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A Highly Stereoselective Asymmetric Synthesis of (−)-Lobeline and (−)-Sedamine†

François-Xavier Felpin and Jacques Lebreton*

Laboratoire de Synthèse Organique, Faculté des Sciences et des Techniques, CNRS UMR 6513, 2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France

lebreton@chimie.univ-nantes.fr

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A highly stereoselective asymmetric synthesis of (−)-sedamine and (−)-lobeline is described from benzaldehyde in 16 and 17 steps with an overall yield of 20% and 14%, respectively. The key intermediate *syn*-3,4-epoxyalcohol was prepared in a highly diastereomeric fashion (>99% ee, dr) and served as a common intermediate for both alkaloids.

Introduction

The herb of *Lobelia inflata* contains more than 20 piperidine alkaloids. The most important of them is (−)-lobeline (**1**) (see Figure 1). The herb was named after Matthias de Lobel (1570 (Lille) to 1616 (London)), a French botanist and physician. The plant was also known as Indian tobacco because the American Indians smoked the dried leaves to obtain the effects of **1** on the central nervous system (CNS). It is an erect annual or biannual herb, 1−2 ft high with lower leaves. The flowers are pale violet blue in color, tinted pale yellow within.[1] At the end of the 19th century, *Lobelia* was considered to be one of the most important plants in medicinal preparation. At one time, **1** was used as a respiratory stimulant, but its use became obsolete due to its unpredictable effects. Because it possesses actions similar to those of (−)-nicotine **3**, lobeline **1** is currently under investigation for use as a smoking deterrent.

Lobeline **1** has been reported to have many nicotine **3** like effects, including learning disorders and anxiolitic effects. Lobeline **1** binds to the neuronal nicotinic receptor with high affinity (K_i = 4−30 nM), leading to its classification as a nicotinic agonist. Thus, lobeline **1** resembles nicotine **3** in behavioral and pharmacological experiments, but no obvious structural resemblance of lobeline **1** to nicotine **3** is apparent. Moreover several studies have shown that lobeline **1** sometimes acts as a nicotinic antagonist.[2] Thus, considerable evidence suggests that nicotine **3** and lobeline **1** may not be acting via a common CNS mechanism.[3] As part of our program

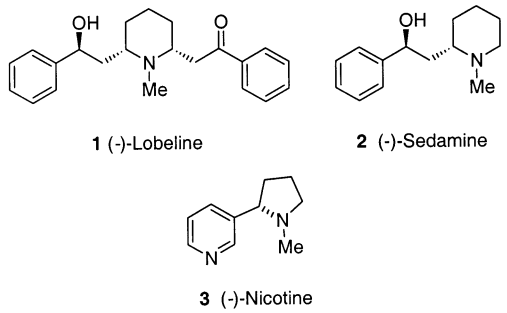

FIGURE 1.

of studying the chemistry and biology of natural products active on CNS diseases,[4] we recently initiated a project directed toward the total synthesis of **1** and (−)-sedamine **2** (see Figure 1) to elucidate the mechanism of action and structure−function relationships. Our strategy was to design a route leading to the preparation of analogues of these natural products to evaluate them. To date, only one asymmetric synthesis of lobeline **1** has been reported, by Marazano.[5] Moreover, to our knowledge, only a few analogues have been prepared with minor modifications, principally to the carbonyl or hydroxyl functions.[6] Here we report the total synthesis of **1** and the structurally simplified natural analogue **2**.[7]

* To whom correspondence should be addressed. Phone: + 33 2 51 12 54 03. Fax: + 33 2 51 12 54 02.

† This paper is dedicated with deep admiration to our close colleague and outstanding scientist Dr. Jean Villiéras on the occasion of his retirement.

(1) Millspaugh, C. F. *Lobelia inflata*. In *American medicinal plants: an illustrated and descriptive guide to plants indigenous to and naturalized in the United States which are used in medicine*; Dover: New York, 1974; pp 385−388.

(2) For reviews on the pharmacology of lobeline, see: (a) Damaj, M. I.; Patrick, G. S.; Creasy, K. R.; Martin, B. R. *J. Pharmacol. Exp. Ther.* **1997**, *282*, 410−419. (b) Mccurdy, C. R.; Miller, R. L.; Beach, J. W. *Biol. Act. Nat. Prod.* **2000**, 151−162.

(3) For a relevant and novel mechanism of action, see: Dwoskin, L. P.; Crooks, P. A. *Biochem. Pharmacol.* **2002**, *63*, 89−98.

(4) (a) Girard, S.; Robins, R. J.; Villiéras, J.; Lebreton, J. *Tetrahedron Lett.* **2000**, *41*, 9245−9249. (b) Felpin, F.-X.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *Synlett* **2000**, 1646−1648. (c) Felpin, F.-X.; Girard, S.; Vo-Thanh, G.; Robins, R. J.; Villiéras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305−6312. (d) Felpin, F.-X.; Vo-Thanh, G.; Villiéras, J.; Lebreton, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1121−1124.

(5) Compère, D.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 4528−4532. The (−)-lobeline is obtained in 18 steps from a commercial product.

(6) (a) Flammia, D.; Dukat, M.; Damaj, M. I.; Martin, B.; Glennon, R. A. *J. Med. Chem.* **1999**, *42*, 3726−3731. (b) Terry, A. V.; Williamson, R.; Gattu, M.; Beach, J. W.; McCurdy, C. R.; Sparks, J. A.; Pauly, J. R. *Neuropharmacology* **1998**, *37*, 93−102. (c) Dwoskin, L. P.; Crooks, P. A.; Jones, M. D. Patent WO 01/08678, 2001.

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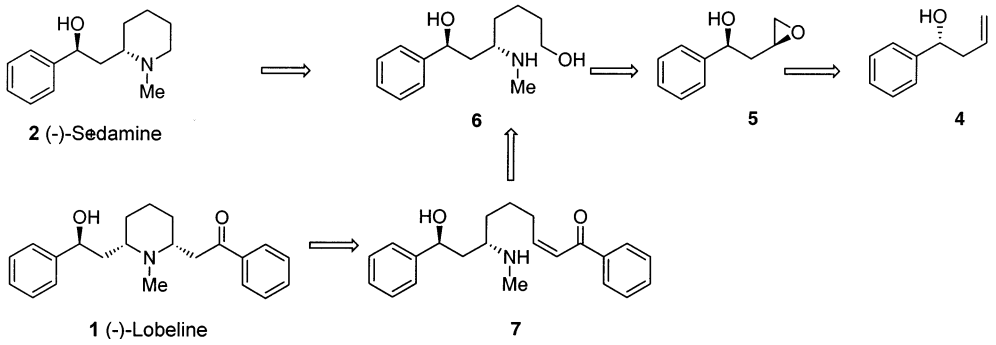
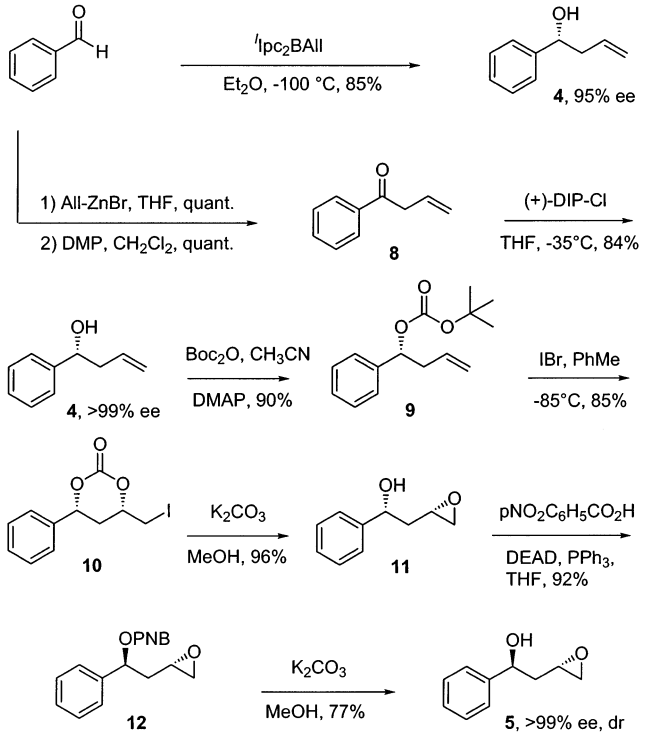


FIGURE 2.

Results and Discussion

Our retrosynthetic analysis of these alkaloids is illustrated in Figure 2 and indicated to us that compound **6** could serve as the key intermediate for both targets. We anticipated that, from the chiral homoallylic alcohol **4**, the chirality induction should direct the diastereoselective epoxidation of the double bond to afford the *syn*-epoxy alcohol and the inversion of the absolute configuration of the alcohol would lead to the desired *anti*-epoxy alcohol **5**. Then, regioselective ring-opening of the terminal epoxide with an allylorganometallic reagent should not only lead to the desired carbon skeleton but also, in the meantime, introduce a terminal double bond precursor of primary alcohol, and liberate the secondary alcohol, which by nucleophilic displacement with an *N*-methyl equivalent would furnish the key intermediate **6**. From this latter intermediate, in situ cyclization of the correctly activated primary alcohol would enable the first target, **2**, to be reached.[8] To pursue our work, oxidation of the key intermediate **6** to the corresponding aldehyde followed by the Wittig reaction with an appropriate reagent should give the adduct **7**, which undergoes an intramolecular Michael reaction to produce lobeline[9] **1**.

