The structure was solved with direct methods; an E map revealed maxima for the 25 C, N, O, and S atoms. The structure refinement was by the method of full-matrix least-squares with anisotropic temperature factors for C, N, O, and S and isotropic terms for H. Several H atoms were fixed at precalculated positions, and the three atoms in one methyl group were described by an appropriately located circle of 12 0.25-weight atoms. The function minimized was $\sum w(F_o - F_c)^2$, where $w = 1/\sigma(F_o)^2$. Only those data for which I_c was greater than $3\sigma(I_o)$ were included in the refinement. The final R and R_w ($[\sum w(F_o - F_c)^2/w\sum F_o^2]^{1/2}$) factors were 0.082 and 0.068, respectively. Sattering factors for C, N, O, and S were calculated from the analytical expressions of Cromer and Mann[35] and the H values were interpolated from the data of Stewart et al.[36] A final difference electron map contained two ca. 0.65 e Å^{-3} maxima near C15. Earlier attempts to fit a split-atom model to this region were unsuccessful.

The crystallographic computations were performed on a UNIVAC 1108 in the University of Maryland's Computer Science Center with the X-RAY 76[37] package of programs.

Acknowledgment. We thank Dr. Ruth S. McDiarmid (NIAMDD) for helpful discussions and Ms. Joan V. Todd for the preparation of this manuscript. This work was supported, in part, by NIH Contract 263-MD-012893 to H.L.A. and through the facilities of the University of Maryland's Computer Science Center.

Registry No. **3**, 61214-21-9; **4**, 61214-22-0; **5**, 61214-24-2; **6**, 61214-25-3; *o*-phthalaldehyde, 643-79-8; ethanethiol, 75-08-1; *n*-propylamine, 107-10-8; DMAC, 762-42-5.

Supplementary Material Available: The visible spectrum of the adduct **6** (Figure 3), pictures of the CPK space-filling models of **6** (Figure 4), the temperature-dependent ^{1}H NMR spectra of the NCH_2Et methylene protons of **6** (Figure 5), and a list of the atomic fractional coordinates and temperature factors for the X-ray structure of **6** (Table III) are given (6 pages). Ordering information is given on any current masthead page.

(35) Cromer, D. T.; Mann, J. B. *Acta Crystallogr. Sect. B* **1968**, *B31*, 418-422.
(36) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175-3187.
(37) Stewart, J. M.; Machin, P. A.; Dickinson, C.; Ammon, H. L.; Heck, H.; Flack, H. Technical Report 446; Computer Science Center, University of Maryland: College Park, MD, 1976.

Absolute Configurations of the *cis*- and *trans*-13-Methyltetrahydroprotoberberines. Total Synthesis of (+)-Thalictricavine, (+)-Canadine, (±)-, (-)-, and (+)-Thalictrifoline, and (±)-, (-)-, and (+)-Cavidine

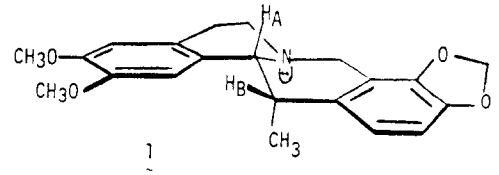
Kinuko Iwasa, Yash Pal Gupta, and Mark Cushman*

Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907

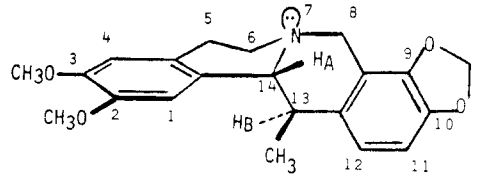
Received May 29, 1981

The tetrahydroprotoberberine alkaloids (+)-thalictricavine [(+)-**6**] and (+)-canadine [(+)-**23**] have been synthesized from an optically resolved (+)-13-carboxy-7,8,13,14-tetrahydro-9-oxoprotoberberine [(+)-**26**]. This establishes the absolute configuration of (+)-thalictricavine as 13*S*,14*R*. (+)-Thalictrifoline [(+)-**2**] and (+)-cavidine [(+)-**1**] have also been prepared from a common intermediate, (+)-**32**, whose absolute configuration was established by correlation with (+)-**26**. This determines the absolute configuration of (+)-thalictrifoline as 13*R*,14*R*, of (+)-corydalic acid methyl ester (**22**) as 3*R*,4*R*, and of the protopine (+)-corycavine (**20**) as 13*R*.

The 13-methyltetrahydroprotoberberine alkaloids are a group of metabolites which occur in various species of *Corydalis*. Compounds in which protons H_A and H_B are cis [e.g., cavidine (**1**)] are referred to as cis diastereomers,



1



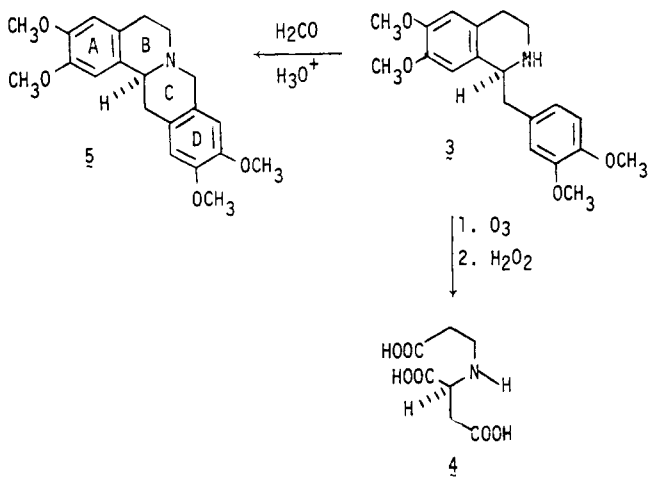
2

while in the trans isomers [e.g., thalictrifoline (**2**)] these protons are trans. As portrayed in structures **1** and **2**, the cis isomers exist in the *trans*-quinolizidine conformation, while the trans diastereomers exist in the *cis*-quinolizidine conformation in solution in order to avoid a nonbonded interaction between the C-13 methyl group and the C-1 hydrogen atom.[1]

The absolute configurations of the tetrahydroprotoberberines which lack substituents in the B and C rings were determined by the conversion of (-)-*N*-norlaudanosine (**3**) to *N*-(β-carboxyethyl)-L-aspartic acid (**4**) of known absolute configuration and (-)-norcoralydine (**5**), which therefore must have the 14*S* configuration.[2] The tetrahydroprotoberberines related to compound **5** which are

(1) (a) Bersch, H. W. *Arch. Pharm. (Weinheim, Ger.)* **1958**, *291*, 595. (b) Jeffs, P. W. *Experientia* **1965**, *21*, 690. (c) Yu, C. K.; MacLean, D. B.; Rodrigo, R. G. A.; Manske, R. H. F. *Can. J. Chem.* **1970**, *48*, 3673. (d) Govindachari, T. R.; Nagarajan, K.; Charubala, R.; Pai, B. R.; Subramanian, P. S. *Indian J. Chem.* **1970**, *8*, 769. (e) Takao, N.; Iwasa, K.; Kamigauchi, M.; Sugiura, M. *Chem. Pharm. Bull.* **1977**, *25*, 1426. (f) Takao, N.; Iwasa, K. *Ibid.* **1976**, *24*, 3185.
(2) Corrodi, H.; Hardegger, E. *Helv. Chim. Acta* **1956**, *39*, 889.

