Chiral Amino Alcohols As Intermediates in the Stereocontrolled Synthesis of 1,3-Disubstituted Tetrahydroisoquinolines and Protoberberines

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Received July 8, 1998

An efficient stereocontrolled synthetic approach to (3*S*)-3-aryltetrahydroisoquinoline **3d** and (1*S*,3*S*)-3-aryl-1-methyltetrahydroisoquinolines **3a**−**c** by a Pictet−Spengler heterocyclization reaction of optically active (95% ee) (*S*)-1,2-diarylethylamines **2a**−**c** is presented. An alternative route toward obtaining the epimeric derivative of **3a**, tetrahydroisoquinoline (1*R*,3*S*)-**6**, was also achieved by a stereocontrolled ring opening process carried out on the oxazolotetrahydroisoquinoline **9**. Tetrahydroisoquinoline **8** was employed for the stereoselective preparation of (5*S*,6*S*,14*S*)-6-phenyl-2,3,10,11-tetramethoxyprotoberberin-5-ol **(12)**, a new type of 5,6-disubstituted protoberberine derivative with excellent (d.e>95% by ^{1}H NMR) stereoselection.

Introduction

During the last years a lot of attention has been paid to the development of new strategies directed toward the stereocontrolled preparation of heterocyclic systems, and in this context, much progress has been made in the field of tetrahydroisoquinolines, a family of alkaloids with a widespread occurrence in nature and with an important physiological action.[1] Thereby, several original methodologies for the synthesis of chiral 1-substituted tetrahydroisoquinolines have been reported.[2] However, very few examples of the enantioselective syntheses of 1,3-disubstituted tetrahydroisoquinolines are known,[3] and in all cases reported, alkyl, but not aryl, substituents were placed at C-3. Only one example reported by our group, an enzyme-mediated enantioselective synthesis of 3-phenyl-1-methyl-1,2,3,4-tetrahydroisoquinolin-4-ols, has been described, but the reported procedure suffers from serious limitations.[4]

Our continuous interest in the synthesis of alkaloids incorporating the isoquinoline core encouraged us to find versatile methodologies for the stereoselective preparation of 3-aryltetrahydroisoquinolines and epimeric C-1 methyl-substituted 3-aryltetrahydroisoquinolines. Moreover, in connection with a related project aiming at the stereocontrolled synthesis of isopavines and tetrahydroisoquinolin-4-ols, we have recently achieved the synthesis of a series of optically active β-amino alcohols **1** (95% ee) by reaction of a chiral imine with benzylic Grignard reagents.[5] Now, we wish to present the results obtained when β-amino alcohols **1** were used as starting materials for the stereocontrolled synthesis of the pair of epimeric C-1 methylated 6,7-dimethoxy-3-(3,4-dimethoxyphenyl)tetrahydroisoquinolines (**3a**) and (**6**).

Finally, having established an optimum strategy for the access to enantiopure 3-aryltetrahydroisoquinolines of type **3**, in order to extend its applicability, a new stereoselective synthetic route to 5- and/or 6-substituted protoberberine derivatives has also been developed. To the best of our knowledge, the projected approach would lead to the first example of a stereocontrolled preparation of a protoberberine derivative with three stereogenic centers.

Results and Discussion

To accomplish the enantioselective preparation of the (3*S*)-3-aryl-tetrahydroisoquinoline **3d**, amine **2a**, which is easily obtained by removal (H_2, Pd−C) of the chiral appendage of the corresponding (+)-β-amino alcohol **1a**,[5b] was made to react with formaldehyde in acidic medium (see Scheme 1), thus, affording the target heterocycle **3d** in high yield (80%) without racemization. When acetaldehyde was used instead of formaldehyde under similar

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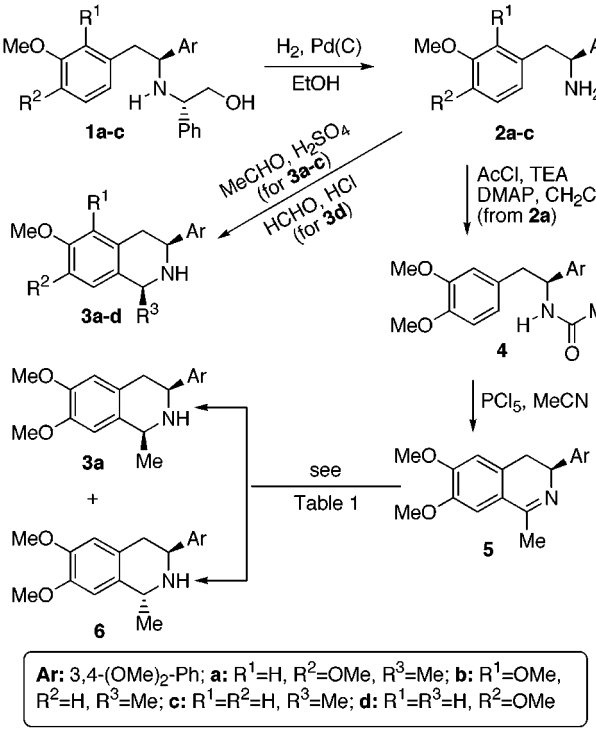
10.1021/jo981326h CCC: $18.00
Published on Web 01/27/1999

Scheme 1



cyclization conditions, a series of (1*S*,3*S*)-1-methyl-3-aryltetrahydroisoquinolines **3a**−**c** was obtained from amines **2a**−**c**, respectively, in good yield (70−82%), as a single enantiomer in each case. Extensive NMR studies (NOE experiments) proved the 1,3-cis relationship between the substituents at both stereogenic centers. This result can be explained by assuming that, in the transition state, the iminium salt is stabilized in a chairlike conformation, with the aryl substituent in an equatorial position and where the C=N bond adopts the (*E*) configuration, as has been previously rationalized for the cyclization of related compounds.[6] In this preferred conformation, the attack of the aryl ring leads to the observed stereochemistry in isoquinolines **3a**−**c**. Moreover, since the unique stereoisomer obtained is the less sterically hindered one, the corresponding heterocyclization reaction seems to be a thermodynamically controlled process.[3b]

Once the stereocontrolled synthesis of 1,3-cis disubstituted tetrahydroisoquinolines **3a**−**c** had been optimized, a second synthetic alternative was evaluated and optimized for the transformation of **2a** into **6**. For that purpose, (see Scheme 1) dihydroisoquinoline **5** was prepared from the common precursor, amine **2a**, via heterocyclization of the acetamide intermediate **4**,[7] and then the reduction of the azomethine function in dihydroisoquinoline **5** was studied under different conditions (see Table 1).

