Total Synthesis of (±)-Roserine†

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Received September 3, 1997[⊗]

Electrophilic cyclization of amino ketals **14a** and **14b** with 6 M HCl at 23 °C, followed by oxidation with air in 6 M HCl at 100 °C, gave tetrahydrophenanthridines **16a** and **16b**, respectively, which were transformed into the pyrrolophenanthridinium salts **1a** and **1b**. Compound **1b** was shown to be the correct structure of the *Narcissus pallidulus* constituent, roserine.

Introduction

Roserine is a novel pyrrolophenanthridinium alkaloid recently isolated in small quantity from *Narcissus pallidulus* by Codina et al.[1a] Structure **1a** was originally proposed for roserine on the basis of its high-resolution mass spectrum, routine ^{1}H and ^{13}C NMR spectra, and a ^{1}H−^{1}H COSY spectrum; however, three additional isomeric pyrrolophenanthridinium structures **1b**−**d**, all of which are compatible with much of the spectroscopic data, were implicitly rejected "on the basis of the H(6) and H(7) correlation observed in a complete COSY experiment" (Figure 1).[1b] Although the structure proposed for roserine contains an asymmetric center at C(4), there is currently no evidence for an absolute configuration of the natural material or, indeed, whether the alkaloid is even optically active.

Two structural features of **1a** appear to be unusual upon comparison with related natural products. With the single exception of roserine, all 16 or so pyrrolophenanthridinium alkaloids currently known from plant sources[2a] contain a fully aromatic C-ring. It is also notable that within the broader class of *Amaryllidaceae* phenanthridine alkaloids, which includes a variety of pyrrolophenanthridines and pyrrolophenanthridones structurally related to the known pyrrolophenanthridinium salts, several members exhibit a pattern of three contiguous oxidized carbon atoms in the aromatic A-ring; however, all such examples appear to be 7,8,9-trisubstituted in contrast to the 8,9,10-trimethoxy substitution pattern that has been proposed for roserine.[2b]

A number of pyrrolophenanthridinium alkaloids were investigated for their potential utility as antineoplastic agents by Cheng et al.[3] A notable example from this structural class, ungeremine, showed low toxicity coupled with remarkable efficacy during preclinical testing.[3a,4]

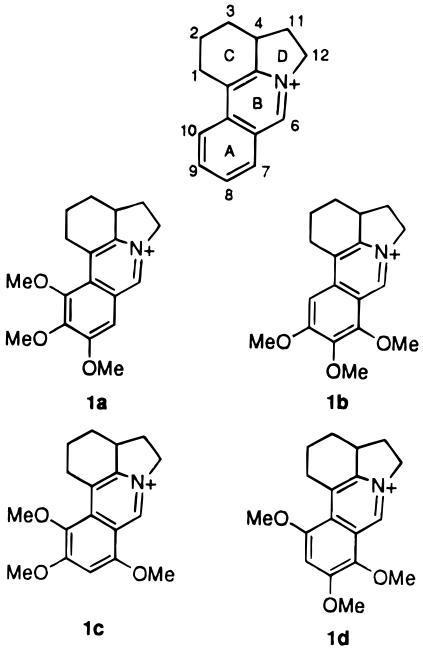
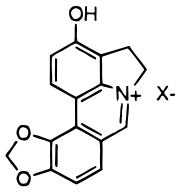


Figure 1. Numbering scheme[1] and isomeric candidates (**1a**−**d**) for the structure of roserine.



ungeremine

Ungeremine was advanced to human clinical trials in the People's Republic of China where it reportedly showed good overall efficacy against ovarian and uterine cervix carcinomas but relatively poor activity against gastric and "miscellaneous" carcinomas.[5] Thus, a clear rationale exists for the continued preclinical SAR (structure−activity relationship) study of novel and structurally diverse pyrrolophenanthridinium alkaloids.

The novelty of roserine's reported structure, its apparent scarcity from a single natural source, and the need for an assessment of its biological activity make total synthesis an attractive route for the procurement of useful amounts of this natural product. However, the

† Dedicated to Kenneth O. Hartley on the occasion of his 83rd birthday.

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(1) (a) Bastida, J.; Codina, C.; Viladomat, F.; Rubiralta, M.; Quirion, J.-C.; Weniger, B. *J. Nat. Prod.* **1992**, *55*, 134. (b) The numbering system used by Codina et al., was adopted in this paper to facilitate discussion and comparison of our results. A widely accepted alternative numbering scheme for the pyrrolo[3,2,1-*de*]phenanthridinium ring system may be found in *The Ring Systems Handbook*; American Chemical Society: Columbus, OH (1993). coden: RSHAEE 1629RSF-3262RSF (1993).

(2) (a) CAS Online substructure search. (b) *The Dictionary of Natural Products* (CD-ROM version); Chapman & Hall: London, 1996.

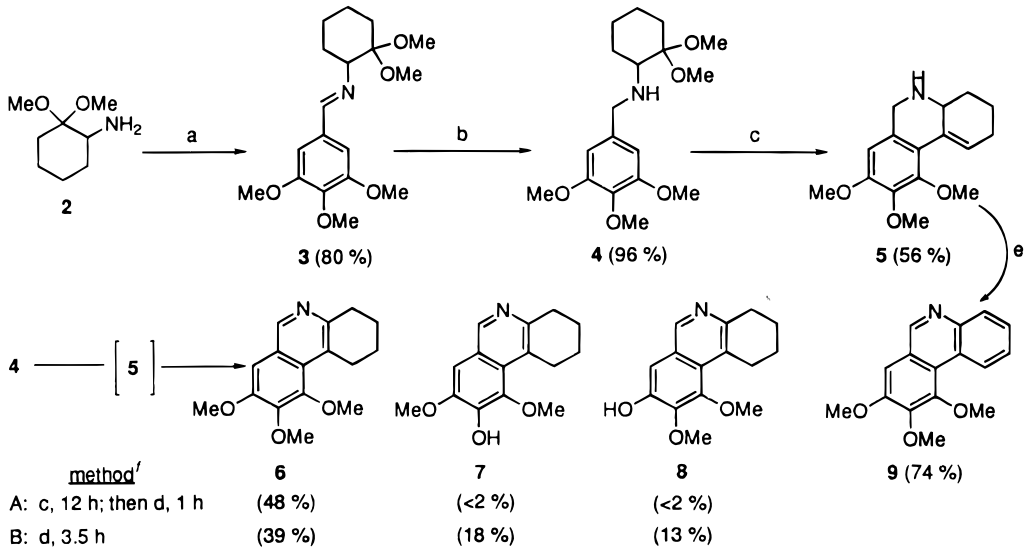
(3) (a) Zee-Cheng, R. K.-Y.; Yan, S.-J.; Cheng, C. C. *J. Med. Chem.* **1978**, *21*, 199. (b) Samoilova, M. Ye.; Akhvlediani, R. N.; Frolova, Ye. P.; Kurkovskaya, L. N.; Yershova, Yu. A.; Safonova, T. S.; Korovin, B. V.; Suvorov, N. N. *Khim.-Farm. Zh.* **1994**, *28*, 10.

(4) Lu, D. Y.; Xu, J.; Xu, B.; Zhou, A. M. *Chin. Biochem. J.* **1993**, *9*, 626.

(5) (a) Xu, B.; Wang, X.-W. *Drugs Future* **1997**, *22*, 123. (b) Fei, C.; Liu, G. Z.; Dong, M. G.; Hua, Z. D.; Wu, Q. F.; Li, S. J.; Hu, L. Y. *New Drugs Clin. Rem. (China)* **1985**, *4*, 1.

S0022-3263(97)01641-1 CCC: $14.00

Scheme 1[a]



[a]Reaction conditions: (a) 3,4,5-trimethoxybenzaldehyde, MeOH, reflux; (b) PtO_2, EtOH, H_2 (1 atm); (c) aqueous 6 M HCl, 23 °C, nitrogen atmosphere; (d) aqueous 6 M HCl, 100 °C, air atmosphere; (e)20% Pd-C, decalin, reflux. [f]See Experimental Section for complete details.

nonaromatic C-ring of roserine presents a synthetic challenge that is not readily amenable to any of the currently available methods for construction of the pyrrolophenanthridinium skeleton.[6] In this report, we describe (1) a total synthesis of structure **1a**, (2) correction of the structure proposed by Codina et al. for roserine, and (3) the first total synthesis of structure **1b** and its spectroscopic correlation with natural roserine.

Results and Discussion

Our initial approach to **1a** was predicated on the assumption that 8,9,10-trimethoxy-1,2,3,4-tetrahydrophenanthridine, **6**, might be induced to undergo directed lateral metalation at C(1) and subsequent functionalization with a two-carbon D-ring fragment.[7] The preparation of intermediate **6** is shown in Scheme 1. Amino ketal **2**[8] was used in a two-step reductive amination of 3,4,5-trimethoxybenzaldehyde to give amino ketal **4** in 80% overall yield. Aqueous 6 M HCl at room temperature, which has previously been described for the conversion of electron-rich *N*-benzyl aminoacetaldehyde acetals to 4-hydroxy-1,2,3,4-tetrahydroisoquinolines,[9] promoted the cyclization of amino ketal **4** to hexahydrophenanthridine **5** in 56% yield. Tetrahydrophenanthridine **6**, probably formed by reaction of **5** with adventitious traces of oxygen, was also isolated in 7% yield from this reaction mixture. When the cyclization−aromatization of **4** was carried out in 6 M HCl starting at 100 °C in the presence of air, tetrahydrophenanthridine **6** was the major product but significant amounts of mono-demethylated tetrahydrophenanthridines **7** and **8** were also formed. Limited attempts to selectively aromatize the heterocyclic ring of compound **5** did not give satisfactory results. Thus, isolated **5** reacted with 20% Pd−C (decalin, reflux, 4 h) to give fully aromatized 8,9,10-trimethoxyphenanthridine, **9**, in 74% yield, while addition of 1 equiv of DDQ to crude **5** in aqueous 6 M HCl gave a complex product mixture containing only a small amount of compound **6**. Ultimately, a two-stage reaction sequence performed without isolation of intermediate **5** was found to be optimal for the preparation of **6**. Thus, compound **4** was allowed to stand in 6 M HCl at room temperature under a nitrogen atmosphere for 20 h; the nitrogen atmosphere was replaced with air, and the rapidly stirred mixture was heated to 100 °C for 2 h to give compound **6** in 48% yield. These reaction conditions, which minimize exposure of the final product to hot 6 M HCl, appeared to completely avoid detectable formation of side-products **7** and **8**.

