Stereoselective Synthetic Approaches to Highly Substituted Cyclopentanes via Electrophilic Additions to Mono-, Di-, and Trisubstituted Cyclopentenes

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Received January 25, 2000

Electrophilic additions to allylically substituted alkenes are of broad synthetic utility. The control of stereoselectivity in such reactions has attracted considerable interest. However, the effect of allylic and homoallylic substituents in cyclopentenyl systems has not been investigated systematically. Studies on a series of mono, di-, and trisubstituted cyclopentenes are reported in which *trans*-vicinal-additions favor a *syn*-selective approach of electrophiles to the cyclopentene system. The formal addition of HOBr, HOCl, CH_3SCl, and dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF)/NaN_3 with a variety of cyclopentene substrates has been carried out, and the effects of various allylic substituents on these selectivities have been examined. Additions of HOBr, HOCl, and DMTSF to highly functionalized substrates proceed predictably with *syn* selectivity, giving predominantly or exclusively one product. Methanesulfenyl chloride additions are less predictable, but can be tuned by suitable alteration of solvent and substrate. Results have proven useful in total syntheses of (+)-trehazolin and (+)-allosamidin.

Introduction

The promising biological activity of several new cyclopentane-containing natural products has generated considerable interest in their total synthesis. The polyhydroxylated cyclopentane rings in allosamidin **1** (Figure 1), trehazolin **2**, the keruffarides and crasserides **3**, and mannostatins A and B (**4** and **5**, respectively) are thought to mimic the structure of carbohydrates. As a result, many of these substances inhibit glycoside-processing enzymes, and total syntheses of several have been reported.[1−4]

In previous synthetic studies reported by our laboratory, penta- and hexasubstituted cyclopentane units were constructed in a two-stage process (Scheme 1). Stage 1 involved the well-precedented heterocycloaddition of a monosubstituted cyclopentadiene like **6**, which, upon reduction of the intermediate bicyclic adduct **7**, afforded 3,4,5-trisubstituted cyclopentenes such as **8**. Stage 2 of the process involved a vicinal functionalization of the bis-allylically substituted alkene group in **8** to introduce two additional substituents leading to **9**. For many stage 2 additions, the factors affecting stereoselectivity are not well-understood. In the case of vicinal dihydroxylation, numerous reports of the osmylation of such cyclopentenes have appeared,[5] although no clear stereochemical trend

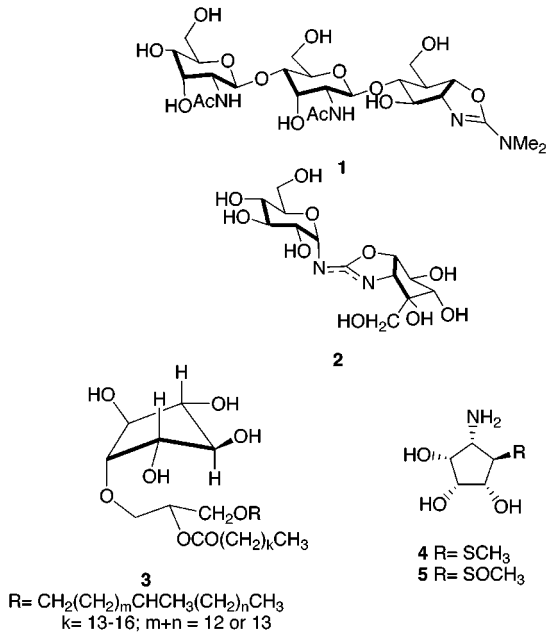


Figure 1. Structures of some naturally occurring cyclopentitols.

(1) Allosamidin: (a) Kassab, D.; Ganem, B. *J. Org. Chem*. **1999**, *64*, 1782−1783. (b) Goering, B. K.; Ganem, B. *Tetrahedron Lett*. **1994**, *35*, 6997−7000. (c) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 1261−1263. (d) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1991**, *113*, 5863−5864. (e) Takahashi, S.; Terayama, H.; Kuzuhara, H. *Tetrahedron Lett.* **1992**, *33*, 7565−7568.

(2) Trehazolin: (a) Goering, B. K.; Li. J.; Ganem, B. *Tetrahedron Lett*. **1995**, *36*, 8905−8908. (b) Li, J.; Lang, F. R.; Ganem, B. *J. Org. Chem*. **1998**, *63*, 3403−3410. (c) Ogawa, S.; Uchida, C. *Chem. Lett.* **1993**, 173−176. (d) Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Org. Chem*. **1994**, *59*, 813−822. (e) Ledford, B. E.; Carreira, E. M. *J. Am. Chem. Soc.* **1994**, *117*, 11811−11812.

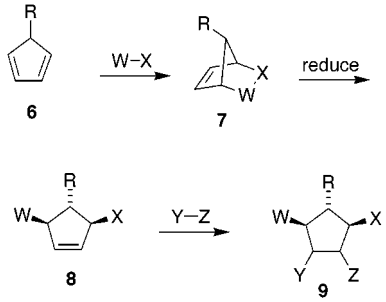
(3) Mannostatins (a) King, S. B.; Ganem, B. *J. Am. Chem. Soc*. **1991**, *113*, 5089−5090. (b) King, S. B.; Ganem, B. *J. Am. Chem. Soc*. **1994**, *116*, 562−570. (c) Knapp, S.; Phar, T. G. M. *J. Org. Chem*. **1991**, *56*, 4096−4097. (d) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1991**, *113*, 6317−6318. (e) Ogawa, S.; Kimura, H.; Uchida, C.; Ohashi, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1695−1705. (f) Ling, R.; Mariano, P. S. *J. Org. Chem*. **1998**, *63*, 6072−6076.

(4) For a recent review, see (g) Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev*. **1999**, *99*, 779−844.

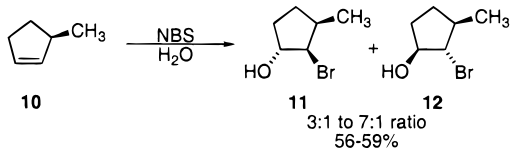
(5) See inter alia: (a) Hanselaer, R.; Samson, M.; Vandewalle, M. *Tetrahedron* **1978**, *34*, 2393−2397. (b) Trost, B. M.; Kuo, G.-H.; Benneche, T. J. *Am. Chem. Soc.* **1988**, *110*, 621−622. (c) Poli, G. *Tetrahedron Lett*. **1989**, *30*, 7385−7388. (d) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc*. **1992**, *114*, 980−985. (e) Donohoe, T. J.; Garg, R.; Moore, P. R. *Tetrahedron Lett*. **1996**, *37*, 3407−3410. (f) Donohoe, T. J.; Moore, P. R.; Waring, M. J.; Newcombe, N. J. *Tetrahedron Lett.* **1997**, *38*, 5027−5030.

10.1021/jo000101f CCC: $19.00
Published on Web 06/06/2000

Scheme 1



Scheme 2



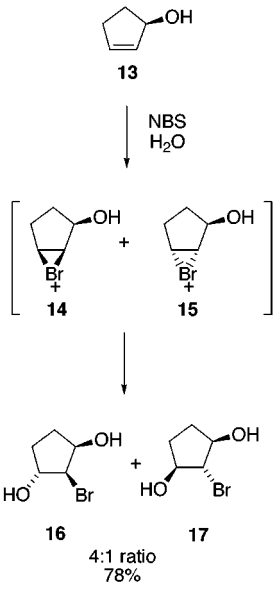
has emerged.[6] Electrophilic addition reactions to allylically substituted alkenes are of broad synthetic utility, and the control of stereoselectivity in such reactions has attracted considerable interest[7,8] However, the effect of allylic and homoallylic substituents in cyclopentenyl systems has not been investigated systematically.[9]

Here we report studies on a series of mono, di-, and trisubstituted cyclopentenes in which we have observed a pattern of *trans*-vicinal-additions derived from the approach of electrophiles *syn* to allylic substituents on the cyclopentene system. The stereochemical outcome with a variety of substrates and the effect of various allylic substituents on these selectivities have been examined. Our results have proven useful in total syntheses of (+)-trehazolin[2a,b] and (+)-allosamidin[1a]

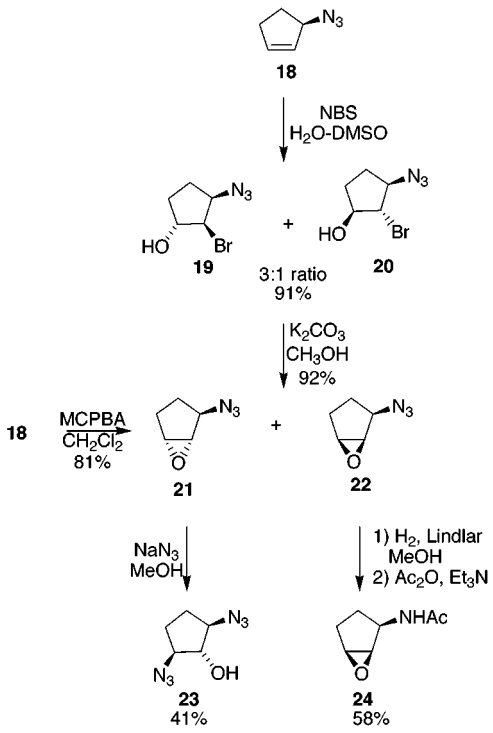
Results

HOX Additions. Prior to the present study, the stereoselectivity of HOBr addition to a substituted cyclopentene, formally achieved using NBS−H_2O, has been examined in the case of 3-methylcyclopentene **10** (Scheme 2).[10] Reaction of **10** with NBS in water was reported to give a mixture of bromohydrins **11** and **12**, in ratios of 3:1 to 7:1. Encouraged by that finding, our laboratory subsequently examined the reaction of 2-cyclopentenol **13** (Scheme 3) with NBS in H_2O which afforded bromodiols **16** and **17** (4:1 ratio) in 78% overall yield.[11] Direct NMR monitoring of the addition in D_2O confirmed that **13** was completely consumed, that no other products were formed, and that the 4:1 product ratio was unaffected by the workup and isolation. The minor product **17** arises by the expected *trans*-opening of *anti*-bromonium ion **15**,

Scheme 3



Scheme 4



and its *meso*-structure was readily established by NMR. The major product **16** can be seen to arise from the *syn*-bromonium ion **14** by a similar mechanism.[1b]

As an additional test of the method, 3-azidocyclopentene[12] **18** (Scheme 4) was exposed to NBS in H_2O (with DMSO as a cosolvent to improve solubility), affording a mixture of two products (3:1 ratio) in 91% yield. The

(6) Goering, B. K.; Ph.D. Dissertation, Cornell University, 1995.

(7) For studies on electrophilic additions, see: De La Mare, P. B. D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems*; Elesevier: Amsterdam, 1982. Fahey, R. C. *Top. Stereochem*. **1968**, *3*, 237−342.

(8) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650−663.

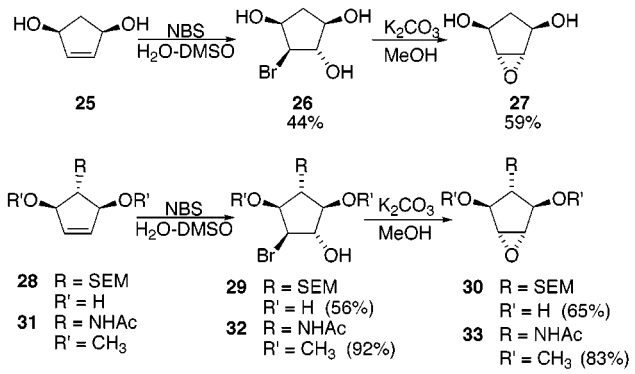
(9) For seminal work on the stereochemistry of additions to substituted cyclohexenes, see (a) Barili, P. L.; Bellucci, G.; Marioni, F.; Morelli, I.; Scartoni, V. *J. Org. Chem*. **1972**, *37*, 4353−4357. (b) Bellucci, G.; Berti, G.; Ingrosso, G.; Mastrorilli, E. *Tetrahedron Lett*. **1973**, 3911−3914. (c) Bellucci, G.; Berti, G.; Bianchini, R.; Ingrosso, G.; Mastrorilli, E. *Gazz. Chim. Ital*. **1976**, *106*, 955−966. (d) Bellucci, G.; Bianchini, R.; Ingrosso, G.; Mastrorilli, E. *Gazz. Chim. Ital*. **1978**, *108*, 643−650.

