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Synthesis of 2-Spirocyclopropylglucose via Condensation of Erythrose with the Lithium Enolate of 2,6-Di-*tert*-butyl-4-methylphenyl Cyclopropanecarboxylate

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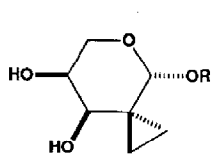
Summary: Glyceraldehyde, erythrose, and threose are condensed with the enolate derived from cyclopropanecarboxylic acid BHT ester. The conversion of two diastereomeric products of this condensation into new 2-spirocyclopropyl-substituted aldopyranoses is described.

Glycosidases, which participate in primary metabolism[1] and the processing of cell-surface carbohydrates,[2] constitute a broad class of enzymes which cleave glycosidic linkages, presumably through the intermediacy of an enzyme-bound glycosyl oxocarbonium intermediate.[3] In an earlier report[4] we described the synthesis of benzyl 2-spirocyclopropyl-L-arabinopyranoside (1) as a potential mechanism-based inactivator of β-galactosidases,[5] for which 2 is the normal substrate. Huber and coworkers[6] have recently described a related approach to the inactivation of glycosidases using 5-spirocyclopropylglycosides. Both classes of compound failed to produce time-dependent loss of glycosidase activity; in the former case this is due at least in part to the poor affinity of 1 for the active site of the enzyme (as evidenced by their poor activity as competitive inhibitors). Aside from the spirocyclopropyl group, the structural feature which distinguishes 1 from 3 is the absence of the terminal hydroxymethyl group. Though earlier studies[7] suggested that this substituent is not an essential component of active substrates accepted by the enzyme (both with respect to k_{cat} and K_M), the construction of 3 was warranted to allow a fair test of the original proposition.[4]

With a view towards screening a broad array of glycosidases, we sought a general method for constructing all four possible 2-spirocyclopropyl-substituted aldohexoses. Formally, this could be accomplished by an aldol condensation between cyclopropanecarboxaldehyde and erythrose or threose. However, cyclopropyl anions stabilized by an α-carbonyl are notoriously unsatisfactory because of their tendency to undergo self-condensation.[8] Seebach et al.[9] have discovered that the lithium enolate of 2,6-di-*tert*-butyl-4-methylphenyl cyclopropanecarboxylate (BHT ester 4) adds cleanly to a variety of electrophiles. We have extended these studies and demonstrated that 4 serves as a synthetic equivalent to the necessary aldol.



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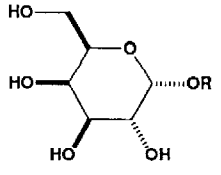

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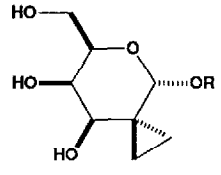

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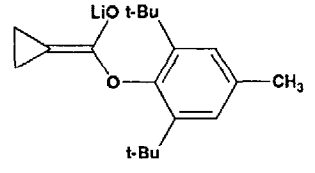
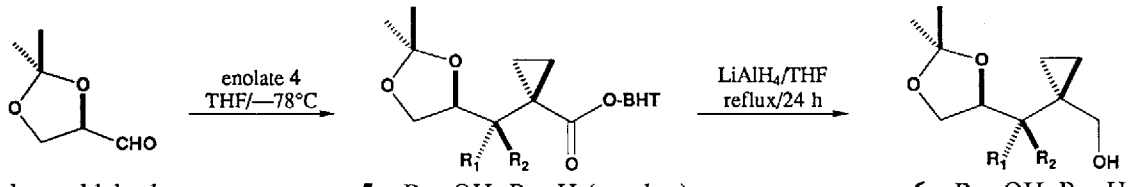


4

Enolate **4**, produced by exposure of the BHT ester of cyclopropanecarboxylic acid to *tert*-butyllithium in THF at —78°C, reacts with glyceraldehyde acetonide (see Scheme I) cleanly to afford **5** as a 12.5:1 (*erythro:threo*) mixture of diastereomers (71% yield). Reduction of the mixture ($LiAlH_4$/THF/24 h) leads to the diols **6a** and **6b** (80% yield) which can be separated by column chromatography. Assignment of *erythro*-**6a** as the major product by ^{1}H-NMR was confirmed by single crystal x-ray analysis of the minor isomer (see Figure 1).[10] The preferred sense of addition agrees with the predictions of Felkin.[11] Having established the efficiency and stereoselectivity of the addition of Seebach's enolate to a protected aldose, we turned our attention to the construction of the desired 2-spirocyclopropylaldohexoses.

