JOC*Article*

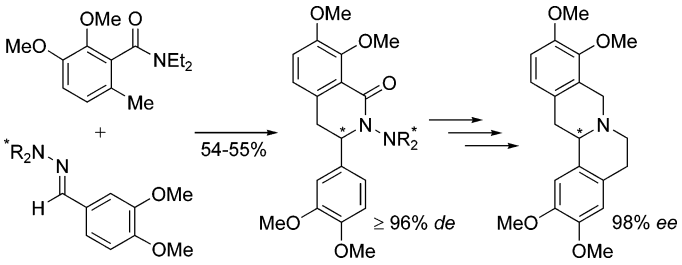
Asymmetric Synthesis of Tetrahydropalmatine via Tandem 1,2-Addition/Cyclization

Marine Boudou and Dieter Enders*

Institut für Organische Chemie, RWTH Aachen, Landoltweg 1, D-52074 Aachen, Germany

enders@rwth-aachen.de

Received July 26, 2005



The enantioselective synthesis of both enantiomers of tetrahydropalmatine (**2**) (ee = 98%), a natural alkaloid belonging to the tetrahydroprotoberberine family, is described. The key step of this total synthesis is based on our tandem 1,2-addition/ring-closure methodology employing lithiated methylbenzamide and benzaldehyde SAMP or RAMP hydrazones as substrates. An initial route was investigated for the formation of N- and 3-substituted dihydroisoquinolones starting from 2-substituted benzaldehyde SAMP hydrazones, but although high diastereoselectivity was achieved, only disappointing yields were obtained. In our subsequent synthetic strategy, 2,3-dimethoxy-6-methylbenzamide **6** and 3,4-dimethoxybenzaldehyde SAMP or RAMP hydrazone **19** gave the dihydroisoquinolones **20** in high diastereomeric purity (de ≥ 96%) and reasonable yield (54−55%), taking into account the complex functionalities established in one step. Cleavage of the N−N bond of the chiral auxiliary and reduction of the carbonyl group of the amide moiety were performed in the same step, and the resulting tetrahydroisoquinolines **22** (ee = 99%) were N-functionalized by treatment with various electrophiles to investigate the ring closure by Pummerer, Friedel−Crafts, and Pomeranz−Fritsch reactions. The Pummerer cyclization led to the formation of (*S*)-(−)-**2** with slight racemization (ee = 89%), whereas the Friedel−Crafts reaction proved to be unsuccessful. Finally, Pomeranz−Fritsch-type cyclization afforded the desired title compound (*R*)-(+)-**2** in excellent enantioselectivity in 9% overall yield over seven steps and after optimization of the last step (*S*)-(−)-**2** in 17% overall yield.

Introduction

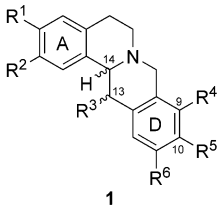
The protoberberines, a large class of naturally occurring alkaloids, possess antitumor, antimicrobial, and other biological activities.[1,2] The tetrahydroprotoberberines **1**, a subclass occurring in at least eight botanical families, are characterized by a tetracyclic skeleton containing an isoquinoline core.[1] Alkoxy or hydroxy substituents of the A ring are always situated at the same positions, whereas the substitution pattern of the D ring can slightly vary. In addition to their stereogenic center in C-14, these alkaloids can possess alkyl or hydroxy substitution at the C-13 position.[3]

(1) (a) Bhakuni, D. S.; Jain, S. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, p 95. (b) Santavý, F. In *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. 17, 385. (c) Santavý, F. In *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1970; Vol. 12, p 333. (d) Jeffs, P. W. In *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, p 41. (e) Manske, R. H. F.; Ashford, W. R. In *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Holmes, H. L., Eds.; Academic Press: New York, 1954. Vol. 4, p 78.

(2) (a) Memetzidis, G.; Stambach, J. F.; Jung, L.; Schott, C.; Heitz, C.; Stoclet, J. C. *Eur. J. Med. Chem.* **1991**, *26*, 605. (b) Suffnees, M.; Cordell, A. C. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, FL, 1985; Vol. 25, p 3. (c) Cushman, M.; Dekow, F. W.; Jacobsen, L. B. *J. Med. Chem.* **1979**, *22*, 331. (d) Wilson, W. D.; Gough, A. N.; Doyle, J. J.; Davison, M. W. *J. Med. Chem.* **1976**, *19*, 1261. (e) Zee-Cheng, R. K. Y.; Cheng, C. C. *J. Med. Chem.* **1976**, *19*, 882.

(3) *Römpp-Lexikon Naturstoffe*; Fugmann, B., Ed.; Thieme: Stuttgart, 1997; pp 519−520.

10.1021/jo051554t CCC: $30.25
Published on Web 10/14/2005



1

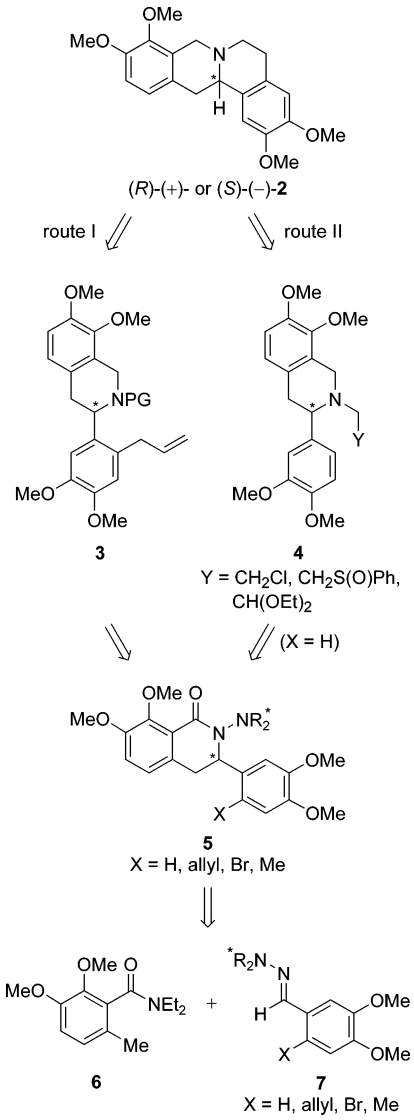
R^1 = OH, OMe; R^2 = OMe or $R^1 + R^2$ = OCH_2O
R^3 = H, OH, Me
R^4 = H, OH, OMe; R^5 = OMe or $R^4 + R^5$ = OCH_2O
R^6 = H, OH, OMe

Among the different strategies described for the construction of the tetrahydroprotoberberine core, the classical Pictet−Spengler[4] or Bischler−Napieralski/reduction[5] procedures occupy a prominent position. Unfortunately, the use of these heterocyclization procedures to effect the final ring closure between the isoquinoline core, containing rings A and D, has strong limitations. Indeed, the electronic requirements of the cyclization restrict the scope of the substitution pattern at the aromatic ring of the tetrahydroprotoberberine skeleton. Those methods are unsuitable for the synthesis of 9,10-disubstituted derivatives as for example tetrahydropalmatine (**2**). Several approaches have been developed to overcome these difficulties, but currently, the three described asymmetric syntheses of tetrahydropalmatine have not been fully selective.[6]

Very recently, we reported the asymmetric synthesis of 3-substituted dihydro-2*H*-isoquinolin-1-ones, dihydro- and tetrahydroisoquinolines via a tandem 1,2-addition/ring-closure sequence[7] employing lithiated *N*,*N*-diethyl-2-methylbenzamides and aromatic hydrazones derived from enantiomerically pure hydrazines SAMP or RAMP ((*S*)- or (*R*)-1-amino-2-(methoxymethyl)pyrrolidine).[8] We were hoping that an application of this methodology to the asymmetric total synthesis of 9,10-disubstituted tetrahydroprotoberberines, and more particularly tetrahydropalmatine, should prove the validity of our synthetic strategy.

Both enantiomers of **2** as well as the racemate are present in nature. Although (*R*)-(+)-tetrahydropalmatine seems to have been isolated as early as 1903,[9] it was not before 1923 that the structure elucidation of this alkaloid

SCHEME 1



was accomplished after its isolation from tubers of *Corydalis cava*.[10] Among the biological activities attributed to tetrahydropalmatine, the racemic form was shown to possess an insecticidal activity against larvae and adults of *Drosophila melanogaster*,[11] whereas the (*S*)-(−) enantiomer might be valuable as an antitumor promoter (inhibitory effect on *Epstein−Barr* virus).[12] The (*R*)-(+) enantiomer was shown to inhibit the activity of GABA-T by 46%, this irreversible inhibition being the basic action mechanism of drugs used in the treatment of convulsive disorders.[13]

The target molecules (*R*)-(+)- and (*S*)-(−)-tetrahydropalmatine (**2**) should either be obtained after ozonolysis, deprotection, and reductive amination of precursor **3** (Scheme 1, route I) or should result from the ring closure of tetrahydroisoquinoline **4** employing a Friedel−Crafts,

(4) For a review on Pictet−Spengler cyclization, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. For examples, see: (a) Munchoff, M. J.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 4607. (b) Miller, R. B.; Tsang, T. *Tetrahedron Lett.* **1988**, *29*, 6715. (c) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095. (d) Meyers, A. I.; Boes, M.; Dickman, D. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 458. (e) McMurtrey, K. D.; Meyerson, L. R.; Cashaw, J. L.; Davis, V. E. *J. Org. Chem.* **1984**, *49*, 947. (f) Kametani, T.; Nakano, K.; Shishido, K.; Fukumoto, K. *J. Chem. Soc. C* **1971**, 3350.

