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Chiral Auxiliary Mediated Pictet-Spengler Reactions: Asymmetric Syntheses of (-)-Laudanosine, (+)-Glaucine and (-)-Xylopinine.

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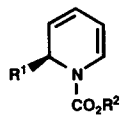
Abstract: Cyclohexyl-based chiral auxiliaries can be used effectively in an asymmetric Pictet-Spengler synthesis of tetrahydroisoquinoline, aporphine and protoberbine alkaloids. Using this strategy, concise asymmetric syntheses of (-)-laudanosine, (+)-glaucine and (+)-xylopinine have been accomplished.

During the last few years, the synthesis and synthetic utility of enantiopure *N*-acyl-1,2-dihydropyridines **1** and *N*-acyl-2,3-dihydro-4-pyridones **2** have been studied in our laboratories.[1,2] These versatile chiral building blocks were used in the synthesis of several alkaloid natural products. The heterocycles **1** and **2** are readily available as either antipode by addition of nucleophiles to enantiopure *N*-acylpyridinium salts **3**. The most effective acyl salts were those prepared containing cyclohexyl-based chiral auxiliaries attached to



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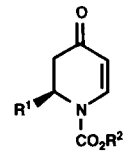

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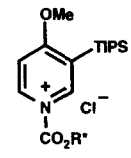
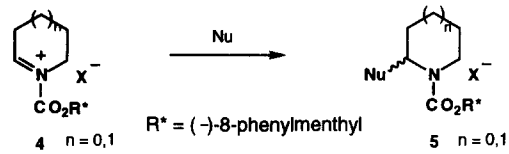


3

R* = cyclohexyl-based chiral auxiliaries

the *N*-acyl carbonyl. The efficient transfer of chirality (80-95% de) has been attributed to a favorable rotamer population and π-π stacking interactions.[3]

To determine if good asymmetric induction could be obtained with other types of related *N*-acyliminium ions, we briefly investigated the addition of nucleophiles to *N*-acyl salts **4** (Scheme 1). The results were disappointing in that poor diastereoselectivity was obtained (4-30% de).[4] Apparently the factors affecting chirality transfer from the cyclohexyl-based chiral auxiliary to the pyridinium ring in **3** are not present in these "non-aromatic" *N*-acyliminium ions.[5] We reasoned that an *intramolecular* addition to similar chiral



Scheme 1

N-acyliminium ions might result in a higher degree of stereocontrol, a thought which led us to investigate a chiral auxiliary mediated Pictet-Spengler reaction.

The Pictet-Spengler reaction is one of the most important methods for the construction of tetrahydroisoquinoline and β-carboline alkaloids.[6] In general, the Pictet-Spengler reaction involves the condensation of a β-arylethylamine with an aldehyde to give tetrahydroisoquinolines. The reaction proceeds via iminium or *N*-acylimium ion formation and subsequent intramolecular aromatic electrophilic substitution. Asymmetric versions of the Pictet-Spengler reaction involve the presence of chirality either in the amine component or the aldehyde substrate. Enantioselective alkaloid syntheses starting with tryptophan esters or chiral aldehydes have been reported.[7] Only in a few isolated cases has the Pictet-Spengler reaction been carried out asymmetrically by employing a recoverable chiral auxiliary group.[8]

Our initial studies involved the preparation of chiral carbamate **6**, from 3,4-dimethoxyphenethylamine and 8-phenylmenthyl chloroformate,[3a] and subsequent condensation with vinyl ether **7** to give a 68% yield of diastereomers **8a** and **8b** in a ratio of 83:17 (Scheme 2).[8b] The vinyl ether **7** was used instead of the corresponding aldehyde due to its increased stability to storage and the reaction conditions. The diastereomers **8** could not be conveniently separated by chromatography, so the mixture was reduced with $LiAlH_4$ to give (-)-laudanosine (**9**) in 73% yield and 63% ee. This is the unnatural form (*R*) of the alkaloid. The observed stereochemical outcome is consistent with the rationalization depicted in Figure 1. The correct absolute

