Enantioselective Allyltitanations and Metathesis Reactions. Application to the Synthesis of Piperidine Alkaloids (+)-Sedamine and (−)-Prosophylline

Janine Cossy,* Catherine Willis, Véronique Bellosta, and Samir BouzBouz

Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

janine.cossy@espci.fr

Received June 26, 2001

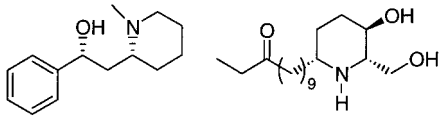
An enantioselective synthesis of the piperidine alkaloids (+)-sedamine and (−)-prosophylline is reported. The synthesis of (+)-sedamine has been achieved in 12 steps with an overall yield of 20% from benzaldehyde, and (−)-prosophylline was obtained in 15 steps with an overall yield of 9.2%, starting from D-glyceraldehyde acetonide **14**. The key steps are enantioselective allyltitanation reactions and ring-closing or cross-metathesis reactions.

Introduction

Piperidine alkaloids constitute a large family of compounds, many of which exhibit a wide range of physiological activities. As a result of this aspect, intense activity has been devoted to the isolation and structure determination of bases of this class and to the development of general methodologies and routes for their synthesis.[1] In this context, during the past few years, several methods were developed for the synthesis of 2-substituted piperidine alkaloids, as well as for the synthesis of 2,6-disubstituted piperidine alkaloids.[2]

Sedamine was the first alkaloid isolated from *Sedum acre*[3] and was obtained later from a number of *Sedum* species.[4] Both levorotatory (−)-sedamine and the dextrorotatory enantiomer were found in all of the *Sedum* species mentioned above. Numerous syntheses of sedamine have been reported either in racemic form[5] or as a single enantiomer.[6] (−)-Prosophylline is a prosopis alkaloid that contains a 2,6-disubstituted-3-piperidinol skeleton. This alkaloid was isolated from the leaves of *Prosopis africana*[7] and possesses noteworthy antibiotic and anesthetic properties.[8] Surprisingly, only one synthesis of racemic prosophylline[9] and two enantioselective synthesis of (−)-prosophylline[10] have been reported to date.

Among the different methods that allow the formation of a piperidine ring,[11] the intramolecular nucleophilic displacement of an activated alcohol moiety (e.g., tosylate, mesylate or triflate) by an amine is certainly one of the most useful and reliable methods.[11] Furthermore, during the past 10 years, the ring-closing metathesis reaction (RCM) has been developed into a powerful method for the preparation of both carbo- and heterocyclic ring systems.[12] Furthermore, piperidine rings can be very efficiently constructed from allylbutenylamines.[12g] However, these two approaches require that the stereochemistry has already been established in previous steps using either chiral pool-derived cyclization precursors or ste-



(+)-Sedamine (-)-Prosophylline

Figure 1.

(1) Strunz, G. M.; Findlay, J. A. In *The Alkaloids;* Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, pp 89−174.

(2) Numata, A.; Ibuka, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31.

(3) (a) Marion, L.; Lavigne, R.; Lemay, L. *Can. J. Chem*. **1951**, *29*, 347. (b) Franck, B. *Chem. Ber.* **1958**, *91*, 2803.

(4) (a) Logar, S.; Mesicek, M.; Perpar, M.; Seles, E. *Farm. Vestn.* **1974**, *21*; *Chem. Abstr.* **1975**, *82*, 82916h. (b) Krasnov, E. A.; Petrova, L. V.; Bekker, E. F. *Khim. Prir. Soedin.* **1977**, 585; *Chem. Abstr.* **1977**, *87*, 164249k.

(5) (a) Tufariello, J. J.; Ali, S. A. *Tetrahedron Lett.* **1978**, *47*, 4647. (b) Shono, T.; Matsumura, Y.; Tsubaka, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172. (c) Tirel, P. J.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1989**, *30*, 1947. (d) Pilli, R. A.; Dias, L. C. *Synth. Commun.* **1991**, *21*, 2213. (e) Ozawa, N.; Nakajima, S.; Zzoya, K.; Hamaguchi, F.; Nagasaka, T. *Heterocycles* **1991**, *32*, 889. (f) Driessens, F.; Hootelé, C. *Can. J. Chem*. **1991**, *69*, 211. (g) Ghiaci, M.; Adibi, M. *Org. Prep. Proced. Int*. **1996**, *38*, 474.

(6) (a) Beyerman, H. C.; Eveleens, W.; Muller, Y. M. F. *Recl. Trav. Chim. Pays-Bas* **1956**, *75*, 63. (b) Beyerman, H. C.; Eenshuistra, J.; Eveleens, W.; Zweistra, A. *Recl. Trav. Chim. Pays-Bas* **1959**, *78*, 43. (c) Schöpf, C.; Dummer, G.; Wüst, W. *Liebigs Ann. Chem.* **1959**, *626*, 134. (d) Wakabayashi, T.; Watanabe, K.; Kato, Y.; Saito, M. *Chem. Lett.* **1977**, 223. (e) Irie, K.; Aoe, K.; Tanaka, T.; Saito, S. *J. Chem. Soc., Chem. Commun.* **1985**, 633. (f) Pyne, S. G.; Bloem, P.; Chapman, S. L.; Dixon, C. E.; Griffith, R. *J. Org. Chem.* **1990**, *55*, 1086. (g) Kiguchi, T.; Nakazono, Y.; Kotera, S.; Ninomiya, I.; Naito, T. *Heterocycles* **1990**, *31*, 1525. (h) Comins, D. L.; Hong, H. *J. Org. Chem.* **1993**, *58*, 5035. (i) Poerwono, H.; Higashiyama, K.; Takahashi, H. *Heterocycles* **1998**, *47*, 262. (j) Yu, C. Y.; Meth-Cohn, O. *Tetrahedron Lett.* **1999**, *40*, 6665. (k) Compère, D.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 4528.

(7) (a) Ratle, G.; Monseur, X.; Das, B. C.; Yassi, J.; Khuong-Huu, Q.; Goutarel, R. *Bull. Soc. Chim. Fr.* **1966**, 2945. (b) Khuong-Huu, Q.; Ratle, G.; Monseur, X.; Goutarel, R. *Bull. Soc. Chim. Belg.* **1972**, *81*, 443.

(8) (a) Bourinet, P.; Quevauviller, A. *Compt. Rend. Soc. Biol.* **1968**, *162*, 1138; *Chem. Abstr. 70*, 95233k. (b) Bourinet, P.; Quevauviller, A. *Ann. Pharm. Fr.* **1968**, *26*, 787; *Chem. Abstr. 71*, 29012g.

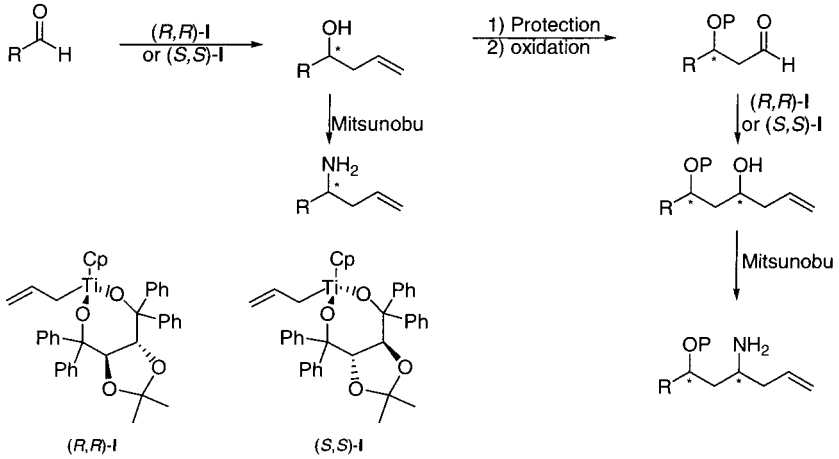
(9) Natsume, M.; Ogawa, M. *Heterocycles* **1981**, *16*, 973.

(10) (a) Koulocheri, S. D.; Haroutounian, S. A. *Tetrahedron Lett.* **1999**, *40*, 6869. (b) Toyooka, N.; Yoshida, Y.; Yotsui, Y.; Momose, T. *J. Org. Chem*. **1999**, *64*, 4914.

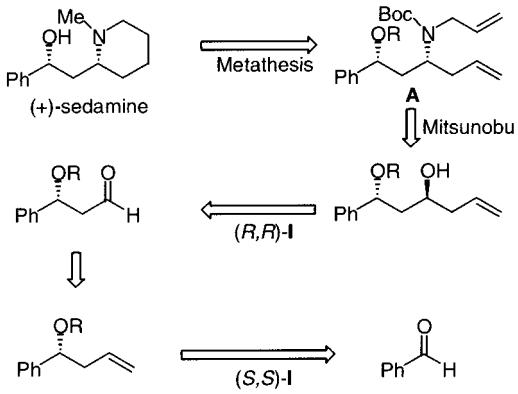
(11) For reviews see: (a) Wang, C. L. J.; Wuonola, M. A. *Org. Prep. Proced. Int*. **1992**, *24*, 585. (b) Lashat, S.; Dickner, T. *Synthesis* **2000**, 1781.

10.1021/jo010653d CCC: $22.00
Published on Web 01/22/2002

Scheme 1



Scheme 2. Retrosynthetic Scheme



reoselective C−N bond formation such as a Mitsunobu reaction on alcohols of the appropriate configuration. Recently, we have shown that enantioselective allyltitanation reactions of aldehydes by the (*R*,*R*)-**I** or (*S*,*S*)-**I** complex (Scheme 1), followed by a Mitsunobu reaction, appear to be methods of choice for obtaining amines and/or 1,3-amino alcohols of high enantiomeric excess. The considerable potential of these reactions has been applied to the synthesis of (+)-sedamine.[13] Herein, we would like to give a full account of this work and also to report the synthesis of (−)-prosophylline.

Synthesis of (+)-Sedamine. We recently reported that the addition of enantioenriched allyltitanium complexes **I** can convert protected 3-hydroxy aldehydes to monoprotected 1,3-diols with high selectivity. This methodology was applied to the synthesis of enantiopure piperidines such as (+)-sedamine in combination with a Mitsunobu reaction and a ring closing metathesis reaction of diene **A** according to the retrosynthetic scheme (Scheme 2).

When benzaldehyde was treated with the (*S*,*S*)-**I** allyltitanium complex (Scheme 3) according to the reported procedure,[14] homoallylic alcohol (+)-**1** was produced in 90% yield with an enantiomeric excess of 93%.[15] Protection of this product as the *p*-methoxybenzyl ether (*t*-BuOK, PMB-Br, THF, 96% yield) followed by oxidative cleavage of the double bond by using $NaIO_4/OsO_4$, in THF/H_2O (1/1), led to the unstable aldehyde **3**, which was immediatly treated with the (*R*,*R*)-**I** complex in ether at −78 °C, to give the alcohol (+)-**4** with a diastereomeric ratio of 96:4 (75% yield for the two steps). The next step of the synthesis was the transformation of the homoallylic alcohol (+)-**4** to the corresponding amine **6**. For this purpose, a two-step sequence was used. The first step was a Mitsunobu reaction. When alcohol (+)-**4** was treated by $Zn(N_3)_2 \cdot 2pyr$ (0.6 equiv)[16] in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine, the expected azide **5** was not formed and the starting material was recovered. On the contrary, when (+)-**4** was treated with diphenylphosphoryl azide (DPPA)[17] in the presence of DEAD and PPh_3 in THF at 0 °C and the temperature was raised immediatly to room temperature, the azide (+)-**5** was isolated in 40% yield. The yield of (+)-**5** was increased to 82% when the temperature was increased from 0 °C to room temperature over 12 h. When the reduction of azide (+)-**5** to amine **6** was achieved by using PPh_3/H_2O or PPh_3/NH_4OH in THF, the amine **6** could not be extracted from the aqueous phase. On the contrary, the reduction of azide (+)-**5** with $LiAlH_4$ in THF proceeded in 94% yield, and the homoallylic amine **6** was isolated and converted directly to carbamate (+)-**7** (Boc_2O, dioxane) with a diastereomeric ratio of 97.5:2.5 (85% yield). Compound (+)-**7** was then alkylated with allyl bromide in the presence of KHMDS to produce (+)-**8** in 91% yield. Treatment of (+)-**8** with the Grubbs' catalyst $\mathbf{G_1}$[18] (Scheme 3) in benzene furnished the 3,4-dehydropiperidine (+)-**9** in 94% yield. After catalytic hydrogenation of the double bond of (+)-**9** in EtOAc over PtO_2, the *p*-methoxybenzyl group was removed with 1.1 equiv of DDQ in a mixture of CH_2Cl_2/H_2O (18/1, rt, 15 min). Under these conditions, the alcohol (+)-**11** was obtained in 75% yield and 15% of the starting material (+)-**10** was recovered. These two

(12) (a) Schrock, R. R.; Murdzek, J. S.; Bazar, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3575. (b) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 3974. (c) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3875. (d) Fu, G. C.; Nguyen, S. T.; Grubbs R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (e) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (f) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012 and references therein. (g) Phillips, A. J.; Abell., A. D. *Aldrichimica Acta* **1999**, *32*, 75.

(13) Cossy, J.; Willis, C.; Bellosta, V.; Bouzbouz, S. *Synlett* **2000**, 1461.

(14) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Swarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.

