Enantioselective Approaches to Aminocyclopentitols: A Total Synthesis of (+)-6-Epitrehazolin and a Formal Total Synthesis of (+)-Trehazolin

Jun Li, Fengrui Lang, and Bruce Ganem*

Department of Chemistry, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

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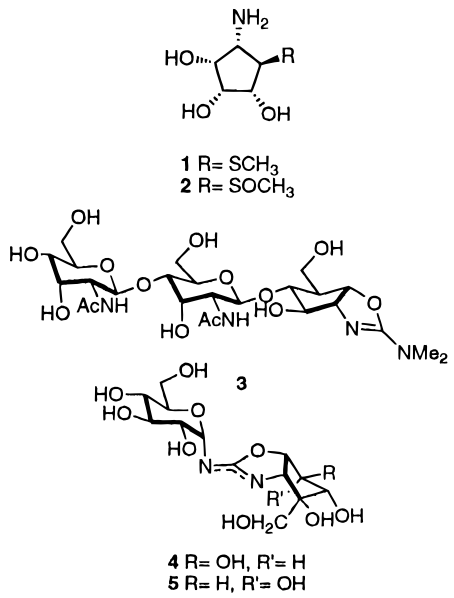
Potent inhibitors of trehalase, such as trehazolin and its congeners, represent an attractive approach to the design of effective new insect control agents. In this report, enantioselective total syntheses of (−)-6-epitrehazolin and (+)-trehazolin were achieved using the asymmetric heterocycloaddition between [(benzyloxy)methyl]cyclopentadiene and the acylnitroso compound arising from in situ oxidation of *(S)*-mandelohydroxamic acid with tetrabutylammonium periodate. Further functionalization of the resulting 3,4,5-trisubstituted cyclopentene, either involving osmylation or epoxidation of the double bond, efficiently created pentasubstituted cyclopentanes. Introduction of the quaternary carbon in both synthesis targets was achieved via stereoselective osmylation of an intermediate 2,3,4,5-substituted 1-methylenecyclopentane.

Introduction

Inhibitors of glycosidases, which are the enzymes that catalyze the hydrolysis of glycosidic bonds, figure prominently in many of the major advances of modern glycobiology.[1] Recently, several new aminocyclopentitol-containing natural products have been discovered that display potent and selective effects on a variety of biologically important glycosidases. Examples include mannostatins A and B (**1**−**2**, Scheme 1), which are selective mannosidase inhibitors,[2] allosamidin (**3**), representing a new family of pseudotrisaccharide chitinase inhibitors,[3] and trehazolin (**4**),[4] which inhibits the trehalase-catalyzed breakdown of trehalose to two molecules of glucose.

Apart from **4**, known trehalase inhibitors include validoxylamine A,[5] salbostatin,[6] and 1-deoxynojirimycin,[7] the last being much less active. Potent, substrate-specific inhibitors of trehalase represent an attractive approach to the design of effective new insect control agents, since trehalose is the principal blood sugar and mobile energy source of insects. Moreover, trehalase inhibitors should exhibit little human toxicity, since trehalose plays no significant role in mammalian metabolism.[8]

Scheme 1



The chemical and biological properties of trehazolin have been studied by several research groups,[9] from which have emerged some interesting synthetic analogues, such as (+)-6-epitrehazolin **5**,[10] as well as a variety of useful structure−activity relationships.[11] Several partial or total enantioselective syntheses of trehazolin, whose correct absolute configuration is depicted in **4**, have also been reported.,[12−15] In most syntheses,

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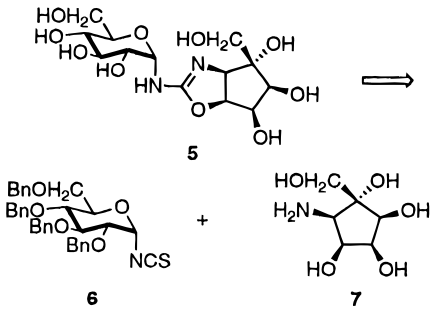
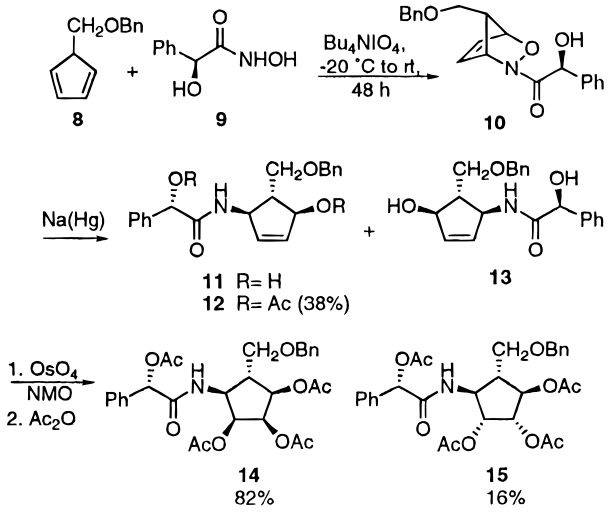
Scheme 2



Scheme 3



access to the core aminocyclopentitol was achieved either by (a) functionalization of an enantiomerically pure starting material, typically a carbohydrate, drawn from the chiral pool[16] or (b) hydroxylation of preassembled di- and trisubstituted cyclopentenes using osmylation or epoxidation reactions.[17]

Our own approach to the synthesis of trehazolin, as developed in earlier syntheses of cyclopentane-based glycosidase inhibitors,[14,18,19] focused on the enantioselective heterocycloaddition of substituted cyclopentadienes or fulvenes to create 3,4,5-trisubstituted cyclopentenes, which undergo stereoselective additions with strongly electrophilic reagents syn to the allylic substituents, thus resulting in pentasubstituted cyclopentanes.[20] Here, we report enantioselective syntheses of (+)-trehazolin (**4**) and (+)-6-epitrehazolin (**5**) in which we demonstrate the practicality of our approach in assembling the requisite hexasubstituted aminocyclopentitol components.

Synthesis of (+)-6-Epitrehazolin

The convergent strategy we envisioned was formulated around a late-stage assembly of the aminooxazoline ring by the condensation of appropriate carbohydrate and cyclopentane intermediates. One likely endgame involved reaction of the known tetra-*O*-benzyl-α-D-glucopyranosylisothiocyanate (**6**)[21] with aminocyclopentitol **7** (Scheme 2) to give a thiourea whose cyclization and deprotection, following the precedent of Shiozaki et al.,[12b] should afford **5**.

The enantioselective synthesis of **7** began with an asymmetric heterocycloaddition between the known [(benzyloxy)methyl]cyclopentadiene **8** (Scheme 3),[22] prepared from thallous cyclopentadienide, and the acylnitroso compound arising from in situ oxidation of (*S*)-mandelohydroxamic acid **9** with tetrabutylammonium periodate. Cycloaddition led to a mixture of the desired product **10** together with its diastereomer (not shown). The inseparable mixture was reduced using sodium amalgam to afford pure cyclopentene **11**, which was characterized as its diacetate **12**, in 40% overall yield from thallous cyclopentadienide. The minor cycloadduct **13** was also obtained in 11% yield. Consistent with an earlier precedent,[19] the catalytic osmylation of **11** favored syn addition. However, the osmylation of diacetate **12** was more selective and nearly quantitative, affording **14** and **15** in >5:1 ratio after acetylation. Pure **14** was obtained in 82% overall yield from **12** after chromatography. Nuclear Overhauser enhancements observed between the four cis methine ring hydrogens confirmed the assigned relative stereochemistry in **14**.