Scheme I



glyceraldehyde acetonide

5a, R_1=OH, R_2=H (*erythro*)
5b, R_1=H, R_2=OH (*threo*)

6a, R_1=OH, R_2=H
6b R_1=H, R_2=OH

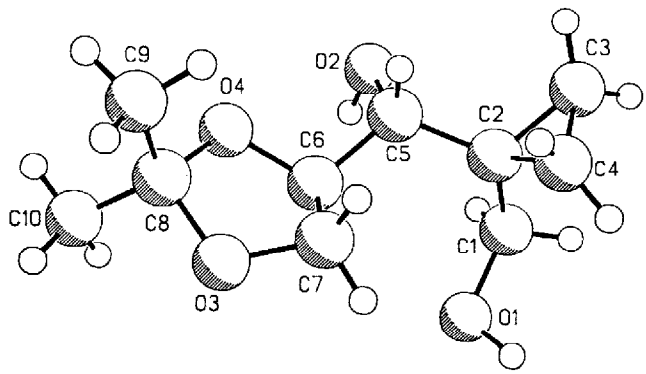
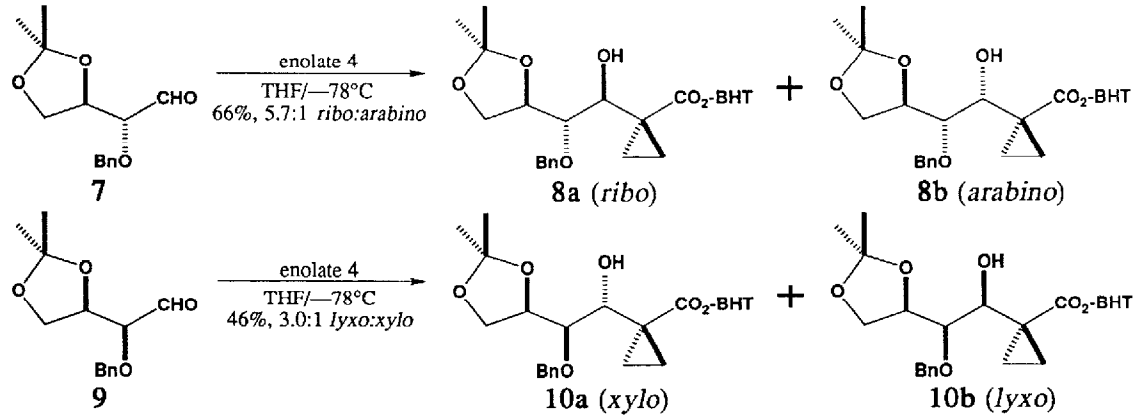


Figure 1. Structure of **6b** as determined by x-ray crystallography.[10]

Protected D-erythrose **7**, available from D-arabinose,[12] upon exposure to enolate **4** gives a 5.7:1 mixture (as determined by ^{1}H-NMR and analytical HPLC, 94:6 hexanes:EtOAc) of diastereomers **8a** and **8b** in 66% yield (see Scheme II). Similarly, protected D-threose **9**[13] gives **10a** and **10b** (3.0:1, 46% yield). The stereochemical assignments were made on the basis of several features in their ^{1}H-NMR spectra which were analogous to the spectra of **6a** and **6b**. In particular, the chemical shift of the 3-OH in the minor diastereomer (*threo* addition) was ≥0.6 ppm upfield of the corresponding proton in the major diastereomer in each case.[14]

