JOC*Article*

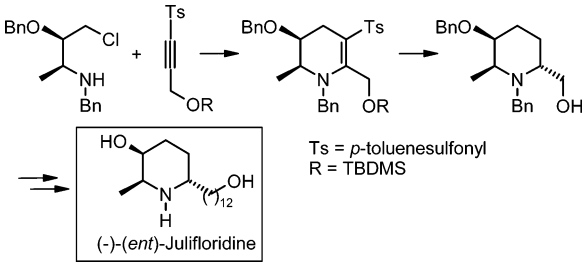
A Highly Stereoselective Synthesis of (−)-(*ent*)-Julifloridine from the Cyclization of an Alanine-Derived Chloroamine with an Acetylenic Sulfone

Huimin Zhai, Masood Parvez, and Thomas G. Back*

Department of Chemistry, University of Calgary, Calgary, AB, Canada, T2N 1N4

tgback@ucalgary.ca

Received February 14, 2007



The cyclization of γ-chloroamine **11**, derived from L-alanine, and acetylenic sulfone **12** afforded the dehydropiperidine **19** via conjugate addition followed by intramolecular alkylation of the corresponding sulfone-stabilized anion. An unexpected acid-catalyzed desulfonylation of **19** occurred in one step via desilylation and tautomerization of the enamine moiety to the corresponding aldehyde, followed by elimination of *p*-toluenesulfinic acid. The highly stereoselective reduction of the resulting unsaturated aldehyde **25** with sodium cyanoborohydride produced piperidine **23** with a diastereomeric ratio of >98:2. (−)-(*ent*)-Julifloridine (**8**) was obtained by Swern oxidation of **23**, followed by Wittig olefination and hydrogenation/debenzylation.

Introduction

2,6-Disubstituted piperidinols (**1**) occur widespread in nature, particularly among the alkaloids of various species of the plant genera *Cassia* and *Prosopis*.[1,2] Numerous compounds possessing either the 2,6-cis or 2,6-trans substitution pattern have been discovered, in addition to ones with 3α- and 3β-configurations. Members of this class are reported to display a wide range of bioactivities,[3] including inhibitory activity toward acetylcholine esterase,[3a] as well as cytotoxic,[3b] antibacterial,[3c−f] antimycotic[3c,e] and DNA-binding activity.[3g] Juliflorine **(2)** and julifloricine **(3)**, the main alkaloids of *Prosopis juliflora*, as well as the less abundant alkaloid (+)-julifloridine **(4)**, were first isolated by Ahmad et al.[4] The absolute stereochemistry of **4** was deduced to be 2*R*,3*R*,6*R*,[5] based on a comparison of its ^{13}C NMR

* Address correspondence to T.G. Back, Tel.: (403) 220-6256, Fax: (403) 289-9488.

(1) For selected reviews of piperidine alkaloids, see: (a) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1985; Vol. 26, pp 89−183. (b) Fodor, G. B.; Colasanti, B. In *Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 1−90. (c) Angle, S. R.; Breitenbucher, J. G. *Stud. Nat. Prod. Chem.* **1995**, *16*, 453−502. (d) Schneider, M. J. *Alkaloids: Chem. Biol. Perspect.* **1996**, *10*, 155−299. (e) Andersen, R. J.; Van Soest, R. W. M.; Kong, F. *Alkaloids: Chem. Biol. Perspect.* **1996**, *10*, 301−355. (f) Ojima, I.; Iula, D. M. *Alkaloids: Chem. Biol. Perspect.* **1999**, *13*, 371−412. (g) Plunkett, O.; Sainsbury, M. In *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Sainsbury, M., Ed.; Elsevier: Amsterdam, 1998; Part F/Part G (partial)), pp 365−421. (h) Rodriguez, J. *Stud. Nat. Prod. Chem.* **2000**, *24* (Part E), 573−681.

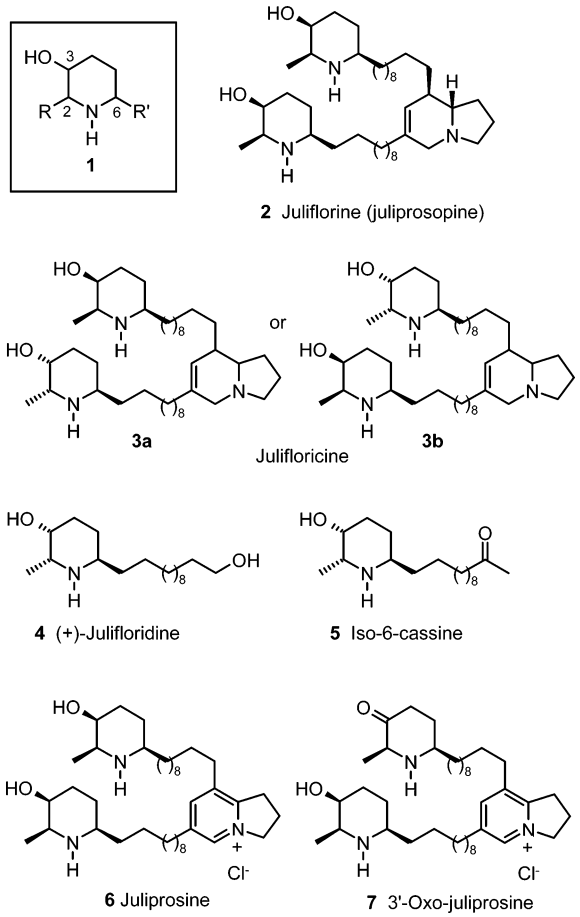
(2) For selected reviews of the synthesis of piperidines, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701−1729. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693−3712. (c) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989. (d) Laschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781−1813. (e) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379−423.