(10) Finnegan, R. A.; Wepplo, P. J. *Tetrahedron* **1972**, *28*, 4267−4271.

(11) Ratios were obtained by integration of ^1H NMR spectra of mixtures. Typically, one or more pairs of peaks were sufficiently well-resolved to obtain accurate integration values with ±10% precision. Most reported yields are unoptimized. Because of the water-solubility and/or volatility of many low-molecular weight target compounds, the ratios of products, whenever appropriate, were measured using NMR for in situ reaction monitoring and the results compared with the ratios of isolated products.

(12) Chmielowiec, U.; Uzarewicz, I.; Uzarewicz, A. *Pol. J. Chem*. **1990**, *64*, 613−619.

Scheme 5

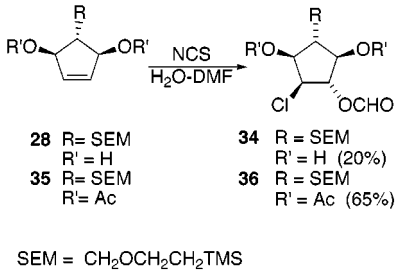


major and minor products were assigned structures **19** and **20**, respectively, on the basis of the following transformations. The product mixture was treated with K_2CO_3 in methanol to furnish two epoxyazides, **21** and **22**. Peracid epoxidation of **18** also afforded **21** and **22** in a 1.3:1 ratio, and the two compounds were readily separated by chromatography. The structure of the major isomer was established as the *trans*-epoxyazide **21** by its reaction with NaN_3, which afforded the *meso*-hydroxydiazide **23**. The structure of the minor *cis*-epoxyazide **22** was confirmed by reduction of the azide and acetylation of the resulting amine to afford *cis*-epoxyacetamide **24**, which was spectroscopically indistinguishable from an authentic sample prepared according to a literature method.[13] Thus, the addition of HOBr to **18** proceeded predominantly via the *syn*-bromonium ion to afford **19** as the major addition product.

The formal addition of HOBr to several more highly substituted cyclopentenes also favored products arising from an initial *syn*-bromonium ion (Scheme 5). Reaction of *cis*-cyclopentene-1,4-diol **25**[14] with NBS in H_2O gave bromotriol **26** as the only product in 44% yield. That **26** was the only product formed was confirmed by ^1H NMR monitoring of a parallel reaction performed in DMSO-d_6 and D_2O, which indicated <10% formation of other stereoisomers. The structure of **26** was established by cyclization in base to the *meso*-epoxydiol **27**, whose spectroscopic properties were distinct from those of the isomeric *meso*-epoxydiol obtained by the *syn*-selective peracid epoxidation of **25**.[15] Addition of HOBr in DMSO−H_2O to the protected triol **28** afforded bromohydrin **29** in 56% yield (Scheme 5).[1b] Reaction of **29** with K_2CO_3 furnished epoxide **30**, whose spectral properties differed from those of the corresponding epoxide arising from peracid oxidation of **28**.

The reaction of NBS−H_2O with dimethoxyacetamide **31** (Scheme 5) was studied under similar conditions. Compound **31** was prepared by the photolysis of pyridinium perchlorate in methanol.[16] A single bromohydrin **32** was isolated in 92% yield, which was transformed in base to the corresponding epoxyacetamide **33**. Compound **33** was identical with the product of peracid oxidation of **31**, and its structure was unambiguously established by X-ray crystallography.

Scheme 6



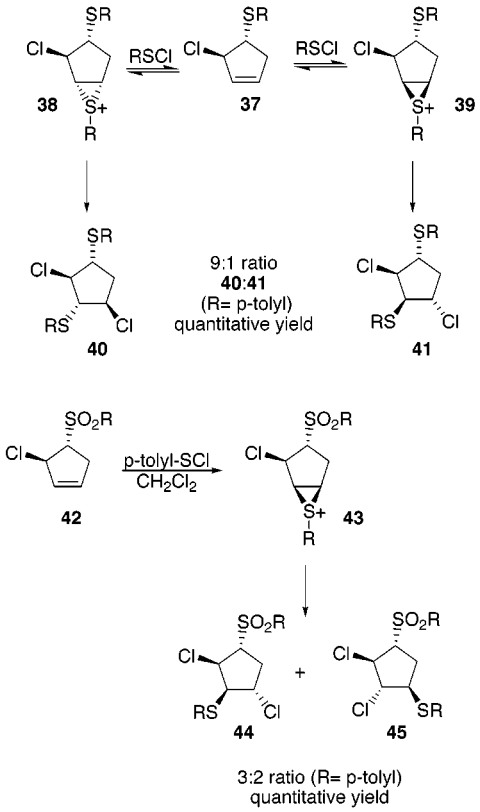
The formal addition of HOCl to substituted cyclopentenes also favored products arising from *syn*-chloronium ion formation. Reaction of *N*-chlorosuccinimide in H_2O−DMF with diol **28** furnished the halohydrin formate **34**, although only in 20% yield. The structure of **34** was confirmed by reaction with base to afford epoxide **30**, which was identical with an authentic sample. The reaction of NCS−H_2O with diacetate **35**[1a] gave better results, producing **36** (65% yield), which also formed **30** upon treatment with base.In summary, the addition of hypohalous acids to substituted cyclopentenes afforded predominantly *trans*-1,2-halohydrins arising from *syn*-addition of X^+ to the allylic substituent. This preference for 1,2-addition products derived from intermediate *syn*-halonium ions appears to be independent of the nature of the substituent (i.e., alkyl, OH, OR) and is most pronounced with polysubstituted cyclopentenes.

MeSCl Additions. The stereochemistry of alkyl- and arylsulfenyl chloride additions to substituted cyclopentenes was first examined by Hartke et al. (Scheme 7).[17] In contrast to HOBr and HOCl additions, no clear stereochemical trend was apparent in this study. Addition of *p*-tolyl sulfenyl chloride to a solution of chlorosulfide **37** in CH_2Cl_2 afforded dichlorodisulfides **40** and **41** as a 9:1 ratio in high yield. The predominant product **40** apparently arose from the intermediate **38** in which a putative thiiranium ion intemediate was oriented *anti* to the allylic substituent. In contrast, the same addition to the corresponding chlorosulfone **42** afforded products **44** and **45** apparently arising from the regioisomeric opening of a common *syn*-thiiranium ion of structure **43**.

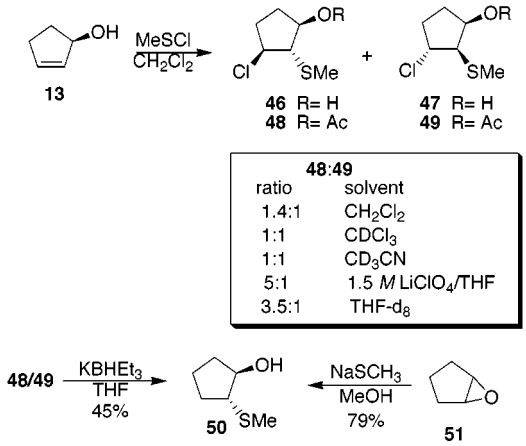
The present study examined the addition of MeSCl to 2-cyclopenten-1-ol **13** in a variety of solvents (Scheme 8). When CH_3SCl was combined with **13** in CH_2Cl_2, a 1.4:1 ratio of products was obtained in 60% yield after acetylation. Since the two products were unstable to chromatography, the mixture was immediately acetylated. The product mixture displayed well-resolved NMR signals for the two components, consistent with 1-chloro-2-thio-3-acetoxycyclopentanes. However, pure samples of each product could not be obtained by chromatography, and nuclear Overhauser enhancement (NOE) measurements on the mixture were unable to provide unambiguous stereochemical assignments. Ultimately, the two addition products were assigned structures **46** (major) and **47** (minor) on the basis of the following chemical correlation of their derived acetates **48** and **49**. After a number of unsuccessful attempts using Bu_3SnH, Na−NH_3, and Na−naphthalene, the dehalogenation−deacetylation of a

(13) Vince, R.; Daluge, S. *J. Med. Chem.* **1974**, *17*, 578−583.
(14) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876−877.
(15) (a) Sable, H. Z.; Adamson, T.; Tolbert, B.; Posternak, Th. *Helv. Chim. Acta* **1963**, *66*, 1157−1165. (b) Theil, F.; Schick, H.; Winter, G.; Reck, G. *Tetrahedron* **1991**, *47*, 7569−7582.
(16) Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439−4449.
(17) Hartke, K.; Jung, M.-H.; Zerbe, H.; Kampchen, T. *Liebigs Ann. Chem.* **1986**, 1268−1280.

Scheme 7



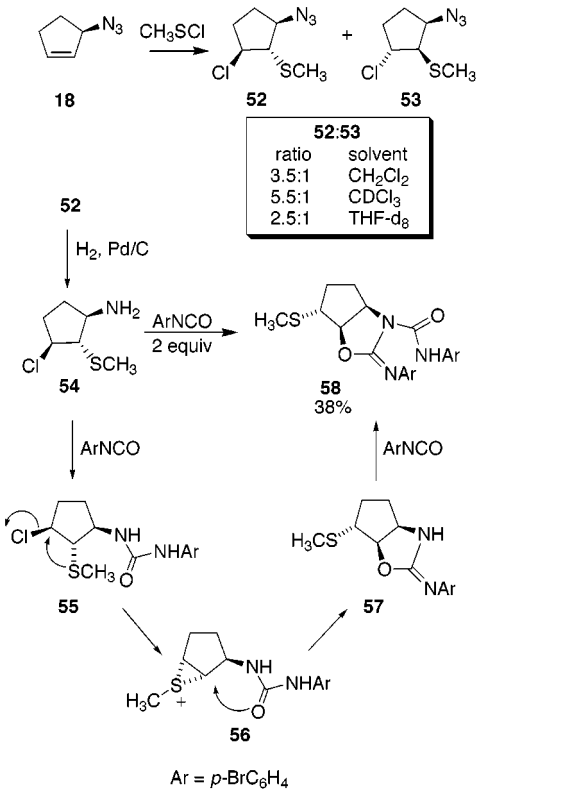
Scheme 8



sample enriched in **48** was achieved using potassium triethylborohydride to afford *trans*-2-(methylthio)cyclopentanol **50**, which was identical with an authentic sample[18] prepared from epoxycyclopentane **51** by a known method.[19]

The addition of CH_3SCl to **13** was monitored by ^1H NMR, and the product mixture was studied as a function of solvent (Scheme 8). No stereoselectivity was observed when CH_3SCl additions were performed in $CDCl_3$ or CD_3CN, but a modest preference for **46**, the product of *anti*-thiiranium ion opening, was noted when the reaction was conducted in THF-d_8. The reaction in THF was little affected when carried out in the presence of 1.5 M $LiClO_4$, which has been shown to increase the ionic character of sulfenyl chloride additions.[20]

Scheme 9



A similar study of the reaction of CH_3SCl with 3-azidocyclopentene **18** was carried out to afford a mixture of two addition products (Scheme 9). While NMR chemical shifts and coupling constants indicated that each product was a 1-chloro-2-(methylthio)-3-azidocyclopentane, no clear-cut stereochemical assignments could be made. The major product was ultimately assigned structure **52** by hydrogenation over palladium on carbon, and condensation of the resulting amine with *p*-bromophenyl isocyanate (2 equiv). That two-step process, which was intended to prepare the corresponding crystalline *N*-arylurea for X-ray diffraction analysis, afforded instead an unxpected bicyclic urea in 38% yield, whose solid-state structure was unambiguously shown to be **58** by X-ray analysis (Figure 2).

