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Asymmetric Synthesis of (*S*)-(−)-Xylopinine. Use of the Sulfinyl Group as an *Ipso* Director in Aromatic S_E

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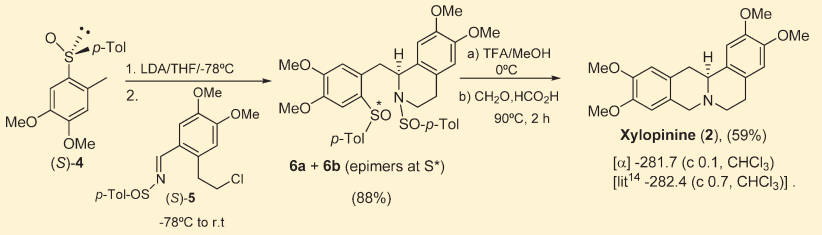
Supporting Information

ABSTRACT:



Optically pure (*S*)-(−)-xylopinine **2** was prepared in three steps in 52% overall yield. Thus, condensation of the carbanion derived from (*S*)-**4** with the (*S*)-(*E*)-sulfinylimine **5** gave a 2:1 mixture of tetrahydroisoquinolines **6a** and **6b**, differing only in configuration at sulfur. *N*-Desulfinylation of this mixture gave the diastereomeric sulfoxides which, without separation, were converted into (*S*)-(−)-xylopinine (**2**) with loss of the sulfinyl moieties under Pictet−Spengler conditions. This unprecedented *ipso* electrophilic substitution of a sulfinyl group may have synthetic implications beyond that described in this work.

INTRODUCTION

Protoberberines are a large group of naturally occurring alkaloids characterized by a tetracyclic ring skeleton containing an isoquinoline core.[1] These alkaloids possess a wide range of biological properties including antimicrobial, antitumor, antileukemic, and antiinflammatory activities.[2] The tetrahydroprotoberberines **1** are a subclass of protoberberines occurring in at least eight families of the plant kingdom.[3] Alkoxy (methoxy, methylenedioxy) or hydroxy substituents at the A ring are always located at the same positions, whereas the substitution pattern of the D ring is variable. Moreover, the stereogenic center at C-14 and an alkyl or hydroxyl group at C-13 are sometimes present[4] (Figure 1). Among the variety of strategies developed for the asymmetric synthesis of tetrahydroprotoberberines, two classical procedures, the Pictet−Spengler[5] and the Bischler−Napieralski cyclization/reduction,[6] have been the most frequently used for the construction of the tetrahydroisoquinoline nucleus.

Recently, one of us has reported that 2-(*p*-tolylsulfinyl)benzyl carbanions are highly efficient in transferring chiral benzyl groups to various electrophilic species. Their reaction with compounds containing the C=N bond has provided one of the best methods for preparing compounds containing the 2-phenylethylamine skeleton in high optical purity. Thus, *N*-sulfinylaldimines[7] and *N*-sulfinylketimines[8] react with these carbanions with complete stereocontrol and high yields to produce *anti*-1,2-diarylpropylamines. These reactions were also employed in the synthesis of *anti*-1,2-amino alcohols and *anti*-1,2-amino sulfides starting from the corresponding oxygen-[8,9] and sulfur-containing[10] carbanions. Reactions with *N*-arylarylideneamines generate mixtures of *syn* and *anti* isomers, epimers at the amine-bearing carbon, with the stereoselectivity being dependent on the electronic effect of the aromatic ring substituents of the acceptor.[11] Given that tetrahydroprotoberberines contain a 2-arylethylamine fragment, we reasoned that they could be prepared making use of this methodology.[7−11] In this paper, we report an application of this strategy for the synthesis of (*S*)-(−)-xylopinine (**2**) (Figure 1), a prototypical member of the tetrahydroprotoberberines isolated from *Xylopia discreta*.[12]

Several asymmetric syntheses of (*S*)-(−)-xylopinine can be found in the literature,[5b−c,13] with that reported by Davis[14] being remarkable because it also used the *N*-sulfinylimine's methodology. However, the syntheses are not completely satisfactory because they involve long synthetic sequences and/or require the separation of mixture of diastereoisomers because of the moderated stereoselectivity control of the key asymmetric transformation. In our case, these problems have been avoided by using the bond disconnection between N-7 and C-8 indicated in Figure 2, which provides the ring-opened 1-benzylisoquinoline **6a**. Further cleavage of the C-13 and C-14 bond gives two

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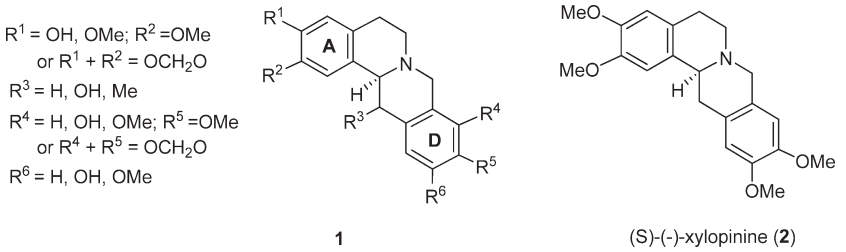


Figure 1. Natural tetrahydroprotoberberines.