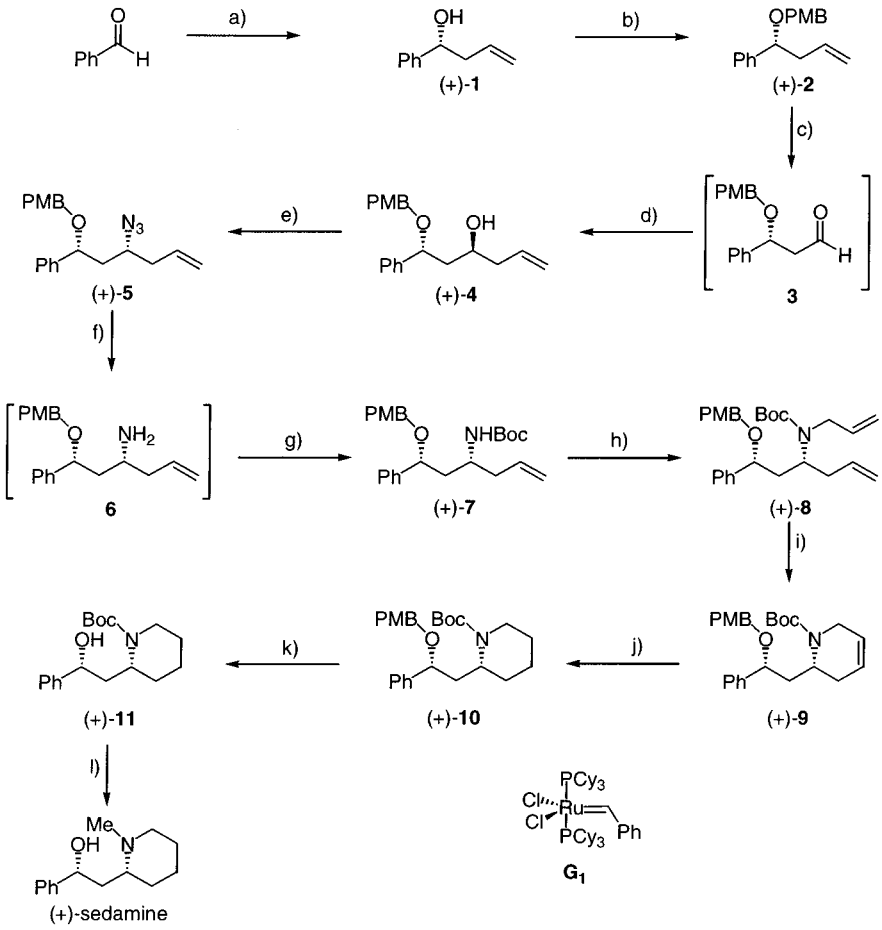
(15) The enantiomeric excess was determined by HPLC; column, Chiralpak AD_2; eluent, 3% isopropyl alcohol in *n*-hexane.

(16) Viaud, M. C.; Rollin, P. *Synthesis* **1990**, 130.

(17) Irako, N.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1992**, *48*, 7251.

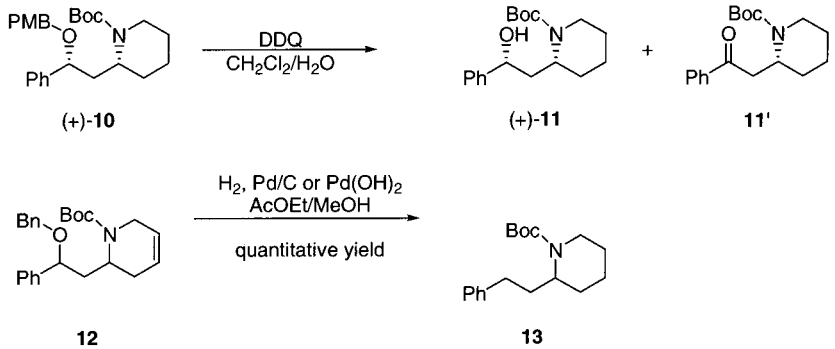
(18) Miller, S. J.; Blackwell, M. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606.

Scheme 3. Synthesis of (+)-Sedamine[a]



[a] Reagents and conditions: (a) (*S,S*)-**I**, Et_2O, −78 °C, 90%; (b) *t*-BuOK, PMB-Br, THF, 96%; (c) $OsO_4/NaIO_4$, THF/H_2O; (d) (*R,R*)-**I**, Et_2O, −78 °C, 75% for the two steps; (e) DEAD, PPh_3, DPPA, THF, 0 °C to rt, 82%; (f) $LiAlH_4$, Et_2O, 94%; (g) Boc_2O, dioxane, 85%; (h) allylbromide, KHMDS, THF/DMF = 3/1, 91%; (i) **G**$_1$, C_6H_6, 94%; (j) H_2, PtO_2, AcOEt, 94%; (k) DDQ, CH_2Cl_2/H_2O = 18/1, 75%; (l) $LiAlH_4$, THF, reflux, 78%.

Scheme 4

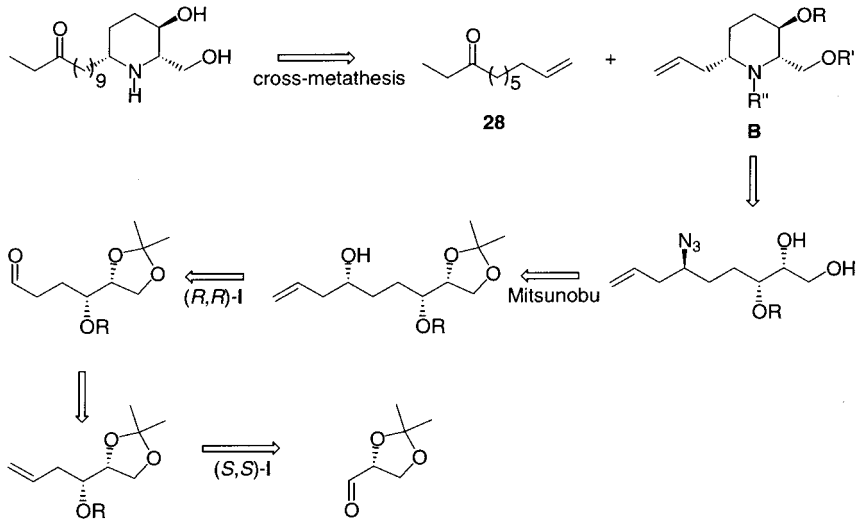


compounds could be separated easily. We note that when 1.5 equiv of DDQ was used, (+)-**10** was entirely consumed and a chromatographically separable mixture of alcohol (+)-**11** (80%) and ketone **11′** [5d] (10%) was formed (Scheme 4). After reduction of the Boc group of (+)-**11** with $LiAlH_4$ in refluxing THF for 6 h, (+)-sedamine was obtained after crystallization in 78% yield with a diastereoselectivity of 98%. The properties were identical to those reported in the literature.[6]

The replacement of the *p*-methoxybenzyl protecting group by a benzyl group would shorten the synthesis of (+)-sedamine provided that reduction of the dehydropiperidine and hydrogenolysis of the benzyl group could be achieved in a one-pot reaction. Accordingly, the benzylic ether **12** was also prepared and hydrogenated, but contrary to expectation compound **13** was obtained instead of **11**, with either Pd/C or $Pd(OH)_2$ as catalyst (Scheme 4). Nonetheless the synthesis of (+)-sedamine was still efficient as this compound was obtained with high diastereoselectivity (98%) in 12 steps in an overall yield of 20%.

Synthesis of (−)-Prosophylline. The enantioselective allyltitanation of aldehydes with (*R,R*)-**I** and (*S,S*)-**I** was also used to synthesize (−)-prosophylline. The construction of the piperidine ring of prosophylline was envisaged to arise by intramolecular nucleophilic displacement of a mesylate by an amine. The stereogenic centers at C-6 and C-3 could be controlled through

Scheme 5. Retrosynthetic Scheme



enantioselective allyltitanations of aldehydes, and the stereogenic center at C-2 could come from D-glyceraldehyde acetonide. Furthermore the ketonic side chain could be built up by using a cross-metathesis reaction between the substituted piperidine **B** and the unsaturated enone **28** (Scheme 5).

When D-glyceraldehyde acetonide **14**[19] was treated with the allyltitanium complex (*S*,*S*)-**I**,[14] homoallylic alcohol (+)-**15** (dr = 98:2) was isolated in 86% yield.[14] Protection of (+)-**15** as the benzyl derivative (+)-**16** was achieved in the presence of *t*-BuOK and benzyl bromide in THF (91%). Compound (+)-**16** was then transformed to the unstable aldehyde **18** in a two step-sequence. Olefin (+)-**16** was hydroborated (BH_3·THF, THF; NaOH, H_2O_2) and transformed to the primary alcohol (+)-**17** in 83% yield. After Swern oxidation of (+)-**17**, aldehyde **18** was immediately treated with the allyltitanium complex (*R*,*R*)-**I** at −78 °C in ether to give the homoallylic alcohol (+)-**19** in a 98:2 diastereomeric ratio (yield 81%). The next step of the synthesis was the transformation of the homoallylic alcohol (+)-**19** to the azide by a Mitsunobu reaction. When homoallylic alcohol (+)-**19** was treated with DPPA in the presence of PPh_3 and DEAD in THF at 0 °C and the temperature was raised to room temperature over 12 h, according to the procedure used for the synthesis of (+)-sedamine, the azide **20** was formed, but it could not be separated from DPPA. However, after the azide was reduced by $LiAlH_4$ (ether, 0 °C) amine (+)-**21** was obtained in 41% overall yield for the two steps. With the aim of obtaining the precursor of the piperidine ring of prosophylline, compound (+)-**21** was treated with acid in order to deprotect the diol. However, **22** could not be obtained when CSA in MeOH or an acidic resin in a mixture of MeOH/H_2O were used (Scheme 6).

In an alternative route, the impure azide acetal **20** was treated with AcOH/H_2O (80/20) and transformed to the corresponding diol (−)-**23** in 76% yield (two steps). Protection of the primary alcohol of (−)-**23** as the *tert*-butyldiphenylsilyl ether (TBDPSCl, imidazole, CH_2Cl_2) afforded (−)-**24** in 96% yield. Treatment with methanesulfonyl chloride in the presence of DMAP and pyridine gave the mesylate (+)-**25** in 98% yield (Scheme 7). The next step of the synthesis was the formation of the piperidine ring. For this purpose, a two-step sequence was used. First, reduction of the azide (+)-**25** to the amine (+)-**26**, with PPh_3 in aqueous THF at 50 °C for 12 h, was achieved in 89% yield. Treatment of amine (+)-**26** with Et_3N in refluxing methanol furnished the desired piperidine (−)-**27** in 88% yield. It is worth noting that the transformation of the azido compound (+)-**25** to amine (+)-**27** in a one-pot procedure by addition of PPh_3 in THF followed by the addition of aqueous Et_3N afforded piperidine (−)-**27** in lower yield (37%).

As a possible method that would introduce the ketonic side chain at C-6, we examined the cross-metathesis reaction[20] between the substituted piperidine (−)-**27** and the unsaturated ketone **28**.[21] Unfortunately when a mixture of (−)-**27** and unsaturated ketone **28** were treated with the "new generation" Grubbs' catalyst $\mathbf{G_2}$[22] (10 mol %), the desired coupling product **29** was not obtained and the starting material was recovered (Scheme 8). However, when piperidine (−)-**27** was transformed to its benzylcarbamate (+)-**30** (CbzCl, Na_2CO_3, CH_2Cl_2/H_2O, quantitative yield) and treated with the Grubbs' catalyst $\mathbf{G_2}$ in the presence of the unsaturated ketone **28**, the desired coupling product (+)-**31** was isolated in 58% yield after 4 h in refluxing CH_2Cl_2. The synthesis of (−)-prosophylline was completed by hydrogenation of the olefin and deprotection of the hydroxyl and amino groups. When compound (+)-**31** was hydrogenated over Pd/C, reduction of the double bond was achieved, as well as the deprotection of the piperidine nitrogen and the secondary alcohol. The resulting hydroxylated amine (−)-**32** was then treated with tetrabutylammonium fluoride in THF to afford (−)-prosophylline in 54% yield. The spectral and physical data were in accordance with the literature data.[9] (−)-Prosophylline was obtained by the above route in 15 steps with a diastereomeric ratio of 98:2 and with an overall yield of 9.2%.

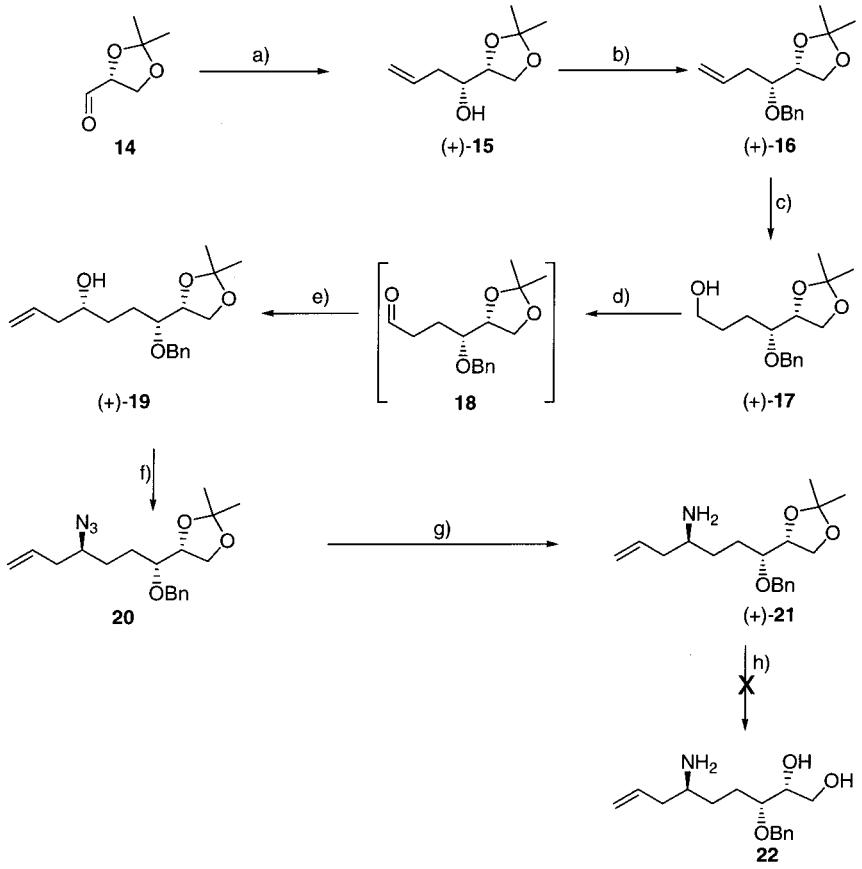
(19) Schmid, C. R.; Bryant, J. D. *Org. Synth*. **1995**, *72*, 6.