0022-3263/81/1946-4744$01.25/0



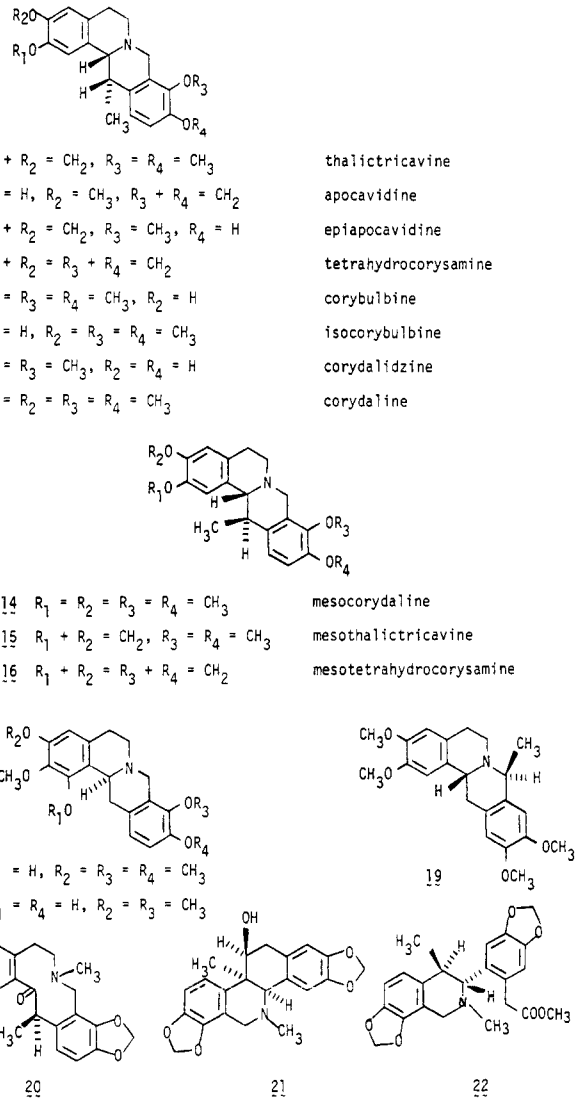
5 3 4

unsubstituted in the B and C rings adopt a *trans*-quinolizidine conformation similar to that of the *cis*-13-methyl diastereomers.[3] The absolute configuration of the naturally occurring (+)-*cis*-13-methyltetrahydroprotoberberines (**1**, **6–13**; Chart I) are therefore believed to be as shown here with the assumption that the axial 13-methyl groups do not make a significant contribution to the molecular rotations.[1b,4]

This correlation of positive rotation with a 14β-hydrogen should not be extended to the *trans*-13-methyltetrahydroprotoberberine series (**2**, **14–16**)[5] because of the difference in the quinolizidine conformation. In this regard, it should be pointed out that the absolute configurations of (-)-capaurine (**17**) hydrobromide,[6] the mono-*p*-bromobenzoate of (-)-capaurimine (**18**),[7] and (+)-*O*-methylcorytenchirine (**19**)[8] have been determined by X-ray analysis. Since these compounds also adopt a *cis*-quinolizidine conformation in the solid state similar to that of the *trans*-13-methyltetrahydroprotoberberine series in solution, it might be argued that a 14β-hydrogen does correlate with a positive rotation in the latter series. However, this argument is not a good one because it has been demonstrated that tetrahydroprotoberberines bearing an oxygen substituent at C-1 such as capaurine and certain capaurimine derivatives exist in solution at room temperature as a mixture of the trans- and cis-fused quinolizidine conformations.[1e,f]

Both (±)-mesotetrahydrocorysamine (**16**) and (±)-tetrahydrocorysamine (**9**) are converted by *Corydalis incisa* plants and callus cells to the protopine alkaloid corycavine (**20**), which is an intermediate in the biosynthesis of the benzophenanthridine alkaloids (+)-corynoline (**21**) and (+)-14-epicorynoline.[9] Knowledge of the absolute configurations of the (+)- and (-)-13-methyltetrahydroprotoberberines would allow the assignment of the absolute configuration of naturally occurring (+)-corycavine because (+)-corycavine has been chemically converted to (+)-mesotetrahydrocorysamine (**16**).[10] Methyl (+)-corydalate (**22**) of unknown absolute configuration has also been isolated from *Corydalis incisa*.[11] This metabolite or a closely related compound might also serve as an intermediate in the biosynthetic conversion of certain protoberberines to benzophenanthridine alkaloids. Determination of the absolute configuration of (+)-mesotetrahydrocorysamine (**16**) would also allow the assignment of the absolute configuration of methyl (+)-corydalate (**22**) since (+)-**22** has already been chemically converted to (+)-**16** by methods which did not disturb the absolute configurations of the two asymmetric centers.[11] We now report chemical correlations of optically active 13-methyltetrahydroprotoberberines which establish their absolute configurations. This work entailed the execution of the first total syntheses of naturally occurring (+)-thalictrifoline (**2**) and (+)-cavidine (**1**).[12]

Chart I



6	$R_1 + R_2 = CH_2$, $R_3 = R_4 = CH_3$	thalictricavine
7	$R_1 = H$, $R_2 = CH_3$, $R_3 + R_4 = CH_2$	apocavidine
8	$R_1 + R_2 = CH_2$, $R_3 = CH_3$, $R_4 = H$	epiapocavidine
9	$R_1 + R_2 = R_3 + R_4 = CH_2$	tetrahydrocorysamine
10	$R_1 = R_3 = R_4 = CH_3$, $R_2 = H$	corybulbine
11	$R_1 = H$, $R_2 = R_3 = R_4 = CH_3$	isocorybulbine
12	$R_1 = R_3 = CH_3$, $R_2 = R_4 = H$	corydalidzine
13	$R_1 = R_2 = R_3 = R_4 = CH_3$	corydaline

14	$R_1 = R_2 = R_3 = R_4 = CH_3$	mesocorydaline
15	$R_1 + R_2 = CH_2$, $R_3 = R_4 = CH_3$	mesothalictricavine
16	$R_1 + R_2 = R_3 + R_4 = CH_2$	mesotetrahydrocorysamine

17, $R_1 = H$, $R_2 = R_3 = R_4 = CH_3$
18, $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$

19

20 **21** **22**

(3) Shamma, M. "The Isoquinoline Alkaloids"; Academic Press: New York, 1972; pp 293–295. Kametani, T.; Ujiie, A.; Ihara, M.; Fukumoto, K.; Koizumi, H. *Heterocycles* **1975**, *3*, 371.

(4) Kondo, Y. *Yakugaku Zasshi* **1963**, *83*, 1017. Snatzke, G.; Hrbek, J., Jr.; Hruban, L.; Horeau, A.; Santavy, F. *Tetrahedron* **1970**, *26*, 5013.

(5) (+)-Thalictrifoline (**2**) is the only *trans*-13-methyltetrahydroprotoberberine which has thus far been isolated as a natural product: Manske, R. H. F. *Can. J. Chem.* **1943**, *21B*, 111. Compounds **14–16** have been prepared by chemical modification of natural products: Gadamer, J. *Arch. Pharm. (Weinheim, Ger.)* **1902**, *240*, 19. Tani, C.; Takao, N.; Takao, S. *Yakugaku Zasshi* **1962**, *82*, 748. Tani, C.; Takao, N.; Takao, S.; Tagahara, K. *Yakugaku Zasshi* **1962**, *82*, 751.

(6) Shimanouchi, H.; Sasada, Y.; Ihara, M.; Kametani, T. *Acta Crystallogr., Sect. B* **1969**, *B25*, 1310.

(7) Kametani, T.; Ihara, M.; Honda, T.; Shimanouchi, H.; Sasada, Y. *J. Chem. Soc. C* **1971**, 2541.

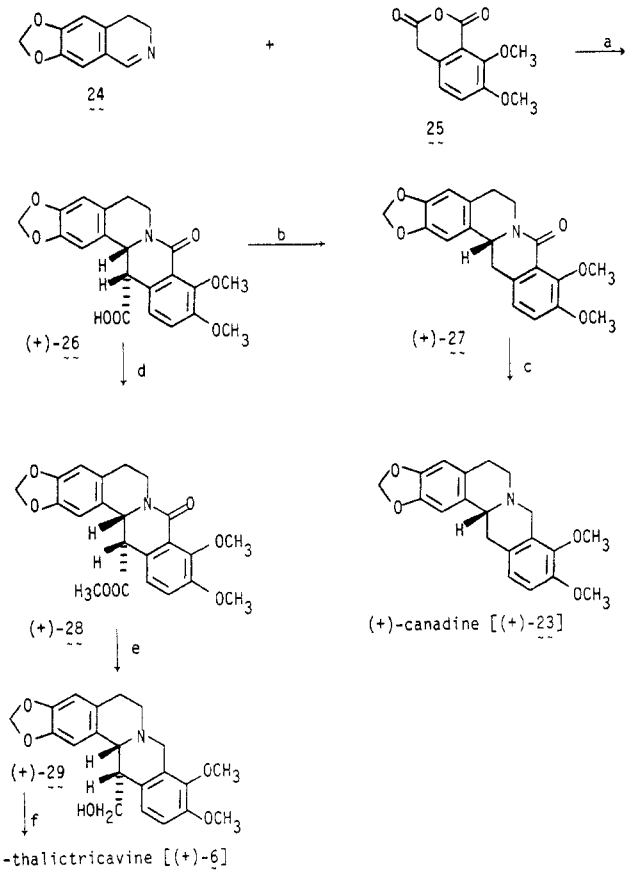
(8) Bruderer, H.; Metzger, J.; Brossi, A.; Daly, J. J. *Helv. Chim. Acta* **1976**, *59*, 2793.

