a [4n + 2]annulene have been yet reported.

We hope that this report will now stimulate a search for further examples and more definitive evidence for a ground-state triplet. We ourselves are actively attempting the synthesis of **10**, **13**, **16**, and **18** in the hope of providing more data, and also we are further probing the nature of **3** by ESR.[32]

Acknowledgment. We thank the Natural Sciences and Engineering Research Council and the University of Victoria for financial assistance.

Registry No. **1**, 206-92-8; **2**, 120-12-7; **3**, 80664-93-3; **4**, 85-01-8; **5**, 27786-82-9; **6**, 58746-77-3; **7**, 83561-31-3; **8**, 83561-32-4; **9**, 83561-33-5; **10**, 83561-34-6; **11**, 83561-35-7; **12**, 83561-36-8; **13**, 83561-37-9; **14**, 83561-38-0; **15**, 83561-39-1; **16**, 83561-46-0; **17**, 83561-47-1; **18**, 83561-48-2; **19**, 83561-40-4; **20**, 66965-78-4; **21**, 83561-41-5; **22**, 83561-49-3; **23**, 83561-42-6; **24**, 83561-43-7; **25**, 83561-44-8; **26**, 83561-45-9.

(31) See for example: D. Kearns and S. Ehrenson, *J. Am. Chem. Soc.*, 84, 739 (1962); E. Wasserman, R. S. Hutton, V. J. Kuck, and E. A. Chandross, *ibid.*, **96**, 1965 (1974); W. D. Laidig and H. F. Schaefer, *ibid.*, 101, 7184 (1979).

(32) To date, attempts to record an ESR signal of **3a** both in solution and in the solid state have not been successful between 300 and 77 K. In contrast, Yang's biradical[30b] and bisgalvanoxy[30c] both gave ESR spectra[33] as have more recent examples.[34]

(33) R. Kreilick, *J. Chem. Phys.*, **43**, 308 (1965).

(34) P. W. Kopf and R. W. Kreilick, *J. Am. Chem. Soc.*, **91**, 6569 (1969); A. M. McPherson, et al., *ibid.*, 101, 3425 (1979).

A Simplified Synthesis of (±)-4-Hydroxy-*N*-methylmorphinan-6-one[1,2]

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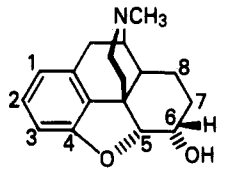
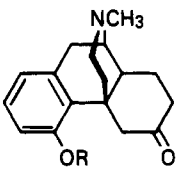
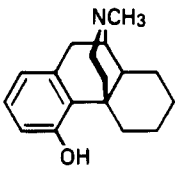
The finding of exceptional antinociceptive activity[3-7] of the morphine derived[4,8] 6-oxomorphinan (−)-**2** and its methyl ether (−)-**3**, and the observation[8] that the former could serve as a key intermediate to (−)-3-deoxy-7,8-dihydromorphine [(−)-**1**], made **2** and **3** particularly attractive candidates for total synthesis. This preparation[8] of **2** also provided access to (−)-4-hydroxy-*N*-methylmorphinan (**4**) that showed morphine-like antinociceptive activity and had previously[9] only been prepared by nonregiospecific Grewe-type cyclization. Total synthesis of racemic **2**[10,11]



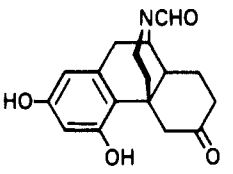
1



2 R = H
3 R = CH_3



4



5

and **3**[11] was accomplished from 2,4-dihydroxy-*N*-formylmorphinan-6-one (**5**), but the route utilized was cumbersome since it afforded **2** only after the 4,5-oxide bridge has been closed and then reopened through a reductive fission. A regioselective O-alkylation of **5** with 5-chloro-1-phenyl-1*H*-tetrazole followed by hydrogenolysis[12] seemed a more attractive path to follow. Initial attempts in pursuing this approach, however, resulted in the formation of a rather complex mixture of O- and C-5 alkylated products.[13] It seemed likely that these complications, obviously originating from alkylation of the enolate ion, could be avoided if the 6-keto group was reduced to an alcohol prior to alkylation of the 2-hydroxy function and subsequent hydrogenolysis. We now report on a successful completion of this variant.[2]