(20) For cross-metathesis reactions see: Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783 and references therein.

(21) Compound **28** was prepared from ethyl vinyl ketone by 1,4-addition of the Grignard reagent prepared from 6-bromo-1-hexene in the presence of CuBr·Me_2S, in THF.

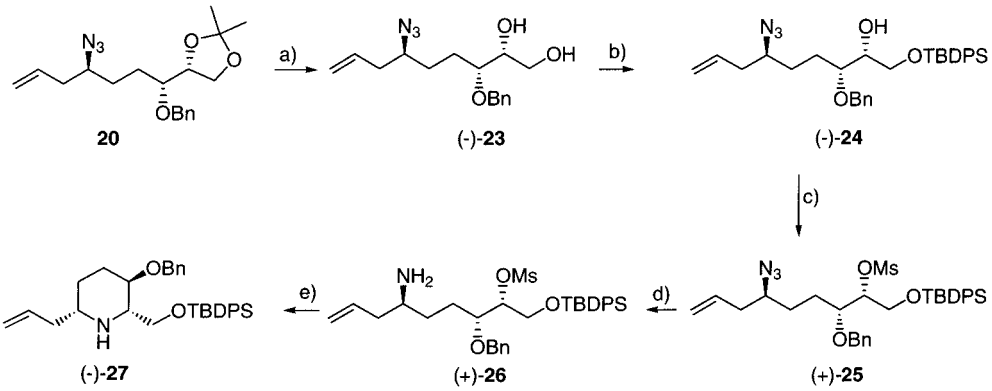
(22) Scholl, M.; Ding, S.; Woo Lee, C.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 953.

Scheme 6[a]



[a] Reagents and conditions: (a) (*S*,*S*)-**I**, Et_2O, −78 °C, 86%; (b) *t*-BuOK, BnBr, THF, 91%; (c) (i) BH_3·THF, (ii) H_2O_2, NaOH, H_2O, 83%; (d) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, quantitative yield; (e) (*R*,*R*)-**I**, Et_2O, −78 °C, 81%; (f) PPh_3, DEAD, DPPA, THF, 0 °C to rt; (g) $LiAlH_4$, Et_2O, 0 °C, 41% for the two steps; (h) CSA/MeOH or H^+ resin, MeOH/H_2O.

Scheme 7[a]



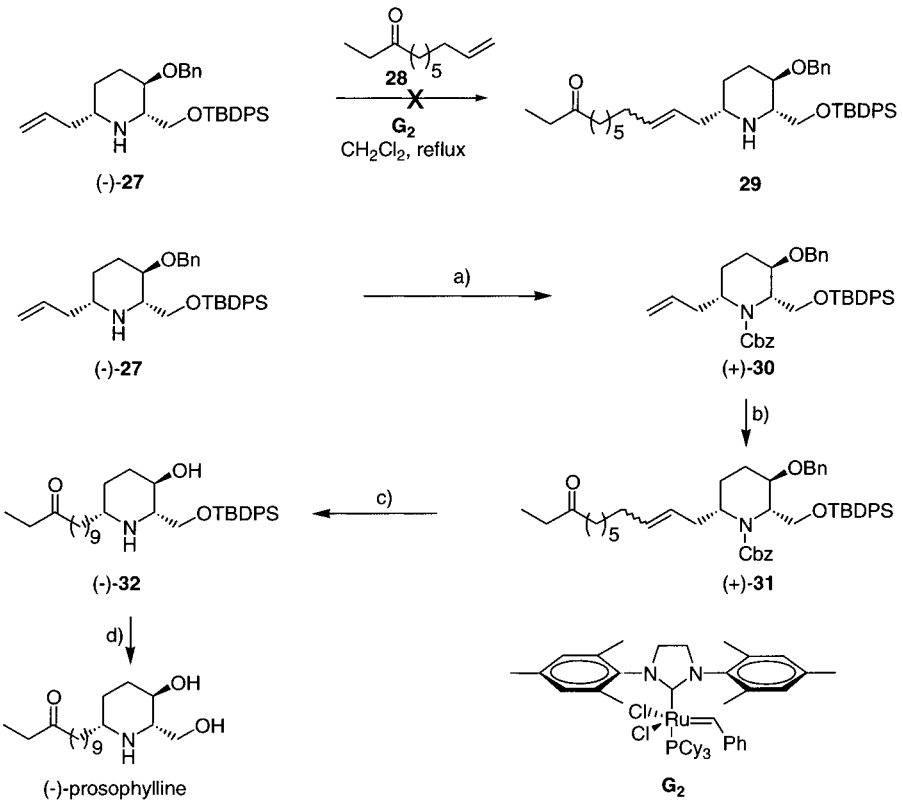
[a] Reagents and conditions: (a) AcOH/H_2O, 80/20, 76% for the two steps; (b) TBDPSCl, imidazole, CH_2Cl_2, 96%; (c) MsCl, DMAP, pyridine, 98%; (d) PPh_3, THF/H_2O, 89%; (e) Et_3N, MeOH, reflux, 88%.

The application of the enantioselective allyltitanation methodology to the synthesis of (+)-sedamine and (−)-prosophylline was efficient, as these compounds could be obtained in relatively few steps with high diastereoselectivity. As both the (*R*,*R*)-**I** and (*S*,*S*)-**I** allyltitanium complexes are available, (−)-sedamine and (+)-prosophylline could also be prepared by these routes.

Experimental Section

General Procedures. Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium/benzophenone ketyl immediately before use. Benzene, dichloromethane, DMF and triethylamine were distilled from calcium hydride under argon. Benzaldehyde and allyl bromide were distilled prior to use. Moisture-sensitive reactions were conducted in oven- or flame-dried glassware under an argon atmosphere. Flash chromatography was carried out on Kieselgel 60 (230−400 mesh, Merck) and analytical thin-layer chromatography was performed on Merck precoated silica gel (60 F_{254}). Melting points are uncorrected. Microanalyses were performed at the Service de Microanalyse de l'Université Pierre et Marie Curie in Paris. Mass spectra were obtained by GC/MS with electron impact ionization by using a 5971 Hewlett-Packard instrument at 70 eV; only

Scheme 8[a]



[a] Reagents and conditions: (a) CbzCl, Na_2CO_3, CH_2Cl_2/H_2O, quantitative yield; (b) **28**, **G**$_2$, CH_2Cl_2, reflux, 58%; (c) H_2, Pd/C 10%, MeOH/HCl, 50/1, 60%; (d) TBAF, THF 90%.

selected ions are reported. HRMS and CIMS were performed at the Laboratoire de Spectrochimie de l'Ecole Normale Supérieure in Paris. ^{1}H and ^{13}C spectra were respectively recorded on a Bruker AC 300 spectrometer at 300 and 75 MHz. Unless otherwise specified, spectra were recorded in $CDCl_3$ as solvent; chemical shifts (δ) were expressed in ppm and coupling constant (J) in hertz. IR spectra were recorded as neat films (NaCl cell) and KBr pellets or $CHBr_3$ solutions for solids on a Perkin-Elmer 298. Optical rotations were determined operating at the sodium D line. HPLC analyses were conducted using Chiralpak AD_2 column. Cyclopentadienyl[(4*S*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*′]titanium chloride was prepared following the reported procedure.[14]

(1*R*)-1-Phenylbut-3-en-1-ol[14] **(+)-1.** Allylmagnesium chloride (5.19 mL, 2 M in THF, 10.4 mmol, 1.1 equiv) was added at 0 °C to a mixture of cyclopentadienyl[(4*S*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*′]titanium chloride (7.51 g, 12.3 mmol, 1.3 equiv) in anhydrous Et_2O (150 mL). The orange mixture was stirred for 2 h at 0 °C and cooled to −78 °C. To this mixture was added dropwise a solution of benzaldehyde (0.96 mL, 1.0 g, 9.4 mmol, 1 equiv) in Et_2O (12 mL). After 3 h at −78 °C, the reaction was quenched by addition of a 45% aqueous NH_4F solution (50 mL). The mixture was stirred overnight at room temperature and then filtered through Celite. The organic phase was washed with brine (300 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was diluted with pentane (150 mL) and filtered to afford (4S,*trans*)-2,2-diméthyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol ((*S*,*S*)-taddol) (4.98 g, 10.7 mmol, 87%). The organic layer was concentrated in vacuo, and the crude residue was purified on silica gel (CH_2Cl_2/hexanes/Et_2O, 4/4/1) to afford (+)-**1** (1.26 g, 8.5 mmol, 90%) as a yellow oil (93% ee, determined by chiral HPLC, column Chiralpak AD_2, *n*-hexane/*i*-PrOH, 97/3, (+)-**1** 96.6%, t_R = 14.10 min; (−)-**1** 3.4%, t_R = 14.70 min). Physical and spectral data were identical to those previously reported:[14] R_f = 0.53 (CH_2Cl_2/hexanes/Et_2O, 4/4/1); $[\alpha]^{20}_D$ = +51.5 (*c* 1.0, C_6H_6) {lit.[14] $[\alpha]^{20}_D$ = +47.9 (*c* 5.0, C_6H_6)}; IR (neat) 3360, 1640, 1595 cm^{-1}; ^{1}H NMR (300 MHz) δ (ppm) 7.40−7.26 (m, 5H), 5.83 (m, 1H), 5.22−5.13 (m, 2H), 4.74 (m, 1H), 2.57−2.50 (m, 2H), 2.22 (d, 1H, J = 3.3 Hz); ^{13}C NMR (75.5 MHz) δ (ppm) 143.7 (s), 134.3 (d), 128.3 (d), 127.4 (d), 125.7 (d), 118.2 (t), 73.2 (d), 43.7 (t); MS (EI, 70 eV) *m*/*z* 148 (M, 1), 129 (1), 128 (2), 115 (1), 108 (8), 107 (100), 105 (8), 91 (2), 79 (58), 77 (33), 51 (7).

1-Methoxy-4-{[((1*R*)-1-phenylbut-3-enyl)oxy]methyl}-benzene (+)-2. To a solution of (+)-**1** (1.20 g, 8.1 mmol, 1 equiv) in THF (10 mL) at 0 °C was added *t*-BuOK (1.27 g, 11.4 mmol, 1.4 equiv). The mixture was stirred for 5 min, and *p*-methoxybenzyl bromide (2.00 g, 9.7 mmol, 1.2 equiv) was added dropwise. After 4 h at room temperature, the reaction was quenched by addition of a 20% aqueous NH_4Cl solution (50 mL). After extraction of the aqueous phase with EtOAc (3 × 85 mL), the combined organic phases were washed with water (45 mL) and brine (45 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (Et_2O/petroleum ether, 2/98 to 5/95) to afford (+)-**2** as a yellow oil (2.10 g, 7.8 mmol, 96%): R_f = 0.57 (Et_2O/petroleum ether, 1/9); $[\alpha]^{20}_D$ = +67.3 (*c* 1.0, C_6H_6); IR (neat) 1640, 1610, 1585 cm^{-1}; ^{1}H NMR (300 MHz) δ (ppm) 7.47−7.35 (m, 5H), 7.32−7.25 (m, 2H), 6.97−6.89 (m, 2H), 5.85 (m, 1H), 5.14−5.04 (m, 2H), 4.48 (d syst AB, 1H, J = 11.4 Hz), 4.41 (dd, 1H, J = 7.7, J = 5.9 Hz), 4.27 (d syst AB, 1H, J = 11.4 Hz), 3.85 (s, 3H), 2.69 (m, 1H), 2.49 (m, 1H); ^{13}C NMR (75.5 MHz) δ (ppm) 159.0 (s), 141.9 (s), 134.9 (d), 130.5 (s), 129.2 (d), 128.3 (d), 127.5 (d), 126.8 (d), 116.7 (t), 113.7 (d), 80.7 (d), 69.9 (t), 55.2 (q), 42.6 (t); MS (EI, 70 eV) *m*/*z* 268 (M, 1), 227 (1), 162 (1), 150 (1), 135 (1), 131 (1), 129 (1), 122 (10), 121 (100), 115 (1), 105 (2), 91 (4), 77 (6), 65 (1), 51 (1). Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.57; H, 7.51. Found: C, 80.55; H, 7.56.

