Bischler−Napieralski Cyclization−*N*/*C*-Alkylation Sequences for the Construction of Isoquinoline Alkaloids. Synthesis of Protoberberines and Benzo[*c*]phenanthridines *via* C-2′-Functionalized 3-Arylisoquinolines[1]

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Efficient synthetic routes to isoquinoline alkaloids of the protoberberine and benzo[*c*]phenanthridine classes are reported. The key transformations are derived from the intramolecular cyclization of C-2′-functionalized *N*-(1,2-diarylethyl)amides or enamides *via* 3-arylisoquinoline derivatives. Thus, under Bischler−Napieralski reaction conditions (PCl_5, nitrile as solvent, room temperature) *N*-(1,2-diarylethyl)amides **12** regioselectively yielded 2,3-disubstituted 13,14-dihydroprotoberberinium salts **20**, a scarcely studied oxidation state in this class of alkaloids. Subsequent reduction of the iminium bond gave the known coralydine (**21a**) and *O*-methylcorytenchirine (**21b**) and their 8-phenyl analogue **21c**. The one-pot preparation of these dihydroprotoberberinium salts **20** is shown to proceed with cleavage of the silyl ether and immediate halogenation of the resulting hydroxyl group, followed by cyclization of the obtained *N*-(1,2-diarylethyl)amide **18** to a 3,4-dihydroisoquinoline derivative **19** and subsequent intramolecular *in situ N*-alkylation of the latter imine. Ready access to planar 8,9-dialkoxylated benzo[*c*]phenanthridinium salts is also described. Condensation of ketoester **23** with benzylamine in the presence of titanium(IV) chloride, followed by acetylation, afforded a mixture of naphthylamide **24** and (*E*)-enamide **25**. Both enamides were efficiently cyclized by $POCl_3$. While the planar benzo[*c*]phenanthridinium salt **26** was directly produced from **24**, the (*E*)-enamide **25** gave the 3-arylisoquinolinium salt **27**, which was reduced and intramolecularly *C*-alkylated to yield the tetracyclic nucleus of these alkaloids.

Introduction

Benzo[*c*]phenanthridine and protoberberine alkaloids have represented continuing challenge for organic synthesis due to their widespread occurrence in nature and broad range of biological activities.[2,3] Protoberberines have been found to exert physiological activities of diverse nature (antimicrobial, antitumor, antineoplastic, etc....). Much interest has been focused on their effectiveness as antileukemic agents, and research in this area has revealed that the intercalation of coralyne and berberine with DNA may play a critical role in their antileukemic action.[4] Recently, benzo[*c*]phenanthridines have attracted considerable attention because nitidine and other 8,9-disubstituted planar benzophenanthridinium salts such as fagaronine have been shown to have antitumor activity in animal tumor models, an activity which could be related to inhibition of DNA topoisomerase.[5] Interestingly, 7,8-disubstituted benzophenanthridine alkaloids such as chelerythrine have not generally been found to have antitumor activity.[6] However, the toxicological problems associated with the most active members of these groups have led to development of new synthetic methods of these compounds, in order to study structure−activity relationships.[7]

Although a wide variety of methods have been utilized for the synthesis of these classes of natural products,[8] especially attractive are those in which the key step for the construction of the protoberberine or benzo[*c*]phenanthridine skeleton is the annelation of an isoquinoline derivative.[9] However, only a few examples have been reported on the preparation and synthetic applications of C-2′-functionalized 3-arylisoquinolines. Onda[10] and Hanaoka[11] have developed a biomimetic approach in which 2′-vinyl-3-aryl-1-isoquinolones are obtained by Hofmann degradation of protoberberinium salts and further cyclized to the benzo[*c*]phenanthridine skeleton photochemically or by derivatization of the vinyl group, respectively. Other approaches rely on the ammonolysis of benzopyrylium salts,[12] $S_{RN}1$ reaction of iodobenzamides

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(9) For a few representative examples, see the following. Protoberberine synthesis from (a) 1-benzylisoquinolines: Suau, R.; Valpuesta, M. *Tetrahedron* **1990**, *46*, 4421. (b) *N*-Phenethyl-1,4-dihydroisoquinolinium salts: Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 2115; *J. Org. Chem.* **1978**, *43*, 4183. (c) *N*-acylalkylidenetetrahydroisoquinolines: Naito, T.; Katsumi, K.; Toda, Y.; Ninumiya, I. *Heterocycles* **1983**, *20*, 775. Lenz, G. R. *J. Org. Chem.* **1977** *42*, 1117. (d) *N*-functionalized 3-arylisoquinolines: Dyke, S. F.; Brown, D. W.; Sainsbury, M.; Hardy, G. *Tetrahedron* **1971**, *27*, 3495. Benzo[*c*]phenanthridine synthesis from (e) 4-phenylacetylisoquinolones: Onda, M.; Harigaya, Y.; Suzuki, T. *Chem. Pharm. Bull.* **1977**, *23B*, 79. (f) C-4-functionalized isoquinolines: Sainsbury, M.; Dyke, S. F.; Moon, B. J. *J. Chem. Soc., Chem. Commun.* **1970**, 1797. (g) C-4-functionalized isoquinolones: Cushman, M; Abbaspour, A.; Gupta, Y. P. *J. Am. Chem. Soc.* **1983**, *105*, 2873.

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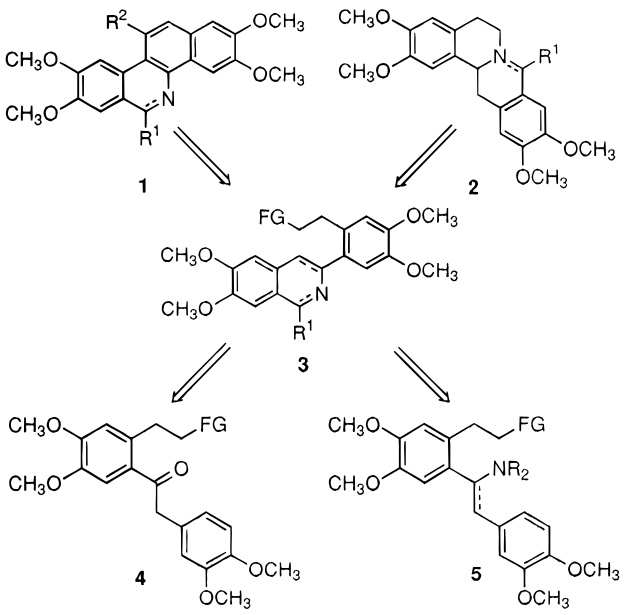
Scheme 1



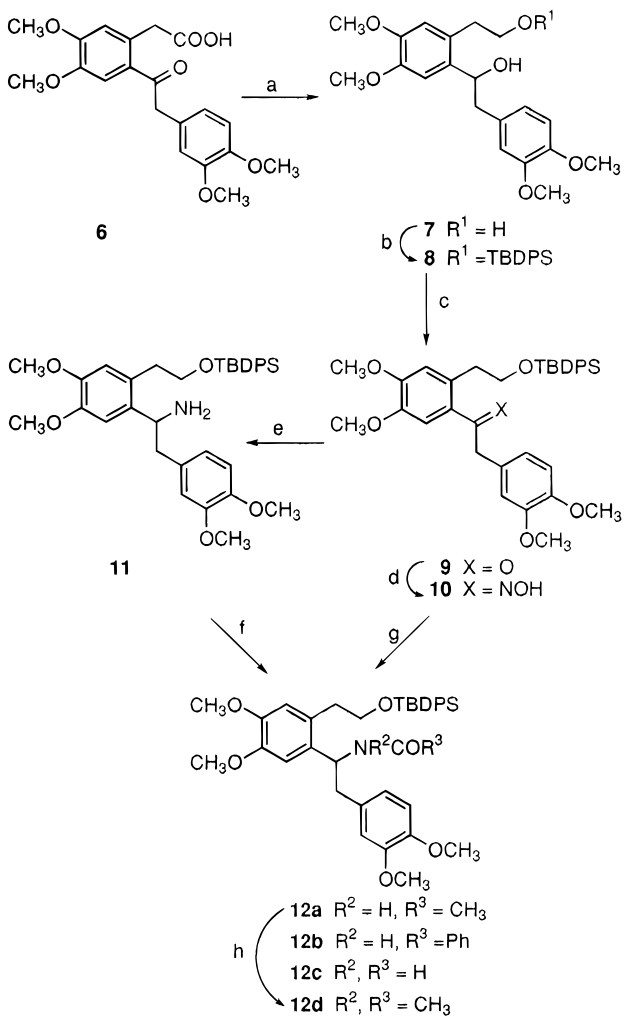
with 2-acetylhomoveratric acid enolates,[13] cycloaddition of lithiated toluamides and benzaldimines,[14] or cycloaddition of *N*-(2-ethenylbenzoyl)-*N*,2-dimethylbenzamide derivatives.[15]

In formulating a general strategy for the synthesis of benzo[*c*]phenanthridines **1** and protoberberines **2**, we recognized the potential of the Bischler−Napieralski cyclization reaction to generate these alkaloids *via* a common and versatile synthetic intermediate: a C-2′-functionalized 3-arylisoquinoline derivative (Scheme 1). On the basis of previous methodological studies, we anticipated that 13,14-dihydroprotoberberines (7,8-dehydroberbines), a scarcely studied oxidation stage in the chemistry of protoberberines, could arise from intramolecular *N*-alkylation of C-2′-functionalized 3-aryl-3,4-dihydroisoquinolines (imines), whereas benzo[*c*]phenanthridines could be obtained by *C*-alkylation or acylation of *N*-substituted 3-aryl-1,2-dihydroisoquinolines (enamines). Two different methods were studied for the synthesis of the key C-2′-functionalized 3-arylisoquinolines. The first relied on assembling the isoquinoline nucleus *via* Bischler−Napieralski cyclization of *N*-(1,2-diarylethyl)amides[16] or enamides[17] **5**. The second approach was the joining of the pertinent deoxybenzoin **4** and nitrile units *via* a Ritter-type reaction.[18] We now wish to present the findings from our investigations of the Bischler−Napieralski cyclization−*N*/*C*-alkylation sequences for the construction of protoberberine and benzo[*c*]phenanthridine skeletons. A retrosynthetic analysis for these alkaloids is depicted in Scheme 1.

Results and Discussion

Preparation of the requisite 1,2-diarylethylamines and amides is outlined in Scheme 2. Since LAH reduction of

Scheme 2[a]



[a] Reagents: (a) $NaBH_4$, $TiCl_4$, DME (81%); (b) *t*-$BuPh_2SiCl$, imidazole, DMF (94%); (c) PCC, CH_2Cl_2 (88%); (d) $NH_2OH{\cdot}HCl$, pyridine (89%, *anti*-**10a**/*syn*-**10b** 1.2/1.0); (e) $NaBH_4$, $TiCl_4$, DME (60%); (f) Et_3N, DMAP, R_3COCl, CH_2Cl_2, **12a** (85%) and **12b** (89%); **12c**: $HCONH_2$, (85%); (g) Bu_3P, PhSSPh; then $NaBH_3CN$, AcOH, then Ac_2O, **12a** (45%); (h) MeI, KOH, DMSO (60%).

the 2-[(3,4-dimethoxyphenyl)acetyl]-4,5-dimethoxyphenylacetic acid (**6**)[19] to the corresponding dialcohol **7** has been reported[20] to proceed in moderate yield (65%), other reduction agents were tried. Best results (81%) were obtained with $NaBH_4$−$TiCl_4$ in DME,[21] while $NaBH_4$−$AlCl_3$[22] gave only a low yield of **7** (40%). In the latter case, competitive lactone formation was an important side reaction, affording isochromanone **13** as a byproduct (31%) (Figure 1). Attempts for selective reduction of the carboxyl group *via* boranes[23] were unsuccessful: only small quantities of the dialcohol **7** were obtained by using BH_3−DMS (35%). Selective protection of the primary hydroxyl group with *tert*-butyldiphenylchlorosilane[24] (94%), followed by PCC oxidation,[25] afforded the deoxybenzoin **9** (88%). PDC[26] or Swern[27] oxidation gave lower yields

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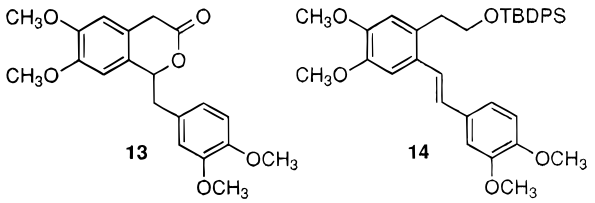
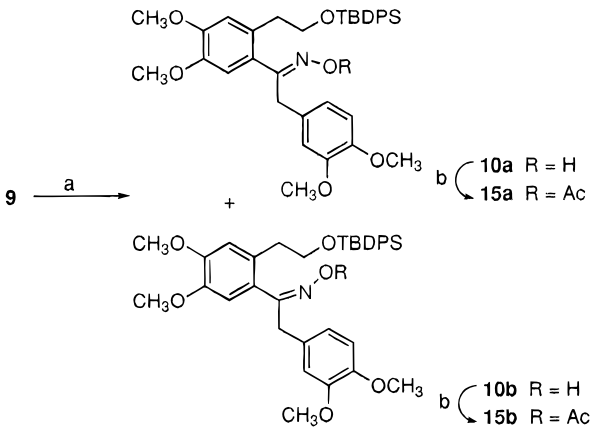


Figure 1.