Reduction of ketone **5** with L-Selectride in DMF and THF at −70 °C afforded the triol **6** in 93% yield (Scheme I). The α-configuration in **6** followed from its successful conversion into **14** of established stereochemistry.[1,3] O-Alkylation of **6** with 5-chloro-1-phenyl-1*H*-tetrazole in DMF in the presence of potassium carbonate at 70–75 °C afforded by crystallization and chromatography of the mother liquor 57% of the ether **7**, and 3% of the isomeric ether **8** as the slower moving eluate. The catalytic reduction of **7** over Pd/C in acetic acid at 60 °C and under 50-psi hydrogen pressure gave after chromatography over silica gel 28% of the faster moving acetate **10** and 32% of the slower moving diol **9**.

Hydrolysis of **9** and **10** with methanolic HCl afforded the amine **11** in 84% and 79% yield, respectively, which was converted by reductive N-methylation into the diol **12** (69%). Oppenauer oxidation of **12** with benzophenone in the presence of potassium *tert*-butoxide afforded the interesting diphenylmethylene ketone **13** as the major product and 27% of the desired ketone **2** after chromatography. The structure of **13** followed from spectral data and is apparently formed in an aldol type of reaction. A superior conversion of diol **12** into the desired compounds was accomplished by a reversal of the reaction sequence. O-Methylation of **12** with phenyltrimethylammonium chloride afforded the ether alcohol **14** in 65% yield. This alcohol was found identical by ^{1}H NMR, MS, and TLC with the α epimer obtained earlier in the (−) series.[1] Op-

(1) The compounds described here are (±) entities except those that are marked with the prefix (−), originating from natural morphine.

(2) Presented by one of us (F.L.H.) at the 183rd National Meeting of the American Chemical Society, Las Vegas, NV, March 1982; ORGN 214.

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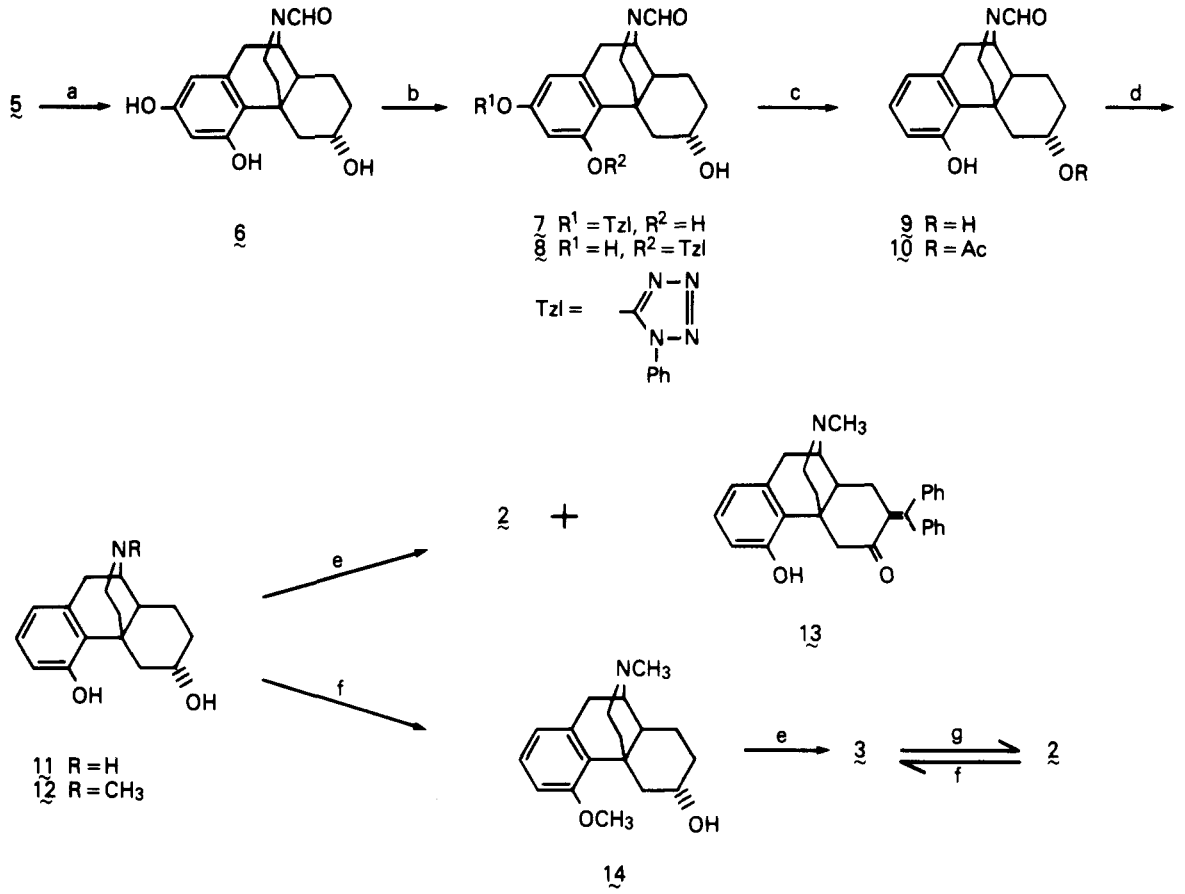
(13) Hsu, F.-L.; Rice, K. C.; Brossi, A. *Heterocycles*, **1982**, in press.