(3*R*)-3-[(4-Methoxybenzyl)oxy]-3-phenylpropanal 3. To a solution of (+)-**2** (2.10 g, 7.8 mmol, 1 equiv) in THF/H_2O (1/1) (60 mL) was added OsO_4 (0.50 mL, 4% aqueous solution, 0.078 mmol, 0.01 equiv). The black solution was stirred for 5 min at room temperature, and $NaIO_4$ (6.70 g, 31.3 mmol, 4 equiv) was added by small portions over 2 h. After additional

stirring for 2 h, the reaction was quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (72 mL). After 30 min, Et_2O (115 mL) and brine (72 mL) were added to the reaction mixture. The aqueous phase was extracted with Et_2O (3 × 120 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product (2.17 g) was used for the next step without further purification: $R_f = 0.45$ (Et_2O/petroleum ether, 1/2); IR (neat) 1725, 1610 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 9.77 (dd, 1H, $J = 2.6$, $J = 1.5$ Hz), 7.46−7.34 (m, 5H), 7.26−7.18 (m, 2H), 6.93−6.85 (m, 2H), 4.91 (dd, 1H, $J = 9.2$, $J = 4.0$ Hz), 4.44 (d syst AB, 1H, $J = 11.0$ Hz), 4.25 (d syst AB, 1H, $J = 11.0$ Hz), 3.81 (s, 3H), 2.97 (ddd, 1H, $J = 16.5$, $J = 9.2$, $J = 2.6$ Hz), 2.64 (ddd, 1H, $J = 16.5$, $J = 4.0$, $J = 1.5$ Hz); ^{13}C NMR (75.5 MHz) δ (ppm) 200.5 (d), 159.2 (s), 140.5 (s), 129.8 (s), 129.4 (d), 128.7 (d), 128.1 (d), 126.5 (d), 113.7 (d), 75.7 (d), 70.1 (t), 55.1 (q), 51.5 (t); MS (EI, 70 eV) *m*/*z* 270 (M, 4), 197 (1), 163 (1), 138 (21), 137 (77), 132 (16), 131 (26), 122 (14), 121 (100), 109 (17), 105 (19), 103 (15), 92 (11), 77 (26), 65 (4), 51 (8).

(1*R*,3*S*)-1-[(4-Methoxybenzyl)oxy]-1-phenylhex-5-en-3-ol (+)-4. Allylmagnesium chloride (4.30 mL, 2 M in THF, 8.6 mmol, 1.1 equiv) was added at 0 °C to a mixture of cyclopentadienyl[(4*R*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*′]titanium chloride (6.23 g, 10.2 mmol, 1.3 equiv) in anhydrous Et_2O (125 mL). The orange mixture was stirred for 2 h at 0 °C and cooled to −78 °C, and a solution of **3** (2.17 g of crude) in Et_2O (27 mL) was then added dropwise to this mixture. After 3 h at −78 °C, the reaction was quenched by addition of a 45% aqueous NH_4F solution (45 mL). The mixture was stirred overnight at room temperature and was then filtered through Celite. The organic phase was washed with brine (320 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was diluted with pentane (120 mL) and filtered to afford (*R*,*R*)-taddol (3.18 g, 6.8 mmol, 67%). The filtrate was concentrated in vacuo, and the crude residue was purified on silica gel (CH_2Cl_2/hexanes/Et_2O, 4/4/1) to afford (+)-**4** as a yellow oil (1.82 g, 5.8 mmol, 75% from (+)-**2**), with a diastereomeric ratio of 96:4 (determined by ^1H NMR): $R_f = 0.48$ (CH_2Cl_2/hexane/Et_2O, 4/4/1); $[\alpha]^{20}_D = +80.0$ (*c* 1.1, C_6H_6); IR (neat) 3440, 1640, 1610 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.41−7.28 (m, 5H), 7.27−7.21 (m, 2H), 6.92−6.85 (m, 2H), 5.81 (m, 1H), 5.13−5.01 (m, 2H), 4.70 (dd, 1H, $J = 9.2$, $J = 3.3$ Hz), 4.45 (d syst AB, 1H, $J = 11.2$ Hz), 4.23 (d syst AB, 1H, $J = 11.2$ Hz), 3.97 (m, 1H), 3.80 (s, 3H), 2.61 (d, 1H, $J = 4.4$ Hz), 2.27−2.19 (m, 2H), 1.96 (ddd, 1H, $J = 14.5$, $J = 9.2$, $J = 2.6$ Hz), 1.76 (ddd, 1H, $J = 14.5$, $J = 8.8$, $J = 3.3$ Hz); ^{13}C NMR (75.5 MHz) δ (ppm) 159.2 (s), 142.0 (s), 134.8 (d), 130.1 (s), 129.4 (d), 128.5 (d), 127.5 (d), 126.4 (d), 117.4 (t), 113.8 (d), 78.0 (d), 70.2 (t), 67.5 (d), 55.1 (q), 44.5 (t), 41.8 (t); MS (EI, 70 eV) *m*/*z* 312 (M, 1), 294 (1), 270 (1), 227 (1), 197 (1), 176 (1), 158 (2), 137 (56), 121 (100), 117 (7), 105 (9), 91 (5), 77 (7), 65 (1). Anal. Calcd for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.69; H, 7.94.

1-{[(1*R*,3*R*)-3-Azido-1-phenylhex-5-enyl)oxy]methyl}-4-methoxybenzene (+)-5. To a solution of (+)-**4** (1.82 g, 5.8 mmol, 1 equiv) in anhydrous THF (70 mL), cooled at 0 °C, was added PPh_3 (1.68 g, 6.4 mmol, 1.1 equiv). The mixture was stirred for 5 min at 0 °C, and then DEAD (1.01 mL, 1.12 g, 6.4 mmol, 1.1 equiv) and DPPA (1.38 mL, 1.77 g, 6.4 mmol, 1.1 equiv) were added dropwise. The mixture was allowed to warm slowly at room temperature with stirring for 12 h, and the solution was concentrated in vacuo. The crude residue was purified on silica gel (EtOAc/petroleum ether, 5/95) to afford (+)-**5** (1.62 g, 4.8 mmol, 82%): $R_f = 0.92$ (EtOAc/petroleum ether, 1/4); $[\alpha]^{20}_D = +13.2$ (*c* 1.0, C_6H_6); IR (neat) 2100, 1640, 1610 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.49−7.31 (m, 5H), 7.31−7.20 (m, 2H), 6.96−6.87 (m, 2H), 5.77 (m, 1H), 5.19−5.05 (m, 2H), 4.49 (dd, 1H, $J = 7.2$, $J = 7.2$ Hz), 4.41 (d syst AB, 1H, $J = 11.2$ Hz), 4.21 (d syst AB, 1H, $J = 11.2$ Hz), 3.83 (s, 3H), 3.31 (m, 1H), 2.39−2.06 (m, 3H), 1.86 (m, 1H); ^{13}C NMR (75.5 MHz) δ (ppm) 159.1 (s), 141.2 (s), 133.4 (d), 130.1 (s), 129.3 (d), 128.6 (d), 127.7 (d), 127.1 (d), 118.3 (t), 113.7 (d), 78.0 (d), 69.9 (t), 58.7 (d), 55.2 (q), 41.9 (t), 38.4 (t); MS (EI, 70 eV) *m*/*z* 310 (1), 309 (M − N_2, 1), 268 (1), 218 (1), 202 (1), 170 (3), 162 (5), 137 (18), 135 (7), 132 (65), 121 (100), 104 (23), 91 (8), 77 (13); HRMS (IC$^+$, CH_4) calcd for $C_{20}H_{24}N_3O_2$ (MH^+) *m*/*z* 338.1869, found 338.1904.

(1*R*,3*R*)-1-[(4-Methoxybenzyl)oxy]-1-phenylhex-5-en-3-amine 6. A suspension of $LiAlH_4$ (0.54 g, 14.3 mmol, 3 equiv) in anhydrous Et_2O (37 mL) was stirred for 5 min at 0 °C, and a solution of (+)-**5** (1.60 g, 4.75 mmol, 1 equiv) in Et_2O (37 mL) was then added dropwise. The mixture was stirred for 1 h at 0 °C and for 1 h at room temperature. Water (0.56 mL), a 15% aqueous NaOH solution (0.56 mL), and water (1.12 mL) were successively added, and the resulting mixture was then diluted with EtOAc (120 mL) and water (25 mL). The aqueous phase was extracted with EtOAc (3 × 110 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product (1.39 g, 4.5 mmol, 94%) was used in the next step without further purification: $R_f = 0.07$ (EtOAc); IR (neat) 3370, 1640, 1610 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.43−7.28 (m, 5H), 7.26−7.19 (m, 2H), 6.93−6.85 (m, 2H), 5.73 (m, 1H), 5.15−4.96 (m, 2H), 4.48 (dd, 1H, $J = 8.6$, $J = 5.3$ Hz), 4.39 (d syst AB, 1H, $J = 11.2$ Hz), 4.17 (d syst AB, 1H, $J = 11.2$ Hz), 3.81 (s, 3H), 2.90 (m, 1H), 2.17 (m, 1H), 2.05−1.62 (m, 5H); ^{13}C NMR (75.5 MHz) δ (ppm) 159.0 (s), 142.2 (s), 135.3 (d), 132.9 (s), 129.3 (d), 128.4 (d), 127.4 (d), 126.7, (d), 117.4 (t), 113.7 (d), 79.9 (d), 69.8 (t), 55.1 (q), 48.7 (d), 45.9 (t), 42.5 (t); MS (EI, 70 eV) *m*/*z* 312 (M + 1, 1), 270 (1), 227 (2), 192 (1), 177 (8), 175 (7), 160 (14), 134 (12), 121 (100), 117 (13), 104 (10), 91 (5), 72 (11), 63 (1), 51 (1).

***tert*-Butyl (1*R*)-1-{(2*R*)-2-[(4-Methoxybenzyl)oxy]-2-phenylethyl}but-3-enylcarbamate (+)-7.** To a solution of **6** (1.39 g, 4.5 mmol, 1 equiv) in dioxane (11 mL), cooled at 0 °C, was added dropwise a solution of Boc_2O (1.56 g, 7.15 mmol, 1.6 equiv) in dioxane (9 mL). The mixture was stirred for 19 h at room temperature and was then diluted with water (26 mL) and Et_2O (75 mL). The aqueous phase was extracted with Et_2O (2 × 80 mL). The combined organic phases were washed with brine (73 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (EtOAc/pentane, 5/95 to 20/80) to afford (+)-**7** (1.56 g, 3.8 mmol, 85%) as yellow crystals: $R_f = 0.17$ (EtOAc/pentane, 0.5/9.5); $[\alpha]^{20}_D = +34.7$ (*c* 1.1, C_6H_6); mp = 87−89 °C; IR (neat) 3410, 3360, 1700, 1640, 1610, 1585 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.44−7.28 (m, 5H), 7.27−7.20 (m, 2H), 6.92−6.84 (m, 2H), 5.71 (m, 1H), 5.12−4.96 (m, 2H), 4.93 (m, 1H), 4.40 (dd, 1H, $J = 7.7$, $J = 5.1$ Hz), 4.34 (d syst AB, 1H, $J = 11.0$ Hz), 4.17 (d syst AB, 1H, $J = 11.0$ Hz), 3.80 (s, 3H), 3.72 (m, 1H), 2.30−2.13 (m, 2H), 2.02−1.88 (m, 1H), 1.85−1.72 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (75.5 MHz) δ (ppm) 159.1 (s), 155.3 (s), 142.0 (s), 134.2 (d), 130.2 (s), 129.5 (d), 128.5 (d), 127.7 (d), 126.6 (d), 117.6 (t), 113.7 (d), 79.2 (d), 78.8 (s), 70.0 (t), 55.1 (q), 48.6 (d), 42.4 (t), 39.6 (t), 28.3 (q); MS (EI, 70 eV) *m*/*z* 339 (MH^+ − *t*BuO, 1), 277 (1), 221 (7), 204 (7), 178 (4), 160 (16), 137 (43), 121 (100), 105 (7), 91 (5), 77 (7), 59 (6); HRMS (IC$^+$, CH_4) calcd for $C_{25}H_{34}NO_4$ (MH^+) *m*/*z* 412.2488, found 412.2495.