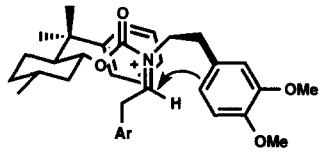
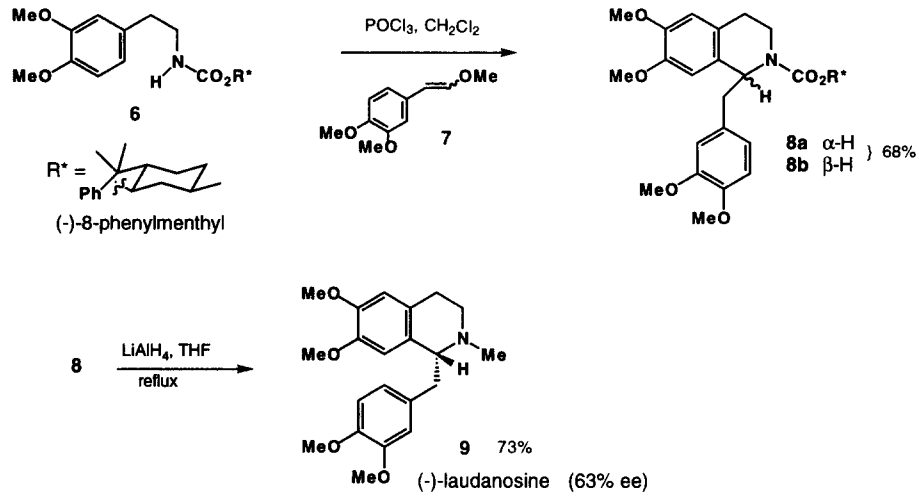


Figure 1. Ar = 3,4-dimethoxyphenyl

stereochemistry would be introduced by using the antipode of the chiral auxiliary present in carbamate **6**. Encouraged by this result, the study was expanded. Since 8-phenylmenthol (8-PhMen) is only readily accessible as the (-)-enantiometer,[9] we moved to the more available (+)- and (-)-*trans*-2-(α-cumyl)cyclohexanol (TCC) chiral auxiliaries.[10] Since initial work with the 8-PhMen-derived carbamate **6** and vinyl ether **7**

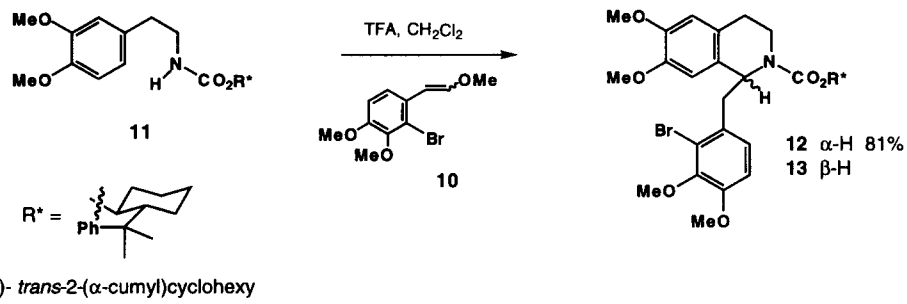


Scheme 2

provided only moderate asymmetric induction, we decided to see if a C-2 substituent on the ring of the vinyl ether substrate would enhance the stereoselectivity. Accordingly, commercially available methoxymethyltriphenylphosphonium chloride[11] was treated with KHMDS at 0 °C followed by slow addition of 6-bromoveratraldehyde at -78 °C to give an 86% yield of vinyl ether **10** as a 2:1 mixture of (*E*) and (*Z*) isomers, as determined by ^{1}H NMR analysis.

It was found that the Pictet-Spengler reaction of **10** and carbamate **11** (Scheme 3) proceeds with better selectivity when trifluoroacetic acid is used in place of $POCl_3$, which was used in the earlier studies. Several runs were performed and the results are shown in Table 1. The optimum conditions found used 5 equiv of trifluoroacetic acid in CH_2Cl_2 at -10 °C for 56 h. Lowering the temperature makes the reaction sluggish resulting in lower yield (entry 4), and increasing the reaction time slightly decreases the stereoselectivity (entry 2). Under the best conditions found (entry 1), a 9:1 mixture of (+)-**12** and **13** was obtained. The presence of the C-2

bromine substituent not only led to an increase in the degree of asymmetric induction during the Pictet-Spengler reaction, but the products, **12** and **13**, could now be conveniently separated by chromatography.



Scheme 3

Table 1. Asymmetric Pictet-Spengler Reaction of **10** and **11**.

entry	catalyst[a]	solvent	time	temperature[b]	% de	yield[c] of **12**
1	TFA (5 eq)	CH_2Cl_2	56 h	0 °C to -10 °C	79	75%
2	TFA (5 eq)	CH_2Cl_2	64 h	0 °C to -10 ° C	74	81%
3	TFA (5 eq)	CH_2Cl_2	56 h	0 °C to -20 °C	76	66%
4	TFA (5 eq)	CH_2Cl_2	56 h	-30 °C to -35 °C	78	48%
5	TFA (5 eq)	CH_2Cl_2	72 h	-30 °C to -35 °C	76	60%
6	TFA (15 eq)	CH_2Cl_2	56 h	0 °C to -10 °C	72	61%

[a]Reactions were generally performed on 0.1 to 0.3 mmol scale. [b]Reaction temperatures of 0 °C to -20 °C were maintained using a freezer: A Cryotrol was used for all the reactions temperatures below -20 °C. [c]Yields are for isolated products obtained from radial PLC (silica gel, EtOAc/hexanes).

