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A New Synthesis of Carbapentofuranoses from Carbohydrates

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Abstract : Carbafuranosides were synthesized in one step from various *O*-protected 1,2,6-trideoxy-6-iodo-hex-1-enitols by cobalt catalyzed 5-*exo* radical-cyclization under molecular oxygen. Yields were fair to good with interesting selectivities. © 1997 Elsevier Science Ltd.

Carbocyclic sugar analogs of furanoses[1] are found in various classes of biologically important products, enzyme inhibitors and carbanucleosides[2] showing antiviral or antibiotic activity. Synthetic studies towards the elaboration or these compounds have been described starting from sugar precursors[3] or non-carbohydrate materials.[4,5] Other methodologies using samarium diiodide and relevant to the synthesis of polyoxygenated cyclopentanes from carbohydrates have also been described.[6]

Our strategy to carbofuranosides from carbohydrates relies on the reductive ring-opening of *O*-protected methyl 6-deoxy-6-iodo-hexopyranosides **I** with zinc according to Vasella[7] (figure 1) and further elaboration of the open-chain aldehyde **II** to an hexenitol derivative **III** containing a primary radical precursor (X = I, figure 1). A 5-*exo* radical cyclization/oxygenation sequence[8] would then give in one step the required hydroxymethyl substituted polyoxygenated cyclopentane core of the carbafuranoside **IV**. Our recently described cobalt-catalyzed system for radical cyclization under molecular oxygen[9] was used for this study.

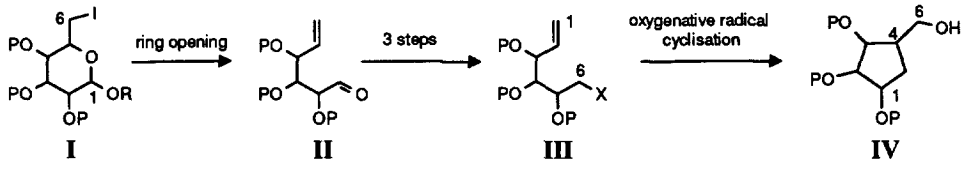

Figure 1

O-Protected 1,2-dideoxy-hex-1-enitols[10] (III, X = OH, Figure 1) of the L-*xylo*-, L-*ribo*-, L-*lyxo*- and

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D-*arabino*- configuration were obtained by zinc opening of the corresponding methyl 6-deoxy-6-iodo-hexopyranosides **I** in the D-*gluco*-, D-*allo*-, D-*galacto*- and D-*manno*- series followed by sodium borohydride reduction of the intermediate aldehyde **II**.[7] Conversion of the primary hydroxyl group to an iodide was done directly (PPh_3, I_2)[11] for compound **5** but a two-steps procedure (TsCl, pyridine then NaI, HMPA, 60°C) had to be used for the synthesis of products **1**, **3**, **4** and **6** because of competitive nucleophilic intramolecular attack of the C-3 benzyloxy oxygen atom and tetrahydrofuran formation.[12] A small amount of α-deoxygenated aldehyde (25%) which was formed during the zinc opening of methyl 2,3,4-tri-*O*-benzyl-6-deoxy-6-iodo-α-D-glucopyranoside[7] was also transformed according to the general synthetic scheme to 3,4-di-*O*-benzyl-1,2,5,6-tetradeoxy-6-iodo-D-*threo*-hex-1-enitol **2**.

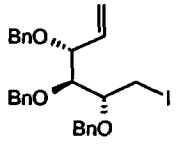
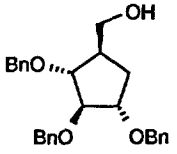
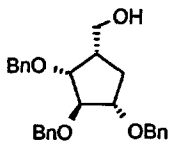
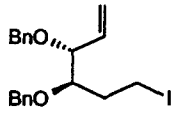
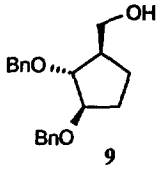
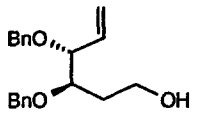
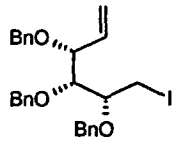
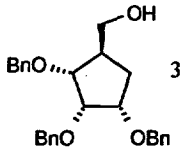
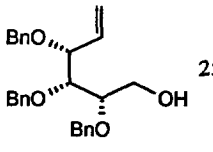
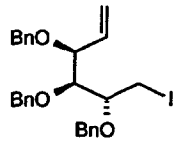
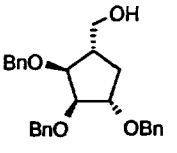
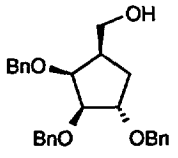
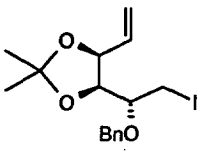
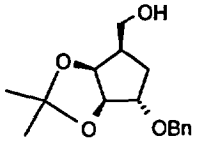
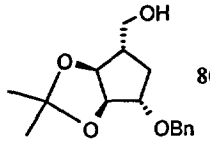
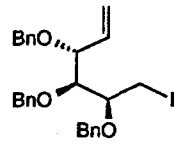
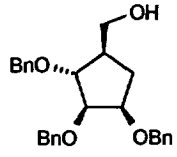
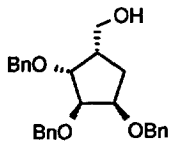
Cyclizations were carried out in basic (1.7 eq. NaOH) ethanolic solution at 40°C with 2-5% of Co(salen) complex[13] and 2-4 eq. of $NaBH_4$ under air and gave the carbafuranosides in a few hours at 40°C (see Table 1). Only products of 5-*exo* cyclization were observed and the main by-product was the hex-1-enitol resulting from oxygenation of the uncyclized radical. Small amounts of starting material and reduced compounds were also isolated.[8,9] Assignment of configuration of the new asymetric center was deduced from the one and two-dimensional ^1H NMR data and by comparison with known compounds when possible.[14]