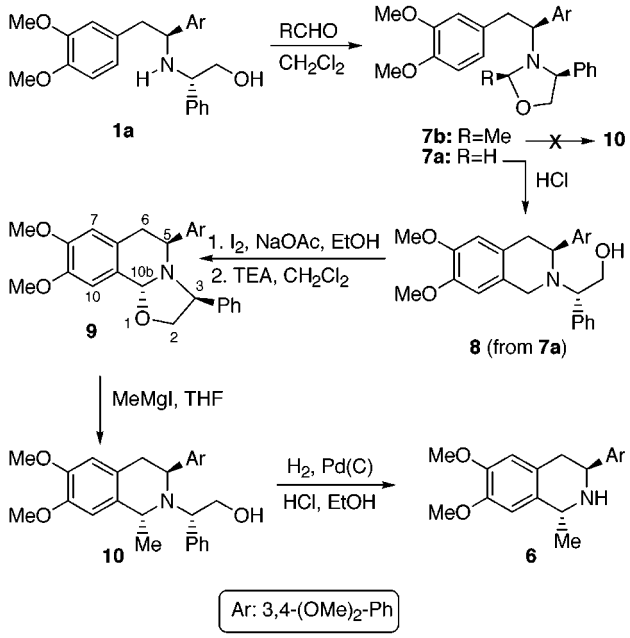
As shown in Table 1, catalytic hydrogenation[8] of dihydroisoquinoline **5** or the use of the bulky reagent[9] $NaBH(OAc)_3$ in refluxing CH_2Cl_2 afforded the corresponding 1,3-*cis*-tetrahydroisoquinoline **3a** with very high diastereoselection. Besides, whereas the use of LAH or $LAH/AlCl_3$ in refluxing THF[10] only afforded unreacted starting material, other nucleophilic reducing systems such as $NaBH_4$/MeOH led to mixtures of both epimers at C-1, where the desired 1,3-trans epimer **6** was obtained as the minor stereoisomer (27% of the reaction mixture by ^1H NMR). Finally, and according to previous reports by Bringmann,[3b] we expected the pair $LAH/AlMe_3$ to afford the 1,3-*trans*-tetrahydroisoquinoline **6**, but unfortunately, in the present case the 1,3-cis derivative **3a** was the one obtained as the major stereoisomer, probably due to an electrostatic repulsive interaction between the incoming hydride and the electron-enriched aryl ring.

Table 1. Reductive Assays Carried out on Dihydroisoquinoline 5

reagent and conditions	yield[a] (%)	**3a**:**6**
H_2, Pd/C, EtOH, rt	95	>95:5
$NaBH_4$, MeOH, rt	70	73:27
$NaBH(OAc)_3$, CH_2Cl_2, reflux	88	>95:5
LAH, THF, reflux	*b*	
$LAH/AlCl_3$, THF, reflux	*b*	
$LAH/AlMe_3$, THF, −78 °C → rt	90	80:20

[a] Combined yield for both stereoisomers. [b] No reaction was observed.

Scheme 2



At this point in the research, a new approach to the stereoselective synthesis of 1,3-trans disubstituted tetrahydroisoquinolines was envisaged as depicted in Scheme 2. Oxazolidines **7a**,**b**, quantitatively prepared from the common precursor **1a** by reaction with aqueous formaldehyde and acetaldehyde, respectively, were heated in 1 N HCl to attempt heterocyclization. In the former case, oxazolidine **7a** yielded the expected tetrahydroisoquinoline **8**, but unfortunately, analogous behavior was not observed for oxazolidine **7b** since, under the same reaction conditions, unreacted starting material and amine **2a** were the only products found in the crude reaction mixture.

(6) See ref 3b. See also: Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164−168, and Domínguez, E.; Lete, E.; Badía, D.; Villa, M. J.; Castedo, L.; Domínguez, D. *Tetrahedron* **1987**, *43*, 1943−1948.

(7) Domínguez, E.; Lete, E. *Heterocycles* **1983**, *20*, 1247−1254.

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(9) Cimarelli, C.; Palmieri G. *Tetrahedron: Asymmetry* **1994**, *5*, 1455−1458.

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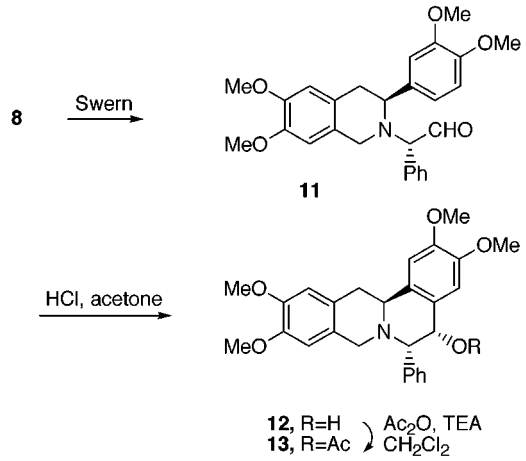
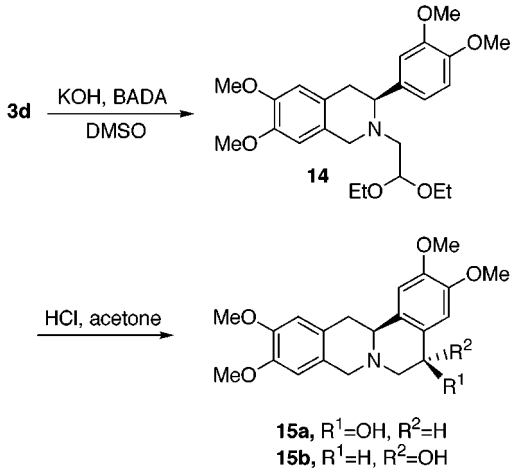
Scheme 3