This five-step route to enantiomerically pure, differentially protected amidocyclopentitol **14** made it possible to introduce stereoselectively the quarternary center in 6-epitrehazolin, as shown in Scheme 4. Catalytic hydrogenolysis of both the benzylic ether and acetate groups in **14** using palladium hydroxide furnished alcohol **16** in quantitative yield. Using the method of Grieco et al.,[23] nitrophenylselenation followed by in situ oxidative elimination cleanly transformed **16** into alkene **17** in 83% yield. Flanked by two allylic substituents shielding the top face of the five-membered ring, the exocyclic alkene in **17** underwent vicinal hydroxylation exclusively from the opposite face using OsO_4 and *N*-methylmorpholine *N*-oxide to afford diol **18**. Further evidence for its structure came from the observation that **18** underwent slow intramolecular 1,5-acetyl migration to the corresponding primary acetate. The resulting mixture was converted to a single pentaacetate **19** in 96% overall yield from **17**. Exhaustive hydrolysis of **19** furnished aminocyclopentitol **7** (96%).

The overall stereochemical configuration of **7** was unambiguously confirmed by its successful transformation into (+)-**5**, as shown in Scheme 5. Condensation of **7** with isothiocyanate **6** gave thiourea **20** (80% yield),

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(13) (a) Ogawa, S.; Uchida, C. *Chem. Lett.* **1993**, 173−176. (b) Uchida, C.; Yamagishi, T.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 589−602.

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(15) Ledford, B. E.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 11811−11812.

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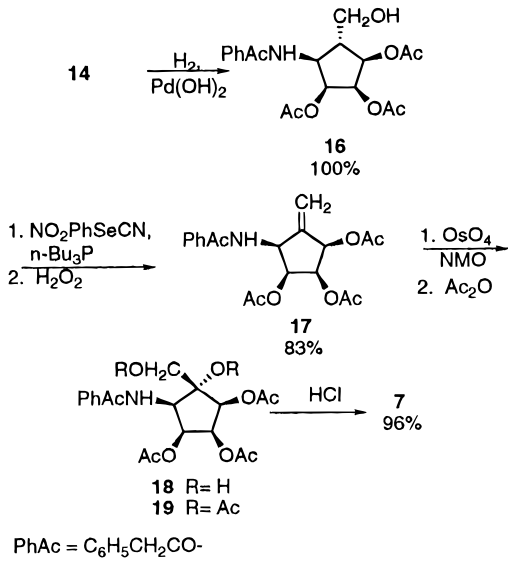
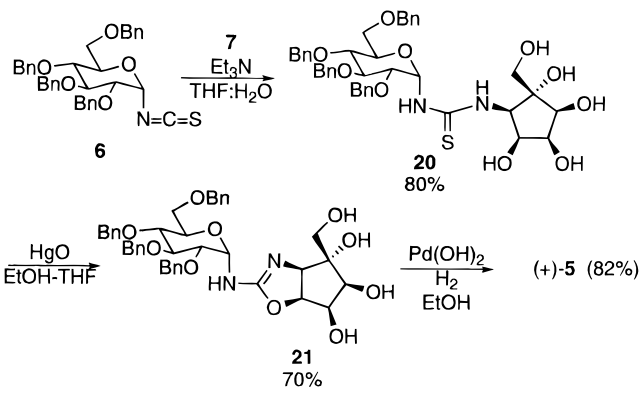
(22) Corey, E. J.; Koelliker, U.; Neuffer, J. *J. Am. Chem. Soc.* **1971**, 1489−1490.

(23) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485−1486.

Scheme 4



Scheme 5

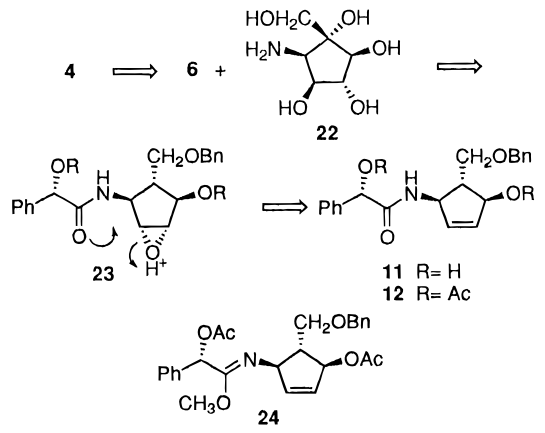


which could be cyclized to aminooxazoline **21** using yellow mercuric oxide in 70% yield. Deprotection of **21** by hydrogenolysis afforded (+)-**5** (82%), whose physical and spectrometric properties agreed with previously published values.[10] Overall, the synthesis of **5** proceeded in 14 steps and 11% overall yield from cyclopentadiene **8**.

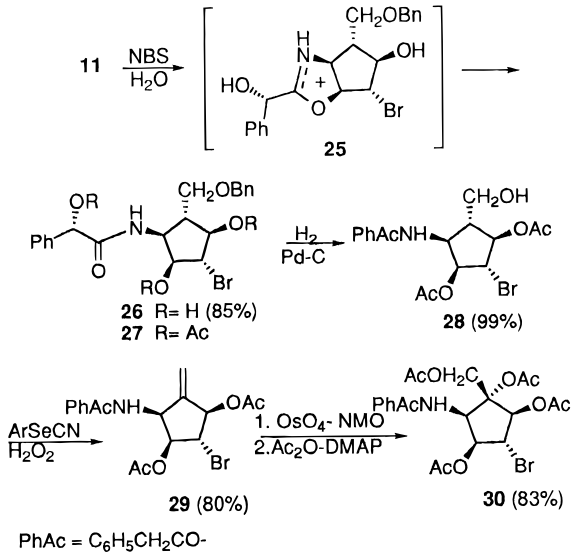
6-Bromo-6-deoxytrehazolin Approach to Trehazolin

On the basis of the successful synthesis of (+)-**5**, an attractive route to (+)-**4** was envisioned (Scheme 6) involving condensation of isothiocyanate **6** with the trehazolin aminocyclopentitol **22**, which had previously been synthesized.[12b] Compound **22** was expected to arise from amide carbonyl participation in the opening of epoxide **23**, for which we hoped to develop a synthesis from diacetate **12** (Scheme 3) or some other protected form of diol **11**. Peracids are known to interact more strongly with secondary allylic amides than with allylic hydroxyl groups in effecting syn epoxidation reactions.[17a,24] To ascertain whether steric hindrance at the remaining allylic carbon could override the syn directing effect of the mandelamide group, the epoxidation of several ether derivatives of **11** (R= *tert*-butyldimethylsilyl, triisopropylsilyl, trityl) was studied using using *m*-chloroperoxybenzoic acid, CF_3CO_3H, HOF−CH_3CN,[25] and dimethyldioxirane. In all cases, however, the product was predominantly or exclusively the undesired *syn*-epoxide, an authentic sample of which was prepared in quantitative yield by the direct epoxidation of **11** itself (vide infra). To eliminate the hydrogen-bond-donor properties of the acylamino group, diacetate **12** was transformed to the corresponding *O*-methyl imino ether **24**. However, epoxidation of **24** afforded a complex mixture of products that was not investigated further.

Scheme 6



Scheme 7

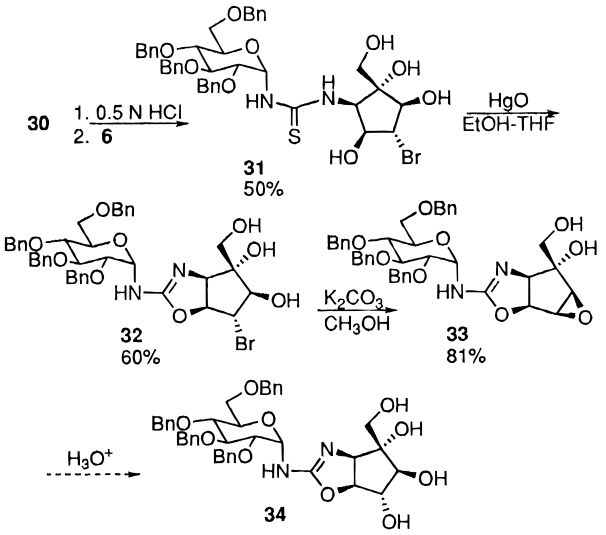


As expected, reaction of *N*-bromosuccinimide−H_2O with amide **11** occurred with anchimeric participation by the mandelamide carbonyl as depicted in **25** (Scheme 7) to afford a single HOBr adduct **26** in 85% yield. It occurred to us that a sequence of steps paralleling those in Schemes 4 and 5 might be used to transform **26** into 6-bromo-6-deoxytrehazolin, which itself might serve as a potential precursor for trehazolin (vide infra). Following that rationale, **26** was exhaustively acetylated to give triester **27**. When subjected to hydrogenolysis conditions, **27** underwent benzylic deoxygenation with no trace of dehalogenation to afford **28** in quantitative yield. Selenation of **27** with subsequent oxidative elimination furnished **29** in 80% yield. Vicinal dihydroxylation of **29** was highly stereoselective, with acetylation of the product affording pure hexasubstituted cyclopentane **30** in 83%

(24) Berti, G. *Topics Stereochem.* **1973**, *7*, 93−251.

