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Supplementary Material Available: Problem specification with constraints that were used in the IGOR2 exploration of hydroboration and the complete set of reactions generated (35 pages). Ordering information is given on any current masthead page.

A General Synthetic Strategy toward Aminocyclopentitol Glycosidase Inhibitors. Application of Palladium Catalysis to the Synthesis of Allosamizoline and Mannostatin A

Barry M. Trost* and David L. Van Vranken

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94302.
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Abstract: A general strategy for the synthesis of aminocyclopentitol glycosidase inhibitors has been applied to the synthesis of allosamizoline and mannostatin A. These cyclic pseudosugars are members of a growing family of highly potent and selective glycosidase inhibitors. A palladium-catalyzed ionization/cyclization reaction for preparing oxazolidinones from *meso*-alkenediols forms the cornerstone for this approach toward the synthesis of highly functionalized cyclopentane rings.

Glycosidase inhibitors are aiding in developing an understanding of glycoprotein processing in which glycoconjugates present on the surface of mammalian cells constitute functional domains for carbohydrate protein interactions involved in recognition, adhesion, transport, etc.[1] Possible applications in immunology, diabetes, virology, and cancer stimulates general interest into structures with specific biological function.[2] Inhibitors of glycoside-processing enzymes have traditionally been molecules which share direct structural homology with the natural enzymatic substrate—often polyhydroxylated six-membered heterocyclic rings.[3-5] The reported isolation of allosamidin in 1986[6] opened the way to recognition that aminohydroxy-substituted five-membered carbocyclic rings can have powerful and specific inhibitory activity against glycosidases which normally accept six-membered pyranoside substrates. Since this initial report, four other such aminohydroxycyclopentanes have been reported—the mannostatins,[7] the trehalase inhibitors trehalostatin[8] and trehazolin,[9] and Merrell Dow's cyclopentylamine[10] (Figure 1).[11] The intensitive synthetic investigations of aminohydroxycyclopentanes are a result not just of the challenging density and juxtaposition of functionality but of their biological activity as glycosidase inhibitors. The compounds in Figure 1 are the most potent and specific known competitive inhibitors for their respective enzymes. The superiority of five-membered ring inhibitors over six-membered ring analogs (which more closely resemble the enzymatic substrates) may be related to the energetic costs associated with distortion of the natural chair conformation of six-membered rings to match the enzymatic transition state. The potential therapeutic applications of this newly emerging class of glycosidase inhibitors demands a general and flexible approach to their synthesis.

A Unified Approach to Aminocyclopentitols Involving Palladium Catalysis

Pd(0) catalyzed reactions provide selective entry to amino alcohols of varying regio- and stereoselectivity. The *cis*-vicinal amino alcohols may derive either from epoxides in a single step as in eq 1, path a[12] or their synthetic equivalents such as 2-alkene-1,4-diols as illustrated in the one-pot sequence of eq 1, path b,[12,13] wherein the bisurethane is generated in situ. In both cases, the regio- and diastereoselectivity is assured by covalent tethering of the nitrogen nucleophile to the substrate. An asymmetric synthesis of the amino alcohol via the vinyl epoxide requires an asymmetric synthesis of the latter. On the other hand, the use of *meso*-2-alkene-1,4-diols permits asymmetric induction by differentiation of the enantiotopic leaving groups.

Two approaches for dissymmetrization of the *meso*-diols are feasible. Enzymatic hydrolysis of a diester[14] or transacylation[15] (eq 2) may provide the enantiomeric monoesters which then may

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(9) Ando, O.; Satake, H.; Itoi, K.; Sato, A.; Nakajima, M.; Takahashi, S.; Haruyama, H.; Ohkuma, Y.; Kinoshita, T.; Enokita, R. *J. Antibiot.* **1991**, *44*, 1165.

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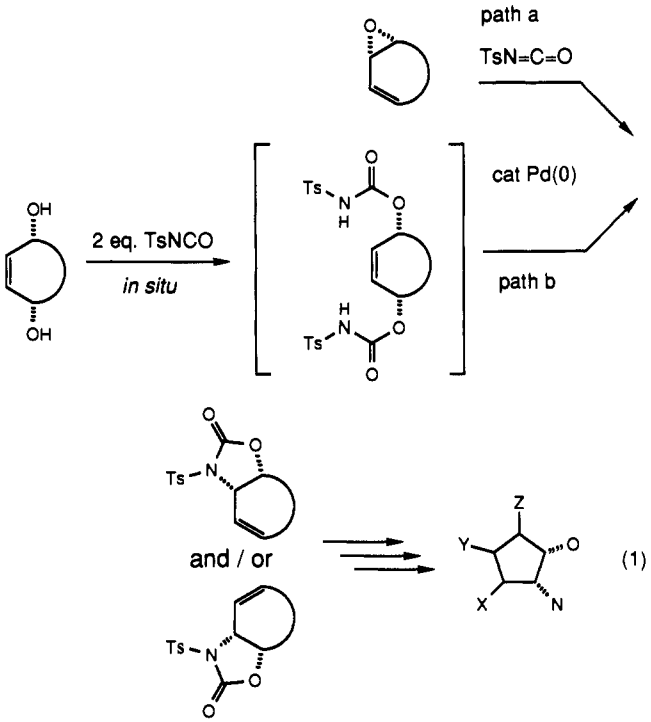
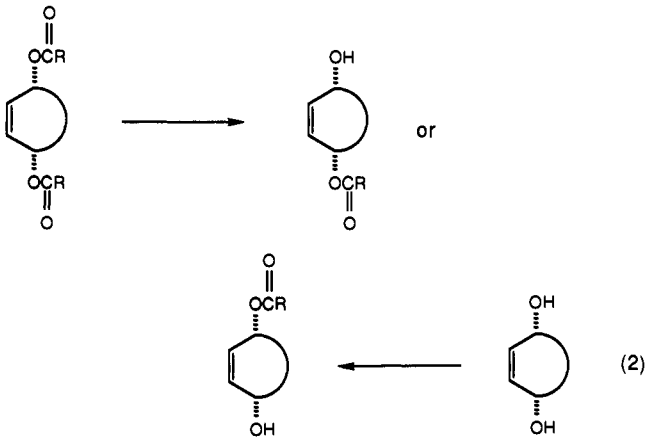


(1)

be entered into the synthetic sequence. With one notable exception, the achievement of high ee's frequently requires either the sacrifice of conversion or of overreaction with a corresponding decrease in yield.[14-16] Furthermore, an enzyme that functions well in one system does not routinely extend to different substrates.[16]



(2)

The greater strategic efficiency of asymmetric transition metal-catalyzed reactions over the more commonly employed protocol of enzymatic hydrolysis followed by functional group interconversion stems from the ability of transition metals to orchestrate complex bond reorganization (e.g., bond breakage and/or formation) directly on the synthetic pathway concomitant with the induction of asymmetry. While enantioselective transition metal-catalyzed reactions involving hydrogen[17] or oxygen atom transfer[18] are abundant, useful asymmetric transformations involving other transition metal-catalyzed processes are less common. Particular difficulties for Pd-catalyzed allylic alkylations as illustrated in eq 1 stem from the fact that bond breaking and making occur on the face of the substrate distal to Pd and therefore remote from the chiral environment provided by the asymmetric ligands.[19,20] Nevertheless, we have found that significant levels of enantioselectivity may be achieved in this ionization process and have developed a class of easily prepared chiral phosphine ligands which allow the prediction of the absolute stereochemistry of the oxazolidinone product based on the stereochemistry of the ligand precursors (see Figure 2).[21] Starting from meso substrates, this single palladium-catalyzed reaction thus determines the chirality of the final synthetic target.

The feasibility of regio-, diastereo-, and enantioselective syntheses of vinyloxazolidin-2-ones via organopalladium reactions provides the opportunity for a general and flexible strategy for the synthesis of five-membered ring aminocyclitol glycosidase inhibitors from a simple and inexpensive building block, cyclopentadiene. To realize this potential, efforts directed toward the syntheses of allosamidin and mannostatin were initiated.

Synthesis of (±)-Allosamizoline

In 1986 Suzuki and co-workers in Japan reported the isolation of a pseudotrisaccharide from the mycelial extract of *Streptomyces* sp.[6] This compound, allosamidin and its congeners (**1**) were shown to possess specific inhibitory activity against chitinases from various sources. The unique pseudotrisaccharide structure of this molecule is composed of two β-1,4-linked *N*-acetyl-D-allosamine residues connected to a cyclopentanoxazoline core which is almost invariant among the various active congeners of allosamidin. The cyclopentanoxazoline portion of this molecule, allosamizoline, **2a**, bears structural similarity to the recently reported α,α-trehalase inhibitors trehalostatin and trehazolin. Subsequently, new analogues have been discovered wherein the *N*-acetylallosamine units are modified but retaining the allosamizoline unit except for one in which the dimethylamino group is demethylated. The original structure reported for allosamizoline based on NMR spectroscopy assigned the vicinal hydroxy groups to have the cis-3*S*,4*R* configuration **5a**. Subsequent 2D NMR investigations led to a structural revision to the trans isomer **2a**. Two different stereoisomeric structures have been assigned to trehalostatin/trehazolin.[8] The uncertainties of assignment of the stereochemistry of five-membered ring systems by NMR methods requires more definitive evidence which may be provided by synthesis.

To provide confirmation of the revised assignment and initiate a synthetic strategy to this interesting class of potent and specific chitinase inhibitors, we sought to apply the palladium-catalyzed methodology developed for synthesis of oxazolidinones to allosamizoline **2a** as well as the gulo, galacto, and allo analogs **3a–5a**, respectively.[23] Our retrosynthetic analysis derives both *cis*- and both *trans*-dihydroxy isomers from a common intermediate, the corresponding olefin (Scheme I). The oxazoline results from the oxazolidinone which in turn, derives directly from the palladium-catalyzed reaction of a known cyclopentenediol[24] derived in one operation from cyclopentadiene.[25,26]

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(23) The nomenclature is somewhat misleading—allosamizoline **1a** (originally thought to have pseudoallosamine stereochemistry as in **4a**) would be more appropriately named glucosamizoline to reflect its stereochemical homology with glucosamine.

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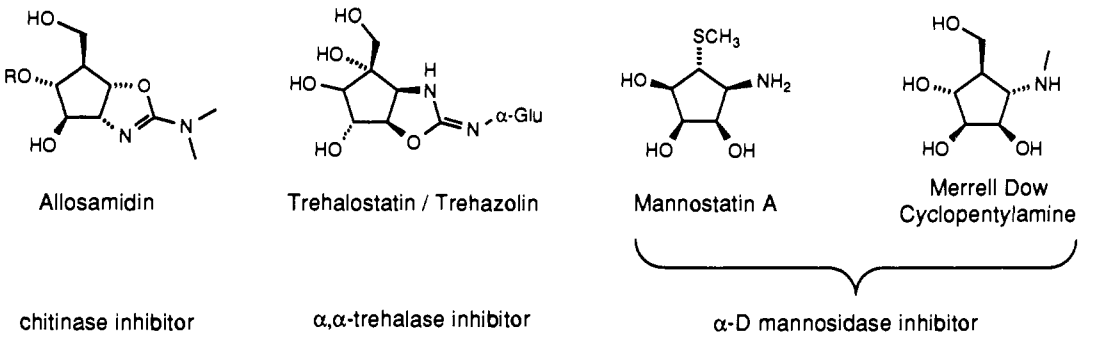


Figure 1. Five-membered ring aminocyclitol glycosidase inhibitors.

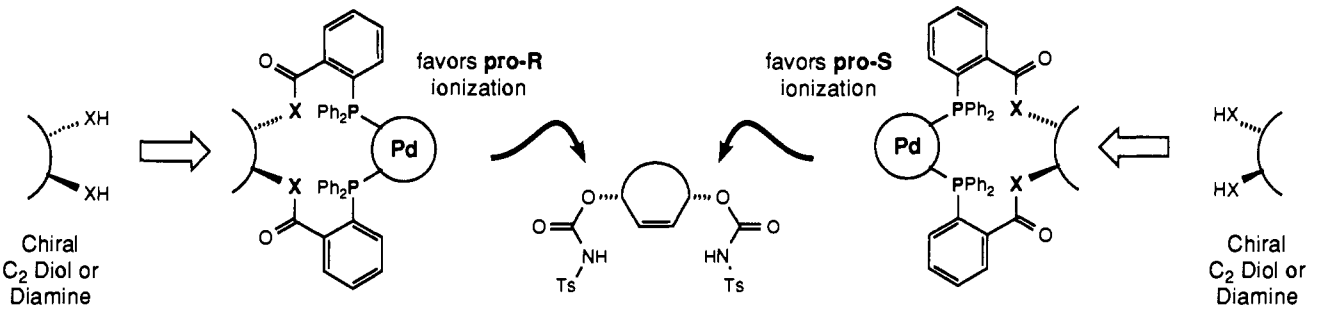
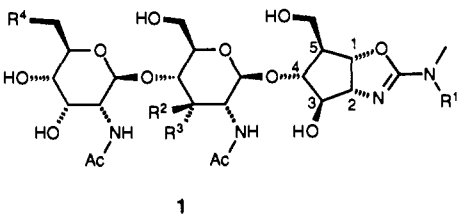


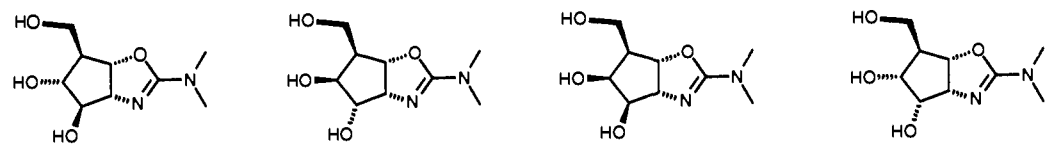
Figure 2. Correlation of the enantiotopicity of the ionization step with the stereochemistry of the chiral linker in the phosphine ligand.

Chart I



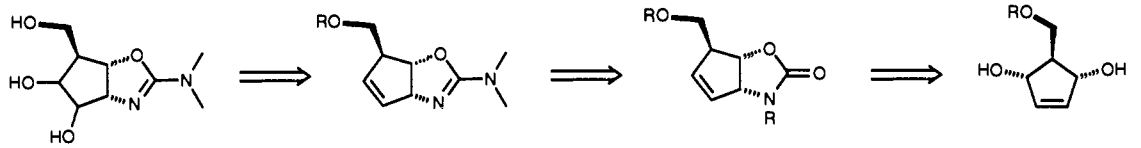
1

a) $R^1 = CH_3$, $R^2 = R^4 = H$, $R^3 = OH$ allosamidin
b) $R^1 = R^2 = R^4 = H$, $R^3 = OH$
c) $R^1 = R^2 = H$, $R^3 = OH$, $R^4 = CH^3$
d) $R^1 = R^4 = CH_3$, $R^2 = H$, $R^3 = OH$
e) $R^1 = R^4 = CH_3$, $R^2 = OH$, $R^3 = H$
f) $R^1 = R^3 = H$, $R^2 = OH$, $R^4 = CH_3$



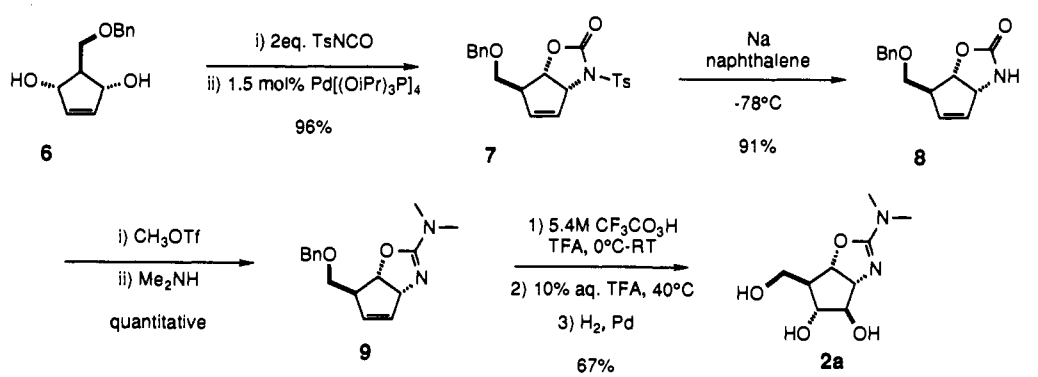
2a **3a** **4a** **5a**

Scheme I



2a - 5a

Scheme II



6 **7** **8** **9** **2a**

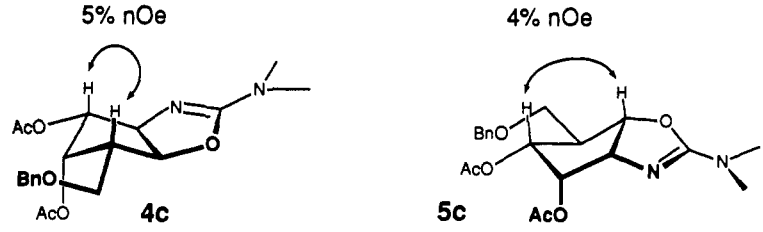
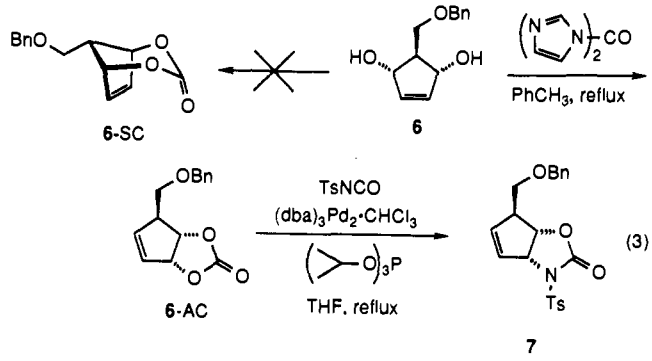


Figure 3. Assignment of stereochemistry of galacto and allo isomers by NOE.

