Carbocycles from carbohydrates *via* free radical cyclizations: new synthetic approaches to glycomimetics

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Free radical cyclization of enantiomerically pure, acyclic presursors derived from carbohydrates is an excellent method for the synthesis of complex, densely functionalized chiral carbohydrate mimics ('glycomimetics'). The extent of the acyclic diastereoselection can be modulated and is closely associated with the structure, rigidity and conformational aspects of the radical precursors. General models for a rationale of the stereochemical outcome of the cyclizations are shown.

1 Introduction

Carbohydrates are readily available and inexpensive building blocks for the synthesis of natural products.[1] In the last decade, particular emphasis has been devoted to the preparation of polyfunctionalized carbocycles from sugars.[2] Carbocyclization based on free radical chemistry has been recognized as an efficient tool because radical cyclization methods tolerate high levels of substrate functionalization.[3] The general process includes monosaccharide protection, opening, functionalization and finally cyclization to a carbocyclic ring of five or six carbons.

These efforts have culminated in the design of some new free radical based methodologies for the synthesis of mimetics of natural sugars ('glycomimetics') such as aminocyclopentitols, inositols, branched chain cyclitols or carbasugars. Glycomimetics play critical roles in biological systems and, by controlling cell–cell interactions or interfering with carbohydrate metabolic processes, are potential candidates for new pharmaceutical drugs.[4]

In the last nine years, our group has been actively working in this area. In this review we present the most relevant results for the synthesis of aminocyclopentitols and cyclitols by free radical cyclization of acyclic monosaccharide derivatives. Particular emphasis is placed on the stereochemical aspects of these reactions. Most of the conversions are straightforward examples that illustrate the utility, scope and generality of this strategy for the synthesis of enantiomerically pure carbocycles.

2 Aminocyclopentitols *via* cyclization of δ-functionalized *O*-alkyl oxime ethers derived from carbohydrates

The aminocyclopentitol nucleus is present in a wide variety of natural products. The synthesis of these polyhydroxylated cyclopentylamines has been an area of growing interest due to the discovery of their potent biological properties. For example, allosamidin (**1**), trehazolin (**3**), mannostatins (**4**), and Merrel Dow's cyclopentylamine (**5**), have been found to have powerful and specific inhibitory activity against glycosidases. As a consequence, they have attracted the interest of organic chemists and many synthetic approaches have been reported.[5] Another important group of aminocyclopentitols, the 4-amino-1,2,3-cyclopentanetriols, are also versatile and valuable inter-

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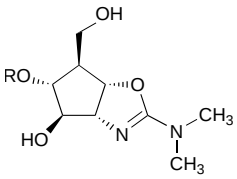
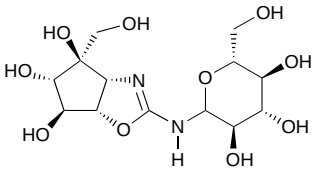
mediates for the synthesis of cyclopentane-type glycosidase inhibitors and carbocyclic nucleosides.[6]

The 5-*exo* radical cyclization reaction of acyclic carbohydrate derivatives has been applied to the synthesis of a broad range of polyhydroxylated cyclopentanes using different types of radical acceptors: olefins and enol ethers,[7] unsaturated esters,[8] alkynes,[9] imines,[10] oxime ethers[11] and hydrazones.[12]

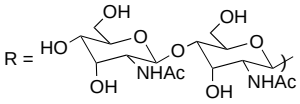
In this section, we present a range of free radical cyclizations of acyclic δ-functionalized *O*-alkyl oxime ethers derived from carbohydrates to obtain different aminocyclopentitols.



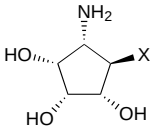
(–)-Allosamidin (**1**)



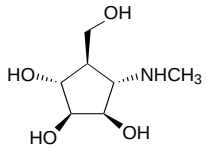
Trehazolin (**3**)



(–)-Allosamizoline (**2**, R = H)



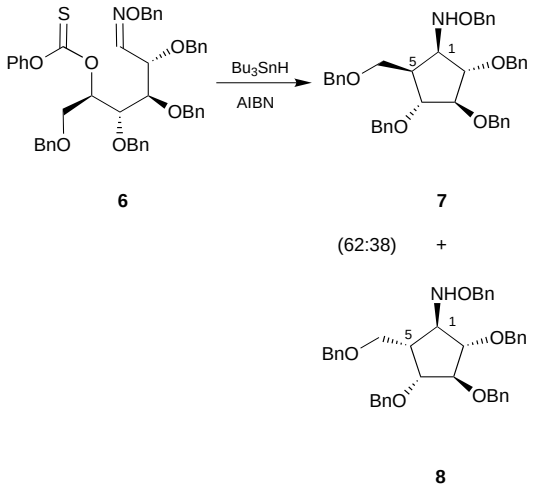
Mannostatin A (**4a**, X = SCH_3)
Mannostatin B [**4b**, X = $S(O)CH_3$]



