Asymmetric Synthesis of the Protoberberine Alkaloid (*S*)-(−)-Xylopinine Using Enantiopure Sulfinimines

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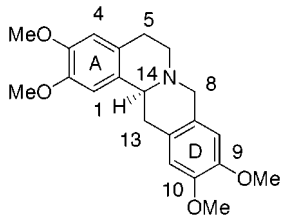
A concise enantioselective synthesis of (*S*)-(−)-xylopinine (**1**) is described involving the addition of the laterally lithiated derivative of *o*-tolunitrile of **16** to enantiopure sulfinimine (+)-**14**. Treatment of the resulting cyano sulfinamide adduct (−)-**17b** with DIBAL-H accomplishes five operations in a single pot and furnishes the cyclic imine (+)-**18** in good yield. Reduction and cyclization affords (*S*)-(−)-**1**. Alternatively basic hydrolysis of **17b**,**c** gives isoquinolone **21** that is cyclized and reduced to give (*S*)-(−)-**1**.

Xylopinine (**1**) is a prototypical member of the protoberberines, a large family of naturally occurring alkaloids characterized by a tetracyclic ring skeleton and an isoquinoline core.[1] Various alkoxy (methoxy, methylenedioxy) substitution patterns are found in the A- and D-rings, and a stereogenic center at C(14) is present as are alkyl and hydroxy groups at C(13). The protoberberines play key roles as precursors in the biosynthesis of many isoquinoline alkaloids such as rhoeadine, secoberbine, and benzo[*c*]phenanthridine.[2] The various biological properties that have been attributed to this class of alkaloids include antimicrobial, antileukemic, antitumor, and antiinflammatory activities.Although several racemic syntheses of the protoberberines have been reported, the small number of asymmetric syntheses undoubtedly reflects the lack of general methods to prepare them in enantiopure form that have the desired ring substitution patterns.[3] Indeed the majority of these asymmetric syntheses has been of (*S*)-(−)-xylopinine (**1**) (Figure 1). Meyers reported two asymmetric synthesis of (−)-**1** employing his chiral formamidine anions[4] and chiral bicyclic lactam technologies.[5] A chiral auxiliary mediated Pictet−Spengler synthesis was used by Comins[6] and by Czarnocki[7] to prepare this alkaloid while Kametani employed a photochemical cyclization strategy with an enantiomerically pure eneamide.[8]



(*S*)-(-)-Xylopinine (**1**)

Figure 1.

As part of a program aimed at developing new strategies for the asymmetric synthesis of biorelevant tetrahydroisoquinolines, we have been examining the reactions of laterally lithiated species **2** with enantiopure sulfinimines **3** (Scheme 1).[9] Cyclization of the resulting sulfinamide **4** gives the isoquinolone **5** or cyclic imine **6**, both of which can be further elaborated to the tetrahydroisoquinonine **7**. This methodology has the potential for avoiding many of the limitations of the Bischler−Napieralski and Pictet−Spengler protocols as well as providing isoquinolines with substitution patterns not easily accessible by other means. In this context we reported highly stereoselective asymmetric syntheses of (2*R*,4*S*)-(−)-6-methoxy-*N*-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinolin-4-ol (**7**, R = 4-MeO, $R^1 = R^2 = H$, $R^3 = Ph$, $R^4 = OH$) using the laterally lithiated amide derived from 4-methoxy-*N*,*N*-diethyl-*o*-toluamide (**2**, $X = C(O)NEt_2$, R = 4-MeO).[10] However, when this protocol was applied to the synthesis of *trans*-(1*R*,3*R*)-(−)-6,8-dimethoxy-1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**7**, R = 6,8-diMeO, $R^1 = R^3 = Me$, $R^2 = H$), the isoquinoline segment of the anti-HIV michellamines, it resulted in the formation of a complex mixture of sulfinamide **4** atropisomers.[11] These atropisomers are caused by restricted rotation of the *N*,*N*-diethylamide group, which prevents determination of the dr and eliminates the possibility of a obtaining a diastereomerically pure product. Use of the laterally lithiated *o*-tolylnitriles not only avoids this problem, but

(1) For a review see Bhakuni, D. S.; Jain, S. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: Orlando, FL, 1986; Vol. 28, pp 95−181.

(2) For reviews, see (a) Iwasa, K. In *The Alkaloids: Chemistry and Pharmacology*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 1995; Vol 46, pp 273−346. (b) Hanaoka, M. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: Orlando, FL, 1988; Vol. 33, pp 141−222.

(3) For references to the asymmetric synthesis of other protoberberine alkaloids, see (a) Matulenko, M. A.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 573. (b) Pyne, S. G.; Dikie, B. *J. Org. Chem.* **1990**, *55*, 1932. (c) Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 4183.

(4) Meyers, A. I.; Boes, M.; Dickman, D. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 458.

(5) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 4607.

(6) Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327.

(7) Czarnocki, Z.; Arazny, Z. *Heterocycles* **1999**, *51*, 2871.

(8) Kametani, T.; Takagi, N.; Toyata, M.; Honda, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2830.

(9) For a reviews on lateral lithiation reactions, see: (a) Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 5. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

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(11) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*, 3901.

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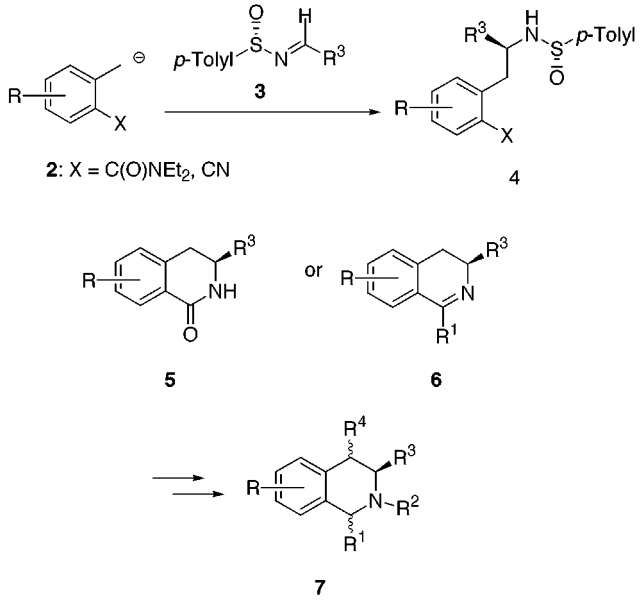
Scheme 1



the corresponding sulfinamide **4** (X = CN) can be converted, in one pot, to the cyclic imine **6**.[11] As an extension of this new protocol we describe a concise stereoselective asymmetric synthesis of (*S*)-(−)-xylopinine (**1**).

