Vinyl and Alkynyl Pyrimidines as Michael Acceptors: An Approach to a Cylindrospermopsin Substructure

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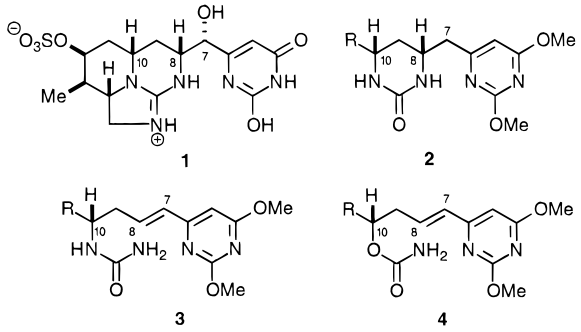
Vinyl pyrimidine **9** and alkynyl pyrimidine **24** undergo base-mediated intramolecular conjugate addition reactions in which a carbamate and a urea, respectively, behave as nitrogen nucleophiles. The cyclic carbamate derived from **9** was converted to **11** via a metalation−oxidation reaction in which 2-phenylsulfonyl-3-phenyloxaziridine behaves as a hydroxylation reagent. The cyclic urea derived from **24** was converted to cylindrospermopsin substructure **30** using dimethyldioxirane to introduce the C_7 hydroxyl group.

Cylindrospermopsin (**1**) is a structurally complex guanidinium sulfate produced by the cyanobacterium *Cylindrospermopsis raciborskii*.[1] Contamination of freshwater drinking sources by these blue green algae is believed to have caused the 1979 outbreak of hepatoenteritis in Queensland, Australia,[2] as well as other public health problems.[3] Cylindrospermopsin, whose structure was assigned in 1992 on the basis of extensive NMR studies, is believed to be the agent responsible for the toxicity of these cyanobacteria. This alkaloid has recently been isolated from several other cyanobacteria[4] and has been shown to inhibit production of cell-reduced glutathione.[5]

The interesting structure of cylindrospermopsin, the biological consequences of its consumption, and the fact that its structure assignment rests principally on NMR data make cylindrospermopsin a compelling target for synthesis. Both the Snider and Weinreb groups have reported studies directed toward cylindrospermopsin.[6,7] Both groups have described novel chemistry that addresses several of the key problems that must be overcome in any synthesis of cylindrospermopsin, including control of stereochemistry around the piperidine ring and establishment of the stereochemistry at C_7 relative to stereogenic centers residing in the tricyclic core of the natural product. This paper will describe our own efforts to address the problem of establishing the relative stereochemistry at C_7, C_8 and C_{10} of cylindrospermopsin.



Our approach to cylindrospermopsin (**1**) is outlined through the structures presented above. It was imagined that the target alkaloid could be prepared from a structure of type **2**. The C_{10} substituent (R) would have to be suitable for completion of the tricyclic guanidinium core of **1**, and metalation−oxidation chemistry would be used to introduce the C_7 hydroxyl group in a stereoselective manner. It was hoped that **2** might be prepared by intramolecular conjugate addition of a urea to a vinyl pyrimidine, using a substrate of type **3**. There existed some precedence for the conjugate addition portion of this plan, albeit with an oxygen nucleophile rather than a nitrogen nucleophile.[8,9] In the event, we began with a conservative approach to the problem and first examined this chemistry using a carbamate of type **4** as the cyclization substrate.

The specific target first chosen for study was carbamate **9a**. This substrate was prepared as shown in Scheme

(1) Ohtani, I.; Moore, R. E.; Runnegar, M. T. C. *J. Am. Chem. Soc.* **1992**, *114*, 7941. Moore, R. E.; Ohtani, I.; Moore, B. S.; de Koning, C. B.; Yoshida, W. Y.; Runnegar, M. T. C.; Carmichael, W. W. *Gazz. Chim. Ital.* **1993**, *123*, 329. For a recent investigation of the biosynthesis of cylindrospermopsin, see: Burgoyne, D. L.; Hemscheidt, T. K.; Moore, R. E.; Runnegar, M. T. C. *J. Org. Chem.* **2000**, *65*, 152. For the structure of C_7-epimer of cylindrospermopsin, see: Banker, R.; Teltsch, B.; Sukenik, A.; Carmeli, S. *J. Nat. Prod.* **2000**, *63*, 387.

(2) Hawkins, P. R.; Runnegar, M. T. C.; Jackson, A. R. B.; Falconer, I. R. *Appl. Environ. Microbiol.* **1985**, *50*, 1292.

(3) Saker, M. L.; Thomas, A. D.; Norton, J. H. *Environ. Toxicol.* **1999**, *14*, 179. Saker, M. L.; Eaglesham, G. K. *Toxicon* **1999**, *37*, 1065.

(4) Harada, K.-I.; Ohtani, I.; Iwamoto, K.; Suzuki, M.; Watanabe, M. F.; Watanabe, M.; Terao, K. *Toxicon* **1994**, *32*, 73. Banker, R.; Carmeli, S.; Hadas, O.; Teltsch, B.; Porat, R.; Sukenik, A. *J. Phycol.* **1997**, *33*, 613. Hawkins, P. R.; Chandrasena, N. R.; Jones, G. J.; Humpage, A. R.; Falconer, I. R. *Toxicon* **1997**, *35*, 341. Shaw, G. R.; Sukenik, A.; Livne, A.; Chiswell, R. K.; Smith, M. J.; Seawright, A. A.; Norris, R. L.; Eaglesham, G. K.; Moore, M. R. *Environ. Toxicol.* **1999**, *14*, 167.

(5) Runnegar, M. T.; Kong, S.-M.; Zhong, Y.-Z.; Ge, J.-L.; Li, S. C. *Biochem. Biophys. Res. Commun.* **1994**, *201*, 235. Runnegar, M. T.; Kong, S.-M.; Zhong, Y.-Z.; Lu, S. C. *Biochem. Pharmacol.* **1995**, *49*, 219.

(6) Snider, B. B.; Harvey, T. C. *Tetrahedron Lett.* **1995**, *36*, 4587. Snider, B. B.; Xie, C. *Tetrahedron Lett.* **1998**, *39*, 7021. The first total synthesis of cylindrospermposin was reported while this submission was undergoing review: Xie, C.; Runnegar, M. T. C.; Snider, B. B. *J. Am. Chem. Soc.* **2000**, *122*, 5017. In addition model studies were reported by two other groups: McAlpine, I. J.; Armstrong, R. W. *Tetrahedron Lett.* **2000**, *41*, 1849. White, J. E.; Hansen, J. D. *Book of Abstracts*, 219th National Meeting of the American Chemical Society, San Francisco, CA, March 26−30, 2000; American Chemical Society: Washington, DC, 2000.

(7) Heintzelman, G. R.; Parvez, M.; Weinreb, S. M. *Synlett* **1993**, 551. Heintzelman, G. R.; Weinreb, S. M.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 4594.

(8) Renz, H.; Schlimme, E. *Liebigs Ann. Chem.* **1986**, *6*, 957.

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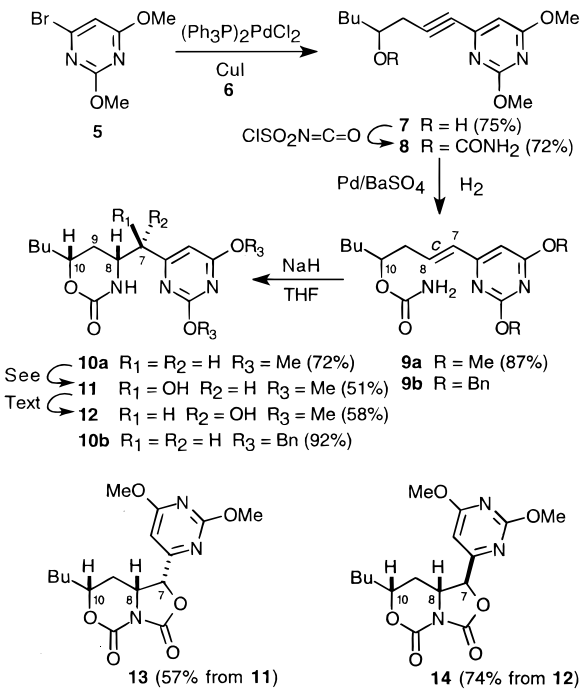
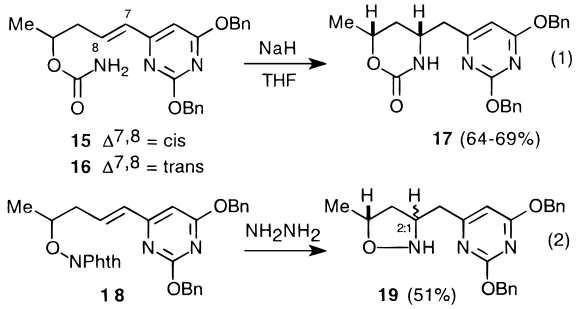
Scheme 1



1. Sonogashira coupling of 6-bromo-2,4-dimethoxypyrimidine (**5**)[10] with 1-octyn-4-ol (**6**)[11] gave alkynyl pyrimidine **7** in 75% yield.[12] Treatment of **7** with chlorosulfonyl isocyanate followed by hydrolysis of the crude product gave carbamate **8** in 72% yield.[13] Catalytic hydrogenation of **8** over palladium on barium sulfate in the presence of pyridine provided *cis*-alkene **9a** (87%).

