VOLUME 70, NUMBER 6

JOC Articles

MARCH 18, 2005

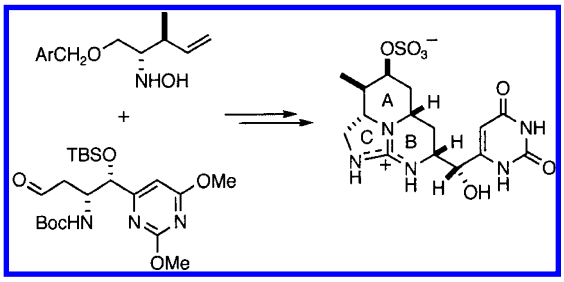
Total Synthesis of (−)-7-Epicylindrospermopsin, a Toxic Metabolite of the Freshwater Cyanobacterium *Aphanizomenon ovalisporum*, and Assignment of Its Absolute Configuration

James D. White* and Joshua D. Hansen

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331-4003

james.white@oregonstate.edu

Received August 5, 2004



The *Z* and *E* nitrones **38** and **39** from condensation of aldehyde **20** with hydroxylamine **36** underwent intramolecular dipolar cycloaddition to give the substituted 1-aza-7-oxobicyclo[2.2.1] heptanes **40** and **41** in a ratio of 2:1, respectively. Reductive N−O bond cleavage of **40** followed by carbonylation gave cyclic urea **47** in which inversion of the secondary alcohol was effected via an oxidation−reduction sequence. After conversion of the *p*-bromobenzyl ether **50** to azide **54**, activation of the cyclic urea as its *O*-methylisourea and reduction of the azide led to spontaneous cyclization to afford the tricyclic nucleus **59** of cylindrospermopsin. Global deprotection, including hydrolysis of the 2,4-dimethoxypyrimidine appendage to a uracil, and then monosulfation of the resultant diol **60** afforded a substance identical with natural (−)-7-epicylindrospermopsin (**1**). The asymmetric synthesis of (−)-7-epicylindrospermopsin defines its absolute configuration as 7*S*,8*R*,10*S*,12*S*,13*R*,-14*S*.

Introduction

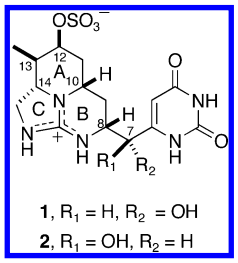
An outbreak of hepatoenteritis in 1979 among the human population of Palm Island, situated off the Queensland coast of Australia, was later traced to the presence of a cyanobacterium *Cylindrospermopsis raciborskii* in the drinking water supply.[1] *C. raciborskii*, originally discovered in Indonesia, is now quite common in phytoplankton of temperate waters and is often the dominant species in algal blooms where incidence of gastrointestinal disease is found.[2] For example, blooms of the organism have been noted in eutrophicated lakes and rivers in Hungary, Israel, Brazil, Japan, and Florida, and consequently, *C. raciborskii* must now be considered an environmental hazard of some importance.[3]

Aqueous extraction of *C. raciborskii* by Moore and co-workers furnished a novel alkaloid which they named cylindrospermopsin and to which they assigned structure **1**.[4] The same alkaloid was isolated from the alga *Umezakia natans* by Harada[5] and from *Aphanizomenon ovalisporum* by Banker.[6] *A. ovalisporum* was also found to produce a minor toxic metabolite which was shown to be a stereoisomer of **1** and which was assigned structure **2**.[7] A substance designated deoxycylindrospermopsin has also been isolated from *C. raciborskii*,[8] but the structure of this metabolite remains uncertain.

Cylindrospermopsin was found to be cytotoxic to rat hepatocytes with an in vivo LD_{50} of 2.1 mg/kg for a 24 h assay, decreasing to 0.2 mg/kg when a 5-day kill rate was

(1) Byth, S. *Med. J. Aust.* **1980**, *2*, 40.
(2) Hawkins, P. R.; Runnegar, M. T.; Jackson, A. R.; Falconer, I. R. *Appl. Environ. Microbiol.* **1985**, 1292.

10.1021/jo0486387 CCC: $30.25
Published on Web 11/02/2004



1, R_1 = H, R_2 = OH
2, R_1 = OH, R_2 = H

measured.[9] Unlike other hepatotoxic metabolites of cyanobacteria such as the microcystins,[10] cylindrospermopsin does not exert its toxic effect through specific inhibition of protein phosphatases but through interruption of the biosynthetic steps leading to cell-reduced glutathione.[11] This inhibition is complete at 2.5 μM but the precise mechanism of inhibition is unknown. Renal toxicity as well as neurotoxicity have also been associated with cylindrospermopsin.[12] Interestingly, although 7-epicylindrospermopsin possesses toxicity similar to its stereoisomer,[7] deoxycylindrospermopsin is reported to be devoid of biological activity.[8]

The structure assignment made to cylindrospermopsin by Moore[4] rested on the precarious assumption that the uracil moiety existed as an anomalous enol tautomer which permitted intramolecular hydrogen bonding with a guanidine nitrogen and fixed a conformation in which H-7 would occupy a gauche relationship to H-8. The same assumption when applied to 7-epicylindrospermopsin would place H-7 and H-8 in an antiperiplanar orientation. Although the NMR evidence reported by Moore was not entirely consistent with these conclusions, a synthesis of (±)-cylindrospermopsin by Snider appeared to confirm Moore's structural attribution to this alkaloid.[13] It was apparent, however, that the Snider synthesis does not distinguish between cylindrospermopsin stereoisomers which differ in configuration at C-7. On the other hand, the synthesis of 7-epicylindrospermopsin by Weinreb does define the relative configuration at this center and proves that the assignments previously made to cylindrospermopsin and 7-epicylindrospermopsin must be reversed.[14]

Thus, cylindrospermopsin is correctly represented by **2**, and **1** is 7-epicylindrospermopsin. The absolute configuration of the two metabolites was unknown, however, and biosynthetic evidence[15] provided no reason to favor enantiomers **1** and **2** over their antipodes. A major purpose of our synthesis, therefore, was to establish the absolute configuration of **1** and/or **2** while exploring an asymmetric intramolecular dipolar cycloaddition strategy as a key step in constructing a portion of the cylindrospermopsin framework.[16]

Our goal at the outset was an asymmetric synthesis of the presumed structure of cylindrospermopsin, i.e., **1**, but as events unfolded it became clear that the relative configuration of cylindrospermopsin was incorrectly represented by this structure. When it was shown by Weinreb that **1** was the C-7 epimer of cylindrospermopsin,[14] our target was redefined as the natural enantiomer of 7-epicylindrospermopsin. It was hoped, nevertheless, that by determining the absolute configuration of the 7-epi compound we could establish the absolute stereochemistry of cylindrospermopsin as well even though no structural correlation existed between the two compounds at that time. Our synthesis plan for **1** is shown in Scheme 1 and centers upon construction of a 1-aza-7-oxabicyclo-[2.2.1]heptane **3** as the prelude to elaboration of the tetrasubstituted piperidine (ring A) of **4**. The logical precursor to **3** is (*Z*)-nitrone **5**, which we anticipated would undergo a stereoselective intramolecular dipolar cycloaddition to the vinyl substituent in a boat conformation which has minimal steric interactions between intervening substituents.[18] Nitrones are typically assembled from condensation of an aldehyde with a hydroxylamine, and hence, the requisite building blocks for the synthesis of **5** are projected as **6** (Western Fragment) and **7** (Eastern Fragment). This plan partitions the four stereogenic centers of **5** equally between its two precursors and also positions members of each pair of stereocenters in a vicinal relationship. This enables a single center in each subunit to exercise stereocontrol in the asymmetric construction of that subunit. The uracil substituent of **1** is concealed as a 2,4-dimethoxypyrimidine through most of the synthesis, to be unmasked at a late stage by hydrolysis, as was done in the Snider[13] and Weinreb[14] routes.

Results and Discussion

Synthesis of Eastern Fragment 7. Construction of the dimethoxypyrimidine unit needed for this fragment began with improvement to a procedure reported by Langely[19] for the synthesis of 2,4,6-tribromopyrimidine from barbituric acid (**8**).[20] Treatment of **8** with phosphorus oxybromide and triethylamine in hot toluene was found to give the volatile tribromopyrimidine in quantitative yield if toluene was removed azeotropically from

(3) (a) Nagy, L.; Hiripi, L.; Kovacs, A.; Voros, L. *Hidrol. Kozl*. **1998**, *78*, 298. (b) Presing, M.; Herodek, S.; Voros, L.; Kobor, I. *Arch. Hydrobiol.* **1996**, *136*, 553. (c) Sukenik, A.; Rosin, C.; Porat, R.; Telsch, B.; Banker, R.; Carmeli, S. *Isr. J. Plant Sci.* **1998**, *46*, 109. (d) de Souza, R. C. R.; Carvalho, M. C.; Truzzi, A. *Environ. Toxicol. Water Qual.* **1998**, *13*, 73. (e) Chapman, A. D.; Schelske, C. L. *J. Phycol*. **1997**, *33*, 191.

(4) Moore, R. E.; Ohtani, I.; Runegar, M. T. C. *J. Am. Chem. Soc.* **1992**, *114*, 7941.

(5) Harada, K.; Ohtani, I.; Iwamoto, K.; Suzuki, M.; Watanabe, M. F.; Watanabe, M.; Terao, K. *Toxicon* **1994**, *32*, 73.

(6) Banker, R.; Teltsch, B.; Sukenik, A.; Carmeli, S.; Hadas, O.; Porat. R. *J. Phycol.* **1997**, *33*, 613.

(7) Banker, R.; Teltsch, B.; Sukenik, A.; Carmeli, S. *J. Nat. Prod.* **2000**, *63*, 387.

(8) Norris, R. L.; Eaglesham, G. K.; Pierens, G.; Shaw, G. R.; Smith, M. J.; Chiswell, R. K.; Seawright, A. A.; Moore, M. R. *Environ. Toxicol.* **1999**, *14*, 163.

(9) Runnegar, M. T.; Kong, S.-M.; Zhong, Y.-Z.; Ge, J.-L.; Lu, S. C. *Biochem. Biophys. Res. Commun.* **1994**, *201*, 235.

(10) Carmichael, W. *Sci. Am.* **1994**, *270*, 78.

(11) Runnegar, M.; Kong, S.-M.; Zhong, Y.-Z.; Lu, S. *Biochem. Pharmacol.* **1995**, *49*, 219.

(12) Falconer, I. R.; Hardy, S. J.; Humpage, A. R.; Froscio, S. M.; Tozer, G. J.; Hawkins, P. R. *Environ. Toxicol.* **1999**, *14*, 143.

(13) Xie, C.; Runnegar, M. T. C.; Snider, B. B. *J. Am. Chem. Soc.* **2000**, *122*, 5017.

(14) Heintzelman, G. R.; Fang, W.-K.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **2002**, *124*, 3939 and references therein.

(15) Burgoyne, D. L.; Hemscheidt, T. K.; Moore, R. E.; Runnegar, M. T. C. *J. Org. Chem.* **2000**, *65*, 152.

(16) White, J. D.; Hansen, J. D. *J. Am. Chem. Soc*. **2002**, *124*, 4950.

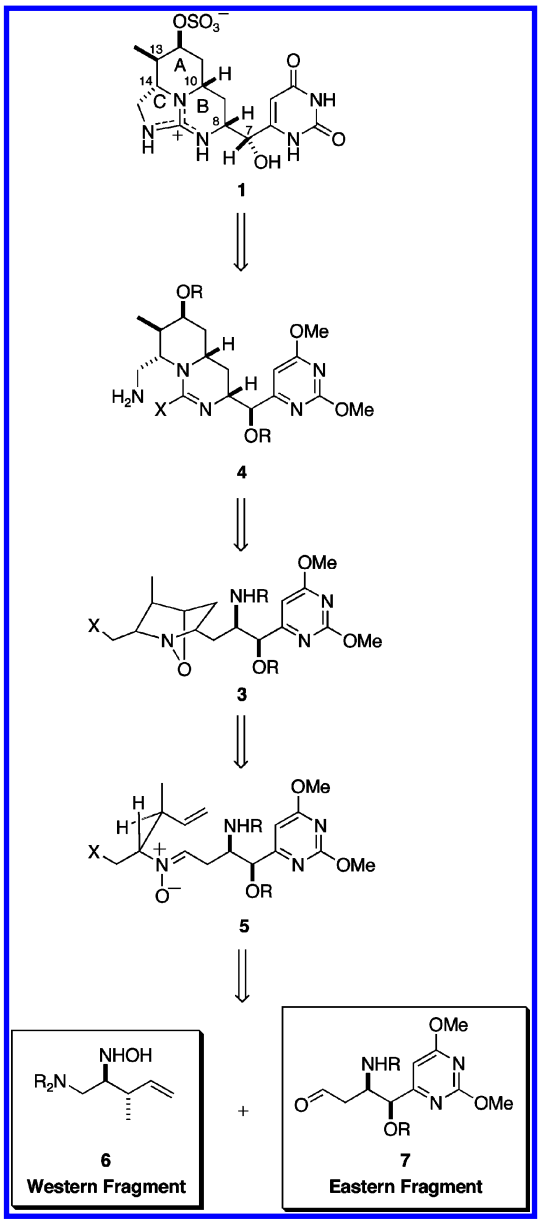
(17) For a review of the biological properties and synthetic approaches to cylindropsermopsin, see: Murphy, P. J.; Thomas, C. W. *Chem. Soc. Rev.* **2001**, *30*, 303.

(18) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497.

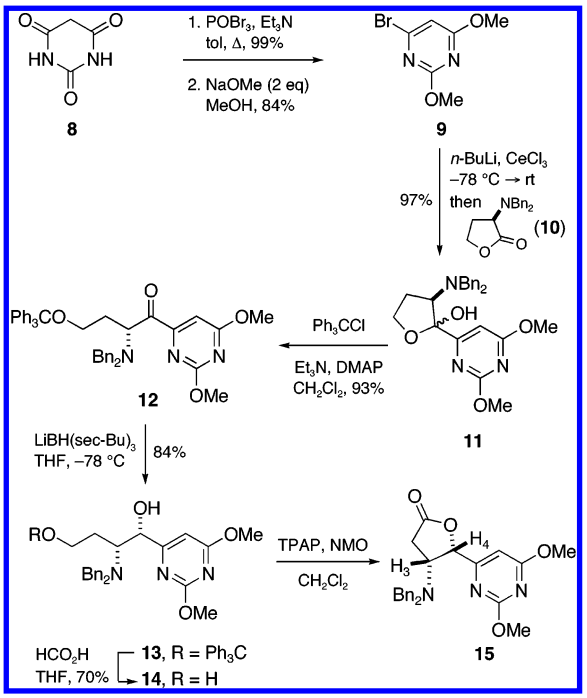
(19) Langley, B. W. *J. Am. Chem. Soc.* **1956**, *78*, 2136.

