Articles

A Simple and Efficient Synthetic Route to Chiral Isopavines. Synthesis of (−)-*O*-Methylthalisopavine and (−)-Amurensinine

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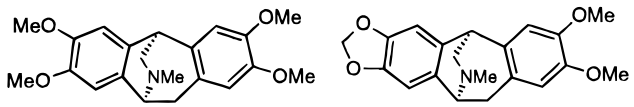
The isopavinan alkaloids (−)-*O*-methylthalisopavine (**7a**) and (−)-amurensinine (**7d**) have been synthesized in good yield and high ee from the appropriate 1,2-diarylethylamine derivatives using optically active *β*-amino alcohols as chiral support. This synthetic route employs as key steps the alkylation reaction of the azomethine derivatives **2** with Grignard reagents **1** and a novel one-pot double-intramolecular cyclization of the adequately functionalized 1,2-diarylethylamines **5** to afford a series of optically active isopavines **6a**−**d** and **7a**−**d**.

Introduction

Over the last years we have been engaged in a major effort to study the synthesis and reactivity of different isoquinoline derivatives, such as 3-arylisoquinolines, protoberberines, and benzo[*c*]phenanthridines.[1] As a result of our interest in this field, we have extended our investigations to the synthesis of natural and non-natural isopavines because of their important pharmacological properties for the treatment of the nerve system disorders recently reported: Alzheimer's disease, Hungtington's chorea, amyotrophic lateral sclerosis, and Parkinson's and Down's syndromes.[2]

Isopavines are a small group of natural products characterized by a tetracyclic skeleton with an isoquinoline core, as shown below for natural (−)-*O*-methylthalisopavine and (−)-amurensinine (Figure 1). Few examples of syntheses of these compounds have been reported to date.[3] Moreover, the enantioselective synthesis of isopavines has not been extensively developed yet, although their interest for future pharmacological studies should be emphasized. As far as we know, in the literature there is only one example where the synthesis of an enantiomerically enriched isopavine does not involve a resolution step of any of the intermediates,[4] and furthermore, in all the cases reported, the final cyclization step takes place in moderate yields requiring rather long reaction times.



(-)-O- Methylthalisopavine *(-)-Amurensinine*

Figure 1.

In this paper, and in connection with our studies on the asymmetric synthesis of isoquinoline alkaloids,[5] we describe a suitable and general route for the asymmetric synthesis of optically pure isopavines starting from chiral 1,2-diarylethylamine precursors **4**. Then, a sequence of stereocontrolled transformations (*N*-alkylations and double acid cyclization) was envisaged to prepare the isopavine core. The described protocol is interesting from a synthetic point of view taking into account the large number of diarylethylamines of type **4** available by this method, as it allows any arylic substitution pattern, thus leading to the synthesis of a wide range of naturally and unnaturally occurring isoquinoline derivatives.[6]

Results and Discussion

The synthesis of 1,2-diarylethylamines **4** (see Scheme 1) started with the reaction between freshly prepared Grignard benzylic reagents **1** and imines **2**. These imines were synthesized, in turn, in good yields by condensation of the corresponding *β*-amino alcohol (readily prepared by reduction of their respective α-amino acids[7]) with aryl aldehydes in refluxing benzene. The *S* enantiomer of the *β*-amino alcohol chiral auxiliary was employed because it would eventually lead to the corresponding levogire isopavines, the unique isomers found in nature.

[⊗] Abstract published in *Advance ACS Abstracts*, September 1, 1997.

(1) See, for example: (a) Tellitu, I.; Badía, D.; Domínguez, E.; Carrillo, L. *Heterocycles* **1996**, *43*, 2099−2112. (b) Badía, D.; Domínguez, E.; Tellitu, I. *Tetrahedron* **1992**, *48*, 4419−4430.

(2) For pharmacological activities, see: (a) Weber, E.; Keana, J.; Barmettler, P. PCT Int. Appl. WO 12575, **1990**; *Chem. Abstr.* **1991**, *115*, 106019w. (b) Childers, W. E., Jr.; Abou-Gharbia, M. A. U.S. Patent 4940789, 1990; *Chem. Abstr.* **1990**, *113*, 191190w.

(3) For syntheses of natural and non-natural isopavines, see, for example: (a) Gözler, B. In *The Alkaloids*; Academic Press: New York, 1987; Vol. 31, pp 342−355. (b) Yasuda, M.; Hamasuna, S.; Yamano, K.; Kubo, J.; Shima, K. *Heterocycles* **1992**, *34*, 965−977. (c) Kametani, T.; Higashiyama, K.; Honda, T. *Chem. Pharm. Bull.* **1984**, *32*, 1614−1618. (d) Jung, M. E.; Miller, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 1984−1992. (e) Dyke, S. F.; Kinsman, R. G.; Warren, P.; White, A. W .C. *Tetrahedron* **1978**, *34*, 241−245 . (f) Dyke, S. F.; ; Ellis, A. C.; Kinsman, R. G.; White, A. W .C. *Tetrahedron* **1974**, *30*, 1193−1199. (g) Rice, K. C.; Ripka, W. C.; Reden, J.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 601−607.

(4) (a) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095−5108. (b) Gottlieb, L.; Meyers, A. I. *J. Org. Chem.* **1990**, *55*, 5659−5662.

(5) Tellitu, I.; Badía, D.; Domínguez, E.; García, F. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1567−1578.

(6) Carrillo, L.; Badía, D.; Domínguez, E.; Tellitu, I. Unpublished results.

(7) (*S*)-(+)-Valinol and (*S*)-(+)-phenylglycinol were prepared by reduction of L-valine and L-phenylglycine, respectively, using $LiBH_4$−Me_3SiCl in THF at room temperature for 24 h. Nicolás, E.; Russell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766−770.

S0022-3263(97)00810-4 CCC: $14.00

Scheme 1

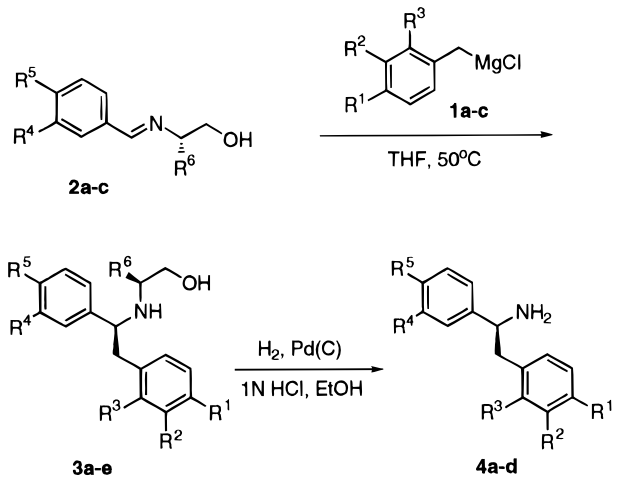


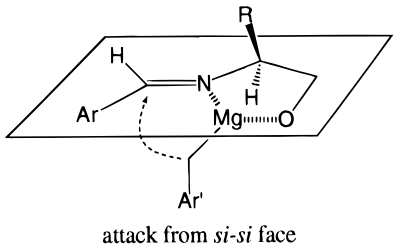
Table 1. Nucleophilic Alkylation of Chiral Imine Derivatives 2a−c

entry	substr	prod	R^1	R^2	R^3	R^4	R^5	R^6	yield[a] (%)	de[b] (%)
1	**1a** + **2a**	**3a**	OMe	OMe	H	OMe	OMe	^{i}Pr	80	80
2	**1a** + **2b**	**3b**	OMe	OMe	H	OMe	OMe	Ph	80	>95
3	**1b** + **2b**	**3c**	H	OMe	OMe	OMe	OMe	Ph	77	>95
4	**1c** + **2b**	**3d**	H	OMe	H	OMe	OMe	Ph	76	>95
5	**1a** + **2c**	**3e**	OMe	OMe	H	OCH_2O		Ph	75	>95

[a] Isolated yield of the mixture of diastereomers. [b] Determined by ^{1}H NMR spectroscopy.

