A New Synthetic Approach to the Carbocyclic Core of Cyclopentane-Type Glycosidase Inhibitors: Asymmetric Synthesis of Aminocyclopentitols *via* Free Radical Cycloisomerization of Enantiomerically Pure Alkyne-Tethered Oxime Ethers Derived from Carbohydrates

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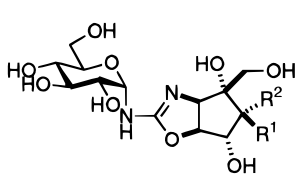
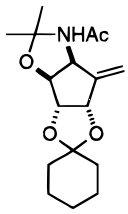
The synthesis of compounds **6**-**8**, derived from 2,3:5,6-bis-*O*-isopropylidene-D-mannofuranose (**3**), and the preparation of products **16** and **17**, obtained from 2,3-*O*-isopropylidene-D-ribose (**13**) is reported. The first free radical cyclization of enantiomerically pure alkyne-tethered oxime ethers derived from carbohydrates (**6**, **8**, **16**, and **17**) is described. These radical precursors have been submitted to cyclization with tributyl or triphenyltin hydride plus triethylborane to yield, after ring closure, the aminocyclopentitols **9**−**12** and **18**−**20**, respectively. These carbocycles have been obtained as mixtures of *Z* and *E* vinyltin isomers, but with excellent diastereoselection at the new stereocenter formed during the ring closure. After protodestannylation, only one diastereoisomer was detected and isolated. The absolute configuration at the new stereocenter formed during the carbocyclization has been established by detailed ^{1}H NMR analysis. The specific transformation of compound **19** (or **20**) into aminocyclitol **24** is described. Compound **24** is an analogue of the aminocyclopentitol moiety of trehazolin (**1a**), a known and powerful glycosidase inhibitor of trehalase. From these results, we can conclude that a new method for the asymmetric synthesis of aminocyclitols of biological interest is now available.

Introduction

Free radical inter- and intramolecular carbon−carbon bond-forming reactions are of paramount importance in organic synthesis.[1] In recent years, complex and densely functionalized carbocycles have been efficiently prepared from chiral, radical precursors, using free radical-based methodologies.[1e] As a part of our ongoing research in this area,[2] we describe here *the first examples of the free radical cycloisomerization of enantiomerically pure, polyoxygenated alkyne-tethered oxime ethers.*[3,4] This strategy has resulted in a new and highly stereospecific method[5] for the asymmetric synthesis of aminocyclopentitols.[6] These compounds are key intermediates for the preparation of carbonucleosides[7] and cyclopentane type glycosidase inhibitors,[8] such as trehazolin (**1a**) and trehalostatin (**1b**).[9]



1a R^1 = OH, R^2 = H Trehazoline
1b R^1 = H, R^2 = OH Trehalostatin



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Results and Discussion

The synthetic approach used is described in Scheme 1. The essential aspects of this scheme include nucleophilic attack of an ethyne anion to an aldose **A**[10] followed by selective protection and activation to afford the conveniently functionalized chiral, radical precursor **B**. This compound, upon attack by the appropriate tin hydride reagent, provides the vinyl radical[11] species **C** which was expected to lead to the aminocyclopentitol **D**. These molecules are conveniently designed for further

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(1) (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: New York, 1986. (b) Curran, D. P. *Synthesis* **1988**, 417, 489. (c) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (d) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (e) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139. (f) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1992.

(2) (a) Marco-Contelles, J.; Martínez, L.; Martínez-Grau. A.; Pozuelo, C.; Jimeno, M. L. *Tetrahedron Lett.* **1991**, *32*, 6437. (b) Marco-Contelles, J.; Pozuelo, C.; Jimeno, M. L.; Martínez, L.; Martínez-Grau. A. *J. Org. Chem.* **1992**, *57*, 2625. (c) Marco-Contelles, J.; Sánchez, B.; Pozuelo, C. *Nat. Prod. Lett.* **1992**, *1*, 187. (d) Marco-Contelles, J.; Sánchez, B. *J. Org. Chem.* **1993**, *58*, 4293. (e) Marco-Contelles, J.; Bernabé, M.; Ayala, D.; Sánchez, B. *J. Org. Chem.* **1994**, *59*, 1234. (f) Marco-Contelles, J.; Sánchez, B.; Pozuelo, C. *Tetrahedron: Asymmetry* **1992**, *3*, 689. (g) Marco-Contelles, J.; Martínez, L.; Martínez-Grau, A. *Tetrahedron: Asymmetry* **1991**, *2*, 961.

(3) Booth, S. E.; Jenkins, P. R.; Swain. C. J.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans 1* **1994**, 3499, and references cited therein.

(4) Although the free radical cyclization of terminal alkynes with oxime ethers has been known for some years, its high synthetic potential has been almost neglected: (a) Enholm, E. J.; Burroff, J. A.; Jaramillo, L. M. *Tetrahedron Lett.* **1990**, *31*, 3727. For the analogous cyclization of β-allenic oxime ethers, see: (b) Hatem, J.; Henriet-Bernard, C.; Grimaldi, J.; Maurin, R. *Tetrahedron Lett.* **1992**, *33*, 1057.

(5) A preliminary account of this work has been published: Marco-Contelles, J.; Destabel, C.; Chiara, J. L.; Bernabé, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1547.

(6) For some recent synthetic approaches, see reference 8 and the following: (a) Kiguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T.; Hiramatsu, H. *Tetrahedron Lett.* **1995**, *36*, 253. (b) Gallos, J. K.; Goga, E. G.; Koumbis, A. E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 613. (c) Marco-Contelles, J.; Bernabé, M. *Tetrahedron Lett.* **1994**, *35*, 6361. (d) Maycock, C. D.; Barros, M. T.; Santos, A. G.; Godinho, L. S. *Tetrahedron Lett.* **1993**, *34*, 7895. (e) Marco-Contelles, J.; Ruiz, P.; Martínez, L.; Martínez-Grau, A. *Tetrahedron* **1993**, *49*, 6669. (f) Elliot, R. P.; Hui, A.; Fairbanks, A. J.; Nash, R. J.; Winchester, B. G.; Way, G.; Smith, C.; Lamont, R. B.; Storer, R.; Fleet, G. W. J. *Tetrahedron Lett.* **1993**, *34*, 7949. (g) Chiara, J. L.; Marco-Contelles, Khiar, N.; Destabel, C.; Gallego, P.; Bernabé, M. *J. Org. Chem.* **1995**, *60*, 6010.

(7) Borthwick, A. D.; Biggadike, K. *Tetrahedron* **1992**, *48*, 571.

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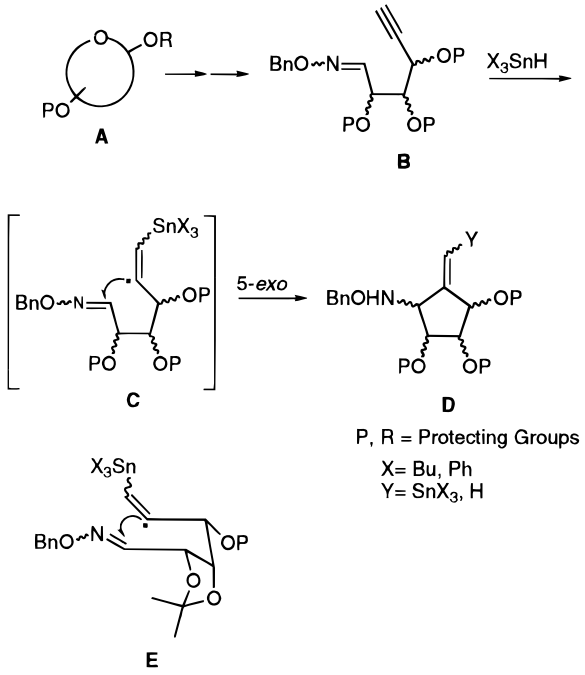
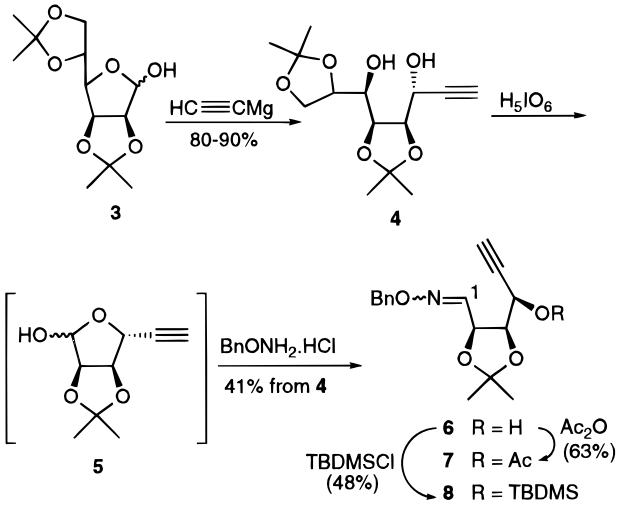
Scheme 1



synthetic manipulation. In fact, an example of compound type **D**, 1,2-*O*-cyclohexylidene-3,4-*N*,*O*-isopropylidene of D- and L-(1,2/3,4)-4-acetamido-5-methylenecyclopentane-1,2,3-triol (**2**), has been prepared from 1,2-*O*-cyclohexylidene-*myo*-inositol in poor yield, in a time-consuming process (an additional step was required for resolution of the racemate), and it has been finally transformed into trehazolin (**1a**) and trehalostatin (**1b**).[12] In addition, starting from different aldoses, it is possible to synthesize a large spectrum of compounds of type **D**, natural or analogues, having different absolute configuration at the carbons bearing the protected hydroxyl groups. The particular stereodirecting properties and conformational bias of the acyclic sugar derivatives also offer potential high degrees of stereochemical control in the formation of the new stereocenters.