(9) (a) Takao, N.; Iwasa, K.; Kamigauchi, M.; Sugiura, M. *Chem. Pharm. Bull.* **1973**, *21*, 1020. (b) Takao, N.; Kamigauchi, M.; Iwasa, K. April 1978 Meeting of the Pharmaceutical Society of Japan, Okayama, Japan, Abstracts, p 343.

(10) Takao, N.; Kamigauchi, M.; Iwasa, K.; Kriyama, H., August 1979 Meeting of the Pharmaceutical Society of Japan, Sapporo, Japan, Abstracts, p 196.

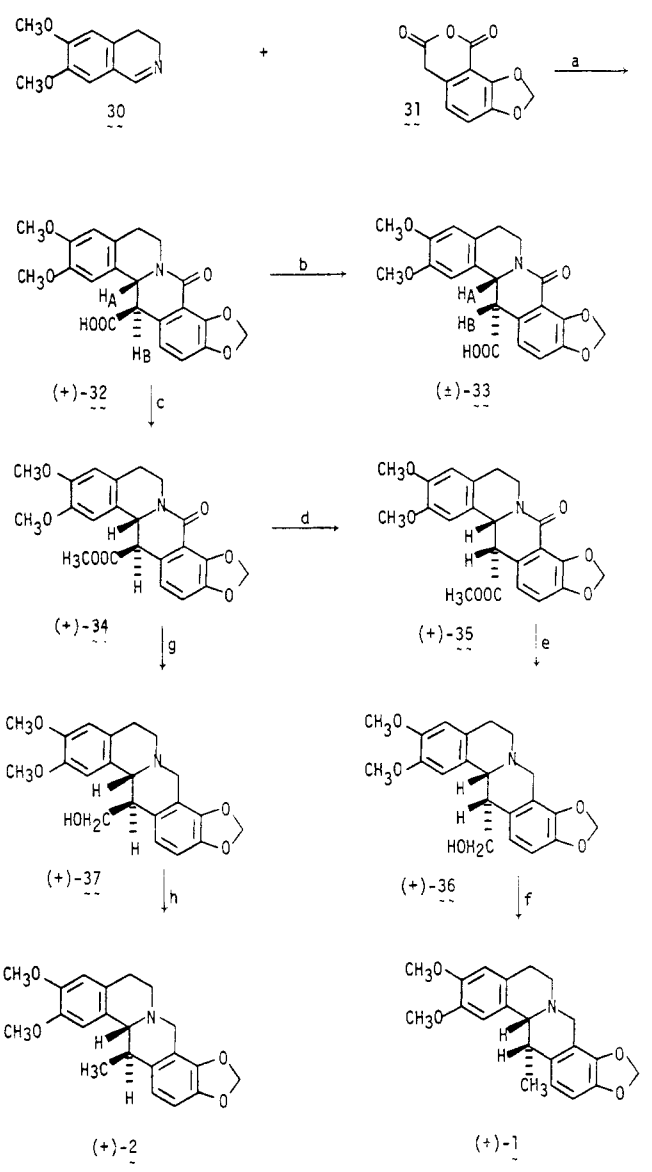
(11) Nonaka, G.; Kodera, Y.; Nishioka, I. *Chem. Pharm. Bull.* **1973**, *21*, 1020.

Scheme I



[a] (1) $CHCl_3$, room temperature (30 min); (2) AcOH, reflux (24 h); (3) (−)-strychnine, Me_2CO. [b] 240–244 °C (5 min). [c] $LiAlH_4$, Et_2O, 0–23 °C (2 h). [d] CH_2N_2, Et_2O, 0 °C (12 h). [e] $LiAlH_4$, THF-Et_2O, reflux (2 h). [f] (1) MsCl, Py, 0 °C (1 h); (2) $LiAlH_4$, THF-Et_2O, reflux (2 h).

Scheme II



[a] (1) $CHCl_3$, room temperature (1 h); (2) (−)-strychnine, $CHCl_3$-MeOH. [b] AcOH, reflux (23 h). [c] CH_2N_2, $CHCl_3$-EtOH, 0 °C (1 h). [d] CH_3ONa, MeOH, room temperature (96 h). [e] $LiAlH_4$, THF-Et_2O, reflux (27 h). [f] (1) MsCl, pyridine, room temperature (1.5 h); (2) $LiAlH_4$, THF-Et_2O, room temperature (2 h). [g] $LiAlH_4$, THF-Et_2O, reflux (6 h). [h] (1) MsCl, pyridine, room temperature (4 h); (2) $LiAlH_4$, THF-Et_2O, reflux (3.5 h).

The first goal of the present study was to prove the absolute configuration of (+)-thalictricavine (**6**). Our recent total synthesis of (±)-thalictricavine (**6**) and (±)-canadine (**23**) from a common intermediate, (±)-**26** (Scheme I), suggests that the absolute configuration of (+)-thalictricavine (**6**) could be determined by chemical correlation with (+)-canadine (**23**).[13] Since changes in the substituents on the A and D rings of tetrahydroprotoberberines have only a minor effect on the specific rotation, the absolute configuration of (+)-canadine, as shown in structure (+)-**23**, has been established by comparison with (−)-*N*-norlaudanosine (**3**).[2]

The racemic intermediate (±)-**26**[13] afforded a crystalline salt (mp 164–171 °C; $[\alpha]_D$ +174°) when treated with (−)-strychnine in acetone followed by recrystallization from acetone. The free acid (+)-**26** ($[\alpha]_D$ +412°) was provided by decomposition of the salt. The enantiomeric acid (−)-**26** ($[\alpha]_D$ -416°) was also obtained by decomposition of the mother liquors with hydrochloric acid followed by recrystallization of the free acid from acetone. The (+) cis acid (+)-**26** yielded an optically impure lactam [(+)-**27**, $[\alpha]_D$ +48°] when heated at 240–244 °C. The levorotatory acid (−)-**26** was also decarboxylated thermally, which afforded optically impure (−) lactam (−)-**27**, $[\alpha]_D$ −38°. Lithium aluminum hydride reduction of (+)-**27** gave (±)-canadine (**23**) and optically impure (+)-canadine ($[\alpha]_D$ +86°) while similar treatment of (−)-**27** yielded (−)-canadine, $[\alpha]_D$ −38°. Consequently, the absolute configuration of the intermediate (+)-**26** must be 13*S*,14*R* as displayed in Scheme I. The amino alcohol (+)-**29** ($[\alpha]_D$ +278°) was prepared by lithium aluminum hydride reduction of the methyl ester (+)-**28**, $[\alpha]_D$ +417°. Reduction of the mesylate of (+)-**29** with lithium aluminum hydride afforded (+)-thalictricavine [(+)-**6**; $[\alpha]_D$ +312° (lit.[14] $[\alpha]^{23}_D$ +291.9°)]. This proves

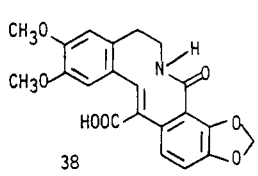
(12) Dr. B. R. Pai, Amrutanjan Research Center, Madras, has notified us of their synthesis of (±)-thalictrifoline (**2**) and (±)-cavidine (**1**) by essentially the same route as shown in Scheme II. Dr. Pai reported the details of their work at a symposium entitled "New Reagents, Reactions, and Rearrangements" held at the Department of Organic Chemistry at the University of Madras on Jan 21, 1981. (±)-Cavidine (**1**) has also previously been synthesized by using the enamide photocyclization reaction: Ninomiya, I.; Takasugi, H.; Naito, T. *Heterocycles* **1973**, *1*, 17; *J. Chem. Soc., Perkin Trans. 1* **1975**, 1791. Our own work was previously outlined in two preliminary communications: Iwasa, K.; Cushman, M. *Heterocycles* **1981**, *16*, 901. Iwasa, K.; Gupta, Y. P.; Cushman, M. *Tetrahedron Lett.* **1981**, 2333.

(13) Cushman, M.; Dekow, F. W. *J. Org. Chem.* **1979**, *44*, 407.

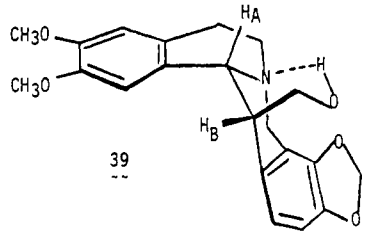
(14) Manske, R. H. F. *J. Am. Chem. Soc.* **1953**, *75*, 4928.

that the absolute configuration of (+)-thalictricavine is 13*S*,14*R* as shown in structure **6**.