(20) Dimethylaniline facilitates the preparation of 2,4,6-trichloropyrimidine from barbituric acid and phosphorus oxychloride, see: Baddiley, J.; Topham, A. *J. Chem. Soc.* **1944**, 678.

SCHEME 1



SCHEME 2



the mixture (Scheme 2). The tribromopyrimidine was used without purification in a reaction with sodium methoxide which displaced two of the three bromo substituents selectively from the pyrimidine nucleus. Optimal conditions for this reaction required dropwise addition of two equivalents of sodium methoxide in methanol to the pyrimidine and afforded 4-bromo-2,6-dimethoxypyrimidine (**9**) in excellent yield.

The second component required for the Eastern Fragment was (*R*)-2-(dibenzylamino)butyrolactone (**10**), the enantiomer of which was previously prepared from (*S*)-(+)-methionine by Reetz.[21] We adapted Reetz' method to (*R*)-(−)-methionine and found that reaction of the amino acid with benzyl bromide and potassium carbonate in aqueous tetrahydrofuran gave γ-lactone **10** with an acceptable enantiomeric purity (90% ee) which could be improved to >98% ee by recrystallization. The optimal reaction time for the formation of **10** was 5−6 h; shorter reactions resulted in significant quantities of the monobenzylamino lactone, whereas longer reaction periods degraded the enantiomeric purity of **10**.

As a prelude to coupling the pyrimidine unit with **10**, halogen−metal exchange of bromopyrimidine **9** was carried out with *n*-butyllithium. Exchange occurred rapidly at −78 °C, but treatment of the lithio pyrimidine alone with lactone **10** was accompanied by ca. 25% racemization as measured by a deuterium incorporation experiment. The addition of cerium trichloride to the reaction mixture completely suppressed racemization of **10**,[22] and the adduct **11** was produced in high yield as a mixture of two diastereomeric hemiketals. Not surprisingly, there was no evidence of an equilibrium between **11** and its ring-opened isomer, but exposure of **11** to trityl chloride in the presence of triethylamine containing a catalytic quantity of 4-(dimethylamino)pyridine led smoothly to the protected primary alcohol **12**. The reduction of chiral α-aminoketones has been examined by Reetz,[23] who showed that tertiary amines do not direct hydride reagents and that reduction follows the Felkin−Anh model in yielding predominantly a syn amino alcohol. Accordingly, the reaction of **12** with sodium borohydride in methanol was found to yield **13** and its anti epimer in the ratio 8.5:1, respectively. This ratio was improved to 12:1 in favor of **13** when L-Selectride was used as the reducing agent at −78 °C. Proof of configuration of the major syn diastereomer **13** was obtained by its hydrolysis in formic acid to give diol **14**, which upon oxidation with catalytic tetra-*n*-propylammonium perruthenate and excess *N*-methylmorpholine *N*-oxide[24] produced γ-lactone **15**. The relationship between H-3 and

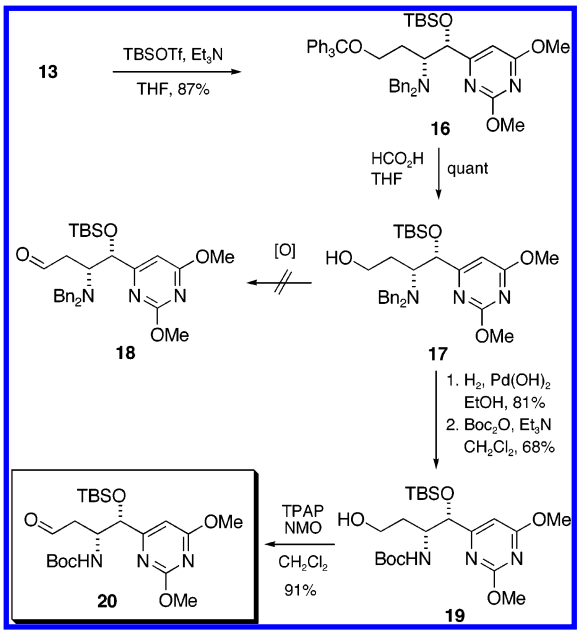
(21) Reetz, M. T.; Schmitz, A.; Holdgroen, X. *Tetrahedron Lett.* **1989**, *30*, 5421.

(22) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

(23) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.

(24) Ley, S.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

SCHEME 3

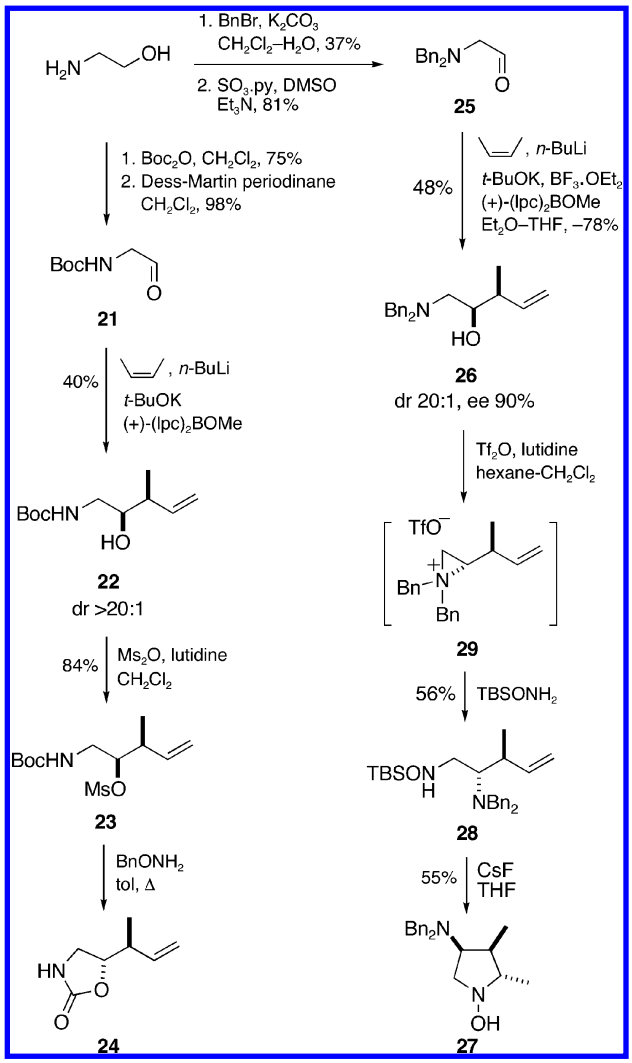


H-4 in this lactone was shown conclusively to be cis by means of an NOE experiment in which H-4 was irradiated. A signal enhancement of 18% was observed for H-3 confirming that the amino alcohol **13** from which **15** originated must have possessed syn configuration. There was also an opportunity with **13** to determine its enantiomeric purity and thus be reassured that no racemization of **12** had occurred during its reduction. For this purpose, racemic **13** was prepared and the enantiomers were shown to be separable by HPLC on a chiral (OJ) column. By this criterion, the enantiomeric ratio of **13** was found to be >97:3.

Completion of the Eastern Fragment from **13** required only protection of the secondary alcohol, release of the primary alcohol from its trityl ether, and oxidation of the latter to an aldehyde. To this end, **13** was converted to its *tert*-butyldimethylsilyl ether **16** and the trityl group was removed with formic acid to afford **17** in high yield (Scheme 3). Unfortunately, no oxidant could be found which would transform primary alcohol **17** to aldehyde **18**. In every case, mixtures were produced which were predominantly the result of a retro-Mannich reaction of the initially generated β-aminoaldehyde **18** or of *N*-oxide formation from this amine. It was clear from this outcome that the reactivity of the tertiary amine of **17** should be suppressed in order to accomplish oxidation of the primary alcohol, and when the two benzyl groups were removed by hydrogenolysis in the presence of palladium hydroxide and the resulting primary amine was protected as carbamate **19**, oxidation of the alcohol took place to give aldehyde **20** in high yield. The sequence to Eastern Fragment **20** requires nine steps from (*R*)-(−)-methionine (10 from barbituric acid) and proceeds in an overall 20% yield.

Synthesis of the Western Fragment. Our initial plan for constructing homoallylic hydroxylamine **6**, the designated reaction partner for **20**, envisioned aldehyde **21** as the starting point. The latter was prepared in straightforward fashion from ethanolamine and was converted to its oxime in the hope that asymmetric

SCHEME 4



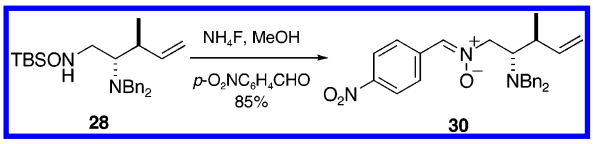
crotylation of this material would afford the (2*S*,3*S*) configuration required for **6** (Scheme 4). Unfortunately, treatment of the oxime of **21** with the (*E*)-crotylborane prepared from *trans*-2-butene and (−)-diisopinylcampheylmethoxyborane gave an impractically low yield of the desired hydroxylamine.[25] The same reagent with O-protected versions of the oxime were also unsuccessful. This failure prompted an alternative approach to the Western Fragment from aldehyde **21**. Syn homoallylic alcohol **22**[26] was obtained with high enantio- and diastereoselectivity from the reaction of **21** with the (*Z*)-crotylborane prepared from (+)-diisopinylcampheylmethoxyborane and was converted to its mesylate **23** in anticipation that displacement with *O*-benzylhydroxylamine would lead to a protected version of **6**. Instead, the sole product of this reaction was oxazolidinone **24** resulting from intramolecular displacement of the mesylate by the Boc group.

In an attempt to find a route to **6** which would avoid neighboring group participation in the displacement seen with **23**, the Boc protecting group of **21** was replaced by

(25) For a similar result, see: Itsuno, S.; Watanabe, K.; Ito, K.; El-Shehawy, A. A.; Sarhan, A. A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 109.

(26) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

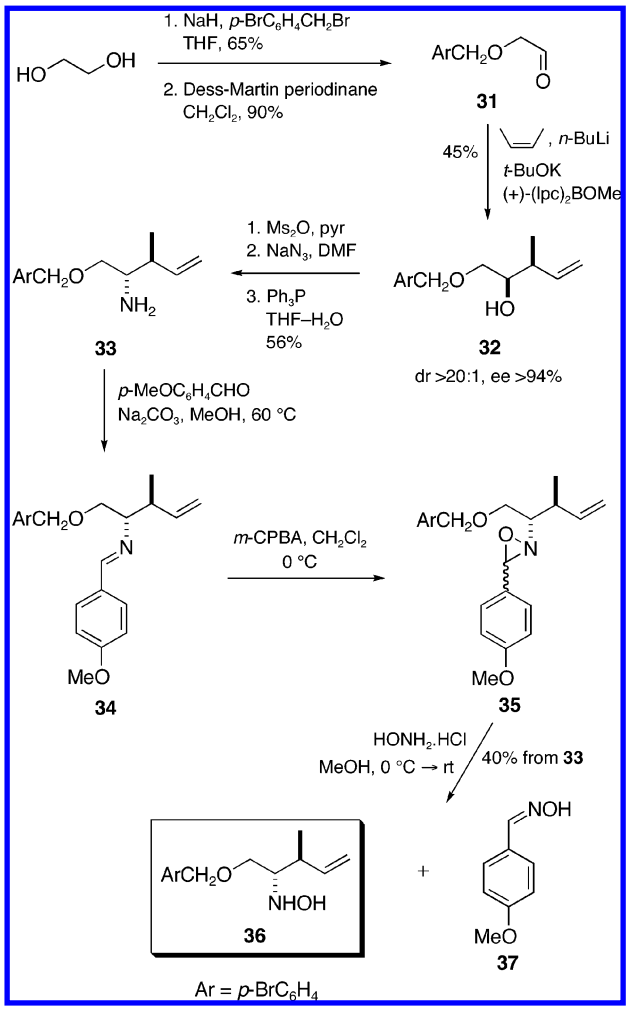
SCHEME 5



a pair of benzyl substituents. *N*,*N*-(Dibenzylamino)-acetaldehyde (**25**) was prepared from ethanolamine and was subjected to the same asymmetric crotylation[26] used with **21** (Scheme 4). The resulting homoallylic alcohol **26** was treated with triflic anhydride and then with the *tert*-butyldimethylsilyl ether of hydroxylamine in the expectation that displacement would give **6**. The first indication that events had taken a different turn came when the silyl group was removed from the product under basic conditions and *N*-hydroxypyrrolidine **27** was obtained. This result suggested that the product from **26** was the rearranged hydroxylamine derivative **28**, implying the intervention of azidirinium ion **29** in the displacement of triflate from **26**.[27] A firm assignment of structure to **28** became possible when it was reacted with *p*-nitrobenzaldehyde in the presence of ammonium fluoride to yield crystalline nitrone **30** (Scheme 5). X-ray crystallographic analysis of **30** confirmed its relative stereostructure and proved that an inversion consistent with 1,2-migration of the dibenzylamino group had taken place in **28**.