Scheme 2



Synthesis and Free Radical Cyclization of D-Manno Derivatives 6−8. The synthesis was carried out starting from 2,3:5,6-bis-*O*-isopropylidene-D-mannofuranose (**3**)[13] (Scheme 2). Treatment of **3** with ethynylmagnesium bromide[14] gave compound **4** as the only isolated isomer.[15] Sequential "one-pot" acid hydrolysis plus diol cleavage[16] gave lactol **5**, which after oxime ether formation, afforded the radical precursor **6**, in 41% overall yield from **4**. Standard manipulations allowed us to prepare also from this intermediate the acetyl (**7**) and the *tert*-butyldimethylsilyl (**8**) derivatives. These compounds were isolated as inseparable mixtures of *E* and *Z* isomers in 2:1 ratio, respectively, as determined by analysis of the ^{1}H NMR spectrum of the mixture, integrating the well resolved H-1 signal of each isomer [(*E*) δ H-1 $\approx$ 7.60 ppm; J = 7.3 Hz; (*Z*) δ H-1 $\approx$ 7.00 ppm; J = 4.2 Hz)]. Since, under the experimental conditions described by Enholm[4a] no cyclization was observed, we turned our attention to the triethylborane plus triphenyltin hydride-mediated carbocyclization of enynes, as described by Oshima.[17] Under these conditions[18] precursors **6**-**8** gave the vinyltin derivatives **9**−**11** in good yield (Scheme 3). These products were obtained as mixtures of *Z* and *E* isomers (for compound **10** only the *Z* isomer was detected and isolated), that we could separate and isolate by flash chromatography.[19] Each geometrical isomer was stereochemically homogeneous at the new stereocenter formed during the cyclization (C-4) and, in all the cases, only the isomer having the *R* absolute configuration, was detected. This was evident after analysis of the corresponding ^{1}H NMR spectra. In

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(9) Ando, O.; Satake, H.; Itoi, K.; Nakajima, M.; Takahashi, S.; Haruyama, H. *J. Antibiot.* **1991**, *44*, 1165.

(10) The incorporation of a triple bond into a carbohydrate precursor can be achieved by Wittig-type reagents and dehydrobromination: Mella, M.; Panza, L.; Ronchetti. F.; Toma, L. *Tetrahedron* **1988**, *44*, 1673. (b) McIntosh, M.; Weinreb, S. *J. Org. Chem.* **1993**, *58*, 4823, or by simple Grignard addition to the corresponding hemiacetals: Gaudino, J. J.; Wilcox, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 4374.

(11) For some free radical cyclization of vinyl radicals, see: (a) Clive, D. L. J.; Manning, H. W. *J. Chem. Soc., Chem. Commun.* **1993**, 666. (b) Moriya, O.; Okawara, M.; Ueno, Y. *Chem. Lett.* **1984**, 1437. (c) Moufid, N.; Chapleur, Y. *Tetrahedron Lett.* **1991**, *32*, 1799. (d) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Soc. Chem. Jpn.* **1987**, *60*, 3415.

(12) (a) Uchida, C.; Yamagashi, T.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 589. (b) Uchida, C.; Kitahashi, H.; Yamagashi, T.; Iwaisaki, Y. Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2775. (c) Ogawa, S.; Uchida, C.; Yuming, Y. *J. Chem. Soc., Chem. Commun.* **1992**, 886. (d) Ogawa, S.; Uchida, C. *Chem. Lett.* **1993**, 173. (e) Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *Tetrahedron Lett.* **1993**, *34*, 1505. (f) Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Org. Chem.* **1994**, *59*, 813.

(13) Lee, B.; Nolan, T. J. *Tetrahedron* **1967**, 2789.

(14) (a) Buchanan, J. G.; Dunn, A. D.; Edgar, A. R. *Carbohydr. Res.* **1974**, C5−C7. (b) Buchanan, J. G.; Dunn, A. D.; Edgar, A. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1191.

(15) Shing, T. K. H.; Elsley, D. A.; Gillhouley, J. G. *J. Chem. Soc., Chem. Commun.* **1989**, 1280.

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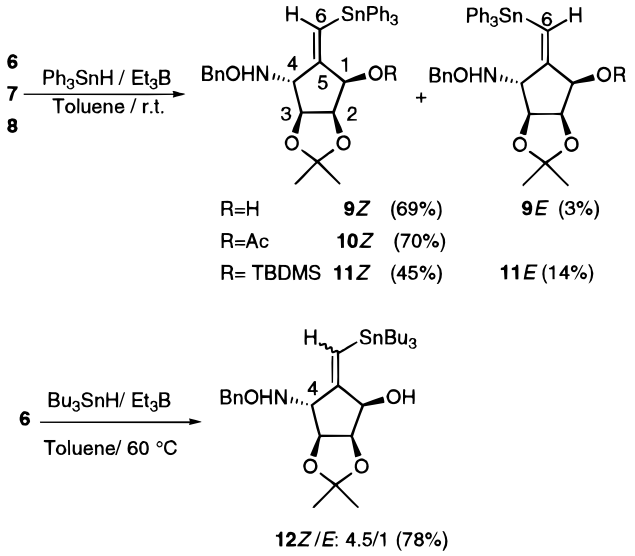
(17) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547.

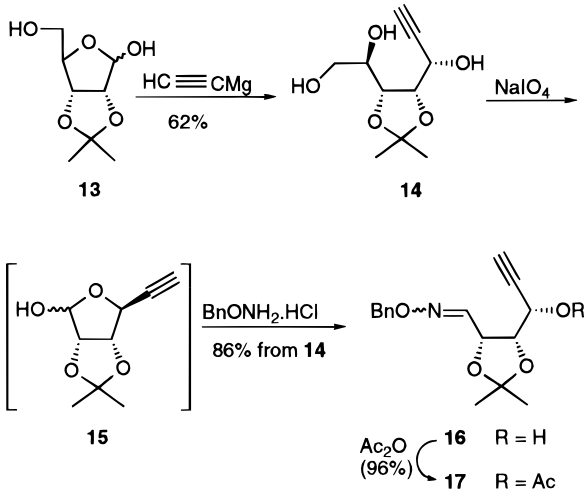
(18) See Experimental Section.

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Scheme 3



Scheme 4

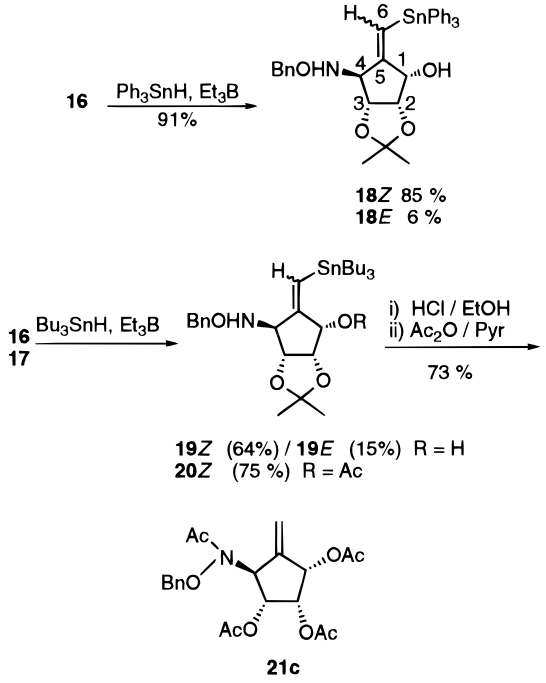


fact, for compounds **9***Z* or **9***E* we could observe $J_{3,4} = 0$ Hz; furthermore, in **9***Z* a strong NOE effect, absent in compound **9***E*, was observed between H-4 and H-6, and, in addition, an NOE effect was detected between H-6/OH in **9***E*. Similar trends were also observed in the other cyclized products **10** and **11**. Treating **6** with triethylborane and tributyltin hydride gave carbocycle **12** in good yield and high stereospecificity, as an inseparable 4.5:1 mixture of *Z*:*E* isomers (Scheme 3).

Synthesis and Free Radical Cyclization of D-Ribo Derivatives 16 and 17. In order to broaden the scope of this method, the synthesis of the D-ribo radical precursors **16** and **17** was attempted. These products were prepared from 2,3-*O*-isopropylidene-D-ribose (**13**)[20] following the same synthetic sequences as for the synthesis of **6** and **8** (see above) and were isolated as mixtures of *E* and *Z* isomers, in 2:1 ratio, respectively (Scheme 4). The free radical cyclization of these precursors, under the same experimental conditions, gave in high yield the corresponding aminocyclopentitol derivatives **18**, **19** (as a mixture of *E*/*Z* isomers that we could separate and isolate), and **20**, as the exclusive *Z* isomer (Scheme 5).

(20) (a) Bichard, C. J. F.; Fairbanks, A. J.; Fleet, G. W. J.; Ramsden, N. G.; Vogt, K.; Doherty, O.; Pearce, L.; Watkin, D. J. *Tetrahedron: Asymmetry* **1991**, *2*, 901. (b) Mandal, S. B.; Achari, B. *Synth. Commun.* **1993**, *23*, 1239.

Scheme 5



The detailed analysis of the high field ^{1}H NMR spectrum of these compounds has shown that all these products were also stereochemically homogeneous and have the *S* absolute configuration at the new stereocenter. In fact, the ^{1}H and ^{13}C NMR spectra of compounds **18***Z* {$[\alpha]^{25}_D$ −76.3 (*c* 1.19, $CHCl_3$)} (Scheme 5) and **9***Z* {$[\alpha]^{25}_D$ +80.1 (*c* 1.08, $CHCl_3$)}(Scheme 3) are superimposable. These compounds differ only in their chiroptical properties. *Thus, starting from two readily available and cheap* D*-sugars, we have prepared an enantiomeric pair in a short synthetic sequence, with complete diastereoselection.*

The high degree of stereochemical control observed in the cyclization of precursors **16** and **17** (the same argument is also valid for compounds **6**−**8**) can be explained according to Beckwith's guidelines,[1c] assuming that, in the early transition state, the favored vinyl radical species is in a chairlike conformation with most of the substituents in the preferred pseudoequatorial orientation (see radical species **E** in Scheme 1). The formation of mixtures with major or exclusive *Z* isomers in these vinyltin intermediates is in agreement with the results observed by Oshima[17] but has no negative influence for our synthetic purposes (see below).