The cyclization of **9a** proceeded as anticipated. Thus, treatment of **9a** with excess sodium hydride in tetrahydrofuran at reflux afforded oxazinone **10a** as a white solid in 72% yield. The *cis*-relationship of the C_8 and C_{10} side chains of **10a** was established by the appearance of $H_{9\beta}$ (δ 2.01), which exhibited a large geminal coupling (J = 14 Hz) to $H_{9\alpha}$ and only small vicinal couplings to H_8 and H_{10}. In addition, a comparison of spectral data with those obtained for **17** (vide infra) also supported this stereochemical assignment.[14] These data suggest that **10a** occupies a conformation in which the C_8 and C_{10} side chains are equatorially disposed. It is possible that the stereochemical outcome of this cyclization is controlled by thermodynamics.

This type of cyclization has some generality. For example, similar treatment of **9b** with sodium hydride gave conjugate adduct **10b** in 92% yield.[14] Furthermore, the stereochemical outcome of this process does not seem to be a function of olefin geometry. For example, similar treatment of *cis*-alkene **15** or *trans*-alkene **16** gave conjugate adduct **17** in 64% and 69% yields, respectively (eq 1). Finally, it was shown that treatment of *N*-alkoxyphthalimide **18** with hydrazine in CH_2Cl_2 gave isoxazolidine **19** in 51% yield as a 2:1 mixture of diastereomers (eq 2).[14] One interpretation of this result is that the presumed intermediate hydroxylamine adds irreversibly to the vinyl pyrimidine, and thus the product ratio reflects kinetics rather than thermodynamics. An alternative explanation is that the thermodynamic partitioning between *cis* and *trans* isomers is simply different in the case of five-membered ring formation.



Attention was next turned to introduction of the C_7 hydroxyl group (Scheme 1). This was eventually accomplished by treatment of **10a** with 2.1 equiv of *n*-butyllithium followed by reaction of the presumed intermediate dianion with 2-phenylsulfonyl-3-phenyloxaziridine.[15,16] This reaction provided a 51% yield of a single alcohol, eventually assigned structure **11**.[17] The stereochemistry of **11** was established by converting it to a structure in which all stereogenic centers were part of a fused ring system. Thus, treatment of **11** with carbonyldiimidazole and 4-DMAP in benzene gave cyclic carbamate **13** in 57% yield. Irradiation of H_7 and H_{10} in **13** gave 6% and 3.3% enhancements, respectively, of the signal due to H_8, suggesting a *cis*-relationship between these protons. Furthermore, treatment of **11** with *p*-nitrobenzoic acid, diethyl azodicarboxylate, and triphenylphosphine gave the corresponding inverted *p*-nitrobenzoate (80%), which upon treatment with methanolic potassium carbonate gave alcohol **12** (62%).[18] This alcohol was then converted to the corresponding cyclic carbamate **14** in 74% yield. Irradiation of H_7 and H_{10} in **14** gave 2% and 5.4% enhancements, respectively, of the signal due to H_8, consistent with the structure assignment when compared with the NOE results obtained with **13**.

One explanation for the observed stereoselectivity in the oxidation of **10a** is that the presumed intermediate dianion forms a structure in which one lithium bridges

(9) This plan was patterned after the well-known ability of vinyl pyridines to behave as Michael acceptors. For references of some relevance, see: Gray, A. P.; Platz, R. D.; Chang, T. C. P.; Leverone, T. R.; Ferrick, D. A.; Kramer, D. N. *J. Med. Chem.* **1985**, *28*, 111 (vinyl pyridines). Macor, J. E.; Ordway, T.; Smith, R. L.; Verhoest, P. R.; Mack, R. A. *J. Org. Chem.* **1996**, *61*, 3228 (5-vinyl-1,2,4-oxadiazoles). Schroeder, A. C.; Bloch, A.; Perman, J. L.; Bobek, M. *J. Med. Chem.* **1982**, *25*, 1255 (6-ethynyluracils). For other chemistry of some relevance to this research, see: Jacobi, P. A.; Liu, H. *J. Am. Chem. Soc.* **1999**, *121*, 1958.

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

(11) The required alkyne was prepared in 81% yield by reaction of 1,2-epoxyhexane with lithium acetylide ethylenediamine complex in DMSO at room temperature (see Experimental Section).

(12) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(13) Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1976**, *76*, 389.

(14) Experimental procedures for the preparation of **9b** and its conversion to **10b** are described in the Supporting Information. Experimental procedures for the chemistry described in eqs 1 and 2 and the preparation of starting materials for that chemistry also appear in the Supporting Information. The stereochemistry of **17** was supported by NOE experiments. Thus, irradiation of C_{10} (δ 4.24) gave a 6.3% enhancement of the signal due to H_8 (δ 3.92) and a 5% enhancement of the signal due to H_{9b} (δ 2.01), establishing the *cis*-relationship of these three protons. In addition $H_{9\beta}$ exhibited a large geminal coupling to $H_{9\alpha}$ (J = 14 Hz) and only small vicinal couplings to H_8 and H_{10}.

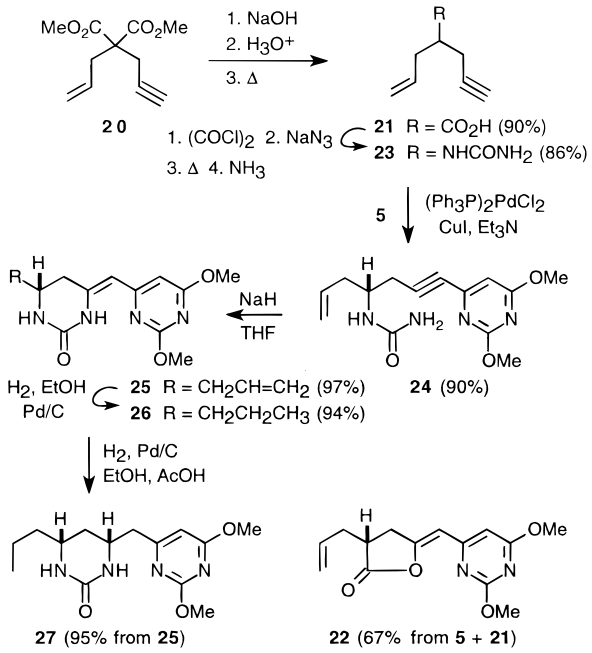
(15) Vishwakarama, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1988**, *66*, 203.

(16) Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919.

(17) It is notable that similar treatment of **10b** gave only a 15% yield of the corresponding alcohol. It was suspected that metalation of the benzyl groups might have been problematic with this substrate.

(18) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

Scheme 2



the C_8-nitrogen and a pyrimidine nitrogen to form a six-membered ring chelate. The C_7 carbanion then reacts with the oxaziridine from the sterically least hindered β-face.

The studies described in Scheme 1 established that the conjugate addition−metalation−oxidation plan outlined in the Introduction was reasonable. Therefore attention was turned to preparation of substrates related to ureas **2** (R = *n*-Pr) and **3** (R = allyl) as described in Scheme 2. The known diester **20** was prepared by sequential alkylation of dimethyl malonate with allyl bromide and propargyl bromide.[19] Saponification of the malonate followed by acidification and decarboxylation gave **21** in 90% yield. It had been planned to couple **21** with 6-bromo-2,4-dimethoxypyrimidine and subject the expected acid to a Curtis degradation to provide urea **24**. This plan was thwarted, however, as coupling **21** with the bromopyrimidine under Sonogashira conditions provided enol lactone **22** in 67% yield.[20] Thus, the presumed intermediate alkynyl pyrimidine cyclized efficiently. Given this result, acid **21** was first converted into urea **23** in 86% yield via a straightforward reaction sequence (acid → acid chloride → acyl azide → isocyanate → urea) and then coupled with 6-bromo-2,4-dimethoxypyrimidine to afford **24** in 90% yield. Rather than reducing **24** to a substrate of type **3**, it was decided to use **24** itself as a cyclization substrate. In the event, treatment of **24** with sodium hydride in tetrahydrofuran resulted in clean formation of **25** (97%).[21] The geometry of the trisubstituted olefin in **25** was proven by NOE experiments that established the proximity of H_7 and the C_9 methylene protons. Finally, catalytic hydrogenation of **25** over palladium on charcoal in ethanol provided **26** (94%), whereas addition of acetic acid to the reaction mixture provided **27** in 95% yield. The *cis* relationship between the C_8 and C_{10} side chains was established in the same manner used to determine stereochemistry in **10a** (vide supra).

