1-Thio-1,2-*O*-isopropylidene Acetals: Novel Precursors for the Synthesis of Complex *C*-Glycosides

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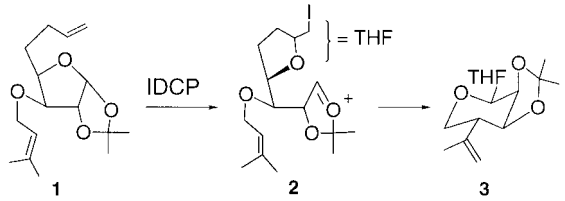
The implication of carbohydrates in important biological mechanisms has led to interest in carbomimetic structures as potential therapeutic agents and biochemical tools.[1,2] First generation analogues of the native carbohydrate with functional group replacements allow for systematic analysis of carbohydrate-receptor contacts and are natural starting points.[3] Among these are *C*-glycosides, derivatives in which the exocyclic acetal oxygen is replaced by a methylene.[4] *C*-glycosides are expected to have conformational and steric properties similar to those of the *O*-analogues[5,6] and are especially interesting as hydrolytically stable carbomimetics or molecular scaffolding.[7,8]

Application of existing *C*-glycoside methodologies[4,9] toward the synthesis of "true" *C*-glycosides[10] of complex structures such as glycolipids and disaccharides is not generally practical. The most common approach to such structures involves the coupling of sugar-derived THP components. This includes the addition of C1 nucleophiles to aglycon aldehydes, C1 radicals to activated or tethered aglycon alkenes, and aglycon nucleophiles to C1 electrophiles.[11−14] These methods are often limited by experimentally difficult or low-yielding coupling protocols and lengthy processing sequences for the THP precursors and the coupled product. Strategies based on C1-nucleophiles with aglycon aldehydes are the most general but are only reliable for 2-deoxy and Man-α-*C*-glycosides.[11] Extension to the *gluco* and *galacto* series is severely hampered by competing elimination of the 2-substituent. 2-Phenyl-sulfinyl-lithio glycals have been used to address this problem, and high yields with complex aldehydes have been obtained.[12] However, the synthesis and handling of these lithio reagents are not trivial, and the conversion of the coupled product to the *C*-glycoside is somewhat cumbersome. Herein we describe a highly convergent, de novo approach[15−17] to β-C-galactosides, which alleviates these problems.

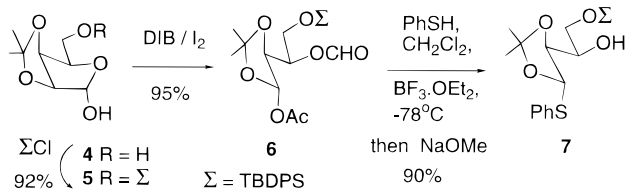
The methodology originates in our earlier observation that the iodoetherification of C5 allylated 1,2-*O*-isopropylidene furanose **1** on treatment with IDCP gave the linked bis-ether **3**, which may be regarded as a "1-deoxy-L-*galacto*pyranose."[18] The reaction was extremely facile and proceeded in high yield with formation of only a single THP isomer. The proposed mechanism for the formation of **3** involves the intramolecular capture of the isopropylidinated oxocarbenium ion **2** by the alkene residue. (Scheme 1). The efficiency of the reaction apparently derives from

Scheme 1



the cyclic nature of **2**. This led to interest in less substituted 1,2-*O*-isopropylidinated oxocarbenium ion precursors as potential annulating synthons for highly oxygenated structures. Toward this goal the 1-thio-1,2-*O*-isopropylidine **7** was prepared (Scheme 2).

Scheme 2



Compound **7** was obtained on large scale in four straightforward operations from commercially available D-lyxose.[19] Acetonation of D-lyxose provided the known derivative **4**[20] which was converted to the silyl ether **5**. The reaction of **5** with (diacetoxyiodo)-benzene (DIB)/I_2 according to the Suarez procedure, led to the acetate **6** in high yield.[21] Treatment of **6** with thiophenol and boron trifluoride etherate at low temperature, followed by basic hydrolysis of the crude product gave **7** in 90% from **6**.

The plan for *C*-glycoside synthesis requires the esterification of **7**, the glycone segment, with an acid **8** which corresponds to

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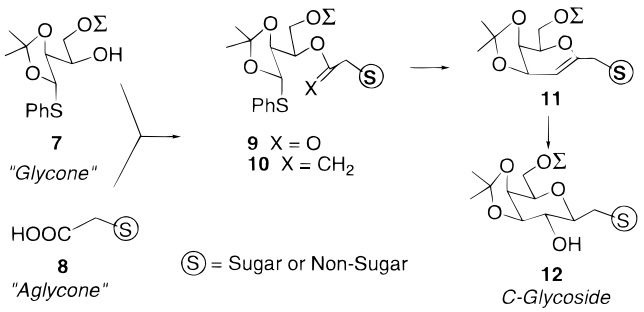
Scheme 3



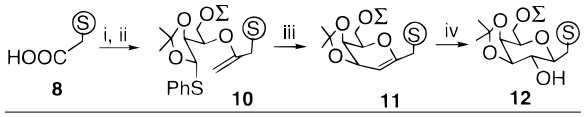
the aglycon. Olefination of the ester **9** to an enol ether **10**, followed by activation of the thioacetal in **10**, should lead to the C1-substituted glycal **11**. Finally hydroboration of **11** would provide a β-C-galactoside **12** (Scheme 3).