Merrel Dow's cyclopentylamine (**5**)

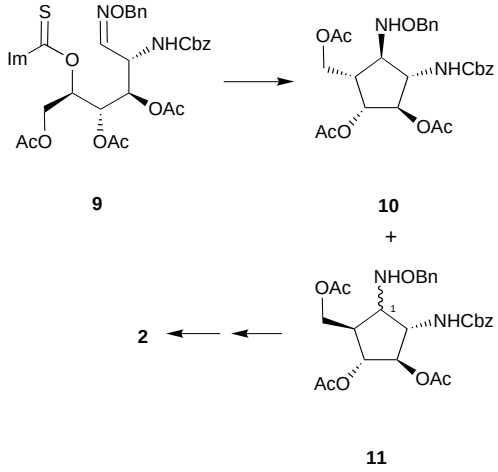
2.1 Bu_3SnH-mediated 5-*exo* radical cyclizations

The ability of *O*-alkylaldoximes to act as intramolecular radical traps is well known. Bartlett was the first to synthesize aminocyclopentitols by cyclization of 5-oximinoalkyl radicals derived from D-glucose (Scheme 1).[11] Four stereoisomers can arise in the cyclization of radical precursor **6**; however, only carbocycles **7** and **8** were obtained in a 62 : 38 ratio, respectively. The 1,5-*cis* product is the major one and this result can be explained by assuming that the intermediate radical preferentially adopts a chair-like conformation with the substituents at C2, C3 and C4 in pseudoequatorial positions.[13]



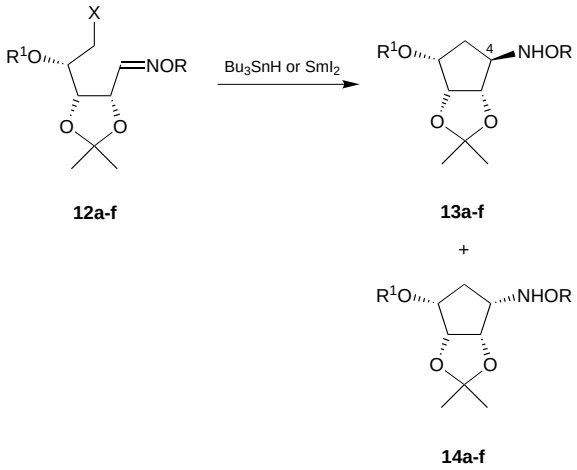
Scheme 1

Following a similar strategy, Simpkins designed a short enantiospecific route to allosamizoline (**2**), the aminocyclopentitol aglycon of allosamidin (**1**) starting from D-glucosamine (Scheme 2).[14] The cyclization of radical precursor **9** showed poor diastereoselectivity; three compounds were obtained: the minor **10**, and the major **11**, isolated as a mixture of epimers in C1.

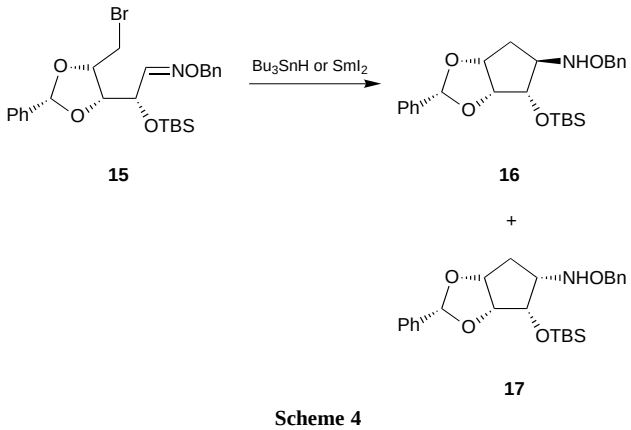


Scheme 2

In our group, we carried out a new synthesis of enantiomerically pure 4-amino-1,2,3-cyclopentanetriols[15] *via* free radical cyclization of a series of oxime ethers **12a**–**f** (Scheme 3) and **15** (Scheme 4); these compounds were easily prepared from D-ribono-γ-lactone. All precursors were obtained and used as inseparable mixtures of *E* and *Z* oxime isomers (7 : 3 ratio, respectively), and were submitted together to typical conditions for radical cyclization promoted by tributyltin hydride or samarium diiodide.