(5) See, for example: (a) Venkov, A. P.; Ivanov, I. I. *Tetrahedron* **1996**, *52*, 12299. (b) Larsen, R. D.; Reamer, R. A.; Corley, E. G.; Davis, P.; Grabowski, E. J. J.; Reider, P. J.; Shinkai, I. *J. Org. Chem.* **1991**, *56*, 6034. (c) Pandey, G. D.; Tiwari, K. P. *Heterocycles* **1980**, *14*, 59. (d) Patra, A.; Mukhopadhyay; Mitra, A. K. *Indian J. Chem., Sect. B* **1980**, *19*, 561. (e) Pai, B. R.; Natarajan, S.; Manikumar, G.; Rajaraman, R.; Suguna, H. *J. Org. Chem.* **1978**, *43*, 1992. (f) Rajaraman, R.; Pai, B. R.; Premila, M. S.; Suguna, H. *Indian J. Chem., Sect. B* **1977**, *15*, 876.

(6) (a) Cutter, P. S.; Miller, R. B.; Schore N. E. *Tetrahedron* **2002**, *58*, 1471. (b) Matulenko, M. A.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 573. (c) Pyne, S. G.; Dikic, B. *J. Org. Chem.* **1990**, *55*, 1932.

(7) Enders, D.; Braig, V.; Boudou, M.; Raabe, G. *Synthesis* **2004**, 2980.

(8) (a) Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173. (b) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 2933.

(9) Heyl, G. *Arch. Pharm. (Weinheim, Ger.)* **1903**, *241*, 318.

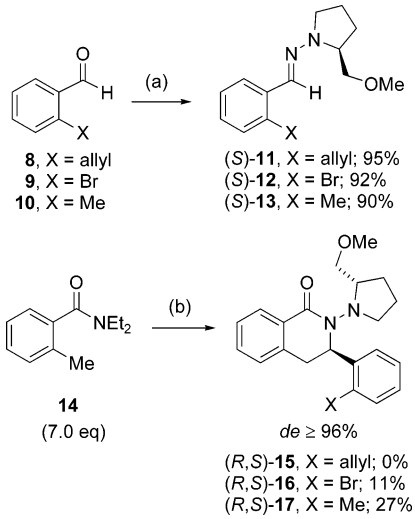
(10) Späth, E.; Mosettig, E.; Tröthandl, O. *Chem. Ber.* **1923**, *56*, 875.

(11) Miyazawa, M.; Yoshio, K.; Ishikawa, Y.; Kameoka, H. *J. Agric. Food Chem.* **1998**, *46*, 1914.

(12) Ito, C.; Itoigawa, M.; Tokuda, H.; Kuchide, M.; Nishino, H.; Furukawa, H. *Planta Med.* **2001**, *67*, 473.

(13) Choi, S. Y.; Bang, M.-H.; Lee, E. J.; Kwon, O.-S.; Kang, T.-C.; Lee, Y.-H.; Rho, Y.-D.; Baek, N.-I. *Agric. Chem. Biotechnol.* **2003**, *46*, 67 and references cited therein.

SCHEME 2[a]



[a] Reagents and conditions: (a) SAMP, MS 4 Å, Et_2O, 0 °C to room temperature, 20−25 h. (b) LDA (7.0 equiv), THF, −78 °C then (*S*)-**11**, (*S*)-**12** or (*S*)-**13**, $AlMe_3$ (1.1 equiv), THF, −40 °C, 16−20 h.

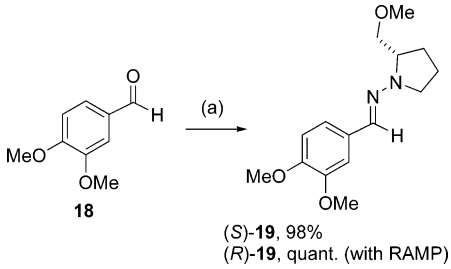
a Pummerer, or a Pomeranz−Fritsch reaction (route II). Both routes should ensure the correct methoxy substitution pattern present in ring A of **2** during the ring closure. In addition, the formation of tetrahydroisoquinolines **3** or **4**, containing the D ring with the correct substitution pattern, gives then access to the 9,10-disubstituted derivatives. Both tetrahydroisoquinolines could be derived from a common precursor, namely N-substituted 3-phenyl-substituted dihydroisoquinolinone **5**, after N−N cleavage of the chiral auxiliary, reduction of the amide functionality, and protection or functionalization of the resulting free amine. However, to introduce the allyl chain in **3**, the protected bromide or methyl-substituted amines derived from **5** would have to be submitted to further functionalization. The generation of **5** was envisaged by our tandem 1,2-addition/ring-closure methodology[7] starting from 2,3-dimethoxy-6-methylbenzamide **6** and 3,4-dimethoxy benzaldehyde SAMP or RAMP hydrazone **7**, respectively (Scheme 1).

Results and Discussion

As the tandem reaction had never been performed with a 2-substituted SAMP hydrazone before, first a model system of route I was investigated. Indeed, a reaction of simple 2-methylbenzamide **14** with 2-substituted benzaldehyde SAMP hydrazones (*S*)-**11**, (*S*)-**12**, or (*S*)-**13** should function as a guide in terms of the possible yield and diastereoselectivity offered by this tandem process (Scheme 2).

The syntheses of SAMP hydrazones (*S*)-**11**, (*S*)-**12**, and (*S*)-**13** were achieved in excellent yields by condensation of SAMP with the corresponding benzaldehydes **8**,[14] **9**, and **10** in Et_2O using molecular sieves to remove the water formed during the reaction.[15] Following the conditions developed for our methodology,[7] 7 equiv of 2-methylbenzamide **14** were deprotonated using an equimolar amount of LDA at −78 °C to minimize the risk of self-condensation.[16] The lithiated species was then reacted with 2-substituted benzaldehyde SAMP hydrazones (*S*)-**11**, (*S*)-**12**, or (*S*)-**13** previously complexed to $AlMe_3$ at −40 °C. However, instead of dihydroisoquinolinone (*R*,*S*)-**15**, a complex mixture of products was isolated containing (*S*)-**11** together with its isomer, namely (2*E*)-2-propenyl benzaldehyde SAMP hydrazone. For the bromide-substituted SAMP hydrazone (*S*)-**12**, only 11% of dihydroisoquinolone (*R*,*S*)-**16** could be isolated with an excellent diastereoselectivity of 96%. A comparison with the 65% yield previously reported for *para*-bromobenzaldehyde SAMP hydrazone indicated a strong steric hindrance for this ortho-equivalent.[7] In fact, a slight increase in the yield of this reaction was observed by switching from the bromide to the methyl substituent. This time the tandem 1,2-addition/ring closure between 2-methylbenzamide **14** and 2-methylbenzaldehyde SAMP hydrazone (*S*)-**13** gave 27% of the desired dihydroisoquinolone (*R*,*S*)-**17** with a diastereomeric excess ≥96% (Scheme 2).

SCHEME 3[a]



[a] Reagents and conditions: (a) SAMP or RAMP, MS 4 Å, Et_2O, 0 °C to room temperature, 18−21 h.

This series of reactions showed that ortho-substitution on the benzaldehyde SAMP hydrazone was poorly tolerated by our system. It should be mentioned that the Meyers route to tetrahydropalmatine[6b] was also thwarted by the ortho-substitution in one of the reaction components. Therefore, a second strategy (route II) was investigated where the ring closure of the tetrahydropalmatine core does not require the help of an ortho-substituent on the phenyl ring of our 3-substituted dihydroisoquinolone system.

3,4-Dimethoxybenzaldehyde SAMP or RAMP hydrazones **19** were obtained in virtually quantitative yield by condensation of commercial 3,4-dimethoxybenzaldehyde (**18**) and SAMP or RAMP, respectively, under the conditions described above (Scheme 3).

The deprotonation of 2,3-dimethoxy-6-methylbenzamide (**6**), prepared in 92% yield over two steps starting from commercially available 2,3-dimethoxybenzoic acid,[17,18]

(14) Kampmeier, J. A.; Harris, S. H.; Mergelsberg, I. *J. Org. Chem.* **1984**, *49*, 621.

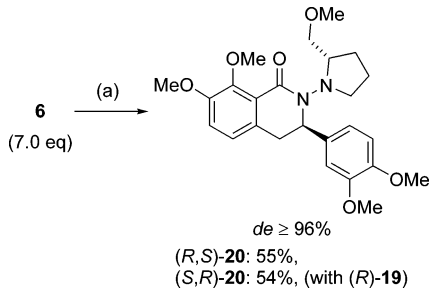
(15) For recent reviews on the SAMP/RAMP-hydrazone method, see: (a) Enders, D.; Voith, M.; Lenzen, A. *Angew. Chem.* **2005**, *117*, 1330; *Angew. Chem., Int. Ed.* **2005**, *44*, 1304. (b) Enders, D.; Boudou, M.; Gries, J. In *New Methods for the Asymmetric Synthesis of Nitrogen Heterocycles*; Vicario, J. L., Badía, D., Carillo, L., Eds.; Research Signpost: Trivandrum, India, 2005; p 1. (c) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.

(16) Clark, R. D.; Jahangir, A. *Org. React.* **1995**, *47*, 1.

(17) Zhuang, L.; Wai, J. S.; Embrey, M. W.; Fisher, T. E.; Egbertson, M. S.; Payne, L. S.; Guare, J. P., Jr.; Vacca, J. P.; Hazuda, D. J.; Felock, P. J.; Wolfe, A. L.; Stillmock, K. A.; Witmer, M. V.; Moyer, G.; Schleif, W. A.; Gabryelski, L. J.; Leonard, Y. M.; Lynch, J. J., Jr.; Michelson, S. R.; Young, S. D. *J. Med. Chem.* **2003**, *46*, 453.