Scheme 4



To circumvent the difficulties found during the preparation of the target 1,3-trans disubstituted heterocycle **6**, a modified synthetic route was evaluated (see Scheme 2). Thus, after oxidation of isoquinoline **8** and the subsequent treatment of it with the base, the 5,10b-*trans*-oxazolotetrahydroisoquinoline **9** (no NOE was observed between the protons at C-10b and C-5 or C-3) was obtained as a single diastereoisomer. To conclude the projected synthesis, the stereoselective methylation of **9** was performed, affording the target tetrahydroisoquinoline **10**, which, under treatment with H_2 (Pd−C), produced the (1*R*,3*S*)-6,7-dimethoxy-3-(3,4-dimethoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline **6** (de>95% by ^{1}H NMR). The observed stereocontrol at C-1 during the formation of tetrahydroisoquinoline **10** can be attributed to the nucleophilic attack on the less hindered face of the developing iminium intermediate formed with simultaneous opening of the oxazolidine ring.[11] This stereochemical proposal was confirmed a posteriori by measurements of NOE experiments carried out on the target heterocycle **6**.

Once the feasibility of the proposed strategies for the preparation of different nonracemic tetrahydroisoquinoline derivatives had been demonstrated, we moved to our second synthetic goal, which was the stereoselective synthesis of protoberberine derivatives of type **12** (see Scheme 3). This protocol illustrates the possible stereoselection that the presence of the adjacent asymmetric carbon would induce in the generation of the new stereogenic center.

Thereby, the already available isoquinoline **8** was oxidized under Swern conditions[12] to give the labile aldehyde **11**. As already anticipated,[5c] when treated with an acetone solution of aqueous HCl, the latter derivative **11** was diastereoselectively transformed into (5*S*,6*S*,14*S*)-5-hydroxy-6-phenyl-2,3,10,11-tetramethoxyprotoberberine **(12)** as a result of a 1,2-induction due to the presence of an adjacent stereogenic center (de > 95% by ^{1}H NMR). The relative configuration at the newly created stereogenic center accounts for the observation of an intense NOE between H-5 and H-6. Besides, since no chromatographic resolution could be achieved for the signals attributed to each enantiomer, the ee determination (95%) had to be performed on its acetylated derivative **13**.

(11) Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083−1092.

(12) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660.

To demonstrate that the presence of a substituent (i.e., a phenyl) adjacent to the new stereogenic center was required to get stereoselection in the above-mentioned synthesis of protoberberine **12**, the following experiment was designed (see Scheme 4). Acetal **14**, prepared from tetrahydroisoquinoline **3d** (KOH, BADA (bromoacetaldehydediethylacetal)-, DMSO), was submitted to the same cyclization conditions as mentioned above. In this case, the acidic treatment[13] of acetal **14** yielded protoberberine **15**, a hydroxylated analogue of the naturally occurring protoberberine (−)-*xylopinine*,[14] as a separable 1:1 diastereomeric mixture of protoberberines (5*R*,14*S*)-**15a** and (5*S*,14*S*)-**15b**. The relative configuration at C-5 was elucidated by means of extensive NMR studies. Thus, the observation —and the absence— of NOE between H-14 and H-5 was used as a diagnosis for the stereostructure assignments of **15a** and **15b**, respectively. In both cases, the ee (95%) was determined by chiral HPLC analysis after chromatographic separation of both diastereoisomers.

In summary, the first enantioselective synthesis of 3-aryltetrahydroisoquinolines from optically active (95% ee) amino alcohols **1** is reported. Besides, the diastereodivergent synthesis of the pair that is epimeric at C-1, 1-methyl-3-aryl-1,2,3,4-tetrahydroisoquinolines **3a** and **6**, has been achieved with great success. At the same time, the same type of precursor, **1**, led to the obtaining of isoquinoline **8** and then (5*S*,6*S*,14*S*)-6-phenylprotoberberin-5-ol **12**, a new kind of protoberberine derivative. In this case, the high overall and optical yields, the small number of steps, and the chemical economy (the chiral auxiliary is included in the skeleton of the target molecule) feature the described synthesis. Ee determinations (95% by chiral HPLC) were carried out on isoquinolines **3a**−**d** and **6** and also on protoberberines **13** and **15a**,**b**, indicating that no racemization took place in any of the performed transformations.

Experimental Section[15]

Typical Procedure for Synthesis of Tetrahydroisoquinolines 3a−c. Synthesis of (−)-(1*S*,3*S*)-6,7-Dimethoxy-3-(3,4-dimethoxyphenyl)-1-methyl-1,2,3,4-tetrahydroiso-

(13) Tellitu, I.; Badía, D.; Domínguez, E.; Carrillo, L. *Heterocycles* **1996**, *43*, 2099−2112.

(14) For a stereocontrolled synthesis of (−)-xylopinine, see, for example: Comins, D. L.; Thakker, P. M.; Baevsky, M. F. *Tetrahedron* **1997**, *53*, 16327−16340.

(15) For general procedures, see ref 5a.

quinoline (3a). Over a suspension of amine **2a** (0.65 g, 2.05 mmol) in 6 N H_2SO_4 (1 mL) was added acetaldehyde (0.27 g, 6.15 mmol) in three portions. After the first addition the mixture was heated to reflux for 24 h. Then, the mixture was allowed to reach room temperature, a new portion of acetaldehyde was added, and the suspension was stirred for 24 h. Finally, the third portion was added and the mixture was stirred at reflux for 5 h. Then, after cooling with an ice bath, the mixture was basified with NaOH (10%) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was distilled under vacuum, and the resulting oil was crystallized from Et_2O to afford tetrahydroisoquinoline **3a** as a white solid (0.49 g, 1.43 mmol, 70%) $[\alpha]^{20}_D$: −1.7 (*c* = 1.0, CH_2Cl_2). Mp: 130−133 °C. ^{1}H NMR (*δ*, ppm): 1.50 (d, *J* = 6.5, 3H), 1.74 (br s, 1H), 2.82 (dd, *J* = 15.6, 3.8, 1H), 2.96 (dd, *J* = 15.6, 10.8, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.97 (dd, *J* = 10.8, 3.8, 1H), 4.23 (q, *J* = 6.5, 1H), 6.57 (s, 1H), 6.72 (s, 1H), 6.86 (d, *J* = 8.2, 1H), 6.97 (dd, *J* = 8.2, 1.8, 1H), 7.02 (d, *J* = 1.8, 1H). ^{13}C NMR (*δ*, ppm). 22.4, 38.3, 53.2, 55.9, 56.0, 58.6, 108.5, 109.7, 111.1, 111.5, 118.7, 127.2, 131.7, 137.2, 147.4, 147.5, 148.2, 149.1. IR (KBr): 3320−3280. EI-MS *m*/*z*: 339 (M^+ − 4, 100). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.94; H, 7.34; N, 4.08. Found: C, 69.65; H, 7.33, 3.71.