(14) Rice, K. C. *J. Med. Chem.* **1977**, *20*, 164.

Scheme I



6

7 R^1 = Tzl, R^2 = H
8 R^1 = H, R^2 = Tzl

9 R = H
10 R = Ac

2 +

13

11 R = H
12 R = CH_3

3 ⇌ 2 (g; f)

14

(a) L-selectride, THF, −70 °C, 93%. (b) Tzl-Cl, K_2CO_3, DMF, 70-80 °C, 60%. (c) 10% Pd-C, HOAc, 60 °C, 60%. (d) conc. HCl, CH_3OH, 80-85%. (e) $PhC(=O)Ph$, KO^{t}Bu, benzene. (f) $PhN^{\oplus}Me_3Cl^{\ominus}$, K_2CO_3, DMF, 65%. (g) BBr_3, $CHCl_3$, −70 °C, 68%

penauer oxidation of **14** afforded the desired methyl ether **3** in 85% yield and O-demethylation[13] of **3** with BBr_3 in chloroform gave the phenol **2** in 67% yield.

Both samples of **2** and **3** were identical by ^1H NMR, MS, and TLC with the corresponding samples prepared in the natural (−) series,[3,8] and (±)-**3** showed approximately half of the antinociceptive activity (ED_{50} 0.51 mg/kg, mice, hot-plate, sc) of the natural enantiomer (−)-**3** (ED_{50} 0.29 mg/kg).

Experimental Section

Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this Laboratory. IR spectra were recorded on a Beckman IR4230 instrument. Melting points were determined with a Thomas-Hoover or Fisher-Johns apparatus and are corrected. NMR spectra were obtained with either a Varian HR 220 or JEOL LNM-FX100 spectrometer with $(CH_3)_4Si$ as the internal reference. Electron-ionization (EI) mass spectra (MS) were determined with a Hitachi Perkin-Elmer RMU-6E instrument (70 eV) and chemical-ionization (CI) mass spectra were obtained with a Finnigan 1015D spectrometer with a Model 6000 data collection system. Short-range Hydrion paper was used for pH determinations. Silica gel GF plates for thin-layer chromatography (TLC) were purchased from Analtech, Inc. Silica gel 60 (230–400 mesh) and aluminia Woelm N (activity III) were purchased from EM Laboratories and Woelm Pharmaceutical Co., respectively.

***N*-Formyl-2,4,6α-trihydroxymorphinan (6).** The dihydroxymorphinan **5**[10,11] (7.0 g, 23.2 mmol) was dissolved in 30 mL of hot DMF, cooled to room temperature, and mixed with 60 mL of dry THF. L-Selectride (1 M/THF, 70 mL, 70 mmol) was added dropwise to this stirred solution at −70 °C under argon. The reaction was complete in 30 min and the mixture was allowed to warm to room temperature, quenched with 15 mL of H_2O, and then acidified with 10% HCl. The THF was evaporated and the solution was extracted with $CHCl_3$/*i*-PrOH (3:2). The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated to afford a yellow oil. Trituration of this crude product with EtOAc gave crystalline **6** (5.3 g). The filtrate gave another 1.3 g of **6** after column chromatography (silica gel, $CHCl_3$/MeOH/c-NH_4OH = 120:10:1). Compound **6** (total 6.6 g, 93%) was recrystallized from DMF–EtOAc: mp >250 °C; IR (KBr) 3400, 3280, 1640 cm^{-1}; NMR (Me_2SO-d_6) δ 8.80, 9.03 (2 s, 2 H, 2 OH), 7.85, 8.00 (2 s, 1 H, NCHO), 6.02 (d, 1 H, Ar H, J = 3 Hz), 5.91 (d, 1 H, Ar H, J = 3 Hz); MS (EI), m/e 303 (M^+).