(3) (a) Choudhary, M. I.; Nawaz, S. A.; Zaheer-ul-Haq; Azim, M. K.; Ghayur, M. N.; Lodhi, M. A.; Jalil, S.; Khalid, A.; Ahmed, A.; Rode, B. M.; Atta-ur-Rahman; Gilani, A.-H.; Ahmad, V. U. *Biochem. Biophys. Res. Commun.* **2005**, *332*, 1171−1179. (b) Bolzani, V. S.; Gunatilaka, A. A. L.; Kingston, D. G. I. *Tetrahedron* **1995**, *51*, 5929−5934. (c) Sansores-Peraza, P.; Rosado-allado, M.; Brito-Loeza, W.; Mena-Rejón, G. J.; Quijano, L. *Fitoterapia* **2000**, *71*, 690−692. (d) Aqeel, A.; Khursheed, A. K.; Viqarud-din, A. *Arzneimittel Forsch.* **1991**, *41*, 151−154. (e) Aqeel, A.; Khursheed, A. K.; Viqaruddin, A.; Sabiha, Q. *Arzneimittel Forsch.* **1989**, *39*, 652−655. (f) Ahmad, A.; Khan, K. A.; Ahmad, V. U.; Qazi, S. *Planta Med.* **1986**, *4*, 285−288. (g) Luis, A. S.; Karin, J. S.; Schmeda-Hirschmann, G.; Griffith, G. A.; Holt, D. J.; Jenkins, P. R. *Planta Med.* **1999**, *65*, 161−162.

(4) Ahmad, V. U.; Basha, A.; Haque, W. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1978**, *33B*, 347−348.

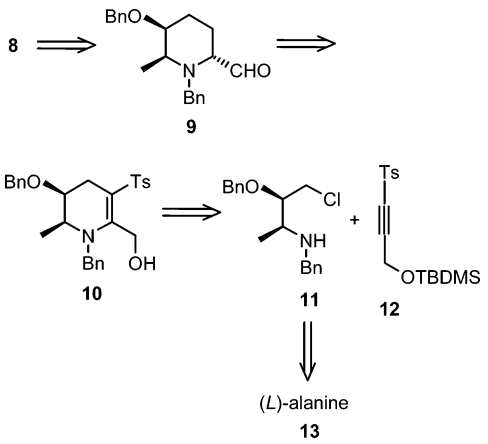
10.1021/jo0703101 CCC: $37.00
Published on Web 04/17/2007

spectrum with that of iso-6-cassine **(5)**, but it was not possible to distinguish between structures **3a** and **3b** for julifloricine. Two alkaloids named juliprosopine[6a] and juliprosine[6b] were later isolated from *Prosopis juliflora* by Hesse and co-workers. Juliprosopine proved to be identical to julifloricine (**2**),[3f] while **2**, juliprosine **(6)**, 3′-oxojuliprosine (**7**), and several congeners showed growth inhibitory activity against both monocotyledonous and dicotyledonous plants.[7] The first syntheses of **2** and **6** were reported recently by Snider and Neubert,[8] who also assigned the indicated stereochemistry to the indolizidine moiety of **2**.

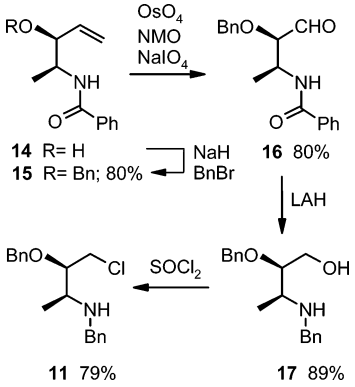


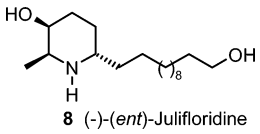
Although relatively little studied, the alkaloid (+)-julifloridine (**4**) has nevertheless been the subject of several synthetic approaches. Thus, Paterne and Brown reported a racemic synthesis in 1983,[9] followed by enantioselective syntheses by Naito et al.[10] and more recently by Lemire and Charette.[11] We now report the first synthesis of (−)-(*ent*)-julifloridine (**8**), the antipode of the naturally occurring alkaloid **4**, from L-alanine. Since D-alanine is also readily available, our approach should serve equally for the preparation of the (+)-enantiomer **4**.

SCHEME 1



SCHEME 2





Results and Discussion

The general approach to **8** is shown retrosynthetically in Scheme 1. Thus, we envisaged the formation of the product from aldehyde **9** by means of a Wittig reaction followed by hydrogenation/hydrogenolysis. The latter compound was expected from the stereoselective reduction of the enamine double bond, reductive desulfonylation, and oxidation of the primary alcohol of dehydropiperidine **10**. Cyclization of γ-chloroamine **11**, in turn obtained from L-alanine (**13**), with acetylenic sulfone **12** via conjugate addition, intramolecular alkylation, and desilylation would afford the key intermediate **10**.

The required γ-chloroamine **11** was obtained from allylic alcohol **14**, which is readily available from (L)-alanine by the method of Ibuka et al.[12] This was followed by O-benzylation, oxidative cleavage, reduction with lithium aluminum hydride, and chlorination to afford **11**, as shown in Scheme 2. Acetylenic sulfone **12** was obtained as described previously.[13]

(5) Ahmad, V. U.; Qazi, S. *Z. Naturforsch. B: Anorg. Chem., Org. Chem.* **1983**, *38B*, 660.