The protocol was applied to **7** and the acids **8a**−**e**. Compounds **8b**−**e** were prepared by standard procedures on known precursors.[22] Esterifications were promoted by DCC with DMAP as catalyst and performed in dry benzene.[23] The enol ethers were prepared by the Tebbe reaction on the esters.[24] Treatment of the enol ether with methyl triflate and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) in anhydrous dichloromethane led to a single endo-glycal product in all cases except for the reaction of **11c**, which gave a small amount of the exo-glycal. This was smoothly converted to the endo isomer on heating in benzene. *C*-glycoside **12e** illustrates that the protocol may be extended to aglycon components which contain amino groups. Notably, the sulfonyl-protecting group is compatible with the conditions of the Tebbe and the key cyclization reaction. In general the esterification-Tebbe sequence and the cyclization step each occurred in approximately 70−80% (see Table 1). Hydroboration of the glycals with BH_3·Me_2S, provided in each case the β-C-galactoside, as a single product in high yield. The galacto configuration of the *C*-glycoside was confirmed by ^{1}HNMR analysis of the hydroboration products or their acetate derivatives. The coupling constants for **12a** are representative and in agreement with those expected for the 3,4-*O*-isopropylidene galacto residue ($J_{1,2} = 9.9$, $J_{2,3} = 7.2$, $J_{3,4} = 4.5$, and $J_{4,5} = 2.2$ Hz).[25]

C-glycosides **12a**−**e** are analogues of, or model compounds for, important β-galactosides such as those contained in the blood group antigens, tumor-associated antigens, receptors for pathogenic bacteria, and glycolipids.[26,27] In particular, *O*-glycolipids related to **12a** and the *O*-saccharide of **12b** have recently attracted attention as selectin ligands.[28,29]

To illustrate the synthesis of other THP motifs, the thioacetal **7** was converted to **13** by alkylation with 1-bromo-2-methyl-2-butene. Treatment of **13** with IDCP in anhydrous dichloromethane

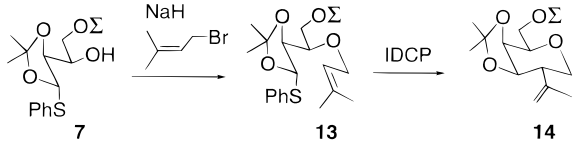
Table 1*



Aglycone Ⓢ	Enol Ether (% Yield)[a]	Glycal (% Yield)	C-Glycoside (% Yield)
$CH_3(CH_2)_{15}$ **8a**	**10a** (80)	**11a** (76)	**12a** (76)
8b	**10b** (83)	**11b** (72)[b]	**12b** (75)
8c	**10c** (62)	**11c** (72)[b, c]	**12c** (75)
8d	**10d** (72)	**11d** (86)	**12d** (77)
8e	**10e** (73)	**11e** (76)[b]	**12e** (84)

*(i) **7**, DCC, DMAP, PhH; (ii) Tebbe; (iii) MeOTf, DTBMP, CH_2Cl_2; (iv) BH_3·DMS then Na_2O_2 [a]1.2−1.5 equiv of acid used, yield based on **7**. [b]Reaction quenched at ca. 80% completion, based on recovered starting material. [c]Includes the product obtained from isomerization of the exo-glycal isomer (10%).

Scheme 4



provided a single THP **14**,[30] in which the isopropenyl substituent was *trans* to the *cis*-isopropylidenedioxy residue (Scheme 4). The stereochemical result is identical to that observed for the more substituted oxo-carbenium ion precursor **1**, and remains to be further investigated.

In summary a highly general synthesis of Gal-β-C-galactosides has been described. Noteworthy aspects are the highly convergent design, the easy availability and stability of the glycone synthon, and the applicability to a variety of complex aglycon segments. Glyconic analogues of these structures would be obtainable by using diastereomers of **7** which are available from the corresponding furanoses. It should be also possible to use 1-thio-1,2-*O*-isopropylidenes as synthons for highly oxygenated cyclohexanes and carbasugars. These directions are currently being pursued.

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Supporting Information Available: Synthetic procedures and physical data for compounds **7**, **8b**−**e**, **9a**, **9b**, **9d**, **9e**, **10a**−**d**, **11a**−**e**, **12a**−**e**, and **14** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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