solution of diisopropylamine (0.43 mL, mmol) in dry DME (4 mL) at −78 °C under N_2 followed by stirring for 30 min at 0 °C. A solution of the lactone (3.5 mmol) in DME (7 mL) was added dropwise to the solution of LDA at −78 °C. After being stirred for 30 min at −78 °C, the mixture was added dropwise to a stirred solution of the nitro enamine (1 mmol) in DME (3 mL) at −78 °C. The reaction was performed under the condition shown in Table II, and then the resulting mixture was quenched by the method A or B and purified by flash column chromatography (silica gel, AcOEt–hexane) to give the desired nitroolefins. Results are given in Table II. The % ee was determined by chiral shift 400-MHz ^1H NMR analysis ($CDCl_3$, $Eu(hfc)_3$).

The zinc enolates were prepared from lithium enolate by adding an equimolar amount of $ZnCl_2$ (0.69 M solution in ether) at −78 °C and stirring at −20 °C for 30 min. The copper enolates were prepared by adding the powdered CuI to a lithium enolate at −78 °C and stirring at 0 °C for 30 min.

Quenching Method A. The reaction mixture was poured into cold 0.5 N HCl through a bridge slowly.

Quenching Method B. The reaction mixture was poured into a stirred suspension of *p*-TsOH (5–10 equiv of base) in CH_2Cl_2 through a tube. The CH_2Cl_2 layer was washed with water twice, dried ($MgSO_4$), and evaporated.

Examination of Quenching Conditions (Table IV). To a solution of nitro enamine **2a** (22.3 mg, 0.12 mmol) in DME (1 mL) was added lithium enolate **5** (0.6 mmol) in DME (2 mL) with phenanthrene as an internal standard at −78 °C under N_2, and the mixture was stirred at −78 to −20 °C for 2 h. Part of the resulting mixture was transferred through a tube into 0.5 N HCl–CH_2Cl_2 and a suspension of *p*-TsOH (ca. 5 equiv of base) in CH_2Cl_2 or water–CH_2Cl_2, and each was extracted with CH_2Cl_2 using Extrelut 3 column. The residue obtained after evaporation was analyzed by HPLC (column, Jasco fine-pack SIL (25 × 0.46); hexane–isopropanol (2:1); flow rate, 3 mL/min; detector, 25 nm).

Crossover Experiments between 4 and 5 (Table V). To a solution of nitro enamine **2a** in DME was added lithium enolate **4** or **5** prepared in DME with phenanthrene as an internal standard at −78 °C, and the mixture was stirred under the reaction conditions in Table V. Part of the resulting mixture was transferred through a tube into a suspension of *p*-TsOH (ca. 5 equiv of base) in CH_2Cl_2 and extracted by means of Extrelut 3 column. The remaining reaction mixture was cooled to −78 °C again, and the enolate **5** or **4** was added. After the reaction was performed under the conditions in Table V, the products were analyzed by HPLC.

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Supplementary Material Available: General experimental details, spectral data on **2b,c**, **7a–c**, **8a–c**, **9a–c**, **12**, and **13**, procedures and data on **14** and **15**, Table I, Table III, and tables of crystal data, bond lengths, bond angles, atomic coordinates, and thermal parameters for **2b** (13 pages). Ordering information is given on any current masthead page.

Synthesis and Evaluation of Hypothetical Intermediates in the Biosynthetic Conversion of Protoberberine to Benzo[*c*]phenanthridine Alkaloids. Evidence for Oxidative C–N Bond Fission Followed by Intramolecular Recyclization in Cell Cultures of *Corydalis incisa*

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Abstract: In order to clarify the nitrogen–carbon cleavage process in the biosynthetic conversion of protoberberine to benzo[*c*]phenanthridine alkaloids, the novel, deuterated, 6-hydroxylated protoberberines **19** and **26** have been synthesized as hypothetical intermediates and studied in *Corydalis incisa* callus cell cultures. The syntheses relied on the in situ conversion of the unstable amino aldehydes **17** and **23** to the acetals **18** and **24**, which afforded the desired products **19** and **26** under acidic conditions. The structure of **26c** was confirmed by X-ray analysis. In solution, both **19** and **26** were found to exist as an equilibrium mixture of at least two carbinol ammonium species and one amino aldehyde form. Of these two novel diastereomeric carbinol ammonium compounds **19** and **26**, only the 13,14-cis isomer **26** was transformed into the labeled benzo[*c*]phenanthridines corynoline (**11**) and corynoloxine (**12**). However, corycavine (**8**) was incorporated more effectively into **11** and **12** than **26**. Both **19** and **26** were bioconverted via the corresponding amino alcohols **30** and **25** to the dehydro derivative **29**. Mass spectral analysis of the biosynthetic products indicated that unexpectedly, some H–D exchange at C-8 had occurred.

The benzophenanthridine alkaloids (±)- and (+)-corynoline (**11**), as well as (±)- and (+)-corynoloxine (**12**), have been isolated from *Corydalis incisa* Pers. (Scheme I).[1,9] A number of studies involving the incorporation of labeled precursors[2-11] have confirmed the earlier suggestion that the benzophenanthridines arise biosynthetically from the protoberberines (e.g., **1–3**)[12,13] via the protopines (e.g., **7** and **8**).[14] The commonly postulated intermediate is compound **9**. Nucleophilic addition of the enamine to the aldehyde in **9** would give an iminium ion, which could then

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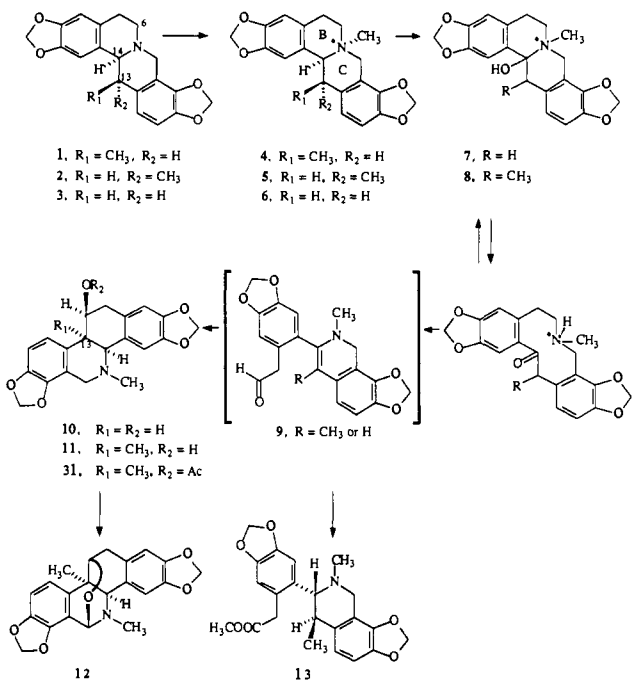
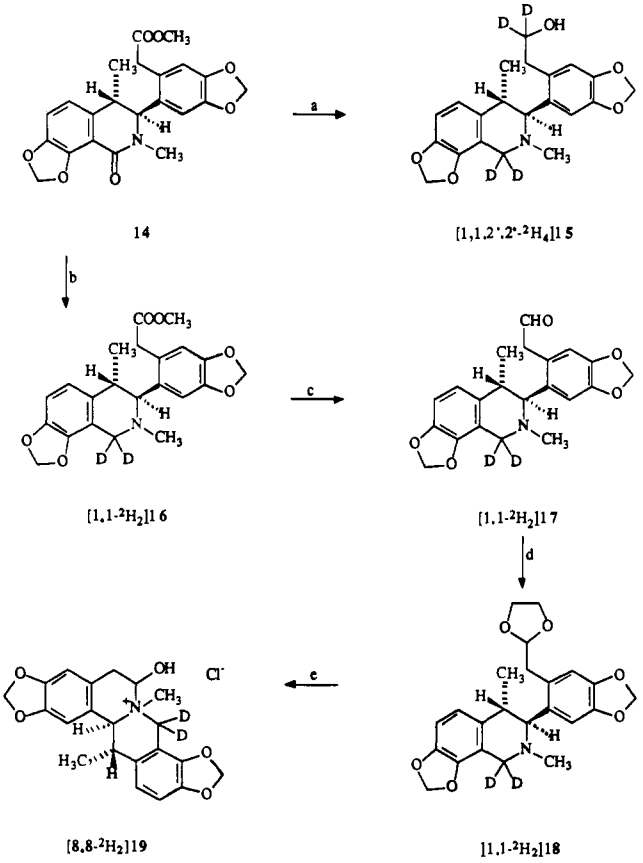
Scheme I



