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New Synthesis of (±)-Emetine from Tetrahydroprotoberberine Precursors via an α-Diketone Monothioketal Intermediate

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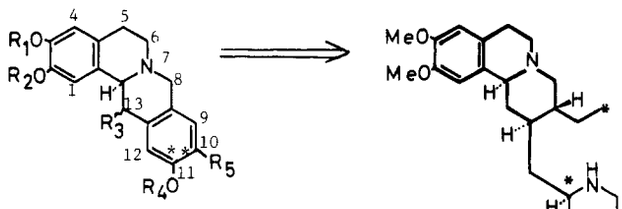
A new route to (±)-emetine (**2**) via the protoemetine derivative **29** has been developed. Protoberberine derivatives **3, 4, 5,** and **6** were converted into the α-diketone monothioketal **25,** which upon cleavage with potassium hydroxide, followed by desulfurization and esterification, yielded the protoemetine derivative **29.**

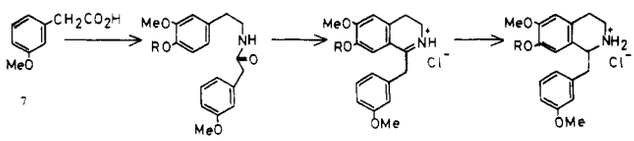
Because of the structural and biosynthetic parallelism between the ipecac and various indole alkaloids,[1] the development of efficient synthetic methods which could cover both of these classes of alkaloids has a significant practical value. We report here a new synthesis of (±)-emetine (**2**),[2] a representative ipecac alkaloid and one of the most synthesized natural products known,[3] by a completely new method which would be generally applicable to the synthesis of both the ipecac and the indole alkaloids.[4]



1 : $R_1=R_2=R_3=R_4=H$, $R_5=OH$
3 : $R_1=R_2=R_4=Me$, $R_3=R_5=H$
4 : $R_1=R_2=R_4=Me$, $R_3=CN$, $R_5=H$
5 : $R_1=R_4=Me$, $R_2=CH_2C_6H_5$, $R_3=R_5=H$
6 : $R_1=R_4=Me$, $R_2=CH_2C_6H_5$, $R_3=CN$, $R_5=H$

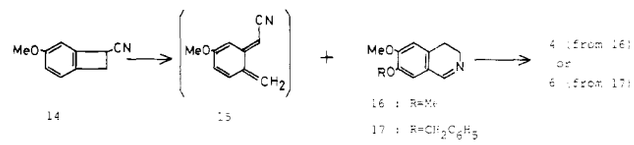
The present method proceeds through Woodward fission,[5] which had been once thought to be involved in the biogenetic pathways of the ipecac and some of the indole alkaloids. The fission between C-10 and C-11 of a tetrahydroprotoberberine precursor (e.g., **1**) was realized chemically by the cleavage reaction[6] of an α-diketone monothioketal intermediate **25** derived from tetrahydroprotoberberine precursors **3, 4, 5,** and **6.**

The starting tetrahydroprotoberberine framework was prepared by two different approaches. In the first approach, the tetrahydroprotoberberine **3** was obtained in 47% overall yield from 3-methoxybenzyl cyanide. Hydrolysis of 3-methoxybenzyl cyanide, prepared from *o*-chloroanisole and acetonitrile by a benzyne reaction[7] with methanolic potassium hydroxide, gave 3-methoxyphenylacetic acid (**7**), which on condensation with homoveratrylamine at 180 °C yielded the phenylacetamide **8** in 92% yield. The Bischler–Napieralski cyclization by phosphorus oxychloride provided the 3,4-dihydroisoquinoline **10** in 98% yield. This material was reduced with sodium borohydride followed by treating with ethereal hydrogen chloride to form the 1,2,3,4-tetrahydroisoquinoline hydrochloride **12** nearly quantitatively. Mannich condensation of the hydrochloride with 35% formalin in methyl alcohol produced the crystalline hydrochloride of 2,3,11-trimethoxytetrahydroprotoberberine (**3**) in 85% yield.