Scheme 3[a]



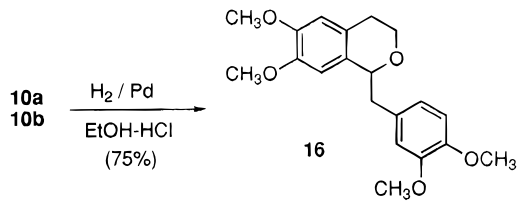
[a] Reagents: (a) $NH_2OH{\cdot}HCl$, pyridine (89%, **10a**:**10b** 1.2:1); (b) Ac_2O, py (96%, **15a**:**15b** 1.2:1).

(67 and 51%, respectively). During the latter reduction, a side product, the (*E*)-stilbene **14**, was also isolated (10%) (Figure 1).

Reductive amination of the ketone **9** was carried out *via* oximes. Thus, treatment of **9** with hydroxylamine hydrochloride afforded the oxime **10** as a mixture of the *anti* (**10a**) and *syn* (**10b**) isomers in a 1.2:1 *anti*/*syn* ratio. The similar size of both oxime carbon substituents could explain this product distribution. The pure diastereomers were obtained by careful column chromatography and unambiguously identified by NMR spectroscopy. The differences among the chemical shift values of the α-methylene protons and the α-carbons in the NMR spectra of both isomers were used to assign the stereochemistry. It has been observed that these protons experience a downfield shift for the isomer in which they are in a *cis* disposition to the hydroxyl group (*anti* isomer in this case) relative to the other isomer (*trans* disposition),[28] while the corresponding α-carbon is shifted upfield. We observed similar trends for our oximes: the α-methylene protons resonated at δ 3.67−3.74 and 3.84 ppm for the *syn* (**10b**) and *anti* (**10a**) isomers, respectively (Scheme 3). In addition, a difference of around 6 ppm was observed in the α-carbon chemical shift values, which appeared at 42.41 (*syn*) and 36.19 (*anti*) ppm, respectively. Since the oxime esters can be reduced to amines under milder conditions than the oximes themselves,[23] the oxime acetates **15a** (*anti)* and **15b** (*syn*) were quantitatively prepared (Ac_2O, pyridine) (Scheme 3) and their stereochemistry assigned using the same criteria as described above for the oximes **10**.

Several procedures for the reduction of the oximes **10** and their acetates **15** to the corresponding amine **11** were examined. Reduction of **15a** with BH_3−THF in diglyme at 110 °C[29] resulted in isomerization of the starting material to a mixture of oxime acetates **15a** and **15b**

Scheme 4



(1.2:1 ratio). Since hydrogenation in the presence of Pd/charcoal in EtOH/HCl has been shown to be a mild high-yielding procedure for the reduction of oximes,[30] this method was applied to the oximes **10**. However, the isochroman **16** was obtained in high yield (75%) instead of the desired amine (Scheme 4). Formation of this cyclic ether **16** could be explained by hydrolysis of the oxime moiety, followed by reduction of the resulting ketone, and subsequent intramolecular cyclization of the obtained dialcohol. Attempts to perform the catalytic hydrogenation under neutral conditions[31] were unsuccessful: starting material was recovered even at high pressures of H_2 (30 atm). In view of the failure of oximes **10** to undergo catalytic hydrogenation, we next considered the reduction with hydrides, although it was anticipated that this might be problematic. For example, it has been reported that LAH reduction of benzyl ketone oximes yielded aziridines,[32] while the use of DIBALH promoted Beckman-type rearrangement.[33] In our case, after considerable optimization, we found that the oximes **10** could be reduced selectively with the pair $NaBH_4$−$TiCl_4$ to give the amine **11** in a moderate yield (60%). It is worth mentioning that attempts to convert the alcohol **8** to the amine **11** by activation and displacement of the secondary hydroxyl group failed. Thus, when **8** was treated with NaH/sulfamoyl chloride,[34] β-elimination was the main reaction and the stilbene **14** was obtained as the major product (83%). The alcohol-to-amine Mitsunobu reaction (PPh_3, DEAD, phthalimide)[35] gave a similar result.

Smooth reductive amidation of the ketone **9** was observed upon conversion to the oxime **10**, followed by reduction and acylation (Scheme 2). Thus, treatment of this oxime with Bu_3P−PhSSPh,[36] operating under strictly anhydrous conditions at room temperature, led to an intermediate imine. Subsequent reduction with $NaBH_3CN$ and acetic acid, followed by *in situ* acetylation of the so-obtained amine with Ac_2O, generated the acetamide **12a** in a moderate yield (45%). Alternatively, acylation of the amine **11** with acetyl and benzoyl chloride[37] afforded 85−90% isolated yields of **12a** and **12b**, respectively. Formylation of **11** was accomplished with $HCONH_2$ at 150 °C to give the formamide **12c** in good yield (85%). Methylation of acetamide **12a** (MeI, KOH, DMSO)[38] afforded the *N*-methyl derivative **12d**. It should be noted that, due to restricted rotation about the CO−N bond, the amides **12c** and **12d** were obtained as mixtures of the *cis* and *trans* rotamers in a 2.5:1 ratio. Their ratio

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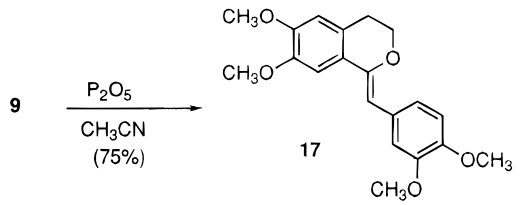
Scheme 5



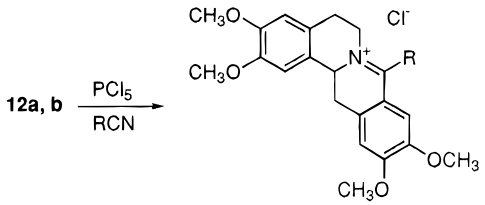
and stereochemistry were established by NMR.[39] Thus, though in the ^{1}H NMR spectrum of formamide **12c** most of the signals for both rotamers were overlapped, separate ^{13}C NMR resonances could be observed for both rotamers. For instance, the carbonyl carbon signal appears at higher field for the *cis* rotamer (160.18 ppm) than for the *trans* isomer (164.20 ppm). The *cis*/*trans* rotamers of the *N*-methylacetamide **12d** could be easily detected by both ^{1}H and ^{13}C NMR.[40] In this case, for example, the methinic proton signal is shifted downfield in the *cis* isomer (6.18 ppm) relative to the *trans* isomer (5.08 ppm). Acetamide **12a** and benzamide **12b** were obtained as single rotamers, presumably the more stable *cis* isomer.[40]

Protoberberine Synthesis. With amine **11** and amides **12** in hand, we investigated the synthesis of the target protoberberine derivatives. We have recently reported[41] the preparation of several C-2′-functionalized 3-aryl-1,2,3,4-tetrahydroisoquinolines **3** (Scheme 1) by $TiCl_4$-induced cyclization of bis(methoxymethyl)amines under mild conditions ($TiCl_4$, −78 °C). However, attempts to obtain the tetrahydroprotoberberine skeleton *via* intramolecular *N*-alkylation reactions of these tetrahydroisoquinoline derivatives were unsuccessful.[42] A direct and efficient approach to 3-arylisoquinolines is the condensation of deoxybenzoins with nitriles promoted by P_2O_5, a procedure based on a Ritter-type reaction, reported earlier from our laboratory.[18] However, treatment of the deoxybenzoin **9** with acetonitrile in the presence of P_2O_5 resulted in isolation of isochroman **17** as the major product (75%) (Scheme 5). Presumably, deprotection of the hydroxyl group occurred in the reaction medium, despite the reported stability of the TBDPS protecting group under acidic conditions.[43] Subsequent intramolecular nucleophilic attack of the resulting hydroxyl group to the carbonyl group, followed by dehydration, afforded the cyclic ether **17**.

Our next approach to the isoquinoline nucleus of the C-2′-functionalized 3-arylisoquinolines was the Bischler−Napieralski reaction of amides **12**. From our experience in the Bischler−Napieralski cyclization applied to the synthesis of 3-aryl-3,4-dihydroisoquinolines, we did not anticipate any difficulty in the analogous transformation here, since elimination of the amide group as a nitrile *via* a retro-Ritter reaction could be avoided by using PCl_5 as condensing agent and the "appropriate" nitrile as solvent.[16] Although it was expected that the silyl ether would be stable under the reaction conditions,[43] when amides **12a** and **12b** were treated with PCl_5 at room temperature for 14 h, the C-8-substituted 2,3,10,11-tetramethoxy-13,14-dihydroprotoberberinium chlorides **20a** (67%) and **20b** (54%) were obtained, respectively, in a one-pot procedure (Scheme 6). An explanation for the latter results involves initial cleavage of the silyl ether and halogenation, followed by Bischler−Napieralski cyclization of the resulting 1,2-diarylethylamide to a 3-aryl-3,4-dihydroisoquinoline derivative and subsequent *in situ* intramolecular *N*-alkylation of the imine. In order to establish that we were correct in assuming this pathway, modification of the reaction conditions was undertaken to isolate the proposed intermediates. Thus, we were able to obtain C-2′-chloroethyl-substituted amide **18** and 3-aryl-3,4-dihydroisoquinoline **19a**, after workup, from amide **12a** by varying the reaction time and PCl_5/amide ratio (Scheme 7). Nevertheless, under the same reaction conditions, the formamide **12c** afforded a mixture of products, from which only the 3,4-dihydroisoquinoline **19b** could be isolated (28%) (Scheme 8). We suspected that the failure of this reaction was due to the presence of the highly electrophilic unsubstituted C-1 carbon atom, which could suffer from nucleophilic attack and/or subsequent oxidation. Therefore, this procedure affords the quinolizidine nucleus of the protoberberine alkaloids in one pot, starting from *N*-(1,2-diarylethyl)amides.