Hydroxylation of urea **27** failed using the protocol established with urethane **10a**. Thus, treatment of **27** with 3 equiv of *n*-butyllithium, followed by 2-phenylsulfonyl-3-phenyloxaziridine, returned only small amounts of starting material along with other intractable materials.[22] This disappointing result suggested that introduction of the C_7 hydroxyl group might be best accomplished by the formal addition of water across the C_7-C_8 bond of enamides such as **25** or **26**. Initial studies were discouraging.[23] It was eventually found, however, that treatment of **25** with dimethyldioxirane[24] in the presence of methanol provided an unstable mixture of *N*,*O*-acetals **28**, which were converted, upon reaction with sodium cyanoborohydride at pH 4,[25] to a 78:22 mixture of isomeric alcohols **29** and **30** in 97% overall yield from **25**.[26] Although **29** and **30** could not be separated by chromatography or crystallization, they could be separated upon conversion to the corresponding cyclic *N*,*O*-acetals or carbamates. Thus, treatment of the aforementioned mixture with 2,2-dimethoxypropane and a catalytic amount of 10-camphorsulfonic acid gave **31** (58%) and **32** (16%) after separation by column chromatography. Furthermore, treatment of the mixture of **29** and **30** with carbonyldiimidazole provided separable cyclic carbamates **33** (65%) and **34** (20%). The stereochemistry of the *N*,*O*-acetals and cyclic carbamates were established by difference NOE experiments. For example, irradiation of H_8 in **31** gave 10%, 3.5%, and 4.7% enhancements of signals due to H_7, H_{9eq}, and H_{10}, respectively, whereas irradiation of H_8 in **32** gave 1%, 3.2%, and 4.4% enhancements of signals due to H_7, H_{9eq}, and H_{10}, respectively. Similar results were obtained with **33** and **34**. Finally, hydrolysis of **31** and **32** in aqueous HCl provided **29** (70%) and **30** (60%), respectively (Scheme 3).[27]

The stereochemical course of the conversion **25** to **29** and **30** can be rationalized as follows. The stereochemistry at C_7 is set in an initial epoxidation of the enamide. This presumably occurs largely from the face of the cyclic urea opposite the C_{10} allyl group. Reduction of an *N*-acyliminium ion, presumably generated at pH 4 from **28**, occurs almost exclusively from the β-face of the cyclic urea either because of a steric effect (avoidance of an interaction with the C_{10} allyl group) and/or stereoelectronic effect (axial delivery of hydride such that the product is born with a staggered array of substituents

(19) Mook, R. Jr.; Sher, P. M. *Org. Synth.* **1988**, *66*, 75.

(20) The geometry of the trisubstituted olefin was established by NOE experiments. Irradiation of H_7 (δ 5.59) gave a 4.0% enhancement of the pseudoequatorial proton at C_9 (δ 3.13).

(21) It is notable that a carbamate related to **8** (replace OMe with OBn) gave largely the conjugated enyne resulting from elimination upon treatment with NaH in THF (67% yield).

(22) Whereas the oxidation of **27** failed, the hydroxylation of 4-alkyl-2,6-dimethoxypyrimidines with 2-phenylsulfonyl-3-phenyloxaziridine reagent may have some generality. For example, in one experiment, deprotonation of 4-methyl-2,6-dimethoxypyrimidine with *n*-butyllithium followed by reaction with the oxaziridine gave equal amounts of 4-hydroxymethyl-2,6-dimethoxypyrimidine and the product derived from addition of the initially formed anion to *N*-phenylsulfonylbenzaldimine generated during the course of the hydroxylation reaction.

(23) For example, treatment of **25** with osmium tetroxide or *m*-chloroperoxybenzoic acid gave complex product mixtures. Attempts at hydroboration−oxidation were also unsuccessful. Treatment of **25** with NBS in MeOH, however, did give a mixture of diasteromeric dibromides derived from bromination at C_7 and C_9.

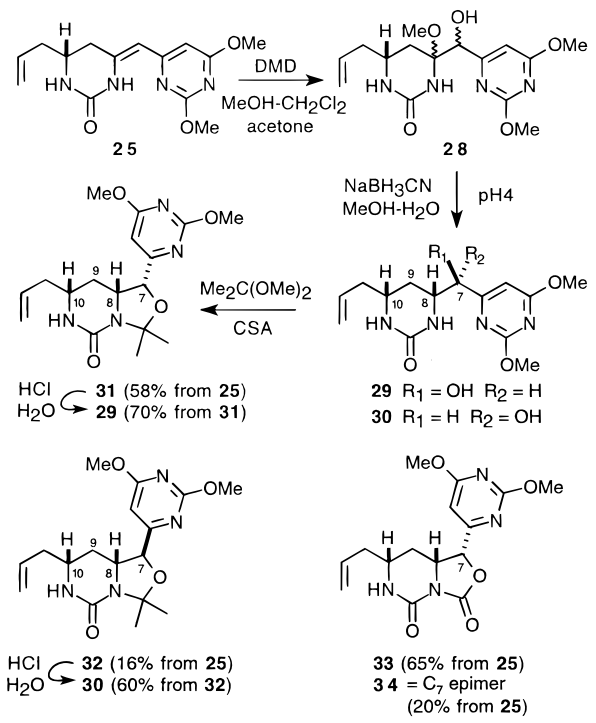
(24) Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91.

(25) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

(26) This material appeared to contain a trace amount of a third stereoisomer based on the appearance of a very small doublet at δ 4.40 in the ^{1}H NMR spectrum of the mixture.

(27) All of the chemistry described for **25** has also been accomplished with **26**. Details will appear in the Ph.D. Thesis of J.F.D.

Scheme 3



across C_8, C_9, and C_{10}). Whereas the stereoelectronic argument is speculation, it is notable that in both **29** and **30**, the hydrogens on C_8 and C_{10} occupy well-defined axial sites, and the hydrogens on C_9 are well-defined as axial and equatorial, on the basis of an analysis of coupling constants (for example for **29**, $J_{8,9eq} = 4.1$ Hz, $J_{8,9ax} = 11.3$ Hz, $J_{9ax,9eq} = 12.6$ Hz, $J_{10,9eq} = 3.5$ Hz and $J_{10,9ax} = 11.3$ Hz; similar values were observed for **30**).

Since the hydration of **25** largely gave stereochemistry at C_7 opposite to that demanded by cylindrospermopsin, the conversion of **29** to **30** was undertaken using the Martin modification of the Mitsunobu reaction.[18] Treatment of **29** with *p*-nitrobenzoic acid, diethyl azodicarboxylate, and triphenylphosphine in tetrahydrofuran under reflux gave a crude *p*-nitrobenzoate that was hydrolyzed in methanolic potassium carbonate to provide **30** in 91% overall yield. Thus, although the hydration of **25** does not directly provide the presumed cylindrospermopsin C_7 stereochemistry, a straightforward separation−inversion protocol has been developed that should allow all of the material to be used in a productive manner.[28]

In summary, a synthesis of a substructure of cylindrospermopsin has been accomplished. The synthesis features an intramolecular conjugate addition of a urea to a 4-alkynylpyrimidine and an enamide-hydration procedure that revolves around oxidation of an enamide with dimethyldioxirane in the presence of monosubstituted olefin. During the course of model studies, the stereoselective hydroxylation of a dianion, derived from a 4-alkylpyrimidine, was accomplished using 2-phenylsulfonyl-3-phenyloxaziridine. From the standpoint of a synthesis of cylindrospermopsin, it is hoped that the allyl group of intermediates such as **30** will serve as a handle for constructing the AB-ring system. For this to be done without compromising stereocontrol, it will be necessary to prepare enantiopure **30**, which should be straightforward if an enantioselective synthesis of **21** can be developed. These studies are underway.

(28) The separation−inversion protocol provides a 55% yield of **30** starting from a 78:22 mixture of **29** and **30**.

Experimental Section[29]

(±)-Oct-1-yn-4-ol (6). To a slurry of 20.28 g (220 mmol) of lithium acetylide ethylenediamine complex in 120 mL of dry dimethyl sulfoxide at room temperature was added 10.0 mL (83.4 mmol) of 1,2-epoxyhexane.[30] The solution was stirred at room temperature for 23 h, cooled to 0 °C, and quenched by slow addition of 500 mL of water. The resulting solution was extracted with four 250-mL portions of Et_2O. The combined organic extracts were washed with three 500-mL portions of water and dried (Na_2SO_4). Diethyl ether was removed via distillation at atmospheric pressure to provide 8.47 g (81%) of alkyne **6** as a brown liquid which was used without further purification: IR (neat) 3366, 3295, 2931, 2861, 2120 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88−0.95 (m, 3H), 1.27−1.59 (m, 6H), 1.85 (s, 1H), 2.06 (t, $J = 2.7$, 1H), 2.25−2.51 (m, 2H), 3.70−3.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (q), 22.6 (t), 27.3 (t), 27.7 (t), 35.9 (t), 69.9 (d), 70.7 (s), 80.9 (d); exact mass calcd for $C_8H_{14}O$ *m/z* 126.1045, found *m/z* 126.1032.

(±)-2,4-Bis(methoxy)-6-[4-(hydroxy)-1-octynyl]pyrimidine (7). To a solution of 4.27 g (19.3 mmol) of 6-bromo-2,4-dimethoxypyrimidine[10] and 3.74 g (29.6 mmol) of alkyne **6** in 35 mL of tetrahydrofuran and 35 mL of triethylamine was added a mixture of 140 mg (0.20 mmol) of bis(triphenylphosphine)palladium(II) chloride and 71 mg (0.37 mol) of copper(I) iodide. The resulting mixture was stirred vigorously at room temperature for 19 h. The reaction mixture was then diluted with 300 mL of Et_2O and washed successively with 250 mL of brine and 250 mL of water. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 80 g of silica gel (eluted with EtOAc−hexanes, 3:7) to give 3.81 g (75%) of alkynyl pyrimidine **7** as a viscous brown oil: IR (neat) 3380, 2940, 2858, 2233 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87−0.94 (m, 3H), 1.25−1.61 (m, 6H), 2.44−2.70 (m, 3H), 3.81−3.92 (m, 1H), 3.95 (s, 3H), 3.98 (s, 3H), 6.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (q), 22.4 (t), 27.6 (t), 28.2 (t), 36.0 (t), 53.7 (q), 54.7 (q), 69.6 (d), 80.3 (s), 91.3 (s), 104.1 (d), 151.4 (s), 165.1 (s), 171.6 (s); exact mass calcd for $C_{14}H_{20}N_2O_3$ *m/z* 264.1474, found *m/z* 264.1458.