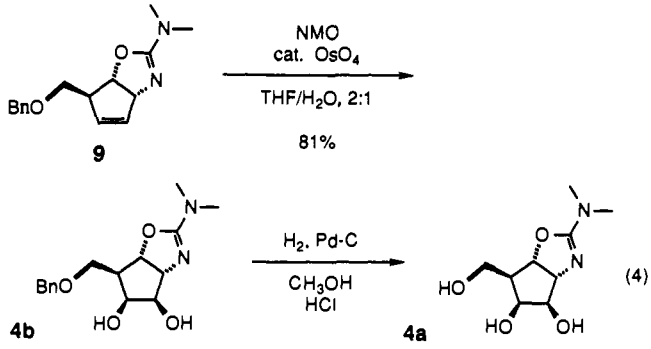
Initial efforts focussed on the cyclic carbonate **6-SC** of the known diol **6** but all attempts at its synthesis lead only to the rearranged cyclic carbonate **6-AC**. Exposure of a 1:1.2 mixture of carbonate **6-AC** and *p*-toluenesulfonylisocyanate to a Pd(0) catalyst produces complete conversion to a single product easily identified as the desired oxazolidin-2-one **7** (eq 3). The major



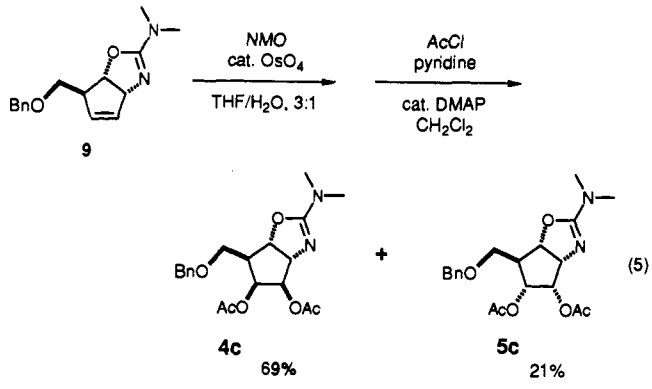
drawback of this strategy lies in the asymmetric nature of the intermediate **6-AC** which precludes a simple strategy for asymmetric induction. Nevertheless, the success of the cyclic carbonate as a precursor for oxazolidin-2-one formation makes it an attractive surrogate of an epoxide in cases where diols are more easily accessible as is the case here where attempts to generate an epoxide corresponding to **6-AC** failed.

The preferred synthetic route (see Scheme II) begins with application of the ionization/cyclization protocol shown in eq 1 to the known diol **6** to afford oxazolidinone **7** in 96% yield. Reductive desulfonylation with sodium naphthalenide gives the parent oxazolidinone **8** in 91% yield. O-Methylation with freshly distilled methyl triflate to give the cyclic imidate followed directly by treatment with anhydrous dimethylamine provides the heterocyclic oxazoline **9** in quantitative yield. Dihydroxylation of the olefin in **9** provides access to the analogs **2a–5a**, respectively.

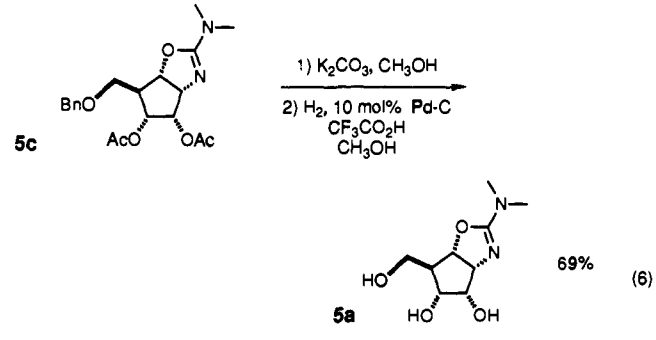
cis-Dihydroxylation is effected with *N*-methylmorpholine-*N*-oxide (NMO) and catalytic osmium tetroxide in 60% aqueous THF to give the galacto isomer **4b** as the major product in 81% yield (eq 4). The minor isomer could not be easily separated in pure form by silica gel chromatography. Hydrogenolytic debenzylation of the hydrochloride salt with 10 mol% palladium on carbon gives the free triol **4a**.



The minor allo isomer **5b** is more easily isolated by peracylation of the mixture of diols. Repetition of the hydroxylation under slightly modified reaction conditions followed by acetylation gives the easily separated diacetates **4c** and **5c** in 69% and 21% yields, respectively (eq 5). The change in diastereofacial selectivity from eq 3 may reflect the change in water content in the two runs. Our initial assignment of stereochemistry was based on the prediction



that the major product would result from addition of osmium tetroxide to the convex face of the bicyclo[3.3.0] ring system. The stereochemistry of these two isomers is confirmed by the cross-ring NOEs observed by NMR spectroscopy (Figure 3). Irradiation of proton H(5) in **4c** leads to a 5% NOE in the proton at the 3 position. In **5c**, irradiation of proton H(2) leads to a 4% NOE in the proton at the 4 position. The free triol **5a** is readily obtained by saponification of the acetate groups of **5c** with methanolic potassium carbonate and palladium-catalyzed hydrogenolysis of the trifluoroacetate salt of the resulting benzyl ether in 69% yield (eq 6).



Our attempts to find a protocol which would favor the allo isomer **5b** using Woodward–Prevost and related oxidations were foiled by the poor nucleophilicity of the double bond of **9** under acidic conditions. An alternative strategy envisions inverting the relative steric hindrance of the two diastereotopic faces. To disfavor attack from the convex face of the [3.3.0] ring system, the osmium-catalyzed oxidation was performed on the cyclodextrin complex. The benzyl group should sit in the cavity of the cyclodextrin thereby introducing the latter as a shield for the convex face (see Figure 4). After warming an aqueous mixture of benzyl ether **9** and β-cyclodextrin (to form the more sterically demanding benzyl ether–cyclodextrin complex) the solution is treated with NMO and catalytic osmium tetroxide to give a mixture of diols

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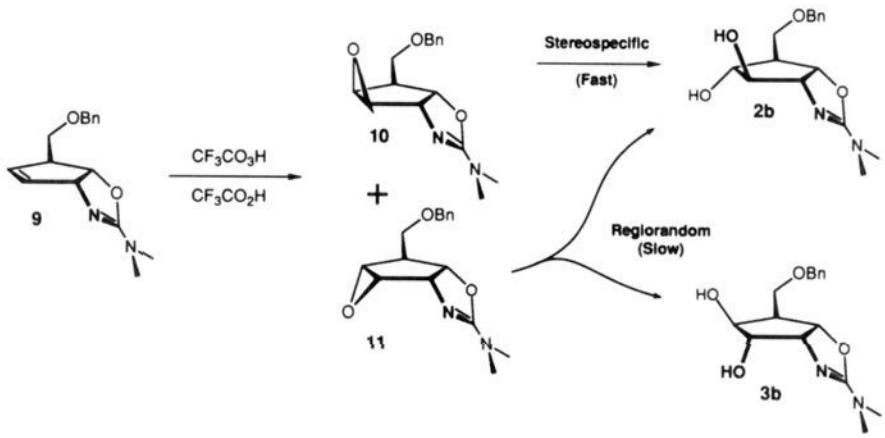
Scheme III



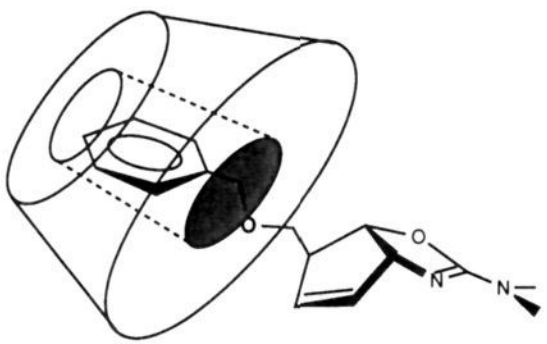
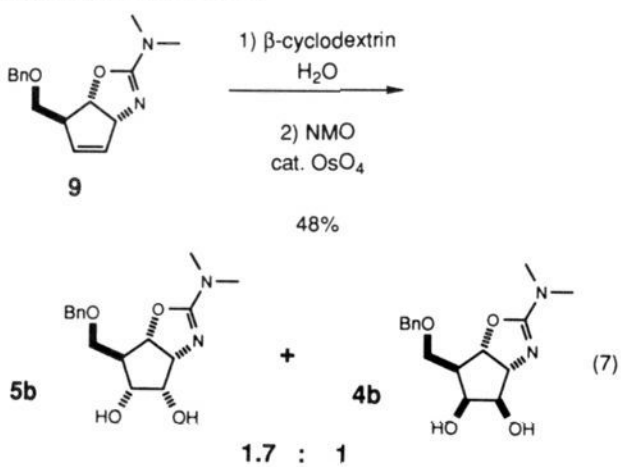


Figure 4. Cyclodextrin as a steric shield.

in 48% yield (eq 7). The allo isomer **5b** predominated (^{1}H NMR) over the galacto isomer **4b**.



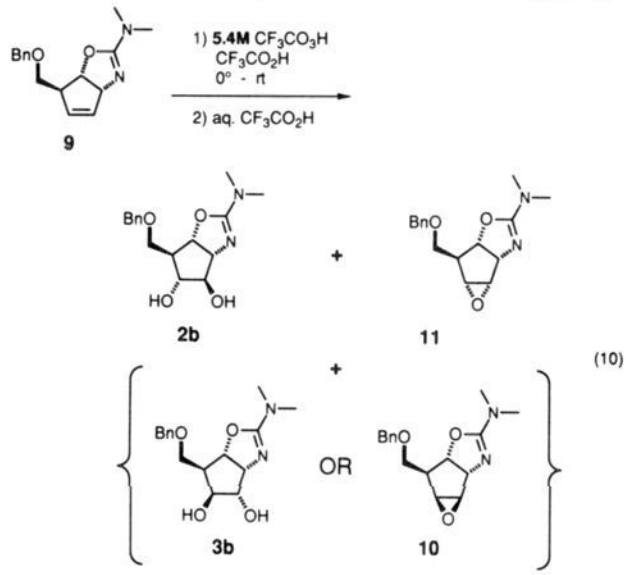
(7)

For the synthesis of allosamizoline, we sought to employ a sequence of epoxidation/hydrolysis to provide the desired *trans*-3,4-diol, **2b**. Alkene **9** is a very unreactive substrate toward the typical electrophilic epoxidizing reagents. As previously observed, reactions of this substrate which are performed under acidic conditions lead to protonation of the allylic nitrogen functionality; the positive charge inductively deactivates the olefin. After running the gamut of available epoxidizing reagents (metal-catalyzed[27] and peracid[28]) it is found that epoxidation with excess (usually about 8 eq) trifluoroperacetic acid[29] in trifluoroacetic acid at 0 °C gives the best results.[30] The peracid solution may be generated with either 30% or 90% hydrogen peroxide (eqs 8 and 9). In each case, sufficient trifluoroacetic anhydride is added to react with all water and hydrogen peroxide at 0 °C. The more concentrated

$$30\%\ H_2O_2 + (CF_3CO)_2O \rightarrow 1.2\ M\ CF_3CO_3H \text{ in } CF_3COOH \quad (8)$$

$$90\%\ H_2O_2 + (CF_3CO)_2O \rightarrow 5.4\ M\ CF_3CO_3H \text{ in } CF_3COOH \quad (9)$$

trifluoroperacetic acid solution MUST BE USED AT/OR BELOW 0 °C. **[Caution: Such mixtures may be explosive.]**[31] When a chloroform solution of **9** is treated with the 5.4 M peracid solution at 0 °C followed by hydrolysis, a mixture of **2b**, **11**, and either **3b** or **10** is obtained (eq 10). If the hydrolysis conditions used for the mixture of epoxides **10** and **11** are forcing enough



(10)

to produce **3b**, epoxide **10** will not survive; conversely, if conditions are mild enough to isolate epoxide **10**, **3b** is generally not formed (see Scheme III). Partial debenzylation is observed when 5.4 M trifluoroperacetic acid is used, so the procedure is best followed directly by palladium-catalyzed hydrogenolysis of the benzyl ether/alcohol mixture.

The structures of the two epoxides **10** and **11** are assigned by correlating the observed coupling of H-5 (next to the hydroxymethyl group) in the ^{1}H NMR spectra of each with the dihedral

(27) (a) Gao, Y.; Hansen, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Jorgenson, K. A. *Chem. Rev.* **1987**, *109*, 5765.

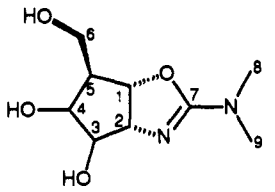
(28) (a) Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015. (b) Rastetter, W. H.; Richard, T. J.; Lewis, M. D.; Lewis, M. D. *J. Org. Chem.* **1978**, *43*, 3163.

(29) Fieser, L. F.; Fieser, M. L. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1987; Vol. 1, p 821.

(30) For general reviews, see: (a) Rao, A. S. *Tetrahedron* **1983**, *39*, 2323–2367. (b) Gorzynski-Smith, J. *Synthesis* **1984**, 629.

(31) We experienced a small explosion when **neat** alkene was treated with concentrated peroxytrifluoroacetic acid at room temperature.

Table I. ^1H NMR and ^{13}C NMR Shifts for Allosamizoline and Its 3,4-Epimers in D_2O[d]



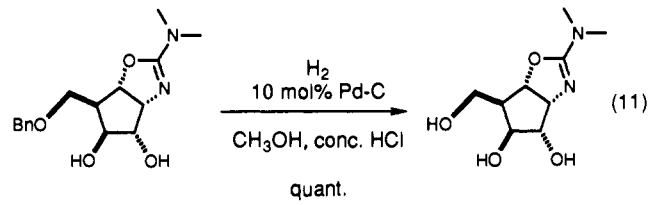
pos	**2a** (HCl salt) natural[a,b] ^1H[b]	^{13}C	**2a** (HCl salt) synthetic ^1H[b]	^{13}C	**2a** (free base)[c] ^1H[b]	^{13}C	**5a** (CF_3CO_2H salt)[c] ^1H[b]	^{13}C	**4a** (HCl salt)[c] ^1H[b]	^{13}C	**3a** (free base)[c] ^1H[b]	^{13}C
1	5.37 (5.34)	87.2	5.35	(87.3) 89.6	4.80	86.7	5.27	91.5	5.36	92.0	4.85	89.1
2	4.34 (4.31)	64.2	4.32	(64.2) 66.5	3.98	73.4	4.54	62.8	4.45	67.6	4.47	71.1
3	4.14 (4.06)	82.2	4.06	(82.3) 84.6	3.75	85.1	4.68	75.4	4.22	81.7	4.03	79.1
4	3.83 (3.81)	75.4	3.82	(75.4) 77.7	3.64	77.3	3.98	74.7	4.29	75.4	4.16	78.9
5	2.43 (2.4)	51.9	2.4	(51.8) 54.1	2.12	54.0	2.55	53.7	2.54	52.3	2.41	52.4
6a	3.72 (3.88)	59.9	3.72	(59.9) 62.2	3.70	63.0	3.64	62.2	3.84	61.4	3.73	61.8
6b	3.92 (3.88)	59.9	3.88		3.87	63.0	3.83	62.2	3.94	61.4	3.87	61.8
7		161.2		(161.5) 163.8		166.3		163.9		163.4		167.2
8a	3.08 (3.07)	37.9	3.07	(37.8) 40.1	2.89	39.8	3.07	39.9	3.07	39.9	2.90	40.0
8b	3.11 (3.09)	38.1	3.09	(38.1) 40.4	2.89	39.8	3.08	40.2	3.08	40.2	2.90	40.0

[a] From ref 6. [b] Values in parentheses were obtained in our laboratories from an authentic sample provided by A. Suzuki. [c] Values in parentheses are corrected by δ2.3 for differences in the reference between our spectrum and that reported in the literature.