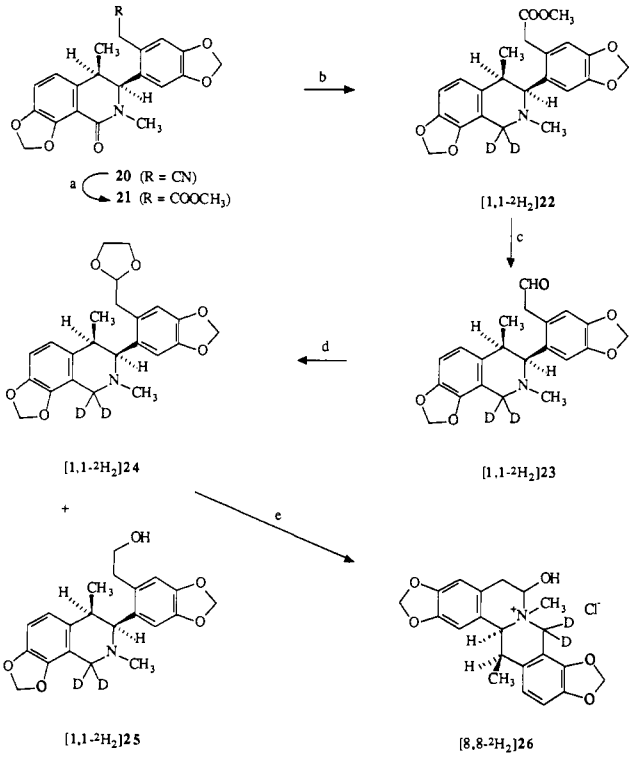
Scheme II[a]



[a] Key: (a) $LiAlD_4$, THF, reflux (29 h). (b) (1) $POCl_3$, 60 °C (3 h); (2) $NaBD_4$, EtOH, dry glyme, room temperature (18 h). (c) DIBAH, CH_2Cl_2, −78 °C (5 h). (d) TsOH, $HOCH_2CH_2OH$, benzene, reflux (13 h). (e) HCl, THF, 0 °C to room temperature (0.5 h).

be reduced to afford the benzophenanthridines (e.g., **10** and **11**). Although the formation of the hypothetical intermediate **9** from

Scheme III[a]



[a] Key: (a) (1) HCl, CH_3OH, −20 to −40 °C (2.25 h), 0 °C (17 h); (2) H_2O. (b) (1) $POCl_3$, 57 °C (3 h); (2) $NaBD_4$, EtOH, dry glyme, room temperature (17 h). (c) DIBAH, CH_2Cl_2, −78 °C (1.5 h). (d) TsOH, $HOCH_2CH_2OH$, reflux (12 h). (e) HCl, THF, 0 °C to room temperature (0.5 h).

the protoberberines obviously involves N-methylation, oxidative cleavage of the C(6)–N bond, and a removal of a total of three hydrogen atoms from C-6, C-13, and C-14, the exact sequence of these events, as well as the intermediates and mechanisms involved, have not been clearly delineated.

In any case, it is established that all three hydrogen atoms are lost from the same α-face of the molecule during the conversion of (−)stylopine (**3**) to chelidonine (**10**) in *Chelidonium majus* plants.[7,8,15] Work in *C. incisa* plants has demonstrated the transformation of both tetrahydrocorysamine (**1**) and meso-tetrahydrocorysamine (**2**) to corynoline (**11**),[9,11] so that the biosynthesis proceeds without regard for the relative configurations at C-13 and C-14. In contrast, only the cis-B/C fused *N*-methyl salts **4**–**6**, and not the corresponding trans-fused salts, are converted into benzophenanthridine alkaloids.[9,16] The intermediacy of the protopine alkaloids **7** and **8** in the biosynthesis of benzophenanthridines has also been demonstrated.[9,16] These studies have served to define the biosynthetic pathway illustrated in Scheme I for the conversion of protoberberines to benzophenanthridines.

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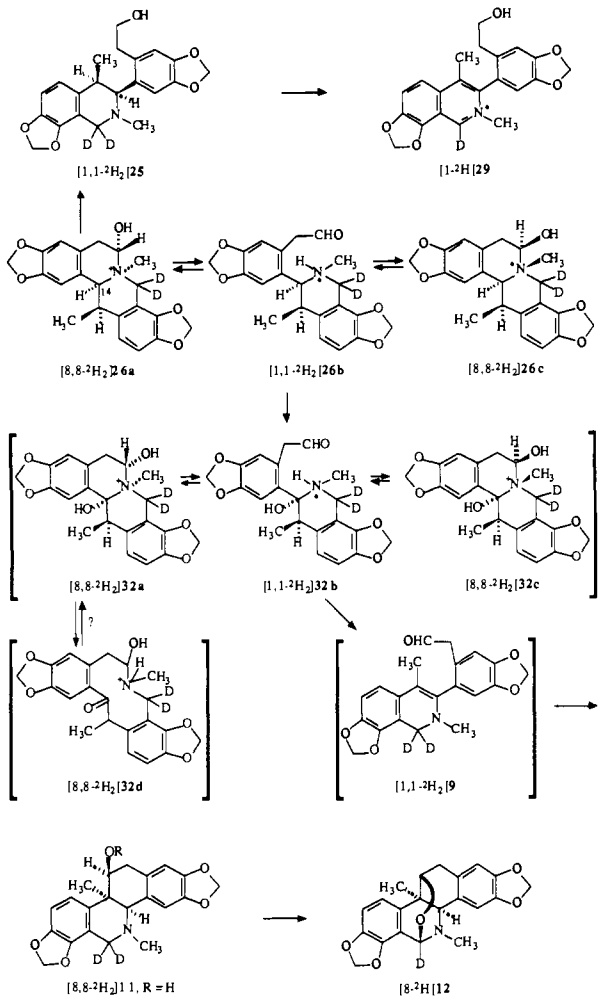
Scheme IV



The present report describes our efforts to delineate the chemistry surrounding the production and utilization of the hypothetical intermediate enamino aldehyde **9** shown in Scheme I. This study has involved the synthesis of some of the hypothetical intermediates between the N-methylated salts **4–6** and intermediate **9**. Preliminary accounts describing the preparation and incorporation studies of several of these intermediates have appeared.[17]

Synthesis. The compounds selected for synthesis as hypothetical biosynthetic intermediates were the C-6 hydroxylated derivatives [8,8-$^2H_2$]**19** and [8,8-$^2H_2$]**26** (Schemes II and III) of the quaternary *N*-methyl salts **5** and **4**. A study of the metabolism of these compounds might be useful in answering the question of whether C-6 or C-14 is oxidized first during the conversion of the N-methylated quaternary protoberberine salts **4–6** to intermediate **9**. The strategy employed for their preparation involved an extension of our previous synthesis of corydalic acid methyl ester (**13**)[18] in order to obtain the required compounds.

