Investigation of a Dialkylation Approach for Enantioselective Construction of Vicinal Quaternary Stereocenters

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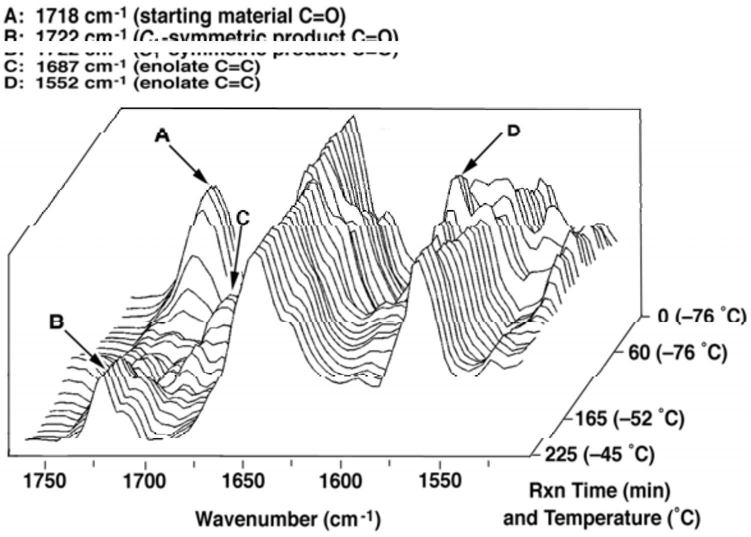
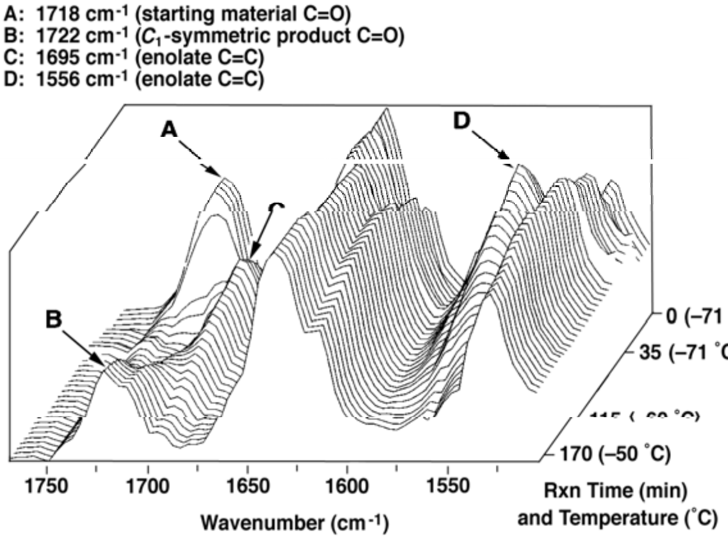
Supporting Information

A. IR Data for the NaHMDS-Mediated Dialkylation:



NaHMDS was added at –76 ˚C and the reaction was stirred at –76 ˚C for 1h. Ditriflate **2** then was added and the reaction was allowed to slowly warm from –71 ˚C to –50 ˚C over 3 h.

B. IR Data from the KHMDS-Mediated Dialkylation:



KHMDS was added at –71 ˚C and the reaction was stirred at –71 ˚C for 1h. Ditriflate **2** then was added and the reaction was allowed to slowly warm from –71 ˚C to –50 ˚C over 2 h.

C. Experimental Procedures

Representative Procedure for Experiments Summarized in Table 2. Nitrogen was bubbled through a solution of dihydroisoindigo **1** (0.159 g, 0.358 mmol) and HMPA (0.36 mL) for 1 h. The solution was cooled to –40 ˚C, LHMDS (1.0 M/THF, 0.82 mL, 0.82 mmol) was added, and the resulting dark green solution was stirred at –40 ˚C for 1h. Ditriflate **2** (0.176 g, 0.413 mmol) then was added and stirring was continued at –40 ˚C for 16h. The resulting red solution was diluted with Et_2O (20 mL), washed sequentially with H_2O (5×5 mL) and brine (5 mL), dried ($MgSO_4$), filtered through a plug of silica gel and the eluent was concentrated *in vacuo* to give a crude red oil. Analysis of the crude product mixture by HPLC (Alltima silica column with guard, 98:2 hexanes-isopropanol, flow rate = 1 mL/min, UV detection at 254 nm) revealed a product ratio of **3**:**4**:**5** = 101:13:1.