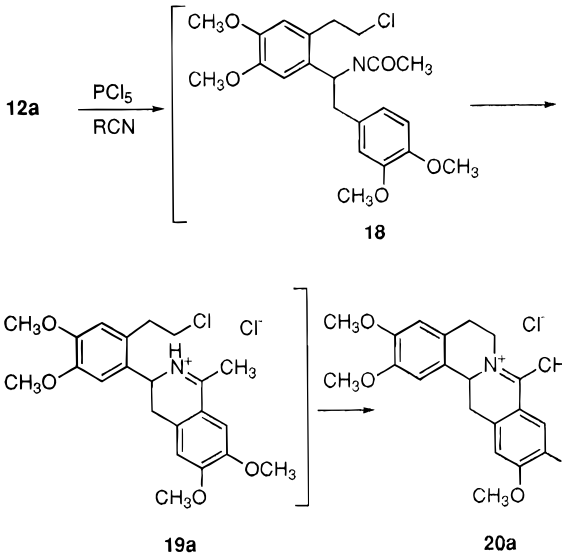
To further extend the synthetic utility of the dihydroprotoberberine synthesis, these compounds were transformed into berbines (tetrahydroprotoberberines) very

Scheme 6



20a R = CH_3 (67%)
20b R = Ph (54%)

Scheme 7



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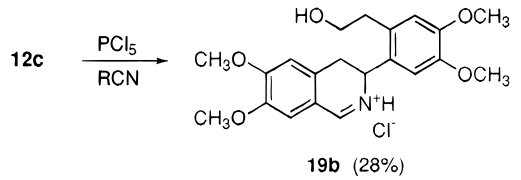
(42) Treatment of 3-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxytetrahydroisoquinoline (ref 41) with PCC in CH_2Cl_2, PCl_5 in acetonitrile, $SOCl_2$ in benzene, or PBr_3 in pyridine gave only complex mixtures of products. No formation of the desired tetrahydroprotoberberine could be detected.

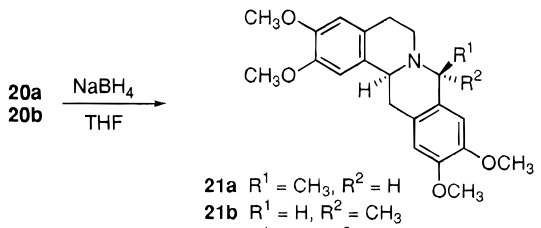
(43) The TBDPS group has been reported to be stable under the acidic conditions that may cause the removal of other silicon protecting groups (Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1981; pp 47). However, in order to test its stability under the reaction conditions that were going to be used, 2-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]benzene was prepared from 2-phenylethanol [*tert*-$BuPh_2SiCl$, imidazole, DMF, rt, 1.5 h (95%)] and used as a model compound. This silyl ether was stable when treated with P_2O_5, PCl_5, or $POCl_3$ under the conditions used later on.

Scheme 8



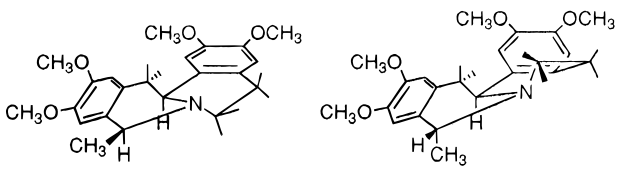
19b (28%)

Scheme 9



21a $R^1 = CH_3$, $R^2 = H$
21b $R^1 = H$, $R^2 = CH_3$
21c $R^1 = Ph$, $R^2 = H$

efficiently. Thus, reduction of the dehydroberbines **20a** and **20b** with $NaBH_4$ in THF provided tetrahydroprotoberberines **21a** and **21b** (as a 4:1 ratio of α/β C-8 diastereomers) and **21c** (as a single C-8 diastereomer), respectively (Scheme 9). As frequently happens,[44] in the reduction of imine **20a**, the amines **21a** and **21b** were isolated as very stable borane adducts. This is reflected in the presence of three bands in the IR spectrum in $CHCl_3$ (ν_{max} = 2300−2400 cm^{-1}, BH) and a downfield shift for most of the ^1H NMR signals relative to the free amine; i.e., the resonances of the H-14 proton appeared at δ 4.05 and δ 4.34−4.41 ppm for the adducts of **21a** and **21b**, respectively, and at δ 3.71 and 4.24 ppm for the free bases. Hydrolysis (3 M HCl, methanol, rt, overnight) of the borane−amine complexes gave the known natural alkaloids coralydine (**21a**) and *O*-methylcorytenchirine (**21b**), whose data are identical to those reported,[45] and their 8-phenyl-substituted analogue **21c**. The stereochemistry of coralydine and *O*-methylcorytenchirine has been previously determined by NMR[45] and X-ray crystallography.[46] Thus, coralydine (**21a**) presents a *trans*-fused B/C ring system in chairlike arrangements with the C-8 substituent in a *pseudo*equatorial disposition. This is associated with high-field chemical shifts for H-14 and H-8 in the ^1H NMR spectrum (3.71 and 3.72 ppm, respectively) and Bohlman bands in the IR spectrum. However, *O*-methylcorytenchirine (**21b**) was reported to adopt a *cis* form at the B/C ring junction with the C-8-Me in *pseudo*axial disposition, which is reflected in the absence of Bohlman bands and lower field shifts for H-14 and H-8 (4.24 and 4.10 ppm, respectively) (Figure 2). The most likely stereochemistry for the single diastereomer **21c**, obtained from the $NaBH_4$ reduction of **20b**, would be that resulting from hydride attack on the *re* face, leaving the phenyl group in a *pseudo*equatorial disposition. Thus, the ^1H NMR chemical shift of H-8 (4.49 ppm) and the presence of Bohlman bands in the IR spectrum (2740 cm^{-1}) were consistent with a *trans* B/C ring junction, with the C-8-Ph in a *pseudo*equatorial disposition, in accordance with the data reported for other 8-phenyltetrahydroprotoberberines.[47] Besides comparative criteria, the stereochemistry of **21c** was confirmed



21a *Coralydine* **21b** *O-Methylcorytenchirine*

Figure 2.

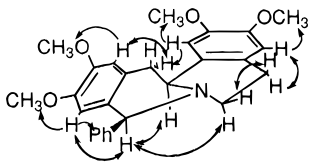


Figure 3. NOE enhancements observed for **21c**.

by nuclear Overhauser effect difference spectroscopy and $^1H-^1H$ decoupling experiments. Berbine **21c** demonstrated an H-8 hydrogen signal enhancement upon irradiation of H-14 methine hydrogen, and *vice versa*, which confirms that they are in a *cis* disposition. On the other hand, the NOE observed between axial H-6 and H-8 and the absence of NOE between H-13 and H-6 indicate a *trans* B/C ring junction[48] (Figure 3). The rest of the NOE experiments carried out are consistent with the proposed stereochemistry and have allowed us to unequivocally assign the chemical shifts of all protons.

Benzo[*c*]phenanthridine Synthesis. Our next concern was the preparation of the planar benzo[*c*]phenanthridinium salts. The key step for the cyclization to the benzo[*c*]phenanthridine skeleton would be the C-4 alkylation of C-2′ functionalized 1,2-dihydroisoquinolines (enamines). These compounds can be readily prepared by reduction of the iminium bond of *N*-alkylisoquinolinium salts by classical procedures.[49] However, because of the instability of these enamines, which easily undergo oxidation or disproportionation reactions, they are usually generated *in situ* and immediately alkylated. Several approaches to the synthesis of isoquinolinium salts were investigated. First, we reasoned that the Bischler−Napieralski reaction of *N*-substituted amides would afford *N*-protected 3,4-dihydroisoquinolines, thus preventing cyclization of the C-2′ side chain to the protoberberine skeleton. However, the reactions of the *N*-methylacetamide **12d** under the previously tested conditions (PCl_5 or $POCl_3$, CH_3CN) gave mixtures of products, and the desired dihydroisoquinoline could not even be detected (^1H NMR). Next, we tried the reduction−alkylation sequence on 3-arylisoquinolinium salts, previously prepared by oxidation of the corresponding C-2′-functionalized 3-aryl-1,2,3,4-tetrahydroisoquinolines.[50] Unfortunately, all attempts to perform the intramolecular cyclization on these substrates were unsuccessful: the intermediate 1,2-dihydroisoquinoline was detected by ^1H NMR, but no alkylation was observed.[51]

In view of these results, we planned a route to the benzo[*c*]phenanthridine skeleton on the basis of our earlier report of the synthesis 3-arylisoquinolinium salts

(44) Pelter, A.; Smith, K.: Boron-Hydrogen Compounds. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, 1979; Vol. 3; p 766.
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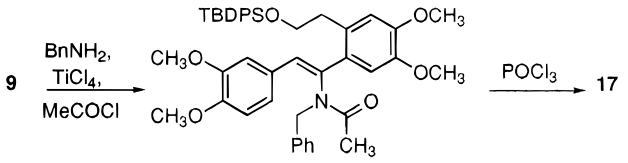
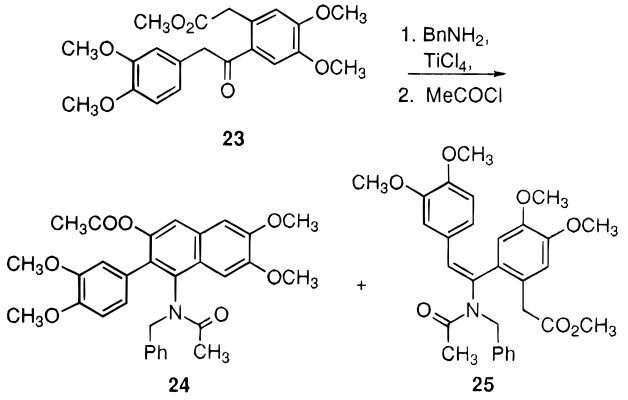
Scheme 10



Scheme 11

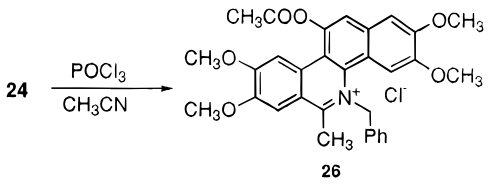


via enamides.[17] The overall strategy involved the synthesis and Bischler−Napieralski cyclization of appropriately functionalized *N*-1,2-diarylethylenamides. This may offer a rapid entry into the benzo[*c*]phenanthridine skeleton, and we were interested in trying this methodology to simplify the synthesis of planar 8,9-disubstituted benzophenanthridinium salts. Since treatment of the enamide **22**, derived from deoxybenzoin **9**, has been shown[17] to produce the isochroman **17**, instead of the expected isoquinoline (Scheme 10), we decided to test the above-mentioned strategy on the keto ester **23**.

The starting keto ester **23** was prepared by esterification of keto acid **6** with methyl iodide in acetone using potassium carbonate. Treatment of **23** with benzylamine in the presence of triethylamine and titanium tetrachloride in dimethoxyethane at −83 °C under strictly anhydrous conditions led to an intermediate imine, which was *in situ* acetylated with acetyl chloride to afford a 1:1.1 mixture of naphthylamide **24** and the (*E*)-enamide **25** (overall yield 60%). These products were separated by HPLC and the stereochemistry of **25** assigned on the basis of NOE difference experiments. Thus, the large NOE from the enamidic proton to the methyl protons of the acetyl group, and *vice versa*, is only compatible with an *E* configuration for this compound. Presumably, **24** is formed by intramolecular acylation of the initially formed *Z*-isomer of **25** to give the corresponding naphthol, which is *in situ* acetylated to afford **24** (Scheme 11).

Both products, the naphthylamide **24** and the (*E*)-enamide **25**, proved to be useful precursors of benzo[*c*]phenanthridines. Since **24** and **25** are *N*,*N*-disubstituted amides, we thought that cyclization must proceed through an intermediate chloriminium salt, a highly electrophilic species, because of the impossibility of formation of

Scheme 12



nitrilium salts, proposed intermediates in the Bischler−Napieralski cyclization.[52] Consequently, the presence of the *N*-benzyl group would avoid the retro-Ritter reaction. On the other hand, isomerization of the (*E*)-enamide to the synthetically useful (*Z*)-enamide could take place under the reaction conditions as we have observed for related systems.[17] Preliminary experiments which employed PCl_5 as condensing agent revealed that these enamides could not be cyclized under several different conditions. However, treatment of **24** with $POCl_3$ in acetonitrile under reflux provided the benzophenanthridinium salt **26** in high yield (80%) (Scheme 12). Although the use of naphthylamides in the synthesis of benzo[c]-phenanthridines is well precedented,[8a] their preparation usually involves lengthy synthetic sequences. For instance, the synthesis of sanguilutine of Ishii[53] requires the preparation of a naphthylamide from a 2-aryltetralone (four steps), which was obtained by the Robinson method[54] (five steps). Ishikawa[55] has recently reported a novel synthesis of macarpina whose last step is a Bischler−Napieralski cyclization of a naphthylformamide. The latter amide was prepared from a deoxybenzoin by a sequence that involved, as key steps, a Reformatsky reaction, intramolecular acylation, and aromatic nitrosation (11 steps). Furthermore, Bisagni and Janin have also reported[56] new access to benzophenanthridines through thermal cyclization of ethyl carbamates of 2-aryl-1-naphthylamines. The requisite urethanes for the key cyclization step were prepared from 2-aryltetralones. Our methodology considerably reduces the number of steps and therefore simplifies the synthesis of this type of alkaloid.