Observed selectivities were good to very high and could be rationalized with the reported preferences for these 5-*exo* radical cyclizations.[15] The influence of the C-3 substituent of the hex-1-enitol on the stereochemical outcome of the reaction was preponderant and products with a *trans* relationship for the C-3 and C-4 substituents of the carbafuranose were obtained.[16] Substrates **1** and **2**, where all substituents could occupy equatorial positions in the six-membered *chair* transition state gave very high selectivity: 12:1 in favor of α-D-*arabino*-carbafuranose derivative **7** from the reaction of **1** and none of the C-4 epimer of **9** could ever be detected in the reaction mixture from **2**. Substrate **3** was very reluctant to cyclize but gave only α-D-*ribo*-carbafuranose derivative **11** together with considerable amounts of hex-1-enitol **12** coming from oxygen quench of the uncyclized radical.

Cyclization of the L-*lyxo*-hex-1-enitol derivative **4** gave a 4/1 mixture of the expected β-L-*ribo*- and α-D-*lyxo*-carbafuranoses **13** and **14** but in 50% yield only. In an attempt to increase the yield, the 3 and 4 positions of the L-*lyxo*-hex-1-enitol **5** were tethered with an isopropylidene group which should give a much favorable conformation for the radical cyclization. Indeed, a 80% yield of carbafuranoses was isolated in four hours from the reaction of **5** but with almost complete loss of selectivity (see table 1); in this case, the 3,4 *cis* product **15** was formed in slightly higher amount than the *trans* compound **16**.

Despite the lower cyclization rate of 5-hexenyl radicals compared to their 3-oxa- analogs,[15] the cobalt(salen)/sodium borohydride/molecular oxygen system[9] was found to be efficient for the control of the radical-cyclization oxygenation sequence and carbafuranoses were obtained as the major products in every

Table 1

Substrate	Time(h)[a]	Products		Yield(%)[b]
 **1**	20	 **7**	 **8**	69 12/1
 **2**	6	 **9**	 **10**	57 4/1[c]
 **3**	20	 **11**	 **12**	35 25
 **4**	5	 **13**	 **14**	50 4/1
 **5**	4	 **15**	 **16**	80 1.2/1
 **6**	6	 **17**	 **18**	30 4/1

a: all reactions were run at 40°C with a continuous stream of ethanol-saturated air bubling throught the solution.
b: isolated yields. The selectivity was measured by ^{1}H NMR on the mixture before isolation of the individual isomers.
c: these compounds could not be separated by chromatography.

case. The system is very easy to use and the mildness of the reaction conditions has to be emphasized; however, severe competition with oxygenation of the radical prior to cyclization occurs if the cyclization rate is not high enough, which is obviously the case for substrate **3** in our conditions.[17] Further work is currently in progress to overcome this limitation.

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14. Benzyl groups were hydrogenolyzed (H_2, Pd/C) and the tetrol was peracetylated. Selected data: **7** : tetrol $[\alpha]_D^{20}$ +45 (c 1.08, methanol) lit.[3c] $[\alpha]_D^{20}$ +40, lit.[3d] $[\alpha]_D^{20}$ -40.5 for the enantiomer. **13** : tetrol $[\alpha]_D^{20}$ -4 (c 1.70, methanol), lit.[3d] $[\alpha]_D^{16}$ +6.6 for the enantiomer. **17**. tetrol : $[\alpha]_D^{20}$ +4 (c 1.00, methanol), lit.[3c] $[\alpha]_D^{20}$ +6; tetracetate : $[\alpha]_D^{20}$ -3 (c 1.20, $CHCl_3$) lit.[3a] $[\alpha]_D^{23}$ +4.1 for the enantiomer.
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