With a method in hand to provide diastereomerically pure (+)-**12** in good yield and stereoselectivity, we turned our attention to the synthetic utility of **12** as an intermediate for the synthesis of aporphine and protoberbine alkaloids.

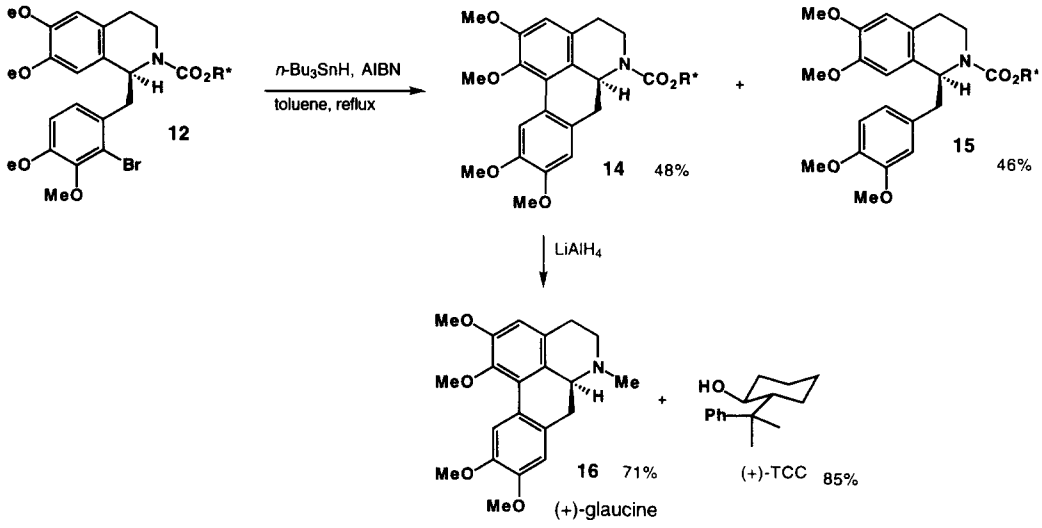
Synthesis of (+)-Glaucine.

The tetramethoxyaporphine, (+)-glaucine (**16**), was isolated from *Glaucicium flauvum* by Fischer.[12] The structure and stereochemistry were confirmed by Gadamer via synthesis and resolution.[13] In 1990 Meyers[14]

reported the first asymmetric synthesis of (+)-glaucine using a chiral formamidine directed enantioselective alkylation to incorporate the correct absolute stereochemistry at C-1 of **16**.

Our approach to (+)-glaucine required converting **12** to the aporphine derivative **14** by aryl-aryl bond formation (Scheme 4). A modification of a free radical cyclization reported by Estevéz[15] was used to carry out the desired conversion.

The best yield of biaryl **14** was obtained when a solution of Bu_3SnH and AIBN in toluene was added to **12** in refluxing toluene over a period of 3-4 hours using a syringe pump. Careful chromatography afforded 48% of aporphine **14** and 46% of debrominated product **15**. All attempts at decreasing the amount of reduction leading to **15** were unsuccessful. Bringmann[16] reported a useful method of biaryl coupling using bis(triphenylphosphine)palladium(II) chloride. Unfortunately, with **12** this method gave a very low yield of desired product along with recovery of starting material.



