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An Improved Synthesis of 1,2,9,9a-Tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (CBI): A Simplified Analogue of the CC-1065 Alkylation Subunit

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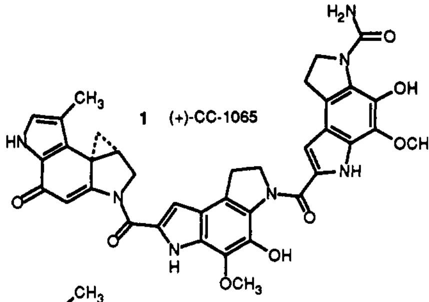
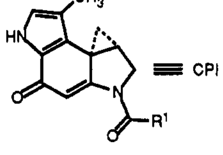
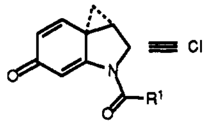
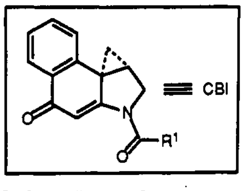
A concise and improved synthesis of **11**, the immediate precursor to *N*-BOC-CBI and related analogues of CC-1065 incorporating the 1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one alkylation subunit, is detailed based on a direct 5-*exo-trig* aryl radical–alkene cyclization for 3-hydroxymethylindoline generation.

(+)-CC-1065 (**1**),[1] a potent antitumor antibiotic which participates in a sequence-selective minor groove alkylation of DNA, has been the subject of extensive chemical, mechanistic, and biological studies.[2] In recent efforts, we have detailed the preparation of CC-1065 analogues bearing deep-seated changes in the CPI alkylation subunit[3-7] with the intent of defining the fundamental structural features contributing to polynucleotide molecular recognition and functional reactivity.[4-10] In these studies, agents incorporating the simplified and chemically more stable 1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (CBI) alkylation subunit[6] proved especially interesting. Such agents have displayed more potent in vitro cytotoxic activity[6] than the corresponding CPI agent, and selected agents within the CBI series have displayed efficacious antitumor activity.[7] Despite the decreased reactivity of the CBI-based agents, they have been found to participate in the characteristic adenine N-3 alkylation of DNA at a greater rate and with a higher intensity (efficiency) than the corresponding agents incorporating the authentic CPI alkylation subunit.[9] Consequently, in the course of the continued examination of the CBI-based agents, we have had the occasion to examine alternative, more direct approaches to their synthesis. Herein, we detail a concise synthesis of **11**, the immediate precursor to the CBI alkylation subunit, incorporating two significant improvements over our initially disclosed route.









We have found the *N-tert*-butyloxycarbonyl derivative of 1-hydroxy-3-naphthylamine (**4**) to be readily accessible through the condensation of ammonia[11] with commercially available 1,3-dihydroxynaphthalene[12] (**2**) followed by *N*-BOC protection (82–87%, two steps), Scheme I. This has proven to be a significant improvement over its preparation