(25) Rozen, S.; Bareket, Y.; Dayan, S. *Tetrahedron Lett.* **1996**, *37*, 531−534.

Scheme 8



yield after chromatography. No trace of any isomeric product was detected.

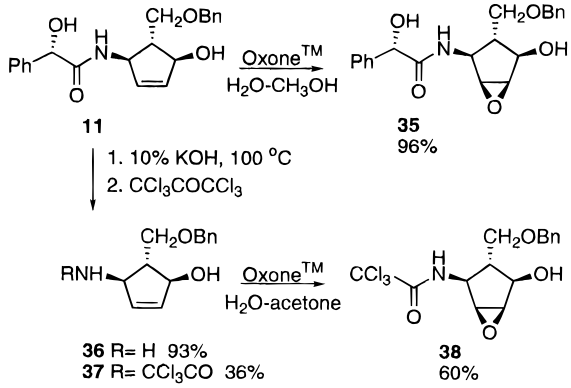
Hydrolysis of **30** in dilute HCl afforded the corresponding aminobromocyclopentitol, which, without purification, was reacted as before with glucosylisothiocyanate **6**. The desired thiourea **31** (Scheme 8) was obtained in 50% yield and was cyclized using yellow HgO to aminooxazoline **32** (60% yield), which represents a protected form of 6-bromo-6-deoxytrehazolin. To cyclize the *trans*-bromohydrin unit, **32** was stirred in a suspension of potassium carbonate−methanol and thus formed epoxide **33** in 81% yield.

Our interest in epoxide **33** as a precursor to (+)-trehazolin arose from the knowledge that electronegative substituents strongly influence the direction of acid-catalyzed epoxide opening.[16a,26] Adjacent hydroxy and acyloxy groups have been shown to destabilize the incipient positive charge in such openings, causing the incoming nucleophile to bond at the more remote epoxide carbon. In the case of **33**, it was hoped that the combination of steric hindrance from the quaternary center, together with the two electron-withdrawing hydroxyl groups,[26b] would outweigh the inductive effect of the iminocarbamate substituent and thus favor the stereochemical outcome shown in **34**. In the event, a dilute solution of epoxide **33** in 10:1 water−trifluoroacetic acid (TFA) was unchanged upon prolonged stirring at room temperature. Even in 1:1 H_2O/TFA, little or no hydrolysis of **33** was evident after 24 h at room temperature. Control experiments in our laboratory had previously established that the glycosidic linkage in **4** and **5** was stable to these conditions. Unfortunately, the use of 1:1 H_2O/TFA under more forcing conditions (50−60 °C) led to fragmentation of the aminoisoxazoline linkage, judging from the thin layer chromatogram, in which a spot appeared that comigrated with tetrabenzyl-D-glucopyranose. Similar results were observed in reactions of **33** with dilute perchloric acid in tetrahydrofuran, and no trace of the desired epoxide hydrolysis product could be detected under any conditions tested.

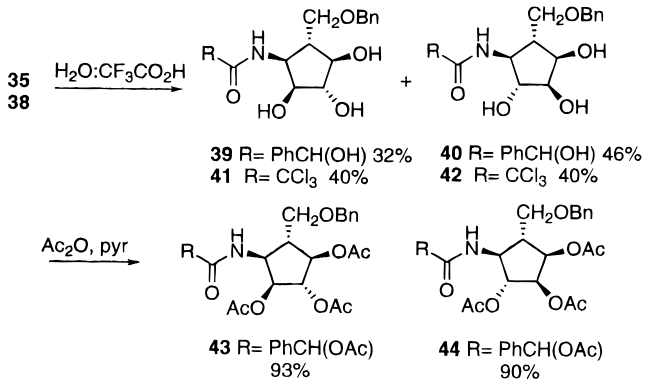
Formal Total Synthesis of (+)-Trehazolin

To investigate an alternative approach to aminocyclopentitol **22** for the synthesis of trehazolin, the effect of varying the electronegativity of adjacent substituents on the regiochemistry of epoxide ring opening was explored using mandelamide **35** and trichloroacetamide **38** (Scheme 9). Starting from trisubstituted cyclopentene **11**, *syn*-epoxidation with *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded **35** in 96% yield. In addition, alkaline hydrolysis of **11** furnished **36**, which could be trichloroacetylated using hexachloroacetone to afford **37** in 36% yield from **36**. Treatment of **37** with Oxone formed the corresponding *syn*-epoxide **38** (60% yield).

Scheme 9



Scheme 10

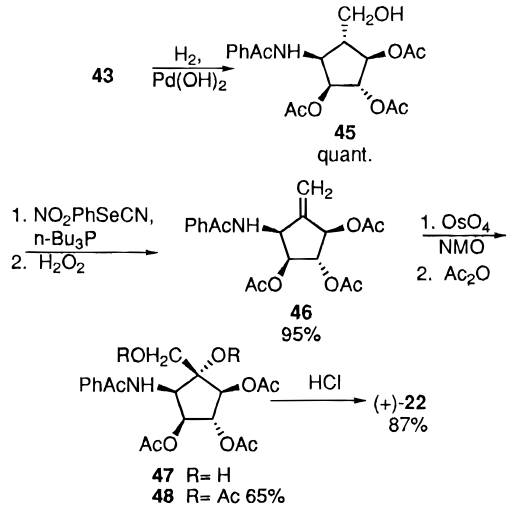


Not surprisingly, epoxide **35** proved resistant to acid but did undergo slow hydrolysis using 2:1 H_2O/TFA (rt, 60 h) to afford a 1:1.6 ratio of the desired product **39** (32%) and its isomer **40** (52%, Scheme 10), which for further characterization were transformed to the corresponding peracetates **43** (93%) and **44** (90%). Under similar conditions, the combined halogen electron-withdrawing effects in epoxytrichloroacetamide **38**, which were expected to influence the regiochemistry of opening, had only a modest effect on the product distribution, leading to a 1:1 ratio of **41** and **42**. Therefore, the synthesis of **22** was completed from the more readily available **43**.

The route to **22** (Scheme 11) closely paralleled the synthesis of **7** shown in Scheme 4. Reductive cleavage of both the benzylic ether and ester substituents in **43** by hydrogenolysis with palladium hydroxide gave hydroxy phenylacetamide **45** in quantitative yield. Nitrophenylselenation of the primary alcohol in **45** followed by in situ oxidative elimination furnished alkene **46** in 95% yield. Stereoselective osmylation of the exocyclic alkene in **46** using OsO_4−*N*-methylmorpholine *N*-oxide gave diol **47**, which was additionally characterized as its pentaacetate ester **48** (65% yield). Acidic hydrolysis of **48** furnished aminocyclopentitol (+)-**22** (87%), whose

(26) (a) Franks, J. A., Jr.; Tolbert, B.; Steyn, R.; Sable, H. Z. *J. Org. Chem.* **1965**, *30*, 1440−1446. (b) Tolbert, B.; Steyn, R.; Franks, J. A., Jr.; Sable H. Z. *Carbohydr. Res.* **1967**, *5*, 62−81.

Scheme 11



spectral and physical properties were in agreement with earlier reported values. Since this unprotected aminocyclitol has previously been converted to (+)-trehazolin,[12b] a formal total synthesis of **4** was thus achieved.