Synthetic Manipulation of the Carbocyclic Vinyltin Derivatives. Synthesis of Aminocyclopentitols. After having developed a simple protocol for the synthesis of vinyltin cyclopentane-type derivatives of high synthetic potential, we analyzed different synthetic protocols for transforming these useful intermediates[21] into defined aminocyclopentitol derivatives.

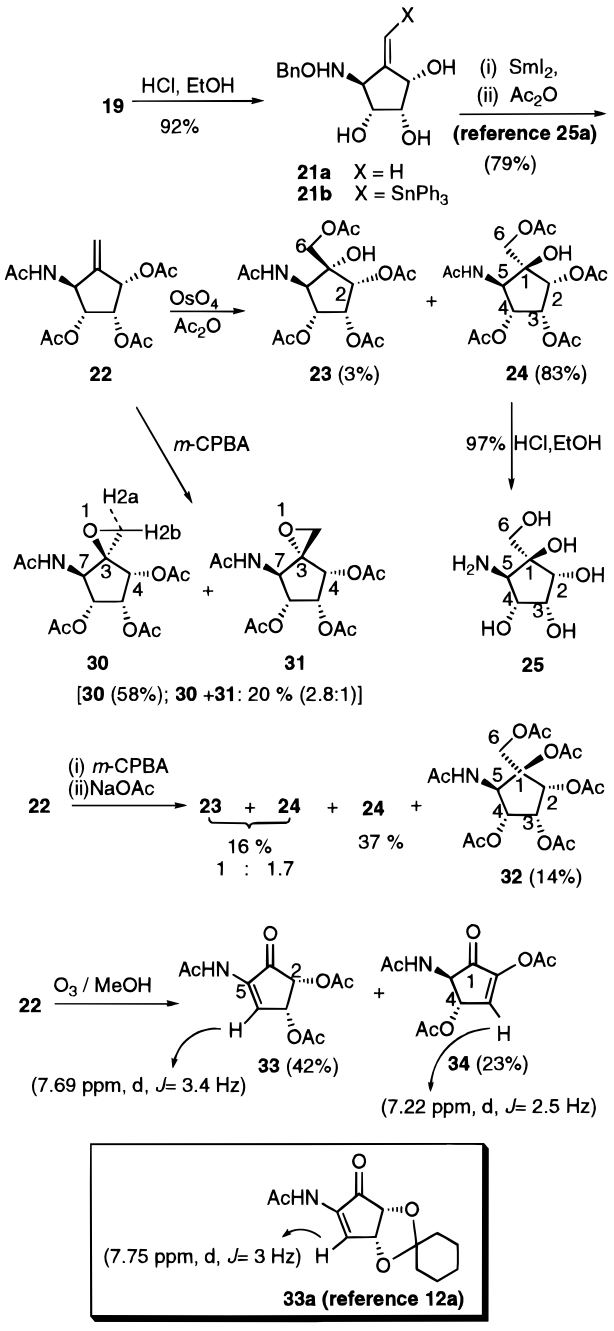
First, we tested different conditions for the protodestannylation of the vinyl intermediates. In the first experiments, compound **9***Z* (Scheme 3) proved unusually stable to typical protodestannylation conditions (SiO_2[21] or methanol in acetic acid[4a]). After some experimentation we found that acid hydrolysis promoted by ethanol saturated with hydrogen chloride was the method of choice for effecting the protodestannylation of these

(21) Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*, Butterworths: London, 1986.

vinyltin intermediates.[22] Reaction of compound **19**(*E*/*Z*) with anhydrous ethanol saturated with hydrogen chloride resulted in simultaneous protodestannylation[22] and hydrolysis of the acetonide, leading to triol **21a** in high yield. Note that, when methanol in acetic acid (catalytic) was used,[4a] compound **20***Z* (Scheme 5) gave the same triol **21a**, but in only 20% yield.[23] When **20***Z* was submitted to reaction with anhydrous ethanol saturated with hydrogen chloride, followed by acetylation, the corresponding peracetylated aminocyclitol **21c** (Scheme 5) was obtained in good overall yield (73%).[23] It is interesting to point out that, when we submitted the analogous vinyl intermediate **18***Z* (Scheme 5) to the same conditions for protodestannylation, compound **21b** resulted in low yield (16%),[23] while trifluoromethanosulfonic acid or cerium ammonium nitrate in methanol[24] did not work.

Once we found a convenient method for this hydrolysis, the synthetic power of this methodology was demonstrated by transforming compound **19** (or **20**) into **24** (Scheme 6). This compound is the C-1,2,4-tri-epimer of the aminocyclitol moitey of trehazolin (**1a**) and the C-1,4-di-epimer of the aminocyclitol moitey of trehalostatin (**1b**); the C-4 epimer of aminocyclitol **24** has been prepared previously and converted into an analogue of these glycosidase inhibitors.[12a] The transformation (**19** → **24**) was accomplished as follows. Acid hydrolysis of compound **19** (→**21a**) was followed by samarium diiodide-mediated[25a] cleavage of the nitrogen−oxygen bond in the *O*-benzyl hydroxylamine **21a**, followed by acetylation in a "one-flask" operation, afforded peracetate **22** {$[\alpha]^{25}_D$ −30.2 (*c* 0.83, $CHCl_3$)} in good overal yield (79%) from **21a**. Treatment of this allylic acetamide with osmium tetroxide, NMO, 80% aqueous acetone[12a,26] gave almost exclusively, after partial acetylation, the aminocyclopentitol **24** {$[\alpha]^{25}_D$ +1.9 (*c* 0.96, $CHCl_3$)} in excellent yield; only traces of the minor isomer **23**, obtained by reaction from the α face, were isolated. A similar high *syn*-stereoselectivity has also been observed in the osmylation of some allylic substituted cyclopentanes.[27] The absolute configuration at the new stereocenter (C-1) was established by ^{1}H NMR analysis. Thus, the 2D-NOESY spectrum of **24** shows cross peaks for H-5/H-6a, and also OH/H-2, indicating that the methylene C-H6 is *cis* to H-5, and that the OH group is *cis* to H-2. On the other hand, the 2D-NOESY spectrum of aminocyclopentitol **23** exhibits cross peaks for H-2/H-6a and H-2/H-6b, thus indicating that C-H6 is now *cis* to H-2. Finally, acid hydrolysis of compound **24** gave in good yield the fully deprotected aminocyclopentitol **25**.

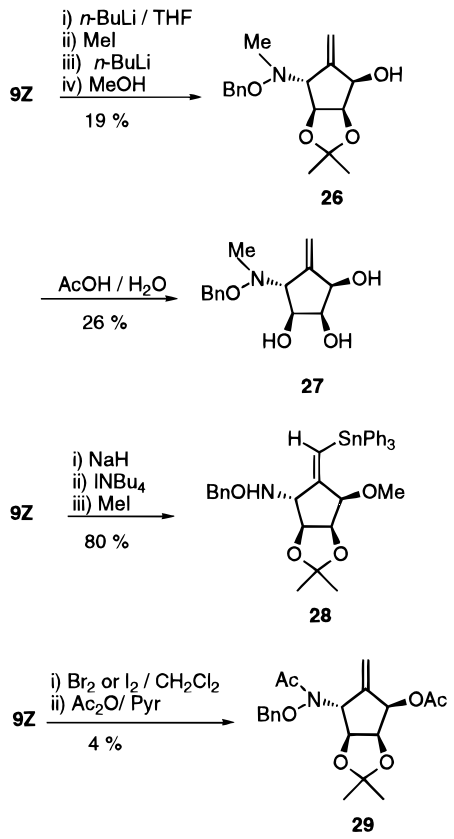
Scheme 6



Under the conditions described above for destannylation, all the blocking groups present in compound **19** were removed. More selective and milder reaction conditions were desired. However, we found unexpected difficulties for destannylating the D-*manno* derivatives **9**−**12** (Scheme 3) using BuLi[28] (similar problems have been found in the D-*ribo* derivatives **18** and **20**). Under these conditions only recovered starting materials, without traces of the desired product, were obtained; compound **10***Z* gave only the deacetylated intermediate **9***Z* in 38% yield.[23] We reasoned that these unexpected problems were probably due to the formation of the corresponding lithium alkoxide salts (**9***Z*, **10***Z*, **12**) that, by serious electronic repulsion or simple steric hindrance (**11***Z*) with the incoming butyl

(22) Ardisson, J.; Férézou, J. P.; Julia, M.; Pancrazi, A. *Tetrahedron Lett.* **1987**, *28*, 2001.
(23) See supporting information.
(24) Hanessian, S.; Léger, R. *J. Am. Chem. Soc.* **1992**, *114*, 3115.
(25) Although the reduction of oximes to amines *via* SmI_2 is known (Mukaiyama, T.; Yorozu, K.; Kato, K.; Yamada, T. *Chem. Lett.* **1992**, 181), the specific reduction of *O*-alkyl hydroxylamines to amines *via* SmI_2 seems to be unprecedented. For the first very recent reports on the nitrogen−oxygen samarium diiodide-mediated cleavage, see refs 5, 6g, and the following: (a) Chiara, J. L.; Destabel. C.; Gallego, P.; Marco-Contelles, J. *J Org. Chem.* **1996**, *61*, 359. (b) Keck, G. E.; McHardy, S. F.; Murry, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7289. (c) Keck, G. E.; McHardy, S. F.; Wager, T. T. *Tetrahedron Lett.* **1995**, *36*, 7419 (personal communication; we thank Professor Keck for sending us a copy of this manuscript prior to publication).
(26) We have found also that the direct osmylation or epoxidation of vinyl derivative **20** (Scheme 5) proved unsuccessful.
(27) (a) Ganem, B.; King, S. B. *J. Am. Chem. Soc.* **1994**, *116*, 562. (b) Trost, B. M.; Kuo, G.-H.; Benneche, T. J. *J. Am. Chem. Soc.* **1988**, *110*, 621. (c) Poli, G. *Tetrahedron Lett.* **1989**, *30*, 7385. However, it has been shown that the complexation of amides with OsO_4 does not take place in the hydroxylation of certain acyclic sulfoxide-substituted allylic amides: Hauser, F. M.; Ellenberger, S. R.; Clardy, J. C.; Bass, L. S. *J. Am. Chem. Soc.* **1984**, *106*, 2458.
(28) Chen, S.-M. L.; Schaub, R. E.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3450.