Tetrahydrophenanthridine **6** requires only two additional carbon atoms to complete the skeleton of target **1a**; however, we were unable to laterally metalate and alkylate **6** at C(4) despite several attempts to do so.[10]

(6) (a) Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S.; Sada-Costa, M. *Tetrahedron* **1997**, *53*, 299. (b) Xiong, Y.; Moore, H. *J. Org. Chem.* **1996**, *61*, 9168. (c) Hutchings, R. H.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 1004. (d) Parnes, J. S.; Carter, D. S.; Kurz, L. J.; Flippin, L. A. *J. Org. Chem.* **1994**, *59*, 3497 and references therein. (e) Lauk, U.; Durst, D.; Fischer, W. *Tetrahedron Lett.* **1991**, *32*, 65. (f) See also, Banwell, M. G.; Wu, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2671.

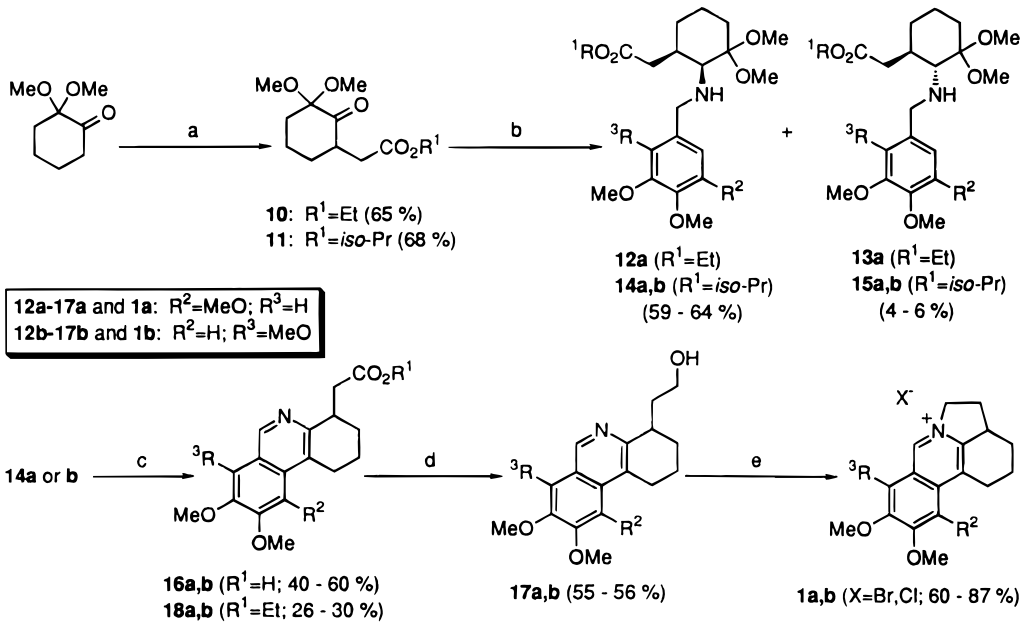
(7) For a general discussion of this topic, see Clark, R. D.; Jahangir, A. *Org. Reac.* **1995**, *47*, 30−33.

(8) (a) Driguez, H.; Vermes, J. P.; Lessard, J. *Can. J. Chem.* **1978**, *56*, 119. (b) We thank Mr. David Repke for the large-scale preparation of amino ketal **2** by an unpublished method. Thus, 2-chlorocyclohexanone was converted to **2** in 85% yield via azide substitution, ketalization, and reduction of the azido group.

(9) (a) Oppolzer, W.; Robbiani, C. *Helv. Chim. Acta* **1983**, *66*, 1119. (b) Bobbit, J. M.; Sih, J. C. *J. Org. Chem.* **1968**, *33*, 856. (c) Euerby, M. R.; Waigh, R. D. *J. Chem. Res., Synop.* **1987**, *2*, 36.

(10) Tetrahydrophenanthridine **6** proved highly resistant toward metalation with a variety of strong, nonnucleophilic bases. Thus, THF solutions of LDA or LTMP and ether solutions of LTMP−KO^{t}Bu or mesityllithium all failed to generate a colored anion from **6** over 1−3 h between −78 °C and +23 °C. After quenching these reaction mixtures with a two-carbon fragment (ethylene oxide) or methyl iodide to determine possible sites of metalation, the only detectable tetrahydrophenanthridine in each crude product mixture was unreacted **6**. Treatment of **6** with *n*-BuLi in THF followed by a methyl iodide quench gave a very complex mixture comprised in part from direct addition of an *n*-butyl group to the C=N bond; however, no recognizable methyl group incorporation, aside from *N*-methylation, could be detected from the ^{1}H NMR spectrum of the crude reaction mixture. The metalation of 3-methylisoquinoline was briefly examined as a potential model system for the metalation of **6**; however, in distinct contrast to **6**, 3-methylisoquinoline readily gave a deep red-colored anion with LTMP (THF, −78 °C). This anion was quenched with methyl iodide (−78 °C) to give 3,4-dimethylisoquinoline rather than the expected product, 3-ethylisoquinoline (see also, Gisby, G. P.; Sammes, P. G.; Watt, R. A. *J. Chem. Soc., Perkin Trans. 1* **1982**, 249).

Scheme 2[a]



[a]Reaction conditions: (a) KO^{t}Bu, THF; then $R^1O_2CCH_2I$; (b) trimethoxybenzylamine, Ti(O^{i}Pr)$_4$; then $NaBH_4$, ^{i}PrOH; (c) aqueous 6 M HCl, 23 °C, nitrogen atmosphere; then, 100 °C, air atmosphere, 1 h; (d) 1.05 equiv BMS, THF, 23 °C, 5 h; (e) PX_3, benzene, reflux, 10 - 30 min.

We next investigated an approach to structure **1a** that would potentially allow incorporation of the C(11)−C(12) D-ring fragment at an earlier stage in the synthesis via elaboration of ketone **10**[11] (Scheme 2). The mild reaction conditions used for the preparation of aldimine **3** gave no apparent reaction between ketone **10** and 3,4,5-trimethoxybenzylamine, while several attempts to generate an imine from these reactants under Dean−Stark conditions (toluene, reflux, molecular sieves or catalytic *p*-TsOH) gave complex product mixtures which were not investigated further. However, when ketone **10** and 3,4,5-trimethoxybenzylamine were allowed to react according to the method of Bhattacharyya[12] in neat Ti(O^{i}Pr)$_4$ followed by reduction with methanolic $NaBH_4$, the resulting crude mixture appeared to be composed primarily of reductive amination products. After careful analysis this product mixture was shown to consist of ethyl esters **12a** and **13a** (4:1 ratio) and isopropyl esters **13a** and **15a** (4:1 ratio); the ratio of total ethyl esters (**12a**+**13a**) to isopropyl esters (**14a**+**15a**) was approximately 3:2. The partial transesterification of **10** during imine formation could be avoided by replacing Ti(O^{i}Pr)$_4$ with Ti(OEt)$_4$ in Bhattacharyya's procedure; however, the use of Ti(OEt)$_4$ caused the reaction mixture to solidify after a short time, and, following reduction with $NaBH_4$−EtOH, the isolated yield of diastereomeric esters **12a** and **13a** (4:1 ratio) was poor. A single attempt to conduct the imine formation using 0.29 M Ti(OEt)$_4$ in abs EtOH, followed by reduction with ethanolic $NaBH_4$, also gave **12a** and **13a** in poor yield. Finally, 2,2-dimethoxycyclohexanone was alkylated with isopropyl iodoacetate[13] to give 1,2-cyclohexanedione monoketal **11** in 68% yield. Treatment of **13** with 3,4,5-trimethoxybenzylamine in neat Ti(O^{i}Pr)$_4$ followed by addition of ethanolic $NaBH_4$ afforded the cis and trans diastereomers **14a** and **15a** in a 4:1 ratio. However, when the reduction step of the procedure was carried out with a slurry of $NaBH_4$ in 2-propanol, the **14a:15a** diastereomer ratio improved to 10:1. Employing the latter method, pure cis diastereomer **14a** was isolated in 59% yield and used for all subsequent work toward the synthesis of target structure **1a**. Treatment of **14a** with 6 M HCl at room temperature under a nitrogen atmosphere for 14 h, followed by introduction of an air atmosphere and warming the reaction mixture to 100 °C for 1 h, gave tetrahydrophenanthridine **16a** in 60% yield. Reduction of **16a** with borane−methyl sulfide complex (BMS) in THF at room temperature for 16−20 h gave the desired primary alcohol **17a** in 40−55% yield; however, this problematic transformation was accompanied by formation of an incompletely characterized over-reduction product when sufficient BMS was used to ensure complete consumption of the starting material. Several attempts to optimize the lithium aluminum hydride reduction of **16a** in ether also gave **17a** in 40−50% yield. Eventually it was found that careful treatment of **16a** with 1.05 equiv of BMS in THF minimized over-reduction while reproducibly giving 55% of alcohol **17a** and 35% of a recyclable ethyl ester, **18a**, after workup of the reaction mixture with ethanolic HCl. Reaction of **17a** with a large excess of PBr_3 in refluxing benzene for 2.5 h[14] gave pyrrolophenanthridinium bromide **1a** (Br^-) in fair yield; however, this procedure was significantly improved by the use of 1 equiv of either PCl_3 or PBr_3 in refluxing benzene for 30 min to give **1a** (Cl^-) or **1a** (Br^-) in 76 and 87% yield, respectively.