Given the regiochemistry assigned by NMR, the origin of **58** was best rationalized from the all-*trans*-aminocyclopentane **54** as shown in Scheme 9. Following the initial formation of urea **55**, a formal 1,2-methylthio shift via thiiranium **56** led to **57**, which then reacted with a second equiv of ArNCO. The structural assignment established that CH_3SCl additions to **18** afforded a major product **52** formally arising from the *anti*-azidothiiranium ion intermediate predominated, with ratios of **52** to **53** ranging from 2.5:1 in THF to 5.5:1 in $CDCl_3$.

The reaction of more highly substituted cyclopentenes with CH_3SCl was also investigated. In the case of *cis*-1,4-diacetoxy-2-cyclopentene **59** (Scheme 10), reaction with CH_3SCl in CH_2Cl_2 or CCl_4 produced a single diacetoxychlorosulfide in 80−85% yield. The product was assigned structure **60** based on its saponification and

(18) Goodman, L.; Benitez, A.; Baker, B. R. *J. Am. Chem. Soc.* **1958**, *80*, 1680−1686.

(19) Conte, V.; DiFuria, F.; Modena, G.; Sbampato, G.; Valle, G. *Tetrahedron: Asymmetry* **1991**, *2*, 257−276

(20) Smit, W. A.; Zefirov, N. S.; Bodrikov, I. V.; Krimer, M. Z. *Acc. Chem. Res.* **1979**, *12*, 282−288.

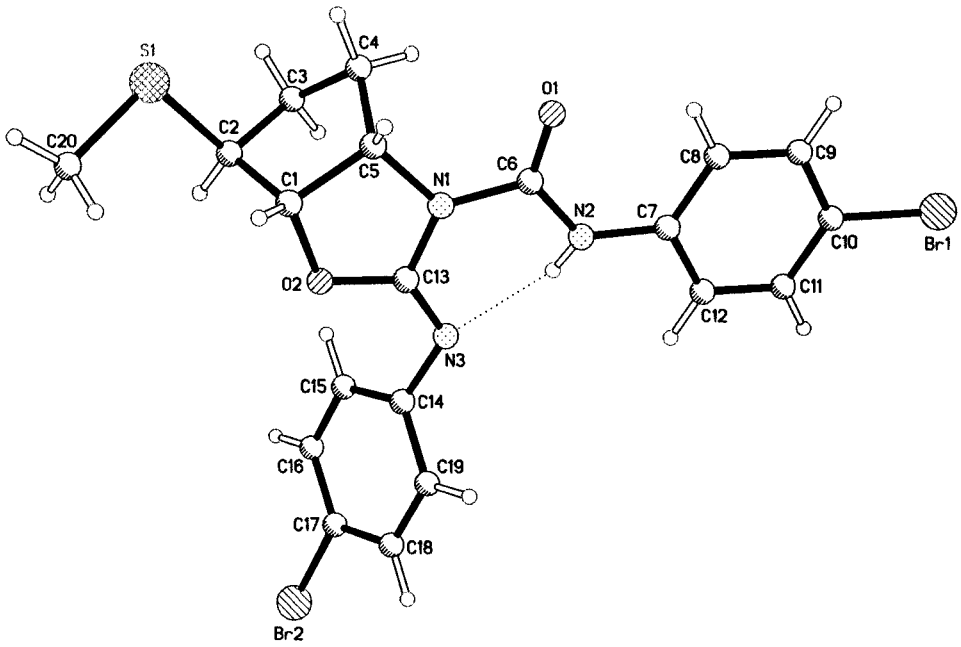
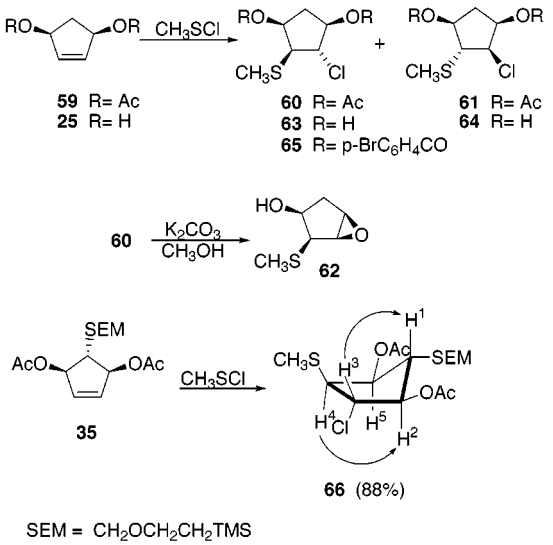


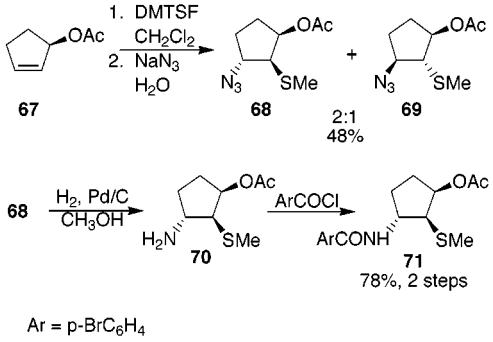
Figure 2. X-ray crystal structure of rearrangement product **58**.

Scheme 10



SEM = $CH_2OCH_2CH_2TMS$

Scheme 11



Ar = p-BrC_6H_4

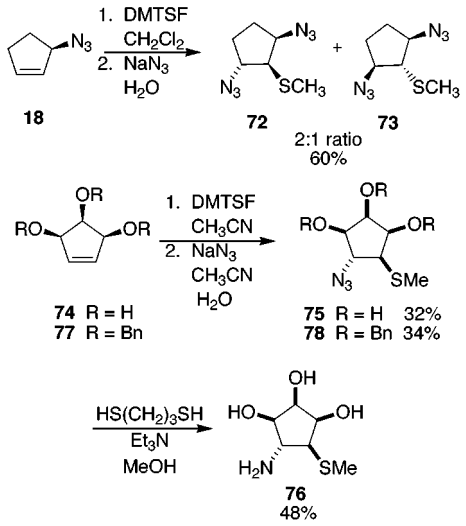
cyclization in K_2CO_3−CH_3OH to form non-*meso* epoxide **62**. The corresponding *cis*-cyclopentene-1,4-diol **25** reacted with CH_3SCl to afford a 2:1 mixture of adducts in 81% yield. The isomeric products could be separated by chromatography, and the major diol was shown to be **63** by acetylation and correlation with **60**. Stereochemical assignments were further secured by conversion of **63** to the corresponding crystalline bis-*p*-bromobenzoate **65**, whose structure was solved by X-ray diffraction analysis. Interestingly, the stereoselectivity of CH_3SCl addition to **25** was reversed in d_8-THF, giving a 1:1.5 ratio of **63** and **64**. Addition of CH_3SCl to diacetate **35**[1a] proceeded via *syn*-episulfonium ion formation to afford chlorothioether **66** as the sole product (88% yield). The structure of **66** was confirmed by nuclear Overhauser enhancement (NOE) spectroscopy, where NOE effects were observed between H2 and H4, and between H1 and H3. No H1/H4 or H3/H5 NOE effects were observed.

DMTSF Additions. Dimethyl(methylthio)sulfonium tetrafluoroborate [DMTSF; CH_3SS^+ $(CH_3)_2$ BF_4^-] has been utilized for methylsulfenylation reactions of alkenes in conjunction with sources of cyanide, azide, or other nucleophiles.[21] The process results in *trans*-vicinal addition to the alkene by nucleophilic opening of a putative thiiranium ion. Attempts to react DMTSF with cyclopentenol **13** under a variety of conditions afforded complex, oligomeric products. Alternatively, a solution of cyclopentenyl acetate **67** (Scheme 11) was treated with DMTSF in CH_2Cl_2, with subsequent addition of aqueous NaN_3, and afforded a 2:1 mixture of diastereomeric products, identified as **68** and **69**, in 48% overall yield. Some deacetylation and oligomerization occurred, which lowered the yield. After careful chromatography to separate the two azidothioethers, the major isomer **68** was hydrogenated using excess Pd/C to the corresponding amine **70**, and directly aroylated using *p*-bromobenzoyl chloride to give **71**, whose structure was unambiguously established by X-ray diffraction.

Similarly, reaction of 3-azidocyclopentene **18** with DMTSF/CH_2Cl_2 and subsequently with aqueous NaN_3 afforded a 2:1 mixture of isomeric diazidomethyl sulfides **72** and **73** (Scheme 12) in 60% yield. The minor isomer

(21) (a) Trost, B. M.; Shibata, T. *J. Am. Chem. Soc.* **1982**, *104*, 3225−3228. (b) Trost, B. M.; Shibata, T.; Martin, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 3228−3230. (c) Caserio, M. C.; Kim, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3231−3233. (d) Trost, B. M.; Martin, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 4263−4265.

Scheme 12



was assigned the *meso*-diazide structure **73** by NMR. The major product **72** formally arises from azidolysis of the *syn*-azidothiiranium ion, suggesting that the stereochemistry of electrophilic DMTSF-promoted sulfenylations more closely resembles NBS−H_2O−DMSO than MeSCl additions.

Application of the DMTSF-mediated *trans*-1,2-azidosulfenylation reaction to the known[22] all-*cis*-cyclopentenetriol **74** was of interest as a short, convergent route to analogues of the potent α-mannosidase inhibitor, mannostatin. Reaction of **74** with DMTSF in CH_3CN followed by NaN_3 afforded **75** as the only isolable product in 32% yield. The stereochemistry of **75** was established by reduction of the azide group to the corresponding amine using propane-1,3-dithiol.[23] The resulting racemic aminotriol was shown to be spectroscopically distinct from synthetic (−)-mannostatin A,[3a] and assigned structure **76** corresponding to 1,5-bis-epi-mannostatin A. The same reaction of DMTSF/NaN_3 with tribenzyl ether **77** afforded **78** as the only addition product in 34% yield. Both **75** and **78** result from methanesulfenylation *syn* to the three oxygen substituents on the cyclopentene ring.

Discussion and Conclusions

The results of the present study indicate that additions of NBS−H_2O, NCS−H_2O, and DMTSF/NaN_3 to a range of hydroxy, alkoxy, and azide-containing mono-, di-, and trisubstituted cyclopentenes proceed with fair to good stereoselectivities. With these electrophiles, the stereochemistry of addition favors products derived from *syn*-approach of the initial electrophile with respect to the allylic substituent. In reactions of CH_3SCl with cyclopentenol **13** and cyclopentenyl azide **18**, the major products were derived from *anti*-addition of the electrophile, whereas the reaction of CH_3SCl with *cis*-cyclopentene-1,4-diol **25** and the corresponding diacetate **59** gave products derived exclusively from *syn*-oriented electrophilic approach.

Kahn et al., who have developed theoretical models to better understand the regio- and stereochemistry of electrophilic additions to cyclic and acyclic allylically substituted alkenes,[8,24] cite at least three factors that can affect the overall reaction. These include the relative abundance at equilibrium of each conformational isomer, the relative reactivity of each conformer, and the regio- and stereoselectivities observed in the reaction of each conformer. Moreover, some electrophilic additions may proceed stepwise via reversible, rapidly equilibrating intermediates, from which stereoisomeric products may be formed at different rates. Such intermediates may differ widely in structure and net charge (e.g., cationic, bridged halonium ions; neutral, 4-coordinate sulfuranes) and may undergo subsequent nucleophilic addition via stereochemically distinct mechanisms. While we hoped to devise a general strategy for assembling a broad range of functionalized cyclopentanes, it was evident that variations in the nature of the allylic substituent (which may coordinate, participate, or eliminate during addition) could also influence the regio- and stereochemical outcome.

