# Applications of Organosulfur Chemistry to Organic Synthesis: Total Synthesis of (+)-Himbeline and (+)-Himbacine

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*Received April 4, 1997*[⊗]

Total syntheses of (+)-himbacine (**1**) and (+)-himbeline (**2**) are described. The synthesis involves the preparation of sulfone **38** and aldehyde **42** as single enantiomers followed by coupling of these compounds using a Julia−Lythgoe olefination. The preparation of sulfone **38** features an acid-promoted intramolecular Diels−Alder reaction of an α,β-unsaturated thioester while the synthesis of **42** features a Beak alkylation of piperidine **39**.

## Introduction

The isolation of himbacine (**1**) from samples of bark of *Galbulimima baccata* collected in North Queensland and New Guinea was first reported in 1956.[2] The structural formula of himbacine was reported in 1961,[3] and stereochemical aspects of the structure were secured by X-ray crystallography as reported in 1962.[4] The structurally related alkaloids himbeline (**2**) and himgravine (**3**), along with other alkaloids, have also been isolated from *Galbulimima baccata*.[5,6] There was relatively little interest in himbacine until it was reported that it is a potent muscarinic antagonist that displays selectivity for the $M_2$ receptor.[7] Since blockage of presynaptic inhibitory muscarinic receptors leads to an elevation of synaptic levels of acetylcholine, it was anticipated that appropriate himbacine analogs might offset some of the losses in the cholinergic system that occurs in Alzheimer's disease.[8] Thus, himbacine became a lead compound for identifying possible new drug candidates for the treatment of Alzheimer's dementia. Initial SAR studies suggested that while certain himbacine substructures retained antimuscarinic activity, they failed to retain receptor selectivity. For example, lactone **4** binds to the $M_1$ and $M_2$ receptor subtypes with $K_d$ values of 9.7 and 1.2 μM, respectively, while analog **5** shows $K_d$ values of 1.5 and 3.2 nM, respectively. For comparison, himbacine binds to the $M_1$ and $M_2$ receptors with $K_d$ values of 168 and 9 nM, respectively.[7] To lay the foundation for further medicinal chemical efforts in the area, a total synthesis of himbacine was undertaken.[9] It is notable that synthesis efforts in other laboratories have also recently been reported.[10] This paper presents the full details of total syntheses of (+)-himbacine (**1**) and (+)-himbeline (**2**), accompanied by observations made along the way.

Our plan to address the eight stereogenic centers in himbacine revolved around preparing perhydronaphthalene and piperidine fragments and coupling them using an appropriate olefination procedure. Our initial targets for synthesis were aldehyde **6** and sulfone **7** (Chart 1), which were to be coupled using the Julia−Lythgoe olefination protocol.

**Preparation of Aldehyde 6.** An intramolecular Diels−Alder approach was taken to the synthesis of aldehyde **6**. Ozonolysis of cycloheptene (**8**) using the Schreiber protocol gave aldehyde **9** (Scheme 1).[11] Treatment of the crude aldehyde with (carbomethoxymethylidene)triphenylphosphorane in methanol provided unsaturated ester **10** in 72% yield. This material was a 2:1 mixture of *E* and *Z* geometrical isomers, respectively, based on integration of NMR signals due to the β-vinylic hydrogens which appeared at δ 6.95 (dt, $J$ = 15, 7 Hz) and 6.23 (dt, $J$ = 11, 7 Hz), respectively. Deprotonation of **10** with lithium diisopropyamide in HMPT−THF, followed by treatment of the resulting dienolate anion with (*S*)-2-hydroxypropanal[12] gave a 94% yield of β-hydroxy esters **11** as a mixture of geometrical and configurational isomers.[13] Following chemistry precedented in the work of Kende and Wu, treatment of **11** with catalytic *p*-toluenesulfonic acid in methanol gave crude β-hydroxy lactone, which was converted to an 8:1 mixture of butenolides **12** (78% from **10**) upon treatment with

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1997.

(1) This paper is dedicated to the memory of Professor William G. Dauben.

(2) Brown, R. F. C.; Drummond, R.; Fogerty, A. C.; Hughes, G. K.; Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1956**, *9*, 283.

(3) Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1961**, *14*, 106.

(4) Fridrichsons, J.; Mathieson, J. M. *Acta Crystallogr.* **1962**, *15*, 119.

(5) For a review see Ritchie, E.; Taylor, W. C. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1967; Vol. 9, p 529.

(6) *Galbulimima baccata* is not a pine as stated in our earlier communication.[9] It belongs to the Magnoliales order and thus is somewhat related to magnolias. We thank Professor Frank R. Stermitz of Colorado State University for bringing this error to our attention.

(7) Kozikowski, A.; Fauq, A. H.; Miller, J. H.; McKinney, M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 797. Malaska, M. J.; Fauq, A. H.; Kozikowski, A. P.; Aagaard, P. J.; McKinney, M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1247. Malaska, M. J.; Fauq, A. H.; Kozikowski, A. P.; Aagaard, P. J.; McKinney, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 61.

(8) Miller, J. H.; Aagaard, P. J.; Gibson, V. A.; McKinney, M. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 663.

(9) For a communication, see: Hart, D. J.; Wu, W.-L.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1995**, *117*, 9369.

(10) For approaches that are very similar to ours, see: De Baecke, G.; De Clercq, P. J. *Tetrahedron Lett.* **1995**, *36*, 7515. Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russell, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551. For another total synthesis and a different approach, see: Chackalamannil, S.; Davies, R. J.; Asberom, T.; Doller, D.; Leone, D. *J. Am. Chem. Soc.* **1996**, *118*, 9812.

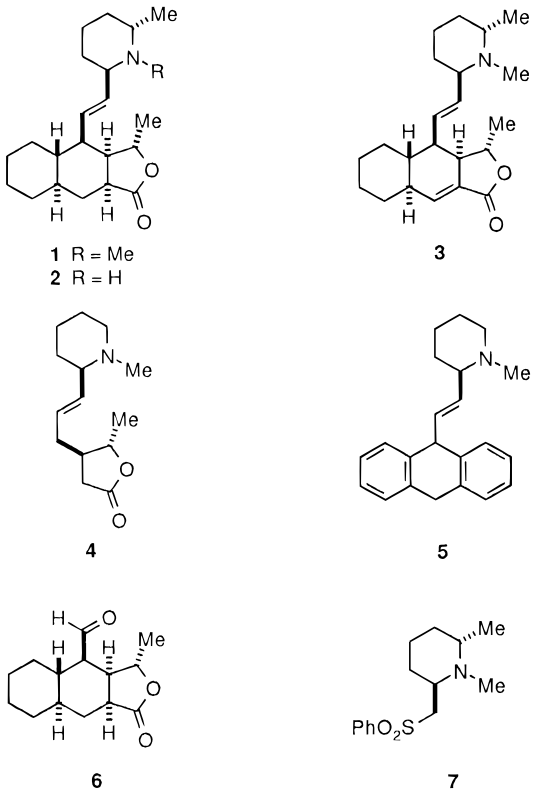
(11) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867.

(12) Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, *45*, 5767.

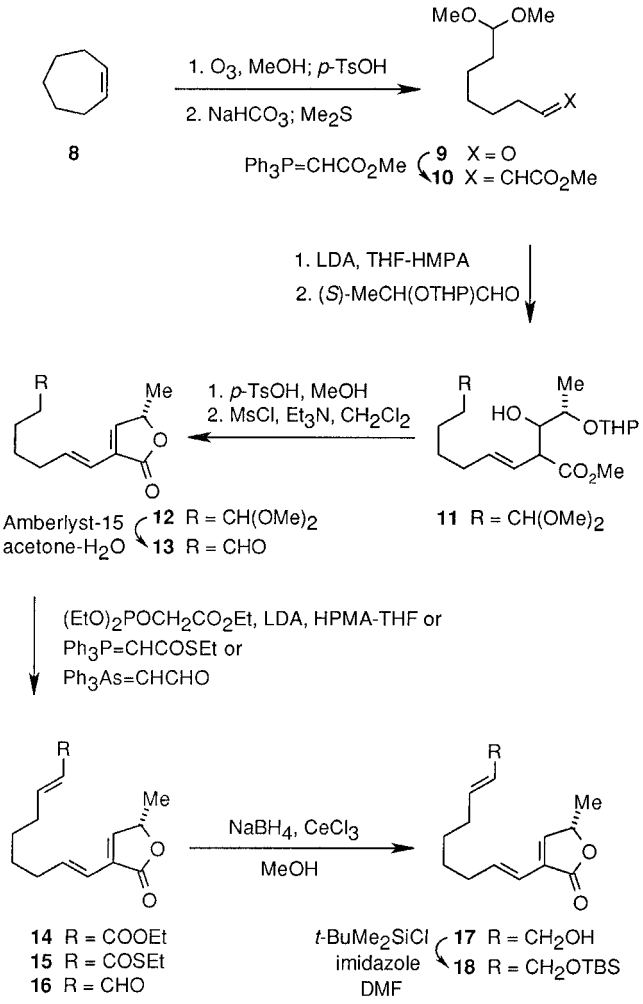
(13) Hermann, J. L.; Kieczykowski, G.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *14*, 2433.

S0022-3263(97)00612-9 CCC: $14.00 

**Chart 1**




**Scheme 1**

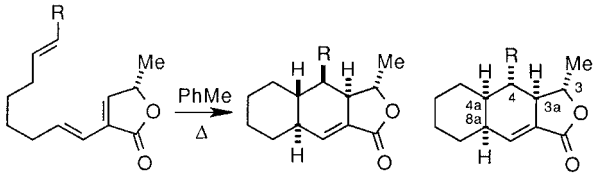



methanesulfonyl chloride and triethylamine in dichloromethane.[14] The *E*:*Z* isomer ratio was improved to 32:1 by allowing a dichloromethane solution of **11** to sit on the windowsill in the presence of iodine on a sunny day.[15]

We next turned to the construction of Diels–Alder substrate **14** and other trienes that were eventually studied. Hydrolysis of acetal **12** was accomplished using Amberlyst-15 in aqueous acetone. The resulting crude aldehyde **13** was subjected to Wadsworth–Horner–Emmons olefination to provide **14** in 71% overall yield.[16] Thioester substrate **15** was also prepared in 67% overall yield from **12** using the appropriate stabilized phosphorane.[17] Finally, crude **13** was allowed to react with the appropriate arsenic ylide to afford unsaturated aldehyde **16** (76%).[18] Luche reduction of **16** ($NaBH_4$–$CeCl_3$) gave allylic alcohol **17** (96%)[19] which was readily converted to the corresponding *tert*-butyldimethylsilyl ether **18** (88%).[20]

The results of a series of intramolecular Diels–Alder reactions are documented in Table 1. We first examined the cycloaddition of unsaturated ester **14**. This substrate underwent cycloaddition when heated to 200 °C in toluene to give a mixture of cycloadducts that were inseparable by column chromatography (entry 1). Signals in the vinylic region of the $^1$H NMR spectrum of the mixture at $\delta$ 6.64 and 6.69 with relative intensities of 1:4 suggested that the cycloaddition had provided a mixture of endo and exo cycloadducts derived from addition anti to the butenolide methyl group. Although

**Table 1. Intramolecular Cycloadditions of Trienes**




| Entry | Substrate | Conditions | %Yield[b] | 19:20 |
|---|---|---|---|---|
| 1 | **14** | 200 C (3h) | 77 | 1:4[c] |
| 2 | **14** | 110 C (24h) | 58 | 1:1[c] |
| 3 | **14** | Acid, 40 C (96h)[a] | 31 | 3:1 |
| 4 | **18** | 210 C (18h) | 82 | 1:4[c] |
| 5 | **15** | 110 C (16h) | 30 | 1:1 |
| 6 | **15** | Acid, 40 C (96h)[a] | 75 | 20:1 |

[a] $SiO_2$–$Et_2AlCl$ was used as an acid promoter. [b] Isolated yield of product mixture. [c] A minor isomer was detected in addition to **19** and **20**.

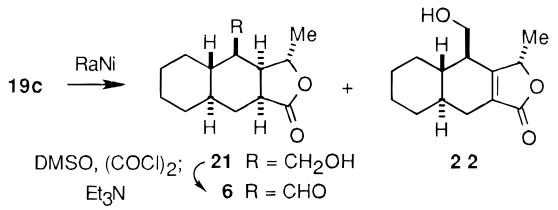
(14) Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163. Yao, Z.-J.; Wu, Y.-L. *Tetrahedron Lett.* **1994**, *35*, 157.
(15) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.
(16) Wadsworth, W. S., Jr. *Organic Reactions*; Wiley: New York, 1977; Vol. 25, pp 73–254.
(17) Keck, G. E.; Boden, E. P.; Mabury, S. A. *J. Org. Chem.* **1985**, *50*, 709.
(18) Huang, Y.-Z., Shi, L.; Yang, J.; Cai, Z. *J. Org. Chem.* **1987**, *52*, 3558.
(19) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(20) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(21) The appearance of a small signal at about $\delta$ 6.79 in the cycloadditions of **19a** and **19b** suggested that a small amount of third stereoisomer was formed in these cycloaddition reactions. This signal did not appear in the Lewis acid promoted reactions.

it was initially not possible to assign stereochemistry to each cycloadduct, evidence was eventually obtained to support assignment of the $\delta$ 6.64 and 6.69 signals to the endo-anti (**19a**) and exo-anti (**20a**) cycloadducts, respectively. Since the endo-anti cycloadduct **19a** was required for the synthesis of himbacine, some other conditions were examined. These studies showed that lowering the reaction temperature to 110 °C gave approximately a 1:1 ratio of **19a** and **20a** (entry 2), but attempts to further improve the endo-exo ratio using homogeneous Lewis acid promotors resulted in no reaction or decomposition products.[22] It is possible that the lactone in **14** competes with the unsaturated ester for the Lewis acid, causing problems with this approach.