(6) (a) Ott-Longoni, R.; Viswanathan, N.; Hesse, M. *Helv. Chim. Acta* **1980**, *63*, 2119−2129. (b) Dätwyler, P.; Ott-Longoni, R.; Schöpp, E.; Hesse, M. *Helv. Chim. Acta* **1981**, *64*, 1959−1963.

(7) (a) Nakano, H.; Nakajima, E.; Fujii, Y.; Shigemori, H.; Hasegawa, K. *Plant Growth Regul.* **2004**, *44*, 207−210. (b) Nakano, H.; Nakajima, E.; Hiradate, S.; Fujii, Y.; Yamada, K.; Shigemori, H.; Hasegawa, K. *Phytochemistry* **2004**, *65*, 587−591.

(8) Snider, B. B.; Neubert, B. J. *Org. Lett.* **2005**, *7*, 2715−2718.

(9) Paterne, M.; Brown, E. *C. R. Acad. Sci. Paris Ser. 2* **1983**, *296*, 433−434.

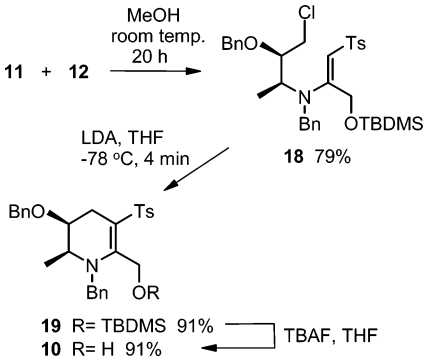
(10) Kiguchi, T.; Shirakawa, M.; Honda, R.; Ninomiya, I.; Naito, T. *Tetrahedron* **1998**, *54*, 15589−15606.

(11) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747−2750.

(12) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370−4382.

(13) Back, T. G.; Nava-Salgado, V. O.; Payne, J. E. *J. Org. Chem.* **2001**, *66*, 4361−4368.

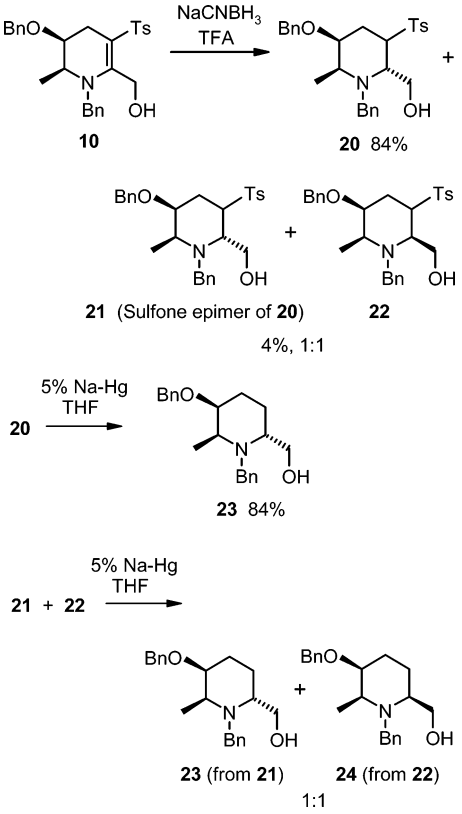
SCHEME 3



The cyclization of acetylenic sulfones with chloroamines or amino esters by tandem conjugate addition and either intramolecular alkylation or acylation, respectively, has provided routes to a variety of alkaloids, including (−)-pumiliotoxin C,[14] indolizidines (−)-167B, (−)-209D, (−)-209B, and (−)-207A,[15] (−)-lasubine II,[16] (±)-myrtine,[16] and quinolone alkaloids from the medicinal shrub *Ruta chalepensis*.[17] In the present instance, the cyclization of **11** with **12** was readily effected by performing the conjugate addition in methanol, followed by brief treatment with 2 equiv of LDA at −78 °C in THF (Scheme 3).[18] The structure of enamine **10**, obtained by desilylation of **19**, was confirmed by X-ray crystallography (see Supporting Information) in order to ensure that epimerization had not occurred in preceding steps.

Attempts to reduce the enamine double bond of silyl ether **19** with either sodium triacetoxyborohydride or sodium cyanoborohydride in the presence of trifluoroacetic acid (TFA) proceeded in high yield, but with a 2,6-trans to 2,6-cis ratio of only ca. 10:1. We therefore investigated the similar reduction of the free alcohol **10** to see if the stereoselectivity could be improved. Indeed, treatment of **10** with sodium cyanoborohydride in the presence of TFA afforded 84% of **20** as a single, easily separated diastereomer, as well as 4% of an unseparable 1:1 mixture of diastereomers **21** and **22**. The 2,6-trans configuration of the major product was confirmed by its ultimate conversion to (−)-julifloridine (**8**) (*vide infra*). Thus, this procedure afforded the 2,6-trans isomers **20** and **21**, differing with respect to their configuration at the sulfone-substituted carbon, in a combined yield of 86% with a 2,6-trans:cis ratio of 43:1. The similar reduction of **10** with sodium triacetoxyborohydride afforded a comparable yield of the combined diastereomers, but with the lower 2,6-trans to 2,6-cis ratio of 19:1. Reductive desulfonylation of the major isomer **20** with sodium amalgam[19] produced **23**. As expected, the similar reduction of the unseparated mixture of **21** and **22** furnished equal amounts of **23** and another diastereomer, which we conclude is the corresponding 2,6-cis isomer **24**. These processes are shown in Scheme 4.[20]