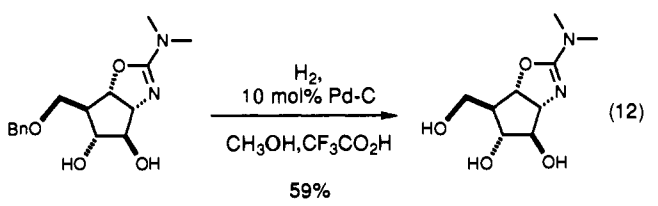
angles derived from MM2 minimization of the corresponding O-debenzylated structures. The dihedral angles H(5)–C–CH (ring) in debenzylated **10** are calculated to be 140.7° and 50.7° which should give rise to couplings of about 3–5 and 1–3 Hz, respectively. In contrast, the corresponding dihedral angles for O-debenzylated **11** are calculated to be 74.5° and 97.6° from which couplings of about 0 Hz are expected. In excellent accord with these results, the absorption for H-5 in the NMR spectrum of O-debenzylated **10** is found as a tdd at δ 2.50 (J = 7.5, 3.3, 1.7 Hz, D_2O); whereas, the corresponding absorption in the isomeric epoxide appears as a triplet at δ 2.56 (J = 5.6 Hz, D_2O) showing coupling only to the methylene group of the hydroxymethyl side chain.

When a chloroform solution of alkene **9** is reacted with 1.2 M peroxytrifluoroacetic acid solution at 0 °C, a mixture of benzylallosamizoline **2b** and the diastereomeric epoxides, **10** and **11** (no debenzylation), is obtained. Under the conditions of the epoxidation, partial solvolysis of the epoxide **10** to benzylallosamizoline **2b** occurs. Following the epoxidation with an acidic hydrolysis (10% aqueous trifluoroacetic acid, 40 °C) converts the remainder of **10** to benzylallosamizoline **2b** (Scheme IV). Epoxide **11** may be separated and hydrolyzed (50% aqueous trifluoroacetic acid, 65 °C) to provide more of **2b** along with **3b**.

The allo isomer **3b** was debenzylated in quantitative yield (eq 11). Debenzylation of the trifluoroacetate salt of benzylallosamizoline formed allosamizoline in 59% yield (eq 12). Alternatively, the crude hydrolysis mixture may be debenzylated and the isomeric *trans*-diol **3a** separated from allosamizoline (**2a**).

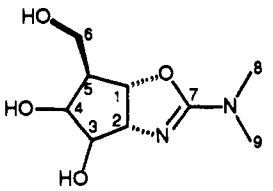


3b **3a** (11)



2b **2a** (12)

Table II. ^1H Coupling Constants for Allosamizoline and Its 3,4-Epimers



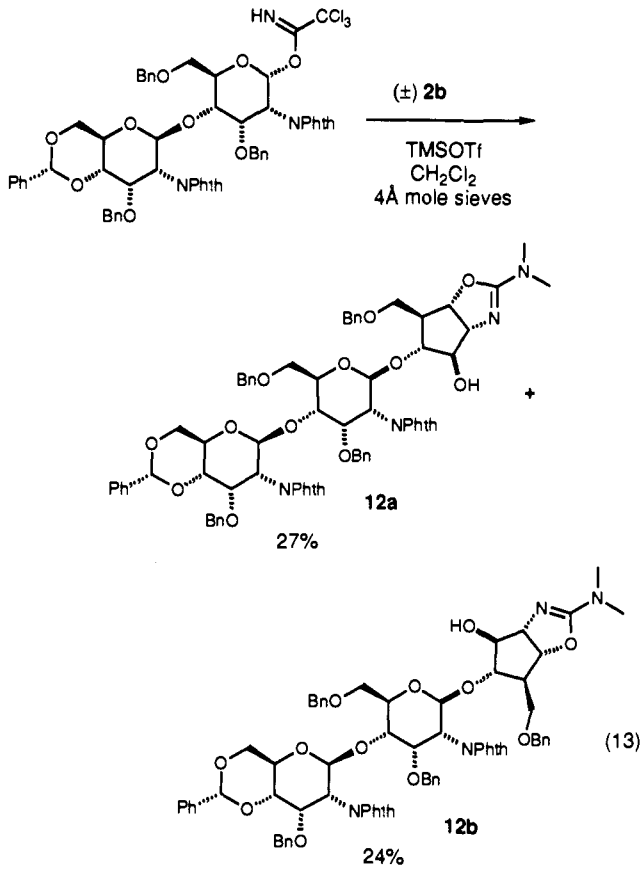
	Natural[a] **2a**·HCl	synthetic **2a**·HCl	**2a** free base	**5a** CF_3CO_2H	**4a**	**3a** free base
J1,2	9 (9.1) Hz	9.0	9.2	8.2	9.2	8.4
J1,5	5 (5.4)	5.2	6.1	3.4	6.4	4.0
J3,4	4 (4.9)	5.0	5.4	5.2	5.5	5.7
J4,5	8 (8.6)	8.5	9.9	7.3	5.5	5.5
J5,6a	7 (7.0)	7.1	7.3	7.1	7.6	7.9
J5,6b	5 (4.5)	4.6	4.3	4.8	7.0	6.7
J6a,6b	12 (11.6)	11.6	11.5	11.6	11.3	11.2

[a] From ref 6. Values in parentheses were obtained in our laboratories from an authentic sample kindly provided by A. Suzuki.

Synthetically, the protocol which best affords benzylallosamizoline, **2b**, is (1) epoxidation with 1.2 M peroxytrifluoroacetic acid at 0 °C (9 h), (2) acidic hydrolysis, (3) separate benzylallosamizoline **2b** from epoxide **11**, and (4) hydrolyze remaining epoxide **11**. The combined yield of benzylallosamizoline **2b** from this procedure is 63% (see Scheme V). The best synthetic protocol which produces allosamizoline (**2a**) in 67% yield involves (1) epoxidation with 5.4 M peroxytrifluoroacetic acid 0 °C to room temperature, (2) acidic hydrolysis, and (3) debenzylation (see Scheme V). Tables I and II show a comparison of the NMR spectral properties of all four diol diastereomers, related to and including allosamizoline.

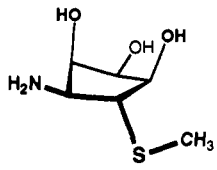
6-*O*-Benzylallosamizoline **2b** is an important intermediate for synthetic approaches toward the active allosamidins and has been used in both published syntheses.[26a,32] In a collaborative effort with Vasella and Maloisel, the racemate undergoes chemoselective glycosylation at the desired 4-0 position with a suitable disaccharide using the trichloroacetamidate to give the protected pseudotrisaccharides **12a** and **12b** (eq 13). Deprotection of **12a** proceeds in 64% yield to afford allosamidin.

(32) Maloisel, J.-L.; Vasella, A.; Trost, B. M.; Van Vranken, D. L. *J. Chem. Soc., Chem. Commun.* **1991**, 1099.

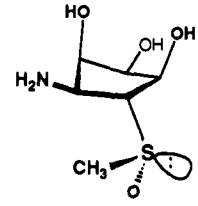


Synthesis of (±)-Mannostatin A

In 1989 Aoyagi and co-workers reported the isolation of the newest class of mannosidase inhibitors from the microorganism *Streptoverticillum verticillus*—the mannostatins.[33] The mannostatins are highly specific competitive inhibitors of α-D-mannosidase (K_i 4.8 × 10^{-8} M against jackbean α-D-mannosidase) and have been shown to be inhibitors of glycoprotein processing.[34] At the inception of this project, the mannostatins were the only known carbocyclic mannosidase inhibitors—subsequent to the initial report of the mannostatins, workers at Merrell-Dow reported a rationally designed potent inhibitor of mannosidases which was also based on an aminocyclopentitol framework.[35] Mannostatin A **13** and mannostatin B **14** differ only by the type of sulfur substituent: mannostatin A contains a thiomethyl group,



Mannostatin A, **13**



Mannostatin B, **14**

while mannostatin B contains a stereogenic methylsulfinyl group with the *R* configuration.

We recognized that the development of an efficient synthesis would require introduction of the sensitive sulfur substituent after any necessary oxidation chemistry. Our retrosynthetic analysis

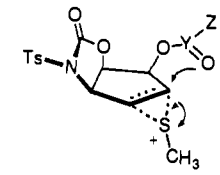
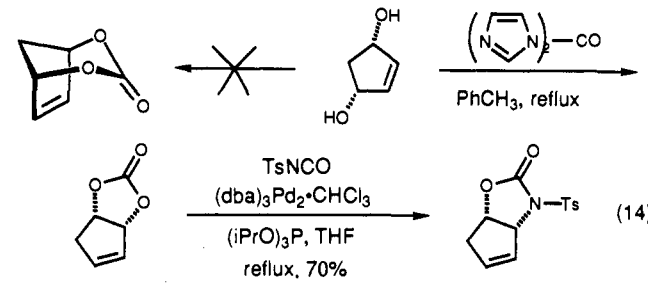


Figure 5. A directed hydroxysulfenylation strategy.

derived the vicinal hydroxysulfur functionality in mannostatin A from regioselective opening of the corresponding epoxide (see Scheme VI). The olefinic precursor to this epoxide **15** contains a hydroxyl group which could be introduced via allylic oxidation of the key oxazolidinone **17**. It now becomes evident that such an oxazolidine may derive by several routes from the well-known cyclopent-2-ene-1,4-diol, available in one step from cyclopentadiene, via our palladium based methodology.[36]

As in our previous synthesis, generation of a cyclic carbonate from the diol leads only to the asymmetrical carbonate rather than the symmetrical one (eq 14). While oxazolidin-2-one formation proceeds readily from the cyclic carbonate, the rendering of an



asymmetric synthesis by a simple asymmetric induction difficult via such an asymmetric intermediate led us to pursue an alternative route based on retaining a meso intermediate for the Pd(0) catalyzed step.

The synthesis begins with the palladium-catalyzed ionization/cyclization reaction by treatment of *meso*-cyclopent-2-ene-1,4-diol with 2 equiv of toluenesulfonyl isocyanate followed by 1.8 mol% tetrakis(triisopropyl phosphite)palladium to afford oxazolidinone **17** in 97% yield on a 13-g scale (Scheme VII). Oxidation with 5 equiv of selenium dioxide in refluxing diglyme at 170 °C affords the β-allylic alcohol **16b** sometimes admixed with ketone **18**. Addition of disodium acid phosphate helps minimize overoxidation. Best results derive from use of higher temperatures and shorter reaction times. To obtain good conversions, quartz sand must be added to maintain dispersion of this heterogeneous mixture. The crude mixture is directly subjected to the Dess-Martin periodinane buffered with sodium bicarbonate which proves to be an extremely mild and effective method for oxidizing the product mixture completely to enone[18] in 64% yield from alkene **17**. Manganese dioxide gives good yields (77%) of the desired ketone but requires 12.4 equiv of reagent and still returns starting material. On the other hand, chromium or ruthenium based reagents or catalysts and Moffatt-Swern type oxidations prove less satisfactory. The enone is reduced under Luche conditions at 0–5 °C to give a 7:1 mixture of α- and β-alcohols **16a** and **16b**, respectively. The desired α epimer **16a** was isolated in 81% yield. Good diastereoselectivity was also achieved with DIBAL-H (THF, CH_2Cl_2, −78 °C) and 9-BBN-H (THF, 0 °C) but in lower yields (55% and 47% yields, respectively). Our assignment of the stereochemistry was initially based on the assumption that selenium dioxide would add from the convex face of the bicyclo[3.3.0] ring system to give alcohol **16b** and that hydride reduction of the carbonyl group gives the opposite stereochemistry. The finding that the epimer **16a** undergoes facile

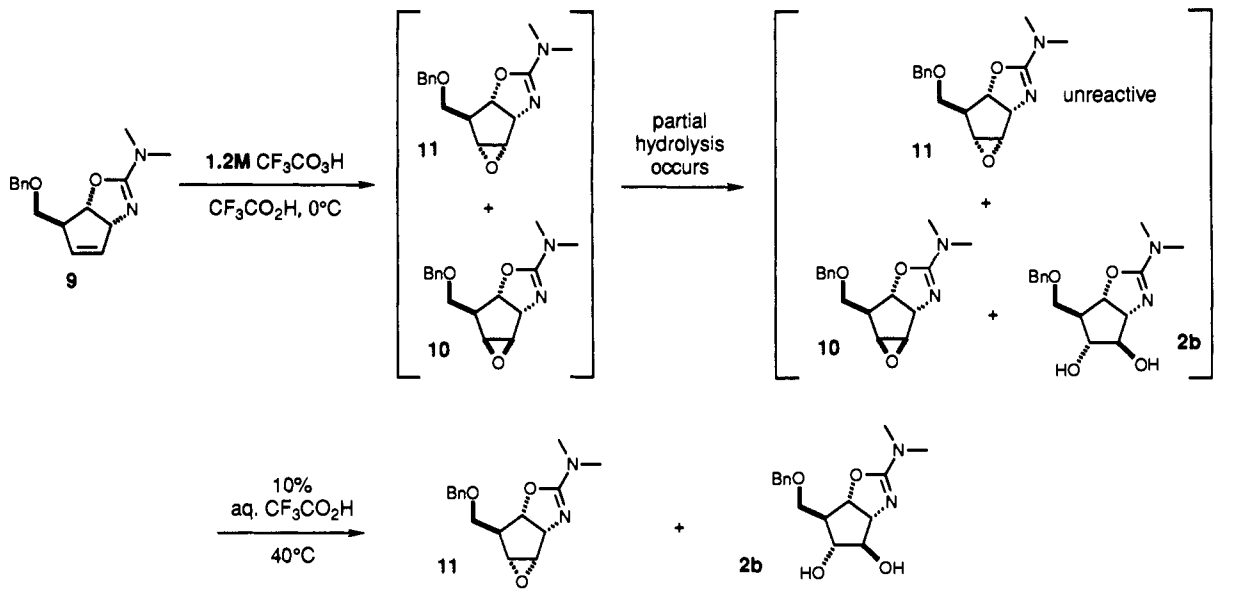
(33) (a) Aoyagi, T.; Yamamoto, T.; Morishima, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1989**, *42*, 883. (b) Morishima, H.; Kojiri, K.; Yamamoto, T.; Aoyagi, T.; Nakamura, H.; Iitaka, Y. *J. Antibiot.* **1989**, *42*, 1008.

(34) Tropea, J. E.; Kaushal, G. P.; Pastuszak, I.; Mitchell, M.; Aoyagi, T.; Molyneaux, R. J.; Elbein, A. D. *Biochemistry* **1990**, *29*, 10062.

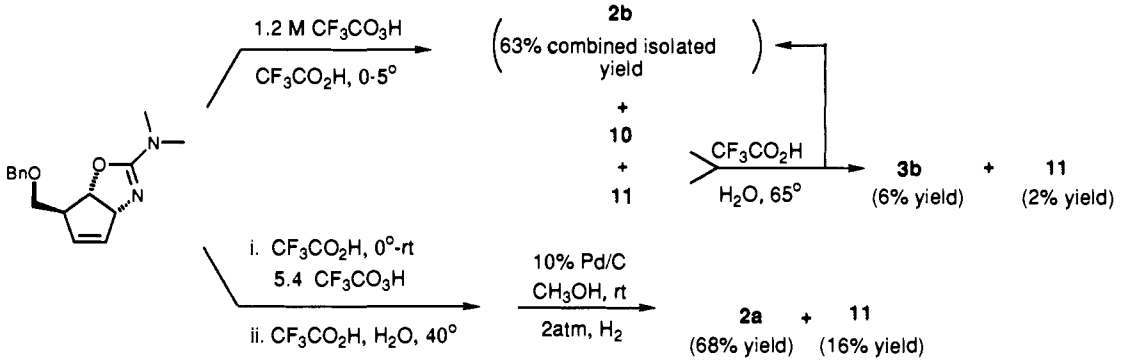
(35) Farr, R. A.; Peet, N. R.; Kang, M. S. *Tetrahedron Lett.* **1990**, *49*, 7109.

(36) For a preliminary report of a portion of this work, see: Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 6317. For other syntheses of mannostatin A: (a) Knapp, S.; Dhar, T. G. M. *J. Org. Chem.* **1991**, *56*, 4096. (b) Kimg, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089. (c) Ogawa, S.; Yuming, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 890.