(11) Compound **10** has been previously mentioned as a minor reaction product without physical characterization: Langschwager, W.; Hoffmann, H. M. R. *Liebigs Ann* **1995**, 797. Note: There is a typographical error in the experimental section of this paper that matches the compound number for ethyl (3,3-dimethoxy-2-oxocyclohexyl)acetate with physical properties of ethyl (3,3-diethoxy-2-oxocyclohexyl)acetate.

(12) (a) Bhattacharyya, S. *Tetrahedron Lett.* **1994**, *35*, 2401. (b) See also Seebach, D.; Hungerbuhler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Zuger, M. *Synthesis* **1982**, 138.

(13) Chuchani, G.; Hernandez, J. A.; Yepez, M.; Alonso, M. E. *Int. J. Chem. Kinet.* **1977**, *9*, 811.

(14) These reaction conditions were previously described for a related D-ring closure in a synthesis of vasconine: See ref 6a.

Table 1. Effect of Solvent and Counterion on ^{13}C NMR Shifts of 1a[a]

carbon number	**1a** (Br^-) $CDCl_3$[b]	**1a** (Br^-) 1:1 $CDCl_3-CD_3OD$[c]	**1a** (Br^-) CD_3OD[c]	**1a** (Cl^-) $CDCl_3$	**1a** (Cl^-) 1:1 $CDCl_3-CD_3OD$	**1a** (Cl^-) CD_3OD	**1a** mean(s)[d]	Δ (ppm) $\mathbf{1a}_m$, lit.[e]
C(8)	155.3	156.7	157.3	155.6	156.8	157.3	156.5(0.9)	−5.9
C(9)	150.4	151.7	152.2	150.8	151.8	152.2	151.5(0.8)	1.0
C(10)	149.2	150.4	150.1	149.4	150.5	151.1	150.1(0.7)	3.3
C(4a)	144.3	145.7	146.7	144.2	145.8	146.8	145.6(1.1)	3.6
C(6)	142.0	141.2	142.2	143.3	141.5	142.2	142.1(0.7)	3.6
C(10a)	129.0	130.7	131.0	129.0	130.7	131.0	130.2(1.0)	−5.3
C(10b)	128.9	130.2	130.6	128.8	130.2	130.6	129.9(0.8)	2.8
C(6a)	125.3	126.3	126.9	125.7	126.4	126.9	126.3(0.6)	7.0
C(7)	106.6	106.0	106.5	107.1	106.1	106.6	106.5(0.4)	9.7
10-MeO	61.7	62.4	62.5	61.9	62.4	62.5	62.2(0.3)	−0.3
9-MeO	61.3	62.0	62.0	61.6	62.0	62.0	61.8(0.3)	−0.6
C(12)	57.3	57.9	58.5	57.2	58.0	58.4	57.9(0.5)	0.5
8-MeO	57.0	57.1	57.2	57.1	57.1	57.2	57.1(0.1)	0.3
C(4)	40.9	41.9	42.5	41.2	42.0	42.5	41.8(0.7)	1.8
C(11)	31.8	32.4	32.8	32.0	32.4	32.7	32.4(0.4)	0.7
C(3)	26.5	27.2	27.7	26.8	27.3	27.7	27.2(0.5)	0.4
C(1)	26.0	27.0	27.5	26.3	27.1	27.5	26.9(0.6)	3.9
C(2)	22.8	23.5	24.1	23.1	23.6	24.1	23.5(0.5)	1.7

[a] Solute concentration was 0.04 M. [b] Referenced to the center peak of $CDCl_3$ ($\delta = 77.2$). [c] Referenced to the center peak of CD_3OD ($\delta = 49.2$). [d] Mean (standard deviation); $N = 6$. [e] Roserine values from reference 1.

A comprehensive ^1H and ^{13}C NMR characterization of structure **1a** was carried out using **1a**(Br^-) in $CDCl_3$ solution. The position and relative configuration of the aliphatic protons of rings C and D were assigned on the basis of $^1H-^1H$ coupling and NOE correlations observed with 2D COSY and NOESY experiments.[15] The NOESY spectrum of **1a**(Br^-) also showed, as expected, strong NOE's for H(6) with H(7) and H(12α,β); *however, the COSY spectrum did not show a detectable correlation between H(6) and H(7).* Proton H(7) also showed an NOE with the singlet at δ 4.09 allowing assignment of the 8-methoxy group, while an NOE between both H(1) protons and the singlet at δ 3.97 was used to establish the 10-methoxy group. The ^{13}C NMR spectrum of **1a** (Br^-) showed a discreet resonance for each carbon atom while an APT experiment gave the number of protons attached to each. The protonated carbons were assigned by their chemical shift values and one-bond heteronuclear ($^{13}C-^1H$) correlations were obtained from a 2D HETCOR experiment. The unambiguous assignment of all carbon atoms of **1a** (Br^-), including the quaternary centers, was carried out by analysis of long-range 2D COLOC and 2D HMBC experiments optimized for three bonds. Solvent effects on the 1D proton and carbon NMR spectra of **1a** (Cl^-) and **1a** (Br^-) were studied using $CDCl_3$, CD_3OD, and 1:1 $CDCl_3-CD_3OD$ solutions. The ^{13}C NMR spectra of **1a** (Table 1) showed little solvent-dependence or counterion-dependence; thus, the standard deviation, *s*, for every ^{13}C resonance of **1a** (2 counterions × 3 solvents; $N = 6$ for each resonance line) was ≤1.1 ppm. In contrast, the ^1H NMR signals assigned to H(6), H(7), and H(12α) of structure **1a** were observed to be strongly solvent-dependent.[16] Halide counterion effects on the ^1H NMR spectra of **1a** were negligible over the range of solvents examined.

Aside from the three important signals mentioned above, the ^1H NMR spectra of **1a** were essentially constant over the range of solvents studied; thus, the isolated multiplets assigned to H(1α,β), H(3α), H(4), H(11α,β), and the three methoxy singlets seemed likely to be reliable diagnostic signals for a partial comparison with the published spectral data for roserine. The absence of significant solvent-induced shifts in the ^{13}C NMR spectra of **1a** suggested that all of these data would be crucial for an unambiguous synthetic confirmation of roserine's identity. *Direct comparison of the solvent-independent portions of the ^1H NMR spectra of **1a**, as well as the entire set of ^{13}C NMR data for **1a**, with the corresponding published spectral data for roserine clearly revealed that they are isomeric structures.*

Several lines of evidence suggested the likely identity of roserine with structure **1b**. The 1D ^1H and ^{13}C NMR data reported for roserine are consistent with the general skeletal features of all four structures **1a**−**d**, whereas the 8,9,10-trimethoxy pattern of structure **1a** was specifically proposed for roserine on the basis of a $^1H-^1H$ COSY experiment which suggested coupling between proton H(6) at δ 9.50 and the proton at δ 6.95 (assigned as H(7)). Codina et al. apparently did not attempt to confirm the H(7) assignment with an NOE experiment.[17] A $^1H-^1H$ COSY spectrum of authentic **1a** showed no detectable correlation between H(6) and H(7) (vide supra); however, this result is not very surprising in light of the corresponding $^1H-^1H$ coupling information known for isoquinoline[18] (Figure 2).

There is no apparent coupling between H(1) and H(6), H(7), or H(8) in isoquinoline: The only readily observable $^1H-^1H$ coupling constant for H(1) with an A-ring proton appears to be $J_{H(1)-H(5)} = 0.9$ Hz. An additional example of transannular $^1H-^1H$ coupling that is especially relevant to the isoquinolinium moiety of roserine is provided by the related pyrrolophenanthridinium alkaloid vasconine[6d] (Figure 2). Protons H(7) and H(10) of vasconine were unambiguously assigned from a NOESY experiment but, while the $^1H-^1H$ COSY spectrum shows a clear H(6)−H(10) correlation, there is no evidence of an H(6)−H(7) correlation in this alkaloid. We inferred from these data that, of the four possible isomers **1a**−**d**, only structure **1b** might be confidently expected to exhibit a coupling relationship between H(6) and an A-ring proton; therefore, **1b** is an appropriate candidate for the correct

(15) The relative configuration of protons in structures **1a** and **1b** were determined experimentally relative to H(4). Proton H(4) in **1a** and **1b** is arbitrarily assigned the β-configuration in Figure 2.

(16) Complete details are available in the Supporting Information.

(17) Bastida, J. Personal communication: May 28, 1997.

(18) Kook, A. M.; Smith, S. L.; Brown, E. V. *Org. Magn. Reson.* **1984**, *22*, 730.