SCHEME 4

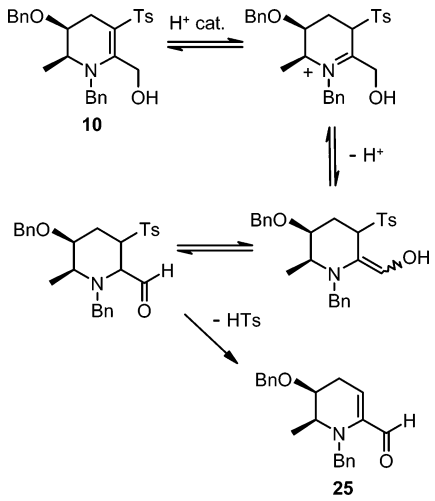


A remarkable protocol for the conversion of the enamine silyl ether **19** to piperidinol **23** in two steps was discovered fortuitously during the routine NMR analysis of the free alcohol **10**. It was observed that **10** was transformed into the α,β-unsaturated aldehyde **25** in high yield when allowed to stand in $CDCl_3$ solution for several hours, presumably as the result of catalysis by traces of HCl present in the solvent. We postulate that the presence of an acid catalyst results in equilibration of the enamine **10** with its enol tautomer via the corresponding iminium ion. Further tautomerization to the keto form, followed by the facile elimination of *p*-toluenesulfinic acid, affords the conjugated aldehyde **25** (Scheme 5).

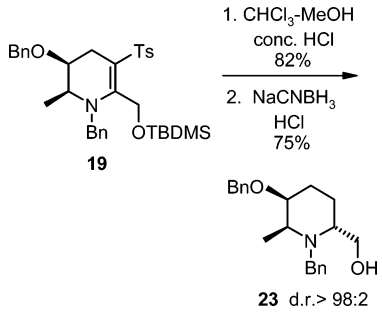
Since the cleavage of TBDMS ethers can be carried out in the presence of strong acids,[21] we treated **19** in chloroform−methanol containing concentrated hydrochloric acid. Desilylation to **10**, followed by tautomerization and elimination of the sulfinic acid, as shown in Scheme 5, afforded the aldehyde **25** directly. Moreover, the reduction of **25** with sodium cyanoborohydride in the presence of hydrochloric acid produced the 2,6-*trans*-piperidinol **23** as essentially a single diastereomer (d.r. >98:2),

(14) Back, T. G.; Nakajima, K. *J. Org. Chem.* **1998**, *63*, 6566−6571.
(15) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543−4552.
(16) Back, T. G.; Hamilton, M. D.; Lim, V. J. J.; Parvez, M. *J. Org. Chem.* **2005**, *70*, 967−972.
(17) Back, T. G.; Parvez, M.; Wulff, J. E. *J. Org. Chem.* **2003**, *68*, 2223−2233.
(18) The reaction was quenched with neutral alumina after only 4 min at −78 °C. Significant reductions in yield were observed with longer reaction times or when the mixture was allowed to warm to room temperature prior to workup.
(19) (a) For a review of desulfonylation methods, see: Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547−10658. (b) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477−3478.
(20) The stereoselectivity of hydride reductions or other nucleophilic additions to cyclic iminium ions, which can be generated from the corresponding enamines in the presence of acid catalysts, has been extensively studied and can often be rationalized by consideration of steric and stereoelectronic effects. For a review, see (a) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289−296. The role of $A^{(1,2)}$ strain is particularly important in determining the stereoselectivity of reduction of iminium species derived from *N*,2-substituted piperidines; see (b) Toyooka, N.; Yoshida, Y.; Yotsui, Y.; Momose, T. *J. Org. Chem.* **1999**, *64*, 4914−4919. Similar arguments presumably apply here.
(21) Greene, T. W.; Wuts, P. G. M. in *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 133−141.

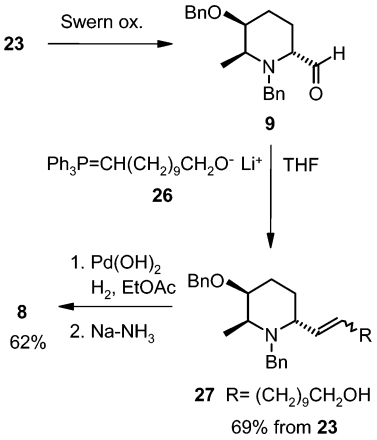
SCHEME 5



SCHEME 6



SCHEME 7



as indicated in Scheme 6.[20] Thus, desilylation, enamine reduction, and desulfonylation were achieved in two steps with excellent diastereoselectivity and in high yield under the above conditions. Moreover, this procedure avoids the use of sodium amalgam and the required manipulation and disposal of mercury. Unfortunately, selective reduction of the carbon−carbon double bond in the presence of the aldehyde was not possible.

The completion of the synthesis of (−)-julifloridine (**8**) is shown in Scheme 7. The alcohol **23** was oxidized to aldehyde **9**, followed by installation of the side chain by means of the Wittig reagent **26**.[22] The resulting alkene **27** (*E*:*Z* = 1:9) was hydrogenated and O-debenzylated simultaneously. Unfortunately, the *N*-benzyl group proved resistant to hydrogenolysis under these conditions and was therefore removed with sodium in liquid ammonia. The product **8** was obtained in a high state of purity, as evidenced by its NMR spectra (see the Supporting Information) and a comparison of its optical rotation with that of the known (+)-enantiomer[23] (see the Experimental Section).