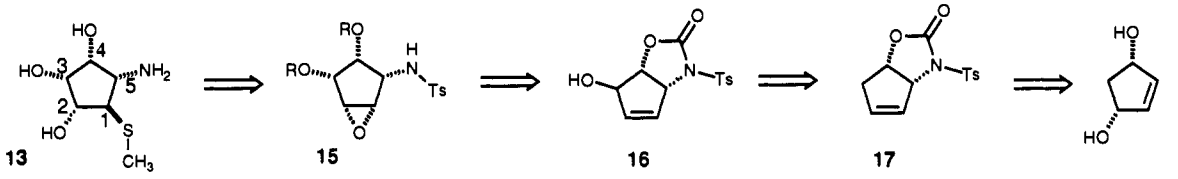
Scheme IV



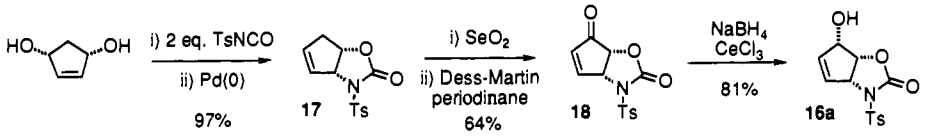
Scheme V. Synthetic Protocols for Allosamizoline and Its Monobenzyl Ether



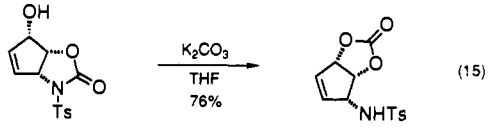
Scheme VI



Scheme VII



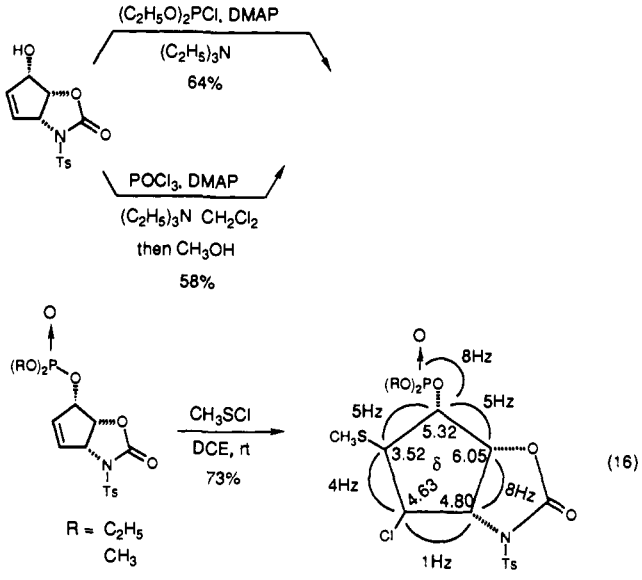
rearrangement under basic conditions (K_2CO_3, THF) to give a cyclic carbonate supports our stereochemical assignment (eq 15).



A desirable strategy for completion of the synthesis envisions a directed hydroxysulfenylation (Figure 5). Initial problems arose during derivatization of the secondary alcohol because of the ease of internal transacylation (eq 15). For example, attempts to form the diethyl phosphate using potassium carbonate as base only leads to cyclic carbonate. Catalysis of phosphorylation with a soluble base like DMAP allows generation of the desired phosphate (eq 16). The unreactivity of the double bond toward electrophiles requires the use of a reactive RS+ synthon. While DMTSF proves insufficient,[37] methylsulfenyl chloride[38] does react to give a single adduct in good yield. Detailed analysis of the NMR spectrum with spin decoupling reveals the assignments given in eq 16. Most importantly, the proton on the carbon bearing sulfur is clearly

(37) Trost, B. M.; Shibata, T. *J. Am. Chem. Soc.* **1982**, *104*, 3225. Trost, B. M.; Shibata, T.; Martin, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 3328. Trost, B. M.; Martin, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 4263.

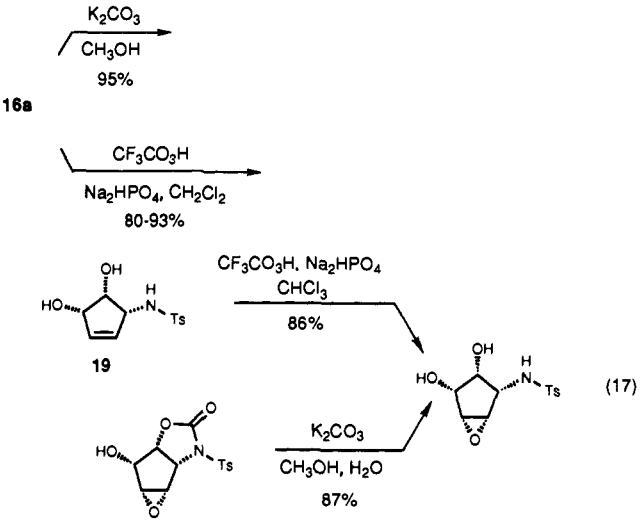
(38) Brintzinger, H.; Pfaunstiehl, K.; Koddebusch, H.; Kling, K. *Chem. Ber.* **1950**, *83*, 87. Müller, W. H.; Butler, P. E. *J. Am. Chem. Soc.* **1986**, *90*, 2075. Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208.



(16)

vicinal to the proton on carbon bearing phosphate. Thus, the regioselectivity is opposite that required for mannostatin but is interesting to generate analogues. Inaccuracies associated with assigning stereochemistry on the basis of NMR coupling constants combined with poor agreement of predicted coupling constants for the various diastereomers derived from molecular mechanics calculations preclude our assigning a stereochemistry to this adduct at this time.

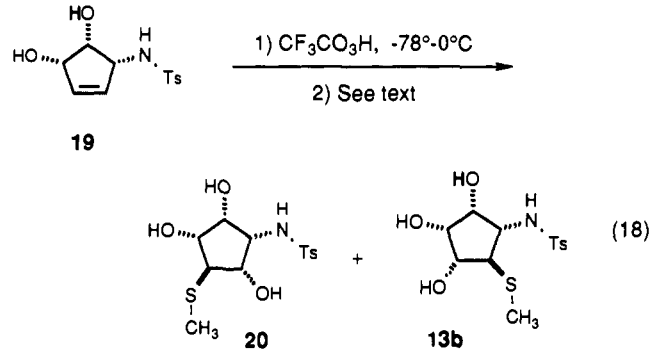
An alternative strategy emerges from the expectation of the ability to effect a diastereoselective epoxidation. Free diol **19** is prepared by hydrolysis of the carbamate of **16a** with methanolic potassium carbonate (eq 17). With three syn-directing groups, epoxidation with anhydrous peroxytrifluoroacetic acid buffered with disodium hydrogen phosphate (−78 °C to room temperature) proceeds with 100% diastereoselectivity to give the *syn*-epoxide (eq 17).[39] The same epoxide results by inverting the two steps,



(17)

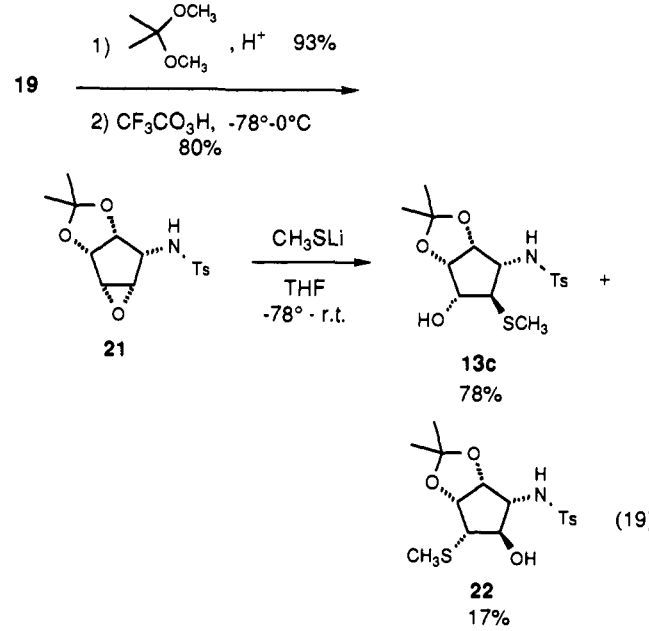
i.e., initial epoxidation followed by hydrolysis. Thus, an allylic alcohol seems sufficient to direct the diastereofacial selectivity even to the concave face of this bicyclic oxazolidin-2-one.

The regioselective epoxide ring opening proved to be the most difficult step of the sequence. Using lithium thiomethoxide the product mixture consistently favors not *N*-tosylmannostatin **13b** but product derived from regioisomeric ring opening **20**. After much searching we find that addition of excess titanium tetraisopropoxide could favor the desired isomer **13b** by 2:1 but the isolated yield is never over 25% (eq 18).



(18)

Conformational effects which favor trans diaxial ring opening are well established in the reactions of six-membered ring epoxides (Furst–Plattner rule[40]). The application of this concept to the conformationally more flexible five-membered ring system has not normally been considered because of the relatively low-energy differences of the various ring conformers. To influence the regioselectivity in this epoxide opening we seek to convert the substrate to a bicyclic ring system where steric and conformational effects might drive the selectivity. A bicyclo[3.3.0] ring system normally favors a butterfly (extended) conformation. Thus, we envision that a more pseudochairlike transition state would be favored over a more pseudoboatlike transition state which would also have the additional disadvantage of unfavorable interactions between the sulfonamido group and the incipient alkoxide (Figure 6).[41] To test this idea, conversion into a bicyclo[3.3.0] system by ketalization should be a simple protocol. Although ketalization of the *cis*-aminoalcohol moiety could compete with ketalization of the *cis*-diol, the latter should dominate thermodynamically. In the event, diol **19** is converted to the acetonide and epoxidized to give the epoxide **21** (eq 19). When treated with lithium thiomethoxide in THF (−78 °C to room temperature), the major product is the mannostatin isomer **13c** isolated in 78% yield along with the isomeric ring-opening product **22** (eq 19).[42]



(19)

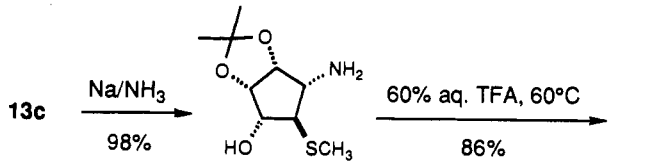
The regiochemistry of the major product **13c** derives from proton–proton decoupling in the NMR spectrum. The proton α to the sulfonamide group at δ 3.26 (ddd, J = 11.4, 9.7, 4.8 Hz) is coupled to the proton at δ 2.61 (dd, J = 11.4, 10.3 Hz) with a coupling constant of 11 Hz. Further, the proton α to the thiomethyl group couples to that α to the hydroxyl group at δ 3.56

(39) McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895.

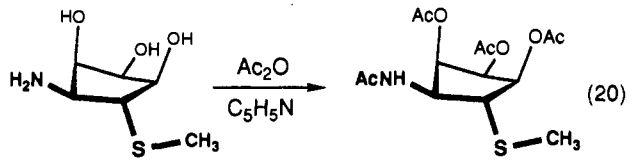
(40) Fürst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275. Smith, J. G. *Synthesis* **1984**, 629. Winterfeldt, E. *Stereoselektive Synthese, Prinzipien und Methoden*; F. Vieweg & Sohn: Braunschweig, 1988; pp 32–7.

(ddd, J = 10.2, 9.2, 5.4 Hz) with a coupling constant of 10 Hz.

Deprotection of **13c** is accomplished by reductive desulfonylation with sodium in ammonia followed by hydrolysis of the acetonide with 60% aqueous trifluoroacetic acid at 60 °C to give mannostatin A as the racemate (eq 20). Further characterization is provided by conversion to its tetraacetate (acetic anhydride, pyridine). Both mannostatin A and the tetraacetate give spectral data identical to that reported.[33] Attempts to form mannostatin B by oxidation of the N-tosyl derivative gave diastereomeric mixtures of sulfoxides and sulfone.



13d

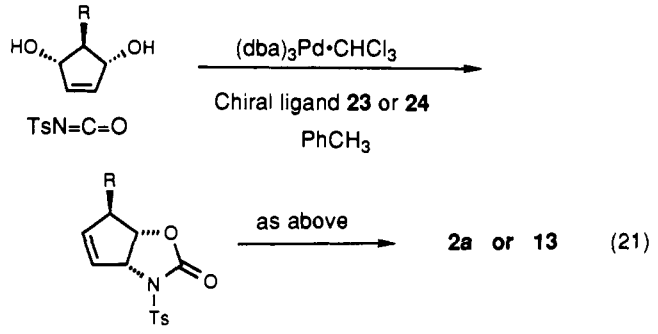


(20)

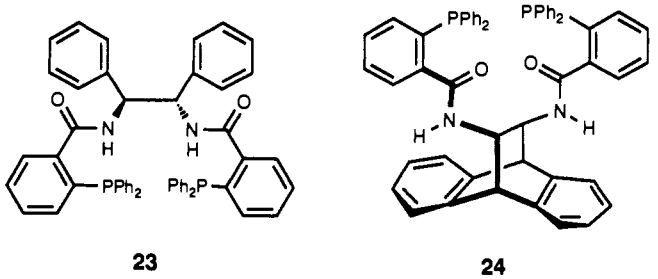
(±)-Mannostatin A, **13**

Conclusion

The completion of the syntheses of allosamizoline and mannostatin A demonstrate the general effectiveness of strategies that evolve from the palladium-catalyzed oxazolidinone-forming reaction (eq 1) for the synthesis of aminocyclopentitol glycosidase inhibitors. We have used this methodology in preparing allosamizoline in six steps and 59% overall yield and mannostatin A in 27% yield over ten steps from the appropriate cyclic diols. The unequivocal establishment of the correct stereochemistry of allosamizoline as the gluco structure **2a** rather than the originally assigned allo structure **5a** suggests that a more proper name may be glucosamizoline to indicate its structural relationship to *N*-acetylglucosamine. Subsequent to completion of these syntheses we have shown that substitution of triisopropyl phosphite in the palladium reaction with an appropriate chiral ligand provides the carbamates **7** and **17** (eq 21) with enantiomeric excesses of 70% and 88%, respectively.[21,43] Thus, the synthetic routes developed here require no changes to complete asymmetric syntheses and



(21)



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thus correspond to formal asymmetric syntheses of these two natural products of allosamizoline and mannostatin A. We are continuing our development of the asymmetric version of this reaction and applying it in asymmetric syntheses of other highly functionalized carbocyclic enzyme inhibitors.

Experimental Section

General Methods. All reactions were run under an atmosphere of dry nitrogen unless otherwise indicated. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer or a Nicolet 205 spectrophotometer. Elemental analyses were performed by Spang Microlabs, Eagle Harbor, MI; Robertson Laboratories, Madison, NJ; M-H-W Laboratories, Phoenix, AZ. High-resolution mass spectra (HRMS) and low-resolution mass spectra (LRMS) were obtained from the Mass Spectrometry Resource, School of Pharmacy, University of California—San Francisco on a Kratos MS9. ^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded using a Varian XL-400 or Varian Gemini 200 or 300. Unless otherwise indicated, spectra recorded in deuterium oxide were referenced to DSS (3-methylsilyl)-1-propanesulfonic acid, sodium salt) or to an external reference. Proton NMR spectra used for analytical determinations (e.g, product ratios) were run with an increased delay (0.5–1.0 s) to minimize effects of differential relaxation times.

(±)-4*S*-[(Benzyloxy)methyl]-1-[(4′-methylphenyl)sulfonyl]cyclopent-5-eno[4,5-*d*]-3a*R*,6a*S*-1,3-oxazolidinone (7). To a stirred solution of diol **6** (1.521 g, 6.905 mmol) in anhydrous THF (10 mL) under nitrogen at room temperature was added *p*-toluenesulfonyl isocyanate (2.16 mL, 2.80 g, 14.2 mmol) dropwise. The reaction was stirred at room temperature for 5 h and then at 70 °C for 40 min. To a flask containing tris(dibenzylideneacetone)dipalladium chloroform complex (0.107 g, 104 μmol) in anhydrous THF (6 mL) under nitrogen was added triisopropyl phosphite (0.155 mL, 129 mg, 0.619 mmol). The mixture was stirred at room temperature for 15 min until a clear yellow solution was obtained. An aliquot of the catalyst solution (1 mL, 0.005 equiv) was added, and the solution was stirred at 70 °C for 24 h at which point thin-layer chromatography showed little reaction. More catalyst solution (2 mL, 0.01 equiv) was added, and the mixture was stirred at reflux for 1 h. Solvent was removed in vacuo, and the product was chromatographed on a column of silica gel with 10% ethyl acetate/hexanes to afford the oxazolidinone **7** as a beige solid (2.66 g, 96.4%): mp 105.0–106.0 °C (recrystallized from ethyl acetate as colorless plates); IR ($CDCl_3$) 3060, 3030, 2860, 1780 (s), 1600, 1495, 1450, 1360, 1180, 1090, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, J = 8.4 Hz, 2 H), 7.16–7.33 (m, 7 H), 6.03 (dt, J = 5.9, 1.8 Hz, 1 H), 5.84 (d, J = 5.9 Hz, 1 H), 5.22 (ddd, J = 7.1, 2.9, 1.4 Hz, 1 H), 4.83 (d, J = 7.0 Hz, 1 H), 4.41 (s, 2 H), 3.50 (dd, J = 9.5, 4.5 Hz, 1 H), 3.29 (dd, J = 9.5, 5.5 Hz, 1 H), 3.09 (br s, 1 H), 2.37 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.46, 137.55, 135.23, 134.90, 129.71 129.53, 128.44, 128.29, 127.80, 127.47, 79.82, 73.09, 69.36, 66.11, 52.39, 21.65. HRMS Calcd for $C_{21}H_{21}NO_5S$: 399.1141. Found: 399.1145.