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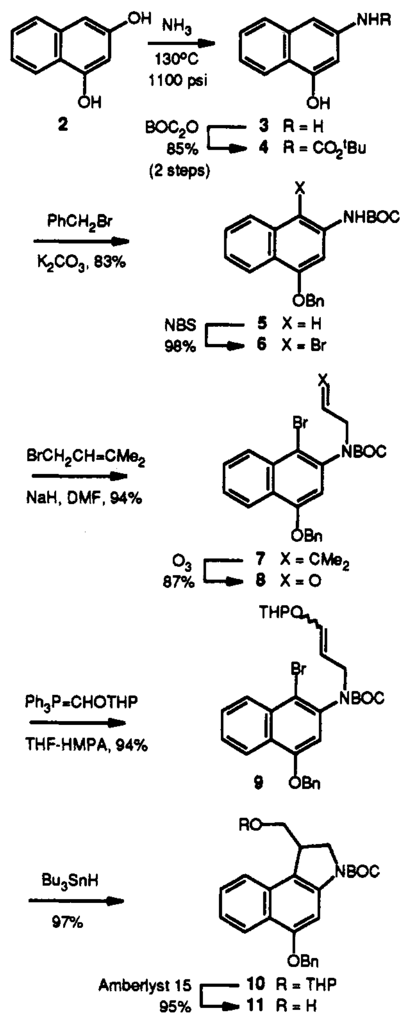
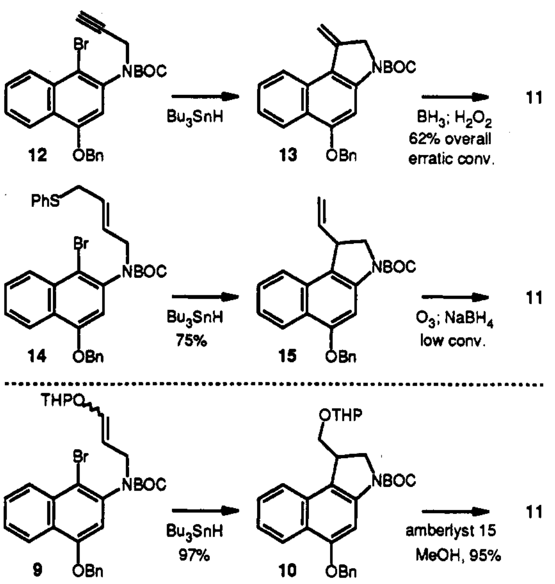
(12) 1,3-Dihydroxynaphthalene is commercially available from Sigma Chemical Corp.

Scheme I



Scheme II



from 1-methoxy-3-nitronaphthalene derived from methoxide addition to 1,3-dinitronaphthalene.[6,11] Employing this new procedure, multigram quantities of 4 have proven readily available.

More problematic has been the free-radical closure with generation of a C3 functionalized indoline. In our initial efforts,[6] this was most effectively addressed through 5-*exo-dig* aryl radical–alkyne cyclization of 12 followed by immediate hydroboration–oxidation of the unstable 3-methyleneindoline 13, Scheme II. While satisfactory conversions to the 3-(hydroxymethyl)indoline were achieved under carefully defined reaction conditions (50–62%), the competitive isomerization of 13 to the corresponding 3-methylindole could never be eliminated completely. Nonetheless, this approach proved expedient for the initial generation of 11 and more successful than an alternative indirect approach based on the self-terminating 5-*exo-trig* aryl radical–alkene cyclization of 14. In this latter approach, the 5-*exo-trig* free-radical ring closure was especially productive (>75%) but the subsequent conversion of 15 to 11 through oxidative cleavage of the terminal olefin proved problematic. In both indirect approaches, the free-radical ring closure has proven effective but the subsequent functionalization of the cyclization product to provide the 3-(hydroxymethyl)indoline has proven technically challenging. Consequently, in the design of alternative approaches to 11, we elected to examine free-radical ring closures on appropriate precursors that would directly provide the functionalized 3-(hydroxymethyl)indoline.

Alkylation of the sodium salt of 6 with 1-bromo-3-methyl-2-butene (94%, DMF, 25 °C) followed by carefully controlled ozonolysis of the olefin 7 and subsequent reductive workup (Me_2S) of the crude ozonide provided 8 (87%). In the optimization of the ozonolysis reaction, the use of extended reaction times was found to lead to the rapid generation of a further oxidation product.[13] Consequently, the attentive adherence to the reaction conditions and particularly the reaction time we have detailed has proven critical to the success of the conversion of 7 to 8. Wittig introduction of the vinyl ether 9 proved most effective through use of [(2-tetrahydropyranyloxy)methylene]triphenylphosphorane[14] with low-temperature generation of the ylide in THF followed by reaction with 8 in THF–HMPA[15] over a sustained reaction period (24 h, 94% versus 6 h, 45–60%). In preliminary studies of the Wittig reaction, the observed conversions in the absence of HMPA proved much lower and [(2-tetrahydropyranyloxy)methylene]triphenylphosphorane proved superior to (methoxymethylene)triphenylphosphorane or [(benzyloxy)methylene]triphenylphosphorane although this was not investigated in detail. Treatment of 9 with Bu_3SnH (2.0 equiv, 0.2 equiv AIBN, C_6H_6, 80 °C, 1 h) provided 10, the product of the 5-*exo-trig* aryl radical–alkene cyclization, in excellent yield (97%). Subsequent THP deprotection[16] of 10 provided 11 identical to material previously detailed.[6]