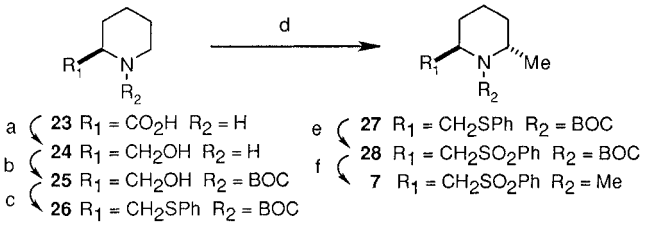
On the basis of the notion that we might be involved with an inverse electron demand Diels–Alder, silyl ether **18** was selected as the next substrate for study. Unfortunately, this substrate offered no improvement over unsaturated ester **14**. Once again, two major cycloadducts, whose vinylic protons appeared a $\delta$ 6.61 (minor) and 6.65 (major), were obtained in a 1:4 ratio, respectively (entry 4).[21] This time, however, the major cycloadduct was obtained in pure form by recrystallization of the product mixture, and 2D-NMR spectroscopy clearly established its structure as **20b**. For example, COSY spectra showed that $H_{3a}$, $H_4$, $H_{4a}$, and $H_{8a}$ appeared at $\delta$ 2.7, 1.55, 1.9, and 2.4, respectively. In difference NOE experiments, irradiation of $H_{4a}$ gave 8% and 7% enhancements of the signals due to $H_{8a}$ and $H_{3a}$, respectively, suggesting a cis relationship between these hydrogens. Furthermore, irradiation of the $H_{3a}$, $H_{4a}$, and $H_{8a}$ signals failed to show an NOE at $H_4$, consistent with a trans relationship between $H_4$ and other hydrogens on the cyclohexene ring. Finally, irradiation of the lactone methine at $\delta$ 4.2 showed a small NOE of 2% at $H_{3a}$ and a larger NOE of 4% at $H_4$, establishing the stereochemical relationship between stereogenic centers in the lactone and cyclohexene rings.

Based on knowledge that thioesters are more reactive than esters as Diels–Alder dienophiles, we next examined unsaturated thioester **15**.[23] This change had little effect on product ratios in the thermal cycloaddition (entry 5). For example, warming **15** at 110 °C gave nearly equal amounts of **19c** (vinyl proton at $\delta$ 6.63) to **20c** (vinyl proton at $\delta$ 6.68). Once again we examined Lewis acid promotors. Although homogeneous Lewis acids again met with failure, excellent results were obtained using a heterogeneous promotor prepared by the reaction of diethylaluminum chloride with silica gel (entry 6).[24] When treated with this promotor, thioester **15** gave a 75% yield of a mixture of cycloadducts **19c** and **20c** (20:1, respectively) from which the desired endo isomer could be crystallized in 67% yield. Given this result, we reinvestigated ester **14** as a substrate and found that although it underwent cycloaddition upon treatment with $SiO_2$–$Et_2AlCl$, the yield and endo–exo ratios were inferior to those obtained with thioester **15** (entry 3). The precise reasons for the difference in behavior of **14** and **15** are not known. The results, however, are consistent with observations that Lewis acids such as ethylaluminum dichloride and titanium tetrachloride seem to activate unsaturated thioesters in preference to unsaturated esters in competitive situations.[23] In the case of **15**, perhaps the Lewis acid promotor complexes the thioester and not the lactone, thus activating the dienophile without deactivating the diene.

**Scheme 2**




**Scheme 3**




(a) $BF_3$•$Et_2O$, $BH_3$•$Me_2S$, THF (b) NaOH, (*t*-BuOCO)$_2$O, THF, $H_2O$ (c) PhSSPh, pyridine, $Bu_3P$ (d) *s*-BuLi, TMEDA-$Et_2O$; $CH_3I$ (e) *m*-CPBA, $NaHCO_3$, $CH_2Cl_2$ (f) $CF_3CO_2H$, $CH_2Cl_2$; HCHO, $H_2O$, $NaBH_3CN$, *p*H7

It turns out that use of a thioester in the critical Diels–Alder reaction was beneficial in the next stage of the synthesis (Scheme 2). Although treatment of **19c** with sodium borohydride under several different conditions failed to accomplish reduction of the thioester without disturbing the lactone, treatment of **19c** with Raney nickel in ethanol accomplished chemoselective reduction of both the thioester and alkene in the presence of the lactone to provide alcohol **21** (81%),[25] whose structure was confirmed by X-ray crystallography, along with butenolide **22** (9%).[26] Swern oxidation of **21** gave aldehyde **6** (70–90%) as a sensitive oil that was best used directly in subsequent reactions.[27]

**Preparation of Sulfone 7.** The original plan called for the coupling of aldehyde **6** with sulfone **7**, whose preparation is described in Scheme 3. (*R*)-Piperidine-2-carboxylic acid (**23**) was resolved via its tartrate salt using a published procedure.[28] Treatment of **23** with boron trifluoride etherate followed by borane–dimethyl sulfide complex gave crude amino alcohol **24**,[29] which was reacted with di-*tert*-butyl dicarbonate and sodium hydroxide to provide **25** in 88% overall yield.[30] Treatment of alcohol **25** with diphenyl disulfide and tri-*n*-butylphosphine in the presence of pyridine gave sulfide **26** (94%).[31]

(22) An exhaustive list of Lewis acids was not tried, but it is notable that diethylaluminum chloride (not supported on silica gel) failed to afford cycloadducts.

(23) Wladislaw, B.; Marzorati, L.; Gruber. J. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1991**, *59*, 479. Chen, C.-Y.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 3840. Byeon, C.-H. Ph.D. Thesis, The Ohio State University, Columbus, OH, 1994.

(24) Cativiela, C.; Fraile, J. M.; Garcia, J. I.; Mayoral, J. A.; Pires, E.; Royo, A. J.; Figueras, F.; de Menorval, L. C. *Tetrahedron* **1993**, *49*, 4073.

(25) McIntosh, A. V., Jr.; Meinzer, E. M.; Levin, R. H. *J. Am. Chem. Soc.* **1948**, *70*, 2955.

(26) We thank Dr. Judith Gallucci of the Department of Chemistry Crystallography Facility for determining the crystal structures of **21**, **31**, and **35**.

(27) Mancuso, A. J.; Swern, E. *Synthesis* **1981**, 165.

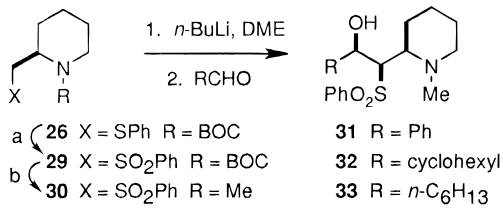
(28) Shiraiwa, T.; Shinjo, K.; Kurokawa, H. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3251.

(29) Dickman, D. A.; Meyers, A. I.; Smith, G. A.; Gawley, R. E. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. 7, p 530.

(30) Tarbell, D. S.; Yamamoto, Y.; Pope, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *69*, 730.

(31) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, *16*, 1409.

**Scheme 4**

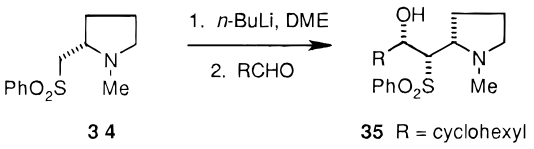



Metalation of **26** in diethyl ether−TMEDA using a cyclohexane solution of *sec*-butyllithium, followed by treatment of the resulting carbanion with iodomethane, gave **27** in 41% yield.[32] Oxidation of **27** to sulfone **28** was accomplished in 87% yield using *m*-chloroperoxybenzoic acid. Treatment of **28** with trifluoroacetic acid, followed by neutralization and Borch methylation of the resulting amine, completed the synthesis of sulfone **7** (90%).[33]

**Attempted Coupling of Aldehyde 6 with Sulfone 7.** All attempts to couple aldehyde **6** with the anion derived from metalation of sulfone **7** met with failure.[34] This was a mild surprise since metalated $\beta$-amino sulfone−aldehyde couplings had been used during the course of preparing several himbacine analogs.[7a,b] The problem appeared to be that the aldehyde was too hindered, and we speculate that either proton transfer reactions and/or nucleophilic addition of the carbanion to the lactone carbonyl group caused problems. No tractable products were ever isolated from these reactions, although it was demonstrated that metalation of the sulfone was not the problem. For example, treatment of **7** with *n*-butyllithium in tetrahydrofuran followed by benzaldehyde gave a mixture of $\beta$-hydroxy sulfone adducts.

Although dissapointing, this approach was not without some benefit as during attempts to find conditions to effect the desired Julia−Lythgoe olefination,[35] some useful solvent effects on carbonyl addition reactions of metalated sulfones were discovered.[36] In addition, some interesting diastereoselectivities in coupling reactions of the simpler $\beta$-amino sulfones **30** and **34** with aldehydes were observed. Sulfone **30** was prepared from racemic sulfide **26** as described in Scheme 4. Thus, oxidation of the sulfide gave sulfone **29** (89%) which was converted to **30** in 90% yield using standard conditions. On the basis of our experience with sulfone **7**, it was not surprising to find that metalation of **30** with *n*-butyllithium in DME followed by reaction with benzaldehyde gave a mixture of four diastereomeric $\beta$-hydroxy sulfones in a 9:1:1:1 ratio and 84% combined yield. It was possible to separate all four diastereomers and determine the stereochemistry of the major isomer (**31**) by X-ray crystallography.[26] It was more surprising to find that the anion derived from **30** gave better stereoselectivity upon reaction with cyclohexanecarbaldehyde and propanal. The reaction with cyclohexanecarbaldehyde gave four diastereomers (93%) in an 18:1:1:1 ratio, and the major diastereomer was assigned structure **32** by analogy with the benzaldehyde results and supported by similarities in their $^1$H NMR spectra. The reaction of **30** with heptanal similarly provided an 18:1:1:1 mixture of adducts (81%) with the major isomer assigned as structure **33**.

**Scheme 5**

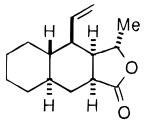



Unfortunately, this diastereoselectivity appears to be sensitive to sulfone structure. For example, metalation of sulfone **34** followed by reaction with cyclohexanecarbaldehyde gives a 59:27:7:7 mixture of diastereomers with **35** as the major product (Scheme 5).[26,37] Finally, treatment of $\beta$-(dimethylamino)ethyl phenyl sulfone[38] with *n*-butyllithium followed by cyclohexanecarbaldehyde provides a 1:1 mixture of diastereomeric $\beta$-hyroxysulfones, an indication that the asymmetric induction observed with sulfones **30** and **34** is due to the ring stereogenic center.

**A Successful Coupling Strategy: Synthesis of Himbacine.** Due to lack of success in the coupling of **6** and **7**, the approach was revised in a manner that switched the polarity of the coupling partners. Thus, it was hoped that the carbanion derived from metalation of sulfone **38** would couple with aldehyde **42**. The synthesis of **38** is described in Scheme 6. Treatment of alcohol **21** with *p*-toluenesulfonyl chloride and pyridine provided the corresponding tosylate which was treated with thiophenol and potassium *tert*-butoxide in DMSO to afford sulfide **36** (94%). Anticipating that a lactone and metalated sulfone would be incompatible, **36** was treated with diisobutylaluminum hydride and the resulting lactol was converted to acetal **37** (94%) using boron trifluoride etherate and methanol.[39] Oxidation of **37** with *m*-chloroperoxybenzoic acid completed the preparation of **38** (94%).

The synthesis of aldehyde **42** is described in Scheme 7. Alcohol **25** was converted to silyl ether **39** in 96% yield using standard conditions.[20] Metalation and methylation of **25** using the Beak protocol gave **40** in 71% yield.[32] Deprotection of the alcohol using tetra-*n*-butylammonium

(32) Beak, P.; Lee, W. K. *J. Org. Chem.* **1990**, *55*, 2578.
(33) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(34) On one occasion, treatment of the anion derived from sulfone **7** with aldehyde **6** followed by benzoyl chloride gave crude material, which upon treatment with sodium amalgam clearly gave olefin **I** in about 15% overall yield [$^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.75 (m, 1H), 1.0−1.3 (m, 6H), 1.38 (d, $J$ = 7 Hz, 3H), 1.6−1.8 (m, 4H), 1.9 (m, 1H), 2.10 (m, 1H), 2.25 (m, 1H), 2.6 (m, 1H), 4.65 (dq, $J$ = 12, 7 Hz, 1H), 5.1 (m, 2H), 5.5 (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 22.0 (q), 26.0 (t), 26.3 (t), 31.1 (t), 31.9 (t), 33.5 (t), 39.8 (d), 41.0 (d), 42.1 (d), 46.9 (d), 48.6 (d), 76.7 (d), 116.7 (t), 139.7 (d), 178.1 (s)]. This material could have resulted from sequential carbonyl addition, alcohol acylation, a Grob fragmentation, and vinyl sulfone reduction.