The so-obtained condensation derivatives were stable and proved to consist of the typical imine−oxazolidine tautomeric mixture.[8] The aldimines **2** were assumed to be in the *E* configuration on the basis of the report by Hine[9] and ^{13}C NMR studies which showed only a single resonance for the amino carbon (163 ppm). At this point, imines **2a**−**c** were submitted to addition reactions with various Grignard reagents **1a**−**c**, prepared *in situ*,[10] exhibiting good to excellent levels of diasteroselection. The transformations were carried out with 5 equiv of the organometallic reagent at −10 °C; then, the crude was later heated at 45−50 °C for 5 h, quenched with ammonium chloride, and worked up in the usual manner.

The ratio of a diasteromeric mixture of amines **3** was determined by ^{1}H NMR spectroscopy, and it was found to be dependent on the nature of the chiral support used (see entries 1 and 2 in Table 1). Phenylglycinol-derived imine **2b** gave better stereoselectivity than the valinol-derived imine **2a**; therefore phenylglycinol was selected in order to prepare series of chiral (1*S*,1*S*′)-amines **3b**−**e**. We presume that the remarkable stereocontrol observed in the reported alkylation reactions can be attributed to the formation of an internal chelate between the magnesium atom of the Grignard reagent with the hydroxy group and the lone pair electrons of the nitrogen atom. Thus, the *re* and *si* faces are differentiated toward the attack of the nucleophile because of the bulkiness of the group at the α position of the imines. Consequently, the attack of the benzylic group occurs from the *si*−*si* face (Figure 2), the less hindered face (Figure 2), of the C=N bond leading to the (1*S*,1′*S*) isomer formation.[11] This stereochemical proposal was *a posteriori* confirmed on the heterocycles obtained by comparison with data found in the literature.



attack from *si-si* face

Figure 2.

Table 2. Chiral Amines 4a−d and Isopavines 7a−d Prepared

substr	prod	R^1	R^2	R^3	R^4	R^5	R^6	t_R (min)[a]	t_R (min)[b]	ee (%)	yield (%)
3b	**4a**[c]	OMe	OMe	H	OMe	OMe		13.6	15.9	95	92[e]
3c	**4b**	H	OMe	OMe	OMe	OMe		9.7	10.6	94	70[f]
3d	**4c**	H	OMe	H	OMe	OMe		10.2	13.3	94	80[f]
3e	**4d**	OMe	OMe	H	OCH_2O			10.7	14.0	95	76[e]
6a	**7a**[d]	OMe	OMe	H	OMe	OMe	Me	23.1	19.1	95	96[e]
6b	**7b**	H	OMe	OMe	OMe	OMe	Me	23.3	15.7	94	93[f]
6c	**7c**	H	OMe	H	OMe	OMe	Me	18.9	14.5	94	88[f]
6d	**7d**	OMe	OMe	H	OCH_2O		Me	21.6	23.4	95	95[e]

[a] Retention time for (*S*)-amines **4** or (5*R*,12*S*)-isopavines **7**. [b] Retention time for (*R*)-amines **4** or (5*S*,12*R*)-isopavines **7**. [c] The HPLC conditions (Chiralcel OD, UV detector, *n*-hexane/2-propanol 50:50 as eluent; flow rate 0.9 mL/min) were optimized using a racemic mixture of **4a**.[12] [d] The HPLC conditions (Chiralcel OD, UV detector, *n*-hexane/2-propanol 8:2 as eluent; flow rate 0.5 mL/min) were optimized using a racemic mixture of **7a**. [e] Crystallized. [f] Oil.

Moreover, the chiral appendage was cleanly removed from (1*S*,1*S*′)-**3b**−**e** by hydrogenolysis, thus providing the corresponding primary (*S*)-amines **4a**−**d** in high yield without racemization. As shown in Table 2, the optical purity in all the cases studied was shown to be greater than 94% by HPLC.

In order to complete the synthesis (Scheme 2), the amines **4a**−**d** were alkylated with bromoacetaldehyde diethyl acetal (BADA) to afford the corresponding acetals **5a**−**d**. At this stage of the research, isopavines **6a**−**d** were successfully obtained in one step by acid-catalyzed double cyclization. The observed behavior can be explained by assuming that the synthetic route involves two sequential electrophilic cyclizations probably through a 1-benzyltetrahydroisoquinoline intermediate.[13] It is noteworthy to point out that, when compared with other previously reported synthesis of isopavines,[3] the method employed by our group, which uses H_2SO_4/HOAc as cyclizing agent at room temperature, allows the preparation, in a short reaction time, of the isopavine framework in almost quantitative yield. Besides, racemization processes are not observed under the reaction conditions chosen. These conditions gave better results than other

(8) When the ^{1}H NMR spectra were carried out in $CDCl_3$, equilibrium mixtures of the imines **2** and the corresponding tautomeric oxazolidines were observed, whereas the ^{1}H NMR in CD_3OD showed resonances for only the open chain structures. For studies in imine−oxazolidine tautomerism, see: (a) Lambert, J. B.; Majchrzak, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3588−3591. (b) Lázár, L.; Lakatos, A. G.; Fülöp, F.; Bernáth, G.; Riddell, F. G. *Tetrahedron*. **1997**, *53*, 1081−1088 and references therein.

(9) Hine, J.; Yeh, C. H. *J. Am. Chem. Soc.* **1967**, *89*, 2669−2676.

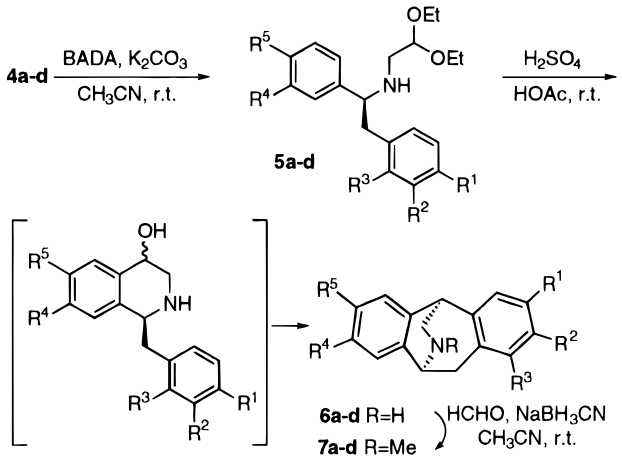
(10) Obtained from activated magnesium by entrainment with 1,2-dibromoethane and iodine. Hashigaki, K.; Kan, K.; Qais, N.; Takeuchi, Y.; Yamato, M. *Chem. Pharm. Bull.* **1991**, *39*, 1126−1131.

