Access to 1-Hydroxymethylpyrrolizidines Utilizing Malate Enolate−Imine Condensation and Ring-Closing Methathesis: Synthesis of (−)-Croalbinecine

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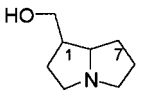
Pyrrolizidine alkaloids are nitrogen-fused bicyclo[3.3.0]-octanes and have long attracted synthetic interest due to their relatively simple structural features and wide range of pharmacologic activity.[1] Diverse and elegant synthetic methods have been developed for the construction of this core structure, especially for the 1-hydroxymethylpyrrolizidines, also called necine bases.[2] Many synthetic methods for these alkaloids rely on an efficient approach to functionalized 2-pyrrolidinones.[3]

In our previous paper, we developed a new approach to highly functionalized 2-pyrrolidinones using the condensation between the enolate dianion of malate and nonenolizable imines.[4] Though the yield and diastereoselectivity of this condensation were less than optimal, this method provides an expedient approach to 2-pyrrolidinones appropriate for the synthesis of necines. In this paper, the synthesis of (−)-croalbinecine (**2**), an enantiomer of the polyhydroxylated pyrrolizidine, is discussed utilizing ester-imine condensation and ring-closing metathesis.[5]



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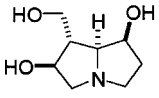
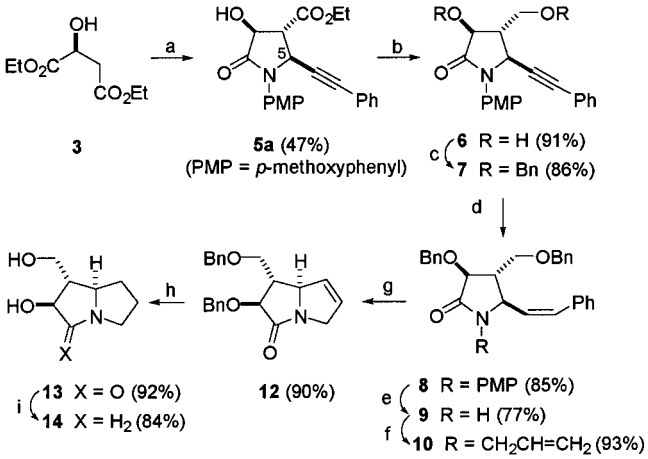


2

The enolate dianion generated from diethyl (*S*)-malate (**3**) by treating with two equivalents of sodium bis-(trimethylsilyl)amide was reacted with phenylpropargylidene *p*-anisidine (**4**)[6] at −78 °C in THF to give **5a** (47%) and its C(5)-epimer **5b** (11%) (Scheme 1). Selective reduction of the ester moiety of pyrrolidinone **5a** with $LiBH_4$ followed by the protection of the resulting diol **6** provided **7**. We proposed in our earlier study the stereochemistry of **5a** on the basis of the NOE results and further confirmed it in this study by X-ray crystallographic analysis of **7**.[7] Partial reduction of the triple bond of **7** followed by oxidative removal of the *p*-methoxyphenyl group on nitrogen provided **9**, which was *N*-allylated for the second ring formation. Ring-closing olefin metathesis of **10** to **12** with Grubbs catalyst **11** was successful despite the possible deactivation of the intermediate by the neighboring amide carbonyl.[8] Addition of 0.3 equiv of $Ti(O\text{-}^iPr)_4$ together with Grubbs catalyst gave essentially the same results.[9] The neighboring benzyloxy group may play a steric effect to inhibit the chelation between the amide oxygen and the ruthenium intermediate. Catalytic hydrogenation of **12** smoothly produced **13**, which was reduced with LAH to give the dihydroxylated pyrrolizidine **14,** C(1)-epimer of (+)-petasinecine.[10]

Scheme 1[a]



[a] Reagents: (a) $2NaN(TMS)_2$, Ph-C≡C-CH=N-PMP (**4**); (b) $LiBH_4$, diglyme; (c) NaH, BnBr, DMF; (d) H_2, Lindlar cat.; (e) $(NH_4)_2Ce(NO_3)_6$, H_2O-CH_3CN; (f) $CH_2=CHCH_2Br$, NaH; (g) $(Cy_3P)_2Cl_2Ru$=CHPh (**11**, 3 mol %), PhH; (h) H_2, $Pd(OH)_2$, CH_3OH; (i) $LiAlH_4$, THF.