SCHEME 1



The synthesis started with the preparation of the *anti*-3,4-epoxy alcohol **5** as presented in Scheme 1. At first, we turned our effort to the preparation of the chiral homoallylic alcohol **4**.

Although the direct allylation of benzaldehyde, and more generally aldehydes, with chiral reagents or catalysts is well documented in the literature[10] and successfully provided the desired homoallylic alcohol **4** in good

(7) For racemic syntheses of sedamine, see: (a) Tufariello, J. J.; Ali, S. A. *Tetrahedron Lett.* **1978**, *47*, 4647−4650 (b) Shono T.; Matsumura Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172−1176. (c) Hootelé, C.; Ibebeke-Bomangwa, W.; Driessens, F.; Sabil, S. *Bull. Soc. Chim. Belg.* **1987**, *96*, 57−61. (d) Tirel, P. J.; Vaultier, M.; Carrie, R. *Tetrahedron Lett.* **1989**, *30*, 1947−1950 (e) Driessens, F.; Hootelé, C. *Can. J. Chem.* **1991**, *69*, 211−217. (f) Ozawa, N.; Nakajima, S.; Zaoya, K.; Hamaguchi, F.; Nagasaka, T. *Heterocycles* **1991**, *32*, 889−894. (g) Pilli, R. A.; Dias, L. C. *Synth. Commun.* **1991**, *21* 2213−2229 (h) Ghiaci, M.; Adibi, M. *Org. Prep. Proced. Int.* **1996**, *28*, 474−477. For asymmetric synthesis, see: (i) Beyerman, H. C.; Eveleens, W.; Muller, Y. M. F. *Recl. Trav. Chim. Pays-Bas* **1956**, *75*, 63−75. (j) Beyerman, H. C.; Eenshuistra, J.; Eveleens, W.; Zweistra, A. *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 43−58. (k) Schöpf, C.; Dummer. G.; Wüst, W. *Liebigs Ann. Chem.* **1959**, *626*, 134−1149. (l) Wakabayashi, T.; Watanabe, K.; Kato, Y.; Saito, M. *Chem. Lett.* **1977**, 223−228. (m) Irie, K.; Aoe, K.; Tanaka, T.; Saito, S. *J. Chem. Soc., Chem. Commun.* **1985**, 633−635. (n) Wanner, K. T.; Kärtner, A. *Heterocycles* **1987**, *26*, 921−924. (o) Wanner, K. T.; Kärtner, A. *Arch. Pharm.* **1987**, *320*, 1253−1267. (p) Pyne, S. G.; Bloem, P.; Chapman, S. L.; Dixon, C. E.; Griffith, R. *J. Org. Chem.* **1990**, *55*, 1086−1093. (q) Kiguchi, T.; Nakazono, Y.; Kotera, S.; Ninomiya, I.; Naito, T. *Heterocycles* **1990**, *31*, 1525−1535. (r) Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035−5036. (s) Poerwono, H.; Higashiyama, K.; Takahashi, H. *Heterocycles* **1998**, *47*, 263−270. (t) Yu, C.-Y.; Meth-Cohn, O. *Tetrahedron Lett.* **1999**, *40*, 6665−6668. (u) Meth-Cohn, O.; Yau, C. C.; Yu, C.-Y. *J. Heterocycl. Chem.* **1999**, *36*, 1549−1553. (v) Cossy, J.; Willis, C.; Bellosta, V.; Bouzbouz, S. *Synlett* **2000**, 1461−1463. (w) Cossy, J.; Willis, C.; Bellosta, V.; Bouzbouz, S. *J. Org. Chem.* **2002**, *67*, 1982−1992.

(8) An enantiomeric synthesis of (−)-allosedamine, a diastereoisomer of (−)-sedamine, using this strategy was previously published as a communication; see: Felpin, F.-X.; Lebreton, J. *Tetrahedron Lett.* **2002**, *43*, 225−227.

(9) Lobeline exists in solution as a *cis*/*trans* mixture; see also ref 5.

(10) For a review, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293. For representative examples of enantioselective allylations, see: Masamune, S.; Short, R. P. *J. Am. Chem. Soc.* **1989**, *111*, 1892−1894. (b) Roush, W. R.; Hoong, L. K.; Palmer. M. A. J.; Park, C. J. *J. Org. Chem.* **1990**, *55*, 4109−4117. (c) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827−7828. (d) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723−4724. (e) Loh, T. P.; Zhou, J. R. *Tetrahedron Lett.* **1999**, *40*, 9115−9118. (f) Kii, S.; Maruoka, K. *Tetrahedron Lett.* **2001**, *42*, 1935−1939. For recent applications in total synthesis, see: (a) Provencal D. P.; Gardelli, C.; Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett.* **1995**, *36*, 6033−6036. (b) Onoda, T.; Shirai, R.; Koiso, Y.; Iwasaki, S. *Tetrahedron Lett.* **1996**, *37*, 4397−4400. (c) Yu, W.; Zhang, Y.; Jin, Z. *Org. Lett.* **2001**, *3*, 1447−1450. (d) Cossy, J.; Willis, C.; Bellosta, V.; Saint-Jalmes, L. *Synthesis* **2002**, 951−957.

ee (around 90−95%), this methodology suffers, in many cases, from the difficulty in preparing and handling these chiral reagents. The most popular agent of this class is the *B*-allyldiisopinocampheylborane[11] (Ipc_2BAll) developed by Brown. Brown's reagent was prepared from the commercially available *B*-chlorodiisopinocampheylborane (DIP-Chloride (DIP-Cl))[12] and allylmagnesium bromide. Its preparation and use required careful manipulation at low temperature (−100 °C), and the presence of the magnesium salts significantly complicated the reaction, particularly by decreasing the reaction rate. Also during the course of our ongoing work, we have carefully investigated the enantioselective allylation of aromatic and heteroaromatic aldehydes[13] with Brown's reagent and found that in every case in our study the ee was not superior to 95%. For example, Brown's asymmetric allylation of benzaldehyde afforded the chiral homoallylic alcohol (*R*)-**4** in 85% yield and 95% ee[14] (best value). In this context, we found that an efficient alternative strategy on a large scale was an enantioselective reduction[15] of the corresponding allyl phenyl ketone **8**. The β,γ-unsaturated ketone **8**[16] was prepared by treatment of benzaldehyde with an excess of allylzinc bromide followed by oxidation with the Dess−Martin periodinane reagent[17] (DMP). Although the preparation of the β,γ-unsaturated aryl ketone **8** required two steps from benzaldehyde, it should be pointed out that nearly quantitative overall yield was obtained, no silica gel purification was needed, and this sequence could be readily adapted to a large scale. Also, it should be noted that the treatment of the commercially available *N*-methoxy-*N*-methylbenzamide with allylmagnesium chloride led cleanly to the β,γ-unsaturated **8** in quantitative[18] crude yield. In our opinion, a two-step allylation/oxidation[19] sequence of benzaldehyde is more convenient and less costly on a large scale.

The enantioselective reduction of the crude β,γ-unsaturated ketone **8** with (+)-DIP-Cl proceeded smoothly in THF at −35 °C to afford the chiral homoallylic alcohol (*R*)-**4** in 84% yield and >99% ee. To the best of our knowledge, only one example of enantioselective reduction of the ketone **8** has been reported using 0.55 equiv of chiral Corey oxazaborolidine in the presence of a borane−dimethyl sulfide complex at −20 °C: the chiral homoallylic alcohol was then isolated in 90% yield and in 96% ee (on a 20 mmol scale).[20] The enantiomerically pure homoallylic alcohol (*R*)-**4** was then obtained in good overall yield of 80% from benzaldehyde in three steps, requiring only one purification at the end.