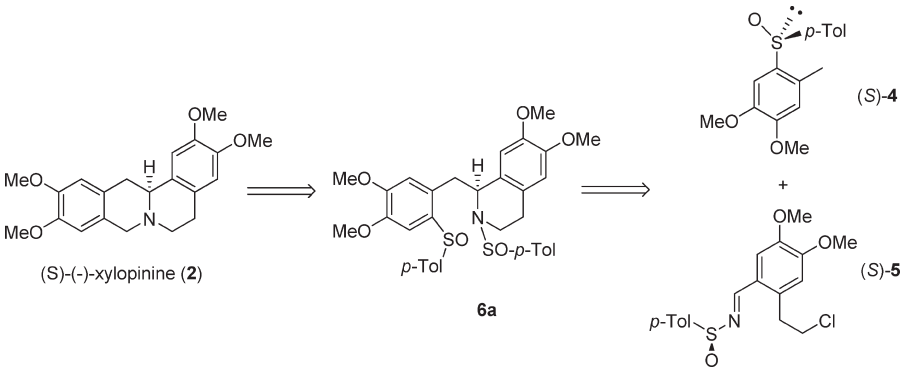
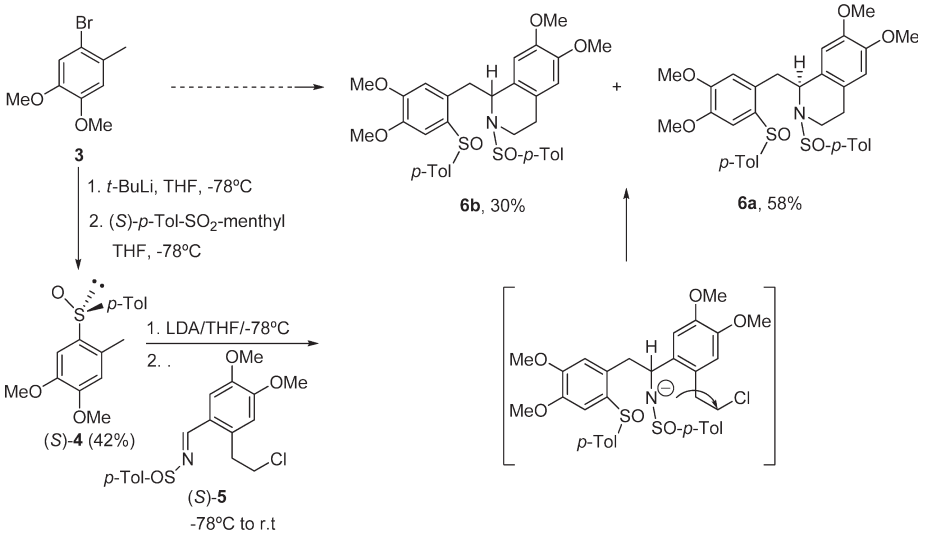


Figure 2. Retrosynthetic approach to (*S*)-(−)-xylopinine (**2**).

Scheme 1. Synthesis of 6a and 6b from (*S*)-4 and (*S*)-5



fragments: the 2-*p*-tolylsulfinyl-4,5-dimethoxytoluene (*S*)-**4** and the substituted *N*-*p*-tolylsulfinylaldimine (*S*)-**5**. Nucleophilic addition of the *o*-sulfinyl carbanion derived from (*S*)-**4** with the imine is the key step of the sequence.

RESULTS AND DISCUSSION

The synthesis of the intermediate **6a** was performed according to the synthetic sequence depicted in Scheme 1. Compound (*S*)-**4** was prepared in 42% yield by the Andersen synthesis from 1-bromo-4,5-dimethoxy-2-methylbenzene **3**. We chose the sulfinylimine (*S*)-**5** as the electrophile because of the (*S*) configuration of the xylopinine.[15] The enantiopure sulfinylimine (*S*)-**5** was obtained in 83% yield by condensation of 2-(2-chloroethyl)-4,5-dimethoxybenzaldehyde[16] with (*S*)-*p*-toluenesulfinamide[17] according to Davis' procedure.[18] Deprotonation of (*S*)-**4** at the benzylic position with LDA at −78 °C, followed by the addition of the *N*-sulfinylimine (*S*)-**5** at this temperature and stirring overnight at room temperature, produced a 2:1 diastereomeric mixture of 1-benzyltetrahydroisoquinolines **6a** and **6b** in 88% combined isolated yield. The diastereomeric tetrahydroisoquinolines **6a** and **6b** were readily separable by flash chromatography. The major diastereoisomer **6a** was used for completing the synthetic