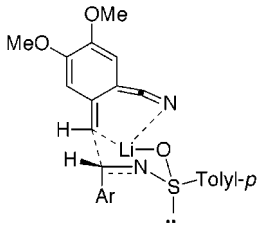
Results and Discussion

Our synthesis begins with preparation of the requisite sulfinimines **13**−**15** as outlined in Scheme 2. Commercially available 3,4-dimethoxyphenethanol (**8**) was protected either as the benzyl or TBDMS ethers **9** in excellent yields. Refluxing of **9** with NBS in $CHCl_3$ selectively furnished the desired bromides **10** in good yield. Lithium halogen exchange was accomplished by treating **10** with *sec*-BuLi at −78 °C, which was then treated with dry DMF to give the protected aldehydes **11** in 82% yield. Sulfinimines **13**−**15** were prepared in 85−87% yield, as previously described,[12] by reacting the aldehydes with (*S*)-(−)-*p*-toluenesulfinamide (**12a**),[12] (*S*)-(−)-2-methoxynaphthalenesulfinamide (**12b**)[13] or (*R*)-(+)-*tert*-butanesulfinamide (**12c**),[14] in the presence of Ti(OEt)$_4$.

3,4-Dimethoxy-6-methylbenzonitrile (**16**), prepared from the corresponding bromide and CuCN in 90% yield,[11] reacts with LDA at −78 °C in THF to give the intensively red-colored solution of the laterally lithiated *o*-tolylnitrile. To this solution was added 1 equiv of sulfinimine (*S*)-(+)-**13a** (PG = Bn) (Scheme 3). After 0.5 h at −78 °C the reaction mixture was quenched at this temperature with aqueous NH_4Cl. The de, readily determined by ^{1}H NMR on the crude reaction mixture, was an acceptable 80%. However, all attempts to separate the diastereomeric sulfinamides **17a** by conventional chromatography (flash, preparative TLC) were unsuccessful. Attempts to improve the diastereoselectivity by varying the solvent, base, or by the addition of additives had no effect on the diastereomeric ratio (Table 1).

One of the advantages of our isoquinoline synthetic strategy (Scheme 1) is that it offers many opportunities to enhance the diastereomeric ratio and/or give chromatographically separable products by altering the reaction partners, i.e., the sulfinyl auxiliary (R) or the hydroxyl protecting group (PG) in sulfinimines **13**−**15**. Thus reaction of the laterally lithiated nitrile of **16** with the *O*-*tert*-butyldimethylsilyl-protected sulfinimine (*S*)-(+)-**13b** gave the corresponding sulfinamide (S_S,*S*)-**17b** in 68% yield with a slightly lower dr of 88:12 (76% de) (Table 1: entry 8). Importantly, the diastereoisomers were readily separable by flash chromatography. A significantly improved dr of 98:2 (96% de) was observed for the benzyl-protected 2-methoxynaphthylsulfinimine (*S*)-(+)-**14** affording the major diastereoisomer (S_S,*S*)-(−)-**17c** in 68% yield (Table 1, entry 9). With the *tert*-butanesulfinimine (*R*)-(−)-**15** the laterally lithiated nitrile of **16** gave a complex mixture of products and the corresponding sulfinamide was not detected (Table 1, entry 10).

The major diastereoisomer is predicted to have the (*S*)-configuration at the newly created chiral center in **17**. This assumption, confirmed in the synthesis of (*S*)-(−)-**1**, is based on our mechanistic hypothesis[11] wherein the *o*-quinomethane structure derived from the nitrile anion is chelated through the lithium cation to the sulfinyl oxygen and approaches the *Si*-face of the sulfinimine via six-membered chairlike transition state **TS-1**.



TS-1

Treatment of (S_S,*S*)-(−)-**17b** with a slight excess of DIBAL-H at 0 °C in toluene followed by hydrolysis with 3 N HCl resulted in the cyclic imine (*S*)-(+)-**18** in 70% isolated yield (Scheme 4). This accomplishes five operations in a single-pot. DIBAL-H reduces the nitrile to the aldimine (operation 1), and then hydrolysis deprotects TBDMS-ether (operation 2), converts the aldimine to the aldehyde (operation 3), removes the sulfinyl group to give the free amine (operation 4), which cyclizes to the imine (operation 5). Reduction of (+)-**18** with $NaBH_4$ gave the tetrahydroisoquinoline (*S*)-(+)-**19** as the only detected isomer in 85% yield. Cyclization was easily accomplished by conversion of alcohol **19** into its tosylate **20** with TsCl in pyridine solvent, isolation of the crude tosylate by extraction into EtOAc, and treating with NaH. (*S*)-(−)-Xylopinine (**1**) was isolated in 73% yield for the two steps. The spectral properties of (*S*)-(−)-**1** were consistent with literature values and confirms its absolute configuration.

Synthesis of (*S*)-(−)-**1** from (*S*)-(−)-8-oxoxylopine (**23**) was also explored because of the possibility that the corresponding laterally lithiated amide species could provide access to diversely C(13)-substituted protober-

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(13) Davis, F. A.; Lee, T.; Zhang Z. Unpublished results. (*S*)-(−)-2-Methoxynaphthalenesulfinamide (**12b**), mp 148−150 °C, $[\alpha]^{20}_D$ −81.2 (*c* 1.0, $CHCl_3$) was prepared in the similar manner as (*S*)-(−)-**12a** in 85% yield. Full details will appear in due course.