Although 3,4-epoxy alcohols are attractive synthetic intermediates,[21] only a few enantioselective syntheses are reported in the literature, and none of these describe efficient preparations of chiral *anti*-3,4-epoxy alcohols. In this context, with the homoallylic alcohol (*R*)-**4** in hand, we investigated the stereoselective epoxidation of the C−C double bond. As a more direct approach,[22] the diastereoselective epoxidation of the homoallylic alcohol (*R*)-**4** was examined without success using the Sharpless protocol[23] with *tert*-butyl hydroperoxide in the presence of vanadium acetylacetonate: the desired *syn*-epoxy alcohol[24,25] **11** was isolated in moderate yield (73%) with low (<4:1) selectivity.[26]

To achieve this transformation with an excellent level of diastereoselectivity, the above results forced us to plan an alternative strategy with a three-step sequence based on a modified Cardillo[27] iodocyclization procedure. Following this methodology, the homoallylic *tert*-butyl carbonate **9** was prepared from the corresponding alcohol (*R*)-**4** in 90% yield by treatment with di-*tert*-butyl dicarbonate (Boc_2O) in the presence of DMAP in acetonitrile. On our substrate, this procedure is more convenient than the one originally described by Smith et al.,[28] in which the homoallylic *tert*-butyl carbonate **9** is obtained by deprotonation of the homoallylic alcohol with *n*-BuLi followed by treatment with Boc-ON (2-(((*tert*-butoxycarbonyl)oxy)imino)-2-phenylacetonitrile).[29] Then, diastereoselective iodine-induced electrophilic cyclization of the homoallylic *tert*-butyl carbonate **9** was carried out by simple treatment with IBr at low temperature (−85 °C) to furnish the corresponding iodocarbonate **10**, which under basic conditions (K_2CO_3 in methanol) led to the desired *syn*-epoxy alcohol **11** as a single diastereoisomer.[30,31]

(11) (a) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401−404. (b) Racherla, U. S.; Liao, Y.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 6614−6617.

(12) DIP-Chloride is a trademark of Aldrich Chemical Co.

(13) Felpin, F.-X.; Bertrand, M.-J.; Lebreton, J. *Tetrahedron* **2002**, *58*, 7381−7389.

(14) All enantiomeric excesses were determined by chiral HPLC analysis on a Chiralcel OD-H column, 46 × 15 cm.

(15) For reviews on enantioselective reduction of prochiral ketones, see: (a) Singh, V. K. *Synthesis* **1992**, 605−617. (b) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475−1504. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.

(16) This β,γ-unsaturated aryl ketone, **8**, is quite sensitive to basic or acidic treatment, as well as purification on silica gel, and evolved slowly to the more stable α,β-unsaturated compound. However, when this crude material was immediately engaged in the next step, no side reaction occurred.

(17) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552. (c) Boeckmann, R. K., Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **1999**, *77*, 141−152.

(18) This compound was >95% pure as judged from proton NMR analysis.

(19) Other oxidations such as with Jones reagent or PCC failed to give β,γ-unsaturated aryl ketone **8**.

(20) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 2880−2888.

(21) (a) Lipshutz, B. H.; Kotsuki, H.; Lew, W. *Tetrahedron Lett.* **1986**, *27*, 4825−4828. (b) Guo, J.; Duffy, K. J.; Stevens, K. L.; Dalko, P. I.; Roth, R. M.; Hayward, M. M.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 187−192. (c) Hayward, M. M.; Roth, R. M.; Duffy, K. J.; Dalko, P. I.; Stevens, K. L.; Guo, J.; Kishi, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 192−196.

(22) Epoxidation of homoallylic alcohol (*R*)-**4** with *m*-chloroperbenzoic acid proceeded without diastereoselectivity.

(23) Sharpless K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136−6137.

(24) Mihelich has shown that this method gave much higher diastereoselectivity with 2-substituted homoallylic alcohols with a *cis*-double bond: Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690−7692.

(25) The absolute configuration of the major diastereoisomer was assigned as (1*R*,3*S*) by analogy with the literature and in accord with the proposed mechanism.

(26) The mixture of the two diastereoisomers could not be resolved on a silica gel column.

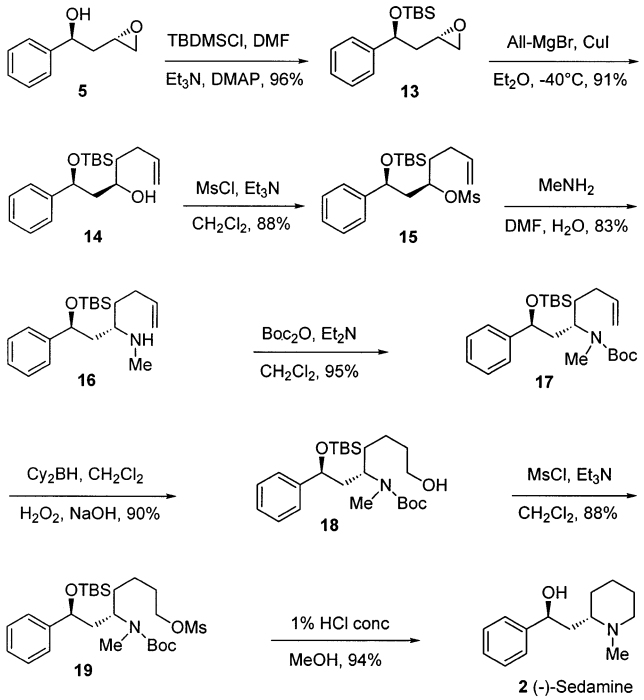
(27) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626−4633.

(28) Duan, J. J.-W.; Smith, A. B., III. *J. Org. Chem.* **1993**, *58*, 3703−3711.

(29) Under Smith's conditions compound **9** was isolated with similar yield. However, the use of *n*-BuLi on a large scale is less convenient.

(30) To confirm this high selectivity, a sample of a racemic mixture of *syn*/*anti*-3,4-epoxy alcohol (1/1) was prepared via epoxidation of the racemic homoallylic alcohol **4** with *m*CPBA.

SCHEME 2



This synthesis provided efficient diastereoselective access to the key (1*R*,3*S*)-epoxy alcohol **11** in three steps from the homoallylic alcohol in 73% overall yield and was amenable to multigram scale-up. Unambiguous proof of the stereochemistry of epoxy alcohol **11** was provided by its conversion to **2** (vide infra). The methodologies developed by Sharpless[23] and Cardillo[27] from the chiral homoallylic alcohols lead to the *syn*-3,4-epoxy alcohols. Also, from these substrates the inversion of the alcohol configuration could give the corresponding *anti*-diastereoisomers. Thus, the inversion of alcohol configuration of (1*R*,3*S*)-epoxy alcohol **11** was efficiently accomplished using a Mitsunobu reaction using the conditions of Dodge.[32] The *syn*-3,4-epoxy alcohol **11** was treated with *p*-nitrobenzoic acid in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine to afford the corresponding inverted ester **12** in 92% yield after purification on a silica gel column. Treatment of this ester **12** in methanol with a catalytic amount of K_2CO_3 led to the desired *trans*-3,4-epoxy alcohol **5** in 77% yield.

To proceed with our synthesis of **2**, the hydroxyl group of **5** was protected as the *tert*-butyldimethylsilyl ether under standard conditions as depicted in Scheme 2. Then, the epoxide **13** was treated with the allyl Grignard reagent and a catalytic amount of CuI to afford the alcohol **14** as the sole[33] product in 91% yield after purification.

Our initial attempts to introduce the amine function from the corresponding alcohol **14** via an azido met with failure. Thus, the alcohol function was transformed into a leaving group by mesylation under standard conditions to afford the compound **15**, which was treated with sodium azide in DMF at 50 °C, leading to a complex mixture.[34] So, we envisaged in the Mitsunobu[35] reaction the possibility of carrying out this step at low temperature to avoid the intramolecular 1,3-dipolar cycloaddition reaction. The alcohol **14** was reacted with a mixture of diphenylphosphoroazide and triphenylphosphine at 0 °C, leading cleanly to an apolar product (supposedly the corresponding azide) as judged by a TLC analysis (R_f = 0.8; EtOAc/hexane, 1/9) of the reaction mixture. However, during the workup of the reaction,[36] complete decomposition occurred. At this point, it became clear that the azido group was the source of the problem. To overcome this difficulty, we therefore moved to another amine precursor: the *N*-phthalimide.[37] Thus, the alcohol **14** was treated with DEAD, triphenylphosphine, and phthalimide to give the expected *N*-phthalimide in 70% yield after purification. However, its hydrolysis with hydrazine in ethanol at reflux afforded the corresponding pure amine in low yield (<40%) due to the difficult purification on silica gel to separate close byproducts. After considerable experimentation, we were rewarded to find a simple method in which mesylate **15** underwent nucleophilic displacement with a total S_N2 process with aqueous methylamine[38] in DMF at 60 °C to afford the *N*-methylamine compound **16** in 83% yield.

At this stage of our synthesis, we found that protection of the *N*-methylamine function of **16** was important not only to facilitate the purification of the intermediates but also to avoid side reactions during the hydroboration step. We chose a protecting group prone to cleavage in acidic conditions, concomitantly with the silyl ether. Accordingly, *N*-methylamine **16** was treated with Boc_2O, employing a standard procedure, to afford the Boc derivative **17** in high yield (95%). Upon successive exposure to dicyclohexylborane and hydrogen peroxide, compound **17** underwent hydroboration/oxidation to afford the primary alcohol **18** in 90% yield after purification. This alcohol **18** was then converted to its corresponding mesylate **19** under standard conditions. Exposure of the crude material to 1% concentrated HCl in methanol at 65 °C effected hydrolysis of both Boc and *tert*-butyldimethylsilyl ether protecting groups. The corresponding hydrochloric salt formed was treated with basic aqueous solution during the workup to liberate the amine function, leading, by intramolecular substitution[39] of the mesylate, to the formation of the piperidine ring of the sedamine **2**, which was then isolated in 95% yield after purification. A

(31) To make this method shorter, we attempted to directly treat the reaction mixture of the iodocarbonate **10** with a solution of K_2CO_3 in methanol. Unfortunately, the desired compound was accompanied by substantial amounts of undefined products, which greatly complicated the purification on a silica gel column.