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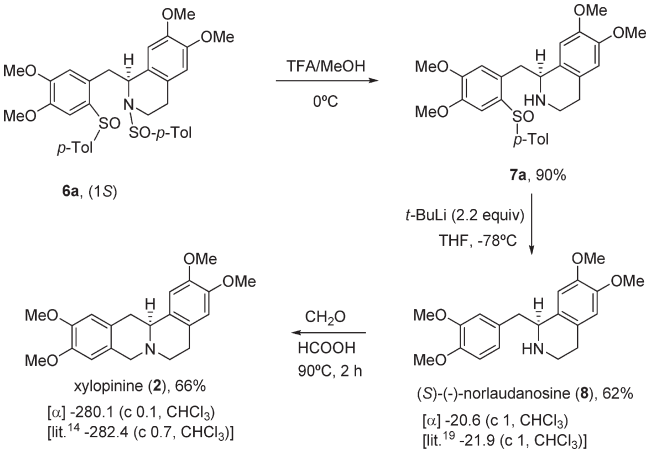
sequence because we assumed that it would have the (*S*)-configuration at the newly created chiral center.[15] This assumption was later confirmed by the synthesis of (*S*)-(−)-**2**.

The synthesis of (*S*)-(−)-xylopinine (**2**) from **6a** is depicted in Scheme 2. *N*-Desulfinylation of **6a** was performed with TFA at 0 °C in methanol, which afforded the secondary amine **7a** in 90% yield. To ensure the regioselective cyclization that would allow the synthesis of **2**, we first proceeded to eliminate the SOTol group from **7a** by reaction with 2.2 equiv of *t*-BuLi at −78 °C in THF, thus producing the (*S*)-(−)-norlaudanosine (**8**) in 62% yield. Finally, the Pictet−Spengler cyclization of **8** afforded (*S*)-(−)-xylopinine (**2**) in 66% yield. The spectral properties of **2** and **8** were fully consistent with their literature values, and their specific rotations (Scheme 2), very similar to those reported for the corresponding natural compounds of known configuration,[14,19] indicated that both exhibited the (*S*) configuration at their amine-bearing carbon atom. This assignment confirms that **6a** and **7a** also have the (*S*) configuration at this carbon atom. The complete regiocontrol observed in the cyclization step is not unexpected on the basis of electronic requirements which yield predominantly or exclusively the 10,11-disubstituted derivatives.

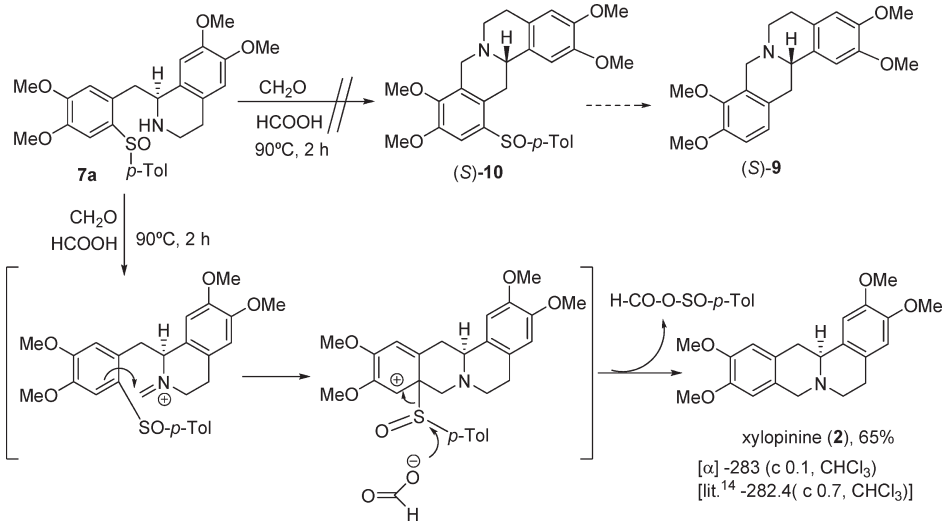
Scheme 2. Preparation of (*S*)-(−)-Xylopinine (2) from 6a



We now tried to obtain the isomer of the xylopinine, that is, (*S*)-(−)-tetrahydropalmatine (**9**) starting from **7a** by changing the order of the steps of Scheme 2. The results are depicted in Scheme 3. The Pictet−Spengler cyclization applied to **7a** should generate sulfoxide **10**, which would yield **9** by C-desulfinylation. To our surprise, however, when compound **7a** was subjected to Pictet−Spengler reaction conditions (aqueous CH_2O, HCOOH, 90 °C, 2 h), (*S*)-(−)-xylopinine (**2**) was obtained as the only isolable product (65% yield, Scheme 3). From a synthetic point of view, this process for preparing (*S*)-(−)-xylopinine is considerably more efficient than that shown in Scheme 2. This reaction presumably occurs by electrophilic attack of the iminium species on the sulfur-bearing carbon atom of the very electron-rich aromatic ring followed by expulsion of the arylsulfinyl moiety, perhaps as the formic−*p*-toluenesulfinic mixed anhydride (Scheme 3). To our knowledge, this is the first example of the participation of an arylsulfinyl group in an electrophilic *ipso* aromatic substitution reaction.[20] It potentially opens up a large number of new synthetic applications of sulfoxides, particulary with respect to the synthesis of optically pure isoquinolines via the reaction of *o*-sulfinylbenzyl carbanions with imines.[7−10]