The foregoing difficulties associated with carrying a protected amine into the sequence designed to afford **6** persuaded us to postpone introduction of the amino function to a later stage when it would be needed for the eventual cyclization of **4** to the amidine moiety of **1**. This revision to the synthesis plan required versions of **3** and **5** (Scheme 1) in which the X group is a protected alcohol, and our starting point would now be ethylene glycol rather than ethanolamine. The mono-*p*-bromobenzyl ether of ethylene glycol was oxidized to aldehyde **31** which underwent asymmetric crotylation[26] to give syn homoallylic alcohol **32** with excellent stereoselectivity (Scheme 6). Attempts to effect displacement of derivatives of **32**, such as its triflate, with *O*-*tert*-butyldimethylsilylhydroxylamine led primarily to a conjugated diene by elimination, but reaction of the mesylate of **32** with sodium azide in dimethylformamide was more successful. The inverted (anti) azide was obtained in good yield accompanied by ca. 10% of elimination product, and the azide was reduced to amine **33** with triphenylphosphine.[28] This left us with the task of oxidizing the amine to a hydroxylamine without causing oxidation of the vinyl group. Fortunately, an excellent protocol has been published by Holmes for exactly this transformation,[29] and we exploited this method by first condensing **33** with *p*-anisaldehyde and then oxidizing the resultant imine **34** with *m*-chloroperbenzoic acid. Rapid oxaziridine formation took place at 0 °C, uncomplicated by epoxidation of the vinyl group, and gave **35** as a 1:1 mixture of diastereomers at the oxaziridine carbon. This mixture, upon exposure to hydroxylamine hydrochloride, smoothly

SCHEME 6

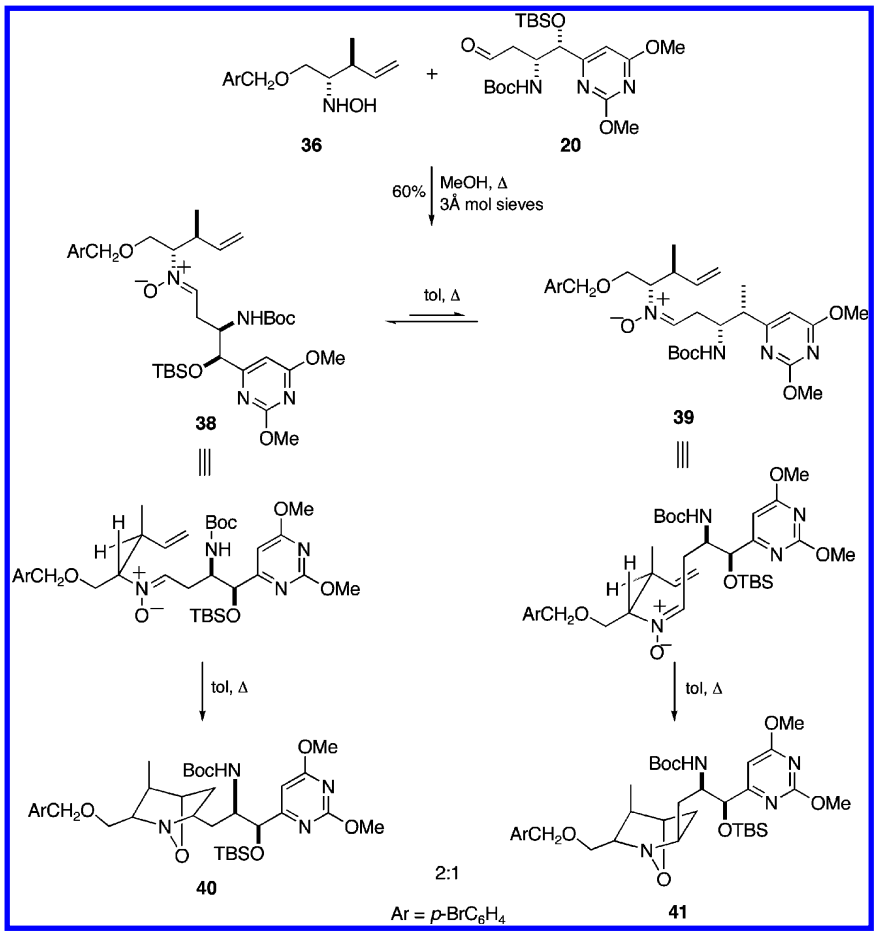


furnished hydroxylamine **36** after removal of the byproduct, *p*-anisaldoxime (**37**). The sequence from ethylene glycol to **36**, although somewhat lengthier than was originally projected, was amenable to scale-up and allowed us to prepare multigram quantities of the hydroxylamine **36** for condensation with aldehyde **20**.

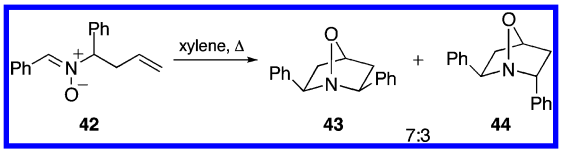
Union of Fragments and Completion of the Synthesis. The coupling of Eastern and Western Fragments **20** and **36** proceeded efficiently in refluxing methanol when 3 Å molecular sieves were present to remove the water of condensation (Scheme 7). Under these conditions, (*Z*)-nitrone **38** was obtained as a single isomer. With the stage now set for an intramolecular 1,3-dipolar cycloaddition leading to ring A of **1**, we invested substantial effort in optimizing the conditions for this key step. We quickly found that the preferred solvent was toluene and that there was a narrow temperature window within which cycloaddition was practical. Above 110 °C, the nitrone decomposed rapidly, whereas below 95 °C there was little reaction. In addition, we found that within the 95−110 °C range there was slow isomerization of the (*Z*)-nitrone **38** to its (*E*)-isomer **39** and that the (*E*) isomer also underwent intramolecular cycloaddition. The (*Z*)- to (*E*)-nitrone isomerization was accelerated by Lewis acid catalysts such as 5 M lithium perchlorate in ether,[30] with no benefit to the cycloaddition process. The optimized conditions for intramolecular cycloaddition of

(27) For a similar rearrangement, see: Gmeiner P.; Junge, D.; Kaertner, A. *J. Org. Chem.* **1994**, *59*, 6766.
(28) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353.
(29) (a) Smith, A. L.; Williams, S. F.; Holmes, A. B.; Hughes, L. R.; Swithenbank, C.; Lidert, Z. *J. Am. Chem. Soc.* **1988**, *110*, 8696. (b) Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Swithenbank, C.; Lidert, Z. *J. Org. Chem.* **1991**, *56*, 1393.

SCHEME 7



SCHEME 8



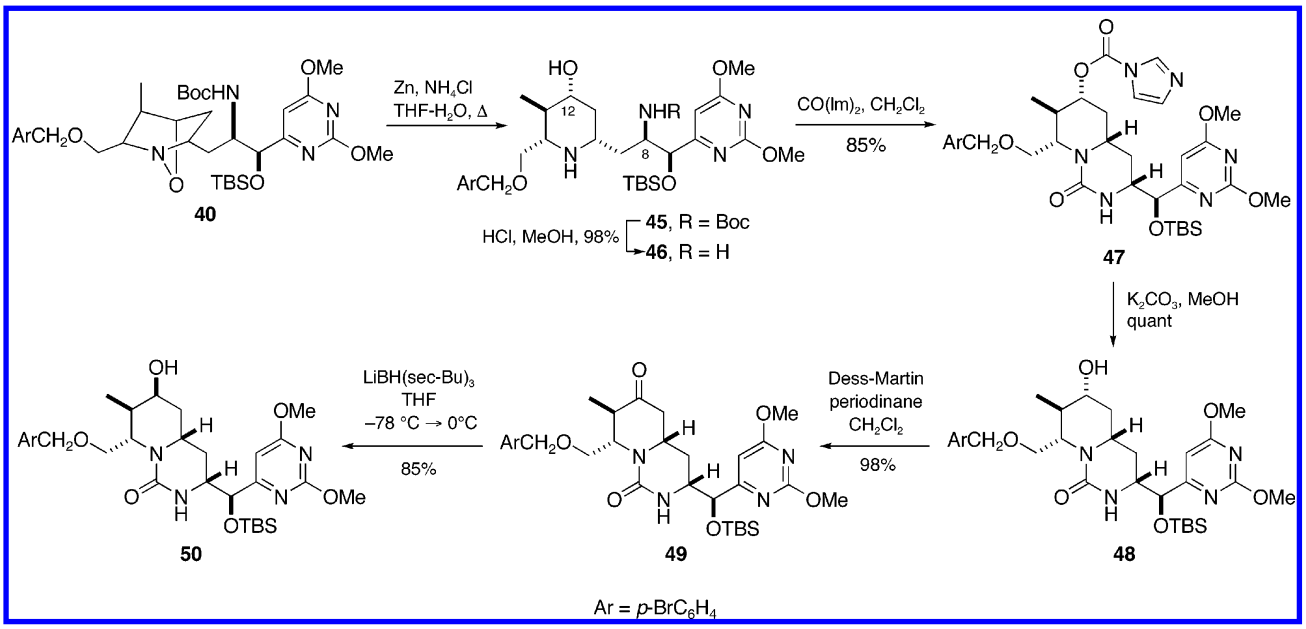
38 led to a 2:1 mixture of isomeric oxazabicyclo[2.2.1]-heptanes **40** and **41** which could only be separated chromatographically with substantial loss of material. High dilution proved unnecessary for the reaction since no products of intermolecular cycloaddition were ever observed. The mode of cycloaddition of **38** conforms to results published by Oppolzer who examined the influence of chain length between the nitrone and olefin on the regiochemistry of the reaction[18] and is also consistent with findings of Hoffman and Endesfelder,[31] who showed that (*Z*)-nitrone **42** in xylene at reflux gave a 7:3 mixture of exo,exo and exo,endo cycloadducts **43** and **44**, respectively (Scheme 8).

Since both **40** and **41** were unstable to chromatography on silica and appreciable loss of material occurred when their purification was attempted by this means, the mixture of cycloadducts was subjected to immediate reductive cleavage of the N−O bond. The resulting piperidine **45** was stable and could be purified without difficulty (Scheme 9). Although both samarium diiodide and Raney nickel were effective reagents for the reduction of **40**, the most convenient method involved the use of zinc dust and ammonium chloride at elevated temperature. An important attribute of this relatively mild reduction was preservation of the silyl ether, and after removal of the Boc protecting group in acidic methanol the piperidine **46** was obtained in an overall 68% yield from nitrone **38**.

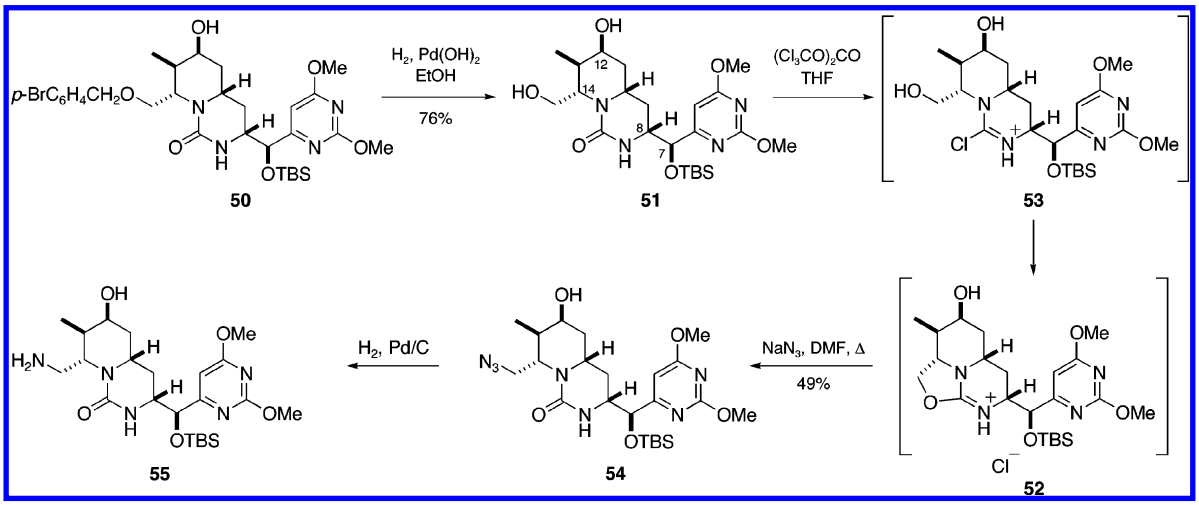
With **46**, a substantial portion of the cylindrospermopsin functionality and five of the six stereocenters of **1** were in hand. However, the aberrant configuration at C-12 remained a significant challenge since it appeared unlikely for steric reasons that a Mitsunobu-type inversion would be effective at this site. On the other hand, reduction of a C-12 ketone by a bulky hydride reagent should deliver an axial alcohol with the required (*S*) configuration. Our concern with this tactic was that the keto piperidine from oxidation of **45** or **46** could undergo retro-Mannich fragmentation which would scramble the stereochemistry of substituents attached to the piperidine. Indeed, when oxidation of alcohol **45** was attempted, it became clear that this fear was well grounded. Removal of basicity from the piperidine nitrogen prior to oxidation at C-12 was an obvious remedy for this situation, and the proximal amino group at C-8 afforded a handy partner for this purpose. Exposure of **46** to carbonyldimidazole conveniently bridged the amine and piperidine nitrogens to produce a cyclic urea **47** in which acylation of the C-12 alcohol had accompanied urea formation. The

(30) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.
(31) Hoffman, R. W.; Endesfelder, A. *Justus Liebig Ann. Chem.* **1986**, 1823.

SCHEME 9



SCHEME 10



imidazoyl carbamate was readily cleaved from **47** with methanolic potassium carbonate to give alcohol **48**, and oxidation of this secondary alcohol now proceeded uneventfully. As expected, reduction of ketone **49** with L-Selectride[32] yielded a single alcohol **50** which was clearly epimeric with **46** at C-12.