Conclusion

In summary, we have shown that the asymmetric cycloaddition of 1-substituted-2,4-cyclopentadienes with heterodienophiles, which has previously been used to construct pentasubstituted cyclopentanes, can also be extended to the preparation of hexasubstituted cyclopentanes featuring quaternary carbon centers. An enantioselective synthesis of (+)-6-epitrehazolin from thallous cyclopentadienide was achieved in 14 steps and 11% overall yield. Aminocyclopentitol (+)-**22** was similarly prepared from **8** in 11 steps, constituting a formal total synthesis of (+)-trehazolin.

Experimental Section[27]

Synthesis of Trisubstituted Cyclopentene 11. (Benzyloxy)methyl chloride ($PhCH_2OCH_2Cl$, 3.48 g, 22.3 mmol) was added dropwise to a suspension of freshly sublimed cyclopententadienylthallium (4 g, 14.8 mmol) in diethyl ether (150 mL) at −30 °C under Ar, and the mixture was stirred for 30 h at −20 °C. The suspension was rapidly filtered at −30 °C into a 500 mL flask, and to the resulting yellow filtrate were added *n*-Bu_4NIO_4 (6.44 g, 14. 87 mmol) and cold methanol (50 mL). The mixture was warmed to −20 °C, and a solution of (*S*)-mandelohydroxamic acid (2.48 g, 14.8 mmol) in methanol (20 mL) was added dropwise under Ar. The reaction mixture was stirred at −20 °C for 24 h and then slowly warmed to room temperature over 20 h and filtered through a short silica gel column. The filtrate was concentrated to give impure **10** (5 g), which was carried on directly to the next step.

To a suspension of **10** and Na_2HPO_4 (10.1 g) in 2:1 THF/methanol (120 mL) at 0 °C was added sodium amalgam (22 g, 6% w/w). After the mixture was stirred for 8 h at 0 °C, 1:1 THF/EtOAc (200 mL) was added, and the mixture was filtered through Celite. The filtrate was concentrated in vacuo and purified by silica gel chromatography (50:1 CH_2Cl_2/CH_3OH) to give **11** (1.98 g, 40% for three steps) as a clear oil: $[\alpha]^{25}_D$ +25.7° (*c* 0.3, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41−7.25 (m, 10 H), 6.36 (d, 1 H, J = 7.8 Hz), 5.97−5.91 (m, 1 H), 5.70−5.65 (m, 1 H), 5.01 (d, 1 H, J = 3.3 Hz), 4.59−4.51 (m, 3 H), 4.52 (s, 2H), 3.70−3.57 (m, 3 H), 3.30 (d, 1 H, J = 3.4 Hz), 2.67 (d, 1 H, J = 5.9 Hz), 2.19−2.13 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 139.4, 137.8, 135.6, 132.7, 128.6, 128.4, 127.7, 127.6, 126.7, 78.3, 74.0, 73.1, 70.5, 56.2, 55.9; IR ($CDCl_3$) 3600, 3400, 3100, 3050, 2750, 1660, 1525, 1100 cm^{-1}; HRMS (FAB) for $C_{21}H_{24}NO_4$ (M + 1) calcd 354.1705, found 354.1701.

Synthesis of Diacetate 12. To a room-temperature solution of **10** (80 mg, 0.28 mmol) in pyridine (1.5 mL) were added 4-(dimethylamino)pyridine (DMAP, 8 mg, 0.07 mmol) and acetic anhydride (0.20 mL, 2.12 mmol) under Ar. After the mixture was stirred for 20 h, the solvent was removed and the residue was purified by silica gel column (hexanes/EtOAc 2:1) to give diacetate **12** (98 mg, 100%) as a clear oil: $[\alpha]^{25}_D$ +53.2° (*c* 0.5, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49−7.22 (m, 10 H), 6.26 (d, 1 H, J = 8.1 Hz), 6.06 (s, 1 H), 6.00−5.87 (m, 2 H), 5.54 (d, 1 H, J = 3.1 Hz), 4.90−4.80 (m, 1 H), 4.51 (s, 2 H), 3.75−3.58 (m, 2 H), 2.30−2.19 (m, 1 H), 2.17, 2.05 (2 s, each 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 169.0, 167.7, 138.1, 135.4, 135.3, 132.6, 129.0, 128.7, 128.3, 127.5, 127.4, 127.3, 79.9, 75.4, 73.2, 69.6, 56.0, 53.1, 21.1, 21.0; IR ($CHCl_3$) 3410, 3070, 3040, 1730, 1675 cm^{-1}; FABMS *m/e* 438 (M + 1, 35), 378 (M + 1 − HOAc, 100%).

Osmylation of 12: Synthesis of 14. To a solution of diacetate **12** (245 mg, 0.55 mmol) and *N*-methylmorpholine *N*-oxide (130 mg, 1.10 mmol) in 10:1 acetone/H_2O (11 mL) at 0 °C was added OsO_4 (0.35 mL, 5% w/w in H_2O). The reaction was slowly warmed to room temperature and monitored by TLC. After 48 h, $NaHSO_3$ (0.57 g, 5.50 mmol) in H_2O (10 mL) was added, and the mixture was stirred for 4 h at room temperature. The acetone was removed under reduced pressure, and the aqueous residue was extracted with CH_2Cl_2 (4 × 20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was dissolved in pyridine (4 mL) and treated with DMAP (13 mg, 0.11 mmol) and acetic anhydride (0.52 mL, 5.5 mmol) under Ar. The resulting solution was stirred at room temperature for 24 h and concentrated in vacuo. The residue was flash chromatographed (2:1 hexanes/EtOAc) to give tetraacetates **14** (256 mg, 82%) and **15** (52 mg, 16%) as clear oils. For **14**: $[\alpha]^{25}_D$ +28.7° (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.22 (m, 10 H), 6.32 (d, 1 H, J = 8.3 Hz), 6.06 (s, 1 H), 5.37 (t, 1 H, J = 4.4 Hz), 5.28−5.18 (m, 2 H), 4.64−4.42 (m, 3 H), 3.59 (ddd, 2 H, J = 3.8, 9.3, 13 Hz), 2.35−2.22 (m, 1 H), 2.19 (s, 3 H), 2.03, 2.01, 1.93 (3 s, each 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 169.1, 168.9, 168.8, 167.6, 137.8, 135.2, 129.2, 128.9, 128.3, 127.6, 127.6, 75.3, 73.4, 72.4, 71.4, 70.6, 68.2, 50.5, 50.0, 20.9, 20.6, 20.5, 20.3; IR ($CDCl_3$) 3450, 2870, 1760, 1680 cm^{-1}; MS (FAB) 556, 496, 468, 309; HRMS (FAB) for $C_{29}H_{34}NO_{10}$ (M + 1), calcd 556.2183, found 556.2185.

Hydrogenolysis of 14: Synthesis of 16. To a solution of **14** (256 mg, 0.46 mmol) in absolute ethanol (50 mL) was added $Pd(OH)_2$ on carbon (50 mg). The system was flushed with hydrogen and the reaction mixture stirred under a balloon of hydrogen. After 8 h at room temperature, ethyl acetate (25 mL) was added, and the mixture was filtered through Celite. The filtrate was concentrated in vacuo to give **16** (187 mg, 100%) as a white solid: $[\alpha]^{25}_D$ +15.0° (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49−7.21 (m, 5 H), 5.95 (d, 1 H, J = 7.8 Hz), 5.31 (t, 1 H, J = 4.2 Hz), 5.15 (dd, 1 H, J = 3.7, 6.8 Hz), 4.93 (dd, 1 H, J = 5.0, 7.8 Hz), 4.30 (dd, 1 H, J = 7.6, 15.3 Hz), 3.75−3.55 (m, 2 H), 2.21−2.11 (m, 1 H), 2.00, 1.89 (2 s, each 3 H), 1.88 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.4, 170.1, 169.1, 168.8, 134.3, 129.6, 129.2, 127.7, 71.5, 70.8, 70.4, 61.3, 53.4, 50.1, 43.5, 20.5, 20.3, 20.2; IR ($CDCl_3$) 3430, 2920, 1750, 1650 cm^{-1}; FABMS *m/e* 408 (M + 1, 100).