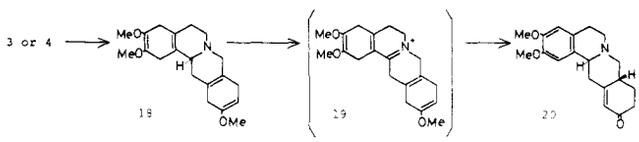
8 : R=Me
9 : $R=CH_2C_6H_5$
10 : R=Me
11 : $R=CH_2C_6H_5$
12 : R=Me
13 : $R=CH_2C_6H_5$

In the second approach, the tetrahydroprotoberberine **4,** a synthetic equivalent of **3,** was prepared by a more straightforward way using the method developed by Kametani et al.[8] Thermolysis of a 1:1 mixture of 1-cyano-5-methoxybenzocyclobutene (**14**)[9] and 3,4-dihydro-6,7-dimethoxyisoquinoline (**16**)[10] without solvent at 140–150 °C resulted in regioselective intermolecular cycloaddition to form 13-cyano-2,3,11-trimethoxytetrahydroprotoberberine (**4**) via the *o*-quinodimethane intermediate **15** in 50% yield. The product **4** possessed a superfluous cyano group at C-13. However, this could be easily removed in a subsequent stage.



16 : R=Me
17 : $R=CH_2C_6H_5$

Dissolving metal reduction of the tetrahydroprotoberberines **3** and **4** using lithium in liquid ammonia in the presence of *tert*-butyl alcohol afforded the enol ether **18** in 76 and 74% yields, respectively. In the latter case, reductive decyanation occurred in preference to reduction of the aromatic rings, as observed in a related system.[11] Although attempts at selective reduction of ring D to give **23** under Birch conditions were unsuccessful, a selective aromatization of ring A of the enol



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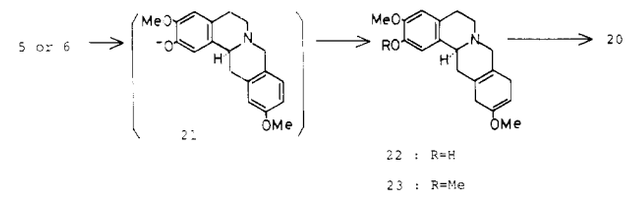
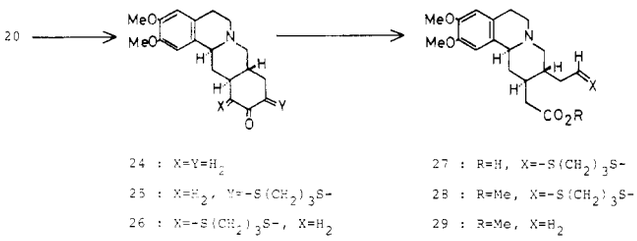
ether **18** could be accomplished by using *N*-chlorosuccinimide.

Upon treatment of the enol ether **18** with an equivalent molar amount of *N*-chlorosuccinimide in methylene chloride, the α,β-unsaturated ketone **20**[12] was obtained directly in 63% yield. During the conversion an immonium salt **19** could be formed initially,[13] and concurrent hydrolysis of the enol ether group on the D ring by moisture contained in the solvent and subsequent isomerization of the double bonds could occur to give the thermodynamically more stable compound **20.**

In order to avoid overreduction under the Birch conditions, alternative tetrahydroprotoberberines, **5** and **6,** possessing a 2-benzyloxy group as a regiocontrol element were prepared by employing the same two approaches as above. Birch reduction of the protoberberine **5,** obtained in 62% overall yield from the phenylacetic acid **7** by the first approach, followed by treating with ethereal diazomethane afforded the ring D enol ether **23** in 84% yield. Similarly, the 13-cyanoprotoberberine **6,** generated in 60% yield of thermolysis of the 3,4-dihydroisoquinoline **17**[14] and the benzocyclobutene **14,**[9] afforded the identical enol ether **23**[9] in 76.5% yield. In these conversions, initial formation of the phenolate anion **21** through reductive cleavage of the benzyl ether could allow a preferential reduction of the D ring to give **23.** Conversion of the enol ether **23** into the α,β-unsaturated ketone **20**[12] was achieved in 84% yield by heating with methanolic hydrochloric acid.



Catalytic hydrogenation of the α,β-unsaturated ketone **20** on 10% palladized carbon in methyl alcohol achieved a highly stereospecific reduction to furnish the C/D trans ketone **24** in 89% yield, although an actual stereochemistry could not be determined at this stage since none of the characteristics appeared spectroscopically.