Reduction of the trans-substituted lactam ester **14**[18] with lithium aluminum deuteride in tetrahydrofuran gave the tetradeuterated alcohol [1,1,2′,2′-$^2H_4$]**15**, while treatment of **14** with phosphorus oxychloride followed by sodium borodeuteride in dry glyme gave the desired dideuterated intermediate [1,1-$^2H_2$]**16**. Not surprisingly, the phenylacetaldehyde [1,1-$^2H_2$]**17** obtained by reduction of the ester [1,1-$^2H_2$]**16** with diisobutylaluminum hydride in dichloromethane proved to be rather unstable and, accordingly, the crude product was converted without purification into the acetal [1,1-$^2H_2$]**18** by heating with ethylene glycol and *p*-toluenesulfonic acid. Treatment of the acetal [1,1-$^2H_2$]**18** with hydrochloric acid in tetrahydrofuran then gave the desired carbinol ammonium compound [8,8-$^2H_2$]**19** in which the protons at C-13 and C-14 are trans.

An analogous synthesis of the carbinol ammonium salt [8,8-$^2H_2$]**26** having cis protons at C-13 and C-14 is presented in Scheme III. The chemistry proceeded as before with the exception of the isolation of the reduced alcohol [1,1-$^2H_2$]**25** in low yield (3.9%) as a side product accompanying the ketal [1,1-$^2H_2$]**24**.

Determination of the Structures of the Carbinol Ammonium Compounds [8,8-$^2H_2$]19 and [8,8-$^2H_2$]26. The carbinol ammonium chlorides [8,8-$^2H_2$]**19** and [8,8-$^2H_2$]**26** possess novel structures. Although several carbinol ammonium compounds have appeared in the literature,[19–23] they are derived from the transannular additions of tertiary amines to ketones in 9- and 10-membered rings, as in the protopine salts **7** and **8**. The cyclization of an amino aldehyde under acidic conditions to form the type of stable carbinol ammonium chloride represented by structures [8,8-$^2H_2$]**19** and [8,8-$^2H_2$]**26** is distinct from the transannular additions referenced

Table I. Proportion (%) of the Major Forms of **26** and **19** in Different Solvents

	CD_3OD	DMSO-d_6	TFA-*d*
[8,8-$^2H_2$]**26**	73	80	>90
[8.8-$^2H_2$]**19**	75	>90	>90

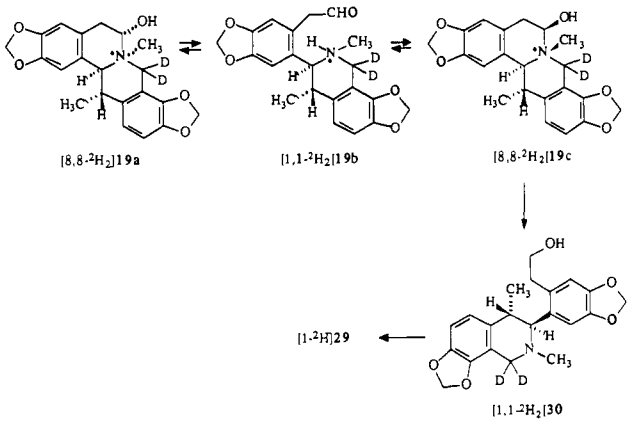
Table II. The Chemical Shifts of the *C*-Methyl Group in the ^1H NMR Spectra of **26**, **19**, **27**, and **28**

	CD_3OD	TFA-*d*
[8,8-$^2H_2$]**26c** major	1.41	1.48
[8,8-$^2H_2$]**26a** minor	1.00	
[8,8-$^2H_2$]**19a** major	1.49	1.65
[8,8-$^2H_2$]**19c** minor	1.21	
27 trans-B/C fused salt	1.38	1.51
27 cis-B/C fused salt	1.02	1.14
28 cis-B/C fused salt	1.45	1.60

Table III. Coupling Constants (Hz) in the ^1H NMR Spectra of the Major Isomers of **26** and **19**

	$J_{5\alpha,6}$	$J_{5\beta,6}$	$J_{13,14}$
[8,8-$^2H_2$]**26c**	5.8	9.5	5.4
[8,8-$^2H_2$]**19a**	9.0	5.8	10

Scheme V



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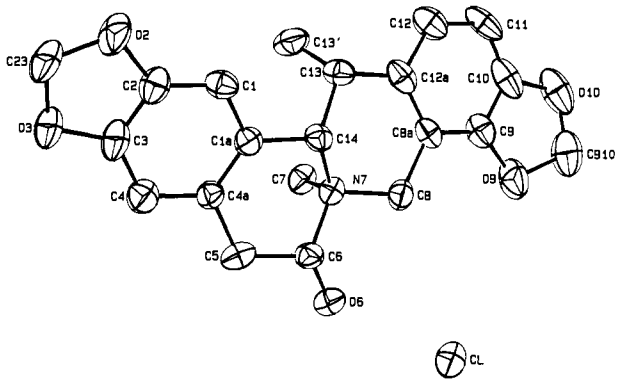
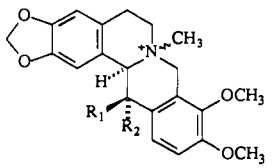


Figure 1.

above. An effort was therefore made to determine the structural details of these substances.

The ^1H NMR spectra of the carbinol ammonium compounds [8,8-$^2H_2$]**26** and [8,8-$^2H_2$]**19** in CD_3OD each showed two sets of signals, indicating that principally two species were present in each sample. The percent compositions were found to be solvent dependent (Table I). An increase in temperature resulted in signal broadening, indicating that [8,8-$^2H_2$]**26** and [8,8-$^2H_2$]**19** exist as an equilibrium mixture of the trans-B/C and cis-B/C fused salts (Schemes IV and V), which interconvert through the amino aldehyde forms [8,8-$^2H_2$]**26b** and [8,8-$^2H_2$]**19b**. Analogous behavior has been observed in the salts of protopine-type alkaloids (e.g., **7** and **8**, Scheme I).[23,24] The major isomers of [8,8-$^2H_2$]**26** and [8,8-$^2H_2$]**19** were found to be the trans-fused salt [8,8-$^2H_2$]**26c** and the cis-fused salt [8,8-$^2H_2$]**19a** by comparison of the chemical shifts of the *C*-methyl groups in the ^1H NMR spectra with those of the corresponding trans-B/C and cis-B/C fused protoberberine *N*-methyl salts **27** and **28** (Table II).[24] The configuration of the



27, $R_1 = CH_3$, $R_2 = H$
28, $R_1 = H$, $R_2 = CH_3$

hydroxyl group at C-6 in the major isomers [8,8-$^2H_2$]**26c** and [8,8-$^2H_2$]**19a** is assigned equatorial on the basis of the coupling constants of the H-5 and H-6 protons (Table III). The hydroxyl groups in the minor forms of the salts are assumed also to be equatorial by analogy to the results observed with the major forms.

Additional evidence for structure [8,8-$^2H_2$]**26c** was obtained from an X-ray analysis on a sample obtained by crystallization from methanol, and an ORTEP drawing is shown in Figure 1. This corresponds to the major form of [8,8-$^2H_2$]**26** in solution as indicated from the ^1H NMR studies.

Biosynthesis. Cultured *C. incisa* cells were grown on agar medium containing racemic [8,8-$^2H_2$]**26** and [8,8-$^2H_2$]**19** at 25 °C for 5 weeks (Table IV, experiments 1 and 2). After incubation, the medium and cells were extracted for alkaloids. Four bases were isolated by preparative thin-layer chromatography of the extracts from the fraction to which [8,8-$^2H_2$]**26** was fed. The structures of three of them were confirmed to be the deuterated corynoline [[8,8-$^2H_2$]**11**], corynoloxine [[8-^2H]**12**], and the cis amino alcohol [1,1-$^2H_2$]**25** by comparison of the mass and ^1H NMR spectra with those of the authentic samples. The structure [1-^2H]**29** was assigned to the last one on the basis of the ^1H NMR spectrum. Two compounds obtained from the fraction to which [8,8-$^2H_2$]**19** was administered were found to be the trans amino alcohol [1,1-$^2H_2$]**30** (Scheme V) and its dehydro derivative [1-^2H]**29**. The deuterium distribution of the products was determined by ^1H NMR and mass spectrometry (Table V).