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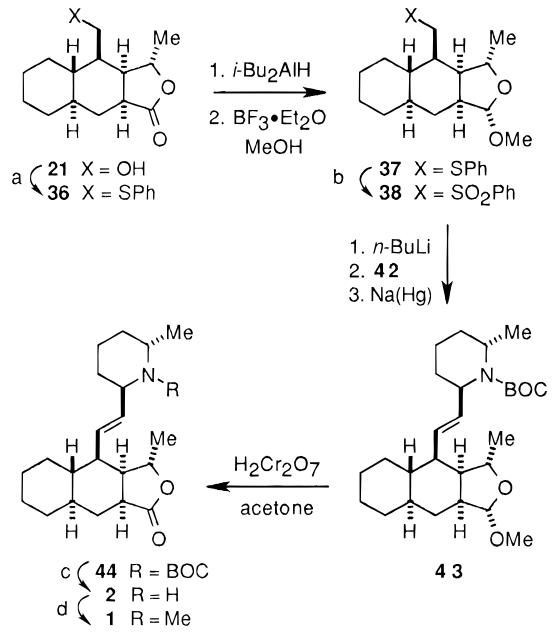
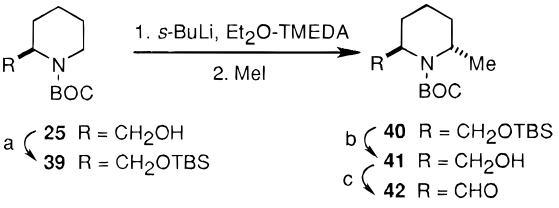
(35) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833.
(36) Hart, D. J.; Wu, W.-L. *Tetrahedron Lett.* **1996**, *37*, 5283.
(37) The preparation of sulfone **35** followed the same general path used to prepare sulfone **30** (see Experimental Section), only (*S*)-2-(hydroxymethyl)pyrrolidine was used as the starting material (Jing Li, unpublished results).
(38) Metalation of $\beta$-(dimethylamino)ethyl phenyl sulfone (Barlow, K. N.; Marshall, D. R.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1920) with *n*-BuLi followed by reaction of the resulting carbanion with cyclohexanecarbaldehyde gave a 58:42 mixture of diastereomeric $\beta$-hydroxy sulfones in 91% yield.
(39) Acetal **37** is a single isomer whose stereochemistry at the acetal carbon was not proven, but is most likely as shown. We note that the stereochemistry shown in the communication describing this research is most likely in error.[9]

**Scheme 6**




(a) TsCl, pyridine; PhSH, KO-*t*-Bu, DMSO (b) *m*-CPBA
(c) TFA, $CH_2Cl_2$ (d) $NaBH_3CN$, HCHO

**Scheme 7**




(a) *t*-$BuMe_2SiCl$, imidazole, DMF (b) *n*-$Bu_4NF$, THF
(c) $(n\text{-}Pr)_4NRuO_4$, NMO, $CH_2Cl_2$

fluoride gave **41** (93%), and oxidation using the Ley procedure provided aldehyde **42** (86%).[40]

The synthesis was completed as outlined in Scheme 6. Metalation of **38** in 1,2-dimethoxyethane followed by addition of excess aldehyde **42** provided a diastereomeric mixture of $\beta$-hydroxy sulfones in 67% yield along with 25% of recovered sulfone. Treatment of the mixture of sulfones with sodium amalgam and disodium hydrogen phosphate in methanol gave olefin **43** in 68% yield.[41] Thus, the overall yield of this Julia−Lythgoe coupling was 45% (or 60% taking into account recovered **38**). Oxidation of **43** with Jones reagent provided **44** (95%),[42] and removal of the nitrogen protecting group using trifluoroacetic acid provided (+)-himbeline (**2**) in 92% yield.[43] Borch methylation of himbeline afforded (+)-himbacine (**1**) in 70% yield. The synthetic alkaloid was identical in all respects with a sample of the natural product (TLC, $^1H$ NMR, $^{13}C$ NMR, IR, mp, optical rotation) and a 1:1 mixture of the synthetic and natural materials melted undepressed.[44]

## Experimental Section

**7,7-Dimethoxyheptanal (9).** A solution of 7.0 g (71.3 mmol) of cycloheptene (**8**) in 250 mL of $CH_2Cl_2$ and 50 mL of MeOH was cooled to −78 °C, and ozone (Welsbach ozone generator) was bubbled through the mixture. When the solution turned blue, ozone addition was stopped and argon was passed through the mixture until the blue color was discharged. The cold bath was removed, and 1.215 g (6.4 mmol) of *p*-TsOH monohydrate was added. The solution was allowed to warm to rt over a 2.5-h period with stirring under an atmosphere of argon. To the mixture was added 2.15 g (25.6 mmol) of anhydrous sodium bicarbonate. The mixture was stirred for 20 min, and 12 mL (163 mmol) of dimethyl sulfide was added. After being stirred overnight, the mixture was concentrated to approximately 50 mL in vacuo, 100 mL of $CH_2Cl_2$ and 75 mL of water were added, and the aqueous phase was extracted with two 100-mL portions of $CH_2Cl_2$. The combined organic layers were washed with 100 mL of water. The aqueous layer was extracted with 100 mL of $CH_2Cl_2$, and the combined extracts were dried ($Na_2SO_4$) and concentrated to give 12.5 g (97%) of crude aldehyde **9**, suitable for use in subsequent reactions without further purification: IR (neat) 2720, 1724 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.30−1.65 (m, 8H), 2.38 (dt, $J$ = 7.3, 1.6 Hz, 2H), 3.29 (s, 6H), 4.33 (t, $J$ = 5.7 Hz, 1H), 9.74 (t, $J$ = 1.7 Hz, 1H); mass spectrum *m*/*e* (relative intensity) 174 ($M^+$, 1), 173 (9), 141 (12).

**Methyl 9,9-Dimethoxy-2-nonenoate (10).** To a solution of 12.5 g (71.8 mmol) of crude aldehyde **9** in 200 mL of MeOH was added 25.0 g (73.3 mmol) of (carbomethoxymethylidene)triphenylphosphorane at 0 °C. The mixture was stirred at 0 °C for 5 h and then at rt for 2 h. The solvent was removed in vacuo, and the residue was extracted with three 100-mL portions of diethyl ether−hexane (1:1). The combined extracts were concentrated and chromatographed over silica gel (eluted with ethyl acetate−hexane, 1:9 plus 1% triethylamine) to give 11.93 g (72% from **8**) of ester **10** as a 3:2 mixture of *E* and *Z* isomers, respectively: IR (neat) 1725, 1657 $cm^{-1}$; $^1H$ NMR of mixture (250 MHz, $CDCl_3$) $\delta$ 1.35−1.61 (m, 8H), 2.19−2.80 (m, 2H), 3.31 (s, 6H), 3.73 (s, 3H), 4.35 (t, $J$ = 5.7 Hz, 1H), 5.70−7.0 (m, 2H); exact mass calcd for $C_{12}H_{22}O_4$ *m*/*e* 230.1518, found *m*/*e* 230.1501.

**(*S*)-3-[(*E*)-7,7-Dimethoxy-1-heptenyl]-5-methyl-2(5*H*)-furanone (12).** To a solution of 36.7 mL (55.0 mmol) of LDA in THF and 9.5 mL (55.0 mmol) of HMPA in 150 mL of THF at −78 °C was introduced via syringe 11.58 g (50.3 mmol) of ester **10**. The solution was stirred for 30 min, and then 8.70 g (55.0 mmol) of the tetrahydropyranyl ether of (*S*)-2-hydroxypropanal[12] was added dropwise. The mixture was stirred at −78 °C for 1 h , quenched with 200 mL of water, and then extracted with three 100-mL portions of diethyl ether. The combined extracts were washed with 100 mL of brine, dried ($Na_2SO_4$), and concentrated in vacuo. Chromatagraphy of the residue over silica gel (eluted with ethyl acetate−hexane, 1:3 plus 1% triethylamine) gave 18.3 g (94%) of $\beta$-hydroxy ester **11** as a colorless oil: IR (neat) 3444 (br), 1738 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.0−1.9 (m, 10H), 2.0−2.2 (m, 2H), 2.3−3.2 (m, 4H), 4.33(t, $J$ = 5.7 Hz, 1H), 4.60−4.90 (m, 2H), 5.35−5.70 (m, 2H); exact mass calcd for $C_{20}H_{36}O_7$ *m*/*e* 388.2462, found *m*/*e* 388.2471. This material was used directly in the next reaction.

A solution of 18.3 g (47.1 mmol) of **11** in 150 mL of MeOH containing 1.20 g of *p*-TsOH was stirred at rt overnight. After addition of 3.0 mL of triethylamine, the solvent was removed by rotary evaporation to give 11.8 g of crude $\beta$-hydroxy lactone: IR (neat) 3443, 1771 $cm^{-1}$; exact mass calcd for $C_{14}H_{24}O_5$ *m*/*e* 272.1624, found *m*/*e* 272.1614. This material was used in the following reaction without further purification.

The crude $\beta$-hydroxy lactone was dissolved in 150 mL of $CH_2Cl_2$ and cooled to 0 °C, and 4.7 mL (6.87 g, 60.0 mmol) of methanesulfonyl chloride and 16.8 mL (12.1 g, 120.0 mmol)

(40) Griffith, W. P.; Ley, S. V.; Whitcombe, F. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 39.
(41) For alternative methods for conducting this elimination which were not tried, see: Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194.
(42) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.
(43) Synthetic himbeline gave a melting point and specific rotation in agreement with those reported for the natural product.[2] Spectral data were also in accord with the assigned structure.
(44) We thank Professor Viresh Rawal for kindly providing a sample of the natural product.

of triethylamine were added successively. The reaction mixture was stirred at 0 °C for 2 h and diluted with 250 mL of $CH_2Cl_2$ and 150 mL of water. The aqueous layer was extracted with an additional 100 mL of $CH_2Cl_2$. The combined extracts were washed with 100 mL of brine, dried ($Na_2SO_4$), and concentrated to dryness. Chromatography of the residue over silica gel (eluted with ethyl acetate−hexane, 1:4 plus 1% triethylamine) afforded 1.60 g of pure *E*-**12** and 7.7 g of a mixture of *E*-**12** and *Z*-**12** (78% for two steps). ***E*-12**: $[\alpha]^{20}_D$ +30.3 (*c* 0.54, $CHCl_3$); IR (neat) 1756, 1661 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.36 (d, $J$ = 6.7 Hz, 3H), 1.19−1.50 (m, 4H), 1.52−1.57 (m, 2H), 2.11 (q, $J$ = 7.0 Hz, 2H), 3.25 (s, 6H), 4.29 (t, $J$ = 5.7 Hz, 1H), 4.96 (q, $J$ = 6.7 Hz, 1H), 6.04 (d, $J$= 15.4 Hz, 1H), 6.71 (dt, $J$ = 15.3, 7.0 Hz, 1H), 7.00 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 19.0 (q), 24.0 (t), 28.4 (t), 32.0 (t), 33.1 (t), 52.5 (q), 76.7 (d), 104.3 (d), 118.5 (d), 129.1 (s), 138.1 (d), 147.0 (d), 171.8 (s); exact mass calcd for $C_{14}H_{22}O_4$ *m*/*e* 254.1519, found *m*/*e* 254.1498.

A solution of 4.30 g (16.9 mmol) of the mixture of *E* and *Z* isomers in 150 mL of $CH_2Cl_2$ containing 0.20 g of iodine was irradiated with sunlight for 10 h. After isomerization was complete by TLC analysis (silica gel, ethyl acetate−hexane, 1:3), the mixture was washed with 50 mL of 10% aqueous sodium thiosulfate, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with ethyl acetate−hexane, 1:4 plus 1% triethylamine) to give 3.56 g (83%) of pure *E*-**12**.

**Ethyl (2*E*,8*E*)-9-[(*S*)-Dihydro-5-methyl-2-oxo-3-furyl]-2,8-nonadienoate (14).** To a solution of 8.0 mL (12.0 mmol) of 1.5 M LDA in cyclohexane, 40 mL of THF, and 5 mL of HMPA was added 2.69 g (12.0 mmol) of triethyl phosphonoacetate at 0 °C. The solution was stirred at 0 °C for 15 min, and then 1.71 g (8.2 mmol) of crude aldehyde **13** (prepared from **12** as described in the preparation of **15**) was added. The mixture was stirred at 0 °C for 30 min, diluted with 100 mL of saturated aqueous ammonium chloride, and then extracted with three 100-mL portions of diethyl ether. The combined extracts were washed with 100 mL of brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:10) to give 1.84 g (83% from acetal **12**) of ester **14** as a colorless oil: $[\alpha]^{20}_D$ +26.4 (*c* 0.50, $CHCl_3$); IR (neat) 1756, 1715, 1652 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.25 (t, $J$ = 7 Hz, 3H), 1.38 (d, $J$ = 7 Hz, 3H), 1.4−1.5 (m, 4H), 2.1−2.2 (m, 4H), 4.14 (q, $J$ = 7 Hz, 2H), 5.00 (q, $J$ = 6.8 Hz, 1H), 5.77 (d, $J$ = 15.6 Hz, 1H), 6.06 (d, $J$ = 15.3 Hz, 1H), 6.74 (dt, $J$ = 15.9, 7 Hz, 1H), 6.91 (dt, $J$= 15.6, 7 Hz, 1H), 7.01 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 14.1 (q), 19.0 (q), 27.4 (t), 28.1 (t), 31.8 (t), 32.9 (t), 60.0 (t), 76.8 (d), 118.6 (d), 121.4 (d), 129.1 (s), 137.8 (d), 147.1 (d), 148.7 (d), 166.5 (s), 171.8 (s); exact mass calcd for $C_{16}H_{22}O_4$ *m*/*e* 278.1519, found *m*/*e* 278.1517.

