General Procedure for the Benzylation of Substituted Benzyl Alcohols (1) with Benzene in the Presence of Nafion-H. A mixture of substituted benzyl alcohols (1) (30 mmol) and Nafion-H (10 wt %) in benzene (0.9 mol) was refluxed with stirring until completion of the reaction as monitored by GLC analysis (OV-1, 2 m). The solid resinsulfonic acid was then filtered off, and the filtrate was analyzed by GLC. The reaction conditions and yields are summarized in Table I.

General Procedure for the Benzylation of Benzyl Alcohol (1) with Alkylbenzenes (2) in the Presence of Nafion-H. A mixture of benzyl alcohol (1) (30 mmol) and Nafion-H (10 wt %) in alkylbenzenes (0.9 mol) was heated at 90–95 °C with stirring until completion of the reaction as monitored by GLC analysis (OV-1, 2 m). The solid resinsulfonic acid was then filtered off, and the filtrate was analyzed by GLC. The reaction conditions and yields are summarized in Table II.

Competitive Benzylation of Benzene and Toluene with Benzyl Alcohols. A mixture of benzyl alcohol (1) (30 mmol) and Nafion-H (10 wt %) in benzene (0.45 mol) and toluene (0.45 mol) was refluxed with stirring for 2 h. The solid resinsulfonic acid was then filtered off, and the filtrate was analyzed by GLC. The reaction conditions and yields are summarized in Table III.

General Procedure for the Benzylation of Bis(hydroxymethyl)benzenes (5) in the Presence of Nafion-H. A mixture of bis(hydroxymethyl)benzenes (5) (1.45 mmol) and Nafion-H (300 mg) in 30 mL of benzene was refluxed with stirring for 2 h. The reaction mixture was treated as described above to give **6a** and **6b** in yields of 76% and 75%, respectively.

Benzylation of 2-(Hydroxymethyl)diphenylethane (7) with Benzene in the Presence of Nafion-H. A mixture of 2-hydroxydiphenylethane (7) (1 mmol) and Nafion-H (300 mg) in 30 mL of benzene was refluxed with stirring for 2 h. The reaction mixture was treated as described above to give 193 mg (99.5%) of **9** as colorless prisms (hexane): mp 75–76 °C (lit.[10] mp 78–79 °C).

General Procedure for the Trimerization and Tetramerization of Methoxybenzyl Alcohols (10 and 12). A mixture of methoxybenzyl alcohols (10 mmol) and 300 mg of Nafion-H in 30 mL of CH_2Cl_2 was refluxed with reflux for 2 h. The reaction mixture was treated as described above to give 70% of **11** and 80% of **13**, respectively.

11: colorless prisms (benzene); mp 232–234 °C (lit.[7] mp 234 °C).

13: colorless prisms (CH_2Cl_2); mp >300 °C (lit.[8] mp 335–365 °C); mass spectrum, *m/e* 592 (M^+).

Regeneration of Nafion-H Catalyst. The recovered catalyst was washed several times with acetone and deionized water, followed by drying at 105 °C for 10 h. The catalyst activity of regenerated catalyst was as good as that of fresh catalyst.

(10) Bestmann, H. J.; Hartl, R.; Haberlein, H. *Liebigs Ann. Chem.* **1968**, *718*, 33.

Asymmetric Synthesis of the Corynantheine Alkaloids via an Intramolecular Blaise Reaction. (−)-Corynantheidol and (−)-Dihydrocorynantheol

Richard L. Beard and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

Received October 1, 1990

An asymmetric total synthesis of the corynantheine family of alkaloids has been accomplished, leading to corynantheidol (**1a**) and dihydrocorynantheol (**1b**). Formal syntheses to corynantheidine and dihydrocorynantheine are also shown. The key to this asymmetric route is the use of (1) chiral β-carboline formamidines, which allow high degrees of diastereoselection at C-3 with chloroacetonitrile, and (2) a new version of the Blaise reaction using Zn–Ag couple and ultrasonic radiation. These two synthetic techniques combine to allow an efficient entry into the title compounds. The overall yield of **1a** was 16.4% in seven steps from starting carboline **5**.

The class of indole alkaloids related to yohimbine and known as the ring E seco equivalents are called the corynantheines.[1] There have been several beautiful total syntheses of these substances, although all provided racemic material.[2] Our program on asymmetric synthesis of various alkaloids and other medicinally important substances[3-8] has relied on the use of chiral formamidines. These versatile synthons, in both chiral and achiral forms, have provided a large array of elaborated nitrogen compounds since their introduction in 1980.[9]

We now report a further advance in this methodology that incorporates the use of the old, seldom-employed, Blaise reaction[10a] and its application toward the asymmetric total synthesis of the corynantheine alkaloids corynantheidol (**1a**) and dihydrocorynantheol (**1b**). Furthermore, the route to these systems also allows entry into two related seco alkaloids, corynantheidine (**2a**) and dihydrocorynantheine (**2b**).

Pivotal intermediates to **1** and **2** have been the tetracyclic ketones **3** and **4**, the latter of which have been prepared in racemic form by Szantay,[11] Weisbach,[12]

(1) Isolation: Kerner, P.; Schwyzer, R.; Flan, A. *Helv. Chim. Acta* **1952**, *35*, 851. Structure determination: Prelog, V.; Janot, M. M.; Goutarel, R. *Helv. Chim. Acta* **1951**, *34*, 1207. Stereochemistry: Van Tamelen, E. E.; Aldrich, P. E.; Katz, T. J. *J. Am. Chem. Soc.* **1957**, *79*, 6426.

(2) For a review on the various total syntheses of the corynantheine series, see: *Total Synthesis of Natural Products*; Apsimon, J. A., Ed.; Wiley: New York, 1977; Vol. 3, pp 315–344.

(3) Meyers, A. I.; Loewe, M. F.; Sohda, T. *J. Org. Chem.* **1986**, *51*, 3108.

(4) Meyers, A. I.; Miller, D. B.; White, F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778.

(5) Meyers, A. I.; Dickman, D. A.; Bailey, T. R. *J. Am. Chem. Soc.* **1985**, *107*, 7974.

(6) Meyers, A. I.; Bailey, T. R. *J. Org. Chem.* **1986**, *51*, 872.

(7) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095.

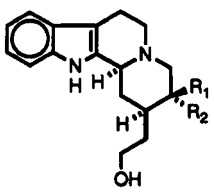
(8) Meyers, A. I.; Guiles, J. *Heterocycles* **1989**, *28*, 295.

(9) For earlier work on chiral and achiral formamidines see: Meyers, A. I. *Aldrichimica Acta* **1985**, *18*, 59; *Lect. Heterocycl. Chem.* **1984**, *7*, 75.

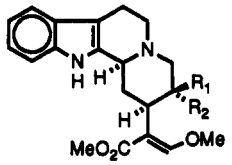
(10) (a) Blaise, E. E. *C. R. Hebd. Seances Acad. Sci.* **1901**, *132*, 478. (b) For a recent use of this reaction, see: Kishi, Y.; Hannick, S. M. *J. Org. Chem.* **1983**, *48*, 3833.

(11) Szantay, C.; Toke, L.; Hordy, K.; Kalans, G. *J. Org. Chem.* **1967**, *32*, 423.