In order to establish the absolute configuration of the minor isomer **6b**, obtained by reaction of **4** and **5** (Scheme 2), we decided to sequentially eliminate the two chiral centers. First, we removed the *N*-sulfinyl group with TFA/MeOH (Scheme 4) and obtained **7b**, differing from **7a** in its spectroscopic parameters, and therefore with only one of the two chiral centers being different. C-Desulfinylation of **7b** with *t*-BuLi afforded (*S*)-(−)-norlaudanosine **8** (67% yield). The sign of the specific rotation of **8**[21] thus obtained was identical to that reported for the (*S*)-enantiomer,[19] which indicated that the configuration at the amine-bearing trisubstituted carbon atom was identical for **6a** and **6b**. Thus, **7a** and **7b** (and therefore **6a** and **6b**) differ only in the configuration of the *p*-TolSO group joined to the aromatic ring.[22] Partial racemization of this sulfur group must take place during the condensation of **4** with **5** as a consequence of the prolonged reaction time required[23] (overnight) to complete the reaction. Finally, this also indicates that reaction of the sulfinylimine (*S*)-**5** with the carbanion derived from **4** is stereounique,

Scheme 3. Unexpected Evolution of 7a under Pictet−Spengler Conditions



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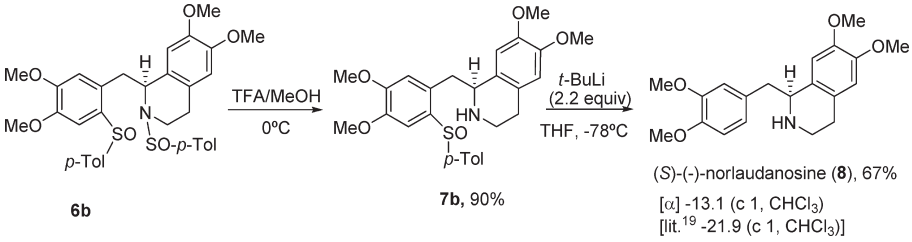
Scheme 4. Determination of the Absolute Configuration of 6b

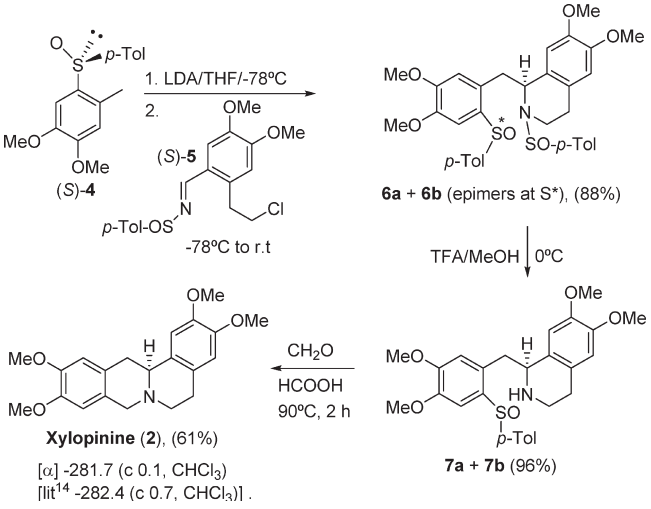


6b

7b, 90%

(*S*)-(-)-norlaudanosine (**8**), 67%
[α] -13.1 (c 1, $CHCl_3$)
[lit.[19] -21.9 (c 1, $CHCl_3$)]

Scheme 5. Asymmetric Synthesis of (*S*)-(−)-Xylopinine in Three Steps from (*S*)-4 and (*S*)-5



only yielding amines with the (*S*) configuration at carbon, as has been previously observed for other carbanions.[7]

Since the configuration at the chiral carbon of compounds **6a** and **6b** is identical, we studied the synthesis of (*S*)-(−)-xylopinine (**2**) from the mixture obtained in the reaction of (*S*)-**4** and (*S*)-**5** (Scheme 5). *N*-Desulfinylation of the 2:1 mixture of **6a** and **6b** with TFA at 0 °C in methanol (96% yield) followed by the Pictet−Spengler cyclization of the resulting mixture afforded (*S*)-(−)-xylopinine (**2**) in 61% yield, with specific rotation identical to that reported for the natural product.[14]

In conclusion, the synthesis of the optically pure (*S*)-xylopinine (**2**) was performed in three steps by reaction of the *o*-sulfinyl benzyl carbanion derived from (*S*)-**4** and *N*-sulfinylamine (*S*)-**5**, *N*-desulfinylation of the resulting mixture of products, and subsequent Pictet−Spengler cyclization. The overall isolated yield was 52%, and the optical purity of the xylopinine thus obtained is very high or complete. The previously unreported participation of the sulfinyl group in an *ipso* electrophilic aromatic substitution reaction was the key step in the reaction sequence. This observation may well have important synthetic implications, and this possibility is currently under investigation in our group.

