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Free Radical Cycloisomerization of Enantiomerically Pure Alkyne-Tethered Oxime Ethers: A New Method for the Asymmetric Synthesis of Aminocyclopentitols

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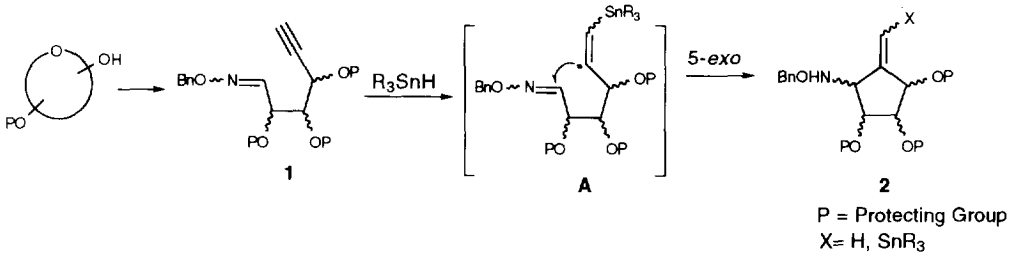
Abstract: We describe for the first time the free radical cyclization of enantiomerically pure alkyne-tethered oxime ethers obtained from carbohydrates. The synthesis of compounds **6** and **7**, obtained from 2,3-*O*-isopropylidene-D-ribose **3** is reported. These radical precursors have been submitted to cyclization with tributyl or triphenyltin hydride plus triethylborane, to yield, after ring closure, the aminocyclopentitols **8-10**. These carbocycles have been obtained as mixtures of *Z* and *E* vinyltin isomers, but with excellent diastereoselection. After protodestannylation only one diastereoisomer was detected. The absolute configuration at the new stereocenter formed during the ring closure has been established by detailed ^{1}H NMR analysis. The specific transformation of compound **9** (or **10**) into aminocyclitol **14** is described. From these results, we can conclude that a new method for the asymmetric synthesis of aminocyclopentitols of biological interest is now available.

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.[2] As part of our ongoing research in this area,[3] we report here a new and highly stereospecific method for the asymmetric synthesis of aminocyclopentitols.[4] These compounds are key intermediates for the preparation of carbonucleosides[5] and cyclopentane type glycosidase inhibitors.[6,7] In this communication we describe *the first examples of the free radical cycloisomerization of enantiomerically pure, polyoxygenated alkyne-tethered oxime ethers.*[8,9]

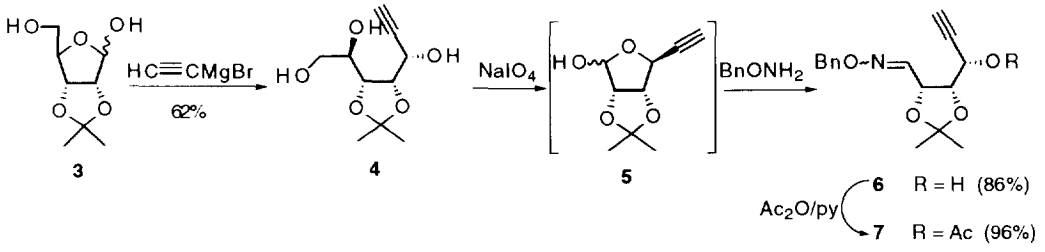
Scheme 1



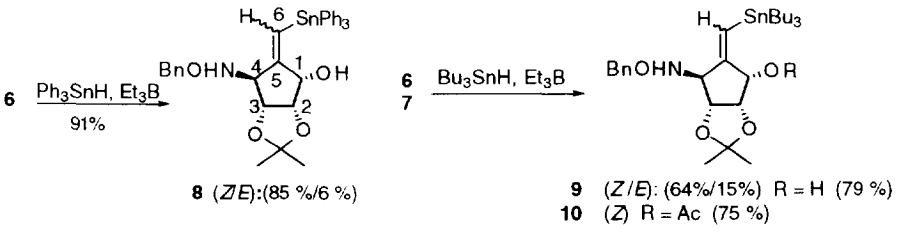
Our approach is shown in Scheme 1. The essential aspects of this strategy include nucleophilic attack of an ethyne anion to aldoses followed by selective protection and activation to afford the chiral radical precursor **1**. This product, upon attack by the appropriate tin hydride reagent, provides the vinyl radical[10] species (**A**) which is expected to lead to the aminocyclopentitol **2**. These molecules are conveniently designed for further synthetic manipulation: in fact, an example of compounds of type **2**: 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, 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 has been transformed into trehazolin and trehalostatin.[11] As the required starting materials, the aldoses, are readily available, it is possible to synthesize almost all the desired compounds of type **2** in different stereogenic configurations at the carbons bearing the hydroxyl groups. The particular stereodirecting properties and conformational bias of acyclic sugar derivatives also offer opportunities for high stereochemical control in the formation of new stereocenters.