***S*-Ethyl (2*E*,8*E*)-9-[(*S*)-2,5-Dihydro-5-methyl-2-oxo-3-furyl]-2,8-nonadienethioate (15).** A solution of 3.30 g (13.0 mmol) of acetal **12** in 50 mL of acetone containing 0.5 g of Amberlyst-15 and 0.8 mL of water was stirred at rt for 24 h. The resin was removed by filtration, and the filtrate was concentrated in vacuo to give 2.81 g of crude aldehyde **13**, which was used in the next step without further purification.

A solution of the above aldehyde and 6.20 g (17.0 mmol) of *S*-ethyl ((thiocarboxy)methylene)triphenylphosphorane[17] in 150 mL of chloroform was heated at reflux for 2 h. The solution was cooled to rt, 50 mg of 4-(dimethylamino)pyridine was added, and the mixture was stirred at rt for another 2 h. The solution was concentrated in vacuo, and the residue was chromatographed over silica gel (eluted with ethyl acetate−hexane, 1:4) to provide 2.55 g (67% from **12**) of thioester **15** as a colorless oil: $[\alpha]^{20}_D$ +26.5° (*c* 0.81, $CHCl_3$); IR (neat) 1756, 1668, 1631 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 1.2 (t, $J$ = 7.4 Hz, 3H), 1.38 (d, $J$ = 6.8 Hz, 3H), 1.39−1.51 (m, 4H), 2.11−2.21 (m, 4H), 2.90 (q, $J$ = 7.4 Hz, 2H), 5.00 (q, $J$ = 6.8 Hz, 1H), 6.03 (d, $J$ = 15.5 Hz, 2H), 6.70−6.90 (two dt, 2H), 7.02 (s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 14.7 (q), 19.0 (q), 22.9 (t), 27.4 (t), 28.1 (t), 31.8 (t), 32.9 (t), 76.8 (d), 118.7 (d), 128.8 (d), 129.1 (s), 137.8 (d), 144.7 (d), 147.1 (d), 171.8 (s), 189.9 (s); FAB mass for $C_{16}H_{22}O_3S$ *m*/*e* ($M^+$ + 1) 295.17 (100).

**(2*E*,8*E*)-9-[(*S*)-2,5-Dihydro-5-methyl-2-oxo-3-furyl]-2,8-nonadienal (16).** A mixture of 0.84 g (4.0 mmol) of crude aldehyde **13** (prepared from **12** as described above), 2.06 g (4.8 mmol) of (formylmethyl)triphenylarsonium bromide,[18] 0.66 g (4.8 mmol) of potassium carbonate, and 40 mL of THF−diethyl ether (v/v = 7:3, containing 0.2 mL of water) was stirred at rt for 3 h. The solution was decanted, and the residue was washed with diethyl ether. The combined solutions were concentrated in vacuo, and the residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:4) to give 0.71 g (76% from acetal **12**) of aldehyde **16** containing a small amount of impurities. This material was suitable for use in the next reaction: IR (neat) 2733, 1754, 1688, 1638 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.39 (d, $J$= 7 Hz, 3H), 1.4−1.7 (m, 4H), 2.1−2.5 (m, 4H), 5.02 (q, $J$ = 7 Hz, 1H), 6.06 (d, $J$ = 15 Hz, 1H), 6.10 (dd, $J$ = 15, 7.5 Hz, 1H), 6.76 (m, 2H), 7.03 (s, 1H), 9.50 (d, $J$ = 7.5 Hz, 1H).

**(*S*)-3-[(1*E*,7*E*)-9-Hydroxy-1,7-nonadienyl]-5-methyl-2(5*H*)-furanone (17).** To a solution of 0.71 g (3.0 mmol) of aldehyde **16** and 1.12 g (3.0 mmol) of cerium chloride heptahydrate in 7.5 mL of MeOH was added 0.11 g (3.0 mmol) of sodium borohydride over a 3-min period. The mixture was stirred for 5 min, diluted with 30 mL of water, and extracted with three 30-mL portions of diethyl ether. The combined extracts were washed with 30 mL of brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:3) to give 0.69 g (96%) of alcohol **17** as a colorless oil: $[\alpha]^{20}_D$ +27.8 (*c* 0.2, $CHCl_3$); IR (neat) 3418, 1752 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.42 (d, $J$ = 7 Hz, 3H), 1.4−1.6 (m, 4H), 2.05 (m, 2H), 2.18 (m, 2H), 4.09 (m, 2H), 5.03 (dq, $J$ = 7, 1.6 Hz, 1H), 5.65 (m, 2H), 6.08 (d, $J$ = 16 Hz, 1H), 6.79 (dt, $J$ = 16, 7 Hz, 1H), 7.03 (d $J$= 1.6 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 19.1 (q), 28.1 (t), 28.5 (t), 31.8 (t), 33.1 (t), 63.7 (t), 77.1 (d), 118.4 (d), 129.1 (d), 132.9 (d), 138.4 (d), 146.8 (d), the carbonyl and adjacent olefinic carbon were not observed.

**(*S*)-3-[(1*E*,7*E*)-9-(*tert*-Butyldimethylsiloxy)-1,7-nonadienyl]-5-methyl-2(5*H*)-furanone (18).** To a solution of 0.48 g (2.0 mmol) of alcohol **17** in 10 mL of dry DMF were added 0.375 g (2.6 mmol) of *tert*-butyldimethylsilyl chloride and 0.544 g (8.0 mmol) of imidazole. The mixture was stirred at rt overnight, diluted with 30 mL of water, and then extracted with three 30-mL portions of diethyl ether. The combined extracts were washed with 30 mL of brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:9) to give 0.62 g (88%) of slightly impure silyl ether **18** as a colorless oil: $[\alpha]^{20}_D$ +21.3 (*c* 0.57, $CHCl_3$), IR (neat) 1759, 1662 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$), $\delta$ 0.069 (s, 6H), 0.91 (s, 9H), 1.43 (d, $J$ = 7 Hz, 3H), 1.35−1.50 (m, 4H), 2.05 (m, 2H), 2.18 (m, 2H), 4.15−4.25 (m, 2H), 5.03 (dq, $J$ = 7, 2 Hz, 1H), 5.40−5.68 (m, 2H), 6.08 (d, $J$ = 15 Hz, 1H), 6.79 (dt, $J$ = 16, 7 Hz, 1H), 7.03 (d, $J$ = 2 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −5.2 (q), 18.2 (s), 19.0 (q), 25.8 (q), 28.1 (t), 28.5 (t), 31.8 (t), 33.0 (t), 63.8 (t), 76.7 (d), 118.4 (d), 129.1 (s), 129.3 (d), 130.8 (d), 138.2 (d), 146.9 (d), 171.8 (s); exact mass calcd for $C_{20}H_{34}O_3Si$ *m*/*e* 350.2305, found *m*/*e* 350.2258.

**Ethyl (3*S*,3a*R*,4*R*,4a*S*,8a*S*)-1,3,3a,4,4a,5,6,7,8,8a-Decahydro-3-methyl-1-oxonaphtho[2,3-*c*]furan-4-carboxylate (19a) and Ethyl (3*S*,3a*R*,4*S*,4a*R*,8a*S*)-1,3,3a,4,4a,5,6,7,8,8a-Decahydro-3-methyl-1-oxonaphtho[2,3-*c*]furan-4-carboxylate (20a). A. Thermal Reaction.** A solution of 1.67 g (6.0 mmol) of triene **18** in 25 mL of toluene was heated in a sealed tube (bath temperature 200 °C) under an argon atmosphere for 27 h. The mixture was cooled to rt, and the residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:20 → 1:15 → 1:10) to give 1.29 g (77%) of a 1:4 mixture (by NMR) of **19a** and **20a**, respectively: $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.25 (t, $J$ = 7 Hz, $CH_3$), 1.35 (d, $J$ = 7 Hz, $CH_3CH$), 6.64 (t, $J$ = 3 Hz, =CH for **19a**), 6.69 (t, $J$ = 3 Hz, =CH for **20a**), 6.79 (t, $J$ = 3 Hz, =CH for third isomer), other overlapping signals appeared at appropriate chemical shifts. **B. $SiO_2$−$Et_2AlCl$-Promoted Reaction.** A mixture of 36 mg (0.13 mmol) of triene **14** and 78 mg of $SiO_2$−$Et_2AlCl$ in 2 mL of dry toluene was stirred at 40 °C for 4 days and then cooled to rt and concentrated in vacuo. The residue was subjected

to preparative TLC (eluted with ethyl acetate−hexane, 1:25) to provide 18 mg (50%) of recovered **14** and 11 mg (31%) of a 3:1 mixture (by NMR) of **19a** and **20a**, respectively. A small signal due to a third isomer also appeared at $\delta$ 6.79.

**(3*S*,3a*R*,4*R*,4a*S*,8a*S*)-4-[(*tert*-Butyldimethylsiloxy)-methyl]-3a,4,4a,5,6,7,8,8a-octahydro-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one (19b) and (3*S*,3a*R*,4*S*,4a*R*,8a*S*)-4-[(*tert*-Butyldimethylsiloxy)methyl]-3a,4,4a,5,6,7,8,8a-octahydro-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one (20b).** A solution of 0.176 g (0.5 mmol) of triene **18** in 15 mL of toluene containing 3 mg of hydroquinone was heated in a sealed tube (bath temperature 210 °C) under an argon atmosphere for 18 h. The mixture was cooled to rt and concentrated in vacuo, and the residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:9) to give 0.144 g (82%) of a 4:1 mixture (by NMR) of **20b** and **19b**, respectively. Recrystallization of a sample from EtOAc−hexane provided 41 mg of pure exoadduct **20b** as a white solid: mp 126−127 °C; $[\alpha]^{20}_D$ −36.1 (*c* 0.44, $CHCl_3$); IR (neat) 1765, 1685 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 0.061 (s, 3H), 0.069 (s, 3H), 0.89 (s, 9H), 1.17−1.23 (m, 2H), 1.30−1.44 (m, 2H), 1.45−1.58 (m, 1H), 1.52 (d, $J$ = 6 Hz, 3H), 1.58−1.62 (m, 1H), 1.70 (m, 2H), 1.85 (m, 1H), 1.95 (m, 1H), 2.37 (m, 1H), 2.90 (tt, $J$ = 9, 3 Hz, 1H), 3.65 (dd, $J$ = 10.5, 3 Hz, 1H), 3.77 (dd, $J$ = 10.5, 4 Hz, 1H), 4.24 (dq, $J$ = 8.5, 6 Hz, 1H), 6.64 (t, $J$ = 3.5 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −5.7 (q), −5.6 (q), 18.0 (s), 21.5 (q), 21.8 (t), 25.6 (q), 25.8 (t), 26.9 (t), 29.5 (t), 34.8 (d), 37.7 (d), 38.2 (d), 46.3 (d), 60.5 (t), 81.0 (d), 129.8 (s), 139.7 (d), 170.0 (s); exact mass calcd for $C_{20}H_{34}O_3Si$ *m*/*e* 350.2305, found *m*/*e* 350.2290. Anal. Calcd for $C_{20}H_{34}O_3Si$: C, 68.63; H, 9.78. Found: C, 68.39; H, 9.73.

***S*-Ethyl (3*S*,3a*R*,4*R*,4a*S*,8a*S*)-1,3,3a,4,4a,5,6,7,8,8a-Decahydro-3-methyl-1-oxonaphtho[2,3-*c*]furan-4-carbothioate (19c).** A mixture of 4.70 g (16.0 mmol) of triene **15** and 9.6 g of $SiO_2$−$Et_2AlCl$ in 150 mL of dry toluene was stirred at 40 °C for 4 days and then cooled to rt and filtered through a short column of silica gel. Concentration of the filtrate and chromatography of the residue over silica gel (eluted with ethyl acetate−hexane, 1:9) afforded 3.51 g (75%) of a 20:1 mixture of two diastereomeric cycloadducts (by $^1H$ NMR) and 0.46 g (10%) of recovered **16**. Recrystallization of the cycloadducts from ethyl acetate−hexane gave 3.17 g (67%) of pure endo adduct **19c** as a white solid: mp 72−73 °C; $[\alpha]^{20}_D$ +2.7 (*c* 0.6, $CHCl_3$); IR (neat) 1770, 1682 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.04 (dq, $J$ = 8.4, 1.9 Hz, 1H), 1.28 (t, $J$ = 7.4 Hz, 3H), 1.37 (d, $J$ = 6.0 Hz, 3H), 1.20−1.50 (m, 4H), 1.70−1.95 (m, 4H), 2.06 (m, 1H), 2.80 (tt, $J$ = 9.5, 3.5 Hz, 1H), 2.90 (q, $J$ = 7.4 Hz, 2H), 2.96 (dd, $J$ = 11.1, 9.6 Hz, 1H), 4.40 (dq, $J$ = 9.1, 6.0 Hz, 1H), 6.63 (t, $J$ = 2.8 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 14.4 (q), 20.5 (q), 23.7 (t), 25.7 (t), 25.8 (t), 30.7 (t), 32.3 (t), 39.5 (d), 41.9 (d), 44.6 (d), 55.4 (d), 77.0 (d), 130.0 (s), 140.6 (d), 168.6 (s), 200.1 (s); exact mass calcd for $C_{16}H_{22}O_3S$ *m*/*e* 294.1219, found *m*/*e* 294.1286. Anal. Calcd for $C_{16}H_{22}O_3S$: C, 65.28; H, 7.54; S, 10.87. Found: C, 65.29; H, 7.49; S, 10.79.