Selective introduction of the hydroxy group at the C(7) position of **12** was accomplished by epoxidation followed by ring opening with LAH. Epoxidation of **12** with *m*-CPBA gave a chromatographically separable mixture of the epoxides **15** (61%) and **16** (10%) (Scheme 2). Simultaneous epoxide opening and amide reduction with LAH produced **17** in 65% yield together with the regioisomer **18** (9%). Hydrogenolysis of the benzyl groups from **17** with cat. $Pd(OH)_2$ in methanol produced (−)-croalbi-

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(1) Liddell, J. R. *Nat. Prod. Rep.* **1999**, *16*, 499−507. Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619−636. Robins, D. J. *Nat. Prod. Rep.* **1995**, *12*, 413−418. Dai, W.-M.; Nagao, Y.; Fujita, E. *Heterocycles* **1990**, *30*, 1231−1261.

(2) Kim, S.-H.; Kim, S.-I.; Lai, S.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 6771−6775. Bertrand, S.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* **1999**, *40*, 3173−3174. Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125−137. Ito, H.; Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5469−5470. Mulzer, J.; Shanyoor, M. *Tetrahedron Lett.* **1993**, 34, 6545−6548.

(3) Himstra, H.; Speckamp. W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: London, 1991; Vol. 2, p 1047. Hart, D. J. In *Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1988; Vol. 6, p 227.

(4) Ha, D.-C.; Yun, K.-S.; Park, H.-S.; Choung, W.-K.; Kwon, Y.-E. *Tetrahedron Lett.* **1995**, *36*, 8445−8448. For the synthesis of 2-azetidinones using ester enolate-imine condensation, see: Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1988**, *89*, 1447−1465.

(5) White, J. D.; Hrnciar, P.; Yokoshi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359−7360. Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857.

(6) Matsui, S.; Hashimoto, Y.; Saigo, K. *Synthesis* **1998**, 1161−1165. Layer, R. W. *Chem. Rev.* **1963**, *63*, 489−510.

(7) Details are described in the Supporting Information.

(8) White, J. D.; Hrnciar, P.; Yokoshi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359−7360. Martin, S. F.; Liao, Y.; Chen, H.-J.; Pätzel, M.; Ramser, M. N. *Tetrahedron Lett.* **1994**, *35*, 6005−6008.

(9) Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130−9136.

(10) Aasen, A. J.; Culvenor, C. C. J. *J. Org. Chem.* **1969**, *34*, 4143−4147.

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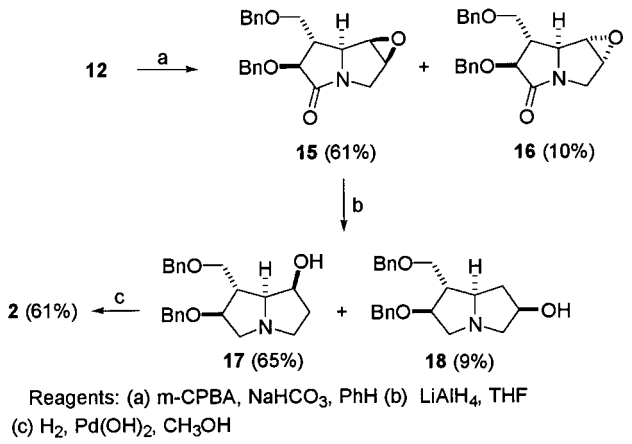
Scheme 2



necine (**2**) in 61% yield. Spectroscopic and physical data of **2** except for the sign of the optical rotation were identical to those of natural and synthetic materials.[11,12]

In summary, we have shown that the condensation between the enolate dianion of diethyl malate and imine combined with ring-closing olefin metathesis provides an expedient approach to 1-hydroxymethylpyrrolizidines, necine bases. The synthesis of pyrrolizidine alkaloid, (−)-croalbinecine, from diethyl (*S*)-malate in 10 steps demonstrates the synthetic utility of this approach for diverse pyrrolizidine alkaloids and their analogues.