Preparative Scale Dialkylation Using Conditions Optimized for Formation of 3. Nitrogen was bubbled through a solution of dihydroisoindigo **1** (3.14 g, 7.06 mmol) and HMPA (7.2 mL) for 1 h. The solution was cooled to –40 ˚C, LHMDS (1.0 M/THF, 16.5 mL, 16.5 mmol) was added, and the resulting dark green solution was stirred at –40 ˚C for

1h. Ditriflate **2** (3.81 g, 8.93 mmol) then was added and stirring was continued at –40 ˚C for 14h. The resulting red solution was diluted with Et_2O (400 mL), washed sequentially with H_2O (3×100 mL) and brine (50 mL), dried ($MgSO_4$), filtered through a plug of silica gel and the eluent was concentrated *in vacuo* to give a crude red oil. Purification of this crude product by flash chromatography on silica gel (9:1 hexanes-EtOAc) gave 2.34 g (58%) of C_2–symmetric product **3** as a pale yellow solid and 0.481 g (12%) of C_1–symmetric product **4** as a colorless solid.[1]

Representative Procedure for Experiments Summarized in Table 3. Nitrogen was bubbled through a solution of dihydroisoindigo **1** (0.163 g, 0.367 mmol), 18-crown-6 (0.489 g, 1.85 mmol) and THF (1.2 mL) for 1 h. The solution was cooled to –40 ˚C, KHMDS (0.176 g, 0.882 mmol) was added, and the resulting dark green solution was stirred at –40 ˚C for 1.5 h. Ditriflate **2** (0.177 g, 0.415 mmol) then was adde, and stirring was continued at –40 ˚C for 17h. The resulting red solution was diluted with Et_2O (20 mL), washed sequentially with H_2O (5×5 mL) and brine (5 mL), dried ($MgSO_4$), filtered through a plug of silica gel and the eluent was concentrated *in vacuo* to give a crude red oil. Analysis of the crude product mixture by HPLC (Alltima silica column with guard, 98:2 hexanes-isopropanol, flow rate = 1 mL/min, UV detection at 254 nm) revealed a product ratio of **4**:**3**:**5** = 8.6:2.8:1.

(4*S*,5*S*)-Trifluoromethanesulfonic acid-2,2-dimethyl-5-(triisopropylsiloxy-methyl)-[1,3]dioxolan-4-yl methyl ester (6). Trifluoromethanesulfonic anhydride (1.0 mL, 1.7 g, 6.0 mmol, freshly distilled from P_2O_5) was added to a colorless solution of (4*S*,5*S*)-[2,2-dimethyl-5-(triisopropylsiloxymethyl)-[1,3]dioxolan-4-yl]-methanol (1.58 g, 4.96 mmol),[1] *i*-Pr_2NEt (1.5 mL, 1.1 g, 8.6 mmol) and Et_2O (60 mL) at 0 ˚C. The resulting yellow mixture was stirred at 0 ˚C for 30 min, then filtered. The filtrant was rinsed with Et_2O (100 mL), and the combined filtrate was concentrated *in vacuo* to give a yellow oil. Purification of this crude product by flash chromatography on silica gel (9:1 hexanes-EtOAc) afforded 1.98 g (89%) of triflate **6** as a pale yellow oil: $[\alpha]^{24}_{D}$ –0.7, $[\alpha]^{24}_{577}$ –1.4, $[\alpha]^{24}_{546}$ +1.0, $[\alpha]^{24}_{435}$ –6.2, $[\alpha]^{24}_{405}$ –0.3, (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 4.75 (dd, *J* = 10.7, 2.6 Hz, 1H), 4.52 (dd, *J* = 10.7, 5.4 Hz, 1H), 4.23 (ddd, *J* = 7.9, 5.4, 2.6 Hz, 1H), 4.0 (dd, *J* = 9.8, 4.0 Hz, 1H), 3.93 (ddd, *J* = 7.7, 7.7, 4.1 Hz, 1H), 3.75 (dd, *J* = 9.8, 7.5 Hz, 1H), 1.41 (s, 3H), 1.40 (s, 3H), 1.15–1.05 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 118.6 (q, $J_{C\text{-}F}$ = 320 Hz), 110.5, 77.4, 76.2, 75.5, 64.1, 26.9, 26.6, 17.8, 11.8; IR (film)

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[1] Taunton, J.; Collins, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10412-10422.

2945, 2894, 2869, 1464, 1418, 1384, 1373, 1246, 1213, 1149, 1098, 1069, 954, 883, 802, 777 cm^{-1}; HRMS (CI) *m/z* 451.1810 (451.1797 calcd for $C_{17}H_{33}F_3O_6SSi$, M+H).