Table IV. Feeding Experiments in Cell Static Cultures of *Corydalis Incisa*

expt no.	substrate	substr, mg	medium, L	incub time, days	dry cell wt, g	product wt, mg (yield or recovery, %), $[\alpha]_D$					
						11	**12**	**8**	**25**	**29**	**15**	**31**
1	[8,8-$^2H_2$]**26**	86	1.2	35	4.75	2 (2.6) [+91°]	4 (5.2) [+34°]		10 (12.8) [−40°][a]	2 (2.4)		
2	[8,8-$^2H_2$]**19**	90	2.0	37	8.86					trace	20 (24.0)	
3	[8,8-$^2H_2$]**26**	87	1.2	36	7.58	0.5 (0.7)	1.3 (1.7) [+90°]		2 (2.6) [−29°]	trace		
4	**8**	87	1.2	36	7.02	2.8[b] (3.5) [+28°]	8.1[b] (10.3) [+119°]	5.3[b] (6.0) [−14°]				4.0[b] (4.5) [+41°]
5	[1,1-$^2H_2$]**25**·HCl	60	1.0	21	3.52			11 (18.0) [−21°]	1 (1.7)			
6	[1,1,2′,2′-$^2H_4$]**15**·HCl	65	1.0	35	5.33					1 (1.5)	19 (32.0)	

[a] Measured as the hydrochloride. [b] Nondeuterated compound.

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Table V. Deuterium Distribution Determined by ^1H NMR and Mass Spectra

expt no.	substrate	product	D distribution, % from ^1H NMR (D at C-8 or C-1)	from mass[a] D_0	D_1	D_2	D_3	D_4
1	[8,8-$^2H_2$]**26**		84(D_α) 84(D_β)					
		11	24(D_α) 56(D_β)	44	32	24		
		12	28(D_α)	79	21			
		25	51(D_α) 77[b](D_β)	17	48	35		
		29	48(D_α)					
2	[8,8-$^2H_2$]**19**		91(D_α) 91(D_β)					
		29	45					
		30	90(D_α + D_β)	18	42	40		
5	[1,1-$^2H_2$]**25**		83(D_α) 77[b](D_β)	5	30	65		
		25	72(D_α) 81[b](D_β)	6	34	60		
		29	43					
6	[1,1,2′,2′-$^2H_4$]**15**		100[c](D_α) 100[c](D_β)				6	94
		29	35[c]					
		15	78[c](D_α) 88[c](D_β)				24	76

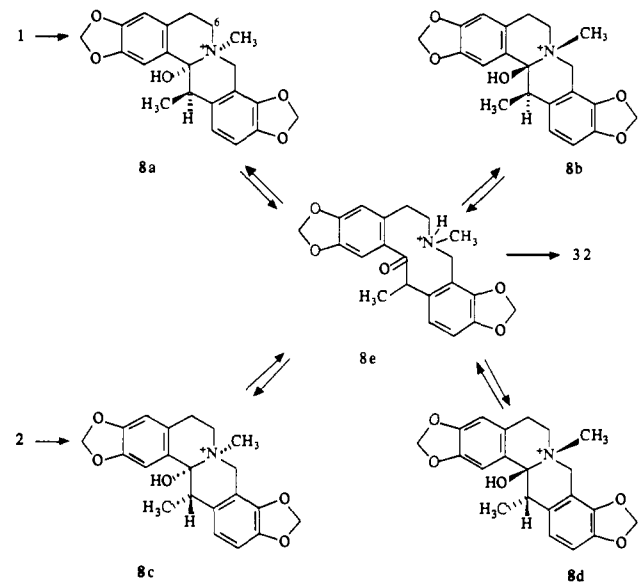
[a] The figures given are the percentages of the molecules containing 4, 3, 2, 1, and 0 atoms of deuterium, respectively. [b] There is an error since some overlap of the signal of a hydrogen at C-8 occurs with the resonance of a hydrogen at C-6. [c] D distribution at C-1.

It is therefore evident that the 6-hydroxy-13-methylprotoberberine [8,8-$^2H_2$]**26**, having the cis configuration of protons at C-13 and C-14, was converted into [8,8-$^2H_2$]**11** and [8-^2H]**12**, but [8,8-$^2H_2$]**19**, possessing the trans configuration, was not (Schemes IV and V). This is in marked contrast to the situation with the 13-methylprotoberberines **1** and **2**, both of which are converted to corycavine **8**.[9] This difference may be explained as follows (Schemes IV–VI). The intermediate protopine derived from either **1** or **2** exists as an equilibrium mixture of four forms **8a–8d**, which interconvert through **8e**.[23,24] Either hydroxylation of **8** at C-6 or hydroxylation of [8,8-$^2H_2$]**26** at C-14 would lead to an intermediate shown here as forms [8,8-$^2H_2$]**32a** and [8,8-$^2H_2$]**32c**, which interconvert through [8,8-$^2H_2$]**32b**. It is presently not clear whether or not the 6,14-dihydroxy-13-methylprotoberberines **32a** and **32c** are interconverted through the 10-membered ring compound **32d**. On the other hand, the hypothetical intermediate [8,8-$^2H_2$]**19** is evidently not converted to the intermediate **32**. Formation of [8,8-$^2H_2$]**11** from [8,8-$^2H_2$]**26** provides evidence supporting the intermediacy of a 6-hydroxyprotoberberine during the conversion of the 13-methylprotoberberines into **11**.

The hypothetical enamino aldehyde **9** might be generated either by stereospecific hydroxylation at C-14 followed by the elimination of water or by a direct dehydrogenation at C-13 and C-14. If the dehydrogenation mechanism were operating, then one would expect that [8,8-$^2H_2$]**26** would be a more effective precursor than **8**. In order to clarify this point, experiments with [8,8-$^2H_2$]**26** and **8** were carried out under the same conditions (Table IV, experiments 3 and 4). Corycavine (**8**) was incorporated 4 times and 6 times better into corynoline (**11**) and corynoloxine (**12**), respectively, than was [8,8-$^2H_2$]**26**. Acetylcorynoline (**31**, Scheme I), which is formed from **11**, was isolated from the fraction to which **8** was fed. Since **8** is a more effective precursor than [8,8-$^2H_2$]**26**, the 13-methylprotoberberines likely undergo hydroxylation at C-14 prior to hydroxylation at C-6 in the major biosynthetic pathway to corynoline (**11**), and it is unlikely that the enamino aldehyde intermediate **9** is generated by a direct cis-dehydrogenation of **26**. It is also true that even though the hypothetical intermediate **26** undergoes bioconversion to corynoline (**11**), it may not be a true metabolite of *C. incisa*, since it has not been detected in the plant.

Two further statements can be made from experiments with [8,8-$^2H_2$]**26**. In the first place, the retention of deuterium in [8-^2H]**12** corresponds to that of the axial C-8α deuterium in

Scheme VI



[8,8-$^2H_2$]**11** (Table V). This is in keeping with a stereospecific removal of hydrogen from C-8 of **11** in the bioconversion into **12**. Secondly, biotransformation of [8,8-$^2H_2$]**26** into [8,8-$^2H_2$]**11** or [1,1-$^2H_2$]**25** involves the inequivalent loss of deuterium from C-8 of [8,8-$^2H_2$]**26** (Table V). This deuterium loss indicates that C-8 is affected during the conversion of [8,8-$^2H_2$]**26** into [8,8-$^2H_2$]**11** or [1,1-$^2H_2$]**25**. This is in disagreement with the result in *Ch. majus* plants that C-8 is unaffected during the transformation of stylopine (**3**) into chelidonine (**10**).[15]

Finally, feeding experiments with the cis and trans amino alcohols [1,1-$^2H_2$]**25** and [1,1,2′,2′-$^2H_4$]**15** were carried out in order to clarify whether or not they are effective as precursors of **11**. The racemic cis and trans amino alcohols **25** and **15** are incorporated into the dehydro derivative **29** in callus cell cultures of *C. incisa* (Tables IV and V, experiments 5 and 6), and they are not effective as precursors of **11**.