In summary, the (−)-antipode **8** of naturally occurring (+)-julifloridine (**4**) was obtained for the first time from **11** and **12** in eight steps and an overall yield of 19%, via a sulfone-mediated cyclization, using readily available and easily handled reagents. The discovery of the acid-catalyzed conversion of the piperidinol silyl ether **19** to the desulfonylated aldehyde **25** in one step is noteworthy, as is the very high diastereoselectivity in the subsequent reduction of **25** to **23**. It is also evident that the enantiomer of γ-chloroamine **11** would be equally accessible from readily available D-alanine, thereby permitting the synthesis of (+)-julifloridine by the same route. Finally, this approach should serve for the synthesis of either enantiomer of the many other 2,6-trans-disubstituted 3-piperidinols that have been reported to date from various sources.

Experimental Section

General Experimental. Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ solution and mass spectra were obtained by electron impact. Chromatography refers to flash chromatography on silica gel (230−400 mesh). Organic solutions were dried using anhydrous $MgSO_4$.

Enamine Sulfone 18. γ-Chloroamine **11** (2.38 g, 7.83 mmol; see Supporting Information) was added to a solution of acetylenic sulfone **12**[13] (2.80 g, 8.63 mmol) in 50 mL of dry methanol. The solution was stirred at room temperature for 20 h and then concentrated *in vacuo* to give a yellow oil. The residue was chromatographed using 20% ethyl acetate−hexane to give 3.87 g (79%) of enamine **18,** obtained as fine white crystals: mp 106−107.5 °C (from ethyl acetate−hexanes); $[\alpha]^{22}_D = +149$ (*c* 0.34, $CHCl_3$); IR (KBr) 1557, 1284, 1255, 1130, 1086 cm^{-1}; ^1H NMR (300 MHz) δ 7.46−7.31 (m, 7 H), 7.22−7.17 (m, 3 H), 7.11−7.03 (m, 4 H), 5.37 (d, *J* = 13.3 Hz, 1 H), 4.85 (s, 1 H), 4.68 (d, *J* = 11.8 Hz, 1 H), 4.61−4.50 (m, 1 H), 4.47 (d, *J* = 12.8 Hz, 1 H), 4.40 (d, *J* = 11.8 Hz, 1 H), 4.32 (d, *J* = 16.9 Hz, 1 H), 3.93 (d, *J* = 16.9 Hz, 1 H), 3.85−3.76 (m, 1 H), 3.58−3.50 (m, 2 H), 2.36 (s, 3 H), 1.24 (d, *J* = 7.2 Hz, 3 H), 0.85 (s, 9 H), 0.07 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz) δ 158.1, 142.9, 141.7, 137.0, 136.2, 129.0, 128.6, 128.5, 128.4, 128.1, 126.8, 126.1, 125.9, 99.3, 79.1, 72.1, 55.8, 55.1, 47.4, 43.1, 25.6, 21.3, 17.9, 15.4, −5.6, −5.7); MS (*m*/*z*, %) 627 (M^+, 5), 458 (63), 149 (65), 91 (100); HRMS calcd for $C_{26}H_{37}{}^{35}ClNO_2Si$ ($M^+ - CH_2Ts$): 458.2282. Found: 458.2304. Anal. Calcd for $C_{34}H_{46}ClNO_4SSi$: C, 64.99; H, 7.38; N, 2.23. Found: C, 65.06; H, 7.30; N, 2.06.

(5*S*,6*S*)-*N*-Benzyl-5-benzyloxy-2-(*tert*-butyldimethylsilyloxymethyl)-6-methyl-3-(*p*-toluenesulfonyl)-2,3-dehydropiperidine (19). Sulfone **18** (3.14 g, 5.00 mmol) was dissolved in 20 mL of dry THF and cooled to −78 °C under argon. A solution of LDA (10.0 mmol) in 30 mL of dry THF was added via syringe over 5 min. The resulting orange solution was stirred at −78 °C for 4 min and was then filtered through neutral alumina. The alumina was washed with THF and the clear filtrate was concentrated *in vacuo*. Compound **19** was obtained as a colorless oil (2.69 g, 91%) that was used in subsequent steps without further purification: $[\alpha]^{22}_D$

(22) Lermer, L.; Neeland, E. G.; Ounsworth, J. P.; Sims, R. J.; Tischler, S. A.; Weiler, L. *Can. J. Chem.* **1992**, *70*, 1427−1444.

(23) Our specific rotation for **(−)-8** was $[\alpha]^{22}_D = -8.2$ (*c* 0.34, MeOH). This was in close agreement to that reported by Lemire and Charette (ref. 11) for (+)-julifloridine (**4**), $[\alpha]^{20}_D = +7.3$ (*c* 0.23, MeOH), but different from that reported by Naito et al. (ref 10), $[\alpha]^{25}_D = +18$ (*c* 0.84, MeOH). It should be noted that Lemire and Charette prepared the Mosher ester derivative of their synthetic (+)-julifloridine and were thus able to confirm that their synthetic product had an ee of 98.6% by ^{19}F NMR analysis.