Table 2. Effect of Solvent and Counterion on ^{13}C NMR Shifts of 1b[a]

carbon number	**1b** (Br^-) $CDCl_3$[b]	**1b** (Br^-) 1:1 $CDCl_3$–CD_3OD[c]	**1b** (Br^-) CD_3OD[c]	**1b** (Cl^-) $CDCl_3$	**1b** (Cl^-) 1:1 $CDCl_3$–CD_3OD	**1b** (Cl^-) CD_3OD	**1b** mean(s)[d]	Δ (ppm) $\mathbf{1b}_m$, lit.[e]
C(9)	162.3	163.6	164.2	162.2	163.7	164.2	163.4(0.9)	1.0
C(7)	150.6	150.8	151.6	150.5	150.8	151.5	151.0(0.5)	0.5
C(4a)	146.7	147.4	148.4	146.6	147.4	148.3	147.5(0.8)	0.7
C(8)	142.1	142.6	143.4	142.1	142.6	143.4	142.7(0.6)	0.7
C(6)	138.7	137.9	138.9	140.0	138.0	138.9	138.7(0.8)	0.2
C(10a)	135.5	136.4	137.2	135.4	136.5	137.2	136.4(0.8)	0.9
C(10b)	127.0	128.4	129.0	126.8	128.4	129.0	128.1(1.0)	1.0
C(6a)	119.3	119.9	120.5	119.4	119.9	120.5	119.9(0.5)	0.6
C(10)	97.0	97.8	98.8	96.8	97.9	98.8	97.9(0.9)	1.1
7-MeO	62.9	62.7	63.0	62.8	62.7	63.0	62.9(0.1)	0.4
8-MeO	61.5	62.0	62.1	61.6	62.1	62.1	61.9(0.3)	−0.5
C(12)	57.8	57.8	58.4	57.7	57.8	58.3	58.0(0.3)	0.6
9-MeO	57.1	57.5	57.7	56.9	57.5	57.7	57.4(0.3)	0.6
C(4)	40.3	41.0	41.7	40.2	41.1	41.7	41.0(0.7)	1.0
C(11)	32.0	32.5	33.0	32.0	32.5	32.9	32.5(0.4)	0.8
C(3)	27.2	27.7	28.3	27.2	27.8	28.3	27.8(0.5)	1.0
C(1)	23.4	23.9	24.3	23.3	23.9	24.3	23.9(0.4)	0.9
C(2)	22.1	22.6	23.4	22.1	22.7	23.4	22.7(0.6)	0.9

[a] Solute concentration was 0.04 M. [b] Referenced to the center peak of $CDCl_3$ ($\delta = 77.2$). [c] Referenced to the center peak of CD_3OD ($\delta = 49.2$). [d] Mean (standard deviation); $N = 6$. [e] Roserine values from reference 1.

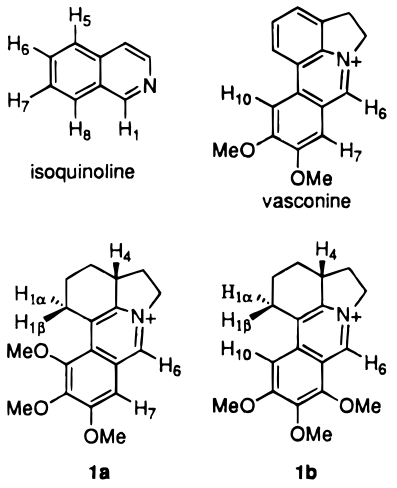


Figure 2. Selected $^1H-^1H$ coupling and NOE relationships: See text for discussion.

structure of roserine. Structures **1a**, **1c**, and **1d** also share the structural motif of a C(10) methoxy substituent proximal to H(1α) and H(1β) of the saturated C-ring. In structure **1a** this substitution pattern leads to large, solvent-independent downfield shifts in H(1β), $\Delta\delta = 0.6$ ppm, and H(1α), $\Delta\delta = 0.35$ ppm, relative to the H(1α,β) signals reported for roserine. It seemed likely that the corresponding methylene protons of structures **1c** and **1d** would be similarly deshielded, whereas the H(1) methylene protons of **1b** would be shielded relative to **1a**.

Fortunately, the optimized synthetic approach that afforded the bromide and chloride salt forms of compound **1a** also proved entirely satisfactory for a synthesis of both salt forms of structure **1b**. Thus, reductive amination of ketone **11** with 2,3,4-trimethoxybenzylamine gave cis diastereomer **14b** in 73% isolated yield (crude mixture *cis*-**14b**:*trans*-**15b** = 13:1), and the three-step transformation of **14b** into pyrrolophenanthridinium salts **1b** (Cl^-) and **1b** (Br^-) proceeded without incident.

The structure of **1b** was fully assigned[15] by analysis of 2D NOESY, COSY, HETCOR, HMBC, and COLOC experiments recorded using a $CDCl_3$ solution of **1b** (Br^-). A carbon NMR study of **1b** (Br^-) and **1b** (Cl^-), each examined in $CDCl_3$, 1:1 $CDCl_3$–CD_3OD, and CD_3OD solution, revealed that the ^{13}C NMR spectra of **1b** are essentially independent of counterion or solvent effects (Table 2). The standard deviation for each ^{13}C resonance of **1b** (2 counterions × 3 solvents; $N = 6$ for each line) was $s \leq 1.0$ ppm. We were therefore gratified to observe that the mean value for each ^{13}C spectral line of **1b** precisely matched a corresponding spectral line reported for natural roserine ($|\delta_{\mathbf{1b}(\text{mean})} - \delta_{\text{roserine}}| \leq 1.1$ ppm for each line). When the ^{13}C NMR spectral lines reported for natural roserine in $CDCl_3$ were included in a statistical calculation with the corresponding values for **1b** (Cl^- and Br^-) recorded only in $CDCl_3$ ($N = 3$ for each of the 18 lines), the standard deviation was $s \leq 0.8$ ppm for each line, while the mean of all the standard deviations (s_{mean}) was only 0.2 ppm.

Not surprisingly, the ^{1}H NMR spectra of **1b** showed marked solvent-dependent behavior for H(6), H(10), and H(12α), while the chemical shifts for all other proton resonances were virtually constant over the range of our solvent study.[16] Aside from the three highly solvent-variable signals, the chemical shift and multiplicity (or signal bandwidth in the case of unresolved multiplets) of every resonance in the ^{1}H NMR spectrum of **1b** correlated with a matching signal reported for roserine.[19]

We were initially puzzled by our inability to precisely match the entire set of ^{1}H NMR spectral data reported for natural roserine using $CDCl_3$ solutions of compound **1b**; furthermore, it was disappointing to learn that we could not directly compare **1b** with roserine because no authentic sample of the natural product had been retained by the Codina group.[20] However, inspection of

(19) The solvent-independent signals for **1b** (Cl^-) and **1b** (Br^-) in $CDCl_3$ were uniformly offset downfield from the corresponding reported roserine signals by 0.11 ± 0.03 ppm. Differences of this magnitude have been ascribed to minor variances in solute concentration (ref 6f) or solvent composition (ref 6d) in previous ^{1}H NMR studies of pyrrolophenanthridinium alkaloids. The proton signals of greatest diagnostic value in a comparison of **1b** with the reported data for roserine were H(1β): $\delta_m = 3.27$ (br dd, $J_m = 17$, 6 Hz) [lit.[1] $\delta = 3.13$ (dd, $J = 16$, 6 Hz)], H(1α): $\delta_m = 2.95$ (symmetrical multiplet) [lit.[1] $\delta = 2.85$ (ddd, $J = 16$, 6, 1.5 Hz)], and H(10): $\delta_m = 7.06 \pm 0.11$ (singlet) [lit.[1](assigned as H(7)) $\delta = 6.95$ (singlet)]. When corrected for the global 0.11 ppm offest (vide supra), all other proton NMR signals reported for roserine were statistically indistinguishable from the corresponding signals recorded for either **1a** or **1b**. See the Supporting Information for a complete tabulated solvent-effect and counterion-effect study of **1a** and **1b** in three solvents.

Codina's original $^1H-^1H$ COSY spectrum for roserine in $CDCl_3$, which includes the 1-D proton spectrum on the *x* and *y* axes, revealed the presence of a previously unreported large, broad signal (δ 3.6−3.9) that is not correlated with any ^1H nucleus from the natural product structure. The sum of the ^1H and ^{13}C NMR signals reported for roserine, plus the four heteroatoms necessary for the simplest rationalization of the chemical shift information, requires an empirical formula of $C_{18}H_{22}NO_3$: Since a high-resolution mass spectrum of the natural product satisfactorily verified the NMR-predicted formula[1] it is clear that the newly discovered ^1H NMR signal is due to an unrelated impurity in Codina's sample. We have made several unsuccessful attempts to identify this substance with the aim of evaluating its effect on the ^1H NMR chemical shifts of **1b**; however, without recourse to the original roserine sample or further information about the exact nature of its contaminant, it is unlikely that the solvent-dependent proton signals of **1b** and roserine can be precisely matched until the natural product is isolated again.[21]

Proton H(4) of **1b** (Cl^-) did not exchange at a measurable rate in neat D_2O (neutral pH, ambient temperature) over the course of three weeks; therefore it may be reasonable to expect that the absolute configuration of roserine, if it is not a natural racemate, can eventually be determined following reisolation from the plant source.

Conclusions

This work demonstrates the structure correction and first total synthesis of the pyrrolophenanthridinium alkaloid, (±)-roserine. The optimized synthetic route appears to be general and practical; thus, substantial amounts of synthetic roserine, **1b** (Cl^-), and an isomer, **1a** (Cl^-), are currently available for biological assessment. The biological activity of these compounds will be reported in due course.

Experimental Section

Routine ^1H and ^{13}C spectra were recorded at 300.13 and 75.40 MHz, respectively, using $CDCl_3$ solutions with internal tetramethylsilane as the reference unless otherwise noted. Routine operating procedures and solvent purification methods used in this work have been characterized elsewhere.[22] Elemental analyses were performed by Analytical Services, Central Research and Development, of Roche Bioscience.