Treatment of the ketone **24** with pyrrolidine in boiling benzene for 2 h followed by trimethylene dithiotosylate[15] yielded the α-diketone monothioketal **25** in 65% yield accompanied by its regioisomer **26** in 9% yield. Similar to the ketone **24,** the actual structures of the products could not be assigned at this point. In this transformation, the ratio of the products was greatly influenced by the amount of enamine formed. Longer heating resulted in a higher yield of the unwanted isomer **26,** while a minimum heating period was desirable for the preferential formation of the target compound **25.**

Cleavage of the α-diketone monothioketal **25** by potassium hydroxide[16] afforded the crude thioacetal carboxylic acid **27,** which on esterification with diazomethane gave rise to the corresponding thioacetal ester **28** in a well-defined crystalline form in 94% overall yield. Heating **28** with Raney nickel catalyst (W-2) in boiling methyl alcohol effected the desulfurization of the thioacetal group to give the crystalline protoemetine derivative **29** in 92% yield. Although the physical properties were in agreement with the reported data[17] and the synthesis of the compound **29** constitutes a formal synthesis of (±)-emetine (**2**), further structure confirmation was made by the conversion into (±)-emetine (**2**) via a three-step sequence developed by Battersby and Turner.[18] Complete identity with the authentic material led to confirmation of structures **24, 25,** and **28.**

Since the indole analogues of the tetrahydroprotoberberines have been prepared,[19] the synthesis of structurally parallel indole alkaloids, such as the corynantheine-type alkaloids, can be conceived by appropriate modification of the present approach.

Experimental Section

Melting points were determined on a Yanagimoto MP-S2 apparatus and are uncorrected. Infrared absorption spectra were recorded on a Shimadzu IR 400 instrument, and proton magnetic resonance spectra, for deuteriochloroform solutions, were recorded on Jeol PS 100 and PMX 60 spectrometers with tetramethylsilane as an internal reference. Mass spectra were recorded on a Hitachi RMU-7 spectrometer.

3-Methoxyphenylacetic Acid (7). A solution of 3-methoxybenzyl cyanide (58.0 g, 0.41 mol) in ethyl alcohol (1110 mL) containing KOH (132.2 g, 2.2 mol) was refluxed for 14 h. The solvent was removed in vacuo, and the residue was dissolved in water (300 mL). The aqueous layer was washed twice with methylene chloride and acidified with concentrated HCl to liberate the carboxylic acid. The mixture was extracted with methylene chloride, washed with water, dried over Na_2SO_4, and evaporated to leave a crystalline mass which was recrystallized from *n*-hexane to give **7** (59.6 g, 91%) as colorless prisms: mp 67.5–68.5 °C (lit.[20] mp 67 °C); IR ν_{max} (Nujol) ~2400, 1695 cm^{-1}; NMR δ 11.9 (1 H, s), 7.4–6.85 (4 H, m), 3.75 (3 H, s), 3.6 (2 H, s).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-3-methoxyphenylacetamide (8).** A mixture of 2-(3,4-dimethoxyphenyl)ethylamine (1.34 g, 7.4 mmol) and 3-methoxyphenylacetic acid (**7;** 1.23 g, 7.4 mmol) was heated at 130 °C for 0.5 h and then at 170–180 °C for 2.5 h, removing water by means of an aspirator. After cooling, the crystalline residue was recrystallized from benzene and *n*-hexane to give **8** (2.26 g, 92%) as colorless prisms: mp 104.5–106 °C; IR ν_{max} (Nujol) 3270, 1640 cm^{-1}; NMR δ 5.50 (1 H, brd s; disappeared with D_2O), 3.80 (3 H, s), 3.75 (3 H, s), 3.70 (3 H, s), 3.45 (2 H, s), 3.40 (2 H, t, J = 7.0 Hz), 2.70 (2 H, t, J = 7.0 Hz); MS *m/e* 329 (M^+). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.26; H, 7.19; N, 4.29.