Scheme 7



lithium, would prevent further destannylation. With this idea in mind we decided to protect the free nitrogen or the hydroxyl group in these substrates. As shown in Scheme 7, after treatment with BuLi and MeI, followed by reaction *in situ* with more BuLi and workup with methanol, product **26** was obtained albeit in low yield (19%). Final hydrolysis of the acetonide gave the fully deprotected aminocyclopentitol **27** again in low yield (26%). In this synthetic sequence we have observed only N-methylation, that proved satisfactory for our purposes, although the yield could not be improved. In fact, when the methylation of **9***Z* was promoted by sodium hydride with methyl iodide in the presence of catalytic amounts of tetrabutylammonium iodide,[29] the *O*-methylated product **28** was obtained and proved reluctant to react with BuLi to give the desired destannylated product.[23]

We have also tested in our vinyltin intermediates the bromine or iodine method,[28] for the synthesis of the corresponding vinyl halides, with deceiving result (Scheme 7; **9***Z* → **29**: 4% yield; note that in this case we have surprisingly isolated not the corresponding vinyl halide, but the dehalogenated material[23]) or without success (**18**, **20***Z*).

In summary, we were unable to find conditions for the selective protodestannylation of our substrates. However, this was not a serious problem, because ethanol/HCl reagent effectively removed all the protecting groups, that could be reinstalled in "one-pot" protocols (see above). And, in addition, excellent stereochemical control was observed in the osmylation of the peracetylated intermediate **22**. This fact moved us to follow our project according to these trends.

Then we considered the reaction with other oxidizing reagents for transforming the exo-double bond in the same key intermediate **22**. For instance, epoxidation (*m*-CPBA[18]) of compound **22** gave the expected epoxides **30** and **31** (Scheme 6), in a 10:1 ratio, as determined from the ^{1}H NMR of the crude reaction mixture. After careful chromatography, the major compound **30** and a mixture of **30** + **31** (2.8:1) were isolated in 58% yield and in 20% yield, respectively (combined overall yield: 78% yield). The absolute configuration at C-3 (the new stereocenter) in the major isomer **30** has been assigned by NOE experiments; in fact, a strong NOE effect was detected between H-2a and H-7 and a very weak one between H-2b and H-4, and between H-2a and NH. This assignment has also been definitively established by chemical correlation. When compound **22** was epoxidized and the resulting mixture treated with sodium acetate in DMF,[12a] followed by acetylation of the crude, compounds **23**, **24**, and a new compound **32** (Scheme 6) were detected. After purification by column chromatography product **24** (37%), a mixture of **23** and **24** (in 1.7:1 ratio; 16% yield) and peracetate **32** (14%) were isolated. The absolute configuration at C-1 in aminocyclitol **32** has been determined by detailed ^{1}H NMR analysis. In the NOESY spectrum of compound **32** a strong cross peak H-5/H-6a was observed, which allowed us to determine the *S* absolute configuration at C-1, as shown in Scheme 6. Then, this product comes from the total peracetylation of the major product **24**.

With the promising results obtained in the osmylation and epoxidation, we next attempted the hydroboration of compound **22**. We wanted an easy way to prepare related hydroxymethyl derivatives. Unexpectedly, in spite of the several experiments and different typical conditions tested in products **21a** and **22**, we were unable to prepare the desired molecule. In contrast, ozonolysis (O_3, MeOH at −78 °C, followed by reaction with DMS) gave the ketones **33** and **34** (Scheme 6) in 42% and 23% yield, respectively. Straightforward assignment of the structures for the major and minor isomers to **33** and **34**, respectively, was deduced from the corresponding ^{1}H NMR analysis.[18] A similar substrate (**33a**; Scheme 6) has also been recently obtained and characterized by Ogawa;[12a] the comparison of the corresponding spectroscopic data in **33a** are in full agreement with those observed for **33**. Obviously, these products arise from β-elimination of the presumed, unstable β-acetoxy ketone intermediates; H-5 being more acidic, due to the acetamido substituent, than H-2 accurately explains the formation of major isomer **33**. These compounds are extremely interesting substrates for further development towards the synthesis of mannostatin A analogues.[12]

Conclusions

From the results reported here, we can conclude that the (tributyl)triphenyltin hydride-mediated free radical cycloisomerization of polyoxygenated, enantiomerically pure alkyne-tethered oxime ethers:[30] (a) is possible, (b) the presence of triethylborane is absolutely necessary for the success of the process, (c) gives chiral, highly functionalized vinyltin[21] derivatives with large potential synthetic applications, and (d) the correct selection of the radical precursor allowed us to obtain very high diastereoselection, independent of the type of substituents at the propargylic position. In summary, the present method has proven to be very useful for the synthesis of some aminocyclopentitols of potential biological interest.

(29) Czernecki, S.; Georgoulis, C.; Provelenghiou, C. *Tetrahedron Lett.* **1976**, 3535.

Experimental Section

General Methods. See reference 2d.

1-[(Benzyloxy)imino]-5,6-dideoxy-2,3-*O*-isopropylidene-D-*allo*-hex-5-yne (6). 4,5:7,8-Di-*O*-isopropylidene-3,4,5,6,7,8-D-*talo*-oct-1-ynitol (**4**)[15] (3.70 g, 12.92 mmol) [prepared according to the reported procedure[14b] using 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose in 90% yield: ^{1}H NMR (200 MHz; $CDCl_3$) δ 1.36, 1.40, 1.42, 1.54 (4 × 3 H, 4 × s), 2.53 (1 H, d, $J_{1,3}$ = 2.3 Hz), 4.05−4.76 (7 H, br m)], dissolved in dry diethyl ether (25 mL), was added to a stirred suspension of periodic acid (6.01 g, 26.34 mmol) in dry diethyl ether (100 mL). The reaction mixture was stirred at room temperature (rt) for 4.5 h, more periodic acid (6.00 g, 26.32 mmol) was added, and the reaction mixture was stirred overnight. More periodic acid (3.00 g, 13.16 mmol) was added again, and the reaction mixture was stirred for another 3.5 h. The solution was washed with 5% aqueous $NaHCO_3$ solution, followed by extraction with CH_2Cl_2 (4 × 80 mL); the combined organic extracts were washed with 5% aqueous sodium thiosulfate solution, 5% aqueous $NaHCO_3$ solution, and brine, and then dried over Na_2SO_4 and concentrated under reduced pressure. The crude lactol **5** (1.60 g) was dissolved in CH_2Cl_2 (65 mL), and *O*-benzylhydroxylamine hydrochloride (2.086 g, 13.07 mmol) and pyridine (2.1 mL, 26 mmol) were added. The reaction mixture was refluxed for 8 h, cooled, poured into water (60 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product (3.10 g) was purified by flash column chromatography. Elution with EtOAc/hexane (5/95 to 15/85) gave compound **6** (1.54 g, 41%) as an inseparable mixture of *syn*/*anti* isomers (1:2), as a pale yellow oil. R_f = 0.38 (25% EtOAc/hexane). IR, ^{1}H NMR, and mass spectra identical to those of 1-[(benzyloxy)-imino]-5,6-dideoxy-2,3-*O*-isopropylidene-D-*talo*-hex-5-yne (**16**) (see below). ^{13}C NMR (50.32 MHz; $CDCl_3$) δ 149.6, 147.6, 137.3, 136.6, 128.5, 128.3, 128.3, 128.2, 127.9, 110.3, 109.9, 81.2, 80.1, 80.0, 74.5, 71.6, 62.6, 61.6, 75.4, 75.1, 76.6, 76.2, 27.0, 26.4, 25.0, 24.5. EIMS (*m*/*z*) 274 (5), 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.12; H, 6.31; N, 5.10.

1-[(Benzyloxy)imino]-4-*O*-acetyl-5,6-dideoxy-2,3-*O*-isopropylidene-D-*allo*-hex-5-yne (7). Oxime ether **6** (1.208 g, 4.17 mmol) was stirred in pyridine (6 mL) and acetic anhydride (6 mL) at rt overnight, and then the solvent was removed under reduced pressure. The crude product (1.87 g) was purified by flash column chromatography. Elution with EtOAc/hexane (10/90) gave compound **7** (0.839 g, 63%) as an inseparable mixture of *syn*/*anti* isomers (1:2) as a white solid. R_f = 0.35 (20% EtOAc/hexane). IR and ^{1}H NMR, identical to those of the 1-[(benzyloxy)imino]-4-*O*-acetyl-D-*talo*-hex-5-yne **17** (see below). EIMS (*m*/*z*) 332 (M^+ + 1, 1), 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.40; H, 6.59; N, 4.50.