Scheme 3



Scheme 4

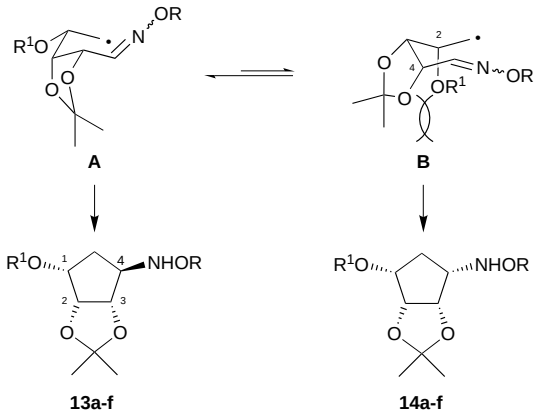
From precursors **12a**–**f** (Scheme 3), using tributyltin hydride, all the cyclizations showed good yields and high stereoselectivity (Table 1), favouring the formation of the *exo* products **13a**–**f**. When samarium diiodide was used, the yields were lower due to several competititve processes: epoxide ring formation and/or elimination; however, compounds **13a**–**f** were the only diastereomers obtained.[15]

Table 1 Free radical cyclization of precursors **12** using Bu_3SnH

12	X	R	R^1	**13**/**14**	Total yield (%)
a	Br	Bn	H	100/0	75
b	Br	Bn	Bu^tMe_2Si	100/0	53
c	Br	Bn	Ac	100/0	52
d	Br	Bn	Bz	89/11	58
e	Br	Me	Bz	80/20	71
f	I	Bn	H	100/0	85

The cyclization of precursor **15** (Scheme 4), using the tin hydride method, provided a mixture of **16** and **17** in a 1.8 : 1.0 ratio and 80% total yield. The samarium diiodide ring closure gave the major product **16**, in 40% yield, with traces of **17**.[15]

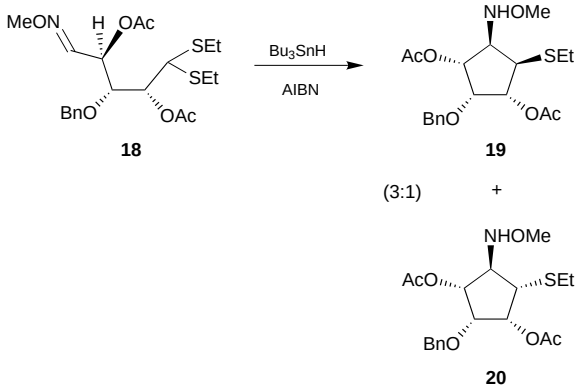
The stereochemical outcome of these free radical cyclizations is consistent with the transition state model proposed by Beckwith,[13] in which the radical species is in a chair-like conformation having most of the substituents in the preferred pseudo-equatorial positions. This is in agreement with the results reported by Wilcox for the cylization of analogous α,β-unsaturated esters.[8] In Scheme 5 hypothetical lowest energy transition states for the intermediate radicals are presented. In conformation B, the unfavourable 1,3-diaxial interaction between the substituents at C2 and C4 (radical numbering) destabilizes the transition state leading to the *endo* product. We have not found a satisfactory explanation for the formation of small amounts of the *endo* product during the cyclization of precursors **12d**–**e** (Table 1) with a benzoyl group at R^1 (compare with the results obtained in the cyclization of precursors **12a**–**c,f** with different protecting groups at this position). The higher diastereoselectivity observed in samarium-mediated carbocyclization, compared with tributyltin hydride cyclization, is difficult to rationalize at this moment. We can hypothesize that a chelated samarium–ligand transition state[12] should impose some limits to the conformational freedom in the reactive species, leading to higher stereochemical control.



Scheme 5

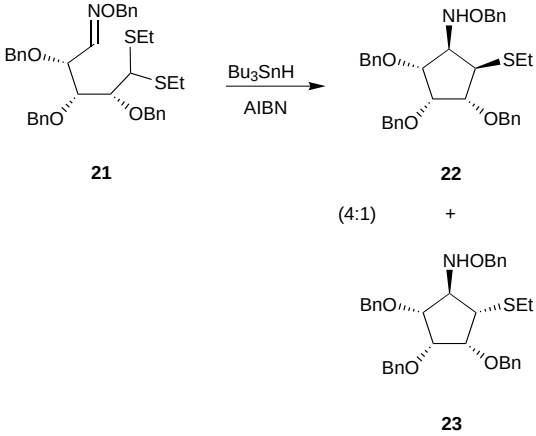
In summary, the free radical cyclization of δ-functionalized *O*-alkyl oxime ethers derived from D-ribose is a good method for the synthesis of (1*R*,2*R*,3*S*,4*R*)-4-amino-1,2,3-cyclopentanetriol derivatives in terms of chemical yield and acyclic diastereoselection. Major *trans* (C1–C4 and C3–C4) isomers are formed (Scheme 5). Comparing both cyclizations methods, the tin-mediated cyclization of 5-oximinoalkyl radicals derived from monosaccharides is clearly superior to the corresponding SmI_2-mediated reaction, in terms of chemical yield and experimental manipulation.

The use of dithioketals as a radical precursor in this type of cyclization has also been studied. Roberts was the first to use, as a key step to prepare new mannostatin analogues, a free radical carbocyclization of an α-sulfenyl radical on oxime ethers, starting from D-allose (Scheme 6).[16] The cyclization of radical precursor **18** occurs in high yield (80%), but the stereoselectivity was moderate (3 : 1) and unfortunately both isomers **19** and **20** were obtained as an inseparable mixture.