3,4-Dihydro-6,7-dimethoxy-1-(3-methoxybenzyl)isoquinoline Hydrochloride (10). A solution of **8** (37.15 g, 113 mmol) in benzene (250 mL) was refluxed with phosphorus oxychloride (34.94 g, 226 mmol) for 4 h. The solvent was removed in vacuo, and the residue was washed several times with hot *n*-hexane to leave a crystalline mass which was recrystallized from isopropyl alcohol and *n*-hexane to give **10** (39 g, 98%) as colorless prisms: mp 118.5–120 °C; IR ν_{max} (Nujol) 1640 cm^{-1}; NMR ($CDCl_3$ + CF_3CO_2H) δ 4.38 (2 H, s), 4.10 (3 H, s), 3.87 (3 H, s), 3.82 (3 H, s), 3.11 (2 H, t, J = 8.0 Hz); MS *m/e* 311 (M^+). Anal. Calcd for $C_{19}H_{22}NO_3Cl{\cdot}H_2O$: C, 62.35; H, 6.61; N, 3.83. Found: C, 62.43; H, 6.13; N, 3.64.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(3-methoxybenzyl)isoquinoline Hydrochloride (12). To an ice-cooled solution of **10** (2.5 g, 6.8 mmol) in methyl alcohol (20 mL) was added $NaBH_4$ (1.55 g, 41 mmol) in small portions with stirring. The solvent was evaporated in vacuo, and the residue was treated with 10% NH_4OH (40 mL) and extracted with methylene chloride. The extract was washed with saturated NaCl, dried over K_2CO_3, and evaporated to leave a crystalline residue (1.53 g, 71.3%) which was converted into the hydrochloride **12** by treating with saturated ethereal hydrogen chloride in isopropyl alcohol: colorless prisms; mp 102–104 °C; NMR ($CDCl_3$ + CF_3CO_2H) δ 3.80 (3 H, s), 3.77 (3 H, s), 3.75 (3 H, s); MS *m/e* 313 (M^+). Anal. Calcd for $C_{19}H_{24}NO_3Cl{\cdot}H_2O$: C, 62.03; H, 7.12; N, 3.81; Cl, 9.64. Found: C, 61.79; H, 6.81; N, 3.82; Cl, 9.57.

2,3,11-Trimethoxytetrahydroprotoberberine Hydrochloride (3). A solution of **12** (0.1 g, 0.29 mmol) in ethyl alcohol (10 mL) was refluxed with 37% formalin (0.54 g, 18 mmol) for 45 min. Removal of the solvent in vacuo left a crystalline mass which was recrystallized from isopropyl alcohol to give **3** (0.085 g, 85%) as colorless prisms: mp 185–187 °C; IR ν_{max} (Nujol) 2850–2700, 1600 cm^{-1}; NMR ($CDCl_3$ + CF_3CO_2H) δ 3.85 (3 H, s), 3.80 (3 H, s), 3.75 (3 H, s); MS *m/e* 325 (M^+). Anal. Calcd for $C_{20}H_{24}NO_3Cl{\cdot}H_2O$: C, 63.23; H, 6.90; N, 3.69; Cl, 9.33. Found: C, 63.45; H, 6.94; N, 3.65; Cl, 9.45.

13-Cyano-2,3,11-trimethoxytetrahydroprotoberberine (4). A mixture of 3,4-dihydro-6,7-dimethoxyisoquinoline (**16**; 2.32 g, 12.2 mmol) and 1-cyano-5-methoxybenzocyclobutene (**14**; 1.93 g, 12.2 mmol) was heated at 150 °C for 5.5 h under an atmosphere of nitrogen. The reaction mixture was crystallized from ethyl alcohol to give practically pure **4** (2.09 g, 50%) as pale yellow prisms: mp 174–176 °C; IR ν_{max} (Nujol) 2850–2750, 2230 cm^{-1}; NMR δ 6.67 (1 H, s), 6.64 (1 H, s), 4.29 (1 H, d, J = 3.0 Hz), 3.92 (6 H, s), 3.84 (3 H, s); MS m/e 350 (M^+). Anal. Calcd for $C_{21}H_{22}O_3N_2$: C, 71.98; H, 6.33; N, 8.00. Found: C, 71.94; H, 6.25; N, 8.00.

1,4,9,12-Tetrahydro-2,3,11-trimethoxytetrahydroprotoberberine (18). A. To a stirring solution of **3** (3.5 g, 10.7 mmol) in a mixture of tetrahydrofuran (48 mL), *tert*-butyl alcohol (48 mL), and liquid ammonia (200 mL) was added lithium (2.56 g, 0.37 g-atom) in small portions. After the stirring was continued for 1 h, the reaction mixture was treated with NH_4Cl (25 g) and ammonia was evaporated. The residue was extracted with methylene chloride, washed with water, dried over Na_2SO_4, and evaporated to leave a crystalline mass which was recrystallized from isopropyl alcohol to give **18** (2.7 g, 76%) as pale yellow prisms: mp 111.5–114 °C; NMR δ 4.60 (1 H, brd s), 3.62 (3 H, s), 3.60 (3 H, s), 3.50 (3 H, s); MS m/e 329 (M^+). Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.07; H, 8.12; N, 4.19.

B. To a stirring solution of **4** (0.7 g, 2 mmol) in a mixture of tetrahydrofuran (5 mL), *tert*-butyl alcohol (6 mL), and liquid ammonia (130 mL) was added lithium (1.5 g, 0.22 g-atom) in small portions. After the stirring was continued for 6 h, the reaction mixture was treated with NH_4Cl (10 g) and ammonia was evaporated. The residue was extracted with methylene chloride, washed with water, dried over Na_2SO_4, and evaporated to leave a crystalline mass which was recrystallized from isopropyl alcohol to give **18** (0.487 g, 74%) as pale yellow prisms, mp 111.5–114 °C.