Anal. Calcd for $C_{17}H_{21}NO_4 \cdot 0.5H_2O$: C, 65.37; H, 7.10; N 4.48. Found: C, 65.45; H, 6.99; N, 4.78.

4,6α-Dihydroxy-*N*-formyl-2-[(1-phenyltetrazol-5-yl)oxy]morphinan (7) and 2,6α-Dihydroxy-*N*-formyl-4-[(1-phenyltetrazol-5-yl)oxy]morphinan (8). A mixture of **6** (6.0 g, 19.8 mmol), 5-chloro-1-phenyltetrazole (4.0 g, 22.1 mmol), and anhydrous K_2CO_3 (6.8 g, 49.2 mmol) in 120 mL of DMF was heated and stirred at 70–75 °C overnight under argon. The mixture was filtered and the filtrate was evaporated under high vacuum to give a residue, which was dissolved in $CHCl_3$ and washed with 10% HCl. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to a foam. This mixture was treated with 20 mL of CH_3OH and allowed to stand at room temperature to afford crystalline **7** (2.2 g). The filtrate was evaporated and chromatographed over silica gel ($CHCl_3$/CH_3OH = 40:1) to give another 2.9 g of **7** (total 5.1 g, 57%). Recrystallization from DMF–CH_3OH afforded an analytical sample: mp 244–246 °C; IR (KBr) 3580, 3440, 3180, 1650 cm^{-1}; NMR

(Me_2SO-d_6) δ 9.72 (s, 1 H, OH), 7.90, 8.04 (2 s, 1 H, NCHO), 7.55–7.84 (m, 5 H, Ar H), 6.66 (d, 1 H, Ar H, J = 3 Hz), 6.59 (d, 1 H, Ar H, J = 3 Hz); MS (CI/NH_3), m/e 448 (M^+ + 1).

Anal. Calcd for $C_{24}H_{25}N_5O_4$: C, 64.42,; H, 5.63; N, 15.65. Found: C, 64.11; H, 5.74; N, 15.85.

The slow moving fractions gave **8** (260 mg, 3%), which was recrystallized from DMF–MeOH: mp 199–200 °C; IR (KBr) 3450, 3240, 1635 cm^{-1}; NMR (Me_2SO-d_6) δ 9.52 (s, 1 H, OH), 8.04 (s, 0.5 H, 0.5 NCHO), 7.56–7.92 (m, 5.5 H, Ar H, 0.5 NCHO), 6.76 (d, 1 H, Ar H, J = 3 Hz), 6.44 (d, 1 H, Ar H, J = 3 Hz); MS (CI/NH_3), m/e 448 (M^+ + 1).

Anal. Calcd for $C_{24}H_{25}N_5O_4 \cdot 0.5H_2O$: C, 63.14; H, 5.74; N, 15.34. Found: C, 62.93; H, 6.01; N, 15.11.

4,6α-Dihydroxy-*N*-formylmorphinan (9) and 6α-Acetoxy-*N*-formyl-4-hydroxymorphinan (10). A mixture of 2-tetrazolyl ether **7** (4.4 g, 9.8 mmol), 10% Pd–C (6.0 g) in 180 mL of HOAc was hydrogenated at 50 psi at 60 °C for 2 days. The catalyst was filtered and the filtrate was evaporated to give a residue, which was dissolved in $CHCl_3$ and washed with 5% HCl, brine, and dried (Na_2SO_4). Evaporation of solvent gave a foam (5.0 g), which was chromatographed on silica gel ($CHCl_3$/MeOH = 50:1). The fast-moving component was collected and recrystallized from DMF–CH_3OH to yield **10** (900 mg, 28%): mp 252–254 °C; IR (KBr) 3250, 1730, 1640 cm^{-1}; NMR (Me_2SO-d_6) δ 9.04 (s, 1 H, OH), 7.73, 7.89 (2 s, 1 H, NCHO), 6.70 (t, 1 H, Ar H, J = 7 Hz), 6.40 (d, 1 H, Ar H, J = 7 Hz), 6.36 (d, 1 H, Ar H, J = 7 Hz), 4.86 (m, 1 H, C_6-H), 3.85 (d, 1 H, C_5-H, J = 13 Hz), 1.54 (s, 3 H, $OCOCH_3$); MS (CI/NH_3), m/e 330 (M^+ + 1).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 68.97; H, 7.11; N, 4.24.