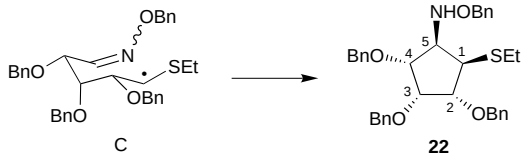
Scheme 6

In parallel work, we reported the synthesis of new mannostatin A analogues by free radical cyclization of precursor **21**, prepared from D-ribose *via* a shorter route (Scheme 7).[17] The yield was also high (80%) and, although the stereoselectivity was only slightly better (4 : 1), the major compound **22** was isolated in almost pure form.

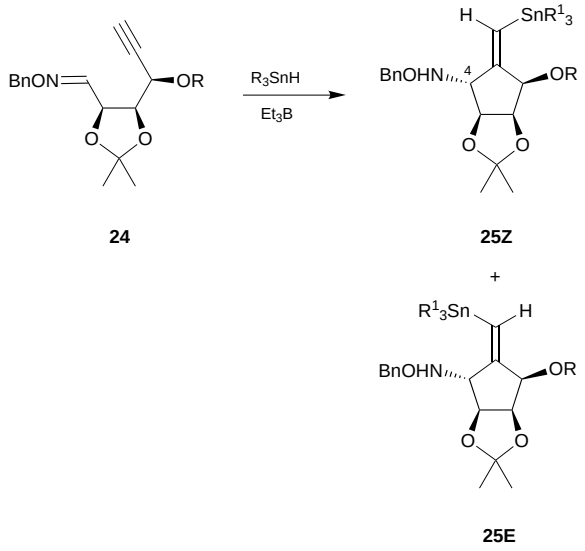


Scheme 7

The *cis* stereochemistry at the new stereocenters (C1 and C5) in the major compound can be explained by assuming a chair-like conformation in the transition state of the 5-*exo*-*trig* ring closure (Scheme 8), with the oxime ether and most of the substituents in the preferred pseudo-equatorial positions (conformation C) to avoid 1,3-diaxial interactions in other possible conformers.



Scheme 8



Scheme 9

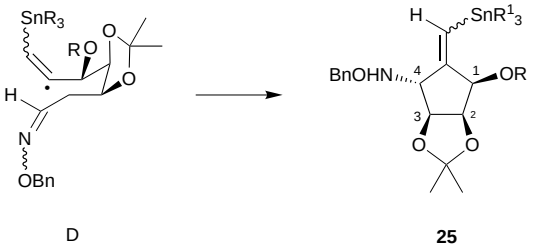
2.2 R_3SnH-mediated 5-*exo* cyclization of δ-alkyne tethered *O*-alkyl oxime ethers

The intramolecular coupling of oxime ethers tethered to terminal alkynes to prepare acyclic sugar derivatives has been carried out using a hydrostannylation reaction.[18] Derived from D-mannose, the radical precursor **24** (Scheme 9) was cyclized using tributyltin or triphenyltin hydride plus Et_3B to give the vinyl stannanes **25** as a mixture of the separable *Z*/*E* isomers (Table 2). Each geometric isomer was diastereomerically pure at the new stereocenter (C4) with the absolute configuration shown in Scheme 9. The synthesis and cyclization of a similar radical precursor, prepared from D-ribose, leads to enantiomers of compounds **25*Z*/*E*** in good yield and complete diastereoselection at the newly formed stereocenter.

Table 2 Free radical cyclization of precursor **24**

Entry	R	R^1	**25Z** (%)	**25E** (%)
1	H	Ph	69	3
2	H	Bu	78 (4.5 : 1 ratio)	
3	Ac	Ph	70	—
4	TBDMS	Ph	45	14

The diastereoselectivity observed in the cyclization can be explained according to Beckwith's guidelines,[13] assuming that, in the early transition state, the favoured intermediate vinyl radical is in a chair-like conformation D with most of the substituents in the preferred pseudoequatorial orientation (Scheme 10). As in the cyclization of precursors **12** (Scheme 3), major isomers having a *trans* relationship between C1/C4 and C3/C4 are obtained.



D **25**

Scheme 10

2.3 SmI_2-mediated intramolecular reductive coupling of δ-carbonyl tethered *O*-alkyl oxime ethers

In 1989, Enholm was the first to describe the samarium-mediated intramolecular cyclization of aldehydes tethered to α,β-unsaturated esters in substrates derived from carbohydrates.[19]

Our group has recently developed the samarium-mediated intramolecular reductive coupling of carbonyl-tethered *O*-alkyl oxime ethers to provide a new and synthetically useful method for the construction of aminocyclopentitols.[15] This procedure was applied to the synthesis of trehazolamine analogous **26** (Scheme 11) by reductive coupling of δ-carbonyl tethered *O*-alkyl oxime ethers derived from D-glucose. Reaction of precursor **27** using samarium iodide, gave only isomer **28** in 80% yield. Simultaneously, Naito also analyzed this protocol using Bu_3SnH as a reagent for carbocyclization.[20] Reaction of **27** (Scheme 11) with tributyltin hydride gave a 1.0 : 1.4 mixture of **28** and **29**, respectively, in 68% overall yield.