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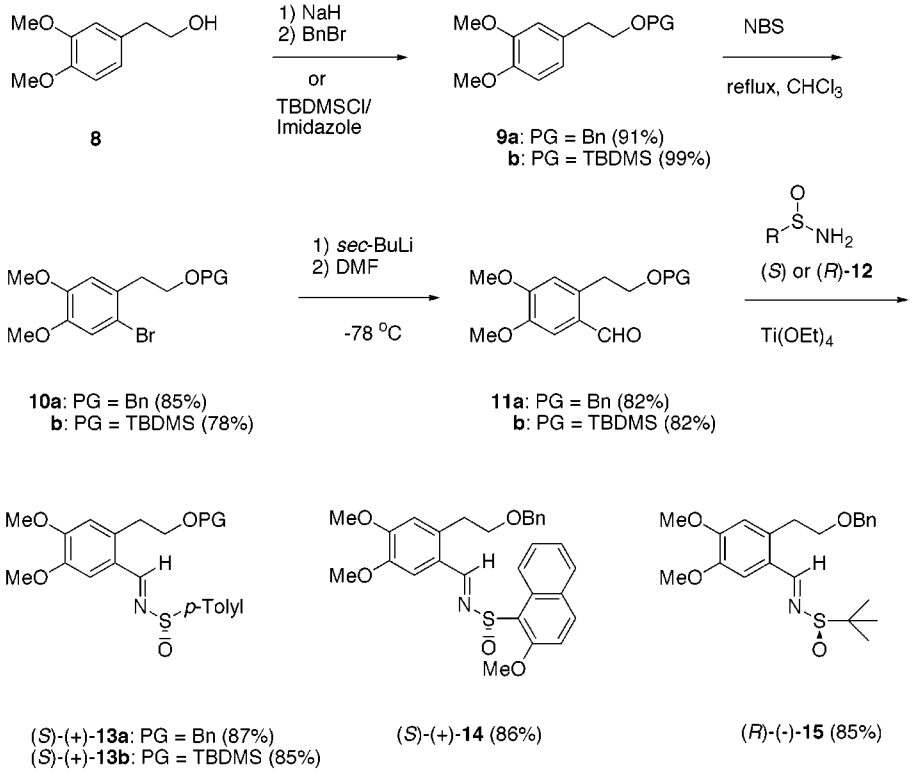
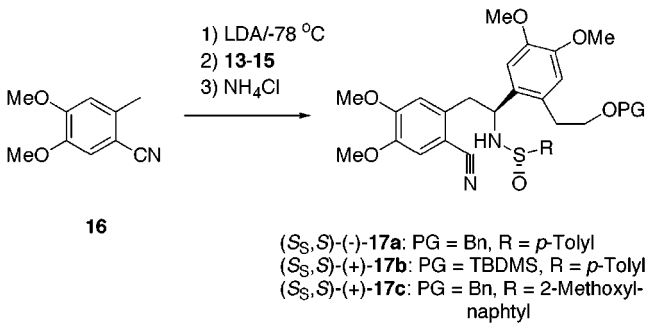
Scheme 2[a]



[a] **a**: R = (*S*)-(−)-*p*-tolyl, **b**: R = (*S*)-(−)-2-methoxynaphthyl, **c**: R = (*R*)-(+)-*tert*-butylsulfinyl.

Scheme 3



berines by reaction with electrophiles. Iinitial attempts to hydrolyze the nitrile group in **17b**,**c** under acidic conditions failed. Although refluxing **17b** in concentrated HCl for 10 h removed the sulfinyl auxiliary, the desired acid was not obtained, affording instead the amino nitrile. Fortunately, heating **17b**,**c** in aqueous MeOH with 4 equiv of LiOH for 8 h produced a 77−78% yield of **21a**,**b**. For the TBDMS protected ether, **17b**, the alcohol **21a** was obtained directly in 78% yield. Hydrogenation of **21b** over H_2/$Pd(OH)_2$ was necessary and furnished **21a** in 96% yield. The isoquinolone alcohol **21a** was converted, as before, into the tosylate **22**, which was treated with NaH to give (*S*)-(−)-**23** in 75% overall yield for the two operations.All attempts to generate the laterally lithiated amide of (+)-**23** by treatment with LDA failed and starting material was recovered. Stronger bases such as *n*-butyllithium are reported to prefer 1,2-addition at the 8-oxo group in **23** to give enamines.[18] Inspection of molecular models suggest that steric constraints may prevent the requisite planar conformation necessary for formation of the *o*-quinomethane structure, i.e., **TS-1**.

In summary, concise asymmetric synthesis of naturally occurring (*S*)-(−)-xylopinine (**1**) from readily available sulfinimine derived cyclic imine (*S*)-(+)-**18** and (*S*)-(−)-8-oxoxylopine (**23**) is described. Application of this protocol (Scheme 1) to the enantioselective synthesis of other protoberberine alkaloids is underway.

Experimental Section

General Procedures. Column chromatography was performed on silica gel, Merck grade 60 (230−400 mesh). TLC plates were visualized with UV, in an iodine chamber or with phosphomolybdic acid, unless noted otherwise. Melting points were recorded on a Mel-Temp apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter and IR spectra were recorded, using NaCl plates or as KBr disks, on a Mattson 4020 FTIR polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a GE Omega 500, operating at 500 and 125 MHz, respectively. HRMS were performed in the Department of Chemistry, Drexel University, Philadelphia, PA, using a Fissions ZAB HF double-focusing mass spectrometer. Elemental analyses were performed in the Department of Chemistry, University of Pennsylvania, Philadelphia, PA.

Dichloromethane was distilled over calcium hydride under an inert atmosphere. THF and ether were freshly distilled under nitrogen from a purple solution of sodium and benzophenone ketyl. Unless stated otherwise, all reagents were purchased from commercial sources and used without additional purification.

2-Bromo-4,5-dimethoxytoluene. In a 250-mL two-necked round-bottom flask equipped with a stirring bar and rubber

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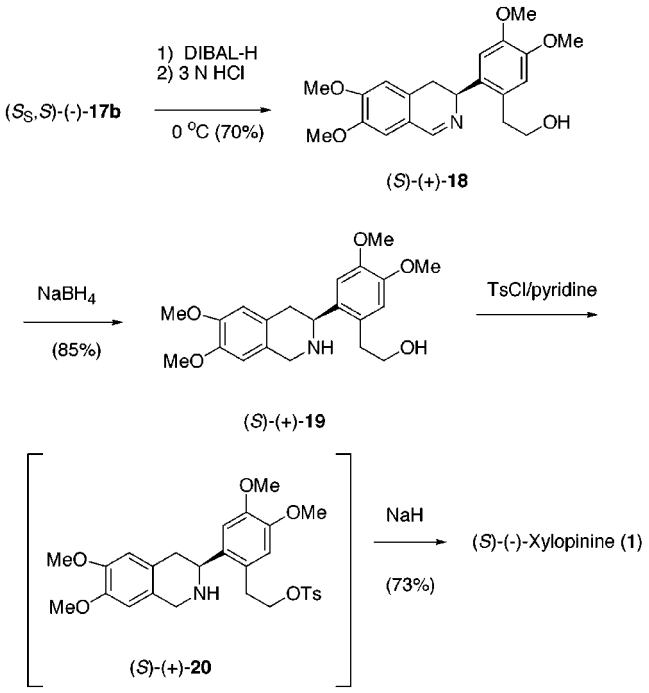
(18) Lenz, G. R. *J. Org. Chem.* **1974**, *39*, 2846.