***tert*-Butyl Allyl-(1*R*)-1-{(2*R*)-2-[(4-methoxybenzyl)oxy]-2-phenylethyl}but-3-enylcarbamate (+)-8.** A solution of (+)-**7** (1.53 g, 3.7 mmol, 1 equiv) in a mixture of THF/DMF (3/1) (29.3 mL) was cooled at 0 °C, and KHMDS (7.88 mL, 0.5M in toluene, 3.9 mmol, 1.06 equiv) was added dropwise. The mixture was stirred for 30 min at 0 °C, and freshly distilled allyl bromide (0.35 mL, 0.49 g, 4.1 mmol, 1.1 equiv) was added dropwise. After 2 h at room temperature, the reaction was quenched by addition of an aqueous 1 M HCl solution (14.4 mL). The reaction mixture was diluted with EtOAc (86 mL), and the aqueous phase was extracted with EtOAc (3 × 120 mL). The combined organic phases were washed with water (120 mL) and brine (120 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified on silica gel (Et_2O/petroleum ether, 5/95 to 15/85) to afford (+)-**8** (1.52 g, 3.4 mmol, 91%) as a pale yellow oil: $R_f = 0.43$ (Et_2O/petroleum ether, 2/8); $[\alpha]^{20}_D = +32.0$ (*c* 1.0, C_6H_6); IR (neat) 1690, 1640, 1610, 1585 cm^{-1}; ^1H NMR(300 MHz) δ (ppm) 7.44−7.29 (m, 5H), 7.26−7.17 (m, 2H), 6.92−6.84 (m, 2H), 5.82 (m, 1H), 5.61 (m, 1H), 5.21−4.91 (m, 4H), 4.34 (d syst AB, 1H, $J = 11.2$ Hz), 4.29 (dd, 1H, $J = 7.2$, $J = 7.2$ Hz), 4.13 (d syst AB, 1H, $J = 11.2$ Hz), 3.81 (s, 3H), 3.92−3.69 (m, 2H), 3.64 (m, 1H), 2.32−2.02 (m, 3H), 1.87 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (75.5 MHz)

(rotamers) δ (ppm) 159.0 (s), 155.4 (s), 141.9−141.6 (s), 136.1 (d), 135.7 (d), 135.3 (d), 130.4 (s), 129.3 (d), 128.3 (d), 127.7 (d), 127.1 (d), 116.8−116.6 (t), 116.0−115.6 (t), 113.6 (d), 79.4−79.1 (s), 78.3 (d), 69.7 (t), 55.1 (q), 53.3−52.8 (d), 46.5 (t), 41.5−41.2 (t), 38.2−37.5 (t), 28.3 (q); MS (EI, 70 eV) *m*/*z* 352 (1), 332 (1), 310 (MH^+-allyl-Boc, 7), 274 (1), 261 (9), 232 (5), 218 (14), 204 (4), 188 (2), 174 (5), 160 (16), 156 (15), 137 (4), 121 (100), 112 (20), 104 (3), 91 (4), 57 (11); HRMS (IC^+, CH_4) calcd for $C_{28}H_{38}NO_4$ (MH^+) *m*/*z* 452.2801, found 452.2805.

***tert*-Butyl (2*R*)-2-{(2*R*)-2-[(4-Methoxybenzyl)oxy]-2-phenylethyl}-1,2,3,6-tetrahydropyridine-1-carboxylate (+)-9.** To a solution of (+)-**8** (1.52 g, 3.4 mmol, 1 equiv) in anhydrous benzene (37 mL) was added a solution of $\mathbf{G_1}$ (0.14 g, 0.2 mmol, 0.05 equiv) in benzene (3.5 mL) over 4 h at room temperature. The mixture was stirred for 12 h at room temperature and was then concentrated in vacuo. The crude residue was purified on silica gel (Et_2O/petroleum ether, 1/9 to 3/7) to afford (+)-**9** (1.34 g, 3.2 mmol, 94%): R_f = 0.51 (Et_2O/petroleum ether, 3/7); $[\alpha]^{20}_D$ = +27.1 (*c* 1.0, C_6H_6); IR (neat) 1700, 1610, 1585 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.43−7.28 (m, 5H), 7.27−7.19 (m, 2H), 6.92−6.85 (m, 2H), 5.73−5.53 (m, 2H), 4.61 (br s, 1H), 4.35 (d syst AB, 1H, *J* = 11.4 Hz), 4.35−4.21 (m, 2H), 4.18 (d syst AB, 1H, *J* = 11.4 Hz), 3.82 (s, 3H), 3.54 (br m, 1H), 2.32 (m, 1H), 2.16 (m, 1H), 1.88−1.63 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (75.5 MHz) δ (ppm) 158.9 (s), 154.7 (s), 142.3 (br s), 130.5 (s), 129.2 (d), 128.3 (d), 127.5 (d), 126.8 (d), 123.6 (d), 122.6 (d), 113.6 (d), 79.3 (s), 78.7 (d), 69.7 (t), 55.1 (q), 45.8−45.1 (br d), 40.4 (t), 39.9 (t), 28.32 (q), 28.3 (t); MS (EI, 70 eV) *m*/*z* 322 (M − Boc, 1), 302 (2), 287 (2), 231 (50), 202 (13), 184 (9), 170 (2), 158 (2), 137 (15), 127 (22), 126 (44), 121 (100), 105 (8), 91 (6), 82 (60), 57 (27). Anal. Calcd for $C_{26}H_{33}NO_4$: C, 73.73; H, 7.85; N, 3.31. Found: C, 73.72; H, 7.99; N, 3.19.

***tert*-Butyl (2*R*)-2-{(2*R*)-2-[(4-Methoxybenzyl)oxy]-2-phenylethyl}piperidine-1-carboxylate (+)-10.** To a solution of (+)-**9** (1.34 g, 3.2 mmol, 1 equiv) in EtOAc (64 mL) was added PtO_2 (0.04 g, 0.2 mmol, 0.05 equiv). After 1 h under H_2 (1 atm), the mixture was filtered through Celite and concentrated in vacuo. The crude residue was purified on silica gel (Et_2O/petroleum ether, 1/9 to 3/7) to afford (+)-**10** (1.62 g, 3.0 mmol, 94%) as a yellow oil: R_f = 0.51 (Et_2O/petroleum ether, 3/7); $[\alpha]^{20}_D$ = +68.6 (*c* 1.2, C_6H_6); IR (neat) 1685, 1610, 1585 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.41−7.27 (m, 5H), 7.26−7.20 (m, 2H), 6.90−6.84 (m, 2H), 4.34 (d syst AB, 1H, *J* = 11.0 Hz), 4.45−4.26 (m, 2H), 4.16 (d syst AB, 1H, *J* = 11.0 Hz), 3.98 (m, 1H), 3.81 (s, 3H), 2.85 (m, 1H), 2.23 (m, 1H), 1.84 (m, 1H), 1.65−1.30 (m, 6H), 1.46 (s, 9H); ^{13}C NMR (75.5 MHz) δ (ppm) 158.9 (s), 154.9 (s), 142.3 (s), 130.6 (s), 129.2 (d), 128.3 (d), 127.5 (d), 126.9 (d), 113.6 (d), 79.0 (s), 78.7 (d), 69.7 (t), 55.1 (q), 47.7 (d), 39.0 (t), 38.5 (t), 28.3 (q), 27.9 (t), 25.5 (t), 18.9 (t); MS (EI, 70 eV) *m*/*z* 324 (M − Boc, 1), 289 (3), 233 (33), 206 (2), 204 (5), 189 (5), 186 (4), 184 (3), 172 (3), 160 (3), 137 (8), 128 (100), 121 (63), 104 (4), 84 (81), 77 (6), 57 (17); HRMS (IC^+, CH_4) calcd for $C_{26}H_{36}NO_4$ (MH^+) *m*/*z* 426.2644, found 426.2643.

***tert*-Butyl (2*R*)-2-((2*R*)-2-Hydroxy-2-phenylethyl)piperidine-1-carboxylate (+)-11.** To a solution of (+)-**10** (1.12 g, 2.6 mmol, 1 equiv) in a mixture of CH_2Cl_2 and H_2O (18/1) (43.3 mL) was added DDQ (0.66 g, 2.9 mmol, 1.1 equiv). After 15 min, the reaction mixture was quenched with an aqueous saturated $NaHCO_3$ solution (3.5 mL). The mixture was diluted with water (25 mL) and CH_2Cl_2 (40 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (CH_2Cl_2/Et_2O, 30/1 to 30/10) to afford (+)-**11** as a white solid (0.61 g, 2.0 mmol, 75%) and (+)-**10** (0.17 g, 0.39 mmol, 15%). (+)-**11**: R_f = 0.09 (CH_2Cl_2/Et_2O, 30/1); $[\alpha]^{20}_D$ = +121.1 (*c* 1.2, C_6H_6); mp = 59−61 °C; IR (neat) 3390, 1670 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.41−7.21 (m, 5H), 4.75 (br m, 1H), 4.40 (br m, 1H), 4.04−3.73 (br m, 2H), 2.78 (br m, 1H), 2.10 (m, 1H), 1.87 (m, 1H), 1.71−1.51 (6H), 1.46 (s, 9H); ^{13}C NMR (75.5 MHz) δ (ppm) 155.4 (br s), 144.6 (br s), 128.2 (d), 127.1 (d), 125.6 (d), 79.6 (s), 72.5 (d), 48.4 (br d), 40.2 (br t), 39.3 (br t), 29.1 (br t), 28.3 (q), 25.3 (t), 19.0 (t); MS (EI, 70 eV) *m*/*z* 305 (M, 1), 249 (4), 230 (4), 202 (32), 186 (5), 184 (7), 128 (100), 120 (4), 105 (23), 84 (80), 79 (6), 57 (41). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.66; H, 9.07; N, 4.55.

(2*R*)-2-((2*R*)-2-Hydroxy-2-phenylethyl)-1-methylpiperidine (+)-Sedamine. To a mixture of $LiAlH_4$ (0.17 g, 4.35 mmol, 5.2 equiv) in THF (11 mL) was added dropwise a solution of (+)-**11** (0.26 g, 0.84 mmol, 1 equiv) in THF (11 mL). After 6 h under reflux, the reaction mixture was quenched by addition of H_2O (0.17 mL), followed by the addition of a 15% aqueous NaOH solution (0.17 mL) and water (0.34 mL). The mixture was filtered through Celite, and the filtrate was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (CH_2Cl_2/MeOH, 12/1 to 0/1) to afford (+)-sedamine (0.15 g, 0.68 mol, 78%). The product was crystallized in pentane at 0 °C to afford white crystals; their spectral and physical data were in accordance with the literature data:[6] R_f = 0.07 (CH_2Cl_2/Et_2O, 30/1); $[\alpha]^{20}_D$ = +87.0 (*c* 1.1, EtOH) {lit.[6i] $[\alpha]^{20}_D$ = +88.4 (*c* 1.1, EtOH)}; mp = 54−56 °C {lit.[6i] mp = 59−61 °C}; IR (KBr) 3533, 3467, 1604 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.45−7.21 (m, 5H), 6.47 (br s, 1H), 4.92 (dd, 1H, *J* = 10.7, *J* = 2.6 Hz), 3.10 (m, 1H), 2.89 (m, 1H), 2.57 (m, 1H), 2.51 (s, 3H), 2.14 (m, 1H), 1.85−1.22 (m, 7H); ^{13}C NMR (75.5 MHz) δ (ppm) 145.5 (s), 128.1 (d), 126.9 (d), 125.4 (d), 74.7 (d), 60.8 (d), 51.0 (t), 39.8 (q), 39.6 (t), 25.5 (t), 22.2 (t), 20.3 (t); MS (EI, 70 eV) *m*/*z* 219 (M, 2), 198 (1), 176 (1), 144 (1), 128 (1), 120 (1), 112 (2), 105 (2), 98 (100), 91 (2), 84 (1), 79 (4), 77 (5), 70 (8), 55 (1). Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.65; H, 9.71; N, 6.26.

2-[2-(Benzyloxy)-2-phenylethyl]-1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridine 12. Compound **12** was synthesized with an analogous strategy as for (+)-**9**: R_f = 0.35 (pentane/EtOAc, 95/5); IR (neat) 3330, 1740, 1690 cm^{-1}; ^1H NMR (300 MHz) (2 diastereomers) δ (ppm) 7.49−7.25 (m, 10H), 5.80−5.52 (m, 2H), 5.05−4.10 (m, 3H), 4.44 (d syst AB, 1H, *J* = 11.8 Hz), 4.27 (d syst AB, 1H, *J* = 11.8 Hz), 3.77−3.38 (m, 1H), 2.64−1.72 (m, 4H), 1.60−1.40 (m, 9H); ^{13}C NMR (75.5 MHz) (2 diastereomers) δ (ppm) 155.4 (s), 143.0 (br s), 139.1 (s), 129.2 (d), 129.1 (d), 128.3 (d), 128.0 (d), 127.5 (d), 127.1 (d), 124.3 (br d), 123.7 (br d), 123.4 (br d), 80.0 (s), 79.5 (br d), 71.9 (br t), 71.3 (br t), 70.9 (br t), 46.9 (br d), 46.0 (br d), 41.2 (t), 40.7 (t), 39.9 (t), 30.3 (t), 30.1 (t), 29.1 (q); MS (EI, 70 eV) *m*/*z* 320 (M − *t*BuO, 1), 292 (8), 213 (17), 229 (47), 202 (17), 184 (15), 172 (6), 158 (5), 140 (1), 126 (43), 104 (19), 91 (100), 82 (69), 77 (7), 65 (6), 57 (40).

1-(*tert*-Butoxycarbonyl)-2-(2-phenylmethyl)piperidine 13. Method A. To a solution of **12** (0.09 g, 0.24 mmol, 1 equiv) in a mixture of EtOAc and MeOH (4/1) (2 mL) was added 20% $Pd(OH)_2$ (0.01 g, 0.02 mmol, 0.07 equiv). After 1 h under H_2 (1 atm) at room temperature, the reaction mixture was filtered through Celite and concentrated in vacuo to afford **13** (0.06 g, 0.22 mmol, 94%). **Method B.** To a solution of **12** (0.10 g, 0.26 mmol, 1 equiv) in EtOAc (5 mL) was added 10% Pd/C (0.02 g, 0.02 mmol, 0.07 equiv). After 1 h under H_2 (1 atm) at room temperature, the reaction mixture was filtered through Celite and concentrated in vacuo to afford **13** (0.08 g, 0.29 mmol, quantitative yield): R_f = 0.55 (pentane/EtOAc, 95/5); IR (neat) 1690 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.35−7.15 (m, 5H), 4.32 (br m, 1H), 4.04 (m, 1H), 2.82 (m, 1H), 2.71−2.47 (m, 2H), 2.03 (m, 1H), 1.82−1.52 (m, 7H), 1.47 (s, 9H); ^{13}C NMR (75.5 MHz) δ (ppm) 155.1 (s), 142.1 (s), 128.3 (d), 128.2 (d), 125.6 (d), 79.0 (s), 50.2 (d), 38.7 (br t), 32.7 (t), 31.8 (t), 28.4 (t), 28.4 (q), 25.5 (t), 18.9 (t); MS (EI, 70 eV) *m*/*z* 289 (M, 1), 233 (17), 216 (4), 188 (2), 184 (8), 160 (1), 144 (1), 128 (100), 117 (3), 112 (2), 105 (3), 91 (16), 84 (52), 77 (2), 65 (2), 57 (25).