(±)-1-[2,6-Bis(methoxy)-6-pyrimidinyl]-1-octyn-4-ol Carbamate (ester) (8). To a solution of 1.40 mL (16.8 mmol) of chlorosulfonyl isocyanate in 30.0 mL of dry CH_2Cl_2 at 0 °C was added dropwise via cannula a solution of 3.70 g (14.0 mmol) of alcohol **7** in 30.0 mL of dry CH_2Cl_2. The resulting solution was stirred for 1 h at room temperature. The reaction mixture was then cooled with an ice/water bath, and a solution of 5.0 mL of water in 25.0 mL of THF was added. The reaction mixture was then heated to reflux for 20 min. After cooling to room temperature the reaction mixture was diluted with 50 mL of CH_2Cl_2 and washed with two 200-mL portions of water. The aqueous phase was extracted with 50 mL of CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The resulting residue was chromatographed over 50 g of silica gel (eluted with EtOAc−hexanes, 1:1) to give 3.08 g (72%) of carbamate **8** as a sticky noncrystalline solid: IR (thin film) 3471, 3349, 3195, 2960, 2858, 2238, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83−0.89 (m, 3H), 1.25−1.36 (m, 4H), 1.64−1.71 (m, 2H), 2.64 (dd, $J = 17.4$, 5.2, 1H), 2.72 (dd, $J = 17.4$, 5.7, 1H), 3.91 (s, 3H), 3.95 (s, 3H), 4.80−4.88 (m, 1H), 5.22 (br s, 2H), 6.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (q), 22.3 (t), 25.0 (t), 27.2 (t), 32.9 (t), 53.8 (q), 54.8 (q), 72.0 (d), 80.4 (s), 89.5 (s), 104.6 (d), 151.2 (s), 156.6 (s), 165.2 (s), 171.6 (s); exact mass calcd for $C_{15}H_{23}N_3O_4$ *m/z* 307.1532, found *m/z* 307.1518.

(29) General procedures can be found at the beginning of the Experimental Section of: Atarashi, S.; Choi, J.-K.; Ha, D.-C.; Hart, D. J.; Kuzmich, C.; Lee, C.-S.; Ramesh, S.; Wu, S. C. *J. Am. Chem. Soc.* **1997**, *119*, 6226.

(30) Available from a commercial source.

(±)-(1*Z*)-1-[2,6-Bis(methoxy)-4-pyrimidinyl]-1-octen-4-ol Carbamate (ester) (9a). A mixture of 1.46 g (4.76 mmol) of alkyne **8** and 714 mg of 5% palladium on barium sulfate in 15.0 mL of pyridine was degassed and flushed with a hydrogen atmosphere three times. The reaction mixture was stirred vigorously under 1 atm of hydrogen for 2 h at room temperature, during which time 105 mL (4.7 mmol) of hydrogen was taken up. The reaction mixture was then filtered through a pad of Celite, and the filter cake was rinsed with three 50-mL portions of MeOH. The filtrate was concentrated in vacuo, and the residue was chromatographed over 50 g of silica gel (eluted with EtOAc−hexanes, 1:1) to give 1.28 g (87%) of alkene **9a** as a sticky viscous oil: IR (thin film) 3471, 3354, 3190, 2954, 2865, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85−0.90 (m, 3H), 1.26−1.37 (m, 4H), 1.53−1.64 (m, 2H), 3.08−3.15 (m, 2H), 3.96 (s, 3H), 4.00 (s, 3H), 4.58 (br s, 2H), 4.86−4.95 (m, 1H), 6.01 (dt, J = 11.9, 7.2, 1H), 6.25 (s, 1H), 6.30 (d, J = 11.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9 (q), 22.5 (t), 27.4 (t), 33.8 (t), 34.1 (t), 53.7 (q), 54.7 (q), 74.5 (d), 101.3 (d), 128.0 (d), 136.1 (d), 157.0 (s), 164.8 (s), 165.0 (s), 172.2 (s); exact mass calcd for $C_{15}H_{23}N_3O_4$ *m/z* 309.1688, found *m/z* 309.1662.

(±)-(4*R,6*S**)-6-Butyl-4-[(2,6-methoxy-4-pyrimidinyl)-methyl]tetrahydro-2*H*-1,3-oxazin-2-one (10a).** To a solution of 1.52 g (4.92 mmol) of carbamate **9a** in 165 mL of dry THF at room temperature was added 297 mg (7.43 mmol) of a 60% dispersion of NaH in mineral oil. The reaction mixture was heated to reflux for 2 h, then cooled to room temperature, and quenched by addition of 2.0 mL of saturated aqueous NH_4Cl. The reaction mixture was then dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over 40 g of silica gel (eluted with EtOAc−hexanes, 1:1) to give 1.10 g (72%) of **10a** as a white solid: mp 108−110 °C; IR (KBr pellet) 3366, 3224, 3119, 2955, 2861, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.1, 3H), 1.30−1.63 (m, 5H), 1.67−1.77 (m, 2H), 1.98−2.05 (m, 1H), 2.69 (dd, J = 14.3, 8.9, 1H), 2.79 (dd, J = 14.3, 4.0, 1H), 3.88−3.96 (m, 1H), 3.97 (s, 3H), 4.00 (s, 3H), 4.20−4.28 (m, 1H), 6.22 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5 (q), 22.0 (t), 26.3 (t), 32.8 (t), 34.4 (t), 42.4 (t), 49.4 (d), 53.4 (q), 54.4 (q), 76.4 (d), 100.7 (d), 154.2 (s), 164.9 (s), 167.2 (s), 171.6 (s); exact mass calcd for $C_{15}H_{23}N_3O_4$ *m/z* 309.1688, found *m/z* 309.1711.

(±)-(4*R,6*S**)-6-Butyl-4-[(2,6-bisbenzyloxy-4-pyrimidinyl)methyl]tetrahydro-2*H*-1,3-oxazin-2-one (10b).** To a solution of 960 mg (2.72 mmol) of carbamate **9b** in 70 mL of dry THF at room temperature was added 125 mg (3.13 mmol) of a 60% dispersion of NaH in mineral oil. The reaction mixture was heated to reflux for 1.5 h, then cooled to room temperature, and quenched by addition of 1.0 mL of saturated aqueous NH_4Cl. The reaction mixture was then diluted with 30 mL of EtOAc, dried ($MgSO_4$), and concentrated in vacuo to give 882 mg (92%) of **10b** as a white solid, mp 110−113 °C, which was used without further purification: IR (KBr pellet) 3354, 3119, 3025, 2947, 2840, 1696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87−0.94 (m, 3H), 1.34−1.70 (m, 7H), 1.89−2.00 (m, 1H), 2.72−2.76 (m, 2H), 3.83−3.96 (m, 1H), 4.12−4.26 (m, 1H), 5.41 (s, 2H), 5.42 (s, 2H), 6.17 (br s, 1H), 6.28 (s, 1H), 7.33−7.50 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (q), 22.2 (t), 26.5 (t), 32.8 (t), 34.5 (t), 42.8 (t), 49.4 (d), 68.1 (t), 69.0 (t), 76.5 (d), 101.3 (d), 127.7 (d), 127.9 (d), 128.0 (d), 128.2 (d), 128.3 (d), 135.7 (s), 136.3 (s), 154.3 (s), 164.3 (s), 167.6 (s), 171.2 (s), one carbon not observed; exact mass calcd for $C_{27}H_{31}N_3O_4$ *m/z* 416.2314, found *m/z* 461.2324.

(±)-(4*R,6*R**)-6-Butyl-4-[(*R**)-(2,6-bismethoxy-4-pyrimidinyl)hydroxymethyl]tetrahydro-2*H*-1,3-oxazin-2-one (11).** To a solution of 680 mg (2.20 mmol) of **10a** in 20.0 mL of dry THF at −70 °C was added 1.85 mL (4.63 mmol) of a 2.5 M solution of *n*-BuLi in hexanes. The reaction mixture was warmed to −40 °C for 1 h in an acetonitrile−dry ice bath. After the reaction mixture was cooled to −70 °C, a solution of 863 mg (3.30 mmol) of (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine[16] in 7.0 mL of dry THF, precooled in a dry ice−acetone bath, was added. After stirring for 75 min, the reaction was quenched by addition of 1 mL of saturated aqueous NH_4Cl, diluted with 50 mL of EtOAc, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over 90 g of silica gel (eluted with EtOAc−hexanes, 3:1, to separate excess oxaziridine, then EtOAc) to give 120 mg (18%) of recovered **10a** and 364 mg (51%) of alcohol **11** as a white solid: mp 131−133.5 °C; IR (KBr pellet) 3354, 3107, 2955, 2872, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (t, J = 6.9, 3H), 1.25−1.67 (m, 8H), 3.85−4.02 (m, 1H), 3.95 (br s, 6H), 4.13−4.22 (m, 1H), 4.71 (d, J = 3.2, 1H), 6.63 (s, 1H), 6.93 (br s, 1H), 1H not observed; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (q), 22.3 (t), 26.1 (t), 26.7 (t), 34.7 (t), 53.9 (q), 54.7 (q), 54.8 (d), 72.7 (d), 76.8 (d), 98.6 (d), 156.5 (s), 164.8 (s), 170.2 (s), 172.4 (s); calcd for $C_{15}H_{24}N_3O_5$ (M + 1) *m/z* 326.1716, found (M + 1) *m/z* 326.1740 (parent not observed).