Our next objective was to determine the absolute configuration of (+)-thalictrifoline [(+)-**2**]. The required 3,4-(methylenedioxy)homophthalic anhydride (**31**, Scheme II) was already available in large quantities made possible by a route utilized as part of a recent total synthesis of the benzophenanthridine alkaloid chelidonine.[15] Condensation of compounds **30** and **31** afforded (±)-*trans*-**32** (J_{AB} = 8 Hz) in 78% yield. The cis acid (±)-**33** was obtained by heating the remaining material in acetic acid. The trans acid (±)-**32** was resolved with the aid of (−)-strychnine. The trans stereochemistry of **32** was established by the conversion of (+)-**32** into the thermodynamically more stable cis diastereomer (±)-**33** (J_{AB} = 4 Hz) on heating in refluxing acetic acid.[16] The fact that this reaction proceeds with racemization suggests involvement of an achiral intermediate **38**. Treatment of (+)-**32** ([α]$_D$ +250°) with



38



39

diazomethane yielded the methyl ester (+)-**34**, [α]$_D$ +265°. Epimerization of (+)-**34** (J_{AB} = 9.4 Hz) proceeded without racemization by using sodium methoxide in methanol to give (+)-**35** (J_{AB} = 4 Hz; [α]$_D$ +428°). Since the conformations of (+)-**35** and (+)-**28** are identical as evidenced by the ^{1}H NMR data and the optical rotations are almost identical, they must have the same absolute configurations. The structure of (+)-**35** shown in Scheme II is also consistent with its reduction to (+)-cavidine (**1**,[α]$_D$ +323°) whose absolute configuration is now known by comparison with (+)-thalictricavine (**6**). These results also establish the absolute configuration of the intermediate (+) trans ester **34**, which was reduced to an amino alcohol (+)-**37**. Compound (+)-**37** displayed a low optical rotation ([α]$_D$ +4.8°) uncharacteristic of the protoberberine series. There are actually two cis quinolizidine conformations possible for the protoberberines. The compounds in this series which adopt a cis conformation usually exist with the nitrogen lone pair of electrons axial with respect to the B ring as shown in structure **2** (J_{AB} = 8 Hz). The low optical rotation of (+)-**37** is explained by the fact that it populates the other possible cis quinolizidine conformation represented by structure **39** in which the nonbonded electrons are equatorial with respect to the B ring.[16] This is evidenced by the small coupling constant J_{AB} = 2 Hz which is consistent with conformation **39**. This conformation is unusual for the protoberberine series and results in the present case from stabilization due to intramolecular hydrogen bonding.

The reduction of (+)-**34** to (+)-thalictrifoline [(+)-**2**, [α]$_D$ +199° (lit.[19] [α]$_D$ +218°)] determines the absolute configurations of (+)-thalictrifoline [(+)-**2**] as 13*R*,14*R* and that of methyl (+)-corydalate (**22**) as 3*R*,4*R*. This work also establishes the absolute configuration of naturally occurring (+)-corycavine (**20**) as 13*R* since it has been chemically converted to (+)-mesotetrahydrocorysamine (**16**).[10] All of the chemistry reported in Scheme II was also performed by starting from (±)- and (−)-**32**.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on a Varian EM-360 60-MHz instrument. The high-resolution 470-MHz NMR spectra were obtained by using a Nicolet NTC-470 spectrometer and the data accumulated by using 32K free induction decays. Except where noted, the samples for NMR analyses were dissolved in $CDCl_3$. Chemical shifts are reported in parts per million relative to Me_4Si as an internal standard. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Optical rotations were determined in chloroform with a Perkin-Elmer 241 unless otherwise indicated. Preparative thin-layer chromatography (TLC) was performed on Merck silica gel 60 F-254. Microanalyses were performed by the Purdue Microanalytical Laboratory. The mass spectra were determined on a CEC 21-110 or a Du Pont 21-492 B double-focusing spectrometer using an ion-source temperature of 150–270 °C and an ionization potential of 70 eV. Organic solutions were dried over $MgSO_4$.

(+)-*cis*-2,3-(Methylenedioxy)-8-oxo-9,10-dimethoxy-13-carboxytetrahydroprotoberberine [(+)-26]. A solution of (−)-strychnine (170 mg, 0.51 mmol) in $CHCl_3$ (5 mL) was added to a solution of (±)-**26**[13] (200 mg, 0.50 mmol) in Me_2CO (10 mL) and $CHCl_3$ (5 mL). The mixture was allowed to stand for 3 days at room temperature. The solvent was evaporated and the residue was dissolved in Me_2CO (20 mL). After the mixture was allowed to stand in the refrigerator overnight, the first crop (10 mg; [α]$_D$ −54°) was filtered off. The mother liquors then deposited a second crop [158 mg; mp 164–171 °C; [α]$_D$ +168° (*c* 0.11)] which was recrystallized from Me_2CO to afford the salt: mp 164–171 °C; [α]$_D$ +174° (*c* 0.086). Aqueous HCl (10%) was then added to a solution of the salt (119 mg) in hot water (30 mL). After cooling, the acidic solution was extracted with Et_2O. The organic layer was washed with water, dried, and evaporated. The residue was crystallized from Me_2CO to give the free (+) cis acid (+)-**26**: 38 mg; mp 242–243 °C; [α]$_D$ +412° (*c* 0.08); mass spectrum, *m*/*e* (relative intensity) 397 (M$^+$, 6), 353 (21), 351 (30), 339 (28), 337 (36), 336 (28), 322 (43), 236 (18), 222 (16), 194 (14), 193 (15), 178 (51), 176 (100).

(−)-*cis*-2,3-(Methylenedioxy)-8-oxo-9,10-dimethoxy-13-carboxytetrahydroprotoberberine [(−)-26]. The filtrate from above was evaporated, and the residue was dissolved in $CHCl_3$. The solution was extracted with 5% HCl and washed with water. The organic solution was dried and evaporated. The residue was crystallized from Me_2CO to give (−)-**26**: 27 mg; mp 238–240 °C; [α]$_D$ −416° (*c* 0.07); mass spectrum, *m*/*e* (relative intensity) 397 (M$^+$, 18), 353 (18), 351 (7), 337 (4), 336 (6), 322 (6), 236 (10), 222 (18), 194 (18), 178 (31), 176 (100).

(±)-2,3-(Methylenedioxy)-8-oxo-9,10-dimethoxytetrahydroprotoberberine [(±)-27]. The cis acid (±)-**26** (50 mg, 0.13 mmol) was heated at 243–245 °C for 5 min during which gas evolved from the melt. Preparative TLC (silica gel, C_6H_6–Et_2O, 1:1) yielded a product which was recrystallized from MeOH–$CHCl_3$ to afford the lactam (±)-**27**: 11 mg (24%); mp 215 °C; IR ($CHCl_3$) 1645 cm^{-1}; NMR δ 7.05 (s, 2 H), 6.75 (s, 2 H), 6.03 (s, 2 H), 5.30–4.30 (m, 2 H), 4.07 (s, 3 H), 3.93 (s, 3 H), 3.30 2.70 (m, 5 H); chemical-ionization mass spectrum, *m*/*e* (relative intensity) 354 (M$^+$ + 1, 100).

(+)-2,3-(Methylenedioxy)-8-oxo-9,10-dimethoxytetrahydroprotoberberine [(+)-27]. The cis acid (+)-**26** (32 mg, 0.08 mmol) was heated at 240–244 °C for 5 min during which gas evolved from the melt. The residue was separated by preparative TLC (silica gel, C_6H_6–Et_2O 1:1) to yield a product which was recrystallized from $CHCl_3$–MeOH to give the optically impure lactam (+)-**27**: 14 mg (50%); mp 214–215 °C; [α]$_D$ + 48° (*c* 0.11); IR ($CHCl_3$) 1645 cm^{-1}; mass spectrum, *m*/*e* (relative intensity) 353 (M$^+$, 44), 178 (100), 176 (77), 163 (57).

(−)-2,3-(Methylenedioxy)-8-oxo-9,10-dimethoxytetrahydroprotoberberine [(−)-27]. The cis acid (−)-**26** (60 mg, 0.15 mmol) was heated at 242–248 °C for 20 min during which gas

(15) Cushman, M.; Choong, T.-C.; Valko, J. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067.
(16) Cushman, M.; Gentry, J.; Dekow, F. W. *J. Org. Chem.* **1977**, *42*, 1111.
(17) "The Merck Index", 9th ed.; Merck and Co., Inc.: Rahway, NJ, 1976.
(18) Taguchi, H.; Imaseki, I. *Yakugaku Zasshi* **1964**, *84*, 955.
(19) Kametani, T. "The Chemistry of the Isoquinoline Alkaloids"; Hirokawa Publishing Co., Inc., Tokyo, 1969; p 121.

evolved from the melt. The residue was subjected to preparative TLC (silica gel, 95:5 $CHCl_3$–MeOH followed by 1:1 C_6H_6–Et_2O) to yield the optically impure lactam (–)-**27**: 26 mg (49%); mp 216–217 °C; $[\alpha]_D$ –38° (*c* 0.10); mass spectrum, *m/e* (relative intensity) 353 (M^+, 78), 178 (100), 176 (65), 163 (52).

