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Diastereoselectivity of the Cyclization of Hexos-5-uloses by Sm$_2$-mediated Pinacol Coupling

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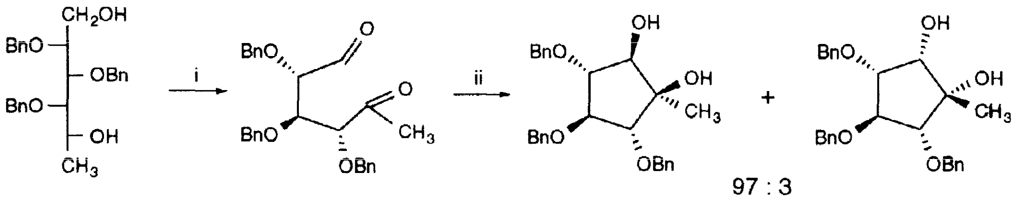
Abstract : 2,3,4,6-Tetra-*O*-benzyl-hexos-5-uloses derived from D-glucose, D-mannose and D-galactose have been cyclized to *cis*-diols by a one pot Swern oxidation/SmI$_2$-mediated pinacol coupling procedure. The effect of the substituent orientation on the diastereoselectivity of the coupling step is examined. © 1998 Elsevier Science Ltd. All rights reserved.

We have recently described the total synthesis of the complex carbocyclic monosaccharide caryose.[1] One of the key steps of the synthesis was the SmI$_2$-induced cyclization of compound **2** (see Scheme 1), which was obtained through a double Swern oxidation of compound **1**.



1 **2** **3** **4**

Scheme 1: i) (COCl)$_2$/DMSO/Et$_3$N/CH$_2$Cl$_2$; ii) SmI$_2$/*t*-BuOH/THF, -78°C → r.t. (64% from **1**)

The preponderant product of this intramolecular pinacolic condensation was the desired compound **3**, having the same configuration at its quaternary carbocyclic centre as the corresponding C-8 position of caryose. As expected,[2] in this main product the *cis* hydroxyl groups were *trans*-oriented with respect to the adjacent alkoxy groups. Interestingly, the analogous cyclization of dialdehyde **5** (which differs from **2** in carrying an hydrogen atom in place of the methyl group) has been reported[3] to occur with a comparable

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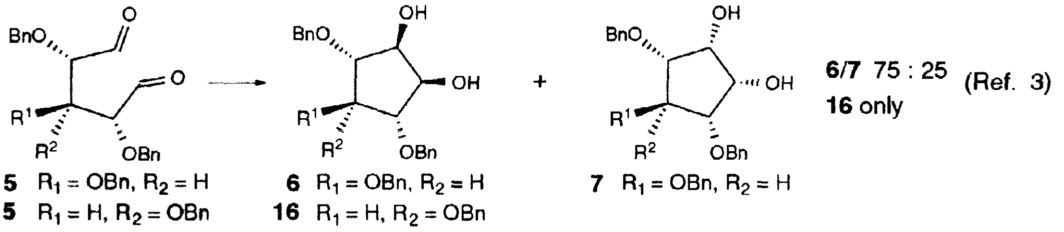
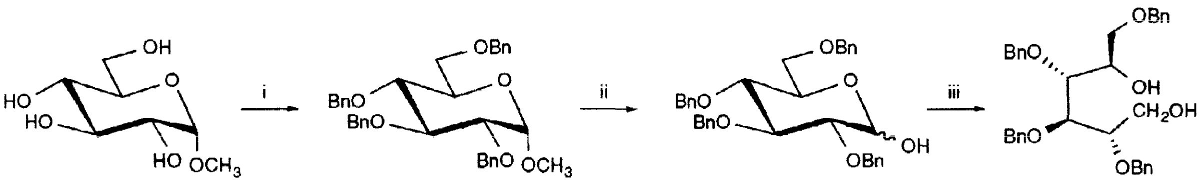
overall yield of carbocyclic *cis*-diols but with much lower diastereoselectivity (Scheme 2). Assuming a greater electrodonating power of a methyl group with respect to an hydrogen atom, the sensibly higher selectivity found in the cyclization of compound **2** should suggest a particularly important role played by electrostatic interactions in the stereochemical control of this type of cyclizations.