On the other hand, under the same cyclization conditions the (*E*)-enamide **25** was isomerized to the *Z* diastereomer (^{1}H NMR monitoring), which is readily cyclized to the 3-arylisoquinolinium salt **27**. Because of its instability, **27** was transformed into the dihydrobenzophenanthridine **28** without further purification. Thus, reduction of **27** with $NaBH_4$ in THF at room temperature, followed by intramolecular acylation (HCl/MeOH)[12] of the resulting 1,2-dihydroisoquinoline, led to **28** (overall yield 35%, from enamide **25**). Since this phenolic benzophenanthridine also decomposed rapidly, it was *O*-acetylated (Ac_2O/pyridine) to give quantitatively **29** (Scheme 13).

Fortunately, we discovered that treatment of the mixture of naphthylamide **24** and (*E*)-enamide **25** with $POCl_3$ in acetonitrile under reflux gave a mixture of the benzophenanthridine **26** and the 3-arylisoquinoline **27**, which was subjected to the above-described synthetic sequence to afford **29**: (a) reduction ($NaBH_4$, THF), (b) intramolecular acylation (HCl/MeOH), and (c) acylation of the phenolic hydroxyl group (Ac_2O, pyridine). This considerably improved the overall yield of the process (60% *vs* 35%).

(51) The 3-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-*N*-methylisoquinolinium chloride **31** was prepared by deprotection of 3-[2-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-4,5-dimethoxyphenyl]-6,7-dimethoxy-*N*-methylisoquinolinium iodide **30** with methanolic HCl (see the supporting information for data). Treatment of **31** with $NaBH_4$ afforded the corresponding 1,2-dihydroisoquinoline, which could be detected (^{1}H NMR) but was too labile to be fully characterized. Treatment of the crude product with PCC or PBr_3, under previously described conditions for similar substrates (ref 13), gave only mixtures of products.

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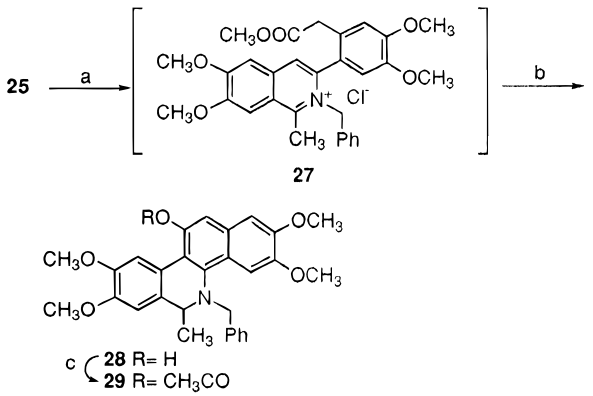
Scheme 13[a]



[a] Reagents: (a) $POCl_3$, CH_3CN; (b) (1) $NaBH_4$, THF, (2) 12 M HCl, MeOH; (c) $(AcO)_2O$, pyridine.

Conclusions

Convenient approaches to the target protoberberine and benzo[*c*]phenanthridine derivatives *via* Bischler−Napieralski cyclization−*N*/*C*-alkylation sequences have been developed. It has been demonstrated that reactions of C-2′-functionalized 1,2-diarylethylamides under Bischler−Napieralski cyclization conditions allow the one-pot preparation of 2,3-disubstituted 13,14-dihydroprotoberberines, which could not be synthesized by direct oxidation of the corresponding tetrahydroprotoberberines,[57] and represent additional examples of this novel oxidation stage in the chemistry of protoberberine alkaloids. In addition, the Bischler−Napieralski reaction of C-2′-functionalized 1,2-diarylethylenamides constitutes a very direct route into planar 8,9-dialkoxylated benzo[*c*]phenanthridinium salts in a reduced number of steps (three to four steps from keto acid **4**, one more from commercial homoveratric acid), with comparatively high overall yields.

Experimental Section

General Procedures. Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or $CHCl_3$ solution (oils). NMR spectra were recorded at 20−25 °C, running at 250 MHz for ^1H and 62.8 MHz for ^{13}C in $CDCl_3$ solutions, unless otherwise stated. $^1H-\{^1H\}$ NOE experiments were carried out in the difference mode by irradiation of all the lines of a multiplet.[58] Assignment of individual ^{13}C resonances are supported by DEPT experiments. Mass spectra were recorded by the Universities of La Laguna and Santiago de Compostela. TLC was carried out with 0.2 mm thick silica gel plates (Merck Kiesegel GF_{254}). Visualization was accomplished by UV light or by spraying with Dragendorff's reagent.[59] Flash column chromatography[60] on silica gel was performed with Merck Kiesegel 60 (230−400 mesh). HPLC was performed using a LiChrosorb Si60 (7 μm) column. All solvents used in the reactions were anhydrous and purified according to standard procedures.[61]

2-(3,4-Dimethoxyphenyl)-1-[2-(2-hydroxyethyl)-4,5-dimethoxyphenyl]ethanol (7). Method A. BH_3−DMS (0.3 mL of a 2 M solution in THF, 0.6 mmol) was added dropwise to a solution of the keto acid **6** (200 mg, 0.5 mmol) in THF (10 mL) at rt, under argon atmosphere. The reaction mixture was stirred at rt for 2 h. After this period, the reaction was quenched with MeOH (0.5 mL), the solvent was removed *in vacuo*, and the reaction mixture was dissolved in CH_2Cl_2 (20 mL). The solution was washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash column chromatography (silica gel, 9:1 hexane/ethyl acetate) afforded the alcohol **7** (70 mg, 35%) as a white solid which was recrystallized from ethyl acetate: mp 135−136 °C (lit.[20] mp 139−141 °C).

Method B. Keto acid **6** (500 mg, 1.3 mmol) was added in portions to a mixture of $NaBH_4$ (223 mg, 51.5 mmol) and $AlCl_3$ (193 mg, 1.5 mmol) in diglyme (10 mL) at 0 °C. The reaction mixture was stirred at rt for 14 h and then poured into an ice (5 g)−12 M HCl (1 mL) mixture and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 2:8 hexane/ethyl acetate) to afford two fractions:

Fraction 1: 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3-isochromanone (13): 146 mg, 31%; mp (MeOH) 174−175 °C (lit.[20] mp 173−175 °C).

Fraction 2: alcohol 7: 200 mg, 40%; mp (EtOAc) 135−136 °C (lit.[20] mp 139−141 °C).

Method C. Keto acid **6** (16.30 g, 43.5 mmol) was added in portions to a mixture of $NaBH_4$ (7.27 g, 0.2 mol) and $TiCl_4$ (4.7 mL, 47.8 mmol) in dry DME (300 mL) at 0 °C, under argon atmosphere. The reaction mixture was stirred at rt for 16 h, and then the reaction was quenched with water (150 mL) and the solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate to afford **7** (13.18 g, 81%) as a white solid: mp 135−136 °C (lit.[20] mp 139−141 °C).

1-[2-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)ethanol (8). To a stirred solution of the alcohol **7** (1.00 g, 2.7 mmol) and imidazole (413 mg, 6.1 mmol) in dry DMF (15 mL) was added dropwise *tert*-butyldiphenylchlorosilane (0.79 mL, 3.0 mmol) at rt under argon atmosphere. After 1.5 h, water (5 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 50% hexane/ethyl acetate) to afford **8** (1.55 g, 94%) as a white solid which was recrystallized from hexane: mp 89−90 °C; IR (KBr) 3600, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) 1.01 (s, 9H), 2.00 (broad s, 1H), 2.76 (t, J = 6.7 Hz, 2H), 2.86 (m, 2H), 3.77 (t, J = 6.7 Hz, 2H), 3.78 (s, 6H), 3.87 (s, 3H), 3.88 (s, 3H), 4.92 (t, J = 7.4 Hz, 1H), 6.54 (s, 1H), 6.59 (d, J = 1.9 Hz, 1H), 6.66 (dd, J = 8.1, 1.9 Hz, 1H), 6.76 (d, J = 8.1 Hz), 6.94 (s, 1H), 7.25−7.60 (m, 10H); ^{13}C NMR ($CDCl_3$) 19.11, 26.73, 34.88, 44.77, 55.62, 55.66, 55.78, 55.84, 65.00, 71.37, 109.02, 111.04, 112.67, 113.06, 121.34, 127.52, 127.94, 129.54, 130.76, 133.28, 133.35, 134.19, 135.43, 135.45, 147.54, 147.77, 148.56; MS (EI) *m*/*z* (rel intensity) 582 (29, $M^+ - 18$), 449 (24), 199 (59), 194 (28), 193 (100), 165 (20), 152 (65), 151 (51). Anal. Calcd for $C_{36}H_{44}O_6Si$: C, 71.96; H, 7.39. Found: C, 71.98; H, 7.44.

2-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-4,5-dimethoxyphenyl 3,4-Dimethoxybenzyl Ketone (9). Method A. A solution of DMSO (0.26 mL, 3.8 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a stirred solution of oxalyl chloride (0.14 mL, 1.8 mmol) in CH_2Cl_2 (5 mL) at −83 °C under argon atmosphere. After 10 min, a solution of the alcohol **8** (984 mg, 1.6 mmol) in CH_2Cl_2 (4 mL) was added, and the reaction mixture was stirred at −83 °C for 20 min. Triethylamine (1.1 mL, 8.2 mmol) was added, and the resulting solution was allowed to warm to rt (1 h). Water (12 mL) was added, the mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were washed with HCl (5 mL, 1% aqueous), water (5 mL), Na_2CO_3 (5 mL, 5% aqueous), and water (5 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 7:3 hexane/ethyl acetate) to afford two fractions:

Fraction 1: (*E*)-1-[2-[2-[(*tert*-butyldiphenylsilyl)oxy]-ethyl]-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)-ethene (14): 95 mg, 10%; colorless oil; IR ($CHCl_3$) 1610, 1520

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cm^{-1}; ^1H NMR ($CDCl_3$) 1.01 (s, 9H), 2.98 (t, J = 6.7 Hz, 2H), 3.81 (s, 3H), 3.85 (t, J = 6.7 Hz, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 6.61 (s, 1H), 6.78 (d, J = 16.0 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.99−7.07 (m, 2H), 7.07 (s, 1H), 7.18 (d, J = 16.0 Hz, 1H), 7.23−7.58 (m, 10H); ^{13}C NMR ($CDCl_3$) 19.07, 26.76, 35.97, 55.73, 55.79, 55.89, 64.76, 108.37, 109.15, 111.25, 113.46, 119.26, 124.45, 127.50, 128.30, 129.45, 129.05, 129.48, 130.98, 133.59, 135.46, 147.60, 148.35, 148.61, 149.00; MS (EI)-*m/z* (rel intensity) 582 (M^+, 71), 525 (29), 477 (81), 199 (49), 151 (85), 135 (100), 43 (81). Anal. Calcd for $C_{36}H_{42}O_5Si$: C, 74.19; H, 7.27. Found: C, 74.35; H, 7.15.