Additions of NBS−H_2O and NCS−H_2O with **10**, **13**, **18**, **25**, **28**, and **31** likely involve three-membered halonium ions and were consistently *syn*-selective. Those results were in agreement with the reactivity model developed by Kahn et al. for conformers of acyclic allylic alcohols and ethers most closely corresponding to the envelope conformation of the cyclopentene ring.[8] In that model, the alkene face *syn*- to the oxygen substituent was made more reactive by interaction of nonbonded n-electrons on oxygen both with the alkene's p-electron cloud and with the incipient electrophile. Whereas such effects would be expected to be less significant in the case of allylic azide or alkyl substituents, both 3-azidocyclopentene and 3-methylcyclopentene displayed *syn* selectivities comparable to that observed with 2-cyclopentenol **13**, suggesting that other steric or stereoelectronic factors might also be involved.

For formal 1,2-additions of HOBr and HOCl to alkenes, additional stabilization of the intermediate *syn*-halonium ions might be achieved by a hyperconjugative generalized anomeric effect. In the original anomeric effect, electron donation from the nonbonded n-electrons on the pyranose oxygen into the adjacent C−O σ^* orbital of an electronegative anomeric substituent results in preferential stabilization of the less sterically favored axial (α) stereoisomer.[25] A related phenomenon, termed the "gauche effect", has been invoked to explain the preferred gauche-conformations of certain 1,2-disubstituted ethanes,[26] and involves similar (C−H)σ-(C−X)σ^* orbital interactions. Allylically substituted cyclopentenes such as **10**, **13**, and **18** would be expected favor an envelope conformation having an equatorial CH_3 or N_3 substituent, as shown in Scheme 13. Addition of X^+ may lead to two cyclic halonium ions, **79** and **80** (Scheme 13). A generalized anomeric effect may stabilize the *syn*-adduct **79**, where the axial allylic C−H σ-bond can serve as an electron-releasing group to stabilize the strongly electronegative halonium ion by back-donation into the C−X σ^*-bond. For cyclopentene-derived *syn*-halonium ions such as **79**, molecular modeling studies indicate an almost perfect (180

(22) Borcherding, D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem.* **1987**, *52*, 5457−5461.

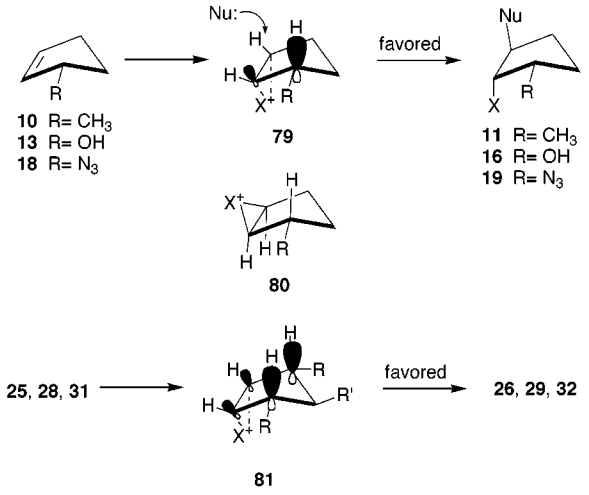
(23) Bayley, H.; Standring, D. N.; Knowles, J. R. *Tetrahedron Lett.* **1978**, 3633−3634.

(24) See ref 8 for a comprehensive review of additions of a variety of electrophiles to a broad range of cyclic and acyclic alkenes.

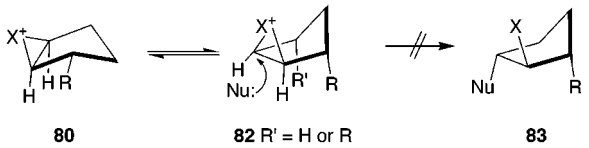
(25) (a) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527−548. (b) Kirby, A. J. *The Anomeric Effect and Related Stereochemical Effects at Oxygen*; Springer: New York, 1983.

(26) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102−111.

Scheme 13



Scheme 14



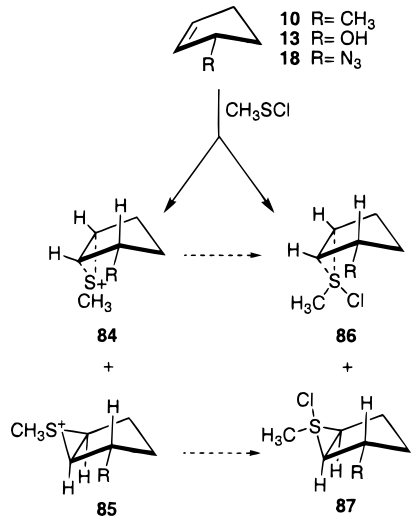
± 5°) antiperiplanar orbital overlap between the C−H s and C−X σ*-bonds. Models further established that dihedral angles in substituted onium ions in the corresponding cyclohexenyl and cycloheptenyl systems deviated significantly (±15 to 25°) from antiperiplanarity. Moreover, such a generalized anomeric effect should be additive in the case of two bis-allylically substituted cyclopentenes such as **25**, **28**, and **31**, which would further stabilize the corresponding diequatorial conformation **81**.

If the intermediate halonium ions such as **79**−**81** were formed reversibly, as has been suggested for highly substituted, bridged bromonium ions,[27] then the product distribution in HOX additions would be determined not by the thermodynamically more stable halonium ion, but by the rate of halonium ion opening. On the basis of steric factors, the transition state for the opening of the *syn*-halonium ion **79** to the observed products (**11**, **16**, **19**) would be expected to be lower in energy than that for the *anti*-halonium ion **80**. Intermediate **80** must undergo a conformational change to **82** (Scheme 14) in order for nucleophilic attack at the distal carbon to proceed via *trans*-diaxial opening. The incipient H_2O or DMSO nucleophile in **82** would experience a 1,3-diaxial interaction with the substituent R. Additional steric repulsions would result in 1,4-disubstituted cyclopentenes such as **25**, **28**, and **31**.

Unlike NBS−H_2O additions, the reaction of MeSCl with allylically substituted cyclopentenes displayed no consistent stereochemical trend. In previously reported studies on the reaction of methyl and *p*-tolylsulfenyl chloride with **37** and **42**, modest changes in the remote (homoallylic) substituent led to a reversal in the overall stereochemistry of addition.[17] In the present study, cyclopentenol **13** and cyclopentenyl azide **18** afforded mostly *anti* products, whereas bis-allylically substituted cyclopentenes give increasing proportions of *syn* products.

(27) Brown, R. S. *Acc. Chem. Res.* **1997**, *30*, 131−137.

Scheme 15



Such wide variations in selectivity may indicate that the intermediates formed in electrophilic additions of MeSCl are different in structure and/or reactivity from the cyclic halonium ions implicated in NBS−H_2O and NCS−H_2O additions.

While electrophilic additions of halogens and sulfenyl chlorides to alkenes and alkynes both afford *trans*-products, the intermediacy of discrete, three-membered, cyclic thiiranium and thiirenium ions in RSCl additions remains controversial.[20] Whether such ions can form reversibly is not known, and their subsequent reactivity toward nucleophiles is not fully understood. In the case of allylically substituted cyclopentenes such as **10**, **13**, and **18**, electrophilic addition of CH_3SCl might proceed via stereoisomeric thiiranium ions **84/85** (Scheme 15) and/or a-sulfurane adducts **86/87**. Moreover, nucleophiles can attack **84/85** at one of the three-membered ring carbons (to afford overall *anti*-addition) or at sulfur, giving rise to α-sulfuranes **86/87**, respectively. A recent report documents both modes of reactivity in stereoisomeric thiiranium ions.[28] The relative rates of formation of such intermediates and of nucleophilic ring opening likely determine the overall stereoselectivity of addition.

Earlier kinetic studies on MeSCl additions to alkenes indicate that chloride is retained in the solvent cage, and that the first-formed intermediate, thought to be the α-sulfurane or thiiranium ion pair, undergoes rapid nucleophilic attack.[20] Under those conditions, the product distribution would be determined solely by the relative rates of electrophilic attack, which would explain the *anti* selectivity observed for simple cyclopentenes **10**, **13**, and **18**. Sterically demanding or electronegative substituents on the cyclopentene would be expected retard nucleophilic opening of the sulfurane or thiiranium ion,[29] and reduce the preference for *anti*-addition. Such a trend is evident in comparing products derived from **13**, cyclopentenediol **25**, and the corresponding diacetate **59** (Scheme 10), as well as products from chlorosulfide **37** and the corre-

(28) Fachini, M.; Lucchini, V.; Modena, G.; Pasi, M.; Pasquato, L. *J. Am. Chem. Soc.* **1999**, *121*, 3944−3950.

(29) Similar effects of inductively withdrawing substituents have been observed in acid-catalyzed epoxide openings: (a) Bronsted, J. N.; Kilpatrick, M.; Kilpatrick, M. *J. Am. Chem. Soc.* **1929**, *51*, 428−461. (b) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557−1560, and references therein; (c) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696−5704.

sponding chlorosulfone **42** (Scheme 7). Alternatively, the electron-deficient π-systems in **25** and **59** may be too unreactive to form α-sulfuranes directly, reacting instead via the corresponding *syn*-thiiranium ions, which can be stabilized by the generalized anomeric effect noted earlier. Unfortunately, no simple mechanistic picture rationalizes the various solvent and dissolved electrolyte effects on CH_3SCl additions in the present study. For example, THF gives higher amounts of *anti* product than CH_2Cl_2 or $CDCl_3$ in the case of cyclopentenol, yet the situation is reversed in the case of azidocyclopentene.

Although not as thoroughly studied, additions of thiosulfonium salts such as DMTSF to substituted cyclopentenes followed a more predictable and consistent trend, exhibiting modest to excellent *syn* selectivity. DMTSF and CH_3SCl additions differ significantly in that nucleophiles are only introduced into the former once the initial electrophilic addition has been completed, and the process of nucleophilic addition is slow. Thus, as with NBS−H_2O and NCS−H_2O additions, the preferential *syn*-stereoselectivity observed in DMTSF additions might be the result of kinetically controlled opening of rapidly interconverting thiiranium intermediates, formed in the presence of a weak disulfide nucleophile. Consistent with this rationale, a recent study demonstrated the rapid interchange of *S*-alkyl thiiranium groups with alkyl disulfides, likely involving a rapid alkene−thiiranium ion equilibrium.[28]

The results reported here demonstrate that electrophilic additions to cyclopentenes can be a useful and stereoselective tool in organic synthesis. Additions of NBS−H_2O, NCS−H_2O, and DMTSF to functionalized substrates proceed with *syn* selectivity, giving predominantly or exclusively one product. MeSCl additions are less predictable, but can be tuned by suitable alteration of solvent and substrate. Such stereoselective electrophilic additions have played an important role in preparing aminocyclopentitols and other densely functionalized cyclopentanes, and will be of continuing utility as more such substances are discovered and synthesized.