The use of this approach to the preparation of the CBI subunit in the synthesis of functional analogues of (+)-CC-1065 is in progress and will be disclosed in due course.

Experimental Section

***N*-(*tert*-Butyloxycarbonyl)-4-hydroxy-2-naphthylamine (4).** 1,3-Dihydroxynaphthalene 2[12] (800 mg, 5.00 mmol) was dissolved in 35 mL of liquid NH_3 at −78 °C. This solution was sealed in a 600-mL steel bomb containing a glass liner. The reaction mixture was warmed to 130 ± 5 °C and 1100 psi for 16

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[13] For the byproduct of overoxidation: (*Z*)-3-bromo-3-[2′-(benzyloxycarbonyl)phenyl]-2-[*N*-(*tert*-butyloxycarbonyl)-*N*-(formylmethyl)amino]-2-propenal ($CDCl_3$, 200 MHz, ppm) 9.80 (m, 1 H, CHO), 9.19 (s, 1 H, CHO), 8.15 (dd, *J* = 2, 8 Hz, C3′-H), 7.5–7.7 (m, 3 H, C4′-H, C5′-H, C6′-H), 7.39 (m, 5 H, $CH_2C_6H_5$), 5.30 (s, 2 H, $OCH_2C_6H_5$), 3.7–4.0 (m, 2 H, CH_2CHO), 1.48 and 1.50 (two s, 9 H, $OC(CH_3)_3$); IR (neat) ν_{max} 2978, 1716, 1456, 1420, 1370, 1332, 1262, 1230, 1156, 1098, 1008, 742 cm^{-1}; CIMS (isobutane) *m/e* 502/504 (M^+ + H), 446/448 (100/92).

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h with vigorous stirring. The vessel was allowed to cool to 80 °C, and the NH_3 was released slowly. By the time the vessel reached 50 °C the NH_3 had evaporated and the remaining traces were removed under a stream of dry N_2 at 40 °C. This slurry containing **3** was protected from oxidation by air with a steady flow of dry N_2. The intermediate amine **3** was not isolated but was protected immediately as the *tert*-butyl carbamate. Di-*tert*-butyl dicarbonate (4.4 g, 20 mmol) in dioxane (100 mL) was added to the bomb. The bomb was resealed, and the contents were warmed at 100 °C with stirring for 4 h. The bomb was cooled to room temperature and opened and the residue partitioned between saturated aqueous NaCl (50 mL) and EtOAc (50 mL). The aqueous phase was reextracted with EtOAc (50 mL × 2). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Chromatography (4 × 10-cm SiO_2, 20–40% EtOAc–hexane gradient elution) provided pure **4** (1.09 g, 1.30 g theoretical, 84%) as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 8.08 (d, 1 H, J = 8.2 Hz, C5-H), 7.63 (d, 1 H, J = 8.1 Hz, C8-H), 7.39 (dd, 1 H, J = 6.8, 8.2 Hz, C6-H), 7.32 (dd, 1 H, J = 6.8, 8.1 Hz, C7-H), 7.14 (br s, 1 H, NH), 7.23 (d, 1 H, J = 1.8 Hz, C1-H), 6.80 (br s, 1 H, OH), 6.64 (s, 1 H, C3-H), 1.52 (s, 9 H, $OC(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) 153.3, 152.7, 135.8, 134.8, 126.9, 126.8, 123.6, 123.5, 121.6, 107.2, 102.4, 81.0, 28.3; IR (film) ν_{max} 3344, 3056, 2979, 2933, 1701, 1636, 1586, 1536 cm^{-1}; FABMS (NBA) *m/e* (relative intensity) 259 (M$^+$, 85), 203 (100); FABHRMS *m/e* 259.1200 ($C_{15}H_{17}NO_3$ requires 259.1208).

Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.30; H, 6.78; N, 5.44.

***N*-(*tert*-Butyloxycarbonyl)-4-(benzyloxy)-2-naphthylamine (5).** A solution of *N*-(*tert*-butyloxycarbonyl)-4-hydroxy-2-naphthylamine (**4**, 5.00 g, 19.3 mmol) in dry DMF (50 mL) under an atmosphere of dry N_2 was treated with anhydrous K_2CO_3 (3.7 g, 27.0 mmol), benzyl bromide (4.0 g, 23.1 mmol), and *n*-Bu_4NI (70 mg, 0.01 mmol), and the mixture was stirred for 8 h at 23 °C. The reaction mixture was concentrated under reduced pressure. Chromatography (4 × 10-cm SiO_2, 10–20% EtOAc–hexane gradient elution) provided pure **5** (5.48 g, 6.74 g theoretical, 83%) as a cream colored powder identical with authentic material:[6] mp 137.5 °C sharp (hexanes, needles); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 8.22 (d, 1 H, J = 8.1 Hz, C5-H), 7.68 (d, 1 H, J = 8.2 Hz, C8-H), 7.3–7.5 (m, 8 H, C1-H, C6-H, C7-H, $CH_2C_6H_5$), 7.06 (d, 1 H, J = 1.1 Hz, C3-H), 6.62 (br s, 1 H, NH), 5.23 (s, 2 H, $OCH_2C_6H_5$), 1.55 (s, 9 H, $OC(CH_3)_3$); IR (KBr) ν_{max} 3318, 3058, 3032, 3007, 2970, 2934, 2882, 1701, 1633, 1606, 1585, 1543, 1502 cm^{-1}; EIMS *m/e* (relative intensity) 349 (M$^+$, 2.6) 91 (100); CIMS (isobutane) *m/e* (relative intensity) 350 (M + H$^+$, 44), 294 (100); EIHRMS *m/e* 349.1677 ($C_{22}H_{23}NO_3$ requires 349.1677).

Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.24; H, 6.95; N, 4.11.

***N*-(*tert*-Butyloxycarbonyl)-4-(benzyloxy)-1-bromo-2-naphthylamine (6).** A solution of **5** (500 mg, 1.43 mmol) in 25 mL of THF under N_2 was cooled to −60 °C and treated with a drop of concentrated H_2SO_4 in 5 mL of THF. After the solution was stirred for 5 min (−60 °C), NBS (306 mg, 1.72 mmol, 1.2 equiv) was added to the reaction mixture. The mixture was stirred for 5 h (−60 °C) and diluted with Et_2O (60 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and saturated aqueous NaCl (30 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (2.5- × 15-cm SiO_2, 10% EtOAc–hexane) afforded **6** (601 mg, 613 mg theoretical, 98%) as a pale yellow solid: mp 111 °C (sharp, EtOAc–hexane, pale yellow plates); ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) 8.28 (d, 1 H, J = 8.5 Hz, C5-H), 8.11 (dd, 1 H, J = 1.8, 8.3 Hz, C8-H), 8.10 (s, 1 H, C3-H), 7.4–7.6 (m, 8 H, C6-H, C7-H, $CH_2C_6H_5$, NH), 5.29 (s, 2 H, $OCH_2C_6H_5$), 1.58 (s, 9 H, $OC(CH_3)_3$); IR (KBr) ν_{max} 3407, 2979, 1735, 1625, 1601 cm^{-1}; EIMS *m/e* (relative intensity) 427/429 (M$^+$, 0.8/0.7), 91 (100); CIMS (isobutane) *m/e* (relative intensity) 428/430 (M + H$^+$, 5.7/4.0), 372/374 (100/67); EIHRMS *m/e* 427.0781 ($C_{22}H_{22}BrNO_3$ requires 427.0783).