(±)-4*S*-[(*Benzyloxy*)methyl]cyclopent-5-eno[4,5-*d*]3a*R*,6a*S*-oxazolidin-2-one (8). To a flame dried flask containing naphthalene (7.00 g, 54.6 mmol) under nitrogen were added sodium (1.1 g, 47.8 mmol, washed with hexanes) and anhydrous DME (44 mL). The mixture was stirred at room temperature for 2 h to give a green-black solution. To a flame dried flask containing *N*-tosylcarbamate **7** (2.64 g, 6.61 mmol) equipped with an addition funnel was added anhydrous THF (20 mL). The stirred solution was cooled to −78 °C, and the solution of sodium naphthalenide was cannulated into the addition funnel. The sodium naphthalenide solution was titrated into the solution of carbamate to give a deep green-black solution. (TLC indicated complete consumption of starting material.)

Ammonium chloride (4 g) was added, and the stirred mixture was allowed to warm to room temperature. Aqueous pH 7 phosphate buffer (0.20 M, 50 mL) was added followed by dichloromethane (50 mL). The layers were separated, and the aqueous layer was extracted with more dichloromethane (50 mL). The combined organic layers were washed with saturated aqueous sodium chloride and dried over magnesium sulfate. Solvent was removed in vacuo, and the residue was chromatographed on a column of silica gel with 50% ethyl acetate/hexanes to give the oxazolidinone **8** as an off-white solid (1.484 g, 91.5%): mp 85–86 °C; IR ($CDCl_3$) 3470, 3270, 3080, 3040, 2880, 1760, 1460, 1400, 1370, 1335, 1230, 1100, 1050, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26–7.44 (m, 5 H), 6.80 (s, 1 H), 5.84 (m, 2 H), 5.01 (d, J = 7.0 Hz, 1 H), 4.72 (d, J = 7.1 Hz, 1 H), 4.52 (s, 2 H), 3.57 (dd, J = 9.3, 4.8 Hz, 1 H), 3.39 (dd, J = 9.3, 5.9 Hz, 1 H), 3.24 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.66, 137.81, 133.57, 131.41, 128.38, 127.67, 127.44, 82.31, 73.02, 70.06, 61.77, 52.63. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.46; H, 6.36; N, 5.71; MW, 245.1052. Found: C, 68.48; H, 6.36; N, 5.47; MW, 245.1057.

(±)-4*S*-[(Benzyloxy)methyl]-2-(*N*,*N*-dimethylamino)cyclopent-5-eno[4,5-*d*]-3a*S*,6a*R*-oxazoline (9). To a flask (equipped with an empty

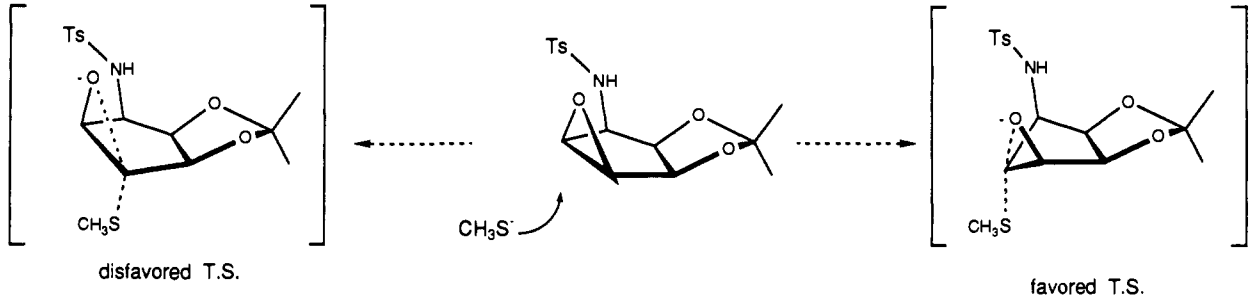

Figure 6. Conformational bias for regioselective epoxide ring opening.

dry ice condenser) containing a stirred solution of oxazolidinone **8** (1.477 g, 6.02 mmol) in anhydrous dichloromethane (12 mL) under nitrogen was added freshly distilled methyl triflate (1.22 mL, 1.77 g, 10.8 mmol). The solution was stirred at 0–5 °C for 0.5 h and then at room temperature for 35 h.

The solution was cooled to −78 °C, and the condenser was charged with a dry ice/acetone slurry. Anhydrous dimethylamine (ca. 5–8 mL) was condensed into the flask, and the mixture was allowed to warm to 0 °C, stirred at this temperature for 2 h, and then warmed to room temperature over 9 h. The mixture was taken up in chloroform (100 mL) and washed with saturated aqueous potassium carbonate (40 mL). The aqueous phase was extracted with dichloromethane (50 mL), and the combined organic layers were washed with saturated aqueous sodium chloride and dried over potassium carbonate. Removal of solvent in vacuo gave the oxazoline **9** as an orange brown oil (1.654 g, 100%): IR ($CHCl_3$) 3000, 2920, 1750, 1650 (s), 1450, 1400, 1250, 1210, 1180, 1080, 1010, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.40 (m, 5 H), 5.94 (dt, J = 5.8, 1.8 Hz, 1 H), 5.66 (d, J = 5.8 Hz, 1 H), 5.02 (dd, J = 7.1, 1.6 Hz, 1 H), 4.90 (d, J = 7.0 Hz, 1 H), 4.54 (s, 2 H), 3.51 (dd, J = 9.2, 5.1 Hz, 1 H), 3.29 (dd, J = 9.3, 7.6 Hz, 1 H), 3.18 (br s, 1 H), 2.90 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.18, 138.11, 135.02, 129.95, 128.44, 127.65, 85.84, 74.71, 73.17, 71.21, 53.21, 37.71. HRMS Calcd for $C_{16}H_{20}N_2O_2$: 272.1526. Found: 272.1525.

(±)-5*S*,6*R*-Bisacetoxy-4*S*-[(benzyloxy)methyl]cyclopentano[4,3-*d*]-3a*S*,6a*S*-oxazolidin-2-one (4c) and (±)-5*R*,6*S*-Bisacetoxy-4*S*-[(benzyloxy)methyl]cyclopentano[4,3-*d*]-3a*S*,6a*S*-oxazolidin-2-one (5c). To a flask containing alkene **9** (24.6 mg, 90.3 μmol) was added NMO (21.4 mg, 181 μmol). Anhydrous THF (150 μL) was added followed by deionized water (50 μL) and osmium tetroxide (1 small crystal, ca. 1 mg). After stirring 17 h, sodium bisulfite (18 mg) and Celite (18 mg) were added. A small amount of ethanol and water (3 drops each) were added to assist in homogenization, and the mixture was stirred vigorously for 3 h. The reaction mixture was filtered through a short pad of silica gel with 50% methanol/ether and then 45:5:50 methanol/triethylamine/chloroform. After removal of solvent in vacuo, the residue was taken up in ethyl acetate and filtered through a plug of cotton to remove the silica gel. Following removal of solvent in vacuo, the resulting residue was directly peracylated.

To a flask containing the mixture of diols was added a small stir bar and DMAP (2 mg, 16 μmol) followed by a solution of 10% (v/v) pyridine/dichloromethane (180 μL, 217 μmol). After cooling to 0 °C, acetyl chloride (14 μL, 200 μmol, distilled from CaH_2) was added dropwise with stirring, and the mixture was allowed to warm to room temperature over 7 h. The reaction mixture was taken up in dichloromethane (25 mL) and washed with saturated aqueous potassium carbonate followed by saturated aqueous sodium chloride. After drying over potassium carbonate and removal of solvent in vacuo, an oil was obtained (two isomers by ^1H NMR). Flash chromatography afforded the diacetates **5c** (7.3 mg, 20.7% from **9**) and **4c** (24.2 mg, 68.7% from **9**).

5c: IR (CH_2Cl_2) 2920, 2870, 1745, 1660, 1420, 1410, 1375, 1190, 1110, 1030, 985, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32 (m, 5 H), 5.37 (dd, J = 5.3, 4.2 Hz, 1 H), 5.11 (dd, J = 8.4, 4.0 Hz, 1 H), 4.74 (dd, J = 8.0, 3.8 Hz, 1 H), 4.55 (d, J = 12.0 Hz, 1 H), 4.51 (d, J = 12.2 Hz, 1 H), 4.49 (dd, J = 8.0, 5.4 Hz, 1 H), 3.64 (dd, J = 9.5, 4.0 Hz, 1 H), 3.50 (dd, J = 9.5, 4.7 Hz, 1 H), 2.91 (s, 6 H), 2.60 (m, 1 H), 2.05 (s, 3 H), 1.99 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 170.3, 163.0, 138.1, 128.6, 127.9, 127.8, 83.3, 73.8, 73.2, 72.8, 68.5, 67.5, 48.7, 37.6, 20.6, 20.5; LRMS (m/z) 331 (12), 330 (11), 271 (33), 245 (4), 223 (9), 209 (31), 203 (9), 181 (10), 167 (22), 165 (23), 121 (9), 113 (34). HRMS Calcd for $C_{18}H_{23}N_2O_4$ ($C_{20}H_{26}N_2O_6$–CH_3CO_2): 331.1658. Found: 331.1627.

4c: IR (CH_2Cl_2) 3060, 2990, 1745 (s), 1660 (s), 1420, 1375, 1190, 1100, 1080, 1045, 1030, 980, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.33 (m, 5 H), 5.52 (t, J = 4.3 Hz, 1 H), 5.03 (t, J = 4.3 Hz, 1 H), 4.79 (dd, J = 8.8, 5.2 Hz, 1 H), 4.55 (d, J = 12.0 Hz, 1 H), 4.49 (d, J = 12.0 Hz, 1 H), 4.41 (dd, J = 8.8, 4.9 Hz, 1 H), 3.60 (m, H), 2.89 (s, 6 H), 2.59 (m, 1 H), 2.00 (s, 3 H), 1.96 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.21, 170.17, 162.43, 138.22, 128.57, 127.87, 127.81, 111.56, 83.59, 80.34, 72.99, 72.80, 71.97, 71.91, 66.71, 47.64, 37.45, 20.54, 20.37; LRMS (m/z) 347 (2), 331 (23), 330 (10), 272 (9), 271 (50), 269 (4), 224 (3), 209 (11), 203 (11), 167 (10), 165 (8), 155 (8), 125 (6), 113 (41), 112 (36), 92 (10), 91 (100). HRMS Calcd for $C_{18}H_{23}N_2O_4$ ($C_{20}H_{26}N_2O_6$–CH_3CO_2): 331.1658. Found: 331.1638.

(±)-4*S*-[(Benzyloxy)methyl]-2-(dimethylamino)-5*S*,6*R*-dihydroxycyclopentano[4,3-*d*]-3a*S*,6a*S*-oxazoline (4b). To a 10-mL, round-bottomed flask containing alkene **9** (93.8 mg, 0.345 mmol) and NMO (60.9 mg, 0.520 mmol) at ambient temperature was added THF (0.6 mL) and deionized water (0.3 mL). Osmium tetroxide (1.5 mg, 5.9 μmol, 1 crystal) was added, and the biphasic mixture was rapidly stirred for 26 h. Sodium bisulfite (3 mg) was added, and the mixture was stirred 7 h. Following removal of solvent in vacuo, the mixture was chromatographed on a column of silica gel with 10–15% methanol/ethyl acetate + 1% triethylamine to afford diol **4b** (86.1 mg, 81.6%): IR ($CHCl_3$) 3010, 2930, 2870, 1650 (s), 1450, 1410, 1360, 1260, 1190, 1110, 1080, 1050, 1020, 980, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35 (m, 3 H), 7.31 (m, 2 H), 4.85 (dd, J = 8.8, 5.5 Hz, 1 H), 4.61 (d, J = 11.9 Hz, 1 H), 4.29 (dd, J = 8.8 Hz, 3.9 Hz, 1 H), 4.20 (m, 1 H), 4.00 (dd, J = 7.1, 3.4 Hz, 1 H), 3.83 (dd, J = 9.4, 7.1 Hz, 1 H), 3.77 (dd, J = 9.2, 6.0 Hz, 1 H), 2.88 (s, 6 H), 2.32 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.0, 137.8, 128.7, 128.1, 127.9, 85.9, 79.9, 74.8, 73.4, 72.7, 67.5, 49.1, 37.5, 29.5. HRMS Calcd for $C_{16}H_{22}N_2O_4$: 306.1580. Found: 306.1581.

(±)-4*S*-[(Benzyloxy)methyl]-3a*S*,6a*R*-dihydro-2-(dimethylamino)-5*R*,6*S*-dihydroxycyclopentano[4,3-*d*]oxazole (5b). To a flask containing diacetate **5c** (17.1 mg, 43.8 μmol) was added anhydrous potassium carbonate (1 crystal, 3.6 mg, 26.1 μmol) followed by absolute methanol (0.20 mL). The mixture was stirred at room temperature for 3 h. Chloroform was added, and the mixture was filtered through a short plug of silica gel. The filter cake was washed with 5:95:0.5 methanol/chloroform/concentrated aqueous ammonia. The filtrate was combined and concentrated in vacuo. The residue was chromatographed on a column of silica gel with 10:90:1 methanol/chloroform/concentrated aqueous ammonia. (No yield determined.) IR ($CHCl_3$) 3550, 3410 (b), 3005, 2940, 2870, 1650 (s), 1520, 1490, 1480, 1455, 1415, 1365, 1265, 1120, 1075, 1025, 985, 930, 890, 850, 625 cm^{-1}; ^1H NMR ($CDCl_3$ 400 MHz); δ 7.30–7.36 (m, 5 H), 4.80 (dd, J = 8.2, 4.1 Hz, 1 H), 4.53 (s, 2 H), 4.43 (dd, J = 8.1, 5.9 Hz, 1 H), 4.11 (dd, J = 5.9, 4.6 Hz, 1 H), 3.90 (dd, J = 6.8, 4.6 Hz, 1 H), 3.67 (dd, J = 9.4, 4.0 Hz, 1 H), 3.59 (dd, J = 9.4, 4.7 Hz, 1 H), 2.93 (s, 6 H), 2.39 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.73, 138.09, 123.38, 127.65, 127.50, 85.22, 74.88, 73.24, 71.96, 69.48, 68.72, 51.24, 37.64. HRMS Calcd for $C_{16}H_{22}N_2O_4$: 306.1579. Found: 306.1563.

Dihydroxylation of the β-Cyclodextrin Complex of 9. To a dry 25-mL flask containing alkene **9** (35.2 mg, 129 μmol) and β-cyclodextrin (147 mg, 129 μmol, Chemical Dynamics Corp.) was added deionized water (9 mL). The mixture was stirred at 65 °C for 2 min to effect solution and then allowed to cool to room temperature over 7 h with stirring resulting in a heterogeneous suspension. NMO (45.4 mg, 0.194 mmol) was added followed by osmium tetroxide (3.5 mg, 13.8 μmol). The mixture was stirred at room temperature for 52 h. A small amount of sodium bisulfite (ca. 10 mg) was added, and the mixture was stirred at room temperature for 0.5 h. The suspension was saturated with sodium chloride and extracted with chloroform. Removal of solvent in vacuo afforded a mixture of diols **5b** and **4b** (12 mg, 2:1 ratio by ^1H NMR); a small amount of more material was isolated by extraction with toluene with similar NMR ratios.