In conclusion, it is likely that the hexahydrobenzo[*c*]-phenanthridine alkaloids are biosynthesized from protoberberine alkaloids via oxidation at C-14 and then at C-6, followed by C(6)–N bond fission and elimination of water leading to an en-

amino aldehyde, followed by nucleophilic addition of the enamine to the aldehyde and reduction of the iminium ion (Scheme IV).

Experimental Section

All reactions were performed under a nitrogen atmosphere. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. NMR spectra were recorded on Varian FT-80 80-MHz, XL-200 200-MHz, and VXR-500S 500-MHz spectrometers in $CDCl_3$ solvent, except where noted. 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. IR spectra were recorded on a Beckman IR-33 spectrophotometer. Microanalyses were performed by the Purdue Microanalytical Laboratory. The mass spectra were determined on a Finnigan 4000 spectrometer using an ionization potential of 70 eV, or with a Hitachi M80 instrument operating at 75 eV. The chemical ionization mass spectra (CIMS) were obtained by using isobutane as the ionizing gas. Fast atom bombardment mass spectra (FABMS) were run on a Kraytos MS50 spectrometer at room temperature using a glycerol matrix. Optical rotations were determined with a Na-D, DIP-SL (Jasco) polarimeter. TLC and preparative TLC were performed on silica gel 60F-254 glass plates.

[1,1,2′,2′-$^2H_4$]-(±)-*trans*-*N*-Methyl-1,2,3,4-tetrahydro-4-methyl-7,8-(methylenedioxy)-3-[2-(2′-hydroxyethyl)-4,5-(methylenedioxy)phenyl]-isoquinoline (15). Lactam ester **14** (258 mg, 0.627 mmol) was added to a suspension of $LiAlD_4$ (280 mg, 6.67 mmol) in THF (30 mL). The reaction mixture was heated at reflux for 29 h. The mixture was cooled to 0 °C and quenched with water (0.28 mL), 15% aqueous NaOH (0.28 mL), and water (0.84 mL). The aluminates were filtered and washed with chloroform. The combined organic layer was dried ($MgSO_4$) and evaporated to give a brown oil, which was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel (10 g, 60–200 mesh) eluting with EtOAc–hexane (1:1), yielding the free base as a solid: 187 mg (92%), mp 73–75 °C dec; IR ($CHCl_3$) 3360, 3000, 2940, 2870, 1475, 1450, 1250-1175, 1015, 910 cm^{-1}; NMR (80 MHz) δ 1.14 (d, 3 H, J = 6.5 Hz, C Me), 2.12 (s, 3 H, N Me), 2.85 (s, 1 H, H-1′), 2.89 (s, 1 H, H-1′), 3.20 (m, 1 H, H-4), 3.59 (d, 1 H, J = 10.2 Hz, H-3), 4.40 (br s, 1 H, OH), 5.94 (s, 4 H, 2 OCH_2O), 6.75 (s, 2 H, Ar H), 6.77 (s, 1 H, Ar H), 6.85 (s, 1 H, Ar H); EIMS m/e (relative intensity) 373 (M^+, 10), 372 (1), 164 (100), 163 (16), 162 (2); CIMS m/e (relative intensity) 374 (MH^+, 73), 373 (57), 164 (100); high-resolution MS calcd for $C_{21}H_{19}D_4NO_5$ 373.1927, found 373.1930.

Alcohol **15** (165 mg, 0.44 mmol) was dissolved in dry THF (2 mL) in an oven-dried vial and cooled to −10 to −20 °C. Dry HCl gas was passed into the solution for 10 min. The precipitate was filtered and washed with THF to give the hydrochloride salt: 151 mg (83%). The analytical sample was recrystallized from EtOH: mp 249–251 °C; CIMS, m/e (relative intensity) 374 ($M^+ - Cl^-$, 100). Anal. Calcd for $C_{21}H_{20}D_4NO_5Cl \cdot {}^1/_2H_2O$: C, 60.21; H + D, 6.98; N, 3.34. Found: C, 60.25; H + D, 6.98; N, 3.34.

[1,1-$^2H_2$]-(±)-*trans*-*N*-Methyl-1,2,3,4-tetrahydro-4-methyl-7,8-(methylenedioxy)-3-[2-[(methoxycarbonyl)methyl]-4,5-(methylenedioxy)-phenyl]isoquinoline (16). The lactam ester **14** (450 mg, 1.02 mmol) in $POCl_3$ (3.4 mL) was heated at 60 °C for 3 h. The solution was evaporated and the residue was dried under high vacuum for 30 min. The residue was dissolved in dry glyme (4.5 mL) and the mixture was cooled to 0 °C. A solution of $NaBD_4$ (275 mg, 4.24 mmol) in absolute ethanol (9.45 mL) was then added dropwise at 0 °C. The reaction mixture was stirred at room temperature for 18 h. The mixture was cooled to 0 °C and decomposed with 2% HCl (6 mL). The organic solvent was evaporated and water (11 mL) was added. The aqueous solution was neutralized with 20% aqueous K_2CO_3 (18 mL) at 0 °C. The mixture was extracted with EtOAc (3 × 12 mL). The combined organic extract was dried and evaporated to yield the crude product, which was purified by column chromatography on silica gel (23 g, 60–200 mesh), eluting with hexane–EtOAc (2:1) to give the product. Further elution with hexane–EtOAc (2:3) yielded the unreacted starting material: 77 mg (17%). The desired product could be further purified by recrystallization from $CHCl_3$–hexane: 260 mg (60%); mp 133–135 °C; IR ($CHCl_3$) 3100–3000, 2950, 2880, 2780, 1725, 1455, 1475 cm^{-1}; NMR (80 MHz) δ 1.03 (d, 3 H, J = 6.4 Hz, C Me), 2.06 (s, 3 H, N Me), 3.13–3.03 (m, 2 H, H-3 and H-4), 3.64 (s, 3 H, O Me), 3.70 (s, 2 H, H-1′), 5.94 (s, 4 H, 2 OCH_2O), 6.70 (s, 3 H, Ar H), 6.88 (s, 1 H, Ar H); CIMS m/e (relative intensity) 400 (MH^+, 100), 399 (M^+, 89); high-resolution MS calcd for $C_{22}H_{21}D_2NO_6$ 399.1651, found 399.1651.