(11) (a) Suzuki, Y.; Takahashi, H. *Chem. Pharm. Bull.* **1983**, *31*, 31−40. (b Takahashi, H.; Suzuki, Y.; Hori, T. *Chem. Pharm. Bull.* **1983**, *31*, 2183−2191.

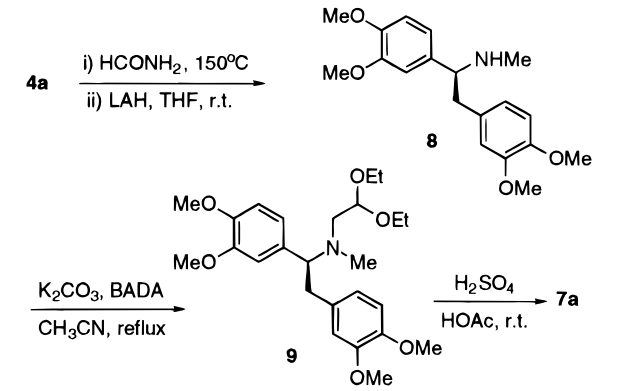
(12) The 1,2-diarylethylamine **4a** was prepared following the procedure described by Dyke, S. F.; Brown, D. W.; Sainsbury, M.; Hardy, G. *Tetrahedron* **1971**, *27*, 3495−3502.

(13) Dyke, S. F.; Ellis, A. C.; Kinsman, R. G.; White, A. W .C. *Tetrahedron* **1974**, *30*, 1193−1199.

Scheme 2



Scheme 3



methods previously reported for this kind of double cyclization.[14] Finally, in order to accomplish the final products, a *N*-methylation reaction was carried out, thus affording a series of *N*-methylated isopavines (**7a**−**d**) with optical purities greater than 94% (see Table 2).

We would also like to report that an alternative sequence of steps in the route toward the synthesis of *N*-methylisopavines **7** was also studied. In this case (see Scheme 3), when the methylation step was carried out *prior* to the final cyclization process, a partial racemization was detected in the final product. This low optical purity was also observed in dialkylated amine **8** and was calculated to be ca. 88% by HPLC (Chiralcel OD, UV detector, *n*-hexane/2-propanol 75:25 as eluent; flow rate 0.5 mL/min; retention times 16.9 min for the *R* isomer, 19.4 min for the *S* isomer).

In summary, a simple and very efficient synthetic route to obtain optically pure isopavine alkaloids has been developed starting from chiral 1,2-diarylethylamines, which, in turn, were obtained enantiomerically pure by using phenylglycinol as chiral auxiliary, and it has been applied with great success to the preparation of natural (−)-*O*-methylthalisopavine (**7a**) and (−)-amurensinine (**7d**).

Experimental Section[15]

Typical Procedure for the Synthesis of Imines 2a−c. Synthesis of (−)-(1′*S*)-(*E*)-*N*-(2-Hydroxy-1-isopropylethyl)-3,4-dimethoxybenzylideneamine (2a). A mixture of L-valinol [or (*S*)-(+)-phenylglycinol for **2b,c**] (0.98 g, 8.5 mmol), 3,4-dimethoxybenzaldehyde (1.42 g, 9.5 mmol), and molecular sieves (4 Å) in 60 mL of benzene was heated to reflux during 4 h. Then, after cooling, the mixture was filtered and the solvent was distilled under vacuum to afford a residue that was crystallized from Et_2O−pentane (1.96 g, 92%): mp 102−104 °C; $[\alpha]^{20}_D = -42.0$ ($c = 0.2$, EtOH); ^{1}H NMR (CD_3OD) 0.89 (d, 3H, $J = 6.7$), 0.97 (d, 3H, $J = 6.7$), 1.87−1.95 (m, 1H), 3.28−3.31 (m, 1H), 3.65 (dd, 1H, $J = 11.2, 8.4$), 3.83 (dd, 1H, $J = 11.2, 3.6$), 3.86 (s, 3H), 3.87 (s, 3H), 6.99 (d, 1H, $J = 8.3$), 7.24 (dd, 1H, $J = 8.3, 1.8$), 7.52 (d, 1H, $J = 1.8$), 8.17 (s, 1H); ^{13}C NMR (CD_3OD) 19.7, 20.2, 31.1, 56.4, 64.8, 80.4, 110.8, 112.1, 124.8, 130.3, 150.7, 153.1, 163.9; IR (KBr) ν 3330−3100, 1680 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 251 (M^+, 11), 220 ($M^+ - 31$, 100), 208 (21), 178 (12), 151 (28), 55 (12). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.81; H, 8.62; N, 5.21.

(−)-(1′*S*)-(*E*)-*N*-(2-Hydroxy-1-phenylethyl)-3,4-dimethoxybenzylideneamine (2b). According to the typical procedure imine **2b** was obtained from (*S*)-(+)-phenylglycinol and 3,4-dimethoxybenzaldehyde in 95% yield: mp 69−72 °C (*n*-heptane); $[\alpha]^{20}_D = -65.6$ ($c = 0.2$, EtOH); ^{1}H NMR (CD_3OD) 3.81 (s, 3H), 3.84 (s, 3H), 3.87 (d, 2H, $J = 6.5$), 4.43 (t, 1H, $J = 6.5$); 6.99 (d, 1H, $J = 8.0$), 7.23−7.51 (m, 7H), 8.39 (s, 1H); ^{13}C NMR (CD_3OD) 56.3, 67.6, 78.1, 110.8, 112.1, 124.9, 128.4, 129.5, 130.5, 142.3, 150.7, 153.2, 163.9; IR (KBr) ν 3600−3200, 1638 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 285 (M^+, 4), 254 ($M^+ - 31$, 100), 149 (12), 91 (8), 71 (8), 57 (11). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.95. Found: C, 71.31; H, 6.93; N, 4.98.

(−)-(1′*S*)-(*E*)-*N*-(2-Hydroxy-1-phenylethyl)-3,4-(methylenedioxy)-benzylideneamine (2c). According to the typical procedure imine **2c** was obtained from (*S*)-(+)-phenylglycinol and 3,4-(methylenedioxy)benzaldehyde in 91% yield: mp 101−103 °C (*n*-heptane); $[\alpha]^{20}_D = -111.2$ ($c = 1.0$, EtOH); ^{1}H NMR (CD_3OD) 3.92 (d, 2H, $J = 6.5$), 4.46 (t, 1H, $J = 6.5$), 6.04 (s, 2H), 6.91 (d, 1H, $J = 8.0$), 7.24−7.56 (m, 7H), 8.36 (s, 1H); ^{13}C NMR (CD_3OD) 67.8, 77.9, 102.9, 107.5, 108.9, 126.2, 128.4, 129.5, 132.1, 142.4, 149.7, 151.5, 163.2; IR (KBr) ν 3330−3100, 1635 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 269 (M^+, 2), 238 ($M^+ - 31$, 100), 180 (9), 77 (15). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.19; H, 5.59; N, 5.14.