Anal. Calcd for $C_{22}H_{22}BrNO_3$: C, 61.69; H, 5.18; N, 3.27. Found: C, 61.68; H, 5.47; N, 3.65.

2-[*N*-(*tert*-Butyloxycarbonyl)-*N*-(3-methyl-2-buten-1-yl)amino]-4-(benzyloxy)-1-bromonaphthalene (7). A suspension of NaH (73 mg, 1.82 mmol, 1.3 equiv) in 4 mL of DMF at 24 °C under Ar was treated with **6** (601 mg, 1.40 mmol), and the reaction mixture was stirred for 30 min (24 °C). The mixture was cooled to 0 °C, and 4-bromo-2-methyl-2-butene (0.49 mL, 4.2 mmol, 3 equiv) was added slowly to the mixture. The mixture was allowed to warm to 24 °C and was stirred for 8 h (24 °C) before being poured onto H_2O (30 mL). The mixture was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were washed with H_2O (30 mL) and saturated aqueous NaCl, dried ($MgSO_4$), and concentrated in vacuo. The oily residue was crystallized from EtOAc–hexane to afford 503 mg of **7** as pale yellow prisms. Chromatography of the recrystallization mother liquor (1.5 × 15-cm SiO_2, 0–10% EtOAc–hexane gradient elution) provided an additional 149 mg (total yield 94%, 652 mg, 696 mg theoretical) of **7**: mp 128.5–129 °C (EtOAc–hexane): ^{1}H NMR ($CDCl_3$, 200 MHz, ppm) 8.34 (d, 1 H, J = 8 Hz, C5-H), 8.28 (d, 1 H, J = 8 Hz, C8-H), 7.4–7.8 (m, 7 H, C6-H, C7-H, $CH_2C_6H_5$), 6.70 and 6.78 (two s, 1 H, C3-H), 5.30 (m, 1 H, CH=C), 5.24 and 5.21 (AB q, 2 H, J = 12 Hz, $OCH_2C_6H_5$), 4.48 (dd, 1 H, J = 6, 15 Hz, CHHC=C), 4.04 (dd, 1 H, J = 6, 15 Hz, CHHC=C), 1.62 (s, 3 H, $=CCH_3$), 1.38 (s, 3 H, $=CCH_3$), 1.31 and 1.57 (two s, 9 H, $OC(CH_3)_3$); IR (KBr) ν_{max} 3070, 2968, 2932, 1690, 1654, 1618, 1594, 1506 cm^{-1}; CIMS (isobutane) *m/e* (relative intensity) 496/498 (M + H$^+$, 5/5), 440/442 (100/99); FABHRMS (NBA-CsI) *m/e* 628.0463 (M + Cs$^+$, $C_{27}H_{30}BrNO_3$ requires 628.0463).

Anal. Calcd for $C_{27}H_{30}BrNO_3$: C, 65.32; H, 6.09; N, 2.82. Found: C, 65.00; H, 5.84; N, 3.14.