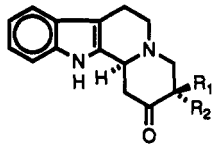
0022-3263/91/1956-2091$02.50/0



(-)-1a, R_1=Et, R_2=H
(-)-1b, R_1=H, R_2=Et



(-)-2a, R_1=Et, R_2=H
(-)-2b, R_1=H, R_2=Et



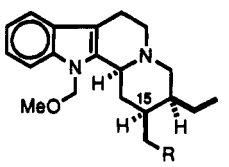
(-)-3, R_1=Et, R_2=H
(-)-4, R_1=H, R_2=Et

Bosch,[13a] Ninomiya, and Winterfeldt[13b] using various clever routes. The only difference between **3** and **4** is the stereochemistry in ring D where the ethyl group is either β (axial) or α (equatorial), respectively.

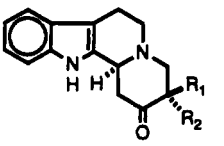
Our route to enantiomerically pure **1** was initiated by metalation of the β-carboline **5**[3,4] followed by rapid addition of chloroacetonitrile–KH (-90 °C) and then hydrazine to remove the formamidine group (Scheme I). This produced the (*S*)-(cyanomethyl)carboline **6** in 60–65% yield and 80–85% ee. The enantiomeric purity was determined on a chiral Pirkle column after **6** had been converted to the 1-naphthamide. Integration of the peaks showed that the *S* to *R* ratio was 92:8 ± 2.[14] The amide **7** was prepared by treating the carboline with 2-bromobutanoyl bromide and the 1:1 diastereomeric mixture subjected, without delay, to a zinc–silver couple in THF and agitated by ultrasonic radiation.[15] In this fashion, the intramolecular Blaise reaction proceeded smoothly at 25–40 °C to give the cyclic product **8** in 84% yield. In the absence of the zinc–silver couple, or by use of the various reported forms[16] of activated zinc, or without the use of ultrasound, the yields of this step were poor to nonexistent and cluttered with a variety of side and decomposition products. Kishi[10b] has described the apparent utility of activated zinc in the classical Blaise reaction in an intermolecular fashion to reach cyclic intermediates for the synthesis of saxitoxins. To demonstrate the generality of this intramolecular version of the Blaise reaction, we performed several additional experiments on the cyano ester and amides shown in Scheme II. The bromo ester of the cyanoethanol derivative **15** was smoothly transformed into the enamino ester **16** in 70% yield while the bromo amides **17** and **20** were readily converted into enamino amides **18** and **21** in 80% and 79% yields, respectively. In the latter two examples, hydrolysis was performed to furnish the dicarbonyl derivatives **19** and **22** in 95% and 87% yields, respectively. It is clear from these results that this ring closure of cyano bromo amides or esters will be quite useful.

The Blaise cyclization product **8** was hydrolyzed in 20% H_3PO_4 to the keto lactam **9**, which was isolated as a 10:1 mixture ($[\alpha]_D$ -170°, mp 145–148 °C) presumed at the time to be mainly the axial ethyl epimer, due to minimization of nonbonded interaction with the flanking carbonyls.

Lithium aluminum hydride reduction of **9** gave the hydroxy amines **10** as a 4:1 mixture of carbinols in 73% combined yield. Without further characterization, these carbinols were oxidized under Swern conditions (TFAA–DMSO, Et_3N, CH_2Cl_2, -78 °C)[17] and after flash chromatography gave ketone **11** as a single pure material (85%, $[\alpha]_D$ -260°, mp 128–129 °C). It is noteworthy that the ethyl group maintained its axial position during the two-step sequence from **9**. Treatment of **11** with sodium dimethyl [(methoxycarbonyl)methyl]phosphonate according to the procedure of Weisbach[12] produced a 1:1 mixture of *E* and *Z* unsaturated esters **12a**, which was hydrogenated with use of Pd/C in ethyl acetate to give the saturated ester **13a** in 96% yield (two steps) as an 8:1 mixture of β to α C-15 acetic esters. Separation of the latter mixture



13a, R=CO_2Me (8:1, β/α)
14a, R=CH_2OH



3, R_1=Et, R_2=H $[\alpha]_D$ -126°
4, R_1=H, R_2=Et $[\alpha]_D$ -89.5°

was not easy, and the mixture was therefore reduced with lithium aluminum hydride to the C-15 hydroxyethyl group. Separation was now possible, and this was readily performed on silica (flash chromatography) to give pure **14a** as the β (2-hydroxyethyl) epimer in 81% yield. Removal of the MOM group with 3 N HCl followed by 6 N KOH gave (-)-corynantheidol (**1a**) ($[\alpha]_D$ -95 ± 2°, mp 189–190 °C (lit.[18] $[\alpha]_D$ -99 ± 2°, mp 185–186, 195–196 °C)). The epimer of **1a**, namely dihydrocorynantheol (**1b**), required that we have access to the tetracyclic ketone (-)-**4**. As it happened, removal of the MOM group in **11** (3 N HCl, 6 N KOH) gave an 84% yield of the epimeric ketones **3** and **4** in a ratio of 1:10. This mixture was readily separated (SiO_2, flash chromatography) to pure material, and each compound was completely characterized. Treatment of either **3** or **4** with 10% KOH returned the 10:1 equilibrium mixture. With pure **4** as the major thermodynamic epimer,[19] it was now possible to carry on the approach to dihydrocorynantheol (**1b**) by essentially repeating the route described above to reach **1a**. This was performed with **4** and gave (-)-**1b**, in all respects identical with the natural material.[18]

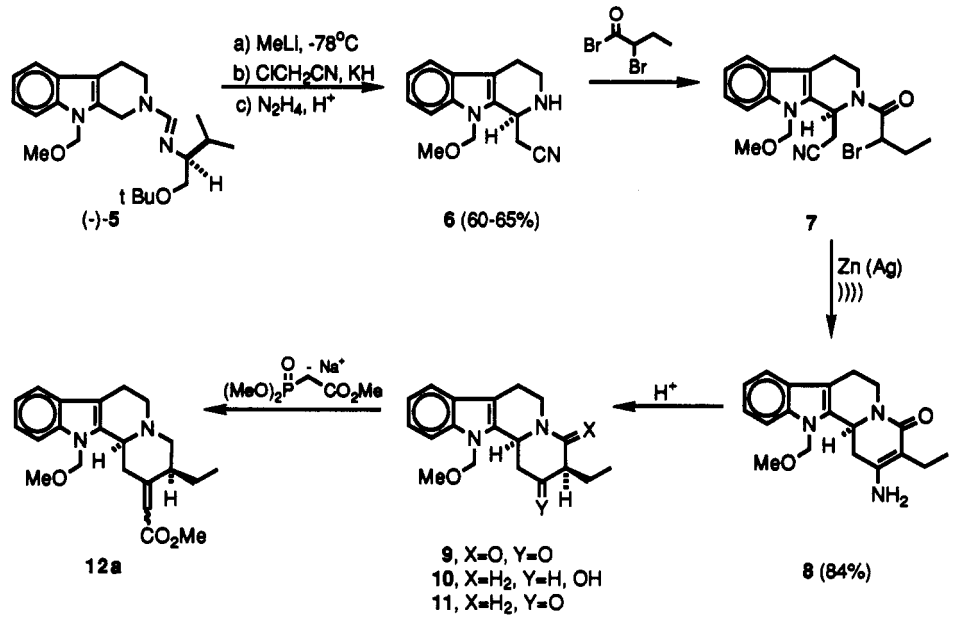
In summary, we have demonstrated excellent access to the corynantheine family of alkaloids in enantiomerically pure form using the chiral formamidine methodology along with the intramolecular Blaise process. Other alkaloids of various families are under study and will be reported in due course.