EXPERIMENTAL SECTION

General Methods. All moisture-sensitive reactions were carried out in flame-dried glassware under argon atmosphere and monitored by TLC. Flash chromatography was performed with silica gel 60 (230−400 mesh ASTM). Melting points were determined in open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (concentration in g/100 mL). The IR spectra were recorded with an FT-IR spectrophotometer. The NMR spectra were acquired in $CDCl_3$ solutions at 300 and 75 MHz for ^1H and ^{13}C NMR, respectively. *J* values are given in hertz. The diastereomeric excesses were determined by 300 MHz ^1H NMR spectroscopy. Mass spectra were measured at 70 eV and 190 °C. All described compounds were over 97% pure by NMR analysis.

(*S*)-(−)-1,2-Dimethoxy-4-methyl-5-(*p*-tolylsulfinyl)benzene (*S*)-(4). To a stirred solution of 1-bromo-4,5-dimethoxy-2-methylbenzene **3** (0.40 g, 1.73 mmol, 1 equiv) in THF (4 mL) cooled at −78 °C was added dropwise a 1.6 M pentane solution of *t*-BuLi (2.16 mL, 3.46 mmol, 2 equiv). After 5 min, a solution of (*S*)-menthyl-*p*-toluenesulfinate (0.560 g, 1.90 mmol, 1.1 equiv) in THF (4 mL) cooled at −78 °C was added via cannula. When the reaction was completed (20 min), the mixture was hydrolyzed with saturated aqueous NH_4Cl (8 mL) at −78 °C and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography eluting with hexane/EtOAc 2:1 to produce 0.212 g (42%) of (*S*)-**4** as a white solid: mp 123−124 °C; $[\alpha]_D$ −23.3 (*c* 1, $CHCl_3$); IR (KBr) ν_{max} 1593, 1502, 1262, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 2.36 (s, 3H), 3.88 (s, 3H), 3.91 (s, 3H), 6.65 (s, 1H), 7.24 and 7.45 (AA′BB′system, 4H), 7.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.0, 21.3, 56.0, 56.1, 106.9, 113.3, 125.6, 128.6, 129.9, 133.8, 141.3, 142.0, 148.2, 150.9; EIMS *m*/*z* 290 (76, M^+), 273 (100), 271 (23), 242 (49), 167 (34), 138 (16); HRMS-FAB *m*/*z* $[M + 1]^+$ calcd for $C_{16}H_{19}O_3S$ 291.1055, found 291.1059.

(*S*)-(+)-(*E*)-*N*-[2-(2-Chloroethyl)-4,5-dimethoxybenzylidene]-4-methylbenzenesulfinamide (*S*)-(5). A mixture of (*S*)-(+)-*p*-toluenesulfinamide[17] (4.93 mmol, 0.766 g, 1.01 equiv), 2-(2-chloroethyl)-4,5-dimethoxybenzaldehyde[16] (1.111 g, 4.88 mmol, 1 equiv), and titanium(IV) ethoxide (4.05 mL, 19.52 mmol, 4 equiv) in CH_2Cl_2 (30 mL) was refluxed for 3 h. The reaction mixture cooled at 0 °C was quenched by addition of cold water (20 mL). The mixture was filtered through Celite, and the filtrate was washed with CH_2Cl_2. The phases were separated, the aqueous phase was washed with CH_2Cl_2 (15 mL), and the combined organic portions were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography using hexane/EtOAc 2:1 as eluent to give 1.47 g (83%) of (*S*)-**5** as a white solid: mp 91−92 °C; $[\alpha]_D$ +46.8 (*c* 1, $CHCl_3$); IR (KBr) ν_{max} 1585, 1514, 1275, 1068 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3H), 3.27−3.48 (m, 2H), 3.68 (t, 2H, *J* 7.2), 3.89 (s, 3H), 3.93 (s, 3H), 6.75 (s, 1H), 7.31 and 7.63 (AA′BB′system, 4H), 7.39 (s, 1H), 8.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 35.9, 44.8, 56.0, 56.1, 112.9, 113.9, 124.7, 129.8 (2C), 133.8, 141.6, 142.1, 148.2, 152.3, 158.2; EIMS *m*/*z* 365 (2, M^+), 278 (16), 226 (32), 225 (32), 191 (23), 176 (100), 139 (38), 91 (22); HRMS-FAB *m*/*z* $[M + 1]^+$ calcd for $C_{18}H_{21}ClNO_3S$ 366.0931, found 366.0924.