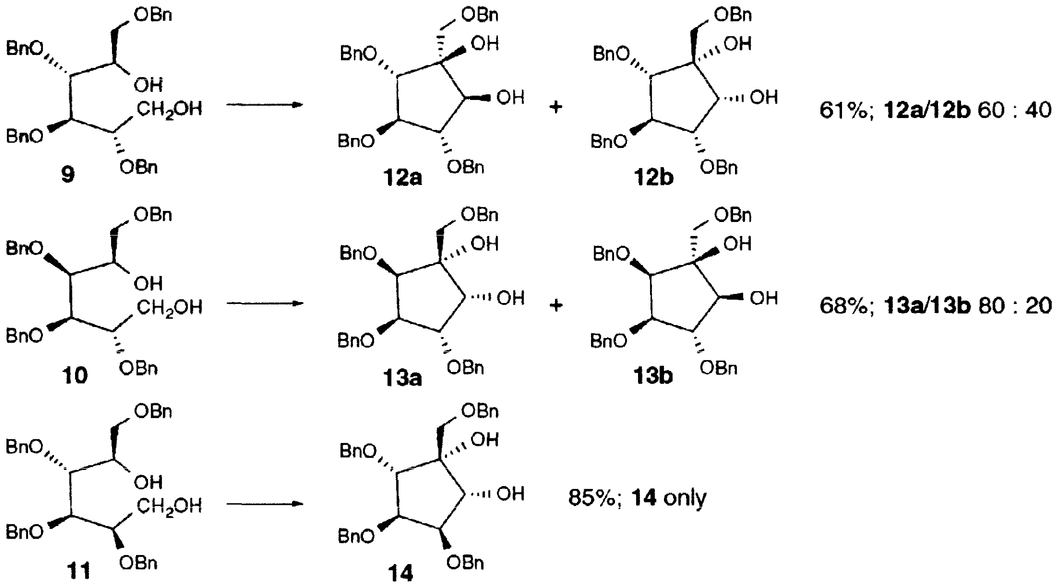
Scheme 2

Starting from these observations we investigated the effect of the substituent orientation on the diastereoselectivity of the pinacol coupling in view of the possible extension of the procedure followed for the preparation of the caryose precursor **3** to a more general approach aimed at the diastereoselective preparation of higly functionalized cyclopentanes possessing a quaternary chiral centre. The procedure was based on a three step (benzylation, hydrolysis to hemiacetals and $NaBH_4$ reduction at C-1) easy conversion of methyl α-hexopyranosides into alditols unprotected at C-1 and C-5. These intermediates were transformed into the corresponding 1,5-dicarbonylic derivatives, which underwent the intramolecular pinacolic condensation promoted by SmI_2. In Scheme 3 the sequence of reactions needed to convert the methyl α-D-glucopyranoside into its corresponding partially protected alditol (**9**, yield: 65% from **8**), is summarized. A similar procedure was used starting from methyl α-D-manno- and α-D-galactopyranoside to prepare respectively, 2,3,4,6-tetra-*O*-benzyl-D-galactitol **10** (yield: 65%) and 2,3,4,6-tetra-*O*-benzyl-D-mannitol **11** (yield: 56%), respectively.



Scheme 3: i) BnBr, NaH, DMF, 0°C→r.t.; ii) 7:1 AcOH/2N H_2SO_4, reflux; iii) $NaBH_4$, 2:1 $MeOH/H_2O$, reflux.