The slower moving component was collected and recrystallized from CH_3OH to afford **9** (890 mg, 32%): mp 230–231 °C; IR (KBr) 3540, 3420, 3150, 1645 cm^{-1}; NMR (Me_2SO-d_6) δ 8.96 (s, 1 H, OH), 7.71, 7.87 (2 s, 1 H, NCHO), 6.66 (t, 1 H, J = 7 Hz), 6.37 (d, 1 H, Ar H, J = 7 Hz), 6.33 (d, 1 H, Ar H, J = 7 Hz), 3.84 (m, 1 H, C_6-H); MS (CI/NH_3), m/e 288 (M^+ + 1).

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.06; H, 7.35; N, 4.91.

4,6α-Dihydroxymorphinan (11). A. From 9. A solution of **9** (660 mg, 2.3 mmol) in 1.5 mL of 37% HCl and 15 mL of CH_3OH was refluxed for 16 h. The CH_3OH was evaporated and the aqueous solution was rendered alkaline to pH 8–9 with concentrated aqueous NH_3 and extracted with $CHCl_3$/i-PrOH = 3:2. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give a solid, which was recrystallized from DMF to yield **11** (500 mg, 84%): mp 245–246 °C dec; IR (KBr) 3420, 3260 cm^{-1}; NMR (Me_2SO-d_6) δ 6.71 (t, 1 H, Ar H, J = 7 Hz), 6.44 (m, 2 H, Ar H); MS (EI), m/e 259 (M^+).

Anal. Calcd for $C_{16}H_{21}NO$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.81; H, 7.97; N, 5.55.

B. From 10. Compound **11** was prepared in 79% yield from **10** by the procedure used in A above.

4,6α-Dihydroxy-*N*-methylmorphinan (12). A mixture of **11** (820 mg, 3.16 mmol), 37% HCHO (0.95 mL, 12.6 mmol), NaOAc (1.1 g, 13.4 mmol), and 10% Pd–C (160 mg) in 100 mL of 2 N HOAc was hydrogenated at 45 psi at room temperature overnight. The catalyst was filtered and the filtrate was adjusted to pH 8 with concentrated aqueous NH_3 and extracted with $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated to afford a gum (1.0 g), which was crystallized from acetone to yield **12** (595 mg, 69%): mp 181–182 °C; IR (KBr) 3200 cm^{-1}; NMR (CD_3OD) δ 6.85 (t, 1 H, Ar H, J = 7 Hz), 6.56 (d, 1 H, Ar H, J = 7 Hz), 6.50 (d, 1 H, Ar H, J = 7 Hz), 4.08 (m, 1 H, C_6-H), 3.79 (d, 1 H, C_5-H, J = 14 Hz), 2.32 (s, 3 H, NCH_3); MS (CI/NH_3), m/e 274 (M^+ + 1).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.67; H, 8.67; N, 4.93.

7-(Diphenylmethylene)-4-hydroxy-*N*-methylmorphinan-6-one (13). To a suspension of KO-t-Bu (890 mg, 7.9 mmol) in 30 mL of benzene was added a suspension of benzophenone (3.6 g, 19.7 mmol) and **12** (540 mg, 1.98 mmol) in 60 mL of benzene dropwise under argon. The reaction mixture was refluxed for 1.5 h and TLC indicated two products. The mixture was cooled to room temperature and treated with 20 mL of 10% HCl. The benzene layer was separated and the acidic solution was washed with ether (3 × 20 mL), rendered alkaline to pH ~8 with concentrated aqueous NH_3, extracted with $CHCl_3$/i-PrOH = 3:2. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. Column chromatography of the residue (alumina, $CHCl_3$/CH_3OH = 250:1) gave **13** as a white solid (410 mg, 48%), which was recrystallized from CH_3OH: mp 196–197 °C; IR (KBr) 3400, 1685 cm^{-1}; NMR ($CDCl_3$) δ 6.98–7.11 (m, 6 H, Ar H), 6.77–6.89 (m, 4 H, Ar H), 6.60 (t, 1 H, Ar H, J = 7.5 Hz), 6.40 (d, 1 H, Ar H, J = 7.5 Hz), 5.89 (d, 1 H, Ar H, J = 7.5 Hz), 4.36 (d, 1 H, C_5-H, J = 13.5 Hz), 2.31 (s, 3 H, NCH_3); MS (CI/NH_3), m/e 436 (M^+ + 1).