(±)-Canadine [(±)-23]. A solution of the lactam (±)-**27** (8 mg, 0.02 mmol) in THF (5 mL) was added to a solution of $LiAlH_4$ (70 mg) in Et_2O (10 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was stirred for 2 h at room temperature before addition of water (70 μL), 15% NaOH (70 μL), and water (210 μL). The solid was filtered and washed with $CHCl_3$. The combined filtrates were washed with water, dried, and evaporated. The residue was crystallized from Me_2CO to give (±)-canadine: 4.00 mg (52%); mp 164–165 °C (lit.[17] mp 172 °C); mass spectrum, *m/e* (relative intensity) 339 (M^+, 100), 174 (11), 164 (39), 149 (39).

(+)-Canadine [(+)-23]. The optically impure lactam (+)-**27** (10 mg, 0.028 mmol) was reduced by the same procedure described above for the preparation of (±)-**23**. The residue was crystallized from Me_2CO to afford (±)-canadine: 3.8 mg (40%); $[\alpha]_D$ 0° (*c* 0.76). The residue obtained from the mother liquors was purified by preparative TLC (silica gel, 7:3 C_6H_6–Et_2O) to give optically impure (+)-canadine: 4.3 mg (45%); mp 118–157 °C; $[\alpha]_D$ +86° (*c* 0.086); mass spectrum, *m/e* (relative intensity) 339 (M^+, 100), 174 (18), 164 (81), 149 (66).

(–)-Canadine [(–)-23]. The lactam (–)-**27** (23 mg, 0.065 mmol) was reduced by the same method as described above for the preparation of (±)-canadine to give optically impure (–)-canadine: 15 mg (68%); mp 115–160 °C; $[\alpha]_D$ –38° (*c* 0.246); mass spectrum, *m/e* (relative intensity) 339 (M^+, 100), 174 (27), 164 (72), 149 (55).

(+)-*cis*-2,3-(Methylenedioxy)-8-oxo-9,10-dimethoxy-13-(methoxycarbonyl)tetrahydroprotoberberine [(+)-28]. A solution of the cis acid (+)-**26** (38 mg, 0.096 mmol) in EtOH (15 mL) was slowly added to a solution of an excess of CH_2N_2 in Et_2O (50 mL) at 0 °C. After the mixture was allowed to stand overnight in the refrigerator the excess CH_2N_2 was decomposed by addition of AcOH. The solvent was evaporated and the residue was purified by preparative TLC (silica gel, 1:1 C_6H_6–Et_2O) to yield the cis ester (+)-**28**, 38 mg (97%). The analytical sample was recrystallized from Me_2CO–Et_2O: mp 176–177 °C; $[\alpha]_D$ +417° (*c* 0.082); IR ($CHCl_3$) 1730, 1645 cm^{-1}; mass spectrum, *m/e* (relative intensity) 411 (M^+, 37), 352 (12), 236 (100), 221 (9), 208 (12), 193 (22).

(+)-*cis*-2,3-(Methylenedioxy)-9,10-dimethoxy-13-(hydroxymethyl)tetrahydroprotoberberine [(+)-29]. A solution of the cis ester (+)-**28** (75 mg, 0.18 mmol) in THF (10 mL) was added to a solution of $LiAlH_4$ (100 mg, 2.64 mmol) in Et_2O (15 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was heated at reflux for 2 h. The mixture was decomposed by addition of water (75 μL), 15% NaOH (75 μL), and finally water (225 μL). The aluminates were filtered and washed with $CHCl_3$. The combined filtrates were dried and evaporated. The residue was crystallized from $CHCl_3$–MeOH to give the cis amino alcohol (+)-**29**: 58 mg (75%); mp 199–200 °C; $[\alpha]_D$ +278° (*c* 0.07); IR ($CHCl_3$) 3400–3100 cm^{-1}; mass spectrum, *m/e* (relative intensity) 369 (M^+, 100), 338 (43), 194 (62), 179 (38), 176 (36), 165 (48).

(+)-Thalictricavine [(+)-6]. Methanesulfonyl chloride (45 mg, 0.39 mmol) was added slowly to a solution of the cis amino alcohol (+)-**29** (54 mg, 0.15 mmol) in pyridine (1 mL) with stirring at 0 °C. After 1 h at 0 °C, water was added to the reaction mixture. The solution was extracted with $CHCl_3$. The organic layers were dried and evaporated. The resulting mesylate was dissolved in THF (25 mL), and the solution was added to a mixture of $LiAlH_4$ (90 mg, 2.4 mmol) and Et_2O (15 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was heated at reflux for 2 h before the addition of water (90 μL), 15% NaOH (90 μL), and water (270 μL). The aluminates were filtered and washed with $CHCl_3$. The combined filtrates were dried and evaporated. The residue was subjected to preparative TLC (silica gel, 7:3 C_6H_6–Et_2O). The starting material (+)-**29** (8 mg, 15%) was recovered along with (+)-thalictricavine: 9 mg (17%); mp 149–150 °C (lit.[14] mp 140 °C); $[\alpha]_D$ +312° (*c* 0.056); mass spectrum, *m/e* (relative intensity) 353 (M^+, 50), 338 (11), 178 (100), 174 (20), 163 (20).

(±)-*trans*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-carboxytetrahydroprotoberberine [(±)-32]. A solution of norhydrastinine (**30**; 1.825 g, 10.42 mmol) in $CHCl_3$ (20 mL) was added to a stirred suspension of 3,4-(methylenedioxy)homophthalic anhydride (**31**; 0.950 g, 4.61 mmol) in $CHCl_3$ (20 mL) during 1 h at room temperature under a nitrogen atmosphere. After an additional 1.5 h the solvent was evaporated, and Me_2CO was added. The solid (±)-**32** (1.346 g, 78%) was filtered and recrystallized from EtOAc–MeOH–$CHCl_3$: mp 252–254 °C; IR (KBr) 3600–2400, 1723, 1620, 1585 cm^{-1}; NMR ($CDCl_3$–pyridine-d_5, 3:1) δ 7.12 (s, 1 H), 6.93 (s, 2 H), 6.68 (s, 1 H), 6.08 (m, 2 H), 5.42 (d, 1 H, J_{AB} = 8 Hz), 5.01 (m, 1 H), 4.22 (d, 1 H, J_{AB} = 8 Hz), 3.75 (s, 3 H), 3.67 (s, 3 H), 3.30–2.40 (m, 3 H); mass spectrum, *m/e* (relative intensity) 397 (M^+, 4), 351 (20), 206 (31), 192 (49), 191 (100), 176 (60), 162 (30), 134 (82).

Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82, N, 3.52. Found: C, 63.51; H, 5.06; N, 3.40.

(±)-*cis*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-carboxytetrahydroprotoberberine [(±)-33]. Method A. The mother liquor from above was evaporated, and the residue was dissolved in AcOH (10 mL). The solution was heated at reflux for 26 h. The AcOH was evaporated, and the residue was crystallized from Me_2CO to give (±)-**33**: 261 mg (15%); mp 259–261 °C dec; IR (KBr) 3600–2400, 1715, 1620, 1580 cm^{-1}; NMR ($CDCl_3$–pyridine-d_5, 3:1) δ 8.92 (br s, 1 H), 7.03 (s, 3 H), 6.77 (s, 1 H), 6.20 (m, 2 H), 5.30 (d, 1 H, J_{AB} = 4 Hz), 5.00 (m, 1 H), 4.40 (d, 1 H, J_{AB} = 4 Hz), 3.97 (s 3 H), 3.87 (s, 3 H), 3.30–2.40 (m, 3 H); mass spectrum, *m/e* (relative intensity) 397 (M^+, 23), 353 (21), 351 (26), 206 (25), 192 (100), 178 (14), 176 (12), 162 (17), 134 (20).

Method B. A solution of the trans acid (+)-**32** (50 mg, 0.13 mmol) in AcOH (5 mL) was heated at reflux for 23 h. The AcOH was evaporated, and the residue purified by thin-layer chromatography to yield (±)-**33**: 19 mg (38%); mp 262–263 °C; $[\alpha]_D$ 0°. The mass spectrum was identical with that of the sample above.

Anal. Calcd for $C_{21}H_{19}NO_7$: C, 63.47; H, 4.82; N, 3.52. Found: C, 63.67; H, 4.98; N, 3.24.