Scheme 4

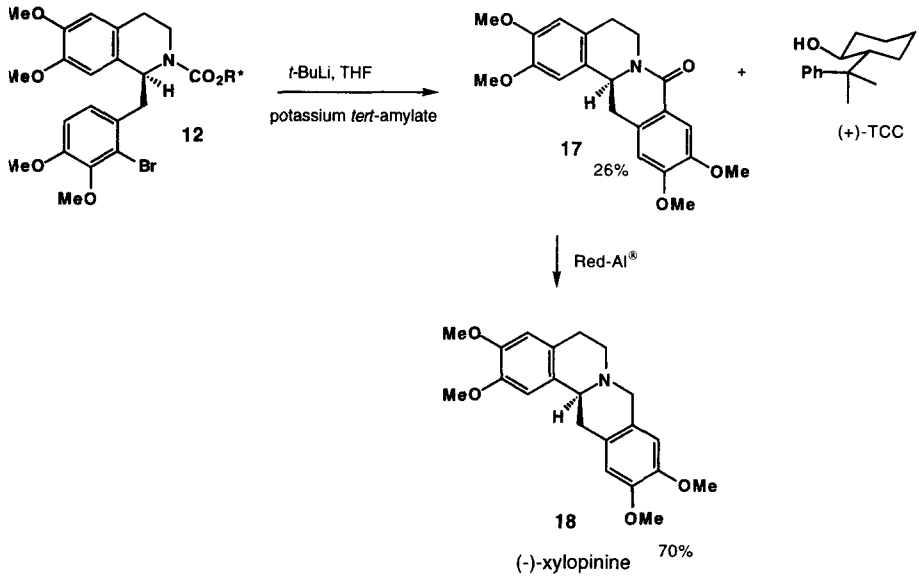
The synthesis was completed by reduction of carbamate **14** with $LiAlH_4$ in THF to produce 71% of (+)-glaucine (**16**) as a white solid and an 85% yield of recovered chiral auxiliary, (+)-TCC. The spectral data and

optical rotation of **16** [$[\alpha]_D^{23}$ +104 (*c* 0.32, $CHCl_3$)] were comparable to that obtained by the Meyers group[14] [$[\alpha]_D^{23}$+100 (*c* 3.2, $CHCl_3$)].

Synthesis of (-)-Xylopinine.

Investigation of *Xylopia decreta*, a member of the Annonaceae family, by Schmutz[16] led to isolation of the protoberbine alkaloid, (-)-xylopinine **(18)**. The absolute configuration of the alkaloid was determined to be 14*R* by Corrodi and Hardegger.[17]

A desire to demonstrate the versatility of our asymmetric Pictet-Spengler reaction prompted us to investigate benzylisoquinoline **12** as an intermediate to (-)-xylopinine. We envisioned that an aryl organometallic nucleophile could be prepared in situ from the aryl bromide present in **12** and then would attack the N-acyl carbonyl carbon of the carbamate in an intramolecular fashion to form the 8-oxoberbine **17** with simultaneous elimination of the TCC chiral auxiliary (Scheme 5).



Scheme 5

Accordingly, we explored various metalation reactions and conditions to convert **12** to **17** as shown in Table 2. The cyclization proved to be difficult. The best conditions found (entry 7) involved adding *t*-BuLi in THF at -78 °C, followed by addition of potassium *tert*-amylate at 0 °C, and stirring at ambient temperature overnight. In this manner, a 26% yield of 8-oxoberbine **17** was isolated as a white solid.

Table 2. Cyclization to form 8-oxoberbine 17

entry	reagent	conditions[a]	yield[b] of **17**
1	*t*-BuLi (2.1 eq), BF_3•OEt2 (2 eq), THF	-78 °C (1 h); slowly warmed to 25 °C (24 h)	25%
2	*t*-BuLi (2 eq), THF	-78 °C (1 h), then heated at 60 °C (16 h)	17%
3	*t*-BuLi (2.2 eq), ether	-78 °C (1 h); then 25 °C (12 h)	11%
4	*t*-BuLi (2.2 eq), $MgBr_2$ (2 eq), THF	-78 °C (0.5 h), then heated at 60 ° C (52 h)	22%
5	*t*-BuLi (2.2 eq), $MgBr_2$ (2 eq), BF_3•OEt_2 (1.2 eq), THF	-78 °C (1 h), then 25 ° C (2 h), then reflux (16 h)	9%
6	Reicke's Mg[c], THF, diglyme	25 °C (0.5 h), then heated to 80 °C (12 h)	0[d]
7	*t*-BuLi, K-*t*-amylate, THF	-78 °C (1 h), then 0 ° C (3 h) and 25 °C (12 h)	26%
8	*t*-BuLi, K-*t*-amylate, BF_3•OEt_2 (1.2 eq), THF	-78 °C (1 h), then 0 °C (3 h) and 25 °C (12 h)	9%

[a]Reactions were generally performed on 0.1 to 0.3 mmol scale. [b]Yields are for isolated products obtained from radial PLC (silica gel, EtOAc/hexanes). [c]Riecke's Mg was synthesized *in situ* by adding K metal to freshly prepared $MgBr_2$ and refluxing in THF. [d]Starting material was recovered.

With the 8-oxoberbine **17** in hand, the final step of the synthesis was assured. Following the protocol of Lenz[18] for reduction of racemic 8-oxoberbine, (-)-**17** was treated with Red-Al® in refluxing benzene to give a 70% yield of (-)-xylopinine (**18**) as a white solid. The spectral data were in agreement with the literature values,[19] and the optical rotation $[[\alpha]_D^{23}$ - 266 (*c* 0.8, $CHCl_3$)] was also comparable to the reported value[23] $[[\alpha]_D^{23}$ - 277 (*c* 1.0, $CHCl_3$)].