Typical Procedure for the Synthesis of Amines 3a−e. Synthesis of (+)-(1*S*,1′*S*)-1,2-Bis(3,4-dimethoxyphenyl)-*N*-(2-hydroxy-1-isopropylethyl)-ethylamine (3a). A solution of imine **2a** (1.7 g, 6.77 mmol) in THF (20 mL) was added to a freshly prepared solution of (3,4-dimethoxybenzyl)magnesium chloride (**1a**) (5 equiv) in 55 mL of the same solvent, and the mixture was heated at 45−50 °C during 5 h. Then, after cooling, the reaction was quenched with 20 mL of a saturated solution of NH_4Cl, and decanted, and the aqueous layer was extracted twice with 20 mL of Et_2O. The combined organic extracts were dried over Na_2SO_4, and the solvent was distilled under vacuum. The residue was column chromatographed (hexanes/ethyl acetate, 1:1) to afford **3a** (3.41 g, 80%) as a colorless oil. An analytically pure sample was obtained by crystallization from *n*-heptane: mp 94−95 °C; $[\alpha]^{20}_D = +63.5$ ($c = 0.1$, EtOH); ^{1}H NMR ($CDCl_3$) 0.83 (d, 3H, $J = 6.8$), 0.87 (d, 3H, $J = 6.8$), 1.61−1.75 (m, 1H), 2.22−2.28 (m, 1H), 2.84 (d, 1H, $J = 7.1$), 2.85 (d, 1H, $J = 7.1$), 3.35 (dd, 1H, $J = 11.0, 4.4$), 3.55 (dd, 1H, $J = 11.0, 4.2$), 3.77 (s, 3H), 3.80−3.86 (m, 10H), 6.52 (d, 1H, $J = 1.9$), 6.62 (dd, 1H, $J = 8.0, 1.9$), 6.68−6.80 (m, 4H); ^{13}C NMR ($CDCl_3$) 19.1, 19.5, 29.5, 44.8, 55.7, 55.8, 59.9, 61.1, 61.6, 109.9, 110.7, 110.9, 112.5, 119.5, 121.3, 131.3 136.4, 147.4, 147.9, 148.5, 148.9; IR (KBr) ν 3500−3300 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 300 (100), 285 (55), 234 (37), 205 (26), 181 (13), 151 (21), 128 (11), 91 (10). Anal. Calcd for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.07; H, 7.95; N, 3.80.

(+)-(1*S*,1′*S*)-1,2-Bis(3,4-dimethoxyphenyl)-*N*-(2-hydroxy-1-phenyl-ethyl)ethylamine (3b). According to the typical procedure amine **3b** was obtained from imine **2b** and (3,4-dimethoxybenzyl)magnesium chloride (**1a**) in 80% yield: mp 104−106 °C (*n*-heptane); $[\alpha]^{20}_D = +62.3$ ($c = 0.1$, EtOH); ^{1}H NMR ($CDCl_3$) 2.10 (br s, 2H), 2.88 (dd, 1H, $J = 13.4, 6.9$), 2.97 (dd, 1H, $J = 13.4, 6.4$), 3.53 (dd, 1H, $J = 10.6, 6.9$), 3.66−3.88

(14) See refs 3b, 3c, and 13.

(15) For general procedures, see: Sotomayor, N.; Domínguez, D.; Lete, E. *J. Org. Chem.* **1996**, *61*, 4062−4074.

(m, 15H), 6.44 (d, 1H, J = 1.9), 6.51−6.73 (m, 5H), 7.14−7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) 43.5, 55.6, 55.7, 55.8, 61.6, 61.8, 65.5, 110.2, 110.7, 110.8, 112.6, 119.3, 121.3, 127.1, 127.3, 128.4, 131.0, 136.0, 141.1, 147.3, 147.9, 148.4, 148.7; IR (KBr) υ 3520−3200 cm^{-1}; MS (EI) m/z (rel intensity) 300 (100), 285 (51), 225 (16), 207 (9), 151 (12), 128 (9), 119 (8), 91 (7), 77 (5). Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.15; H, 7.18; N, 3.16.

(+)-(1*S*,1′*S*)-1-(3,4-Dimethoxyphenyl)-2-(2,3-dimethoxyphenyl)-*N*-(2-hydroxy-1-phenylethyl)ethylamine (3c). According to the typical procedure, amine **3c** was obtained from imine **2b** and (2,3-dimethoxybenzyl)magnesium chloride (**1b**) in 77% yield: $[\alpha]^{20}_D$ = +74.2 (c = 0.5, EtOH); ^{1}H NMR ($CDCl_3$) 2.25 (br s, 2H), 2.85 (dd, 1H, J = 13.1, 7.1), 3.11 (dd, 1H, J = 13.1, 6.9), 3.47 (dd, 1H, J = 10.6, 7.2), 3.67−3.73 (m, 7H), 3.80−3.91 (m, 8H), 6.49−6.89 (m, 6H), 7.16−7.24 (m, 5H); ^{13}C NMR ($CDCl_3$) 38.3, 55.6, 55.7, 55.8, 60.4, 60.9, 65.6, 110.2, 110.6, 110.8, 119.0, 122.9, 123.5, 127.1, 127.3, 128.4, 132.7, 136.6, 141.4, 147.3, 147.8, 148.6, 152.6; IR (neat) υ 3500−3300 cm^{-1}; MS (EI) m/z (rel intensity) 438 (M^++1, 4), 301 (23), 286 (100), 166 (81), 151 (13), 121 (17), 103 (20), 91 (18), 77 (14). Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.19; H, 7.22; N, 3.14.

(+)-(1*S*,1′*S*)-1-(3,4-Dimethoxyphenyl)-*N*-(2-hydroxy-1-phenylethyl)-2-(3-methoxyphenyl)ethylamine (3d). According to the typical procedure, amine **3d** was obtained from imine **2b** and (3-methoxybenzyl)magnesium chloride (**1c**) in 76% yield: $[\alpha]^{20}_D$ = +57.0 (c = 0.1, EtOH); ^{1}H NMR ($CDCl_3$) 2.22 (br s, 2H), 2.89 (dd, 1H, J = 13.3, 6.9), 3.02 (dd, 1H, J = 13.3, 6.9), 3.52 (dd, 1H, J = 10.7, 7.0), 3.63−3.69 (m, 12H), 6.55−6.83 (m, 6H), 7.10−7.29 (m, 6H); ^{13}C NMR ($CDCl_3$) 44.2, 55.0, 55.8, 55.9, 61.9, 65.6, 110.7, 111.3, 111.8, 115.1, 119.3, 121.8, 127.2, 127.3, 128.4, 129.0, 136.3, 140.3, 141.4, 148.2, 148.9, 159.5; IR (neat) υ 3550−3250 cm^{-1}; MS (EI) m/z (rel intensity) 286 (100), 271 (17), 218 (32), 190 (10), 166 (66), 121 (17), 91 (13), 77 (13). Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.43. Found: C, 73.33; H, 7.39; N, 3.57.