5,6,8,8a,9,10,13,13a-Octahydro-2,3-dimethoxy-11*H*-dibenzo[*a*,*g*]quinolizin-11-one (20). To a stirring solution of **18** (0.15 g, 0.46 mmol) in methylene chloride (35 mL) was added *N*-chlorosuccinimide (0.061 g, 0.46 mmol) in methylene chloride (5 mL) dropwise at −10 °C, and the stirring was continued for 10 h at room temperature. The reaction mixture was washed with saturated $NaHCO_3$, and the organic layer was dried over Na_2SO_4. Removal of the solvent in vacuo left a crystalline residue which was recrystallized from isopropyl alcohol to give **20** (0.1 g, 63%) as yellow prisms: mp 187–189 °C (lit.[12] mp 185–187 °C) IR ν_{max} (Nujol) 2750–2650, 1660 cm^{-1}; NMR δ 6.70 (1 H, s), 6.68 (1 H, s), 6.05 (1 H, s), 3.89 (3 H, s), 3.88 (3 H, s); MS m/e 313 (M^+), 282.

***N*-[2-(4-Benzyloxy-3-methoxyphenyl)ethyl]-3-methoxyphenylacetamide (9).** A mixture of 2-(4-benzyloxy-3-methoxyphenyl)ethylamine (27.1 g, 100 mmol) and 3-methoxyphenylacetic acid (**7**; 16.5 g, 100 mmol) was heated at 170–180 °C for 1 h, removing generated water by means of an aspirator. The crystalline residue thus formed was recrystallized from benzene to give **9** (37.6 g, 93%) as colorless needles: mp 116.5–117 °C; IR ν_{max} (Nujol) 3280, 1640 cm^{-1}; NMR δ 5.35 (1 H, brd s; disappeared with D_2O), 5.08 (2 H, s), 3.83 (3 H, s), 3.80 (3 H, s), 3.47 (2 H, s), 2.63 (2 H, t, J = 7.5 Hz); MS m/e 405 (M^+). Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.16; H, 6.53; N, 3.53.

7-Benzyloxy-3,4-dihydro-6-methoxy-1-(3-methoxybenzyl)-isoquinoline Hydrochloride (11). A solution of **9** (5.03 g, 12.5 mmol) in benzene (85 mL) was refluxed with phosphorus oxychloride (3.06 g, 20 mmol) for 2.5 h. The solvent was removed in vacuo, and the residue was washed several times with hot *n*-hexane to leave a crystalline mass which was recrystallized from isopropyl alcohol to give **11** (4.92 g, 93%) as pale yellow needles: mp 180.5–181.5 °C; IR ν_{max} (Nujol) 1640 cm^{-1}; NMR ($CDCl_3$ + CF_3CO_2H) δ 7.42 (5 H, s), 5.12 (2 H, s), 4.32 (2 H, s), 4.03 (3 H, s), 3.80 (3 H, s), 3.09 (2 H, t, J = 7.5 Hz); MS m/e 387 (M^+). Anal. Calcd for $C_{25}H_{26}NO_3Cl$: C, 70.82; H, 6.18; N, 3.30; Cl, 8.37. Found: C, 71.03; H, 6.14; N, 3.16; Cl, 8.04.

7-Benzyloxy-1,2,3,4-tetrahydro-6-methoxy-1-(3-methoxybenzyl)isoquinoline Hydrochloride (13). To an ice-cooled solution of **11** (4.21 g, 10 mmol) in methyl alcohol (30 mL) was added $NaBH_4$ (2.4 g, 60 mmol) in small portions with stirring. The solvent was removed in vacuo, and the residue was extracted with benzene, washed with water, dried over Na_2SO_4, and evaporated in vacuo. The residue was dissolved in isopropyl alcohol and treated with saturated ethereal hydrogen chloride to give **13** (3.7 g, 87%) as colorless prisms: mp 194–197 °C; NMR ($CDCl_3$ + CF_3CO_2H) δ 7.40 (5 H, s), 4.99 (2 H, s), 4.78 (1 H, brd s; disappeared with D_2O), 3.88 (3 H, s), 3.76 (3 H, s); MS m/e 389 (M^+). Anal. Calcd for $C_{25}H_{28}NO_3Cl$: C, 70.49; H, 6.63; N, 3.29; Cl, 8.33. Found: C, 70.37; H, 6.37; N, 3.21; Cl, 8.18.