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(1*S*)-1-[4,5-Dimethoxy-2(*S*)-*p*-tolylsulfinyl]benzyl-6,7-dimethoxy-2(*S*)-*p*-tolylsulfinyl)-1,2,3,4-tetrahydroisoquinoline (6a) and (1*S*)-1-[4,5-Dimethoxy-2-(*R*)-*p*-tolylsulfinyl]benzyl-6,7-dimethoxy-2-(*S*)-*p*-tolylsulfinyl)-1,2,3,4-tetrahydroisoquinoline (6b). To a stirred solution of diisopropylamine (0.31 g, 0.43 mL, 3.08 mmol, 1.78 equiv) in THF (10 mL) cooled at −78 °C was added a solution 1.1 M in hexane of *n*-BuLi (1.73 mL, 1.90 mmol, 1.1 equiv). After 30 min, a solution of the sulfoxide (*S*)-**4** (0.5 g, 1.73 mmol, 1 equiv) in THF (8 mL) was added via cannula. After 1 h at −78 °C, a solution of sulfinylimine (*S*)-**5** (0.696 g, 1.90 mmol, 1.1 equiv) in THF (10 mL) was added. The resulting solution was stirred at room temperature for 12 h. The reaction mixture was hydrolyzed with saturated aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), washed with brine (2 × 20 mL), dried (Na_2SO_4), and evaporated. The residue was purified by flash column chromatography using EtOAc/hexane 4:1 as eluent to give 0.942 g (88% yield) of a 2:1 diastereoisomeric mixture of **6a** and **6b**. The mixture of **6a** and **6b** was separated by flash column chromatography using EtOAc/hexane 4:1 as eluent. Major product (**6a**): 0.621 g (58%) as a white solid; mp 104−105 °C; $[\alpha]^{20}_D$ +10.4 (*c* 1.0, $CHCl_3$); IR (deposited film) ν_{max} 1598, 1510, 1265, 1225, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 2.39 (s, 3H), 2.52−2.60 (m, 1H), 3.05−3.42 (m, 5H), 3.75 (s, 3H), 3.76 (s, 3H), 3.83 (s, 3H), 3.91 (s, 3H), 4.99−5.05 (m, 1H), 6.39 (s, 1H), 6.58 (s, 2H), 7.16 −7.23 (m, 6H), 7.36−7.42 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.2, 21.3, 29.1, 38.5, 39.4, 55.9, 56.0 (2C), 56.3, 61.4, 107.9, 109.9, 112.0, 113.6, 125.6, 126.1, 126.2, 128.2, 129.5, 130.0, 130.3, 134.8, 140.6, 141.2, 141.5, 142.1, 147.3, 148.3, 149.0, 151.2; MS-FAB *m*/*z* 620 (13, $M^+ + 1$), 480 (100), 330 (77), 307 (32), 192 (45), 154 (87), 136 (56); HRMS-FAB *m*/*z* $[M + 1]^+$ calcd for $C_{34}H_{38}NO_6S_2$ 620.2141, found 620.2136. Minor product (**6b**): 0.321 g (30%) as a white solid; mp 194−195 °C; $[\alpha]^{20}_D$ +154.5 (*c* 1.0, $CHCl_3$); IR (deposited film) ν_{max} 1599, 1510, 1264, 1225, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H), 2.38 (s, 3H), 2.56−2.65 (m, 1H), 3.08−3.50 (m, 5H), 3.77 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 3.92 (s, 3H), 5.00−5.07 (m, 1H), 6.50 (s, 1H), 6.60 (s, 1H), 6.71 (s, 1H), 7.09 −7.26 (m, 6H), 7.40−7.47 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.2 (2C), 29.1, 38.4, 39.1, 55.8, 55.9, 56.1, 56.2, 62.2, 107.4, 109.9, 111.9, 113.0, 125.2, 126.1, 126.4, 128.1, 129.5, 129.9, 130.3, 135.5, 140.2, 141.2, 141.3, 142.0, 147.2, 148.2, 149.1, 151.4; MS-FAB *m*/*z* 620 (7, $M^+ + 1$), 480 (55), 330 (52), 307 (30), 192 (28), 154 (100), 136 (61); HRMS-FAB *m*/*z* $[M + 1]^+$ calcd for $C_{34}H_{38}NO_6S_2$ 620.2141, found 620.2146.