Acquisition of **50** gave us a structure with all six of the stereocenters of **1** now set correctly, and our next task was elaboration of the guanidine unit embedded in the cylindrospermopsin core. This required replacement of the *p*-bromobenzyl ether with a primary amine which, it was hoped, could be induced to undergo intramolecular condensation with the urea carbonyl. Cleavage of ether **50** by hydrogenolysis over Pearlman's catalyst furnished diol **51** which proved to be a crystalline substance (Scheme 10). X-ray crystallographic analysis of **51** (Figure 1) fully confirmed its structure and demonstrated that rings A and B occupied chair conformations with the C-12 hydroxyl group in an axial orientation. The spatial relationship between hydrogens at C-7 and C-8 is gauche, consistsent with the coupling constant measured in the ^{1}H NMR spectrum of **51**, and the equatorial hydroxymethyl substituent at C-14 is positioned relative to the urea carbonyl in a manner which suggests that ring

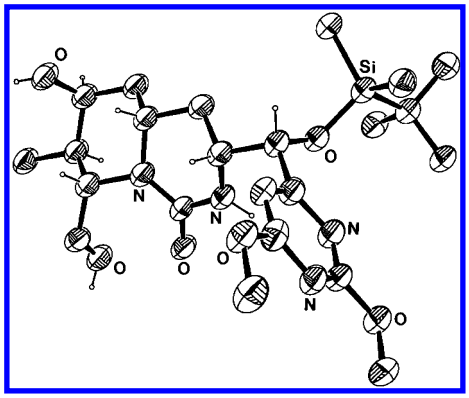
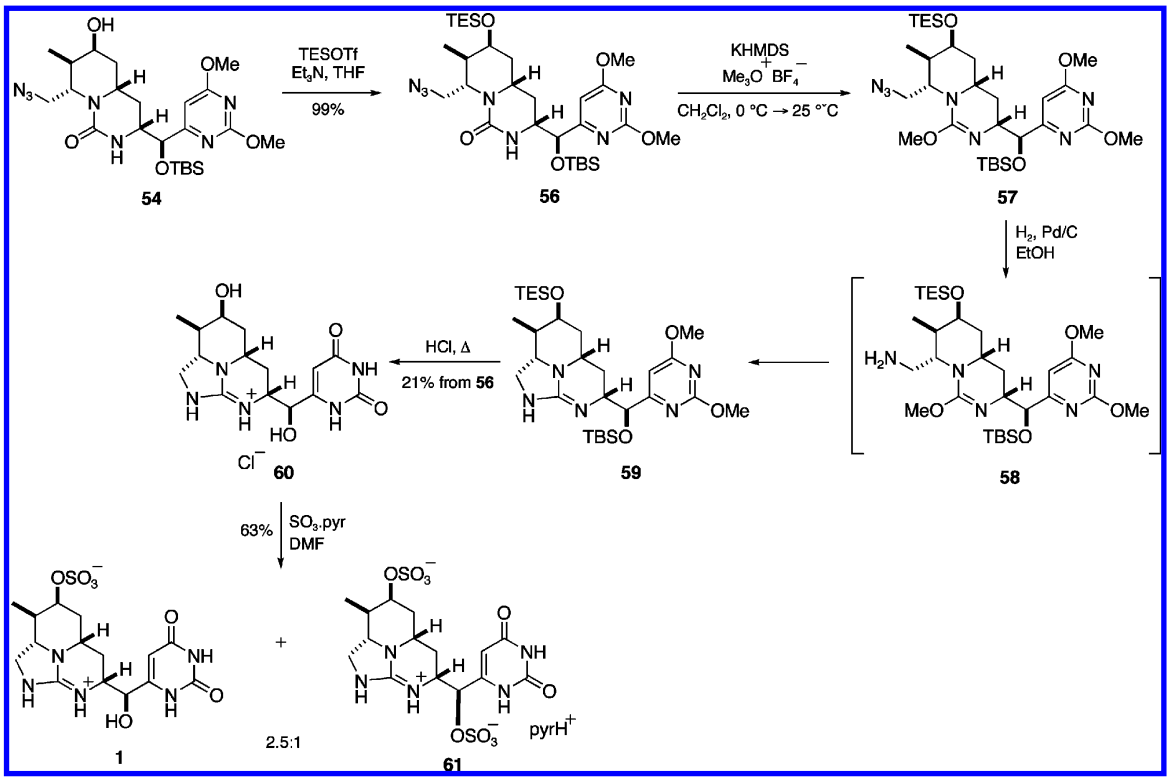


FIGURE 1. ORTEP representation of the X-ray crystal structure of **51**. Ellipsoids are at the 20% probability level.

(32) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

SCHEME 11



closure to a cyclic imidate should be facile. Indeed, when **51** was treated with triphosgene a substance presumed to be **52** was detected by mass spectrometry, and we conjecture that this imidate is formed by intramolecular displacement of chloride from **53**. In any event, cyclic imidate **52** was reopened by sodium azide in hot dimethylformamide to give azide **54** which was reduced to primary amine **55** under an atmosphere of hydrogen. Unfortunately, many attempts to force cyclization of amino urea **55** all met with failure, neither thermal conditions (1,2-dichlorobenzene at 170 °C) nor Lewis acids such as diethylaluminum chloride affording any evidence for the formation of a guanidine moiety. Most of these reactions returned the urea unchanged, indicating that modification of this functional group would be required in order to assemble a guanidine in the manner we envisioned.

Our inability to close amino urea **55** forced us to return to azide **54** so that a suitable modification protocol could be applied to the urea without interference from the amino group. First, however, it was necessary to protect the hydroxyl function of **54**, and reaction of this alcohol with triethylsilyl triflate gave ether **56** in excellent yield. Interestingly, no silylation of the urea moiety took place with this reagent, although when trimethylsilyl triflate was used for protection of **54**, some O-silylation at the urea did occur. With the urea of **56** open for derivatization, its exposure to potassium hexamethyldisilazide and then to trimethyloxonium fluoroborate furnished the unstable methylisourea **57** along with two minor products which arose from monomethylation at each of the pyrimidine nitrogens. Since chromatographic purification of **57** resulted in substantial loss of material, the crude azide was hydrogenated over palladium-on-carbon with the result that the transient primary amine **58** cyclized spontaneously to yield **59**. Although the facility with which **58** underwent ring closure to guanidine **59** seemed surprising, a similar observation was reported by Weinreb in his synthesis of 7-epicylindrospermopsin when an azido urea similar to **56** was reacted with methyl triflate and then was hydrogenated.

Conversion of **56** to **1** proved to be straightforward since we could now take advantage of known chemistry[13] for the global deprotection of this substance. Thus, exposure of **59** to hot concentrated hydrochloric acid accomplished hydrolysis of the dimethoxypyrimine to the uracil residue as well as removal of the two silyl groups to yield hydrochloride **60** after purification by reversed-phase HPLC. The ^{1}H and ^{13}C NMR spectra of diol **60** matched those of the racemic hydrochloride synthesized by Weinreb,[14] confirming that our synthesis had led to 7-epicylindrospermopsin rather than cylindrospermopsin itself. Finally, treatment of diol **60** with sulfur trioxide−pyridine complex as described by Snider[13] gave 7-epicylindrospermopsin (**1**) accompanied by bissulfate **61** in the approximate ratio 2.5:1. These two substances were readily separated by reversed-phase HPLC and pure **1** was shown to have spectral properties which agreed with those reported for natural 7-epicylindrospermospin.[7] The optical rotation of our synthetic compound ($[\alpha]_D^{25}$ −17.2) closely matched the value reported for natural material ($[\alpha]_D^{25}$ −20.5)[7] and established that the absolute configuration of natural 7-epicylindrospermopsin is correctly represented by **1**, i.e., 7*S*,8*R*,10*S*,12*S*,13*R*,14*S*.[33] Since 7-epicylindrospermopsin has been correlated chemically with cylindrospermopsin by Weinreb[14] and the two compounds are known to differ in configuration only at

(33) A recent asymmetric synthesis of 7-epicylindrospermopsin by Williams confirms this assignment (Looper, R. E.; Williams, R. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2930).

C-7, cylindrospermopsin is represented in absolute configuration by **2**, i.e., 7*R*,8*R*,10*S*,12*S*,13*R*,14*S*.

The asymmetric synthesis of (−)-7-epicylindrospermopsin described above corroborates the structural correction made to this natural product by Weinreb in the course of his synthesis of the racemic substance. The stereochemical error in Moore's assignment of relative configuration to cylindrospermopsin,[4] and which passed unnoticed in Snider's synthesis of this compound,[13] must now be attributed to an incorrect assumption regarding the conformation of the molecule about the C-7−C-8 bond. This led to a misinterpretation of the 4.0 Hz coupling between H-7 and H-8 as that of a syn-vicinal relationship. An analogous conformation for 7-epicylindrospermopsin would place H-7 and H-8 in an antiperiplanar orientation, a stereochemical relationship difficult to reconcile with the 6.8 Hz coupling between these two protons. Although the solution conformations of **1** and **2** are presently unknown, the structural revisions made to cylindrospermopsin and its epimer remove the awkward postulate of a previously unknown tautomer of uracil as the agency which, through hydrogen bonding, was thought to stabilize the conformations previously proposed for these metabolites.

Experimental Section

2,4,6-Tribromopyrimidine. To a flame-dried, argon-filled flask were added phosphorus(V) oxytribromide (17.88 g, 62.4 mmol), dry toluene (30 mL), barbituric acid (**8**, 2.00 g, 15.6 mmol), and *N*,*N*-dimethylaniline (3.60 mL, 28.8 mol). The mixture turned red and was heated to reflux for 3 h and then cooled to room temperature, and ice (ca 50 g) was added. The aqueous layer was separated and extracted with benzene (10 mL), and the extract was dried over $MgSO_4$, filtered, and diluted with MeOH (60 mL). The solution was concentrated under reduced pressure to give 4.89 g (99%) of 2,4,6-tribromopyrimidine as a yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.1, 150.7, 153.0. This material was used without purification for the next reaction.

4-Bromo-2,6-dimethoxypyrimidine (9). To a solution of 2,4,6-tribromopyrimidine (4.89 g, 15.4 mmol) in anhydrous MeOH (40 mL) and dry Et_2O (20 mL) was added dropwise sodium methoxide (0.50 M, 61.7 mL, 30.9 mmol) during 1 h, and the mixture was stirred for 20 h. After concentration of the mixture under reduced pressure, the residue was diluted with water (10 mL), and the mixture was extracted with Et_2O (100 mL). The extract was concentrated under reduced pressure to give 2.83 g (84%) of pure **9** as a colorless solid: IR (neat) 1588, 1568, 1466, 1360, 1344 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3H), 3.88 (s, 3H), 6.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.2, 55.2, 104.8, 151.8, 164.3, 171.5; MS (FAB) *m/z* 219 (M + 1) 149, 136; HRMS (FAB) *m/z* 218.9767 (calcd for $C_6H_8N_2O_2{}^{79}Br$ 218.9769).

(*R*)-2-Dibenzylamino-4-hydroxybutyric Acid Lactone (10). (*R*)-Methionine (5.00 g, 34.0 mmol) was added to a solution of K_2CO_3 (13.9 g, 101 mmol) in water (100 mL), and the mixture was heated to reflux. Benzyl bromide (24.0 mL, 0.20 mol) was added dropwise, and the mixture was heated at reflux for 3 h and then cooled to room temperature. The aqueous phase was separated and extracted with Et_2O (150 mL), and the extract was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the excess benzyl bromide and benzyl alcohol were distilled off (1 Torr, 60 °C). The residual oil was purified by chromatography (hexanes−ethyl acetate, 7:3) to yield a solid which was crystallized from hexanes−Et_2O to yield 5.91 g (62%) of **10** as colorless prisms: [α] +28.3 (*c* 1.0, $CHCl_3$); IR (neat) 1757, 1643, 1602 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33−2.24 (m, 2H), 3.70 (d, *J* = 13.7 Hz, 2H), 3.78 (t, *J* = 9.9 Hz,1H), 3.95 (d, *J* = 13.7 Hz, 2H), 4.10−4.01 (q, *J* = 8.8 Hz, 1H), 4.35−4.28 (m, 1H), 7.49−7.26 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.5, 54.5, 57.6, 65.1, 127.1, 128.2, 128.4, 138.7, 175.8; MS-(EI) *m/z* 282 (M + 1)$^+$, 254, 196, 190, 181, 146, 91; HRMS (El) *m/z* 282.1494 (calcd for $C_{18}H_{19}NO_2$ 281.1416).

(2*R*,3*R*)- and (2*S*,3*R*)-3-Dibenzylamino-2-hydroxy(2,6-dimethoxy-4-pyrimidinyl)tetrahydrofuran (11). A flask containing anhydrous $CeCl_3$ (dried at 120 °C and 0.5 Torr for 2 h, then cooled to room temperature) was filled with argon, and 15 mL of dry THF was added. The suspension was stirred for 5 min before addition of **10** (423 mg, 1.50 mmol), and the mixture was stirred for 30 min at room temperature and then cooled to −78 °C. In a separate flask, a solution of **9** (657 mg, 3.0 mmol) in THF−Et_2O (1:1, 40 mL) was stirred at −78 °C for 5 min, and ice-cold *n*-butyllithium (1.6 M, 1.82 mL, 2.92 mmol) was added. The resulting solution was immediately transferred via cannula to the solution containing **10**, the mixture was stirred at −78 °C for 45 min and then was allowed to warm to room temperature during 5 h. Aqueous saturated NH_4Cl solution (6 mL) was added, followed by saturated aqueous $NaHCO_3$ (20 mL) and water (5 mL), and the aqueous layer was separated and extracted with Et_2O (30 mL). The extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (petroleum ether−EtOAc, 9:1 to 8:2 + 5% MeOH) of the residue yielded 617 mg (97%) of **11** as a pale yellow oil: [α] − 43.3 (c 0.28, $CHCl_3$); IR (neat) 3600−3100, 2955, 1720, 1567, 1448, 1352 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38−2.15 (m, 2H), 3.51 (d, *J* = 14.0 Hz, 2H), 3.69 (t, *J* = 8.1 Hz, 1H), 4.01 (d, *J* = 22.8 Hz, 2H), 4.08−4.00 (m, 1H), 4.20 (ddd, *J* = 8.8, 8.8, 4.4 Hz, 1H), 6.36 (s, 1H), 7.31−6.93 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 53.9, 54.7, 55.5, 66.9, 97.9, 102.0, 126.9, 128.0, 128.1, 128.4, 128.5, 128.7, 139.1, 164.5, 170.9, 172.4; MS (CI) *m/z* 422 (M + 1), 340, 323, 279, 209, 185, 91; HRMS (CI) *m/z* 422.2078 (calcd for $C_{24}H_{27}N_3O_4$ 421.2002).

(R)-2,6-Dimethoxy-4-(2′-dibenzylamino-4′-trityloxybutanoyl)pyrimidine (12). A solution of **11** (617 mg, 1.46 mmol), Et_3N (0.365 mL, 2.62 mmol), triphenylmethyl chloride (569 mg, 2.00 mmol), and 4-(dimethylamino)pyridine (7.2 mg, 0.06 mmol) in 10 mL of CH_2Cl_2 was stirred at room temperature for 48 h and then at reflux for 5 h. The solution was cooled to room temperature and diluted with saturated aqueous NH_4Cl (2 mL) and saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was separated and extracted with Et_2O (30 mL), and the extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography (petroleum ether−Et_2O, 9:1, to petroleum ether−EtOAc, 8:2) afforded 900 mg (93%) of **12** as a pale yellow oil: [α] +36.5 (*c* 1.0, $CHCl_3$); IR (neat) 1711, 1595, 1568, 1359 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11−2.02 (m, 1H), 2.28−2.19 (m, 1H), 3.18 (q, *J* = 5.5 Hz, 2H), 3.46 (s, 3H), 3.73 (ABq, *J* = 14.3 Hz, 4H), 4.03 (s, 3H), 5.19 (t, *J* = 7.5 Hz, 1H), 6.85 (s, 1H), 7.36−7.13 (m, 25H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.0, 54.2, 54.3, 54.8, 57.2, 60.6, 86.6, 99.9, 126.8, 127.2, 127.6, 127.8, 128.1, 128.6, 139.5, 144.0 162.4, 165.2, 172.8, 200.8; MS (FAB) *m/z* 664 (M + 1), 496, 391, 243, 136, 91; HRMS (FAB) *m/z* 664.3099 (calcd for $C_{43}H_{42}N_3O_4$ 664.3097).