**(3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-4-(hydroxymethyl)-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one (21) and (3*S*,4*R*,4a*S*,8a*R*)-4,4a,5,6,7,8,8a,9-Octahydro-4-(hydroxymethyl)-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one (22).** A suspension of approximately 40 g of active Raney nickel[25] in 75 mL of EtOH and 75 mL of diethyl ether was stirred for 15 min followed by the addition of 2.35 g (8.0 mmol) of thioester **19c**. The mixture was stirred for 30 min at rt and then passed through a short column of silica gel which was washed with three 50-mL portions of EtOAc. The combined organic solutions were concentrated in vacuo, and the residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:4) to give 1.54 g (81%) of alcohol **21** as a white solid and 0.29 g of a mixture of other products. Recrystallization of the mixture from EtOAc−hexane afforded **22** as a white solid. **Alcohol 21**: mp 162−163.5 °C; $[\alpha]^{20}_D$ +53.9 (*c* 0.51, $CHCl_3$); IR (neat) 3482, 1735 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.85−1.30 (m, 6H), 1.51 (d, $J$ = 5.9 Hz, 3H), 1.50−1.90 (m, 7H), 2.43 (m, 1H), 2.57 (dt, $J$ = 12.8, 6.7 Hz, 1H), 3.63−3.78 (m, 2H), 4.70 (dq, $J$ = 10.1, 5.9 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 21.1 (q), 25.7 (t), 26.2 (t), 29.8 (t), 32.1 (t), 33.6 (t), 38.4 (d), 40.3 (d), 42.5 (d), 42.8 (d), 45.7 (d), 61.3 (t), 77.5 (d), 178.5 (s); exact mass calcd for $C_{14}H_{22}O_3$ *m*/*e* 238.1570, found *m*/*e* 238.1572. Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.54; H, 9.31. Found: C, 70.47; H, 9.28. The structure of **21** was confirmed by X-ray crystallography.[45] Alcohol **22**: mp 164−165 °C; $[\alpha]^{20}_D$ −19.3 (*c* 0.44, $CHCl_3$); IR (neat) 3468, 1731, 1673 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.95−1.37 (m, 6H), 1.41 (d, $J$ = 6.7 Hz, 3H), 1.65−2.0 (m, 5H), 2.08 (m, 1H), 2.15 (m, 1H), 2.30 (m, 1H), 3.66 (dd, $J$ = 10.6, 6.3 Hz, 1H), 3.89 (dd, $J$ = 10.7, 3.4 Hz, 1H), 5.17 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 18.7 (q), 25.8 (t), 26.1 (t), 27.2 (t), 31.4 (t), 33.6 (t), 37.9 (d), 39.1 (d), 43.5 (d), 61.7 (t), 79.0 (d), 126.6 (s), 166.0 (s), 173.4 (s); exact mass calcd for $C_{14}H_{20}O_3$ *m*/*e* 236.1413, found *m*/*e* 236.1422. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.14; H, 8.54. Found: C, 71.11; H, 8.55.

***tert*-Butyl (*R*)-2-(Hydroxymethyl)-1-piperidinecarboxylate (25).** To a solution of 6.45 g (50 mmol) of (*R*)-2-piperidinecarboxylic acid[28] and 6.5 mL (53 mmol) of boron trifluoride etherate in 30 mL of THF was added, under reflux, 25 mL (50 mmol) of 2.0 M borane−dimethyl sulfide complex in THF over a 3-h period. The light brown solution was heated under reflux for an additional 18 h and then cooled to rt. To the residue was added 44 mL (176 mmol) of 4.0 M aqueous NaOH. The mixture was refluxed for 4 h, cooled to rt, and extracted with four 100-mL portions of chloroform. The combined extracts were dried ($K_2CO_3$) and concentrated to give 5.88 g of crude **24** as a thick oil. This material was used directly in the next step without further purification. To a solution of 5.88 g of crude **24** in 300 mL of THF−water (1:1) were added successively 10 mL of aqueous 6 N NaOH and 13.1 g (60 mmol) of di-*tert*-butyl dicarbonate in 60 mL of THF through a dropping funnel. The mixture was stirred at rt overnight and then extracted with two 150-mL portions of EtOAc. The combined extracts were washed with 100 mL of brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:1) to give 9.5 g (88% from 2-piperidinecarboxylic acid) of alcohol **25** as a white solid: mp 86−87 °C; $[\alpha]^{20}_D$ +35.9 (*c* 2.0, $CHCl_3$); IR (neat) 3443, 1652 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.42 (s, 9H), 1.36−1.70 (m, 6H), 2.47 (br, 1H), 2.83 (t, $J$ = 12.2 Hz, 1H), 3.57 (m, 1H), 3.75 (m, 1H), 3.90 (br d, $J$ = 13.3 Hz, 1H), 4.25 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 19.4 (t), 25.0 (t), 25.1 (t), 28.3 (q), 39.8 (t), 52.3 (d), 61.3 (t), 79.6 (s), 156.1 (s); exact mass calcd for $C_{11}H_{21}O_3N$ *m*/*e* 215.1522, found *m*/*e* 215.1498. Anal. Calcd for $C_{11}H_{21}O_3N$: C, 61.37; H, 9.83. Found: C, 61.15; H, 9.90.

***tert*-Butyl (*R*)-2-[(Phenylthio)methyl]-1-piperidinecarboxylate (26).** A mixture of 21.5 g (100 mmol) of alcohol **25**, 32.7 g (150 mmol) of diphenyl disulfide, and 31.2 g (150 mmol) of 97% tri-*n*-butylphosphine in 24 mL (300 mmol) of dry pyridine was stirred at rt for 24 h and then diluted with 500 mL of diethyl ether and 200 mL of water. The organic layer was washed with 100 mL of dilute aqueous sodium bicarbonate and 100 mL of brine, dried ($K_2CO_3$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:20) to give 28.9 g (94%) of sulfide **26** as a white solid: mp 57−58 °C; $[\alpha]^{20}_D$ +13 (*c* 1.15, $CHCl_3$); IR (neat) 3057, 1694, 1584 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.40 (s, 9H), 1.35−1.63 (m, 5H), 1.94 (m, 1H), 2.75 (dt, $J$ = 14, 2 Hz, 1H), 3.03−3.17 (m, 2H), 4.03 (broad d, 1H), 4.38 (m, 1H), 7.14−7.39 (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 18.6 (t), 25.1 (t), 26.3 (t), 28.3 (q), 33.3 (t), 38.9 (t), 49.5 (d), 79.4 (s), 125.8 (d), 128.8 (d), 129.0 (d), 136.2 (s), 154.7 (s); exact mass calcd for $C_{17}H_{25}O_2NS$ *m*/*e* 307.1608, found *m*/*e* 307.1604. Anal. Calcd for $C_{17}H_{25}O_2NS$: C, 66.41; H, 8.20. Found: C, 66.27; H, 8.30.

***tert*-Butyl (2*S*,6*R*)-2-Methyl-6-[(phenylthio)methyl]-1-piperidinecarboxylate (27).** To a solution of 27.6 g (90 mmol) of sulfide **26** in 250 mL of diethyl ether at −78 °C was added 15.7 g (135 mmol) of TMEDA followed by 97 mL (126 mmol) of 1.3 M *s*-BuLi in cyclohexane. The mixture was stirred at −78 °C for 6 h, and then 25.4 g (180 mmol) of methyl iodide was added dropwise. The mixture was slowly warmed to rt overnight. The mixture was diluted with 300 mL of

(45) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

water, extracted with three 200-mL portions of diethyl ether, dried ($K_2CO_3$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:25) to give 11.8 g (41%) of sulfide **27** as a white solid: mp 56−57 °C; $[\alpha]^{20}_D$ +7.8 (*c* 1.0, $CDCl_3$); IR (neat) 1682, 1584, 1391, 1372 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.21 (d, $J$ = 6.7 Hz, 3H), 1.44 (s, 9H), 1.5−1.75 (m, 3H), 1.75−1.86 (m, 2H), 2.03−2.11 (m, 1H), 2.89 (dd, $J$ = 13, 11 Hz, 1H), 3.34 (dd, $J$= 13, 3 Hz, 1H), 4.0 (m, 2H), 7.16−7.43 (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 13.1 (t), 20.4 (q), 21.9 (t), 26.6 (t), 28.4 (q), 36.8 (t), 47.0 (d), 50.8 (d), 79.3 (s), 125.8 (d), 128.7 (d), 129.2 (d), 154.9 (s), an aromatic singlet was not detected; exact mass calcd for $C_{18}H_{27}O_2NS$ *m/e* 321.1764, found *m/e* 321.1754. Anal. Calcd for $C_{18}H_{27}O_2NS$: C, 67.25; H, 8.47. Found: C, 67.02; H, 8.47.

***tert*-Butyl (2*S*,6*R*)-2-Methyl-6-[(phenylsulfonyl)methyl]-1-piperidinecarboxylate (28).** To an ice-cooled and well-stirred heterogeneous solution of 9.63 g (30 mmol) of sulfide **27** and 11.3 g (135 mmol) of sodium bicarbonate in 150 mL of $CH_2Cl_2$ was added 19.0 g (66 mmol) of 60% *m*-chloroperoxybenzoic acid. The mixture was stirred at rt for 3 h and quenched with 50 mL of dilute aqueous ammonium hydroxide. The organic layer was washed with 50 mL of dilute aqueous ammonium hydroxide, dried ($K_2CO_3$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:20) to give 9.2 g (87%) of sulfone **28** as a white solid: mp 104−105 °C; $[\alpha]^{20}_D$ +20.8 (*c* 1.74, $CHCl_3$); IR (neat) 1689, 1477, 1391, 1376 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.18 (d, $J$ = 7 Hz, 3H), 1.39 (s, 9H), 1.52−1.76 (m, 4H), 1.86 (m, 1H), 2.05 (m, 1H), 3.32 (dd, $J$ = 14, 10 Hz, 1H), 3.58 (dd, $J$ = 14, 3.5 Hz, 1H), 3.98 (m, 1H), 4.25 (m, 1H), 7.50−7.95 (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 14.3 (t), 19.8 (q), 24.4 (t), 26.9 (t), 28.3 (q), 46.7 (d), 47.9 (d), 58.9 (t), 79.8 (s), 127.8 (d), 129.1 (d), 133.5 (d), 140.0 (s), 154.6 (s); exact mass calcd for $C_{18}H_{27}O_4NS$ *m/e* 353.1662, found *m/e* 353.1681. Anal. Calcd for $C_{18}H_{27}O_4NS$: C, 61.16; H, 7.70. Found: C, 61.05; H, 7.69.

**(2*S*,6*R*)-2-Methyl-6-[(phenylsulfonyl)methyl]-1-piperidine (7).** A mixture of 6.35 g (18.0 mmol) of carbamate **28** and 5 mL of trifluoroacetic acid in 5 mL of $CH_2Cl_2$ was stirred at rt for 2 h and then diluted with 200 mL of $CH_2Cl_2$ and 50 mL of 6 N aqueous NaOH. The aqueous layer was extracted with 100 mL of $CH_2Cl_2$, and the combined extracts were dried ($K_2CO_3$) and concentrated in vacuo to give 4.91 g of crude amine. This material was used in the following reaction without purification.

To a stirred solution of the crude amine and 5 mL of aqueous 37% formaldehyde in 80 mL of acetonitrile was added 2.0 g (30 mmol) of sodium cyanoborohydride. A vigorous exothermic reaction ensued. The mixture was stirred for 30 min while glacial acetic acid was added dropwise to maintain a pH of 7. Stirring was continued for an additional 1 h, and the solvents were removed in vacuo. To the residue was added 60 mL of aqueous 2 N NaOH, and the solution was extracted with three 100-mL portions of $CH_2Cl_2$. The combined extracts were washed with 50 mL of 1 N aqueous sodium hydroxide, dried ($K_2CO_3$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 9:1 plus 2.5% triethylamine) to give 4.32 g (90% from **28**) of sulfone **7** as a white solid: mp 54.4−55.5 °C; $[\alpha]^{20}_D$ +1.7 (*c* 0.7, $CHCl_3$); IR (neat) 2933, 2776, 1446, 1378 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.93 (d, $J$ = 7 Hz, 3H), 1.20 (m, 1H), 1.35−1.65 (m, 3H), 1.76 (m, 2H), 2.12 (s, 3H), 2.15 (m, 1H), 3.17 (dd, $J$ = 14, 8 Hz, 1H), 3.29 (dd, $J$ = 14, 2.4 Hz, 1H), 3.45 (m, 1H), 7.52−7.93 (m, 5H); $^{13}C$ NMR (75 MHz, $CHCl_3$) $\delta$ 19.2 (t), 20.1 (q), 29.2 (t), 33.4 (t), 38.9 (q), 51.4 (t), 51.9 (d), 55.3 (d), 127.8 (d), 129.1 (d) 133.5 (d), 139.9 (s); exact mass calcd for $C_{14}H_{21}O_2NS$ *m/e* 267.1294, found *m/e* 267.1291. Anal. Calcd for $C_{14}H_{21}O_2NS$: C, 62.89; H, 7.92. Found: C, 62.78; H, 7.92.