(2,2-Dimethoxycyclohexyl)(3,4,5-trimethoxybenzylidene)amine (3). 3,4,5-Trimethoxybenzaldehyde (372 mg, 1.9 mmol) and amino ketal **2**[8] (300 mg, 1.9 mmol) were combined in 50 mL of anhydrous MeOH, and the mixture was brought to reflux under a nitrogen atmosphere. The reaction mixture was periodically concentrated by distillation (1 atm), and the solvent was replaced with fresh MeOH; after 4 h the mixture was concentrated with a rotary evaporator to give a crude yellow solid. Recrystallization of the crude material from hexanes gave 490 mg of **3** as white needles (80% yield): mp 112.5−113 °C; ^1H NMR δ 8.21 (s, 1 H), 7.03 (s, 2 H), 3.91 (s, 6 H), 3.87 (s, 3 H), 3.55 (br m, 1 H), 3.24 (s, 3 H), 3.15 (s, 3 H), 2.08 (ddd, J = 13.5, 10.8, 3.9 Hz), 1.95−1.35 (m, 7 H); ^{13}C NMR 159.2, 153.4, 140.2, 132.4, 105.3, 100.9, 70.3, 60.9, 56.2, 47.7, 47.4, 32.4, 29.0, 22.9, 20.9; EI-MS *m/z* 337 (M, 5%), 323 (20%), 322 (100%), 306 (8%), 222 (16%), 196 (12%), 181 (8%), 176 (8%), 149 (25%). Anal. Calcd for $C_{18}H_{27}HNO_5$: C, 64.07; H, 8.05; N, 4.36. Found: C, 64.35, H, 8.05; N, 4.36.

(2,2-Dimethoxycyclohexyl)(3,4,5-trimethoxybenzyl)amine (4). A mixture of imine **3** (500 mg, 1.5 mmol) and 34 mg of PtO_2 in 10 mL of abs EtOH was hydrogenated (23 °C, 1 atm H_2) for 6 h. The reaction mixture was filtered through Celite and concentrated under vacuum to give 490 mg of **4** (96%) as a clear, colorless oil: ^1H NMR δ 6.59 (s, 2 H), 3.86 (s, 6 H), 3.83 (s, 3 H), 3.83 (d, J = 13.4 Hz, 1 H), 3.61 (d, J = 13.4 Hz, 1 H), 3.18 (s, 3 H), 3.10 (s, 3 H), 2.88 (br t, J = 3 Hz), 1.8−1.25 (m, 8 H); ^{13}C NMR δ 153.2, 137.0, 136.7, 105.2, 101.4, 60.9, 56.1, 55.6, 51.7, 47.7, 47.2, 27.9, 25.3, 22.5, 19.4; EI-MS *m/z* 339 (M, 8%), 324 (12%), 308 (5%), 196 (12%), 181 (100%); LSIMS−HRMS Calcd for $C_{18}H_{30}NO_5$ (M + H): 340.2124. Found: 340.2122. Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13. Found: C, 63.28; H, 8.65; N, 4.12.

8,9,10-Trimethoxy-2,3,4,4a,5,6-hexahydrophenanthridine (5). Amino ketal **4** (100 mg, 0.3 mmol) was dissolved in 3 mL of aqueous 6 M HCl under a nitrogen atmosphere. The reaction mixture was allowed to stir at 23 °C for 16 h; TLC analysis (silica gel, 95:5 $CH_2Cl_2-CH_3OH$) showed complete consumption of **4** and the presence of a major product **5** (R_f = 0.26) and a minor product **6** (R_f = 0.56). The reaction mixture was made strongly basic with 3 M NaOH and extracted with 3 × 15 mL of ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 71 mg of a crude, pink oil. Preparative TLC (silica gel; 95:5 $CH_2Cl_2-CH_3OH$) afforded 46 mg of **5** (56%) and 6 mg of **6** (7%). Compound **5** was a colorless oil: ^1H NMR δ 6.88 (br t, J = 4 Hz, 1 H), 6.33 (s, 1 H), 4.11 (d, J = 16.4 Hz, 1 H), 3.94 (d, J = 16.4 Hz, 1 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.37−3.28 (m, 1 H), 2.30−2.21 (m, 2 H), 2.21−2.12 (m, 1 H), 1.86−1.74 (m, 1 H), 1.69−1.53 (m, 1 H), 1.49−1.34 (m, 1 H); ^{13}C NMR δ 152.8, 151.9, 141.6, 131.8, 130.5, 125.7, 120.3, 104.8, 61.0, 59.9, 55.9, 53.8, 49.0, 31.6, 27.0, 20.9; EI-MS *m/z* 275 (M, 100%), 274 (88%), 259 (10%), 258 (10%), 245 (43%), 246 (45%), 232 (12%), 216 (10%); LSIMS−HRMS Calcd for $C_{16}H_{22}NO_3$ (M + H): 276.1600. Found: 276.1605.

8,9,10-Trimethoxy-1,2,3,4-tetrahydrophenanthridine (6). Method A. Amino ketal **4** (878 mg, 2.6 mmol) was allowed to react in aqueous 6 M HCl at 23 °C for 20 h under a nitrogen atmosphere. An air atmosphere was applied to the vessel, and the rapidly stirred reaction mixture was warmed to 100 °C for 2 h. The reaction mixture was cooled to 0 °C, made strongly basic with 30% NaOH, and extracted with 3 × 20 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give a clear yellow oil. The crude product was purified by flash chromatography (silica gel, 40:1 $CH_2Cl_2-CH_3OH$) to afford 340 mg of **6** (48%) as a colorless oil: ^1H NMR δ 8.82 (s, 1 H), 7.00 (s, 1 H), 3.99 (s, 3 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.38 (br t, J = 6 Hz, 2 H), 3.05 (br t, J = 6 Hz, 2 H), 1.96−1.80 (m, 4 H); ^{13}C NMR δ 152.0, 149.4, 148.6, 147.8, 145.5, 126.5, 124.7, 124.4, 102.5, 60.9, 60.6, 55.5, 33.1, 27.1, 23.1, 22.2; EI-MS *m/z* 273 (M, 100%), 258 (50%), 243 (20%), 242 (20%). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.40; H, 7.00; N, 4.79.

Method B. Amino ketal **4** (400 mg, 1.2 mmol) was dissolved in 12 mL of aqueous 6 M HCl, and the solution was heated to reflux for 3.5 h under an air atmosphere. The reaction mixture was made strongly basic with NaOH and extracted with CH_2Cl_2 to give a dark crude product. Flash chromatography (silica gel, 97:3 $CH_2Cl_2-CH_3OH$) gave 129 mg of **6** (39%) and two phenolic products, **7** (55 mg, 18%) and **8** (41 mg, 13%). Routine ^1H NMR spectra of **7** and **8** indicated that they were isomeric mono-demethylated derivatives of structure **6**; their exact structures were assigned from a series of proton NOE

(20) Bastida, J.; Codina, C. Personal communication: June 18, 1997.

(21) For example, pure **1b** (Cl^-) was subjected to the unusual preparative TLC conditions outlined in ref 1; however, the ^1H NMR spectrum ($CDCl_3$) of **1b** isolated from this experiment was unchanged. Mixtures of CD_3OD, DMSO-d_6, D_2O, or H_2O with $CDCl_3$ caused variable, pronounced shifts in the solvent-dependent proton signals of **1b** (Cl^-), but none of these experiments provided a precise match to the original roserine data. Interestingly, a proton NMR spectrum of **1b** (Cl^-) in neat D_2O did provide a nearly exact match to all of the data reported for roserine (see Supporting Information). A fresh analysis of all the original spectral data for roserine might prove useful in probing the identity of the impurity peak; however, beyond the $^1H-^1H$ COSY spectrum, we have been unable to obtain any further original physical data or information concerning the isolation of natural roserine from the Codina group.

(22) Flippin, L. A.; Berger, J.; Parnes, J. S.; Gudiksen, M. S. *J. Org. Chem.* **1996**, *61*, 4812.

experiments. **9-Hydroxy-8,10-dimethoxy-1,2,3,4-tetrahydrophenanthridine (7).** ^{1}H NMR δ 8.78 (s, 1 H), 7.13 (s, 1 H), 4.07 (s, 3 H), 3.89 (s, 3 H), 3.38 (br t, J = 6 Hz, 2 H), 3.07 (br t, J = 6 Hz, 2 H), 1.96−1.80 (m, 4 H). **8-Hydroxy-9,10-dimethoxy-1,2,3,4-tetrahydrophenaanthridine (8).** ^{1}H NMR δ 8.70 (s, 1 H), 7.20 (s, 1 H), 3.92 (s, 3 H), 3.81 (s, 3 H), 3.33 (br t, J = 6 Hz, 2 H), 3.00 (br t, J = 6 Hz, 2 H), 1.89−1.73 (m, 4 H).