This reaction, using samarium diiodide, was also carried out with precursors obtained from D-mannose and D-galactose.[15] Ketone **30**, derived from D-mannose, afforded a mixture of three aminocyclopentitols **31**–**33** (Scheme 11) in a ratio 15 : 3 : 1, respectively. The reductive coupling of precursor **34**, obtained from D-galactose, gave only compound **35**. In all cases, the cyclization gave major compounds showing a *trans* relationship between the hydroxy at C1 and the benzyloxyamino group at C5, and between C4 and C5. There is also a *trans* relationship between the hydroxy at C1 and the benzyloxy group at C2 (except for the cyclization of the D-glucose derivative **27**, that led to isomer **28**). The stereochemistry obtained was independent of the geometry of the starting oxime ether. Surprisingly, no additives such as HMPA were necessary.

These results can be rationalized in terms of a nine-membered ring chelate[12] as shown in Scheme 12. The anion radical species adopt chair-like conformations in which the *O*-alkyl oxime ether at C5 (radical numbering) is in the preferred pseudoequatorial position.

In order to explore the scope of the method, related aldehydes were also studied.[15] To this end, alcohol **36** prepared from D-arabinose was submitted to a one-pot sequence of Swern oxidation and reductive coupling promoted by SmI_2 (Scheme 13). A mixture of **37a** and **37b** was obtained in a 8 : 1 ratio, respectively. Following the same procedure, appropriate and conveniently functionalized alcohols derived from D-ribose and D-xylose were also cyclized in good yield and from excellent to moderate diastereoselectivity.[15] In the SmI_2-promoted cyclization of δ-aldehyde *O*-alkyl oxime ethers, we have observed a *trans* relationship between C1/C2 and C4/C5 in the major isomers.

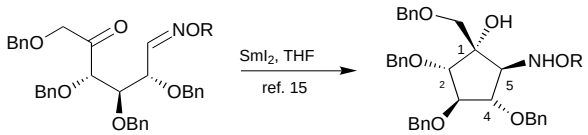
Collectively, the experiments above suggest that the samarium diiodide mediated 5-*exo* intramolecular cyclization of δ-carbonyl tethered *O*-alkyl oxime ethers derived from sugars is a good method for the synthesis of aminocyclopentitols in enantiomerically pure form.

2.4 SmI_2-mediated intramolecular reductive coupling of α,β-unsaturated esters tethered *O*-alkyl oxime ethers

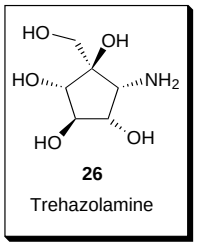
As a complement of the well known SmI_2-mediated reductive coupling of sugar-derived α,β-unsaturated esters tethered to carbonyl groups,[19] we have also described the first SmI_2-promoted intramolecular cyclization of unsaturated esters to *O*-alkyl oxime ethers (Scheme 14).[15] The cyclization of *E*-isomers **38** provided compound **39** in 52% yield as a single isomer.

3 Cyclitols from sugars *via* free radical cyclization

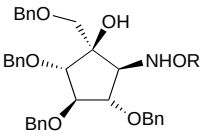
Cyclitols and aminocyclitols are polyhydroxylated cyclohexanes with important biological activities.[4] Different methodologies have been developed for the synthesis of these compounds.[21] Sugars have been commonly used as chiral starting materials. However, among the numerous methods reported for the conversion of carbohydrates into cyclitols, free radical cyclization is not so frequently used when a cyclohexane is the target ring.