(32) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Dodge, J. A.; Trujillo, J. I.; Presnell, M. *J. Org. Chem*. **1994**, *59*, 234−236.

(33) The regioselectivity of cuprate attack observed was significantly dependent on the temperature: at −40 °C only the desired regioisomer was formed.

(34) This failure is not so surprising since the 1-azide-4-alkenes are prone to intramolecular [2 + 3] dipolar cycloaddition at high temperature (above 80 °C) to form a thermally labile triazoline, which may undergo a 1,2-hydrogen shift with nitrogen loss to give a 1-pyrroline; see: Pearson, W. H.; Lin, K.-C. *Tetrahedron Lett*. **1990**, *31*, 7571−7574.

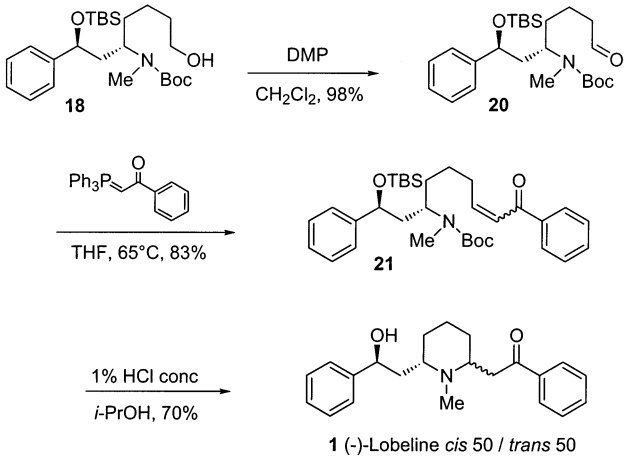
(35) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett*. **1977**, 1977−1980.

(36) This intramolecular 1,3-dipolar cycloaddition reaction occurring on 1-azide-4-alkenes seems to be very substrate dependent. In some cases, it is possible by working quickly to obtain the azide in correct yield. See: Taber, D. F.; Rahimizadeh, M.; You, K. K. *J. Org. Chem*. **1995**, *60*, 529−531.

(37) Busacca, C. A.; Grossbach, D.; Spinelli, E. *Tetrahedron: Asymmetry* **2000**, *11*, 1907−1910.

(38) A. De Mesmaeker, A.; Waldner, A.; Lebreton, J.; Hoffmann, P.; Freirer, S. M.; Fritsch, V.; Wolf, R. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 226−229.

SCHEME 3



comparison of synthetic and natural sedamine **2** showed that the ^{1}H and ^{13}C NMR, IR, and mass spectral data are identical, and the optical rotation of our synthetic material was in agreement with the literature ($[\alpha]^{20}_D = -87.1$ (*c* 0.93, EtOH); lit.[7r] $[\alpha]^{20}_D = -86.8$ (*c* 0.53, EtOH)).

To complete our work, the aldehyde **20** was obtained in nearly quantitative yield by oxidation of primary alcohol **18** with the Dess−Martin periodinane (see Scheme 3).

Aldehyde **20** could be transformed into the α,*β*-unsaturated aryl ketone **21** by a Wittig olefination in good yield using the commercially available (benzoylmethylene)triphenylphosphorane.[40] The proton NMR analysis of this *E*/*Z* mixture was complicated by the presence of rotamers due to the Boc protecting group, and it was not possible to determine the *E*/*Z* ratio. Nevertheless, the geometry of the double bond is unimportant for the synthesis since it is lost on Michael addition. All attempts to cleave the protecting groups of **21**, using the previous conditions with concentrated HCl in methanol described for **2**, failed. Surprisingly, a striking difference between methanol and 2-propanol as solvent was noted for this hydrolysis step. Reaction of the protected compound **21** under acidic conditions in 2-propanol led to **1** in 70% yield. A comparison of synthetic and natural **1** showed that the ^{1}H and ^{13}C NMR, IR, and mass spectral data are identical, and the optical rotation of our synthetic material was in agreement with the literature ($[\alpha]^{20}_D = -39.1$ (*c* 0.975, $CHCl_3$); lit.[41] $[\alpha]^{20}_D = -38.2$ (*c* 1.986, $CHCl_3$)).

As already noted by Marazano et al.,[42] we found that when the crystalline lobeline **1** was dissolved in $CDCl_3$ and the proton NMR spectrum was immediately run, only the *cis* isomer was detected. After a few hours at room temperature, the NMR spectrum of the sample showed the presence of the *cis* and *trans* isomers in a 1/1 ratio. This fact indicated that in solution a slow isomerization occurred via a retro-Michael reaction to afford a *cis*/*trans* mixture of lobeline **1** (Scheme 4).

Conclusion

This highly enantioselective synthesis of **2** and **1** requires 16 and 17 steps from benzaldehyde and gives 20% and 14% overall yields, respectively. Moreover, the overall efficiency and versatility of our strategy could be extended to the preparation of chiral analogues with improved pharmacological activities. We are currently applying this strategy to the preparation of other piperidines and substituted aromatic analogues of both **1** and **2**.

Experimental Section

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz using residual $CDCl_3$ (7.26 ppm) and $CDCl_3$ (77.16 ppm) as internal standard, respectively. Flash column chromatography was performed on 60 Å silica gel (230−400 mesh). HMRS spectra were recorded at the "Service Commun d'Analyse Spectroscopique d'Anger". Chiral HPLC was performed with a Chiralcel OD-H column, 46 × 15 cm, flow rate 0.5 mL/min. (+)-DIP-Cl is available commercially. All reactions were performed under N_2 in a flame-dried flask using anhydrous solvents. Grignard reagents were titrated by Watson and Eastham's method.[43]

(1*R*)-1-Phenylbut-3-en-1-ol (4): Chiral Allylboration. A solution of commercial allylmagnesium bromide in ether (48 mL, 1 M, 48 mmol) was added to a solution of (+)-*B*-chlorodiisopinocampheylborane ((+)-DIP-Cl) (16.0 g, 49.9 mmol) in ether (50 mL) at 0 °C. The resulting mixture was stirred for 1 h at room temperature and then concentrated in vacuo. The residue was extracted with anhydrous pentane (3×): stirring was discontinued to permit the Mg^{2+} salts to settle, and the supernatant pentane extract was filtered through a pad of Celite. Pentane was evaporated under reduced pressure to give *B*-allyldiisopinocampheylborane ($^{l}Ipc_2Ball$) (15.6 g, 96%) as a colorless oil.

To a solution of $^{l}Ipc_2Ball$ (3.91 g, 12 mmol) in ether (25 mL) at −100 °C was slowly added via a cannula a solution of benzaldehyde (1.02 mL, 10 mmol) in ether (20 mL). After 1 h of stirring at −100 °C, the reaction mixture was quenched with methanol (1 mL). The resulting mixture was then allowed to warm to room temperature and extracted with 1 N aqueous HCl. The combined aqueous layers were treated with 30% aqueous NaOH solution until pH 12−13, and then extracted with CH_2Cl_2 (4×). The combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography gave **4** (1.26 g, 85%) as a pale yellow oil: 95% ee, determined by chiral HPLC (hexane/*i*-PrOH = 99/1, 25.0 min for (*R*)-alcohol and 31.7 min for (*S*)-alcohol); $[\alpha]^{20}_D = +44$ (*c* 1.1, benzene) [lit.[44] $[\alpha]^{20}_D = -44.92$ (*c* 7.38, benzene)]; IR (KBr) ν 1641, 2980, 3075, 3380 cm^{-1}; ^{1}H NMR δ (ppm) 2.04 (s br, 1H), 2.49−2.57 (m, 2H), 4.75 (dd, 1H, $J = 5.9$ Hz, $J = 7.2$ Hz), 5.13 (s, 1H), 5.18−5.23 (m, 1H), 5.73−5.94 (m, 1H), 7.27−7.39 (m, 5H); ^{13}C NMR δ (ppm) 43.4, 73.3, 117.7, 125.7, 127.2, 128.1, 134.3, 143.8; MS (CI/NH_3) *m*/*z* 148 (M^+), 166 ($M + NH_4^+$).