Experimental Section

General Procedures. Reagents obtained from commercial sources were used as received, and solvents were dried prior to use. All reactions, unless otherwise noted, were performed in flame-dried glassware under an atmosphere of dry argon. Column chromatography was performed on silica gel. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C NMR at 75 MHz. Infrared spectra were recorded in the FT mode. Data for high-resolution mass spectra and elemental analyses were obtained from Organic Chemistry Research Center, Sogang University at Seoul, Korea.

(3*S*,4*R*,5*S*)-4-Ethoxycarbonyl-3-hydroxy-1-(4-methoxyphenyl)-5-phenylpropargyl-2-pyrrolidinone (5a). To a solution of hexamethyldisilazane (7.5 mL, 35.5 mmol) and *n*-BuLi (1.6M in hexane, 22.2 mL) in 50 mL of THF stirred for 1 h at −78 °C was added a solution of diethyl malate (**3**, 3.0 mL, 17.6 mmol) in 20 mL of THF slowly over a 5-min period. The solution was stirred for 30 min at −78 °C, and a solution of phenlpropargylidene *p*-anisidine (**4**, 3.0 g, 12.7 mmol) in 60 mL of THF was added slowly for 1.5 h. The mixture was slowly warmed to 0 °C over 1.5 h, quenched with 300 mL of saturated NH_4Cl solution, and extracted three times with 200-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (1:1, EtOAc/hexanes) gave **5a** (2.28 g, 47%) as a white solid and its C(5)-epimer **5b** (0.53 g, 11%) as a light yellow solid. **5a**: R_f = 0.20 (1:1, EtOAc/hexanes); mp 129−130 °C; $[\alpha]^{25}_D$ −57.7 (*c* 0.75, $CHCl_3$); IR (KBr, cm^{-1}) 3389, 1724, 1683; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, 2H, *J* = 7 Hz), 7.28 (m, 5H), 6.92 (d, 2H, *J* = 7 Hz), 5.16 (d, 1H, *J* = 9 Hz), 4.68 (d, 1H, *J* = 9 Hz), 4.34−4.29 (m, 3H), 3.79 (s, 3H), 3.45 (t, *J* = 9 Hz), 1.35 (t, 1H, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.2, 170.5, 158.2, 131.6, 128.9, 128.2, 125.7, 121.5, 114.1, 87.3, 84.1, 72.1, 62.1, 55.4, 53.7, 50.9, 14.2; MS (EI) *m/e* (relative intensity) 379 (M$^+$, 91), 128 (100). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.73; H, 5.66; N, 3.58.

(3*S*,4*S*,5*S*)-3-Hydroxy-4-hydroxymethyl-1-(4-methoxyphenyl)-5-phenylethynyl-2-pyrrolidinone (6). To a slurry of $NaBH_4$ (689 mg, 18.2 mmol) in 80 mL of diglyme was added LiCl (850 mg, 20.2 mmol) followed by stirring for 30 min at ambient temperature. A solution of **5a** (1.72 g, 4.6 mmol) in 30 mL of diglyme was added slowly for 10 min to the above solution at 0 °C and the resulting mixture was stirred for 24 h at ambient temperature. The mixture was quenched with 200 mL of saturated NH_4Cl solution and extracted three times with 200-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (2:1, EtOAc/hexanes) gave **6** (1.40 g, 91%) as a white solid: R_f = 0.13 (2:1, EtOAc/hexanes); mp 133−134 °C; $[\alpha]^{20}_D$ −91.9 (*c* 2.13, EtOH); IR (KBr, cm^{-1}) 3342, 1687, 1249; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (d, 2H, *J* = 9 Hz), 7.25 (s, 5H), 6.90 (d, 2H, *J* = 9 Hz), 5.04 (s, 1H), 4.93 (d, 1H, *J* = 9 Hz), 4.62 (d, 1H, *J* = 9 Hz), 4.13 (d, 1H, *J* = 11 Hz), 3.99 (d, 1H, *J* = 11 Hz), 3.77 (s, 3H), 3.23 (s, 1H), 2.63 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6, 157.9, 131.6, 129.3, 128.7, 128.2, 125.5, 121.8, 114.0, 86.6, 84.8, 69.3, 57.8, 55.4, 51.8, 49.6; MS (EI) *m/e* (relative intensity) 337 (M$^+$, 100). Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.47; H, 5.73; N, 4.01.