Differently from compound **2**, any attempt to isolate the hexosuloses produced by the Swern oxidation of **9-11** was limited by the remarkable propensity of these compounds to be hydrated during the extractive work-up.[4] Actually, we observed that hydration of these intermediates decreases sensibly their reactivity in the cyclization step. Therefore, the Swern oxidation and the subsequent pinacolic condensation were both carried out in THF, adopting a one pot procedure. Satisfying yields of carbocyclic compounds were thus obtained in all cases (see Scheme 4). In a typical procedure, the reaction mixture of the Swern double oxidation[5] in THF was concentrated with a gentle stream of argon and then treated at -70°C with a 0.1 M solution in THF of samarium diiodide (5 eq) and with *t*-BuOH (1 eq). After overnight stirring, a standard work up procedure was employed.[1]



Scheme 4

As usual for this type of cyclizations[2,6] in all cases carbocyclic *cis*-diols turned out to be the most abundant products. On the other hand we have observed relevant differences in the diastereoselectiviy of the cyclizations depending on the saccharidic precursor. In fact, a lower diastereoselective ratio (**12a/12b** 60:40) was noticed in the case of **9**, despite the cooperative *trans* orienting effect of the alkoxy substituents at C-2 and C-4[7] closer to the hydroxylated positions of the produced cyclopentane, than in the cases of **11** (only carbocycle **14** was produced) and **10** (**13a/13b** 80:20), where the *trans* orienting effects of the substituents at C-2 and C-4, located on opposite sides of the ring, contrasted. Actually, in a more careful analysis of the three predominant products, it can be observed that in all cases the hydroxyl groups are located on the side of the ring having the lower number of alkoxy substituents. This evidence suggests that a *trans*-orienting contribute is furnished also by the 3-OBn group, although the actual nature of this supposed long-range effect is not clear. This effect favours **14** over its undetected diasteroisomer and **13a** over **13b**, accounting for the higher diastereoselectivity than in the case of **9**, where it favours **12b** over **12a**, opposing the main effect exerted by the C-2 and C-4 alkoxy substituents. This hypothesis is supported by other reported instances. Cyclization of the 1,5 dialdehyde **15** from 2,3,4-tri-O-benzyl ribitol proceeds[3] with complete diastereoselectivity to give

16, differently from the analogous *xylo* derived compound **5** (scheme 2). In addition, the apparently anomalous stereochemical behaviour reported by Chiara[8] for the SmI_2-promoted one-pot conversion of 6-iodinated galactosides into cyclopentanes is consistent with this view.

A further effect can be invoked to account for the sensibly different diastereoselectivity found in the three cases. In fact, the only product obtained from **11** presents a more favourable *trans* relationship between the sterically demanding 4-OBn and 5-CH_2OBn groups. A *cis* relationship occurs instead for the substituents at C-4 and C-5 in the main products from **9** and **10**. The resulting steric repulsion of these bulky groups contributes to explain the detectable formation of the diastereomers **13b** and **12b**.

In conclusion, this work presents a wider insight into the factors governing the stereochemical outcome of the intramolecular pinacolic condensation of hexos-5-uloses mediated by SmI_2. This cyclization is here exploited as the key step of an efficient synthesis of highly functionalized cyclopentanes containing a quaternary chiral centre. In addition, a generalizable expeditious procedure for the preparation of protected hexos-5-uloses is proposed.[9,10]

ACKNOWLEDGMENTS

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3. Perrin, E.; Mallet, J-M.; Sinaÿ, P. *Carbohydr. Letters.* **1996**, *1*, 215-216.
4. Angyal, S. J. *Adv. Carbohydr. Chem. Biochem.* **1991**, *42*, 19-36.
5. The Swern oxidation step was performed as in reference 1, but in THF as the solvent.
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7. For sake of clarity, the carbon numbering of alditols **9-11** is retained for compounds **12a-14**.
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9. For other procedures to obtain hexos-5-uloses see Baxter, E. W., Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175-3185; Barili, P. L.; Berti, G.; Catelani, G.; D'Andrea, F.; De Rensis, F. *Tetrahedron* **1997**, *53*, 8665-8674; and references cited therein.
10. All new compounds were characterized by spectroscopic methods (^{1}H and ^{13}C NMR, MS). The stereochemistry of the new centres was determined by NOE studies.