(1*R*)-1-Phenylbut-3-en-1-ol (4): *Chiral Reduction.* To a solution of (+)-DIP-Cl (8.44 g, 26.3 mmol) in THF (20 mL) cooled at −35 °C was added a solution of ketone **8** (3.20 g, 21.92 mmol) in THF (10 mL). The resulting mixture was stirred overnight. After completion, acetaldehyde (1.68 mL, 30 mmol) was added to consume the excess (+)-DIP-Cl. The mixture was

(39) For selected examples of cyclization, see: (a) Han, G.; LaPorte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *J. Org. Chem.* **2000**, *65*, 6293−6306. (b) Razavi, H.; Polt, R. *J. Org. Chem.* **2000**, *65*, 5693−5706.

(40) Domínguez, C.; Csákÿ, A. G.; Magano, J.; Plumet, J. *Synthesis* **1989**, 172−175.

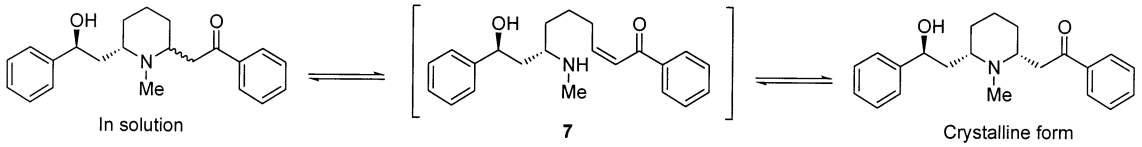
(41) Ebnöther, A. *Helv. Chim. Acta.* **1955**, *38*, 386-396.

(42) Marazano et al. described similar phenomena on the lobeline hydrochloride salt; see ref 5.

(43) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, 165−168.

(44) Jadhav, P. K.; Bhat, K. S.; Perumal, T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432−439.

SCHEME 4



allowed to warm to room temperature and stirred for 1 h. The solvent was removed under reduced pressure, and (−)-α-pinene formed during the reaction was collected by bulb to bulb distillation (50 °C, 10 mmHg, 1 h). The residue was dissolved in ether and quenched with 4 N aqueous HCl. The mixture was basified with solid KOH until pH 11−12 and extracted with ether (3×). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. Removal of the solvent left an oil which was purified by flash chromatography, affording **4** (2.72 g, 84%) as a colorless oil: >99% ee, determined by chiral HPLC (hexane/*i*-PrOH = 99/1, 25.0 min for (*R*)-alcohol and 31.7 min for (*S*)-alcohol); $[\alpha]^{20}_D = +45.9$ (*c* 1.3, benzene).

(1*R*)-Phenylbut-3-en-1-ol (4): Racemic Allylation. A flask fitted with a dropping funnel and a condenser was filled with Zn (15 g, 0.23 mol) and covered with THF (1 mL). A solution of allyl bromide (17.2 mL, 0.2 mol) in THF (10 mL) was slowly added to maintain the temperature at 25−30 °C. After the addition, the mixture was stirred for 1 h at room temperature. Then, a solution of benzaldehyde (9.14 mL, 0.09 mol) in THF (10 mL) was slowly added, and the resulting mixture was stirred for an additional 1 h. After completion, the resulting mixture was hydrolyzed with saturated aqueous NH_4Cl (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine (2×), dried over anhydrous $MgSO_4$, and concentrated in vacuo to give **4** (13.32 g, quantitative) as a pale colorless oil.

1-Phenylbut-3-en-1-one (8). To a solution of DMP (22.92 g, 54.06 mmol) in CH_2Cl_2 (50 mL) at room temperature was added a solution of alcohol **4** (5.0 g, 33.78 mol) in CH_2Cl_2 (40 mL). After 60 min of stirring, the mixture was diluted with ether (40 mL) and washed with 1/1 10% $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ solution (1×), followed by brine (2×). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give **8** (4.93 g, quantitative) as a colorless oil which was quickly used in the next step: IR (KBr) ν 1644, 2882, 3081 cm^{-1}; ^1H NMR δ (ppm) 3.75 (dt, 2H, $J = 6.5$ Hz, $J = 1.4$ Hz), 5.16−5.26 (m, 2H), 5.99−6.19 (m, 1H), 7.41−7.61 (m, 3H), 7.94−8.00 (m, 2H); ^{13}C NMR δ (ppm) 43.5, 118.8, 128.4, 128.7, 131.2, 133.3, 136.7, 198.1; MS (CI/NH_3) *m*/*z* 164 ($M + NH_4^+$), 147 ($M + H^+$).

(1*R*)-Carbonic Acid tert-Butyl Ester 1-Phenylbut-3-enyl Ester (9). To a solution of alcohol **4** (5.43 g, 36.7 mmol) in CH_3CN (160 mL) were added Boc_2O (12.00 g, 55.03 mmol) and DMAP (1.79 g, 14.7 mmol). After 5 h of stirring, the solvent was evaporated under reduced pressure. The residue was taken up in EtOH (110 mL), and imidazole (12.47 g, 0.18 mol) was added. The resulting mixture was stirred at room temperature for 15 min, and then CH_2Cl_2 was added. The organic phase was washed with 5% HCl solution (3×), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (2% ethyl acetate/hexane) gave **9** (8.19 g, 90%) as a yellow oil: $[\alpha]^{20}_D = +51.5$ (*c* 1.04, CH_2Cl_2); IR (KBr) ν 1643, 1741, 2981, 3079 cm^{-1}; ^1H NMR δ (ppm) 1.47 (s, 9H), 2.51−2.80 (m, 2H), 5.04−5.17 (m, 2H), 5.55 (dd, 1H, $J = 6.6$ Hz, $J = 7.6$ Hz), 5.64−5.84 (m, 1H), 7.28−7.39 (m, 5H); ^{13}C NMR δ (ppm) 27.8, 41.0, 78.3, 82.0, 118.1, 126.4, 128.0, 128.4, 133.2, 140.0, 153.0; HRMS (CI/NH_3) *m*/*z* calcd for $C_{15}H_{24}N_1O_3$ ($M + NH_4^+$) 266.1756, found 266.1755. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.41; H, 8.10.

(4*R*,6*S*)-4-Iodomethyl-6-phenyl[1,3]dioxan-2-one (10). To a solution of carbonate **9** (4.7 g, 18.95 mmol) in toluene (150 mL) at −85 °C was slowly added a solution of IBr (1 M in CH_2Cl_2, 30.3 mL, 30.3 mmol). After being stirred at −85 °C for 1 h, the resulting mixture was quenched with 20% $Na_2S_2O_3$/5% $NaHCO_3$ solution (1/1) and diluted with ether (120 mL). The aqueous phase was extracted with ether (2×). The organic extracts were washed with brine (1×), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ethyl acetate/hexane) to give **10** (5.12 g, 85%) as a white solid which was quickly used in the next step due to extensive decomposition: $[\alpha]^{20}_D = +23.1$ (*c* 1.08, CH_2Cl_2); IR (KBr) ν 1722, 3024 cm^{-1}; ^1H NMR δ (ppm) 2.04 (dt, 1H, $J = 11.7$ Hz, $J = 14.3$ Hz), 2.65 (dt, 1H, $J = 2.9$ Hz, $J = 14.3$ Hz), 3.33 (dd, 1H, $J = 7.3$ Hz, $J = 10.7$ Hz), 3.47 (dd, 1H, $J = 4.4$ Hz, $J = 10.7$ Hz), 4.58−4.71 (m, 1H), 5.49 (dd, 1H, $J = 2.9$ Hz, $J = 11.9$ Hz), 7.38 (s br, 5H); ^{13}C NMR δ (ppm) 5.7, 35.5, 77.2, 79.4, 125.9, 128.9, 129.2, 137.1, 148.3.

(1*R*,3*S*)-2-Oxiranyl-1-phenylethanol (11). To a solution of cyclic carbonate **10** (4.14 g, 13.02 mmol) in anhydrous MeOH (52 mL) at room temperature was added K_2CO_3 (5.57 g, 40.36 mmol), and the reaction was stirred for 2 h. The mixture was diluted with ether (200 mL) and quenched with saturated aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ solution (1/1). The aqueous phase was extracted with ether (3×). The organic extracts were washed with brine (1×), dried over anhydrous $MgSO_4$, and filtered. Removal of solvent left an oil which was purified by flash chromatography (30% ethyl acetate/hexane), affording **11** (2.05 g, 96%) as a colorless oil: $[\alpha]^{20}_D = +30.7$ (*c* 1, CH_2Cl_2); IR (KBr) ν 2921, 3061, 3418 cm^{-1}; ^1H NMR δ (ppm) 1.83−2.09 (m, 2H), 2.49 (dd, 1H, $J = 2.7$ Hz, $J = 4.9$ Hz), 2.74 (dd, 1H, $J = 4.4$ Hz, $J = 4.9$ Hz), 2.87 (s br, 1H), 2.95−3.04 (m, 1H), 4.91 (dd, 1H, $J = 5.5$ Hz, $J = 7.8$ Hz), 7.29−7.40 (m, 5H); ^{13}C NMR δ (ppm) 41.7, 46.8, 50.2, 72.5, 125.8, 127.7, 128.5, 143.9; HRMS (CI/NH_3) *m*/*z* calcd for $C_{10}H_{16}NO_2$ ($M + NH_4^+$) 182.1181, found 182.1177.