The readily available (+)-TCC alcohol has proven to be an effective chiral auxiliary for the asymmetric Pictet-Spengler reaction, which can be used to synthesize benzylisoquinoline, aporphine and protoberbine

alkaloids in an enantioselective manner. The bromo-benzylisoquinoline **12** was prepared in 3 steps from readily available compounds and utilized as a common intermediate for the concise asymmetric syntheses of (+)-glaucine and (-)-xylopinine.

EXPERIMENTAL

General. All reactions were performed in oven-dried glassware under an argon atmosphere and were stirred magnetically. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl prior to use. Methylene chloride, toluene, and diisopropylamine were distilled from calcium hydride and stored over 3-Å molecular sieves under N_2. Methanol was distilled from magnesium and stored over 3-Å molecular sieves and used without further purification. *n*-Butyllithium was titrated periodically against diphenylacetic acid according to the procedure of Kofron and Baclawski.[24] Melting points were determined in open capillary tubes with a Meltemp melting point apparatus and are uncorrected. Radial preparative-layer chromatography (radial PLC) was performed with a Chromatotron (Harris Associates, Palo Alto, CA). High-pressure liquid chromatography (HPLC) was carried out using μ-Porasil or chiral columns with a Waters Model 501 pump and a Model 440 absorbance detector. Optical rotations were determined with an Autopol II automatic polimeter (Rudolph Research, Flanders, NJ). Combustion analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. High-resolution mass spectral analyses (HRMS) were carried out at North Carolina State University. Infrared spectra were recorded on a Perkin-Elmer Model 1430 spectrophotometer. NMR spectra were recorded on a GN 300 or a Varian Gemini 300 spectrometer.

***N*-[((*1R,2S,5R*)-8-phenylmenthoxyl)carbonyl]-2-(3,4-dimethoxyphenyl)ethylamine (6).**

A solution of (-)-8-phenylmenthyl chloroformate (882 mg, 3.0 mmol) in freshly distilled CH_2Cl_2 (10 mL) was added to a well stirred mixture containing 3,4-dimethoxyphenethylamine (544 mg, 3.0 mmol), 1N NaOH (5 mL) and CH_2Cl_2 (20 mL). The mixture was stirred vigorously at 25 °C for 3 h. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (15 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated. The crude product was purified by radial PLC (silica gel 10-20% EtOAc/hexanes) to afford 1.07 g (81%) of **6** as a colorless viscous oil: IR (film) 1698, 1514 cm^{-1}; H^1 NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5 H), 7.1 (m, 1 H), 6.6-6.8 (m, 2 H), 4.6 (m, 1 H), 3.85 (bs, 6 H), 3.3 (m, 2 H), 2.7 (m, 2 H), 1.9 (m, 2 H), 1.7 (m, 3 H), 0.9 - 1.4 (m, 10 H), 0.8, (d, 3 H, $J = 7$ Hz). Anal. Calcd for $C_{27}H_{37}NO_4$: C, 73.80; H, 8.43; N, 3.19. Found: C, 73.65; H, 8.53; N, 3.17.

***N*-[((*1R*, *2S*, *5R*)-8-phenylmenthoxy)carbonyl]-1-(4,5-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8).**

To a mixture of carbamate **6** (510 mg, 1.16 mmol) and 3,4-(dimethoxyphenyl)-2-methoxyethylene (280 mg, 1.44 mmol) in 20 mL of methylene chloride was added 1.0 mL of phosphorous oxychloride while stirring under nitrogen at room temperature for two hours, and stirring was continued for another hour. The reaction mixture was treated with dilute ammonium hydroxide solution. After the organic phase separated, it was washed with saturated aqueous sodium chloride solution, dried ($MgSO_4$), and the solvent removed under reduced pressure to give 0.8 g of crude product. On HPLC analysis, the mixture showed a diastereometric ratio of 83:17 (retention time 22 and 21 min; 20% ethyl acetate/hexane). The product was purified by radial PLC using 20-30% ethyl acetate/hexane as an eluent to afford 475 mg (68%) of **8** of the same diastereomeric ratio (83:17) as an oil: IR (film) 1695, 1515 cm^{-1}; H^1NMR (300 MHz, $CDCl_3$) δ 6.9 - 7.3 (m, 5 H), 6.8 - 6.3 (m, 4 H), 6.1 (d, 1 H), 5.2 - 4.7 (m, 1 H), 3.6 - 3.9 (m, 8 H), 2.4 - 3.2 (m, 6 H), 0.7 - 2.2 (m, 19 H), 0.85 (m, 3 H).