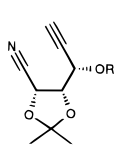
1-[(Benzyloxy)imino]-4-*O*-(*tert*-butyldimethylsilyl)-5,6-dideoxy-2,3-*O*-isopropylidene-D-*allo*-hex-5-yne (8). TBDMSCl (0.227 g, 1.51 mmol) was added portionwise over 45 min to a stirred solution of oxime ether (**6**) (0.171 g, 0.59 mmol) and imidazole (0.243 g, 3.57 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C under argon. The reaction mixture was stirred at rt for 21 h and at reflux for 18 h and concentrated under reduced pressure. The crude product (0.64 g) was purified by flash column chromatography. Elution with EtOAc/hexane (0/100 to 20/80) gave compound **8** (0.115 g, 48%) as an inseparable mixture of *syn*/*anti* isomers (1:2), as a colorless oil: R_f = 0.38 (5% EtOAc/hexane). IR (film) ν_{max} 3300, 1455 cm^{-1}. ^{1}H NMR (200 MHz; $CDCl_3$) δ 0.12, 0.13 and 0.18 (6 H + 3 H, 3 s), 0.91 (9 H + 4.5 H, s), 1.37 and 1.58 (2 × 1.5 H, 2 s), 1.39 and 1.51 (2 × 3 H, 2 s), 2.40 (1 H + 0.5 H, d, J = 2.2 Hz), 4.27 (1 H, t, J = 6.3 Hz), 4.40 (1 H, m), 4.51 (1 H, dd, J = 2.2 and 5.9 Hz), 4.79 (1 H, dd, J = 6.5 and 8.1 Hz) 5.10 (2 H, s) 5.14 (1 H, s), 5.32 (0.5 H, dd, J = 5.2 and 7.2 Hz), 7.05 (0.5 H, d, J = 5.2 Hz), 7.32 (5 H and 2.5 H, m), 7.58 (1 H, d, J = 8.1 Hz). EIMS (*m*/*z*) 234 (12), 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{22}H_{33}NO_5Si$: C, 65.47; H, 8.24; N, 3.47. Found: C, 65.30; H, 8.11; N, 3.34.

(*Z*,*E*)-(1*R*,2*R*,3*S*,4*R*)-4-[(Benzyloxy)amino]-2,3-*O*-isopropylidene-6-(triphenylstannyl)-5-methylenecyclopentane-1,2,3-triol (9*Z*/*E*). (General procedure for radical cyclization). Triethylborane (1 M in hexanes, 1.6 mL, 1.6 mmol) was added to a degassed solution of oxime **6** (0.876 g, 3.03 mmol) and triphenyltin hydride (1.350 g, 3.84 mmol) in dry toluene (180 mL) under argon. The reaction mixture was stirred at rt for 4 h, triethylborane (1 M in hexanes, 1.6 mL, 1.6 mmol) and triphenyltin hydride (1.350 g, 3.84 mmol) were added, and the reaction mixture was stirred overnight. The reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product (3.65 g) was purified by flash column chromatography. Elution with EtOAc/hexane (5/95fi10/90) gave **9***Z* (1.341 g, 69%) and **9***E* (49 mg, 3%). **9*Z***: Colorless oil. R_f = 0.33 (20% EtOAc/hexane). $[\alpha]^{25}_D$ +80.1 (*c* 1.08, $CHCl_3$). IR (film) ν_{max} 3530, 1640 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.16 and 1.22 (2 × 3 H, 2 s), 2.12 (1 H, d, J = 10.4 Hz), 3.74 (1 H, d, J = 3.0 Hz), 4.30 (1 H, d, J = 5.7 Hz), 4.37 (1 H, t, J = 5.9 Hz), 4.47 (1 H, dddd, J = 10.4, 5.9, 2.7, 1.4 Hz), 4.57 (2 H), 5.39 (1 H, d, J = 3.0 Hz), 6.52 (1 H, d, J = 2.7 Hz), 7.25 (15 H, m), 7.52 (5 H, m). ^{13}C NMR (50.32 MHz; $CDCl_3$) δ 160.4, 141.6, 137.7, 137.6, 137.2, 136.9, 129.3, 129.2, 129.0, 128.9, 128.8, 128.5, 128.3, 127.1, 111.2, 80.6, 78.5, 74.3, 71.0, 77.4, 26.5, 24.9. EIMS (*m*/*z*) 564 (100). Anal. Calcd for $C_{34}H_{35}NO_4Sn$: C, 63.77; H, 5.51; N, 2.19. Found: C, 63.71; H, 5.76; N, 2.23. **9*E***: Colorless oil. R_f = 0.25 (20% EtOAc/hexane). $[\alpha]^{25}_D$ −75.2 (*c* 6.2, $CHCl_3$). IR (film) ν_{max} 3500, 3060, 1640 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.28 and 1.41 (2 × 3 H, 2 s), 2.32 (1 H, d, J = 10.7 Hz), 3.61 (1 H, d, J = 3.8 Hz), 4.31 (1 H, d, J = 11.8 Hz), 4.35 (1 H, d, J = 5.8 Hz), 4.36 (1 H, d, J = 11.8 Hz), 4.48 (1 H, t, J = 5.9 Hz), 4.53 (1 H, dddd, J = 10.7, 5.9, 2.1, 1.2 Hz), 4.83 (1 H, d, J = 3.8 Hz), 6.68 (1 H, d, J = 2.1 Hz), 7.12 (2 H, m), 7.31 (13 H, m), 7.59 (5 H, m). ^{13}C NMR (50.32 MHz; $CDCl_3$) δ 162.1, 138.1, 137.4, 137.3, 136.9, 136.5, 129.2, 129.1, 129.0, 128.8, 128.6, 128.5, 128.4, 128.2, 128.0, 127.7, 123.9, 110.4, 80.0, 78.2, 74.7, 69.0, 26.0, 24.3. EIMS (*m*/*z*) 564 (1), 91 (100). Anal. Calcd for $C_{34}H_{35}NO_4Sn$: C, 63.77; H, 5.51; N, 2.19. Found: H, 5.68; N, 2.19.

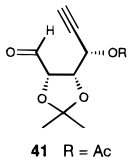
(*Z*)-(1*R*,2*R*,3*S*,4*R*)-4-[(Benzyloxy)amino]-2,3-*O*-isopropylidene-1-*O*-acetyl-6-(triphenylstannyl)-5-methylenecyclopentane-1,2,3-triol (10*Z*). This product was prepared according to the general procedure for carbocyclizations. Oxime ether **7** (0.163 g, 0.49 mmol), triethylborane (1 M in hexanes, 0.25 mL, 0.25 mmol), and triphenyltin hydride (0.230 g, 0.66 mmol) in dry toluene (30 mL) (reaction time: 17 h) gave compound (**10*Z***) (0.236 g, 70%) as a colorless oil. R_f = 0.30 (20% EtOAc/hexane). $[\alpha]^{25}_D$ +93.8 (*c* 1.53, $CHCl_3$). IR (film) ν_{max} 3400, 1750 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ 1.03 (3 H, s), 1.20 and 1.40 (2 × 3 H, 2 s), 3.80 (1 H, d, J = 2.2 Hz), 4.35 (1 H, d, J = 5.7 Hz), 4.63 (2 H, m), 4.75 (1 H, t, J = 5.8 Hz), 5.32 (1 H, ddd, J = 5.8, 2.6, 1.3 Hz), 5.47 (1 H, d, J = 2.2 Hz), 6.37 (1 H, d, J = 2.6 Hz), 7.25 (15 H, m), 7.50 (5 H, m). EIMS (*m*/*z*) 606 (2), 91 (100). Anal. Calcd for $C_{36}H_{37}NO_5Sn$: C, 63.37; H, 5.47; N, 2.05. Found: C, 63.09; H, 5.36; N, 1.87.

**(*Z*,*E*)-(1*R*,2*R*,3*S*,4*R*)-4-[(Benzyloxy)amino]-2,3-*O*-isopropylidene-1-*O*-(*tert*-butyldimethylsilyl)-6-(triphenylstan-

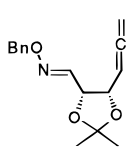
(30) In simultaneous experiments we have analyzed without success (see supporting information): (a) the tributyltin hydride-mediated carbocyclization of alkyne-tethered nitrile **37**, (b) the samarium diiodide-mediated cyclization of compound **17** (Scheme 4) and the alkyne-tethered aldehydes **41** or **42**, and (c) the synthesis of the allene-related radical precursor **44** from compound **17** (Scheme 4) *via* palladium-catalyzed reduction with samarium diiodide: (a) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5237−5240. (b) Tabuchi, T.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1987**, 2275−2278.



37



41 R = Ac
42 R = Bn



44

nyl)-5-methylenecyclopentane-1,2,3-triol (**11*Z*/*E***) was prepared according to the general procedure. Oxime ether **8** (0.067 g, 0.17 mmol), triethylborane (1 M in hexanes, 2 × 0.08 mL, 0.16 mmol), and triphenyltin hydride (2 × 0.074 g, 0.42 mmol) in dry toluene (10 mL) (reaction time: 23 h) gave **11*E*** (0.018 g, 14%) and **11*Z*** (0.057 g, 45%). **11*E***: Colorless oil. R_f = 0.36 (7% EtOAc/hexane). $[\alpha]^{25}_D$ +62.9 (*c* 1.02, $CHCl_3$). IR (film) ν_{max} 3060, 1430 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$) δ 0.18 and 0.19 (6 H, 2 s), 1.00 (9 H, s), 1.27 and 1.45 (2 × 3 H, 2 s), 3.59 (1 H, br s), 4.32 (3 H, m), 4.42 (1 H, t, *J* = 5.5 Hz), 4.96 (1 H, m), 4.90 (1 H, br s), 6.56 (1 H, d, *J* = 2.1 Hz), 7.10- 7.40 (15 H, m), 7.65 (5 H, m). EIMS (*m*/*z*) 677 (2), 91 (100). Anal. Calcd for $C_{40}H_{49}NO_4SiSn$: C, 63.64; H, 6.55; N, 1.86. Found: C, 63.90; H, 6.31; N, 1.58. **11*Z***: Colorless oil. R_f = 0.26 (7% EtOAc/hexane). $[\alpha]^{25}_D$ +87.3 (*c* 0.45, $CHCl_3$). IR (film) ν_{max} 3060, 1430 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$) δ −0.05 (6 H, s), 0.60 (9 H, s), 1.28 and 1.45 (2 × 3 H, 2 s), 3.72 (1 H, br s), 4.27 (1 H, d, *J* = 5.7 Hz), 4.75 (1 H, t, *J* = 5.5 Hz), 4.72 (2 H, s), 4.96 (1 H, ddd, *J* = 5.5, 2.3, 1.0 Hz), 5.47 (1 H, br s), 6.12 (1 H, d, *J* = 2.3 Hz), 7.25 (15 H, m), 7.56 (5 H, m). EIMS (*m*/*z*) 677 (2), 91 (100). Anal. Calcd for $C_{40}H_{49}NO_4SiSn$: C, 63.64; H, 6.55; N, 1.86. Found: C, 63.51; H, 6.62; N, 1.58.