Experimental Section

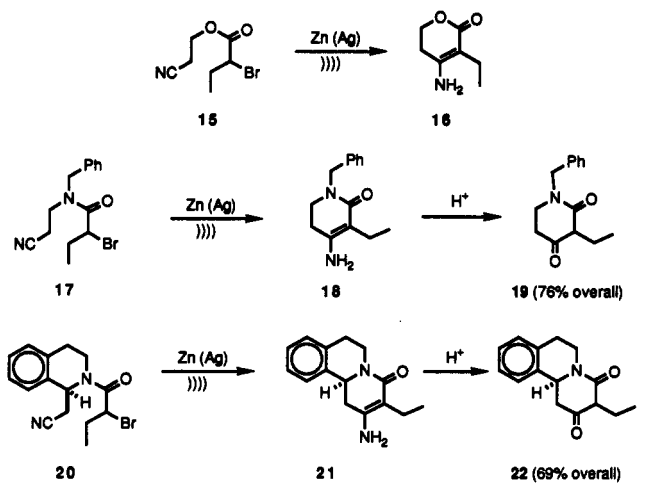
General Procedures. Solvents were distilled under an argon atmosphere as follows: tetrahydrofuran (THF) and diethyl ether from sodium benzophenone ketyl; dichloromethane, dimethyl

(12) Weisbach, J. A.; Kirkpatrick, J. C.; Williams, K. R.; Anderson, E. L.; Yim, E. C.; Douglas, B. *Tetrahedron Lett.* **1965**, 3457.
(13) (a) Ribaralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.* **1989**, *54*, 5591. (b) Ninomiya, I.; Naito, T.; Miyata, O.; Shinada, T.; Winterfeldt, E.; Freund, R.; Ishida, T. *Heterocycles* **1990**, *30*, 1031.
(14) Determined by converting **6** to its naphthamide and analysis by HPLC on a chiral Pirkle Column (Baker). The ratio of *S* to *R* was 92:8 ▶ 2.
(15) The zinc–silver couple was prepared as described: Denis, J. M.; Girard, C.; Conia, J. M. *Synthesis* **1972**, 549.
(16) Fürstner, A. *Synthesis* **1989**, 571.
(17) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(18) (a) Vamvacas, C.; Phillipsborn, W. V.; Schlittler, E.; Schmidt, H.; Karrer, P. *Helv. Chim. Acta* **1957**, *40*, 1793. (b) Gilbert, B.; Antonaccio, L. D.; Djerassi, C. *J. Org. Chem.* **1962**, *27*, 4702. (c) Dastoor, N. J.; Gorman, A. A.; Schmidt, H. *Helv. Chim. Acta* **1967**, *50*, 213.
(19) This material was identical with the racemic ketone reported by Bosch (ref 13 above) except for chiroptical properties.

Scheme I



Scheme II



sulfoxide (DMSO), hexanes, triethylamine, pyridine, and tetramethylethylenediamine (TMEDA) from calcium hydride, and stored over activated 3A molecular sieves. When deemed necessary, reaction flasks were flame-dried, cooled under vacuum (<0.5 Torr), and flushed several times with dry argon before any reagents were added.

Most reactions were monitored by analytical thin-layer chromatography (TLC) using Merck TLC aluminum sheets precoated with silica gel 60 F_{254} (0.2 mm thick). Flash chromatography was performed with use of Aldrich grade 951 silica gel. Analytical gas chromatography (GC) was performed on a Hewlett-Packard 5890 instrument using flame ionization detection with helium carrier gas, 300 °C detector temperature, and 270 °C injector temperature and by using one of the following methods: (A) a 30 m × 0.20 mm Hewlett-Packard 5% phenyl methyl silicone fused column and oven temperature programmed at 240 °C initial at 5 °C/min to 285 °C final; (B) a 15 m × 0.25 mm Alltech RSL 150 column and oven temperature programmed at 200 °C initial at 5 °C/min to 280 °C final; or (C) a 15 m × 0.25 mm Alltech RSL 150 column and oven temperature programmed at 85 °C initial at 5 °C/min to 200 °C final. Retention times are given in minutes.

Melting points and boiling points are uncorrected. Unless the use of an internal thermometer is indicated, temperatures are reported as bath temperatures.

Elemental analyses were performed by Desert Analytics, Tucson, AZ. High-resolution mass spectral analyses were performed by Bristol-Myers Squibb Co.

β-Carboline 6. To a flame-dried two-necked 50-mL round-bottom flask containing a magnetic stir bar and fitted with a low-temperature thermometer and rubber septum was added KH (35% in mineral oil, 0.207 g, 1.81 mmol). The hydride was washed with three 5-mL portions of hexane, the flask was evacuated and flushed with dry argon five times, and the formamidine (-)-5[4] (0.465 g, 1.21 mmol) in dry THF (35 mL) was added via cannula. The flask was cooled to −74 °C, and then a solution of 1.40 M MeLi in hexane (1.3 mL, 1.81 mmol) was added dropwise over 10–12 min so as to keep the temperature of the solution below −72 °C. After 1 h, the solution was cooled below −90 °C (−90 to −100 °C) and a precooled (−78 °C) solution of chloroacetonitrile (0.214 mL, 3.38 mmol) in 1.5 mL of THF was added as fast as possible by cannula down the inside of the flask. After 30 min, the reaction was quenched at −90 °C by addition of 1 mL of HOAc–THF (1:1), and the solution was carefully allowed to warm to room temperature. The solution was diluted with 35 mL of ether and poured into 15 mL of water, the layers were separated, and the aqueous layer was extracted with ether (2×). The combined organic extracts were washed with brine, dried (K_2CO_3), and filtered and the solvents removed under reduced pressure. The brown residue was filtered through silica gel (7:3:1 hexane–ethyl acetate–triethylamine) to give 500 mg of the crude cyanocarboline. Hydrazinolysis[3,4] and purification by flash chromatography (SiO_2, 5:3:2 hexane–ethyl acetate–methanol) provided the substituted β-carboline **6** (0.198 g, 64.3%) as a light yellow solid: mp 145–146.5 °C; $[\alpha]_D$ −15.9° (c 2.46, $CHCl_3$); FTIR (paste) 3324, 3048, 2920, 2910, 2831, 2239, 1464, 1335, 1182, 1104, 1059, 906, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.12 (br s, 1 H), 2.78 (dd, 2 H, J = 4.53 Hz, J = 7.05 Hz), 2.92 (dd, 1 H, J = 10.1 Hz, J = 17.1 Hz), 3.23 (m, 2 H), 3.34 (s, 3 H), 4.47 (dd, 1 H, J = 8.24 Hz, J = 10.0 Hz), 5.35 (AB q, 2 H), 7.18 (t, 1 H, J = 7.24 Hz), 7.28 (t, 1 H, J = 6.94 Hz), 7.44 (d, 1 H, J = 8.21 Hz), 7.54 (d, 1 H, J = 8.69 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.2 (CH_2), 23.4 (CH_2), 38.2 (CH_2), 47.8 (CH), 55.9 (CH_3), 73.7 (CH_2), 109.0 (CH), 111.7 (C), 118.4 (C), 118.6 (CH), 120.2 (CH), 122.7 (CH), 126.9 (C), 131.2 (C), 135.6 (C), 137.6 (C). Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.50; H, 6.60; N, 16.50.