= +128 (*c* 0.90, $CHCl_3$); IR (film) 1568, 1296, 1141 cm^{-1}; ^1H NMR (300 MHz) δ 7.80 (d, J = 8.4 Hz, 2 H), 7.38−7.21 (m, 8 H), 7.20−7.09 (m, 4 H), 5.45 (d, J = 12.8 Hz, 1 H), 4.99 (d, J = 16.4 Hz, 1 H), 4.59 (d, J = 12.8 Hz, 1 H), 4.39 (d, J = 11.8 Hz, 1 H), 4.34 (d, J = 11.8 Hz, 1 H), 4.22 (d, J = 16.4 Hz, 1 H), 3.58−3.48 (m, 1 H), 3.38−3.27 (m, 1 H), 2.86 (dd, J = 15.9, 6.2 Hz, 1 H), 2.43 (s, 3 H), 2.16 (dd, J = 16.2, 10.5 Hz, 1 H), 0.92 (d, J = 6.6 Hz, 3 H), 0.92 (s, 9 H), 0.14 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (75 MHz) δ 150.7, 142.5, 141.1, 138.1, 138.0, 129.5, 128.9, 128.5, 127.8, 127.69, 127.67, 127.2, 126.6, 99.6, 72.6, 70.7, 56.3, 53.6, 53.0, 27.0, 26.0, 21.6, 18.3, 11.2, −5.1, −5.3; MS (*m/z*, %) 591 (M^+, 2), 534 (7), 149 (81), 91 (100); HRMS calcd for $C_{30}H_{36}NO_4SSi$ ($M^+ - C_4H_9$): 534.2134. Found: 534.2147.

(5*S*,6*S*)-*N*-Benzyl-5-benzyloxy-2-hydroxymethyl-6-methyl-3-(*p*-toluenesulfonyl)-2,3-dehydropiperidine (10). Compound **19** (632 mg, 1.07 mmol) was dissolved in 4 mL of THF, cooled to 0 °C, and treated with 1.0 M TBAF in THF (1.5 mL, 1.5 mmol). The solution was stirred at room temperature for 2 h and washed with brine, dried, and concentrated *in vacuo*. The residue was chromatographed using 35% ethyl acetate−hexane as eluent to give 464 mg (91%) of the free alcohol **10** as a white solid: mp 97−98 °C (from ethyl acetate−hexanes); $[\alpha]^{22}_D$ = +177 (*c* 0.44, acetone); IR (KBr) 3500, 1597, 1289, 1118 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 7.77 (d, J = 8.2 Hz, 2 H), 7.45−7.10 (m, 12 H), 5.01 (d, J = 12.8 Hz, 1 H), 4.94 (d, J = 16.4 Hz, 1 H), 4.44 (d, J = 16.4 Hz, 1 H), 4.52−4.34 (m, 3 H), 4.06 (br s, 1 H), 3.62−3.46 (m, 2 H), 2.75 (dd, J = 16.2, 6.2 Hz, 1 H), 2.41 (s, 3 H), 2.22 (dd, J = 16.2, 10.6 Hz, 1 H), 0.91 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 152.8, 143.4, 142.8, 139.4, 130.4, 129.6, 129.2, 128.5, 128.4, 128.3, 128.2, 127.2, 101.3, 73.5, 71.2, 56.8, 54.5, 53.4, 27.8, 21.5, 11.4; ESI MS 478 $(M + H)^+$, 500 $(M + Na)^+$. Anal. Calcd for $C_{28}H_{31}NO_4S$: C, 70.41; H, 6.54; N, 2.93. Found: C, 70.71; H, 6.12; N, 2.73. The X-ray crystallographic data for structure **10** is provided in the Supporting Information.

(2*S*,5*S*,6*S*)-*N*-Benzyl-5-benzyloxy-2-hydroxymethyl-6-methyl-3-(*p*-toluenesulfonyl)piperidine (20). Trifluoroacetic acid (0.80 mL, 10 mmol) was added dropwise to a suspension of alcohol **10** (464 mg, 0.973 mmol) and sodium cyanoborohydride (668 mg, 10.6 mmol) in 15 mL of dichloromethane at 0 °C, and the mixture was stirred at 0 °C for 1 h and then at room temperature for another 1 h. It was washed with aqueous KOH solution, dried, and concentrated *in vacuo* to provide a light yellow oil, which was purified by chromatography (45% ethyl acetate−hexanes) to afford 20 mg (4%) of an inseparable 1:1 mixture of the less polar byproducts **21** and **22** as a clear oil (*vide infra*). Further elution with 55% ethyl acetate−hexanes afforded 391 mg (84%) of 2,6-*trans*-piperidine **20** as a colorless oil: $[\alpha]^{22}_D$ = −62.1 (*c* 1.24, $CHCl_3$); IR (film) 3411, 1597, 1316, 1145 cm^{-1}; ^1H NMR (400 MHz) δ 7.75 (d, J = 8.1 Hz, 2 H), 7.39−7.31 (m, 5 H), 7.30−7.16 (m, 5 H), 7.04−7.00 (m, 2 H), 4.53 (d, J = 11.9 Hz, 1 H), 4.34 (d, J = 11.9 Hz, 1 H), 4.17 (d, J = 14.3 Hz, 1 H), 3.84−3.71 (m, 3 H), 3.58 (s, 1 H), 3.43 (d, J = 14.3 Hz, 1 H), 3.18−3.07 (m, 2 H), 2.98−2.79 (br, s, 1 H), 2.49 (s, 3 H), 2.40 (d, J = 13.9 Hz, 1 H), 2.02 (dt, J = 2.5, 13.7 Hz, 1 H), 1.32 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz) δ 144.8, 139.5, 138.0, 134.9, 130.0, 128.7, 128.38, 128.36, 128.2, 127.6, 127.3, 127.1, 76.0, 71.5, 55.5, 54.5, 53.6, 51.8, 50.2, 23.6, 21.6, 16.2; MS (*m/z*, %) 448 ($M^+ - CH_2OH$, 76), 187 (30), 91 (100); HRMS calcd for $C_{27}H_{30}NO_3S$ ($M^+ - CH_2OH$): 448.1946. Found: 448.1982.