[1,1-$^2H_2$]-(±)-*trans*-*N*-Methyl-1,2,3,4-tetrahydro-4-methyl-7,8-(methylenedioxy)-3-[2-[2′-(1,3-dioxolan-1-yl)ethyl]-4,5-(methylenedioxy)-phenyl]isoquinoline (18). A solution of DIBAH in THF (1 M, 33 mL) was added dropwise to a solution of the amino ester **16** (2.61 g, 6.54 mmol) in dichloromethane (76 mL) over a period of 5 h at −78 °C. Saturated aqueous NaCl (76 mL) was then added to the solution. The organic layer was separated and the aqueous layer was extracted with chloroform (2 × 50 mL). The combined organic layer was dried ($MgSO_4$) and evaporated to give the crude product **17** (1.56 g). Without further purification, the aldehyde **17** (1.56 g) was heated with *p*-toluenesulfonic acid (1.89 g) and ethylene glycol (48 drops) in benzene (89 mL) at reflux for 13 h in the presence of a Dean–Stark trap. Benzene (89 mL) was then added into the reaction mixture. The mixture was washed with 10% aqueous NaOH (5 × 30 mL) and water (5 × 30 mL) and dried ($MgSO_4$). The solvent was evaporated to give the crude product (1.55 g), which was purified by column chromatography (60 g, 60–200 mesh), eluting with EtOAc–hexane (1:3): 1.25 g (46%); mp 50–53 °C; IR ($CHCl_3$) 3060–3000, 2950, 2870, 1470, 1450, 1300–1150, 1115 cm^{-1}; NMR (500 MHz) δ 1.06 (d, 3 H, J = 6.9 Hz, C Me), 2.12 (s, 3 H, N Me), 3.02 (m, 3 H, H-4 and H-1′), 3.37 (br s, 1 H, H-3), 3.83 (m, 2 H, OCH_2CH_2O), 3.96 (m, 2 H, OCH_2CH_2O), 5.03 (t, 1 H, J = 5.0 Hz, H-2′), 5.92 (m, 3 H, OCH_2O), 5.94 (d, 1 H, J = 1.4 Hz, OCH_2O), 6.69 (d, 1 H, J = 8.2 Hz, Ar H), 6.72 (d, 1 H, J = 8.2 Hz, Ar H), 6.80 (s, 1 H, Ar H), 6.89 (s, 1 H, Ar H); CIMS m/e (relative intensity) 414 (MH^+, 100); high-resolution MS calcd for $C_{23}H_{23}D_2NO_6$ 413.1807, found 413.1802.

[8,8-$^2H_2$]-(±)-*trans*-*N*-Methyl-6-hydroxy-13-methyl-2,3-(methylenedioxy)-9,10-(methylenedioxy)tetrahydroprotoberberinium Chloride (19). Concentrated HCl (14 mL) was added dropwise to a solution of ketal **18** (1.25 g, 3.03 mmol) in THF (14 mL) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h. The solution was concentrated until white solid precipitated out. Acetonitrile (20 mL) was added to the mixture and the mixture was stored at 0 °C overnight. The white solid was then filtered and dried: 1.01 g (82%); mp 238–240 °C dec; IR (KBr) 3420, 3060, 1495, 1470, 1270, 1240, 1035, 925 cm^{-1}; NMR (CF_3COOH, 470 MHz) δ 1.65 (d, 3 H, J = 6.7 Hz, C Me), 3.19 (s, 3 H, N Me), 3.20 (m, 1 H, H-13), 3.26 (dd, 1 H, J = 18.7, 9 Hz, H-5), 3.71 (dd, 1 H, J = 18.7, 6.8 Hz, H-5), 4.41 (d, 1 H, J = 10 Hz, H-14), 5.08 (t, 0.18 H, H-8α and H-8β), 5.65 (dd, 1 H, J = 9.0, 6.8 Hz, H-6), 6.12 (d, 1 H, J = 1 Hz, OCH_2O), 6.13 (d, 1 H, J = 1 Hz, OCH_2O), 6.14 (d, 1 H, J = 1 Hz, OCH_2O), 6.16 (d, 1 H, J = 1 Hz, OCH_2O), 6.88 (s, 1 H, Ar H), 6.90 (s, 1 H, Ar H), 6.98 (d, 1 H, J = 8.2 Hz, Ar H), 7.04 (d, 1 H, J = 8.2 Hz, Ar H); FABMS, m/e (relative intensity) 370 ($M^+ - Cl^-$, 100); high-resolution MS calcd for $C_{21}H_{20}D_2NO_5$ 370.1623, found 370.1633.

(±)-*cis*-*N*-Methyl-4-methyl-7,8-(methylenedioxy)-3-[2-[(methoxycarbonyl)methyl]-4,5-(methylenedioxy)phenyl]-3,4-dihydro-1(2*H*)-isoquinolone (21). Hydrogen chloride gas was passed through a $CaCl_2$ tube into a suspension of (±)-*cis*-*N*-methyl-4-methyl-7,8-(methylenedioxy)-3-[2-(cyanomethyl)-4,5-(methylenedioxy)phenyl]-3,4-dihydro-1(2*H*)-isoquinolone (**20**)[18] (1.133 g, 3.00 mmol) in absolute methanol (110 mL) stirred and maintained at −20 to −40 °C. After 2.25 h, the clear solution was stored at 0 °C for 17 h. The solution was then concentrated to half its original volume and poured into cold water (200 mL). The mixture, after saturation with NaCl, was extracted with EtOAc (3 × 50 mL). The extract was washed with water (50 mL), 5% aqueous $NaHCO_3$ (50 mL), and water (50 mL), dried ($MgSO_4$), filtered, and concentrated to give pale yellow crystals: 0.312 g (97%). An analytical sample was acquired by recrystallization from benzene: mp 191–194 °C; IR 2970, 2940, 2880, 1735, 1730, 1640, 1600, 1480, 1455, 1180, 1120 cm^{-1}; ^1H NMR (500 MHz) δ 1.08 (d, 3 H, J = 7.0 Hz, C Me), 2.95 (s, 3 H, N Me), 3.55 (d, 1 H, J = 15.3 Hz, H-1′), 3.64 (m, 1 H, H-4), 3.69 (s, 3 H, OMe), 3.78 (d, 1 H, J = 15.3 Hz, H-1′), 4.79 (d, 1 H, J = 6.4 Hz, H-3), 5.83 (d, 1 H, J = 1.5 Hz, OCH_2O), 5.85 (d, 1 H, J = 1.5 Hz, OCH_2O), 6.13 (d, 1 H, J = 1.3 Hz, OCH_2O), 6.16 (d, 1 H, J = 1.3 Hz, OCH_2O), 6.21 (s, 1 H, Ar H), 6.51 (dd, 1 H, J = 8.0, 1.3 Hz, Ar H), 6.68 (s, 1 H, Ar H), 6.83 (d, 1 H, J = 8 Hz, Ar H); CIMS, m/e (relative intensity) 412 (MH^+, 100). Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.14; N, 3.40. Found: C, 64.18; H, 5.19; N, 3.24.

[1,1-$^2H_2$]-(±)-*cis*-*N*-Methyl-1,2,3,4-tetrahydro-4-methyl-7,8-(methylenedioxy)-3-[2-[(methoxycarbonyl)methyl]-4,5-(methylenedioxy)-phenyl]isoquinolone (22). A suspension of lactam ester **21** (91 mg, 0.22 mmol) in $POCl_3$ (1.5 mL) was heated at 57 °C for 3 h. The $POCl_3$ was evaporated and the residue was dried under vacuum for 40 min. The residue was then dissolved in dry glyme (0.9 mL) and cooled to 0 °C. A solution of $NaBD_4$ (59 mg, 1.194 mmol) in absolute ethanol (1.9 mL) was added, and the reaction mixture was stirred at room temperature for 17 h. The mixture was quenched with 2% HCl (1.2 mL). The organic solvent was evaporated. Water (4.7 mL) was added to the suspension and the mixture was cooled to 0 °C. The suspension was then basified with 20% aqueous K_2CO_3. The mixture was extracted with EtOAc (3 × 30 mL) after the aqueous layer was saturated with NaCl. The combined organic layer was dried ($MgSO_4$) and evaporated to give a yellow oil (107 mg), which was dissolved in $CHCl_3$ and subjected to column chromatography on silica gel (5 g, 60–200 mesh), eluting with EtOAc–hexane (1:3): 73 mg (82.6%); mp 140.5–143.5 °C; IR (KBr) 3050–3020, 2940, 2880, 2760, 1730, 1475, 1450, 1250, 1180, 1140 cm^{-1}; NMR (80

MHz) δ 1.07 (d, 3 H, J = 7 Hz, C Me), 2.24 (s, 3 H, N Me), 2.81 (m, 1 H, H-4), 3.59 (s, 2 H, H-1′), 3.64 (s, 3 H, OMe), 3.78 (d, 1 H, J = 4.3 Hz, H-3), 5.91 (s, 2 H, OCH_2O), 5.93 (s, 2 H, OCH_2O), 6.57 (d, 1 H, J = 8.1 Hz, Ar H), 6.65 (s, 1 H, Ar H), 6.74 (d, 1 H, J = 8.1 Hz, Ar H), 6.80 (s, 1 H, Ar H); CIMS, m/e (relative intensity) 400 (MH^+, 100); high-resolution MS calcd for $C_{22}H_{21}D_2NO_6$ 399.1650, found 399.1643.

