Asymmetric Synthesis of the CBI Alkylation Subunit of the CC-1065 and Duocarmycin Analogs

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Dedicated to Professor E. J. Corey in recognition of his significant contributions to the art of organic synthesis

Abstract: Two exceptionally short and effective asymmetric syntheses of N-BOC-CBI are detailed based on an asymmetric hydroboration (80% ee) or Jacobsen epoxidation (92% ee) of a 3,4-dihydrobenzo[*f*]quinoline followed by direct, transannular spirocyclization for introduction of the activated cyclopropane.

CC-1065 (**1**)[1] and the duocarmycins (**2–3**)[2] represent the parent members of a class of potent antitumor antibiotics that derive their biological properties through a sequence selective alkylation of duplex DNA (Figure 1).[3] In the course of studies to define fundamental relationships between their structure, chemical reactivity, and biological properties, the 1,2,9,9a-tetrahydrocyclopropa[*c*]benzo[*e*]-indol-4-one (CBI) analog of the authentic alkylation subunits has been found to possess especially interesting properties.[4] The natural enantiomers of the CBI analogs have been shown to be 4× more stable, 4× more potent, and synthetically more accessible than the corresponding agents incorporating the natural CPI alkylation subunit of CC-1065.[4–11] In addition, they alkylate DNA with an unaltered sequence selectivity at an enhanced rate and with a greater efficiency than the corresponding CPI analogs indicating that they possess characteristics that make them especially attractive to pursue.[9–11] Herein we report two asymmetric syntheses of CBI potentially applicable to the natural and related analog alkylation subunits employing an asymmetric hydroboration[12] (80% ee) or Jacobsen epoxidation[13] (92% ee) of N-BOC-6-benzyloxy-3,4-dihydro-benzo[*f*]quinoline followed by a direct transannular spirocyclization of the resulting alcohol for introduction of the activated cyclopropane.

The approaches were first examined with racemic N-BOC-CBI (Scheme 1). N-Alkylation of **4**[6] with **5**[14] (1.2 equiv NaH, DMF, 25 °C, 30 min, 90%) followed by Pd(0)-catalyzed Stille cross-coupling of **6**[15] (0.2 equiv $(Ph_3P)_4Pd$, toluene, 50 °C, 1.5 h, 91%) cleanly provided **7**.[15] Subsequent epoxidation with *m*-CPBA (1.5 equiv, CH_2Cl_2, –78 to –30 °C, 2 h, 84%) followed by regiospecific Dibal-H reductive ring opening of the epoxide **8**[15] (2 equiv Dibal-H, THF, –78 to –30 °C, 1 h, 80%) provided exclusively the key alcohol **9**,[15] mp 116–117 °C, derived from hydride delivery to the benzylic position. Alternatively, hydroboration–oxidation of **7** (1.0 equiv BH_3–SMe_2, THF, 0 °C, 2 h; $NaBO_3$–$4H_2O$) provided predominantly **9** (71%) and a small amount of the isomeric hydroboration product (10%). Hydrogenolysis of the benzyl ether (cat 10% Pd–C, 1 atm H_2, CH_3OH, 25 °C, 30 min, 97%) and direct transannular Ar-3' spirocyclization upon Mitsunobu activation of the secondary alcohol[15] (mp 172 °C, 3 equiv ADDP, 3 equiv Bu_3P, toluene, 50 °C, 1 h, 72%)