Experimental Section[30]

Addition of HOBr to 2-Cyclopentenol 13; Synthesis of 1-Bromo-2,5-dihydroxycyclopentanes 16 and 17. To a stirred solution of **13** (160 mg, 1.92 mmol) in H_2O (11 mL) at 0 °C was added *N*-bromosuccinimide (380 mg, 2.10 mmol) in one portion. After 1 h, the solution was warmed to room temperature and then concentrated in vacuo. The solid residue was triturated with cold ether (2 × 10 mL), and the combined organic layers were then dried ($MgSO_4$), filtered, and concentrated. The residue was purified by SiO_2 flash chromatography (4:1 toluene:CH_3CN) to afford 273 mg of a 4:1 mixture of bromohydrins **16** and **17** (78% yield). Analytically pure samples of each isomer could be obtained by further chromatography (SiO2, 1:1 EtOAc:hexanes). For **16**: R_f = 0.24 (1:1 EtOAc:hexanes); ^{1}H NMR (300 MHz, D_2O) δ 4.24 (m, 1 H), 4.11 (m, 1 H), 3.95 (dd, 1 H, J = 6.5, 4.6), 2.15−1.98 (m, 2 H), 1.61 (m, 1 H), 1.38 (m, 1 H); ^{13}C NMR (75 MHz, D_2O) δ 77.2, 71.7, 61.0, 28.5, 28.3; IR (film) 3400, 2950, 2850, 1340, 1300, 1180, 1100, 1040 cm^{-1}; CIMS *m*/*z* 262 (2M + 1 + CH_4 − HBr − 2 H_2O, 47%), 244 (2M + 1 + CH_4 − HBr - 3H_2O, 27%), 100 (100%). For **17**: R_f = 0.28 (1:1 EtOAc:hexanes); ^{1}H NMR (300 MHz, D_2O) δ 4.08 (m, 2 H), 3.69 (t, 1 H, J = 7.9 Hz), 1.95 (m, 2 H), 1.57 (m, 2 H); ^{13}C NMR (75 MHz, D_2O) 76.4, 61.1, 28.4; IR (film) 3400, 2950, 2850, 1350, 1190, 1040 cm^{-1}; CIMS *m*/*z* 181 (M^+), 163 (M−H_2O), 100 (M − HBr), 83 (M − H_2O − HBr).

Addition of HOBr to 3-Azidocyclopentene; Synthesis of 3-Azido-2-bromocyclopentanols 19 and 20. *N*-Bromosuccinimide (460 mg, 2.6 mmol) was added to a stirred solution of 3-azidocyclopentene **18** (143 mg, 1.3 mmol) in DMSO (20 mL) containing H_2O (1.2 mL). After 2 h, the solution was diluted with H_2O (75 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to a yellow oil, which was chromatographed on SiO_2 (3:1 hexanes:EtOAc) to afford a 3:1 mixture of **19** and **20** (247 mg, 91%; R_f 0.56 in 1:1 hexanes:EtOAc). For **19**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.45 (m, 1 H), 4.12 (m, 2 H), 2.4−1.6 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.1, 63.4, 60.2, 29.4, 27.1; **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (m, 1 H), 4.03 (m, 1 H), 3.91 (t, 1 H, J = 5.9 Hz), 2.4−1.6 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 79.0, 67.7, 59.0, 30.4, 28.1; IR (mixture, neat) 3350 (b), 2950, 2100, 1260 cm^{-1}; EIMS *m*/*z* 205/207 (M^+, 1%), 162/164 (M − HN_3, 15%), 83 (M − HN_3 − Br, 80%).

Conversion of 19 and 20 to *cis*- and *trans*-3-Azidocyclopentene Oxides 21 and 22. Potassium carbonate (104 mg, 0.75 mmol) was added to a stirred solution of **19** and **20** (62 mg, 0.30 mmol) in dry CH_3OH (6 mL). After stirring 20 h, the solution was partitioned between H_2O (30 mL) and CH_2Cl_2 (30 mL). The aqueous layer was then extracted with CH_2Cl_2 (15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give a yellow oil (35 mg, 92%) containing epoxides **21** and **22**.

Authentic samples of **21** and **22** were prepared as follows. To a stirred solution of **18** (114 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added *m*-chloroperoxybenzoic acid (350 mg, 2.0 mmol) in CH_2Cl_2 (5 mL). The resulting solution was stirred for 1 h at 40 °C, then at room temperature overnight. After diluting with CH_2Cl_2 (20 mL), the solution was washed with 10% $NaHSO_3$ (2 × 10 mL), filtered through Celite, and washed with 2 N NaOH (2 × 10 mL). The organic phase was then dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed (SiO_2, 4:1 hexanes:EtOAc) to afford **21** (58 mg, 46%) and **22** (44 mg, 35%), both as clear oils. For **21**: R_f 0.49 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.03 (d, 1 H, J = 4.8 Hz), 3.57 (d, 1 H, J = 2.2 Hz), 3.49 (d, 1 H, J = 1.9 Hz), 2.1−1.8 (m, 4 H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 61.4, 57.5, 56.9, 26.2, 25.6; IR (neat) 2900, 2100, 1240, 850 cm^{-1}; EIMS 125 (M^+, 10%), 83 (M − N_3, 20%). For **22**: R_f 0.30 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.72 (t, 1 H, J = 8.0 Hz), 3.57 (m, 1 H), 3.48 (d, 1 H, J = 2.7 Hz), 2.18 (dd, 1 H, J = 14.2 Hz, 8.3 Hz), 1.92 (dt, 1 H, J = 12.3 Hz, 8.1 Hz), 1.8−1.6 (m, 1 H), 1.6−1.4 (m, 1 H); ^{13}C NMR δ (75 MHz, $CDCl_3$) 61.9, 57.7, 55.5, 26.4, 23.4; IR (neat) 2950, 2100, 1250, 850 cm^{-1}, EIMS *m*/*z* 125 (M^+, 25%), 83 (M − N_3, 10%).

Synthesis of *meso*-2,5-Diazidocyclopentanol 23. To a stirred solution of *trans*-epoxyazide **21** (13 mg, 0.10 mmol) in MeOH (1 mL) was added NaN_3 (20 mg, 0.30 mmol). The solution was heated at reflux for 5 h and then stirred for 20 h at room temperature. The reaction was partitioned between H_2O (2 mL) and Et_2O (2 mL). The aqueous layer was removed and extracted with Et_2O (2 × 2 mL). The combined ether layers were dried ($MgSO_4$) and concentrated in vacuo, and the residue was chromatographed on SiO_2 (4:1 hexanes:EtOAc) to afford a colorless oil (7 mg, 41%): R_f 0.27 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (t, 1 H, J = 7.6 Hz); 3.71 (m, 2 H), 2.25 (bs, 1 H), 2.11 (m, 2 H), 1.75 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.1, 65.6, 26.3; IR (neat) 3400 (b), 2100 1250 cm^{-1}, EIMS *m*/*z* 168 (M^+, 2%), 83 (M − HN_3 − N_3, 15%).

Hydrogenation of 22; Synthesis of *cis*-3-Acetamidocyclopentene Oxide 24. A solution of **22** (28 mg, 0.22 mmol) in dry MeOH (2 mL) containing Lindlar's catalyst (10 mg) was stirred at room temperature under 1 atm H_2. After 4 h, TLC showed complete disappearance of starting material. The mixture was then cooled to 15 °C and purged with Ar. Triethylamine (0.15 mL, 1.1 mmol) and acetic anhydride (0.10 mL, 1.1 mmol) were added, and after 20 h, catalyst was removed by filtration through Celite. The solvents were removed in vacuo, and the resulting residue was chromatographed on SiO_2 (12:1 CH_2Cl_2:MeOH) to afford 18 mg (58%)

(30) General procedures: King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1994**, *116*, 562−570.

of a low-melting solid whose spectral data matched those of an authentic sample of **24** prepared by the literature method.[13]

Addition of HOBr to *cis*-Cyclopentene-1,4-diol 25; Synthesis of 1-Bromo-2,3,5-trihydroxycyclopentane 26. To a stirred solution of **25** (94 mg, 0.94 mmol) in H_2O (2 mL) at 0 °C was added NBS (333 mg, 1.87 mmol) in one portion. After stirring for 1 h at room temperature, the mixture was diluted with 5 mL of H_2O and extracted with EtOAc (4 × 5 mL). The aqueous layer was then frozen and lyophilized to give a white solid, which was purified by flash chromatography over SiO_2 (5% MeOH:EtOAc), affording pure **26** (80 mg, 44%) as a colorless oil: $R_f = 0.36$ (5% MeOH:EtOAc), ^{1}H NMR (300 MHz, D_2O) δ 3.96 (m, 2 H), 3.87 (m, 1 H), 3.75 (m, 1 H), 2.41 (m, 1 H), 1.54 (m, 1 H); ^{13}C NMR (75 MHz, D_2O) δ 85.3, 76.1, 71.4, 60.0, 40.7; IR (film) 3400, 2950, 1300, 1100 cm^{-1}; CIMS *m/z* 395 (2M + 1), 359 (2M + 1 − 2H_2O), 295 (2M + 1 − H_2O − Br), 197 (M^+), 179 (M − H_2O), 99 (M − H_2O − Br, 100%).

Conversion of 26 to *trans*-1,4-Dihydroxycyclopentene Oxide 27. To a stirred solution of bromohydrin **26** (22 mg, 0.11 mmol) in MeOH (4 mL) at room temperature was added anhydrous Na_2CO_3 (61 mg, 0.57 mmol) in one portion. The heterogeneous mixture was then stirred at room temperature for 10 h. After cooling to 0 °C, the reaction was quenched with by the addition of NH_4Cl (0.57 g) in H_2O (1 mL). The methanol was removed in vacuo, and the aqueous residue was frozen and lyophilized to afford a white solid, which was triturated several times with 1:9 MeOH:EtOAc. The triturates were then concentrated in vacuo to furnish pure **27** (7.6 mg, 59%) as a white solid: R_f 0.53 (1:9 MeOH:EtOAc); ^{1}H NMR (300 MHz, D_2O) δ 4.15 (d, 2 H, $J = 5.9$ Hz), 3.49 (s, 2 H), 1.76 (dt, 1 H, $J = 15.8$, 4.6 Hz), 1.43 (d, 1 H, $J = 15.8$ Hz); ^{13}C NMR (75 MHz, D_2O) δ 72.2, 61.3, 41.1; IR (film) 3300, 2950, 1350, 1100, 1020, 860 cm^{-1}; CIMS *m/z* 117 (M + 1), 99 (M + 1 − H_2O), 81 (M + 1 − 2H_2O), 69 (100%).

Peracid Epoxidation of 25; Synthesis of *cis*-1,4-Dihydroxycyclopentene Oxide. To a stirred solution of cyclopentene-1,4-diol (81.8 mg, 0.81 mmol) in THF (4 mL) at 0 °C was added MCPBA (154 mg, 0.90 mmol). The resulting solution was stirred at room temperature for 20 h. The THF was then removed in vacuo and replaced with H_2O (2 mL). The H_2O layer was extracted with EtOAc (2 × 2 mL); the aqueous layer was then frozen and lyophilized to give a crude solid which was chromatographed over SiO_2 (19:1 EtOAc:MeOH) to afford pure *cis*-1,4-dihydroxycyclopentene oxide (64 mg, 68%) as a colorless oil: R_f 0.20 (19:1 EtOAc:MeOH); ^{1}H NMR (300 MHz, D_2O) δ 4.04 (t, 2 H, $J = 8.4$ Hz), 3.41 (s, 2 H), 2.08 (dt, 1 H, $J = 12.4$, 7.3 Hz), 1.05 (dt, 1 H, $J = 12.3$, 8.6 Hz); ^{13}C NMR (75 MHz, D_2O) δ 71.6, 60.6, 34.4; IR (film) 3300, 2950, 1350, 1100, 1020, 860 cm^{-1}; CIMS *m/z* 117 (M + 1), 99 (M + 1 − H_2O, 100%).