(3*S*,4*S*,5*S*)-3-Benzyloxy-4-benzyloxymethyl-1-(4-methoxyphenyl)-5-phenyethynyl-2-pyrrolidinone (7). To a slurry of 60% NaH (85 mg, 3.54 mmol) in 5 mL of DMF was added a solution of **6** (398 mg, 1.18 mmol) in 7 mL of DMF. The mixture was stirred for 30 min, and benzyl bromide (0.42 mL, 3.54 mmol) was added followed by stirring at ambient temperature for 1 h. The mixture was quenched with 50 mL of saturated NH_4Cl solution, and the aqueous layer was extracted twice with 100-mL portions of CH_2Cl_2. The combined organic layers was dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (1:6, EtOAc/hexanes) gave **7** (527 mg, 86%) as a light yellow solid: R_f = 0.25 (1:4, EtOAc/hexanes); mp 104−105 °C; $[\alpha]^{20}_D$ −63.6 (*c* 0.55, $CHCl_3$); IR (KBr, cm^{-1}) 2889, 1709, 1248; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44−6.90 (m, 19H) 5.15 (d, 1H, *J* = 12 Hz), 4.89 (d, 1H, *J* = 8 Hz), 4.84 (d, 1H, *J* = 12 Hz), 4.50 (d, 1H, *J* = 12 Hz), 4.43 (d, 1H, *J* = 12 Hz), 4.34 (d, 1H, *J* = 8 Hz), 3.79 (s, 3H), 3.82−3.76 (m, 1H), 3.68−3.64 (m, 1H), 2.73(m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 157.6, 137.8, 137.7, 131.6, 129.9, 128.6, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 125.2, 122.0, 113.0, 86.1, 85.6, 75.2, 73.2, 72.7, 65.6, 55.4, 49.9, 48.2; MS (EI) *m/e* (relative intensity) 517 (M$^+$, 3), 91 (100). Anal. Calcd for $C_{34}H_{31}NO_4$: C, 78.89; H, 6.04; N, 2.71. Found: C, 79.02; H, 6.19; N, 2.47.

(3*S*,4*S*,5*R*)-3-Benzyloxy-4-benzyloxymethyl-1-(4-methoxyphenyl)-5-[(*Z*)-2-phenylethenyl]-2-pyrrolidinone (8). A mixture of **7** (704 mg, 1.36 mmol) and Lindlar catalyst (49 mg, 7% w/w) in 10 mL of benzene was reacted under 40 psi hydrogen pressure using Parr hydrogenator for 40 min. The mixture was filtered over Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel (1:7, EtOAc/hexanes) to give **8** (597 mg, 85%) as a light yellow oil: R_f = 0.32 (1:3, EtOAc/hexanes); $[\alpha]^{20}_D$ −26.7 (*c* 8.87, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 1704; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43−7.18 (m, 15H) 7.04 (d, 2H, *J* = 9 Hz), 6.77 (d, 2H, *J* = 9 Hz), 6.61 (d, 1H, *J* = 11 Hz), 5.37(t, 1H, *J* = 11 Hz), 5.16−5.07 (m, 2H), 4.86 (d, 1H, *J* = 11 Hz), 4.40−4.27 (3H, m), 3.76 (s, 3H), 3.65−3.57 (m, 2H), 2.34 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 157.2, 137.9, 137.6, 135.8, 134.5, 130.4, 129.9, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 125.1, 113.6, 75.5, 73.2, 72.7, 65.4, 55.3, 54.3, 47.5; MS (EI) *m/e* (relative intensity) 519 (M$^+$, 1), 91(100). Anal. Calcd for $C_{34}H_{33}NO_4$: C, 78.59; H, 6.40; N, 2.70. Found: C, 78.61; H, 6.46; N, 2.66.