Table 1. Reaction of Laterial Lithiated *o*-Tolylnitrile 16 with Sulfinimines 13−15

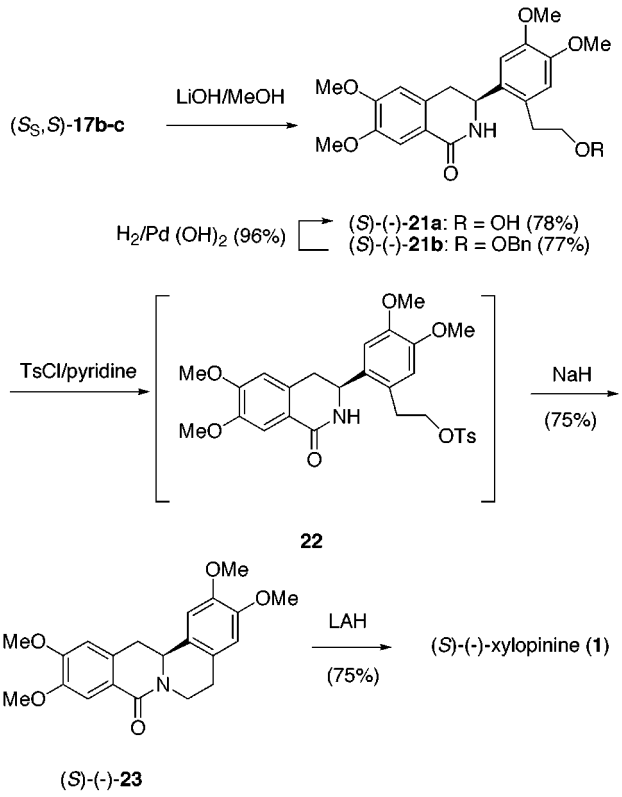
entry	sulfinimine	conditions	products	% yield[a]	dr (% de)[b]
1	(*S*)-(+)-**13a**	THF, 0.5 h	(S_S,*S*)-(−)-**17a**	70	90:10 (80%)[c]
2		THF, CuI 1:1 THF:EtO_2		68	90:10 (80%)[c]
3		THF/DMPU		68	90:10 (80%)[c]
4		THF/Me_3Al		68	90:10 (80%)[c]
5		toluene	no reaction		
6		THF/sec-BuLi,TMEDA	complex mixture and **13a** recovered		
7		THF/LiHMDS	no reaction		
8	(*S*)-(+)-**13b**	THF, 0.5 h	(S_S,*S*)-(−)-**17b**	68	88:12 (76%)
9	(*S*)-(+)-**14**	THF, 0.5 h	(S_S,*S*)-(−)-**17c**	68	98:2 (96%)
10	(*R*)-(−)-**15**	THF, 0.5 h	complex mixture of products		

[a] Isolated yield of pure major diastereoisomer. [b] Determined from the ^{1}H NMR of the crude reaction mixtures. [c] Could not be separated by conventional chromatography.

Scheme 4



Scheme 5



septa under an argon atmosphere was placed 2.0 g (13.14 mmol) of 3,4-dimethoxytoluene (Aldrich) in $CHCl_3$ (60 mL). *N*-Bromosuccinamide, 2.38 g (13.40 mmol), was added under an argon atmosphere, and the reaction mixture was refluxed for 4 h. The organic phase was extracted with $CHCl_3$ (2 × 30 mL), H_2O (20 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc 50:1) gave 3.29 g (85%) of an oil. Spectral properties are consistent with literature values.[16]

3,4-Dimethoxy-6-methylbenzonitrile (16). In a 250-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 2.0 g (8.65 mmol) of 2-bromo-4,5-dimethoxytoluene in DMF (40 mL). To the reaction mixture was added 1.16 g (12.97 mmol) of CuCN, and the solution was stirred at 120 °C for 16 h and cooled to room temperature, and H_2O (30 mL) was added. The organic phase was extracted with $CHCl_3$ (2 × 30 mL) and organic portion was washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc 5:1) gave 1.38 g (90%) of a white solid, mp 79−80 °C (lit.[17] 81 °C); IR (KBr) 2214 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 1 H), 3.80, 3.86 (2 s, 6 H), 6.74, 6.99 (2 s, 2 H).

1,2-Dimethoxy-4-(2-benzyloxyethyl)benzene (9a). In a 100-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 3.0 g (16.46 mmol) of 3,4-dimethoxyphenethyl alcohol (Aldrich) in THF (50 mL). To the solution was added 0.59 g (24.69 mmol, 95% dry) of sodium hydride at 0 °C, and the solution was stirred for 30 min. At this time 1.95 mL (16.46 mmol) of benzyl bromide was added dropwise, and the reaction mixture was stirred for 2 h. Cold H_2O (5 mL) was added, the solution was extracted with EtOAc (2 × 30 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc 25:1) gave 4.12 g (91%) of an oil; IR (neat) 2935, 2857, 1516, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.88 (t, J = 6.9 Hz, 2 H), 3.68 (t, J = 6.9 Hz, 2 H), 3.85, 3.86 (2 s, 6 H), 4.53 (s, 2 H), 6.77 (m, 3 H), 7.329 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 36.53, 56.34, 56.45, 72.00, 73.54, 111.78, 112.88, 121.39, 128.11, 128.19, 128.92, 129.94, 132.27, 148.06, 149.35. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97, H 7.40. Found: C, 75.13; H, 7.54.

1,2-Dimethoxy-4-(2-*tert*-butyldimethylsiloxyethyl)benzene (9b). In a 100-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 3.0 g (16.5 mmol) of 3,4-dimethoxyphenethyl alcohol (Aldrich) in DCM (50 mL) at 0 °C. Imidazole (1.34 g, 19.75 mmol) and *tert*-butyldimethylsilyl chloride (2.72 g, 18.10 mmol) were added at 0 °C, and the reaction mixture was stirred for 2 h. At this time the solution was extracted with DCM (2 × 25 mL) and the organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc 10:1) gave 4.83 g (99%) of an oil; IR (neat) 2952, 2856, 1516, 1260,

1031, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (s, 6 H), 0.88 (s, 9 H), 2.78 (t, J = 6.9 Hz, 2 H), 3.85, 3.86 (2 s, 6 H), 6.75 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ −4.70, 18.98, 26.45, 39.83, 56.43, 56.56, 65.35, 111.78, 113.21, 121.64, 132.60, 148.08, 149.32. Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.52. Found: C, 64.70; H, 9.46.

1-Bromo-4,5-dimethoxy-2-(2-benzyloxyethyl)benzene (10a). In a 100-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 4.0 g (14.69 mmol) of **9a** in $CHCl_3$ (60 mL), and 2.66 g (14.98 mmol) of *N*-bromosuccinamide was added. The reaction mixture was refluxed for 4 h, the organic phase was extracted with DCM (50 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc 30:1) gave 4.38 g (85%) of a colorless oil; IR (neat) 2934, 2848, 1507, 1257, 1099 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.00 (t, J = 6.9 Hz, 2 H), 3.69 (t, J = 6.9 Hz, 2 H), 3.82, 3.85 (2 s, 6 H), 4.55 (s, 2 H), 6.80, 7.00 (2 s, 2 H), 7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 36.83, 56.66, 56.81, 70.35, 73.63, 114.45, 114.92, 116.07, 128.24, 128.27, 129.03, 130.92, 139.06, 148.78, 148.84. Anal. Calcd for $C_{17}H_{19}BrO_3$: C, 58.13; H, 5.45. Found: C, 58.35; H, 5.07.