2-[*N*-(*tert*-Butyloxycarbonyl)-*N*-(formylmethyl)-amino]-4-(benzyloxy)-1-bromonaphthalene (8). A solution of **7** (456 mg, 0.92 mmol) in 46 mL of CH_2Cl_2 and 9 mL of CH_3OH at −78 °C was treated with a stream of 3% O_3/O_2 (200 L/h, 55 s). The reaction was quenched quickly with the addition of 2.3 mL of Me_2S. The reaction mixture was stirred at −78 °C for 5 min and at 24 °C for 3 h before the solvent was removed in vacuo. Chromatography (2 × 25-cm SiO_2, 20–40% EtOAc–hexane gradient elution) afforded **8** (375 mg, 432 mg theoretical, 87%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) amide rotamers 9.82, 9.79, and 9.76 (three s or apparent t, 1 H, CHO), 8.37, 8.32, 8.28, 8.26, 8.13 and 8.10 (six d, 2 H, J = 8.0 Hz, C5-H and C8-H), 7.66–7.35 (m, 7 H, C6-H, C7-H, $CH_2C_6H_5$), 7.02, 7.01 and 6.98 (three s, 1 H, C3-H), 5.27, 5.25, 5.30 and 5.18 (two s and two d, 2 H, J = 11.2 Hz, $OCH_2C_6H_5$), 4.71, 4.69 and 4.57 (three d, 1 H, J = 18.6 Hz, CHHCHO), 4.01, 3.99 and 3.96 (three d, 1 H, J = 18.6 Hz, CHHCHO), 1.56, 1.35 and 1.34 (three s, 9 H, $OC(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) 198.0 and 197.7 (CHO), 154,8, 154.5 and 154.3 (2 C), 139.0 and 138.9 (C), 136.3 (C), 132.8 and 132.7 (C), 128.8, 128.7 and 128.6 (2 CH), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.5 (2 CH), 126.5 (CH), 126.2 and 126.0 (C), 122.5 (CH), 114.2 and 113.9 (C), 107.4 and 107.1 (CH), 82.0, 81.5 and 81.4 (C), 70.7 and 70.5 (CH_2), 60.2, 59.2 and 59.1 (CH_2), 29.7, 28.3 and 28.1 ($3CH_3$); IR (neat) ν_{max} 2977, 2930, 2820, 2716, 1733, 1699, 1620, 1593 cm^{-1}; FABHRMS (NBA-CsI) *m/e* 601.9949 (M + Cs$^+$, $C_{24}H_{24}BrNO_4$ requires 601.9943).

2-[*N*-(*tert*-Butyloxycarbonyl)-*N*-[3-(tetrahydropyranyloxy)-2-propen-1-yl]amino]-4-(benzyloxy)-1-bromonaphthalene (9). A suspension of triphenyl[(2-tetrahydropyranyloxy)methyl]phosphonium chloride[14] (1.13 g, 2.74 mmol, 3 equiv) in 9.3 mL of THF at −78 °C was treated dropwise with *n*-BuLi (1.4 mL, 1.83 M in pentane, 2.56 mmol, 2.86 equiv). The reaction mixture was stirred at −78 °C for 5 min and allowed to warm to 24 °C over 30 min. The mixture was recooled to −78 °C, and hexamethylphosphoramide (HMPA, 3.85 mL, 22.0 mmol, 24 equiv) was added followed immediately by addition of **8** (422 mg, 0.897 mmol) in 4.5 mL of THF (dropwise addition). The reaction mixture was stirred for 1.5 h at −78 °C and 24 h at 24 °C before being quenched with the addition of 150 mL of phosphate buffer (pH = 7.4). The mixture was extracted with EtOAc (150 mL × 3), and the combined organic phase was dried (Na_2SO_4) and concentrated in vacuo. Chromatography (Florisil, 200 mesh, 2 × 25 cm, 20–40% EtOAc–hexane containing several drops of Et_3N, gradient elution) afforded **9** (477 mg, 510 mg theoretical, 94%) as an off-white oil as a mixture of *E*- and *Z*-olefin isomers: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) *E*- and *Z*-isomers, amide rotamers 8.47–8.13 (m, 2 H, C5-H and C8-H), 7.63–7.36 (m, 8 H, C6-H, C7-H, C3-H, $CH_2C_6H_5$), 6.84–6.71 (m, 1 H, CH=CH), 6.24–6.10 (m, 1 H, CH=CH), 5.24–5.15 (m, 2 H, $OCH_2C_6H_5$), 4.86–4.33 (m, 3 H, CH_2CH=CH, $OCHCH_2$), 3.98–2.67 (m, 2 H, OCH_2CH_2), 1.77–1.26 (m, 15 H, $OC(CH_3)_3$, $OCHCH_2CH_2CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) 154.4, 154.2, 154.1, 153.8 and 153.6 (2