(*Z*,*E*)-(1*R*,2*R*,3*S*,4*R*)-4-[(Benzyloxy)amino]-2,3-*O*-isopropylidene-6-(tributylstannyl)-5-methylenecyclopentane-1,2,3-triol (12*Z*/*E*). This carbocycle was prepared according the general procedure replacing triphenyltin hydride by tributyltin hydride. Oxime **6** (0.256 g, 0.88 mmol), tributyltin hydride (0.3 mL + 0.6 mL, 0.99 g, 3.40 mmol) and triethylborane (1 M in hexanes, 0.4 mL + 0.8 mL, 1.2 mmol) in dry toluene (50 mL) (reaction time: 41 h) gave a mixture of **12*Z*/*E*** (0.399 g, 78%) in a ratio of 4.5:1, respectively, and as a colorless oil. R_f = 0.36 (10% EtOAc/hexane). IR (film) ν_{max} 3530, 1455 cm^{-1}. **12*Z***: ^1H NMR (200 MHz; $CDCl_3$) δ 0.84−1.65 (33 H, m), 2.29 (1 H, d, *J* = 10.2 Hz), 3.68 (1 H, d, *J* = 3.3 Hz), 4.35−4.66 (5 H, m), 5.37 (1 H, d, *J* = 3.3 Hz), 6.24 (1 H, d, *J* = 1.2 Hz), 7.35 (5 H). For **12*E***: ^1H NMR (200 MHz; $CDCl_3$) δ 0.84−1.65 (33 H, m), 2.15 (1 H, d, *J* = 10.7 Hz), 3.51 (1 H, d, *J* = 3.5 Hz), 4.35−4.76 (5 H, m), 5.20 (1 H, d, *J* = 3.5 Hz), 6.32 (1 H, d, *J* = 1.8 Hz), 7.35 (5 H, m). Anal. Calcd for $C_{28}H_{47}NO_4Sn$: C, 57.95; H, 8.16; N, 2.41. Found: C, 58.01; H, 7.98; N, 2.31.

1-[(Benzyloxy)imino]-5,6-dideoxy-2,3-*O*-isopropylidene-D-*talo*-hex-5-yne (16). 1,2-dideoxy-4,5-*O*-isopropylidene-D-*allo*-hept-1-ynitol (14) (1.755 g, 8.11 mmol) [prepared as reported[14b] (62%); ^1H NMR (200 MHz; $CDCl_3$) δ 1.37 and 1.44 (2 × 3 H, 2 s), 2.05 (1 H, m), 2.55 (1 H, d, *J* = 2.2 Hz), 3.36−3.98 (5 H, br m), 4.15 (1 H, dd, *J* = 5.3, 9.2 Hz), 4.26 (1 H, dd, *J* = 5.3, 8.3 Hz), 4.60 (1 H, m)] was dissolved in water (40 mL); sodium periodate (2.644 g, 12.36 mmol) and $NaHCO_3$ (0.937 g, 11.15 mmol) were added, and the reaction mixture was stirred at rt for 1.5 h. The solution was extracted with CH_2Cl_2 (4 × 30 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give crude **5,6-dideoxy-2,3-*O*-isopropylidene-*ribo*-hex-5-ynofuranose (15)**.[14b] The crude furanose **15** (1.534 g) was dissolved in CH_2Cl_2 (70 mL), and *O*-benzylhydroxylamine hydrochloride (1.942 g, 12.17 mmol) and pyridine (2 mL, 24.73 mmol) were added. The reaction mixture was refluxed for 4.5 h, cooled, poured into water (70 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product (4.30 g) was purified by flash column chromatography. Elution with EtOAc/hexane (25/75) gave **1-[(benzyloxy)imino]-5,6-dideoxy-2,3-*O*-isopropylidene-D-*talo*-hex-5-yne (16)** (2.028 g, 86%) as a mixture of *syn*/*anti* isomers (1:2) and as a pale yellow oil. R_f = 0.38 (25% EtOAc/hexane). IR (film) ν_{max} 3450, 3290, 2120 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$) δ 1.38 and 1.59 (2 × 1.5 H), 1.40 and 1.54 (2 × 3 H), 2.46 (3 H with 1.5 H, d, *J* = 2.2 Hz and 1.5 H) 4.17 (0.5 H, ddd, *J* = 2.2, 3.8, 8.5 Hz), 4.31 (1 H, dd, *J* = 5.5, 6.5 Hz), 4.40 (1 H, dt, *J* = 2.2, 5.5 Hz), 4.50 (0.5 H, dd, *J* = 3.8, 7.3 Hz), 4.81 (1 H, dd, *J* = 6.5, 7.3 Hz), 5.10 (2 H, s), 5.12 (1 H, s), 5.22 (0.5 H, dd, *J* = 4.2, 7.3 Hz), 7.05 (0.5 H, d, *J* = 4.2 Hz), 7.35 (5 H and 2.5 H, m), 7.63 (1 H, d, *J* = 7.3 Hz). EIMS (*m*/*z*) 274 (1), 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.70; H, 6.51; N, 4.70.

4-*O*-acetyl-5,6-dideoxy-2,3-*O*-isopropylidene-D-*talo*-hex-5-yne (17). Oxime ether **16** (1.123 g, 3.88 mmol) was stirred in pyridine (6 mL) and acetic anhydride (6 mL) at room temperature for 2 h, and then the solvent was removed under reduced pressure. The crude product (1.30 g) was purified by flash column chromatography. Elution with EtOAc/hexane (20/80) gave **17** (1.236 g, 96%) as an inseparable mixture of *syn*/*anti* isomers (1:2) and as a white solid. R_f = 0.35 (20% EtOAc/hexane). IR (film) ν_{max} 3300, 1745 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$) δ 1.39 and 1.62 (2 × 1.5 H), 1.41 and 1.55 (2 × 3 H), 2.06 (3 H, s), 2.09 (1.5 H, s), 2.47 (1 H, d, *J* = 2.2 Hz), 2.49 (0.5 H, d, *J* = 2.2 Hz), 4.44 (1 H, dd, *J* = 5.3, 6.8 Hz), 4.56 (0.5 H, dd, *J* = 3.6, 7.3 Hz), 4.85 (1 H, dd, *J* = 6.8, 8.0 Hz), 5.11 (2 H, s), 5.17 (1 H, 2 × d, *J* = 12.0 Hz), 5.28 (0.5 H, dd, *J* = 4.3, 7.3 Hz), 5.38 (0.5 H, dd, *J* = 2.2, 3.6 Hz), 5.44 (1 H, dd, *J* = 2.2, 5.3 Hz), 7.04 (0.5 H, d, *J* = 4.3 Hz), 7.35 (5 H and 2.5 H, m), 7.53 (1 H, d, *J* = 8.0 Hz). EIMS (*m*/*z*) 91 ($C_7H_7^+$, 100). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 64.98; H, 6.50; N, 4.39.

(*Z*,*E*)-(1*S*,2*S*,3*R*,4*S*)-4-[(Benzyloxy)amino]-2,3-*O*-isopropylidene-6-(triphenylstannyl)-5-methylenecyclopentane-1,2,3-triol (18). This compound was prepared according to the general procedure for carbocyclizations. Oxime **16** (1.005 g, 3.48 mmol), triphenyltin hydride (1.462 g + 0.765 g, 6.34 mmol) and triethyl borane (1M in hexanes, 1.8 mL + 1 mL, 2.8 mmol) in dry toluene (200 mL) gave **18*Z*** (1.640 g, 74%) and a mixture of **18*Z*/*E*** (0.375 g) (in a ratio of 2/1, 0.250 g *Z* and 0.125 g *E*; total **18*Z***: 1.890 g, 85%; total **18*E***: 0.125 g, 6% [(colorless oil. R_f = 0.33 (20% EtOAc/hexane). $[\alpha]^{25}_D$ +69.3 (*c* 1.37, $CHCl_3$)]. **18*Z***: colorless oil. R_f = 0.33 (20% EtOAc/hexane). $[\alpha]^{25}_D$ −76.3 (*c* 1.19, $CHCl_3$). IR and ^1H NMR (300 MHz; $CDCl_3$) identical to those of **(*Z*)-(1*R*,2*R*,3*S*,4*R*)-4-[(Benzyloxy)amino]-2,3-*O*-isopropylidene-6-(triphenylstannyl)-5-methylenecyclopentane-1,2,3-triol (9*Z*)**. EIMS (*m*/*z*) 564 (70), 91 (100). Anal. Calcd for $C_{34}H_{35}NO_4Sn$: C, 63.77; H, 5.51; N, 2.19. Found: C, 63.48; H, 5.45; N, 1.98.