2-Bromobutyramide 7. β-Carboline **6** (0.400 g, 1.64 mmol) was dissolved in 25 mL of dichloromethane. A solution of 4-(*N*,*N*-dimethylamino)pyridine (10 mg) and triethylamine (0.251 mL, 1.80 mmol) in 5 mL of dichloromethane was added, and the resulting solution was cooled to 0 °C. 2-Bromobutyryl bromide (0.211 mL, 1.80 mmol) was added slowly over about 5 min, and stirring was continued for an additional 30 min at 0 °C. The solution was diluted with 25 mL of dichloromethane and poured into 10 mL saturated aqueous $NaHCO_3$, and the layers separated. The aqueous layer was extracted with dichloromethane (2 × 10

mL), the organic fractions were collected, washed with brine, dried ($MgSO_4$), and filtered, and the solvents were removed under reduced pressure to give 2-bromobutyramide **7** (589 mg, 88.8%) as an inseparable 1:1 mixture of diastereomers after flash chromatography (SiO_2, 3:1 hexane–ethyl acetate): FTIR (paste) 3056, 2931, 2850, 2250, 1643, 1463, 1417, 1378, 1341, 1310, 1211, 1186, 1064, 911, 742 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) two diastereomers (1:1) δ 1.03 (t, 1.5 H, J = 7.13 Hz), 1.10 (t, 1.5 H, J = 7.08 Hz), 2.17 (m, 1 H), 2.24 (m, 1 H), 2.71–3.43 (m, 4 H), 3.35 (s, 3 H), 3.81 (m, 0.5 H), 3.91 (m, 0.5 H), 4.26 (m, 1 H), 4.39 (m, 0.5 H), 4.57 (m, 0.5 H), 5.41 (AB q, 2 H), 5.98 (br t, 0.5 H), 6.16 (br t, 0.5 H), 7.15–7.32 (m, 2 H), 7.42–7.53 (m, 2 H). Anal. Calcd for $C_{19}H_{22}BrN_3O_2$: C, 56.41; H, 5.49; N, 10.37. Found: C, 56.36; H, 5.47; N, 9.74.

Eneamino Amide 8. Zn–Ag couple[15] (0.746 mg, 11.4 mmol) was suspended in 40 mL of THF and subjected to ultrasonic irradiation at 40 °C for 10 min under an argon atmosphere. A solution of the 2-bromobutyramide **7** (1.61 g, 3.80 mmol) in 10 mL of THF was added via syringe while the flask was swirled, and the flask was placed back in the sonicator and irradiated at 40 °C until all of the starting material was absent from the reaction vessle as judged by TLC (30 min–2 h). About 1 mL of water was added, and the flask was removed from the bath to cool and to allow the excess zinc to settle. The liquid was decanted into another flask and the zinc rinsed with THF until all of the product was transferred to the second flask. Four milliliters of 50% aqueous K_2CO_3 was added and the solution stirred for 1 h at room temperature. The layers were separated, and the aqueous layer was rinsed twice with THF. The collected organic fractions were dried (K_2CO_3) and filtered and the solvents removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, 2:3 hexane–ethyl acetate) to give 1.09 g (87.9%) of eneamino amide **8** as a colorless solid: mp 107–109 °C; $[\alpha]_D$ –407° (*c* 2.41, $CHCl_3$); FTIR (paste) 3548, 3344, 3222, 2961, 2927, 2851, 1644, 1591, 1463, 1417, 1372, 1344, 1312, 1268, 1184, 1107, 1063, 748 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (t, 3 H, J = 7.44 Hz), 2.36 (m, 2 H), 2.75 (m, 1 H), 2.80 (m, 4 H), 3.33 (s, 3 H), 4.02 (br s, 2 H), 5.00 (m, 1 H), 5.38 (AB q, 2 H), 7.15 (t, 1 H, J = 7.45 Hz), 7.26 (t, 1 H, J = 8.31 Hz), 7.43 (d, 1 H, J = 8.09 Hz), 7.53 (d, 1 H, J = 7.61 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.8 (CH_3), 17.6 (CH_2), 21.5 (CH_2), 36.0 (CH_2), 38.7 (CH_2), 50.4 (CH), 56.0 (CH_3), 74.2 (CH_2), 103.9 (C), 109.3 (CH), 112.6 (C), 118.6 (CH), 120.5 (CH), 122.5 (CH), 126.7 (C), 134.1 (C), 138.4 (C), 147.5 (C), 168.3 (C); exact mass for $C_{19}H_{24}N_3O_2$ (MH^+), calcd 328.1868, found 328.1864.

β-Keto Amide 9. Eneamino amide **8** (1.08 g, 3.32 mmol) was dissolved in 110 mL of THF, 27.5 mL of water and 27.5 mL of concentrated H_3PO_4 were added, and the solution was stirred at room temperature until all of **8** was consumed as determined by TLC. Solid K_2CO_3 was added carefully to neutralize the mixture, and after the solution was stirred for about 10 min, the layers were separated. The aqueous layer was washed twice with THF, the organic layers were separated, combined, dried (K_2CO_3), and filtered, and the solvents were removed under reduced pressure to give 1.03 g (95.4%) of β-keto amide **9** and its C-3 epimer as an inseparable mixture of diastereomers (10:1) after purification by flash chromatography (SiO_2, 1:1 hexane–ethyl acetate): mp 143–148 °C; $[\alpha]_D$ –170° (*c* 3.41, $CHCl_3$); FTIR (paste) 3055, 2933, 1729, 1661, 1652, 1464, 1412, 1307, 1250, 1184, 1108, 1064, 1014, 969, 910, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major diastereomer) δ 1.05 (t, 3 H, J = 7.38 Hz), 2.04 (m, 2 H), 2.41 (dd, 1 H, J = 11.2 Hz, J = 18.3 Hz), 2.93 (m, 3 H), 3.30 (s, 3 H), 3.37 (m, 2 H), 4.97 (dd, 1 H, J = 12.5 Hz, J = 14.5 Hz), 5.38 (AB q, 2 H), 7.19 (t, 1 H, J = 7.20 Hz), 7.29 (t, 1 H, J = 7.11 Hz), 7.44 (d, 1 H, J = 8.01 Hz), 7.54 (d, 1 H, J = 7.62 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 16.9, 20.7, 40.0, 46.4, 48.1, 56.0, 59.1, 74.1, 109.3, 111.9, 118.7, 120.6, 123.0, 126.3, 131.9, 138.4, 168.3, 203.4; exact mass for $C_{19}H_{23}N_2O_3$ (MH^+), calcd 327.1709, found 327.1699; judged to be >98% pure by GC (method A, General Procedures); retention time 17.18 (both diastereomers).