(–)-*trans*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-carboxytetrahydroprotoberberine [(–)-32]. A solution of (–)-strychnine (1.120 g, 3.35 mmol) in $CHCl_3$ (20 mL) was added to a solution of (±)-**32** (1.316 g, 3.31 mmol) in $CHCl_3$ (40 mL) and MeOH (40 mL). The clear solution was allowed to stand overnight at room temperature. EtOAc (50 mL) was added. The solution was then concentrated to half the original volume and was stored overnight in the refrigerator. The first crop of salt crystals [582 mg; $[\alpha]_D$ –96° (*c* 0.204)] was filtered. Evaporation of solvent from the filtrate gave a residue which was recrystallized several times from $CHCl_3$–EtOAc to afford a second crop of the salt: 375 mg; $[\alpha]_D$ –85° (*c* 0.154). The analytical sample was recrystallized several times from $CHCl_3$–EtOAc: mp 230–233 °C dec; $[\alpha]_D$ –103° (*c* 0.116).

Anal. Calcd for $C_{42}H_{41}N_3O_9 \cdot 0.5H_2O$: C, 68.03; H, 5.71; N, 5.67. Found: C, 67.69; H, 5.75; N, 5.38.

A sample of the above salt (582 mg) was dissolved in $CHCl_3$–Me_2CO, and 10% HCl was added to the solution. The resulting solid was filtered and washed with hot water to give the free acid (–)-**32** (285 mg). The analytical sample was recrystallized several times from $CHCl_3$–MeOH–EtOAc: mp 235–240 °C; $[\alpha]_D$ –245° (*c* 0.112, $CHCl_3$–MeOH, 3:1); IR (KBr) 3600–2400, 1720, 1620, 1587 cm^{-1}; mass spectrum, *m/e* (relative intensity) 397 (M^+, 29), 353 (62), 351 (38), 206 (46), 192 (90), 191 (100), 176 (62), 162 (55), 138 (75).

(+)-*trans*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-carboxytetrahydroprotoberberine [(+)-32]. The mother liquors were obtained from filtration of the second crop of salt crystals above. Me_2CO and 10% HCl were added to the solution. The solid was filtered and triturated with hot water to give the free acid (+)-**32**: 346 mg; mp 233–235 °C dec; $[\alpha]_D$ +250° (*c* 0.106, $CHCl_3$–MeOH 3:1); IR (KBr) 3600–2400, 1720, 1620, 1587 cm^{-1}; mass spectrum, *m/e* (relative intensity) 397 (M^+, 9), 353 (67), 351 (63), 206 (33), 192 (40), 191 (100), 176 (71), 162 (62), 134 (95).

(±)-*trans*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(methoxycarbonyl)tetrahydroprotoberberine [(±)-34]. A solution of the trans acid (±)-**32** (300 mg, 0.75 mmol) in $CHCl_3$ (10 mL) and EtOH (30 mL) was slowly added to a solution of CH_2N_2 in Et_2O (10 mL) with stirring at 0 °C. After 1 h the solution was decolored, and a large excess of CH_2N_2 in Et_2O was added. The reaction mixture was stirred for an additional 2 h at 0 °C. The excess CH_2N_2 was decomposed by addition of AcOH, the solution was concentrated, and EtOAc was added. The colorless crystals (301 mg, 96%) were filtered: mp 235–236 °C;

IR ($CHCl_3$) 1720, 1630 cm^{-1}; NMR δ 6.93 (d, 1 H, J = 8 Hz), 6.78 (s, 2 H), 6.63 (d, 1 H, J = 8 Hz) 6.20 (m, 2 H), 5.27 (d, 1 H, J = 9.5 Hz), 5.10–4.70 (m, 1 H), 4.07 (d, 1 H, J = 9.4 Hz), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.80 (s, 3 H), 3.30–2.50 (m, 3 H); mass spectrum, m/e (relative intensity) 411 (M^+, 9), 352 (16), 351 (10), 220 (100), 192 (21), 177 (55).

Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.15; N, 3.40. Found: C, 64.19; H, 5.09; N, 3.18.

(−)-*trans*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(methoxycarbonyl)tetrahydroprotoberberine [(−)-34]. A solution of the trans acid (−)-**32** (695 mg, 1.69 mmol) in $CHCl_3$ (35 mL) and EtOH (35 mL) was added to a stirred solution of a large excess of CH_2N_2 in Et_2O (20 mL) at 0 °C. After 1.5 h the excess diazomethane was decomposed by addition of AcOH. The solvent was evaporated, and the residue crystallized from Me_2CO to give the trans ester (−)-**34**: 628 mg (87%); mp 182–183 °C; $[\alpha]_D$ −266° (c 0.134); mass spectrum, m/e (relative intensity) 411 (M^+, 29), 352 (28), 351 (21), 220 (100), 192 (25), 177 (50).

(+)-*trans*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(methoxycarbonyl)tetrahydroprotoberberine [(+)-34]. The trans acid (+)-**32** (432 mg, 1.09 mmol) was dissolved in $CHCl_3$ (20 mL) and EtOH (20 mL), and the solution was added to excess CH_2N_2 in Et_2O with stirring at 0 °C. After 1 h the product was isolated as described above to afford the trans ester (+)-**34**: 366 mg (82%); mp 182–183 °C; $[\alpha]_D$ +265° (c 0.134); mass spectrum, m/e (relative intensity) 411 (M^+, 52), 352 (18), 351 (14), 220 (100), 192 (15), 177 (29).

(±)-*cis*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(methoxycarbonyl)tetrahydroprotoberberine [(±)-35]. Method A. A solution of the cis acid (±)-**33** (260 mg, 0.65 mmol) in EtOH (30 mL) and $CHCl_3$ (10 mL) was slowly added to a solution of diazomethane in Et_2O (15 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at 0 °C before the excess diazomethane was decomposed by addition of AcOH. The solvent was evaporated, and EtOAc was added to the residue. The crystalline product (244 mg, 90%) was isolated by filtration: mp 205–206 °C; IR ($CHCl_3$) 1730, 1640 cm^{-1}; NMR δ 7.00 (br s, 2 H), 6.88 (s, 1 H), 6.82 (s, 1 H), 6.30 (m, 2 H), 5.28 (d, 1 H, J = 4 Hz), 5.10 (m, 1 H), 4.25 (d, 1 H, J = 4 Hz), 4.00 (s, 6 H), 3.42 (s, 3 H), 3.10–2.30 (m, 3 H); mass spectrum, m/e (relative intensity) 411 (M^+, 26), 352 (16), 351 (10), 220 (90), 192 (26), 191 (17), 177 (100), 176 (20).

Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.15, N, 3.40. Found: C, 64.31; H, 5.34; N, 3.38.

Method B. A solution of the trans ester (±)-**34** (50 mg, 0.12 mmol) in MeOH (30 mL) and $CHCl_3$ (0.5 mL) was added slowly to a solution of NaOMe (2 mg) in MeOH (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 71 h. The solvent was removed, and the residue was purified by preparative TLC (silica gel, $CHCl_3$–EtOH, 98:2) to give the cis ester (±)-**35**: 44 mg (88%); mp 203–204 °C; mass spectrum, m/e (relative intensity) 411 (M^+, 39), 352 (16), 351 (10), 220 (100), 192 (14), 177 (29).

(−)-*cis*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(methoxycarbonyl)tetrahydroprotoberberine [(−)-35]. A solution of the trans ester (−)-**34** (440 mg, 1.07 mmol) in MeOH (50 mL) and $CHCl_3$ (3 mL) was added to a solution of NaOMe (20 mg) in MeOH (30 mL) at 0 °C. The reaction mixture was stirred for 96 h at room temperature. The solvent was evaporated and the residue dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and evaporated to give the cis ester (−)-**35**: 315 mg (72%): mp 229–230 °C; $[\alpha]_D$ −438° (c 0.122); mass spectrum, m/e (relative intensity) 411 (M^+, 41), 352 (12), 351 (7), 220 (100), 192 (14), 177 (28).

(+)-*cis*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(methoxycarbonyl)tetrahydroprotoberberine [(+)-35]. A solution of the trans ester (+)-**34** (316 mg, 0.77 mmol) in MeOH (30 mL) was added to a solution of NaOMe (15 mg) in MeOH (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 96 h. The cis ester (+)-**35** (257 mg, 81%) was isolated as described above: mp 230–231 °C; $[\alpha]_D$ +428° (c 0.108); mass spectrum, m/e (relative intensity) 411 (M^+, 31), 352 (10), 351 (7), 220 (100), 192 (38), 177 (21).