(18) de Silva, S. O.; Ahmad, I.; Snieckus, V. *Can. J. Chem.* **1979**, *57*, 1598.

SCHEME 4[a]



[a] Reagents and conditions: (a) TMEDA (7.0 equiv)/*s*-BuLi (6.5 equiv), Et_2O/THF (5/1), −78 °C then (*S*)-**19** or (*R*)-**19**, $AlMe_3$ (3.1 equiv), Et_2O, −40 °C, 17 h.

was first attempted with LDA. To our surprise, the solution did not turn burgundy red, a typical color for lithiated species of 2-methylbenzamide derivatives. As there is a literature precedence for the deprotonation of 2 equiv of 2,4-dimethoxy-6-methylbenzamide with 3 equiv of LDA[19] and assuming that LDA probably forms a chelate with the methoxy groups of the aromatic ring and the amide group, an additional experiment was performed using 3 equiv of LDA compared to the benzamide. The reaction mixture turned bright orange, but no product could be isolated. We then turned to the use of 7 equiv of an equimolar mixture of *s*-BuLi and TMEDA. A small amount of THF had to be used to maintain a good solubility of the lithiated species when deprotonating 2,3-dimethoxy-6-methylbenzamide **6** in Et_2O.[20] Taking into account that the methoxy substituents can play an important role in this reaction, we increased the amount of $AlMe_3$ to 3.1 equiv for the complexation with hydrazone **20**. Finally, cyclized product (*R*,*S*)-**20** was obtained with excellent diastereoselectivity and in reasonable yield (55%), taking into account the complex functionalities set up in one step (Scheme 4).

The absolute configuration of the generated stereogenic center could be assigned as (*R*) based on our previous work.[7] The high diastereoselectivity of the reaction may be explained through complexation between one molecule of lithiated 2-methylbenzamide **6** and the methoxymethylpyrrolidine moiety of the auxiliary. Another equivalent of lithiated 2-methylbenzamide would then add to the CN double bond of hydrazone **19** on the less hindered Re face, activated by complexation to 1 equiv of $AlMe_3$. The resulting intermediate **21** possessing (*R*) configuration at the new stereocenter would then cyclize to (*R*,*S*)-**20** (Scheme 5). This proposed mechanism is supported by the fact that in our previously reported model reaction with 2-methylbenzamide **14** and benzaldehyde SAMP hydrazone,[7] one untouched equivalent of **14** could always be isolated after the 1,2-addition/ring-closure process independent of the time of the reaction and despite the self-condensation.

Analogously, (*S*,*R*)-**20** could also be obtained in a similar yield, demonstrating the reproducibility of the reaction.

BH_3·THF complex (20 equiv) was used to cleave the N−N bond of the chiral auxiliary of dihydroisoquinolinone (*R*,*S*)-**20** and to reduce the carbonyl group of the amide moiety in the same step (Scheme 6). After hydrolysis of the borane using a 1 N aqueous solution of HCl and a basic workup, we obtained tetrahydroisoquinoline (*R*)-**22** in an excellent yield of 82% and with an enantiomeric excess of 99% (determined by chiral stationary phase HPLC). Analogously, (*S*)-**22** was obtained in the same enantiomeric purity and a reproducible yield of 83%.

The synthesis of (*S*)-(−)-tetrahydropalmatine was then attempted by ring closure via Pummerer reaction. The generation of Pummerer precursor (*S*)-**23** was easily carried out by a Michael reaction of tetrahydroisoquinoline (*S*)-**22** with phenyl vinyl sulfoxide in refluxing methanol. A diastereoisomeric mixture of (*S*)-**23** (ratio of 64/36 determined by HPLC) was obtained in 94% yield. The Pummerer reaction was realized by subjecting (*S*)-**23** to 3 equiv of TFAA and 6 equiv of TFA in refluxing toluene.[21] Phenylsulfanyl tetrahydrodibenzoquinolizine (*S*)-**24** was passed through silica gel and then directly subjected to the next step. We were pleased to see that, after reductive desulfurization with Raney nickel, 31% yield of (*S*)-(−)-tetrahydropalmatine (**2**) could be obtained over two steps (Scheme 7). However, slight racemization occurred during this sequence (ee = 89% determined by chiral stationary phase HPLC), which may have to do with the harsh TFA conditions necessary for this transformation.

The possibility to synthesize (*S*)-(−)-tetrahydropalmatine by Friedel−Crafts reaction was subsequently investigated. After reflux of a solution of tetrahydroisoquinoline (*S*)-**22** and iodoethanol in MeCN in the presence of $NaHCO_3$, the alcohol (*S*)-**25** was obtained in 80% yield. The conversion of the primary alcohol into the corresponding chloride was performed after mesylation and nucleophilic attack of the intermediate anion in the presence of four additional equivalents of LiCl.[22] A yield of 70% of the desired chloroethyl tetrahydroisoquinoline (*S*)-**26** was achieved. A cyclization experiment was conducted with only 1.1 equiv of $AlCl_3$ to prevent possible demethylation of the methoxy substituents,[23] but only starting material was recovered. Because demethylation had obviously not taken place and assuming that $AlCl_3$ might complex with the methoxy substituents, four more equivalents of $AlCl_3$ were added to the reaction mixture. Unfortunately, after 7 h reflux **2** could not be observed by NMR analysis of the crude mixture, and it seemed that the main products were starting material and a phenol derivative (Scheme 8).

Because the final ring closure might as well be effected by a Pomeranz−Fritsch reaction, the respective precursors were prepared. First, the synthesis of diethyl acetal (*R*)-**27** was attempted starting from (*R*)-**22** in the presence of bromoacetaldehyde diethyl acetal and K_2CO_3 in refluxing MeCN. Unfortunately, only 33% of the desired

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

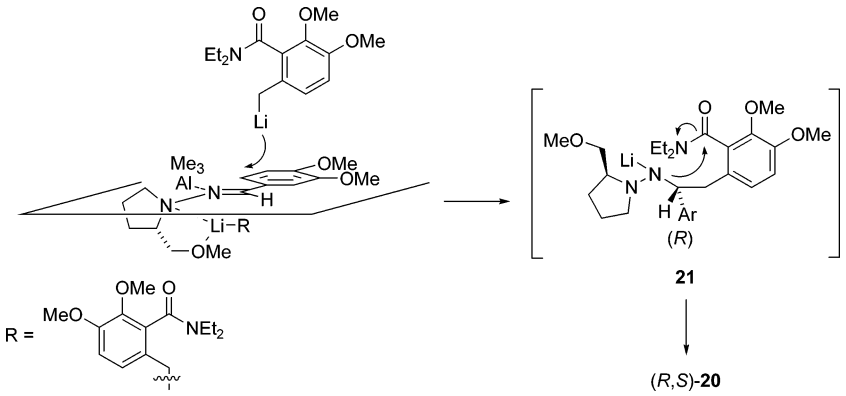
(20) A further optimization of the model tandem reaction of methylbenzamide **14** with benzaldehyde SAMP-hydrazone was realized by switching the solvent of the reaction from THF to Et_2O. This resulted in an increase of the yield from 70 to 80%.

(21) Takano, S.; Iida, H.; Inomata, K.; Ogasawara, K. *Heterocycles* **1993**, *35*, 47.

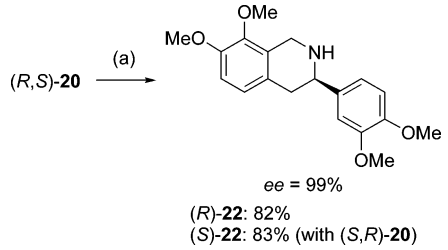
(22) In a model reaction, it was found that 61% of (*S*)-2-(2-chloroethyl)-3-phenyl-1,2,3,4-tetrahydroisoquinoline could be obtained by addition of 1.1 equiv of Et_3N and 1.1 equiv of MsCl to a solution of 2-((*S*)-3-phenyl-3,4-dihydro-1*H*-isoquinolin-2-yl)-ethanol in absence of LiCl.

(23) Hudlicky, T.; Butora, G. U.S. Patent 5912347, 1999.

SCHEME 5

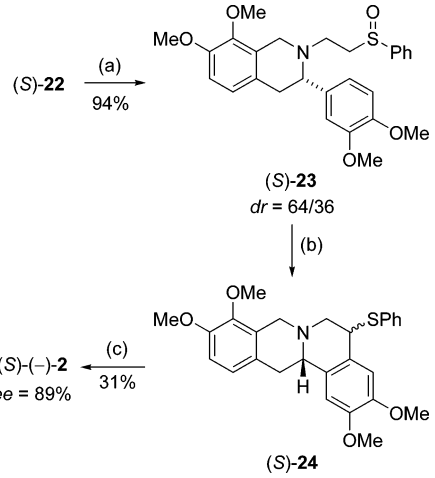


SCHEME 6[a]



[a] Reagents and conditions: (a) BH_3·THF (20 equiv), THF, Δ, 2 h then 1 N aq. HCl, −5 °C to Δ, 15 min.