(3*S*,4*S*,5*R*)-3-Benzyloxy-4-benzyloxymethyl-5-(2-phenylethenyl)-2-pyrrolidinone (9). To a solution of **8** (87 mg, 0.17 mmol) in 16 mL of acetonitrile cooled at 0 °C was added a solution of ceric ammonium nitrate (275 mg, 0.50 mmol) in 4 mL of water over a 5-min period. The mixture was stirred for 1 h at 0 °C, warmed to 10 °C, and diluted with 60 mL of water. The aqueous layer was extracted three times with 100-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification

(11) Rüeger, H.; Benn, M. *Heterocycles* **1983**, *20*, 1331−1334. Mohanraj, S.; Kulanthaivel, P.; Subramanian, P. S.; Herz, W. *Phytochemistry* **1981**, *20*, 1991−1995. Sawhney, R. S.; Atal, C. K.; Culvenor, C. C. J.; Smith, L. W. *Aust. J. Chem.* **1974**, *27*, 1805−1808.

(12) Conversion of **17** to C(7)-epimer of (−)-croalbinecine through Mitsunobu reaction was studied. Experimental details and ^{1}H NMR data for this study are in the Supporting Information.

of the residue by chromatography on silica gel (1:2, EtOAc/hexanes) gave **9** (53 mg, 77%) as a white solid: $R_f = 0.13$ (1:2, EtOAc/hexanes); mp 106−107 °C; $[\alpha]^{22}_D$ −95.9 (*c* 1.4, $CHCl_3$); IR (KBr, cm^{-1}) 3330, 1724; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.07 (m, 15H), 6.67 (d, 1H, $J = 12$ Hz), 6.26 (s, 1H), 5.50 (dd, 1H, $J = 11$, 10 Hz), 5.07 (d, 1H, $J = 12$ Hz), 4.75 (d, 1H, $J = 12$ Hz), 4.61 (t, 1H, $J = 9$ Hz), 4.25 (m, 2H), 4.16 (d, 1H, $J = 8.7$ Hz), 3.46 (m, 2H), 2.27(m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3, 137.9, 137.7, 135.7, 133.9, 130.6, 128.5, 128.4, 128.2, 127.7, 127.5, 127.4, 75.2, 73.0, 72.6, 65.6, 50.0. 49.0; MS (EI) *m/e* (relative intensity) 414 (M^+, 0.04), 91 (100). Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.65; H, 6.76; N, 3.16.

(3*S*,4*S*,5*R*)-1-Allyl-3-benzyloxy-4-benzyloxymethyl-5-(2-phenylethenyl)-2-pyrrolidinone (10). To a mixture of **9** (193 mg, 0.47 mmol) and NaH (22 mg, 0.93 mmol) in 8 mL of THF were added allyl bromide (0.081 mL, 0,93 mmol) and tetra-*n*-butylammonium iodide (17 mg, 0,04 mmol). The mixture was stirred for 1 h at ambient temperature and quenched with 50 mL of saturated NH_4Cl solution. The aqueous layer was extracted three times with 50-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (1:4, EtOAc/hexanes) gave **10** (201 mg, 95%) as a white solid: $R_f = 0.20$ (1:4, EtOAc/hexanes); mp 72 °C; $[\alpha]^{24}_D$ −115 (*c* 1.08, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 1698; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39−7.12 (m, 15H), 6.76 (d, 1H, $J = 11$ Hz), 5.57 (m, 1H), 5.45 (t, 1H, $J = 11$ Hz), 5.09 (d, 1H, $J = 11$ Hz), 4.94 (m, 2H), 4.78 (d, 1H, $J = 11$ Hz), 4.62 (dd, 1H, $J = 11$, 7 Hz), 4.26 (m, 2H), 4.16 (m, 2H), 3.46 (m, 3H), 2.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 138.0, 137.7, 135.7, 134.6, 132.1, 130.3, 128.4, 128.3, 128.2, 127.7, 127.6, 127.5, 127.3, 117.9, 75.9, 73.1, 72.5, 66.0, 53.2, 47.5, 43.4; MS (EI) *m/e* (relative intensity) 454 (M^+, 0.04), 91(100). Anal. Calcd for $C_{30}H_{31}NO_3$: C, 79.44; H, 6.89; N, 3.09. Found: C, 79.67; H, 7.17; N, 2.81.