(1′S,2′R)-2,6-Dimethoxy-4-(2′-dibenzylamino-1′-hydroxy-4′-trityloxybutyl)pyrimidine (13). To a solution of **12** (291 mg, 0.438 mmol) in THF (4.5 mL) at −78 °C was added dropwise L-Selectride (1.0 M, 0.526 mL, 0.526 mmol). After 1.5 h, the mixture was warmed to 25 °C, and EtOH (2.5 mL) and water (1.5 mL) were added. The mixture was stirred for 30 min, NaOH (1 M, 2.5 mL) and H_2O_2 (30%, 2.0 mL) were added, and the mixture was stirred for a further 45 min and was extracted with CH_2Cl_2 (3 × 5 mL). The extract was dried over $MgSO_4$ and concentrated, and the residual oil was purified by flash chromatography (9:1−8:2, hexanes−EtOAc) to give 275 mg (84%) of **13**: [α] −25.0 (*c* 1.0, $CHCl_3$); IR (neat) 3600−3150, 1590, 1580, 1470, 1346; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24−1.95 (m, 2H), 3.08−2.98 (m, 3H), 3.43 (d, *J* = 13.1 Hz,

2H), 3.88 (m, 1H), 3.93 (s, 3H), 3.96 (s, 3H), 4.35 (d, J = 6.6 Hz, 1H), 4.72, (br, 1H), 6.01 (s, 1H), 7.44−7.09 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 20.9, 25.8, 53.6, 54.4, 54.5, 54.6, 59.6, 60.3, 61.8, 73.5, 86.6, 98.6, 126.9, 127.0, 127.7, 128.2, 128.5, 129.0, 139.0, 143.9, 164.3, 171.7, 172.2; MS (CI) *m/z* 666 (M + 1), 496, 243, 267, 91; HRMS (CI) *m/z* 666.3351 (calcd for $C_{43}H_{44}N_3O_4$ 666.3332).

(1′*R*,2′*R*)-2,6-Dimethoxy-4-(2′dibenzylamino-1′,4′-dihydroxybutyl)pyrimidine (14). To **13** (330 mg, 0.496 mmol) were added diethyl ether (13 mL) and formic acid (20 mL). The mixture was stirred at room temperature for 12 h and then was diluted with Et_2O (30 mL) and washed with brine (3 × 15 mL) and saturated aqueous $NaHCO_3$ (3 × 20 mL). The separated organic phase was dried over $MgSO_4$, filtered, and concentrated. Purification of the residual oil by flash chromatography (1:1, hexanes−EtOAc) gave 146 mg (70%) of **14**: [α] − 20.0 (*c* 1.0, $CHCl_3$); IR (neat) 3200−3650, 1594, 1569, 1450, 1355 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70−1.85 (m, 1 H), 1.95−2.10 (m, 1 H), 2.25−2.50 (bs, 1H), 3.04 (q, J = 13.2, 6.6, 6.6 Hz, 1 H), 3.40−3.52 (m, 2 H), 3.78 (dd, J = 17.3, 13.2 Hz, 4 H), 3.91 (s, 3H), 3.93 (s, 3H), 4.49 (d, J = 8.1 Hz, 1H), 4.47−4.62 (bs, 1 H), 6.18 (s, 1 H), 7.18−7.32 (m, 10 H); ^{13}NMR ($CDCl_3$) δ 29.0, 53.9, 54.5, 54.7, 59.8, 60.7, 74.2, 98.8, 127.2, 128.4, 129.2, 139.0, 164.6, 172.0, 172.7; MS (FAB) *m/z* 424.2 (M + 1)$^+$, 285.2, 154.1, 91.1; HRMS (FAB) *m/z* 424.2149 (calcd for $C_{24}H_{30}N_3O_4$ 424.2158).

(1′*S*,2′*R*)-2,6-Dimethoxy-4-[2′dibenzylamino-1′-(*tert*-butyldimethylsilanyloxy)-4′-trityloxybutyl]pyrimidine (16). To a solution of **13** (195 mg, 0.294 mmol) in CH_2Cl_2 (0.7 mL) were added 2,6-lutidine (0.066 mL, 0.572 mmol) and *tert*-butyldimethylsilyl triflate (0.429 mmol, 0.098 mL), and the mixture was stirred for 1.25 h. Aqueous NH_4Cl (1 mL) was added, and the mixture was diluted with Et_2O. The aqueous phase was separated and extracted with Et_2O (3 × 5 mL), and the combined extract was dried over $MgSO_4$, filtered, and concentrated. The residual oil was purified by flash chromatography (9:1 to 8:2 petroleum ether−Et_2O) to give 199 mg (87%) of **16**: [α] −43.3 (*c* 0.28, $CHCl_3$); IR (neat) 2947, 2900, 1602, 1570, 1355 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.20 (s, 3H), −0.18 (s, 3H), 0.88 (s, 9H), 1.90−2.08 (m, 1H), 2.2−2.38 (m, 1H), 3.20−3.32 (m, 1H), 3.30−3.40 (m, 1H), 3.36 (s, 4H), 3.42 (s, 1H), 3.46−3.55 (m, 1H), 4.05 (s, 4H), 3.95−4.09 (bs, 1H), 4.55 (d, J = 2.7 Hz, 1H), 6.72 (s, 1H), 7.05−7.57 (m, 25 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.2, −4.7, 17.9, 25.0, 25.8, 53.8, 54.3, 55.4, 57.6, 60.9, 77.4, 86.5, 99.6, 126.3, 126.7, 127.6, 127.8, 128.5, 128.7, 140.5, 144.2, 164.4, 171.6, 174.8; MS (FAB) *m/z* 780 (M + 1), 652, 496, 368, 243, 91; HRMS (FAB) *m/z* 780.4186 (calcd for $C_{49}H_{58}N_3O_4Si$ 780.4197).

(1′*S*,2′*R*)-2,6-Dimethoxy-4-[2′dibenzylamino-1′-(*tert*-butyldimethylsilanyloxy)-4′-hydroxybutyl]pyrimidine (17). A solution of **16** (235 mg, 0.301 mmol) in Et_2O (10 mL) and formic acid (15 mL) was stirred for 12 h. The mixture was diluted with Et_2O (50 mL), and the solution was washed with brine (3 × 50 mL) and with saturated aqueous $NaHCO_3$ (3 × 40 mL). The organic phase, which contained a mixture of **17** and its formate ester, was concentrated to 20 mL, and MeOH (30 mL) and K_2CO_3 (663 mg, 4.80 mmol) were added. The mixture was stirred for 1 h and extracted with Et_2O (3 × 15 mL), and the combined extract was dried over $MgSO_4$, filtered, and concentrated. The residual oil was purified by flash chromatography (9:1 to 8:2 hexane/EtOAc) to give 156 mg (100%) of **17**: [α] −43.3 (*c* 0.28, $CHCl_3$); IR (neat) 2940, 1595, 1560, 1365 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.07 (s, 3 H), 1.00 (s, 9 H), 0.17 (s, 3 H), 1.42−1.58 (m, 1H), 1.98−2.09 (m, 1H), 2.60−2.90 (bs, 1H), 3.28 (q, J = 6.6, 11.0 Hz, 1H), 3.48−3.60 (m, 1H), 3.63 (d, J = 13.7 Hz, 2H), 3.82 (s, 3H), 3.91 (d, J = 13.7 Hz, 2H), 4.06 (s, 3H), 4.71 (d, J = 4.4 Hz, 1H), 6.73 (s, 1H), 7.23−7.33 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -4.9, −4.4, 18.0, 25.9, 29.4, 29.6, 53.9, 54.5, 54.8, 54.9, 58.8, 58.9, 60.9, 61.2, 78.6, 78.8, 99.4, 126.8, 128.1, 129.1, 140.0, 164.5, 171.8, 174.5; MS (CI) *m/z* 538 (M + 1), 522, 492, 480; HRMS (CI) *m/z* 538.3101 (calcd for $C_{30}H_{44}N_3O_4Si$ 538.3101).

(1′*S*,2′*R*)-2,6-Dimethoxy-4-[2′(*tert*-butoxycarbonyl)amino-1′-(*tert*-butyldimethylsilanyloxy)-4′-hydroxybutyl]pyrimidine (19). To a solution of **17** (201 mg, 0.372 mmol) in EtOH (5 mL) was added $Pd(OH)_2$/C (20%, 100 mg), and the mixture was stirred vigorously under an atmosphere of H_2 for 7 h. The suspension was filtered through Celite, and the filtrate was concentrated under reduced pressure to give 108 mg (81%) of an amino alcohol: IR (neat) 3600−3400, 2926, 1573, 1360 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.22 (s, 3H), 0.93 (s, 9H), 1.23 (m, 1H), 1.46 (t, J = 7 Hz, 1H), 1.56−1.87 (m, 2H), 3.66−3.88 (m, 2H), 3.98 (s, 6H), 4.94 (d, J = 3 Hz, 1H), 6.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −5.0, −4.7, 14.1, 17.9, 25.8, 29.7, 54.0, 55.1, 55.5, 59.4, 72.1, 99.3, 164.5, 170.5, 172.4. This material was used immediately in the next reaction.

To a solution of the amino alcohol obtained above (125 mg, 0.350 mmol) in CH_2Cl_2 (6 mL) were added Boc_2O (84.4 mg, 0.386 mmol) and Et_3N (35.3 mg, 0.350 mmol), and the resulting solution was stirred for 24 h at room temperature. The solvent was removed, and the residual oil was purified by chromatography on silica gel, with hexane/EtOAc (7:3, then 1:1) as eluent, to give 131 mg (68%) of **19**: [α] −9.4 (*c* 0.5, $CHCl_3$); IR (neat) 2953, 2926, 1689, 1595, 1570, 1370 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.11 (s, 3H), 0.93 (s, 9H), 1.37 (s, 9H), 1.97−1.79 (m, 1H), 3.72−3.41 (m, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 4.63 (d, J = 2.2 Hz, 1H), 5.58 (d, J = 9.5 Hz, 1H), 6.49 (s, 1H);^{13}C NMR (75 MHz, $CDCl_3$), δ −5.0, −4.9, 14.1, 18.1, 20.9, 25.8, 28.2, 34.9, 51.8, 53.8, 54.7, 58.7, 75.5, 79.6, 98.8, 156.9, 164.7, 172.1, 172.3; MS (FAB) *m/z* 446 (M + 1), 358, 285, 185, 91; HRMS (FAB) *m/z* 446.2528 (calcd for $C_{20}H_{40}N_3O_6Si$ 446.2530).

(3*R*,4*S*)-3-(*tert*-Butoxycarbonyl)amino-4-(*tert*-butyldimethylsilanyloxy)-4-(2,6-dimethoxy-4-pyrimidinyl)butanol (20). To a solution of **19** (111 mg, 0.240 mmol) in CH_2Cl_2 (2.5 mL) under argon were added powdered molecular sieves (4 Å, 50 mg), *N*-methylmorpholine *N*-oxide (117 mg, 0.360 mmol), and tetra-*n*-propylammonium perruthenate (8.6 mg, 0.02 mmol), and the resulting green mixture was stirred at room temperature for 45 min. The mixture was filtered through a pad of silica which was washed with EtOAc. The filtrate was concentrated under reduced pressure to leave 102 mg (91%) of **20** as a colorless oil: [α] −34.1 (*c* 0.66, $CHCl_3$); IR (neat) 3482−3205, 2959, 2928, 2858, 1720, 1598, 1568, 1477, 1358, 1096, 841, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.13 (s, 3H), 0.95 (s, 9H), 1.37 (s, 9H), 2.34 (ddd, J = 2.6, 8.2, 15.0 Hz, 1H), 2.53 (ddd, J = 2.6, 5.1, 15.0 Hz, 1H), 3.96 (s, 3H), 3.99 (s, 3H), 4.43−4.55 (m, 1H), 4.69 (d, J = 3 Hz, 1H), 5.66 (d, J = 9.5 Hz, 1H), 6.49 (s, 1H), 9.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ −4.8, −4.6, 18.4, 26.1, 28.5, 46.1, 51.2, 54.1, 55.0, 75.0, 79.8, 99.5, 155.4, 165.1, 171.2, 172.6, 200.5; MS (FAB) *m/z* 456 (M + 1), 312, 285, 227, 154, 91; HRMS (FAB) *m/z* 456.2523 (calcd for $C_{21}H_{38}N_3O_6Si$ 456.2530).

2-(*tert*-Butoxycarbonyl)aminoacetaldehyde (21). To 2-(*tert*-butoxycarbonyl)aminoethanol (40.0 mg, 0.248 mmol) in CH_2Cl_2 (2 mL) was added Dess−Martin periodinane (130 mg, 0.306 mmol) in one portion. A milky suspension formed, and the mixture was stirred for 2 h. To the mixture was added 2 mL of saturated aqueous $NaHCO_3$−$Na_2S_2O_4$. Within 20 min the solution became clear and biphasic. The mixture was extracted with CH_2Cl_2, and the extract was washed with brine and dried over $MgSO_4$. Filtration through a plug of Celite and concentration gave 38.6 mg (98%) of **21** which was used without further purification: IR (neat) 3400, 2990, 1702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9 H), 4.07 (d, J = 4.6 Hz, 2 H), 5.18 (bs, 1 H), 9.65 (s, 1 H); ^{13}C NMR (300 MHz, $CDCl_3$), δ 27.8, 51.24, 80.0, 155.7, 197.4; HRMS (FAB) *m/z* 160.088 (calcd for $C_7H_{14}NO_3$ 160.0895).