SCHEME 7[a]

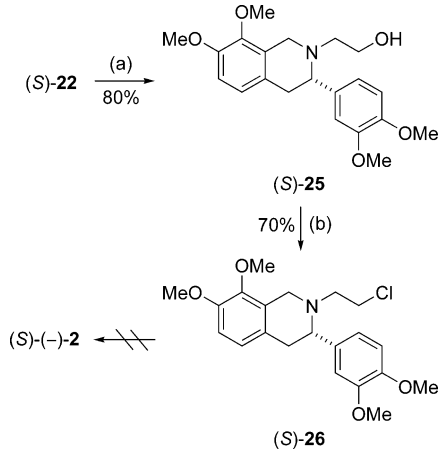


[a] Reagents and conditions: (a) phenyl vinyl sulfoxide, MeOH, reflux, 22 h. (b) TFAA (3 equiv), TFA (6 equiv), PhMe, reflux, 15 h. (c) Ra Ni, H_2, EtOH, reflux, 22 h.

Pomeranz−Fritsch precursor could be obtained. In a second attempt, a stoichiometric amount of KI was employed to perform a bromide−iodide exchange in situ before the nucleophilic attack, and indeed the yield of (*R*)-**27** could be increased to 75% (Scheme 9). When this reaction was repeated under the same conditions for the other enantiomer, 63% of (*S*)-**27** were obtained. The enantiomeric excess for both enantiomers of **27** remained excellent (ee = 99% determined by chiral stationary phase HPLC).

Slightly modifying a protocol described in the literature,[24] we exposed the diethyl acetals **27** to concentrated HCl in acetone overnight to perform the Pomeranz−Fritsch-type cyclization. Each quinolizin-5-ol **28** was obtained in very good yield as a mixture of diastereoisomers (ratio determined by chiral stationary phase HPLC). The deoxygenation of alcohols **28** still had to be accomplished to obtain both enantiomers of the target molecule tetrahydropalmatine (**2**), and to our knowledge no examples other than dehydration reactions are reported in the literature for the removal of the hydroxy group.[25]

SCHEME 8[a]



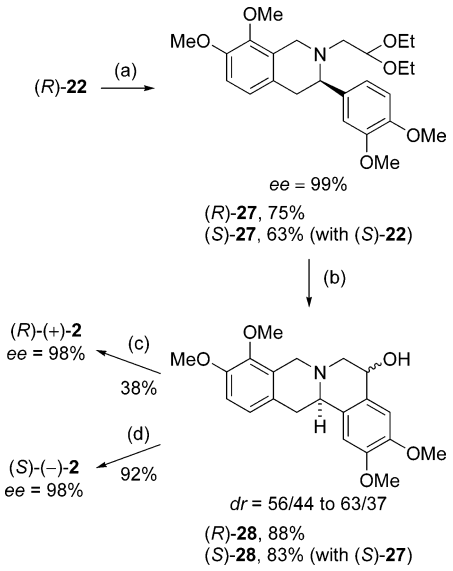
[a] Reagents and conditions: (a) $NaHCO_3$, 2-iodoethanol, MeCN, reflux, 24 h. (b) Et_3N, MsCl, LiCl, CH_2Cl_2, 0 °C to room temperature, 5 h.

First, a combination of 2.5 equiv of BF_3·OEt_2 and Et_3-SiH was applied on the diastereoisomeric mixture of quinolizin-5-ol (*R*)-**28** for 2 h at −78 °C. The choice of these smooth conditions proved to be appropriate because (*R*)-(+)-tetrahydropalmatine (**2**) was obtained in excellent enantiomeric purity, although in a low yield (Scheme 9). Possible reasons could be either that the number of equivalents of both reagents had to be higher, as often employed in the literature for this combination, or that the Lewis acid promoted the demethylation of the methoxy substituents. Because no traces of phenol could be detected in the NMR spectra of the crude mixture, another attempt was made with 5 equiv of both reagents

(24) Carillo, L.; Badía, D.; Domínguez, E.; Anakabe, E.; Osante, I.; Tellitu, I.; Vicario, J. L. *J. Org. Chem.* **1999**, *64*, 1115.

(25) (a) Badía, D.; Domínguez, E.; Iriondo, C. *J. Heterocycl. Chem.* **1986**, *23*, 1599. (b) Tellitu, I.; Badía, D.; Domínguez, E.; Carillo, L. *Heterocycles* **1996**, *43*, 2099.

SCHEME 9[a]



[a] Reagents and conditions: (a) bromoacetaldehyde diethyl acetal (1.2 equiv), KI (1.2 equiv), K_2CO_3 (1.1 equiv), DMF, 110 °C, 24 h. (b) Concentrated HCl, acetone, 0 °C to room temperature, 16−18 h. (c) $BF_3{\cdot}OEt_2$ (2.5 equiv), Et_3SiH (2.5 equiv), CH_2Cl_2, −78 °C, 2 h. (d) $BF_3{\cdot}OEt_2$ (5 equiv), Et_3SiH (5 equiv), CH_2Cl_2, −78 °C to room temperature, 19 h.

slowly warming up to room temperature overnight. The isolated yield for (*S*)-(−)-tetrahydropalmatine (**2**) improved to 92%, and the enantiopurity remained excellent (determined by chiral stationary phase HPLC) (Scheme 9).

Conclusion

Our tandem 1,2-addition/ring-closure methodology proved to be applicable to the synthesis of tetrahydroprotoberberines. Indeed, the enantioselective synthesis of both enantiomers of tetrahydropalmatine was achieved in seven steps (including the synthesis of the 2,3-dimethoxy-6-methylbenzamide (**6**)). The overall yield was 9% (not optimized) for (*R*)-(+)-tetrahydropalmatine (ee = 98%) and after optimization 17% for (*S*)-(−)-tetrahydropalmatine (ee = 98%). This total synthesis compares favorably in terms of yield and enantioselectivity with the previous asymmetric syntheses of **2**.[6]

Experimental Section

[1-(2-Allylphenyl)-meth-(1*E*)-ylidene]-((2*S*)-2-methoxymethylpyrrolidin-1-yl)-amine [(*S*)-11]. According to the general procedure described for the synthesis of hydrazones, 2-allylbenzaldehyde (**8**) (1.038 g, 7.10 mmol) and SAMP (1.079 g, 7.81 mmol, 94% purity (GC)) were reacted overnight. After purification by column chromatography (*n*-pentane/Et_2O = 20/1 to 3/1 + 2% Et_3N), 1.747 g (95%) of (*S*)-**11** was obtained as a pale yellow liquid; $[\alpha]^{24.5}_D$ −156.2 (*c* 1.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84−2.09 (m, 4H), 2.98−3.06 (m, 1H), 3.40 (s, 3H), 3.41−3.56 (m, 4H), 3.64−3.70 (m, 2H), 4.99 (dq, J = 1.7 Hz, J = 17.0 Hz, 1H), 5.05 (dq, J = 1.7 Hz, J = 10.1 Hz, 1H), 5.92 (tdd, J = 6.0 Hz, J = 10.1 Hz, J = 17.0 Hz, 1H), 7.10−7.22 (m, 3H), 7.39 (s, 1H), 7.81 (dd, J = 1.4 Hz, J = 7.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 26.8, 37.5, 49.0 (CH_2), 59.2 (CH_3), 63.1 (CH), 74.5, 115.4 (CH_2), 124.9, 126.3, 126.8, 129.8, 130.7 (CH), 134.8, 135.9 (C), 137.0 (CH) ppm; MS (EI) *m/z* (%) 258 (M^+, 17), 214 (17), 213 (100), 144 (16), 130 (13), 129 (33), 116 (12), 115 (17), 114 (10), 85 (22), 70 (44); IR (in $CHCl_3$) ν 3062, 2974, 2880, 2827, 1636, 1580, 1552, 1477, 1450, 1382, 1342, 1305, 1285, 1248, 1197, 1119, 995, 975, 911, 756 cm^{-1}; Anal. Calcd for $C_{16}H_{22}N_2O$: C, 74.38; H, 8.58; N, 10.84. Found: C, 74.14; H, 8.09; N, 11.18.

[1-(2-Bromophenyl)-meth-(1*E*)-ylidene]-((2*S*)-2-methoxymethylpyrrolidin-1-yl)-amine [(*S*)-12]. According to the general procedure described for the synthesis of hydrazones, 2-bromobenzaldehyde (1.17 mL, 10.0 mmol) and SAMP (1.658 g, 12.0 mmol, 94% purity (GC)) were reacted overnight. After distillation under high vacuum, 2.743 g (92%) of (*S*)-**12** was obtained as a yellow liquid; bp 115−122 °C/0.04 mbar; $[\alpha]^{25}_D$ −132.6 (*c* 2.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85−2.11 (m, 4H), 3.11−3.17 (m, 1H), 3.40 (s, 3H), 3.45−3.52 (m, 1H), 3.53 (dd, J = 6.6 Hz, J = 9.3 Hz, 1H), 3.67 (dd, J = 3.9 Hz, J = 9.3 Hz, 1H), 3.70−3.77 (m, 1H), 6.99−7.05 (m, 1H), 7.21−7.26 (m, 1H), 7.42 (s, 1H), 7.48 (dd, J = 1.1 Hz, J = 8.0 Hz, 1H), 7.89 (dd, J = 1.7 Hz, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 26.9, 48.8 (CH_2), 59.2 (CH_3), 62.9 (CH), 74.4 (CH_2), 121.9 (C), 125.7, 127.0, 127.6, 130.2, 132.5 (CH), 135.7 (C) ppm; MS (EI) *m/z* (%) 298 (M^+, 10), 296 (M^+, 13), 254 (12), 253 (100), 251 (98), 70 (37); IR (capillary) ν 2972, 2924, 2878, 2826, 1568, 1544, 1463, 1436, 1375, 1342, 1308, 1284, 1248, 1197, 1156, 1114, 1019, 974, 870, 851, 753 cm^{-1}; Anal. Calcd for $C_{13}H_{17}BrN_2O$: C, 52.54; H, 5.77; N, 9.43. Found: C, 52.10; H, 6.16; N, 9.92.