Fraction 2: ketone 9: 500 mg, 51%; colorless oil; IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) 1.00 (s, 9H), 3.08 (t, J = 6.1 Hz, 2H), 3.77 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H)*, 3.87 (s, 3H)*, 3.83−3.87 (m, 2H)*, 4.04 (s, 2H), 6.67−6.79 (m, 4H), 7.24−7.37 (m, 7H), 7.50−7.54 (m, 4H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 19.18, 26.87, 37.27, 44.91, 55.76, 55.84, 56.13, 64.87, 111.27, 112.32, 112.74, 115.47, 121.45, 127.50, 129.11, 129.43, 133.86, 135.14, 135.53, 146.46, 147.91, 148.98, 151.07, 199.43; MS (EI) *m/z* (rel intensity) 598 (M^+, <1), 541 (35), 447 (29), 199 (58), 197 (41), 151 (83), 135 (100). Anal. Calcd for $C_{36}H_{42}O_6Si$: C, 72.21; H, 7.07; Found: C, 72.30; H, 6.86.

Method B. A solution of the alcohol **8** (600 mg, 1 mmol) in CH_2Cl_2 (8 mL) was added to a suspension of PCC (323 mg, 1.5 mmol) in CH_2Cl_2 (2 mL), and the reaction mixture was stirred at rt for 2 h. The resulting solution was diluted with Et_2O and filtered through a short pad of silica gel. The filtrate was evaporated to dryness *in vacuo*, and the residue was purified by flash column chromatography (silica gel, 7:3 hexane/ethyl acetate) to afford the ketone **9** (526 mg, 88%) as a colorless oil, identical with a sample prepared as in method A.

Method C. According to the procedure described in method B, alcohol **8** (210 mg, 0.4 mmol) was treated with PDC (129 mg, 0.4 mmol) for 16 h. Workup and column chromatography afforded the ketone **9** (176 mg, 67%) as a colorless oil, identical with a sample prepared as in method A.

***anti- and syn*-α-(3,4-Dimethoxybenzyl)-2-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-4,5-dimethoxyphenyl 3,4-dimethoxybenzaldehyde Oxime (10a) and (10b).** A solution of the ketone **9** (598 mg, 1 mmol) and hydroxylamine hydrochloride (417 mg, 6 mmol) in dry pyridine (10 mL) was refluxed for 1.5 h. The reaction mixture was allowed to cool to rt and evaporated to dryness *in vacuo*, and the residue was partitioned between water (15 mL) and CH_2Cl_2 (40 mL). The organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography (silica gel, 6:4 hexane/ethyl acetate) gave the oxime **10** in 89% overall yield (545 mg) as a separable *anti/ syn* 1.2:1 mixture of diastereomers. ***anti*-Oxime 10a**: white solid; mp 129−131 °C (MeOH); IR (KBr) 1605, 3260 cm^{-1}; ^1H NMR ($CDCl_3$) 1.02 (s, 9H), 2.73 (t, J = 7.1 Hz, 2H), 3.64 (s, 3H), 3.69 (s, 3H), 3.73 (s, 3H)*, 3.77 (s, 3H)*, 3.73−3.77 (m, 2H)*, 3.84 (s, 2H), 6.41 (s, 1H), 6.61−6.62 (m, 4H), 7.23−7.38 (m, 6H), 7.58−7.62 (m, 4H), 7.84 (broad s, 1H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 19.14, 26.87, 35.32, 36.19, 55.70, 55.78, 65.42, 110.93, 111.75, 112.49, 113.32, 121.46, 127.57, 128.16, 128.52, 129.53, 129.90, 133.87, 135.58, 146.75, 147.53, 148.60, 148.89, 158.75; MS (EI) *m/z* (rel intensity) 613 (8, M^+), 556 (44), 388 (97), 199 (47), 151 (100). Anal. Calcd for $C_{36}H_{43}NO_6Si$: C, 70.44; H, 7.06; N, 2.28. Found: C, 70.39; H, 7.06; N, 2.45. ***syn*-Oxime 10b**: colorless oil; IR ($CHCl_3$) 1605, 3450 cm^{-1}; ^1H NMR ($CDCl_3$) 1.03 (s, 9H), 2.59 (t, J = 6.9 Hz, 2H), 3.60 (s, 3H), 3.71 (s, 3H)*, 3.72 (s, 3H)*, 3.77 (s, 3H), 3.67−3.74 (m, 4H)*, 6.09 (s, 1H), 6.56−6.69 (m, 4H), 7.03−7.39 (m, 6H), 7.57−7.61 (m, 4H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 19.14, 26.87, 36.06, 42.41, 55.67, 55.78, 55.81, 64.61, 109.81, 110.96, 112.48, 112.53, 121.71, 125.41, 127.61, 128.45, 128.76, 129.58, 133.76, 135.56, 146.91, 147.88, 148.62, 148.77, 158.90 ; MS (EI) *m/z* (rel intensity) 614 (MH^+), 199 (15), 152 (13), 151 (100), 107 (12), 91 (10), 77 (13). Anal. Calcd for $C_{36}H_{43}NO_6Si$: C, 70.44; H, 7.06; N, 2.28; Found: C, 70.63; H, 7.43; N, 2.58.

***anti*- and *syn*-*O*-Acetyl α-(3,4-Dimethoxybenzyl)2-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-4,5-dimethoxybenzaldehyde Oximes (15a) and (15b).** A solution of a 1.2:1 mixture of the oximes **10a** and **10b** (613 mg, 1mmol) and acetic anhydride (2.7 mL, 30 mmol) in dry pyridine (15 mL) was stirred at rt for 4 h. The reaction mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water (2 × 5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (silica gel, 7:3 hexane/ethyl acetate) afforded the oxime acetate **15** in 96% overall yield (628 mg) as a separable *anti/syn* 1.2:1 mixture of diastereomers. ***Anti* diastereomer 15a**: colorless oil; IR ($CHCl_3$) 1610, 1770 cm^{-1}; ^1H NMR ($CDCl_3$) 1.03 (s, 9H), 2.20 (s, 3H), 2.78 (t, J = 6.6 Hz, 2H), 3.68 (s, 3H), 3.71 (s, 3H), 3.75 (s, 3H), 3.80 (s, 3H)*, 3.77−3.82 (m, 2H)*, 3.92 (s, 2H), 6.46 (s, 1H), 6.55−6.71 (m, 4H), 7.30−7.43 (m, 6H), 7.56−7.64 (m, 4H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 19.13, 26.83, 36.07, 37.64, 55.71, 55.77, 55.85, 65.17, 111.09, 111.91, 112.34, 113.31, 121.48, 126.38, 126.85, 127.56, 129.54, 130.34, 133.70, 133.47, 146.82, 147.96, 148.80, 149.26, 165.52, 169.04; MS (EI) *m/z* (rel intensity) 596 (M^+ − 59, <1), 199 (48), 151 (100), 135 (33), 77 (17), 43 (13). Anal. Calcd for $C_{38}H_{45}NO_7Si$: C, 69.59; H, 6.92; N, 2.14. Found: C, 69.61; H, 6.87; N, 2.23. ***Syn* diastereomer 15b**: colorless oil; IR ($CHCl_3$) 1610, 1770 cm^{-1}; ^1H NMR ($CDCl_3$) 1.05 (s, 9H), 2.03 (s, 3H), 2.50 (t, J = 6.6 Hz, 2H), 3.61 (s, 3H), 3.75 (s, 3H)*, 3.78 (s, 3H)*, 3.80 (s, 3H)*, 3.75−3.82 (m, 4H)*, 6.41 (s, 1H), 6.53−6.72 (m, 4H), 7.31−7.41 (m, 6H), 7.56−7.62 (m, 4H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 19.89, 26.83, 36.07, 42.43, 55.63, 55.71, 55.78, 55.84, 65.35, 109.19, 110.56, 110.94, 112.51, 121.98, 125.09, 126.97, 127.64, 128.36, 129.64, 133.54, 135.48, 146.65, 148.11, 148.74, 148.85, 166.33, 168.48. Anal. Calcd for $C_{38}H_{45}NO_7Si$: C, 69.59; H, 6.92; N, 2.14. Found: C, 69.72; H, 6.74; N, 2.24.

1-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisochroman (16). To a solution of a 1.2:1 mixture of the oximes **10a** and **10b** (200 mg, 0.3 mmol) and 12 M HCl (2 mL) in methanol (8 mL) was added 10% Pd/C (40 mg). The resulting suspension was stirred under H_2 atmosphere (2 atm) at rt for 6 h. The catalyst was filtered off and the filtrate basified with NaOH (40% aqueous). The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried (Na_2SO_4), and evaporated to dryness i*n vacuo*. The residue was purified by flash chromatography (silica gel, 6:4 hexane/ethyl acetate) to afford **16** (69 mg, 75%) as a white solid which was recrystallized from methanol: mp 70−71 °C (lit.[20] mp 69−71 °C).

1-[2-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)ethylamine (11). A solution of a 1.2:1 mixture of the oximes **10a** and **10b** (613 mg, 1 mmol) in DME (3 mL) was added dropwise to a stirred mixture of $NaBH_4$ (160 mg, 4.2 mmol) and $TiCl_4$ (0.2 mL, 2.1 mmol) in dry DME (10 mL) at 0 °C, under argon atmosphere. The reaction mixture was stirred at rt for 14 h, water (10 mL) was added, and the mixture was basified with NaOH (40% aqueous). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (silica gel, 9.8:0.2 CH_2Cl_2/MeOH) afforded the amine **11** (359 mg, 60%) as a yellowish oil: IR ($CHCl_3$) 3360 cm^{-1}; ^1H NMR ($CDCl_3$) 0.95 (s, 9H), 1.29 (broad s, 2H), 2.52−2.80 (m, 4H), 3.66−3.71 (m, 2H)*, 3.68 (s, 3H)*, 3.70 (s, 3H)*, 3.77 (s, 3H), 3.82 (s, 3H), 4.16 (dd, J = 8.4, 4.9 Hz, 1H), 6.47 (s, 1H), 6.48 (d, J = 1.8 Hz, 1H), 6.57 (dd, J = 8.1, 1.8 Hz, 1H), 6.67 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 7.19−7.34 (m, 6H), 7.46−7.51 (m, 4H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 19.01, 26.73, 35.27, 45.37, 52.09, 55.56, 55.61, 55.73, 55.86, 65.00, 108.90, 111.06, 112.37, 113.17, 121.03, 127.48, 127.78, 129.47, 131.55, 133.42, 133.49, 135.43, 147.19, 147.41, 147.57, 148.51. Anal. Calcd for $C_{36}H_{45}NO_5Si$: C, 72.08; H, 7.56; N, 2.34. Found: C, 72.14; H, 7.50; N,.2.27.

***N*-[1-[2-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)ethyl]acetamide (12a). Method A.** Bu_3P (1.1 mL, 4.4 mmol) was added to a stirred solution of a 1.2:1 mixture of the oximes **10** (1 g, 1.6 mmol) and diphenyl disulfide (391 mg, 1.8 mmol) in THF (6 mL) at rt, under argon atmosphere. After 2 h, $NaBH_3CN$ (307 mg, 4.7 mmol) was added, followed by glacial AcOH (1.15

mL), and the reaction mixture was stirred for 2 h. After this period, Ac_2O (1.15 mL) was added, and the mixture was stirred for a further 62 h. The reaction was quenched with K_2CO_3 (5 mL, 5% aqueous) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*, and the residue was purified by flash chromatography (silica gel, 5:5 hexane/ethyl acetate) to obtain the acetamide **12a** (470 mg, 45%) as a colorless oil: IR ($CHCl_3$) 1650, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) 1.01 (s, 9H), 1.81 (s, 3H), 2.68−2.89 (m, 3H), 3.09 (dd, J = 13.4, 5.7 Hz, 1H), 3.67 (s, 3H)*, 3.73 (s, 3H), 3.77 (s, 3H), 3.83 (s, 3H), 3.62−3.71 (m, 2H)*, 5.22 (ddd, J = 8.0, 6.8, 5.7 Hz, 1H), 5.57 (d, J = 6.8 Hz, 1H), 6.43 (d, J = 1.8 Hz, 1H), 6.49 (dd, J = 8.1, 1.8 Hz, 1H), 6.57 (s, 1H), 6.62 (d, J = 8.1 Hz, 1H), 6.67 (s, 1H), 7.26−7.38 (m, 6H), 7.40−7.57 (m, 4H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 19.08, 23.27, 26.80, 35.41, 41.48, 50.90, 55.63, 55.67, 56.14, 64.52, 109.58, 110.82, 112.46, 113.91, 121.41, 127.57, 129.50, 129.93, 131.12, 133.69, 133.78, 135.52, 147.49, 147.80, 148.44, 168.90; MS (EI) *m/z* (rel intensity) 584 (M^+-57, 1), 490 (21), 431 (21), 311 (21), 240 (15), 199 (54), 197 (24), 192 (22), 151 (72), 135 (100), 120 (75), 107 (75), 107 (21), 91 (21), 77 (21), 75 (24), 57 (25), 43 (60). Anal. Calcd for $C_{38}H_{47}NO_6Si$: C, 71.10; H, 7.39; N, 2.18. Found: C, 71.20; H, 7.43; N, 2.16.