Dehydration of 16: Synthesis of 17. To a solution of alcohol **16** (124 mg, 0.30 mmol) and *o*-nitrophenylselenocyanate (138 mg, 0.61 mmol) in dry THF (3 mL) at room temperature was added *n*-Bu_3P (148 mg, 0.73 mmol 182 μL) dropwise under Ar. After 4 h, the solvent was removed in vacuo, and the residue was filtered through a short column of silica gel eluting with 1:1 hexanes/EtOAc to afford impure selenide (162 mg), which was immediately dissolved in THF (3 mL) and treated with H_2O_2 (0.13 mL, 30% w/w) dropwise at room

(27) For general experimental procedures, see ref 19.

temperature. After 5 h, the solvent was removed at reduced pressure, and the residue was flash chromatographed (1:1 hexanes/EtOAc) to afford methylenecyclopentane **17** (100 mg, 84% from **16**) as a syrup: $[\alpha]^{25}_D$ −21.3° (*c* 1.9, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.22 (m, 5 H), 5.55−5.65 (m, 2 H), 5.41−5.36 (m, 2 H), 5.31 (dd, 1 H, J = 3.7, 4.8 Hz), 5.24 (dd, 1 H, J = 3.3, 5.8 Hz), 5.17−5.07 (m, 1 H), 3.66 (s, 2 H), 2.05, 1.91, 1.87 (3 s, each 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 169.6, 169.1, 169.0, 145.5, 134.5, 129.5, 129.0, 127.5, 115.7, 70.9, 70.3, 70.2, 50.1, 43.8, 20.6, 20.34, 20.32; IR ($CDCl_3$) 3460, 2920, 1750, 1670 cm^{-1}; FABMS *m/e* 390 (M + 1).

Osmylation of 17: Synthesis of 19. Aqueous OsO_4 (0.32 mL, 5% w/w in H_2O) was added to a solution of methylenecyclopentane **17** (130 mg, 0.33 mmol) and *N*-methylmorpholine *N*-oxide (117 mg, 1.10 mmol) in 10:1 acetone/H_2O (6.6 mL) at 0 °C. The reaction was warmed to room temperature and monitored by TLC. After 36 h, the solvent was removed in vacuo, and the resulting cyclopentanediol was dissolved in pyridine (3 mL) to which were added DMAP (16 mg, 0.13 mmol) and acetic anhydride (0.50 mL, 5.3 mmol) under Ar. The solution was stirred at room temperature for 24 h and then concentrated in vacuo. The residue was flash chromatographed (1:1 hexanes/EtOAc) to afford pentaacetate **19** (163 mg, 96%) as a syrup: $[\alpha]^{25}_D$ −9.1° (*c* 2.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.24 (m, 5 H), 5.82 (d, 1 H, J = 10.0 Hz), 5.57 (d, 1 H, J = 5 Hz), 5.50 (t, 1 H, J = 4.6 Hz), 5.37 (dd, 1 H, J = 4.3, 6.9 Hz), 5.11 (dd, 1 H, J = 6.8, 10.0 Hz), 4.37, 4.49 (AB q, 2 H, J = 12.5 Hz), 3.59, 3.66 (AB q, 2 H, J = 16.6 Hz), 2.09, 2.06, 1.96, 1.94, 1.75 (5 s, each 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 170.2, 169.9, 168.6, 168.4, 168.3, 134.2, 129.6, 129.1, 127.6, 87.7, 73.8, 71.6, 68.5, 60.3, 54.9, 43.7, 21.5, 20.6, 20.1, 20.1, 20.0; IR ($CDCl_3$) 3450, 2925, 1760, 1680 cm^{-1}; FABMS (M + 1) 508.3; HRMS (FAB) for $C_{24}H_{30}NO_{11}$ (M + 1) calcd 508.1819, found 508.1822.

Hydrolysis of 19: Synthesis of 7. A solution of pentaacetate **19** (158 mg, 0.31 mmol) in anhydrous HCl−CH_3OH (0.5 M, 5 mL) was stirred and heated at 90 °C in a sealed tube for 24 h. The solvent was removed in vacuo, and the residue was dissolved in H_2O (2.5 mL) and then extracted with ether (3 × 2.5 mL) and ethyl acetate (1 × 2.5 mL). The aqueous layer was lyophilized to afford **7**·HCl (64 mg, 96%) as a syrup: $[\alpha]^{25}_D$ = −13.0° (*c* 2.0, CH_3OH); ^{1}H NMR (D_2O, 300 MHz) δ 4.27 (t, 1 H, J = 5.9 Hz), 4.11 (t, 1 H, J = 4.9 Hz), 3.82 (d, 1 H, J = 4.6 Hz), 3.72 (s, 2 H), 3.41 (d, 1 H, J = 6.4 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 80.6, 77.8, 72.2, 68.5, 62.7, 59.9; IR (film) 3300 cm^{-1}; FABMS *m/e* 180 (M + 1).

Coupling of 7 with Isothiocyanate 6: Synthesis of 20. Isocyanate **6** (118 mg, 0.20 mmol) in THF (1.5 mL) was added to a solution of **7**·HCl (29 mg, 0.14 mmol) and Et_3N (0.1 mL) in 10:3 THF/H_2O (1.3 mL). The reaction was stirred at room temperature for 4 h, and the solvent was removed in vacuo. The residue was flash chromatographed (25:2 CH_2Cl_2/CH_3OH) to give thiourea **20** (81 mg, 80%) as a syrup: $[\alpha]^{25}_D$ +140.4° (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, 1 H, J = 7.4 Hz), 7.38−7.18 (m, 20 H), 7.07−7.14 (m, 2 H), 6.87 (br, 1 H), 5.20 (bs, 1 H), 4.71−4.96 (m, 4 H), 4.62 (s, 2 H), 4.56−4.38 (m, 4 H), 4.13 (bs, 2 H), 4.02−3.83 (m, 3 H), 3.43−3.82 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.2, 138.1, 137.6, 137.1, 136.7, 128.6, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 127.9, 127.9, 127.8, 127.8, 83.0, 81.6, 79.4, 78.8, 76.9 75.9, 75.1, 73.4, 73.1, 72.4, 71.1, 70.4, 68.3, 64.6, 63.3; IR (film) 3400, 3350, 1525 cm^{-1}; FABMS *m/e* 761 (M + 1, 100).

Cyclization of 20: Synthesis of 21. Freshly prepared yellow HgO (3 g, 14.4 mmol) was added in three portions to a solution of thiourea **20** in 5:1 ether/THF (6 mL) at room temperature. The reaction was stirred at room temperature for 2 d, and then the mixture was filtered through Celite. After the filtrate was concentrated, the residue was purified by silica gel chromatography (10:1 CH_2Cl_2/CH_3OH) to afford aminooxazoline **21**: $[\alpha]^{25}_D$ +91.0° (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.18 (m, 20 H), 7.10−7.00 (m, 2 H), 5.31 (d, 1 H, J = 4.6 Hz), 4.91 (d, 1 H, J = 10.9 Hz), 4.80−4.70 (m, 3 H), 4.66−4.34 (m, 6 H), 4.32 (t, 1 H, J = 4.3 Hz), 4.12 (d, 1 H, J = 6.4 Hz), 4.04−3.70 (m, 5 H), 3.50−3.69 (m, 2 H), 3.45−3.23 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.2, 137.7, 137.4, 137.3, 137.1, 128.5, 128.4, 128.4, 128.3, 128.2, 128.0, 128.0, 127.9, 127.6, 83.8, 82.3, 81.6, 78.4, 77.5, 76.5, 76.5, 75.6, 75.0, 73.8, 73.4, 72.3, 69.8, 69.2, 62.4; IR (film) 3350, 1660, 1550 cm^{-1}; FABMS *m/e* 727 (M + 1, 100).