1-Bromo-4,5-dimethoxy-2-(2-*tert*-butyldimethylsiloxyethyl)benzene (10b). In a 100-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 2.2 g (10.79 mmol) of **9b** in $CHCl_3$ (50 mL) and 1.95 g (6.11 mmol) of *N*-bromosuccinamide. The reaction mixture was refluxed for 4 h, cooled to room temperature, and extracted with DCM (2 × 20 mL). The organic phase was washed with H_2O (20 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc 50:1) gave 3.16 (78%) of a colorless oil; IR (neat) 2953, 2855, 1509, 1257, 1096, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 6 H), 0.86 (s, 9 H), 2.88 (t, J = 6.9 Hz, 2 H), 3.79 (t, J = 6.9 Hz, 2 H), 3.84 (s, 6 H), 6.78, 6.98 (2 s, 2 H), ^{13}C NMR ($CDCl_3$) δ −5.44, 18.22, 25.86, 39.20, 55.86, 56.06, 62.57, 114.16, 115.26, 130.37, 147.96. Anal. Calcd for $C_{16}H_{27}BrO_3Si$: C, 51.19; H, 7.25. Found: C, 51.39; H, 7.21.

4,5-Dimethoxy-2-(benzyloxyethyl)benzaldehyde (11a). In a 100-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 3.0 g (8.54 mmol) of **10a** in THF (50 mL) at −78 °C. To the reaction mixture was added dropwise 13.1 mL (1.3 M in cyclohexane, 17.08 mmol) of *sec*-BuLi at −78 °C. The solution was stirred for 45 min and 1.24 g (17.08 mmol) of DMF in THF (2 mL) was added. After stirring for 15 min at −78 °C, the reaction mixture was warmed to room temperature and stirred for 2 h, and a saturated solution of NH_4Cl (3 mL) was added. The organic phase was extracted with Et_2O (2 × 50 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc 10:1) gave 2.10 g (82%) of a gum; IR (neat) 2955, 2856, 1675, 1515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28 (t, J = 6.9 Hz, 2 H), 3.70 (t, J = 6.9 Hz, 2 H), 3.92 (s, 6 H), 4.49 (s, 2 H), 6.76, 7.37 (2 s, 2 H), 7.30 (m, 5 H), 10.19 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 32.70, 56.64, 56.71, 71.74, 73.07, 111.99, 114.18, 127.98, 128.16, 128.24, 129.00, 137.72, 138.82, 148.53, 154.22, 190.75. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.82; H, 6.90.

4,5-Dimethoxy-2-(2-*tert*-butyldimethylsilyoxyethyl)-benzaldehyde (11b). In a 100-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was place 3.0 g (7.99 mmol) of **10b** in THF (50 mL) at −78 °C. To the reaction mixture was added dropwise 10.62 mL (15.98 mmol) of *sec*-BuLi at −78 °C, and the solution was stirred for 45 min and 1.16 g (15.98 mmol) of dry DMF in THF (2 mL) was added. After stirring for 15 min, the reaction mixture was warmed to room temperature, stirred for 2 h, and quenched with saturated NH_4Cl (3 mL). The organic phase was extracted with Et_2O (2 × 25 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/EtOAc 10:1) gave 2.12 g (82%) of a gum; IR (neat) 2953, 2856, 1675, 1215 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6 H), 0.82 (s, 9 H), 3.16 (t, J = 6.9 Hz, 2 H), 3.82 (t, J = 6.9 Hz, 2 H), 3.91, 3.93 (2 s, 6 H), 6.74, 7.37 (2 s, 2 H), 10.18 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ −5.58, 18.20, 25.79, 34.76, 55.95, 64.33, 110.68, 113.56, 127.45, 137.46, 147.75, 153.44, 190.13. Anal. Calcd for $C_{17}H_{28}O_4Si$: C, 62.92; H, 8.70. Found: C, 62.68; H, 8.69.

(*S*)-(+)-2-[(2-Benzyloxyethyl)-4,5-dimethoxybenzylidine]-*p*-toluenesulfinamide (13a). General Method. In a 100-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 1.0 g (3.33 mmol) of **11a** in DCM (30 mL) at 0 °C. To the reaction mixture were placed 0.568 g (3.36 mmol) of (*S*)-(−)-*p*-toluenesulfinamide (**12**)[12] and 2.79 mL (13.36 mmol) of titanium(IV) ethoxide, and the reaction mixture was stirred for 8 h. At this time H_2O (1.5 mL) was added, and the organic phase was filtered through Celite and concentrated. Purification by flash chromatography (hexane/EtOAc 10:3) gave 1.26 g (87%) of a solid. mp 101−102 °C. $[\alpha]^{20}_D$ +97.2 (*c* 1.5, $CHCl_3$); IR (KBr) 1596, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.39 (s, 3 H), 3.22 (m, 2 H), 3.66 (t, J = 6.6 Hz, 2 H), 3.88 (s, 6 H), 4.46 (s, 2 H), 6.76, 7.46 (2 s, 2 H), 7.28 (m, 7 H), 7.62 (d, J = 8.1 Hz, 1 H), 8.98 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.37, 32.66, 55.92, 70.93, 72.91, 110.88, 113.27, 124.66, 124.76, 127.44, 128.17, 129.74, 135.46, 138.20, 141.51, 142.29, 147.71, 152.33, 158.15. Anal. Calcd for $C_{25}H_{27}NO_4S$: C, 68.62; H, 6.22; N 3.20. Found: C 68.32, H 6.26; N 2.98.

(*S*)-(+)-2-[(2-*tert*-Butyldimethylsiloxyethyl)-4,5-dimethoxybenzylidine]-*p*-toluenesulfinamide (13b). Purification by flash chromatography (hexane/EtOAc 10:2) gave 0.81 g (85%) of a gum; $[\alpha]^{20}_D$ +40.8 (*c* 0.25, $CHCl_3$), IR (neat) 2953, 2855, 1584, 1520, 1269 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H), 0.82 (s, 9 H), 2.39 (s, 3 H), 3.10 (m, 2 H), 3.79 (m, 2 H), 3.88, 3.91 (2 s, 6 H), 6.71, 7.47 (2 s, 2 H), 7.29, 7.63 (2 d, J = 8.1 Hz, 4 H), 8.94 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ −4.91, 18.85, 22.01, 26.46, 36.18, 56.52, 56.58, 64.84, 111.33, 114.26, 125.36, 125.41, 130.39, 136.55, 142.15, 143.01, 148.35, 152.89, 158.81. Anal. Calcd for $C_{24}H_{35}NO_4SSi$: C, 62.44; H, 7.64; N, 3.03. Found: C, 62.45; H, 7.76; N, 2.76.