(2*S*,3*S*,6*R*)-*N*-Benzyl-3-benzyloxy-6-(hydroxymethyl)-2-methylpiperidine (23). Sulfone **20** (314 mg, 0.655 mmol) was suspended in 15 mL of dry THF, and finely ground 5% sodium amalgam (4.44 g, 9.65 mmol of Na) was added. The mixture was refluxed under nitrogen for 22 h and filtered through a Celite pad, followed by washing with THF. The filtrate was concentrated *in vacuo* to provide a yellow oil, which was purified by chromatography (elution with 55% ethyl acetate−hexanes) to afford 179 mg (84%) of **23** as a colorless oil: $[\alpha]^{22}_D$ = −16.0 (*c* 0.21, $CHCl_3$); IR (film) 3424, 1091, 1071 cm^{-1}; ^1H NMR (400 MHz) δ 7.38−7.18 (m, 10 H), 4.51 (d, J = 12.0 Hz, 1 H), 4.42 (d, J = 12.0 Hz, 1 H), 3.88 (d, J = 14.2 Hz, 1 H), 3.78 (d, J = 14.2 Hz, 1 H), 3.61 (dd, J = 11.0 Hz, 4.4 Hz, 1 H), 3.55−3.47 (m, 2 H), 3.23 (dq, J = 3.4, 6.7 Hz, 1 H), 2.86−2.80 (m, 1 H), 2.21 (br, s, 1 H), 1.86−1.70 (m, 3 H), 1.59−1.43 (m, 1 H), 1.12 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz) δ 140.2, 138.8, 128.5, 128.28, 128.26, 127.4, 127.3, 127.0, 76.3, 70.3, 61.7, 54.6, 52.8, 52.1, 24.2, 23.0, 8.6; MS (*m/z*, %) 294 (100), 234 (57), 91 (100); HRMS calcd for $C_{20}H_{24}NO$ ($M^+ - CH_2OH$): 294.1858. Found: 294.1838.

The mixture of **21** and **22** was treated similarly to afford an unseparated 1:1 mixture of two desulfonylated compounds. One was identical to **23** (NMR), and the other was assumed to be **24** by the process of elimination.

(5*S*,6*S*)-*N*-Benzyl-5-benzyloxy-6-methyl-2,3-dehydropiperidine-2-carbaldehyde (25). Silyl ether **19** (591 mg, 1.00 mmol) was dissolved in 8 mL of chloroform−methanol (5:2) and treated with 1.0 mL of concentrated HCl under argon. The solution was stirred at room temperature for 1 d and washed with saturated aqueous $KHCO_3$ solution. The aqueous layer was extracted with chloroform, the combined organic layers were dried and concentrated, and the residue was purified by chromatography (18% ethyl acetate−hexanes) to give 263 mg (82%) of aldehyde **25** as a pale yellow oil: $[\alpha]^{22}_D$ = −70.2 (*c* 1.20, $CHCl_3$); IR (film) 2733, 1685, 1458, 1361, 1092 cm^{-1}; ^1H NMR (300 MHz) δ 9.24 (s, 1 H), 7.41−7.20 (m, 10 H), 5.69 (dd, J = 5.1, 3.1 Hz, 1 H), 4.49 (d, J = 12.3 Hz, 1 H), 4.41 (d, J = 11.8 Hz, 1 H), 4.40 (d, J = 14.9 Hz, 1 H), 4.31 (d, J = 14.9 Hz, 1 H), 3.46 (ddd, J = 10.3, 5.9, 4.3 Hz, 1 H), 3.33−3.23 (m, 1 H), 2.53 (dt, J = 5.8, 12.6 Hz, 1 H), 2.27 (m, 1 H), 0.89 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (75 MHz) δ 190.3, 143.5, 139.2, 138.2, 128.33, 128.30, 128.26, 127.6, 127.5, 127.1, 125.4, 71.4, 70.5, 54.2, 52.4, 27.0, 11.0; MS (*m/z*, %) 321 (M^+, 28), 230 (28), 215 (30), 186 (26), 110 (70), 91 (100); HRMS calcd for $C_{21}H_{23}NO_2$: 321.1729. Found: 321.1715.

Stereoselective Reduction of Aldehyde 25. Concentrated HCl (1.0 mL) was added dropwise to a suspension of aldehyde **25** (263 mg, 0.82 mmol) and sodium cyanoborohydride (601 mg, 9.54 mmol) in 15 mL of dichloromethane at −10 °C, and the mixture was stirred at 0 °C for 10 h, then at room temperature for 2 h. The mixture was washed with 10 mL of aqueous 20% KOH solution, dried, and concentrated *in vacuo* to provide a light yellow oil, which was purified by chromatography (elution with 55% ethyl acetate−hexanes) to afford 200 mg (75%) of **23** as a colorless oil. The product was identical to that prepared by the desulfonylation of **20** (*vide supra*) and contained at least 98% of the indicated diastereomer (NMR analysis).

12-[(2*R*,5*S*,6*S*)-*N*-Benzyl-5-benzyloxy-6-methylpiperidin-2-yl]-dodec-11-en-1-ol (27). To a solution of oxalyl chloride (114 mg, 0.898 mmol) in dry dichloromethane (4 mL) at −78 °C was added a solution of DMSO (140 mg, 1.79 mmol) in dichloromethane (2 mL). After 10 min, a solution of alcohol **23** (202 mg, 0.621 mmol) in dichloromethane (2 mL) was added. The mixture was allowed to stir for 45 min at −65 °C, triethylamine (182 mg, 1.80 mmol) was added, and it was warmed to room temperature. After 1 h, the reaction was quenched with 10% aqueous $NaHCO_3$ solution and extracted with dichloromethane. The organic layers were combined, dried, and evaporated *in vacuo* to afford 200 mg (100%) of aldehyde **9** as a yellow oil, which was used immediately without further purification.