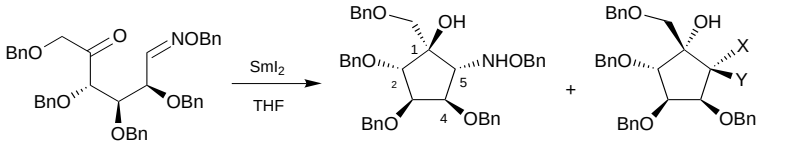
27 **28**



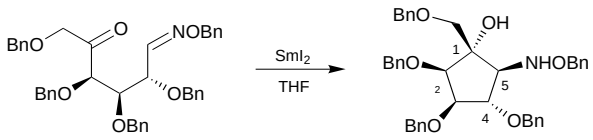
26
Trehazolamine



29

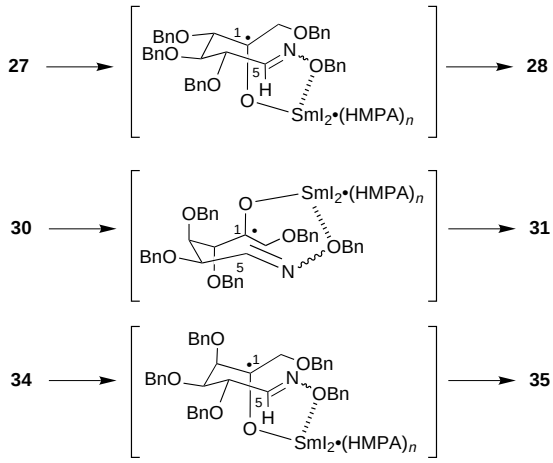


30 **31** **32**, X = H; Y = NHOBn
33, Y = H; X = NHOBn

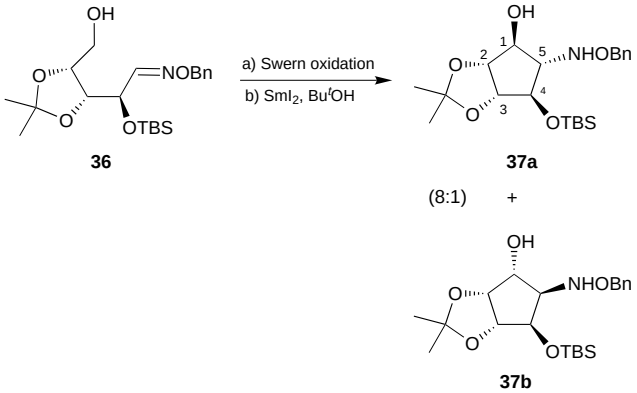


34 **35**

Scheme 11

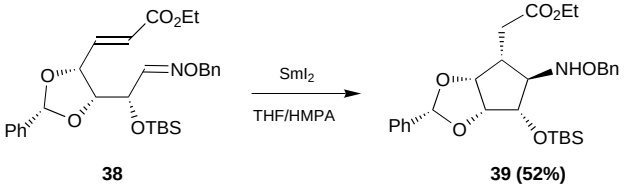


Scheme 12



36 **37a** **37b**

Scheme 13



38 **39 (52%)**

Scheme 14

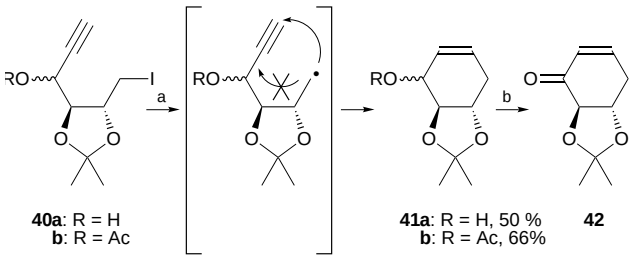
3.1 Bu_3SnH-mediated 6-*endo* cyclization

Hex-5-ynyl radicals cyclize preferentially *via* the kinetically favoured 5-*exo* pathway. Nevertheless, the regioselectivity can be changed by structural factors.[22] This feature has been used in a novel strategy for the synthesis of cyclitols.[23]

We thought that in the cyclization of 1-iodoalk-5-ynes of type **40** (Scheme 15), the 6-*endo*-*dig* ring closure should be preferred because the *trans* located 1,3-dioxolane moiety prevents the 5-*exo*-*dig* pathway leading to thermodynamically disfavoured *trans* fused cyclopentanes. The cyclohexenes **41** were obtained in good yield; the diastereomeric mixture of **41a** was oxidized to cyclohexanone **42**, a highly functionalized, chiral intermediate for the synthesis of cyclitols.[24]

3.2 Bu_3SnH-mediated 6-*exo* cyclization

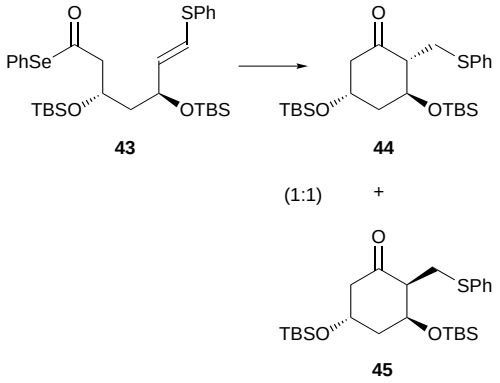
Most of the free radical cyclizations of acyclic carbohydrate derivatives to obtain carbocycles use hex-5-enyl radicals, whereas the 6-*exo* closure to give cyclohexane rings has been used less frequently, because the cyclization of hept-6-enyl radicals is about 40 times slower than the cyclization of the hexenyl radical. Therefore, reactions competing with the



Scheme 15

cyclization (*e.g.* reduction of the initial radical) become important. Another potential problem of the heptenyl radical is due to a 1,5-hydrogen transfer that leads to allyl radicals. Nevertheless, the 6-*exo* cyclization is a well known procedure in the synthesis of branched chain sugars where the cyclization of hept-6-enyl radicals is accelerated by the introduction of electron-withdrawing groups in the radical acceptor.[25]