Hydroxyindoloquinolizidine 10. β-Keto amide **9** (0.268 g, 0.821 mmol) in 10 mL of THF was added via syringe pump over 4 h to a suspension of lithium aluminum hydride (0.125 g, 3.28 mmol) in 10 mL of THF at reflux. After the addition was complete (30 min), the suspension was cooled to 0 °C and 0.13 mL of water was added carefully. The solution was diluted with 10 mL of ether, 0.13 mL of 10% aqueous NaOH and 0.26 mL of water were added, and stirring continued for 30 min at room temperature. The ether was decanted from the granular solids into another flask, and the solids were triturated twice with ether. The collected organic layers were dried (K_2CO_3–$MgSO_4$) and filtered and the solvents removed under reduced pressure to give 237 of residue. The diastereomeric alcohols were purified by flash column chromatography (SiO_2, 8:2:1 hexane–ethyl acetate–triethylamine) to give 186 mg of alcohols **10** (72.7%) as a 4:1 mixture of diastereomers: IR (paste) 3391, 3051, 2926, 1463, 1372, 1341, 1306, 1183, 1108, 1064, 911, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) (major diastereomer) δ 0.97 (t, 3 H, J = 7.35 Hz), 1.26 (m, 2 H), 1.55 (m, 2 H), 1.70 (m, 1 H), 2.04 (m, 1 H), 2.30 (dt, 1 H, J = 13.2 Hz), 2.60 (dd, 1 H, J = 4.6 Hz, J = 11.7 Hz), 2.62 (dd, 1 H, J = 1.5 Hz, J = 11.7 Hz), 2.95 (m, 2 H), 3.29 (s, 3 H), 3.74 (m, 1 H), 3.97 (m, 1 H), 5.41 (AB q, 2 H), 7.17 (m, 2 H), 7.37 (d, 1 H, J = 8.0 Hz), 7.47 (d, 1 H, J = 7.4 Hz); judged to be >98% pure by GC (method B, General Procedures); retention times 11.27 (major), 11.79 (minor).

Ketoindoloquinolizidine 11. To a stirred solution of dimethyl sulfoxide (0.220 mL, 3.10 mmol) in dry dichloromethane (3.0 mL) cooled to –78 °C under a static pressure of dry argon was added a solution of trifluoroacetic anhydride (0.330 mL, 2.33 mmol) in 1.5 mL dichloromethane over about 10 min. Afterward, a solution of alcohol **10** (0.338 mg, 1.07 mmol) in 3.0 mL of dichloromethane was added dropwise over about 10 min. The solution was stirred at –78 °C for an additional 30 min, and then triethylamine (0.620 mL) was added over about 10 min. The dry ice bath was removed, and the temperature of the solution was allowed to warm to room temperature slowly over 40 min. Water was added, the layers separated, and the aqueous layer was extracted with two 5-mL portions of dichloromethane. The collected organic layers were washed with brine, dried ($MgSO_4$), and filtered and the solvents removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, 1:1 hexanes–ethyl acetate) to give 286 mg of **11** (85.2%): mp 128–129.5 °C; $[\alpha]_D$ –260° (*c* 0.60, THF); IR (paste) 3049, 2930, 2814, 2750, 1712, 1667, 1575, 1464, 1372, 1263, 1183, 1135, 1108, 1080, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3 H, J = 7.46 Hz), 1.25 (m, 2 H), 1.81 (2 m, 2 H), 2.34 (m, 1 H), 2.69 (dd, 1 H, J = 9.5 Hz, J = 13.1 Hz), 2.77 (m, 1 H), 3.01 (several d, 4 H), 3.27 (s, 3 H), 3.91 (br d, 1 H), 5.34 (AB q, 2 H), 7.18 (m, 2 H), 7.39 (d, 1 H, J = 8.1 Hz), 7.50 (d, 1 H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 22.1, 24.5, 44.7, 51.3, 52.3, 55.8, 57.8, 58.0, 74.6, 109.3, 111.2, 118.3, 120.1, 122.2, 126.9, 134.9, 138.2, 211.4; judged to be >98% pure by GC (method B, General Procedures); retention time 10.65.

Unsaturated Ester 12a. Sodium hydride (22 mg, 60% in mineral oil, 0.544 mmol) was added to a dry 10-mL round-bottom flask and washed with hexanes (3×) and the flask evacuated at 0.5 Torr. The vacuum was broken with dry argon, the hydride suspended in 4.0 mL of dry THF, and the suspension cooled in an ice–water bath. Trimethyl acetophosphonate (0.097 mL, 0.6 mmol) in 1 mL of THF was added dropwise over 15 min, and after an additional 15 min, a solution of ketone **11** (85 mg, 0.272 mmol) in 2 mL of THF was added dropwise. The solution was stirred for 10 min at 0 °C and then warmed to 50 °C for about 4 h (or until all of **11** was consumed as judged by TLC). The solution was diluted with 5 mL of ether and poured into a separatory funnel containing 5 mL of water. The layers were separated, and the aqueous layer was extracted twice more with ether. The collected organic extracts were washed with brine, dried ($MgSO_4$), and filtered and the solvents removed under reduced pressure to produce 83 mg of **12a** (83%) as a 1:1 mixture of *E* and *Z* isomers, which were used in the next step without further purification. Data refer to a mixture of *E* and *Z* isomers: IR (paste) 3053, 2924, 2856, 2810, 2750, 1716, 1646, 1464, 1378, 1224, 1160, 1108, 1076, 741 cm^{-1}; judged to be >98% pure by GC (method A, General Procedures); retention times 15.66 (45.8%), 16.05 (54.2%).

Ester 13a. Crude unsaturated ester **12a** (as a 1:1 mixture of *E* and *Z* isomers) (68 mg, 0.185 mmol) was dissolved in ethyl acetate (8 mL) in a 100-mL round-bottom flask, and hydrogen was bubbled through the solution for 10 min. Potassium carbonate (25 mg) and 10% palladium on carbon (10 mg) were added to the flask, the septum was replaced, and the flask was evacuated at 1 Torr and flushed with hydrogen five times. The suspension was rapidly stirred under an atmosphere of hydrogen overnight at room temperature. The suspension was diluted with ethyl

acetate and filtered through Celite, and the solvents were removed under reduced pressure to yield 65.3 mg (96%) of the saturated ester **13a** as an 8:1 mixture of C-15 epimers that were used in the next step without further purification. Data refer to an 8:1 mixture of diastereomers: IR (paste) 3050, 2922, 2850, 2807, 2745, 1738, 1463, 1344, 1307, 1160, 1109, 1076, 740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) (major diastereomer) δ 0.94 (t, 3 H, J = 7.3 Hz), 1.2–1.4 (m, 2 H), 1.4–1.85 (m, 3 H), 2.19 (br d, 1 H, J = 12.3 Hz), 2.34 (AB q, 2 H), 2.61 (m, 3 H), 2.92 (m, 2 H), 3.08 (dd, 1 H, J = 2.1 Hz, J = 11.9 Hz), 3.27 (s, 3 H), 3.36 (br d, 1 H, J = 11.0 Hz), 3.71 (s, 3 H), 5.35 (AB q, 2 H), 7.19 (m, 2 H), 7.37 (dd, 1 H, J = 1.1 Hz, J = 7.5 Hz), 7.46 (dd, 1 H, J = 1.5 Hz, J = 6.8 Hz); judged to be >98% pure by GC (method A, General Procedures); retention times 16.35 (major diastereomer), 16.86 (minor diastereomer).