**(±)-*tert*-Butyl (*R**)-2-[(Phenylsulfonyl)methyl]-1-piperidinecarboxylate (29).** To a well-stirred heterogeneous solution of 16.3 g (53 mmol) of racemic sulfide **26** and 20.0 g (239 mmmol) of sodium bicarbonate in 500 mL of $CH_2Cl_2$ cooled in an ice bath was added 33.6 g (117 mmol) of 60% *m*-chloroperoxybenzoic acid. The mixture was stirred at rt for 3 h and then quenched with 300 mL of dilute aqueous ammonium hydroxide. The organic layer was washed with 300 mL of dilute aqueous ammonium hydroxide, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over 100 g of silica gel (eluted with ethyl acetate−hexane, 1:4) to give 16.1 g (89%) of sulfone **29** as a white solid: mp 98−99 °C; IR (neat) 3064, 1694, 1682, 1586, 1478 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.27 (s, 9H), 1.18−1.60 (m, 5H), 1.70 (m, 1H), 2.43 (m, 1H), 3.24 (m, 2H,), 3.74 (br, 1H), 4.68 (m, 1H), 7.39−7.79 (m, 5H); $^{13}C$ NMR (75 MHz, $CHCl_3$) $\delta$ 18.6 (t), 24.7 (t), 28.0 (t), 28.1 (q), 39.1 (t), 46.0 (d), 55.5 (t), 79.7 (s), 127.6 (d), 129.1 (d), 133.5 (d), 139.7 (s), 153.9 (s); exact mass calcd for $C_{17}H_{25}O_4NS$ *m/e* 339.1506, found *m/e* 339.1502.

**(±)-(*R**)-1-Methyl-2-[(phenylsulfonyl)methyl]-1-piperidine (30).** A mixture of 16.1 g (47.5 mmol) of carbamate **29** and 15 mL of trifluoroacetic acid in 20 mL of $CH_2Cl_2$ was stirred at room temperature for 15 h and then diluted with 200 mL of $CH_2Cl_2$ and 150 mL of 6 N aqueous NaOH. The aqueous layer was extracted with 100 mL of $CH_2Cl_2$, and the combined extracts were dried ($K_2CO_3$) and concentrated in vacuo to give 12.4 g of crude amine. This material was used in next step without further purification. To a stirred solution of the crude amine and 25 mL of aqueous 37% formaldehyde in 150 mL of acetonitrile was added 6.25 g (100 mmol) of sodium cyanoborohydride. The mixture was stirred for 30 min, and acetic acid was then added dropwise until the solution tested neutral on wet pH paper. The solution was stirred for an additional 1 h, and the solvents were evaporated in vacuo. To the residue was added 100 mL of aqueous 2 N NaOH. The resulting solution was extracted with three 100-mL portions of chloroform. The combined extracts were washed with 50 mL of aqueous 1 N NaOH, dried ($K_2CO_3$), and concentrated in vacuo. The residue was chromatographed over 50 g of activity II alumina (eluted with EtOAc−hexane, 1:9 plus 1% methanol) to give 10.7 g (90% from carbamate **29**) of sulfone **30** as a colorless thick oil: IR (neat) 3063, 1585, 1446 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.35 (m, 1H), 1.50 (m, 4H), 1.87 (m, 1H), 2.10 (m, 3H), 2.20 (m, 1H), 2.52 (m, 1H), 2.83 (m, 1H), 3.05 (dd, $J$ = 14.5, 7.8 Hz, 1H), 3.36 (dd, $J$ = 14.4, 2.2 Hz, 1H), 7.52−7.92 (m, 5H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 21.5 (t), 25.0 (t), 31.6 (t), 42.7 (q), 53.7 (t), 55.9 (t), 56.6 (d), 127.8 (d), 129.2 (d), 133.6 (d), 139.9 (s); exact mass calcd for $C_{13}H_{19}O_2NS$ *m/e* 253.1138, found *m/e* 253.1133.

**(±)-(α*R**,*βR**,2*R**)-1-Methyl-α-phenyl-*β*-(phenylsulfonyl)-2-piperidineethanol (31).** To a solution of 0.253 g (1 mmol) of sulfone **30** in 2.0 mL of DME, cooled in a dry ice−acetone bath, was added 0.63 mL (1.0 mmol) of 1.6 M *n*-BuLi in hexanes. The resulting red solution was stirred for 20 min, and then 0.106 g (1.0 mmol) of benzaldehyde in 1.0 mL of DME was added. The mixture was stirred for 30 min, quenched with 50 mL of saturated aqueous ammonium chloride, and then extracted with three 50-mL portions of diethyl ether. The combined extracts were washed with 30 mL of brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over 15 g of silica gel (eluted with EtOAc−hexane, 1:9 → 1:6 → 1:4 → 1:2 with 1% MeOH) to give 20 mg of a diastereomer of **31**: mp 89−91 °C; IR ($CCl_4$) 3500, 1548, 1447 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.20−1.70 (m, 3H), 1.80 (m, 1H), 2.00−2.30 (m, 3H), 2.19 (s, 3H), 2.80−2.95 (m, 2H), 4.03 (t, $J$ = 2.9 Hz, 1H), 5.50 (d, $J$ = 2.1 Hz, 1H), 7.07−7.54 (m, 10H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 24.2 (t), 25.4 (t), 27.6 (t), 43.5 (q), 57.8 (t), 63.1 (d), 68.8 (d), 69.4 (d), 125.4 (d), 126.9 (d), 127.6 (d), 127.9 (d), 128.6 (d), 132.9 (d), 141.3 (s), 142.0 (s). This was followed by 27 mg of another diasteromer of **31**: mp 168−170 °C; IR ($CCl_4$) 3150, 3066, 1449 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.20−1.75 (m, 3H), 1.85−2.30 (m, 3H), 2.43 (m, 1H), 2.53 (s, 3H), 3.05 (m, 1H), 3.33 (dt, $J$ = 10.4, 2.6 Hz, 1H), 4.12 (dd, $J$ = 10.4, 2.6 Hz, 1H), 5.39 (d, $J$ = 10.4 Hz, 1H), 6.97−7.33 (m, 10H), the hydroxyl proton was not observed; $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 23.6 (t), 25.6 (t), 26.7 (t), 44.1 (q), 57.9 (t), 63.9 (d), 65.8 (d), 72.8 (d), 126.9 (d), 128.0 (d), 128.2 (d), 128.36 (d), 128.43 (d), 132.1 (d), 140.0 (s), 141.0 (s). This was followed by yet another diasteromer of **31**: mp 120−122 °C; IR ($CCl_4$) 3400, 2930, 1446 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.25−1.68 (m, 3H), 1.70−1.90 (m, 2H), 2.10−2.30 (m, 2H), 2.60 (s, 3H), 2.94 (m, 1H) 3.37 (dt, $J$ = 8.7, 1.8 Hz, 1H), 3.56 (dd, $J$ = 8.2, 1.9 Hz, 1H), 5.43 (d, $J$ = 8.2 Hz,

1H), 6.95 (br, 1H), 7.10−7.41 (m, 10H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 24.1 (t), 24.4 (t), 34.0 (t), 45.3 (q), 56.6 (t), 61.0 (d), 72.7 (d), 73.7 (d), 127.5 (d), 127.9 (d), 128.2 (d), 128.5 (d), 132.7 (d), 140.5 (s), 140.9 (s), one aromatic carbon was obscured. This was finally followed by 242 mg of a mixture of **31** and starting sulfone **30** from which was crystallized 217 mg of pure **31**: mp 110−112 °C; IR ($CCl_4$) 3200, 2938, 1448 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.0 (m, 1H), 1.15−1.35 (m, 2H), 1.45 (m, 1H), 1.63 (m, 1H), 1.75−1.90 (m, 1H), 2.10−2.25 (m, 1H), 2.22 (s, 3H), 2.65 (m, 1H), 2.85 (ddd, $J$ = 12.4, 6.4, 3.6 Hz, 1H), 4.05 (t, $J$ = 5.7 Hz, 1H), 5.60 (d, $J$ = 5.2 Hz, 1H), 6.0 (br, 1H), 7.25−7.84 (m, 10H); $^{13}$CNMR (75 MHz, $CDCl_3$) $\delta$ 21.9 (t), 22.3 (t), 24.3 (t), 42.2 (q), 53.5 (t), 60.7 (d), 69.8 (d), 72.2 (d), 127.0 (d), 127.8 (d), 128.1 (d), 128.7 (d), 133.1 (d), 140.0 (s), 142.2 (s), one aromatic carbon was obscured; exact mass calcd for $C_{20}H_{24}O_3NS$ ($M^+$-H) *m/e* 358.1478, found *m/e* 358.1449.

**(±)-(α*R*,βR*,2R**)-α-Cyclohexyl-1-methyl-*β*-(phenylsulfonyl)-2-piperidine-ethanol (32).** Treatment of 253 mg (1.0 mmol) of **30** with 112 mg (1.0 mmol) of cyclohexanecarbaldehyde as described for the preparation of **31** gave 49 mg (13%) of a roughly equal mixture of three diastereomers of **32** (by $^1$H NMR) and 291 mg (80%) of **32** as a colorless oil: IR (neat) 3450, 3065, 1585, 1447 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.05−1.30 (m, 6H), 1.40 (m, 2H), 1.50−1.80 (m, 8H), 1.90−2.15 (m, 2H), 2.12 (s, 3H), 2.70−2.90 (m, 2H), 3.70 (t, $J$ = 5.0 Hz, 1H), 3.99 (t, $J$ = 5.2 Hz, 1H), 7.55 (m, 2H), 7.65 (m, 1H), 7.95 (m, 2H), the OH was not observed; $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 22.8 (t), 23.0 (t), 25.7 (t), 25.9 (t), 26.1 (t), 26.2 (t), 27.2 (t), 30.4 (t), 40.4 (d), 43.0 (q), 54.8 (t), 62.1 (d), 68.3 (d), 73.8 (d), 128.5 (d), 128.6 (d), 133.1 (d), 142.3 (s); exact mass calcd for $C_{20}H_{31}O_3NS$ *m/e* 365.2026, found *m/e* 365.1994.

**(±)-(α*R*,βR*,2R**)-α-Hexyl-1-methyl-*β*-(phenylsulfonyl)-2-piperidineethanol (33).** Treatment of 253 mg (1.0 mmol) of **30** with 114 mg (1.0 mmol) of heptanal as described for the preparation of **31** gave 52 mg of a nearly equal mixture of three diastereomers of **33** (by $^1$H NMR), 16 mg (6%) of recovered **30**, and 276 mg (75%) of **33** as a colorless oil: IR (neat) 3500, 3064, 1585, 1462, 1446 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.87 (t, $J$ = 6.8 Hz, 3H), 1.05−1.70 (m, 13H), 1.82−2.10 (m, 3H), 2.50 (s, 3H), 2.45−2.55 (m, 1H), 3.01 (dt, $J$ = 11.4, 3.2 Hz, 1H), 3.47 (dt, $J$ = 10.5, 4.2 Hz, 1H), 3.57 (broad d, $J$ = 10.8 Hz, 1H), 3.94 (dd, $J$ = 10.7, 2.9 Hz, 1H), 7.52−7.90 (m, 5H), the OH was not observed; $^{13}$C NMR (75 MHz,$CDCl_3$) $\delta$ 13.9 (q), 18.9 (t), 20.5 (t), 21.5 (t), 22.5 (t), 26.4 (t), 29.1 (t), 31.7 (t), 32.7 (t), 40.5 (q), 49.0 (t), 57.2 (d), 65.3 (d), 71.8 (d), 128.1 (d), 129.1 (d), 133.5 (d), 140.0 (s); exact mass calcd for $C_{20}H_{33}O_3NS$ *m/e* 367.2183, found *m/e* 367.2194.

**(α*S*,*βS*,2*S*)-α-Cyclohexyl-1-methyl-*β*-(phenylsulfonyl)-2-pyrrolidineethanol (35).** Treatment of 240 mg (1.0 mmol) of **34** with 137 mg (1.2 mmol) of cyclohexanecarbaldehyde as described for the preparation of **31** gave 267 mg (76%) of a mixture of diastereomeric *β*-hydroxy sulfones from which **35** could be crystallized as a white solid using ethyl acetate−hexane: mp 122−123 °C; $[\alpha]^{20}_D$ −25.5 (*c* 0.69, MeOH); IR (neat) 3432 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 0.9−2.1 (m, 15H), 2.26 (s, 3H), 2.35 (dt, $J$ = 8, 6 Hz, 1H), 2.99 (m, 1H), 3.27 (m, 1H), 3.33 (t, $J$ = 3.5 Hz, 1H), 3.85 (dd, $J$ = 8, 3.5 Hz, 1H), 5.97 (s, 1H), 7.52 (dd, $J$ = 7, 2 Hz, 2H), 7.60 (tt, $J$ = 6, 2 Hz, 1H), 7.95 (dd, $J$ = 7, 2 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 24.0 (t), 25.7 (t), 25.8 (t), 26.2 (t), 28.6 (t), 29.7 (t), 31.1 (t), 39.9 (d), 42.2 (q), 57.7 (t), 64.0 (d), 67.8 (d), 74.1 (d), 128.5 (d), 128.6 (d), 133.1 (d), 142.0 (s); exact mass calcd for $C_{19}H_{29}NO_3S$ *m*/e 351.1870, found *m/e* 351.1857. Anal. Calcd for $C_{19}H_{29}NO_3S$: C, 64.92; H, 8.32. Found: C, 64.94; H, 8.34.