Crich obtained a 1 : 1 mixture of the cyclohexanones **44** and **45** (Scheme 16), in 90% yield after cyclization of an acyclic acyl radical.[26]



Scheme 16

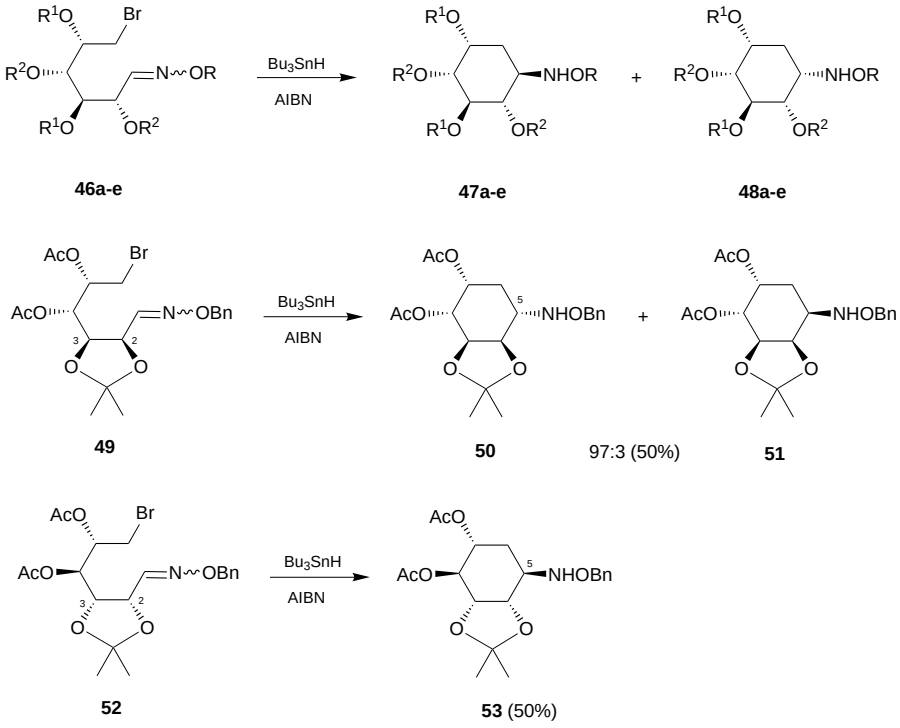
Redlich carried out a very interesting study on the cyclization of 7-deoxy-7-iodohept-1-enitols of the allo-, manno-, galacto- and gulo-series using tributyltin hydride.[27] The cyclization of radical precursors provided carba-6-deoxyhexoses in very good yield. The authors studied the effect of varying the protecting groups adjacent to the reaction centers and the influence of the stereochemistry. They rationalized the observed selectivities in terms of chair- and boat-like transition states depending on the *threo* or *erythro* disposition of the substituents contiguous to the reaction centers.

Of particular interest has been the application of the 6-*exo* free radical cyclization to the synthesis of aminocyclitols. In our group, we carried out the first synthesis of 5-amino-1,2,3,4-cyclohexanetetrols by 6-*exo* cyclization of 6-bromo-6-deoxyhexose derivatives using oxime ethers as radicals acceptors (Scheme 17).[28] All the precursors were obtained as inseparable mixtures of *E* and *Z* isomers in a 70 : 30 ratio. The radical is generated at an appropriate distance from the double bond to give 6-*exo* ring closure. The precurosrs **46a**–**e**, prepared from D-glucose with different protecting groups (Table 3), and the D-manno **49** and D-gulo **52** derivatives were cyclized in moderate yield and good diastereoselectivity. The incorporation of an isopropylidenedioxy at C2 and C3 in radical precursors **49** and **52** dramatically increased the diastereoselection (Scheme 17), giving almost a single isomer at the newly formed stereocenter (C5).

Table 3 Free radical cyclization of precursors **46**

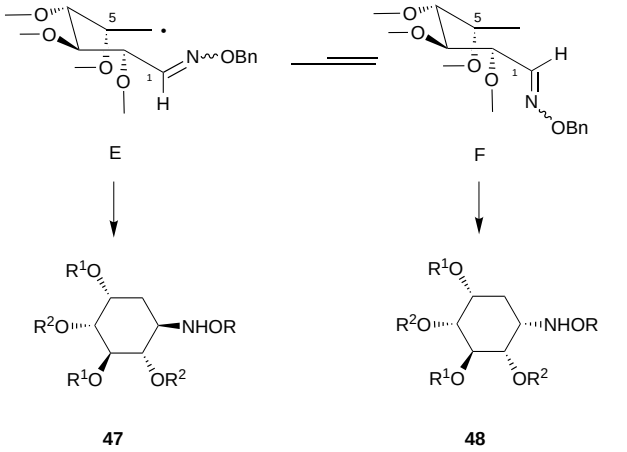
46	R^1	R^2	R	**47**/**48**	Yield (%)
a	Ac	Ac	Bn	83/17	52
b	Bz	Bz	Bn	75/25	55
c	Bz	Bz	Me	73/27	50
d	Bn	H	Bn	80/20	40
e	Bn	Ac	Bn	78/22	42