N^a-(Methoxymethyl)corynantheidol (14a). Ester **13a** (65 mg, 0.175 mmol) was dissolved in 2 mL of dry THF, and the resultant mixture was added to a rapidly stirred suspension of lithium aluminum hydride (20 mg) in 6 mL of THF at ambient temperature under argon. The suspension was stirred for 1 h at room temperature, and 0.020 mL of water, 0.020 mL of 10% aqueous NaOH, and 0.040 mL of water were added sequentially. Stirring was continued for 30 min, and the salts were separated by decantation and washed twice with ether. The collected organic layers were dried ($MgSO_4$) and filtered and the solvents removed under reduced pressure to give 59.2 mg of residue containing an 8:1 mixture of C-15 epimeric alcohols, which were separated by flash chromatography (SiO_2, 5:3:1 hexanes–ethyl acetate–methanol) to produce 48.6 mg of **14a** as a single diastereomer (81%): mp 143–145 °C; $[\alpha]_D$ –189° (c 1.03, THF); ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3 H, J = 7.3 Hz), 1.26 (br s, 1 H), 1.33 (m, 1 H), 1.45–1.84 (m, 5 H), 1.93 (m, 1 H), 2.16 (br d, 1 H, J = 12.6 Hz), 2.62 (m, 3 H), 2.92 (m, 2 H), 3.08 (dd, 1 H, J = 2.16 Hz, J = 11.8 Hz), 3.26 (s, 3 H), 3.42 (br d, 1 H, J = 11.1 Hz), 3.72 (m, 2 H), 5.38 (AB q, 2 H), 7.16 (m, 2 H), 7.37 (d, 1 H, J = 8.1 Hz), 7.46 (d, 1 H, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 17.9, 22.5, 32.7, 36.3, 37.0, 39.5, 52.5, 55.6, 58.3, 60.6, 60.8, 74.9, 109.3, 111.1, 118.1, 119.9, 121.6, 127.4, 136.9, 138.4.

(–)-Corynantheidol (1a). N^a-(Methoxymethyl)corynantheidol (**14a**) (40 mg, 0.12 mmol) was dissolved in 1.5 mL of diethyl ether–THF (3:2), and 3 mL of 3 N aqueous HCl was added. The resulting two-phase solution was stirred rapidly at room temperature for 5 h. The aqueous phase was separated, cooled in an ice–water bath, and basified with 6 N aqueous KOH. The organic products were extracted into diethyl ether, washed with brine, dried ($MgSO_4$), and filtered and the solvents removed under reduced pressure. The residue was recrystallized from hexane and ethyl acetate to give 28.0 mg (80%) of (–)-corynantheidol: mp 189–191 °C; $[\alpha]_D$ –93° (c 0.52, pyridine); lit.[18] mp 185–186 °C, 195–196 °C; $[\alpha]_D$ –99° (c 0.54, pyr); IR (paste) 3411, 3294, 2931, 2872, 2797, 2747, 1459, 1397, 1344, 1321, 1278, 1159, 1055, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 3 H, J = 7.2 Hz), 1.26 (br s, 1 H), 1.46–1.67 (several m, 5 H), 1.84 (br d, 1 H, J = 13.2 Hz), 1.91 (m, 1 H), 2.37 (d, 1 H, J = 9.9 Hz), 2.57 (AB q, 1 H), 2.68 (br d, 1 H, J = 15.0 Hz), 2.85–3.10 (several d, 3 H), 3.20 (br d, 1 H, J = 10.8 Hz), 3.75 (t, 2 H, J = 6.5 Hz), 7.10 (m, 2 H), 7.29 (d, 1 H, J = 6.9 Hz), 7.46 (d, 1 H, J = 6.9 Hz), 7.79 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.7, 17.7, 21.8, 32.1, 36.1, 36.5, 39.7, 53.5, 58.0, 60.4, 60.9, 108.2, 110.7, 118.1, 119.3, 121.2, 127.5, 135.4, 135.9.

Ketones 3 and 4. These C-3 epimeric ketones were prepared by hydrolysis of the N^a-methoxymethyl ether as described for **14** above. In this way, 256 mg (0.819 mmol) of **11** was converted to ketones **3** and **4** (185 mg, 84.2%) in a ratio of 1:10 as judged by ^1H NMR. These diastereomers were easily separated by flash chromatography (SiO_2, 1:1 hexanes–ethyl acetate). Ketone **3**: $[\alpha]_D$ –126° (c 1.28, THF); IR (paste) 3366, 3056, 2959, 2850, 2810, 2747, 1712, 1464, 1383, 1341, 1325, 1285, 1131, 1053, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, 3 H, J = 7.5 Hz), 1.75 (m, 1 H), 1.91 (m, 1 H), 2.40 (m, 1 H), 2.74 (several d, 3 H), 2.85 (dd, 2 H, J = 11.7 Hz, J = 4.2 Hz), 3.03 (m, 1 H), 3.09 (dd, 1 H, J = 11.7 Hz, J = 3.0 Hz), 3.18 (dd, 1 H, J = 11.1 Hz, J = 10.0 Hz), 3.73 (br d, 1 H, J = 9.3 Hz), 7.15 (m, 2 H), 7.33 (dd, 1 H, J = 6.9 Hz, J = 1.0 Hz), 7.52 (d, 1 H, J = 7.4 Hz), 8.14 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 21.2, 24.1, 43.4, 52.1, 52.8, 57.7, 58.7, 108.4, 111.0, 118.2, 119.5, 121.7, 127.0, 133.1, 136.2, 211.4. Ketone **4**: mp 206–207 °C; $[\alpha]_D$ –89.5° (c 1.34, THF); IR (paste) 3373, 3056, 2962, 2883, 2810, 2770, 1712, 1463, 1372, 1341, 1322, 1244, 1125, 1042, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, 3 H, J = 7.4 Hz), 1.27 (m, 2 H), 1.95 (m, 1 H), 2.46 (t, 1 H, J = 11.5 Hz), 2.70 (several d, 3 H), 2.86 (tt, 1 H, J = 15.3 Hz, J = 2.1 Hz), 3.05 (m, 1 H), 3.27 (ddd, 1 H, J = 11.1 Hz, J = 2.7 Hz, J = 2.0 Hz), 3.42 (dd, 1 H, J = 6.15 Hz, J = 11.2 Hz), 3.64 (br d, 1 H, J = 11.8 Hz), 7.16 (m, 2 H), 7.38 (d, 1 H, J = 7.6 Hz), 7.53 (d, 1 H, J = 7.6 Hz), 8.23 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 19.4, 21.9, 45.9, 51.5, 51.6, 59.4, 60.4, 108.3, 111.1, 118.2, 119.5, 121.7, 126.9, 133.2, 136.3, 209.7.

Unsaturated Ester 12b. This compound was prepared according to the procedure described for **12a**. In this way, ketone **4** (70 mg, 0.261 mmol) was converted into 55 mg (65%) of the desired ester **12b** as a 94:6 mixture of E and Z isomers. Data for the major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, 3 H, J = 7.40 Hz), 1.49 (m, 1 H), 1.81 (m, 1 H), 2.35 (m, 2 H), 2.72 (br d, 1 H, J = 14.8 Hz), 2.81 (dd, 1 H, J = 4.3 Hz, J = 13.1 Hz), 2.87 (dd, 1 H, J = 4.3 Hz, J = 11.2 Hz), 3.03 (m, 1 H), 3.19 (AB q, 2 H) 3.73 (m, 1 H), 3.76 (s, 3 H), 3.94 (dd, 1 H, J = 3.3 Hz, J = 13.1 Hz), 5.72 (s, 1 H), 7.12 (m, 2 H), 7.32 (d, 1 H, J = 7.5 Hz), 7.48 (d, 1 H, J = 7.4 Hz), 8.44 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 20.3, 22.6, 29.7, 31.5, 46.1, 51.2, 51.7, 58.2, 59.4, 107.6, 111.0, 112.9, 118.0, 119.3, 121.3, 133.6, 136.0, 161.7, 167.9; judged to be >95% pure by GC (method A, General Procedures); retention times 14.16 (94%), 15.74 (6%).