(2*R*,3*S*)-1-(*tert*-Butyoxycarbonyl)amino-2-hydroxy-3-methyl-4-pentene (22). To a stirred mixture of potassium *tert*-butoxide (113 mg, 1.0 mmol) in THF (1.33 mL) and *cis*-2-butene (2 mL, 22 mmol) was added *n*-butyllithium (1.0 mmol, 0.667 mL, 1.6 M in hexane) at −78 °C. The mixture was stirred

at −45 °C for 10 min, and the resulting orange solution was recooled to −78 °C. To this solution was added dropwise a solution of (+)-methoxydiisopinocampheylborane (387 mg, 1.23 mmol) in Et_2O (2.2 mL). The mixture was stirred at −78 °C for 30 min, $BF_3{\cdot}Et_2O$ (0.137 mmol, 0.14 mL) was added dropwise, and the mixture was stirred for 10 min. A solution of **21** (159 mg, 1 mmol) in THF (1.2 mL) was added dropwise, and the mixture was stirred at −78 °C for 5 h. The mixture was allowed to slowly warm to room temperature and then treated with NaOH (3 M, 3 mL) and H_2O_2 (30%, 1 mL), and the resulting mixture was refluxed for 1 h. The organic phase was separated, washed with water and brine, and dried ($MgSO_4$). After removal of solvent under reduced pressure, the residual oil was chromatographed on silica gel (8:2, hexanes−EtOAc, + 5% CH_2Cl_2) to give 85 mg (40%) of **22**: [α] −28.4 (*c* 1.0, $CHCl_3$); IR (neat) 3550−3300, 2973, 1690, 1516, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (d, *J* = 6.6 Hz, 3H), 1.40 (s, 9H), 2.29−2.14 (m, 1H), 3.00−2.73 (m, 1H), 3.10−3.00 (bs, 1H), 3.38−3.25 (m, 1H), 3.52−3.40 (m, 1H), 4.68−4.58 (bs, 1H), 5.15−4.95 (m, 2H), 5.77−5.65 (ddd, *J* = 18.4, 10.3, 8.1 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 15.4, 28.1, 28.3, 42.3, 44.6, 74.6, 79.5, 115.5, 140.1, 156.8; MS (FAB) *m/z* 216.1$(M + 1)^+$,160.0, 142.1, 104, 75; HRMS (FAB) *m/z* 216.1596 (calcd for $C_{11}H_{22}O_3N$ 216.1599).

(2*R*,3*S*)-1-(*tert*-Butoxycarbonyl)amino-2-methanesulfonyloxy-3-methyl-4-pentene (23). To a solution of **22** (59 mg, 0.274 mmol) in THF (1 mL) were added pyridine (252 mg, 3.2 mmol), DMAP (cat), and methanesulfonyl choride (37.5 mg, 0.329 mmol). The mixture was stirred at room temperature for 0.5 h and then diluted with Et_2O (6 mL) and aqueous NH_4-Cl. The aqueous layer was extracted with Et_2O (2 × 5 mL), and the combined Et_2O extract was washed with brine (5 mL) and dried (MgSO4). Evaporation of the solvent under reduced pressure yielded 67 mg (84%) of **23** which was used without further purification: $[\alpha]^{24}_D$ − 30.9 (*c* 1.0, $CHCl_3$); IR (neat) 3450−3350, 1705, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.6 Hz, 3H)1.43 (s, 9H), 2.61−2.54 (q, *J* = 6.6 Hz, 1H), 3.05 (s, 3H), 3.25−3.18 (m, 1H), 3.53−3.45 (m, 1H), 4.66−4.60 (m, 1H), 5.00−4.85 (bs, 1H), 5.18−4.93 (m, 2H), 5.83−5.72 (ddd, *J* = 18.4, 10.3, 8.1 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 15.4, 27.9, 28.3, 29.2, 38.2, 40.2, 42.2, 79.7, 84.7, 116.9, 137.8, 155.8; MS (FAB) *m/z* 294.1 $(M + 1)^+$, 238.1, 194.1, 142.1; HRMS (FAB) *m/z* 294.13771 (calcd for $C_{12}H_{24}NO_5S$ 294.13752).

2-(Dibenzylamino)ethanol. To a solution of ethanolamine (1.00 g, 16.3 mmol) in CH_2Cl_2−H_2O (33 mL-16 mL) were added Na_2CO_3 (6.90 g, 65.4 mmol) and benzyl bromide (5.60 g, 32.7 mmol), and the solution was stirred at reflux for 3 h. The solution was diluted with H_2O, and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extract was evaporated under reduced pressure, and the excess benzyl bromide was removed by distillation (55 °C, 1 mm) to afford 1.42 g (37%) of the title compound which was used without further purification: IR (neat) 3650−3200, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.55−2.45 (bs, 1H), 2.67 (t, *J* = 5.5 Hz, 2H), 3.59 (m, 2H), 3.63 (s, 4H), 7.34−7.26 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 54.8, 58.3, 58.7, 127.2, 128.5, 129.0, 138.8; MS (FAB) *m/z* 242.2 $(M + 1)^+$, 210.1, 91.1; HRMS (FAB) *m/z* 242.1547 (calcd for $C_{16}H_{20}NO$ 242.1545).

2-(Dibenzylamino)acetaldehyde (25). To a solution of crude 2-(dibenzylamino)ethanol (50.0 mg, 0.207 mmol) and triethylamine (125 mg, 1.24 mmol) in DMSO (1 mL) was added dropwise $SO_3{\cdot}Py$ (154 mg, 0.622 mmol) in DMSO (1 mL). The resulting solution was stirred for 1 h at room temperature and diluted with Et_2O (5 mL) and aqueous NH_4Cl. The mixture was further diluted with H_2O, and the aqueous phase was extracted with Et_2O (2 × 5 mL). The combined Et_2O extract was washed with brine (5 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give 40.1 mg (81%) of **25** which was unstable and was used immediately without purification: ^1H NMR (300 MHz, $CDCl_3$) δ 3.18 (s, 2H), 3.69 (s, 4H), 7.40−7.19 (m, 10H), 9.50 (s, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 57.1, 59.5, 63.5, 122.2, 126.9, 127.5, 128.2, 128.8, 129.1, 138.3, 138.8, 202.1.

(2*R*,3*S*)-1-Dibenzylamino-2-hydroxy-3-methyl-4-pentene (26). To a stirred mixture of potassium *tert*-butoxide (339 mg, 3.03 mmol) in THF (4 mL) and *cis*-2-butene (2.0 mL, 22 mmol) at −78 °C was added *n*-butyllithium (3.2 mmol, 2.0 mL, 1.6 M in hexane), and the mixture was stirred at −45 °C for 10 min. The resulting orange solution was recooled to −78 °C, and a solution of (+)-methoxydiisopinocampheylborane (1.16 g, 3.69 mmol) in Et_2O (3.7 mL) was added dropwise. The mixture was stirred at −78 °C for 30 min, $BF_3{\cdot}Et_2O$ (0.41 mmol, 0.45 mL) was added dropwise, and the mixture was stirred for 10 min. A solution of **25** (980 mg, 4.10 mmol) in THF (4 mL) was added dropwise, and the mixture was stirred at −78 °C for 5 h and was then allowed to warm slowly to room temperature. The mixture was treated with NaOH (3 M, 9.0 mL) and H_2O_2 (30%, 3.0 mL) and was refluxed for 1 h. The organic phase was separated, washed with water and brine, and dried ($MgSO_4$). Isopinocampheol was removed by distillation (75 °C, 1 mm), and the residual oil was chromatographed on silica gel (9:1, then 8:2, hexanes−EtOAc) to give 590 mg (48%) of **26**: [α] − 83.6 (*c* 1.0, $CHCl_3$); IR (neat) 3423, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, *J* = 6.6 Hz, 3H), 2.10 (dd, *J* = 12.1, 6.6 Hz, 1H), 3.39 (d, *J* = 14.0 Hz, 2H), 3.41−3.58 (m, 2H), 3.85 (d, *J* = 14.0 Hz, 2H), 4.95−5.29 (m, 2H), 5.61−5.73 (ddd, *J* = 17.0, 10.3, 8.1 Hz, 1H), 7.35−7.22 (m, 10H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 15.9, 42.5, 57.5, 58.4, 70.0, 114.8, 127.3, 128.5, 129.1, 138.5, 140.5; MS (FAB) *m/z* 296.1 $(M + 1)^+$, 240.1, 210.1, 91.1; HRMS (FAB) *m/z* 296.20113 (calcd for $C_{20}H_{26}NO$ 296.20144).

(2*S*,3*R*,4*R*)-4-Dibenzylamino-1-hydroxy-2,3-dimethylpyrrolidine (27). To a solution of **28** (5.81 mg, 0.014 mmol) in anhydrous THF (1 mL) was added cesium fluoride (3.10 mg, 0.021 mmol), and the mixture was stirred at reflux for 9 h. Anhydrous DMF (2 mL) was added to the solution, which was stirred at 65 °C for 6 h. After the solvent was removed under reduced pressure, the residual material was chromatographed on silica gel (7:3, hexanes−EtOAc) to give 2.31 mg (55%) of **27**: IR (neat) 2921, 1667, 1579, 1452 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25−1.20 (m, 6 H), 1.92−1.86 (m, 1H), 2.72−2.66 (m, 1H), 3.03−2.95 (m, 1H), 3.46−3.36 (m, 2H), 3.58 (d, 14.7 Hz, 2H), 3.68 (d, 14.7 Hz, 2H), 7.41−7.18 (m, 10H); ^{13} C NMR (300 MHz, $CDCl_3$) δ 13.1, 16.7, 56.8, 57.1, 57.8, 71.2, 126.9, 127.3, 128.3, 128.5, 144.0; MS (FAB) *m/z* 311 $(M + 1)^+$, 309, 293, 91; HRMS (FAB) *m/z* 311.2127 (calcd for $C_{20}H_{27}N_2O$ 311.21234).

(2*S*,3*S*)-2-Dibenzylamino-1-(*tert*-butyldimethylsilanyloxy)amino-3-methyl-4-pentene (28). To a stirred solution of **26** (100 mg, 0.34 mmol) in CH_2Cl_2/hexane (1:1, 0.8 mL) at −78 °C were added triflic anhydride (68.7 μL, 0.41 mmol) and lutidine (51.2 μL, 0.44 mmol) during 15 min, followed by dropwise addition of *O*-*tert*-butyldimethylsilanylhydroxylamine (99.9 mg, 0.68 mmol) in CH_2Cl_2/hexane (1:1, 0.8 mL). The mixture was stirred at −78 °C for 3.5 h and warmed to room terperature during 3 h. After removal of the solvent under reduced pressure, the residue was chromatographed on silica gel (100% hexane, then 98:2, then 95:5, and then hexanes−Et_2O) to afford 81 mg (56%) of **28**: $[\alpha]^{24}_D$ +1.8 (*c* 1.0, $CHCl_3$); IR (neat) 2900, 1450, 1249, 836, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 3 H), 0.13 (s, 3 H), 0.94 (s, 9 H),1.02 (d, *J* = 6.6 Hz, 3H), 2.58 (dd, *J* = 14.7, 7.4 Hz, 1H), 2.80 (m, 1H), 2.92 (dd, *J* = 12.5, 4.4 Hz, 1H), 3.14 (m, 1 H), 3.72 (d, *J* = 13.5 Hz, 2H), 3.77 (d, *J* = 13.5 Hz, 2H), 5.30 (m, 2 H), 5.4−5.2 (bs, 1H), 5.88 (ddd, *J* = 16.9, 10.3, 8.1 Hz, 1H), 7.29 (m, 10 H); ^{13} C NMR (300 MHz, $CDCl_3$) δ −5.3, 18.0, 26.4, 39.0, 52.7, 54.6, 59.0, 113.6, 126.8, 128.2, 129.0, 140.2, 143.3; MS (FAB) *m/z* 425 (M + 1), 369, 264, 210, 91; HRMS (FAB) *m/z* 425.2994 (calcd for $C_{26}H_{41}N_2OSi$ 425.2988).

Nitrone 30. To a solution of **28** (124 mg, 0.29 mmol) in anhydrous MeOH (3.0 mL) at room temperature was added *p*-nitrobenzaldehyde (66.3 mg, 0.44 mmol), and the solution was stirred at room temperature for 5 min. To the solution

were added ammonium fluoride (26.1 mg, 0.58 mmol) and 3 Å molecular sieves. The resulting mixture was warmed to 60 °C and stirred for 2 h. After being cooled to room temperature, the mixture was diluted with saturated aqueous $NaHCO_3$ (0.5 mL) and extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The resultant orange solid was crystallized from Et_2O−hexane to give 109 mg (85%) of **30**: $[\alpha]^{24}_D$ −10.0 (*c* 0.64, $CHCl_3$); IR (neat) 1595, 1516, 1340, 746, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (d, J = 6.8 Hz, 3H), 2.62 (ddd, J = 14.4, 14.5, 7.4 Hz, 1H), 3.52−3.59 (m, 1H), 3.78 (ABq, J = 27.1, 13.7 Hz, 4H), 3.99 (dd, J = 12.3, 5.2 Hz, 1H), 4.11−4.21 (m, 1H), 5.08, 5.14 (m, 2H), 5.9 (ddd, J = 18.6, 10.4, 8.2 Hz, 1H), 7.22−7.31 (m, 10 H), 7.35 (s, 1H), 8.32 (ABq, J = 20.0, 9.0 Hz, 4H); ^{13}C NMR (300 MHz, $CDCl_3$), δ 18.6, 39.7, 55.5, 61.2, 67.3, 115.4, 124.2, 127.6, 128.7, 129.0, 129.4, 133.7, 136.6, 139.9, 142.3, 148.1; MS (FAB) *m/z* 444.2 (M + 1)$^+$, 388, 264, 154, 91; HRMS (FAB) *m/z* 444.2291 (calcd for $C_{27}H_{30}N_3O_3$ 444.2287).

2-(4-Bromobenzyloxy)ethanol. To a slurry of NaH (1.18 g, 0.49 mol) in anhydrous THF (90 mL) at room temperature was added ethylene glycol (8.0 mL, 0.14 mol) during 1 h. The mixture was warmed to 50 °C, after which a solution of *p*-bromobenzyl bromide (11.7 g, 0.047 mol) in THF (30 mL) was added during 2 h. The mixture was stirred under reflux for 12 h, cooled to room temperature, and diluted with Et_2O (100 mL) and water (100 mL). The mixture was extracted with Et_2O, and the ethereal extract was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica (hexanes−EtOAc, 8:2) gave 7.30 g (65%) of the title compound: IR (neat) 3600−3111, 2922, 2863, 1482, 1069 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.15−3.21 (bs, 1H), 3.45−3.50 (m, 2H), 3.61−3.68 (m, 2H), 4.41 (s, 2H), 7.13 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.0, 72.1, 72.8, 121.9, 129.8, 131.9, 137.5; MS (FAB) *m/z* 230 (M + 1), 185, 169, 151, 107, 88; HRMS (FAB) *m/z* 229.9941 (calcd for $C_9H_{11}BrO_2$ 229.9942).