**(3*S*,3a*S*,4*R*,4a*S*,8s*R*,9a*S*)-Decahydro-3-methyl-4-[(phenylthio)methyl]naphtho[2,3-*c*]furan-1(3*H*)-one (36).** A solution of 0.48 g (2.0 mmol) of alcohol **21** in 6 mL of pyridine was cooled in an ice−water slurry and treated with 0.76 g (4.0 mmol) of *p*-toluenesulfonyl chloride. The mixture was stirred at 0 °C for 2 h and then placed in a refrigerator overnight (4 °C). The mixture was diluted with 10 mL of 5% aqueous HCl and extracted with two 15-mL portions of $CH_2Cl_2$. The combined extracts were washed with 10 mL of saturated sodium bicarbonate, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:30) to give 0.95 g (95%) of a tosylate suitable for use in the next reaction.

To a solution of 0.27 g (2.5 mmol) of thiophenol in 3 mL of DMSO, stirred under argon at rt, was added 0.375 g (2.5 mmol) of potassium *tert*-butoxide followed by a solution of 0.75 g of the tosylate in 3 mL of DMSO. The reaction mixture was stirred at rt for 1 h, whereupon it was diluted with 30 mL of EtOAc and washed with 20 mL of water. The organic layer was dried ($Na_2SO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:20) to give 0.59 g (94%) of sulfide **36** as a thick oil: $[\alpha]^{20}_D$ +99.4 (*c* 1.1, $CHCl_3$); IR (neat) 3057, 1770, 1582 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.80 (dq, $J$ = 11.1, 2.4 Hz, 1H), 0.99−1.26 (m, 6H), 1.52 (d, $J$ = 6.0 Hz, 3H), 1.64−1.78 (m, 5H), 2.02 (m, 1H), 2.57 (dt, $J$ = 12.8, 6.7 Hz, 1H), 2.60 (dd, $J$ = 13.0, 11.0 Hz, 1H), 2.65 (m, 1H), 3.33 (dd, $J$ = 13.0, 3.5 Hz, 1H), 4.65 (dq, $J$= 10.2, 6.0 Hz, 1H), 7.20−7.30 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 22.0 (q), 25.7 (t), 26.3 (t), 30.1 (t), 32.1 (t), 33.7 (t), 34.9 (t), 40.7 (d), 40.9 (d), 41.5 (d), 42.5 (d), 44.8 (d), 76.7 (d), 126.2 (d), 129.0 (d), 129.1 (d), 136.4 (s), 177.9 (s); exact mass calcd for $C_{20}H_{26}O_2S$ *m/e* 330.1655, found *m/e* 330.1658.

**(1*S*,3*S*,3a*S*,4*R*,4a*S*,8s*R*,9a*S*)-Decahydro-1-methoxy-3-methyl-4-[(phenylthio)methyl]naphtho[2,3-*c*]furan-1(3*H*)-one (37).** To a solution of 0.56 g (1.7 mmol) of lactone **36** in 10 mL of diethyl ether stirred at −78 °C was added 5 mL (5.0 mmol) of a 1 M solution of diisobutylaluminum hydride in hexane. The solution was stirred for 30 min, and then 2 mL of MeOH and 20 mL of 5% aqueous HCl were carefully added. The mixture was extracted with three 30-mL portions of diethyl ether. The combined extracts were washed with 20 mL of brine, dried ($Na_2SO_4$), and cconcentrated to afford 0.543 g (96%) of crude lactol: IR (neat) 3397 cm$^{-1}$; exact mass calcd for $C_{20}H_{28}O_2S$ *m/e* 332.1811, found *m/e* 332.1801. This material was used directly in the next step.

To a stirred solution of 0.52 g (1.5 mmol) of the lactol in 12 mL of MeOH was added 0.2 mL of boron trifluoride etherate at −20 °C. Dichloromethane (3 mL) was added to achieve a homogeneous solution. The reaction was stirred from −20 °C to rt for 2 h, quenched with a few drops of triethylamine, and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:25) to give 0.53 g (98%) of acetal **37**: $[\alpha]^{20}_D$ +138.5 (*c* 0.73, $CHCl_3$); IR (neat) 3057, 1583, 1480, 1375 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.80−1.10 (m, 5H), 1.15−1.30 (m, 2H), 1.41 (d, $J$ = 6.0 Hz, 3H), 1.50−1.80 (m, 5H), 2.03 (m, 1H), 2.14 (m, 1H), 2.59 (dd, $J$ = 12.6, 11.0 Hz, 1H), 2.71 (m, 1H), 3.32 (dd, $J$ = 12.6, 3.3 Hz, 1H), 3.33 (s, 3H), 4.17 (dq, $J$ = 9.1, 6.0 Hz, 1H), 4.47 (s, 1H), 7.10−7.32 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 24.96 (q), 25.85 (t), 26.5 (t), 30.1 (t), 33.3 (t), 34.0 (t), 35.1 (t), 40.7 (d), 41.3 (d), 41.5 (d), 44.4 (d), 46.4 (d), 53.8 (q), 75.2 (d), 108.2 (d), 125.5 (d), 128.5 (d), 128.8 (d), 137.3 (s); exact mass calcd for $C_{21}H_{30}O_2S$ *m/e* 346.1968, found *m/e* 346.1956.

**(1*S*,3*S*,3a*S*,4*R*,4a*S*,8s*R*,9a*S*)-Decahydro-1-methoxy-3-methyl-4-[(phenylsulfonyl)methyl]naphtho[2,3-*c*]furan-1(3*H*)-one (38).** To an ice-cooled suspension of 0.50 g (1.45 mmol) of sulfide and 0.61 g (7.25 mmol) of sodium bicarbonate in 50 mL of $CH_2Cl_2$ was added slowly 1.0 g (3.48 mmol) of 60% *m*-chloroperoxybenzoic acid. The suspension was stirred at rt for 2 h, diluted with 50 mL of $CH_2Cl_2$, and washed with 100 mL of a saturated aqueous sodium bicarbonate. The aqueous layer was extracted with 100 mL of $CH_2Cl_2$. The combined extracts were washed with 50 mL of brine, dried ($Na_2SO_4$), and concectrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:9) to provide 0.513 g (94%) of sulfone **38** as a white solid: mp 127−128 °C; $[\alpha]^{20}_D$ +100 (*c* 0.35, $CHCl_3$); IR (neat) 2928, 1549, 1446, 1377 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 0.60 (dq, $J$ = 11.5 Hz, 1H), 0.8−1.0 (m, 4H), 1.05−1.20 (m, 2H), 1.41 (d, $J$ = 6.1 Hz, 3H), 1.40−1.73 (m, 5H), 2.00−2.20 (m, 2H), 2.73 (dt, $J$ = 8.9, 5.6 Hz, 1H), 2.96 (dd, $J$ = 14.7, 9.4 Hz, 1H), 3.24 (dd, $J$ = 14.7, 1.8 Hz, 1H), 3.27 (s, 3H), 4.06 (dq, $J$ = 9.0, 6.1 Hz, 1H), 4.42 (s, 1H), 7.50−7.90 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 25.5 (q), 25.7 (t), 26.4 (t), 29.8 (t), 32.9 (t), 34.0 (t), 36.6 (d), 40.6 (d), 40.8 (d), 44.9 (d), 46.0 (d), 53.8 (q), 55.6 (t), 75.2 (d), 108.1 (d), 127.8 (d), 129.2 (d), 133.5 (d), 139.8 (s); exact

mass calcd for $C_{21}H_{30}O_4S$ *m/e* 378.1866, found *m/e* 378.1847. Anal. Calcd for $C_{21}H_{30}O_4S$: C, 66.63; H, 7.99. Found: C, 66.70; H, 7.99.

***tert*-Butyl (*R*)-2-[(*tert*-Butyldimethylsiloxy)methyl]-6-methyl-1-piperidinecarboxylate (39).** To a solution of 3.23 g (15 mmol) of alcohol **25** in 40 mL of DMF were added 2.94 g (19.5 mmol) of *tert*-butyldimethylsilyl chloride and 4.08 g (60 mmol) of imidazole. The mixture was stirred at rt overnight, diluted with 80 mL of water, and extracted with three 100-mL portions of diethyl ether. The combined extracts were washed with 100 mL of aqueous saturated sodium bicarbonate and 100 mL of brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:50) to give 4.73 g (96%) of silyl ether **39** as a colorless oil: $[\alpha]^{20}_D$ +34.9 (*c* 0.59, $CHCl_3$); IR (neat) 2931, 1694 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.02 (s, 6H), 0.86 (s, 9H), 1.42 (s, 9H), 1.36−1.55 (m, 5H), 1.82 (d, $J$ = 6.8 Hz, 1H), 2.71 (m, 1H), 3.56 (dd, $J$ = 9.8, 6.3 Hz, 1H), 3.66 (dd, $J$ = 9.4, 8.8 Hz, 1H), 3.95 (br, 1H), 4.13 (br, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −5.52 (q), −5.46 (q), 18.1 (s), 19.0 (t), 24.3 (t), 25.2 (t), 25.8 (q), 28.4 (q), 39.9 (t), 51.5 (d), 60.7 (t), 79.0 (s), 155.1 (s); exact mass calcd for $C_{13}H_{26}O_3NSi$ (M − $C_4H_9$) *m/e* 272.1683, found *m/e* 272.1672.

***tert*-Butyl (2*R*,6*S*)-2-[(*tert*-Butyldimethylsiloxy)methyl]-6-methyl-1-piperidinecarboxylate (40).** A solution of 4.60 g (14.0 mmol) of silyl ether **39** in 45 mL of diethyl ether was cooled to −78 °C, and 2.1 g (18.2 mmol) of TMEDA was added, followed by 14 mL (18.2 mmol) of *s*-BuLi in cyclohexane. The pale yellow mixture was stirred at −78 °C for 6 h, and then 3.36 g (23.8 mmol) of methyl iodide was added. The mixture was slowly warmed to rt with stirring overnight, then diluted with 100 mL of water, and extracted with three 100-mL portions of diethyl ether. The combined extracts were washed with 100 mL of brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:50) to provide 3.41 g (71%) of piperidine **40** as a colorless oil: $[\alpha]^{20}_D$ +38.6 (*c* 0.65, $CHCl_3$); IR (neat) 1692, 1388, 1364 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.002 (s, 6H), 0.83 (s, 9H), 1.17 (d, $J$ = 9.3, 4.3 Hz, 3H), 1.40 (s, 9H), 1.42−1.89 (m, 6H), 3.44 (t, $J$ = 9.5 Hz, 1H), 3.63 (dd, $J$ = 9.3, 4.3 Hz, 1H), 3.74 (m, 1H), 3.93 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ −5.6 (q), −5.4 (q), 13.2 (t), 18.1 (s), 20.4 (q), 20.5 (t), 25.8 (q), 26.9 (t), 28.4 (q), 46.7 (d), 52.6 (d), 63.8 (t), 78.9 (s), 155.0 (s); exact mass calcd for $C_{18}H_{38}O_3NSi$ ($M^+$ + 1) *m/e* 344.2623, found *m/e* 344.2595.

***tert*-Butyl (2*R*,6*S*)-2-(Hydroxymethyl)-6-methyl-1-piperidinecarboxylate (41).** A solution of 2.06 g (6.0 mmol) of silyl ether **40** and 9.0 mL of tetra-*n*-butylammonium fluoride in 20 mL of THF was stirred at 0 °C for 1 h and then at rt for 2 h. The mixture was diluted with 100 mL of diethyl ether, washed with 40 mL of brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:4) to give 1.28 g (93%) of alcohol **41** as a thick oil: $[\alpha]^{20}_D$ +45.4 (*c* 0.97, $CHCl_3$); IR (neat) 3444 (br), 1694 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.18 (d, $J$ = 6.8 Hz, 3H), 1.45 (s, 9H), 1.39−1.75 (m, 6H), 3.61−3.75 (m, 3H), 3.98 (br, 1H), 4.19 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 15.8 (t), 18.4 (q), 25.2 (t), 27.9 (t), 28.3 (q), 48.3 (d), 54.1 (d), 66.1 (t), 79.8 (s), 156.3 (s); exact mass calcd for $C_{11}H_{19}O_3N$ ($M^+$ − $CH_4$) *m/e* 213.1366, found *m/e* 213.1315.