[1,1-$^2H_2$]-(±)-*cis*-*N*-Methyl-1,2,3,4-tetrahydro-4-methyl-7,8-(methylenedioxy)-3-[2-[2′-(1,3-dioxolan-1-yl)ethyl]-4,5-(methylenedioxy)-phenyl]isoquinoline (24). A solution of DIBAH in THF (1 M, 52 mL) was added dropwise to a solution of amino ester **22** (4.18 g, 10.48 mmol) in dichloromethane (121 mL) over a period of 1.5 h at −78 °C. Saturated aqueous NaCl (121 mL) was added. The organic layer was separated, and the aqueous layer was extracted with chloroform (3 × 100 mL). The combined organic layer was dried ($MgSO_4$) and evaporated to give the aldehyde **23** (3.02 g). Without further purification, the aldehyde **23** (3.02 g) was treated with *p*-toluenesulfonic acid (3.02 g) and ethylene glycol (77 drops) at reflux for 12 h in the presence of a Dean–Stark trap. Benzene (143 mL) was added and the mixture was washed with 10% aqueous NaOH (5 × 40 mL) and water (5 × 40 mL) and dried ($MgSO_4$). The solvent was evaporated to afford the crude product (2.76 g), which was dissolved in chloroform and subjected to column chromatography on silica gel (200 g, 60–200 mesh), eluting with EtOAc–hexane (1:2): 1.91 g (44%); mp 136–140 °C; IR (chloroform) 3060–3000, 2950, 2880, 1475, 1455, 1120, 1020 cm^{-1}; NMR (80 MHz) δ 1.06 (d, 3 H, J = 7.1 Hz, C Me), 2.26 (s, 3 H, N Me), 2.94 (m, 3 H, H-4 and H-1′), 3.87 (m, 5 H, OCH_2CH_2O and H-3), 5.00 (t, 1 H, J = 4.8 Hz, H-2′), 5.90 (s, 2 H, OCH_2O), 5.94 (s, 2 H, OCH_2O), 6.56 (d, 1 H, J = 8.4 Hz, Ar H), 6.70 (d, 1 H, J = 8.4 Hz, Ar H), 6.76 (s, 1 H, Ar H), 6.83 (s, 1 H, Ar H); CIMS m/e (relative intensity) 414 (MH^+, 100); high-resolution MS calcd for $C_{23}H_{23}D_2O_6$ 413.1807, found 413.1805.

[1,1-$^2H_2$]-(±)-*cis*-*N*-Methyl-1,2,3,4-tetrahydro-4-methyl-7,8-(methylenedioxy)-3-[2-(2′-hydroxyethyl)-4,5-(methylenedioxy)phenyl]isoquinoline (25). Further elution of the above column with EtOAc–hexane (3:1) gave compound [1,1-$^2H_2$]**25** (150 mg, 3.9%) as an amorphous solid: IR ($CHCl_3$) 3385, 2940, 2885, 1465, 1440, 1370, 1340, 1250–1170, 1015, 920 cm^{-1}; NMR (80 MHz) δ 1.23 (d, 3 H, J = 7.1 Hz, C Me), 2.47 (s, 3 H, N Me), 2.76, 2.96, 3.70, and 3.91 (each m, 1 H, H-1′ and H-2′), 3.29 (qd, 1 H, J = 7.1, 5.5 Hz, H-4), 3.46 and 3.48 (s and d, 0.12 H and 0.05 H, H-8α), 3.85 (m, 0.23 H, H-8β), 3.97 (d, 1 H, J = 5.5 Hz, H-3), 5.90 (d, 1 H, J = 1 Hz, OCH_2O), 5.92 (d, 1 H, J = 1 Hz, OCH_2O), 5.97 (d, 1 H, J = 1 Hz, OCH_2O), 5.98 (d, 1 H, J = 1 Hz, OCH_2O), 6.64 (s, 1 H, Ar H), 6.76 (s, 1 H, Ar H), 6.77 (s, 2 H, Ar H); EIMS m/e (relative intensity) 371 (M^+, 11), 370 (5), 369 (1), 164 (100), 163 (58), 162 (14). The amorphous solid was dissolved in dry THF and treated with several drops of concentrated HCl. The solution was kept at 0 °C. The precipitate was filtered off and dried to give the hydrochloride salt: 144 mg, 87%; mp 250–254 °C dec; FABMS m/e (relative intensity) 372 ($M^+ - Cl^-$, 100); high-resolution MS, calcd for $C_{21}H_{22}D_2NO_5$ ($M^+ - Cl^-$) 372.1779, found 372.1791.

[8,8-$^2H_2$]-(±)-*cis*-*N*-Methyl-6-hydroxy-13-methyl-2,3-(methylenedioxy)-9,10-(methylenedioxy)tetrahydroprotoberberinium Chloride (26). Concentrated HCl (25 mL) was added dropwise to a solution of the ketal **24** (1.91 g, 4.62 mmol) in THF (25 mL) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 H. The solution was concentrated to a syrup on a rotary evaporator upon addition of CH_3CN and H_2O. The solution was kept at 0 °C overnight to give white solid: 1.69 g (90%); mp 239–242 °C. Three recrystallizations from methanol yielded a white solid, 98% of which was one isomer: mp 242–243 °C dec; IR (KBr) 3400, 3100, 2900, 2880, 1475, 1455, 1390, 1260, 1240, 1140, 1025, 910 cm^{-1}; NMR (CF_3COOD, 470 MHz) δ 1.48 (d, 3 H, J = 7.5 Hz, C Me), 2.98 (s, 3 H, N Me), 3.27–3.40 (m, 2 H, H-5), 4.11 (m, 1 H, H-13), 4.43 (br s, 0.16 H, H-8α), 4.91 (br s, 0.16 H, H-8β), 5.09 (d, 1 H, J = 5.4 Hz, H-14), 5.28 (dd, 1 H, J = 9.5, 5.8 Hz, H-6), 6.02 (d, 1 H, J = 1.1 Hz, OCH_2O), 6.04 (d, 1 H, J = 1.1 Hz, OCH_2O), 6.05 (d, 1 H, J = 1.1 Hz, OCH_2O), 6.07 (d, 1 H, J = 1.1 Hz, OCH_2O), 6.77 (s, 1 H, Ar H), 6.83 (s, 1 H, Ar H), 6.99 (d, 1 H, J = 8.3 Hz, Ar H), 7.02 (d, 1 H, J = 8.3 Hz, Ar H); CIMS m/e (relative intensity) 370 ($M^+ - Cl^-$, 100). Anal. Calcd for $C_{21}H_{20}D_2ClNO_5$: C, 62.15; H + D, 5.96; N, 3.45. Found: C, 62.16; H + D, 6.23; N, 3.28.

Callus Cultures and Extraction. The callus of *C. incisa* was subcultured on Murachige and Skoog's (M–S) agar medium fortified with 2,4-dichlorophenoxyacetic acid (1 mg/L), kinetin (0.1 mg/L), and yeast extract (0.1%). Deuterium-labeled compounds were dissolved in water (7.5–15 mL) and introduced into 100-mL Erlenmeyer flasks (30–50) containing ca. 40 mL of the autoclaved M–S medium through a sterile bacterial filter. The callus (ca. 3 g) was transferred to the medium containing each substrate and incubated at 25 °C in the dark for the appropriate time (Table IV). Extraction was carried out as reported in a previous paper.[25] The tertiary-alkaloid fraction soluble in Et_2O was subjected to preparative TLC. The deuterated products (see Table V for deuterium distributions) [8,8-$^2H_2$]**11**, [8,8-$^2H_2$]**12**, and [1,1-$^2H_2$]**25**, and **8** and **31** were purified by preparative TLC with benzene–ether (7:3). Products [1-^2H]**29**, [1,1-$^2H_2$]**30**, and [1,1,2′,2′-$^2H_4$]**15** were obtained by a further preparative TLC (MeOH) of an extract of the low R_f band in TLC with benzene–ether (7:3).