((2*S*)-2-Methoxymethylpyrrolidin-1-yl)-[1-*o*-tolylmeth-(1*E*)-ylidene]-amine [(*S*)-13]. According to the general procedure described for the synthesis of hydrazones, 2-methylbenzaldehyde (1.39 mL, 12.0 mmol) and SAMP (1.382 g, 10.0 mmol, 94% purity (GC)) were reacted overnight. After distillation under high vacuum with the help of a microdistillation apparatus, 2.088 g (90%) of (*S*)-**13** was obtained as a yellow liquid; bp 84 °C/0.02 mbar; $[\alpha]^{25}_D$ −158.9 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84−2.09 (m, 4H), 2.39 (s, 3H), 2.99−3.07 (m, 1H), 3.40 (s, 3H), 3.45−3.58 (m, 2H), 3.64−3.71 (m, 2H), 7.09−7.18 (m, 3H), 7.38 (s, 1H), 7.75 (d, J = 7.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7 (CH_3), 22.2, 26.8, 49.0 (CH_2), 59.2 (CH_3), 63.1 (CH), 74.5 (CH_2), 124.6, 125.8, 126.6, 130.26, 130.9 (CH), 134.2, 134.9 (C) ppm; MS (EI) *m/z* (%) 232 (M^+, 13), 188 (12), 187 (100), 70 (34); IR (capillary) ν 3057, 2879, 1697, 1579, 1553, 1458, 1379, 1342, 1248, 1198, 1154, 1120, 973, 879, 755, 719 cm^{-1}; Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.74; H, 9.20; N, 12.55.

[1-(3,4-Dimethoxyphenyl)-meth-(1*E*)-ylidene]-((2*S*)-2-methoxymethylpyrrolidin-1-yl)-amine [(*S*)-19]. According to the general procedure described for the synthesis of hydrazones, 3,4-dimethoxybenzaldehyde (3.988 g, 24.0 mmol) and SAMP (2.791 g, 20.0 mmol, 93% purity (GC)) were reacted overnight. After distillation under high vacuum using a microdistillation apparatus, 5.466 g (98%) of (*S*)-**19** was obtained as an orange syrup; bp 136 °C/0.03 mbar; $[\alpha]^{25}_D$ −114.7 (*c* 0.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78−2.08 (m, 4H), 2.94−3.05 (m, 1H), 3.40 (s, 3H), 3.42−3.53 (m, 2H), 3.59−3.72 (m, 2H), 3.86 (s, 3H), 3.92 (s, 3H), 6.80 (d, J = 8.2 Hz, 1H), 6.96 (dd, J = 1.8 Hz, J = 8.2 Hz, 1H), 7.20 (s, 1H), 7.25 (d, J = 1.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 26.8, 49.4 (CH_2), 55.8, 55.9, 59.3, 63.2 (CH_3), 74.8, 107.2, 110.0, 119.0 (CH), 130.6 (C), 133.0 (CH), 148.6, 149.2 (C) ppm; MS (EI) *m/z* (%) 278 (M^+, 32), 234 (16), 233 (100), 70 (18); IR (capillary) ν 2933, 2833, 1597, 1563, 1513, 1461, 1416, 1379, 1342, 1268, 1118, 1028, 973, 885, 807, 758 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{22}N_2O_3$ (M^+): 278.1630. Found: 278.1630.

[1-(3,4-Dimethoxyphenyl)-meth-(1*E*)-ylidene]-((2*R*)-2-methoxymethylpyrrolidin-1-yl)-amine [(*R*)-19]. According to the general procedure described for the synthesis of hydrazones, 3,4-dimethoxybenzaldehyde (3.988 g, 24.0 mmol) and RAMP (3.493 g, 20.0 mmol, 75% purity (GC)) were reacted overnight. After distillation under high vacuum using a microdistillation apparatus, 5.539 g (quant.) of (*R*)-**19** was collected as a pale yellow syrup; $[\alpha]^{28}_D$ +114.1 (*c* 1.27, $CHCl_3$).

(3*R*)-3-(2-Bromophenyl)-2-((2*S*)-2-methoxymethylpyrrolidin-1-yl)-3,4-dihydro-2*H*-isoquinolin-1-one [(*R*,*S*)-16]. In a 250-mL Schlenk flask under argon, *n*-BuLi (6.6 mL, 10.50 mmol, 1.59 M in hexane) was added to a solution of (*i*-Pr)$_2$NH (1.5 mL, 10.50 mmol) in abs. THF (50 mL) at 0 °C. The solution was stirred at 0 °C for 15 min and cooled to −78 °C before a solution of *N*,*N*-diethyl-2-methylbenzamide (**14**) (10.50 mmol) in abs. THF (10 mL) was added dropwise. The temperature was raised to −40 °C, and a solution of the SAMP hydrazone (*S*)-**12** (1.50 mmol) in abs. THF (6 mL), previously complexed to $AlMe_3$ (0.83 mL, 1.65 mmol, 2 M in heptane) for at least 1 h, was added dropwise over 30 min. The reaction mixture was stirred overnight (∼18 h) at −40 °C. The reaction was quenched with 10% aqueous potassium and sodium tartrate (5 mL) and sat. aqueous NH_4Cl (10 mL). After warming to room temperature and phase separation, the aqueous layer was extracted 3 times with Et_2O (30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. After purification by column chromatography (*n*-pentane/Et_2O = 8/1 to 1/3), 0.066 g (11%) of (*R*,*S*)-**16** was obtained as a yellow syrup: de ≥ 96% (^{1}H NMR); $[\alpha]^{27}_D$ +62.3 (*c* 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37−1.47 (m, 1H), 1.57−1.68 (m, 1H), 1.92−2.02 (m, 1H), 2.05−2.14 (m, 1H), 2.78−2.85 (dt, J = 4.4 Hz, J = 7.7 Hz, 1H), 3.05 (dd, J = 1.7 Hz, J = 15.9 Hz, 1H), 3.40−3.47 (m, 2H), 3.42 (s, 3H), 3.69−3.78 (m, 2H), 4.00−4.10 (m, 1H), 5.53 (dd, J = 1.7 Hz, J = 7.4 Hz, 1H), 6.93−6.98 (m, 2H), 7.01−7.06 (m, 2H), 7.29−7.34 (m, 2H), 7.51−7.56 (m, 1H), 8.05−8.11 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2, 27.0, 34.2, 51.6 (CH_2), 58.9 (CH_3), 60.7, 65.0 (CH), 77.3 (CH_2), 122.5 (C), 126.8, 126.9, 127.1, 127.5, 127.7, 128.6 (CH), 130.1 (C), 131.8, 133.0 (CH), 134.6, 139.5, 163.5 (C) ppm; MS (EI) *m*/*z* (%) 417 (M^+ + 1, 5), 415 (M^+ + 1, 6), 372 (20), 371 (100), 370 (24), 369 (99), 304 (14), 303 (16), 302 (16), 206 (25), 178 (13), 114 (72), 113 (18), 68 (10); IR (in $CHCl_3$) ν 2925, 2875, 1653, 1604, 1462, 1406, 1329, 1249, 1102, 1025, 754 cm^{-1}; Anal. Calcd for $C_{21}H_{23}BrN_2O_2$: C, 60.73; H, 5.58; N, 6.74. Found: C, 60.27; H, 5.42; N, 7.06.

(3*R*)-2-((2*S*)-2-Methoxymethylpyrrolidin-1-yl)-3-*o*-tolyl-3,4-dihydro-2*H*-isoquinolin-1-one [(*R*,*S*)-17]. According to the procedure described for the synthesis of (*S*,*R*)-**16**, 2-methylbenzamide **14** and SAMP-hydrazone (*S*)-**13** were reacted overnight in abs. THF. After purification by column chromatography (*n*-pentane/Et_2O = 4/1), 0.142 g (27%) of (*R*,*S*)-**17** was obtained as a pale pink crystalline solid: de ≥ 96% (^{1}H NMR); mp 88 °C; $[\alpha]^{21}_D$ +7.7 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36−1.48 (m, 1H), 1.54−1.64 (m, 1H), 1.87−2.01 (m, 1H), 2.04−2.16 (m, 1H), 2.44 (s, 3H), 2.73 (dt, J = 4.2 Hz, J = 7.9 Hz, 1H), 2.86 (dd, J = 1.7 Hz, J = 15.6 Hz, 1H), 3.39−3.43 (m, 2H), 3.40 (s, 3H), 3.66 (dt, J = 7.9 Hz, J = 7.9 Hz, 1H), 3.77 (ddd, J = 0.7 Hz, J = 7.7 Hz, J = 15.6 Hz, 1H), 4.01−4.12 (m, 1H), 5.38 (dd, J = 1.7 Hz, J = 7.7 Hz, 1H), 6.85−6.98 (m, 3H), 7.07 (td, J = 1.7 Hz, J = 7.0 Hz, 1H), 7.11−7.16 (m, 1H), 7.29−7.36 (m, 2H), 8.06−8.13 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3 (CH_3), 23.3, 27.0, 34.6, 51.6 (CH_2), 58.9 (CH_3), 60.4, 62.0 (CH), 77.5 (CH_2), 125.7, 126.0, 127.0, 127.0, 127.3, 127.6 (CH), 130.5 (C), 130.7, 131.9 (CH), 134.6, 135.1, 139.2, 163.6 (C) ppm; MS (EI) *m*/*z* (%) 351 (M^+ + 1, 0.4), 306 (24), 305 (100), 221 (16), 178 (13), 158 (10), 114 (83), 91 (10), 84 (11); IR (KBr) ν 3449, 2923, 2875, 2838, 1648, 1602, 1488, 1458, 1410, 1385, 1331, 1255, 1128, 1105, 1041, 753, 731 cm^{-1}; Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.00; H, 7.14; N; 7.78.

