H), 1.91 (m, J = 3.9 Hz, 1 H), 1.73, (tt, J = 14.4 Hz, J = 4.8 Hz, 1 H), 1.59 (d, J = 13.5 Hz, 1 H), 1.53 – 1.43 (m, 2 H), 1.16 (d, J = 7.5 Hz, 3 H), 1.14 (s, 3 h), 1.07 (s, 3 H); ¹³C NMR (75MHz, CDCl₃) δ 141.7, 141.0, 93.5, 77.4, 62.8, 45.2, 41.9, 38.3, 30.5, 30.4, 30.3, 29.9, 27.9, 20.4; high resolution mass spectrometry (EI) m/z 240.1632 [(M)⁺; calc'd for C₁₄H₂₂O₂: 222.1620]

Note: The ¹H NMR spectra of **11** is identical to the corresponding spectra in the previously reported synthesis

300 MHz ^1H spectra of compound 7

75 MHz ¹³C spectra of compound 7

300 MHz ^1H spectra of compound 5

75 MHz ^{13}C spectra of compound 3

300 MHz ¹H spectra of compound 2

75 MHz ^{13}C spectra of compound 2

600 MHz ^1H spectra of compound 10

300 MHz ^1H spectra of compound 11

75 MHz ^{13}C spectra of compound 11