Ylide **26**[22] (1.23 mmol) in 8 mL of THF was cooled to −78 °C and aldehyde **9** (200 mg, 0.618 mmol) in THF (5 mL) was added. The mixture was stirred at −78 °C for 2 h and then for an additional 2 h at room temperature. The reaction was quenched with water (10 mL), and the solution was extracted with dichloromethane. The combined organic layers were dried and concentrated, and the residue was purified by chromatography (elution with 30% ethyl acetate−hexanes) to give 204 mg (69% from **23**) of olefin **27** (cis:trans = 9:1) as colorless oil: IR (film) 3363, 1453, 1372, 1075 cm^{-1}; ^1H NMR (300 MHz) major cis isomer: δ 7.37−7.14 (m, 10 H), 7.66−7.50 (m, 1 H), 5.43 (dt, J = 10.8, 7.2 Hz, 1 H), 5.23

(crude t, J = ca. 10 Hz, 1 H), 4.41 (d, J = 11.8 Hz, 1 H), 4.36 (d, J = 11.8 Hz, 1 H), 4.00 (d, J = 13.8 Hz, 1 H), 3.65 (t, J = 6.7 Hz, 2 H), 3.56−3.43 (m, 1 H), 3.38 (d, J = 14.3 Hz, 1 H), 3.28−3.15 (m, 1 H), 2.16−2.02 (m, 2 H), 1.86−1.70 (m, 1 H), 1.69−1.48 (m, 3 H), 1.47−1.16 (m, 16 H), 0.99 (d, J = 6.7 Hz, 3 H); minor trans isomer: δ 0.96 (d, J = 7.2 Hz); ^{13}C NMR (75 MHz, major cis isomer) δ 140.5, 138.8, 133.6, 131.3, 128.3, 128.2, 128.1, 127.5, 127.3, 126.5, 77.6, 69.9, 63.1, 53.8, 51.02, 50.96, 32.8, 31.6, 29.6, 29.53, 29.48, 29.43, 29.38, 29.24, 27.7, 25.7, 24.7, 3.0; MS (*m/z*, %) 477 (M^+, 4), 134 (69), 91 (100); HRMS calcd for $C_{32}H_{47}NO_2$: 477.3607. Found: 477.3579.

(−)-(*ent*)-Julifloridine (8). To a stirred solution of olefin **27** (112 mg, 0.234 mmol) in 14 mL of ethyl acetate was added palladium hydroxide (50 mg, 20% on C), and the resulting suspension was stirred under a hydrogen atmosphere at 45 °C and 400 psi for 10 h. The mixture was filtered through Celite, and the filtrate was evaporated to give a colorless oil (92 mg), which was used directly in the next step.

The above oil was dissolved in 5 mL of THF and 15 mL of liquid ammonia at −78 °C. Freshly cut sodium (368 mg, 16.0 mmol) was added while stirring, to afford a dark purple solution. Stirring was continued for 30 min at −78 °C and then under reflux (*ca.*−30 °C) for 3 h. Solid ammonium chloride was added until the color disappeared, and the mixture was warmed to room temperature. Stirring was continued until the evaporation of ammonia was complete, and then 10 mL of water was added. The product was isolated by the procedure of Lemire and Charette[11] to afford 43.3 mg (62%) of (−)-(*ent*)-julifloridine (**8**) as a white solid: mp: 81−83.5 °C, lit.[4] 82−83 °C, lit.[10] 85−87.5 °C, lit.[11] 82−83 °C; $[\alpha]^{22}_D$ = −8.2 (*c* 0.34, MeOH), lit.[10] for (+)-julifloridine **4**: $[\alpha]^{25}_D$ = +18 (*c* 0.84, MeOH), lit.[11] for (**4**): $[\alpha]^{20}_D$ = +7.3 (*c* 0.23, MeOH); IR (film) 3384, 3271, 1456, 1364, 1096 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.70−3.65 (m, 1 H), 3.64 (t, J = 6.7 Hz, 2 H), 3.13 (dq, J = 2.9, 6.5 Hz, 1 H), 2.82 (quintet, J = 5.9 Hz, 1 H), 2.20−1.90 (br, s, 3 H), 1.94−1.84 (m, 1 H), 1.76−1.60 (m, 2 H), 1.58−1.44 (m, 3 H), 1.40−1.20 (m, 20 H), 1.11 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz; CH, CH_2, CH_3 signals assigned by DEPT) δ 68.8 (CH), 63.1 (CH_2), 50.4 (CH), 49.6 (CH), 32.8 (2 × CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (5 × CH_2), 29.4 (CH_2), 27.5 (CH_2), 26.6 (CH_2), 25.7 (CH_2), 15.9 (CH_3); MS (*m/z*, %) 300 (M^+ + 1, 29), 114 (100); HRMS calcd for $C_{18}H_{37}NO_2$: 299.2824. Found: 299.2847.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) and Merck Frosst (Canada) Ltd. for financial support.

Supporting Information Available: The procedure for the preparation of **11**, ^{1}H and ^{13}C NMR spectra of new compounds, and X-ray crystallographic data for **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0703101