Dehydrogenation of 5 with 20% Pd/C. 8,9,10-Trimethoxyphenanthridine (9). Compound **5** (20 mg, 0.07 mmol) and 40 mg of 20% Pd/C were mixed in 2 mL of decalin. The mixture was allowed to reflux for 4 h under a nitrogen atmosphere; TLC (silica gel, 95:5 CH_2Cl_2−CH_3OH) showed complete consumption of **5** and the formation of a single new product. The reaction mixture was diluted with 10 mL of benzene and extracted with 5 mL of aqueous 4 M HCl. The aqueous layer was made strongly basic with NaOH and extracted with ethyl acetate to give 14 mg (74%) of **9**: R_f = 0.6; ^{1}H NMR δ 9.33 (dd, J = 7.8, 2.0 Hz, 1 H), 9.13 (s, 1 H), 8.16 (dd, J = 7.8, 2.0 Hz, 1 H), 7.70 (td, J = 7.1, 1.7 Hz, 1 H), 7.65 (td, J = 7.1, 1.7 Hz, 1 H), 7.25 (s, 1 H), 4.08 (s, 3 H), 4.06 (s, 6 H); ^{13}C NMR δ 153.4, 152.4, 151.5, 146.3, 144.2, 129.9, 127.6, 127.2, 126.2, 124.2, 123.6, 121.6, 105.1, 61.3, 60.5, 56.1; EI-MS m/z 269 (M, 100%), 254 (53%), 239 (16%), 226 (44%), 211 (80%), 196 (20%), 183 (20%), 140 (57%); EI−HRMS Calcd for $C_{16}H_{15}NO_3$: 269.1052. Found: 269.1052. An analytical sample was obtained by recrystallization of the picrate derivative of **9** from methanol: mp (picrate) 201−202 °C. Anal. Calcd for $C_{22}H_{18}N_4O_{10}$: C, 53.02; H, 3.64; N, 11.24. Found: C, 52.93; H, 3.46; N, 11.16.

Ethyl (3,3-Dimethoxy-2-oxocyclohexyl)acetate (10).[11] To a solution of 1.00 g (6.3 mmol) of 2,2-dimethoxycyclohexanone in 5 mL of THF at 0 °C under a nitrogen atmosphere was added 7.6 mL (7.6 mmol) of a 1 M KO^{t}Bu in THF. The reaction mixture was allowed to warm to 23 °C for 1 h, giving a deep burgundy-colored solution. The reaction mixture was cooled to −78 °C, and ethyl iodoacetate (1.35 g, 6.3 mmol) was added dropwise. After 2 h at −78 °C, the reaction mixture was quenched by addition of satd aqueous NH_4Cl and extracted with ether. The ether layers were dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 1.15 g of a crude oily product. Flash chromatography (silica gel, 4:1 hexanes−ethyl acetate) of the crude material afforded 940 mg (65%) of **10** as a colorless oil: ^{1}H NMR δ 4.18−4.05 (m, 2 H), 3.37−3.24 (m, 1 H), 3.31 (s, 3 H), 3.24 (s, 3 H), 2.77 (dd, J = 16.8, 8.5 Hz, 1 H), 2.43 (dq, J = 13.8, 3 Hz, 1 H), 2.20 (dd, J = 16.8, 5.3 Hz, 1 H), 2.12−2.00 (m, 1 H), 1.91 (qd, J = 12.5, 3.9 Hz, 1 H), 1.76−1.66 (m, 1 H), 1.48 (td, J = 13.8, 4.5 Hz, 1 H), 1.35 (qd, J = 13.1, 4.0 Hz, 1 H), 1.25 (t, J = 7.1 Hz, 3). Similarly, alkylation of 2,2-dimethoxycyclohexanone with isopropyl iodoacetate gave keto ester **11** (68%) as a crystalline solid: mp 50−51 °C; ^{1}H NMR δ 4.99 (heptet, J = 6.3 Hz, 1 H), 3.37−3.23 (m, 1 H), 3.31 (s, 3 H), 3.24 (s, 3 H), 2.73 (dd, J = 16.7, 8.7 Hz, 1 H), 2.43 (dq, J = 13.8, 3 Hz, 1 H), 2.18 (dd, J = 16.7, 5.3 Hz, 1 H), 2.11−2.00 (m, 1 H), 1.92 (qd, J = 13.4, 3.9 Hz, 1 H), 1.76−1.66 (m, 1 H), 1.48 (td, J = 13.7, 4.5 Hz, 1 H), 1.35 (qd, J = 13.0, 4.0 Hz, 1 H), 1.24 (d, J = 6.3 Hz, 3), 1.22 (d, J = 6.3 Hz, 3 H); ^{13}C NMR δ 207.1, 171.8, 101.1, 67.9, 49.9, 48.9, 44.7, 35.6, 34.5, 34.0, 21.8, 21.2. Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.59; H, 8.48.

Isopropyl *cis*-[3,3-Dimethoxy-2-[(3,4,5-trimethoxybenzyl)amino]cyclohexyl]acetate (14a) and Isopropyl *trans*-[3,3-Dimethoxy-2-[(3,4,5-trimethoxybenzyl)amino]cyclohexyl]acetate (15a). A. $NaBH_4$−Ethanol Method. Keto ester **11** (500 mg, 1.9 mmol) and 3,4,5-trimethoxybenzylamine (764 mg, 3.9 mmol) were dissolved in 1.11 g (3.9 mmol) of titanium isopropoxide at 23 °C under a nitrogen atmosphere. After 12 h $NaBH_4$ (148 mg, 3.9 mmol) in ca. 20 mL of abs EtOH was added, and the reaction mixture was allowed to stand overnight at 23 °C. The reaction mixture was diluted with 50 mL of CH_2Cl_2 and quenched with 10 mL of 2 M NH_4OH. The mixture was filtered through Celite and extracted with CH_2Cl_2, the combined organic layers were dried ($MgSO_4$) and filtered, and the solution was concentrated to give 1.21 g of a crude product mixture. ^{1}H NMR analysis of the crude material revealed **14a** and **15a** in a 4:1 ratio. **B. $NaBH_4$−2-Propanol Method.** Under conditions identical with those described above, keto ester **11** and 3,4,5-trimethoxybenzylamine were allowed to react in titanium isopropoxide. A slurry of $NaBH_4$ (148 mg, 3.9 mmol) in 10 mL of abs 2-propanol was added, and, after 8 h, the reaction mixture was worked up as above to give 1.10 g of a crude product mixture. ^{1}H NMR analysis of the crude material showed **14a** and **15a** in a 10:1 ratio. Flash chromatography (silica gel, 130:1 CH_2Cl_2−CH_3OH) afforded 490 mg (59%) of cis diastereomer **14a** as a colorless oil, 40 mg of a **14a/15a** mixture, and 5 mg (6%) of slightly impure trans diastereomer **15a**.

14a: ^{1}H NMR δ 6.64 (s, 1 H), 5.02 (heptet, J = 6.2 Hz, 1 H), 3.90 (d, J = 13 Hz, 1 H), 3.88 (s, 3 H), 3.83 (s, 3 H), 3.69 (d, J = 13 Hz, 1 H), 3.22 (s, 6 H), 2.92 (m, bandwidth = 7.3 Hz, 1 H), 2.52−2.47 (m, 1 H), 2.31−2.18 (m, 2 H), 1.80 (br d, J = 10 Hz, 1 H), 1.56−1.28 (m, 6 H), 1.229 (d, J = 6.2 Hz, 3 H), 1.224 (d, J = 6.2 Hz, 3 H); ^{13}C NMR δ 173.0, 153.5, 141.5, 105.5, 103.0, 67.8, 61.2, 59.7, 56.5, 55.9, 48.2, 47.9, 38.9, 28.0, 26.2, 22.3, 21.9; EI-MS m/z 439 (M, 2%), 424 (10%), 181 (100%). Anal. Calcd for $C_{23}H_{37}NO_7$ (0.5 mol H_2O): C, 61.59; H, 8.54; N, 3.12. Found: C, 61.37; H, 8.54; N, 3.29.

15a: ^{1}H NMR δ 6.62 (s, 2 H), 5.02 (heptet, J = 6.3 Hz, 1 H), 3.87 (s, 6 H), 3.83 (s, 3 H), 3.74 (d, J = 13 Hz, 1 H), 3.17 (s, 3 H), 3.05 (s, 3 H), 2.66−2.54 (m, 2 H), 2.45−2.35 (m, 2 H), 1.73−1.58 (m, 4 H), 1.50−1.39 (m, 1 H), 1.24 (d, J = 6.3 Hz, 3 H), 1.22 (d, J = 6.3 Hz, 3 H).

Isopropyl *cis*-[3,3-Dimethoxy-2-[(2,3,4-trimethoxybenzyl)amino)cyclohexyl]acetate (14b) and Isopropyl *trans*-[3,3-Dimethoxy-2-[(2,3,4-trimethoxybenzyl)amino]cyclohexyl]acetate (15b). Keto ester **11** (2.23 g, 8.6 mmol) and 2,3,4-trimethoxybenzylamine[23] (3.4 g, 17.2 mmol) were dissolved in 3.94 g (17.3 mmol) of titanium isopropoxide at 23 °C under a nitrogen atmosphere. The reaction mixture was allowed to stand at room temperature for 24 h, and a solution of 0.653 g (17.3 mmol) of $NaBH_4$ in 45 mL of 2-propanol was added. The reaction mixture was allowed to stand at room temperature for 12 h, diluted with 200 mL of CH_2Cl_2 and 40 mL of aqueous 2 M NH_4OH, and filtered through Celite. The filter cake was washed with additional CH_2Cl_2, and the organic layers were combined, dried ($MgSO_4$), and concentrated to give 5.1 g of crude material. ^{1}H NMR analysis of the crude mixture revealed a 13:1 mixture **14b** and **15b**, respectively. The crude product was purified by flash chromatography (silica gel, 98:2 CH_2Cl_2−CH_3OH) to give 2.40 g (64%) of **14b** and 0.14 g (4%) of **15b**, both as colorless oils.

