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Stereocontrolled Synthesis of 2-Amino-2-Deoxy-α-D-C-Glycopyranosides by Radical Cyclization Reactions

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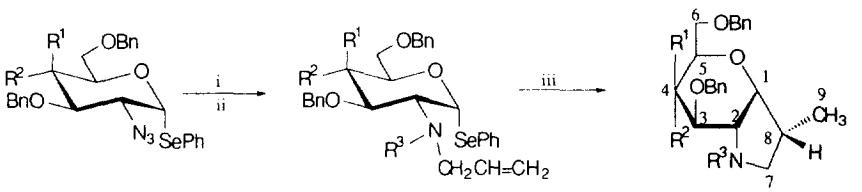
Abstract : *Radical cyclization of phenyl 2-N-allylamino-3,4,6-tri-O-benzyl-2-deoxy-α-D-1-seleno galacto and gluco pyranosides afforded α-D-C-glycopyranosides with high stereoselectivity involving a 5-exo-trig mechanism.* Copyright © 1996 Elsevier Science Ltd

Stereocontrolled intramolecular free-radical cyclization has been widely used for C-C bond formation in organic synthesis.[1] The formation of fused rings by cyclization of hex-5-enyl radicals in the presence of tin hydride is a particularly useful process.[2] Under kinetic control, high regioselectivity affords the five member ring by *exo* cyclization.[3] Although free radical additions have been widely used for the synthesis of C-glycosides,[4,5] few amino C-glycosides have been prepared by this type of reaction.[6] As a continuing programme devoted to the synthesis of C-glycosides, we report herein the radical cyclization of phenyl 2-*N*-allylamino-2-deoxy-α-D-1-selenoglycopyranosides.

Mono- and di-*N*-allylation of the amines obtained by reduction of phenyl 2-azido-3,4,6-tri-*O*-benzyl-2-deoxy-α-D-1-seleno *galacto* (**1**) and *gluco* (**2**) pyranosides[7] afforded the radical precursors **3-5** (Scheme 1).[8]

Scheme 1



1 R^1= OBn, R^2 =H
2 R^2 = H, R^2 =OBn

3 R^1 = OBn, R^2 = H, R^3 =$CH_2CH{=}CH_2$
4 R^1 =OBn, R^2 =R^3 = H
5 R^1 =R^3 = H, R^2 =OBn

6 R^1 = OBn, R^2 = H, R^3 =$CH_2CH{=}CH_2$
7 R^1 =OBn, R^2 =R^3 = H
8 R^1 =R^3 = H, R^2 =OBn

i) $HS(CH_2)_3SH$ (0.2 eq.), $NaBH_4$ (2 eq.), NEt_3 (2 eq.), iPrOH, 45°C, 4h; ii) NaH (1.3 eq. for **4** and **5**, 2 eq. for **3**), $BrCH_2CH{=}CH_2$ (2 eq.), THF, rt, 3h; iii) Bu_3SnH (4 eq.), Et_3B (1.1 eq.), PhH, rt, 10 min. **6** 74%, **7** 72%, **8** 76%

Reaction of **3-5** with *n*-Bu_3SnH in the presence of AIBN in refluxing benzene afforded an inseparable mixture of compounds whatever the reaction conditions were (concentration, reagents quantities, etc).

Triethylborane has been recently used for the initiation of radical reactions and allows the reaction to be carried out under mild conditions (room temperature).[9] Treatment of radical precursor **3** with *n*-Bu_3SnH and

Et_3B in benzene gave the cyclized compound **6**[8] as the sole product in 74% yield. Under the same conditions, compounds **4** and **5** cyclized readily to afford respectively **7**[8](72%) and **8**[8] (76%) (Scheme 1).

The absolute stereochemistry at the newly formed stereocenters (C-1 and C-8) in **6**, **7** and **8** was determined by ^{1}H-NMR spectroscopy and 1 D differential ^{1}H-nOe experiments at 250 MHz in $CDCl_3$ solution. The α configuration at C-1 was established by a small value of the coupling constant between H-1 and H-2 (2.6 Hz for **6**, 4.2 Hz for **7** and 3.9 Hz for **8**). This *cis* relationship was further confirmed by the observation of an Overhauser effect between H-1 and H-2 in the spectrum of compound **6**. Irradiation of H-8 of compounds **6**, **7** and **8** enhanced the signal of H-1, no nucleic Overhauser effect was observed between H-1 and H-9 when H-1 or H-9 was irradiated. Consequently the R configuration for C-8 was tentatively attributed for the three cyclized compounds, althrough confirmation should be obtained by X-ray diffraction.

The conformations of anomeric glucosyl and galactosyl radicals were shown to be different (boat and half-chair respectively) by Giese and coll.[10] De Mesmaeker *et al.* have demonstrated that the stereoselectivity of the 5-*exo* cyclization of anomeric radicals prepared from phenyl 2-*O*-allyl-1-selenoglycopyranosides was influenced by the conformation of these radicals.[5a] In our case, the stereochemical outcome of the cyclization is the same in studied *gluco* and *galacto* series. Epimerization of the C-5 chiral center was also observed in 2-*O*-allyl-1-selenoglycopyranosides, which is depending on the concentration of tributyltin hydride, the temperature, the nature and stereochemistry of the substituents at C-4 and C-6.[5b] No epimerization at C-5 was observed in our experiments after careful examination of the NMR spectra of cyclization products **6-8**. The stereochemical outcome reported here seems not to be influenced by the conformation of the anomeric radicals, which is perhaps due to the rapidity of the cyclization (10 min.) under mild conditions.

In conclusion, we have shown that 2-amino-2-deoxy-α-D-C-glycosides can be readily prepared by radical cyclization from the corresponding phenyl 2-amino-2-deoxy-1-selenoglycoside, in good yield and excellent stereocontrol.

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