(+)-(1*S*,3*S*)-5,6-Dimethoxy-3-(3,4-dimethoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (3b). According to the typical procedure, the reaction of (+)-amine **2b** (0.20 g, 0.63 mmol) with acetaldehyde (1.38 g, 31.50 mmol) afforded, after chromatographic purification, the tetrahydroisoquinoline **3b** as a colorless oil (0.17 g, 0.50 mmol, 80%). $[\alpha]^{20}_D$: +35.0 (*c* = 0.8, CH_2Cl_2). ^{1}H NMR (*δ*, ppm): 1.49 (d, *J* = 6.5, 3H), 2.39 (br s, 1H), 2.78 (dd, *J* = 16.8, 11.4, 1H), 3.12 (dd, *J* = 16.8, 3.5, 1H), 3.77 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.90−3.96 (m, 4H), 4.22 (q, *J* = 6.5, 1H), 6.79 (d, *J* = 8.5, 1H), 6.85 (d, *J* = 8.5, 1H), 6.92−7.04 (m, 3H). ^{13}C NMR (*δ*, ppm): 22.1, 33.3, 53.2, 55.7, 55.9, 58.5, 59.9, 109.7, 110.2, 111.1, 118.7, 120.4, 129.6, 133.0, 137.2, 146.2, 148.2, 149.1, 150.5. IR (neat): 3500−3400. EI−MS *m*/*z*: 343 (M^+, 14).

(−)-(1*S*,3*S*)-3-(3,4-Dimethoxyphenyl)-6-methoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (3c). According to the typical procedure, the reaction of (+)-amine **2c** (0.20 g, 0.69 mmol) with acetaldehyde (1.53 g, 34.80 mmol) afforded the tetrahydroisoquinoline **3c** which was purified by crystallization from Et_2O (0.18 g, 0.57 mmol, 82%). $[\alpha]^{20}_D$: −46.8 (*c* = 1.0, CH_2Cl_2). Mp: 218−221 °C (HCl salt). ^{1}H NMR (*δ*, ppm): 1.49 (d, *J* = 6.4, 3H), 2.87 (dd, *J* = 16.1, 3.8, 1H), 3.03 (dd, *J* = 16.1, 11.0, 1H), 3.77 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 3.99 (dd, *J* = 11.0, 3.8, 1H), 4.23 (q, *J* = 6.4, 1H), 6.61 (d, *J* = 2.6, 1H), 6.76 (dd, *J* = 8.5, 2.6, 1H), 6.84 (d, *J* = 8.2, 1H), 6.97 (dd, *J* = 8.2, 2.0, 1H), 7.01 (d, *J* = 2.0, 1H), 7.14 (d, *J* = 8.5, 1H). ^{13}C NMR (*δ*, ppm): 22.1, 39.0, 52.9, 55.1, 55.8, 58.5, 109.6, 110.9, 112.0, 113.3, 118.6, 126.1, 131.9, 136.3, 137.2, 148.1, 149.0, 158.3 (quaternary C_{arom}). IR (KBr): 3310−3300. EI−MS *m*/*z*: 313 (M^+, 3). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.39; N, 4.47. Found: C, 72.71; H, 7.27; N, 4.40.

(−)-(3*S*)-6,7-Dimethoxy-3-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3d). Over a suspension of amine **2a** (0.44 g, 1.38 mmol) in 8 mL of 1 N HCl was added 35% aqueous formaldehyde (1.08 mL, 13.8 mmol), and the mixture was heated to 60 °C until total consumption of the starting material (TLC, CH_2Cl_2/MeOH, 9.5:0.5). After cooling, the solution was basified with NH_4OH and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with water and dried over Na_2SO_4, and the solvent was evaporated. The so-obtained oil was purified by crystallization from EtOH to afford tetrahydroisoquinoline **3d** as a white solid (0.36 g, 1.10 mmol, 80%). $[\alpha]^{20}_D$: −67.3 (*c* = 0.2, CH_2Cl_2). Mp: 97−98 °C (lit.[16] mp 104−105 °C, racemic MeOH). ^{1}H NMR (*δ*, ppm): 2.11 (s, 1H), 2.84−2.87 (m, 2H), 3.81 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.89−3.92 (m, 1H), 4.04 (d, *J* = 15.1, 1H), 4.14 (d, *J* = 15.1, 1H), 6.54 (s, 1H), 6.56 (s, 1H), 6.82 (d, *J* = 8.2, 1H), 6.92 (dd, *J* = 8.3, 1.8, 1H), 7.00 (d, *J* = 1.8, 1H). ^{13}C NMR (*δ*, ppm): 37.1, 48.7, 55.2, 58.2, 109.0, 109.5, 110.9, 111.5, 118.5, 126.5, 126.6, 136.8, 147.2, 147.4, 148.1, 148.9. IR (KBr): 3350−3275. EI−MS *m*/*z*: 330 (M^+ + 1, 2), 329 (M^+, 7).