14b: ^{1}H NMR δ 7.00 (d, J = 8.4 Hz, 1 H), 6.63 (d, J = 8.4 Hz, 1 H), 5.02 (heptet, J = 6.2 Hz, 1 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.84 (d, J = 12 Hz, 1 H), 3.62 (d, J = 12 Hz, 1 H), 3.20 (s, 3 H), 3.19 (s, 3 H), 2.88 (m, bandwidth = 7.6 Hz, 1 H), 2.50−2.38 (m, 1 H), 2.31−2.15 (m, 2 H), 1.80−1.73 (m, 1 H), 1.55−1.36 (m, 5 H), 1.236 (d, J = 6.2 Hz, 3 H), 1.233 (d, J = 6.2 Hz, 3 H); ^{13}C NMR δ 172.9, 153.0, 152.2, 142.3, 124.3, 110.1, 107.1, 102.6, 67.4, 61.2, 60.8, 59.2, 56.0, 50.4, 47.7, 47.5, 38.4, 36.1, 37.5, 25.7, 21.93, 21.91, 21.5; EI-MS m/z 439 (M, 12%), 424 (80%), 409 (10%), 408 (10%), 181 (100%), 166 (20%); LSIMS−HRMS Calcd for $C_{23}H_{38}NO_7$ (M + H): 440.2648. Found: 440.2645.

15b: ^{1}H NMR δ 6.98 (d, J = 8.4 Hz, 1 H), 6.61 (d, J = 8.4 Hz, 1 H), 5.04 (heptet, J = 6.3 Hz, 1 H), 3.93 (s 3 H), 3.92−3.80 (m, 3 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 3.65 (br d, J = 13 Hz, 1 H), 3.14 (s, 3 H), 2.99 (s, 3 H), 2.64−2.40 (m, 4 H), 2.00−1.84 (m, 1 H), 1.72−1.55 (m, 2 H), 1.48−1.35 (m, 2 H), 1.32−1.26 (m, 1 H), 1.254 (d, J = 6.3 Hz, 3 H), 1.242 (d, J = 6.3 Hz, 3 H); ^{13}C NMR δ 173.7, 153.0, 152.3, 142.2, 124.6, 106.9, 101.7, 77.3, 67.2, 61.0, 60.7, 59.5, 56.0, 47.7, 47.1, 46.9, 37.4, 32.9, 28.0, 24.8, 22.0, 21.9, 18.3; LSIMS−HRMS Calcd for $C_{23}H_{38}NO_7$ (M + H): 440.2648. Found: 440.2651.

(8,9,10-Trimethoxy-1,2,3,4-tetrahydrophenanthridin-4-yl)acetic Acid (16a). Amino ketal **14a** (500 mg, 1.1 mmol) was allowed to react in 10 mL of aqueous 6 M HCl at 23 °C under a nitrogen atmosphere for 12 h. The nitrogen atmosphere was replaced by air, and the reaction mixture was

(23) Gutsche, C. D.; Johnson, H. E. *J. Am. Chem. Soc.* **1954**, *76*, 1776.

stirred rapidly and heated to 100 °C for 1 h. The mixture was cooled to room temperature, brought to pH = 12 using aqueous NaOH, and extracted with 3 × 50 mL of CH_2Cl_2. These CH_2Cl_2 layers were discarded. The strongly basic aqueous layer was neutralized to pH = 7 using 4 M HCl and extracted with 3 × 50 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 271 mg of a crude product. Purification of the crude material by flash chromatography (silica gel, 95:5 CH_2Cl_2−CH_3OH) afforded 228 mg (60%) of **16a** as a white crystalline solid: mp 152−153 °C; ^{1}H NMR δ 8.79 (s, 1 H), 7.06 (s, 1 H), 4.03 (s, 3 H), 4.00 (s, 3 H), 3.94 (s, 3 H), 3.58 (br dt, J = 18.3, 4 Hz, 1 H), 3.5−3.37 (m, 1 H), 3.32−3.18 (m, 1 H), 2.85 (dd, J = 15.6, 10.0 Hz, 1 H), 2.68 (dd, J = 15.6, 1.2 Hz, 1 H), 2.21−2.12 (m, 1 H), 2.10−2.02 (m, 1 H), 1.81−1.54 (m, 2 H); ^{13}C NMR δ 176.9, 155.9, 152.2, 150.9, 149.5, 147.8, 130.0, 129.4, 127.1, 105.2, 63.5, 63.2, 58.2, 46.0, 39.4, 33.4, 30.1, 24.4; LSIMS *m/z* 332 (M + H, 100%), 314 (5%), 286 (5%), 272 (5%). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.11; H, 6.38; N, 4.38.

(7,8,9-Trimethoxy-1,2,3,4-tetrahydrophenanthridin-4-yl)acetic Acid (16b). Compound **14b** (1.00 g, 2.3 mmol) was allowed to react in 100 mL of aqueous 6 M HCl at 23 °C under a nitrogen atmosphere for 36 h. The reaction mixture was then exposed to air and heated to 110 °C for 1.5 h. The reaction mixture was cooled to room temperature, adjusted to pH = 7 with aqueous 3 M NaOH, and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give 600 mg of a crude residue. The crude material was purified using flash chromatography (silica gel, 95:5 CH_2Cl_2−CH_3OH) to afford 300 mg (40%) of **16b** as a white crystalline solid: mp 139−141 °C; ^{1}H NMR δ 9.16 (s, 1 H), 6.91 (s, 1 H), 4.13 (s, 3 H), 4.05 (s, 3 H), 3.98 (s, 3 H), 3.50−3.39 (m, 1 H), 3.16−3.05 (m, 1 H), 2.99−2.76 (m, 1 H), 2.84 (dd, J = 15, 10 Hz, 1 H), 2.67 (dd, J = 15, 1 Hz, 1 H), 2.22−2.10 (m, 2 H), 1.93−1.78 (m, 1 H), 1.67−1.55 (m, 1 H); ^{13}C NMR δ 174.9, 158.6, 149.7, 149.3, 141.8, 140.9, 134.3, 125.3, 118.2, 96.9, 61.9, 61.4, 56.2, 43.5, 36.7, 31.7, 25.4, 21.7; EI-MS *m/z* 331 (M, 35%), 287 (65%), 286 (100%), 272 (30%), 258 (10%), 256 (15%), 242 (20%), 228 (20%). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.15; H, 6.32; N, 4.36.

2-(8,9,10-Trimethoxy-1,2,3,4-tetrahydrophenanthridin-4-yl)ethanol (17a). To a solution of **16a** (200 mg, 0.6 mmol) in 10 mL of THF at 23 °C was added 0.32 mL (0.64 mmol) of neat BMS over 1 h. After 4 h the solvent was removed with a rotary evaporator, and the residue was dissolved in 15 mL of 2 M ethanolic HCl. The reaction mixture was allowed to reflux for 45 min and concentrated to a solid residue under vacuum. The residue was dissolved in ca. 5 mL of water, adjusted to pH = 12 with NaOH, and extracted with CH_2Cl_2 to give 190 mg of a crude product. The crude material was purified using flash chromatography (silica gel, 98:2 CH_2Cl_2−CH_3OH) to give 105 mg (55%) of **17a** and 64 mg (30%) of ester **18a** as colorless oils.

17a: ^{1}H NMR δ 8.79 (s, 1 H), 7.00 (s, 1 H), 4.00 (s, 3 H), 3.98 (s, 3 H), 3.92 (s, 3 H), 3.88−3.72 (m, 2 H), 3.39 (br t, J = 6 Hz, 2 H), 3.27−3.17 (m, 1 H), 2.09−1.64 (m, 6 H); ^{13}C NMR δ 153.3, 151.3, 150.5, 147.7, 146.7, 127.6, 126.2, 125.4, 103.3, 62.6, 61.7, 61.4, 56.3, 41.2, 39.7, 31.0, 28.4, 21.5. EI-MS *m/z* 317 (M, 7%), 286 (7%), 273 (100%), 258 (30%), 242 (12%), 228 (5%). An analytically pure derivative was obtained by recrystallization of the picrate salt of **17a** from abs ethanol: mp (picrate) 123−124 °C. Anal. Calcd for $C_{24}H_{26}N_4O_{11}$: C, 52.75; H, 4.80; N, 10.25. Found: C, 52.78; H, 4.78; N, 10.20.

18a: ^{1}H NMR δ 8.83 (s, 1 H), 7.00 (s, 1 H), 4.27−4.14 (m, 2H), 3.99 (s, 3 H), 3.97 (s, 3 H), 3.92 (s, 3 H), 3.61−3.49 (m, 1 H), 3.43−3.34 (m, 1 H), 3.18 (dd, J = 15.3, 4.3 Hz, 1 H), 2.52 (dd, J = 15.3, 9.8 Hz, 1 H), 2.14−1.67 (m, 4 H), 1.28 (t, J = 7.2 Hz, 3 H); ^{13}C NMR δ 173.4, 152.8, 150.2, 150.1, 148.4, 146.0, 126.7, 125.4, 125.2, 102.8, 61.3, 61.0, 60.2, 55.9, 40.7, 38.6, 27.88, 27.86, 20.7, 14.3; EI-MS *m/z* 359 (M, 64%), 344 (6%), 314 (11%), 298 (4%), 286 (100%); EI−HRMS Calcd for $C_{20}H_{25}NO_5$: 359.1733. Found: 359.1732.

2-(7,8,9-Trimethoxy-1,2,3,4-tetrahydrophenanthridin-4-yl)ethanol (17b). Reduction of 411 mg (1.24 mmol) of **16b** with BMS under conditions identical with those described above gave 220 mg (56%) of **17b** and 114 mg (26%) of ester **18b** as colorless oils.

17b: ^{1}H NMR δ 9.17 (s, 1 H), 6.89 (s, 1 H), 4.09 (s, 3 H), 4.01 (s, 3 H), 3.96 (s, 3 H), 3.86−3.75 (m, 2 H), 3.28−3.18 (m, 1 H), 2.99 (br t, J = 6 Hz, 2 H), 2.10−1.70 (m, 6 H); ^{13}C NMR δ 157.0, 152.0, 149.2, 143.3, 140.4, 133.7, 123.9, 118.0, 96.8, 62.2, 61.9, 61.3, 56.1, 40.5, 38.9, 31.1, 25.6, 20.6; LSIMS−HRMS Calcd for $C_{18}H_{24}NO_4$ (M + H): 318.1705. Found: 318.1700. Anal. Calcd for $C_{18}H_{23}NO_4$ (0.5 mol H_2O): C, 66.24; H, 7.41; N, 4.29. Found: 66.39; H, 7.24; N, 4.46.