4-Bromobenzyloxyacetaldehyde (31). To a solution of 2-(4-bromobenzyloxy)ethanol (23.2 mg, 0.10 mmol) in wet CH_2Cl_2 (1 mL) was added in one portion Dess−Martin periodinane (46.5 mg, 0.11 mmol). After being stirred at room temperature for 2 h, the mixture was diluted with saturated aqueous $NaHCO_3$−$Na_2S_2O_3$ and extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to give 20.6 mg (90%) of **31** which was used without further purification: IR (neat) 2922, 2867, 1730, 1477, 1059, 1014, 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (s, 2H), 4.55 (s, 2H), 7.22 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.5 Hz, 2H), 9.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.2, 75.8, 122.5, 130.0, 132.1, 136.4, 200.3; MS (FAB) *m/z* 230 (M + 1), 185, 169, 90; HRMS (FAB) *m/z* 227.9787 (calcd for $C_9H_9O_2{}^{79}Br$ 227.9786).

(3*S*,4*R*)-5-(4-Bromobenzyloxy)-4-hydroxy-3-methylpent-1-ene (32). To a stirred mixture of potassium *tert*-butoxide (113 mg, 1.00 mmol) in THF (1.3 mL) and *cis*-2-butene (2.0 mL, 22 mmol) was added *n*-butyllithium (1.6 M in hexane, 0.67 mL, 1.00 mmol) at −78 °C. The mixture was stirred at −45 °C for 10 min, the resulting orange solution was recooled to −78 °C, and a solution of (+)-methoxydiisopinocampheylborane (387 mg, 1.23 mmol) in Et_2O (2.2 mL) was added dropwise. The mixture was stirred at −78 °C for 30 min, $BF_3{\cdot}Et_2O$ (0.14 mL, 0.137 mmol) was added dropwise, and the mixture was stirred for 10 min. A solution of **31** (159 mg, 1.00 mmol) in THF (1.2 mL) was added dropwise, and the mixture was stirred at −78 °C for 5 h and then allowed to slowly warm to room temperature. The mixture was treated with NaOH (3 M, 3 mL) and H_2O_2 (30%, 1 mL) and was refluxed for 1 h. The organic phase was separated, washed with water and brine, and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residual oil was chromatographed on silica gel, eluting with hexane/EtOAc (8:2) +5% CH_2Cl_2, to give 95 mg (45%) of **32**: [α] −11.8 (*c* 2.0, $CHCl_3$); IR (neat) 3621−3162, 2964, 2909, 2854, 1646, 1587, 1482, 1098, 1006, 913, 795 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, J = 6.8 Hz, 3H), 2.26 (d, J = 3.8 Hz, 1H), 2.22−2.39 (m, 1H), 3.38 (dd, J = 9.6, 7.9 Hz, 1H), 3.54 (dd, J = 9.6, 3.0 Hz, 1H), 3.61−3.66 (m, 1H), 4.49 (s, 2H), 5.01−5.09 (m, 2H), 5.73 (ddd, J = 17.5, 10.4, 7.9 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 7.48, (d, J = 8.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 41.4, 72.9, 73.4, 73.8, 115.5, 122.0, 129.7, 131.9, 137.5, 140.8; MS (FAB) *m/z* 285 (M + 1), 282, 171, 154, 136, 107, 89; HRMS (FAB) *m/z* 284.0406 (calcd for $C_{13}H_{17}O_2{}^{79}Br$ 284.0412).

(3*S*,4*R*)-5-(4-Bromobenzyloxy)-4-methanesulfonyloxy-3-methylpent-1-ene. To a solution of **32** (100 mg, 0.35 mmol) in anhydrous CH_2Cl_2 (1 mL) were added pyridine (0.28 mL, 3.5 mmol), a catalytic quantity of DMAP (0.05 mol %), and methanesulfonic anhydride (79 mg, 0.45 mmol). After being stirred at room temperature for 16 h, the mixture was concentrated under reduced pressure, and the residue was diluted with Et_2O (4 mL). The solution was washed sequentially with saturated aqueous NH_4Cl, H_2O, and saturated aqueous NaCl and dried over Na_2SO_4. Removal of the solvent under reduced pressure gave 127 mg of the title compound which was used without further purification: [α] −10.9 (*c* 4.0, $CHCl_3$); IR (neat) 2968, 2934, 2871, 1482, 1343, 1170, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (d, J = 6.8 Hz, 3H), 2.55−2.62, (m, 1H), 3.01 (s, 3H), 3.58−3.68 (m, 2H), 4.48 (q, J = 18.6, 11.8 Hz, 2H), 4.69 (ddd, J = 6.8, 6.8, 3.5 Hz, 1H), 5.08−5.16 (m 2H), 5.74 (ddd, J = 17.0, 10.1, 7.6 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.47, (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.1, 39.2, 40.4, 70.7, 73.0, 85.3, 117.1, 122.2, 129.8, 132.0, 136.9, 138.6; MS (FAB) *m/z* 364 (M + 1), 185, 169, 91; HRMS (FAB) *m/z* 362.0190 (calcd for $C_{14}H_{19}O_4{}^{79}BrS$ 362.0187).

(3*S*,4*S*)-4-Amino-5-(4-bromobenzyloxy)-3-methylpent-1-ene (33). To a solution of (3*S*,4*R*)-5-(4-bromobenzyloxy)-4-methanesulfonyloxy-3-methylpent-1-ene (12.1 mg, 0.04 mmol) in anhydrous DMF (0.25 mL) was added sodium azide (9.5 mg, 0.14 mmol), and the mixture was stirred for 16 h in a preheated oil bath at 85 °C. After being cooled to room temperature, the mixture was diluted with Et_2O (2 mL) and washed with H_2O (3 × 2 mL). The ethereal solution was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude azide. This material was taken up into THF (0.5 mL), and triphenylphosphine (11.5 mg, 0.044 mmol) and water (0.05 mL) were added. The mixture was stirred for 4 h at 55 °C, the solvent was removed under reduced pressure, and the residue was taken up into Et_2O−hexane. The resulting suspension was filtered through Celite, and the filtrate was concentrated under reduced pressure. Chromatography of the residue on silica (hexanes−EtOAc, 7:3 to CH_2Cl_2−saturated methanolic ammonia, 5:1) gave 7.0 mg (56%) of **33** as a pale yellow oil: [α] −8.3 (*c* 0.7, $CHCl_3$); IR (neat) 3500−3200 2968, 2934, 2871, 1482, 1343, 1170, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, J = 6.8 Hz, 3H), 2.47−2.54 (m, 1H), 3.41−3.50 (m, 2H), 3.74−3.79 (m, 1H), 4.40 (s, 2H), 5.00−5.06 (m, 2H), 5.73 (ddd, J = 7.4, 9.6, 17.2 Hz, 1H), 7.14 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1, 39.3, 54.4, 71.8, 72.8, 116.2, 121.9, 129.7, 131.9, 137.5, 140.2; MS (FAB) *m/z* 284 (M + 1), 273, 107, 89; HRMS (FAB) *m/z* 284.0649 (calcd for $C_{13}H_{19}ON^{79}Br$ 284.0650).

(3*S*,4*S*)-5-(4-Bromobenzyloxy)-4-hydroxylamino-3-methylpent-1-ene (36). To a solution of **33** (60.8 mg, 0.214 mmol) in anhydrous MeOH (0.30 mL) were added *p*-methoxybenzaldehyde (26 μL, 0.214 mmol) and solid Na_2CO_3 (34.6 mg, 0.321 mmol). The mixture was stirred for 16 h at room temperature and for 50 min at 60 °C. After being cooled to room temperature, the mixture was concentrated under reduced pressure, and the residual oil was taken up in Et_2O (2 mL). The mixture was filtered, and the filtrate was concentrated under reduced pressure to yield 84 mg of crude imine **34**.

A solution of the crude imine obtained above in CH_2Cl_2 (0.4 mL) was cooled to −60 °C, and a solution of *m*-CPBA (0.5 M,

0.314 mL, 0.157 mmol) was added. The mixture was allowed to warm to room temperature during 2 h and was diluted with saturated aqueous $NaHCO_3$ (0.3 mL). The mixture was extracted with CH_2Cl_2, and the extract was washed with H_2O (1 mL) and saturated aqueous NaCl (1 mL) and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded 55.2 mg of oxaziridine **35**.

To a solution of **35** obtained above in MeOH (0.2 mL) was added hydroxylamine hydrochloride (19.8 mg, 0.286 mmol), and the mixture was stirred for 2 h at 0 °C. The mixture was diluted with saturated aqueous $NaHCO_3$ (1 mL) and extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl and concentrated under reduced pressure. Chromatography of the residue on silica (hexanes−EtOAc, 8:2−1:1) gave 25.6 mg (40% from **33**) of **36** as a colorless oil: [α] −10.0 (*c* 1.0, $CHCl_3$); IR (neat) 3490−3111, 2972, 2909, 2867, 1600, 1482, 1237 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, J = 6.8 Hz, 3 H), 2.42−2.49 (m, 1H), 2.91 (ddd, J = 3.8, 7.1, 7.1 Hz, 1H), 3.50 (dd, J = 6.6, 9.6 Hz, 1H), 3.62 (dd, J = 3.6, 9.6 Hz, 1H), 4.47 (ABq, J = 12.3, 17.8 Hz, 2H), 5.03−5.10 (m, 2H), 5.78 (ddd, J = 8.2, 10.4, 18.4 Hz, 1H), 7.20 (d, J = 8.5 Hz, 2 H), 7.46 (d, J = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.8, 37.6, 65.7, 68.3, 73.0, 121.9, 129.0, 129.7, 131.9, 137.6, 141.8; MS (FAB) *m/z* 300 (M + 1), 246, 244, 171, 169, 113; HRMS (FAB) *m/z* 300.0595 (calcd for $C_{13}H_{19}O_2N^{79}Br$ 300.0599).

Nitrone 38. To a flask containing **36** (39.0 mg, 0.129 mmol) and 3 Å molecular sieves (10 mg) was added a solution of **20** (50.8 mg, 0.111 mmol) in CH_2Cl_2 (2 mL). The mixture was immediately concentrated under reduced pressure, and the residue was taken up in anhydrous MeOH (0.3 mL). The solution was stirred under argon for 5 h at room temperature and was concentrated under reduced pressure. Chromatography of the residue on silica (hexanes−EtOAc 6:4−4:6) gave 49.3 mg (60%) of **38**: [α] −16.9 (*c* 1.8, $CHCl_3$); IR (neat) 3469−3162, 2964, 2922, 2854, 1717, 1600, 1570, 1477, 1351, 1166, 1090, 833 cm^{-1};^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.14 (s, 3H), 0.94 (s, 9H), 1.02, (d, J = 6.8 Hz, 3H), 1.34 (s, 9H), 2.37 (ddd, J = 5.2, 11.2, 18.1 Hz, 1H), 2.62−2.74 (m, 2H), 3.57−3.67 (m, 2H), 3.93 (s, 3H), 3.96 (s, 3H), 4.14 (m, 1H), 4.44 (ABq, J = 12.3, 23.3 Hz, 2H), 4.66 (d, J = 2.7 Hz, 1H), 4.97−5.00 (m, 2H), 5.66 (d, J = 9.6 Hz, 1H), 5.74 (ddd, J = 8.2, 10.1, 17.3 Hz, 1H), 6.51 (s, 1H), 6.85 (t, J = 4.9 Hz, 1H), 7.13 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H);^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, −4.4, 16.9, 18.5, 26.2, 28.6, 29.9, 38.0, 53.2, 54.2, 55.1, 68.6, 72.8, 75.4, 79.4, 79.8, 99.5, 116.1, 121.8, 129.5, 131.9, 137.5, 138.1, 139.4, 156.0, 165.1, 172.2, 172.6; MS (FAB) *m/z* 737 (M + 1), 285, 171, 136, 89; HRMS (FAB) *m/z* 737.2937 (calcd for $C_{34}H_{54}N_4O_7Si^{79}Br$ 737.2945).

Piperidine 45. A suspension of **38** (510 mg, 0.691 mmol) and 4 Å molecular sieves (60 mg) in toluene (14 mL) was stirred under argon for 72 h at 96 °C. The mixture containing **40** and **41** (ca. 2:1) was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was taken up into THF (9 mL), and H_2O (9 mL), saturated aqueous NH_4Cl (9 mL), and Zn dust (2.20 g, 34.5 mmol) were added sequentially. The mixture was stirred for 8 h at 65 °C, cooled to room temperature, and diluted with CH_2Cl_2 (30 mL). Saturated aqueous $NaHCO_3$ (30 mL) was added, and the mixture was extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl and dried over Na_2SO_4. Removal of the solvent under reduced pressure afforded 400 mg of crude **45**. The crude material was carried forward to the next reaction without further purification.

Amine 46. A solution of crude **45** obtained above in methanolic HCl (1 M, 2 mL) was concentrated under reduced pressure at 45 °C. This process was repeated three times, and the residue was taken up into methanolic HCl (1 M, 1 mL), MeOH (2 mL), and water (2 mL). The mixture was washed with Et_2O, and the aqueous phase was diluted with CH_2Cl_2 (5 mL). The organic phase was made basic (pH 8−9) with K_2CO_3 and was extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl and concentrated under reduced pressure to yield 301 mg (98%, 68% from **38**) of **46** as a mixture of diastereomers: IR (neat) 3545−3180, 2960, 2926, 2863, 1650, 1595, 1569, 1472, 1367, 1248, 1086, 729 cm^{-1}; MS (FAB) *m/z* 639 (M + 1), 613, 391, 285, 219, 149, 136, 89; HRMS (FAB) *m/z* 639.2603 (calcd for $C_{29}H_{48}N_4O_5Si^{79}Br$ 639.2577).