(−)-(1*S*)-*N*-[1,2-Bis(3,4-dimethoxyphenyl)ethyl]acetamide (4). Over a solution of amine **2a** (0.45 g, 1.42 mmol) in 20 mL of CH_2Cl_2 were added catalytic amounts of DMAP and Et_3N (0.30 mL, 2.13 mmol). The mixture was cooled with an ice bath, AcCl (0.13 mL 1.78 mmol) was added via syringe, and the new solution was stirred overnight at room temperature. Then, the crude was poured onto ice and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent distilled under vacuum. The resulting oil was purified by flash column chromatography (CH_2Cl_2/EtOAc, 6:4) and then crystallized from Et_2O to afford acetamide **4** as a white solid (0.40 g, 1.11 mmol, 79%). $[\alpha]^{20}_D$: −4.8 (*c* = 0.3, EtOH). Mp: 148−150 °C. ^{1}H NMR (*δ*, ppm): 1.97 (s, 3H), 3.03−3.07 (m, 2H), 3.75 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 3.85 (s, 3H), 5.15−5.18 (m, 1H), 5.70 (br d, 1H), 6.50−6.82 (m, 6H). ^{13}C NMR (*δ*, ppm): 23.3, 42.0, 54.1, 55.6, 55.7, 55.8, 110.4, 110.8, 111.0, 112.4, 118.5, 121.3, 129.7, 134.0, 147.5, 148.1, 148.5, 148.8, 169.2. IR (KBr): 3297, 1641. EI−MS *m*/*z*: 300 (M^+ − 57, 12).

(−)-(3*S*)-6,7-Dimethoxy-3-(3,4-dimethoxyphenyl)-1-methyl-3,4-dihydroisoquinoline (5). Over a solution of acetamide **4** (0.54 g, 1.49 mmol) in 25 mL of MeCN was added PCl_5 (2.48 g, 11.9 mmol) under argon in three portions at 0 °C, and after each addition the mixture was allowed to reach room temperature. When the starting material was completely consumed (TLC) the solution was cooled with an ice bath and basified using NaOH (20%), and the stirring was continued for 1 h. Then, the crude reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, the solvent distilled under vacuum, and the resulting oil was purified by flash column chromatography (hexanes/EtOAc/TEA, 6:3.5:0.5) to afford 3,4-dihydroisoquinoline **5** (0.46 g, 1.34 mmol, 90%). $[\alpha]^{20}_D$: −2.9 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (*δ*, ppm): 2.45 (d, *J* = 2.0, 3H), 2.81−2.87 (m, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 4.25 (ddd, *J* = 12.6, 6.6, 2.0, 1H), 6.67 (s, 1H), 6.82 (d, *J* = 8.2, 1H), 6.91 (dd, *J* = 8.2, 1.8, 1H), 7.01 (d, *J* = 1.8, 1H), 7.03 (s, 1H). ^{13}C NMR (*δ*, ppm): 23.3, 34.1, 55.7, 55.8, 55.9, 56.1, 60.4, 109.0, 110.1, 110.4, 111.0, 118.9, 122.1, 130.7, 136.9, 147.6, 147.9, 148.8, 151.1, 163.8. IR (neat): 1625. EI−MS *m*/*z*: 341 (M^+, 100).

Typical Procedure for the Synthesis of Oxazolidines 7. Synthesis of (+)-(4*S*,1′*S*)-3-[1,2-Bis(3,4-dimethoxyphenyl)ethyl]-4-phenyloxazolidine (7a). A solution of *β*-amino alcohol **1a** (1.6 g, 3.80 mmol), HCHO (1.5 mL, 35% aq, 19.0 mmol), and molecular sieves (4 Å) in 10 mL of CH_2Cl_2 was stirred at room temperature until there was total consumption of starting material (TLC, CH_2Cl_2/AcOEt, 6:4). Then, the molecular sieves were filtered, the solvent was distilled at reduced pressure, and the resulting mixture was purified by flash column chromatography (hexanes/EtOAc, 7:3) to afford oxazolidine **7a** as a colorless oil (1.70 g, 3.80 mmol, quantitative yield). $[\alpha]^{20}_D$: +173.5 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR (*δ*, ppm): 2.82 (dd, *J* = 13.1, 9.6, 1H), 3.11 (dd, *J* = 13.1, 4.0, 1H), 3.46 (s, 3H), 3.63 (s, 3H), 3.68 (dd, *J* = 7.9, 4.7, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 3.78−3.82 (m, 1H), 4.03 (dd, *J* = 7.2, 4.8, 1H), 4.15 (t, *J* = 7.7, 1H), 4.72 (d, *J* = 5.1, 1H), 4.87 (d, *J* = 5.1, 1H), 6.20 (d, *J* = 1.8, 1H), 6.37−6.45 (m, 2H), 6.54−6.64 (m, 3H), 7.14−7.24 (m, 5H). ^{13}C NMR (*δ*, ppm): 42.7, 55.3, 55.5, 55.7, 64.8, 69.2, 72.7, 85.2, 109.8, 110.6, 111.3, 112.7, 121.2, 121.5, 126.7, 126.9, 128.1, 130.8, 133.7, 143.5, 147.1, 147.9, 148.1, 148.3. IR (neat): 1520. EI−MS *m*/*z*: 449 (M^+, <1). Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; N, 3.11. Found: C, 71.98; H, 6.94; N, 3.00.

(+)-(2*S*,4*S*,1′*S*)-3-[1,2-Bis(3,4-dimethoxyphenyl)ethyl]-2-methyl-4-phenyloxazolidine (7b). According to the typical procedure the reaction between (+)-amine **1a** (0.8 g, 1.9 mmol) and CH_3CHO (0.51 mL, 9.1 mmol) afforded, after 5 h, oxazolidine **7b** as a 92:8 cis−trans mixture of diastereoisomers (0.70 g, 1.52 mmol, 80%). $[\alpha]^{20}_D$: +94.5 (*c* = 0.2, CH_2Cl_2). ^{1}H NMR (*δ*, ppm): 1.46 (d, *J* = 5.3, 3H), 2.78 (dd, *J* = 13.5, 9.5, 1H), 3.02 (dd, *J* = 13.5, 5.2, 1H), 3.58 (s, 3H), 3.66 (s, 3H), 3.72 (dd,

(16) Vicente, T.; Martínez de Marigorta, E.; Domínguez, E.; Carrillo, L.; Badía, D. *Heterocycles* **1993**, *36*, 2067−2072.