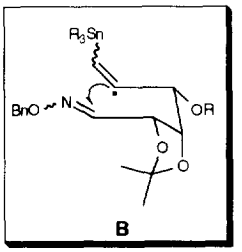
Scheme 2



Scheme 3

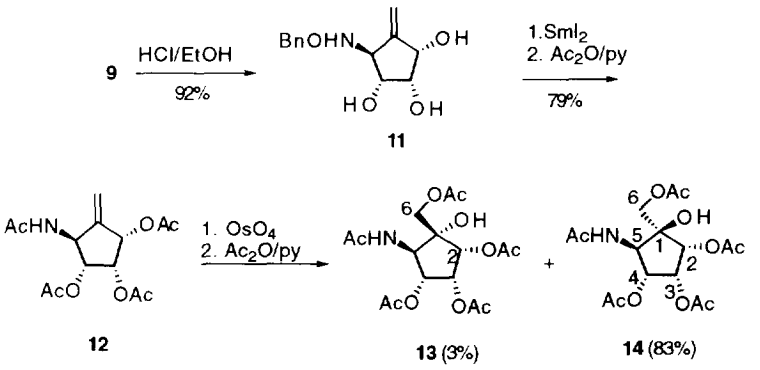


With this scenario in mind and in order to explore the scope of this method, the synthesis of the radical precursors **6** and **7** was attempted. These products have been prepared from 2,3-*O*-isopropylidene-D-ribose **3**[12] (Scheme 2). Treatment of compound **3** with ethynylmagnesium bromide gave product **4**, as the only isolated isomer.[13] Sodium periodate cleavage of the vicinal diol afforded lactol **5**, that after reaction with *O*-benzylhydroxylamine, under standard conditions, provided compound **6**,[14] as a mixture of *E* and *Z* isomers, in 2:1 ratio, respectively. We were unable to separate both isomers and they were submitted to cyclization together. Compound **7** was obtained from **6** by simple acetylation.[14] In the experimental conditions described by Enholm[9] no cyclization was observed. We then turned our attention to the triethylborane plus triphenyltin hydride mediated carbocyclization of enynes, as described by Oshima.[15] In these conditions the free radical cyclization[14] of precursors **6** and **7** gave in high yield the corresponding aminocyclopentitol derivatives **8** and **9** (as *E*/*Z* isomers that we could separate and isolate) and **10**, as the exclusive *Z* isomer (Scheme 3). The detailed analysis of the high field ^{1}H NMR spectrum of these compounds[14] has shown that all these products were chirally homogeneous and have *S* as the absolute configuration at the new stereocenter. In agreement with that, for compound **8***Z* we could observe $J_{3,4}$= 0 Hz and in carbocycle **8***E* a strong n.O.e effect was detected between H1 and H6. The high field ^{1}H NMR spectra of compounds **9** and **10** showed similar spectroscopic trends.



The high degree of stereochemical control observed in the cyclization of precursors **6** and **7** can be explained assuming that in the early transition state, the favored vinyl radical species is in a chair-like conformation with most of the substituents in preferred pseudoequatorial orientation[1] (**B**); this gives the observed *trans* products **8-10**. The formation of major or exclusive *Z* isomers in these vinyltin intermediates is in agreement with the results observed by Oshima.[15]

Scheme 4



These vinyltin derivatives[16] are conveniently functionalized for further synthetic manipulation. For instance, the synthetic power of this methodology has been demonstrated by transforming compound **9** (or **10**) into the aminocyclopentitol **14**[14] (Scheme 4). Compound **14** is an analogue of the aminocyclopentitol moiety of trehazolin, a powerful glycosidase inhibitor of trehalase.[11] This transformation has been accomplished as follows. Reaction of compound **9** with anhydrous ethanol saturated with hydrogen chloride resulted in simultaneous protodestannylation[17] and hydrolysis of the acetonide, leading to the triol **11** in high yield. Efficient samarium diiodide mediated cleavage of the N-O bond of the *O*-benzyl hydroxylamine **11**, followed by acetylation in a "one-flask" operation, afforded the peracetate **12** {$[\alpha]_D^{25}$ -30.2 (*c* 0.83, $CHCl_3$)}. Treatment of this allylic acetamide with osmium tetroxide gave, after partial acetylation, the aminocyclopentitol **14** {$[\alpha]_D^{25}$ +1.9 (*c* 0.96, $CHCl_3$)}in excellent yield (83%); only traces of the minor isomer (**13**), obtained by reaction from the α face, were isolated. A similar high *syn*-stereoselectivity has also been observed in the osmylation of certain allylic substituted cyclopentanes.[18] The absolute configuration at the new stereocenter (C1) has been established by ^1H NMR analysis. In fact, the 2D-NOESY spectrum of compound **14** shows crosspeaks for H5/H6a, and also OH/H2, indicating that the methylene, $C(6)H_2$, is *cis* to

H5, and that the OH group is *cis* to H2. On the other hand, the 2D-NOESY spectrum of aminocyclopentitol **13** exhibits crosspeaks for H2/H6a and H2/H6b, thus demonstrating that $C(6)H_2$ is now *cis* to H2.

In summary, the present method has proven to be a new and very useful method for the synthesis of some aminocyclopentitols of biological interest.

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14 All new compounds gave satisfactory analytical and spectroscopic data. **Typical experiment for carbocyclization**: Triethylborane (1M in hexanes, 0.5 equiv) and tributyltin hydride (1.2-1.3 equiv) were added to a stirred solution of the radical precursor (1 equiv) in dry, degassed toluene (0.018M), under argon, at 60°C (bath temperature). The reaction was stirred for 1 h. Then, the same quantities of the reagents were added, and the reaction was pursued until complete (tlc analysis; ≈10 h). The solvent was removed and the residue was dissolved in ether and treated with 15% aqueous solution of potassium fluoride, overnight at room temperature. The organic phase was separated, dried, evaporated and submitted to chromatography. A similar protocol has been used for the triphenyltin hydride mediated cyclization.

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