(*S*)-(+)-2-[(2-Benzyloxyethyl)-4,5-dimethoxybenzylidine]-1-methoxynaphthalenesulfinamide (14). Prepared from (*S*)-(−)-2-methoxynaphthalenesulfinamide (**12b**)[13] and **11a**; purification by flash chromatography (hexane/EtOAc 10:3) gave 1.44 g (86%) of a gum; $[\alpha]^{20}_D$ +63.2 (*c* 0.7, $CHCl_3$); IR (neat) 2935, 2854, 1568, 1506, 1271 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28 (m, 2 H), 3.70 (m, 2 H), 3.85, 3.89, 3.94 (3 s, 9 H), 4.45 (d, J = 3.5 Hz, 2 H), 6.70, 7.46 (2 s, 2 H), 7.61, 7.95, 8.65 (3 d, J = 3.5 Hz, 3 H), 9.29 (s, 1 H); ^{13}C ($CDCl_3$) δ 32.68, 55.93, 71.19, 73.30, 110.79, 113.22, 113.46, 122.31, 122.48, 124.32, 124.85, 127.49, 127.92, 128.68, 129.29, 129.45, 131.38, 134.43, 134.97, 138.18, 147.73, 152.12, 157.17, 159.07. Anal. Calcd for $C_{29}H_{29}NO_5S$: C, 69.16; H, 5.80; N, 2.78. Found: C, 68.97; H, 5.81; N, 2.87.

(*R*)-(−)-2-[(2-Benzyloxyethyl)-4,5-dimethoxybenzylidene]-*tert*-butylsulfinamide (15). Prepared from (*R*)-(+)-*tert*-butanesulfinamide (**12c**)[14] and **11a**; purification by flash chromatography (hexane/EtOAc 5:1) gave 0.23 g (85%) of a gum; $[\alpha]^{20}_D$ −50.1 (*c* 0.6, $CHCl_3$); IR(neat) 2934, 2871, 1583, 1514, 1280; ^{1}NMR ($CDCl_3$) δ 1.24 (s, 9 H), 2.68 (t, J = 2.5 Hz, 2 H), 3.67 (m, 2 H), 3.90, 3.91 (2 s, 6 H), 4.48 (s, 2 H), 6.78, 7.47 (2 s, 2 H), 7.30 (m, 5 H), 8.71 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.24, 33.43, 56.60, 56.66, 58.20, 71.68, 73.68, 111.69, 114.18, 125.57, 128.19, 129.00, 135.86, 138.91, 148.46, 152.86, 160.97. Anal. Calcd for $C_{22}H_{29}NO_4S$: C, 65.48; H, 7.24; N, 3.47. Found: C, 65.31; H, 7.33; N, 3.32.

(S_S,*S*)-(−)-*N*-[1-(2-(2-Benzyloxyethyl]-4,5-dimethoxyphenyl)-2-(2-cyano-4,5-dimethoxyphenyl]-*p*-toluenesulfinimide (17a). General Procedure. In a 100-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 1.49 mL (1.5 M in THF, 2.24 mmol) of LDA in THF (25 mL) at −78 °C followed by the dropwise addition of 0.20 g (1.12 mmol) of 3,4-dimethoxy-6-methylbenzonitrile (**16**) in THF (2 mL). The reaction mixture was stirred for 0.5 h, and 0.540 g (1.23 mmol) of **13a** in THF (2 mL) was added dropwise. After stirring for 0.5 h, saturated NH_4Cl (5 mL) was added at −78 °C and the solution was warmed to room temperature. The reaction mixture was extracted with Et_2O (2 × 30 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chroma-

tography (hexane/EtOAc 5:1) gave 0.480 g (69%) of **17a** as a gum in de 80% that could not be separated. Major isomer: ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3 H), 2.74 (m, 2 H), 3.36 (m, 4 H), 3.72, 3.76, 3.82, 3.86 (4 s, 12 H), 4.36 (s, 2 H), 4.47 (m, 1 H), 4.97 (m, 1 H), 6.51, 6.75, 6.84, 6.91 (4 s, 4 H), 7.22 (m, 7 H), 7.43 (d, J = 8.5 Hz, 2 H). Minor isomer: ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3 H), 2.79 (m, 2 H), 3.46 (m, 4 H), 3.74, 3.77, 3.84, 3.89 (4 s, 12 H), 4.38 (s, 2 H), 4.51 (m, 1 H), 5.13 (m, 1 H), 6.49, 6.72, 6.82, 6.89 (4 s, 4 H), 7.23 (m, 7 H), 7.46 (d, J = 8.5 Hz, 2 H).

(S_S,*S*)-(+)-*N*-[1-(2-(2-*tert*-Butyldimethylsilyloxyethyl)-4,5-dimethoxyphenyl)-2-(2-cyano-4,5-dimethoxyphenyl]-*p*-toluenesulfinimide (17b). Purification by silica gel column chromatography (hexane/EtOAc 5:1) gave 1.39 g (68%) of **17b** as a gum; $[\alpha]^{20}_D$ +40.3 (*c* 0.3, $CHCl_3$); IR (neat) 3295, 2935, 2218, 1598, 1465 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.82 (s, 6 H), 2.36 (s, 3 H), 2.61 (m, 2 H), 3.30−3.62 (m, 5 H), 3.81, 3.84, 3.85, 3.86 (4 s, 12 H), 4.44 (br s, 1 H), 4.91 (m, 1 H), 6.57, 6.75, 6.82, 6.92 (4 s, 4 H), 7.20, 7.48 (2 d, J = 8.5 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ −4.68, 18.91, 21.96, 26.55, 36.00, 42.23, 54.41, 56.43, 56.71, 56.81, 64.54, 105.12, 110.86, 113.55, 113.93, 114.52, 119.10, 126.21, 129.98, 130.06, 130.99, 136.55, 142.00, 142.07, 148.28, 148.51, 148.93, 153.17. HRMS Calcd for $C_{35}H_{42}N_2O_6SSi$ (M+Na) 661.2756. Found 661.2763.