J = 6.5, 3.6, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 3.89 (dd, J = 9.5, 5.2, 1H), 3.93−4.02 (m, 2H), 4.91 (q, J = 5.3, 1H), 6.51 (d, J = 1.9, 1H), 6.59−6.65 (m, 5H), 7.16−7.13 (m, 5H). ^{13}C NMR (δ, ppm): 22.3, 41.4, 55.6, 55.8, 64.9, 68.1, 73.1, 92.3, 110.0, 110.6, 112.0, 112.6, 121.3, 121.5, 126.8, 127.3, 128.1, 131.6, 132.8, 143.9, 147.1, 148.0, 148.2, 148.3. IR (neat): 1520. EI−MS m/z: 462 ($M^+ - 1$, <1). Anal. Calcd for $C_{28}H_{33}NO_5$: C, 72.55; H, 7.17; N, 3.02. Found: C, 72.88; H, 7.29; N, 2.73.

(+)-(3*S*,1′*S*)-6,7-Dimethoxy-3-(3,4-dimethoxyphenyl)-2-(2-hydroxy-1-phenylethyl)-1,2,3,4-tetrahydroisoquinoline (8). A suspension of oxazolidine **7a** (0.56 g, 1.25 mmol) in 5 mL of 1 N HCl was heated under argon at 50−60 °C for 5 h. Then, the mixture was cooled at 0 °C, basified with 1 M NaOH, and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was distilled under vacuum, and the resulting oil was purified by flash column chromatography (hexanes/EtOAc, 1:1) to afford tetrahydroisoquinoline **8** as a colorless oil (0.39 g, 0.87 mmol, 70%). $[\alpha]^{20}_D$: +35.8 (c = 1.0, CH_2Cl_2). ^{1}H NMR (δ, ppm): 2.86 (dd, J = 16.5, 4.5, 1H), 3.11 (dd, J = 16.5, 5.9, 1H), 3.82 (s, 3H), 3.82 (s, 3H), 3.83−3.99 (m, 11H), 4.23 (dd, J = 5.9, 4.5, 1H), 6.50 (s, 1H), 6.59 (s, 1H), 6.64−6.82 (m, 3H), 7.23−7.39 (m, 5H). ^{13}C NMR (δ, ppm): 32.7, 47.2, 55.6, 55.8, 55.9, 58.1, 62,4, 64.9, 109.1, 110.7, 111.1, 111.2, 119.9, 127.5, 128.4, 125.8, 128.1, 134.9, 139.9, 147.3, 147.6, 148.1, 148.7. IR (neat): 3600−3300. EI−MS m/z: 449 (M^+, 2). Anal. Calcd for $C_{27}H_{31}NO_5$: C, 72.14; H, 6.95; N, 3.11. Found: C, 71.96; H, 6.83; N, 3.25.

(+)-(3*S*,5*S*,10b*R*)-8,9-Dimethoxy-5-(3,4-dimethoxyphenyl)-3-phenyl-2,3,5,6-tetrahydro-10bH-oxazolo-[2,3-a]-isoquinoline (9). Over a solution of tetrahydroisoquinoline **8** (0.38 g, 0.85 mmol) in 30 mL of EtOH were added iodine (0.43 g, 1.7 mmol) and NaOAc (0.09 g, 1.1 mmol) the resulting mixture was refluxed for 1 h, and after cooling, an aqueous solution of sodium thiosulfate (10%) was added dropwise. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic extracts were washed with brine and dried over Na_2SO_4, and after the solvent was distilled under vacuum, the so-obtained solid was dissolved in 15 mL of CH_2Cl_2 and cooled at −78 °C. Then, triethylamine (0.24 mL, 1.7 mmol) was added, the mixture was stirred under argon for 1 h, and the temperature was raised to room temperature. Water was added, the organic phase was decanted and dried over Na_2SO_4, and the solvent was distilled at reduced pressure to afford an oil that was purified by flash column chromatography (hexanes/EtOAc, 1:1) yielding oxazoloisoquinoline **9** as a colorless oil (0.26 g, 0.60 mmol, 70%). $[\alpha]^{20}_D$: +33.4 (c = 1.0, CH_2Cl_2). ^{1}H NMR (δ, ppm): 2.80 (dd, J = 16.0, 3.2, 1H), 3.03 (dd, J = 16.0, 11.3, 1H), 3.55 (s, 3H), 3.79 (dd, J = 7.8, 5.2, 1H), 3.84 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 4.01 (dd, J = 11.3, 3.2, 1H), 4.30 (dd, J = 7.8, 5.2, 1H), 4.41 (t, J = 7.8, 1H), 5.53 (s, 1H), 6.60 (s, 1H), 6.76 (d, J = 8.2, 1H), 6.88 (dd, J = 8.2, 1.8, 1H), 6.94 (s, 1H), 6.97 (d, J = 1.8, 1H), 7.15−7.28 (m, 5H). ^{13}C NMR (δ, ppm): 39.9, 55.4, 55.8, 55.9, 60.5, 66.4, 70.7, 90.9, 109.9, 110.3, 110.6, 120.0, 126.5, 126.8, 128.3, 123.8, 127.5, 135.5, 142.9, 147.8, 148.1, 148.8, 149.1. IR (neat): 1520. EI−MS m/z: 446 ($M^+ - 1$, 100). Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.14; H, 6.53; N, 3.13. Found: C, 72.06; H, 6.35; N, 2.97.