(-)-Laudanosine (9).

A solution of $LiAlH_4$ (2.0 mL, 1M in THF, 2.0 mmol) was added to a solution of **8** (66% de, 275 mg, 0.55 mmol) in 20 mL of THF under argon. The mixture was stirred at ambient temperature for 3 h and then refluxed overnight. The cooled reaction mixture was quenched by successive dropwise addition of 0.4 mL of water and 0.5 mL of 1M NaOH. This produced a dry granular precipitate which was easy to filter. Ether (50 mL) was added to the filtrate, and the mixture was washed with brine, dried over $MgSO_4$, and concentrated to give an oily residue. Purification by radial PLC (silica gel, CH_2Cl_2-10% MeOH/$CHCl_2$) gave 144 mg (73%) of (-)-laudanosine (**9**, 63% ee) [$[\alpha]_D^{23}$ - 63 (*c* 1, EtOH)] as an oil and 98 mg (76% recovery) of (-)-8-phenylmenthol. The spectral properties of **9** were in agreement with reported data.[20]

***N*-[(1*S*,2*R*)-2-[((1-Methyl-1-phenylethyl)cyclohexyloxy)carbonyl]-2-(-3,4-dimethoxylphenyl)ethylamine (11)**

A solution of (+)-*trans*-(α-cumyl)cyclohexyl chloroformate[3a] (1.05 g, 3.75 mmol) in freshly distilled CH_2Cl_2 (7 mL) was added to a well stirred mixture containing 3,4-dimethoxyphenethylamine (0.75 g, 4.15 mmol), 1N NaOH (7.5 mL) and freshly distilled CH_2Cl_2 (10 mL). The mixture was stirred vigorously at 25 °C for 16 h. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by radial PLC (silica gel, 20% EtOAc/hexanes) to afford 1.60 g (86%) of **11** as a colorless

viscous oil: $[\alpha]_D^{27}$ - 2.64 (*c* 1.06, $CHCl_3$); IR (film) 1699, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (m, 5 H), 7.04 (m, 1 H), 6.65 - 6.82 (m, 2 H), 4.58 (m, 1 H), 3.86 (s, 3 H), 3.85 (s, 3 H), 3.26 (m, 2 H), 2.66 (m, 2 H), 1.97 (m, 2 H), 1.67 (m, 3 H), 0.98 - 1.45 (m, 11 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 151.6, 148.5, 147.2, 131.0,127.2, 125.0, 124.2, 120.2, 111.5, 110.9, 74.7, 55.4, 55.3, 51.0, 41.6, 39.3, 35.2, 33.4, 27.2, 26.6, 25.6, 24.4, 24.3. Anal. Calcd for $C_{26}H_{35}NO_4$: C, 73.38; H, 8.29; N, 3.29; Found: C, 73.23; H, 8.24; N, 3.23.

2-Bromo-4,5-dimethoxy-1-(2-methoxyethenyl)benzene (10).

A solution of $KN(TMS)_2$ (0.5M in toluene, 22.5 mL, 11.25 mmol) was added dropwise to a solution of methoxymethyltriphenylphosphonium chloride (3.87 g, 11.25 mmol) in THF (60 mL) at 0 °C under argon. The deep red solution was stirred at 0 °C for 15 min, then cooled to -78 °C, and a solution of 6-bromovertraldehyde (2.304 g, 9.39 mmol) in THF (25 mL) was slowly added. The reaction mixture was stirred at -78 °C for 45 min, the cooling bath was removed, and the mixture was stirred at ambient temperature overnight. The reaction was quenched with water and concentrated under reduced pressure at ambient temperature. Ether (60 mL) and water (20 mL) were added to the residue and the layers were separated. The aqueous phase was extracted twice with ether (20 mL), and the combined organic extracts were washed with water and brine, and then dried over anhydrous K_2CO_3. Evaporation of the solvent gave a crude white solid, which was purified by radial PLC (silica gel, 5% EtOAc/hexanes containing 1% triethylamine) to give 2.32 g (91%) of a mixture of (*E*)-and (*Z*)-2-bromo-4,5-dimethoxy-1-(2-methoxyethenyl)benzene (**10**) (2:1 ratio by ^1H NMR). An analytical sample of the product was obtained by recrystalization from hexanes. ^1H NMR (300 MHz, $CDCl_3$) (*E* isomer): δ 7.01 (s, 1 H), 6.90 (d, 1 H, J = 12 Hz), 6.82 (s, 1 H), 6.01 (d, 1 H, J = 12 Hz), 3.88 (s, 3 H); 3.86 (s, 3 H). (*Z* isomer): δ 7.68 (s, 1 H), 7.01 (s, 1 H), 6.17 (d, 1 H, J = 7 Hz), 5.52 (d, 1 H, J = 7 Hz), 3.79 (s, 3 H), 3.72 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) (E and Z mixture): δ 55.6, 55.7, 55.9, 56.2, 56.4, 60.6, 103.5, 104.1, 108.1, 112.5, 112.7, 114.8, 115.3, 115.5, 127.4, 128.2, 147.3, 147.6, 147.7, 148.3, 149.2. Anal. Calcd for $C_{11}H_{13}BrO_3$: C, 48.37; H, 4.80; Found C, 48.10; H, 4.75.