(1*S*,3*S*)-4-Nitrobenzoic Acid 2-Oxiranyl-1-phenylethyl Ester (12). A 250 mL, double-necked, round-bottomed flask was filled with epoxy alcohol **11** (2.05 g, 12.5 mmol), 4-nitrobenzoic acid (4.18 g, 25 mmol), and PPh_3 (6.55 g, 25 mmol) in THF (70 mL). The flask was immersed in an ice bath, and DEAD (3.93 mL, 25 mmol) was slowly added to maintain the temperature below 10 °C. Upon completion of the addition, the mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was removed in vacuo, and the residue was diluted with ether. The white precipitate was filtered, and the filtrate was washed with saturated aqueous $NaHCO_3$. The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (10% ethyl acetate/hexane) gave **12** (3.43 g, 92%) as a colorless oil: $[\alpha]^{20}_D = +23.4$ (*c* 2.5, CH_2Cl_2); IR (KBr) ν 1726, 2924, 3055 cm^{-1}; ^1H NMR δ (ppm) 2.11 (ddd, 1H, $J = 4.6$ Hz, $J = 6.9$ Hz, $J = 14.5$ Hz), 2.38 (ddd, 1H, $J = 4.7$ Hz, $J = 8.5$ Hz, $J = 14.5$ Hz), 2.54 (dd, 1H, $J = 2.6$ Hz, $J = 5.0$ Hz), 2.80 (dd, 1H, $J = 4.4$ Hz, $J = 5.0$ Hz), 3.03−3.13 (m, 1H), 6.27 (dd, 1H, $J = 4.6$ Hz, $J = 8.4$ Hz), 7.29−7.48 (m, 5H), 8.21−8.33 (m, 4H); ^{13}C NMR δ (ppm) 39.8, 47.1, 48.9, 75.3, 123.7, 126.4, 128.7, 128.9, 130.9, 135.6, 139.4, 150.7, 163.9; HRMS (LSIMS/Cs^+) *m*/*z* calcd for $C_{17}H_{16}NO_5$ ($M + H^+$) 314.1029, found 314.1026.

(1*S*,3*S*)-2-Oxiranyl-1-phenylethanol (5). A solution of nitroester **12** (3.11 g, 10.4 mmol) in MeOH (93 mL) and H_2O (7 mL) at room temperature was treated with K_2CO_3 (1.58 g, 11.5 mmol). After being stirred for 2 h, the resulting mixture was concentrated under reduced pressure. The residue was diluted with AcOEt (100 mL), washed with brine (1×), dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purifica-

tion by flash chromatography (20% ethyl acetate−hexane) gave **5** (1.32 g, 77%) as a colorless oil: $[\alpha]^{20}_D = -63.5$ (*c* 2.36, CH_2Cl_2); IR (KBr) ν 2919, 3061, 3425 cm^{-1}; ^1H NMR δ (ppm) 1.81 (ddd, 1H, $J = 3.7$ Hz, $J = 6.7$ Hz, $J = 14.5$ Hz), 2.16 (ddd, 1H, $J = 4.1$ Hz, $J = 9.0$ Hz, $J = 14.5$ Hz), 2.51 (s br, 1H), 2.62 (dd, 1H, $J = 2.9$ Hz, $J = 4.9$ Hz), 2.85 (t app, 1H, $J = 4.7$ Hz), 3.14−3.23 (m, 1H), 4.95 (dd, 1H, $J = 3.5$ Hz, $J = 9$ Hz), 7.27−7.40 (m, 5H); ^{13}C NMR δ (ppm) 41.5, 47.2, 50.1, 71.8, 125.7, 127.7, 128.6, 144.2; HRMS (CI/NH_3) *m*/*z* calcd for $C_{10}H_{16}NO_2$ ($M + NH_4^+$) 182.1181, found 182.1177.

(1*S*,3*S*)-*tert*-Butyldimethyl(2-oxiranyl-1-phenylethoxy)-silane (13). To a solution of epoxy alcohol **5** (1.32 g, 8.05 mmol) in DMF (25 mL) at room temperature were added Et_3N (2.24 mL, 16.1 mmol), TBDMSCl (1.94 g, 12.9 mmol), and DMAP (50 mg). After being stirred at room temperature for 3 h, the resulting mixture was diluted with ether (75 mL) and quenched with water (50 mL). The aqueous phase was extracted with ether (4×). The combined extracts were washed with brine (3×), dried over anhydrous $MgSO_4$, and filtered. Removal of solvent left an oil which was purified by flash chromatography (2% ethyl acetate/hexane), affording **13** (2.15 g, 96%) as a colorless oil: $[\alpha]^{20}_D = -69.5$ (*c* 1.68, CH_2Cl_2); IR (KBr) ν 2955, 3033 cm^{-1}; ^1H NMR δ (ppm) −0.12 (s, 3H), 0.08 (s, 3H), 0.91 (s, 9H), 1.66 (ddd, 1H, $J = 3.4$ Hz, $J = 7.2$ Hz, $J = 14$ Hz), 1.96 (ddd, 1H, $J = 4.4$ Hz, $J = 9.1$ Hz, $J = 14$ Hz), 2.45 (dd, 1H, $J = 2.8$ Hz, $J = 5.0$ Hz), 2.80 (t, 1H, $J = 9$ Hz), 3.11−3.20 (m, 1H), 4.92 (dd, 1H, $J = 3.4$ Hz, $J = 9.3$ Hz), 7.22−7.34 (m, 5H); ^{13}C NMR δ (ppm) −5.0, −4.5, 18.3, 25.9, 44.5, 47.9, 49.9, 72.8, 125.7, 127.3, 128.3, 145.2. Anal. Calcd for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 69.12; H, 9.33.

(1*S*,3*R*)-1-(*tert*-Butyldimethylsilanoxy)-1-phenylhept-6-en-3-ol (14). To a solution of CuI (207 mg, 1.09 mmol) in ether (4 mL) cooled at −40 °C was added AllMgBr (1 M in ether, 10.85 mL, 10.85 mmol). The resulting mixture was stirred at −30 °C for 15 min, and a solution of epoxide **13** (2.01 g, 7.23 mmol) in ether (14 mL) was added. After being stirred at −40 °C for 30 min, the reaction was quenched with saturated NH_4Cl solution and extracted with ether (4×). The combined extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (5% ethyl acetate/hexane) gave **14** (2.13 g, 92%) as a colorless oil: $[\alpha]^{20}_D = -63.3$ (*c* 2.21, CH_2Cl_2); IR (KBr) ν 1641, 2954, 3065, 3447 cm^{-1}; ^1H NMR δ (ppm) −0.09 (s, 3H), 0.09 (s, 3H), 0.93 (s, 9H), 1.34−1.66 (m, 2H), 1.73−1.93 (m, 2H), 1.95−2.19 (m, 2H), 3.72−3.84 (m, 1H), 4.88−5.03 (m, 2H), 5.10 (t app, 1H, $J = 5.3$ Hz), 5.69−5.89 (m, 1H), 7.23−7.36 (m, 5H); ^{13}C NMR δ (ppm) −5.1, −4.6, 18.3, 26.0, 30.0, 36.9, 46.1, 67.9, 73.8, 114.7, 125.8, 127.2, 128.3, 138.7, 144.3; HRMS (CI/*i*-butane) *m*/*z* calcd for $C_{19}H_{33}O_2Si$ ($M + H^+$) 321.2250, found 321.2264. Anal. Calcd for $C_{19}H_{32}O_2Si$: C, 71.19; H, 10.06. Found: C, 71.14; H, 10.15.

(2′*S*,1*R*)-Methanesulfonic Acid 1-[2-(*tert*-Butyldimethylsilanoxy)-2-phenylethyl]pent-4-enyl Ester (15). A solution of alcohol **14** (2.10 g, 6.56 mmol) and Et_3N (1.83 mL, 13.1 mmol) in CH_2Cl_2 (65 mL) at 0 °C was treated with MsCl (0.76 mL, 9.8 mmol). The resulting mixture was stirred at 0 °C for 10 min and then washed with water (3×). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (5% ethyl acetate/hexane) to give **15** (2.53 g, 97%) as a colorless oil: $[\alpha]^{20}_D = -41.5$ (*c* 2.61, CH_2Cl_2); IR (KBr) ν 1642, 2955, 3031 cm^{-1};

^1H NMR (200 MHz, $CDCl_3$) δ (ppm) −0.26 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 1.81−1.94 (m, 2H), 1.99−2.06 (m, 2H), 2.11−2.23 (m, 2H), 3.01 (s, 3H), 4.84 (dd, 1H, $J = 4.3$ Hz, $J = 7.8$ Hz), 4.92−5.11 (m, 3H), 5.70−5.90 (m, 1H), 7.25−7.34 (m, 5H); ^{13}C NMR δ (ppm) −5.0, −4.4, 18.1, 25.9, 28.9, 34.7, 39.0, 46.0, 71.9, 80.8, 115.6, 126.1, 127.6, 128.3, 137.0, 144.6.