(S_S,*S*)-(+)-*N*-[1-(2-(2-Benzyloxyethyl)-4,5-dimethoxyphenyl)-2-(2-cyano-4,5-dimethoxyphenyl]-1-methoxynaphthalenesulfinamide (17c). Purification by silica gel column chromatography (hexane/EtOAc 5:1) gave 0.65 g (68%) of **17c** as a gum; $[\alpha]^{20}_D$ +35.2 (*c* 0.5, $CHCl_3$); IR (neat) 3296, 2937, 2851, 2218, 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.88 (m, 2 H), 3.23 (dd, J = 14, 6 Hz, 2 H), 3.38−3.57 (m, 3 H), 3.63, 3.90, 3.73, 3.87, 3.97 (5 s, 15 H), 4.42 (s, 2 H), 5.00 (m, 1 H), 6.01 (d, J = 4 Hz, 1 H), 6.66, 6.67, 6.68, 6.99 (4 s, 4 H), 7.30 (m, 5 H), 7.40 (m, 3 H), 7.79, 7.90, 8.22 (3 d, 3.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 33.23, 42.29, 54.10, 56.50, 56.58, 56.79, 57,49, 71.71, 73.57, 105.18, 110.16, 113.66, 113.89, 114.21, 119.13, 122.57, 125.18, 126.52, 128.17, 128.25, 128.53, 128.98, 129.08, 129.48, 129.95, 131.28, 131.91, 133.90, 136.80, 139.04, 148.22, 148.53, 148.99, 152.88, 155.94. HRMS Calcd for $C_{39}H_{40}N_2O_7S$ (M + Na) 703.2453. Found: 703.2475.

(*S*)-(+)-2-[2-(6,7-Dimethoxy-3,4-dihydroisoquinolin-3-yl)-4,5-dimethoxyphenyl]ethanol (18). In a 50-mL of two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 0.25 g (0.38 mmol) of **17b** in toluene (20 mL) at 0 °C, and 1.0 mL (1 M in CH_2Cl_2, 0.53 mmol) of DIBAL-H was added. After stirring for 2 h, 3 N HCl (5 mL) was added, the reaction mixture was stirred for 15 min, and sat. $NaHCO_3$ (20 mL) was added. After 10 min, the organic phase was extracted with EtOAc (2 × 20 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography on silica gel (hexane/EtOAc 3:1) gave 0.1 g (70%) of **18** as a solid, mp 152−153 °C; $[\alpha]^{20}_D$ +42.6 (*c* 0.3, $CHCl_3$); IR (KBr) 3422, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.88−3.02 (m, 4 H), 3.77−3.80 (m, 2 H), 3.82, 3.88, 3.92, 3.93 (4 s, 12 H), 4.81−4.85 (m, 1 H), 6.71, 6.76, 6.86, 6.88 (4 s, 4 H), 8.28 (d, J = 3 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 32.96, 35.66, 56.60, 56.79, 56.85, 58.88, 64.51, 110.94, 111.30, 113.93, 121.64, 130.26, 130.53, 134.26, 148.10, 148.80, 148.90, 152.46, 159.95. HRMS Calcd for $C_{21}H_{25}NO_5$ (M + H) 372.1810. Found: 372.1796.

(*S*)-(+)-2-[2-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-3-yl)-4,5-dimethoxyphenyl]ethanol (19). In a 50-mL of two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 0.080 g (0.21 mmol) of **18** in CH_3OH (15 mL), and 0.008 g (0.21 mmol) of $NaBH_4$ was added at 0 °C. The reaction mixture was stirred for 2 h at room temperature at which time H_2O (0.5 mL) was added, and the solution was concentrated. The residue was extracted with EtOAc (2 × 10 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography (CH_2Cl_2/CH_3OH 20:1, Et_3N) gave 0.068 g (85%) of **19** as a solid, mp 190 °C (dec); $[\alpha]^{20}_D$ +35.6 (*c* 0.3, $CHCl_3$); IR (KBr) 3420, 3200, 2935, 2860 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.77−4.25 (m, 9 H), 3.81, 3.86, 3.87, 3.89 (4 s, 12 H), 4.81 (br s, 1 H), 6.55, 6.66, 6.77, 6.95 (4 s, 4 H); ^{13}C NMR ($CDCl_3$) δ 34.01, 36.08, 47.71, 52.92, 56.56, 56.64, 56.71, 64.54, 109.47, 109.79, 112.40, 114.00, 126.80, 126.85, 132.17, 133.17, 148.12, 148.38, 148.44, 149.20. HRMS Calcd for $C_{21}H_{27}NO_5$ (M + H) 372.181. Found 372.1797.

(*S*)-(−)-Xylopinine. In a 50-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 0.058 g (0.134 mmol) of **19** in pyridine (10 mL) at 0 °C and 0.028 g (0.147 mmol) of *p*-toluenesulfonyl chloride was added. The reaction mixture was stirred for 6 h, sat. $NaHCO_3$ (2 mL) was added, and the organic phase was extracted with EtOAc (2 × 10 mL). The organic phase was dried ($MgSO_4$) and concentrated to give an oil that was transferred to a 25-mL two-necked round-bottom flask containing THF (10 mL). Sodium hydride (0.003 g, 95% dry, 0.20 mmol, Aldrich) was added under argon atmosphere at 0 °C, and the reaction mixture was stirred for 30 min. The organic phase was extracted with EtOAc (2 × 10 mL) and H_2O (5 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc 10:3, the silica gel was pretreated with 10% Et_3N in *n*-hexane) gave 0.040 g (73%) of a solid, mp 177−178 °C [lit.[5] 179−180 °C]; $[\alpha]^{20}_D$ −282.4 (*c* 0.7, $CHCl_3$) [lit.[5] −283.1 (*c* 0.36, $CHCl_3$)]; IR (KBr) 2940, 1509 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.65 (m, 2 H), 2.85 (dd, J = 11.2, 3.6 Hz, 1 H), 3.15 (m, 2 H), 3.25 (dd, J = 16, 3.7 Hz, 1 H), 3.67 (d, J = 14.7 Hz, 1 H), 3.85, 3.86, 3.87, 3.89 (4 s, 12 H), 3.94 (d, J = 14.6 Hz, 1 H), 6.57, 6.62, 6.66, 6.74 (4 s, 4 H); ^{13}C NMR ($CDCl_3$) δ 29.58, 36.95, 51.95, 56.50, 56.56, 56.60, 56.69, 58.78, 60.22, 109.16, 109.65, 112.01, 126.73, 126.81, 127.27, 130.19, 148.12, 148.20, 148.35. Analytical data were in agreement with literature values.[7]

(*S*)-(−)-3-[2-(2-Hydroxyethyl)-4,5-dimethoxy-3,4-dihydro-*2H*-isoquinolin-1-one (21a). In a 50-mL single-necked round-bottom flask equipped with a stirring bar and condenser was placed 0.45 g (0.70 mmol) of **17b** in CH_3OH (30 mL) and H_2O (5 mL). To the reaction mixture was added 0.067 g (2.80 mmol) of LiOH, and the solution was refluxed for 8 h. The reaction mixture was concentrated, and the residue was extracted with EtOAc (2 × 30 mL), dried ($MgSO_4$), and concentrated. Purification by flash chromatography on Et_3N pretreated silica gel (CH_2Cl_2/CH_3OH 20:1) gave 0.211 g (78%) of a gel; $[\alpha]^{20}_D$ −37.5 (*c* 0.2, $CHCl_3$); IR (neat) 3403, 3328, 2954, 1652, 1506, 1457 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (br s, 1 H), 2.90 (m, 3 H), 3.19 (m,1 H), 3.83 (m, 2 H), 3.84, 3.86, 3.92, 3.94 (4 s, 12 H), 5.17, 5.19 (dd, J = 13, 4 Hz, 1 H), 6.26 (br s, 1 H), 6.65, 6.70, 7.08, 7.57 (4 s, 4 H); ^{13}C NMR ($CDCl_3$) δ 35.60, 36.86, 52.63, 56.55, 56.69, 56.74, 56.82, 64.23, 109.99, 110.21, 110.76, 113.64, 121.39, 129.53, 131.91, 132.44, 148.62, 148.83, 149.30, 153.10, 167.42. HRMS Calcd for $C_{21}H_{25}NO_6$ (M + Na) 410.1579. Found: 410.1585.