Addition of HOBr to Diol 28; 1-Bromo-2,3,5-trihydroxy-4-(2′-trimethylsilylethoxy)methylcyclopentane 29. To a stirred solution of diol **28** (1.70 g, 7.4 mmol) under Ar at 10 °C in DMSO (10 mL) were added H_2O (0.27 mL, 14.8 mmol) and *N*-bromosuccinimide (2.63 g, 14.8 mmol). The resulting homogeneous solution was stirred for 30 min, and the reaction was allowed to warm to room temperature. The reaction was then quenched by the slow addition of 5% aqueous $NaHCO_3$ (35 mL) and extracted with Et_2O (4 × 30 mL). The combined ether extracts were washed with brine (30 mL), dried over $MgSO_4$, and concentrated. The resulting brown oil was chromatographed on a column of SiO_2 (3:1 EtOAc:hexanes) to afford bromohydrin **29** (1.4 g, 56%) as a white solid: mp 89−90 °C; R_f 0.41 (3:1 EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (dd, 1 H, $J = 8.5$, 6.5 Hz), 4.06 (dd, 1 H, $J = 8.6$, 5.1 Hz), 3.92 (t, 1 H, $J = 3.5$ Hz), 3.79 (t, 1 H, $J = 6.5$ Hz), 3.53−3.48 (m, 4 H), 2.24 (m, 1 H), 0.91, (t, 2 H, $J = 8.2$ Hz), −0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.5, 71.9, 69.6, 68.8, 59.3, 51.8, 29.6, 18.1, 1.4; IR (film) 3360, 2900, 1400, 1350, 1250, 1100, 1040 cm^{-1}; CIMS *m/z* 327 (M^+, 2%), 73 (100%).

Peracid Epoxidation of 28; Synthesis of *cis*-1,4-Dihydroxy-2,3-oxido-5-(2'trimethylsilylethoxy)methylcyclopentane. To a solution of diol **28** (15 mg, 0.072 mmol) in CH_2Cl_2 (0.5 mL) at room temperature under Ar was added MCPBA (12 mg, 0.07 mmol). The resulting mixture was stirred at room temperature for 8 h and then quenched by washing with 10% sodium bisulfite (2 × 0.5 mL) and satd $NaHCO_3$ (2 × 0.5 mL). The aqueous layers were pooled and extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to afford (10 mg, 62%) *cis*-1,4-dihydroxy-2,3-oxido-5-(2'trimethylsilylethoxy)methylcyclopentane as a clear oil: R_f 0.35 (9:1 CH_2Cl_2:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (d, 2 H, $J = 7.8$ Hz), 3.56 (m, 4 H), 3.51 (t, 2 H, $J = 8.3$ Hz), 1.64 (m, 1 H), 0.89 (t, 2 H, $J = 7.8$ Hz), −0.02 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.2, 68.9, 68.8, 56.9, 47.5, 18.2, −1.3; IR (film) 3400, 2950, 2850, 1260, 1100, 1050 cm^{-1}; CIMS *m/z* 245 (M + CH_4 + 1 − H_2O), 229 (M + 1 − H_2O), 73 (100%).

Conversion of 28 to 1-Chloro-2,4-dihydroxy-5-formyloxy-3-(2′-trimethylsilylethoxymethyl)cyclopentane 34. To a stirred solution of **28** (52 mg, 0.23 mmol) in DMF containing 0.1% water (2.4 mL) at 0 °C was added *N*-chlorosuccinimide (90 mg, 0.68 mmol) in one portion. The resulting solution was allowed to stand at room temperature for 48 h and then diluted with H_2O (5 mL) and extracted with Et_2O (8 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to an oil. Purification by flash chromatography (1:1 hexanes:EtOAc) afforded pure **34** (14 mg, 20%): R_f 0.43 (1:3 hexanes:EtOAc); ^{1}H NMR (300 MHz) δ 8.14 (s, 1 H), 5.16 (t, 1 H, $J = 5.9$ Hz), 4.31 (dd, 1 H, $J = 6.5$, 4.8 Hz), 4.07 (dd, 1 H, $J = 9.0$, 4.5 Hz), 3.98 (dd, 1 H, $J = 8.4$, 5.4 Hz), 3.57 (d, 2 H, $J = 4.4$ Hz), 3.52 (t, 2 H, $J = 8.8$ Hz), 3.52 (t, 2 H, $J = 8.8$ Hz), 2.35 (m, 1 H), 0.91 (t, 2 H, $J = 8.2$ Hz), 0.01 (s, 9 H); ^{131}C NMR (75 MHz $CDCl_3$) δ 161.2, 86.8, 76.3, 72.8, 69.1, 68.8, 63.4, 51.3, 18.1, −1.3; IR (film) 3400, 2950, 2850, 1740 cm^{-1}; FABMS *m/z* 311 (M + 1, 8%), 283 (M + 1 − CO), 97%), 119 (100%).

Conversion of 29 to 1,4-Dihydroxy-2,3-oxido-5-(2′-trimethylsilylethoxy)methylcyclopentane 30. To a solution of bromohydrin **29** (1.72 g, 5.3 mmol) in MeOH (150 mL) at 0 °C under Ar was added anhydrous Na_2CO_3 (2.8 g, 26.5 mmol). The mixture was then stirred at room temperature for 22 h and then cooled to 0 °C and quenched with NH_4Cl (2.8 g, 53 mmol) in H_2O (50 mL). The bulk of MeOH was then removed in vacuo, and the aqueous residue was extracted with EtOAc (3 × 75 mL). The combined EtOAc layers were washed with brine (15 mL) and dried over $MgSO_4$. Concentration gave a crude solid, which was chromatographed over SiO_2 (14:1 CH_2Cl_2:MeOH) to afford epoxide **30** (0.84 g, 65%) as a white crystalline solid: mp 76−81 °C; R_f 0.20 (14:1 CH_2Cl_2:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10 (d, 2 H, $J = 6.2$ Hz), 3.60 (d, 2 H, $J = 0.5$ Hz), 3.47 (t, 2 H, $J = 8.2$ Hz), 3.25 (d, 2 H, $J = 8.1$ Hz), 2.19 (t, 1 H, $J = 8.1$ Hz), 0.92 (t, 2 H, $J = 8.3$ Hz), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.2, 70.7, 68.3, 58.9, 57.6, 18.1, −1.4; IR (film) 3400, 2950, 2850,1450, 1350, 1250 cm^{-1}; CIMS *m/z* 245 (M + 1 + CH_4 − H_2O, 2%), 73 (100%).

Addition of HOBr to 4-Acetamido-3,5-dimethoxycyclopentene 31; Synthesis of Acetamido-1-bromo-2-hydroxy-3,5-dimethoxycyclopentane 32. To a solution of **31** (20 mg, 0.11 mmol) in water (2 mL) was added *N*-bromosuccinimide (58 mg, 0.32 mmol). After stirring for 2 d, the solution was evaporated and the residue chromatographed on SiO_2 (20:1 CH_2Cl_2:MeOH) to afford **32** (30 mg, 92%) as a colorless oil: R_f = 0.31 (9:1 CH_2Cl_2:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (bs, 1 H, $J = 7.0$ Hz), 4.33 (m, 2 H), 4.16 (m, 1 H), 3.82 (m, 1 H), 3.66 (m, 1 H), 3.40 (s, 3 H), 3.39 (s, 3 H), 2.04 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 89.1, 81.6, 78.8, 62.3, 58.1, 58.0, 54.1, 23.9; IR (film) 3250, 1650, 1390, 1100 cm-1; FIMS *m/z* 283, 281 (M^+, 100%), 202 (M − Br, 51%).

Conversion of 32 to 4-Acetamido-3,5-dimethoxycyclopentene oxide 33. To a stirred solution of **32** (26 mg, 0.092 mmol) in MeOH (1 mL) was added K_2CO_3 (32 mg, 0.23 mmol). After 20 h, the mixture was diluted with H_2O (2 mL) and then saturated with K_2CO_3 and extracted with EtOAc (2 × 2 mL). The combined organic layers were evaporated to afford **33** (15 mg, 83%) as a white solid: mp 89−91°C; $R_f = 0.56$ (9:1 CH_2Cl_2:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.48 (bd, 1 H, $J = 9.7$ Hz), 4.38 (d, 1 H, $J = 9.6$ Hz), 3.64 (s, 2 H), 3.57 (s, 2 H), 3.45 (s, 6 H), 1.92 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 85.9,

58.4, 57.7, 55.0, 23.5; IR (film) 3400, 2900, 1660, 1540, 1370, 1100 cm^{-1}; FDMS *m/z* 202 (M + 1, 87%). Crystals of **33** suitable for X-ray analysis were obtained by recrystallization from CH_2Cl_2:hexanes.

Addition of HOCl to Diacetate 35; Synthesis of 1-Chloro-3,5-diacetoxy-2-formyloxy-4-(2′-trimethylsilylethoxy)-methylcyclopentane 36. To a solution of diacetate **35** (15 mg, 0.05 mmol) in DMF (0.5 mL) containing 0.1% H_2O at 0 °C was added *N*-chlorosuccinimide (19 mg, 0.14 mmol). The solution was stirred for 30 s at 0 °C and then sealed in a Kimble vial for 24 h at room temperature. The reaction was then diluted with H_2O (1 mL) and extracted with Et_2O (5 × 1 mL). The combined ether layers were washed with brine (1 mL) and dried over $MgSO_4$. Filtration and concentration afforded a crude oil, which was purified by flash chromatography over SiO_2 (4:1 hexanes:EtOAc) to give pure **36** (12 mg, 65%) as a colorless oil: R_f 0.35 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.1 (s, 1 H), 5.58 (m, 1 H), 5.18 (t, 1 H, J = 5.5 Hz), 5.14 (t, 1 H, J = 4.6 Hz), 4.39 (dd, 1 H, J = 7.9, 4.9 Hz), 3.56 (d, 2 H, J = 3.0 Hz), 3.52 (t, 2 H, J = 8.5 Hz), 2.33 (m, 1 H), 2.15 (m, 3 H), 2.08 (s, 3 H), 0.92 (t, 1 H, J = 8.5 Hz), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 170.1, 159.7, 80.5, 75.6, 74.0, 68.8, 67.7, 58.9, 48.8, 20.9, 20.8, 17.9, −1.4; IR (film) 2950, 2850, 1745, 1740, 1225, 1150, 1100, 1070 cm^{-1}; CIMS *m/z* 412 (M + H_2O), 384 (M + H_2O − CO), 367 (M + H_2O − OCHO, 100%).

Addition of Methanesulfenyl Chloride to 2-Cyclopentenol 13 in CH_2Cl_2; Synthesis of 48 and 49. To a stirred solution of 2-cyclopentenol **13** (130 mg, 1.55 mmol) in dry CH_2Cl_2 (30 mL) was added methanesulfenyl chloride (140 mg, 1.7 mmol) in CH_2Cl_2 (10 mL). After 1 h, the solution was evaporated to afford a brown oil (213 mg) consisting of **46** and **47**. The **46**/**47** mixture was dissolved in pyridine (5 mL) and stirred overnight with acetic anhydride (60 μL, 6.4 mmol). The solution was then diluted with Et_2O (50 mL) and washed with satd $NaHCO_3$ (3 × 30 mL). The combined aqueous layers were back-extracted with Et_2O (2 × 30 mL), and the combined ether extracts were dried over $MgSO_4$ and evaporated. The resulting orange oil was filtered through a short column of neutral alumina (4:1 hexanes:EtOAc) to afford a 1.4:1 mixture of **48** and **49** (191 mg, 60%), contaminated with traces of a regioisomeric impurity; R_f 0.36 (5:1 hexanes:EtOAc). For **48**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 (m, 1 H), 4.06 (m, 1 H), 3.21 (t, 1 H, J = 4.0 Hz), 2.6−1.7 (m, 4 H), 2.18 (s, 3 H), 2.07 (s, 3 H); for **49**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.44 (m, 1 H), 4.23 (q, 1 H, J = 5.4 Hz), 3.27 (t, 1 H, J = 6.3 Hz), 2.6−1.7 (m, 4 H), 2.22 (s, 3 H), 2.06 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture) δ 81.7, 79.4, 74.9, 67.2, 63.3, 62.6, 60.0, 59.9, 52.5, 34.5, 33.30, 30.32, 29.8, 29.6, 29.5, 21.4, 21.3, 21.2, 16.1, 15.5, 15.2; IR (neat) 2976, 1742, 1230 cm^{-1}; EIMS *m/z* 208 (M^+, 35%).