(2′*S*,3*S*)-{1-[2-(*tert*-Butyldimethylsilanoxy)-2-phenylethyl]pent-4-enyl}methylamine (16). To a solution of mesylate **15** (2.53 g, 6.36 mmol) in DMF (30 mL) at room temperature was added methylamine (40% in water, 22 mL, 0.25 mol). After the mixture was stirred at 50 °C for 12 h, another portion of methylamine (11 mL, 0.13 mol) was added, and the resulting mixture was stirred for 8 h at 50 °C. Then, the mixture was diluted with ether (100 mL) and water (30 mL). The aqueous phase was extracted with ether (4×). The combined extracts were washed with water (1×) and brine (2×), dried over anhydrous $MgSO_4$, and filtered. Removal of solvent left an oil which was purified by flash chromatography (5% EtOH/0.5% Et_3N/CH_2Cl_2), affording **16** (1.85 g, 88%) as a colorless oil: $[\alpha]^{20}_D = -50$ (*c* 2.68, CH_2Cl_2); IR (KBr) ν 1641, 2955, 3064, 3367 cm^{-1}; ^1H NMR δ (ppm) −0.22 (s, 3H), 0.04 (s, 3H), 0.90 (s, 9H), 1.46−1.67 (m, 4H), 1.80−1.95 (m, 1H), 2.01−2.12 (m, 2H), 2.36 (s, 3H), 2.50−2.62 (m, 1H), 4.76 (dd, 1H, $J = 4.1$ Hz, $J = 8.7$ Hz), 4.91−5.07 (m, 2H), 5.72−5.93 (m, 1H), 7.22−7.33 (m, 5H); ^{13}C NMR δ (ppm) −4.9, −4.5, 18.1, 25.9, 29.8, 32.9, 33.4, 45.2, 57.1, 74.6, 114.4, 125.9, 127.1, 128.2, 138.8, 145.7; HRMS (CI/NH_3) *m*/*z* calcd for $C_{20}H_{36}NOSi$ ($M + H^+$) 334.2566, found 334.2552.

(2′*S*,3*S*)-{1-[2-(*tert*-Butyldimethylsilanoxy)-2-phenylethyl]pent-4-enyl}methylcarbamic Acid *tert*-Butyl Ester (17). A solution of amine **16** (1.85 g, 5.56 mmol) and Et_3N (1.16 mL, 8.33 mmol) in CH_2Cl_2 (100 mL) at room temperature was treated with $(Boc)_2O$ (1.82 g, 8.33 mmol). The mixture was stirred for 6 h at room temperature, and then the solvent was evaporated under reduced pressure. The residue was diluted in EtOH (50 mL) and treated with imidazole (1.89 g, 27.8 mmol). After the resulting mixture was stirred for 15 min at room temperature, the solvent was evaporated and the residue was diluted with CH_2Cl_2 (50 mL) and washed with 0.5% HCl solution. The organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography (5% ethyl acetate/hexane) gave **17** (2.28 g, 95%) as a colorless oil: $[\alpha]^{20}_D = -35.7$ (*c* 2.74, CH_2Cl_2); IR (KBr) ν 1642, 1695, 2956, 3065 cm^{-1}; ^1H NMR (two rotamers in a 7/3 ratio) δ (ppm) −0.19 (s, 3H), 0.02 (s, 3H), 0.87 (s, 9H), 1.43 (s, 9H × 0.7), 1.49 (s, 9H × 0.3), 1.66−2.08 (m, 6H), 2.66 (s, 3H × 0.3), 2.71 (s, 3H × 0.7), 3.87 (m, 1H), 4.57 (t, 1H, $J =$ 6.9 Hz), 4.89−4.99 (m, 2H), 5.65−5.85 (m, 1H), 7.27−7.30 (m, 5H); ^{13}C NMR (two rotamers) δ (ppm) −4.9, −4.5, 18.2, 25.9, 28.6, 30.4, 32.0, 44.2, 51.6, 51.9, 72.8, 72.9, 79.0, 79.6, 114.8, 126.5, 127.3, 128.2, 138.1, 138.3, 144.8, 145.2, 155.9, 156.2; HRMS (CI/*i*-butane) *m*/*z* calcd for $C_{25}H_{44}NO_3Si$ ($M + H^+$) 434.3090, found 434.3088. Anal. Calcd for $C_{25}H_{43}NO_3Si$: C, 69.23; H, 9.99; N, 3.23. Found: C, 69.16; H, 10.05; N, 3.21.

(2′*S*,3*S*)-{1-[2-(*tert*-Butyldimethylsilanoxy)-2-phenylethyl]-5-hydroxypentyl}methylcarbamic Acid *tert*-Butyl Ester (18). To a solution of cyclohexene (2.75 mL, 27.2 mmol) was added BH_3·Me_2S (2 M in THF, 6.87 mL, 13.7 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C, and then a solution of carbamate **17** (1.95 g, 4.50 mmol) in THF (70 mL) was slowly added over 10 min at 0 °C. The solution was allowed to warm to room temperature, stirred for 6 h, cooled to 0 °C, quenched with EtOH (5 mL), and treated with 1 M aqueous NaOH solution (22.5 mL, 22.5 mmol) and H_2O_2 (50% in water, 5.52 mL, 90 mmol). After being stirred at room temperature for 1 h, the resulting mixture was quenched with 1 M aqueous $Na_2S_2O_3$ solution. The aqueous phase was extracted with AcOEt (4×). The combined organic extracts were washed with 1 M $Na_2S_2O_3$ solution (1×) and brine (1×), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The volatile residues were eliminated by bulb to bulb distillation (6 mmHg, 70 °C), and the residue was purified by flash chromatography (20% ethyl acetate/hexane) to give **18** (1.83 g, 90%) as a colorless oil: $[\alpha]^{20}_D = -31.5$ (*c* 2.13, CH_2Cl_2); IR (KBr) ν 1694, 2929, 3064, 3438 cm^{-1}; ^1H NMR (two rotamers) δ (ppm) −0.18 (s, 3H), 0.02 (s, 3H), 0.88 (s, 9H), 1.19−2.12 (m, 8H), 1.43 (s, 9H × 0.7), 1.49 (s, 9H × 0.3), 2.66 (s, 9H × 0.3), 2.70 (s, 9H × 0.7), 3.56 (q app, 2H, $J = 6.6$ Hz), 3.86 (m, 1H × 0.7), 4.00 (m, 1H × 0.3), 4.57 (t, 1H, $J = 7$ Hz), 7.29−7.33 (m, 5H); ^{13}C NMR (two rotamers in a 7/3 ratio) δ (ppm) −4.9, −4.5, 18.2, 22.0, 22.4, 25.9, 28.6, 32.1, 32.4, 32.6, 44.2, 51.3, 52.1, 62.7, 72.8, 73.0, 79.1, 79.6, 126.5, 127.2, 127.3,

128.2, 144.8, 145.1, 156.1, 156.3; HRMS (CI/*i*-butane) *m*/*z* calcd for $C_{25}H_{46}NO_4Si$ (M + H^+) 452.3196, found 452.3196. Anal. Calcd for $C_{25}H_{45}NO_4Si$: C, 66.47; H, 10.04; N, 3.10. Found: C, 66.53; H, 10.05; N, 3.09.

(5*S*,7*S*)-Methanesulfonic Acid 5-(*tert*-Butoxycarbonylmethylamino)-7-(*tert*-butyldimethylsilanoxy)-7-phenylheptyl Ester (19). A solution of alcohol **18** (0.50 g, 1.11 mmol) and Et_3N (0.31 mL, 2.22 mmol) in CH_2Cl_2 (15 mL) at 0 °C was treated with MsCl (0.13 mL, 1.66 mmol). The resulting mixture was stirred at 0 °C for 40 min and then quenched with water. The aqueous phase was extracted with CH_2Cl_2 (3×). The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and filtered. Removal of solvent left an oil which was purified by flash chromatography (20% ethyl acetate/hexane), affording **19** (0.59 g, 95%) as a colorless oil: $[\alpha]^{20}_D = -26.2$ (*c* 1.16, CH_2Cl_2); IR (KBr) ν 1689, 2857, 2930 cm^{-1}; ^1H NMR (two rotamers in a 6/4 ratio) δ (ppm) −0.19 (s, 3H), 0.01 (s, 3H), 0.87 (s, 9H), 1.40−1.78 (m, 17H), 1.94−2.08 (m, 1H), 2.65 (s, 3H × 0.4), 2.69 (s, 3H × 0.6), 2.98 (s, 3H), 4.14 (m, 2H), 4.56 (m, 1H), 7.30 (s, 5H); ^{13}C NMR (two rotamers) δ (ppm) −4.9, −4.6, 18.2, 22.1, 25.9, 28.5, 28.7, 29.0, 31.7, 31.9, 37.4, 37.6, 44.1, 51.0, 51.8, 69.6, 70.1, 72.7, 72.9, 79.1, 79.6, 126.4, 127.2, 127.4, 128.2, 144.6, 144.9, 155.9, 156.1; HRMS (LSIMS/Cs^+) *m*/*z* calcd for $C_{26}H_{46}NO_6SiS$ (M − H^+) 528.2815, found 528.2821.