Products from Experiment 1. Product [8,8-$^2H_2$]11: NMR δ 1.08 (s, 3 H, C Me), 2.16 (s, 3 H, N Me), 3.07 (dd, 1 H, J = 17.0, 4.0 Hz, H-5), 3.09 (dd, 1 H, J = 17.0, 2.0 Hz, H-5), 3.26 (d, 1 H, J = 2.0 Hz, H-14), 3.41 (d, 0.44 H, J = 16.0 Hz, H-8α), 3.39 (s, 0.32 H, H-8α), 3.91 (dt, 1 H, J = 4.0, 2.0 Hz, H-6), 3.99 (d, 0.44 H, J = 16.0 Hz, H-8β), 5.91, 5.93, and 5.96 [(d, 2 H, J = 1.0 Hz), (d, 1 H, J = 1.0 Hz), and (d, 1 H, J = 1.0 Hz), 2 OCH_2O)], 6.61 (s, 1 H, H-4), 6.63 (s, 1 H, H-1), 6.76 and 6.89 (each d, 1 H, J = 8.3 Hz, H-11 and H-12); EIMS m/e (relative intensity) 369 (29), 368 (40), 367 (40), 351 (51), 350 (74) 349 (71), 336 (37), 335 (47), 334 (53), 321 (20), 320 (31), 319 (43), 318 (49), 309 (24), 308 (31), 307 (23), 306 (23), 192 (39), 191 (65), 190 (77), 189 (56), 188 (38), 178 (38), 177 (52), 176 (100), 175 (60), 174 (26), 165 (27), 164 (49), 163 (82), 162 (92), 161 (44), 160 (32), 149 (50), 148 (23), 147 (30), 146 (21), 135 (40); CIMS m/e (relative intensity) 370 (M^+, 65), 369 (96), 368 (100).

Product [8-^2H]12: NMR δ 1.26 (s, 3 H, C Me), 2.15 (s, 3 H, N Me), 2.87 (br s, 1 H, H-14), 2.96 (dd, 1 H, J = 17.0, 4.0 Hz, H-5), 3.10 (d, 1 H, J = 17.0 Hz, H-5), 3.65 (m, 1 H, H-6), 5.31 (s, 0.72 H, H-8), 5.92, 5.95, 6.0, and 6.02 (each d, 1 H, J = 1.0 Hz, 2 OCH_2O), 6.62 (s, 1 H, H-4), 6.70 (s, 1 H, H-1), 6.84 (s, 2 H, H-11 and H-12); EIMS m/e (relative intensity) 366 (M^+, 9), 365 (24), 203 (28), 202 (100), 189 (22), 188 (21); CIMS m/e (relative intensity) 367 (MH^+, 24), 366 (73), 365 (68), 202 (100).

Product [1,1-$^2H_2$]25: NMR δ 1.23 (d, 3 H, J = 7.5 Hz, C Me), 2.49 (s, 3 H, N Me), 2.81, 2.96, 3.72, and 3.92 (each m, 1 H, H-1′ and H-2′), 3.3 (m, 1 H, H-4), 3.48 (s, 0.32 H, H-1α), 3.51 (d, 0.17 H, J = 16.5 Hz, H-1α), 3.98 (d, 1 H, J = 5.3 Hz, H-3), 5.92 and 5.98 (each m, 2 H, 2 OCH_2O), 6.65 (s, 1 H, Ar H), 6.76 (s, 1 H, Ar H), 6.78 (s, 2 H, Ar H); EIMS m/e (relative intensity) 371 (M^+, 7), 370 (8), 369 (3), 164 (72), 163 (100), 162 (42); CIMS m/e (relative intensity) 371 (M^+, 35), 370 (28), 163 (100).

Product [1-^2H]29: NMR δ 2.42 (s, 3 H, C Me), 2.43 (m, 2 H, H-1′), 3.70 (m, 2 H, H-2′), 4.33 (s, 3 H, N Me), 6.00, 6.12, 6.45, and 6.46 (each br s, 1 H, 2 OCH_2O), 6.61 (s, 1 H, Ar H), 7.0 (s, 1 H, Ar H), 7.73 (s, 2 H, Ar H), 9.79 (s, 0.52 H, H-1).

Products from Experiments 2, 5, and 6. Product [1,1-$^2H_2$]30: (from experiment 2) NMR δ 1.18 (d, 3 H, J = 7.0 Hz, C Me), 2.16 (s, 3 H, N Me), 2.92 (m, 2 H, H-1′), 3.3 (dq, 1 H, J = 11.0, 7.0 Hz, H-4), 3.63 (m, 1 H, H-3), 3.78 (m, 1 H, H-2′), 3.93 (m, 1.1 H, H-2′ and H-1), 6.0 and 6.01 (each s, 2 H, 2 OCH_2O), 6.80 and 6.87 (each d, 1 H, J = 8.0 Hz, Ar H), 6.83 (s, 1 H, Ar H), 6.92 (s, 1 H, Ar H); EIMS m/e (relative intensity) 371 (M^+, 11), 370 (10), 369 (4), 165 (11), 164 (93), 163 (100), 162 (47).

Product [1-^2H]29: (from experiment 2) EIMS m/e (relative intensity) 367 (M^+, 3.5), 366 (4.4), 306 (32), 142 (100).

Product [1,1-$^2H_2$]25: (from experiment 5) NMR δ 3.46 (s, 0.17 H, H-1α), 3.48 (d, 0.11 H, J = 16.5 Hz, H-1α); EIMS m/e (relative intensity) 371 (M^+, 13), 370 (7), 369 (1), 164 (100), 163 (66), 162 (18).

Product [1,2′,2′-$^2H_3$]29: (from experiment 6) NMR δ 2.42 (s, 3 H, C Me), 2.44 and 2.48 (each d, 1 H, J = 14.0 Hz, H-1′), 4.32 (s, 3 H, N Me), 6.08, 6.10, 6.44, and 6.46 (each br s, 1 H, 2 OCH_2O), 6.60 (s, 1 H, Ar H), 6.99 (s, 1 H, Ar H), 7.71 (s, 2 H, Ar H), 9.80 (s, 0.65 H, H-1).

Product [1,1,2′,2′-$^2H_4$]15: (from experiment 6) NMR δ 1.16 (d, 3 H, J = 7.0 Hz, C Me), 2.15 (s, 3 H, N Me), 2.83 and 2.96 (each d, 1 H, J = 14.0 Hz, H-1′), 3.28 (dq, 1 H, J = 9.5, 7.0 Hz, H-4), 3.62 (m, 1 H, H-3), 3.82 (br, 0.22 H, H-1α), 3.93 (br s, 0.12 H, H-1β), 5.97 and 5.98 (each s, 2 H, 2 OCH_2O), 6.77 and 6.83 (each d, 1 H, J = 8.0 Hz, Ar H), 6.79 (s, 1 H, Ar H), 6.90 (s, 1 H, Ar H); EIMS m/e (relative intensity) 373 (M^+, 13), 372 (1), 371 (4), 165 (12), 164 (100), 163 (42), 162 (11); CIMS m/e (relative intensity) 374 (MH^+, 59), 373 (53), 164 (100).

Products from Experiment 4: Products **11**, **12**, and **31** were identical, by IR, ^1H NMR, MS spectra, with each authentic sample.

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Supplementary Material Available: Details of the X-ray analysis of **26c** (1 page). Ordering information is given on any current masthead page.

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