Method B. Acetyl chloride (0.15 mL, 2.1 mmol) was added dropwise to a solution of the amine **11** (1 g, 1.6 mmol), triethylamine (0.31 mL, 2.5 mmol), and DMAP (24 mg, 0.2 mmol) in CH_2Cl_2 (50 mL) at 0 °C, under argon atmosphere. The reaction mixture was stirred at rt for 4 h and then poured into ice (25 g) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (2 × 25 mL) and dried (Na_2SO_4), and the solvent was removed *in vacuo*. Flash chromatography (silica gel, ethyl acetate) yielded the acetamide **12a** (910 mg, 85%), identical with a sample as prepared in method A.

***N*-[1-[2-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)ethyl]benzamide (12b).** According to the procedure described in method B for the synthesis of **12a**, a solution of the amine **11** (680 mg, 1.1 mmol), triethylamine (0.22 mL, 1.7 mmol), and DMAP (24 mg, 0.2 mmol) in CH_2Cl_2 (50 mL) was treated with benzoyl chloride (0.16 mL, 1.4 mmol). After workup and column chromatography (silica gel, 6:4 hexane/ethyl acetate), benzamide **12b** was obtained (707 mg, 89%) as a white solid which was recrystallized from methanol: mp 129−130 °C; IR (KBr) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) 1.00 (s, 9H), 2.75−2.90 (m, 2H), 3.02 (dd, J = 13.6, 7.7 Hz, 1H), 3.19 (dd, J = 13.6, 5.8 Hz, 1H), 3.67 (s, 3H), 3.74 (s, 3H)*, 3.79 (s, 3H)*, 3.82 (s, 3H)*, 3.72−3.82 (m, 2H)*, 5.44 (ddd, J = 7.7, 6.8, 5.8 Hz, 1H), 6.32 (d, J = 6.8 Hz, 1H), 6.51 (d, J = 1.8 Hz , 1H), 6.56 (dd, J = 8.1, 1.8 Hz, 1H), 6.59 (s, 1H), 6.66 (d, J = 8.1 Hz, 1H), 6.73 (s, 1H), 7.26−7.39 (m, 8H), 7.43−7.62 (m, 7H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 18.77, 26.21, 35.17, 41.27, 50.86, 55.24, 55.34, 56.73, 64.28, 109.49, 111.67, 112.24, 113.67, 121.17, 126.51, 127.26, 128.09, 129.20, 129.57, 129.65, 130.98, 135.19, 131.09, 133.32, 133.42, 134.17, 147.21, 147.28, 147.52, 148.23, 166.22; MS (EI) *m/z* (rel intensity) 552 (M^+ − 151, 3), 199 (19), 151 (30), 135 (36), 105 (100), 77 (41). Anal. Calcd for $C_{43}H_{49}NO_6Si$: C, 73.36; H, 7.02; N, 1.99. Found: C, 73.42; H, 7.12; N, 2.04.

***N*-[1-[2-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-4,5-dimethoxyphenyl]-2-(3,4-dimethoxyphenyl)ethyl]formamide (12c).** A solution of the amine **11** (1 g, 1.6 mmol) in formamide (20 mL) was stirred at 150 °C for 15 min and then allowed to cool to rt. The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were washed with brine (2 × 20 mL), dried (Na_2SO_4), and concentrated to *in vacuo*. Flash chromatography (silica gel, 3:7 hexane/ethyl acetate) gave **12c** (890 mg, 85%) as a white solid which was recrystallized from hexane/ethyl acetate. The formamide **12c** was isolated as a mixture of *cis* and *trans* rotamers in a 2.5:1 ratio: mp 50−52 °C; IR (KBr) 1665, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) 1.00 (s, 9H, major rotamer), 1.04 (s, 9H, minor rotamer), 2.68−2.78 (m, 2H, both rotamers), 2.86−2.90 (m, 1H, both rotamers), 3.12 (dd, J = 13.5, 5.7 Hz, 1H, both rotamers), 3.66 (s, 3H, both rotamers), 3.73 (s, 3H, both rotamers), 3.76 (s, 3H, both rotamers), 3.79 (s, 3H, both rotamers)*, 3.79−3.89 (m, 2H, both rotamers)*, 5.19−5.27 (m, 1H, both rotamers), 6.08 (d, J = 6.4 Hz , 1H, both rotamers), 6.39−6.69 (m, 5H, both rotamers), 7.30−7.40 (m, 5H, both rotamers), 7.48−7.57 (m, 5H, both rotamers), 7.94 (s, 1H, both rotamers) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 19.05, 26.78 (both rotamers), 35.24 (major rotamer), 35.32 (minor rotamer), 41.57 (major rotamer), 43.74 (minor rotamer), 50.49 (major rotamer), 53.62 (minor rotamer), 55.59, 55.65, 55.70, 55.76, 55.93, 55.98, 64.65 (both rotamers), 109.03 (minor rotamer), 109.91 (major rotamer), 110.81 (major rotamer), 111.13 (minor rotamer), 112.44 (major rotamer), 112.65 (minor rotamer), 113.39 (minor rotamer), 113.72 (major rotamer), 121.38 (major rotamer), 121.54 (minor rotamer), 127.50, 127.55, 127.64, 129.51, 129.70 (both rotamers), 129.63 (major rotamer), 130.72 (major rotamer), 131.44 (minor rotamer), 133.26 (minor rotamer), 133.39 (minor rotamer), 133.43 (major rotamer), 135.45 (major rotamer), 147.35 (major rotamer), 147.53 (major rotamer), 147.85 (major rotamer), 147.91 (minor rotamer), 147.94 (minor rotamer), 148.40 (major rotamer), 148.68 (minor rotamer), 160.18 (major rotamer), 164.20 (minor rotamer); MS (EI) *m/z* (rel intensity) 583 (M^+-44, <1) 199 (53), 197 (31), 165 (23), 151 (60), 135 (100), 105 (80), 91 (13), 77 (13), 57 (13), 44 (3). Anal. Calcd for $C_{37}H_{45}NO_6Si$: C, 70.78; H, 7.23; N, 2.23. Found: C, 70.92; H, 7.18; N, 2.20.

***N*-Methyl-*N*-[1-[2-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-4,5-(dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)ethyl]-acetamide (12d).** A suspension of KOH (224 mg, 4 mmol) in DMSO (2 mL) was stirred at rt for 5 min. Acetamide **12a** (600 mg, 1 mmol) and MeI (2 mmol, 0.12 mL) were added, and the reaction mixture was stirred at rt until no further evolution of the starting material was observed (TLC monitoring, 16 h). Water (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (2 × 5 mL) and dried (Na_2SO_4), and the solvent was evaporated to dryness *in vacuo*. The residue was purified by flash chromatography (silica gel, 3:7 hexane/ethyl acetate) to obtain recovered starting material (155 mg, 26%) and the acetamide **12d** (370 mg, 60%) as a mixture of rotamers in a 2.5:1 major/minor ratio: IR ($CHCl_3$) 1740, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) 1.01 (s, 9H, both rotamers), 1.55 (s, 3H, minor rotamer), 1.83 (s, 3H, major rotamer), 2.58 (s, 3H, major rotamer), 2.66 (s, 3H, minor rotamer), 2.70−3.22 (m, 4H, both rotamers), 3.60−3.67 (m, 2H, both rotamers) , 3.73 (s, 3H, major rotamer), 3.74 (s, 3H, major rotamer), 3.75 (s, 3H, minor rotamer), 3.78 (s, 3H, both rotamers), 3.84 (s, 3H, minor rotamer), 3.89 (s, 3H, major rotamer), 3.92 (s, 3H, minor rotamer), 5.08 (dd, J = 10.3, 2.8 Hz, 1H, minor rotamer), 6.18 (t, J = 7.9 Hz, 1H, major rotamer), 6.52−6.58 (m, 4H, both rotamers), 6.94−6.97 (m, 1H, both rotamers), 7.29−7.43 (m, 6H, both rotamers), 7.51−7.54 (m, 4H, both rotamers); ^{13}C NMR ($CDCl_3$) 19.13 (both rotamers), 20.58 (minor rotamer), 22.21 (major rotamer), 26.82 (both rotamers), 27.92 (minor rotamer), 30.75 (major rotamer), 34.88, 36.88 (both rotamers), 37.42 (minor rotamer), 55.57, 55.67, (both rotamers), 55.77 (major rotamer), 56.84, 56.28 (both rotamers), 59.24 (minor rotamer), 64.55, (both rotamers) 110.80 (major rotamer), 111.04 (minor rotamer), 111.40 (minor rotamer), 111.85 (major rotamer), 112.09 (major rotamer), 112.36 (minor rotamer), 114.01 (minor *rotamer*), 114.67 (major rotamer), 120.99 (major rotamer), 121.37 (minor rotamer), 128.32 (major rotamer), 129.65 (major rotamer), 130.39 (major rotamer), 131.09 (minor rotamer), 132.64 (major rotamer), 133.34 (minor rotamer), 133.64 (minor rotamer), 133.71 (minor rotamer), 127.55, 129.46, 135.50 (both rotamers), 146.59 (major rotamer), 147.10 (minor rotamer), 147.39 (major rotamer), 147.84 (minor rotamer), 148.04 (minor rotamer), 148.33 (minor rotamer), 148.59, (major rotamer) 149.06 (major rotamer), 169.50 (major rotamer), 170.92 (minor rotamer). Anal. Calcd for $C_{39}H_{49}NO_6Si$: C, 71.41; H, 7.53; N, 2.14. Found: C, 71.32; H, 7.62; N, 2.16.

1-(3,4-Dimethoxybenzylidene)-6,7-dimethoxyisochroman (17). To a solution of the ketone **9** (100 mg, 0.17 mmol) in acetonitrile (10 mL) was added P_2O_5 (97 mg, 0.68 mmol) in portions at rt, under strictly anhydrous conditions. The reaction mixture was stirred at rt for 20 h, the solvent was removed *in vacuo*, and water (5 mL) was added. The resulting solution was basified with NaOH (10% aqueous) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were

washed with brine (2 × 5 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford **17** as a yellow solid which was recrystallized from methanol (36 mg, 75%): mp 169−170 °C (lit.[20] mp 173−175 °C).