(*Z*/*E*)-(1*S*,2*S*,3*R*,4*S*)-4-[(Benzyloxy)amino]-2,3-O-isopropylidene-6-(tributylstannyl)-5-methylenecyclopentane-1,2,3-triol (19). Triethylborane (1 M in hexanes, 3 mL, 3 mmol) was added to a degassed solution of oxime **16** (1.679 g, 5.80 mmol) and tributyltin hydride (2 mL, 2.2 g, 7.6 mmol) in dry toluene (315 mL) under argon. The reaction mixture was stirred at 60 °C for 1.3 h, triethylborane (1 M in hexanes, 3 mL, 3 mmol) and tributyltin hydride (2 mL, 2.2 g, 7.6 mmol) were added, and the reaction mixture was stirred at 60 °C overnight. The reaction mixture was concentrated under reduced pressure and the residue (7.5 g) diluted in Et_2O (50 mL), stirred with 15% aqueous KF solution (50 mL) for several hours, and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product (6.76 g) was purified by flash column chromatography. Elution with EtOAc/hexane (0/100 → 5/95) gave **19*Z*** (2.148 g, 64%) and **19*E*** (0.522 g, 15%). **19*Z***: pale yellow oil. R_f = 0.40 (10% EtOAc/hexane). $[\alpha]^{25}_D$ −55.1 (*c* 2.2, $CHCl_3$). IR (film) ν_{max} 3530, 1450 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$) δ 0.84−1.65 (33 H, m), 2.29 (1 H, d, *J* = 10.0 Hz), 3.68 (1 H, d, *J* = 3.3 Hz), 4.37 (1 H, d, *J* = 5.8 Hz), 4.49 (2 H, m), 4.67 (2 H, s), 5.37 (1 H, d, *J* = 3.3 Hz), 6.24 (1 H, d, *J* = 1.4 Hz), 7.35 (5 H, m). EIMS (*m*/*z*) 524 (100). Anal. Calcd for $C_{28}H_{47}NO_4Sn$: C, 57.95; H, 8.16; N, 2.41. Found: C, 58.12; H, 8.23; N, 2.31. **19*E***: pale yellow oil. R_f = 0.34 (10% EtOAc/hexane). $[\alpha]^{25}_D$ −74.9 (*c* 2.38, $CHCl_3$). IR (film) ν_{max} 3500, 1450 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$) δ 0.84−1.65 (33 H, m), 2.17 (1 H, d, *J* = 10.9 Hz), 3.51 (1 H, d, *J* = 3.5 Hz), 4.37 (1 H, d, *J* = 5.5 Hz), 4.45 (2 H, m), 4,64 (1 H, d, *J* = 12.0 Hz), 4.72 (1 H, d, *J* = 12.0 Hz), 5.19 (1 H, d, *J* = 3.5 Hz), 6.32 (1 H, d, *J* = 1.8 Hz), 7.34 (5 H, m). EIMS (*m*/*z*) 524 (72), 91 (100).

(*Z*)-(1*S*,2*S*,3*R*,4*S*)-4-[(Benzyloxy)amino]-1-*O*-acetyl-2,3-*O*-isopropylidene-6-(tributylstannyl)-5-methylenecyclopentane-1,2,3-triol (20*Z*). This compound was prepared according to the modified general procedure, as reported for the cyclization of oxime **16**. Oxime **17** (0.246 g, 0.74 mmol), tributyltin hydride (2 × 0.25 mL, 0.55 g, 1.9 mmol), and triethylborane (1 M in hexanes, 2 × 0.35 mL, 0.7 mmol) in dry toluene (40 mL) (reaction time: 5.5 h) gave **20*Z*** (0.345 g,

75%) as a pale yellow oil. $R_f = 0.38$ (15% EtOAc/hexane). $[\alpha]^{25}_D$ −8.4 (*c* 0.59, $CHCl_3$). IR (film) ν_{max} 1750 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$) δ 0.84−1.60 (33 H, m), 2.14 (3 H, s), 3.82 (1 H, d, $J = 3.4$ Hz), 4.42 (1 H, d, $J = 5.6$ Hz), 4.67 (2 H, s), 4.80 (1 H, t, $J = 5.9$ Hz), 5.26 (1 H, br d, $J = 6$ Hz), 5.43 (1 H, d, $J = 3.4$ Hz), 6.32 (1 H, d, $J = 2.2$ Hz), 7.35 (5 H, m). EIMS (*m*/*z*) 622 (M^+, 4), 566 (100). Anal. Calcd for $C_{30}H_{49}NO_5Sn$: C, 57.89; H, 7.94; N, 2.25. Found: C, 58.10; H, 7.59; N, 2.02.

(1*S*,2*S*,3*R*,4*S*)-4-[(Benzyloxy)amino]-5-methylenecyclopentane-1,2,3-triol (21a). This compound was prepared using either **19** or **20**. ***(Z)*-6-(Tributylstannyl)-5-methylenecyclopentane-1,2,3-triol (19 *E/Z*)** (2.124 g, 3.66 mmol) was stirred in a solution of HCl/EtOH (60 mL) at rt for 2 h, and the solvent was removed under reduced pressure. The residue was diluted with water (60 mL) and extracted with hexane (3 × 50 mL), and the aqueous extract was then concentrated under reduced pressure to give a pale yellow foam. The foam (1.055 g) was dissolved in EtOH (75 mL), propylene oxide (0.8 mL, 0.66 g, 11.4 mmol) was added, and the reaction mixture was stirred at 50 °C overnight. The reaction mixture was cooled and concentrated under reduced pressure, and the crude product (1.16 g) was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (0/100 to 10/90) gave **21a** (0.846 g, 92%), as a white solid. $R_f = 0.40$ (10% CH_2Cl_2/MeOH). $[\alpha]^{25}_D$ −68.0 (*c* 0.2, MeOH). IR (KBr) ν_{max} 3450, 1650 cm^{-1}. ^1H NMR (200 MHz; D_2O) δ 3.72 (1 H, dt, $J = 7.2$, 2.2 Hz), 3.95 (2 H, m), 4.35 (1 H, t, $J = 3$ Hz), 4.69 (2 H, s), 5.29 (2 H, pseudoquintet, $J = 2.5$ Hz), 7.30 (5 H, m). ^{13}C NMR (75.43 MHz; $CDCl_3$) δ 149.3, 137.2, 128.7, 128.5, 128.4, 128.0, 114.3, 76.9, 74.0, 73.2, 72.6, 68.0. EIMS (*m*/*z*) 252 ($M^+ + 1$, 3), 91 (100). Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.97; H, 6.80; N, 5.31.

(1*R*,2*R*,3*R*,4*R*,5*R*)-5-Acetamido-1-*C*-(acetoxymethyl)-2,3,4-tri-*O*-acetylcyclopentane-1,2,3,4-tetraol (23) and *(1S,-2R,3R,4R,5R)*-5-Acetamido-1-*C*-(acetoxymethyl)-2,3,4-tri-*O*-acetylcyclopentane-1,2,3,4-tetraol (24). A solution of osmium tetraoxide in *t*-BuOH (0.05M, 3.6 mL, 0.18 mmol) and NMO (0.357 g, 2.64 mmol) were added to a stirred solution of compound **22** (obtained from compound **21a**[23,25a]) (0.279 g, 0.89 mmol) in acetone (8 mL)/water (2 mL). The reaction mixture was stirred at 40 °C in the dark overnight. Sodium bisulfite (0.74 g, 7.1 mmol) was added and the reaction mixture stirred at rt for 1.3 h, dried over Na_2SO_4, filtered through Celite, and concentrated under reduced pressure. The crude diol (0.60 g) was dissolved in pyridine (3 mL) and cooled at 0 °C, and acetic anhydride (3 mL) was added. The reaction mixture was stirred at rt for 2 h and then concentrated under reduced pressure and purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (0/100 → 4/96) gave **23** (0.011 g, 3%) as a viscous oil and **24** (0.277 g, 80%), as a white foam. **23**: $R_f = 0.32$ (4% CH_2Cl_2/MeOH). $[\alpha]^{25}_D$ +13.6 (*c* 0.87, $CHCl_3$). ^1H NMR (500 MHz; $CDCl_3$) δ 2.04, 2.12, 2.13, 2.15, 2.19 (5 × 3 H, 5 s), 3.95 (1 H, d, $J = 11.6$ Hz), 4.10 (1 H, d, $J = 11.6$ Hz), 4.57 (1 H, dd, $J = 10.8$, 4.9 Hz), 4.71 (1 H, s), 5.13 (1 H, dd, $J = 5.0$, 10.8 Hz), 5.25 (1 H, d, $J = 4.9$ Hz), 5.52 (1 H, t, $J = 4.9$ Hz), 6.42 (1 H, d, $J = 4.9$ Hz); **24**: $R_f = 0.30$ (4% CH_2Cl_2/MeOH). $[\alpha]^{25}_D$ +1.9 (*c* 0.96, $CHCl_3$). IR (KBr) ν_{max} 3400, 1750 cm^{-1}. ^1H NMR (500 MHz; $CDCl_3$) δ 2.03, 2.06, 2.07, 2.08, 2.12 (5 × 3 H, 5 s), 3.90 (1 H, s), 4.16 (1 H, d, $J = 11.9$ Hz), 4.21 (1 H, d, $J = 11.9$ Hz), 4.64 (1 H, t, $J = 8.8$ Hz), 5.17 (1 H, dd, $J = 6.4$, 7.9 Hz), 5.21 (1 H, d, $J = 4.6$ Hz), 5.50 (1 H, dd, $J = 6.4$, 4.6 Hz), 6.35 ppm (1 H, d, $J = 9.5$ Hz). ^{13}C NMR (50.32 MHz; $CDCl_3$) δ 171.5, 170.9, 170.1, 170.1, 77.8, 75.8, 74.5, 68.8, 56.6, 65.5, 23.3, 21.0, 20.9, 20.8. EIMS (*m*/*z*) 390 ($M^+ + 1$, 2), 43 (100). Anal. Calcd for $C_{16}H_{23}NO_{10}$: C, 49.36; H, 5.95; N, 3.60. Found: C, 49.17; H, 5.77; N, 3.58.