Urea 48. To a solution of **46** (301 mg, 0.470 mmol) in CH_2Cl_2 (9.4 mL) at 0 °C under argon was added carbonyldiimidazole (166 mg, 1.03 mmol), and the mixture was allowed to warm to room temperature during 1 h. The solution was stirred at 40 °C for 7 h and concentrated under reduced pressure to yield a mixture of **47** and **48** which was taken up in MeOH (5 mL). To the resulting solution was added K_2CO_3 (650 mg, 4.7 mmol), and the mixture was stirred at 60 °C for 1 h. The solvent was removed under reduced pressure to afford 306 mg (85%) of **48** (mixture of stereoisomers) as a tan oil: IR (neat) 3545−3166, 2960, 2926, 2863, 1717, 1650, 1595, 1566, 1469, 1360, 1246, 1204, 1086, 905, 833, 728 cm^{-1}; MS (FAB) *m/z* 665 (M + 1), 587, 465, 285, 227, 169; HRMS (FAB) *m/z* 665.2382 (calcd for $C_{30}H_{46}N_4O_6Si^{79}Br$ 665.2397).

Ketone 49. To a solution of **48** (360 mg, 0.470 mmol) in CH_2Cl_2 (9.4 mL) was added Dess−Martin periodinane (237 mg, 0.564 mmol), and the mixture was stirred at room temperature for 1.5 h. The mixture was diluted with saturated aqueous $NaHCO_3$−$Na_2S_2O_3$ and extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to give 355 mg (98%) of **49**. The ketone was used for the next reaction without further purification: IR (neat) 2959, 2934, 2852, 1717, 1653, 1592, 1568, 1455, 1352, 1090, 844 cm^{-1}; HRMS (FAB) *m/z* 663.2202 (calcd for $C_{30}H_{44}N_4O_6Si^{79}Br$ 663.2213).

Alcohol 50. To a solution of **49** (320 mg, 0.483 mmol) in THF (8 mL) at −78 °C under argon was added L-Selectride (0.57 mL, 0.67 mmol), and the mixture was stirred for 1 h at −78 °C. The mixture was allowed to warm to room temperature during 1 h, after which time EtOH (0.2 mL), water (0.2 mL), H_2O_2 (0.2 mL, 30%), and sodium hydroxide (1 M, 0.2 mL) were added sequentially. The mixture was stirred for 4 h at room temperature, diluted with saturated aqueous $NaHCO_3$ (5 mL), and extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to give 273 mg (85%) of **50** which was used for the next reaction without further purification: IR (neat) 3570−3132, 2947, 2926, 2850, 1650, 1578, 1469, 1351, 1204, 1094, 905, 842 cm^{-1}; MS (FAB) *m/z* 665 (M + 1), 587, 465, 285, 227, 169; HRMS (FAB) *m/z* 665.2382 (calcd for $C_{30}H_{46}N_4O_6Si^{79}Br$ 665.2397).

Diol 51. To a solution of the alcohol **50** (262 mg, 0.394 mmol) in EtOH (16 mL) was added $Pd(OH)_2/C$ (20%, 400 mg), and the mixture was stirred at ambient temperature under an atmosphere of H_2 for 16 h. The suspension was filtered through Celite, the filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica (hexanes−EtOAc, 1:1, then EtOAc, then EtOAc−methanolic NH_3 1−6%) to give 149 mg (76%, 66% from **48**) of **51** which was crystallized from EtOH: mp 55−57 °C; [α] −59.3 (*c* 2.0, $CHCl_3$); IR (neat) 3515−3110, 2962, 2922, 2849, 1635, 1595, 1568, 1480, 1459, 1361, 1090, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ −0.08 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 1.03 (d, J = 6.8 Hz, 3H), 1.23 (t, J = 7.3 Hz, 1H), 1.47 (m, 2H), 1.94 (m, 2H), 2.27 (bs, 1H), 3.19 (dd, J = 3.8, 10.1 Hz, 1H), 3.50−3.69 (m, 3H), 3.88 (m, 1H), 3.95 (s, 6H), 4.43 (d, J = 5.5 Hz, 1H), 5.03 (bs, 1H), 5.60 (dd, J = 3.0, 9.6 Hz, 1H), 6.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7, −4.3. 14.5, 18.5, 26.2, 33.7, 36.8, 41.8, 50.9, 54.1, 54.4, 55.3, 61.3, 62.2, 69.9, 76.1, 99.1, 157.9, 165.4, 171.6, 172.7; MS (FAB) *m/z* 497 (M + 1), 465, 285, 154, 136; HRMS (FAB) *m/z* 497.2795 (calcd for $C_{23}H_{41}N_4O_6Si$ 497.2795).

Azide 54. To a solution of **51** (12.4 mg, 0.02 mmol) in THF (1.2 mL) at room temperature under argon was added triphosgene (3.0 mg, 0.01 mmol), and the mixture was stirred for 45 min. To this solution was added MeOH (1 mL), and the mixture was stirred for 5 min and concentrated under reduced pressure. The residue was taken up in anhydrous DMF (1.0

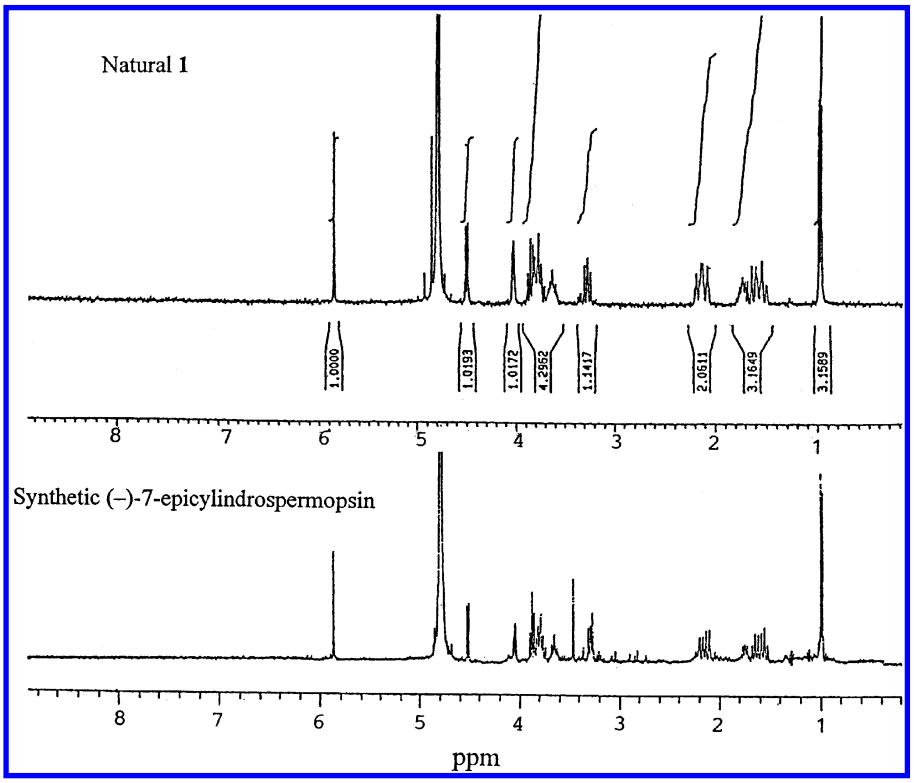


FIGURE 2. ^{1}H NMR spectra of natural and synthetic (−)-7-epicylindrospermopsin (**1**) in MeOH-d_4.

mL), sodium azide (16.2 mg, 0.25 mmol) was added, and the mixture, which darkened to an orange-red color, was stirred at 60 °C for 3 h and then diluted with CH_2Cl_2 (5 mL). The solution was washed with water (3 × 3 mL) and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Chromatography of the residue on silica (EtOAc to EtOAc−methanolic NH_3, 2%) gave 6.4 mg (49%) of **54**: [α] +0.5 (*c* 0.64, $CHCl_3$); IR (neat) 3534−3122, 2956, 2921, 2856, 2101, 1643, 1628, 1593, 1566, 1458, 1351, 1093, 842 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.09 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.53−1.76 (m, 4H), 1.87 (ddd, *J* = 3.8, 7.6, 13.7 Hz, 1H), 1.95−2.06 (m, 1H), 3.30 (dd, *J* = 3.0, 12.6 Hz, 1H), 3.50−3.75 (m, 3H), 3.92−3.98 (m, 1H), 3.97 (s, 3H), 3.98 (s, 3H), 4.10 (dd, *J* = 4.6, 12.6 Hz, 1H), 4.33 (d, *J* = 7.1 Hz, 1H), 5.07 (bs, 1H), 6.46 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, −4.2, 14.5, 16.4, 18.5, 23.1, 26.2, 30.1, 32.3, 33.2, 36.0, 38.3, 47.6. 53.0, 54.3, 55.3, 55.6, 56.1, 67.3, 77.0, 78.4, 99.3, 158.1, 165.4, 171.8, 172.6; MS (FAB) *m/z* 522 (M + 1), 465, 285, 219; HRMS (FAB) *m/z* 522.2863 (calcd for $C_{23}H_{40}N_7O_5Si$ 522.2860).

Triethylsilyl Ether 56. To a solution of **54** (6.0 mg, 12.0 μmol) in CH_2Cl_2 (100 μL) at 0 °C under argon were added triethylsilyl triflate (0.8 μL, 5.0 μmol) and Et_3N (0.5 μL, 5.0 μmol), and the mixture was stirred for 20 min. The mixture was warmed to room temperature, diluted with aqueous NH_4-Cl, and extracted with Et_2O. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford 6.6 mg (99%) of pure **56**: [α] −0.7 (*c* 0.6, $CHCl_3$); IR (neat) 2962, 2922, 2874, 2852, 2095, 1659, 1592, 1568, 1462, 1358, 1115, 1090, 838 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.10 (s, 3H), 0.11 (s, 3H), 0.56 (q, *J* = 7.6 Hz, 6 H), 0.88−0.99 (m, 21 H), 1.50−1.64 (m, 3H), 1.73 (ddd, *J* = 3.8, 7.6, 13.7 Hz, 1H), 1.85−1.93 (m, 1H), 3.2 (dd, *J* = 2.9, 12.4 Hz, 1H), 3.48 (q, *J* = 6.9 Hz, 1H), 3.52−3.69 (m, 2H), 3.83−3.90 (m, 1H), 3.97 (s, 3H), 3.98 (s, 3H), 4.13 (dd, *J* = 4.3, 12.4 Hz, 1H), 4.32 (d, *J* = 6.9 Hz, 1 H), 5.05 (bs, 1H), 6.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.6, −4.2, 5.3, 7.3, 15.7, 16.8, 18.5, 26.2, 30.1, 33.2, 36.7, 39.7, 39.4, 47.9, 52.9, 54.3, 55.3, 55.7, 56.3, 66.3, 67.7, 78.6, 99.3, 158.2, 165.4, 171.9, 172.6; MS (FAB) *m/z* 636 (M + 1) 579, 285, 154, 136, 87; HRMS (FAB) *m/z* 636.3747 (calcd for $C_{29}H_{53}N_7O_5Si_2$ 636.3725).

Diol 60. To a solution of **56** (6.0 mg, 9.4 μmol) in CH_2Cl_2 (400 μL) at 0 °C under argon was added KHMDS (0.5 M in toluene, 90.0 μL, 47.0 μmol), and the mixture was stirred for 10 min. Solid trimethyloxonium tetrafluoroborate (2.8 mg, 18.0 μmol) was added, and the mixture was stirred at 0 °C for 8 h and then was diluted with aqueous NH_4Cl and extracted with Et_2O. The extract was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give crude **57**. This material was taken up in MeOH (1 mL), Pd/C (20%, 3 mg) was added, and the mixture was stirred under an atmosphere of H_2 at room temperature for 8 h. The suspension was filtered through a pad of Celite, the filtrate was concentrated under reduced pressure, and the resulting crude **59** was taken up in concd HCl. The solution was heated at reflux for 7 h and concentrated under reduced pressure, and the residue was purified by HPLC on a Zorbax 300SB-C18 column (9.4 × 250 mm), eluting with 4% MeOH/H_2O containing 0.1% TFA at 4 mL/min (retention time 20.1 min), to provide 0.65 mg (21% from **56**) of pure **60** as a colorless amorphous solid: [α] −8.3 (*c* 0.06, H_2O); ^{1}H NMR (400 MHz, D_2O) δ 0.98 (d, *J* = 6.9 Hz, 3H), 1.51−1.79 (m, 3H), 2.07−2.19 (m, 2H), 3.28 (dd, *J* = 8.8, 10.6 Hz, 1H), 3.58−3.68 (m, 1H), 3.73−3.89 (m, 3 H), 4.03 (s, 1H), 4.50 (d, *J* = 6.6 Hz, 1H), 5.86 (s, 1H); ^{13}C NMR (150 MHz, D_2O) δ 13.1, 30.2, 37.8, 39.7, 44.1, 47.6, 52.6, 56.9, 68.3, 71.2, 99.7; MS (FAB) *m/z* 336 (M^+) 282, 185, 93; HRMS (FAB) *m/z* 336.1673 (calcd for $C_{15}H_{22}N_5O_4$: 336.1672). The ^{1}H and ^{13}C NMR spectra of this compound were identical to those of the corresponding racemic compound prepared by Weinreb.[14]

7-Epicylindrospermopsin (1). To a solution of **60** (0.65 mg, 1.90 μmol) in dry pyridine (0.1 mL) containing Na_2SO_4 (10 mg) was added a solution of SO_3·DMF in DMF (0.1 M, 216 μL, 21.6 μmol, 11 equiv), and the mixture was stirred at ambient temperature for 30 min. The solvent was removed in vacuo, and the residue was taken up in MeOH. The mixture was filtered, and the filtrate was concentrated. Purification of the residual oil by HPLC on a Zorbax 300SB-C18 column (9.4 × 250 mm), eluting with 1.5% MeOH in water containing

0.1% TFA at 4 mL/min, gave 0.51 mg (63%) of **1**: [α] −17.2 (*c* 0.03, H_2O) (lit.[7] [α] −20.5 (*c* 0.06, H_2O)); HRMS (FAB) *m/z* 416.1238 (calcd for $C_{15}H_{22}N_5O_7S$ 416.1240). The ^1H NMR spectrum corresponded closely with that of natural 7-epicylindrospermopsin (Figure 2).

Acknowledgment. We are indebted to Professor Alexandre F. T. Yokochi, Department of Chemical Engineering, Oregon State University, for the X-ray crystal structures of **30** and **51**, and to Professor Steven Weinreb, Pennsylvania State University, for the NMR spectra of **60** and for a preprint of ref 14. Financial support was provided by the National Science Foundation (0076103-CHE) and by the National Institute of General Medical Sciences (GM58889). We are greatful to Dr. Ellen Laird, Array Biopharma, Boulder, CO, for assistance with the preparation of the cover graphic.

Supporting Information Available: X-ray crystallographic data for **30** and **51** and copies of NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0486387