Hydrogenolysis of 21: Synthesis of 6-Epitrehazolin (5). To a solution of **21** (40 mg, 0.055 mmol) in dry EtOH (5 mL) was added $Pd(OH)_2$ on carbon (200 mg), and the mixture was stirred under hydrogen (1 atm) at room temperature for 24 h. The reaction was filtered through Celite, and the filtrate was concentrated. The impure product was chromatographed on Dowex 50WX 2-200 and eluted with deionized water and 0.5 N aqueous ammonia. The desired product was contained in the first few fractions, which were lyophilized to afford 6-epitrehazolin ((+)-**5**) as a white solid (17 mg, 82%): $[\alpha]^{25}_D$ +135.6° (*c* 0.67, H_2O) (lit.[9b] $[\alpha]_D$ +130°); ^{1}H NMR (D_2O, 500 MHz) δ 5.14 (d, 1 H, J = 5.5 Hz), 4.89 (dd, 1 H, J = 6.5, 6.5 Hz), 4.28 (dd, 1 H, J = 4.5, 5.5 Hz), 3.99 (d, 1 H, J = 7.5 Hz), 3.74, 3.78 (AB q, 2 H, J = 3.5, 12.5 Hz), 3.67−3.53 (m, 3 H), 3.49 (dd, 1 H, J = 9.0, 10.0 Hz), 3.39 (m, 1 H), 3.23 (dd, 1 H, J = 9.0, 10.0); ^{13}C NMR (D_2O, 75 MHz) δ 161.0, 83.4, 82.3, 80.4, 75.8, 72.9, 72.6, 71.7, 69.8, 69.5, 61.5, 60.5; IR (KBr) 3370, 2930, 1670 cm^{-1}; FABMS *m/e* 367 (M + 1, 55), 119 (100).

Synthesis of Bromohydrin 26. *N*-Bromosuccinimide (378 mg, 2.1 mmol) was added to a solution of cyclopentene **11** (626 mg, 1.8 mmol) in 1,4-dioxane (50 mL) and H_2O (5 mL) at room temperature. After the reaction mixture was stirred at room temperature for 18 h, the solvents were removed in vacuo, and the residue was purified by flash chromatography on silica gel (10:1 CH_2Cl_2/CH_3OH) to afford **26** (677 mg, 85%) as a white solid: mp 128−135 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 7.61 (d, 1 H, J = 7.0 Hz), 7.48 (d, 2 H, J = 6.5 Hz), 7.35−7.20 (m, 8 H), 5.31 (d, 1 H, J = 4.5 Hz), 5.07 (d, 1 H, J = 4.5 Hz), 4.96 (d, 1 H, J = 5.0 Hz), 4.61 (d, 1 H, J = 6.0 Hz), 4.34 (m, 1 H), 4.42 (s, 2 H), 4.18 (m, 1 H), 4.22 (m, 1 H), 4.00 (dd, 1 H, J = 5.5, 6.5 Hz), 3.62 (dd, 1 H, J = 4.0, 9.5 Hz), 3.54 (dd, 1 H, J = 4.0, 9.5 Hz), 2.15 (m, 1 H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 173.2, 141.9, 139.6, 128.9, 128.8, 128.3, 128.2, 127.5, 78.1, 77.3, 74.8, 73.6, 68.8, 61.6, 51.9, 51.2; IR (film) 3400, 1710, 1670 cm^{-1}; HRMS (FAB) for $C_{21}H_{25}BrNO_5$ (M + 1) calcd 450.0916, found 450.0916.

Synthesis of Bromotriacetate 27. A mixture of bromohydrin **26** (761 mg, 1.7 mmol), acetic anhydride (15 mL), and DMAP (30 mg, 0.25 mmol) was stirred overnight. The mixture was concentrated in vacuo at room temperature to give a brown solid that was purified by flash chromatography on silica gel (20:1 CH_2Cl_2/CH_3OH) to afford **27** (916 mg, 94%) as a white solid: mp 114−115 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.25 (m, 10 H), 6.28 (d, 1 H, J = 7.5 Hz), 6.01 (s, 1 H), 5.35−5.15 (m, 2 H), 4.57 (m, 1 H), 4.49 (s, 2 H), 4.16 (t, 1 H, J = 4.5 Hz), 3.59 (d, 2 H, J = 5.1 Hz), 2.43 (m, 1 H), 2.16, 2.05, 1.93 (3 s, each 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 169.2, 169.1, 168.1, 137.7, 135.0, 129.1, 128.8, 128.3, 127.6, 127.5, 127.3, 79.5, 78.0, 75.2, 73.4, 69.0, 51.5, 50.0, 49.2, 20.8, 20.3; IR (film) 3300, 1750, 1620, 1590 cm^{-1}; $[\alpha]^{25}_D$ +17.2° (*c* 1.1, CH_2Cl_2); HRMS (FAB) for $C_{27}H_{31}BrNO_8$ (M + 1) calcd 576.1233, found 576.1230.

Debenzylation of 27: Synthesis of 28. Benzyl ether **27** (343 mg, 0.60 mmol) was dissolved in anhydrous EtOH (25 mL), and $Pd(OH)_2$ on carbon (110 mg, Aldrich) was added. The solution was stirred at room temperature under a balloon of hydrogen for 4 h and then filtered through Celite and solvent removed to afford 318 mg of impure product. Purification by flash chromatography on silica gel (1:1 hexanes/EtOAc) afforded **28** (252 mg, 99%) as a white foam: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50−7.20 (m, 5 H), 5.77 (d, 1 H, J = 8.1 Hz), 5.18 (dd, 1 H, J = 3.9, 6.9 Hz), 5.07 (dd, 1 H, J = 2.7, 5.4 Hz), 4.63 (ddd, 1 H, J = 5.4, 8.4, 10.2 Hz), 3.97 (dd, 1 H, J = 2.7, 3.9 Hz), 3.69 (d, 2 H, J = 4.2 Hz), 3.64 (s, 2 H), 2.05 (m, 1 H), 2.05, 1.87 (2 s, each 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 170.0, 169.1, 134.2, 129.5, 129.3, 127.7, 79.7, 79.3, 60.1, 52.5, 50.0, 49.7, 43.5, 20.7, 20.3; IR (film) (3500, 1750, 1680 cm^{-1}; $[\alpha]^{25}_D$ −11.9° (*c* 0.5, CH_2Cl_2); HRMS (FAB) for $C_{18}H_{23}BrNO_6$ (M + 1) calcd 428.0709, found 428.0706.

Dehydration of 28: Synthesis of 29. To a mixture of alcohol **28** (170 mg, 0.40 mmol) in anhydrous THF (20 mL)

stirring over 4 Å molecular sieves (1 g) was added 2-nitrophenyl selenocyanate (136 mg, 0.60 mmol). The reaction mixture was stirred under argon while *n*-Bu_3P (150 μL, 0.60 mmol) was added dropwise. After being stirred overnight at room temperature, the intermediate selenide was treated with 30% H_2O_2 (0.7 mL) at room temperature for 50 h. The reaction mixture was filtered through Celite and the filtrate concentrated in vacuo. Purification of the impure alkene by flash chromatography afforded **29** (124 mg, 80%) as a white solid: mp 128−130 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.20 (m, 5 H), 5.66 (s, 1 H), 5.49 (d, 1 H, J = 5.4 Hz), 5.45 (m, 1 H), 5.37 (t, 1 H, J = 2.4 Hz), 5.24 (t, 1 H, J = 2.1 Hz), 5.12 (dd, 1 H, J = 2.1, 5.4 Hz), 4.03 (t, 1 H, J = 2.1 Hz), 3.66 (s, 2 H), 2.06, 1.86 (2 s, each 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 169.7, 169.2, 145.2, 134.5, 129.5, 129.2, 127.6, 115.3, 78.4, 77.7, 51.7, 48.3, 43.8, 20.9, 20.5; IR (film) 3320, 1750, 1680, 1580 cm^{-1}; HRMS (FAB) for $C_{18}H_{21}BrNO_5$ (M + 1) calcd 410.0603, found 410.0598.