(1*R*)-1-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol[14] (+)-15. Allylmagnesium chloride (5.0 mL, 2 M in Et_2O, 10.0 mmol, 1.1 equiv) was added at 0 °C to a mixture of cyclopentadienyl[(4*S*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*′]titanium chloride (7.27 g, 11.9 mmol, 1.3 equiv) in anhydrous Et_2O (145 mL). After 2 h at 0 °C, the orange reaction mixture was cooled to −78 °C, and a solution of **14** (1.19 g, 9.1 mmol, 1 equiv) in Et_2O (12 mL) was added dropwise. After 4 h at −78 °C, the reaction

was quenched by addition of a 45% aqueous NH_4F solution (48 mL). The mixture was stirred overnight at room temperature and then filtered through Celite (Et_2O, 500 mL). The organic phase was washed with brine (350 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was diluted in pentane (150 mL) and filtered to afford (*S*,*S*)-taddol (4.04 g, 8.7 mmol, 73%). The organic layer was concentrated in vacuo and the crude residue was purified on silica gel (pentane/Et_2O, 8/2 to 1/1) to afford (+)-**15** (1.35 g, 7.85 mmol, 86%). The spectral and physical data are in accordance with the literature data:[14] R_f = 0.76 (pentane/Et_2O, 1/2); $[\alpha]^{20}_D$ = +14.2 (*c* 1.0, $CHCl_3$) {lit.[23] $[\alpha]^{20}_D$ = +12.7 (*c* 1.5, $CHCl_3$)}; IR (neat) 3430, 1640, 1210 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 5.85 (m, 1H), 5.18−5.06 (m, 2H), 4.06−3.93 (m, 2H), 3.73 (m, 1H), 3.58 (m, 1H), 2.39 (br s, 1H), 2.26−2.18 (m, 2H), 1.42 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75.5 MHz) δ (ppm) 133.9 (d), 117.7 (t), 109.2 (s), 78.3 (d), 71.4 (d), 65.9 (t), 38.1 (t), 26.4 (q), 25.2 (q); MS (EI, 70 eV) *m*/*z* 157 (M − Me, 74), 131 (14), 115 (4), 103 (2), 101 (100), 97 (12), 83 (9), 79 (9), 73 (23), 72 (11), 67 (4), 61 (11), 59 (43), 55 (23). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.86; H, 9.43.

(4*R*)-4-[(1*R*)-1(Benzyloxy)but-3-enyl]-2,2-dimethyl-1,3-dioxolane (+)-16. To a solution of (+)-**15** (1.33 g, 7.7 mmol, 1 equiv) in THF (10 mL) at 0 °C was added *t*-BuOK (1.21 g, 10.8 mmol, 1.4 equiv). After 5 min at 0 °C, benzyl bromide (1.10 mL, 1.59 g, 9.3 mmol, 1.2 equiv) was added dropwise. The mixture was stirred for 2.5 h at room temperature, and then the reaction was quenched by addition of a 20% aqueous NH_4Cl solution (57 mL). The aqueous phase was extracted with EtOAc (3 × 115 mL), the organic layer was washed with water (85 mL) and brine (85 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (Et_2O/petroleum ether, 5/95 to 20/80) to afford (+)-**16** (1.84 g, 7.0 mmol, 91%): R_f = 0.77 (Et_2O/petroleum ether, 2/1); $[\alpha]^{20}_D$ = +13.9 (*c* 1.1, $CHCl_3$); IR (neat) 1640, 1210 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.45−7.25 (m, 5H), 5.91 (m, 1H), 5.19−5.06 (m, 2H), 4.75 (d syst AB, 1H, *J* = 11.8 Hz), 4.69 (d syst AB, 1H, *J* = 11.8 Hz), 4.24 (ddd, 1H, *J* = 7.4, *J* = 6.6, *J* = 6.2 Hz), 4.01 (dd, 1H, *J* = 8.1, *J* = 6.6 Hz), 3.73 (dd, 1H, *J* = 8.1, *J* = 7.4 Hz), 3.53 (m, 1H), 2.41−2.18 (m, 2H), 1.46 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75.5 MHz) δ (ppm) 138.5 (s), 134.4 (d), 128.2 (d), 127.7 (d), 127.4 (d), 117.1 (t), 109.2 (s), 79.2 (d), 77.8 (d), 72.4 (t), 65.7 (t), 35.2 (t), 26.4 (q), 25.3 (q); MS (EI, 70 eV) *m*/*z* 262 (1), 247 (5), 221 (6), 204 (4), 163 (15), 161 (6), 145 (3), 134 (2), 117 (4), 115 (2), 105 (2), 101 (19), 91 (100), 79 (2), 77 (2), 65 (6), 59 (3). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.32; H, 8.54.

(4*R*)-4-(Benzyloxy)-4-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)butan-1-ol (+)-17. To a solution of (+)-**16** (1.63 g, 6.21 mmol, 1 equiv) in THF (15 mL) at 0 °C was added dropwise BH_3 (6.21 mL, 1 M in THF, 6.21 mmol, 1 equiv). After 2 h at room temperature, the reaction mixture was cooled to 0 °C, and water (0.7 mL), 3 M aqueous NaOH (2.2 mL) and 30% aqueous H_2O_2 (1.5 mL) were successively added. The mixture was stirred for 2.3 h at room temperature and was then diluted with water (62 mL). The pH was adjusted to 6−7 with 10% aqueous HCl. The aqueous phase was extracted with ether (3 × 240 mL), and the combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (155 mL) and brine (155 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (Et_2O/petroleum ether, 40/60 to 70/30) to afford (+)-**17** (1.45 g, 5.2 mmol, 83%). The spectral and physical data are in accordance with the literature data:[24] R_f = 0.64 (Et_2O/petroleum ether, 95/5); $[\alpha]^{20}_D$ = +41.2 (*c* 2.0, $CHCl_3$) {lit.[24] $[\alpha]^{20}_D$ = −42.5 (*c* 1.1, $CHCl_3$) for (−)-**17**}; IR (neat) 3405, 1210 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.41−7.23 (m, 5H), 4.81 (d syst AB, 1H, *J* = 11.8 Hz), 4.63 (d syst AB, 1H, *J* = 11.8 Hz), 4.24 (ddd, 1H, *J* = 7.4, *J* = 6.6, *J* = 6.2 Hz), 4.00 (dd, 1H, *J* = 8.1, *J* = 6.6 Hz), 3.69 (dd, 1H, *J* = 8.1, *J* = 7.4 Hz), 3.62−3.54 (m, 2H), 3.48 (m, 1H), 2.11 (br s, 1H), 1.81−1.47 (m, 4H), 1.45 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75.5 MHz) δ (ppm) 138.4 (s), 128.2 (d), 127.9 (d), 127.5 (d), 109.3 (s), 79.4 (d), 78.2 (d), 72.7 (t), 65.8 (t), 62.4 (t), 28.6 (t), 27.0 (t), 26.4 (q), 25.3 (q); MS (EI, 70 eV) *m*/*z* 281 (M+1, 1), 265 (M − Me, 2), 179 (8), 160 (2), 157 (2), 134 (2), 107 (2), 101 (18), 91 (100), 79 (2), 71 (22), 65 (5), 59 (3); HRMS (CI^+, CH_4) calcd for $C_{16}H_{25}O_4$ (MH^+) *m*/*z* 281.1753, found 281.1745.

(4*R*)-4-(Benzyloxy)-4-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)butanal 18. To a solution of oxalyl chloride (0.99 mL, 1.44 g, 11.4 mmol, 2.2 equiv) in CH_2Cl_2 (79 mL) at −78 °C was added dropwise DMSO (1.03 mL, 1.13 g, 14.5 mmol, 2.8 equiv). After 30 min at −78 °C, a solution of (+)-**17** (1.45 g, 5.2 mmol, 1 equiv) in CH_2Cl_2 (19 mL) was added. After 20 min at −78 °C, Et_3N (3.5 mL) was added, and the mixture was stirred for 15 min at −78 °C and 10 min at 0 °C. The mixture was then diluted with pentane (20 mL) and brine (20 mL). The aqueous phase was extracted with pentane (3 × 235 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude residue was diluted in pentane, filtered on paper, and concentrated in vacuo to afford **18** (1.44 g, 5.2 mmol, quantitative yield) as a yellow oil: R_f = 0.86 (Et_2O/petroleum ether, 9/1); IR (neat) 1720, 1210 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 9.67 (t, 1H, *J* = 1.5 Hz), 7.40−7.22 (m, 5H), 4.76 (d syst AB, 1H, *J* = 11.8 Hz), 4.55 (d syst AB, 1H, *J* = 11.8 Hz), 4.20 (ddd, 1H, *J* = 7.4, *J* = 6.6, *J* = 6.2 Hz), 4.00 (dd, 1H, *J* = 8.1, *J* = 6.6 Hz), 3.73 (dd, *J* = 8.1, *J* = 7.4 Hz), 3.46 (m, 1H), 2.64−2.40 (m, 2H), 1.85−1.61 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75.5 MHz) δ (ppm) 201.7 (d), 138.2 (s), 128.2 (d), 128.0 (d), 127.6 (d), 109.3 (s), 78.4 (d), 78.2 (d), 72.7 (t), 65.7 (t), 39.8 (t), 26.4 (q), 25.2 (q), 23.1 (t); MS (EI, 70 eV) *m*/*z* 278 (M, 1), 263 (M − Me, 3), 245 (1), 220 (1), 202 (2), 177 (20), 157 (1), 134 (5), 129 (1), 116 (1), 107 (2), 101 (27), 91 (100), 83 (3), 73 (6), 65 (7), 59 (4).

(4*R*,7*R*)-7-(Benzyloxy)-7-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-1-en-4-ol (+)-19. Allylmagnesium chloride (2.84 mL, 2 M in THF, 5.7 mmol, 1.1 equiv) was added at 0 °C to a mixture of cyclopentadienyl[(4*R*,*trans*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-*O*,*O*′]titanium chloride (4.12 g, 6.7 mmol, 1.3 equiv) in anhydrous diethyl ether (88 mL). After 2 h at 0 °C, the orange reaction mixture was cooled to −78 °C, and a solution of **18** (1.44 g, 5.2 mmol, 1 equiv) in Et_2O (19 mL) was added dropwise. The mixture was stirred 3 h at −78 °C, and the reaction was quenched by addition of a 45% aqueous NH_4F solution (30 mL). The mixture was stirred overnight at room temperature and filtered through Celite (Et_2O, 290 mL), and the filtrate was washed with brine (250 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was diluted with pentane (100 mL) and filtered to afford (*R*,*R*)-taddol (2.79 g, 6.0 mmol, 89%). The filtrate was concentrated in vacuo, and the crude residue was purified on silica gel (Et_2O/petroleum ether, 2/8 to 7/3 to afford (+)-**19** (1.348 g, 4.2 mmol, 81%): R_f = 0.31 (Et_2O/petroleum ether, 6/4); $[\alpha]^{20}_D$ = +48.1 (*c* 1.1, $CHCl_3$); IR (neat) 3440, 1640, 1215 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.44−7.23 (m, 5H), 5.79 (m, 1H), 5.13 (m, 1H), 5.08 (m, 1H), 4.79 (d syst AB, 1H, *J* = 11.8 Hz), 4.63 (d syst AB, 1H, *J* = 11.8 Hz), 4.23 (ddd, 1H, *J* = 7.7, *J* = 6.6, *J* = 6.3 Hz), 3.99 (dd, 1H, *J* = 8.1, *J* = 6.6 Hz), 3.69 (dd, 1H, *J* = 8.1, *J* = 7.7 Hz), 3.54 (m, 1H), 3.46 (m, 1H), 2.30−2.05 (m, 3H), 1.62−1.49 (m, 4H), 1.45 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75.5 MHz) δ (ppm) 138.5 (s), 134.7 (d), 128.2 (d), 128.0 (d), 127.5 (d), 117.7 (t), 109.2 (s), 79.1 (d), 78.3 (d), 72.6 (t), 70.1 (d), 65.8 (t), 41.9 (t), 32.2 (t), 26.5 (q), 26.4 (t), 25.3 (q); MS (EI, 70 eV) *m*/*z* 305 (M − Me, 1), 279 (7), 262 (1), 203 (1), 183 (2), 171 (3), 157 (1), 141 (2), 129 (2), 117 (3), 111 (20), 101 (13), 91 (100), 83 (2), 73 (4), 65 (4). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.04; H, 8.99.

(4*R*)-4-[(1*R*,4*S*)-4-Azido-1-(benzyloxy)hept-6-enyl]-2,2-dimethyl-1,3-dioxolane 20. To a solution of (+)-**19** (1.348 g, 4.2 mmol, 1 equiv) in THF (50 mL) at 0 °C, was added PPh_3 (1.21 g, 4.6 mmol, 1.1 equiv). DEAD (0.73 mL, 0.81 g, 4.6 mmol, 1.1 equiv) and DPPA (1.0 mL, 1.27 g, 4.6 mmol, 1.1 equiv) were added dropwise, and the mixture was allowed to warm slowly to room temperature with stirring for 12 h. The solution was concentrated in vacuo, and the crude residue was purified on silica gel (Et_2O/petroleum ether, 2/8 to 1/1) to afford a mixture

(23) Mulzer, J.; Angermann, A. Münch, W. *Liebigs Ann. Chem*. **1986**, 825.