(±)-(4*R,6*R**)-6-Butyl-4-[(*S**)-(2,6-bismethoxy-4-pyrimidinyl)hydroxymethyl]tetrahydro-2*H*-1,3-oxazin-2-one (12).** To a suspension of 72 mg (0.22 mmol) of alcohol **11** were added 163 mg (0.975 mmol) of 4-nitrobenzoic acid and 281 mg (1.07 mol) of diethyl azodicarboxylate. The reaction mixture immediately became homogeneous and was stirred at room temperature for 21 h. The solvent was removed in vacuo, and the residue was chromatographed over 50 g of silica gel (eluted first with EtOAc−hexanes, 3:7, to separate residual triphenylphosphine, then with EtOAc−hexanes, 3:1) to provide 84 mg (80%) of the 4-nitrobenzoate of alcohol **12** as a white foam: IR (KBr pellet) 3251, 3125, 2952, 2871, 1733, 1704, 1525, 1358 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J = 7.1, 3H), 1.37−1.71 (m, 7H), 1.96 (dd, J = 13.5, 5.2, 1H), 3.98 (s, 3H), 4.01 (s, 3H), 4.21−4.31 (m, 2H), 5.73 (d, J = 4.7 Hz, 1H), 5.87 (br s, 1H), 6.45 (s, 1H), 8.27 (d, J = 9.1, 2H), 8.33 (d, J = 9.1, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (q), 22.3 (t), 26.7 (t), 29.6 (t), 34.5 (t), 52.4 (d), 54.1 (q), 55.0 (q), 76.1 (d), 77.0 (d), 100.3 (d), 123.6 (d), 131.1 (d), 134.1 (s), 150.8 (s), 154.4 (s), 163.7 (s), 164.7 (s), 165.6 (s), 172.3 (s); exact mass calcd for $C_{22}H_{26}N_4O_8$ *m/z* 474.1750, found *m/z* 474.1743.

To a suspension of 75 mg (0.158 mmol) of the aforementioned 4-nitrobenzoate in 3.0 mL of MeOH at room temperature was added 190 mg (1.37 mmol) of potassium carbonate. The reaction mixture was stirred for 10 min and then filtered through a short column of silica gel (eluted with EtOAc−hexanes, 1:1) to provide 32 mg (62%) of alcohol **12** as a white solid: mp 149−152 °C; IR (KBr pellet) 3271, 3092, 2955, 1688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0, 3H), 1.24−1.78 (m, 8H), 3.63−3.70 (m, 1H), 3.97 (s, 3H), 3.98 (s, 3H), 4.14−4.17 (m, 1H), 4.31 (d, J = 6.5, 1H), 4.32−4.48 (br s, 1H), 6.06 (br s, 1H), 6.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (q), 22.4 (t), 26.7 (t), 29.5 (t), 34.7 (t), 54.1 (q), 54.9 (q), 55.0 (d), 75.1 (d), 76.6 (d), 99.4 (d), 154.8 (s), 165.2 (s), 169.0 (s), 172.3 (s); exact mass calcd for $C_{15}H_{23}N_3O_5$ *m/z* 325.1638, found *m/z* 325.1621.

(±)-(1*R,7R*,8a*R**)-7-Butyl-1-(2,6-dimethoxy-4-pyrimidinyl)tetrahydro-3*H*,5*H*-oxazolo[3,4-*c*][1,3]oxazine-3,5-dione (13).** To a solution of 56 mg (0.17 mmol) of alcohol **11** and 33 mg (0.22 mmol) of 1,1′-carbonyldiimidazole in 2.0 mL of dry benzene at room temperature was added 5 mg (0.04 mmol) of 4-DMAP. The reaction mixture was heated to reflux for 4 h. The solvent was removed under reduced pressure, and the residue was chromatographed over 20 g of silica gel (eluted with EtOAc−hexanes, 1:1) to give 34 mg (57%) of carbamate **13** as a colorless glass: IR (thin film) 2955, 2872, 1819, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, J = 7.0, 3H), 1.11 (dd, J = 13.8, 12.0, 1H), 1.25−1.56 (m, 6H), 2.18 (dt, J = 13.8, 2.9, 1H), 3.96 (s, 3H), 3.99 (s, 3H), 4.39−4.42 (m, 1H), 4.74 (ddd, J = 12.0, 8.1, 3.5, 1H), 5.43 (d, J = 8.1, 1H), 6.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (q), 22.2 (t), 26.7 (t), 29.2 (t), 34.7 (t), 54.3 (q), 55.3 (q), 56.1 (d), 75.9 (d), 79.6 (d), 99.6 (d), 146.4 (s), 151.0 (s), 163.5 (s), 165.5 (s), 172.6 (s); exact mass calcd for $C_{16}H_{21}N_3O_6$ *m/z* 351.1430, found *m/z* 351.1423.

(±)-(1*R,7*S**,8a*S**)-7-Butyl-1-(2,6-dimethoxy-4-pyrimidinyl)tetrahydro-3*H*,5*H*-oxazolo[3,4-*c*][1,3]oxazine-3,5-dione (14).** To a solution of 57 mg (0.18 mmol) of alcohol **12** and 37 mg (0.23 mmol) of 1,1′-carbonyldiimidazole in 3.0 mL of dry benzene at room temperature was added 5 mg (0.04 mmol) of 4-DMAP. The reaction mixture was heated to reflux

for 35 min. The solvent was removed under reduced pressure and the resulting residue was chromatographed over 20 g of silica gel (eluted with EtOAc−hexanes 1:1) to give 46 mg (74%) of carbamate **14** as a white solid: mp 143−145 °C; IR (KBr pellet) 3103, 2955, 2871, 1835, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.1, 3H), 1.30−1.53 (m, 4H), 1.64−1.83 (m, 2H), 1.90−2.02 (m, 1H), 2.63 (dt, J = 13.7, 3.0, 1H), 3.98 (s, 3H), 3.99 (s, 3H), 4.18−4.26 (m, 1H), 4.41−4.50 (m, 1H), 5.07 (d, J = 9.8, 1H), 6.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8 (q), 22.2 (t), 26.6 (t), 31.9 (t), 34.7 (t), 54.2 (q), 54.9 (q), 58.2 (d), 79.2 (d), 80.2 (d), 97.9 (d), 145.8 (s), 150.1 (s), 164.7 (s), 165.5 (s), 172.6 (s); exact mass calcd for $C_{16}H_{21}N_3O_6$ m/z 351.1430, found m/z 351.1423.

(±)-(4*R,6*S**)-6-Methyl-4-[(2,6-bisbenzyloxy-4-pyrimidinyl)methyl]tetrahydro-2*H*-1,3-oxazin-2-one (17).** To a solution of 115 mg (0.274 mmol) of *trans*-carbamate **16** in 9.0 mL of dry THF at room temperature was added 17.0 mg (0.425 mmol) of a 60% dispersion of NaH in mineral oil. The reaction mixture was heated to reflux for 1.5 h, then cooled to room temperature, and quenched by addition of 3.0 mL of saturated aqueous NH_4Cl. The reaction mixture was poured into 50 mL of water and extracted with two 40-mL portions of EtOAc. The combined organic extracts were concentrated in vacuo, and the residue was chromatographed over 32 g of silica gel (eluted first with EtOAc−hexanes 3:7, then with EtOAc) to give 79 mg (69%) of **17** as a white solid, mp 115.5−116.5 °C. Treatment of 53 mg (0.126 mmol) of *cis*-carbamate **15** with 7.4 mg (0.19 mmol) of a 60% dispersion of NaH in mineral oil in 4.2 mL of THF under similar conditions provided 34 mg (64%) of **17** after purification by column chromatography: IR (KBr pellet) 3361, 3227, 3116, 3027, 2938, 1717 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (d, J = 6.3, 3H), 1.40−1.52 (m, 1H), 1.95 (m, 1H), 2.64−2.82 (m, 2H), 3.92 (m, 1H), 4.35 (m, 1H), 5.41 (s, 2H), 5.42 (s, 2H), 6.20 (br s, 1H), 6.27 (s, 1H), 7.28−7.50 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9 (q), 34.9 (t), 42.9 (t), 49.5 (d), 68.3 (t), 69.2 (t), 73.0 (d), 101.5 (d), 127.9 (d), 128.1 (d), 128.2 (d), 128.4 (d), 128.5 (d), 135.8 (s), 136.4 (s), 154.1 (s), 164.6 (s), 167.6 (s), 171.4 (s), one aromatic signal was obscured; exact mass calcd for $C_{24}H_{25}N_3O_4$ m/z 419.1845, found m/z 419.1848.