***tert*-Butyl (2*R*,6*S*)-2-Formyl-6-methyl-1-piperidinecarboxylate (42).** To a mixture of 4 g of 4 Å molecular sieves and 0.404 g (3.5 mmol) of *N*-methylmorpholine *N*-oxide in 25 mL of $CH_2Cl_2$ was added 0.53 g (2.3 mmol) of alcohol **41**. The mixture was stirred for 10 min, 50 mg of tetra-*n*-propylammonium perruthenate (TPAP) was added, and the reaction was stirred at rt overnight. The mixture was diluted with 200 mL of $CH_2Cl_2$, washed with 50 mL of 10% aqueous sodium thiosulfate and 50 mL of brine, and dried ($Na_2SO_4$). The mixture was concentrated, and the residue was chromatographed over silica gel (eluted with EtOAc−hexane, 1:9) to give 0.45 g (86%) of aldehyde **42** as a colorless oil: $[\alpha]^{20}_D$ +121.7 (*c* 0.96, $CHCl_3$); IR (neat) 1732, 1682 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.11 (d, $J$ = 6.8 Hz, 3H), 1.44 (s, 9H), 1.45−1.74 (m, 6H), 3.62 (dt, $J$ = 12.3, 3.9 Hz, 1H), 4.25 (br, 1H), 9.27 (d, $J$= 3.7 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 16.2 (t), 16.4 (q), 25.3 (t), 28.1 (q), 29.2 (t), 47.3 (d), 59.1 (d), 81.2 (s), 156.1 (s), 196.3 (d); exact mass calcd for $C_{11}H_{20}O_2N$ ($M^+$ − CHO) *m/e* 198.1495, found *m/e* 198.1475.

***tert*-Butyl (2*R*,6*S*)-2-[(*E*)-[2-(1*S*,3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Dodecahydro-1-methoxy-3-methylnaphtho[2,3-*c*]furan-4-yl]vinyl]-6-methyl-1-piperidinecarboxylate (43).** To a solution of 0.31 g (0.8 mmol) of sulfone **38** in 10 mL of DME was added 0.5 mL (0.8 mmol) of *n*-BuLi in hexane dropwise. The resulting yellow solution was stirred at −50 °C for 30 min, and then 0.28 g (1.23 mmol) of aldehyde **42** in 2 mL of DME was added slowly. The mixture was stirred at −60 °C for 2 h, then quenched with 30 mL of water, and extracted with two 30 mL portions of diethyl ether. The combined extracts were washed with 30 mL of brine, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (eluted with ethyl acetate−hexane, 1:9) to give 0.334 g (67%) of a diastereomeric mixture of $\beta$-hydroxy sulfones as a white solid and 0.078 g (25%) of recovered sulfone **38**. The $\beta$-hydroxy sulfone mixture was characterized as follows: IR (neat) 3372, 1682 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.61 (m, 1H), 0.88 (m, 4H), 1.23 (two d, $J$ = 7.0 Hz, 6H), 1.39, 1.46 (s, 9H), 1.0−1.70 (m, 13H), 1.80−2.20 (m, 2H), 2.50−2.70 (m, 1H), 3.30 (s, 3H), 3.50−3.85 (m, 1H), 4.20 (m, 1H), 4.40−4.50 (m, 1H), 4.62−4.73 (m, 1H), 4.75−5.34 (m, 1H), 7.45−8.07 (m, 5H); exact mass calcd for $C_{32}H_{48}O_6NS$ ($M^+$ − $OCH_3$) *m/e* 574.3204, found *m/e* 574.3242. Anal. Calcd for $C_{33}H_{51}O_7NS$: C, 65.42; H, 8.49. Found: C, 65.20; H, 8.45.

A mixture of 0.37 g (0.61 mmol) of the $\beta$-hydroxy sulfones, 6.6 g of 6% sodium amalgam, and 1.2 g of disodium hydrogen phosphate in 15 mL of methanol was stirred at room temperature for 3 h, quenched with 20 mL of water, and then extracted with two 30-mL portions of diethyl ether. The combined extracts were dried ($Na_2SO_4$) and concentrated in vacuo. Chromatography of the residue over silica gel (eluted with ethyl acetate−hexane, 1:9) gave 0.186 g (68%) of olefin **43** as a white solid: mp 92−93 °C; $[\alpha]^{20}_D$ +90.5 (*c* 0.38, $CHCl_3$); IR ($CCl_4$) 1690, 1390 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.6−0.7 (m, 1H), 0.92 (m, 4H), 1.22 (d, $J$ = 6.7Hz, 3H), 1.27 (d, $J$ = 6.0 Hz, 3H), 1.15−1.25 (m, 3H), 1.42 (s, 9H), 1.40−1.80 (m, 8H), 1.84−2.08 (m, 3H), 2.17 (m, 2H), 3.29 (s, 3H), 3.96 (m, 1H), 4.16 (dq, $J$ = 8.6, 6.0 Hz, 1H), 4.40 (br, 1H), 4.46 (s, 1H), 5.20 (ddd, $J$ = 15.2, 9.9, 1.3 Hz, 1H), 5.46 (dd, $J$ = 15.2, 6.3 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 13.3 (t), 20.8 (q), 24.6 (q), 25.7 (q), 26.3 (t), 26.4 (t), 26.5 (t), 28.3 (q), 31.3 (t), 32.9 (t), 34.0 (t), 40.2 (d), 41.2 (d), 46.3 (d), 46.4 (d), 46.9 (d), 48.6 (d), 52.3 (d), 53.7 (q), 75.4 (d), 78.8 (s), 108.3 (d), 132.9 (d), 154.9 (s), one carbon was not observed; exact mass calcd for $C_{27}H_{45}O_4N$ *m/e* 447.3351, found *m/e* 447.3347. Anal. Calcd for $C_{27}H_{45}O_4N$: C, 72.44; H, 10.13. Found: C, 72.38; H, 10.16.

***tert*-Butyl (2*R*,6*S*)-2-[(*E*)-[2-(3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Dodecahydro-3-methyl-1-oxonaphtho[2,3-*c*]furan-4-yl]vinyl]-6-methyl-1-piperidinecarboxylate (44).** To a solution of 0.14 g (0.31 mmol) of acetal **43** in 5 mL of acetone was added 0.8 mL of Jones reagent (prepared from 1.03 g of $CrO_3$, 3 mL of water, and 0.87 g of sulfuric acid). The mixture was stirred at rt for 30 min, diluted with 50 mL of diethyl ether, and washed with 20 mL of water. The aqueous layer was extracted with 20 mL of diethyl ether. The combined extracts were dried ($Na_2SO_4$) and concentrated in vacuo. Chromatography of the residue over silica gel (eluted with EtOAc−hexane, 1:9) gave 128 mg (95%) of lactone **44** as a thick oil: $[\alpha]^{20}_D$ +60.6 (*c* 0.55, $CHCl_3$); IR (neat) 1777, 1682 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.66 (m, 1H), 0.97 (m, 3H), 1.10−1.20 (m, 4H), 1.23 (d, $J$ = 6.6 Hz, 3H), 1.40 (d, $J$ = 6.0 Hz, 3H), 1.43 (s, 9H), 1.45−1.80 (m, 8H), 1.80−2.10 (m, 3H), 2.20 (m, 1H), 2.60 (m, 1H), 3.98 (m, 1H), 4.42 (br, 1H), 4.61 (dq, $J$ = 10.2, 5.9 Hz, 1H), 5.21 (ddd, $J$ = 15.2, 10.0, 1.3 Hz, 1H), 5.52 (dd, $J$= 15.2, 6.0 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 13.3 (t), 20.8 (q), 22.0 (q), 25.5 (t), 26.0 (t), 26.3 (t), 28.4 (q), 31.1 (t), 31.9 (t), 33.5 (t), 39.9 (d), 41.5 (d), 42.2 (d), 45.6 (d), 46.9 (d), 48.7 (d), 52.1 (d), 76.8 (d), 79.0 (s), 131.2 (d), 134.1 (d), 154.9 (s), 178.2 (s), one carbon was not observed; exact mass calcd for $C_{26}H_{41}O_4N$ *m/e* 431.3037, found *m/e* 431.3040.

**(3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-Decahydro-3-methyl-4-[(*E*)-2-[(2*R*,6*S*)-6-methyl-2-piperidyl]vinyl]-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one (Himbeline, 2).** To a stirred solution of

0.13 g (0.38 mmol) of carbamate **44** in 2 mL of $CH_2Cl_2$ was slowly added 1 mL of trifluoroacetic acid. The mixture was stirred at rt for 30 min, quenched with 10 mL of 6 N aqueous NaOH, and extracted with four 15-mL portions of $CH_2Cl_2$. The combined extracts were dried ($K_2CO_3$) and concentrated in vacuo. Chromatography over silica gel (eluted with EtOAc−MeOH, 1:1) gave 92 mg (92%) of himbeline (**2**) as a white solid. Further chromatography of a sample over activity II alumina (eluted with EtOAc−hexane, 1:1) afforded salt free himbeline: mp 97.5−98.5 °C (lit.[2] mp 100 °C); $[\alpha]^{20}_D$ +17.1 [*c* 0.56, $CHCl_3$; lit.[2] +19 (2.4% in $CHCl_3$)]; IR (neat) 3325, 1778, 1629, 1452, 1381 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.69 (m, 1H), 0.94−1.08 (m, 3H), 1.08 (d, $J$ = 6.5 Hz, 3H), 1.10−1.27 (m, 4H), 1.40 (d, $J$ = 6.0 Hz, 3H, $CH_3$), 1.38−1.42 (m, 1H), 1.50−1.80 (m, 8H), 1.84 (ddd, $J$ = 11.5, 6.3, 1.7 Hz, 1H), 2.09 (m, 1H), 2.23 (dt, $J$ = 10.1, 6.1 Hz, 1H), 2.60 (dt, $J$ = 12.9, 6.7 Hz, 1H), 3.09 (m, 1H), 3.52 (q, $J$ = 5.0 Hz, 1H), 4.63 (dq, $J$ = 10.2, 6.0 Hz, 1H), 5.24 (ddd, $J$ = 15.4, 9.9, 1.2 Hz, 1H), 5.69 (dd, $J$ = 15.3, 6.7 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 19.6 (t), 21.3 (q), 22.1 (q), 26.0 (t), 26.3 (t), 31.0 (t), 31.2 (t), 31.9 (t), 32.6 (t), 33.5 (t), 39.9 (d), 41.4 (d), 42.2 (d), 45.5 (d), 46.2 (d), 48.9 (d), 52.9 (d), 76.7 (d), 131.1 (d), 135.3 (d), 178.1 (s); exact mass calcd for $C_{21}H_{33}O_2N$ *m/e* 331.2513, found *m/e* 331.2510.

**(3*S*,3a*R*,4*R*,4a*S*,8a*R*,9a*S*)-4-[(*E*)-2-[(2*R*,6*S*)-1,6-Dimethyl-2-piperidyl]vinyl]decahydro-3-methylnaphtho[2,3-*c*]furan-1(3*H*)-one (Himbacine, 1).** To a stirred solution of 75 mg (0.227 mmol) of himbeline (**2**) and 0.2 mL of 37% aqueous formaldehyde in 4 mL of acetonenitrile was added 30 mg of sodium cyanoborohydride. The mixture was stirred for 20 min, and then acetic acid was added dropwise until the solution tested neutral. Stirring was continued for an additional 1 h, the solvent was evaporated in vacuo, 10 mL of 2 N NaOH was added, and the mixture was extracted with four 15-mL portions of $CH_2Cl_2$. The combined extracts were dried ($K_2CO_3$) and concentrated. Chromatography over silica gel (eluted with EtOAc−MeOH, 2:1) gave 71 mg of product as a semisolid, which contained inorganic impurities. Chromatography over a short column of activity II alumina (eluted with EtOAc−hexane, 1:4) afforded 54 mg (70%) of pure himbacine (**1**) as a white solid: mp 129−130 °C [lit.[2] mp 132 °C; standard sample,[44] 129−130 °C]; $[\alpha]^{20}_D$ +51.4 [c 1.01, $CHCl_3$; lit.[2] +63 (2.4% in $CHCl_3$); standard sample,[44] +51.4 (*c* 1.01, $CHCl_3$)]; IR (neat) 2929, 2852, 1777, 1446, 1383 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 0.73 (m, 1H), 0.98 (d, $J$ = 6.5 Hz, 3H), 0.90−1.10 (m, 3H), 1.10−1.30 (m, 3H), 1.38 (d, $J$ = 5.9 Hz, 3H), 1.30−1.46 (m, 2H), 1.50−1.55 (m, 2H), 1.60−1.75 (m, 6H), 1.86 (m, 1H), 2.10 (m, 1H), 2.20 (s, 3H), 2.18−2.25 (m, 1H), 2.60 (dt, $J$ = 12.7, 6.6 Hz, 1H), 2.80−2.85 (m, 1H), 2.98−3.05 (m, 1H), 4.61 (dq, $J$ = 7.3, 5.9 Hz, 1H), 5.24 (dd, $J$ = 15.2, 9.8 Hz, 1H), 5.56 (dd, $J$= 15.2, 9.0 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 13.9 (q), 18.8 (t), 22.1 (q), 26.0 (t), 26.3 (t), 31.3 (t), 31.9 (t), 32.4 (t), 33.1 (t), 33.5 (t), 39.8 (d), 41.0 (q), 41.4 (d), 42.1 (d), 45.6 (d), 49.0 (d), 53.3 (d), 61.2 (d), 76.6 (d), 133.3 (d), 133.4 (d), 178.1 (s); exact mass calcd for $C_{22}H_{35}O_2N$ *m/e* 345.2669, found *m/e* 345.2667.

**Acknowledgment.** We thank the NIH and Interneuron Pharmaceuticals for financial support of this research, Dr. Kurt Loening for help with nomenclature, and the Campus Chemical Instrumentation Center at the Ohio State University for technical support.

**Supporting Information Available:** General experimental and $^1H$ and $^{13}C$ NMR spectra for most new compounds (74 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO970612A