(+)-(1*S*,1′*S*)-2-(3,4-Dimethoxyphenyl)-1-(3,4-(methylenedioxy)phenyl)-*N*-(2-hydroxy-1-phenylethyl)ethylamine (3e). According to the typical procedure, amine **3e** was obtained from imine **2c** and (3,4-dimethoxybenzyl)magnesium chloride (**1a**) in 75% yield: $[\alpha]^{20}_D$ = +55.3 (c = 1.0, EtOH); ^{1}H NMR ($CDCl_3$) 2.61 (br s, 2H), 2.80 (dd, 1H, J = 13.4, 7.3), 2.97 (dd, 1H, J = 13.5, 6.2), 3.50 (dd, 1H, J = 10.7, 7.2), 3.66−3.85 (m, 9H), 5.83 (s, 1H), 5.84 (s, 1H), 6.41−6.70 (m, 6H), 7.14−7.25 (m, 5H); ^{13}C NMR ($CDCl_3$) 42.9, 55.4, 55.5, 61.4, 61.5, 65.3, 100.5, 107.2, 107.6, 110.7, 112.4, 120.3, 121.1, 126.9, 127.1, 128.2, 130.8, 137.3, 140.8, 146.2, 147.1, 147.3, 148.2; IR (neat) υ 3550−3250 cm^{-1}; MS (EI) m/z (rel intensity) 422 (M^+ + 1, 1), 285 (9), 270 (100), 150 (72). Anal. Calcd for $C_{25}H_{27}NO_5$: C, 71.24; H, 6.46; N, 3.32. Found: C, 71.19; H, 6.11; N, 3.14.

Typical Procedure for the Cleavage of *N*-Benzyl Groups. Synthesis of (+)-(1*S*)-1,2-Bis(3,4-dimethoxyphenyl)ethylamine (4a). A solution of the amine **3b** (0.88 g, 2 mmol) in EtOH (20 mL) was hydrogenated in the presence of 10% Pd−C (0.8 g) and 8 mL of 10% HCl. After absorption of hydrogen was complete (45−60 h), the catalyst was filtered off, and the filtrate was made basic with a saturated $NaHCO_3$ solution and extracted twice with 20 mL of CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, and the solvent was evaporated off under reduced pressure. The resulting residue was purified by flash column chromatography to afford **4a** as a colorless oil that was crystallized from EtOH (580 mg, 92%): mp 101−103 °C (lit.[12] mp 106−107 °C, racemate); $[\alpha]^{20}_D$ = +30.0 (c = 0.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 1.55 (br s, 2H), 2.75 (dd, 1H, J = 13.4, 8.4), 2.89 (dd, 1H, J = 13.4, 5.2), 3.81 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 4.12 (dd, 1H, J = 8.4, 5.2), 6.62−6.90 (m, 6H); ^{13}C NMR ($CDCl_3$) 46.0, 55.7, 55.8, 55.9, 57.2, 109.5, 110.9, 111.1, 112.4, 118.4, 121.2, 131.5, 138.2, 147.5, 147.9, 148.6, 148.8; IR (KBr) υ 3260, 3240 cm^{-1}; MS (EI) m/z (rel intensity) 316 (M^+ − 1, 1), 166 (100), 139 (10), 124 (12). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.11; H, 7.30; N, 4.41. Found: C, 68.02; H, 7.12; N, 4.05.

(+)-(1*S*)-1-(3,4-Dimethoxyphenyl)-2-(2,3-dimethoxyphenyl)ethylamine (4b). According to the typical procedure, amine **4b** was obtained from amine **3c** in 70% yield: $[\alpha]^{20}_D$ = +32.0 (c = 0.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 1.56 (br s, 2H), 2.82 (dd, 1H, J = 13.1, 8.5), 2.98 (dd, 1H, J = 13.1, 5.1), 3.79 (s, 3H), 3.83 (s, 6H), 3.84 (s, 3H), 4.18 (dd, 1H, J = 8.5, 5.1), 6.67−6.91 (m, 6H); ^{13}C NMR ($CDCl_3$) 40.8, 55.5, 55.7, 56.1, 60.3, 109.5, 110.6, 110.8, 118.1, 122.7, 123.5, 132.9, 138.7, 147.3, 147.7, 148.7, 152.6; IR (neat) υ 3260, 3240 cm^{-1}; MS (EI) m/z (rel intensity) 316 (M^+ − 1, 1), 166 (100), 139 (12), 124 (15). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.11; H, 7.30; N, 4.41. Found: C, 78.34; H, 7.42; N, 4.17.

(+)-(1*S*)-1-(3,4-Dimethoxyphenyl)-2-(3-methoxyphenyl)ethylamine (4c). According to the typical procedure, amine **4c** was obtained from amine **3d** in 80% yield: $[\alpha]^{20}_D$ = +25.0 (c = 0.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 1.30 (br s, 2H), 2.78 (dd, 1H, J = 13.2, 8.5), 2.95 (dd, 1H, J = 13.2, 5.1), 3.75 (s, 3H), 3.85 (s, 6H), 4.15 (dd, 1H, J = 8.5, 5.1), 6.70−6.89 (m, 6H), 7.18 (t, 1H, J = 7.8); ^{13}C NMR ($CDCl_3$) 46.7, 55.1, 55.9, 56.0, 57.1, 110.1, 111.5, 111.8, 115.0, 118.5, 121.7, 129.3, 138.5, 140.7, 148.2, 149.1, 159.7; IR (neat) υ 3360, 3340 cm^{-1}; MS (EI) m/z (rel intensity) 286 (M^+ − 1, 1), 166 (100), 139 (12), 124 (15). Anal. Calcd for $C_{17}H_{20}NO_3$: C, 71.06; H, 7.36; N, 4.87. Found: C, 71.04; H, 7.46; N, 4.59.

(+)-(1*S*,1′*S*)-2-(3,4-Dimethoxyphenyl)-1-(3,4-(methylenedioxy)phenyl)-ethylamine (4d). According to the typical procedure, amine **4d** was obtained from amine **3e** in 76%: mp 220−222 °C (EtOH−Et_2O as HCl salt) (lit.[12] mp 225−226 °C, racemate); $[\alpha]^{20}_D$ = +38.6 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 1.61 (br s, 2H), 2.74 (dd, 1H, J = 13.4, 8.5), 2.89 (dd, 1H, J = 13.3, 5.1), 3.81 (s, 3H), 3.84 (s, 3H), 4.08 (dd, 1H, J = 8.5, 5.1), 5.92 (s, 2H), 6.60−6.68 (m, 6H); ^{13}C NMR ($CDCl_3$) 45.2, 55.6, 55.7, 57.2, 100.8, 106.8, 107.8, 111.0, 112.4, 119.5, 121.2, 130.7, 131.2, 146.3, 147.0, 147.5, 148.6; IR (neat) υ 3250, 3200 cm^{-1}; MS (EI) m/z (rel intensity) 301 (M^+, 1), 150 (100), 123 (8), 93 (17), 65 (19). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.88; H, 5.99; N, 4.44.