2,3,10,11-Tetramethoxy-8-methyl-13,14-dihydroprotoberberinium Chloride (20a). One-Pot Procedure. To a solution of the acetamide **12a** (256 mg, 0.4 mmol) in dry CH_3CN (10 mL) was added PCl_5 (666 mg, 3.2 mmol) in portions (6 × 111 mg) at 0 °C during 30 min, operating under strictly anhydrous conditions. The reaction mixture was allowed to warm to rt and stirred for 14 h. After this period, the solvent was evaporated *in vacuo*, HCl (10 mL, 10% aqueous) was added, and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine (2 × 10 mL) and dried (Na_2SO_4), and the solvent was removed *in vacuo*. Column chromatography (silica gel, 9.95:0.05 to 9.7:0.3 CH_2Cl_2/MeOH) afforded the dihydroprotoberberinium chloride **20a** (108 mg, 67%) as a yellow solid, which was recrystallized from ethyl acetate: mp 212−213 °C dec; IR (KBr) 1610 cm^{-1}; ^1H NMR ($CDCl_3$) 3.00 (s, 3H), 3.07−3.24 (m, 4H), 3.39 (dd, J = 16.9, 4.5 Hz, 1H), 3.87 (s, 6H), 3.94 (s, 3H), 3.99 (s, 3H), 4.65 (broad d, J = 13.2 Hz, 1H), 5.15 (broad d, J = 14.8 Hz, 1H), 6.72 (s, 1H), 6.80 (s, 1H), 6.91 (s, 1H), 7.30 (s, 1H); ^{13}C NMR ($CDCl_3$) 19.72, 28.44, 35.48, 50.20, 55.99, 56.19, 56.38, 56.66, 59.41, 108.79, 110.18, 111.03, 112.55, 119.71, 123.62, 125.40, 133.88, 148.79, 148.91, 149.24, 157.01, 175.00; MS (EI) *m/z* (rel intensity) 368 (M^+, 3), 366 (24), 365 (100), 364 (71), 352 (20), 351 (12), 350 (47), 348 (13). Anal. Calcd for $C_{22}H_{26}ClNO_4$: C, 65.42; H, 6.48; N, 3.47. Found: C, 65.63; H, 6.90; N, 3.45.

Bischler−Napieralski Cyclization of Acetamide 22. Isolation of Intermediates: (a) *N*-[1-(2-Chloroethyl-4,5-dimethoxyphenyl)-2-(3,4-dimethoxyphenyl)ethyl]acetamide (18). To a solution of the acetamide **22** (189 mg, 0.29 mmol) in dry CH_3CN (7 mL) was added PCl_5 (242 mg, 1.16 mmol) in portions at 0 °C, operating under strictly anhydrous conditions. The reaction mixture was allowed to warm to rt and then stirred for 2.5 h. The solvent was evaporated *in vacuo*, the residue was dissolved in HCl (7 mL; 10% aqueous), and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The organic extracts were washed with brine (2 × 5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (silica gel, 3:7 hexane/ethyl acetate) afforded the chloroacetamide **18** (43 mg, 35%) as a colorless oil: IR ($CHCl_3$) 1660 cm^{-1}; ^1H NMR ($CDCl_3$) 1.72 (s, 3H), 2.87 (t, J = 7.0 Hz, 2H), 2.75−2.94 (m, 1H), 3.08−3.020 (m, 1H), 3.64 (t, J = 7.0 Hz, 2H), 3.68 (s, 3H)*, 3.78 (s, 6H), 3.84 (s, 3H)*, 3.77−3.84 (m, 1H), 4.32 (ddd, J = 13.0, 9.1, 5.4 Hz, 1H), 6.20 (s, 1H), 6.63−6.70 (m, 3H), 6.74 (s, 1H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 22.53, 33.19, 33.36, 43.45, 51.16, 55.83, 56.00, 111.17, 112.78, 120.78, 127.37, 131.38, 134.65, 147.52, 148.23, 148.78, 148.88, 171.10; MS (EI) *m/z* (rel intensity) 423 (M^+ + 2, <1), 421 (M^+ < 1), 259 (14), 257 (43), 221 (15), 192 (10), 178 (32), 164 (15), 161 (12), 151 (24), 107 (15), 91 (15), 77 (17), 65 (11), 43 (100). Anal. Calcd for $C_{22}H_{28}ClNO_5$: C, 62.68; H, 6.70; N, 3.32. Found: C, 62.59; H, 6.72; N, 3.30.

(b) 3-[2-(2-Chloroethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-1-methyl-3,4-dihydroisoquinolinium Hydrochloride (19a). To a solution of the acetamide **12a** (140 mg, 0.22 mmol) in dry CH_3CN (2 mL) was added PCl_5 (366 mg, 1.76 mmol) in portions at 0 °C, very slowly (time, 2 h; PCl_5/amide ratio, 2/1; time, 6 h; PCl_5/amide ratio, 4/1; time, 16 h; PCl_5/amide ratio, 8/1), operating under strictly anhydrous conditions. The solvent was evaporated *in vacuo*, the residue was dissolved in HCl (2 mL, 10% aqueous), and the solution was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were washed with brine (2 × 5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Column chromatography (silica gel, 9.5:0.5 CH_2Cl_2/MeOH) gave the isoquinolinium hydrochloride **19a** (52 mg, 54%): IR ($CHCl_3$) 1610 cm^{-1}; ^1H NMR ($CDCl_3$) 2.71 (s, 3H), 2.82−2.99 (m, 2H), 3.17−3.31 (m, 2H), 3.71−3.76 (m, 2H), 3.87 (s, 3H), 3.91 (s, 3H), 3.95 (s, 3H), 3.96 (s, 3H), 4.58−4.69 (m, 1H), 6.75 (s, 1H), 6.80 (s, 1H), 7.35 (s, 1H), 8.12 (s, 1H); ^{13}C NMR ($CDCl_3$) 21.18, 26.42, 33.19, 43.82, 56.23, 56.60, 56.69, 57.48, 109.80, 110.51, 111.24, 113.26, 119.81, 123.01, 133.16, 134.47, 148.93, 149.77, 150.47, 157.17, 177.68.

2,3,10,11-Tetramethoxy-8-phenyl-13,14-dihydroprotoberberinium Chloride (20b). According to the one-pot procedure described for **20a**, a solution of benzamide **12b** (288 mg, 0.4 mmol) in benzonitrile (10 mL) was treated with PCl_5 (666 mg, 3.2 mmol) and the resulting mixture stirred at rt for 14 h. After workup, the crude reaction mixture was purified by column chromatography (silica gel, 9.9:0.1 to 9.7:0.3 CH_2Cl_2/MeOH) to afford the protoberberinium chloride **20b** (100 mg, 54%) as a yellow solid, which was recrystallized from ethyl acetate: mp 234−235 °C dec; IR (KBr) 1610, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) 2.79−2.86 (m, 1H), 2.99−3.12 (m, 1H), 3.26 (dd, J = 17.6, 16.7 Hz, 1H), 3.59 (s, 3H), 3.67 (dd, J = 17.6, 4.7 Hz, 1H), 3.86 (s, 3H), 3.91 (s, 3H), 4.02 (s, 3H), 4.22−4.25 (m, 2H), 6.16 (dd, J = 16.7, 4.7 Hz, 1H), 6.38 (s, 1H), 6.64 (s, 1H), 7.03 (s, 1H), 7.07 (s, 1H), 7.27−7.31 (m, 1H), 7.56−7.75 (m, 3H), 8.3−8.41 (m, 1H); ^{13}C NMR ($CDCl_3$) 29.00, 36.09, 52.12, 56.02, 56.40, 56.89, 60.33, 109.56, 110.81, 116.01, 120.25, 124.25, 124.96, 125.40, 130.68, 128.48, 128.89, 132.08, 135.58, 148.47, 148.61, 148.92, 157.07, 174.04; MS (EI) *m/z* (rel intensity) 430 (M^+, 10), 429 (33), 353 (26), 352 (100), 336 (16), 214 (6), 176 (8), 77 (2). Anal. Calcd for $C_{27}H_{28}ClNO_4$: C, 69.65; H, 6.06; N, 3.01. Found: C, 69.36; H, 6.20; N, 3.11.

3-[2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-3,4-dihydroisoquinolinium Hydrochloride (19b). According to the one-pot procedure described for **20a**, a solution of formamide **12c** (300 mg, 0.4 mmol) in CH_2Cl_2 (10 mL) was treated with PCl_5 (666 mg, 3.2 mmol), and the resulting mixture was stirred at rt for 16 h. After workup, the crude reaction mixture was column chromatographed (silica gel, 9.9:0.1 to 9.7:0.3 CH_2Cl_2/MeOH) to afford the dihydroisoquinolinium chlorhydrate **19b** (45 mg, 28%): IR ($CHCl_3$) 1610, 3300 cm^{-1}; ^1H NMR ($CDCl_3$) 2.81−2.99 (m, 4H), 3.76 (s, 3H), 3.72−3.77 (m, 2H)*, 3.82 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.76 (ddd, J = 13.8, 6.9, 2.8 Hz, 1H), 6.65 (s, 1H), 6.71 (s, 1H), 6.80 (s, 1H), 6.82 (s, 1H), 8.21 (d, J = 2.8 Hz, 1H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 32.46, 35.87, 55.81, 56.09, 58.43, 63.82, 110.08, 111.10, 111.19, 113.31, 121.22, 129.31, 129.62, 134.09, 148.10, 148.82, 149.03, 153.20. Anal. Calcd for $C_{21}H_{25}NO_5$·HCl: C, 61.83; H, 6.42; N, 3.42. Found: C, 62.10; H, 6.45; N,.3.66.

2,3,10,11-Tetramethoxy-8-phenyl-7,8,13,14-tetrahydroprotoberberine (21c). $NaBH_4$ (8 mg, 0.21 mmol) was added to a suspension of dihydroprotoberberine **20b** (100 mg, 0.21 mmol) in THF (10 mL) at 0 °C. The mixture was stirred for 15 min, going into solution. Water (5 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were washed with brine (2 × 5 mL) and dried (Na_2SO_4), and the solvent was removed *in vacuo* to afford the protoberberine **21c** as a yellow solid, which was recrystallized from hexane/ethyl acetate (86 mg, 95%): mp 160−162 °C; IR ($CHCl_3$) 2740 cm^{-1} (*trans*-quinolizidine); ^1H NMR ($CDCl_3$) 2.29−2.38 (m, 1H), 2.43−2.50 (m, 1H), 2.81−2.87 (m, 1H), 2.94−3.05 (m, 1H), 2.99−3.10 (m, 1H), 3.28 (dd, J = 15.3, 2.8 Hz, 1H), 3.57 (s, 3H), 3.83−3.87 (m, 1H)*, 3.86 (s, 3H)*, 3.87 (s, 3H)*, 3.91 (s, 3H), 4.49 (s, 1H), 6.13 (s, 1H), 6.58 (s, 1H), 6.67 (s, 1H), 6.82 (s, 1H), 7.27−7.41 (m, 5H) (*: partially overlapped signals); ^{13}C NMR ($CDCl_3$) 29.42, 37.24, 48.44, 55.76, 55.81, 56.06, 59.27, 71.76, 108.74, 110.65, 111.20, 111.37, 126.52, 127.30, 127.45, 130.11, 130.62, 128.37, 129.36, 144.87, 147.13, 147.36; MS (EI) *m/z* (rel intensity) 431 (M^+, 39), 354 (17), 241 (25), 240 (100), 239 (45), 225 (10), 210 (11), 209 (63), 192 (15), 191 (10), 176 (9), 165 (13), 91 (14), 77 (11). Anal. Calcd for $C_{27}H_{29}NO_4$: C, 75.15; H, 6.77; N, 3.24. Found: C, 75.22; H, 6.92; N, 3.14.

Coralydine (21a) and *O*-Methylcorytenchirine (21b). According to the procedure described for **21c**, dihydroprotoberberine (**20a**) (100 mg, 0.25 mmol) was treated with $NaBH_4$ (10 mg, 0.25 mmol) in THF (10 mL). After workup, a mixture of coralydine (**21a**) and *O*-methylcorytenchirine (**21b**) was obtained quantitatively, in a 4:1 ratio, as boron complexes: IR ($CHCl_3$) 2300−2400 cm^{-1} (3 bands, BH); ^1H NMR ($CDCl_3$) 1.84 (d, J = 6.5 Hz, 3H, **21a**), 1.97 (d, J = 6.8 Hz, 3H, **21b**), 2.63−3.02 (m, 4H, **21b** and 4H, **21a**), 3.10−3.30 (m, 1H, **21b**), 3.31 (dd, J = 16.6, 3.5 Hz, 1H, **21a**), 3.54 (dd, J = 16.6, 11.5Hz, 1H, **21a**), 3.58−3.71(m, 1H, **21b**), 3.81 (s, 6H, **21b**), 3.84 (s, 6H, **21b**), 3.88 (s, 6H, **21a**), 3.9 (s, 6H, **21a**), 3.96−3.98 (m, 1H, **21a**), 4.05 (dd, J = 11.5, 3.5 Hz, 1H, **21a**), 4.34−4.41 (m,

1H, **21b**), 4.52 (q, J = 6.8 Hz, 1H, **21b**), 6.50 (s, 1H, **21b**), 6.54 (s, 1H, **21b**), 6.8 (s, 1H, **21b**), 6.54 (s, 1H, **21a**), 6.72 (s, 2H, **21a**), 6.74 (s, 1H, **21b**), 6.76 (s, 1H, **21a**); ^{13}C NMR ($CDCl_3$) (**21a**) 15.43, 25.80, 31.09, 55.87, 56.13, 56.19, 57.59, 66.00, 68.44, 108.23, 109.17, 110.81, 125.50, 125.90, 126.06, 127.67, 147.67, 147.90, 148.11.