2-Benzyloxy-3,11-dimethoxytetrahydroprotoberberine Hydrochloride (5). A solution of **13** (9.0 g, 23.1 mmol) in isopropyl alcohol (120 mL) was refluxed with 37% formalin (16.7 g, 205 mmol) for 1 h. After cooling, the separating cyrstalline mass was filtered off and recrystallized from isopropyl alcohol to give **5** (8.0 g, 86%) as pale yellow needles, mp 194–196 °C. The free base obtained from the hydrochloride was recrystallized from methyl alcohol to give pale yellow needles: mp 92–94 °C; NMR δ 7.43 (5 H, s), 5.01 (2 H, s), 3.89 (3 H, s), 3.80 (3 H, s); MS m/e 401 (M^+). Anal. Calcd for $C_{26}H_{27}O_3N$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.49; H, 6.65; N, 3.28.

2-Benzyloxy-13-cyano-3,11-dimethoxytetrahydroprotoberberine (6). A mixture of 7-benzyloxy-3,4-dihydro-6-methoxyisoquinoline (**17**; 1.15 g, 5 mmol) and 1-cyano-5-methoxybenzocyclobutene (**14**; 0.9 g, 5.6 mmol) was heated at 135–140 °C for 3.5 h under an atmosphere of nitrogen. The reaction mixture was treated with ethyl alcohol to give practically pure **6** (1.16 g, 60%) as colorless needles: mp 172–174 °C; IR ν_{max} (Nujol) 2850–2750, 2230 cm^{-1}; NMR δ 7.33 (5 H, s), 5.08 (2 H, s), 3.83 (3 H, s), 3.73 (3 H, s); MS m/e 426 (M^+). Anal. Calcd for $C_{27}H_{26}O_3N_2$: C, 76.03; H, 6.15; N, 6.57. Found: C, 76.34; H, 6.13; N, 6.49.

9,12-Dihydro-2-hydroxy-3,11-dimethoxytetrahydroprotoberberine (22). A. To a stirring solution of **5** (11.0 g, 25 mmol) in a mixture of tetrahydrofuran (60 mL), *tert*-butyl alcohol (70 mL), and liquid ammonia (300 mL) was added lithium (5.5 g, 0.79 g-atom) in small portions. After the stirring was continued for 1 h, the reaction mixture was treated with NH_4Cl (30 g) and ammonia was evaporated. The residue was neutralized with concentrated hydrochloric acid, extracted with methylene chloride, washed with water, dried over Na_2SO_4, and evaporated to leave a crystalline mass which was recrystallized from methyl alcohol to give **22** (6.4 g, 82%) as colorless needles: mp 179.5–180.5 °C; IR ν_{max} (Nujol) 3400, 2750–2650, 1660 cm^{-1}; NMR δ 6.71 (1 H, s), 6.53 (1 H, s), 4.85 (1 H, brd s; disappeared with D_2O), 4.62 (1 H, brd s), 3.80 (3 H, s), 3.53 (3 H, s); MS m/e 313 (M^+). Anal. Calcd for $C_{19}H_{23}O_3N$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.52; H, 7.51; N, 4.55.

B. To a stirring solution of **6** (0.91 g, 2.14 mmol) in a mixture of tetrahydrofuran (5 mL), *tert*-butyl alcohol (5 mL), and liquid ammonia (130 mL) was added lithium (1.5 g, 0.22 g-atom) in small portions. After the stirring was continued for 6 h, the reaction mixture was treated with NH_4Cl (10 g) and ammonia was evaporated. The residue was neutralized with concentrated hydrochloric acid, extracted with methylene chloride, washed with water, and dried over Na_2SO_4, and the solvent was evaporated in vacuo to leave a crystalline mass which was recrystallized from methyl alcohol to give **22** (0.52 g, 78%) as colorless needles, mp 179.5–180.5 °C.

9,12-Dihydro-2,3,11-trimethoxytetrahydroprotoberberine (23). A solution of **22** (1.25 g, 4 mmol) in methyl alcohol (100 mL) was treated with ethereal diazomethane under cooling for 1.5 h. Removal of the solvent left a crystalline residue which was recrystallized from methyl alcohol to give **23** (1.28 g, 98%) as colorless needles: mp 168.5–170 °C; IR ν_{max} (Nujol) 2750–2650, 1660 cm^{-1}; NMR δ 6.62 (1 H, s), 6.53 (1 H, s), 4.60 (1 H, brd s), 3.83 (6 H, s), 3.51 (3 H, s); MS m/e 327 (M^+). Anal. Calcd for $C_{20}H_{25}O_3N$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.26; H, 7.70; N, 4.18.