(3*R*)-3-(3,4-Dimethoxyphenyl)-7,8-dimethoxy-2-((2*S*)-2-methoxymethylpyrrolidin-1-yl)-3,4-dihydro-2*H*-isoquinolin-1-one [(*R*,*S*)-20]. In a 250-mL Schlenk flask under argon, *s*-BuLi (7.5 mL, 9.75 mmol, 1.3 M in hexane) was added to a solution of TMEDA (1.59 mL, 10.50 mmol) in abs. THF (10 mL) and abs. Et_2O (50 mL) at −78 °C. After 15 min, a solution of 2,3-dimethoxy-6-methylbenzamide **6** (2.639 g, 10.50 mmol) in abs. Et_2O (10 mL) was added dropwise. The temperature was raised to −40 °C, and a solution of SAMP hydrazone (*S*)-**19** (0.418 g, 1.50 mmol) in abs. Et_2O (6 mL), previously complexed to $AlMe_3$ (2.3 mL, 4.65 mmol, 2 M in heptane) for at least 1 h, was added dropwise over 45 min. The reaction mixture was stirred overnight (17 h) at −40 °C. The reaction was quenched with 10% aqueous potassium and sodium tartrate (10 mL) and sat. aqueous NH_4Cl (10 mL). After phase separation, the aqueous layer was extracted 4 times with Et_2O (30 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude mixture was purified by column chromatography (*n*-pentane/AcOEt = 1/2) to yield 0.375 g (55%) of (*R*,*S*)-**20** as a pale yellow syrup: de ≥ 96% (^{1}H NMR); $[\alpha]^{24}_D$ +21.18 (*c* 1.67, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40−1.53 (m, 1H), 1.56−1.72 (m, 1H), 1.88−2.02 (m, 1H), 2.06−2.20 (m, 1H), 2.83 (dd, J = 2.2 Hz, J = 15.3 Hz, 1H), 2.95 (dt, J = 3.7 Hz, J = 7.7 Hz, 1H), 3.40 (s, 3H), 3.38−3.50 (m, 2H), 3.65−3.91 (m, 2H), 3.73 (s, 3H), 3.78 (s, 3H), 3.81 (s, 3H), 3.98 (s, 3H), 4.10−4.22 (br, 1H), 4.98 (dd, J = 2.2 Hz, J = 6.2 Hz, 1H), 6.62−6.69 (m, 4H), 6.84 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.9, 26.8, 37.0, 51.7 (CH_2), 55.7, 55.8, 56.1, 58.9 (CH_3), 59.9 (CH), 61.6 (CH_3), 65.8 (CH), 77.2 (CH_2), 109.8, 110.8, 115.3, 118.7, 122.8 (CH), 124.6, 128.9, 133.4, 147.6, 148.5, 149.8, 152.7, 161.8 (C) ppm; MS (EI) *m*/*z* (%) 456 (M^+, 1), 412 (24), 411 (87), 344 (24), 343 (100), 342 (14), 327 (15), 325 (18), 324 (12), 312 (17), 205 (15), 192 (10), 178 (11), 166 (11), 151 (46); IR (in $CHCl_3$) ν 3001, 2937, 2876, 2836, 1653, 1581, 1516, 1484, 1455, 1419, 1389, 1302, 1265, 1140, 1102, 1064, 1033, 1002, 792, 755 cm^{-1}; HRMS *m*/*z* calcd for $C_{23}H_{27}N_2O_5$ ($M^+-C_2H_5O$): 411.1920. Found: 411.1920.

(3*S*)-3-(3,4-Dimethoxyphenyl)-7,8-dimethoxy-2-((2*R*)-2-methoxymethylpyrrolidin-1-yl)-3,4-dihydro-2*H*-isoquinolin-1-one [(*S*,*R*)-20]. In the same manner as described for the synthesis of (*R*,*S*)-**20**, *s*-BuLi (7.5 mL, 9.75 mmol, 1.3 M in hexane), TMEDA (1.59 mL, 10.50 mmol), 2,3-dimethoxy-6-methylbenzamide **6** (2.639 g, 10.50 mmol), RAMP hydrazone (*R*)-**19** (0.418 g, 1.50 mmol), and trimethylaluminum (2.3 mL, 4.65 mmol, 2 M in heptane) were reacted overnight (17 h). The crude mixture was purified twice by column chromatography (pure Et_2O) to yield 0.371 g (54%) of (*S*,*R*)-**20** as a pale yellow syrup: de ≥ 96% (^{1}H NMR); $[\alpha]^{30}_D$ −20.76 (*c* 0.79, $CHCl_3$).

(3*R*)-3-(3,4-Dimethoxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*R*)-22]. In a Schlenk flask under argon fitted with a reflux condenser, BH_3·THF (5.5 mL, 5.52 mmol, 1 M in THF) was added to a solution of dihydroisoquinolinone (*R*,*S*)-**20** (0.126 g, 0.28 mmol) in abs. THF (11 mL), and the reaction mixture was heated at reflux for 4 h. After cooling the solution to 5 °C, we cautiously added 1 N aqueous HCl (2.2 mL). After 1 min reflux, the solvent and most of the water were evaporated under reduced pressure and sat. aqueous $NaHCO_3$ was added to the residue until no evolution of gas could be observed any more. The mixture was extracted 3 times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. After purification by column chromatography (*n*-hexane/acetone = 1/1), 0.075 g (82%) of (*R*)-**22** was obtained as a champagne-beige solid: ee = 99% (Chiralpak AD; *n*-heptane/*i*-PrOH = 65/35; R_t = 14.96 min; λ = 214 nm); mp 103−104 °C; $[\alpha]^{30}_D$ +81.6 (*c* 0.70, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (br, 1H), 2.86−2.96 (m, 2H), 3.83−3.91 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.10 (d, J = 16.4 Hz, 1H), 4.36 (d, J = 16.4 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 6.82 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 8.2 Hz, 1H), 6.95 (dd, J = 1.9 Hz, J = 8.2 Hz, 1H), 7.02 (d, J = 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.3, 44.8 (CH_2), 55.8, 55.9 (CH_3), 58.2 (CH), 60.0 (CH_3), 109.4, 110.7, 110.9, 118.5, 123.9 (CH), 128.0, 128.7, 136.9, 145.1, 148.0, 148.9, 150.1 (C) ppm; MS (EI) *m*/*z* (%) 330 (M^+ + 1, 10), 329 (M^+, 49), 328 (11), 165 (14), 164 (100), 149 (40); IR (KBr) ν 3976, 3459, 3330, 3236, 2990, 2936, 2831, 1596, 1515, 1492, 1461, 1421, 1323, 1272, 1228, 1157, 1080, 1030, 869, 800, 758 cm^{-1}; Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.48; H, 7.36; N, 4.38.

(3*S*)-3-(3,4-Dimethoxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-22]. (*S*)-**22** was prepared in the same manner as described for the synthesis of (*R*)-**22** using dihydroisoquinolinone (*S*,*R*)-**20** (0.300 g, 0.66 mmol) and BH_3·THF (13.1 mL, 13.14 mmol, 1 M in THF). After purification by column chromatography (Et_2O/MeOH = 20/1), 0.182 g (83%) of (*S*)-**22** was obtained as a champagne-beige solid: ee = 99% (Chiralpak AD; *n*-heptane/*i*-PrOH = 65/35; R_t = 11.47 min; λ = 214 nm); $[\alpha]^{27}_D$ −84.8 (*c* 0.70, $CHCl_3$).

(3*S*)-2-(2-Phenylsulfinylethyl)-3-(3,4-dimethoxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-23]. In a 10-mL flask under argon, a solution of tetrahydroisoquinoline (*S*)-**22** (0.109 g, 0.33 mmol) and phenyl vinyl sulfoxide (66 μL, 0.50 mmol) in abs. MeOH (2 mL) was heated at reflux for 22 h. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (pure Et_2O then Et_2O/MeOH = 20/1) to give 0.150 g (94%) of (*S*)-**23** as a yellow syrup: dr = 64/36 (spherical silica; *n*-heptane/*i*-PrOH = 9/1; R_t = 21.82 min; R_t = 27.90 min; λ = 254 nm); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 2.46−2.54 (m, 1H), 2.73−3.18 (m, 11H), 3.55 (d, *J* = 16.1 Hz, 1H), 3.58−3.75 (m, 3H), 3.78 (s, 3H), 3.83 (s, 6H), 3.85 (s, 9H), 3.88 (s, 3H), 3.89 (s, 3H), 4.06 (d, *J* = 16.2 Hz, 1H), 4.18 (d, *J* = 16.1 Hz, 1H), 6.75−6.84 (m, 9H), 6.91 (s, 1H), 7.43−7.49 (m, 8H), 7.51−7.55 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 36.1, 36.7, 47.1, 49.4, 49.5, 54.8, 55.3 (CH_2), 55.7, 55.8, 55.8, 60.1, 60.2 (CH_3), 63.0, 63.6, 110.4, 110.5, 110.6, 111.0, 119.9, 120.0, 123.1, 123.7 (CH), 127.2, 127.3, 127.7, 127.9 (C), 128.9, 128.9, 130.6 (CH), 133.8, 134.1, 143.5, 144.0, 145.0, 148.1, 148.2, 148.8, 149.0, 150.0 (C) ppm; MS (EI) *m*/*z* (%) 466 (10), 465 (31), 464 (M^+ − OH, 100), 355 (10), 354 (12), 313 (17), 164 (27), 149 (11), 137 (25); IR (in $CHCl_3$) ν 3013, 2962, 2935, 1513, 1497, 1461, 1263, 1219, 1143, 1083, 1032, 758, 667 cm^{-1}; HRMS *m*/*z* calcd for $C_{27}H_{30}NO_4S$ (M^+ − OH): 464.1896. Found: 464.1896.