(*S*)-(−)-3-[2-(2-Benzyloxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-3,4-dihydro-*2H*-isoquinolin-1-one (21b). Purification by flash chromatography (hexane/EtOAc 5:20, the silica gel was pretreated with 10% Et_3N in *n*-hexane) gave 0.161 g (77%) of a gel. $[\alpha]^{20}_D$ −85.9 (*c* 1.1, $CHCl_3$); IR (neat) 3326, 2936, 2853, 1662, 1515, 1267 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.91 (m, 3 H), 3.18 (m, 1 H), 3.65 (t, J = 7 Hz, 2 H), 3.87 (s, 6 H), 3.90, 3.96 (2 s, 6 H), 4.49 (s, 2 H), 5.11 (dd, J = 13, 4 Hz, 1 H), 5.87 (br s, 1 H), 6.53, 6.71, 7.03, 7.29 (m, 5 H), 7.63 (4 s, 4 H); ^{13}C NMR ($CDCl_3$) δ 33.25, 37.25, 52.75, 56.58, 56.68, 56.77, 56.84, 74.74, 76.81, 109.71, 110.23, 110.81, 118.71, 121.49, 128.35, 129.05, 129.68, 131.86, 132.41, 138.67, 143.20, 148.64, 148.86, 153.09, 167.26. HRMS Calcd for $C_{28}H_{31}NO_6$ (M+Na) 500.2049. Found: 500.2047.

(*S*)-(−)-3-[2-(2-Hydroxyethyl)-4,5-dimethoxyphenyl]-6,7-dimethoxy-3,4-dihydro-*2H*-isoquinolin-1-one (21a). In a 50-mL of single-necked round-bottom flask equipped with a stirring bar was placed 0.14 g (0.293 mmol) of **21b** and 0.010 g of $Pd(OH)_2$ in CH_3OH (15 mL). The solution was stirred under a hydrogen atmosphere (balloon) for 8 h, filtered through Celite, and concentrated. Purification by silica gel flash chromatography on Et_3N pretreated silica gel (CH_2Cl_2/CH_3OH 20:1,) gave 0.109 g (96%) of a gel, $[\alpha]^{20}_D$ −37.5 (*c* 0.2, $CHCl_3$); IR (neat) 3403, 3328, 2954, 1652, 1506, 1457 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.45 (br s, 1 H), 2.90 (m, 3 H), 3.19 (m,1 H), 3.83 (m, 2 H), 3.84, 3.86, 3.92, 3.94 (4 s, 12 H), 5.17, 5.19 (dd, J = 13, 4 Hz, 1 H), 6.25 (br s, 1 H), 6.65, 6.70, 7.08, 7.57

(4 s, 4 H); ^{13}C NMR ($CDCl_3$) δ 35.60, 36.86, 52.63, 56.55, 56.69, 56.74, 56.82, 64.23, 109.99, 110.21, 110.76, 113.76, 121.39, 129.53, 132.44, 132.91, 148.62, 148.83, 149.30, 153.10, 167.42. HRMS Calcd for $C_{21}H_{25}NO_6$ (M + Na) 410.1579. Found: 410.1585.

(*S*)-(−)-2,3,10,11-Tetramethoxy-5,6,13,13a-tetrahydroisoquino[3,2-*a*]isoquinolin-8-one (23). In a 50-mL two-necked round-bottom-flask equipped with stirring bar and rubber septa under an argon atmosphere was placed 0.190 g (0.49 mmol) of **21a** in pyridine (15 mL) at 0 °C was added. To the reaction mixture was added 0.102 g (0.53 mmol) of *p*-toluenesulfonyl chloride, and the solution was stirred for 8 h, at which time sat. $NaHCO_3$ (2 mL) was added. The solution was extracted with EtOAc (2 × 25 mL), dried ($MgSO_4$), and concentrated. The crude tosylate **22** was placed in a 50-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere in THF (15 mL). To this solution, at 0 °C, was added 0.012 g (95% dry, 0.52 mmol) of sodium hydride, and the reaction mixture was stirred for 30 min. At this time the organic phase was extracted with EtOAc (2 × 25 mL) and H_2O (5 mL), dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc 10:2) gave 0.138 g (85%) of a solid, mp 185−186 °C [lit.[6] 187−188 °C], $[\alpha]^{20}_D$ −297.1 (*c* 0.42, $CHCl_3$) [lit.[6] −296.9 (*c* 0.95, $CHCl_3$)]; IR(KBr): 1654, 1600, 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.79−3.49 (m,5 H), 3.89, 3.90, 3.94, 3.95 (4 s, 12 H), 4.82−4.98 (m, 2 H), 6.69, 6.70, 6.72, 7.64 (4 s, 4 H); ^{13}C NMR ($CDCl_3$) δ 29.93, 38.36, 39.37, 55.95, 56.60, 56.73, 56.81, 77.20, 109.45, 109.84, 111.43, 112.14, 148.62, 148.67, 148.90, 152.57, 165.40. Analytical data were agreement with reported values.[18]

(*S*)-(−)-Xylopinine (1). In a 50-mL two-necked round-bottom flask equipped with a stirring bar and rubber septa under an argon atmosphere was placed 0.075 g (0.20 mmol) of **23** in THF (20 mL). To the reaction mixture was added 0.007 g (0.20 mmol) of $LiAlH_4$ and the solution refluxed for 2 h. At this time the reaction was cooled to 0 °C, and H_2O (0.007 mL), 15% NaOH (0.007 mL), and H_2O (0.02 mL) were added successively. The organic phase was filtered through Celite and concentrated, and the residue was purified by silica gel flash chromatography (hexane/EtOAc 10:3, the silica gel was pretreated with 10% Et_3N in *n*-hexane) to give 0.054 g (75%) of (−)-**1**.

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