5,6,8,8a,9,10,13,13a-Octahydro-2,3-dimethoxy-11*H*-dibenzo[*a*,*g*]quinolizin-11-one (20) Hydrochloride from the Enol Ether 23. A solution of **23** (1.3 g, 4 mmol) in a mixture of methyl alcohol (100 mL), concentrated hydrochloric acid (1 mL), and water (3 mL) was refluxed for 27 h. Removal of the solvent in vacuo left a crystalline residue which was recrystallized from methyl alcohol to give the hydrochloride of **20** (1.12 g, 84%) as pale yellow needles, mp 214–217 °C. The free base converted from the hydrochloride was identical in all respects with an authentic specimen prepared by the above method.

5,6,8,8a,9,10,12,12a,13,13a-Decahydro-2,3-dimethoxy-11*H*-dibenzo[*a*,*g*]quinolizin-11-one (24). A solution of **20** (1.15 g, 3.7 mmol) in methyl alcohol (70 mL) was hydrogenated over 10% Pd–C (300 mg) at atmospheric pressure at room temperature for 13 h until the calculated amount of hydrogen was consumed. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo. Purification of the residue by silica gel column chromatography followed by recrystallization from methyl alcohol gave **24**, (1.02 g, 89%) as pale yellow prisms: mp 139–140 °C; IR ν_{max} (Nujol) 2850–2700, 1700 cm^{-1}; NMR δ 6.66 (1 H, s), 6.58 (1 H, s), 3.87 (6 H, s); MS m/e 315 (M^+), 205, 191. Anal. Calcd for $C_{19}H_{25}O_3N$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.31; H, 7.97; N, 4.38.

5,6,8,8a,9,10,12,12a,13,13a-Decahydro-2,3-dimethoxy-10,10-(propane-1,3-dithio)-11*H*-dibenzo[*a*,*g*]quinolizin-11-one (25) and 5,6,8,8a,9,10,12,12a,13,13a-Decahydro-2,3-dimethoxy-12,12-(propane-1,3-dithio)-11*H*-dibenzo[*a*,*g*]quinolizin-11-one (26). A solution of **24** (1.47 g, 4.7 mmol) in benzene (80 mL) was refluxed with pyrrolidine (0.63 mL, 7.5 mmol) for 2 h with removal of

water by means of a Dean-Stark apparatus. Removal of the solvent in vacuo left the crude enamine which was mixed with 1,3-propane dithiotosylate (1.93 g, 4.7 mmol) and triethylamine (5 mL) in acetonitrile (80 mL), and the mixture was refluxed for 4 h. After evaporation of solvent in vacuo, the residue was extracted with methylene chloride, washed with 3% HCl and 5% $NaHCO_3$, and dried over Na_2SO_4. Removal of the solvent in vacuo left an orange-red caramel (2.13 g) which on silica gel column chromatography followed by recrystallization from methyl alcohol afforded **25** (1.27 g, 65%) as pale yellow needles [mp 202.5–204 °C; IR ν_{max} (Nujol) 2800–2700, 1680 cm^{-1}; NMR δ 6.60 (1 H, s), 6.52 (1 H, s), 3.84 (6 H, s); MS *m/e* 419 (M^+), 232, 205, 191. Anal. Calcd for $C_{22}H_{29}NO_3S_2$: C, 62.97; H, 6.97; N, 3.34; S, 15.28. Found: C, 62.68; H, 7.08; N, 3.24; S, 15.46.] and the isomeric **26** (0.18 g, 9.2%) as pale yellow needles [mp 225.5–227 °C; IR ν_{max} (Nujol) 2800–2700, 1680 cm^{-1}; NMR δ 6.57 (1 H, s), 6.54 (1 H, s), 3.84 (6 H, s); MS *m/e* 419 (M^+), 232, 205, 191. Anal. Calcd for $C_{22}H_{29}NO_3S_2$: C, 62.97; H, 6.97; N, 3.34; S, 15.28. Found: C, 62.71; H, 6.84; N, 3.22; S, 15.29.].