1-[2-Bromo-4,5-dimethoxybenzyl]-2-[((1*S*,2*R*)-(1-methyl-1-phenylmethyl)cyclohexyloxy)carbonyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (12).

To a stirred solution of **11** (0.373 g, 0.877 mmol) and vinyl ether **10** (0.251 g, 0.919 mmol) in 10 mL of freshly distilled CH_2Cl_2 at 0 °C under argon was added trifluoroacetic acid (0.34 mL, 4.38 mmol). The mixture was stirred for 30 min at 0 °C, then allowed to stand in a freezer at -10 °C for 3 d. The reaction mixture was rendered basic with saturated aqueous $NaHCO_3$, the layers were separated, and the aqueous phase was extracted

twice with CH_2Cl_2 (10 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), and then dried over anhydrous $MgSO_4$. Concentration gave an oily product which was determined by HPLC to be a mixture of diastereomers (77% de). Careful chromatography of the residue (radial PLC, silica gel, 15% EtOAc/hexanes) gave the pure major diastereomer **12** (0.398 g, 68%) as an oil: $[\alpha]_D^{23}$ + 64 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.85-7.24 (m, 6 H), 6.26-6.67 (m, 3 H), 5.40 and 4.56 (m, 1 H), 3.65-3.88 (m, 8 H), 2.45-3.25 (m, 6 H), 0.68-2.10 (m, 20 H). Anal. Calcd for $C_{36}H_{44}BrNO_6$: C, 64.86; H, 6.65; N, 2.10; Found: C, 64.76; H, 6.67; N, 2.06.

Carbamate 14.

A solution containing *n*-Bu_3SnH (0.11 mL, 0.405 mmol) and AIBN (0.030 g, 25% by wt) in 2 mL of dry degassed toluene was added over 3-4 h to a solution of **12** (0.135 g, 0.203 mmol) in 3 mL of dry degassed toluene at reflex under argon. The mixture was heated at reflux for 24 h, cooled, and concentrated. The residue was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to afford **14** as a white foamy solid (0.057 g, 48%), and 0.055 g (46%) of debrominated starting material (**15**) was recovered. **14**: $[\alpha]_D^{23}$ + 164 (*c* 0.66, $CHCl_3$); IR (film) 1684, 1515, 1420 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (m, 1 H), 6.28-7.42 (m, 7 H), 4.82 (m, 1 H), 4.65 and 4.38 (m, 1 H), 3.60-4.15 (m, 12 H), 0.75-3.05 (m, 21 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 23.8, 24.8, 26.1, 26.8, 27.0, 29.0, 29.7, 30.0, 30.4, 34.2, 34.8, 38.5, 39.3, 39.7, 50.0, 51.4, 51.8, 55.9, 56.2, 59.9, 75.2, 110.4, 111.0, 111.3, 111.9, 124.4, 124.7, 125.6, 126.0, 127.3, 127.9, 129.7, 130.0, 144.6, 147.5, 148.2, 151.8, 152.1, 152.6, 153.7, 154.4. HRMS calcd for $C_{36}H_{43}NO_6$ 585.3090 (M^+), found 585.3089.

15: ^1H NMR (300 MHz, $CDCl_3$) δ 6.94-7.26 (m, 5 H), 6.78-6.34 (m, 4 H), 5.98 (d, 1 H), 5.20 and 4.70 (m, 1 H), 3.60-3.90 (m, 8 H), 2.40-3.15 (m, 6 H), 0.80-2.15 (m, 20 H).

(+)-Glaucine (16).