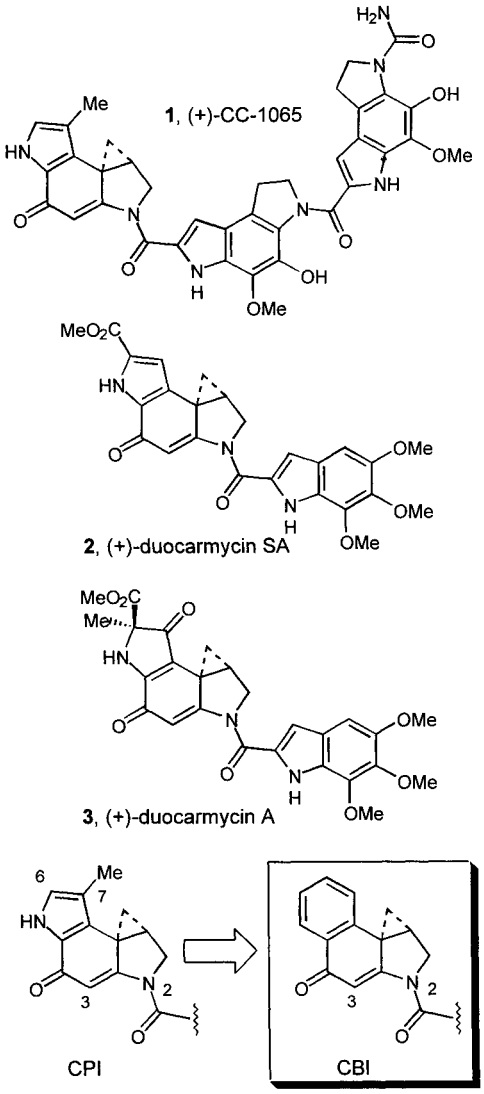
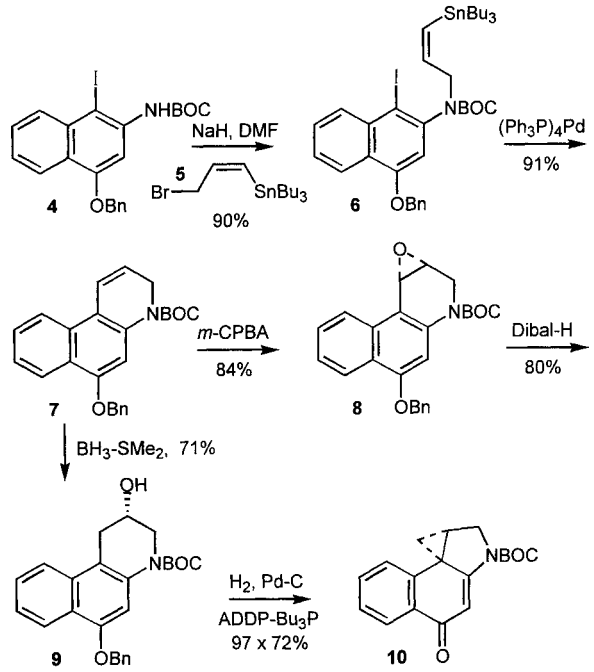


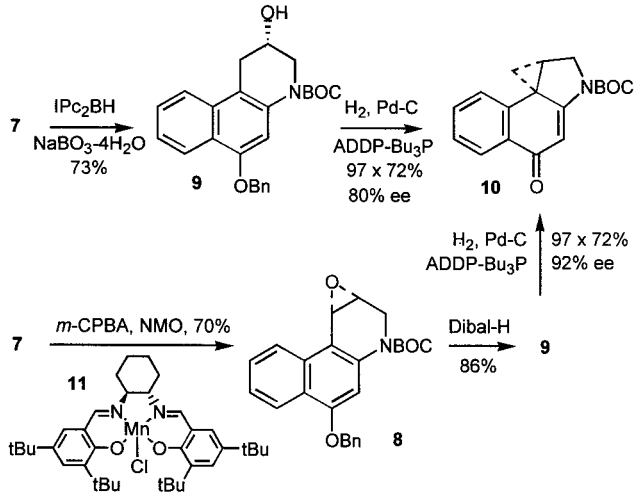
Figure 1



Scheme 1

provided N-BOC-CBI (**10**) identical in all respects with authentic material.[4]

Asymmetric hydroboration of **7** with freshly prepared and crystallized IPc_2BH[12] (prepared from (–)-α-pinene, 2.0 equiv, THF, –20 to 0 °C; $NaBO_3$–$4H_2O$) provided predominantly **9** (73%, 80% ee) and a small amount of the isomeric hydroboration product (9%), (Scheme 2). Hydrogenolysis of **9** and transannular spirocyclization provided (+)-N-BOC-CBI as described above. Assessment of the optical purity and the asymmetric hydroboration % ee was established with **10** by chiral phase HPLC (0.43 × 25 cm ChiralCel OD column, 10% iPrOH–hexane, 1 mL/min, α = 1.13). Assignment of the absolute configuration depicted in Scheme 2 was made by comparison ($[\alpha]_D$, HPLC t_R) with authentic material for which the assignments were unambiguously established by X-ray on a heavy atom derivative.[4]



Scheme 2

In what proved to be the more effective of the two asymmetric syntheses of **10** examined and the most effective approach to an optically active alkylation subunit detailed to date (Scheme 2), treatment of **7** with Jacobsen's (*S,S*)-salen Mn(III) catalyst **11**[13] (0.05 equiv, 5 equiv NMO, CH_2Cl_2, 2 equiv *m*-CPBA, –78 °C, 30 min) provided the optically active epoxide **8** (70%, 92% ee, $[\alpha]^{25}_D$ –19 (*c* 0.3, CH_3OH)). Reductive cleavage of the epoxide (3 equiv Dibal-H, THF, –78 °C, 2 h, 86%) cleanly provided **9**, $[\alpha]^{25}_D$ –35 (*c* 0.1, CH_3OH). Hydrogenolysis of the benzyl ether, transannular spirocyclization, and chiral phase HPLC assessment of the optical purity established that **10**, $[\alpha]^{25}_D$ +173 (*c* 0.15, THF), was 92% ee.

The extension of these observations to the asymmetric synthesis of the authentic alkylation subunits of **1–3** and related analogs is in progress and will be reported in due course.