Monoalkylation Using Less Selective Conditions. Nitrogen was bubbled through a solution of dihydroisoindigo **1** (1.34 g, 3.01 mmol) and DMPU (10 mL) at 0 ˚C for 1 h. LHMDS (0.467 g, 2.79 mmol, plus 5.0 mL, 1.0 M/THF, 5.0 mmol for a total of 7.79 mmol) was added, and the resulting dark green solution was stirred at 0 ˚C for 1 h. Triflate **6** (0.50 g, 1.1 mmol) then was added, and stirring was continued at 0 ˚C for 30 min. The reaction was then diluted with Et_2O (25 mL) and washed with brine (4×25 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a dark red oil. Purification of this crude product first by flash chromatography on silica gel (9:1 hexanes-EtOAc) and then by prep TLC (3:1 hexanes-EtOAc) gave 0.178 g (22%) of the major epimer of **7**, 0.139 g (17%) of the minor epimer of **7**, 0.078 g (9%) of the major epimer of **8** and 0.033 g (4%) of the minor epimer of **8**, all as colorless oils. Major epimer of **7**: $[\alpha]^{24}_{D}$ +104.2, $[\alpha]^{24}_{577}$ +11.5, $[\alpha]^{24}_{546}$ +125.4, $[\alpha]^{24}_{435}$ +224.0, $[\alpha]^{24}_{405}$ +351.2, (*c* 1.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.27 (m, 10H), 7.12–7.10 (m, 2H), 7.03–6.96 (m, 2H), 6.76–6.71 (m, 2H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 1H), 5.23 (d, *J* = 15.7 Hz, 1H), 4.96 (d, *J* = 15.7 Hz, 1H), 4.85 (d, *J* = 15.7 Hz, 1H), 4.69 (d, *J* = 15.8 Hz, 1H), 4.05 (s, 1H), 3.98 (ddd, *J* = 9.5, 6.9, 2.5 Hz, 1H), 3.86–3.79 (m, 3H), 3.33 (dd, *J* = 14.4, 9.8 Hz, 1H), 2.71 (dd, *J* = 14.5, 2.6 Hz, 1H), 1.19–1.06 (m, 24H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 175.2, 143.4, 142.8, 135.6, 135.2, 129.0, 128.6, 128.5, 128.3, 127.7, 127.5, 127.4, 127.3, 124.8, 124.3, 124.2, 122.0, 121.9, 108.7, 108.5, 108.4, 82.1, 74.9, 63.6, 53.0, 50.7, 43.8, 43.7, 38.1, 26.8, 26.7, 18.0, 11.9; IR (film) 2941, 2865, 1709, 1612, 1488, 1466, 1365, 1174 cm^{-1}; HRMS (ES) *m/z* 767.3845 (767.3856 calcd for $C_{46}H_{56}N_2O_5SiNa$, M+Na). Minor epimer of **7**: $[\alpha]^{24}_{D}$ –29.4, $[\alpha]^{24}_{577}$ –4.6, $[\alpha]^{24}_{546}$ –32.7, $[\alpha]^{24}_{435}$ –35.9, $[\alpha]^{24}_{405}$ –98.1, (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.12 (m, 8H), 7.05–6.88 (m, 6H), 6.76 (t, *J* = 7.4 Hz, 1H), 6.62–6.57 (m, 3H), 5.03 (d, *J* = 15.8 Hz, 1H), 4.89–4.81 (m, 2H), 4.57 (d, *J* = 15.8 H, 1H), 4.31 (s, 1H), 4.08–4.04 (m, 1H), 3.89–3.83 (m, 2H), 3.76–3.72 (m, 1H), 3.07 (dd, *J* = 13.0, 13.0 Hz, 1H), 2.57 (dd, *J* = 13.7, 1.8 Hz, 1H), 1.19 (s, 3H), 1.18 (s, 3H), 1.13–1.03 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 174.0, 144.2, 143.7, 135.8, 135.6, 129.6, 128.5, 128.5, 128.3, 127.1, 127.1, 127.0, 126.9, 125.2, 125.0, 124.2, 121.9, 121.7, 109.2, 109.1, 109.1, 81.9, 76.0, 64.0, 52.9, 50.1, 43.9, 43.7, 37.4, 27.0, 26.9, 17.9, 11.8; IR (film) 2942, 2856, 1722, 1715, 1612, 1488, 1467, 1455, 1381, 1366, 1103 cm^{-1}; HRMS (ES) *m/z* 767.3876 (767.3856 calcd for $C_{46}H_{56}N_2O_5SiNa$, M+Na). Major epimer of **8**: $[\alpha]^{24}_{D}$ –93.1, $[\alpha]^{24}_{577}$ –15.9, $[\alpha]^{24}_{546}$ –107.9, $[\alpha]^{24}_{435}$ –211.8, $[\alpha]^{24}_{405}$ –305.0, (*c* 0.8, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.33