A solution of $LiAlH_4$ (1 M in THF, 1 mL, 1 mmol) was added to a solution of **14** (0.83 g, 0.142 mmol) in 4 mL of THF under argon. The mixture was stirred at ambient temperature for 3 h and then refluxed overnight. The cooled reaction mixture was quenched by successive dropwise addition of 0.04 mL of water, 0.04 mL of 15% NaOH, and 0.11 mL of water. This produced a dry granular precipitate which was easy to filter. The precipitate was extracted twice with 10 mL of CH_2Cl_2, and the combined organic extracts were dried over anhydrous K_2CO_3. Concentration afforded a yellow solid (0.075 g), which was purified by radial PLC (silica gel, 10-20% EtOAc/hexanes containing 1% triethylamine) to give (+)-glaucine (**16**) as a white solid (0.04 g, 71%): mp 111-113 °C; lit.[21] mp 120 °C; $[\alpha]_D^{23}$ + 104 (*c* 0.32, $CHCl_3$); lit.[21] $[\alpha]_D^{23}$ + 115 (*c* 3, EtOH); IR

(film) 3022, 1517 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 6.78 (s, 1 H), 6.59 (s, 1 H), 3.93 (s, 3 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 3.65 (s, 3 H), 2.95-3.25 (m, 4 H), 2.57 (s, 3 H), 2.50-2.71 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 29.2, 29.4, 29.9, 31.1, 34.7, 44.2, 53.6, 56.1, 56.2, 60.4, 62.8, 110.7, 111.2, 112.0, 124.8, 127.2, 129.0, 129.5, 144.7, 147.8, 148.3, 152.3.

(*S*)-5,6,13,13a-tetrahydro-2,3,10,11-tetramethoxy-8*H*-dibenzo[*a*,*q*]quinolizin-8-one (17).

To a solution of **12** (0.1258 g, 0.1887 mmol) in 1 mL of THF at -78 °C under argon was slowly added *t*-BuLi (1.7M in pentane, 0.24 mL, 0.415 mmol). The reaction mixture was stirred at -78 °C for 1 h, then gradually warned to 0 °C, and potassium *tert*-amylate (17% in hexanes, 0.216 mL, 0.226 mmol) was slowly added. The reaction mixture was allowed to stir at 0 °C for 3 h and then at ambient temperature overnight. The reaction mixture was quenched with aqueous $NaHCO_3$, the layers were separated, and the aqueous phase was extracted twice with ethyl acetate (5 mL). The combined organic layers were washed with water (5 mL) and brine (5 mL), and then dried over anhydrous $MgSO_4$. The solvent was evaporated and the residue was purified by radial PLC (silica gel, 50% EtOAc/hexanes) to afford **17** (0.018 g, 26%) as a white solid: mp 187-188 °C; $[\alpha]_D^{23}$ - 296.9 (*c* 0.95, $CHCl_3$); IR (film) 1652, 1599, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (s, 1 H), 6.64-6.75 (m, 3 H), 4.78-5.12 (m, 2 H), 3.96 (s, 6 H), 3.91 (s, 3 H), 3.90 (s, 3 H), 2.72-3.20 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.2, 37.6, 38.6, 55.2, 55.9, 56.0, 56.1, 77.2, 108.7, 109.1, 110.7, 111.4, 121.7, 127.3, 127.7, 130.9, 147.9, 148.0, 148.2, 151.9, 164.7. These spectral data are in agreement with the reported values for racemic **17**.[22]

(-)-Xylopinine (18).

Following the procedure of Lenz[22] for the reduction of racemic oxoberbine, a solution of Red-Al® (3.4M in toluene, 0.0275 mL), 0.093 mmol) was added to a solution of **17** (0.0069 g, 0.0187 mmol) in dry benzene (2 mL) under argon, and the mixture was heated at reflux for 16 h. The cooled reaction mixture was quenched with saturated sodium potassium tartarate solution (Rochelle's salt) (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL), and the combined organic extracts were dried over anhydrous K_2CO_3. Concentration afforded a yellow solid (0.007 g) which was purified by radial PLC (silica gel, 25% hexanes/EtOAc containing 1% triethylamine) to give (-)-xylopinine (**18**), (0.005 g, 70%), as a white solid: mp 173-176 °C; lit.[17] mp 177 °C; $[\alpha]_D^{23}$ - 266.3 (*c* 0.8, $CHCl_3$); lit.[23] $[\alpha]_D^{23}$ - 273 (*c* 1.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (s, 1 H), 6.67 (s, 1 H), 6.63 (s, 1 H), 6.58 (s, 1 H), 4.00-3.57 (m, 3 H), 3.90 (s, 3 H), 3.87 (s, 9 H), 3.28-3.04 (m, 3 H),

2.90-2.70 (m, 1 H), 2.59-2.72 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.1, 29.7, 36.5, 51.4, 55.9, 56.0, 56.1, 58.3, 59.7, 108.8, 109.2, 111.5, 111.6, 126.4, 126.5, 126.9, 129.9, 147.5, 147.6.

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