1,3,4,6,7,11b-Hexahydro-9,10-dimethoxy-3-[2,2-(propane-1,3-dithio)ethyl]-2*H*-benzo[*a*]quinolizine-2-acetic Acid Methyl Ester (28). To a solution of **25** (0.073 g, 0.17 mmol) in a mixture of *tert*-butyl alcohol (2 mL) and tetrahydrofuran (2 mL) was added KOH (65 mg, 1 mmol), and the mixture was heated at 60 °C for 3 h with stirring. After cooling, the reaction mixture was acidified with concentrated hydrochloric acid and then treated with ethereal diazomethane. Saturated $NaHCO_3$ solution was added, and the mixture was extracted with methylene chloride, washed with water, and dried over K_2CO_3. The solvent was evaporated in vacuo to leave **28** (0.075 g, 94%) as amorphous powder: IR ν_{max} (neat) 2850–2700, 1720 cm^{-1}; NMR δ 6.70 (1 H, s), 6.62 (1 H, s), 3.90 (6 H, s), 3.70 (3 H, s); MS *m/e* 451 (M^+), 205, 149. Anal. Calcd for $C_{23}H_{33}NO_4S_2$: C, 61.16; H, 7.37; N, 3.10; S, 14.20. Found: C, 60.94; H, 7.22; N, 3.13; S, 14.00.

3-Ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetic Acid Methyl Ester (29). A suspension of W-2 Raney nickel (ca. 3 mL) and **28** (0.447 g, 1 mmol) in methyl alcohol (42 mL) was refluxed for 20 h. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo. The residue was purified by silica gel column chromatography followed by recrystallization from petroleum ether to give **29** (0.32 g, 92.4%) as colorless prisms: mp 77–78.5 °C (lit.[17] mp 78.9–79.2 °C); IR ν_{max} (neat) 2850–2700, 1720 cm^{-1}; NMR δ 6.65 (1 H, s), 6.56 (1 H, s), 3.84 (6 H, s), 3.72 (3 H, s), 0.92 (3 H, collapsed t, J = 7.0 Hz); MS *m/e* 347 (M^+), 246, 205, 191.

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Registry No.—**2,** 65910-27-2; **3** HCl, 19779-81-8; **4,** 67237-59-6; **5,** 67237-60-9; **5** HCl, 67237-61-0; **6,** 67237-62-1; **7,** 1798-09-0; **8,** 67237-63-2; **9,** 67237-64-3; **10,** 1860-59-9; **11,** 67237-65-4; **12** HCl, 67237-66-5; **13** HCl, 67237-67-6; **14,** 1199-31-1; **16,** 3382-18-1; **17,** 15357-92-3; **18,** 65341-27-7; **20,** 19778-10-0; **20** HCl, 19778-11-1; **22,** 67237-68-7; **23,** 67237-69-8; **24,** 65378-14-5; **25,** 65341-28-8; **26,** 65341-29-9; **28,** 65341-30-2; **29,** 3332-90-9; 3-methoxybenzyl cyanide, 19924-43-7; 2-(3,4-dimethoxyphenyl)ethylamine, 120-20-7; formalin, 50-00-0; 2-(4-benzyloxy-3-methoxyphenyl)ethylamine, 22231-61-4; 1,3-propane dithiotosylate, 3866-79-3.

References and Notes

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Studies on Total Synthesis of the Olivomycins

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Studies directed toward total synthesis of olivin (**4**), the aglycon of the olivomycin antitumor antibiotics, are described. The key aldehyde **23,** containing the tricyclic nucleus of olivin, has been prepared in 14 steps from 3,5-dimethoxybenzyl chloride. Methods for construction of the olivin hydroxy ketone side chain were also investigated. Attempted addition of trianion **24** to simple aldehydes was unsuccessful. Cyclohexanecarboxaldehyde, a model for aldehyde **23,** was converted to dithiane **36,** which in two steps was transformed to ketone **38.** Hydroxylation of **38** with *m*-CPBA via a kinetic enolate and trimethylsilyl ether **39** produced a single acyloin, having either structure **40** or **42.**

The olivomycins are a group of antitumor antibiotics first isolated in 1962 from a strain of *Actinomyces olivoreticuli*.[2] The crude antibiotic was subsequently found to be a mixture of three components, olivomycin A, B, and C.[3] Extensive chemical studies led to assignment of absolute stereostructures **1, 2,** and **3,** respectively, to these compounds.[4] The olivomycin antibiotics differ from each other only in the nature of the sugar moieties, and upon hydrolysis all three compounds afford the same aglycon, olivin (**4**). The chromomycins[5] and mithramycins[6] are closely related groups of antitumor antibiotics which differ from the olivomycins in the nature of the carbohydrate residues. In addition both contain a methyl group at the C-7 position of the aglycon. Hydrolysis of the chromomycins and mithramycins affords an aglycon,

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