C), 147.0 and 146.8 (CH), 144.5, 144.4 and 144.1 (CH), 138.8 and 138.6 (C), 136.5 (C), 132.8 (C), 128.7 (2CH), 128.1 (CH), 128.0 and 127.9 (CH), 127.5 (CH), 127.4 and 127.3 (CH), 126.0 and 125.9 (CH), 125.8 (C), 122.4 and 122.3 (CH), 115.0 and 114.3 (C), 109.0, 108.4, 108.3 and 108.0 (CH), 102.9, 102.8 and 102.6 (CH), 98.0, 97.9, 97.8 and 97.5 (CH), 80.6 and 80.1 (C), 70.3 (CH_2), 61.7, 61.6, 61.0 and 60.7 (CH_2), 47.1, 42.9 and 42.3 (CH_2), 29.6 and 29.2 (CH_2), 28.5 and 28.3 ($3CH_3$), 25.0, 24.9 and 24.7 (CH_2), 18.6, 18.5, 18.0, 17.8 and 17.6 (CH_2); IR (neat) ν_{max} 3066, 3034, 2944, 2873, 1703, 1699, 1694, 1674, 1620, 1593 cm^{-1}; FABHRMS (NBA-CsI) m/e 700.0699 (M + Cs$^+$, $C_{30}H_{34}BrNO_5$ requires 700.0675).

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-[(tetrahydropyranyloxy)methyl]-1,2-dihydro-3*H*-benz[*e*]indole (10). A solution of **9** (385 mg, 0.678 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN, 22.3 mg, 0.136 mmol, 0.2 equiv) in 30 mL of C_6H_6 at 24 °C under Ar was treated with Bu_3SnH (0.38 mL, 1.36 mmol, 2.0 equiv), and the reaction mixture was warmed at reflux for 1 h. The reaction mixture was cooled, and the solvent was removed in vacuo. After azeotropic drying with anhydrous THF (10 mL × 2), chromatography (1.5 × 20-cm Florisil, 200 mesh, 20–40% EtOAc–hexane containing several drops of Et_3N, gradient elution) afforded **10** (324 mg, 332 mg theoretical, 97%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) 8.31 (d, 1 *H*, *J* = 8 Hz, C6-H), 7.92 (br s, 1 H, C4-H), 7.77 (d, 1 H, *J* = 6 Hz, C9-H), 7.56–7.31 (m, 7 H, C7-H, C8-H, $OCH_2C_6\mathit{H}_5$), 5.29 (br s, 2 H, $OC\mathit{H}_2C_6H_5$), 4.67 and 4.58 (two br m, 1 H, $OC\mathit{H}CH_2$), 4.27–3.37 (m, 7 H, C1-H, C2-H_2, CH_2OTHP, $OC\mathit{H}_2CH_2$), 1.87–1.53 (m, 15 H, $OC(CH_3)_3$, $OCH_2C\mathit{H}_2C\mathit{H}_2C\mathit{H}_2$); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) 155.5 (C), 152.8 (C), 141.4 (C), 137.0 (C), 130.7 (C), 128.6 (2CH), 127.9 (CH), 127.6 (CH), 127.2 (CH), 127.1 (CH), 123.2 (CH), 122.9 (CH), 122.8 (CH), 122.3 (C), 115.6 (C), 99.9 (CH), 98.5 and 96.5 (CH), 80.6 (C), 70.2 (CH_2), 69.2 (CH_2), 62.6 (CH_2), 52.9 (CH_2), 39.5 and 39.0 (CH), 30.6 (CH_2), 28.5 ($3CH_3$), 25.4 (CH_2), 19.7 (CH_2); IR (neat) ν_{max} 2941, 1699, 1627, 1582, 1517 cm^{-1}; FABHRMS (NBA-CsI) m/e 622.1576 (M + Cs$^+$, $C_{30}H_{34}BrNO_5$ requires 622.1570).

Anal. Calcd for $C_{30}H_{35}NO_5$: C, 73.64; H, 7.21; N, 2.86. Found: C, 73.40; H, 7.23; N, 3.03.