Osmylation of 29: Synthesis of 30. A solution of *N*-methylmorpholine *N*-oxide (98 mg, 0.84 mmol) and 2% aqueous OsO_4 (178 μL, 5 mol %) was added to cyclopentene **29** (110 mg, 0.28 mmol) dissolved in acetone (10 mL) and H_2O (1 mL). The reaction mixture was stirred at room temperature for 40 h, and then the solvents were removed in vacuo and the residue was combined with Ac_2O (10 mL) and DMAP (20 mg). After the mixture was stirred overnight at room temperature, excess Ac_2O was removed in vacuo and the residue purified by flash chromatography on silica gel (1:1 hexanes/EtOAc) to afford **30** (96 mg, 65%) as a white solid: mp 70−72 °C; $[\alpha]^{25}_D$ +8.9° (*c* 1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.20 (m, 5 H), 5.87 (d, 1 H, J = 5.7 Hz), 5.61 (d, 1 H, J = 10.2 Hz), 5.55 (dd, 1 H, J = 6.9, 8.1 Hz), 5.34 (dd, 1 H, J = 8.1, 9.6 Hz), 4.44, 4.24 (AB q, 2 H, J = 12 Hz), 3.88 (dd, 1 H, J = 6.0, 6.3 Hz), 3.65, 3.60 (AB q, 2 H, J = 13.4 Hz), 2.08, 1.97, 1.96, 1.95 (4 s, each 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.5, 170.1, 169.9. 168.9, 168.8, 134.7, 129.7, 128.1, 87.2, 79.1, 77.0, 59.9, 54.2, 49.5, 44.1, 22.0, 21.1, 20.7, 20.6; IR (film) 1750, 1700, 1650 cm^{-1}; HRMS (CI) for $C_{22}H_{27}NO_9Br$ (M + 1) calcd 528.0869, found 528.0856.

Coupling of 30 with Isothiocyanate 6: Synthesis of 31. A mixture of tetraacetate **30** (20 mg, 0.038 mmol) and 0.5 M HCl in CH_3OH (20 mL) was heated at reflux for 60 h. The solvent was removed in vacuo, and the residue was dissolved in H_2O (2 mL) and Et_3N (30 μL) and then added to a solution of isothiocyanate **6** (33 mg, 0.057 mmol) in THF (4 mL) with stirring at room temperature for 5 d. Evaporation of the solvents and purification by flash chromatography on silica gel gave **30** (17 mg, 55%) as a yellow gum: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63−7.05 (m, 21 H), 6.76 (br, s, 1 H), 5.10 (br, s, 1 H), 4.90−4.15 (m, 11 H), 3.85−3.40 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.1, 138.4, 137.9, 137.5, 137.0, 129.0, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 82.0, 80.9, 80.2, 79.9, 77.6, 77.1, 76.3, 75.5, 73.8, 73.7, 71.5, 68.3, 65.7, 58.9, 56.1; IR (film) 3300 cm^{-1}; FABMS *m/e* 743 (M + 1 − HBr, 50), 709 (M + 1 − HBr and H_2S, 65).

Cyclization of 31: Synthesis of 32. To a solution of thiourea **31** (17 mg, 0.021 mmol) in anhydrous THF (5 mL) were added 4 Å molecular sieves (0.5 g) and purified yellow HgO (75 mg). The reaction mixture was protected from light, stirred at room temperature for 16 h, and then filtered through Celite. The solvent was removed in vacuo and the residue purified by flash chromatography to afford **32** (14 mg, 86%) as a white solid: $[\alpha]^{25}_D$ +61° (*c* 0.42, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.05 (m, 20 H), 5.22 (d, 1 H, J = 5.0 Hz), 4.90 (d, 1 H, J = 11.0 Hz), 4.74 (t, 2 H, J = 11.0 Hz), 4.68 (d, 1 H, J = 11.5 Hz), 4.55 (d, 1 H, J = 5.0 Hz), 4.52 (d, 1 H, J = 4.5 Hz), 4.44 (d, 1 H, J = 10.5 Hz), 4.39 (d, 1 H, J = 12.0 Hz), 4.36 (d, 1 H, J = 1.5 Hz), 4.21 (d, 1 H, J = 11.5 Hz), 4.09 (d, 1 H, J = 11.5 Hz), 3.80−3.70 (m, 3 H), 3.66−3.50 (m, 5 H), 3.44 (d, 1 H, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 168.4, 139.1, 138.6, 138.3, 138.2, 129.3, 129.1, 129.08, 129.06, 129.0, 128.88, 128.85, 128.7, 128.58, 128.56, 128.44, 128.36, 82.3, 79.2, 79.1, 78.6, 76.2, 75.6, 74.0, 73.9, 73.1, 71.6, 71.0, 69.2, 60.3, 56.7, 55.6; IR (film) 3450, 2900, 1700 cm^{-1}; FABMS *m/e* 709 (M + 1 − HBr, 100).

Closure of 32 to Epoxide 33. Finely powdered K_2CO_3 (30 mg) was added to a solution of bromohydrin **32** (4 mg, 0.005 mmol) in CH_3OH (2 mL). The heterogeneous reaction mixture was stirred at room temperature for 60 h, and the solvent was removed in vacuo. After the residue was triturated with CH_2Cl_2, the solvent was removed in vacuo and the soluble residue purified by flash chromatography to give epoxide **33** (3 mg, 81%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.10 (m, 20 H), 4.97 (d, 1 H, J = 9.0 Hz), 4.91 (d, 1 H, J = 11.0 Hz), 4.85 (d, 1 H, J = 11.0 Hz), 4.80 (d, 1 H, J = 10.5 Hz), 3.36 (t, 1 H, J = 9.0 Hz), 3.80−3.50 (m, 8 H), 4.02 (d, 1 H, J = 10.5 Hz), 4.79 (d, 1 H, J = 11.0 Hz), 4.75 (d, 1 H, J = 11.5 Hz), 4.58 (d, 1 H, J = 12.5 Hz), 4.50 (d, 1 H, J = 11.0 Hz), 4.48 (d, 1 H, J = 11.5 Hz), 4.40 (d, 1 H, J = 1.5 Hz), 4.20 (d, 1 H, J = 11.5 Hz); IR (film) 3400, 2750, 1700, 1080 cm^{-1}; FABMS *m/e* 709 (M + 1, 100).

Epoxidation of 11: Synthesis of 35. To a solution of cyclopentene **11** (636 mg, 1.80 mmol) in 1,4-dioxane (20 mL) was added *m*-CPBA (374 mg, 2.16 mmol) at room temperature. The reaction mixture was stirred at room temperature overnight and the solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel to give **35** (637 mg, 96%) as an oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42−7.25 (m, 10 H), 6.58 (d, 1 H, J = 7.5 Hz), 5.06 (d, 1 H, J = 3.6 Hz), 4.47 (s, 2 H), 4.31 (dt, 1 H, J = 8.4, 1.5 Hz), 4.10 (dt, 1 H, J = 8.1, 1.4 Hz), 3.61−3.42 (m, 4 H) 3.22 (d, 1 H, J = 3.3 Hz), 2.17 (d, 1 H, J = 6.6 Hz), 1.61 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 139.2, 137.7, 128.8, 128.6, 128.4, 127.8, 127.6, 126.7, 74.3, 73.9, 73.4, 68.6, 57.3, 56.1, 50.6, 45.7; IR (film) 3300, 1650, 1500 cm^{-1}; FABMS *m/e* 370 (M + 1, 98), 119 (100%).