Typical Procedure for the Synthesis of *N*-Alkylated Amines 5a−d. Synthesis of (+)-(1*S*)-1,2-Bis(3,4-dimethoxyphenyl)-*N*-(2,2-diethoxyethyl)ethylamine (5a). Over a stirred suspension of K_2CO_3 (0.97 g, 8.2 mmol) in 25 mL of dry acetonitrile was added a solution of amine **4a** (0.8 g, 2.52 mmol) in 15 mL of the same solvent and the mixture was refluxed during 2 h. Then, BADA (1.52 mL, 10.1 mmol) was added at once and the reflux was continued until the conversion was completed (3 d). After cooling, the mixture was quenched with water and dried over Na_2SO_4 and the solvent was removed *in vacuo* to afford, after crystallization from hexanes, pure amine **5a** as a white solid (1.02 g, 93%): mp 73−75 °C; $[\alpha]^{20}_D$ = +20.5 (c = 0.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 0.98 (t, 6H, J = 7.0), 1.67 (br s, 1H), 2.39−2.44 (m, 2H), 2.69−2.74 (m, 2H), 3.25−3.40 (m, 2H), 3.42−3.48 (m, 2H), 3.60−3.66 (m, 1H), 3.68 (s, 3H), 3.72 (s, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 4.39 (t, J = 5.1, 1H), 6.49−6.78 (m, 6H); ^{13}C NMR ($CDCl_3$) 14.9, 44.7, 49.5, 55.4, 55.5, 61.4, 61.5, 64.2 (C-1), 101.5, 109.9, 110.7, 111.0, 112.4, 119.3, 120.9, 131.2, 136.0, 147.3, 147.8, 148.5, 148.8; IR (KBr) υ 3310, 1260 cm^{-1}. Anal. Calcd for $C_{24}H_{35}NO_6$: C, 66.49; H, 8.13; N, 3.23. Found: C, 66.67; H, 8.29; N, 3.14.

(+)-(1*S*)-*N*-(2,2-Diethoxyethyl)-1-(3,4-dimethoxyphenyl)-2-(2,3-dimethoxyphenyl)ethylamine (5b). According to the typical procedure, amine **5b** was obtained from amine **4b** in 55% yield: $[\alpha]^{20}_D$ = +16.2 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 1.07 (t, 6H, J = 7.0), 2.00 (br s, 1H), 2.48−2.52 (m, 2H), 2.89 (d, 2H, J = 6.8), 3.33−3.47 (m, 2H), 3.50−3.56 (m, 2H), 3.74−3.79 (m, 4H), 3.82 (s, 9H), 4.49 (t, 1H, J = 5.5), 6.60−6.91 (m, 6H); ^{13}C NMR ($CDCl_3$) 14.9, 39.3, 49.5, 55.3, 55.5, 60.2, 61.6, 61.7, 63.0, 101.5, 109.7, 110.5, 119.1, 122.6, 123.3, 128.0, 132.5, 136.3, 147.1, 147.6, 148.6, 152.5; IR (neat) υ 3310, 1270 cm^{-1}; MS (EI) m/z (rel intensity) 301 (15), 282 (53), 236 (100), 190 (32), 151 (30). Anal. Calcd for $C_{24}H_{35}NO_6$: C, 66.49; H, 8.13; N, 3.23. Found: C, 66.29; H, 8.29; N, 3.14.

(+)-(1*S*)-*N*-(2,2-Diethoxyethyl)-1-(3,4-dimethoxyphenyl)-2-(3-methoxyphenyl)ethylamine (5c). According to the typical procedure, amine **5b** was obtained from amine **4b** in 57% yield: $[\alpha]^{20}_D$ = +17.2 (c = 0.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 0.97 (t, 3H, J = 7.0), 0.98 (t, 3H, J = 7.0), 1.79 (br s, 1H), 2.38−2.44 (m, 2H), 2.73−2.78 (m, 2H), 3.23−3.33 (m, 2H), 3.36−3.48 (m, 2H), 3.61 (s, 3H), 3.64−3.69 (m, 1H), 3.72 (s,

3H), 3.74 (s, 3H), 4.39 (t, 1H, J = 5.3), 6.58−6.79 (m, 6H), 7.05 (t, 1H, J = 7.7); ^{13}C NMR ($CDCl_3$) 14.8, 45.1, 49.3, 54.5, 55.3, 61.3, 61.5, 63.9, 101.3, 109.5, 110.5, 111.4, 114.3, 119.1, 121.1, 128.8, 135.8, 139.9, 147.6, 148.6, 159.2; IR (neat) υ 3310, 1260 cm^{-1}; MS (EI) m/z (rel intensity) 358 (M^+ − 45, 1), 309 (10), 282 (59), 271 (30), 236 (100), 190 (41), 151 (21). Anal. Calcd for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.29; H, 8.51; N, 3.19.

(+)-(1*S*)-*N*-(2,2-Diethoxyethyl)-2-(3,4-dimethoxyphenyl)-1-(3,4-(methylenedioxy)phenyl)ethylamine (5d). According to the typical procedure, amine **5d** was obtained from amine **4d** in 57% yield: $[\alpha]^{20}_D$ = +12.9 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 1.02 (t, 3H, J = 7.0), 1.04 (t, 3H, J = 7.0), 1.95 (br s, 1H), 2.41−2.47 (m, 2H), 2.71−2.77 (m, 2H), 3.32−3.45 (m, 2H), 3.47−3.50 (m, 2H), 3.64−3.71 (m, 1H), 3.74 (s, 3H), 3.76 (s, 3H), 4.43 (t, 1H, J = 5.1), 5.84 (s, 2H), 6.51−6.69 (m, 6H); ^{13}C NMR ($CDCl_3$) 14.9, 44.7, 49.4, 55.4, 55.5, 61.5, 61.7, 64.3, 100.5, 101.5, 107.1, 107.6, 110.9, 112.1, 120.3, 120.9, 137.4, 139.9, 146.2, 147.2, 147.5, 148.4; IR (neat) υ 3300, 1270 cm^{-1}. Anal. Calcd for $C_{23}H_{31}NO_6$: C, 67.17; H, 7.48; N, 3.35. Found: C, 67.19; H, 7.59; N, 3.14.

Typical Procedure for the Synthesis of Isopavinanes 6a−d. Synthesis of (−)-(5*R*,12*S*)-2,3,8,9-Tetramethoxyisopavinane (6a). H_2SO_4 (concentrated) (1.31 mL, 23.6 mmol) was added over a stirred solution of amino acetal **5a** (1.02 g, 2.36 mmol) in acetic acid (30 mL), and the mixture was stirred at room temperature during 30 min. Then, the solvent was removed under reduced pressure, and the residue was basified with NH_4OH and extracted twice with 30 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. Isopavine **6a** was purified by crystallization from EtOH (0.75 g, 93%): mp 169−171 °C (EtOH) (lit.[3d] mp 149−159 °C, racemate); $[\alpha]^{20}_D$ = −90.0 (c = 0.1, EtOH); ^{1}H NMR ($CDCl_3$) 2.04 (br s, 1H), 3.11 (dd, 1H, J = 17.2, 3.0), 3.22 (dd, 1H, J = 11.1, 4.3), 3.33 (dd, 1H, J = 17.2, 3.9), 3.58 (d, 1H, J = 11.1), 3.68 (d, 1H, J = 3.9), 3.75 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.22 (t, 1H, J = 3.4), 6.51 (s, 1H), 6.66 (s, 1H), 6.74 (s, 2H); ^{13}C NMR ($CDCl_3$) 41.6, 45.9, 50.9, 54.4, 55.8, 55.9, 56.0, 109.1, 109.2, 111.4, 114.4, 126.7, 131.8, 134.1, 135.1, 146.6, 147.6, 147.8; IR (KBr) υ 3340 cm^{-1}; MS (EI) m/z (rel intensity) 340 (M^+ − 1, 9), 339 (M^+ − 2, 47), 312 (M^+ − 29, 100), 308 (10), 269 (48), 156 (23). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.19; H, 6.59; N, 4.14.