18b: ^{1}H NMR δ 9.21 (s, 1 H), 6.89 (s, 1 H), 4.25−4.13 (m, 2 H), 4.09 (s, 3 H), 4.01 (s, 3 H), 3.96 (s, 3 H), 3.62−3.49 (m, 1 H), 3.20 (dd, J = 15.5, 4.4 Hz, 1 H), 2.98 (br t, J = 5.9 Hz, 1 H), 2.53 (dd, J = 15.5, 9.7 Hz, 1 H), 2.19−1.68 (m, 4 H), 1.28 (t, J = 7.1 Hz, 3 H); ^{13}C NMR δ 173.3, 156.7, 151.2, 149.2, 144.2, 140.4, 133.3, 118.1, 107.1, 96.9, 61.9, 61.3, 60.2, 56.0, 40.1, 37.9, 28.2, 25.5, 20.0, 14.3.

1a (Br$^-$). Method A.[14] Compound **17a** (58 mg, 0.18 mmol) was dissolved in 10 mL of benzene. To this solution was added 0.2 mL of PBr_3 in 2 mL of 1:1 ether−hexane, and the reaction mixture was allowed to reflux under a nitrogen atmosphere for 2.5 h. Methanol (2 mL) was added, and the reaction mixture was concentrated with a rotary evaporator. The crude residue was purified by flash chromatography (silica gel, 95:5 CH_2Cl_2−CH_3OH) to give 30 mg (44%) of **1a** (Br$^-$): ^{1}H NMR δ 10.45 (s, 1 H), 7.89 (s, 1 H), 5.34 (br dd, J = 13.3, 8.3 Hz, 1 H), 4.88 (ddd, J = 13.3, 13.3, 6.3 Hz, 1 H), 4.09 (s, 3 H), 4.07 (s, 3 H), 3.97 (s, 3 H), 3.73 (br dd, J = 18.7, 6.3 Hz, 1 H), 3.51−3.36 (m, 1 H), 3.27−3.12 (m, 1 H), 2.74 (br ddd, J = 12.5, 6.3, 6.3 Hz, 1 H), 2.44−2.26 (m, 2 H), 2.10 (dddd, J = 12.2, 12.2, 12.2, 8.3 Hz, 1 H), 2.02−1.82 (m, 1 H), 1.45 (dddd, J = 11.8, 11.8, 11.8, 2.8 Hz, 1 H); ^{13}C NMR δ 155.5, 150.6, 149.2, 144.1, 142.5, 129.0, 128.9, 125.4, 106.6, 61.7, 61.4, 57.3, 57.0, 41.0, 31.8, 26.6, 26.1, 22.9. See the Supporting Information for proton assignments and detailed results of a ^{1}H NMR solvent-effect study using three solvents. EI-MS *m/s* 300 (M, 2%), 286 (24%), 285 (100%),284 (19%), 271 (22%), 270 (92%), 267 (32%), 266 (52%), 256 (60%), 254 (40%), 242 (86%), 239 (21%), 239 (8%), 238 (48%), 228 (8%), 227 (16%), 226 (15%), 225 (8%), 212 (12%), 199 (33%), 183 (8%), 171 (30%), 170 (12%), 167 (9%), 154 (12%), 143 (15%), 142 (20%), 128 (8%), 127 (6%), 115 (14%), 102 (4%), 89 (4%), 77 (5%); LSIMS−HRMS Calcd for $C_{18}H_{22}NO_3$: 300.1600. Found: 300.1607. **Method B**. Compound **17a** (39 mg, 0.12 mmol) was dissolved in 10 mL of benzene. To this solution was added 33 mg (0.12 mmol) of PBr_3 in 1 mL of 1:1 ether−hexane, and the reaction mixture was allowed to reflux for 10 min. The reaction mixture was concentrated under vacuum, and the residue was purified by flash chromatography (silica gel, 94:6 CH_2Cl_2−CH_3OH) to afford 37 mg (76%) of **1a** (Br$^-$).

1a (Cl$^-$). To a solution of compound **17a** (120 mg, 0.38 mmol) in 10 mL of benzene was added 52 mg (0.38 mmol) of PCl_3 in 1 mL of benzene. The reaction mixture was allowed to reflux for 20 min under a nitrogen atmosphere, 2 mL of methanol was added, and the mixture was concentrated with a rotary evaporator. The crude residue was purified by flash chrmatography (silica gel, 92:8 CH_2Cl_2−CH_3OH) to give 127 mg (87%) of **1a** (Cl$^-$): darkens 92 °C; mp 92.5−93 °C; See the Supporting Information for proton assignments and detailed results of a ^{1}H NMR solvent-effect study using three solvents; EI-MS *m/z* 300 (M, 2%), 286 (20%), 285 (100%), 284 (20%), 271 (16%), 270 (86%), 267 (29%), 266 (46%), 256 (60%), 254 (36%), 242 (60%), 239 (16%), 238 (36%), 228 (4%), 227 (13%), 226 (10%), 225 (4%), 212 (9%), 199 (20%), 183 (6%), 171 (20%), 170 (10%), 167 (7%), 154 (6%), 143 (11%), 142 (10%), 128 (4%), 127 (6%), 115 (10%), 102 (2%), 89 (6%), 77 (6%).

1b (Br$^-$). To a solution of **17b** (14.0 mg, 0.044 mmol) in 4 mL of benzene was added 1 drop of PBr_3. The solution was allowed to reflux for 20 min under a nitrogen atmosphere, cooled to room temperature, diluted with 1 mL of methanol, and concentrated with a rotary evaporator. The crude product was purified by flash chromatography (silica gel, 96:4 CH_2Cl_2−CH_3OH) to give 10.0 mg (60%) of **1b** (Br$^-$): ^{1}H NMR δ 9.93 (s, 1 H), 6.94 (s, 1 H), 5.37 (br dd, J = 12.5, 8.3 Hz, 1 H), 5.07 (ddd, J = 12.5, 12.5, 6.3 Hz, 1 H), 4.27 (s, 3 H), 4.13 (s, 3 H),

3.98 (s, 3 H), 3.63−3.48 (m, 1 H), 3.23 (br dd, J = 17.8, 6.3 Hz, 1 H), 2.99−2.84 (m, 1 H), 2.79 (br ddd, J = 12.5, 6.3, 6.3 Hz, 1 H), 2.48−2.32 (m, 2 H), 2.18 (dddd, J = 12.5, 12.5, 12.5, 8.3 Hz, 1 H), 2.09−1.91 (m, 1 H), 1.47 (dddd, J = 12.6, 12.6, 12.6, 2.7 Hz, 1 H); ^{13}C NMR δ 162.3, 150.6, 146.7, 142.1, 138.6, 135.5, 127.0, 119.3, 97.0, 62.9, 61.6, 57.9, 57.1, 40.3, 32.0, 27.2, 23.4, 22.1. See the Supporting Information for proton assignments and details of a ^{1}H NMR solvent-effect study using three solvents. EI-MS *m*/*z* 300 (M, 2%), 286 (12%), 285 (52%), 284 (26%), 271 (20%), 270 (100%), 256 (16%), 254 (13%), 242 (28%), 239 (26%), 228 (4%), 226 (8%), 225 (7%), 214 (4%), 212 (4%), 199 (12%), 183 (3%), 171 (8%), 154 (3%), 143 (3%), 142 (4%), 115 (4%), 102 (2%), 83 (4%), 77 (5%); LSIMS−HRMS Calcd for $C_{18}H_{22}NO_3$: 300.1600. Found 300.1602.

1b (Cl$^-$). To a solution of **17b** (120 mg, 0.38 mmol) in 10 mL of benzene was added 52 mg (0.38 mmol) of PCl_3 in 1 mL of benzene. The reaction mixture was allowed to reflux for 20 min and worked up as described above, and the crude product was purified by flash chromatography (silica gel, 92:8 CH_2Cl_2−CH_3OH) to give 111 mg (87%) of **1b** (Cl$^-$) as a white, hygroscopic crystalline solid: turns red 105−120 °C prior to melting; mp 126−128 °C dec. See the Supporting Information for proton assignments and detailed results of a ^{1}H NMR solvent-effect study using three solvents. EI-MS *m*/*z* 300 (M, 2%), 286 (12%), 285 (55%), 284 (28%), 271 (19%), 270 (100%), 256 (20%), 254 (13%), 242 (43%), 239 (37%), 238 (4%), 228 (3%), 226 (10%), 225 (8%), 214 (5%), 212 (6%), 199 (24%), 183 (5%), 171 (15%), 170 (8%), 154 (4%), 143 (6%), 142 (6%), 115 (6%), 102 (2%), 83 (3%), 77 (4%); LSIMS−HRMS Calcd for $C_{18}H_{22}NO_3$: 300.1600. Found: 300.1603.

Supporting Information Available: Tabulated results of a ^{1}H NMR study of **1a** (Br$^-$), **1a** (Cl$^-$), **1b** (Br$^-$), and **1b** (Cl^{--}) using $CDCl_3$, 1:1 $CDCl_3$−CD_3OD, and CD_3OD solutions, and copies of representative ^{1}H and ^{13}C NMR spectra of **1a** (Br$^-$), **1b** (Cl$^-$), and **1b** (Br$^-$) in various solvents (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971641O