(±)-4*S*-[(Benzyloxy)methyl]-3a*S*,6a*R*-dihydro-2-(dimethylamino)-5*R*,6*R*-dihydroxycyclopentano[4,3-*d*]oxazole (2b). A solution of peroxytrifluoroacetic acid in trifluoroacetic acid was prepared by carefully adding trifluoroacetic anhydride (12.6 mL, 89.7 mmol) dropwise to a stirred solution of 30% hydrogen peroxide (1.88 g, 16.6 mmol) at 0 °C.

After stirring at 0 °C for 5 min, the mixture was stirred at ambient temperature for 0.5 h.

The peracid solution was cooled to 0 °C and transferred via a Teflon cannula to a flask containing alkene **9** (903 mg, 3.32 mmol) at 0 °C. The flask was swirled by hand at 0 °C to effect solution (10–15 min). The bright yellow solution was stirred at 0–5 °C for 9 h. Solvent was removed in vacuo (rotary evaporator). Solvent removal was repeated with the addition of four portions of chloroform (4 × 30 mL, to assist removal of trifluoroacetic acid) to give a viscous orange oil. The oil was chromatographed (5–10:90:1 methanol/chloroform/concentrated aqueous ammonia) on silica gel to remove the diol, **2b**, and to give a mixture of epoxides (177 mg). The epoxide mixture was stirred with 50% (v/v) aqueous trifluoroacetic acid (2 mL) at 65 °C for 36 h to provide a mixture of the diols **2b**, **3b**, and remaining epoxide **11**. Chromatography on a column of silica gel afforded more **2b** (0.6434 g combined total 63.3%), **3b** (58.8 mg, 5.8%), and epoxide **11** (17.3 mg, 1.8%).

2b: mp 137–9 °C; IR ($CHCl_3$) 3320 (br s), 3020, 2930, 2870, 1650 (s), 1520, 1480, 1450, 1410, 1360, 1260, 1120, 1090, 1030, 980, 930, 900, 850, 630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33 (m, 5 H), 4.72 (dd, J = 9.1, 6.3 Hz, 1 H), 4.55 (s, 2 H), 4.05 (dd, J = 9.2, 4.9 Hz, 1 H), 3.65–3.90 (m, 3 H), 2.86 (s, 6 H), 2.16 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.06, 138.11, 128.38, 127.62, 127.50, 84.64, 81.98, 76.67, 75.17, 73.13, 73.01, 68.99, 50.31, 37.67. Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14; MW, 306.1580. Found: C, 62.39; H, 7.32; N, 9.09; MW, 305.1583.

3b: mp 96–98 °C; IR ($CHCl_3$) 3690, 3610, 3460 (br), 3010, 2940, 1650 (s), 1515, 1480, 1455, 1415, 1365, 1265, 1070, 1025, 980, 930, 890, 850, 624; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.35 (m, 5 H), 5.02 (dd, J = 8.4, 6.0 Hz, 1 H), 4.66 (dd, J = 8.7, 5.9 Hz, 1 H), 4.60 (d, J = 12.0 Hz, 1 H), 4.55 (d, J = 11.9 Hz, 1 H), 4.20 (dd, J = 4.3, 2.7 Hz, 1 H), 4.03 (dd, J = 5.8, 2.6 Hz, 1 H), 3.89 (d, J = 4.2 Hz, 2 H), 2.94 (s, 6 H), 2.37 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.37, 137.48, 128.53, 127.91, 127.62, 85.28, 79.06, 75.42, 73.57, 70.42, 68.14, 48.32, 37.58. HRMS Calcd for $C_{16}H_{22}N_2O_4$: 306.1580. Found: 306.1577.

11: IR ($CHCl_3$) 2940, 2870, 1655 (s), 1490, 1455, 1410, 1335, 1260, 1185, 1100, 1080, 1040, 1030, 980, 895, 870. 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.38 (m, 5 H), 4.75 (d, J = 8.2 Hz, 1 H), 4.54 (d, J = 12.2 Hz, 1 H), 4.50 (d, J = 12.2 Hz, 1 H), 4.48 (dd, J = 8.1, 1.8 Hz, 1 H), 3.66 (s, 1 H), 3.54 (m, 2 H), 2.90 (s, 6 H), 2.76 (t, J = 4.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.39, 137.75, 128.47, 127.80, 127.50, 87.68, 73.30, 70.12, 68.87, 61.43, 46.35, 37.61.

(±)-Allosamizoline, (±)-3a*S*,6a*S*-Dihydro-5*R*,6*R*-dihydroxy-2-(dimethylamino)-4*S*-(hydroxymethyl)cyclopentano[4,3-*d*]oxazole (2a). Method A. (The epoxidation must be performed at or below 0 °C. The use of a safety shield is also recommended for this reaction.) To a 1-mL flask containing 90% hydrogen peroxide (30.5 mg, 0.807 mmol) at 0 °C was carefully added trifluoroacetic anhydride (136 μL, 202 mg, 0.963 mmol). The clear solution was stirred at 0 °C for 5 min and then transferred by glass pipet to a flask containing alkene **9** (21.6 mg, 79.3 μmol) at 0 °C. The mixture was stirred at this temperature for 1 h and then allowed to warm to ambient temperature over 0.5 h. The solvent was removed in vacuo (rotary evaporator). Water was added (0.1 mL), and the solvent was again removed in vacuo. Aqueous trifluoroacetic acid (10% solution, 0.1 mL) was added, and the mixture was stirred at 40 °C for 4.5 h. Solvent was removed in vacuo to give a brown oily residue.

The mixture was transferred with absolute methanol (0.50 mL) to a Griffin–Worden tube containing 10% (w/w) Pd/carbon (10 mol%) and a stir bar. After stirring under a stream of hydrogen for 5 min, the tube was sealed and pressurized with hydrogen (35 psig), and the mixture was stirred for 7 h. The mixture was filtered through Celite and chromatographed on a column of silica gel with 15–25:75:1 methanol/chloroform/concentrated aqueous ammonia to give **2a** (11.5 mg, 67.7% yield) and epoxide **11** (2.5 mg, 15.9%).

2a: mp 203–205 °C; IR (KBr) 3405 (br), 3260 (br), 2940, 2880, 1655 (s), 1480, 1460, 1440, 1420, 1380, 1290, 1280, 1260, 1190, 1120, 1100, 1090, 1040, 980, 950, 905, 895, 810, 720, 620 cm^{-1}; ^1H NMR (D_2O, DSS ref) δ 4.80 (dd, J = 9.2, 6.1 Hz, 1 H), 3.98 (dd, J = 9.2, 5.3, 1 H), 3.87 (dd, J = 11.5, 4.3 Hz, 1 H), 3.75 (dd, J = 7.6, 5.5 Hz, 1 H), 3.70 (dd, J = 11.5, 7.3 Hz, 1 H), 3.64 (dd, J = 9.9, 7.8 Hz, 1 H), 2.89 (s, 6 H), 2.12 (m, 9 peaks, 1 H); ^{13}C NMR (D_2O, DSS ref) δ 166.3, 86.7, 85.1, 77.3, 73.4, 63, 54, 39.8. Anal. Calcd for $C_9H_{14}N_2O_4$: C, 49.99; H, 7.46; N, 12.95; MW, 216.1110. Found: C, 49.6; H, 7.2; N, 12.7. Natural and synthetic allosamizoline (HCl salts) were identical by ^1H NMR and TLC.

11a: IR ($CHCl_3$) 3560 (w), 2600–3500 (br), 3010, 2940, 1740, 1640 (s), 1470, 1410, 1220 (s), 1070, 1040, 1020, 980, 925, 905, 895, 870, 845 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.81 (d, J = 8.1 Hz, 1 H), 4.47 (dd, J = 8.2, 1.8 Hz, 1 H), 3.77 (d, J = 5.25 Hz, 2 H), 3.65 (m, 1 H), 3.57 (dd, J = 2.4, 1.1 Hz, 1 H), 2.90 (s, 6 H), 2.71 (t, J = 5.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.73, 87.51, 69.72, 61.19, 61.22, 61.37, 47.99, 37.50. HRMS Calcd for $C_9H_{14}N_2O_3$: 198.1004. Found: 198.1011.

Method B. To a flask containing benzyl ether **2b** (136.8 mg, 0.447 mmol) at ambient temperature was added 10% (V/V) trifluoroacetic acid/chloroform (1 mL). Solvent was removed in vacuo, and the residue was transferred, using 2 mL absolute methanol, to a Griffin–Worden tube containing 10% Pd/C (47.5 mg, 44.7 μmol) and a stir bar. Extra trifluoroacetic acid (20 μL) was added, and the mixture was stirred at room temperature under hydrogen (40 psig) for 5 h. The mixture was filtered through a pad of Celite with methanol (5 mL) and water (10 mL). Following removal of solvent in vacuo, the residue was chromatographed on a column of silica gel with 10–25:75:1 methanol/chloroform/concentrated aqueous ammonia. To ensure that the product was salt-free, the residue was eluted through a 1 × 20 cm ion exchange column (IRA 400/OH^-) with deionized water (0.25 L). Lyophilization afforded (±)-allosamizoline, **2a**, 57.4 mg as a snow white powder (59.4%).

(±)-3a*S*,6a*S*-Dihydro-5*S*,6*R*-dihydroxy-2-(dimethylamino)-4*S*-(hydroxymethyl)cyclopentano[4,3-*d*]oxazole (4a, Hydrochloride Salt). To a Griffin–Worden tube containing 10% Pd/C (11.0 mg, 10.3 μmol) and a stir bar was added benzyl ether **4b** (31.4 mg, 102.5 μmol) with methanol/concentrated hydrochloric acid (19:1, 0.8 mL). The mixture was stirred under a gentle flow of hydrogen for 5 min. The tube was then pressurized with hydrogen (38 psig) for 7 h. The mixture was filtered through Celite, and the filter cake was washed with ethanol. Solvent was removed in vacuo to give the hydrochloride salt of **4a**. (No yield determined.) IR (KBr) 3100 (br), 2940, 1650 (s), 1460, 1420, 1410, 1380, 1330, 1265, 1190, 1115, 1080, 1050, 1000, 980, 935, 890, 820, 745, 720 cm^{-1}; ^1H NMR (D_2O, DSS ref) δ 5.36 (dd, J = 9.2, 6.4 Hz, 1 H), 4.45 (dd, J = 9.2, 5.5 Hz, 1 H), 4.29 (t, J = 4.06 Hz, 1 H), 4.22 (dd, J = 5.5, 4.0 Hz, 1 H), 3.94 (dd, J = 11.3, 7.0 Hz, 1 H), 3.84 (dd, J = 11.2, 7.6 Hz, 1 H), 3.08 (s, 3 H), 3.07 (s, 3 H), 2.54 (m, 1 H); ^{13}C NMR (D_2O, DSS ref) δ 163.4, 92.0, 81.7, 75.4, 67.6, 61.4, 52.3, 40.2, 39.9. HRMS Calcd for $C_9H_{14}N_2O_4$: 216.1110. Found: 216.1114.

(±)-3a*S*,6a*S*-Dihydro-5*R*,6*S*-dihydroxy-2-(dimethylamino)-4*S*-(hydroxymethyl)cyclopentano[4,3-*d*]oxazole (5a). To benzyl ether **5b** (6.8 mg, 22.2 μmol) at ambient temperature was added 10% (v/v) trifluoroacetic acid in chloroform (0.40 mL). Solvent was removed in vacuo. The salt was taken up in methanol (0.5 mL) and added to a Griffin–Worden tube containing 10% Pd/C (2.3 mg, 2.2 μmol) and a stir bar. The mixture was stirred under a gentle stream of hydrogen for 5 min and then sealed and stirred under hydrogen (40 psig) for 11 h. The reaction mixture was taken up in methanol (10 mL) and filtered through Celite. Solvent was removed in vacuo to give 8.2 mg of residue. The residue was eluted through a 1 × 20 cm ion exchange column (IRA 400, OH^- form) with deionized water to afford **5a** following lyophilization (3.3 mg, 68.8%): mp 140–141 °C; IR (KBr) 3350 (br), 2960, 1650 (s), 1470, 1410, 1340, 1270, 1190, 1115, 1080, 1040, 1020, 980, 955, 920, 895, 860, 855, 845, 800, 720 cm^{-1}; ^1H NMR (trifluoroacetate salt, D_2O, DSS reference, 400 MHz) δ 5.27 (dd, J = 8.2, 3.4 Hz, 1 H), 4.54 (dd, J = 8.2. 5.2 Hz, 1 H), 4.18 (t, J = 4.5 Hz, 1 H), 3.98 (dd, J = 11.6, 4.8 Hz, 1 H), 3.64 (dd, J = 11.6, 7.1 Hz, 1 H), 3.10 (s, 6 H), 2.55 (m, 1 H); ^{13}C NMR (trifluoroacetate salt, D_2O, DSS reference, 100 MHz) δ 163.9, 91.5, 75.4, 74.7, 62.8, 62.3, 53.7, 40.2, 40.1. HRMS Calcd for $C_9H_{16}N_2O_4$: 216.1110. Found: 216.1111.

(±)-3a*S*,6a*S*-Dihydro-5*S*,6*S*-dihydroxy-2-(dimethylamino)-4*S*-(hydroxymethyl)cyclopentano[4,3-*d*]oxazole (3a). To a Griffin–Worden tube containing 10% Pd/C (20.2 mg, 19.0 μmol) and a stir bar was added benzyl ether **3b** (58.8 mg, 192 μmol) with absolute methanol (1.3 mL). Concentrated hydrochloric acid (3 drops) was added, and the mixture was stirred under a gentle flow of hydrogen for 5 min. The tube was pressurized with hydrogen (40 psig) and stirring was continued for 6 h. The mixture was filtered through silica gel with 15:85:1 methanol/chloroform/concentrated aqueous ammonia to give **3a** as a viscous oil (45 mg, 107%). [To ensure that the yield was not inflated due to contamination by silica gel or HCl (as a salt) the product was stirred with aqueous $Hg(OAc)_2$, concentrated in vacuo and filtered through silica gel with 15:85:1 methanol/chloroform/concentrated aqueous ammonia to give 44.7 mg of unchanged product.] IR (KBr) 3404 (br), 2934, 1702, 1648 (s), 1457, 1418, 1384, 1270, 1201, 1112, 1067, 1031, 984, 976, 889, 838, 800, 722, 639 cm^{-1}; ^1H NMR (D_2O, DSS ref, 300 MHz) δ 4.85 (dd, J = 8.4, 4.0 Hz, 1 H), 4.47 (dd, J = 8.2, 5.7 Hz, 1 H), 4.16 (t, J = 4.9 Hz, 1 H), 4.03 (dd, J = 5.5, 4.5 Hz, 1 H), 3.87 (dd, J = 11.2, 6.7 Hz, 1 H), 3.73 (dd, J = 11.2, 7.9 Hz, 1 H), 2.90 (s, 6 H), 2.41 (m, 1 H); ^{13}C NMR (D_2O, DSS ref) δ 167.24, 89.07, 79.09, 78.92, 71.12, 61.82, 52.43, 39.95. HRMS Calcd for $C_9H_{14}N_2O_4$: 216.1110. Found: 216.1105.

(±)-1-[(4′-Methylphenyl)sulfonyl]cyclopent-5-eno[4,3-*d*]-3a*S*,6a*R*-oxazolidin-2-one (17). Addition of anhydrous THF (50 mL) followed by slow addition of *p*-toluenesulfonyl isocyanate (15.65 mL, 102.8 mmol) to *cis*-2-cyclopenten-1,4-diol (5.120 g, 51.14 mmol) resulted in an exo-

thermic reaction. The clear solution was stirred at 60 °C for 2 h to assure complete reaction, and the mixture was then allowed to cool to room temperature.

A solution of tetrakis(triisopropyl phosphite)palladium(0) was prepared by adding triisopropyl phosphite (1.49 mL, 6.04 mmol) to a stirred slurry of tris(dibenzylideneacetone)dipalladium(0)–chloroform complex (0.782 g, 0.756 mmol) in anhydrous THF (25 mL). The catalyst solution was stirred for 2 h at room temperature resulting in a clear yellow solution. (The unused balance of this solution was stored for 2 weeks afterward under nitrogen with no change in appearance.)