(−)-(5*R*,12*S*)-2,3,9,10-Tetramethoxyisopavinane (6b). According to the typical procedure, isopavinane **6b** was obtained from amino acetal **5b** in 98% yield: $[\alpha]^{20}_D$ = −60.5 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 2.17 (br s, 1H), 3.10 (dd, 1H, J = 18.2, 3.2), 3.23 (dd, 1H, J = 11.2, 4.5), 3.31 (dd, 1H, J = 18.2, 3.9), 3.57 (d, 1H, J = 11.2), 3.73−3.78 (m, 7H), 3.84 (s, 6H), 4.30 (t, 1H, J = 3.5), 6.67 (d, 1H, J = 8.2), 6.73 (s, 1H), 6.74 (s, 1H), 6.88 (d, 1H, J = 8.2); ^{13}C NMR ($CDCl_3$) 36.5, 45.8, 50.7, 54.0, 55.6, 55.9, 56.1, 59.5, 109.1, 109.8, 122.6, 129.5, 131.8, 133.7, 136.3, 147.5, 147.8, 148.1, 151.1; IR (neat) υ 3350 cm^{-1}; MS (EI) m/z (rel intensity) 340 (M^+ − 1, 32), 312 (M^+ − 29, 100), 297 (79), 190 (74). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.33; H, 6.69; N, 4.33.

(−)-(5*R*,12*S*)-2,3,9-Trimethoxyisopavinane (6c). According to the typical procedure, isopavinane **6c** was obtained from amino acetal **5c** in 90% yield: mp 93−95 °C (EtOH/Et_2O); $[\alpha]^{20}_D$ = −71.5 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 2.71 (br s, 1H), 3.20 (dd, 1H, J = 11.3, 4.5), 3.39 (dd, 1H, J = 17.6, 3.5), 3.54 (d, 1H, J = 11.3), 3.69 (s, 3H), 3.71−3.75 (m, 2H), 3.83 (s, 6H), 4.24 (t, 1H, J = 3.2), 6.56−6.62 (m, 2H), 6.73 (s, 1H), 6.74 (s, 1H), 7.06 (d, 1H, J = 8.2); ^{13}C NMR ($CDCl_3$) 41.5, 45.0, 50.3, 53.9, 54.7, 55.6, 55.8, 108.8, 110.9, 116.1, 128.4, 131.2, 133.8, 135.0, 136.0, 147.2, 147.5, 157.9; IR (KBr) υ 3360 cm^{-1}; MS (EI) m/z (rel intensity) 309 (M^+ − 2, 25), 282 (M^+ − 29, 100), 251 (15), 239 (40), 208 (35). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.28; H, 6.79; N, 4.49. Found: C, 73.19; H, 6.58; N, 4.22.

(−)-(5*R*,12*S*)-8,9-Dimethoxy-2,3-(methylenedioxy)isopavinane (6d). According to the typical procedure, isopavinane **6d** was obtained from amino acetal **5d** in 95% yield: mp 129−131 °C (EtOH); $[\alpha]^{20}_D$ = −54.0 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 2.56 (br s, 1H), 3.08 (dd, 1H, J = 17.3, 3.1), 3.24 (dd, 1H, J = 11.2, 4.5), 3.35 (dd, 1H, J = 17.3, 3.8), 3.57 (d, 1H, J = 11.2), 3.69 (d, 1H, J = 3.8), 3.76 (s, 3H), 3.86 (s, 3H), 4.24 (t, 1H, J = 3.5), 5.83 (d, 1H, J = 1.1), 5.89 (d, 1H, J = 1.1), 6.51 (s, 1H), 6.64 (s, 1H), 6.69 (s, 1H), 6.70 (s, 1H); ^{13}C NMR ($CDCl_3$) 40.8, 45.8, 50.3, 54.5, 55.7, 55.8, 100.5, 106.1, 106.2, 111.1, 114.1, 126.4, 132.3, 134.7, 134.9, 145.8, 146.1, 146.5, 147.6; IR (KBr) υ 3310 cm^{-1}; MS (EI) m/z (rel intensity) 325 (M^+, 26), 308 (M^+ − 17, 11), 296 (M^+ − 29, 93), 253 (27),174 (100). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.88; N, 4.30. Found: C, 70.19; H, 5.69; N, 4.34.

Typical Procedure for the *N*-Methylation of Isopavinanes 6. Synthesis of (−)-(5*R*,12*S*)-*N*-Methyl-2,3,8,9-tetramethoxyisopavinane (7a) [(−)-*O*-Methylthalisopavine.]. Isopavinane **6a** (0.15 g, 0.44 mmol) was dissolved in dry acetonitrile (20 mL) under argon and 35% aqueous HCHO (0.17 mL, 2.2 mmol) and $NaBH_3CN$ (0.055 g, 0.88 mmol) were added in one portion. The solution was stirred at room temperature until the conversion was complete (90 min). Then, the mixture was quenched with water and extracted twice with 15 mL of CH_2Cl_2. The organic extracts were combined and dried over Na_2SO_4, and the solvent was removed *in vacuo*. Isopavinane **7a** was purified by crystallization from CCl_4 (0.15 g, 96%): mp 157−159 °C (lit.[4a] mp 155 °C); $[\alpha]^{20}_D$ = −103.6 (c = 0.2, EtOH); ^{1}H NMR ($CDCl_3$) 2.48 (s, 3H), 2.85 (dd, 1H, J = 10.4, 5.9), 2.90 (dd, 1H, J = 17.3, 3.0), 3.45−3.63 (m, 3H), 3.76 (s, 3H), 3.85 (s, 6H), 3.86 (s, 3H), 3.89−3.93 (m, 1H), 6.52 (s, 1H), 6.65 (s, 1H), 6.74 (s, 1H), 6.76 (s, 1H); ^{13}C NMR ($CDCl_3$) 38.4, 45.2, 46.0, 55.9, 56.1, 56.3, 60.1, 62.4, 109.3, 110.6, 111.8, 114.8, 126.9, 130.5, 134.2, 134.9, 146.8, 147.8, 147.9, 148.2; MS (EI) m/z (rel intensity) 355 (M^+, 16), 354 (M^+ − 1, 19), 312 (M^+ − 43), 204 (M^+ − 151, 100). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.95; H, 7.09; N, 3.94. Found: C, 70.83; H, 7.15; N, 3.77.

(−)-(5*R*,12*S*)-*N*-Methyl-2,3,9,10-tetramethoxyisopavinane (7b). According to the typical procedure, isopavinane **7b** was obtained from isopavinane **6b** in 93% yield: $[\alpha]^{20}_D$ = −109.6 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 2.46 (s, 3H), 2.82−2.92 (m, 2H), 3.42−3.52 (m, 2H), 3.68 (d, 1H, J = 4.0), 3.73 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 3.90 (t, 1H, J = 3.5), 6.63 (d, 1H, J = 8.3), 6.72 (s, 1H), 6.75 (s, 1H), 6.84 (d, 1H, J = 8.3); ^{13}C NMR ($CDCl_3$) 32.9, 44.9, 45.5, 55.4, 55.7, 55.9, 59.3, 59.5, 61.6, 108.7, 109.6, 109.9, 122.3, 129.2, 130.1, 133.4, 135.7, 147.3, 147.7, 147.9, 151.0; MS (EI) m/z (rel intensity) 354 (M^+ − 1, 30), 312 (39), 297 (31), 204 (100). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.95; H, 7.09; N, 3.94. Found: C, 70.99; H, 7.19; N, 3.74.