Addition of Methanesulfenyl Chloride to 2-Cyclopentenol 13 in THF−$LiClO_4$; Synthesis of 48 and 49. To a solution of **13** (40 mg, 0.47 mmol) in 6 mL of 2 N $LiClO_4$ in dry THF at 0 °C was added MeSCl (43 mg, 0.52 mmol) neat. After 2 h, the solution was diluted with Et_2O (15 mL) and washed with H_2O (3 × 10 mL). The aqueous layers were combined and back-extracted with Et_2O (2 × 15 mL). The combined ether extracts were dried and evaporated to afford a colorless liquid. This crude product was acetylated as described above to afford 74 mg (71%) of **48** and **49** as a 5:1 mixture.

Reductive Dechlorination of 48; Correlation with an Authentic Sample of *trans*-2-Methylthiocyclopentanol 50. To a solution of **48** and **49** (∼5:1, 17 mg, 0.082 mmol) in dry THF (1 mL) was added 1 M Super Hydride−THF (0.12 mL). After stirring 20 h, more Super Hydride solution (0.25 mL) was added. Three hours later, the solution was partitioned between Et_2O (6 mL) and H_2O (6 mL). The aqueous layer was extracted with more Et_2O (5 mL), and the combined ether layers were dried over $MgSO_4$. Evaporation afforded a colorless residue, which was purified by SiO_2 chromatography (5:2 hexanes:EtOAc) to afford pure **50** (45%) whose spectral data matched those of an authentic sample prepared as follows.

Cyclopentene oxide (0.11 mL, 1.3 mmol) was added to a stirred solution of sodium thiomethoxide (91 mg, 1.3 mmol) in dry MeOH (10 mL). The resulting solution was heated at reflux for 4 h and then cooled and diluted with 5% NaOH (25 mL). The reaction mixture was extracted with CH_2Cl_2 (5 × 20 mL), and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo to afford a yellow oil (135 mg, 79%): R_f 0.17 (4:1 hexanes:EtOAc): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.1 (m, 1 H), 2.82 (m, 1 H), 2.2−1.5 (m, 6 H), 2.14 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 78.3, 53.4, 33.4, 30.5, 21.6, 14.3; IR (neat) 3400 (b), 2950, 1400, 975 cm^{-1}; EIMS *m/z* 132 (M^+, 45%).

Addition of Methanesulfenyl Chloride to Cyclopentenyl Azide 18; Synthesis of 3-Chloro-2-methylthiocyclopentyl Azides 52 and 53. To a solution of **18** (200 mg, 1.8 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added methanesulfenyl chloride (170 mg, 2.1 mmol) in one portion. After 1 h, the solvent was removed in vacuo, and the resulting residue was filtered through a plug of SiO_2 (1:19 EtOAc:hexanes) to afford an orange oil (275 mg, 79%) containing a 3.5:1 mixture of **52** and **53** together with minor amounts of a regioisomer. Chromatography on SiO_2 afforded samples enriched in the major product **52**: R_f 0.25 (1:19 EtOAc: hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (m, 1 H), 3.67 (m, 1 H), 3.09 (m, 1 H), 2.4−1.9 (m, 4 H), 2.25 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.9, 63.0, 60.8, 34.4, 29.9, 15.7.

For **53**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.39 (m, 1 H), 4.25 (m, 1 H), 3.27 (m, 1 H), 2.5−1.8 (m, 4 H), 2.21 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$ mixture) δ 69.4, 68.4, 64.3, 63.2, 61.0, 52.3, 33.5, 29.4, 29.1, 29.0, 16.0, 15.0; IR (neat, mixture) 2970, 2100, 1255 cm^{-1}; EIMS *m/z* 191 (M^+, 20%), 149 (M − N_3, 20%).

Reduction of 52; Synthesis of Methylthio-4-bromophenyl Oxazoline 58. A solution of **52** and **53** (>4:1, 31 mg, 0.16 mmol) in MeOH (1.5 mL) was treated with 10% palladium on carbon (40 mg) and stirred under 1 atm H_2 for 2 h. The catalyst was removed by filtration through Celite, and solvent was removed in vacuo to afford impure amine **54** (21 mg, 80%) as a colorless oil. To a solution of **54** in CH_2Cl_2 (1.5 mL) were added triethylamine (22 μL, 0.16 mmol) and 4-bromophenyl isocyanate (95 mg, 0.48 mmol). After stirring 20 h, the resulting white precipitate was filtered through Celite and the filtrate evaporated. The resulting residue was chromatographed (SiO_2, 4:1 hexanes:EtOAc) to afford **58** as a white solid (32 mg, 38%). mp 199−200 °C; R_f 0.33 (4:1 hexanes: EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.74 (s,1 H), 7.43 (m, 6 H), 6.99 (m, 2 H), 5.10 (m, 1 H), 4.93 (d, 1 H, J = 7.5 Hz), 3.31 (m, 1 H), 2.4−1.8 (m, 4 H), 2.17 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 137.2, 132.2, 132.17, 125.4, 121.5, 118.5, 117.6, 116.7, 86.3, 59.9, 51.5, 32.1, 28.8, 15.3; IR (neat) 2977, 1668, 1699, 1592, 1487, 1384, 1307, 1236 cm^{-1}; FDMS *m/z* 525 (M^+, 100%)

Crystals of **58** suitable for crystallographic analysis were obtained by recrystallization from CH_2Cl_2:hexanes.

Addition of CH_3SCl to *cis*-1,4-Diacetoxy-2-cyclopentene 59; Synthesis of 1-Methylthio-2-chloro-3,5-diacetoxycyclopentane 60. To a stirred solution of diacetate **59** (50 mg, 0.27 mmol) in CCl_4 (0.5 mL) at 0 °C was added a 1.6 M solution of MeSCl in CCl_4 (0.51 mL) dropwise. After stirring 8 h at room temperature, the solution was concentrated in vacuo and the resulting yellow oil was purified by flash chromatography (3:1 hexanes:EtOAc) to afford pure **60** (61 mg, 84%) as a clear oil: R_f = 0.28 (3:1 hexanes: EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (m, 1 H), 5.13 (ddd, 1 H, J = 10.0, 6.2, 4.9 Hz), 4.19 (dd, 1 H, J = 10.0, 6.2 Hz), 3.10 (dd, 1 H, J = 10.0, 5.2), 2.71 (ddd, 1 H, J = 15.5, 8.9, 6.5 Hz), 2.22 (s, 3 H), 2.11 (s, 3 H) 2.10 (s, 3 H), 1.81 (ddd, 1 H, J = 15.6, 4.8, 2.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 169.7, 78.8, 72.4, 64.9, 56.9, 36.6, 21.0, 20.8, 15.8; IR (film) 2950, 2850, 1750, 1440, 1370, 1240, 1050 cm^{-1}, FABMS *m/z* 267 (M + 1, 11%), 154 (100%).

Saponification of 60; *all-cis*-1-Hydroxy-2-methylthio-3,4-oxidocyclopentane 62. To a stirred solution of diacetate **60** (56 mg, 0.21 mmol) methanol (7 mL) at 0 °C was added K_2CO_3 (115 mg, 0.83 mmol) in one portion. The resulting heterogeneous mixture was stirred at room temperature for 4 h. The reaction was then cooled to 0 °C and quenched by the addition of NH_4Cl (90 mg, 1.68 mmol) in H_2O (5 mL). Acid (2 N HCl) was added dropwise to pH 7. The mixture was then concentrated in vacuo, and the remaining aqueous portion was

extracted with Et_2O (5 × 10 mL). The combined Et_2O layers were washed with brine (5 mL) and then dried over $MgSO_4$. Filtration and concentration provided an oil. Purification by flash chromatography (3:1 EtOAc:hexanes) gave pure **62** (10 mg, 60%) as a clear oil: R_f 0.41 (3:1 EtOAc:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) 4.05 (m, 1H, 3.69 (s, 2H), 3.24 (d, 1H, J = 5.7 Hz), 2.32 (d, 1H, J = 15.2 Hz), 2.23 (s, 3H), 2.07 (dd, 1H, J = 15.2, 5.9 Hz); ^{13}C$^-$NMR (75 MHz, $CDCl_3$) 69.0, 58.9, 57.2, 53.4, 37.3, 14.8; IR (film) 3400, 2850, 1550, 1400, 1100, 1060 cm^{-1}; FABMS m/z 147 (M + 1, 6%), 119 (100%).

Addition of CH_3SCl to *cis*-Cyclopentene-1,4-diol 25; Synthesis of 2-Chloro-3-methylthio-1,4-cyclopentanediols 63 and 64. To a solution of diol **25** (96 mg, 0.96 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added MeSCl (103 mg, 1.2 mmol). After 3 h, the solution was evaporated, and the orange residue was chromatographed on SiO_2 with 5:1 CH_2Cl_2:acetone to afford a colorless oil (150 mg, 81% yield): R_f 0.37 (9:1 CH_2Cl_2:MeOH). Diastereomers **63** and **64** (2:1 ratio) could be partially separated by the above chromatography procedure. For **63**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (m, 2 H), 3.95 (m, 1 H), 3.12 (dd, 1 H, J = 9.0 Hz, 4.3 Hz), 2.67 (bs, 2 H), 2.4−2.2 (m, 1 H), 2.20 (s, 3 H), 2.1−2.0 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.6, 73.8, 67.9, 60.4, 39.2, 15.2. For **64**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 (m, 1 H), 4.06 (m, 1 H), 3.94 (m, 1 H), 3.22 (m, 1 H), 2.4−2.1 (m, 2 H), 2.27 (s, 3 H); 1^3C NMR (75 MHz, $CDCl_3$) δ 80.2, 71.1, 61.8, 39.2, 15.3; IR of mixture (neat) 3300, 2900, 1100 cm^{-1}; EIMS m/z 185 (M+, 17%), 146 (M − HCl, 50%).

A sample of diol **63** (25 mg, 0.13 mmol) in distilled pyridine (0.4 mL) at room temperature was acetylated by dropwise addition of Ac_2O (82 mg, 0.80 mmol) and stirring of the resulting solution at room temperature for 4 h. The solvent was then removed in vacuo (<2 mm Hg) to give a crude oil. Purification by flash chromatography (3:1 hexanes:EtOAc) provided pure **60** (31 mg, 90%) as a clear oil, which was identical by ^{1}H NMR with the sample of **60** prepared from **59** using MeSCl.

The corresponding bis(4-bromobenzoate) ester **65** of **63** was prepared by adding 4-bromobenzoyl chloride (77 mg, 0.35 mmol) to a stirred solution of **63** (25 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) and pyridine (0.2 mL). After stirring 20 h, H_2O (1 mL) was added, and the resulting mixture was stirred for 45 min. The aqueous layer was separated, and organic layer was washed with 0.2 N HCl (2 × 2 mL) and satd $NaHCO_3$ (2 × 2 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (2 mL) and the combined organic layers then dried over Na_2SO_4 and concentrated in vacuo. Chromatography on SiO_2 (1:1 CH_2Cl_2:hexanes) afforded a white solid (59 mg, 79%). For **65**: mp 108−111 °C; R_f 0.17 (1:1 CH_2Cl_2:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (m, 4 H), 7.65 (m, 4 H), 5.65 (m, 1 H), 5.47 (dd, 1 H, J = 5.3 Hz, 8.8 Hz), 3.39 (dd, 1 H, J = 5.1 Hz, J = 8.9 Hz), 2.90 (m, 1 H), 2.27 (s, 3 H), 2.18 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.3, 165.1, 132.1, 132.1, 131.5, 131.5, 129.0, 128.9, 128.8, 128.5, 80.5, 74.4, 66.2, 58.3, 37.2, 16.4; IR (neat) 1720, 1270, 1095 cm^{-1}; FDMS m/z 547.8 (M − 1, 100%).