Ester 13b. This compound was prepared in the same manner as ester **13a**. In this way, unsaturated ester **12b** (55 mg, 0.170 mmol) was reduced to 50 mg (91%) of ester **13b**: IR (film) 3391, 3062, 2918, 2847, 2805, 2744, 1732, 1574, 1455, 1324, 1156, 740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, 3 H, J = 7.4 Hz), 1.1–1.7 (several m, 4 H), 1.89 (m, 1 H), 2.16 (m, 2 H), 2.26 (dd, 1 H, J = 2.8 Hz, J = 15.6 Hz), 3.00 (m, 1 H), 3.08 (m, 2 H), 3.24 (dd, 1 H, J = 11.3 Hz), 3.72 (s, 3 H), 7.10 (m, 2 H), 7.28 (dd, 1 H, J = 2.8 Hz, J = 8.1 Hz), 7.46 (d, 1 H, J = 7.3 Hz), 7.80 (br s, 1 H).

(–)-Dihydrocorynantheol (1b). This compound was prepared in the manner described for **14a**. In this way, ester **13b** (50 mg, 0.155 mmol) was converted to 38 mg (83%) of (–)-dihydrocorynantheol (**1b**) after recrystallization of the crude product from hexane–dichloromethane: mp 178–180 °C; $[\alpha]_D$ –30 ± 2° (c 0.68, pyridine); lit.[18] mp 181–183 °C; $[\alpha]_D$ –34 ± 2° (c 0.47, pyridine); ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 7.2 Hz), 1.06 (m, 1 H), 1.2–1.5 (several m, 4 H), 1.60 (m, 1 H), 1.87 (m, 1 H), 2.00 (t, 2 H, J = 11 Hz), 2.12 (d, 1 H, J = 11 Hz), 2.55 (m, 1 H), 2.68 (d, 1 H, J = 4.6 Hz), 2.73 (br s, 1 H), 3.00 (several d, 4 H), 3.67 (br t, 2 H, J = 5.9 Hz), 7.09 (m, 2 H), 7.26 (d, 1 H, J = 7 Hz), 7.45 (d, 1 H, J = 7.4 Hz), 8.19 (br s, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 11.0, 21.6, 23.4, 35.3, 35.4, 37.2, 41.6, 53.1, 59.8, 60.2, 60.3, 107.8, 110.8, 118.0, 119.2, 121.1, 127.3, 134.9, 136.1.

β-Cyanoethyl 2-Bromobutyrate (15). This material was prepared in the manner described for **7**. In this way, 1.0 g (14.1 mmol) of 3-hydroxypropionitrile was converted to 2.48 g (80%) of the 2-bromobutyrate **15** after bulb-to-bulb distillation: bp 180–185 °C (0.35 Torr); IR (neat) 2975, 2940, 2880, 2255, 1747, 1462, 1417, 1386, 1301, 1268, 1258, 1206, 1153, 1032 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, 3 H, J = 7.3 Hz), 2.06 (m, 2 H), 2.75 (t, 2 H, J = 6.3 Hz), 4.19 (t, 1 H, J = 7.6 Hz), 4.37 (t, 2 H, J = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.8, 17.7, 28.1, 46.7, 59.8, 116.3, 169.2.

3-Ethyl-4-amino-5,6-dihydropyrone (16) was prepared according to the cyclization procedure described for lactam **8**. In this way, 2.2 g (10.0 mmol) of the 2-bromobutyrate **15** was converted to 0.985 g (69.4%) of **16** after flash chromatography (SiO_2, 5:3:1 hexane–ethyl acetate–methanol): mp 159–160 °C; FTIR (neat) 3354, 3183, 2956, 1625, 1583, 1464, 1400, 1265, 1111, 1054 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.01 (t, 3 H, J = 7.5 Hz), 2.23 (q, 2 H, J = 7.5 Hz), 2.47 (t, 2 H, J = 6.2 Hz), 4.24 (t, 2 H, J = 6.2 Hz), 4.58 (s, 2 H); judged to be >98% pure by GC (method C, General Procedures); retention time 14.61. Anal. Calcd for $C_6H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.46; H, 7.76; N, 9.86.

2-Bromobutyramide 17 was prepared in the manner described for **7**. In this way, 5.0 g of 3-(benzylamino)propionitrile was converted to 10.0 g (104%) of 2-bromobutyramide **17**, which was used in the next step without further purification: FTIR (neat)

3088, 3064, 3031, 2973, 2936, 2877, 2250, 1651, 1496, 1454, 1357, 1273, 1217, 1165, 1112, 1080, 1055, 1029, 960, 919, 809, 732, 699, 617 cm^{-1}.

Eneamino amide 18 was prepared according to the procedure described for **8**. In this way, 2 g (6.47 mmol) of the crude 2-bromobutyramide **17** was converted to 1.1 g (80% from 3-(benzylamino)propionitrile) of **18** after flash chromatography on silica (3:2 hexane–ethyl acetate): mp 144.5–146 °C; FTIR (neat) 3471, 3346, 3222, 3087, 3067, 3025, 2963, 2932, 2870, 1642, 1590, 1477, 1404, 1336, 1247, 1171, 1064, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.92 (t, 3 H, J = 7.3 Hz), 2.21 (m, 4 H), 3.09 (t, 1 H, J = 6.7 Hz), 4.08 (br s, 2 H), 4.51 (s, 2 H), 7.51 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 16.9, 20.7, 40.0, 46.4, 48.1, 56.0, 59.1, 74.1, 109.3, 111.9, 118.7, 120.6, 123.0, 126.3, 131.9, 138.4, 168.3, 203.4.

Keto amide 19 was prepared according to the procedure described for **9**. In this way, 1.0 g (4.34 mmol) of eneamino amide **18** was converted to 0.95 g (95%) of pure **19** as a clear, colorless oil after flash chromatography on silica (3:1 hexanes–ethyl acetate): FTIR (neat) 3050, 3031, 3015, 2966, 2893, 1728, 1668, 1652, 1495, 1454, 1438, 1360, 1275, 1222, 1111, 1080, 736, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.98 (t, 3 H, J = 7.3 Hz), 1.98 (m, 2 H), 2.50 (m, 2 H), 3.17 (t, 1 H, J = 5.8 Hz), 3.45 (m, 2 H), 4.69 (AB q, 2 H), 7.25 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 18.75, 37.9, 41.3, 50.0, 127.4, 127.7 (2 C), 128.5 (2 C), 136.3, 168.2, 204.9; judged to be >96% pure by GC (method C, General Procedures); retention time 22.23. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.68; H, 7.41; N, 6.06. Found: C, 71.95; H, 7.42; N, 6.11. Repeated combustion analyses failed to give satisfactory results due to the apparent hygroscopic nature of **19**.

2-Bromobutyramide 20. (*S*)-1-(Cyanomethyl)-1,2,3,4-tetrahydroisoquinoline (100 mg, 0.581 mmol) (vide infra) was acylated according to the procedure described for **7** to produce 2-bromobutyramide **20** (170 mg, 91.4%) as a 1:1 mixture of diastereomers that was used in the next step without further purification: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.03 (2 t, 3 H), 2.07–2.23 (2 m, 2 H), 2.84–3.07 (several m, 4 H), 3.72–4.50 (several m, 2 H), 4.30 (t, 0.5 H, J = 6.9 Hz), 4.47 (t, 0.5 H, J = 6.7 Hz), 5.59 (t, 0.5 H, J = 5.4 Hz), 5.74 (t, 0.5 H, J = 5.6 Hz), 7.23 (m, 4 H).