The solution of newly formed carbamate in THF was brought to reflux, and an aliquot of catalyst solution (5 mL, 0.59 mol%) was added. The mixture was stirred for 10 min, and another aliquot of catalyst solution (7.5 mL, 0.89 mol%) was added. After stirring 10 min at reflux another aliquot of catalyst solution (2.5 mmol, 0.30 mol%; total of 1.78 mol% catalyst) was added, and vigorous gas (carbon dioxide) evolution was noted while the reaction was stirred at reflux. Within 15 min, gas evolution had stopped, and the reaction began to turn brown (this has always been noted to occur upon completion of reaction). Solvent was removed in vacuo, and the residue was taken up in dichloromethane (250 mL) to give a deep burgandy solution. The organic layer was washed with cold 1.0 N aqueous sodium hydroxide (60 mL, 60 mmol) and the aqueous layer was back extracted with dichloromethane (20 mL). The combined organic layers were washed with saturated aqueous sodium chloride and dried over magnesium sulfate. Solvent was removed in vacuo. The residue was chromatographed on silica gel with 1:1 hexane/ether to give 10.57 g of pure oxazolidinone, **17**, and some impure fractions. The impure fractions were twice rechromatographed to afford 3.33 g more of oxazolidinone, **17**, for a total yield of 13.90 g, 97.3%: mp 131 °C; IR (neat) 3072, 2983, 2925, 1776 (s), 1596, 1365, 1169, 1144, 1091, 1052, 815, 753, 705, 661, 609 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.95 (d, J = 8.4 Hz, 2 H), 7.36 (d, J = 8.1 Hz, 2 H), 6.02 (m, 2 H), 5.29 (dd, J = 7.4, 1.3 Hz, 1 H), 5.11 (ddd, J = 8.3, 5.8, 1.8 Hz, 1 H), 2.83 (m, 1 H), 2.68 (m, 1 H), 2.45 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.35, 145.52, 134.99, 133.86, 129.75, 128.33, 127.97, 76.74, 66.26, 38.95, 21.68. Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01; S, 11.48. Found: C, 55.91; H, 4.57; N, 4.92; S, 11.37.

(±)-4-Oxo-1-[(4′-methylphenyl)sulfonyl]cyclopent-5-eno[5,4-*d*]-3a*R*,6a*R*-oxazolidin-2-one (18). Anhydrous diglyme (50 mL) was added to a neat mixture of alkene **17** (11.88 g, 42.53 mmol), anhydrous dibasic sodium hydrogen phosphate (6.03 g, 42.48 mmol), finely ground selenium dioxide (14.47 g, 130.4 mmol), and oven-dried quartz sand (25 g). The stirred mixture was immersed in a 170 °C oil bath. After stirring for 45 min more, quartz sand (10 g) was added, and the mixture was stirred at reflux for an additional 45 min. The syrupy conglomerate was pushed from the sides of the flask with a spatula, and after stirring at 170 °C for 1.5 h more selenium dioxide (5.20 g, 46.9 mmol) was added. The mixture was stirred for 0.5 h and more selenium dioxide (6.0 g, 54 mmol) was added. The mixture was stirred at 170 °C for 1.5 h longer and then allowed to cool to room temperature over 3 h with stirring. The solids were filtered and washed with dichloromethane (200 mL) to give an orange cloudy filtrate. Dichloromethane was removed via rotary evaporator, and the diglyme was removed under high vacuum (<1 mmHg) at room temperature with stirring. The resulting brown oil was taken up in dichloromethane (175 mL) and washed with saturated aqueous sodium chloride (50 mL), 0.50 N aqueous sodium hydroxide (40 mL), and again with saturated aqueous sodium chloride (50 mL). The aqueous layers were back-extracted with dichloromethane (50 mL), and the combined organic layers were dried over magnesium sulfate. Solvent was removed in vacuo to give a viscous brown oil. The oil was chromatographed/flushed through an 8 × 5 cm column of silica gel with 40–50% ethyl acetate/hexanes to give 9.20 g of beige solid which was subjected directly to oxidation.

Sodium bicarbonate (6.46 g, 76.9 mmol) was added to the product mixture from selenium dioxide oxidation of alkene **17** (8.88 g). The flask was evacuated (<1 mmHg) for 5 min, and freshly prepared Dess–Martin periodinane (15.95 g, 37.6 mmol) was added. The flask was again evacuated for 5 min (<1 mmHg) and then fitted with a septum under nitrogen. The flask was immersed in a room temperature water bath, and 60 mL of anhydrous dichloromethane was added leading to an exothermic reaction. The reaction mixture was stirred at room temperature for 1.6 h and attained a milky consistency. Isopropyl alcohol (0.674 mL, 9.02 mmol) was added, and the mixture was stirred for 5 min to use up any excess periodinane. Sodium bicarbonate (3.2 g, 38 mmol) was added, and the mixture was stirred for 10 min. Solvent was removed in vacuo. The product mixture was adsorbed onto silica gel, loaded onto a 5 × 8 cm column of silica gel, and chromatographed with 40–60% ethyl acetate/hexanes (gradient) to remove most of Dess–Martin byproduct. The obtained solid was rechromatographed to give 8.08 g of enone **18** as a white solid (64.8% starting from alkene **17**): mp 149–153 °C (slight dec); IR ($CDCl_3$) 2840 (w), 1795 (s), 1745 (s), 1380, 1350, 1305, 1205, 1190, 1175 (s), 1145 (s), 1090, 1070, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 8.03 (dd, J = 6.0, 2.3 Hz, 1 H), 7.95 (d, J = 8.4 Hz, 2 H), 7.86 (d, J = 8.1 Hz, 2 H), 6.56 (dd, J = 5.9, 1.0 Hz, 1 H), 5.37 (ddd, J = 7.0, 2.2, 1.0 Hz, 1 H), 4.68 (d, J = 7.09 Hz, 1 H), 2.47 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 197.72, 159.36, 146.66, 136.90, 134.08, 130.24, 128.59, 71.39, 58.53, 21.60. HRMS Calcd for $C_{13}H_{11}NO_5S$–SO_2: 229.0756. Found: 229.0750. Anal. Calcd for $C_{13}H_{11}NO_5S$: C, 53.24; H, 3.78; N, 4.78; S, 10.93. Found: C, 53.04; H, 3.84; N, 4.66; S, 10.73.

(±)-4*S*-Hydroxy-1-[(4′-methylphenyl)sulfonyl]cyclopent-5-eno[5,4-*d*]-3a*R*,6a*R*-oxazolidin-2-one (16a). (If the enone is not completely dissolved before addition of the sodium borohydride, poor selectivity is observed. The low solubility of the enone requires high dilution; however, the reaction is still extremely fast.) A mixture of **18** (3.595 g, 12.17 mmol), 200 mL of anhydrous methanol, and 150 mL of ethyl acetate was stirred with gentle warming from a heat gun until the solid enone went into the solution. After cooling to room temperature, cerium trichloride hexahydrate (4.40 g, 12.4 mmol) was added, and the mixture was cooled to −5 °C. Sodium borohydride (0.470 g, 12.4 mmol) was added immediately in one portion resulting in vigorous gas evolution. The reaction was stirred for 5 min and then neutralized with 1 N hydrochloric acid to pH 6–7 (pH paper). The mixture was concentrated in vacuo to 15 mL, and then chloroform (100 mL) and saturated aqueous sodium chloride (40 mL) were added. Hydrochloric acid (1.0 N) was carefully added to break the resultant emulsion and the layers were separated. The aqueous layer was extracted with 3 × 50 mL of chloroform, and the combined organic layers were dried over magnesium sulfate. Solvent was removed in vacuo, and the residual oil was chromatographed on a 5 × 18 cm column of silica gel with 40–60% ethyl acetate/hexanes (gradient elution) to give the α alcohol **16a**, the β alcohol **16b**, and a set of mixed fractions (211 mg). The mixed fractions were rechromatographed to afford a total of 3.002 g low R_f α alcohol **16a** (82.9%) and 0.4199 g high R_f β alcohol **16b** (11.6%).

16a: IR ($CDCl_3$ solution) 2980, 2930, 1788, 1735, 1597, 1402, 1360, 1215, 1190, 1175, 1149, 1127, 1091, 1069, 1040 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96 (d, J = 8.5 Hz, 2 H), 7.38 (d, J = 8.3 Hz, 2 H), 6.17 (dt, J = 5.8, 1.5 Hz, 1 H), 6.11 (d, J = 5.9 Hz, 1 H), 5.15 (br d, J = 6.6 Hz, 1 H), 4.99 (dd, J = 6.8, 5.7 Hz, 1 H), 4.89 (m, 1 H), 2.46 (s, 3 H), 2.23 (d, J = 10.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.97, 146.12, 137.9, 134.97, 130.09, 129.73, 128.55, 75.32, 63.89, 21.51. HRMS Calcd for $C_{13}H_{13}NO_5S$: 295.0555. Found: 295.0535.

16b: mp 124–125.5 (crystallized from dichloromethane); IR (film from $CDCl_3$ solution) 3550 (br), 3071, 2925, 1781 (s), 1596, 1494, 1362, 1172, 1148, 1110, 1090, 1056, 991, 912, 860, 815, 783, 755, 732, 704, 663, 617 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, J = 8.5 Hz, 2 H), 7.36 (d, J = 8.0 Hz, 2 H), 6.29 (d, J = 5.8 Hz, 1 Hz), 6.11 (ddd, J = 5.8, 1.12, 1.05 Hz, 1 H), 5.38 (ddd, J = 7.2, 3.0, 1.3 Hz, 1 H), 4.91 (br dd, J = 6.0, <1 Hz, 1 H), 4.79 (d, J = 7.0 Hz), 2.45 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.86, 145.86, 136.35, 134.59, 132.67, 129.86, 128.35, 82.9, 80.10, 64.85, 21.71. HRMS Calcd for $C_{13}H_{13}NO_5S$–SO_2: 231.0895. Found: 231.0895. Anal. Calcd for $C_{13}H_{13}NO_5S$: C, 52.87; H, 4.44. Found: C, 52.70; H, 4.70.

(±)-1*S*,2*R*-Dihydroxy-3*R*-[(4′-methylphenyl)sulfonamido]cyclopent-3-ene (19). A mixture of carbamate **16a** (342 mg, 1.16 mmol) and potassium carbonate (190 mg, 1.38 mmol) in methanol/water (19:1, 1.5 mL) was stirred at room temperature for 8 h after adding an additional 1.5 mL of methanol. More potassium carbonate (96 mg, 0.70 mmol) was added, and stirring continued for 10 h, at which time TLC (silica gel, 80% ethyl acetate/hexanes) indicated complete reaction.

The reaction mixture was made acidic with glacial acetic acid, and the solvent was removed in vacuo. The mixture was loaded onto a short column of silica gel and eluted with 80% ethyl acetate/hexanes + 1% acetic acid to afford, upon removal of solvent in vacuo, 294.6 mg of diol **19**, as a white solid, 94.5%: mp 134–135 °C (white solid from chloroform solution); IR (neat film from $CDCl_3$ solution) 3500 (br), 3250 (br), 2923, 1598, 1440, 1401, 1326, 1306, 1290, 1159, 1123, 1088, 1067, 1020, 931, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.81 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.5 Hz, 2 H), 5.91 (dt, J = 5.9, 1.9 Hz, 1 H), 5.67 (dt, J = 5.9, 1.9 Hz, 1 H), 5.15 (br d, J = 8.9 Hz, 1 H, exchangeable), 4.49 (br s, 1 H), 4.15 (m, 1 H), 4.05 (d, J = 10.0, 5.1 Hz, 1 H), 2.82 (br d, J = 4.5 Hz, 1 H, exchangeable); ^{13}C NMR (CD_3CN, 50 MHz) δ 145.05, 139.8, 135.81, 133.04, 131.06, 128.28, 75.02, 72.12, 60.29, 21.58. HRMS Calcd for $C_{12}H_{15}NO_4S/H_2O$: 251.0616. Found 251.0620. Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.52; H, 5.61; N, 5.20; S, 11.91. Found C, 53.20; H, 5.86; N, 5.24; S, 11.72.

(±)-2*R*,3*R*-Dihydroxy-4*S*-[(4-methylphenyl)sulfonamido]-6-oxabicyclo-1*R*,5*S*-[3.1.0]hexane (19a). A solution of peroxytrifluoroacetic acid was prepared by adding trifluoroacetic anhydride (0.678 mL, 4.80 mmol, freshly distilled from calcium hydride) to a suspension of 90%

hydrogen peroxide (150 mg, 3.97 mmol) in 3.3 mL of anhydrous dichloromethane at 0 °C. The solution was allowed to warm to room temperature and stirred for 10 min. The solution was then cooled to 0 °C before addition to the olefin.

To a 50-mL round-bottom flask containing allylic alcohol **19** (294 mg, 1.09 mmol) and a stir bar under nitrogen was added sodium carbonate (463 mg, 4.37 mmol) and chloroform (4 mL, filtered through activated basic alumina). The insoluble stirred mixture was cooled to 0 °C, and the freshly prepared cold peracid solution was added by syringe. A rock-like solid immediately formed (sodium trifluoroacetate?) which made stirring extremely difficult. The mixture was stirred over 6 h while slowly warming to room temperature; during this time the reaction became a paste-like white sludge.

Solvent was removed in vacuo, and the residue was filtered through a 2-in. plug of silica gel with 10% ethanol/ethyl acetate to give, upon removal of solvent in vacuo, about 1.5 g of viscous material. Chromatography on a column of silica gel with 90–95% ethyl acetate/hexanes afforded epoxide **19** as a white crystalline solid (268.5 mg, 86.2%): mp 188–190 °C (ethyl acetate/methanol); IR (KBr) 3536, 3417, 3129, 2954, 2921, 2891, 1599, 1459, 1409, 1349, 1385, 1320, 1299, 1289, 1180, 1158, 1090, 953, 937, 891, 851, 810, 664 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz) δ 7.81 (dt, J = 8.4, 2.0 Hz, 2 H), 7.37 (d, J = 8.1 Hz), 4.05 (dd, J = 6.1, 1.3 Hz, 1 H), 3.81 (dd, J = 6.1, 1.1 Hz, 1 H), 3.46 (dt, J = 3.0, 1.3 Hz, 1 H), 3.41 (td, J = 6.1, 1 Hz, 1 H), 3.35 (m, 1 H, partially hidden by CHD_2OD), 2.41 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 142.85, 139.14, 129.71, 126.81, 70.68, 66.19, 57.65, 56.51, 55.51, 20.78. Anal. Calcd for $C_{12}H_{15}NO_5S$: C, 50.52, H, 5.30; MW, 285.0672. Found: C, 51.14; H, 5.66; MW, 285.0633.

(±)-*N*-Tosylmannostatin A (13b). To a slurry of epoxydiol **19a** (101.0 mg, 0.354 mmol) in anhydrous THF (0.6 mL) at 0 °C was added slowly and dropwise titanium tetraisopropoxide (0.420 mL, 1.41 mmol). The stirred mixture became homogeneous and clear within 1 min.

To a stirred slurry of lithium thiomethoxide (73.5 mg, 1.36 mmol) in THF (0.90 mL) at 0 °C was added the cold Ti(4+) epoxide solution dropwise. The slurry immediately became a yellow, homogeneous solution. The reaction was stirred at 0 °C for 2 h, then warmed to room temperature, and stirred for 13 h.

Aqueous 1 M sodium bisulfate (2.5 mL) and chloroform (20 mL) were added, and the mixture was stirred vigorously for 5 min. The layers were separated, and the aqueous layer was extracted twice more. To the combined organic layers was added methanol (10 mL) and glacial acetic acid (0.30 mL). After stirring 30 min the mixture was filtered through silica gel. The silica gel was washed with 10% methanol/chloroform to remove all the product. Removal of solvent in vacuo afforded a residue which was chromatographed on a 3 × 8 cm column of silica gel with 5–7% methanol chloroform (gradient elution) to afford 24.5 mg of *N*-tosylmannostatin A, **13b**, 20.8%, and 30.1 mg of *N*-tosylisomannostatin A **20**, 25.5% which was directly peracylated for characterization.

13b: IR (neat film from $CDCl_3$ solution) 3450 (br s), 3300 (br s), 2922, 1598, 1434, 1320, 1306, 1291, 1185, 1157, 1092, 1068, 924, 814, 754 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 7.79 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 3.80 (dd, J = 5.9, 4.0 Hz, 1 H, H-2), 3.74 (t, J = 5.2 Hz, 1 H, H-1), 3.71 (t, J = 4.6 Hz, 1 H, H-3), 3.33 (dd, J = 8.4, 4.9 Hz, 1 H, H-4), 3.30 (m, 1 H), 2.82 (dd, J = 8.5, 5.0 Hz, 1 H, H-5), 2.41 (s, 3 H, Ar-CH_3), 1.97 (s, 3 H, $RSCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.04, 137.29, 129.90, 127.63, 75.97, 71.76, 71.38, 58.85, 55.27, 21.31, 13.79. HRMS Calcd for $C_{13}H_{19}NO_5S_2$: 333.0706. Found: 333.0713.