Treatment of these complexes with methanolic 3 M HCl at rt for 16 h afforded coralydine (**21a**) and *O*-methylcorytenchirine (**21b**) quantitatively, whose physical data are identical to those previously reported.[45,46]

Methyl 2-[(3,4-Dimethoxyphenyl)acetyl)-4,5-dimethoxyphenylacetate (23). To a stirred mixture of the acid **6** (1.00 g, 2.7 mmol) and K_2CO_3 (1.51 g, 10.8 mmol) in acetone (50 mL) was added methyl iodide (1.7 mL, 27.0 mmol), and stirring was continued for 1 h at 40−50 °C. The mixture was filtered, the filtrate was evaporated to dryness, and the residue was chromatographed (silica gel, 6:4 hexane/ethyl acetate) to obtain **23** (953 mg, 91%) as a yellowish solid, which was recrystallized from MeOH: mp 130−132 °C; IR (KBr) 1680, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) 3.63 (s, 3H), 3.80 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 3.85 (s, 2H), 3.87 (s, 3H), 4.12 (s, 2H), 6.67 (s, 1H), 6.72 (broad s, 1H), 6.65−6.67 (m, 2H), 7.36 (s, 1H); ^{13}C NMR ($CDCl_3$) 40.01, 47.27, 51.77, 55.74, 55.79, 55.91, 56.03, 111.25, 112.30, 113.42, 115.29, 121.36, 127.43, 128.51, 129.63, 147.17, 147.88, 148.98, 151.61, 172.05, 198.98; MS (EI) *m*/*z* (rel intensity) 389 (MH^+, 42), 388 (M^+, 15), 357 (22), 237 (52), 209 (84), 179 (23), 151 (100). Anal. Calcd for $C_{21}H_{24}O_7$: C, 64.92; H, 6.23. Found: C, 64.65; H, 6.32.

***N*-[3-Acetoxy-2-(3,4-dimethoxyphenyl)-6,7-dimethoxynaphthyl]-*N*-benzylacetamide (24) and Methyl (*E*)-2-[1-(*N*-Benzylacetamido)-2-(3,4-dimethoxyphenyl)ethenyl]-4,5-dimethoxyphenylacetate (25).** $TiCl_4$ (1 mL of a 1 M solution in CH_2Cl_2, 1 mmol) was added dropwise to a solution of keto ester **23** (390 mg, 1 mmol), benzylamine (0.10 mL, 1 mmol), and triethylamine (0.42 mL, 3 mmol) in dry DME (7 mL) at −83 °C, under argon atmosphere. The mixture was allowed to warm to rt and stirred for 30 min. Acetyl chloride (0.21 mL, 3 mmol) and $TiCl_4$ (1 mL of a 1 M solution in CH_2Cl_2, 1 mmol) were added, and the resulting mixture was stirred at rt for 2 h. After this period, K_2CO_3 (5 mL; saturated aqueous) was added, and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was purified by flash column chromatography (silica gel, 4.5:5.5 hexane/ethyl acetate) to give a mixture of the naphthylamide **24** and the enamide **25** in a 1:1.1 ratio (315 mg, 60% overall). Analytical samples of both products could be obtained by HPLC (5:5 hexane/ethyl acetate). **24:** mp 186−188 °C; IR (KBr) 1655, 1770 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.99 (s, 3H), 2.09 (s, 3H), 3.58 (d, J = 14.5 Hz , 1H), 3.86 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 3.98 (s, 3H), 5.27 (d, J = 14.5 Hz, 1H), 6.78−6.83 (m, 2H), 6.92−6.99 (m, 3H), 7.08 (s, 1H), 7.14−7.23 (m, 5H); ^{13}C NMR ($CDCl_3$) 20.38, 22.81, 51.74, 55.63, 55.74, 55.79, 99.86, 106.19, 110.92, 112.56, 121.86, 122.31, 125.10, 126.10, 127.03, 128.07, 128.69, 128.81, 137.09, 137.16, 144.32, 148.48, 150.49, 150.20, 168.76, 170.51; MS(CI) *m*/*z* (rel intensity) 529 (M^+, 57), 488 (43), 446 (42), 445 (32), 444 (33), 396 (19), 395 (19), 355 (37), 354 (19), 323 (25), 322 (22), 91 (72), 57 (10), 43 (69). Anal. Calcd for $C_{31}H_{31}NO_7$: C, 70.29; H, 5.90; N, 2.65. Found: C, 70.06; H, 5.86; N, 2.71.

25: IR ($CHCl_3$) 1650, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.41 (s, 3H), 3.25 (broad s, 2H), 3.49 (s, 3H), 3.51 (s, 3H), 3.70 (s, 3H), 3.81 (s, 3H), 3.89 (s, 3H), 4.53 (broad s, 2H), 6.32 (s, 1H), 6.37 (s, 1H), 6.53-6.55 (m, 2H), 6.65 (d, J = 8.3, 1H), 6.81 (s, 1H), 7.18−7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) 22.54, 36.94, 48.44, 51.82, 55.31, 55.77, 55.97, 110.76, 111.08, 112.54, 113.52, 122.35, 126.36, 127.06, 127.59, 128.24, 129.67, 135.76, 137.80, 148.63, 149.55, 171.03, 171.70; MS(CI) *m*/*z* (rel intensity) 520 (MH^+, 100), 446 (4), 406 (10), 371 (4), 355 (4), 167 (33), 153 (13). Anal. Calcd for $C_{30}H_{33}NO_7$: C, 69.33; H, 6.40; N, 2.70. Found: C, 69.45; H, 6.36; N, 2.69.

11-Acetoxy-*N*-benzyl-6-methyl-2,3,8,9-tetramethoxybenzo[*c*]phenanthridinium Chloride (26). $POCl_3$ (0.23 mL, 3.42 mmol) was added to a solution of naphthylamide **24** in dry acetonitrile (10 mL), and the resulting solution was refluxed for 3 h. The solvent was removed *in vacuo*, HCl (10 mL; 10% aqueous) was added, and the solution was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (2 × 5 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was column chromatographed (silica gel, 9.9:0.1 to 9.5:0.5 CH_2Cl_2/MeOH) to obtain the benzo[*c*]phenanthridinium chloride **26** as a yellow solid, which was recrystallized from ethyl acetate/methanol (116 mg, 80%): mp >380 °C dec; IR (KBr) 1610, 1770 cm^{-1}; ^{1}H NMR ($CDCl_3$ + d_1-TFA) 2.71 (s, 3H), 3.31 (s, 3H), 4.04 (s, 3H), 4.10 (s, 3H), 4.14 (s, 3H), 4.27 (s, 3H), 6.27 (broad s, 2H), 7.16−7.18 (m, 3H), 7.25 (s, 1H), 7.43−7.46 (m, 3H), 7.80 (s, 1H), 8.33 (s, 1H), 8.73 (s, 1H); ^{13}C NMR ($CDCl_3$ + d_1-TFA) 19.51, 21.40, 56.15, 56.34, 56.43, 56.79, 57.25, 98.56, 106.13, 106.95, 109.15, 114.26, 121.16, 123.60, 125.18, 129.17, 130.00, 130.53, 130.97, 131.57, 142.46, 150.87, 152.77, 153.11, 158.02, 169.47; MS-(CI) *m*/*z* (rel intensity) 511(M^+ − 1, 86), 454 (21), 378 (47), 304 (6), 234 (6), 165 (9), 91 (100), 43 (60). Anal. Calcd for $C_{31}H_{30}ClNO_6$: C, 67.94; H, 5.52; N, 2.55. Found: C, 67.66; H, 5.50; N, 2.53.

11-Acetoxy-5-benzyl-2,3,8,9-tetramethoxy-6-methyl-5,6-dihydrobenzo[*c*]phenanthridine (29). (a) *N*-Benzyl-11-hydroxy-2,3,8,9-tetramethoxy-6-methylbenzo[*c*]phenanthridine (28). According to the procedure described for **26**, a solution of the enamide **25** (200 mg, 0.38 mmol) and $POCl_3$ (0.23 mL, 3.42 mmol) in dry acetonitrile (10 mL) was refluxed for 3 h. After workup, the crude reaction mixture, without further purification, was dried under high vacuum and dissolved in THF (10 mL). $NaBH_4$ (20 mg, 0.4 mmol) was added at 0 °C, and the solution was stirred for 45 min. After this period, HCl (2 mL, 50% methanolic) was added, and the resulting mixture was refluxed for 2 h. The reaction mixture was basified with NaOH (40% aqueous), extracted with CH_2Cl_2 (3 × 15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (silica gel, 5:5 hexane/ethyl acetate) to obtain the benzo[*c*]phenanthridine **28** (63 mg, 35%): IR ($CHCl_3$) 3500 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.17 (d, J = 6.5 Hz, 3H), 3.86 (s, 3H), 3.99 (s, 6H), 4.05 (s, 3H), 4.35 (q, J = 6.5 Hz, 1H), 5.01 (d, J = 15.6 Hz, 1H), 5.19 (d, J = 15.6 Hz, 1H), 5.30 (s, 1H), 6.40 (s, 1H), 7.28−7.33 (m, 5H), 7.46 (s, 1H), 7.64 (s, 1H), 8.1 (s, 1H).

(b) 28 turned out to be unstable so, in successive experiments, the crude reaction mixture described in (a), without further purification, was dissolved in pyridine (3 mL) and treated with Ac_2O (0.2 mL) at 60−70 °C for 1 h. Water (3 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed (silica gel, 6:4 hexane/ethyl acetate) to obtain the dihydrobenzo[*c*]phenanthridine **29** (68 mg, 35% overall from **25**): IR ($CHCl_3$) 1770 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.15 (d, J = 6.5 Hz, 3H), 2.40 (s, 3H), 3.88 (s, 3H), 3.96 (s, 3H), 3.96 (s, 6H), 4.21 (q, J = 6.5 Hz, 1H), 4.35 (d, J = 15.0 Hz, 1H), 4.74 (d, J = 15.0 Hz, 1H), 6.58 (s, 1H), 6.81 (s, 1H), 6.90 (s, 1H), 6.99 (s, 1H), 7.29−7.41 (m, 5H), 7.78 (s, 1H); ^{13}C NMR ($CDCl_3$) 16.73, 21.29, 53.68, 55.82, 56.04, 57.58, 100.30, 105.50, 106.80, 108.23, 110.11, 127.13, 127.56, 128.60, 116.39, 116.95, 121.07, 130.23, 134.75, 137.97, 141.74, 142.10, 147.68, 147.90, 148.43, 150.17, 168.57; MS(CI) *m*/*z* (rel intensity) 513 (M^+, 12), 498 (47), 456 (18), 365 (42), 364 (24), 91 (100), 65 (12), 57 (18), 43 (91), 32 (37). Anal. Calcd for $C_{31}H_{31}NO_6$: C, 72.49; H, 6.09; N, 2.73. Found: C, 72.36; H, 6.19; N, 2.88.

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Supporting Information Available: Copies of ^{1}H NMR spectra for new compounds described, assigned NMR data for protoberberine **20c**, and experimental procedure for isoquinoline **31** (26 pages). This material is contained in libraries on microfiche, immediately follows this article in microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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