5-Methyl-3-[(2,6-dimethoxy-4-pyrimidinyl)methyl]isoxazolidines (mixture of *cis* and *trans* isomers) **(19).** To a solution of 166 mg (0.32 mmol) of *N*-alkoxyphthalimide **18** in 1.6 mL of MeOH−CH_2Cl_2 (1:20) was added 35 mL of hydrazine monohydrate. The mixture was stirred at 0 °C for 2 h, another 30 mL of hydrazine monohydrate was added, and stirring was continued for an additional 2 h. The mixture was filtered and concentrated in vacuo. The residue was chromatographed over 20 g of flash silica gel (eluted with EtOAc−hexanes, 3:7) to provide 61 mg (51%) of a mixture of *cis* and *trans* isoxazolidines **19**: ^1H NMR (200 MHz, $CDCl_3$) δ 1.25−1.30 (two d, J = 7, 3H), 1.5−3.0 (m, 4H), 4.0 (m, 2H), 5.4 (two s, 4H), 6.35 (two s, 1H), 7.4−7.5 (m, 10H), 1H not observed; exact mass calcd for $C_{23}H_{25}N_3O_3$ m/z 491.1896, found m/z 491.1895.

(±)-2-(2-Propynyl)-4-pentenoic acid (21). To 20.0 g (0.095 mol) of malonate **20** in 500 mL of THF−MeOH (1:1) cooled in an ice−water bath was added 26.2 g (0.38 mol) of a solution of KOH in 150 mL of THF. The resulting dark orange mixture was warmed under reflux for 10 h. The mixture was slowly cooled to 0 °C and acidified to pH 1 with 3 N aqueous HCl. The organic phase was extracted with two 300-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The resulting light brown oil was heated at 175 °C (1 atm) for 2 h, and the residual liquid was distilled at 180 °C (25 Torr) to afford 11.8 g (90%) of carboxylic acid **21** as a colorless liquid: IR (neat) 3300, 3000, 2150, 1708, 1642 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.01 (t, J = 2.7, 1H), 2.37−2.60 (m, 4H), 2.70 (m, 1), 5.10 (m, 2H), 5.75 (m, 1H), 10.8 (br s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 19.8 (t), 34.6 (t), 43.7 (d), 70.2 (d), 80.7 (s), 118.0 (t), 113.8 (d), 179.9 (s); exact mass calcd for $C_8H_{10}O_2$ m/z 138.0681, found m/z 138.0683.

(±)-3-Allyl-5-[(*Z*)-(2,6-dimethoxy-4-pyrimidinyl)methylene]dihydro-2(3*H*)-furanone (22). To 500 mg (3.62 mmol) of carboxylic acid **21** in 10 mL of dry, degassed THF was added 790 mg (3.62 mmol) of 6-bromo-2,4-dimethoxypyrimidine (**5**) followed by 8.4 mL of triethylamine. The resulting mixture was stirred for 10 min at room temperature under argon. To this mixture was added 25 mg (0.036 mmol) of bis(triphenylphosphine)palladium(II) chloride and 13 mg (0.072 mmol) of copper(I) iodide. The resulting light yellow mixture was stirred at room temperature under argon for 12 h. To the resulting heterogeneous mixture was added 15 mL of water. The organic layer was extracted with two 100-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 1.25 g of a light orange oil. The oil was chromatographed over 30 g of silica gel (eluted with hexanes−EtOAc, 1:1) to afford 670 mg (67%) of lactone **22** as a light yellow oil: IR (neat) 2954, 1812, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (dt, J = 14.5, 7.3, 1H), 2.62 (dt, J = 14.5, 5.2, 1H), 2.80 (ddd, J = 16.4, 7.3, 1.6, 1H), 2.92 (m, 1H), 3.13 (ddd, J = 16.4, 9.4, 1.6, 1H), 3.94 (s, 3H), 3.95 (s, 3H), 5.16 (m, 2H), 5.59 (t, J = 1.6, 1H), 5.74 (ddt, J = 13.5, 9.8, 7.0, 1H), 6.88 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.0 (t), 34.5 (t), 37.7 (d), 53.7 (q), 54.4 (q), 100.0 (d), 104.2 (d), 118.8 (t), 132.9 (d), 153.7 (s), 161.3 (s), 164.9 (s), 172.2 (s), 175.3 (s); exact mass calcd for $C_{14}H_{16}O_4N_2$ m/z 276.1110, found m/z 276.1118. This material contained some trace impurities by ^1H and ^{13}C NMR.

(±)-[1-(2-Propynyl)-3-butenyl]urea (23). To 10 g (72 mmol) of carboxylic acid **21** was added 13 mL of thionyl chloride at 0 °C in one portion. The solution was warmed under reflux for 1.5 h and then distilled at 78 °C under atmospheric pressure to remove excess thionyl chloride. The remaining liquid was distilled at 90 °C (25 Torr) to afford 10.8 g (96%) of the desired acid chloride as a colorless liquid: IR (neat) 3302, 1790, 1643 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.05 (t, J = 2.5, 1H), 2.45−2.60 (m, 4H), 3.07 (q, J = 7.9, 1H), 5.10−5.20 (m, 2H), 5.72 (ddt, J = 17.3, 10.1, 7.2, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2 (t), 34.4 (t), 55.2 (d), 71.3 (d), 79.1 (s), 119.6 (t), 132.3 (d), 174.5 (s); exact mass calcd for $C_8H_9O^{35}Cl$ m/z 156.0342, found m/z 156.0344. This material contained some trace impurities by ^{13}C NMR but could be used in the next reaction sequence. To 5.50 g (35.1 mmol) of the acid chloride was added 30 mL of acetone followed by 3.0 g (45.6 mmol) of sodium azide in 13 mL of water cooled to 0 °C. The resulting solution was stirred for 1 h and then poured into 65 mL of chilled water. The organic phase was extracted with three 250-mL portions of pentane. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to a volume of 30 mL. To the solution was added 65 mL of dry benzene. The mixture was warmed under reflux under argon for 2 h and then cooled in a dry ice−acetone bath. Ammonia gas was passed through a KOH plug and bubbled through the solution for 1 h at −78 °C and then for 30 min at room temperature. The resulting mixture was stirred for an additional 3 h and concentrated in vacuo to afford 5.07 g of a white solid, which was recrystallized from CH_2Cl_2−hexanes (1:12) to afford 4.73 g (89%) of urea **23** as a white solid: mp 90−91.5 °C; IR (KBr) 3308, 2925, 1652, 1532 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.03 (t, J = 2.5, 1H), 2.34−2.43 (m, 4H), 3.87 (sextet, J = 6.5, 1H), 4.85 (br s, 2H), 5.05−5.15 (m, 2H), 5.46 (br d, J = 8.5, 1H), 5.75 (ddt, J = 17.2, 10.2, 7.1, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.0 (t), 37.9 (t), 47.9 (d), 70.8 (d), 80.6 (s), 118.0 (t), 134.0 (d), 158.7 (s); exact mass calcd for $C_8H_{12}ON_2$ m/z 152.0949, found m/z 1542.0948. Anal. Calcd for $C_8H_{12}ON_2$: C, 63.13; H, 7.95. Found: C, 63.00; H, 7.95.

(±)-[1-[3-(2,6-Dimethoxy-4-pyrimidinyl)-2-propynyl]-3-butenyl]urea (24). To 2.44 g (16.0 mmol) of urea **23** in 40 mL of dry, degassed THF was added 3.89 g (17.6 mmol) of 6-bromo-2,4-dimethoxypyrimidine (**5**) followed by 37 mL of triethylamine. The resulting mixture was stirred for 10 min at room temperature under argon. To the mixture was added 112 mg (0.163 mmol) of bis(triphenylphosphine)palladium(II) chloride and 61 mg (0.32 mmol) of copper(I) iodide. The resulting light yellow mixture was stirred at room temperature under argon for 14 h. To the resulting heterogeneous mixture was added 50 mL of water. The organic layer was extracted with two 150-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 4.9 g of a light yellow solid. The residue was chromatographed

over a short plug of 50 g of silica gel (eluted with EtOAc). The desired fractions were concentrated in vacuo to afford 4.15 g (90%) of alkynyl pyrimidine **24** as a white solid: mp 136.5−138 °C; IR (KBr) 3326, 2232, 1651, 1537 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (t, J = 7.0, 2H), 2.62 (dd, J = 17, 4.6, 1H), 2.73 (dd, J = 17, 5.5, 1H), 3.95 (s, 3H), 3.97 (s, 3H), 4.03 (m, 1H), 4.84 (br s, 2H), 5.06−5.16 (m, 2H), 5.55 (br d, J = 9.3, 1H), 5.78 (ddt, J = 14, 10, 7, 1H), 6.40 (s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 25.0 (t), 38.1 (t), 47.7 (d), 53.9 (q), 54.8 (q), 80.6 (s), 90.8 (s), 104.2 (d), 118.0 (t), 134.0 (d), 151.4 (s), 158.5 (s), 165.1 (s), 171.7 (s); exact mass calcd for $C_{14}H_{18}O_3N_4$ m/z 290.1379, found m/z 290.1393. Anal. Calcd for $C_{14}H_{18}O_3N_4$: C, 57.90; H, 6.25. Found: C, 57.90; H, 6.27.