Anal. Calcd for $C_{30}H_{29}NO_2 \cdot {}^1/_3CH_3OH$: C, 81.64; H, 6.85; N, 3.14. Found: C, 81.69; H, 6.77; N, 3.04.

The slower moving material was recrystallized from benzene yield **2** (145 mg, 27%): mp 241–243 °C (lit.[10] mp 243–245 °C).

6α-Hydroxy-4-methoxy-*N*-methylmorphinan (14). A mixture of **12** (350 mg, 1.28 mmol), phenyltrimethylammonium chloride (1.2 g, 7.0 mmol), and anhydrous K_2CO_3 (3.6 g, 26 mmol) in 35 mL of DMF was stirred at 70 °C overnight under argon. The mixture was filtered and the filtrate was evaporated under high vacuum to a brown residue, which was dissolved in $CHCl_3$ and washed with 2 N NaOH and brine. The organic layer was dried (Na_2SO_4) and evaporated to give a gum (400 mg). The crude product was chromatographed on alumina ($CHCl_3$) to give a yellow oil, which was crystallized after trituration with i-Pr_2O. Recrystallization from MeOH/i-Pr_2O afforded **14** (240 mg, 65%): mp 96–98 °C; IR (KBr) 3400 cm^{-1}; NMR ($CDCl_3$) δ 7.04 (t, 1 H, Ar H, J = 7 Hz), 6.68 (m, 2 H, Ar H), 4.05 (m, 1 H, C_6-H), 3.76 (s, 3 H, OCH_3), 3.61 (d, 1 H, C_5-H, J = 14 Hz), 2.32 (s, 3 H, NCH_3); MS (EI), m/e 287 (M^+).

Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.14; H, 8.90; N, 4.80.

4-Methoxy-*N*-methylmorphinan-6-one (3): Compound **3** was prepared in 85% yield from **14** (150 mg, 0.52 mmol) by the procedure used for preparation of **13** and **2**. The product was recrystallized from benzene/petroleum ether: mp 111–112 °C (lit.[11] mp 111–112 °C).

4-Hydroxy-*N*-methylmorphinan-6-one (2). To a solution of **3** (100 mg, 0.35 mmol) in 6 mL of $CHCl_3$ was added BBr_3 (3 g, 12.0 mmol) at −70 °C. The mixture was stirred at −70 °C for 2 h, poured into ice/H_2O, and washed with ether. The aqueous solution was rendered alkaline to pH 8 with concentrated aqueous NH_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with brine, dried (Na_2SO_4), and evaporated to afford a yellow residue. Column chromatography (alumina, $CHCl_3$, then $CHCl_3$/CH_3OH = 50:1) of the crude material gave **2** (65 mg, 68%): mp 241–243 °C (lit.[10] mp 243–245 °C).

Acknowledgment. We thank Ms. Paula Parisius and Alice Wong for combustion analysis and Mr. Noel Whittaker and Mr. William Landis for mass spectra. We also thank Hoffman-La Roche, Inc., Nutley, NJ, for large-scale preparation of an intermediate used in the synthesis of **5**.

Registry No. (±)-**2**, 76786-89-5; (±)-**3**, 83585-95-9; (±)-**5**, 76786-95-3; (±)-**6**, 83585-96-0; (±)-**7**, 83603-84-3; (±)-**8**, 83603-85-4; (±)-**9**, 83585-97-1; (±)-**10**, 83585-98-2; (±)-**11**, 83585-99-3; (±)-**12**, 83586-00-9; (±)-**13**, 83586-01-0; (±)-**14**, 83586-02-1; 5-chloro-1-phenyltetrazole, 14210-25-4.