(24) Miyazaki, H.; Nakamura, N.; Ito, T.; Sada, T., Oshima, T.; Koike, H. *Chem. Pharm. Bull.* **1989**, *37*, 2391.

of **20** and DPPA (1.749 g): R_f = 0.84 (Et_2O/petroleum ether, 6/4); ^1H NMR (300 MHz) δ (ppm) 7.48−7.20 (m, 5H), 5.80 (m, 1H), 5.22−5.09 (m, 2H), 4.80 (d syst AB, 1H, J = 11.8 Hz), 4.62 (d syst AB, 1H, J = 11.8 Hz), 4.24 (ddd, 1H, J = 7.4, J = 6.6, J = 6.2 Hz), 4.02 (dd, 1H, J = 8.5, J = 6.6 Hz), 3.74 (dd, 1H, J = 8.5, J = 7.4 Hz), 3.46 (m, 1H), 3.31 (m, 1H), 2.30 (m, 1H), 1.86−1.50 (m, 4H), 1.48 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (75.5 MHz) δ (ppm) 138.4 (s), 133.6 (d), 128.2 (d), 127.9 (d), 127.6 (d), 118.1 (t), 109.3 (s), 79.4 (d), 78.1 (d), 72.8 (t), 65.7 (t), 62.3 (d), 38.7 (t), 30.1 (t), 27.2 (t), 26.4 (q), 25.2 (q); MS (EI, 70 eV) *m*/*z* 330 (M − Me, 1), 318 (4), 276 (1), 216 (5), 176 (3), 170 (3), 131 (4), 110 (2), 101 (18), 91 (100), 77 (2), 67 (2), 59 (2), 55 (2); HRMS (CI^+, CH_4) calcd for $C_{19}H_{28}N_3O_3$ (MH^+) *m*/*z* 346.2131, found 346.2137.

(4*S*,7*R*)-7-(Benzyloxy)-7-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)hept-1-en-4-amine (+)-21. To a mixture of $LiAlH_4$ (0.08 g, 2.0 mmol, 3 equiv) in Et_2O (5 mL) at 0 °C was added dropwise a solution of **20** (0.23 g of crude) in Et_2O (5 mL). After 1 h at 0 °C and 1 h at room temperature, the reaction was quenched by addition of water (0.16 mL), followed by the addition of a 15% aqueous NaOH solution (0.16 mL) and water (0.32 mL). The mixture was diluted with EtOAc (15 mL) and water (15 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (CH_2Cl_2/MeOH, 98/2 to 0/1) to afford (+)-**21** (0.09 g, 0.27 mmol, 41% from (+)-**19**): R_f = 0.02 (CH_2Cl_2/MeOH, 95/5); $[\alpha]^{20}_D$ = +27.6 (*c* 1.5, $CHCl_3$); IR (neat) 3350, 1640, 1210 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.39−7.23 (m, 5H), 5.75 (m, 1H), 5.14−5.01 (m, 2H), 4.77 (d syst AB, 1H, J = 11.6 Hz), 4.60 (d syst AB, 1H, J = 11.6 Hz), 4.21 (ddd, 1H, J = 7.3, J = 6.6, J = 6.3 Hz), 3.99 (dd, 1H, J = 8.1, J = 6.6 Hz), 3.69 (dd, 1H, J = 8.1, J = 7.3 Hz), 3.42 (m, 1H), 2.73 (m, 1H), 2.21 (m, 1H), 2.10−1.45 (m, 7H), 1.44 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75.5 MHz) δ (ppm) 138.5 (s), 135.3 (d), 128.2 (d), 127.9 (d), 127.5 (d), 117.4 (t), 109.2 (s), 79.8 (d), 78.2 (d), 72.8 (t), 65.8 (t), 50.5 (d), 42.2 (t), 33.3 (t), 27.3 (t), 26.4 (q), 25.2 (q); MS (EI, 70 eV) *m*/*z* 320 (M + 1, 1), 304 (M − Me, 6), 278 (30), 228 (2), 220 (28), 218 (14), 196 (3), 172 (4), 153 (3), 110 (19), 101 (6), 91 (100), 70 (14), 65 (5), 56 (6).

(2*R*,3*R*,6*S*)-6-Azido-3-(benzyloxy)-non-8-ene-1,2-diol (−)-23. A solution of the crude **20** (1.749 g) in AcOH/H_2O (4/1) (10 mL) was stirred 7 h at room temperature. The reaction mixture was then concentrated in vacuo, diluted with EtOAc (200 mL) and washed with water (10 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (Et_2O/petroleum ether, 5/5 to 1/0) to provide (−)-**23** (0.976 g, 3.20 mmol, 76% from (+)-**19**) as a viscous oil: R_f = 0.1 (Et_2O/petroleum ether, 6/4); $[\alpha]^{20}_D$ = −40.1 (*c* 1.0, $CHCl_3$); IR (neat) 3390, 2100, 1640 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.44−7.25 (m, 5H), 5.80 (m, 1H), 5.22−5.10 (m, 2H), 4.63 (d syst AB, 1H, J = 11.4 Hz), 4.52 (d syst AB, 1H, J = 11.4 Hz), 3.77−3.55 (m, 3H), 3.49 (m, 1H), 3.33 (m, 1H), 3.09 (br s, 1H), 2.89 (br s, 1H), 2.36−2.26 (m, 2H), 1.85 (m, 1H), 1.71−1.46 (m, 3H); ^{13}C NMR (75.5 MHz) δ (ppm) 137.7 (s), 133.5 (d), 128.5 (d), 127.9 (d), 118.3 (t), 79.0 (d), 72.7 (d), 72.3 (t), 63.7 (t), 62.1 (d), 38.6 (t), 29.2 (t), 26.4 (t); MS (CI^+, CH_4) *m*/*z* 306 (M+1, 50), 278 (100), 260 (35), 245 (13), 216 (16), 209 (27), 198 (10), 170 (46), 152 (19), 131 (49), 119 (26), 106 (14); HRMS (CI^+, CH_4) calcd for $C_{16}H_{24}NO_3$ (MH^+-N_2) *m*/*z* 278.1756, found 278.1759.

(2*R*,3*R*,6*S*)-6-Azido-3-(benzyloxy)-1-[(*tert*-butyldiphenylsilyl)oxy]non-8-en-2-ol (−)-24. To a solution of (−)-**23** (0.860 g, 2.8 mmol, 1 equiv) and imidazole (0.25 g, 3.7 mmol, 1.3 equiv) in CH_2Cl_2 (3.5 mL) at 0 °C was added dopwise TBDPSCl (0.73 mL, 0.775 g, 2.8 mmol, 1 equiv). The reaction mixture was stirred overnight at room temperature and quenched with a saturated aqueous $NaHCO_3$ solution (4.2 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 21 mL), and the combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (Et_2O/petroleum ether, 5/95 to 3/7) to give (−)-**24** (1.47 g, 2.7 mmol, 96%) as a colorless oil: R_f = 0.78 (Et_2O/petroleum ether, 6/4); $[\alpha]^{20}_D$ = −11.3 (*c* 1.1, $CHCl_3$); IR (neat) 3430, 2080, 1635, 1585 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ (ppm) 7.81−7.68 (m, 4H), 7.26−7.04 (m, 11H), 5.60 (m, 1H), 5.03−4.91 (m, 2H), 4.41 (d syst AB, 1H, J = 11.4 Hz), 4.36 (d syst AB, 1H, J = 11.4 Hz), 3.83−3.78 (m, 2H), 3.73 (m, 1H), 3.55 (m, 1H) 2.92 (m, 1H), 2.40 (d, 1H, J = 5.9 Hz), 2.09−1.87 (m, 2H), 1.76 (m, 1H), 1.55−1.25 (m, 3H) 1.14 (s, 9H); ^{13}C NMR (75.5 MHz, C_6D_6) δ (ppm) 139.5 (s), 136.5 (d), 136.4 (d), 134.6 (d), 134.2 (s), 130.6 (d), 129.1 (d), 128.7 (d), 128.2 (d), 118.6 (t), 79.3 (d), 73.8 (d), 73.1 (t), 65.7 (t), 62.8 (d), 39.4 (t), 30.6 (t), 27.6 (q), 27.5 (t), 19.9 (s); MS (EI, 70 eV) *m*/*z* 441 (2), 420 (1), 390 (4), 333 (18), 309 (3), 289 (3), 273 (9), 267 (8), 259 (4), 253 (4), 207 (4), 199 (22), 177 (14), 163 (6), 135 (10), 121 (98), 105 (5), 91 (100), 69 (7); HRMS (CI^+, CH_4) calcd for $C_{32}H_{42}NSiO_3$ ($MH^+ - N_2$) *m*/*z* 516.2934, found 516.2936.

(4*S*,7*R*,8*R*)-4-Azido-7-(benzyloxy)-9-[(*tert*-butyldiphenylsilyl)oxy]-8-[(methylsulfonyl)oxy]non-1-ene (+)-25. To a solution of (−)-**24** (1.46 g, 2.7 mmol, 1 equiv) and DMAP (49 mg, 0.4 mmol, 0.15 eq) in pyridine (5.3 mL) at 0 °C was added dropwise MsCl (0.31 mL, 0.43 g, 4.0 mmol, 1.5 equiv). After 1.5 h at 0 °C and 1 h at room temperature, the reaction mixture was diluted with Et_2O (42 mL) and washed with water (42 mL), an aqueous saturated solution of $CuSO_4$ (42 mL) and water (17.5 mL). The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (Et_2O/petroleum ether, 2/8) to give (+)-**25** (1.63 g, 2.6 mmol, 98%) as a viscous oil: R_f = 0.55 (Et_2O/petroleum ether, 4/6); $[\alpha]^{20}_D$ = +1.5 (*c* 1.1, $CHCl_3$); IR (neat) 2100, 1640, 1585, 1350, 1175 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.76−7.68 (m, 4H), 7.53−7.29 (m, 12H), 5.79 (m, 1H), 5.22−5.10 (m, 2H), 4.77 (m, 1H), 4.63 (d syst AB, 1H, J = 11.4 Hz), 4.57 (d syst AB, 1H, J = 11.4 Hz), 4.02 (dd, 1H, J = 11.8, J = 3.3 Hz), 3.94 (dd, 1H, J = 11.8, J = 6.2 Hz), 3.81 (m, 1H), 3.29 (m, 1H), 3.03 (s, 3H), 2.33−2.25 (m, 2H), 1.84 (m, 1H), 1.70−1.27 (m, 3H), 1.13 (s, 9H); ^{13}C NMR (75.5 MHz) δ (ppm) 137.9 (s), 135.9 (d), 135.8 (d), 133.9 (d), 133.0 (s), 132.8 (s), 130.4 (d), 130.3 (d), 128.8 (d), 128.5 (d), 128.3 (d), 128.2 (d), 118.7 (t), 84.0 (d), 77.8 (d), 73.3 (t), 63.1 (t), 62.3 (d), 39.0 (t), 38.7 (q), 30.0 (t), 27.1 (q), 26.6 (t), 19.5 (s); MS (CI^+, CH_4) *m*/*z* 622 (M + 1, 9), 594 (69), 552 (14), 526 (18), 498 (100), 486 (15), 420 (31), 390 (14), 330 (12), 315 (10), 257 (7), 179 (9), 107 (15); HRMS (CI^+, CH_4) calcd for $C_{33}H_{44}NSSiO_5$ ($MH^+ - N_2$) *m*/*z* 594.2709, found 594.2708.

(4*S*,7*R*,8*R*)-7-(Benzyloxy)-9-[(*tert*-butyldiphenylsilyl)-oxy]-8-[(methylsulfonyl)oxy]non-1-en-4-amine (+)-26. A solution of (+)-**25** (1.624 g, 2.62 mmol, 1 equiv) and PPh_3 (0.76 g, 2.9 mmol, 1.1 equiv) in THF/H_2O (9/1) (33 mL) was stirred for 12 h at 50 °C under Ar. The reaction mixture was then diluted with Et_2O (75 mL) and acidified with an aqueous 5% HCl solution (66 mL). The aqueous phase was extracted with Et_2O (3 × 75 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (CH_2Cl_2/MeOH/EtOAc, 90/5/5) to give (+)-**26** (1.38 g, 2.33 mmol, 89%) as a very viscous oil: R_f = 0.30 (CH_2Cl_2/MeOH/EtOAc, 8/1/1); $[\alpha]^{20}_D$ = +10.5 (*c* 1.0, $CHCl_3$); IR (neat) 3030, 1640, 1590, 1355, 1175 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.72−7.63 (m, 4H), 7.52−7.21 (m, 11H), 5.75 (m, 1H), 5.14−4.99 (m, 2H), 4.77 (m, 1H), 4.58 (s, 2H), 3.98 (dd, 1H, J = 11.8, J = 3.7 Hz), 3.92 (dd, 1H, J = 11.8, J = 6.2 Hz), 3.74 (m, 1H), 3.01 (s, 3H), 2.69 (m, 1H), 2.18 (m, 1H), 1.95 (m, 1H), 1.77 (m, 1H), 1.58−1.17 (m, 5H), 1.09 (s, 9H); ^{13}C NMR (75.5 MHz) δ (ppm) 137.6 (s), 135.5 (d), 135.3 (d), 134.3 (d), 132.6 (s), 132.4 (s), 129.9 (d), 128.3 (d), 128.0 (d), 127.9 (d), 127.8 (d), 118.1 (t), 83.5 (t), 77.6 (t), 72.7 (t), 62.7 (t), 50.7 (d), 40.9 (t), 38.3 (q), 31.7 (t), 26.7 (q), 26.1 (t), 19.0 (s); MS (EI, 70 eV) *m*/*z* 498 (1), 458 (44), 442 (23), 380 (26), 310 (3), 272 (5), 230 (100), 199 (26), 197 (14), 183 (7), 152 (7), 135 (24), 110 (19), 91 (99), 67 (9); HRMS (CI^+, CH_4) calcd for $C_{33}H_{46}NSSiO_5$ (MH^+) *m*/*z* 596.2866, found 596.2864.