(m, 2H), 7.31–7.22 (m, 7H), 7.18-7.11 (m, 2H), 7.01–6.91 (m, 3H), 6.74 (ddd, *J* = 7.6, 7.6, 0.9 Hz, 1H), 6.59 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 6.38 (dd, *J* = 7.9, 0.7 Hz, 1H), 5.07 (d, *J* = 15.9 Hz, 1H), 4.94 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 4.65 (d, *J* = 15.9 Hz, 1H), 3.96 (s, 1H), 3.84 (ddd, *J* = 8.4, 4.7, 3.8 Hz, 1H), 3.74 (dd, *J* = 10.8, 3.8 Hz, 1H), 3.68 (dd, *J* = 10.7, 4.8 Hz, 1H), 3.61 (dd, *J* = 14.1, 1.9 Hz, 1H), 3.52 (ddd, *J* = 11.1, 7.3, 1.9 Hz, 1H), 2.58 (dd, *J* = 14.2, 11.1, Hz, 1H), 1.39 (s, 3H), 1.11(s, 3H), 1.09–0.99 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.0, 175.3, 143.6, 143.3, 135.8, 135.6, 128.6, 128.5, 128.3, 128.3, 127.7, 127.5, 127.3, 127.3, 126.8, 125.1, 124.4, 123.8, 122.0, 122.0, 109.1, 108.9, 108.5, 81.6, 74.7, 63.1, 53.3, 49.5, 44.3, 43.8, 37.5, 27.1, 26.9, 18.0, 11.8; IR (film) 2940, 2864, 1718, 1709, 1611, 1488, 1466, 1381, 1364, 1169, 1102 cm^{-1}; HRMS (ES) *m/z* 767.3828 (767.3856 calcd for $C_{46}H_{56}N_2O_5SiNa$, M+Na). Minor epimer of **8**: $[\alpha]^{24}_{D}$ –6.2, $[\alpha]^{24}_{577}$ +21.5, $[\alpha]^{24}_{546}$ +8.6, $[\alpha]^{24}_{435}$ –11.6, $[\alpha]^{24}_{405}$ –3.9, (*c* 0.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.14 (m, 10H), 6.94–6.88 (m, 2H), 6.83–6.80 (m, 3H), 6.66–6.62 (m, 1H), 6.57 (dd, *J* = 7.8, 5.0 Hz, 2H), 4.97 (d, *J* = 15.8 Hz, 1H), 4.82 (s, 2H), 4.54 (d, *J* = 15.8 Hz, 1H), 4.13 (s, 1H), 3.84–3.81 (m, 3H), 3.63–3.60 (m, 1H), 3.05–2.98 (m, 1H), 2.58 (d, *J* = 13.1 Hz, 1H), 1.40 (s, 3H), 1.16 (s, 3H), 1.10–1.00 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.9, 173.6, 144.1, 135.9, 135.4, 128.4, 128.4, 128.3, 127.0, 126.9, 126.8, 125.4, 124.9, 122.9, 121.8, 121.6, 109.3, 109.0, 109.0, 81.2, 75.4, 63.9, 52.6, 51.0, 44.5, 43.8, 39.0, 27.3, 27.0, 18.2, 12.1; IR (film) 2941, 2865, 1721, 1714, 1612, 1488, 1468, 1456, 1382, 1361, 1252, 1170, 1102 cm^{-1}; HRMS (ES) *m/z* 767.3876 (767.3856 calcd for $C_{46}H_{56}N_2O_5SiNa$, M+Na).

Monoalkylation Using Conditions Selective for Formation of 7. Nitrogen was bubbled through a solution of dihydroisoindigo **1** (1.38 g, 3.11 mmol), HMPA (3.0 mL) and THF (7.0 mL) at 0 °C for 45 min. The solution was cooled to –40 °C, LHMDS (1.27 g, 7.59 mmol) was added, and the resulting dark green solution was stirred at –40 °C for 1 h. A solution of triflate **6** (0.434 g, 0.963 mmol) in THF (0.25 mL) then was then added, and stirring was continued at –40 °C for 30 min. The reaction was then diluted with Et_2O (25 mL) and washed sequentially with H_2O (4×10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered through a plug of silica and concentrated *in vacuo* to give a dark red oil. Analysis of the crude product mixture by HPLC (Alltima silica column with guard, 98.5:1.5 hexanes-isopropanol, flow rate = 1 mL/min, UV detection at 254 nm) revealed a product ratio of **7**:**8** = 19:1. Purification of the crude product by flash chromatography on silica gel (9:1 hexanes-EtOAc) gave 0.218 g (30%) of the major epimer of **7** plus 0.190 g (26%) of the minor epimer of **7**.