(−)-Sedamine (2). A solution of mesylate **19** (0.40 g, 0.76 mmol) in MeOH (15 mL) was treated with concentrated HCl (0.15 mL). After being stirred at 60 °C for 3 h, the solution was diluted with water and basified with solid $NaHCO_3$ until pH 9−10. The aqueous layer was extracted four times with CH_2Cl_2. The combined organic extracts were washed once with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude extract was purified on neutral alumina (2% EtOH−CH_2Cl_2) to afford **2** (156 mg, 94%) as a white solid: mp 58−60 °C (lit.[7r] mp 59−60 °C); $[\alpha]^{20}_D$ = −87.1 (*c* 0.93, EtOH) [lit.[7r] $[\alpha]^{20}_D = -86.8$ (*c* 0.53, EtOH)]; IR (KBr) ν 2997, 3065, 3277 cm^{-1}; ^1H NMR δ (ppm) 1.28−1.85 (m, 7H), 2.07−2.24 (m, 1H), 2.53 (s, 3H), 2.53−2.65 (m, 1H), 2.96−3.15 (m, 2H), 4.88 (dd, 1H, *J* = 2.7 Hz, *J* = 10.5 Hz), 5.68 (s br, 1H), 7.22−7.41 (m, 5H); ^{13}C NMR δ (ppm) 20.9, 22.3, 26.2, 39.9, 52.2, 61.2, 73.6, 125.6, 127.2, 128.4, 145.4.

(2′*S*,1*S*)-{1-[2-(*tert*-Butyldimethylsilanoxy)-2-phenylethyl]-5-oxopentyl}methylcarbamic Acid *tert*-Butyl Ester (20). To a solution of DMP (0.61 g, 1.43 mmol) in CH_2Cl_2 (4 mL) at room temperature was added a solution of alcohol **18** (0.43 g, 0.95 mmol) in CH_2Cl_2 (4 mL). After 15 min of stirring, the mixture was diluted with ether (10 mL) and washed once with 10% $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ solution (1/1). The aqueous layer was extracted with ether (3×). The combined organic extracts were washed once with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (10% ethyl acetate/hexane) to give **20** (0.41 g, 96%) as a colorless oil: $[\alpha]^{20}_D = -35.1$ (*c* 0.72, CH_2Cl_2); IR (KBr) ν 1690, 1727, 2714, 2857, 3064 cm^{-1}; ^1H NMR (two rotamers in a 7/3 ratio) δ (ppm) −0.19 (s, 3H), 0.02 (s, 3H), 0.87 (s, 9H), 1.40−1.77 (m, 4H), 1.43 (s, 9H × 0.7), 1.48 (s, 9H × 0.3), 1.94−2.08 (m, 2H), 2.39 (m, 2H), 2.66 (s, 3H × 0.3), 2.70 (s, 3H × 0.7), 3.87 (m, 1H × 0.7), 4.03 (m, 1H × 0.3), 4.56 (t, 1H, *J* = 6.8 Hz), 7.30 (s, 5H), 9.69 (s, 1H × 0.3), 9.73 (s, 1H × 0.7); ^{13}C NMR (two rotamers) δ (ppm) −4.9, −4.5, 18.2, 18.6, 18.8, 26.0, 28.6, 31.8, 32.0, 43.5, 43.6, 44.2, 51.0, 51.8, 72.7, 73.0, 79.2, 79.8, 126.5, 127.3, 127.4, 128.3, 144.7, 156.2, 202.1, 202.5; HRMS (CI/*i*-butane) *m*/*z* calcd for $C_{25}H_{44}N_1O_4Si_1$ (M + H^+) 450.3040, found 450.3039.

(2′*S*,1*S*)-{1-[2-(*tert*-Butyldimethylsilanoxy)-2-phenylethyl]-7-oxo-7-phenylhept-5-enyl}methylcarbamic Acid *tert*-Butyl Ester (21). A solution of aldehyde **20** (0.40 g, 0.89 mmol) in THF (20 mL) and phenacylidenetriphenylphosphorane (1.69 g, 4.45 mmol) was stirred for 13 h at 65 °C. Then, removal of solvent left an oil which was purified by flash chromatography (10% ethyl acetate/hexane), affording **21** (0.40 g, 82%) as a yellow oil: $[\alpha]^{20}_D = -26.5$ (*c* 1.97, CH_2Cl_2); IR (KBr) ν 1622, 1653, 1673, 1690, 2929, 3062 cm^{-1}; ^1H NMR (two rotamers in a 7/3 ratio) δ (ppm) −0.18 (s, 3H × 0.7), −0.16 (s, 3H × 0.3), 0.02 (s, 3H), 0.88 (s, 9H), 1.20−1.51 (m, 4H), 1.44 (s, 9H × 0.7), 1.50 (s, 9H × 0.3), 1.73−2.27 (m, 4H), 2.67 (s, 3H × 0.3), 2.72 (s, 3H × 0.7), 3.89 (m, 1H × 0.7), 4.05 (m, 1H × 0.3), 4.58 (t, 1H, *J* = 6.4 Hz), 6.80−7.07 (m, 2H), 7.23−7.33 (m, 5H), 7.44−7.66 (m, 3H), 7.92 (d, 2H, 6.9 Hz); ^{13}C NMR (two rotamers) δ (ppm) −4.9, −4.5, 18.2, 24.7, 25.9, 28.6, 32.1, 32.5, 44.2, 51.2, 51.8, 72.7, 72.9, 79.1, 79.7, 126.2, 126.5, 127.3, 127.4, 128.3, 128.6, 132.7, 138.0, 144.7, 145.1, 149.3, 149.6, 156.0, 156.2, 190.8. Anal. Calcd for $C_{33}H_{49}NO_4Si$: C, 71.82; H, 8.95; N, 2.54. Found: C, 71.92; H, 8.79; N, 2.56.

(−)-Lobeline (1). A solution of **21** (0.40 g, 0.73 mmol) in *i*-PrOH (15 mL) was treated with concentrated HCl (0.15 mL). After being stirred at 60 °C for 3 h, the solution was diluted with water and basified with solid $NaHCO_3$ until pH 9−10. The aqueous layer was extracted four times with CH_2Cl_2. The combined organic extracts were washed once with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude extract was purified on neutral alumina (2% EtOH/CH_2Cl_2) to afford **1** (171 mg, 70%) as a white solid: mp 129−130 °C (lit.[41] mp 130 °C); $[\alpha]^{20}_D = -39.1$ (*c* 0.975, $CHCl_3$) [lit.[41] $[\alpha]^{20}_D = -38.2$ (*c* 1.986, $CHCl_3$)], after 72 h of equilibration (*cis*/*trans* = 1/1) $[\alpha]^{20}_D = -52.0$ (*c* 0.975, $CHCl_3$). Data for the

cis-isomer: ^1H NMR δ (ppm) 1.18−1.29 (m, 1H), 1.46−2.06 (m, 7H), 2.38 (s, 3H), 3.0 (dd, 1H, *J* = 8.5 Hz, *J* = 16.0 Hz), 3.26 (ddm, 2H, *J* = 5.0 Hz, *J* = 16.0 Hz), 3.59−3.65 (m, 1H), 4.97 (dd, 1H, *J* = 2.9 Hz, *J* = 10.8 Hz), 7.22−7.64 (m, 8H), 7.97−8.01 (m, 2H); ^{13}C NMR δ (ppm) 23.4, 23.5, 24.8, 27.4, 40.5, 43.8, 59.1, 64.6, 75.8, 125.6, 127.1, 128.2, 128.3, 128.8, 133.3, 137.1, 145.2, 198.3. Data for the

trans-isomer: ^1H NMR δ (ppm) 1.30−1.39 (m, 1H), 1.46−1.83 (m, 6H), 2.18−2.38 (m, 1H), 2.58 (s, 3H), 3.1 (dd, 1H, *J* = 9.8 Hz, *J* = 14.9 Hz), 3.22−3.32 (m, 2H), 3.80−3.85 (m, 1H), 4.93 (dd, 1H, *J* = 2.6 Hz, *J* = 10.7 Hz), 7.22−7.64 (m, 8H), 8.03−8.07 (m, 2H); ^{13}C NMR δ (ppm) 20.5, 23.0, 23.5, 35.8, 38.8, 43.2, 51.7, 61.1, 75.7, 125.6, 127.0, 128.2, 128.4, 128.8, 133.3, 136.7, 145.5, 198.4.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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