Crystals of **65** suitable for X-ray analysis were obtained by recrystallization from CH_2Cl_2.

Addition of Methanesulfenyl Chloride to Diacetate 35; Synthesis of 1-Methylthio-2-chloro-3,5-diacetoxy-4-(2′ trimethylsilylethoxy)methylcyclopentane 66. To a stirred solution of **35** (34 mg, 0.11 mmol) was added a 1.6 M solution of MeSCl in CCl_4 (0.14 mL, 0.22 mmol) at 0 °C. After stirring for 3 h at 0 °C, the solvent was removed in vacuo to afford a crude oil. Chromatography over SiO_2 (4:1 hexanes:EtOAc) gave pure **66** (39 mg, 88%) as a colorless oil: R_f 0.45 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.25 (dd, 1 H, J = 7.4, 5.5 Hz), 5.20 (dd, 1 H, J = 5.2, 2.2 Hz), 4.18 (dd, 1 H, J = 11.3, 7.7 Hz), 3.59 (m,2 H), 3.53 (t, 2 H, J = 8.0 Hz), 3.20 (dd, 1 H J = 11.3, 5.9 Hz), 2.20 (s, 3 H), 2.10 (s, 6 H), 2.10 (m, 1 H), 0.90 (m, 2 H), 0.01 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 170.1, 80.0, 75.9, 68.8, 68.7, 65.0, 55.5, 50.7, 20.9, 17.9, 15.9, −1.3; IR (film) 2950, 2850, 1750, 1375, 1220, 1090, 1030, 850 cm^{-1}; CIMS m/z 397 (M + 1), 369 (100%).

Addition of DMTSF to Cyclopentenyl Acetate 67; Synthesis of 1-Acetoxy-3-azido-2-methylthiocyclopentanes 68 and 69. To a stirred solution under Ar of **67** (64 mg, 0.51 mmol) in CH_2Cl_2 (2 mL) containing Me_2S (20 μL) was added DMTSF (199 mg, 1.0 mmol). The mixture was stirred for 4 h and then concentrated in vacuo to dryness. The residue was cooled to 0 °C and dissolved in water (2 mL) containing NaN_3 (98 mg, 1.5 mmol). The solution was stirred for 4 d and then extracted with EtOAc (3 × 2 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the residue was filtered through SiO_2 (6:1 hexanes:EtOAc) to afford a 2:1 mixture of **68** and **69** (52 mg, 48%). Careful chromatography afforded pure samples of each isomer. For **68**: R_f 0.44 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.35 (m, 1 H), 3.86 (m, 1 H), 2.90 (m, 1 H), 2.2−1.6 (m, 4 H), 2.18 (s, 3 H), 2.05 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 74.8, 66.5, 57.1, 29.5, 28.8, 21.2, 16.1; IR (film) 2950, 2100, 1740, 1240 cm^{-1}; GC/MS m/z 215 (M$^+$, 20%), 155 (M$^+$ − HOAc, 20%). For **69**: R_f 0.44 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (m, 1 H), 3.66 (m, 1 H), 2,96 (m, 1 H), 2.2−1.6 (m, 4 H), 2.21 (s, 3 H), 2.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 79.1, 66.4, 56.3, 29.9, 29.7, 21.4, 15.3; IR (film) 2950, 2100, 1740, 1240 cm^{-1}; GC/MS m/z 215 (M$^+$, 25%), 155 (M$^+$ − HOAc, 30%).

Reduction and Acylation of 68; Synthesis of 1-Acetoxy-3-(*p*-bromobenzoylamino)-2-methylthiocyclopentane 71. A solution of **68** (26 mg, 0.12 mmol) in CH_3OH (1.5 mL) was stirred with 10% Pd/C (25 mg) under a hydrogen atmosphere for 2.5 h. The catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1 mL), and then triethylamine (67 μL, 0.48 mmol) and *p*-bromobenzoyl chloride (40 mg, 0.18 mmol) were added. After stirring 10 h, the reaction mixture was washed with satd $NaHCO_3$ solution (2 mL) and brine (2 mL). The organic layer was dried (Na_2SO_4) and concentrated, and the residue was purified over SiO_2 (8:1 toluene:CH_3CN) to afford 35 mg (78%) of **71** as a white solid: R_f 0.39 (5:1 toluene:CH_3CN); mp 175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64, 7.56 (2d, 2 H each, J = 8.6 Hz), 6.21 (br. d, 1 H, J = 6.4 Hz), 5.40 (m, 1 H), 4.31 (m, 1 H), 3.04 (m, 1 H), 2.51 (m, 1 H), 2.15 (m, 1 H), 2.14 (s, 3 H), 2.11 (s, 3 H), 1.85 (m, 1 H), 1.62 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 169.2, 135.0, 132.9, 130.3, 127.2,76.1, 56.9, 55.4, 30.2, 29.9, 21.1, 15.6; IR 3290, 1735, 1640, 1545, 1245 cm^{-1}; FIMS m/z 371, 373 (M$^+$, 100%).

Crystals of **71** suitable for X-ray analysis were obtained by recrystallization from EtOH:H_2O:CH_3OH.

Addition of DMTSF to Azidocyclopentene 18; Synthesis of 2,5-Azido-1-methylthiocyclopentanes 72 and 73. To a solution of **18** (36 mg, 0.33 mmol) in CH_2Cl_2 (2 mL) at 0 °C under Ar was added DMTSF (130 mg, 0.66 mmol) in one portion. After stirring 6 h, solvent was evaporated, and the resulting residue was taken up in a solution of NaN_3 (64 mg, 0.99 mmol) in H_2O (2 mL). The solution was stirred for 4 d and then extracted with ether (2 × 2 mL). The combined organic layers were evaporated to a residue that was chromatographed on SiO_2 (4:1 hexanes:EtOAc) to afford 39 mg (60%) of **72** and **73** as a 2:1 mixture: R_f = 0.50 (4:1 hexanes:EtOAc). For **72**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (m, 1 H), 3.75 (m, 1 H), 2.95 (m, 1 H), 2.25 (s, 3 H), 2.2−1.6 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.8, 66.5, 57.9, 29.1, 28.9, 15.9; EIMS m/z 198 (M$^+$, 15%). For **73**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (m, 2 H), 2.82 (t, 1 H, J = 6.4 Hz), 2.25 (s, 3 H), 2.2−1.6 (m, 4 H): ^{13}C NMR (75 MHz, $CDCl_3$) 64.7, 57.6, 29.6, 15.4; EIMS m/z 198 (M$^+$, 20%); IR (film) (mixture) 2900, 2100, 1275 cm^{-1}.

Addition of DMTSF to *all-cis*-Cyclopentenetriol 74; Synthesis of 5-Azido-2,3,4-trihydroxy-1-methylthiocyclopentane 75. To a stirred 0 °C solution of cyclopentenetriol **74** (150 mg, 1.29 mmol) in CH_3CN (7.5 mL) was added DMTSF (304 mg, 1.55 mmol) under Ar. After 6 h at 0 °C, a solution of NaN_3 (252 mg, 3.88 mmol) in water (3 mL) was added. The reaction was warmed to room temperature and stirred for 7 d. Solvent was then removed and the residue triturated with 1:1 CH_2Cl_2:MeOH (3 mL). The triturate was filtered through Celite, rinsing with 10:1 CH_2Cl_2:MeOH (20 mL). The combined organic layers were evaporated, and the residue was chro-

matographed on SiO_2 (10:1 CH_2Cl_2:MeOH) to afford 85 mg (32%) of pure **75** as well as 28 mg of a 1:1 mixture of **74** and **75**: $R_f = 0.35$ (10:1 CH_2Cl_2:MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (m, 1 H), 3.88 (m, 1 H), 3.79 (m, 1 H), 3.63 (m, 1 H) 2.85 (m, 1 H), 2.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 74.8, 71.8, 71.3, 70.8, 51.8, 14.8; IR (film) 3400, 2100, 1500, 1220, 1190 cm^{-1}; FABMS *m*/*z* 205 (M^+, 55%).

Synthesis of 2-Amino-3,4,5-trihydroxy-1-methylthiocyclopentane (bis-epi-mannostatin A) 76. To a solution of azide **75** (95 mg, 0.46 mmol) in MeOH (5 mL) was added triethylamine (388 μL, 2.78 mmol) followed by propane-1,3-dithiol (280 μL, 2.78 mmol). The solution was stirred 72 h at room temperature, during which time a white solid precipitated. The supernatant was then filtered and the filtrate concentrated to a residue that was chromatographed on SiO_2 (50:20:1 CH_2Cl_2:MeOH:NH_4OH) to furnish 39 mg (48%) of **76** as an oil: ^{1}H NMR (300 MHz, D_2O) δ 4.03 (m,1 H), 3.87 (m, 1 H), 3.61 (m, 1 H), 2.91 (m, 1 H), 2.61 (m,1 H), 1.96 (s, 3 H); ^{13}C NMR (75 MHz, D_2O) δ 76.3, 71.6, 71.4, 62.0, 53.6, 15.0; IR (film) 3350, 2900, 1590, 1425, 1125 cm^{-1}; FABMS *m*/*z* 180 (M + 1, 60%), 163 (100%). The ^{1}H NMR spectrum of **76**·HCl was distinctly different from a spectrum of authentic mannostatin A HCl salt.

Addition of DMTSF to *all-cis*-3,4,5-Tribenzyloxycyclopentene 77; Synthesis of 5-Azido-2,3,4-tribenzyloxy-1-methylthiocyclopentane 78. To a stirred 0 °C solution of cyclopentene **77** (200 mg, 0.52 mmol) in CH_3CN (4 mL) was added DMTSF (122 mg, 0.62 mmol). The solution was stirred under argon for 2 h at 0 °C and then warmed to room temperature. After 1.5 h, a solution of NaN_3 (101 mg, 1.55 mmol) in water (1 mL) was added, and the solution was stirred 4 d at room temperature. The reaction mixture was diluted with EtOAc (20 mL) and washed with brine (5 mL). The aqueous layer was back-extracted with EtOAc (3 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by prep TLC to afford **78** (83 mg, 34%) as a colorless oil: R_f 0.31 (4:1 hexanes:EtOAc); ^{1}H NMR (300 MHz, D_2O) δ 7.42−7.25 (m,15 H), 4.84−4.50 (m, 6 H), 4.33 (m, 1 H), 4.01−3.93 (m, 2 H), 3.60 (m,1 H), 2.94 (m, 1 H), 2.22 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 138.4, 137.9, 128.7, 128.65, 128.60, 128.23, 128.18, 128.1, 127.95, 127.90, 81.2, 78.3, 76.4, 73.2, 73.1, 72.4,71.5, 51.0, 15.2; IR (film) 2900, 2100, 1350, 1100 cm^{-1}; FDMS *m*/*z* 479 (M^+,100%).

Acknowledgment. Financial support from the U. S. National Institutes of Health (GM 35712, to B.G.; GM 08500 training grant support for M.A.C.) is gratefully acknowledged. We also thank Emil Lobkovsky of the Departmental X-ray Facility for X-ray crystallographic analyses, and Mr. Ryan Schoenfeld for valuable experimental assistance.

Supporting Information Available: Copies of NMR spectra for all new compounds, as well as ORTEP diagrams and tables of crystallographic data for compounds **33**, **58**, **65**, and **71**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO000101F