Hydrolysis of 35 to Tetrols 39 and 40. To an ice-cold suspension of epoxide **35** (180 mg, 0.49 mmol) in water (2 mL) was added CF_3CO_2H (1.0 mL), and the resulting mixture was stirred at 0 °C for 1 h and then warmed to room temperature. When TLC analysis indicated that no starting material remained (48 h at room temperature), the solvents were removed in vacuo and the residue was dissolved in 5:1 CH_2Cl_2/CH_3OH (10 mL) containing suspended $NaHCO_3$ (0.5 g). After filtration through Celite, the organic phase was concentrated and the residue was purified by flash chromatography (20:1 CH_2Cl_2/CH_3OH) to afford **39** (62 mg, 32%) and **40** (103 mg, 52%) as pale oils. Because of low solubility and broad NMR line widths, both **39** and **40** were directly acetylated (pyridine, 20 equiv of Ac_2O, 0.4 equiv DMAP) and characterized as the corresponding peracetates **43** (93% yield) and **44** (90% yield). For **43**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40−7.31 (m, 10 H), 6.33 (d, NH, J = 7.5 Hz), 6.01 (s, 1 H), 5.18−5.16 (m, 2 H), 5.07−5.03 (m, 1 H), 4.47 (br d, 2 H), 4.42−4.46 (m, 1 H), 3.56 (d, 2 H, J = 4.5 Hz), 2.38−2.35 (m, 1 H), 2.17, 2.03, 2.02, 1.94 (4 s, each 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 169.8, 169.2, 169.0, 168.1, 137.8, 135.2, 129.1, 128.9, 128.4, 127.7, 127.4, 79.2, 76.4, 75.3, 74.9, 73.5, 68.6, 51.1, 47.9, 20.9, 20.8, 20.7, 20.5; IR (film) 3450, 1750, 1690 cm^{-1}; FABMS *m/e* 556 (M + 1, 38), 119 (100). For **44**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45−7.30 (m, 10 H), 6.88 (d, NH, J = 6 Hz), 6.01 (s, 1 H), 5.40−5.24 (m, 3 H), 4.57, 4.48 (AB q, 2 H, J = 12 Hz), 4.14 (br q, 1 H), 3.75, 3.64 (ABX, J = 3.6, 3.9, 9.0 Hz), 2.24 (s 3 H), 2.19−2.10 (m, 1 H), 2.06, 2.04, 2.03 (3 s, each 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 169.7, 169.5, 169.4, 169.1, 138.0, 135.2, 129.0, 128.8, 128.3, 127.5, 127.2, 77.6, 75.3, 73.4, 72.6, 72.5, 69.1, 53.2, 49.3, 21.0, 20.84, 20.80, 20.6; IR (film) 3400, 1745, 1675 cm^{-1}; FABMS *m/e* 556 (M + 1, 100).

Hydrogenolysis of 43 to Alcohol 45. A mixture of benzyl ether **43** (163 mg, 0.29 mmol), anhydrous ethyl alcohol (10 mL), and $Pd(OH)_2$ on carbon (Pearlman's catalyst, 25 mg) was stirred under a balloon of hydrogen at room temperature for 4 h. The reaction mixture was filtered through Celite and solvent evaporated to afford **45** (120 mg, quantitative), which was used without further purification in the next reaction. For analytical purposes, a sample of the product was purified by flash chromatography on silica gel to give **45** as a white solid: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.43−7.32 (m, 3 H), 7.29−7.21 (m, 2 H); 5.75 (d, NH, J = 8.4 Hz), 5.10−4.97 (m, 3 H), 4.49−4.39 (br m, 1 H), 3.63 (s, 2 H), 3.60 (d, 2 H, J = 5.4 Hz), 2.10−1.98 (br m, 1 H), 2.06, 2.05, 1.86 (3 s, each 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.0, 170.2, 169.5, 168.9, 134.0, 129.5,

129.2, 127.7, 79.6, 75.6, 75.1, 57.9, 49.9, 48.3, 43.3, 20.7, 20.6, 20.4; IR (film) 3580−3400, 1750, 1660 cm^{-1}; FABMS *m/e* 408 (M + 1, 100).

Dehydration of 45: Synthesis of 46. To a solution of alcohol **45** (119 mg, 0.29 mmol) and 2-nitrophenyl selenocyanate (132 mg, 0.58 mmol) in anhydrous THF (5 mL) stirring over 4 Å molecular sieves (1 g) under argon was added tributylphosphine (175 μL, 0.70 mmol) dropwise via syringe. After 4 h at room temperature, the solvent was evaporated and the residue filtered through a plug of silica gel to elute the intermediate selenide, which was dissolved in THF (5 mL) and treated with 30% H_2O_2 (164 μL, 1.4 mmol) for 5 h at room temperature. Solvent evaporation followed by flash chromatography on silica gel (1:1 hexanes/ethyl acetate) gave **46** (107 mg, 95%) as a white solid: mp 128−130 °C; $[\alpha]^{27}_D = -53.3°$ (*c* 1.07, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45−7.25 (m, 5 H), 5.53 (d, 1 H, J = 8.5 Hz), 5.48 (dd, 1 H, dd, J = 1.0, 2.0 Hz), 5.22 (dd, 1 H, J = 2.5, 5.5 Hz), 5.19 (dt, 1 H, J = 3.0, 8.5 Hz), 5.09 (t, 1 H, J = 2.5 Hz), 5.07 (dd, 1 H, J = 2.5, 5.5 Hz), 4.99 (t, 1 H, J = 3.0 Hz), 3.68 (d, 1 H, J = 16.5 Hz), 3.65 (d, 1 H, J = 16.5 Hz), 2.10, 2.09, 1.86 (3 s, each 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 170.2, 169.7, 145.2, 134.8, 129.8, 129.5, 128.0, 112.7, 78.4, 75.6, 74.7, 51.7, 44.0, 21.1, 21.0, 20.8; IR (film) 3320, 1750, 1680, 1580 cm^{-1}; HRMS (CI) for $C_{20}H_{24}NO_7$ (M + 1) calcd 390.1553, found 390.1542.

Osmylation of 46: Synthesis of Pentaacetate 48. To an ice-cold solution of alkene **46** (38 mg, 0.098 mmol) in 10:1 acetone/water (1.1 mL) were added *N*-methylmorpholine *N*-oxide (30 mg, 0.29 mmol) and 2% aqueous OsO_4 (62 μL, 5 mol %). After being stirred at room temperature for 24 h, the reaction mixture was concentrated in vacuo, and the residue was treated with acetic anhydride (1.0 mL) and DMAP (10 mg). The mixture was stirred at room temperature overnight, the solvents were removed, and the residue was purified by flash chromatography (1:1 hexanes/ethyl acetate) to afford **48** (32 mg 65%) as a clear gel: $[\alpha]^{26}_D = +8.6°$ (*c* 0.88, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45−7.20 (m, 5 H), 5.79 (d, 1 H, J = 5.6 Hz), 5.68 (d, 1 H, J = 8.8 Hz), 5.41−5.33 (m, 2 H), 5.10 (dd, 1 H, J = 4.6, 5.4 Hz), 4.41, 4.28 (AB q, 2 H, J = 12 Hz), 3.66, 3.60 (AB q, 2 H, d, J = 16.8 Hz), 2.07, 2.04, 1.97, 1.94, 1.92 (5 s, each 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 170.1, 169.9, 169.8, 169.1, 134.6, 129.8, 129.5, 128.0, 87.0, 79.2, 75.8, 73.4, 59.6, 52.5, 43.9, 21.9, 21.0, 20.9, 20.8, 20.6; IR (film) 1750, 1700 cm^{-1}; HRMS (CI) for $C_{24}H_{30}NO_{11}$ (M + 1) calcd 508.1819, found 508.1813.

Synthesis of Aminocyclopentitol 22. A solution of pentaacetate **48** (18 mg, 0.036 mmol) in 0.5 M HCl/MeOH (0.5 mL) was heated to reflux for 4 d. The solvent was removed in vacuo and the residue dried in vacuo overnight to afford aminocyclopentitol **22**·HCl as a white solid (5 mg, 87%). The ^{1}H and ^{13}C NMR spectral data of **22**, as well as of its hexaacetylated derivative, matched values previously reported by Shiozaki.[12b] In addition, the specific rotation of **22**·HCl [+2.1° (*c* 0.2, H_2O)] was in good agreement with the values previously reported for both synthetic [+1.7° (*c* 0.41, H_2O)] and naturally derived [4.5° (*c* 1.1, H_2O)] samples.[12b]

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Supporting Information Available: ^{13}C NMR spectra for **5**, **7**, **12**, **14**, **16**, **17**, **19**−**21**, **26**−**28**, **30**−**32**, **35**, **43**−**46**, **48**, and **22** and ^{1}H NMR spectra for **29** and **33** (33 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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