Benzoquinolizidinone 21 was prepared by the cyclization procedure described for **8**. In this way, 2-bromobutyramide **20** (170 mg) was converted to benzoquinolizidinone **21** (102 mg, 79.7% for two steps) as a white solid after flash chromatography (SiO_2, 5:3:1 hexanes–ethyl acetate–methanol): mp 191–192 °C; $[\alpha]_D$ –410° (c 1.20, THF); IR (paste) 3342, 3212, 2924, 1644, 1622, 1574, 1455, 1418, 1360, 1328, 1270, 1150, 1118, 1065, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, 3 H, J = 7.3 Hz), 2.35 (m, 2 H), 2.39 (m, 2 H), 2.54 (m, 3 H), 4.13 (br s, 2 H), 4.67 (dd, 1 H, J = 11.7 Hz, J = 12.4 Hz), 4.74 (dd, 1 H, J = 4.62 Hz, J = 12.4 Hz), 7.18 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 17.5, 29.8, 37.4, 38.0, 53.4, 103.5, 125.4, 126.3, 126.6, 129.0, 135.4, 136.1, 148.0, 168.2.

Keto amide 22 was prepared according to the procedure given for **9**. In this way, 100 mg of (–)-**21** was converted to 87 mg (87%) of keto amide **22** as an inseparable 3:1 mixture of diastereomers. Data for the major diastereomer: IR (paste) 2932, 2874, 1728, 1651, 1455, 1416, 1362, 1289, 1243, 1116, 1064, 974, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, 3 H, J = 7.0 Hz), 2.03 (m, 2 H), 2.43 (dd, 1 H, J = 11.5 Hz, J = 17.9 Hz), 2.85–3.15 (several m, 4 H), 3.32 (t, 1 H, J = 5.6 Hz), 4.69 (dt, 1 H, J = 3.8 Hz, J = 12.7 Hz), 5.14 (dd, 1 H, J = 3.6 Hz, J = 11.5 Hz), 7.24 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 17.4, 29.1, 39.3, 47.7, 51.7, 58.9, 125.8, 127.0, 127.3, 129.0, 134.0, 134.7, 167.9, 203.9; judged to be >98% pure by GC (method B, General Procedures); retention time 4.89; exact mass for $C_{15}H_{18}NO_2$ (MH^+), calcd 244.1260, found 244.1260.

(*S*)-(–)-1-(Cyanomethyl)-1,2,3,4-tetrahydroisoquinoline, used to prepare **20**, was prepared by alkylation of the lithium salt of the valinol-derived tetrahydroisoquinoline[7] with chloroacetonitrile in the same manner as described for β-carboline **6**. In this way, the valinol-derived tetrahydroisoquinoline formamidine (720 mg, 2.38 mmol) was converted to 0.573 g (69.9%) of the cyanomethyl-substituted formamidine after flash chromatography on silica (8:1:1 hexanes–ethyl acetate–triethylamine): IR (paste) 3090, 3023, 2971, 2940, 2871, 2246, 1645, 1456, 1422, 1387, 1362, 1232, 1197, 1080, 1020, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 3 H, J = 6.5 Hz), 0.92 (d, 3 H, J = 5.8 Hz), 1.12 (s, 9 H), 1.86 (m, 1 H), 2.83 (m, 2 H), 2.95 (m, 2 H), 3.14 (dd, 1 H, J = 7.6 Hz, J = 8.8 Hz), 3.33 (m, 1 H), 3.48 (dd, 1 H, J = 5.15 Hz, J = 8.9 Hz), 3.55 (m, 1 H), 3.62 (m, 1 H), 5.27 (m, 1 H), 7.24 (m, 4 H), 7.45 (s, 1 H). Hydrazinolysis[3,4] gave (*S*)-1-(cyanomethyl)-1,2,3,4-tetrahydroisoquinoline: $[\alpha]_D$ –51° (c 0.60, $CHCl_3$); IR (paste) 3332, 3062, 3021, 2936, 2832, 2247, 1668, 1602, 1494, 1455, 1428, 1379, 1316, 1129, 960, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (br s, 1 H), 2.81 (dd, 2 H, J = 2.5 Hz, J = 7.8 Hz), 2.82 (m, 2 H), 3.10 (m, 1 H), 3.20 (m, 1 H), 4.38 (t, 1 H, J = 6.4 Hz), 7.13 (m, 4 H).

Acknowledgment. We are grateful to Bristol-Myers-Squibb and The National Science Foundation for financial support of this work.

Registry No. (–)-**1a**, 483-27-2; (–)-**1b**, 2270-72-6; (–)-**3**, 131897-80-8; (–)-**4**, 112459-14-0; (–)-**5**, 114926-74-8; **6**, 131831-92-0; **6** (formamidine derivative), 131793-08-3; **7** (isomer 1), 131792-89-7; **7** (isomer 2), 131831-93-1; **8**, 131792-90-0; **9**, 131792-91-1; 3-*epi*-**9**, 131899-62-2; **10** (isomer 1), 131792-92-2; **10** (isomer 2), 131897-81-9; **11**, 131792-93-3; (*E*)-**12a**, 131792-94-4; (*Z*)-**12a**, 131793-06-1; (*E*)-**12b**, 131899-63-3; (*Z*)-**12b**, 132014-10-9; **13a**, 131792-95-5; 15α-**13a**, 131897-82-0; **13b**, 131897-83-1; **14a**, 131792-96-6; (±)-**15**, 131792-97-7; **16**, 131792-98-8; (±)-**17**, 131792-99-9; **18**, 131793-00-5; (±)-**19**, 131793-01-6; **20** (isomer 1), 131793-02-7; **20** (isomer 2), 131793-09-4; **21**, 131793-03-8; *cis*-**22**, 131897-84-2; *trans*-**22**, 131793-04-9; $ClCH_2CN$, 107-14-2; $BrCOCHBrCH_2CH_3$, 26074-52-2; $NC(CH_2)_2OH$, 109-78-4; $NC(CH_2)_2NHCH_2Ph$, 706-03-6; (*E*)-*O*-*tert*-butyl-*N*-[(1,2,3,4-tetrahydroisoquinolin-2-yl)methylene]-(*S*)-valinol, 99395-58-1; (*S*)-(–)-1-(cyanomethyl)-1,2,3,4-tetrahydroisoquinoline, 131793-05-0; (*E*)-*O*-*tert*-butyl-*N*-[[1*S*-(cyanomethyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]methylene]-(*S*)-valinol, 131793-07-2.

Supplementary Material Available: Proton and carbon NMR spectra for **3**, **4**, **8–15**, and **17–22** (33 pages). Ordering information is given on any current masthead page.

Spontaneous Resolution of 2,2′-Dimethoxy-1,1′-binaphthalene

Giovanni Gottarelli* and Gian Piero Spada

Dipartimento di Chimica Organica A. Mangini, Università di Bologna, Via S. Donato, 15, I-40127 Bologna, Italy

Received August 27, 1990

The dimethyl ether of 1,1′-bi-2-naphthol crystallizes as a conglomerate and can be resolved without chiral auxiliaries by entrainment. The direct crystallization of a supersaturated solution of the title compound partially enriched by one enantiomer (ee ≈ 2%) is conducted in anisole at 40 °C and gives, after one crystallization, a compound with ee >98%. Demethylation under nonracemizing conditions gives the enantiomeric 1,1′-bi-2-naphthol.

1,1′-Bi-2-naphthol (**1**) and its derivatives are interesting chiral auxiliaries used for many purposes.[1] Several preparative methods for enantiomerically pure **1** are reported in the literature, ranging from the crystallization

0022-3263/91/1956-2096$02.50/0