(1*S*,2*R*,3*R*,4*R*,5*R*)-5-Amino-1-*C*-(hydroxymethyl)cyclopentane-1,2,3,4-tetraol (25). Pentacetate **24** (0.135 g, 0.35 mmol) was stirred in 2 N HCl (5 mL) at 80 °C for 17 h and then concentrated under reduced pressure. The crude product (0.08 g) was purified on a column of Dowex 50WX4 (H^+) resin. Elution with aqueous 5% ammonia gave aminocyclopentitol **25** (0.060 g, 97%) as a pale yellow solid: mp 135−137 °C. $[\alpha]^{25}_D$ +3.6 (*c* 0.61, MeOH). IR ν_{max} (KBr) 3460, 3360, 1640 cm^{-1}. ^1H NMR (200 MHz; CD_3OD) δ 3.39 (1 H, d, $J = 7.3$ Hz), 3.60 (1 H, d, $J = 11.4$ Hz), 3.68 (1 H, d, $J = 11.4$ Hz), 3.65−4.00 (3 H, m). ^{13}C NMR (50.32 MHz; CD_3OD) δ 78.8, 78.3, 73.2, 71.8, 65.8, 60.5. Anal. Calcd for $C_6H_{13}NO_5$: C, 40.22; H, 7.31; N, 7.82. Found: C, 40.19; H, 7.20; N, 7.77.

(3*S*,4*R*,5*R*,6*R*,7*R*)-7-Acetamido-4,5,6-triacetoxy-1-oxaspiro[2.4]heptane (30) and (*R*)-7-Acetamido-4,5,6-triacetoxy-1-oxaspiro[2.4]heptane (31). *m*-CPBA (57−86%, 0.32 g, 1.1−1.6 mmol) was added to a stirred solution of **22** (0.131 g, 0.42 mmol) in CH_2Cl_2 (8 mL) and phosphate buffer pH 8 (0.30 mL). The reaction mixture was stirred at rt in the dark for 20 h 30, diluted with CH_2Cl_2 (30 mL), washed with saturated sodium thiosulfate solution (10 mL), saturated $NaHCO_3$ solution (10 mL), and water (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product (0.14 g) (^1H NMR of crude, 100% yield, **30**:**31** in a 10:1 ratio) was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (3/97) gave the epoxide **30** (0.080 g, 58%) as a foam. $R_f = 0.45$ (6% CH_2Cl_2/MeOH); $[\alpha]^{25}_D$ +68.5 (*c* 0.53, $CHCl_3$). IR ν_{max} (film) 3350, 1760 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$) δ 1.98 (3 H, s), 2.04 (3 H, s), 2.07 (3 H, s), 2.14 (3 H, s), 2.83 (1 H, d, $J = 4.9$ Hz), 3.06 (1 H, d, $J = 4.9$ Hz), 5.01 (1 H, t, $J = 9.3$ Hz), 5.22 (2 H, dd, $J = 4.5$, 9.4 Hz), 5.61 (1 H, t, $J = 4.5$ Hz), 5.80 (1 H, d, $J = 8.8$ Hz). ^{13}C NMR (50.32 MHz; $CDCl_3$) δ 170.7, 170.3, 169.7, 169.3, 73.2, 71.5, 69.0, 60.9, 50.5, 47.8, 23.1, 20.6, 20.3. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 51.06; H, 5.82; N, 4.25. Found: C, 51.25; H, 5.91; N, 3.84; and a mixture of epoxide **30** and its epimer **31** (0.027 g, 20% in a 2.8:1 ratio) [isolated data for epoxide **31**: $R_f = 0.34$ (6% CH_2Cl_2/MeOH). ^1H NMR (200 MHz; $CDCl_3$) δ 2.02 (3 H, s), 2.08 (3 H, s), 2.14 (3 H, s), 2.15 (3 H, s), 2.80 (2 H, s), 4.21 (1 H, t, $J = 8$ Hz), 5.47 (1 H, dd, $J = 4$, 8 Hz), 5.57 (1 H, d, $J = 4$ Hz), 5.66 (1 H, t, $J = 4$ Hz), 6.06 (1 H, d, $J = 8$ Hz)].

(1*R*,2*R*,3*R*,4*R*,5*R*)-5-Acetamido-1-*C*-(acetoxymethyl)-2,3,4-tri-*O*-acetylcyclopentane-1,2,3,4-tetraol (23) and *(1S,-2R,3R,4R,5R)*-5-Acetamido-1-*C*-(acetoxymethyl)-2,3,4-tri-*O*-acetylcyclopentane-1,2,3,4-tetraol (24). Epoxide **30** and its epimer **31** (0.020 g, 0.06 mmol) and sodium acetate (0.030 g, 0.37 mmol) were stirred in DMF (1.4 mL)/water (0.35 mL) at 120 °C overnight. The reaction mixture was concentrated under reduced pressure, and the residue was stirred in pyridine (0.5 mL) and acetic anhydride (0.5 mL) at rt for 3 h and then concentrated under reduced pressure. The crude product (0.055 g) was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (2/98 and 4/96) gave the pentaacetate **23** and its epimer **24** (0.017 g, 71% in a 1:3 ratio from ^1H NMR).

One-Pot Synthesis of Pentaacetates 23, 24, and (1*S*,2*R*,3*R*,4*R*,5*R*)-5-Acetamido-1-*C*-(acetoxymethyl)-1,2,3,4-tetra-*O*-acetylcyclopentane (32). The same procedure was used for the synthesis of epoxide **30** and its epimer **31**, and the crude was used directly for the epoxide opening followed by acetylation during 24 h. Purification after flash column chromatography gave the fully acetylated product **32** (0.023 g, 14%) as an oil. $R_f = 0.54$ (6% CH_2Cl_2/MeOH). $[\alpha]^{25}_D$ +50.3 (*c* 2.09, $CHCl_3$). IR ν_{max} (film) 3380, 1750 cm^{-1}. ^1H NMR (200 MHz; $CDCl_3$) δ 1.98 (3 H, s), 2.02 (3 H, s), 2.05 (3 H, s), 2.07 (3 H, s), 2.14 (3 H, s), 2.15 (3 H, s), 4.36 (1 H, d, $J = 12.3$ Hz), 4.61 (1 H, d, $J = 12.3$ Hz), 4.88 (1 H, t, $J = 10$ Hz), 5.43 (1 H, dd, $J = 4$, 10 Hz), 5.53 (1 H, t, $J = 4.5$ Hz), 5.83 (1 H, d, $J = 4.7$ Hz), 5.87 (1 H, d, $J = 10$ Hz). ^{13}C NMR (50.32 MHz; $CDCl_3$) δ 171.3, 170.5, 170.3, 169.7, 169.6, 169.1, 84.0, 72.7, 72.2, 69.5, 64.9, 55.0, 23.2, 21.5, 20.7, 20.6, 20.5, 20.3; pentaacetate **23** and its epimer **24** (0.025 g, 16% overall in a 1:1.7 ratio from ^1H NMR); and pentaacetate **24** (0.056 g, 37% overall yield).

(2*R*,3*R*)-Diacetoxy-5-acetamidocyclopent-4-enone (33) and (2,4*S*)-diacetoxy-(5*R*)-acetamidocyclopent-2-enone (34). Ozone was bubbled through a solution of **22** (0.064 g, 0.20 mmol) in MeOH (3 mL) at −78 °C for 3 h. The solution was degassed with argon, and dimethyl sulfide (1 mL, 13.6 mmol) was added. The reaction mixture was stirred overnight, and the temperature was allowed to warm slowly to rt and then concentrated in vacuo. The crude product (0.08 g) was purified by flash column chromatography. Elution with CH_2Cl_2/MeOH (2/98 and 3/97) gave the cyclopentenone **33** (0.022 g, 42%) as a white solid and the cyclopentenone **34** (0.012 g, 23%) as an oil. **33**: $R_f = 0.48$ (5% CH_2Cl_2/MeOH). $[\alpha]^{25}_D$ −16.4 (*c* 1.05, $CHCl_3$). IR ν_{max} (KBr) 3280, 1765, 1725, 1705 cm^{-1}.

^{1}H NMR (200 MHz; $CDCl_3$) δ 2.07 (3 H, s), 2.14 (3 H, s), 2.19 (3 H, s), 5.44 (1 H, d, J = 5.6 Hz), 6.02 (1 H, dd, J = 3.5, 5.6 Hz), 7.69 (2 H, br d, J = 3.4 Hz). ^{13}C NMR (50.32 MHz; $CDCl_3$) δ 195.8, 169.9, 169.4, 169.0, 138.0, 131.2, 68.6, 68.5, 23.8, 20.5, 20.2. Anal. Calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 52.02; H, 5.48; N, 5.19. **34** (this compound was very unstable and decomposed in cold): R_f = 0.29 (5% CH_2Cl_2/MeOH). IR ν_{max} (liquid film) 3380, 1780, 1755, 1740 cm^{-1}. ^{1}H NMR (200 MHz; $CDCl_3$) δ 2.03 (3 H, s), 2.13 (3 H, s), 2.28 (3 H, s), 4.01 (1 H, dd, J = 2.5, 7.0 Hz), 5.82 (1 H, t, J = 2.5 Hz), 6.40 (1 H, d, J = 6.9 Hz), 7.22 (1 H, d, J = 2.5 Hz). ^{13}C NMR (50.32 MHz; $CDCl_3$) δ 192.5, 170.6, 170., 166.9, 149.1, 137.0, 73.8, 59.4, 22.5, 20.8, 20.7. Anal. Calcd for $C_{11}H_{13}NO_6$: C, 51.77; H, 5.13; N, 5.49. Found: C, 52.03; H, 5.31; N, 5.29.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for compounds **21b**, **21c**, **22**,[25a] **26**−**29**, **35**−**44** (13 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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