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-(hydroxymethyl)-1,2-dihydro-3*H*-benz[*e*]indole (11). A solution of **10** (131 mg, 0.267 mmol) in 4 mL of CH_3OH was treated with Amberlyst 15[16] (8.0 mg, 1 mequiv). The reaction mixture was warmed at 45 °C for 6 h. The resin was removed by filtration, and the solvent was concentrated in vacuo. Chromatography (SiO_2, 40–60% EtOAc–hexane gradient elution) afforded **11** (103 mg, 108 mg theoretical, 95%) as a colorless foam identical in all respects to authentic material.[6]

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Registry No. **1**, 69866-21-3; **2**, 132-86-5; **3**, 90923-79-8; **4**, 139975-98-7; **5**, 122745-36-2; **6**, 122745-37-3; **7**, 129918-05-4; **8**, 129918-06-5; (*E*)-**9**, 139975-99-8; (*Z*)-**9**, 139976-00-4; **10**, 139976-01-5; **11**, 122745-39-5; $BrCH_2CH{=}CMe_2$, 870-63-3; $Ph_3P{=}CHOTHP$, 62209-77-2.

Supplementary Material Available: ^{1}H NMR spectra of **4** and **7–10** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Enantiogenic Total Syntheses of (−)-Indolizidines (Bicyclic Gephyrotoxins) 205A, 207A, 209B, and 235B via the Intramolecular Diels–Alder Reaction of a Chiral *N*-Acylnitroso Compound

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A general protocol for the enantiogenic total syntheses of a series of the 5-substituted 8-methylindolizidine class of alkaloids from the arrow poison frog, i.e., (−)-indolizidines **205A** (**1**), **207A** (**2**), **209B** (**3**), and **235B** (**4**), is described, in which a key step is the asymmetric intramolecular Diels–Alder reaction of the chiral *N*-acylnitroso compound **8** leading to the bicyclic oxazinolactam **7** which was utilized as a versatile common chiral intermediate for the preparation of these alkaloids. Subsequent introduction of the C-5 (in future) side chain was elaborated by means of a completely stereocontrolled process involving a Grignard reaction followed by reduction with $NaBH_4$ in acidic media. The bicyclic oxazines **20a**, **24**, and **26** thus obtained were then subjected to reductive N–O bond cleavage followed by cyclodehydration using $PPh_3/CBr_4/Et_3N$, which provided the (−)-enantiomers of the title alkaloids.

Introduction

A number of simple congeneric indolizidine alkaloids, the 5-substituted 8-methylindolizidines, whose mass spectra all show a base peak at $m/z = 138$, have been detected in extracts of the skins of members of the Dendrobatidae family of neotropical arrow-poison frogs.[1] The base peak arises as the result of the loss of the C-5 side chain from the molecular ion. So far, 18 5-substituted 8-methylindolizidines, which together constitute a new subclass of dendrobatis indolizidine alkaloids, have been found,[1,2] mainly by gas chromatographic–mass spectrometric analysis, to be present in certain dendrobatid frogs. Of these, only four, indolizidines (formerly called bicyclic gephyrotoxins) **205A**[3] (**1**),[4] **207A** (**2**),[2] **235B** (**4**),[4] and **235B′**

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(1) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1, pp 1–274.

(2) Edwards, M. W.; Daly, J. W.; Myers, C. W. *J. Nat. Prod.* **1988**, *51*, 1188.

(3) The convention whereby numerical designations are given to dendrobatid alkaloids was originated in 1978 by J. W. Daly's group at the National Institutes of Health. Thus, the identity of an alkaloid is denoted by a series of boldface Arabic numerals (the compound's molecular weight) and a boldface capital letter(s) (a symbol which indicates that the compound is one of two or more isomers). See: Daly, J. W.; Brown, G. B.; Mensah-Dwumah, M.; Myers, C. W. *Toxicon* **1978**, *16*, 163. Daly, J. W. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer-Verlag: Vienna, 1982; Vol. 41, pp 205–340.

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