(+)-(1*R*,3*S*,1′*S*)-3-(3,4-Dimethoxyphenyl)-2-(2-hydroxy-1-phenylethyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (10). Over a stirred and cold (0 °C) solution of MeMgI (0.7 mL of a 3M solution in ether, 2.0 mmol) in 5 mL of THF was added a solution of tetrahydroisoquinoline **9** (0.18 g, 0.40 mmol) in 10 mL of the same solvent. Then, the solution was allowed to reach room temperature, 15 mL of a saturated solution of NH_4Cl was added, the organic phase was decanted, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4, and the so-obtained crude was purified by flash column chromatography (hexanes/EtOAc, 6:4) to afford tetrahydroisoquinoline **10** as a colorless oil (0.19 g, 0.38 mmol, 97%). $[\alpha]^{20}_D$: +21.0 (c = 1.0, CH_2Cl_2). ^{1}H NMR (δ, ppm): 1.66 (d, J = 6.9, 3H), 2.65 (dd, J = 16.0, 4.3, 1H), 2.86 (dd, J = 16.0, 11.8, 1H), 3.27 (dd, J = 9.0, 3.7, 1H), 3.74 (s, 3H), 3.77−3.86 (m, 2H), 3.86 (s, 3H), 3.93 (s, 6H), 4.50 (q, J = 6.9, 1H), 4.63 (dd, J = 11.8, 4.3, 1H), 6.28 (s, 1H), 6.53 (s, 1H), 6.92−7.05 (m, 8H). ^{13}C NMR (δ, ppm): 24.9, 28.9, 51.7, 53.4, 55.7, 55.9, 56.0, 56.1, 61.2, 62.2, 109.4, 110.9, 111.4, 111.5, 119.8, 127.4, 127.7, 128.5, 126.4, 131.9, 133.8, 140.1, 147.1, 147.4, 148.4, 149.2. IR (neat): 3600−3300. EI−MS m/z: 446 ($M^+ - 17$, 100). Anal. Calcd for $C_{28}H_{33}NO_5$: C, 72.55; H, 7.17; N, 3.02. Found: C, 72.76; H, 7.07; N, 2.78.

(−)-(1*R*,3*S*)-6,7-Dimethoxy-3-(3,4-dimethoxyphenyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline (6). A solution of tetrahydroisoquinolines **10** (0.45 g, 1.10 mmol) in a mixture of 10 mL of EtOH and 5 mL of HCl (10%) was hydrogenated at 2 atm in the presence of catalytic amounts of Pd−C (10%). After total consumption of the starting material (TLC, hexanes/EtOAc, 6:4, 20 h) the solution was filtered, basified with a saturated solution of $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was evaporated under reduced pressure, and the resulting colorless oil was purified by flash column chromatography to afford tetrahydroisoquinoline **6** (0.31 g, 0.90 mmol, 82%). $[\alpha]^{20}_D$: −2.4 (c = 0.5, CH_2Cl_2). ^{1}H NMR (δ, ppm): 1.52 (d, J = 6.8, 3H), 1.73 (br s, 1H), 2.87 (d, J = 7.1, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.21 (t, J = 7.1, 1H), 4.30 (q, J = 6.8, 1H), 6.57 (s, 1H), 6.60 (s, 1H), 6.84 (d, J = 8.2, 1H), 6.95 (dd, J = 8.2, 1.9, 1H), 7.02 (d, J = 1.9, 1H). ^{13}C NMR (δ, ppm): 24.1, 37.5, 51.2, 51.6, 55.8, 55.9, 109.7, 110.9, 111.3, 118.7, 126.3, 131.4, 137.1, 147.2, 147.4, 148.1, 148.9. IR (neat): 3350−3200. EI−MS m/z: 343 (M^+, 16). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.94; H, 7.34; N, 4.08. Found: C, 69.84; H, 7.48; N, 4.45.

(−)-(5*S*,6*S*,14*S*)-6-Phenyl-2,3,10,11-tetramethoxy-7,8,13,14-tetrahydroprotoberberin-5-ol (12). Over a cooled (−60 °C) solution of oxalyl chloride (0.13 mL, 1.40 mmol) in 6 mL of CH_2Cl_2 was added dropwise a solution of DMSO (0.20 mL, 2.90 mmol) in 4 mL of the same solvent, and the mixture was stirred for 15 min. Then, a solution of tetrahydroisoquinoline **8** (0.58 g, 1.30 mmol) in 10 mL of CH_2Cl_2 was added dropwise, and the stirring was continued for 30 min. Working at the same low temperature, diisopropylethylamine (1.13 mL, 6.50 mmol) was added slowly, and after being stirred for 15 min, the solution was allowed to reach ambient temperature. The reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were dried over Na_2SO_4, and the solvent was distilled under reduced pressure to afford aldehyde **11**. Crude aldehyde **11** was quickly dissolved in acetone (18 mL), and after cooling with an ice bath, concd HCl (6 mL) was added, and the mixture was stirred for 2 h at room temperature. Then, the crude was cooled again, basified with 1 M NaOH, and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, the solvent was distilled under vacuum, and the resulting oil was purified by flash column chromatography (CH_2Cl_2/EtOAc, 6:4). The resulting colorless oil was crystallized from Et_2O to afford protoberberine **12** as a white solid (0.40 g, 0.91 mmol, yield = 70%, two steps). $[\alpha]^{20}_D$: −94.5 (c = 0.5, CH_2Cl_2). Mp 122−124 °C. ^{1}H NMR (δ, ppm): 2.86 (dd, J = 15.8, 11.1, 1H), 3.18 (dd, J = 15.8, 3.6, 1H), 3.66 (d, J = 15.1, 1H), 3.71−3.94 (m, 2H), 3.77 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 3.94 (s, 3H), 4.41 (d, J = 5.5, 1H), 5.26 (apparent d, 1H), 6.44 (s, 1H), 6.74 (s, 1H), 6.60 (s, 1H), 7.02−7.24 (m, 5H), 7.16 (s, 1H). ^{13}C NMR (δ, ppm): 36.5, 53.8, 54.9, 55.7, 55.9, 67.3, 68.7, 107.5, 108.6, 108.7, 111.0, 125.6, 126.1, 129.4, 129.8, 134.5, 128.1, 128.4, 130.4, 147.2, 147.3, 148.0, 148.2. IR (KBr): 3600−3200. EI−MS m/z: 447 (M^+, 15).