(2*S*,3*R*,6*S*)-6-Allyl-3-(benzyloxy)-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}piperidine (−)-27. A mixture of (+)-**26** (1.30 g, 2.2 mmol, 1 equiv) and Et_3N (0.76 mL, 0.55 g, 5.5 mmol, 2.5 equiv) in MeOH (30 mL) was refluxed (75−80 °C) during 8 h. The solution was then concentrated in vacuo and the crude residue was purified on silica gel (EtOAc/hexanes, 1/10 to 2/10) to afford (−)-**27** (0.962 g, 1.9 mmol, 88%) as a colorless oil: R_f = 0.40 (EtOAc/petroleum ether, 2/8); $[\alpha]^{20}_D$

= −37.4 (*c* 1.0, $CHCl_3$); IR (neat) 3330, 1640, 1585 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.74−7.66 (m, 4H), 7.50−7.35 (m, 6H), 7.27−7.19 (m, 3H), 7.17−7.09 (m, 2H), 5.85 (m, 1H), 5.26−5.09 (m, 2H), 4.55 (d syst AB, 1H, J = 11.4 Hz), 4.30 (d syst AB, 1H, J = 11.4 Hz), 4.13 (dd, 1H, J = 9.6, J = 3.0 Hz), 3.65 (dd, 1H, J = 9.6, J = 8.8 Hz), 3.15 (ddd, 1H, J = 9.9, J = 9.2, J = 4.7 Hz), 2.80 (ddd, 1H, J = 9.2, J = 8.8, J = 3.0 Hz), 2.64 (m, 1H), 2.34−2.06 (m, 3H), 1.77 (m, 1H), 1.47−1.12 (m, 3H), 1.08 (s, 9H); ^{13}C NMR (75.5 MHz) δ (ppm) 138.4 (s), 135.5 (d), 135.4 (d), 133.5 (s), 133.4 (s), 129.5 (d), 128.1 (d), 127.5 (d), 127.4 (d), 127.3 (d), 117.4 (t), 76.3 (d), 70.4 (t), 65.3 (t), 62.4 (d), 54.6 (d), 40.8 (t), 31.2 (t), 30.0 (t), 26.7 (q), 19.2 (s); MS (EI, 70 eV) *m*/*z* 499 (M, 1), 484 (1), 458 (67), 442 (34), 380 (29), 334 (4), 310 (4), 292 (1), 272 (4), 230 (100), 211 (2), 199 (26), 197 (13), 135 (19), 110 (11), 91 (72); HRMS (CI^+, CH_4) calcd for $C_{32}H_{42}NSiO_2$ (MH^+) *m*/*z* 500.2985, found 500.2990.

(2*S*,3*R*,6*S*)-6-Allyl-3-(benzyloxy)-1-[(benzyloxy)carbonyl]-2-{[(*tert*-butyldiphenylsilyl)oxy]methyl}-piperidine (+)-30. To a solution of (−)-**27** (0.680 g, 1.4 mmol, 1 equiv) in CH_2Cl_2 (40 mL) was added dropwise a solution of Na_2CO_3 (0.30 g, 2.9 mmol, 2.1 equiv) in water (7.8 mL), and the mixture was cooled at 0 °C. Benzyl chloroformate (0.31 mL, 0.37 g, 2.2 mmol, 1.6 equiv) was added dropwise to this solution, and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and water (12 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 120 mL). The combined organic phases were washed with water (120 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (EtOAc/petroleum ether, 5/100 to 10/100) to afford (+)-**30** (0.860 g, 1.4 mmol, quantitative yield): R_f = 0.68 (EtOAc/petroleum ether, 2/8); $[\alpha]^{20}_D$ = +8.3 (*c* 1.1, $CHCl_3$); IR (neat) 1660, 1640 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.75−7.54 (m, 4H), 7.54−7.22 (m, 16H), 5.67 (m, 1H), 5.27−5.02 (m, 2H), 5.00−4.45 (m, 5H), 4.25 (m, 1H), 3.85 (m, 1H), 3.71 (m, 1H), 3.55 (m, 1H), 2.25−1.15 (m, 6H), 1.06 (s, 9H); ^{13}C NMR (75.5 MHz) δ (ppm) (rotamers) 156.1 (s), 138.5 (s), 136.9 (s), 135.5 (d), 132.9 (s), 129.7 (d), 128.3 (d), 128.2 (d), 127.6 (d), 127.3 (d), 116.8 (t), 70.7 (d), 70.0 (t), 66.8 (t), 63.9−63.5 (t), 55.9−55.5 (d), 49.6 (d), 39.5−39.0 (t), 26.7 (q), 20.1 (t), 19.2 (s), 19.1 (t); MS (EI, 70 eV) *m*/*z* 458 (63), 442 (31), 408 (2), 380 (30), 334 (12), 272 (4), 230 (100), 207 (20), 199 (25), 197 (12), 183 (9), 135 (21), 110 (14), 91 (89), 67 (9). Anal. Calcd for $C_{40}H_{47}NSiO_4$: C, 75.79; H, 7.47; N, 2.21. Found: C, 75.64; H, 7.46; N, 2.15.

12-((2*S*,5*R*,6*S*)-5-(Benzyloxy)-1-[(benzyloxy)carbonyl]-6-{[(*tert*-butyldiphenylsilyl)oxy]methyl}piperidin-2-yl)-dodec-10-en-3-one (+)-31. To a mixture of $\mathbf{G_2}$ (58 mg, 0.07 mmol, 0.05 equiv) in CH_2Cl_2 (9 mL) was added dropwise at room temperature a solution of (+)-**30** (0.860 g, 1.36 mmol, 1 equiv) and **28** (0.46 g, 2.72 mmol, 2 equiv) in CH_2Cl_2 (3 mL). The solution was stirred under Ar for 4 h at 50 °C and concentrated in vacuo. The crude residue was purified on silica gel (Et_2O/petroleum ether, 2/10 to 3/10) to afford (+)-**31** (0.61 g, 0.79 mmol, 58%) as a colorless oil: R_f = 0.25 (Et_2O/petroleum ether, 3/7); $[\alpha]^{20}_D$ = +8.9 (*c* 1.0, $CHCl_3$); IR (neat) 1690, 1585 cm^{-1}; ^1H NMR (300 MHz, $C_6D_5CD_3$, 363 K) δ (ppm) 7.76−7.63 (m, 4H), 7.28−6.98 (m, 16H), 5.32−5.19 (m, 2H), 5.11 (d syst AB, 1H, J = 12.7 Hz), 5.00 (d syst AB, 1H, J = 12.7 Hz), 4.91 (m, 1H), 4.54 (d syst AB, 1H, J = 12.1 Hz), 4.44 (d syst AB, 1H, J = 12.1 Hz), 4.32 (m, 1H), 3.92−3.80 (m, 2H), 3.71 (m, 1H), 2.21−1.70 (m, 10H), 1.64−1.37 (m, 4H), 1.31−1.01 (m, 6H), 1.10 (s, 9H), 0.91 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75.5 MHz, $C_6D_5CD_3$, 363 K) δ (ppm) 208.8 (s), 157.3 (s), 140.5 (s), 138.4 (s), 136.9 (d), 135.2 (s), 134.0 (d), 133.9 (d), 130.9 (d), 130.0 (d), 129.7 (d), 129.4 (d), 129.3 (d), 129.1 (d), 129.0 (d), 128.6 (d), 73.0 (d), 71.5 (t), 68.1 (t), 66.1 (t), 57.7 (d), 51.8 (d), 43.0 (t), 39.8 (t), 36.5 (t), 33.6 (t), 30.5 (t), 30.3 (t), 30.1 (t), 28.2 (q), 25.0 (t), 22.2 (t), 21.6 (t), 20.6 (s), 8.7 (q); MS (CI^+, NH_3) *m*/*z* 791 ($M + NH_3^+$, 1), 761 (1), 747 (1), 627 (10), 458 (100), 368 (5), 274 (37), 200 (37), 106 (51). Anal. Calcd for $C_{49}H_{63}NSiO_5$: C, 76.03; H, 8.20; N, 1.81. Found: C, 75.71; H, 8.42; N, 1.76.

12-((2*R*,5*R*,6*S*)-6-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-piperidin-2-yl)-5-hydroxydodecan-3-one (−)-32. To a solution of (+)-**31** (0.36 g, 0.47 mmol, 1 equiv) in MeOH/HCl (50/1, 8 mL) was added 10% Pd on carbon (50 mg, 0.05 mmol, 0.1 equiv). After 20 h under H_2 (1 atm) at room temperature, the reaction mixture was filtered through Celite and extracted with EtOAc (200 mL). The organic phase was washed with a saturated aqueous $NaHCO_3$ solution (3 × 50 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified on silica gel (EtOAc/petroleum ether, 3/10 to 6/10) to give (−)-**32** (0.155 g, 0.28 mmol, 60%): R_f = 0.15 (EtOAc/petroleum ether, 4/6); $[\alpha]^{20}_D$ = −1.5 (*c* 1.1, $CHCl_3$); IR (neat) 3405, 1710, 1585 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 7.71−7.58 (m, 4H), 7.45−7.28 (m, 6H), 3.95 (dd, 1H, J = 9.6, J = 5.5 Hz), 3.71 (dd, 1H, J = 9.6, J = 6.6 Hz), 3.38 (m, 1H), 2.64 (m, 1H), 2.48−2.23 (m, 6H), 2.01 (m, 1H), 1.69 (m, 1H), 1.54 (m, 2H), 1.42−1.14 (m, 16H), 1.10 (m, 1H), 1.05 (s, 9H), 1.03 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75.5 MHz) δ (ppm) 211.8 (s), 135.4 (d), 132.9 (s), 132.8 (s), 129.7 (d), 127.6 (d), 71.0 (d), 66.9 (t), 62.8 (d), 55.5 (d), 42.2 (t), 36.4 (t), 35.7 (t), 33.6 (t), 31.1 (t), 29.5 (t), 29.4 (t), 29.3 (t), 29.2 (t), 29.1 (t), 26.7 (q), 26.0 (t), 23.8 (t), 19.0 (s), 7.7 (q); MS (CI, CH_4) *m*/*z* 552 (MH^+, 56), 538 (65), 524 (37), 460 (17), 446 (11), 368 (5), 296 (16), 282 (27), 239 (37), 199 (58), 179 (100); HRMS (CI^+, CH_4) calcd for $C_{34}H_{54}NSiO_3$ (MH^+) *m*/*z* 552.3873, found 552.3868.

(−)-Prosophylline. To a solution of (−)-**32** (155 mg, 0.28 mmol, 1 equiv) in THF (15 mL) was added TBAF (0.56 mL, 1 M in THF, 0.56 mmol, 2 equiv), and after 20 h at room temperature, the reaction mixture was concentrated in vacuo. The crude residue was purified on silica gel (MeOH/CH_2Cl_2, 5/100 to 20/100) to afford (−)-prosophylline (79 mg, 0.25 mmol, 90%) as white crystals. Spectral and physical data are in accordance with the literature data:[7,10] R_f = 0.09 (CH_2Cl_2/MeOH, 10/2); $[\alpha]^{20}_D$ = −17.6 (*c* 1.5, MeOH) {lit.[10] $[\alpha]^{20}_D$ = −13.4 (*c* 1.5, MeOH)}; mp = 77−79 °C {lit.[10] mp = 75−76 °C}; IR (neat) 3300−3200, 1710 cm^{-1}; ^1H NMR (300 MHz) δ (ppm) 3.81 (m, 1H), 3.70 (m, 1H), 3.65−3.27 (m, 4H), 2.58−2.45 (m, 2H), 2.45−2.30 (m, 4H), 2.01 (m, 1H), 1.74 (m, 1H), 1.62−1.46 (m, 2H), 1.45−1.10 (m, 3H), 1.25 (s, 13H), 1.03 (t, 3H, J = 7.4 Hz); ^{13}C NMR (75.5 MHz) δ (ppm) 212.0 (s), 69.5 (d), 63.5 (t), 63.2 (d), 56.0 (d), 42.2 (t), 36.1 (t), 35.7 (t), 33.5 (t), 30.6 (t), 29.6 (t), 29.5 (t), 29.3 (t), 29.2 (t), 29.1 (t), 26.0 (t), 23.7 (t), 7.7 (q); MS (CI^+, CH_4) *m*/*z* 314 (MH^+, 76), 300 (100), 286 (60), 272 (14), 266 (3), 222 (4), 208 (19), 194 (12), 180 (6), 141 (8), 122 (24), 104 (14); HRMS (CI^+, CH_4) calcd for $C_{18}H_{36}NO_3$ (MH^+) *m*/*z* 314.2695, found 314.2693.

Acknowledgment. C.W. thanks Rhodia for a grant. We thank Delphine and Thierry Jouet for kindly providing the picture of *Sedum acre*. A. Duprat is thanked for his help in the realization of the cover art.

JO010653D