(±)-4-Allyl-6-[(*Z*)-(2,6-dimethoxy-4-pyrimidinyl)methylene]tetrahydro-2(1*H*)-pyrimidinone (25). To a solution of 4.0 g (13.78 mmol) of urea **24** in dry THF was added 0.83 g (20.7 mmol) of a 60% NaH dispersion in mineral oil in one portion under argon. The resulting light yellow mixture was stirred for 20 min at room temperature and then was warmed under reflux for 1.5 h. The resulting orange mixture was cooled to room temperature and poured into 100 mL of saturated aqueous ammonium chloride. The organic layer was separated, and the aqueous layer was washed with two 250-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 4.0 g of an orange solid, which was recrystallized from CH_2Cl_2−hexanes (1:13) to yield 3.88 g (97%) of enamide **25** as a light yellow solid: mp 179−181 °C; IR (KBr) 3216, 3101, 1706, 1639 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.18−2.37 (m, 2H), 2.45 (ddd, J = 15, 9, 1, 1H), 2.60 (dd, J = 15, 4, 1H), 3.51 (m, 1H), 3.91 (s, 3H), 4.02 (s, 3H), 5.07 (s, 1H), 5.14−5.20 (m, 2H), 5.52 (br s, 1H), 5.62−5.80 (m, 1H), 5.97 (s, 1H), 11.2 (br s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 33.6 (t), 39.5 (t), 48.1 (q), 53.6 (q), 54.8 (d), 97.5 (d), 98.5 (d), 119.4 (t), 132.5 (d), 143.2 (s), 152.9 (s), 164.4 (s), 164.7 (s), 171.8 (s); exact mass calcd for $C_{14}H_{18}O_3N_4$ m/z 290.1379, found m/z 290.1392. Anal. Calcd for $C_{14}H_{18}O_3N_4$: C, 57.90; H, 6.25. Found: C, 58.10; H, 6.23.

(±)-4-[(*Z*)-(2,6-Dimethoxy-4-pyrimidinyl)methylene]-tetrahydro-6-propyl-2(1*H*)-pyrimidinone (26). To a solution of 100 mg (0.345 mmol) of alkene **25** in 16 mL of EtOAc was added 40 mg of 5% Pd/C. The heterogeneous mixture was placed under 22 psi of hydrogen on a Parr hydrogenator and was shaken for 30 min. The resulting suspension was filtered through a small pad of Celite. The Celite was rinsed with three 40-mL portions of MeOH. The filtrate was concentrated in vacuo to afford 95 mg (94%) of **26** as a white solid: mp 205−206.5 °C; IR (KBr) 3209, 2955, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7, 3H), 1.40−1.51 (m, 4H), 2.40 (dd, J = 15, 10, 1H), 2.65 (dd, J = 15, 4, 1H), 3.45 (m 1H), 3.93 (s, 3H), 4.15 (s, 3H), 5.1 (s, 1H), 5.70 (br s, 1H), 5.90 (s, 1H), 11.4 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (q), 18.4 (t), 33.9 (t), 37.1 (t), 48.7 (d), 53.6 (q), 54.7 (q), 97.4 (d), 98.3 (d), 147.3 (s), 153.1 (s), 164.4 (s), 164.8 (s), 171.8 (s); exact mass calcd for $C_{14}H_{20}O_3N_4$ m/z 292.1535, found m/z 292.1528. Anal. Calcd for $C_{14}H_{20}O_3N_4$: C, 57.50; H, 6.90. Found: C, 58.00; H, 6.88.

(±)-(4*R,6*R**)-4-[(2,6-Dimethoxy-4-pyrimidinyl)methyl]-tetrahydro-6-propyl-2-(1*H*)-pyrimidinone (27).** To a solution of 500 mg (1.72 mmol) of alkene **25** in 15 mL of MeOH was added 150 mg of 10% Pd/C followed by 2 mL of acetic acid. The heterogeneous mixture was placed under 35 psi of hydrogen on a Parr hydrogenator and was shaken for 4 h. The resulting suspension was filtered through a small pad of Celite. The Celite was rinsed with three 100-mL portions of MeOH. The filtrate was concentrated in vacuo to afford a colorless oil. The oil was dissolved in 250 mL of EtOAc and washed with two 200-mL portions of saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford 480 mg (95%) of saturated urea **27** as a white solid: mp 89.5−92 °C; IR (KBr) 3230, 3094, 1682, 1568 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0, 3H), 1.23−1.45 (m, 5H), 1.90 (dt, J = 12.8, 4.6, 1H), 2.65−2.74 (m, 2H), 3.3−3.40 (m, 1H), 3.7−3.90 (m, 1H), 3.90 (s, 3H), 3.94 (s, 3H), 5.10 (br s, 1H), 5.62 (br s, 1H), 6.18 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (q), 18.2 (t), 34.7 (t), 38.1 (t), 43.1 (t), 49.5 (d), 50.0 (d), 53.7 (q), 54.7 (q), 100.9 (d), 156.7 (s), 165.2 (s), 167.8 (s), 171.9 (s). Anal. Calcd for $C_{14}H_{22}O_3N_4$: C, 57.11; H, 7.54. Found: C, 56.87; H, 7.64.

(±)-(4*R,6*R**)-4-Allyl-6-[(*R**)-(2,6-dimethoxy-4-pyrimidinyl)hydroxymethyl]tetrahydro-2(1*H*)-pyrimidinone (29) and (±)-(4*R**,6*R**)-4-Allyl-6-[(*S**)-(2,6-dimethoxy-4-pyrimidinyl)hydroxymethyl]tetrahydro-2(1*H*)-pyrimidinone (30).** Mixture of **29** and **30** from **25**: To a solution of 1.0 g (3.45 mmol) of enamide **25** in 142 mL of MeOH−CH_2Cl_2 (3:1) at −76 °C (internal temperature) was added 44 mL of a 0.09 M solution of dimethyldioxirane[24] in acetone over 15 min. The reaction mixture was stirred for 2 h, the cold bath was removed, and the reaction mixture was concentrated in vacuo to afford 1.2 g of a white solid. To this residue was added 40 mL of MeOH and 1 drop of 5% bromocresol green in MeOH. To this light blue solution was added 2 N HCl in MeOH until the blue solution turned light yellow, followed by 0.542 g (8.63 mmol) of $NaCNBH_3$ under argon at room temperature. The reaction mixture was stirred, and 2 N HCl in MeOH was added dropwise as needed to keep the solution at pH 4 (yellow). The reaction mixture was stirred for 3 h, and then 2 N aqueous NaOH was added to achieve pH 9. The solution was saturated with solid NaCl. The organic phase was extracted with two 250-mL portions of EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford 1.03 g (97%) of diastereomeric hydroxy ureas **29** and **30** as a white solid (mp 136−149 °C). The ratio of 29:30 was 78:22 based on integration of signals for H_7 (cylindrospermopsin numbering), which appeared as doublets at δ 4.3 (J = 6.7 Hz) for **30** and δ 4.65 (J = 3.5 Hz) for **29**. The diastereomers were inseparable by TLC but could be obtained in pure form as follows. Pure **29** from hydrolysis of **31**: To 140 mg (0.402 mmol) of *N*,*O*-acetal **31** in 15 mL of THF was added 3.0 mL of 2 N aqueous HCl. The reaction mixture was warmed under reflux for 4 h. The resulting reaction was cooled to room temperature and basified to pH 9 with 2 N aqueous NaOH. The biphasic mixture was saturated with solid NaCl. The organic layer was extracted with two 75-mL portions of EtOAc. The combined layers were dried ($MgSO_4$) and concentrated in vacuo to afford 90 mg of a white solid. This residue was chromatographed over 3 g of flash silica gel (eluted with 10% MeOH in EtOAc). Desired fractions were concentrated in vacuo to afford 87 mg (70%) of alcohol **29** as a white solid: mp 154.5−155.5 °C; IR (KBr) 3243, 2918, 1697, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.49 (ddd, J = 12.6, 11.3, 11.3, 1H), 1.65 (ddd, J = 12.6, 4.1, 3.5, 1H), 2.08 (dt, J = 13.5, 8.1, 1H), 2.28 (dt, J = 13.5, 5.2, 1H), 3.30−3.42 (m, 2H), 3.90 (dt, J = 11.2, 4.1, 1H), 4.00 (s, 6H), 4.63 (d, J = 4.0, 1H), 5.00 (br s, 1H), 5.11−5.18 (m, 2H), 5.65 (m, 1H), 6.02 (br s, 1H), 6.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8 (t), 40.2 (t), 48.8 (d), 53.9 (q), 54.7 (q), 54.7 (d), 73.2 (d), 98.7 (d), 119.2 (t), 132.9 (d), 157.6 (s), 164.9 (s), 170.0 (s), 172.3 (s); exact mass calcd for $C_{14}H_{21}O_4N_4$ ($M^+ + 1$) m/z 309.1563, found m/z 309.1542. Pure **30** from **29**: To 100 mg (0.325 mmol) of alcohol **29** in 6 mL of dry THF was added 412 mg (1.58 mmol) of triphenylphosphine and 240 mg (1.58 mmol) of 4-nitrobenzoic acid, followed by 0.24 mL (280 mg, 1.60 mmol) of diethyl azodicarboxylate. The resulting orange mixture was stirred at room temperature for 30 min and warmed under reflux for 3 h. The mixture was cooled to room temperature and concentrated in vacuo to afford an orange oil. This residue was dissolved in 200 mL of EtOAc and washed with two 150-mL portions of saturated aqueous sodium bicarbonate solution. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford an orange oil. The oil was dissolved in 30 mL of MeOH, and 200 mg of potassium carbonate was added. The resulting heterogeneous mixture was stirred for 20 min and filtered. To the filtrate was added 15 mL of water and 100 mL of EtOAc. The organic layer was separated, and the aqueous layer was washed with two 50-mL portions of EtOAc. The organic phases were combined, dried ($MgSO_4$), and concentrated in vacuo to afford an orange solid. The residue was chromatographed over 25 g of flash silica gel (eluted with EtOAc, then 10% MeOH in EtOAc). The desired fractions were concentrated in vacuo to afford 91 mg (91%) of alcohol **30** as a white solid: mp 140−142 °C; IR (KBr) 3243, 2917, 1697, 1599 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (ddd, J = 12.6, 11.7,