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(15) For **6**, major rotamer: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, 1H, *J* = 8.2 Hz), 8.18 (d, 1H, *J* = 8.2 Hz), 7.58–7.32 (m, 7H), 6.69–6.62 (m, 1H), 6.65 (s, 1H), 5.86 (d, 1H, *J* = 12.5 Hz), 5.27–5.08 (m, 2H), 4.73 (dd, 1H, *J* = 4.3, 15.0 Hz), 3.60 (dd, 1H, *J* = 8.8, 15.0 Hz), 1.29 (s, 9H), 1.26–1.17 (m, 6H), 1.06–0.97 (m, 6H), 0.71–0.68 (m, 9H), 0.61–0.49 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.1, 154.9, 154.0, 143.7, 135.0, 132.7, 132.1, 128.6, 128.3, 128.1, 127.8, 127.2, 126.1, 125.4, 122.4, 108.5, 108.1, 80.3, 70.3, 54.1, 28.9, 28.3, 27.1, 13.6, 10.0; IR (film) ν_{max} 2955, 1702, 1591, 1374, 1159 cm^{-1}. For **7**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, 1H, *J* = 8.2 Hz), 7.98 (d, 1H, *J* = 8.4 Hz), 7.58–7.48 (m, 3H), 7.44–7.35 (m, 4H), 7.23 (br s, 1H), 7.16 (d, 1H, *J* = 9.6 Hz), 6.06 (dt, 1H, *J* = 4.4, 9.6 Hz), 5.24 (s, 2H), 4.36–4.35 (m, 2H), 1.51 (s, 9H); IR (film) ν_{max} 2973, 2928, 1673, 1590, 1365, 1320, 1240, 1160 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 520.0876 ($C_{25}H_{26}NO_3$ +

Cs^+ requires 520.0889). For **8**: $[\alpha]^{25}_D$ –19.0 (*c* 0.3, CH_3OH); ^1H NMR (C_6D_6, 400 MHz) δ 8.16 (d, 1H, *J* = 8.6 Hz), 7.86 (d, 1H, *J* = 7.4 Hz), 7.72 (s, 1H), 7.25–6.90 (m, 7H), 5.12–5.04 (m, 1H), 5.05 (d, 1H, *J* = 11.3 Hz), 4.97 (d, 1H, *J* = 11.3 Hz), 4.30 (dd, 1H, *J* = 5.0, 13.4 Hz), 4.05–3.97 (m, 1H), 3.68 (dd, 1H, *J* = 2.1, 13.4 Hz), 1.38 (s, 9H); IR (film) ν_{max} 2946, 1704, 1591, 1365, 1246, 1154 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 536.0842 ($C_{25}H_{25}NO_4 + Cs^+$ requires 536.0838). For **9**: $[\alpha]^{25}_D$ –35.0 (*c* 0.1, CH_3OH); mp 116–117 °C (needles, toluene); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.28 (d, 1H, *J* = 8.1 Hz), 7.79 (d, 1H, *J* = 8.4 Hz), 7.53–7.32 (m, 7H), 7.23 (s, 1H), 5.21 (s, 2H), 4.44–4.38 (m, 1H), 3.86 (dd, 1H, *J* = 6.5, 12.8 Hz), 3.78 (dd, 1H, *J* = 2.7, 12.8 Hz), 3.36 (dd, 1H, *J* = 6.1, 17.0 Hz), 3.02 (dd, 1H, *J* = 4.8, 17.0 Hz), 1.92 (d, 1H, *J* = 5.0 Hz), 1.52 (s, 9H); IR (film) ν_{max} 3443, 2926, 1698, 1595, 1368, 1252, 1157 cm^{-1}; FABHRMS (NBA–CsI) *m/z* 538.0999 ($C_{25}H_{27}NO_4 + Cs^+$ requires 538.0994). For N-BOC-2,6-dihydroxy-1,2,3,4-tetrahydrobenzo[*f*]quinoline: mp 172 °C; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.93 (s, 1H), 8.05 (d, 1H, *J* = 7.7 Hz), 7.77 (d, 1H, *J* = 8.4 Hz), 7.48 (t, 1H, *J* = 6.9 Hz), 7.37 (t, 1H, *J* = 7.7 Hz), 7.11 (s, 1H), 5.18 (br s, 1H), 4.07–4.04 (m, 1H), 3.80 (dd, 1H, *J* = 2.9, 12.3 Hz), 3.39 (dd, 1H, *J* = 7.8, 12.3 Hz), 3.23 (dd, 1H, *J* = 6.2, 16.8 Hz), 2.74 (dd, 1H, *J* = 6.1, 16.8 Hz), 1.47 (s, 9H); IR (film) ν_{max} 3347, 2924, 1674, 1368, 1255, 1156, 1069 cm^{-1}.