(−)-(5*S*,6*S*,14*S*)-5-Acetoxy-6-phenyl-2,3,10,11-tetramethoxy-7,8,13,14-tetrahydroprotoberberine (13). Over a solution of protoberberin-5-ol **12** (0.45 g, 1.01 mmol) in 15 mL of CH_2Cl_2 were added TEA (0.20 mL, 1.50 mmol) and a catalytic amount of DMAP. The solution was cooled at 0 °C, Ac_2O (0.12 mL, 1.25 mmol) was added, and the new solution was stirred for 4 h. For the workup, the mixture was poured onto ice and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with brine and dried with Na_2SO_4, and the solvent was evaporated under vacuum. The resulting crude was purified by flash column chromatography (hexanes/EtOAc, 3:7) to afford an oil which was crystallized from Et_2O to yield acetate **13** as a white solid (0.3 g, 0.6 mmol,

60%). $[\alpha]^{20}_D$: −54.2 (*c* = 0.1, CH_2Cl_2). Mp 96−98 °C. ^{1}H NMR (*δ*, ppm): 1.90 (s, 3H), 2.93 (m, 1H), 3.08 (dd, *J* = 16.2, 4.36, 1H), 3.76 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 3.95 (s, 3H), 3.65−3.95 (m, 14H), 4.13 (dd, *J* = 10.5, 4.3, 1H), 4.58 (d, *J* = 5.2, 1H), 6.26 (apparent d, 1H), 6.36 (s, 1H), 6.58 (s, 1H), 6.74 (s, 1H), 6.83 (s, 1H), 7.10−7.31 (m, 5H). ^{13}C NMR (*δ*, ppm): 21.1, 35.0, 52.9, 55.1, 55.8. 55.9, 56.0, 62.7, 70.7, 107.9, 108.9, 109.6, 110.9, 124.3, 125.5, 125.7, 131.5, 135.3, 127.9, 130.1, 147.3, 148.8, 170.7. IR (KBr): 1733. EI−MS *m*/*z*: 167 (40), 149 (100).

(+)-(3*S*)-2-(2,2-Diethoxyethyl)-6,7-dimethoxy-3-(3,4-dimethoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (14). Over a suspension of K_2CO_3 (1.10 g, 8.20 mmol) in 25 mL of dry MeCN was added a solution of tetrahydroisoquinoline **3d** (0.83 g, 2.50 mmol) in 15 mL of the same solvent, and the mixture was heated to reflux for 2 h. After cooling, BADA (1.50 mL, 10.1 mmol) was added, and the reflux was continued until there was total consumption of the starting material (TLC, CH_2Cl_2/EtOAc, 8:2). The mixture was cooled, water (25 mL) was added, and then the mixture was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The resulting crude reaction was purified by flash column chromatography to afford tetrahydroisoquinoline **14** as a colorless oil (0.90 g, 2.02 mmol, 81%). $[\alpha]^{20}_D$: +28.0 (*c* = 0.1, CH_2Cl_2). ^{1}H NMR (*δ*, ppm): 1.15 (t, *J* = 6.9, 3H), 1.20 (t, *J* = 6.9, 3H), 2.36 (dd, *J* = 13.5, 5.1, 1H), 2.73 (dd, *J* = 13.5, 5.3, 1H), 3.05 (dd, *J* = 16.4, 8.9, 1H), 3.65 (m, 6H), 3.84 (s, 3H), 3.86 (s, 6H), 3.88 (s, 3H), 4.12 (d, *J* = 15.3, 1H), 4.61 (t, *J* = 5.1, 1H), 6.56 (s, 2H), 6.80−6.97 (m, 3H). ^{13}C NMR (*δ*, ppm): 15.7, 36.4, 55.7, 56.2, 56.3, 61.7, 62.5, 64.1, 102.6, 109.5, 110.6, 111.0, 111.2, 120.6, 126.4, 126.8, 135.5, 147.7, 147.9, 148.5. IR (neat): 1270. EI−MS *m*/*z*: 445 (M^+, 3).

(−)-(5*R*,14*S*)- and (−)-(5*S*,14*S*)-2,3,10,11-Tetramethoxy-7,8,13,14-tetrahydroprotoberberin-5-ol (15a and 15b). Concentrated HCl (4 mL) was added over a cold (0 °C) solution of acetal **14a** (0.50 g, 1.10 mmol) in 12 mL of acetone, and the mixture was allowed to reach room temperature slowly. The solution was cooled again, basified with 1 M NaOH solution, and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water and dried over Na_2SO_4, and the solvent was evaporated under vacuum. The resulting oil was purified by PTLC to afford protoberberines **15a** and **15b** in a 70% combined yield.

15a. $[\alpha]^{20}_D$: −93.2 (*c* = 0.1, MeOH). ^{1}H NMR (*δ*, ppm): 2.59 (dd, *J* = 11.1, 7.5, 1H), 2.82 (m, 1H), 3.09 (dd, *J* = 15.8, 3.9, 1H), 3.35 (dd, *J* = 11.1, 4.8, 1H), 3.79−3.93 (m, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 4.87 (apparent t, 1H), 6.58 (s, 1H), 6.62 (s, 1H), 6.70 (s, 1H), 7.07 (s, 1H). ^{13}C NMR (*δ*, ppm): 34.2, 55.8, 55.9, 57.1, 57.5, 58.5, 66.7, 107.8, 108.8, 109.3, 111.1, 125.6, 129.8, 130.4, 147.4, 147.5, 147.9, 148.4.

15b. $[\alpha]^{20}_D$: −73.3 (*c* = 0.1, MeOH). ^{1}H NMR (*δ*, ppm): 2.77−2.79 (m, 2H), 3.20−3.31 (m, 2H), 3.57 (dd, *J* = 11.0, 3.8, 1H), 3.73 (d, *J* = 16.2, 1H), 3.85−3.95 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 4.52 (m, 1H), 6.60 (s, 3H), 6.68 (s, 1H), 6.75 (s, 1H), 6.87 (s, 1H). ^{13}C NMR (*δ*, ppm): 36.5, 55.9, 58.7, 59.6, 60.1, 66.7, 107.8, 108.7, 111.1, 111.7, 125.8, 126.0, 128.8, 129.1, 147.4, 147.6, 148.9.

Acknowledgment. Financial support from the Basque Government (Project GV PI 96/53 and fellowships to J.L.V. and to E.A.) and from the University of the Basque Country (Project UPV 170.310-E.A.154/96) is gratefully acknowledged. The authors gratefully acknowledge PETRONOR, S. A. (Muskiz, Bizkaia) for the generous gift of solvents.

Supporting Information Available: Copies of ^{1}H NMR and/or ^{13}C NMR spectra of compounds **3b**,**d**, **4**, **5**, **12**−**14**, and **15a**,**b** (14 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.

JO981326H