(−)-(5*R*,12*S*)-*N*-Methyl-2,3,9-trimethoxyisopavinane (7c). According to the typical procedure, isopavinane **7c** was obtained from isopavinane **6c** in 88% yield: $[\alpha]^{20}_D$ = −111.6 (c = 0.6, EtOH); ^{1}H NMR ($CDCl_3$) 2.50 (s, 3H), 2.89 (dd, 1H, J = 10.8, 4.6), 2.98 (dd, 1H, J = 17.8, 3.2), 3.54−3.70 (m, 6H), 3.84 (s, 3H), 3.85 (s, 3H), 3.95 (t, 1H, J = 3.5), 6.57−6.61 (m, 2H), 6.74 (s, 1H), 6.77 (s, 1H), 7.03 (d, 1H, J = 8.0); ^{13}C NMR ($CDCl_3$) 38.0, 45.0, 55.1, 55.9, 56.1, 59.6, 62.2, 108.8, 110.2, 111.4, 116.3, 128.5, 129.0, 133.7, 134.6, 135.8, 147.6, 148.2, 158.4; MS (EI) m/z (rel intensity) 325 (M^+, 30), 324 (M^+ − 1, 41), 282 (M^+ − 43, 56), 204 (100). Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.79; H, 7.29; N, 4.44.

(−)-(5*R*,12*S*)-*N*-Methyl-2,3-(methylenedioxy)-8,9-dimethoxyisopavinane (7d) [(−)-Amurensinine]. According to the typical procedure, amurensinine **7d** was obtained from isopavinane **6d** in 95%: mp 160−163 °C (EtOH−Et_2O) (lit.[16] mp 162−164 °C); $[\alpha]^{20}_D$ = −145.0 (c = 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 2.47 (s, 3H), 2.80−2.93 (m, 2H), 3.50−3.54 (m, 2H), 3.61 (d, 1H, J = 3.4), 3.76 (s, 3H), 3.77−3.88 (m, 1H), 3.85 (s, 3H), 5.83 (d, 1H, J = 1.2), 5.89 (d, 1H, J = 1.2), 6.51 (s, 1H), 6.61 (s, 1H), 6.70 (s, 1H), 6.71 (s, 1H); ^{13}C NMR ($CDCl_3$) 37.9, 45.1, 45.8, 55.7, 55.8, 59.7, 62.3, 100.5, 106.0, 107.1, 111.1, 114.1, 126.3, 130.9, 134.4, 134.8, 145.8, 146.2, 146.5, 147.6; MS (EI) m/z (rel intensity) 339 (M^+, 25), 322 (11), 296 (35), 188 (100). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.23; N, 4.13. Found: C, 70.69; H, 6.49; N, 4.04.

(16) Santavy, F.; Hruban, L.; Maturova, M. *Collect. Czech. Chem. Commun.* **1966**, *31*, 4286−4295.

Synthesis of (+)-(1*S*)-1,2-Bis(3,4-dimethoxyphenyl)-*N*-methylethylamine (8). A solution of the amine **4a** (0.50 g, 1.5 mmol) in formamide (10 mL) was stirred at 150 °C until complete conversion. Water was added to the mixture, and the resulting solution was then extracted twice with 20 mL of CH_2Cl and washed with H_2O and brine. The organic layers were collected, dried over Na_2SO_4, and filtered, and the solvent was evaporated off under reduced pressure. A THF solution of this crude was carefully added over a stirred solution of LAH (0.114, 3.0 mmol) in the same solvent at 0 °C. The mixture was refluxed until complete conversion (overnight) and then was quenched with MeOH and filtered, water was added, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and filtered, and the solvent was removed *in vacuo* to provide, after flash column chromatography (CH_2Cl_2/EtOAc 1:1), pure amine **8** as a colorless oil (1.12 g, 63%): $[\alpha]^{20}_D = +40.0$ ($c = 0.2$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 2.23 (s, 3H), 2.80 (d, 2H, $J = 7.0$), 2.90 (br s, 1H), 3.58 (t, 1H, $J = 7.0$), 3.69 (s, 3H), 3.74 (s, 3H), 3.76 (s, 3H), 3.77 (s, 3H), 6.51−6.81 (m, 6H); ^{13}C NMR ($CDCl_3$) 33.7, 43.9, 55.2, 55.3, 66.1, 110.1, 110.8, 111.1, 112.4, 119.3, 120.8, 130.6, 134.7, 147.2, 147.6, 148.3, 148.7; IR (KBr) υ 3600−3280 cm^{-1}; MS (EI) m/z (rel intensity) 330 ($M^+ - 1$, 2), 300 (21), 180 (100), 151 (15). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 71.73; H, 7.69; N, 4.64. Found: C, 71.59; H, 7.59; N, 4.29.

Synthesis (+)-(1*S*)-*N*-(2,2-Diethoxyethyl)-1,2-bis(3,4-dimethoxyphenyl)-*N*-methylethylamine (9). Over a stirred suspension of K_2CO_3 (0.21 g, 1.81 mmol) in 25 mL of dry acetonitrile a solution of amine **8** (0.15 g, 0.45 mmol) in 15 mL of the same solvent was added and the mixture was refluxed during 2 h. Then, BADA (1.31 mL, 1.81 mmol) was added and the reflux was continued until the conversion was completed (3 d). After being cooled to room temperature, the mixture was quenched with water and dried over Na_2SO_4 and the solvent was removed *in vacuo* to provide, after flash column chromatography (hexanes/EtOAc, 2:8), pure amine **9** as a colorless oil (0.67 g, 83%): $[\alpha]^{20}_D = +38.5$ ($c = 0.8$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) 1.16 (t, 3H, $J = 7.1$), 1.17 (t, 3H, $J = 7.1$), 2.34 (s, 3H), 2.48 (dd, 1H, $J = 13.5, 5.1$), 2.68 (dd, 1H, $J = 13.5, 5.2$), 2.86 (dd, 1H, $J = 13.4, 9.3$), 3.20 (dd, 1H, $J = 13.4, 5.2$), 3.41−3.62 (m, 4H), 3.69 (s, 3H), 3.78 (s, 3H), 3.81−3.84 (m, 7H), 4.52 (t, 1H, $J = 5.1$), 6.46 (d, 1H, $J = 1.8$), 6.54 (dd, 1H, $J = 8.1, 1.8$), 6.63−6.86 (m, 4H); ^{13}C NMR ($CDCl_3$) 15.2, 38.7, 39.8, 55.6, 55.7, 55.8, 56.8, 61.6, 61.7, 70.7, 101.9, 110.3, 110.7, 111.9, 112.5, 121.1, 132.2, 132.4, 146.9, 147.8, 148.2, 148.4; IR (neat) υ 1130 cm^{-1}; MS (EI) m/z (rel intensity) 402 (3), 300 (90), 296 (100), 285 (47), 195 (52), 151 (40). Anal. Calcd for $C_{25}H_{37}NO_6$: C, 67.09; H, 8.33; N, 3.13. Found: C, 67.22; H, 8.51; N, 3.24.

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