(1*S*)-1-[4,5-Dimethoxy-2-(*S*)-*p*-tolylsulfinyl]benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7a) and (1*S*)-1-[4,5-Dimethoxy-2-(*R*)-*p*-tolylsulfinyl]benzyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7b). To a stirred solution of **6a** or **6b** (0.245 g, 0.39 mmol, 1 equiv) in MeOH (6 mL) cooled at 0 °C was added trifluoroacetic acid (91 μL, 1.18 mmol, 3 equiv). The resulting solution was stirred at 0 °C for 3 h. The volatiles were evaporated, and the residue was chromatographed in a SCX column affording 0.169 g (90%) of the corresponding amine. **7a**: white solid; mp 86−87 °C; $[\alpha]^{20}_D$ −127.3 (*c* 1.0, $CHCl_3$). IR (KBr) ν_{max}: 3459, 1602, 1510, 1460, 1262, 1227, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 2.62−2.81 (m, 2H), 2.89−3.03 (m, 2H), 3.13−3.22 (m, 1H), 3.32 (dd, 1H, *J* 3.9 and 14.1), 3.83 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 4.35 (dd, 1H, *J* 3.9 and 9.6), 6.59 (s, 1H), 6.64 (s, 1H), 6.79 (s, 1H), 7.25 and 7.49 (AA′BB′ system, 4H), 7.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 29.1, 38.6, 40.7, 55.9, 56.1 (2C), 56.2, 56.3, 108.2, 109.5, 112.0, 113.5, 125.6, 127.4, 129.7, 130.0, 131.0, 134.5, 141.4, 142.2, 147.4, 147.8, 148.9, 151.3; EIMS *m*/*z* 482 (2, $M^+ + 1$), 464 (12), 340 (8), 192 (100), 177 (42), 146 (33), 118 (12), 91 (7); HRMS-FAB *m*/*z* $[M + 1]^+$ calcd for $C_{27}H_{32}NO_5S$ 482.2001, found 482.2007. **7b**: white solid; mp 75−76 °C; $[\alpha]^{20}_D$ +110.4 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3459, 1602, 1510, 1460, 1262, 1227, 1047 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 2.73−2.80 (m, 2H), 3.00−3.09 (m, 1H), 3.13−3.23 (m, 2H), 3.39 (dd, 1H, *J* 4.8 and 14.4), 3.79 (s, 3H), 3.80 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.45 (dd, 1H, *J* 4.8 and 8.4), 6.59 (s, 2H), 6.70 (s, 1H), 7.17 (s, 1H), 7.24 and 7.41 (AA′BB′ system, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.3, 28.1, 37.9, 40.0, 53.4, 55.9, 56.0 (2C), 56.1, 109.0, 109.7, 111.8, 113.7, 125.2, 126.7, 127.8, 129.9, 130.7, 134.9, 141.3 (2C), 147.5, 148.0, 148.8, 151.6; EIMS *m*/*z* 482 (2, $M^+ + 1$), 464 (18), 340 (17), 192 (100), 176 (25), 148 (10); HRMS-FAB *m*/*z* $[M + 1]^+$ calcd for $C_{27}H_{32}NO_5S$ 482.2001, found 482.2002.

(*S*)-(-)-Norlaudanosine (8). To a stirred solution of **7a** or **7b** (0.2 g, 0.42 mmol, 1 equiv) in THF (4 mL) cooled at −78 °C was added a solution 1.5 M in pentane of *t*-BuLi (0.91 mmol, 0.61 mL, 2.17 equiv). When the reaction was completed (15 min), the mixture was hydrolyzed with saturated aqueous NH_4Cl (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography using EtOAc/CH_2Cl_2/MeOH 2:2:0.5 as eluent to obtain (*S*)-norlaudanosine (**8**) as a yellow oil [0.089 g (62%), $[\alpha]^{20}_D$ −20.6 (*c* 1, $CHCl_3$) [lit.[19] $[\alpha]^{20}_D$ −21.9 (*c* 1, $CHCl_3$)] from **7a** and 0.097 g (67%) from **7b**, $[\alpha]^{20}_D$ −13.1 (*c* 1, $CHCl_3$)]. Compound **8** was also obtained starting from **6a** or **6b** by using the same procedure. With 2.2 equiv of *t*-BuLi, (*S*)-norlaudanosine was obtained as a yellow oil, 37% yield from **6a** [$[\alpha]^{20}_D$ −18.6 (*c* 1, $CHCl_3$)] and 34% yield from **6b** [$[\alpha]^{20}_D$ −12.1 (*c* 1, $CHCl_3$)]: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.45−2.60 (br s, 1H), 2.70−278 (m, 2H), 2.87−3.00 (m, 2H), 3.12−3.26 (m, 2H), 3.81 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.19 (dd, 1H, *J* 4.8 and 8.4), 6.59 (s, 1H), 6.61 (s, 1H), 6.73−6.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.1, 40.8, 42.1, 55.8 (2C), 55.9, 56.0, 56.7, 109.5, 111.4, 111.9, 112.6, 121.5, 127.1, 129.8, 131.1, 147.1, 147.6, 147.8, 149.0. These data are in accordance with the values reported in the literature.[19]