11.7, 1H), 1.77 (dt, J = 12.6, 3.1, 1H), 2.12 (dt, J = 13.7, 7.8, 1H), 2.28 (dt, J = 13.7, 5.4, 1H), 3.38 (m, 1H), 3.65 (ddd, J = 11.7, 6.1, 3.5, 1H), 3.97 (s, 3H), 3.99 (s, 3H), 4.34 (d, J = 6.1, 1H), 4.73 (br s, 1H), 5.07−5.16 (m, 3H), 5.62−5.75 (m, 2H), 6.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6 (t), 40.2 (t), 48.9 (d), 54.0 (q), 54.8 (q), 54.8 (d), 75.0 (d), 99.2 (d), 119.2 (t), 132.8 (d), 157.0 (s), 165.1 (s), 169.5 (s), 172.2 (s); exact mass calcd for $C_{14}H_{21}O_4N_4$ ($M^+ + 1$) m/z 309.1563, found m/z 309.1600. Pure **30** from **32**: Hydrolysis of 140 mg of of **32**, as described above for the hydrolysis of **31**, gave 75 mg (60%) of **30** as a white solid.

(±)-(1*R,7*S**,8a*S**)-7-Allyl-1-(2,6-dimethoxy-4-pyrimidinyl)tetrahydro-3,3-dimethyl-3*H*-oxazolo[3,4-*c*]pyrimidin-5(1*H*)-one (32)** and **(±)-(1*R**,7*R**,8a*R**)-7-Allyl-1-(2,6-dimethoxy-4-pyrimidinyl)tetrahydro-3,3-dimethyl-3*H*-oxazolo[3,4-*c*]pyrimidin-5(1*H*)-one (31).** To a solution of 530 mg (1.71 mmol) of a 78:22 mixture of alcohols **29** and **30**, respectively, in 15 mL of acetone, was added 5 mL (4.2 g, 40.6 mmol) of 2,2-dimethoxypropane followed by 59 mg (0.25 mmol) of camphorsulfonic acid at room temperature under argon. The reaction mixture was warmed under reflux for 14 h and then cooled to room temperature. The resulting light yellow solution was then concentrated in vacuo to afford 61 mg of a yellow oil. The oil was chromatographed over 60 g of flash silica gel (eluted with EtOAc) to yield 100 mg (16%) of *N*,*O*-acetal **32** as an off-white solid and 350 mg (58%) of *N*,*O*-acetal **31** as a white solid. Properties of **32**: mp 129−131 °C; IR (KBr) 3220, 1668, 1574, 1479, 1359 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (ddd, J = 12.5, 11.5, 11.5, 1H), 1.70 (s, 6H), 2.17 (dt, J = 14.1, 8.2, 1H), 2.33−2.48 (m, 2H), 3.41 (m, 1H), 3.49 (ddd, J = 11.5, 9.0, 3.1, 1H), 3.97 (s, 3H), 3.98 (s, 3H), 4.51 (d, J = 9.0, 1H), 4.75 (br s, 1H), 5.16−5.21 (m, 2H), 5.75 (m, 1H), 6.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2 (q), 26.7 (q), 32.0 (t), 40.3 (t), 50.2 (d), 53.9 (q), 54.6 (q), 60.0 (d), 80.6 (d), 95.1 (s), 97.5 (d), 119.3 (t), 132.8 (d), 152.7 (s), 165.0 (s), 168.2 (s), 172.3 (s); exact mass calcd for $C_{17}H_{24}O_4N_4$ m/z 348.1797, found m/z 348.1811. Properties of **31**: mp 168−169 °C; IR (KBr) 3218, 1666, 1598, 1479, 1354 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (ddd, J = 12.5, 11.7, 11.7, 1H), 1.51 (s, 3H), 1.84 (s, 3H), 1.88−1.99 (m, 2H), 2.19 (dt, J = 12.5, 5.0, 1H), 3.38 (dddd, J = 12.3, 8.6, 7.8, 4.1, 1H), 3.93 (s, 3H), 3.95 (s, 3H), 4.18 (ddd, J = 11.0, 8.1, 2.6, 1H), 4.76 (br s, 1H), 5.02−5.11 (m, 3H), 5.62 (m, 1H), 6.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.2 (q), 27.2 (q), 30.6 (t), 40.6 (t), 50.4 (d), 53.8 (q), 54.7 (q), 56.4 (d), 78.2 (d), 95.4 (s), 98.7 (d), 119.1 (t), 133.1 (d), 153.0 (s), 164.8 (s), 169.4 (s), 173.3 (s); exact mass calcd $C_{17}H_{24}O_4N_4$ m/z 348.1797, found m/z 348.1803.

(±)-(1*R,7*S**,8a*S**)-7-Allyl-1-(2,6-dimethoxy-4-pyrimidinyl)tetrahydro-3*H*-oxazolo[3,4-*c*]pyrimidine-3,5(1*H*)-dione (34) and (±)-(1*R**,7*R**,8a*R**)-7-Allyl-1-(2,6-dimethoxy-4-pyrimidinyl)tetrahydro-3*H*-oxazolo[3,4-*c*]pyrimidine-3,5(1*H*)-dione (33).** To 125 mg (0.40 mmol) of a 78:22 mixture of alcohols **29** and **30**, respectively, in 6 mL of dry benzene was added 75 mg (0.44 mmol) of carbonyl diimidazole in one portion under argon at room temperature. The clear, colorless mixture was warmed under reflux for 1.5 h. The resulting light yellow mixture was cooled to room temperature and concentrated in vacuo to afford 180 mg of a cream colored solid. This residue was chromatographed over 20 g of flash silica gel (eluted with EtOAc) to yield 27 mg (20%) of carbamate **34** as a white solid and 87 mg (65%) of carbamate **33** as a white solid. Properties of **34**: mp 194−196.5 °C; IR (KBr) 3371, 1790, 1682, 1568 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (ddd, J = 13.0, 11.6, 11.6, 1H), 2.22 (dt, J = 13.5, 8.2, 1H), 2.44 (ddd, J = 13.0, 5.4, 4.0, 1H), 2.63 (dt, J = 13.5, 5.1, 4.0, 1H), 3.58 (dddd, J = 11.8, 8.5, 5.4, 4.0, 1H), 3.98 (s, 3H), 3.99 (s, 3H), 4.14 (ddd, J = 11.8, 9.2, 4.0, 1H), 5.01 (d, J = 9.2, 1H), 5.19−5.26 (m, 2H), 5.32 (br s, 1H), 5.72 (m, 1H), 6.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.7 (t), 40.1 (t), 50.7 (d), 54.1 (q), 54.9 (q), 58.4 (d), 78.6 (d), 97.7 (d), 120.3 (t), 131.9 (d), 148.7 (s), 150.4 (s), 165.4 (s), 165.4 (s), 172.5 (s); exact mass calcd for $C_{15}H_{18}O_5N_4$ m/z 334.1277, found m/z 334.1268. Properties of **33**: mp 140−142 °C; IR (KBr) 3368, 1790, 1682, 1568 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (ddd, J = 15.0, 12.1, 12.1, 1H), 2.04 (dt, J = 14.0, 8.2, 1H), 2.17 (ddd, J = 15.0, 5.1, 3.9, 1H), 2.30 (dt, J = 14.0, 5.3, 1H), 3.50 (dddd, J = 15.0, 8.2, 5.4, 3.9, 1H), 3.98 (s, 3H), 4.01 (s, 3H), 4.63 (ddd, J = 11.9, 8.8, 3.5, 1H), 5.12−5.22 (m, 3H), 5.42 (d, J = 8.8 Hz, 1H), 5.65 (m, 1H), 6.50 (s, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 29.8 (t), 40.0 (t), 50.4 (d), 54.2 (q), 55.0 (q), 56.0 (d), 75.2 (d), 99.0 (d), 120.3 (t), 131.9 (d), 149.0 (s), 150.9 (s), 164.5 (s), 165.2 (s), 172.6 (s); exact mass calcd for $C_{15}H_{18}O_5N_4$ m/z 334.1277, found m/z 334.1270.

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Supporting Information Available: Experimental procedures not provided in the Experimental Section, ^{1}H and ^{13}C NMR spectra for most compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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