The stereochemical outcome of the cyclizations could be justified by assuming that the major products arose *via* transition states in which the radical species adopts a preferred chair-like conformation with most of the substituents occupying pseudoequatorial positions to minimize unfavourable 1,3-diaxial steric interactions.[28] In precursors **46** (Scheme 18), the steric interaction between the substituent at C5 and the oxime



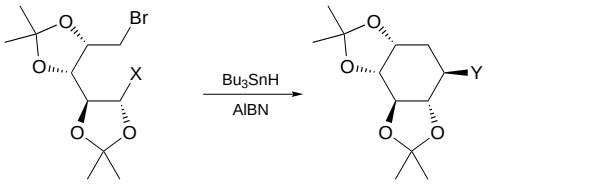
Scheme 17

ether at C1 (radical numbering) displaces the equilibrium to conformer *E*, leading predominantly to compound **47**. Nevertheless, this steric repulsion is not critical, because the results of substrates **49** and **52** point to the significance of the *gauche* interaction between the C2 substituent (isopropylidenedioxy group) and the oxime ether at C1.



Scheme 18

This work has been extended to explore the 6-*exo* cyclization of several 6-bromo-6-deoxy-D-glucose derivatives by changing the nature of the radical trap.[28] As expected, the D-gluco derivative **54a**, with two isopropylidenedioxy groups at C2/C3 and C4/C5, afforded after cyclization only isomer **55a** in 82% diastereomeric excess (Scheme 19). The reactions of enol ether **54b** and α,β-unsaturated ester **54c** with tributyltin hydride gave the major carbocycles **55b**–**c** in high diastereomeric excess (84 and 86% respectively). This improvement in the stereoselectivity, compared with that observed for the analogous precursors **46a**–**e**, confirms the influence of structural factors on the stereochemical outcome of the reaction.



54a: X = CH=NOBn
b: X = CH=CHOMe
c: X = CH=CHCO$_2$Me

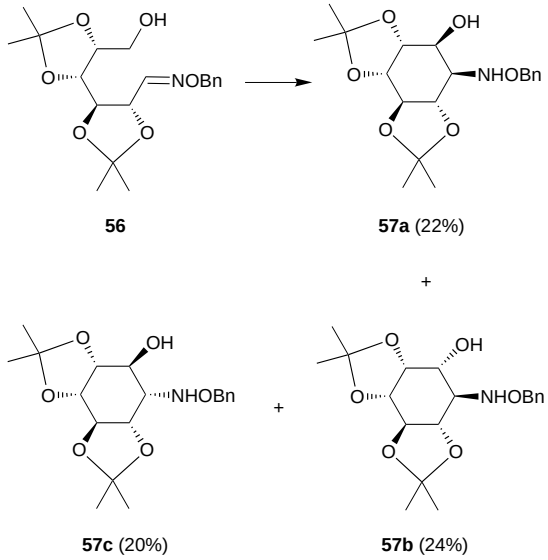
55a: Y = NHOBn (d.e. 82%; 75%)
b: Y = CH$_2$OMe (d.e. 84%; 60%)
c: Y = CH$_2$CO$_2$Me (d.e. 86%; 80%)

Scheme 19

After our initial reports on the synthesis of branched chain cyclitols,[28] several groups have successfully applied this strategy to the synthesis of some natural products.[29,30]

3.3 SmI$_2$-mediated intramolecular reductive coupling of ε-carbonyl tethered *O*-alkyl oxime ethers

Continuing our interest in the synthesis of aminocyclitols, we tried the intramolecular reductive coupling of a sugar-derived oxime ether ε-functionalized with an aldehyde.[15] In order to favor the cyclization we selected the conformationally strained D-glucose derivative **56** (Scheme 20). Dess–Martin oxidation gave the intermediate aldehyde that was submitted to reductive coupling promoted by samarium diiodide yielding the isomers **57a**–**c**. Total yield was good, but the diastereoselection was very poor.



Scheme 20

4 Conclusions

In summary, we have shown that the 5-*exo*, 6-*endo* and 6-*exo* free radical carbocyclization of acyclic, conveniently functionalized radical precursors derived from sugars is a suitable method for the synthesis of polyhydroxylated carbocycles in enantiomerically pure form. The type of radical trap allows us to manipulate the type of carbocycle to be prepared. The appropriate selection of radical precursor and the nature of the functional groups also determines the qualitative and quantitative course of the acyclic diastereoselection in the formation of new stereocenters.

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