(13a*S*)-2,3,9,10-Tetramethoxy-5-phenylsulfanyl-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine [(*S*)-24]. In a 25-mL flask under argon, a solution of sulfoxide (*S*)-**23** (0.124 g, 0.26 mmol), TFAA (0.11 mL, 0.77 mmol), and TFA (0.12 mL, 1.55 mmol) in abs. toluene (12 mL) was heated at reflux for 15 h. The volatiles were removed under reduced pressure, and a part of the resulting crude mixture was purified by preparative TLC (Et_2O/MeOH = 20/1) for analysis whereas the rest was passed through silica (Et_2O/MeOH = 20/1). The combined products were then used for the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 2.71−3.00 (m, 4H), 3.18−3.40 (m, 4H), 3.42−3.71 (m, 4H), 3.78 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 4.15 (d, *J* = 15.9 Hz, 1H), 4.21 (d, *J* = 15.9 Hz, 1H), 4.36 (s, 1H), 4.72 (dd, *J* = 5.2 Hz, *J* = 9.9 Hz, 1H), 6.64 (s, 1H), 6.73 (s, 1H), 6.75−6.90 (m, 4H), 7.24−7.35 (m, 8H), 7.42−7.52 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 35.8, 36.1 (CH_2), 45.9, 47.7 (CH), 53.0, 53.3 (CH_2), 55.8, 55.8, 56.0 (CH_3), 57.7 (CH_2), 58.9, 59.1 (CH), 60.8 (CH_3), 108.0, 108.2, 110.7, 110.8, 110.9, 111.7, 123.6 (CH), 126.2 (C), 127.0 (CH), 128.0 (C), 128.7, 128.9 (CH), 130.8 (C), 131.6 (CH), 132.3, 134.5, 144.9, 147.4, 148.0, 150.1 (C) ppm.

2-[(3*S*)-3-(3,4-Dimethoxyphenyl)-7,8-dimethoxy-3,4-dihydro-1*H*-isoquinolin-2-yl]-ethanol [(*S*)-25]. In a flask under argon, a suspension of tetrahydroisoquinoline (*S*)-**22** (0.097 g, 0.30 mmol), anhydrous MeCN (3 mL), 2-iodoethanol (25 μL, 0.32 mmol), and $NaHCO_3$ (0.027 g, 0.32 mmol) was heated to reflux overnight (24 h). After cooling to room temperature, the reaction mixture was filtered with CH_2Cl_2, and the volatiles were evaporated under reduced pressure. The resulting crude mixture was purified by column chromatography (Et_2O/MeOH = 80/1 to 20/1) providing 0.089 g (80%) of (*S*)-**25** as a pale yellow foam; $[\alpha]^{25}_D$ −36.9 (*c* 0.45, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (dt, *J* = 4.7 Hz, *J* = 12.9 Hz, 1H), 2.59 (br, 1H), 2.80 (ddd, *J* = 4.7 Hz, *J* = 12.9 Hz, 1H), 2.99−3.12 (m, 2H), 3.55 (dt, *J* = 4.7 Hz, *J* = 11.0 Hz, 1H), 3.61 (d, *J* = 16.5 Hz, 1H), 3.71−3.78 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 4.17 (d, *J* = 16.5 Hz, 1H), 6.79−6.88 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.6, 48.8, 54.7 (CH_2), 55.7, 55.8, 55.8 (CH_3), 58.3 (CH_2), 60.1 (CH_3), 63.1, 110.9, 110.8, 110.9, 120.0, 123.2 (CH), 127.3, 127.9, 134.1, 145.1, 148.1, 148.9, 150.1 (C) ppm; MS (EI) *m*/*z* (%) 373 (M^+, 10), 343 (23), 342 (100), 314 (11), 313 (49), 282 (13), 175 (12), 164 (16), 151 (12), 149 (16); IR (in $CHCl_3$) ν 3563, 3536, 3379, 3314, 3012, 2936, 2836, 1596, 1497, 1461, 1423, 1373, 1263, 1233, 1145, 1087, 1030, 986, 877, 756, 667 cm^{-1}; HRMS *m*/*z* calcd for $C_{21}H_{27}NO_5$ (M^+): 373.1889. Found: 373.1890.

(3*S*)-2-(2-Chloroethyl)-3-(3,4-dimethoxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-26]. In a 25-mL Schlenk flask under argon, a solution of the alcohol (*S*)-**25** (0.135 g, 0.36 mmol) in abs. CH_2Cl_2 (12 mL) was cooled to 0 °C. Et_3N (55 μL, 0.40 mmol), methanesulfonyl chloride (31 μL, 0.40 mmol), and LiCl (0.061 g, 1.45 mmol) were successively added, and the temperature was increased to room temperature. After 5 h the reaction was diluted with CH_2Cl_2, and the organic phase was washed twice with sat. aqueous $NaHCO_3$ and twice with H_2O. After drying over $MgSO_4$, filtration, and concentration under reduced pressure, the residue was purified by column chromatography (*n*-pentane/Et_2O = 1/1) to yield 0.097 g (70%) of (*S*)-**26** as a colorless solid; mp 113−115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51−2.62 (m, 1H), 2.88−3.11 (m, 3H), 3.53−3.68 (m, 4H), 3.85 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 4.26 (d, *J* = 16.1 Hz, 1H), 6.85−6.88 (m, 4H), 6.97 (d, *J* = 1.2 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.6, 41.8, 50.2, 55.5 (CH_2), 55.9, 55.9, 60.2 (CH_3), 63.8, 110.5, 110.8, 111.1, 120.1, 123.3 (CH), 127.5, 128.0, 134.9, 145.2, 148.4, 149.2, 150.3 (C) ppm; MS (EI) *m*/*z* (%) 393 (M^+, 22), 392 (18), 391 (M^+, 61), 390 (11), 343 (13), 342 (68), 328 (19), 313 (46), 312 (24), 165 (13), 164 (100), 149 (36); IR (KBr) ν 2999, 2931, 2831, 2362, 1596, 1512, 1458, 1373, 1325, 1263, 1234, 1153, 1081, 1030, 980, 878, 807, 761, 741 cm^{-1}; HRMS *m*/*z* calcd for $C_{21}H_{26}ClNO_4$ (M^+): 391.1550. Found: 391.1551.

(3*R*)-2-(2,2-Diethoxyethyl)-3-(3,4-dimethoxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*R*)-27]. In a 10-mL flask, bromoacetaldehyde diethyl acetal (72 μL, 0.48 mmol) was added to a suspension of tetrahydroisoquinoline (*R*)-**22** (0.132 g, 0.40 mmol), K_2CO_3 (0.061 g, 0.44 mmol), and KI (0.080 g, 0.48 mmol) in anhydrous DMF (5 mL). The reaction mixture was heated at 110 °C for 24 h and diluted with H_2O. The organic phase was kept, and the aqueous phase was extracted 4 times with Et_2O. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 1/3) to yield 0.135 g (75%) of (*R*)-**27** as a yellow syrup: ee = 99% (Chiralpak AD; *n*-heptane/*i*-PrOH = 9/1; R_t = 15.54 min; λ = 230.1 nm); $[\alpha]^{24}_D$ +46.8 (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.2 Hz, 3H), 1.19 (t, *J* = 7.2 Hz, 3H), 2.39 (dd, *J* = 5.2 Hz, *J* = 13.4 Hz, 1H), 2.76 (dd, *J* = 5.2 Hz, *J* = 13.4 Hz, 1H), 2.95 (dd, *J* = 4.7 Hz, *J* = 16.3 Hz, 1H), 3.05 (dd, *J* = 9.2 Hz, *J* = 16.3 Hz, 1H), 3.38−3.72 (m, 6H), 3.84 (s, 3H), 3.85 (s, 6H), 3.87 (s, 3H), 4.38 (d, *J* = 16.6 Hz, 1H), 4.64 (t, *J* = 5.2 Hz, 1H), 6.74 (m, 3H), 6.86 (dd, *J* = 1.7 Hz, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 1.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.3 (CH_3), 36.2, 50.8 (CH_2), 55.8, 55.9 (CH_3), 56.3 (CH_2), 60.2 (CH_3), 61.5, 62.2 (CH_2), 63.6, 102.4, 110.8, 120.3, 123.3 (CH), 127.7, 128.9, 135.3, 145.3, 148.2, 149.0, 150.3 (C) ppm; MS (EI) *m*/*z* (%) 445 (M^+, 6), 400 (12), 399 (11), 343 (32), 342 (100), 329 (13), 314 (20), 313 (50); IR (in $CHCl_3$) ν 2973, 2933, 2903, 2835, 1594, 1497, 1460, 1423, 1373, 1265, 1236, 1138, 1085, 1058, 1030, 988, 803, 757 cm^{-1}; Anal. Calcd for $C_{25}H_{35}NO_6$: C, 67.39; H, 7.92; N, 3.14. Found: C, 67.22; H, 7.90; N, 2.94.