(±)-*cis*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(hydroxymethyl)tetrahydroprotoberberine [(±)-36]. The cis ester (±)-**35** (870 mg, 2.11 mmol) was added to a solution of $LiAlH_4$ (300 mg, 7.91 mmol) in THF–Et_2O (4:1, 100 mL) at 0 °C. The reaction mixture was heated at reflux for 22 h before it was cooled to 0 °C and decomposed by addition of water (300 μL), 15% NaOH (300 μL), and water (900 μL). The aluminates were filtered and washed with $CHCl_3$. The combined filtrates were dried and evaporated to yield a solid: 712 mg (91%); mp 193–195 °C; IR ($CHCl_3$) 3400–3100 cm^{-1}; NMR δ 6.85 (s, 2 H), 6.71 (br s, 2 H), 6.05 (m, 2 H), 4.15 (d, 1 H, J = 16 Hz), 4.05 (br s, 1 H, W_H = 7 Hz), 3.93 (s, 6 H), 3.60 (d, 1 H, J = 16 Hz), 3.80–2.30 (m, 7 H); mass spectrum, m/e (relative intensity) 369 (M^+, 100), 368 (38), 352 (19), 338 (21), 192 (21), 190 (14), 178 (24), 149 (60).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28, N, 3.79. Found: C, 68.26; H, 6.36; N, 3.78.

(−)-*cis*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(hydroxymethyl)tetrahydroprotoberberine [(−)-36]. The cis ester (−)-**35** (270 mg, 0.66 mmol) was added to a solution of $LiAlH_4$ (200 mg, 5.27 mmol) in THF–Et_2O (5:2, 105 mL). The reaction mixture was heated at reflux for 27 h. The product was isolated as described above for the racemate to yield a solid: 177 mg (73%); mp 185–187 °C dec; $[\alpha]_D$ −275° (c 0.114); mass spectrum, m/e (relative intensity) 369 (M^+, 100), 368 (40), 352 (22), 338 (21), 192 (15), 190 (12), 178 (21), 149 (38).

(+)-*cis*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(hydroxymethyl)tetrahydroprotoberberine [(+)-36]. The cis ester (+)-**35** (230 mg, 0.56 mmol) was reduced by the same procedure as described above to yield the cis amino alcohol (+)-**36**: mp 188–189 °C dec; $[\alpha]_D$ +269° (c 0.154); mass spectrum, m/e (relative intensity) 369 (M^+, 100), 368 (39), 352 (25), 338 (25), 192 (20), 190 (18), 179 (29), 149 (61).

(±)-Cavidine [(±)-1]. Methanesulfonyl chloride (148 mg, 1.29 mmol) was added to a solution of (±)-**36** (175 mg, 0.47 mmol) in pyridine (3 mL). The reaction mixture was stirred at room temperature for 2 h and then poured into 5% K_2CO_3 (50 mL). The mixture was extracted with Et_2O. The organic extract was dried and evaporated. The residue was dried in vacuo overnight and then dissolved in THF (15 mL). The solution was added dropwise to a solution of $LiAlH_4$ (200 mg, 5.27 mmol) in THF–Et_2O (4:3, 35 mL) at 0 °C. The reaction mixture was heated at reflux for 3.5 h. The reaction mixture was then cooled to 0 °C and decomposed by addition of water (200 μL), 15% NaOH (200 μL), and water (600 μL). The solid was filtered and washed with $CHCl_3$. The combined filtrates were dried and evaporated. The residue was purified by preparative TLC (silica gel, 1:4 C_6H_6–Et_2O). This yielded the starting material (56 mg, 32%) and (±)-cavidine: 78 mg (46%); mp 188–189 °C (lit.[1c] mp 192 °C); NMR δ 6.75 (s, 3 H), 6.68 (s, 1 H), 6.02 (m, 2 H), 4.12 (d, 1 H, J = 16 Hz), 3.92 (s, 6 H), 3.78 (br s, 1 H, W_H = 6 Hz), 3.58 (d, 1 H, J = 16 Hz), 3.50–2.40 (m, 5 H), 0.93 (d, 3 H, J = 7 Hz); mass spectrum, m/e (relative intensity) 353 (47), 338 (10), 192 (7), 190 (7), 176 (4), 162 (100).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.79. Found: C, 70.92; H, 6.60; N, 3.68.

(−)-Cavidine [(−)-1]. Methanesulfonyl chloride (148 mg, 1.29 mmol) was added to a solution of the cis amino alcohol (−)-**36** (147 mg, 0.40 mmol) in pyridine (2 mL). The solution was stirred at room temperature for 2 h and then poured into 5% K_2CO_3 (50 mL). The mixture was extracted with Et_2O. The organic extract was dried and evaporated. The residue was dried in vacuo overnight and then dissolved in THF (30 mL). The solution was added to a solution of $LiAlH_4$ (200 mg, 5.27 mmol) in THF–Et_2O (1:1, 60 mL). The reaction mixture was heated at reflux for 3.5 h before it was cooled to 0 °C and decomposed by addition of water (200 μL), 15% NaOH (200 μL), and water (600 μL). The solid material was filtered and washed with $CHCl_3$. The combined organic filtrates were dried and the solvent evaporated. The residue was subjected to preparative TLC (silica gel, 2:3 C_6H_6–Et_2O). This resulted in isolation of the starting material (23 mg, 16%) and (−)-cavidine: 24 mg (17%); mp 146–147 °C; $[\alpha]_D$ −330° (c 0.134); mass spectrum, m/e (relative intensity) 353 (M^+, 48), 338 (12), 192 (9), 190 (7), 176 (4), 162 (100).

(+)-Cavidine [(+)-1]. Methanesulfonyl chloride (74 mg, 0.65 mmol) was added to a solution of the cis amino alcohol (+)-**36** (110 mg, 0.30 mmol). The solution was stirred for 1.5 h at room temperature and then poured into 5% K_2CO_3 (50 mL). The mixture was extracted with Et_2O. The organic extract was dried and evaporated. The residue was dried in vacuo overnight and

then dissolved in THF (60 mL). The solution was added dropwise to a solution of $LiAlH_4$ (200 mg, 5.27 mmol) in Et_2O (30 mL). The reaction mixture was stirred for 2 h at room temperature. The (+)-cavidine (23 mg, 22%) was isolated as described above: mp 148–149 °C (lit.[18] mp 144–146 °C); $[\alpha]_D$ +323° (*c* 0.132) [lit.[18] $[\alpha]_D^{12}$ +306 ($CHCl_3$)]; mass spectrum, *m/e* (relative intensity) 353 (M^+, 45), 338 (10), 192 (8), 190 (6), 176 (3), 162 (100).

(±)-*trans*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(hydroxymethyl)tetrahydroprotoberberine [(±)-37]. The trans ester (±)-**34** (440 mg, 1.09 mmol) was added to a solution of $LiAlH_4$ (200 mg, 5.27 mmol) in THF (80 mL) and Et_2O (20 mL) with stirring under a nitrogen atmosphere at 0 °C. The reaction mixture was then heated at reflux for 3 h before it was cooled to 0 °C and decomposed by addition of water (200 μL), 15% NaOH (200 μL), and water (600 μL). The aluminates were filtered and washed with $CHCl_3$. The combined filtrates were dried, and the solvent was evaporated. The residue was dissolved in MeOH and the yellow solution decolored by addition of $NaBH_4$. After the mixture was stirred overnight, water was added. The solution was concentrated and extracted with $CHCl_3$. The $CHCl_3$ extract was dried and the solvent evaporated. The residue was purified by preparative TLC (silica gel, 95:5 $CHCl_3$–EtOH) to yield the trans amino alcohol (±)-**37**: 200 mg (56%); mp 150–151 °C; IR ($CHCl_3$) 3580, 3300–3100 cm^{-1}; NMR (470 MHz, $CDCl_3$–D_2O) δ 6.77 (d, 1 H, *J* = 8 Hz), 6.69 (d, 1 H, *J* = 8 Hz), 6.59 (s, 1 H), 6.58 (s, 1 H), 5.87 (m, 2 H), 4.33 (d, 1 H, *J* = 2 Hz), 4.19 (dd, 1 H, *J* = 10, 3 Hz), 3.98 (dd, 1 H, *J* = 10, 3 Hz), 3.81 (s, 3 H), 3.79 (d, 1 H, *J* = 16 Hz), 3.73 (s, 3 H), 3.60 (d, 1 H, *J* = 16 Hz), 3.40 (m, 1 H), 3.37–3.34 (m, 1 H), 3.25–3.19 (m, 1 H), 3.13–3.04 (m, 1 H), 2.75–2.67 (m, 1 H); mass spectrum, *m/e* (relative intensity) 369 (M^+, 97), 352 (34), 338 (34), 192 (35), 191 (33), 190 (35), 178 (43), 176 (33), 148 (100).

Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.23; H, 6.28; N, 3.79. Found: C, 68.52; H, 6.11; N, 3.70.

(−)-*trans*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(hydroxymethyl)tetrahydroprotoberberine [(−)-37]. A solution of the trans ester (−)-**34** (380 mg, 0.92 mmol) in THF (30 mL) was added to a solution of $LiAlH_4$ (200 mg, 5.27 mmol) in THF–Et_2O (1:1, 60 mL). The reaction mixture was heated at reflux for 5.5 h before it was cooled to 0 °C and decomposed by addition of water (200 μL), 15% NaOH (200 μL), and finally water (600 μL). The aluminates were filtered off and washed with $CHCl_3$. The combined filtrates were dried, and the solvent was evaporated. The residue was treated as described above for the racemate to give the trans amino alcohol (−)-**37**: 230 mg (67%); mp 146–147 °C; $[\alpha]_D$ −8.5° (*c* 0.20); mass spectrum, *m/e* (relative intensity) 369 (M^+, 80), 352 (23), 339 (68), 338 (39), 192 (23), 190 (72), 178 (26), 149 (56), 148 (100).

(+)-*trans*-2,3-Dimethoxy-8-oxo-9,10-(methylenedioxy)-13-(hydroxymethyl)tetrahydroprotoberberine [(+)-37]. A solution of the trans ester (+)-**34** (340 mg, 0.83 mmol) in THF (30 mL) was added to a solution of $LiAlH_4$ (200 mg, 5.27 mmol) in THF–Et_2O (5:2, 70 mL). The reaction mixture was heated at reflux for 6 h before it was cooled to 0 °C and decomposed by addition of water (200 μL), 15% NaOH (200 μL), and water (600 μL). The solid was filtered and washed with $CHCl_3$. The combined filtrates were dried, and the solvent was evaporated. The residue was purified as described above for the racemate to yield the trans amino alcohol (+)-**37**: 208 mg (68%); mp 147–148 °C; $[\alpha]_D$ +4.8 (*c* 0.146); mass spectrum, *m/e* (relative intensity) 369 (M^+, 100), 352 (36), 338 (35), 192 (13), 191 (13), 190 (13), 178 (16), 176 (12), 149 (33).

(±)-Thalictrifoline [(±)-2]. *p*-Toluenesulfonyl chloride (150 mg, 0.79 mmol) was added to a solution of the amino alcohol (±)-**37** (188 mg, 0.51 mmol) in pyridine (2 mL). The reaction mixture was stirred at room temperature for 3 h and then poured into 5% K_2CO_3 (50 mL). The aqueous solution was extracted with $CHCl_3$. The organic extract was dried and the solvent evaporated. The residue was dried in vacuo overnight and then dissolved in THF (10 mL). The solution was added dropwise to a solution of $LiAlH_4$ (350 mg, 9.22 mmol) in THF (30 mL) and Et_2O (30 mL) at 0 °C. The reaction mixture was then heated at reflux for 3 h before it was cooled to 0 °C and decomposed by dropwise addition of water (350 μL), 15% NaOH (350 μL), and water (1050 μL). The aluminates were filtered and washed with $CHCl_3$. The combined organic filtrates were washed with saturated aqueous NaCl, dried, and evaporated. The residue was purified by preparative TLC (silica gel, 1:9 C_6H_6–Et_2O) to give (±)-thalictrifoline [(±)-**2**]: 94 mg (52%); mp 162–164 °C (crystallized from Me_2CO–Et_2O); NMR δ 6.77 (s, 3 H), 6.68 (s, 1 H), 5.98 (s, 2 H), 4.00 (br s, 2 H), 3.88 (s, 6 H), 3.68 (d, 1 H, *J* = 8 Hz), 3.50–2.60 (m, 5 H), 1.44 (d, 3 H, *J* = 6.5 Hz); mass spectrum, *m/e* (relative intensity) 353 (M^+, 40), 338 (11), 192 (10), 191 (13), 190 (11), 176 (13), 162 (100).

Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.79. Found: C, 71.49; H, 6.41; N, 3.91.

(−)-Thalictrifoline [(−)-2]. *p*-Toluenesulfonyl chloride (100 mg, 0.52 mmol) was added to a solution of the amino alcohol (−)-**37** (100 mg, 0.27 mmol) in pyridine (2 mL). The reaction mixture was stirred at room temperature for 15 h and then poured into 5% K_2CO_3. The mixture was extracted with $CHCl_3$. The organic layer was separated, dried, and evaporated. The residue was treated by the same method as described above to afford (−)-thalictrifoline [(−)-**2**]: 10 mg (10%); mp 150.5–151.5 °C; $[\alpha]_D$ −193° (*c* 0.104); mass spectrum, *m/e* (relative intensity) 353 (M^+, 28), 338 (8), 192 (6), 190 (5), 176 (4), 162 (100).

(+)-Thalictrifoline [(+)-2]. Methanesulfonyl chloride (148 mg, 1.29 mmol) was added to a solution of the amino alcohol (+)-**37** (166 mg, 0.45 mmol) in pyridine (3 mL). The reaction mixture was stirred for 4 h at room temperature and then poured into 5% K_2CO_3 (50 mL). The mixture was extracted with Et_2O. The organic extract was dried and evaporated. The residue was dried in vacuo overnight and then dissolved in THF–Et_2O (1:1, 60 mL) at 0 °C. The solution was added dropwise to a solution of $LiAlH_4$ (300 mg) in THF–Et_2O (1:1, 60 mL) at 0 °C. The reaction mixture was heated at reflux for 3.5 h. The reaction mixture was decomposed by addition of water (300 mL), 15% NaOH (300 mL), and water (300 mL). The solid was filtered and washed with $CHCl_3$. The combined filtrates were evaporated, and the residue was purified by preparative TLC (silica gel, 1:9 C_6H_6–Et_2O) to give (+)-thalictrifoline [(+)-**2**], 102 mg (64%). The analytical sample was recrystallized from Me_2CO–Et_2O: mp 149–151 °C (lit.[19] mp 151 °C); $[\alpha]_D$ +199° (*c* 0.136) [lit.[19] $[\alpha]_D$ +218° (MeOH)] mass spectrum, *m/e* (relative intensity) 353 (M^+ 83), 338 (15), 192 (7), 176 (6), 162 (100).

Acknowledgment. This investigation was supported by Grant CA19204, awarded by the National Cancer Institute, DHHS. We are grateful to Mr. John Kozlowski for obtaining the proton spectrum of (±)-**37** on the PUBMRL 470-MHz instrument, which is supported by the National Institutes of Health, Research Grant No. RR01077 from the Department of Research Resources.

Registry No. (±)-**1**, 30342-07-5; (−)-**1**, 79082-01-2; (+)-**1**, 32728-75-9; (±)-**2**, 79082-02-3; (−)-**2**, 79082-03-4; (+)-**2**, 30342-06-4; (+)-**6**, 29550-24-1; (±)-**23**, 29074-38-2; (−)-**23**, 5096-57-1; (+)-**23**, 2086-96-6; (±)-**26**, 68408-57-1; (+)-**26**, 79027-72-8; (+)-**26** (−)-strychnine, 79055-72-4; (−)-**26**, 79082-04-5; (±)-**27**, 76177-41-8; (−)-**27**, 79082-05-6; (+)-**27**, 79027-73-9; (+)-**28**, 79027-74-0; (+)-**29**, 79082-06-7; (+)-**29** mesylate, 78982-17-9; **30**, 3382-18-1; **31**, 75267-21-9; (±)-**32**, 78986-98-8; (−)-**32**, 79055-76-8; (−)-**32** (−)-strychnine, 79082-07-8; (+)-**32**, 79055-77-9; (±)-**33**, 78986-99-9; (±)-**34**, 78987-00-5; (−)-**34**, 79055-78-0; (+)-**34**, 79055-79-1; (±)-**35**, 78987-01-6; (−)-**35**, 79055-80-4; (+)-**35**, 79055-81-5; (±)-**36**, 78987-02-7; (±)-**36** mesylate, 78987-03-8; (−)-**36**, 79082-08-9; (−)-**36** mesylate, 79056-28-3; (+)-**36**, 79082-09-0; (+)-**36** mesylate, 79055-82-6; (±)-**37**, 78987-04-9; (±)-**37** tosylate, 78987-05-0; (−)-**37**, 79082-10-3; (−)-**37** tosylate, 79055-83-7; (+)-**37**, 79082-11-4; (+)-**37** mesylate, 79055-84-8.