(1*S*,2*S*,7a*R*)-2-Benzyloxy-1-benzyloxymethyl-2,5,7a-trihydropyrrolizin-3-one (12). A mixture of **10** (185 mg, 0.41 mmol) and Grubbs catalyst **11** (10 mg, 0.012 mmol) in 30 mL of benzene was heated at reflux for 12 h, and quenched by exposure to air for 4 h. The mixture was filtered over Celite, and the filtrate was concentrate under reduced pressure. The residue was purified by chromatography on silica gel (1:3, EtOAc/hexanes) to give **12** (129 mg, 90%) as a colorless oil: $R_f = 0.21$ (1:3, EtOAc/hexanes); $[\alpha]^{24}_D$ −108 (*c* 2.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3031, 1708; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29 (m, 10H), 5.92 (m, 1H), 5.85 (m, 1H), 5.09 (d, 1H, $J = 12$ Hz), 4.70 (d, 1H, $J = 12$ Hz), 4.51−4.39 (m, 3H), 4.28 (m, 2H), 3.66 (m, 2H), 3.52 (dd, 1H, $J = 10$, 7 Hz), 2.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5, 137.8, 137.7, 128.2, 128.1, 128.0, 127.6, 127.5, 127.3, 77.9, 73.0, 72.4, 68.2, 65.5, 51.7, 50.0; MS (EI) *m/e* (relative intensity) 349 (M^+, 0.02), 91(100). Anal. Calcd for $C_{22}H_{23}NO_3$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.65; H, 6.38; N, 4.03.

(1a*S*,5*S*,6*S*,6a*S*,6b*R*)-5-Benzyloxy-6-(benzyloxymethyl)-perhydroxireno[2,3-*a*]pyrrolizin-4-one (15). A mixture of **12** (98 mg, 0.28 mmol), $NaHCO_3$ (25 mg, 1.12 mmol), and *m*-CPBA (193 mg, 1.12 mmol) in 10 mL of benzene was stirred for 36 h at ambient temperature. The mixture was diluted with 100 mL of EtOAc and sequentially washed with 100 mL of saturated Na_2CO_3 and 100 mL of saturated $NaHCO_3$ solutions. Each aqueous layer was extracted with 50 mL of EtOAc. The aqueous layer was extracted three times with 50-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. Purification of the residue by chromatography on silica gel (1:1, EtOAc/hexanes) to give **15** (63 mg, 61%) and **16** (10 mg, 10%) as a colorless oil. **15**: $R_f = 0.23$ (1:1, EtOAc/Hexane); $[\alpha]^{27}_D$ −103 (*c* 0.6, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 1709; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37−7.25 (m, 10H), 5.02 (d, 1H, $J = 12$ Hz), 4.67 (d, 1H, $J = 12$ Hz), 4.44 (m, 2H), 4.27 (d, 1H, $J = 10$ Hz), 4.03 (d, 1H, $J = 13$ Hz), 3.68−3.56 (m, 4H), 3.50 (dd, 1H, $J = 10$, 7 Hz), 2.95 (d, 1H, $J = 13$ Hz), 2.64 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.8, 137.7, 128.3, 128.2, 128.0, 127.6, 127.4, 78.6, 73.0, 72.1, 67.9, 59.0, 55.7, 55.3, 44.6, 43.9; MS(EI) *m/e* (relative intensity) 366 (M + 1, 0.08), 91 (100). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.34; H, 6.42; N, 3.52.