(3*S*)-2-(2,2-Diethoxyethyl)-3-(3,4-dimethoxyphenyl)-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-27]. (*S*)-**27** was prepared in the same manner as described for the synthesis of (*R*)-**27** using bromoacetaldehyde diethyl acetal (71 μL, 0.47 mmol), tetrahydroisoquinoline (*S*)-**22** (0.129 g, 0.39

mmol), K_2CO_3 (0.060 g, 0.43 mmol), and KI (0.078 g, 0.47 mmol). The resulting crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 1/3) to give 0.111 g (64%) of (*S*)-**27** as a yellow syrup: ee = 99% (Chiralpak AD; *n*-heptane/*i*-PrOH = 9/1; R_t = 14.13 min; λ = 230.1 nm); $[\alpha]^{23.5}_D$ −47.1 (*c* 0.64, $CHCl_3$).

(13a*R*)-2,3,9,10-Tetramethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]-quinolizin-5-ol [(*R*)-28]. In a 10-mL flask, a solution of acetal (*R*)-**27** (0.105 g, 0.24 mmol) in acetone (2.6 mL) was cooled to 0 °C. Concentrated aqueous HCl (86 μL) was added dropwise, and the temperature was slowly increased to room temperature. After 2 h and 30 min, the cooling bath was removed, and the reaction mixture was stirred for an additional 14 h. The temperature was decreased to 0 °C, and 1 N aqueous NaOH was carefully added until pH 10 was reached. The reaction mixture was extracted 4 times with CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (Et_2O/MeOH = 60/1) providing 0.077 g (88%) of (*R*)-**28** as a yellow solid: dr = 44/56 (Chiralcel OD; *n*-heptane/*i*-PrOH = 8/2; R_t = 18.33 min; R_t = 23.72 min; λ = 230 nm); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 2.49 (dd, *J* = 8.1 Hz, *J* = 11.0 Hz, 1H), 2.72−2.85 (m, 3H), 3.12 (dd, *J* = 4.0 Hz, *J* = 16.1 Hz, 1H), 3.24−3.30 (m, 2H), 3.33 (dd, *J* = 4.9 Hz, *J* = 11.0 Hz, 1H), 3.52 (dd, *J* = 3.9 Hz, *J* = 11.2 Hz, 1H), 3.58 (d, *J* = 15.9 Hz, 1H), 3.64 (dd, *J* = 4.0 Hz, *J* = 11.8 Hz, 1H), 3.69 (d, *J* = 16.8 Hz, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.87 (s, 6H), 3.89 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 4.15 (d, *J* = 16.5 Hz, 1H), 4.19 (d, *J* = 16.8 Hz, 1H), 4.53 (s, 1H), 4.86 (dd, *J* = 4.9 Hz, *J* = 8.1 Hz, 1H), 6.69 (s, 1H), 6.74 (s, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 6.89 (s, 1H), 7.06 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 34.6, 36.2, 53.0, 53.5 (CH_2), 55.8, 55.8, 56.0 (CH_3), 58.0 (CH_2), 58.5 (CH), 58.7 (CH_2), 59.0 (CH), 60.1 (CH_3), 66.5, 107.8, 109.1, 110.8, 111.0, 111.7, 123.6, 123.7 (CH), 127.0, 127.1, 127.9, 128.2, 128.7, 129.8, 130.0, 130.1, 144.8, 145.0, 147.8, 148.2, 148.8, 150.1, 150.2 (C) ppm; MS (EI) *m*/*z* (%) 371 (M^+, 41), 370 (13), 355 (10), 354 (47), 165 (32), 164 (100), 163 (16), 150 (13), 149 (69), 121 (11); IR (in $CHCl_3$) ν 1514, 1497, 1460, 1278, 1261, 1218, 1148, 755 cm^{-1}; HRMS *m*/*z* calcd for $C_{21}H_{25}NO_5$ (M^+): 371.1733. Found: 371.1733.

(13a*S*)-2,3,9,10-Tetramethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]-quinolizin-5-ol [(*S*)-28]. According to the procedure described for the synthesis of (*R*)-**28**, acetal (*S*)-**27** (0.105 g, 0.24 mmol) was converted into (*S*)-**28** using concentrated aqueous HCl (86 μL). The resulting crude mixture was purified by column chromatography (Et_2O/MeOH = 60/1) to yield 0.076 g (83%) of (*S*)-**28** as a yellow solid; dr = 63/37 (Chiralcel OD; *n*-heptane/*i*-PrOH = 8/2; R_t = 18.33 min; R_t = 23.72 min; λ = 230 nm).

(13a*R*)-2,3,9,10-Tetramethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine; (*R*)-(+)-Tetrahydropalmatine [(*R*)-(+)-2]. In a 5-mL flask under argon, a solution of alcohol (*R*)-**28** (43 mg, 0.116 mmol) in abs. CH_2Cl_2 (1.5 mL) was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (37 μL, 0.289 mmol) and Et_3SiH (46 μL, 0.289 mmol) were successively added. After 2 h at −78 °C the temperature was increased to room temperature, and the reaction mixture was stirred for an additional 5 h. The solution was then neutralized with sat. aqueous $NaHCO_3$ (∼0.5−1 mL). The organic phase was kept, and the aqueous phase was extracted 4 times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 1/1 + 5% Et_3N) to yield 16 mg (38%) of (*R*)-**2** as a light yellow solid: ee = 98% (Chiralpak AD; *n*-heptane/*i*-PrOH = 8/2; R_t = 9.81 min; λ = 230 nm); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61−2.71 (m, 2H), 2.83 (dd, *J* = 11.4 Hz, *J* = 15.8 Hz, 1H), 3.10−3.24 (m, 2H), 3.27 (dd, *J* = 3.7 Hz, *J* = 15.8 Hz, 1H), 3.51−3.58 (m, 2H), 3.56 (s, 6H), 3.87 (s, 3H), 3.89 (s, 3H), 4.25 (d, *J* = 15.9 Hz, 1H), 6.62 (s, 1H), 6.74 (s, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.1, 36.3, 51.5, 54.0 (CH_2), 55.8, 55.8, 56.0 (CH_3), 59.3 (CH), 60.1 (CH_3), 108.4, 110.8, 111.2, 123.7 (CH), 126.6, 127.6, 128.5, 129.5, 144.9, 147.2, 147.3, 150.1 (C) ppm. All analytical data correspond to those reported in the literature.[26]

(13a*S*)-2,3,9,10-Tetramethoxy-5,8,13,13a-tetrahydro-6*H*-dibenzo[*a*,*g*]quinolizine; (*S*)-(−)-Tetrahydropalmatine [(*S*)-(−)-2]. Method A. In a 25-mL flask under argon, Raney nickel W2 (two spatulas) was added to a solution of crude sulfide (*S*)-**24** (max. 0.26 mmol) in anhydrous EtOH (10 mL). The argon atmosphere was removed under high vacuum until the EtOH started to bubble, and hydrogen gas was added. This operation was repeated twice, and the reaction mixture was heated at reflux for 22 h. The suspension was then filtered with CH_2Cl_2 over a pad of Celite. After evaporation of the solvents, the residue was purified by column chromatography (*n*-pentane/Et_2O = 1/2 to 1/1 + 5% Et_3N) to give 0.029 g (31% over two steps) of (*S*)-**2** as a light yellow solid: ee = 90% (Chiralpak AD; *n*-heptane/*i*-PrOH = 8/2; R_t = 13.74 min; λ = 230 nm).

Method B. In a 5-mL flask, a solution of alcohol (*S*)-**28** (60 mg, 0.162 mmol) in abs. CH_2Cl_2 (3 mL) was cooled to −78 °C. $BF_3{\cdot}OEt_2$ (0.10 mL, 0.808 mmol) and Et_3SiH (0.13 mL, 0.808 mmol) were successively added. After 1 h at −78 °C the temperature was increased to room temperature, and the reaction mixture was stirred for an additional 18 h. The solution was then neutralized with sat. aqueous $NaHCO_3$ (∼1−2 mL). The organic phase was kept, and the aqueous phase was extracted 4 times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude mixture was purified by column chromatography (*n*-pentane/Et_2O = 1/1 + 5% Et_3N) to provide 53 mg (92%) of (*S*)-**2** as a light yellow solid: ee = 98% (Chiralpak AD; *n*-heptane/*i*-PrOH = 8/2; R_t = 13.74 min; λ = 230 nm); mp 138 °C (Lit.[27] 140 °C); $[\alpha]^{24.5}_D$ −268.5 (*c* 0.8, $CHCl_3$, ee = 98%) (Lit.[28] $[\alpha]^{20}_D$ −269 (*c* 0.8, $CHCl_3$)).

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (Sonderforschungsbereich 380, Graduiertenkolleg 440, scholarship to M.B.) and the Fond der Chemischen Industrie. We thank Bayer AG, BASF AG, and Degussa AG for the donation of chemicals.

Supporting Information Available: Chiral HPLC data for **22**, **27**, and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051554T

(26) (a) Blanchfield, J. T.; Sands, D. P. A.; Kennard, C. H. L.; Byriel, K. A.; Kitching, W. *Phytochemistry* **2003**, *63*, 711. (b) Miyazawa, M.; Yoshio, K.; Ishikawa, Y.; Kameoka, H. *J. Agric. Food Chem.* **1998**, *46*, 1914.

(27) Bhakuni, D. S.; Jain, S.; Gupta, S. *Tetrahedron* **1984**, *40*, 1591.

(28) Halbsguth, C.; Meissner, O.; Haeberlein, H. *Planta Med.* **2003**, *69*, 305.