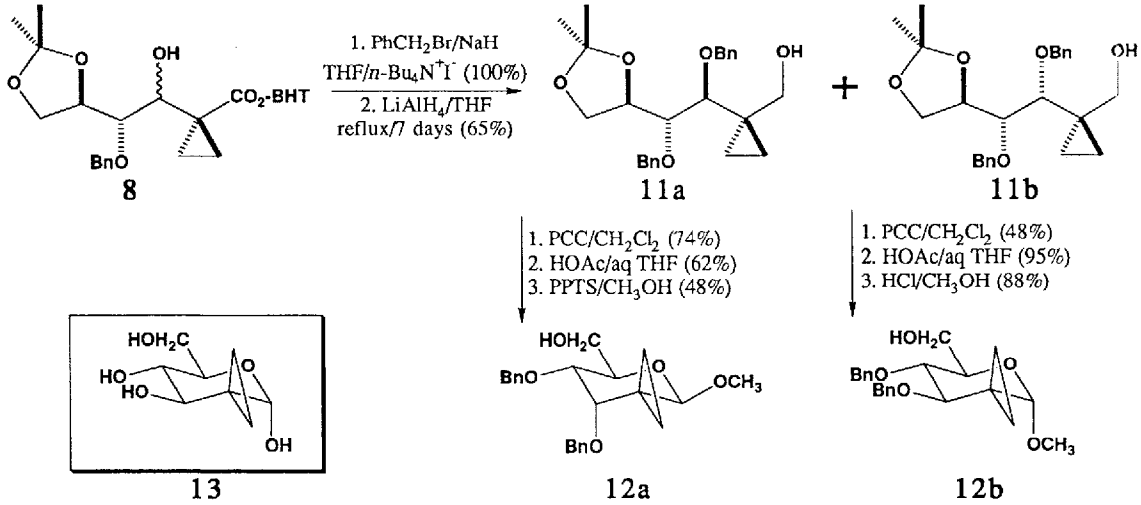
Further confirmation of the stereochemical assignments came from the conversion of **8** to the corresponding pyranosides **12** (see Scheme III): Benzylation[15] and reduction[16] afford **11a** and **11b**, which can be readily separated by column chromatography (3:1 hexanes:EtOAc). Oxidation, hydrolysis, and formation of the methyl glycoside for each diastereomer leads to **12a** and **12b**.

Scheme II



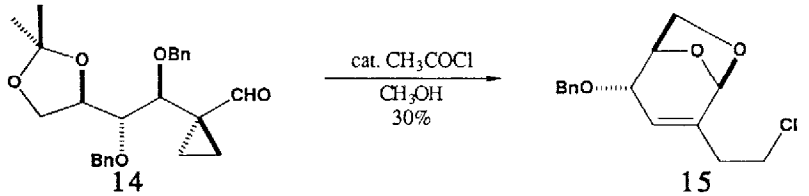
Compound **12a** ($[\alpha]_D^{23}$=—16.7° in benzene) exhibits $^3J_{H3\text{-}H4}$=2.7 Hz, indicating the *ribo* configuration, while **12b** ($[\alpha]_D^{23}$=+42.8° in benzene) has $^3J_{H3\text{-}H4}$=8.8 Hz, consistent with the *arabino* configuration. Hydrogenolysis (H_2/5% Pd-C/1:1 aq CH_3OH, 52%) and hydrolysis of **12b** gives the new sugar "2-spirocyclopropylglucose" (**13**).

Scheme III



Both isomers of **12** are quite sensitive to acid-catalyzed hydrolysis (as evidenced, for example, by rapid degradation from trace DCl in $CDCl_3$); this can be attributed to the adjacent cyclopropane stabilizing the oxocarbonium which results from solvolysis at the anomeric center.[17] An early attempt to produce **12a** directly from **14** (derived from PCC oxidation of **11a**) by treatment with catalytic CH_3COCl in dry CH_3OH gave several products, the most interesting of which is **15** (see Scheme IV, 30% yield). Though the order of steps which leads to **15** is not clear, the isolation of **15** suggests that the cyclopropyl-oxocarbonium ion is sufficiently electrophilic to react at the cyclopropane termini with a nucleophile (Cl^-).

Scheme IV



14 15

This is an efficient route to new 2-spirocyclopropyl-substituted aldoses. Further synthetic exploitation of the cyclopropane may afford new routes to other branched sugars. The activity of glycosides of **13** against glucosidases[19] will be disclosed presently.

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13. **9** is available in four steps from dimethyl D-tartrate; see (a) M. Ohno, K. Fujita, H. Nakai, S. Kobayashi, K. Inoue, S. Nojima *Chem. Pharm. Bull.* **1985**, *33*, 572; (b) D. R. Williams, F. D. Klingler *Tetrahedron Lett.* **1987**, *28*, 869.
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