(1*S*,2*S*,7*S*,7a*S*)-2-Benzyloxy-1-benzyloxymethyl-7-hydroxy-7a-pyrrolizidine (17). To a slurry of $LiAlH_4$ (46 mg, 1.23 mmol) in 5 mL of THF at 0 °C was added slowly a solution of **15** (75 mg, 0.21 mmol) in 5 mL of THF. The resulting mixture was stirred for 2 h at 0 °C and 12 h at ambient temperature. The mixture was cooled to room temperature and a few drops of water were added slowly until no more hydrogen gas evolved. The resulting mixture was filtered over Celite, and the filtrate was concentrate under reduced pressure. The residue was purified by chromatography on silica gel (CH_3OH) followed by dissolving into CH_2Cl_2 to remove the silica gel eluted. Removal of the solvent under reduced pressure gave **17** (47 mg, 65%) and **18** (7 mg, 9%) as a colorless oil. **17**: $R_f = 0.21$ (CH_3OH); $[\alpha]^{24}_D$ −40.7 (*c* 0.55, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 3406; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 10H), 4.50 (s, 4H), 4.19 (m, 1H), 4.00 (q, 1H, $J = 5$ Hz), 3.57 (dd, 1H, $J = 9$, 7 Hz), 3.37 (m, 2H), 3.23 (dd, 1H, $J = 11$, 5 Hz), 3.12 (m, 1H), 2.80 (m, 3H), 1.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 137.4, 128.4, 128.3, 127.7, 127.6, 127.4, 83.1, 73.1, 72.1, 71.8, 71.6, 71.1, 58.1, 53.2, 43.8, 36.1; MS (EI) *m/e* (relative intensity) 353 (M^+, 2), 202 (5), 188 (28), 141 (31), 112 (46), 100 (37), 91 (100).

(1*S*,2*S*,7*S*,7a*S*)-2, 7-Dihydroxy-1-hydroxymethyl-7a-pyrrolizidine [2, (−)-Croalbinecine]. A mixture of **17** (30 mg, 0.085 mmol) and 20% $Pd(OH)_2$ (30 mg, 100% w/w) in 3 mL of ethanol was shaken for 10 days under 45-psi hydrogen pressure using Parr hydrogenator. The mixture was filtered over Celite, and the filtrate was concentrate under reduced pressure. The residue was purified by chromatography on silica gel (20:1, CH_3OH/NH_4OH) to give **2** (9 mg, 61%) as a colorless oil. **2**: $R_f = 0.21$ (20:1, CH_3OH/NH_4OH); $[\alpha]^{24}_D = -35$ (*c* 0.17, EtOH); IR ($CHCl_3$, cm^{-1}) 3326, 2918, 1409, 1090; ^1H NMR (D_2O, 300 MHz) δ 4.28 (m, 1H), 4.18 (m, 1H), 3.74 (dd, 1H, $J = 11$, 5 Hz), 3.63 (dd, 1H, $J = 11$, 7 Hz), 3.27 (m, 2H), 3.13 (m, 1H), 2.75 (m, 1H), 2.55 (t, 1H, $J = 9$ Hz), 2.34 (quint, 1H, $J = 7$ Hz), 2.02 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz) δ 75.4, 72.4, 71.8, 62.8, 62.5, 53.8, 48.0, 37.2; MS (EI) *m/e* (relative intensity) 173 (M^+, 7)

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Supporting Information Available: Experimental procedures and compound characterization data for **5b**, **13**, **14**, **16**, and **18** and X-ray crystallographic data for **7**. Experimental details and ^1H NMR data for the conversion of **17** to the C(7)-epimer of (−)-croalbinecine. This material is available free of charge via the Internet at http://pubs.acs.org.

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