(±)-2,3,5-*O*-Triacetyl-*N*-tosylisomannostatin A (20a). Acetic anhydride (100 μL, 98 mg, 0.98 mmol) was added to triol (±)-*N*-tosylisomannostatin A (**20**) (29.2 mg, 87.6 μmol) and DMAP (2 mg, 16 μmol) in anhydrous pyridine (1 mL). After stirring at room temperature for 8 h, the mixture taken up in dichloromethane, washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. Solvent was removed in vacuo, and the residue was chromatographed on a 1 × 10 cm column of silica gel to afford the triester **20a** as a white residue (7.0 mg, 19%): IR (neat film from $CDCl_3$ solution) 3277, 2925, 2851, 1747 (s), 1440, 1376, 1339, 1221, 1187, 1165, 1093, 1041, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, J = 8.4 Hz, 2 H), 7.31 (d, J = 7.9 Hz, 2 H), 5.15 (br d, J = 10.1 Hz, 1 H, -NH), 5.09 (t, J = 4.9 Hz, 1 H, H-2), 4.98 (m, 2 H, H-1,4), 4.09 (ddd, J = 11.5, 6.7, 5.0 Hz, 1 H, H-3), 3.08 (dd, J = 6.8, 4.6 Hz, 1 H, H-5), 2.43 (s, 3 H), 2.15 (s, 3 H), 2.05 (s, 3 H), 2.02 (s, 3 H), 1.99 (s, 3 H); LRMS (m/z) 340 (13), 339 (16), 298 (23), 297 (32), 296 (12), 292 (11), 281 (11), 281 (13), 280 (91), 268 (20), 250 (40), 249 (10), 244 (14), 228 (14), 226 (10), 215 (14), 186 (21), 184 (41), 157 (13), 142 (80), 141 (14), 139 (36), 126 (22), 115 (20), 112 (16), 103 (22). HRMS Calcd for $C_{19}H_{25}NO_8S_2$–$2(CH_3CO_2)$: 340.0677. Found: 340.0664.

(±)-2,2-Dimethyl-4*S*-[(4-methylphenyl)sulfonamido]cyclopent-5-eno-[4,5-*d*]3a*S*,6a*R*-dioxolane (19b). A mixture of diol **19** (170 mg, 0.631 mmol), (1*R*)-(−)-10-camphorsulfonic acid (3 mg, 12.9 μmol), and dimethoxypropane (0.72 mL, 5.86 mmol) in anhydrous acetone (6 mL, dried over 3 MS) was stirred until TLC (50% ethyl acetate/hexanes) indicated complete consumption of starting material (25 min). Sodium bicarbonate (43 mg, 0.51 mmol) was added, and the slurry was stirred for 5 min. The reaction mixture was filtered through 2 × 5 cm silica gel wetted with 50% ethyl acetate/hexanes, and the silica gel was then eluted with 70 mL of 50% ethyl acetate/hexanes. The filtrate was concentrated in vacuo. The resulting oil was chromatographed on a 2 × 9 cm silica gel column with 20–50% ethyl acetate/hexanes (gradient elution) to afford, upon removal of solvent in vacuo, 181.2 mg of acetonide **19b** as clear crystals (92.8%): mp 107–109 °C (white-beige crystals from ethyl acetate): IR (neat film from $CDCl_3$ solution) 3285 (br), 2987, 2936, 1421, 1381, 1372, 1336, 1224, 1217, 1163, 1093, 1059, 929, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.82 (br d, J = 8.4 Hz, 2 H), 7.32 (d, J = 8.0 Hz, 2 H), 5.81 (dt, J = 5.7, 1.9 Hz, 1 H), 5.63 (ddt, J = 5.7, 1.7, 0.9 Hz, 1 H), 5.29 (br d, J = 9.1 Hz, 1 H, N-H), 4.89 (m, 1 H), 4.225–4.31 (m, 1 H), 4.19–4.225 (m, 1 H), 2.44 (s, 3 H), 1.35 (s, 3 H), 1.23 (s, 3 H); ^{13}C NMR (CD_3CN, 50 MHz) δ 143.74, 137.68, 133.44, 129.70, 127.42, 111.67, 83.43, 76.25, 58.13, 27.34, 26.00, 21.32. HRMS Calcd for $C_{14}H_{16}NO_4S$–CH_3: 294.0801. Found: 294.0800. Anal. Calcd for $C_{14}H_{16}NO_4S$: C, 58.23; H, 6.19; N, 4.53; S, 10.36. Found: C, 58.52; H, 6.22; N, 4.40; S, 10.37.

Epoxide 21. To a solution of acetonide **19b** (98.0 mg, 0.317 mmol) and anhydrous dibasic sodium phosphate (85.2 mg, 0.60 mmol) in anhydrous dichloromethane (2 mL) at −78 °C was added a solution of peroxytrifluoroacetic acid [prepared by the addition of trifluoroacetic anhydride (0.183 mL, 1.30 mmol) to a stirred suspension of 83.8% hydrogen peroxide (38.6 mg, 0.951 mmol) in anhydrous dichloromethane (0.80 mL) at 0 °C followed by warming to room temperature.] The mixture was allowed to warm to room temperature, and the reaction mixture was taken up in chloroform (30 mL) and washed with 10% aqueous sodium bisulfite. (Some of the mixture was spilled!) The mixture was washed with saturated aqueous sodium chloride and dried over magnesium sulfate. Removal of solvent in vacuo afforded 89.5 mg of a mixture of 12.2 mg of starting olefin **19b** and 77.3 mg of epoxide **21** (75.0%, 90.2% based on starting material): mp 132.5–134 °C (white solid residue from acetone/hexanes): IR (neat film from $CDCl_3$ solution) 3481, 2934, 2926, 1338, 1153, 1234, 1091, 1034, 1016, 962, 915, 882, 850, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.83 (dt, J = 6.5, 2.1 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 5.38 (d, J = 10.1 Hz, 1 H, -TsNH), 4.55 (dd, J = 6.6, 1.7 Hz, 1 H), 4.15 (tt, J = 6.8, 1.0 Hz, 1 H), 3.90 (ddd, J = 10.0, 6.9, 1.7 Hz, 1 H), 3.48 (ddd, J = 2.6, 1.7, 1.1 Hz, 1 H), 3.44 (ddd, J = 2.6, 1.7, 0.9 Hz, 1 H), 2.42 (s, 3 H, Ar-CH_3), 1.49 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.43, 138.66, 130.19, 128.13, 101.55, 75.14, 70.88, 62.75, 62.19, 56.47, 27.59, 26.31, 21.66. HRMS Calcd for $C_{15}H_{19}NO_5S$–CH_3: 310.0750. Found: 310.0737. Anal. Calcd for $C_{15}H_{19}NO_5S$: C, 55.37; H, 5.89; N, 4.30; S, 9.86. Found: C, 55.66; H, 5.92; N, 4.18; S, 9.85.

(±)-2,2-Dimethyl-4*R*-hydroxy-6*S*-[(4′-methylphenyl)sulfonamido]-5*R*-(methylthio)cyclopentano[3,4-*d*]-3a*S*,6a*R*-dioxolane (13c) and (±)-2,2-Dimethyl-5*S*-hydroxy-6*R*-[(4′-methylphenyl)sulfonamido]-4*R*-(methylthio)cyclopentano[3,4-*d*]-3a*R*,6a*R*-dioxolane (22). Methyllithium (2.33 mL, 1.4 M in ether) was added to a −78 °C solution of freshly distilled dimethyl disulfide (0.292 mL, 3.26 mmol) in anhydrous ether (1 mL). After stirring 0.5 h at room temperature and then recooling to 0 °C, the resulting slurry was added by syringe to a −5 °C solution of the epoxide **21** (0.2129, 0.652 mmol) in THF (3 mL) (note that warming with a heat gun was required to effect disolution of the epoxide in THF). After 9 h at −5 °C the reaction mixture was taken up in chloroform (80 mL) and washed with saturated aqueous sodium bicarbonate (20 mL) and saturated aqueous sodium chloride (20 mL). The organic layer was dried over magnesium sulfate, and solvent was removed in vacuo.

The residue was chromatographed on a 3 × 11.5 cm column of silica gel with 30–50% ethyl acetate/hexanes (gradient elution) to afford thioether **13c** (190 mg, 78.1%) and thioether **22** (41.8 mg, 17.2%).

Thioether **13c**: mp 180–181 °C (white solid from ethyl acetate); IR (neat film from $CDCl_3$ solution) 3505 (br), 3279 (br), 2987, 2925, 1438, 1400, 1384, 1328, 1251, 1210, 1160, 1092, 1068, 1024, 983, 912, 870, 814 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.83 (br d, J = 8.4 Hz, 2 H), 7.31 (d, J = 7.9 Hz, 2 H), 5.14 (br d, J = 9.9 Hz, 1 H, N-H), 4.45 (dd, J = 5.7, 5.5 Hz, 1 H), 4.19 (dd, J = 5.5, 5.3 Hz, 1 H), 3.56 (ddd, J = 10.2, 9.2, 5.4 Hz, 1 H), 3.26 (ddd, J = 11.4, 9.7, 4.8 Hz, 1 H), 2.61 (dd, J = 11.4, 10.3 Hz, 1 H), 2.44 (s, 3 H, Ar-CH_3), 2.03 (s, 3 H, S-CH_3), 1.47 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.90, 137.57, 111.27, 129.69, 127.54, 76.66, 72.49, 55.67, 51.90, 25.45, 23.80, 21.37, 12.20. HRMS Calcd for $C_{16}H_{23}NO_5S_2$: 373.1019. Found:

373.1017. Anal. Calcd for $C_{16}H_{23}NO_5S_2$: C, 51.54; H, 6.21; N, 3.75; S, 17.17; MW, 373.1019. Found: C, 51.50; H, 6.15; N, 3.47; S, 16.97; MW, 373.1017.

Thioether **22**: IR (neat film from $CDCl_3$ solution) 3527 (br), 3372 (br), 3280 (br), 2986, 2923, 1427, 1380, 1337, 1267, 1210, 1161, 1083, 1046, 936, 880, 848, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.82 (dt, J = 8.4, 2.0 Hz, 2 H), 7.31 (br d, J = 8.0 Hz, 2 H), 5.41 (br d, J = 9.8 Hz, 1 H, N-H), 4.4–4.50 (m, 2 H), 3.88 (dtd, J = 9.7, 4.6, 1.2 Hz, 1 H), 3.72 (bddd, J = 9.2, 4.5, 0.9 Hz, 1 H), 3.17 (s, 1 H), 2.44 (s, 3 H, Ar-CH_3), 2.13 (s, 3 H, S-CH_3), 1.46 (s, 3 H), 1.24 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 143.82, 137.64, 129.80, 127.34, 111.47, 83.69, 78.46, 77.15, 56.69, 52.89, 26.10, 22.98, 21.36, 15.22; LRMS (m/z) 374 (4), 358 (17), 308 (10), 297 (18), 280 (7), 268 (18), 257 (12), 256 (71), 254 (38), 250 (9), 218 (19), 213 (11), 160 (18), 155 (70), 144 (12), 143 (11), 142 (45), 139 (27), 103 (46), 99 (30), 98 (31), 96 (17), 92 (21), 91 (100). HRMS Calcd for $C_{16}H_{23}NO_5S_2$ + H: 374.1097. Found: 374.1103.

(±)-6*S*-Amino-2,2-dimethyl-4*R*-hydroxy-5*R*-(methylthio)cyclopentano[3,4-*d*]-3a*S*,6a*R*-dioxolane (13d). Small pieces of sodium (freshly cut, washed with hexanes, ca. 50 mg) were added to sulfonamide **13c** (202 mg, 0.541 mmol) in 50 mL of liquid ammonia at −78 °C until the solution remained blue. The reaction was quenched by addition of ammonium chloride until the reaction was colorless. The cooling bath was removed, the ammonia was blown off under a stream of nitrogen, and the residue was immediately flushed through a 1.5 × 4 cm column of silica gel with a 10:90:1 methanol/chloroform/concentrated ammonium hydroxide to give the pure amine **13d** as an oil (115.4 mg, 97.3%): IR (neat film from $CDCl_3$ solution) 3400 (br), 3371, 3298, 2986, 2923, 1583, 1438, 1382, 1251, 1209, 1162, 1149, 1097, 1050, 978, 903, 859 cm^{-1}; ^1H NMR ($CDCl_3$ filtered through basic alumina, 300 MHz) δ 4.50 (m, 2 H), 3.63 (dd, J = 9.9, 5.3 Hz, 1 H), 2.63 (dd, J = 11.3, 4.5 Hz, 1 H), 2.45 (t, J = 10.0 Hz, 1 H), 2.15 (s, 3 H), 1.47 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 110.64, 78.79, 76.77, 74.73, 55.58, 53.86, 25.67, 24.03, 12.55. HRMS Calcd for $C_9H_{17}NO_3S$: 219.0930. Found: 219.0928.

(±)-Mannostatin A (13). A solution of the acetonide **13d** (0.115 g, 0.524 mmol) in 60% aqueous trifluoroacetic acid (1 mL, prepared from freshly distilled trifluoroacetic acid and glass-distilled water) was stirred at 60 °C for 6.5 h. Solvent was removed in vacuo. ^1H NMR spectroscopy (D_2O) showed a single compound uncontaminated by starting material. The mixture was loaded onto a 1 × 9 cm column of IRA 400 ion exchange resin (equilibrated to the OH^- form with 1 N sodium hydroxide and washed with deionized water till the eluent was neutral). The column was eluted with 1.1 L of deionized water, and the water was removed in vacuo to afford 59.9 mg (86% yield) of mannostatin A as its free base: IR (HCl salt, KBr) 3390 (br s), 3000, 1610 (br w), 1500, 1125, 1080, 1060 cm^{-1}; ^1H NMR (trifluoroacetate salt; D_2O, referenced to HOD at δ 4.65; 400 MHz) δ 4.06 (dd, J = 6.4, 3.9 Hz, 1 H), 3.88 (t, J = 4.3 Hz, 1 H), 3.78 (dd, J = 7.6, 4.9 Hz, 1 H), 3.32 (t, J = 6.8 Hz, 1 H), 2.89 (dd, J = 7.6, 7.3 Hz, 1 H), 1.93 (s, 3 H); ^1H NMR (free base; D_2O, external reference; TMS in CCl_4; 400 MHz) δ 3.78–3.85 (m, 3 H), 2.76 (dd, J = 8.8, 5.2 Hz, 1 H), 2.59 (dd, J = 8.3, 6.2 Hz, 1 H), 1.97 (s, 3 H); ^{13}C NMR (CD_3OD, 50 MHz) δ 78.26, 73.97, 73.68, 59.72, 58.20, 13.96. HRMS Calcd for $C_6H_{13}NO_3S$: 179.0626. Found: 179.0622.

(±)-Tetraacetylmannostatin A. A mixture of mannostatin A acetonide **13d** (7.6 mg, 34.7 μmol) and dry amberlyst-15 (36 mg) in methanol (0.2 mL) and deionized water (50 μL) was stirred 8 h. The mixture was filtered, the resin was washed with 2 N ammonium hydroxide to remove the product, and the filtrate was concentrated in vacuo to give mannostatin A as an oily residue. The latter was taken up in pyridine (0.30 mL) to which acetic anhydride (30 μL, 32 mg, 0.32 mmol) was added. After 9 h at room temperature, dichloromethane (10 mL) was added. The solution was washed with saturated aqueous sodium bicarbonate (2 mL) and saturated aqueous sodium chloride (2 mL). After drying over magnesium sulfate, solvent was removed in vacuo to afford pure (±)-mannostatin A tetraacetate (8.8 mg, 73.1%): IR (neat film from $CDCl_3$ solution) continued 3320 (br), 2925, 1750 (s), 1655, 1542, 1431 (w), 1375, 1251, 1224, 1160 (w), 1083, 1047, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.68 (d, J = 9.2 Hz, 1 H, AcN-H), 5.40 (dd, J = 5.9, 4.0 Hz, 1 H, H-2), 5.33 (dd, J = 5.6, 4.2 Hz, 1 H, H-2), 5.17 (t, J = 6.2 Hz, 1 H, H-1), 4.53 (ddd, J = 9.1, 8.5, 5.5 Hz, 1 H, H-4), 3.10 (dd, J = 8.3, 6.5 Hz, 1 H, H-5), 2.16 (s, 3 H), 2.12 (s, 3 H), 2.08 (s, 3 H), 2.06 (s, 3 H), 2.04 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.73, 169.65, 169.41, 169.06, 77.21, 73.89, 70.92, 70.58, 53.31, 51.94, 23.02, 20.27, 20.14, 13.29; LRMS (m/z) 287 (3), 227 (22), 186 (34), 185 (100), 170 (10), 168 (9), 167 (22), 144 (24), 143 (29), 142 (12), 138 (27), 137 (76), 128 (13), 127 (19), 126 (91), 125 (15), 114 (18), 103 (32). HRMS Calcd for $C_{14}H_{21}NO_7S$–CH_3CONH: 287.0599. Found: 287.0580.

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