(*S*)-(−)-Xylopinine (2). A mixture of 37% aqueous CH_2O (0.6 mL), HCOOH (1 mL), and (*S*)-norlaudanosine (**8**) (0.044 g, 0.13 mmol) was heated to 90 °C for 2 h. After the resulting mixture had cooled to 25 °C, saturated aqueous $NaHCO_3$ was added until pH > 7 was reached. The mixture was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under vacuum. The residue was purified by flash chromatography using EtOAc/NEt_3 99:1 as eluent to obtain 0.031 g (66%) of (*S*)-xylopinine (**2**) as a solid: mp 177−178 °C (lit.[14] 177−178 °C); $[\alpha]^{20}_D$ −280.1 (*c* 0.1, $CHCl_3$) [lit.[14] $[\alpha]^{20}_D$ −282.4 (*c* 0.7, $CHCl_3$)]. This product also was obtained in 65% yield starting from **7a** or **7b**: $[\alpha]^{20}_D$ −283 (*c* 0.1, $CHCl_3$) from **7a**; $[\alpha]^{20}_D$ −245 (*c* 0.12, $CHCl_3$) from **7b**.

Synthesis of (*S*)-(−)-Xylopinine from a 2:1 Diastereoisomeric Mixture of 6a and 6b. To a stirred solution of a 2:1 mixture of **6a** and **6b** (0.20 g 0.32 mmol) in methanol (5 mL) cooled at 0 °C trifluoroacetic acid (0.96 mmol, 74 μL, 3 equiv) was added. After the mixture was stirred for 3 h at 0 °C, the solvent was evaporated, and the residue was chromatography in a SCX column, affording 0.148 g (96%) of a 2:1 diastereomeric mixture of amines **7a** and **7b**, which was heated to 90 °C during 2 h with a mixture of 37% aqueous CH_2O (1.6 mL) and HCOOH (2.5 mL). After the resulting mixture had cooled to 25 °C, saturated aqueous $NaHCO_3$ was added until pH > 7 was reached. The mixture was then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under vacuum. The residue was purified by flash chromatography using EtOAc/NEt_3 99:1 as eluent to obtain 0.067 g (61%) of (*S*)-xylopinine (**2**) as a solid: mp 177−178 °C; $[\alpha]^{20}_D$ −281.7 (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.56−2.71 (m, 2H), 2.84 (dd, 1H, *J* 11.4 and 15.6), 3.08−3.19 (m, 2H), 3.24 (dd, 1H, *J* 3.6 and 15.6), 3.59 (dd, 1H, *J* 3.9 and 11.4), 3.68 (d, 1H, *J* 14.7), 3.85 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 3.92 (d, 1H, *J* 14.7), 6.58 (s, 1H), 6.62 (s, 1H), 6.67 (s, 1H), 6.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.1, 36.5, 51.4, 55.8, 55.9, 56.0, 56.1, 58.3, 59.6, 108.7, 109.1, 111.4, 111.5, 126.4 (2C),

126.8, 129.9, 147.5 (2C), 147.6, 147.7. Analytical data were in agreement with literature values.[14]

■ ASSOCIATED CONTENT

Supporting Information. Proton and carbon NMR spectra for all new compounds prepared and X-ray data for compound **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The amine used in the synthesis of the (*S*)-xylopinine according to Scheme 1 should have the (*S*) configuration at the amine-bearing carbon atom. Reactions of 2-*p*-tolylsulfinyltoluene with *N*-sulfinylimines, both with (*S*) configuration at their respective sulfur atoms, always evolve in a completely stereoselective manner, only yielding the amine with the (*S*) configuration at this carbon atom (see ref 7). Thus, we assume that, at least, the major compound obtained in the reaction of (*S*)-**4** and (*S*)-**5** would exhibit the (*S*) configuration at the carbon atom.

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(21) The magnitude of the specific rotation of compound **8** obtained from **7b** is clearly lower than that reported for norlaudanosine (see Scheme 4), which indicates that *t*-BuLi should produce epimerization at the chiral carbon of **7b**. It is remarkable that this epimerization was not observed in the reaction of the diastereomer **7a** with *t*-BuLi to form **8** (Scheme 2).

(22) This was unequivocally demonstrated by X-ray diffraction studies of the compound **6b** (see the Supporting Information), which has the (*S*) configuration at the chiral carbon and at the sulfur joined to nitrogen but the (*R*) configuration (the opposite to that of the starting sulfoxide **4**) at the sulfur of the diarylsulfinyl group.

(23) Racemization of sulfoxides with organolithiums has been reported; see: Durst, T.; LeBelle, M. J.; Van del Elzen, R.; Tin, K.-C *Can. J. Chem.* **1974**, *52*, 761. However, this problem had never been detected in the previously studied reactions of *o*-sulfinylbenzyl carbanions with imines (see refs 7−10), probably due to the short reaction times and low temperatures they required to be completed.