

Stereoselective Synthesis of α -C-(alkynyl)-glycosides via Ring-opening of α -1,2-Anhydrosugars

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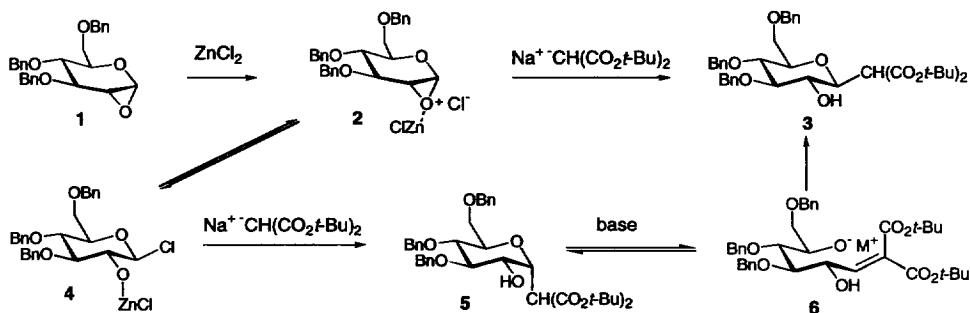
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Abstract: Ring-opening of an α -1,2-epoxide function in sugars with lithium alkynyl derivatives in the presence of zinc chloride proceeds with retention of configuration to afford α -C-(alkynyl)-glycosides in reasonable yields. © 1997 Elsevier Science Ltd.

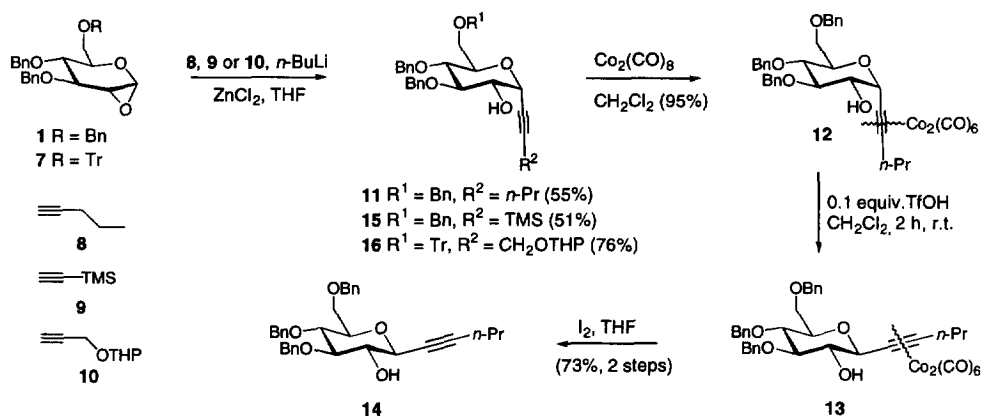
A recent study from this laboratory¹ revealed that ring-opening of 1,2-anhydro-3,4,6-tri-*O*-benzyl- α -D-glucopyranose **1** with an excess of sodio di-*tert*-butyl malonate and the weak Lewis acid zinc chloride proceeded stereoselectively to give the β -C-glucoside **3** in a yield of 75%. The formation of the β -C-glucoside **3** can be explained in several ways. The most obvious one involves stereoselective opening of intermediate **2**, resulting from activation of **1** with zinc chloride, by the malonate anion. On the other hand, the α -C-glucoside **5**, formed by α -attack of the malonate anion on the intermediate β -glucoside **4**, is converted under the prevailing basic conditions into the open-chain sugar derivative **6**, which undergoes an intramolecular Michael reaction to give the thermodynamically more stable β -C-glucoside **3**. Although the latter type of transformation is well established in sugar chemistry,² solid evidence³ in support of the possible existence of intermediate **4** is lacking.

Scheme 1



On the basis of the aforementioned mechanistic considerations, it was conceivable that a similar ZnCl_2 -assisted opening of the 1,2-anhydro function in **1** with an acetylenic instead of a malonate anion would lead to an anomeric mixture of *C*-alkynyl-D-glucopyranosides. In order to assess this proposition (see Scheme 2) the epoxide **1** was transferred to a cooled ($-70\text{ }^\circ\text{C}$) solution of the acetylenic anion (1.2 eq.), prepared *in situ* (*n*-BuLi, THF) from 1-pentyne **8**, followed by the addition of anhydrous ZnCl_2 (1.2 eq.). TLC-analysis, after 2 h at $20\text{ }^\circ\text{C}$, revealed complete conversion of **1** into one major component and a small amount of a polar by-product, which comigrated with the hydrolysis product of **1**. ^1H - and ^{13}C -NMR spectroscopy of the purified (silica gel) main product (55%) showed the presence of one diastereoisomer. In addition, the ^1H -COSY spectrum⁴ of the corresponding *O*-2 acetylated derivative of **11** showed a signal for the anomeric proton at δ 4.98 ppm with $J_{1,2}$ 5.8 Hz, the magnitude of which is in agreement with an axially orientated pentynyl group in compound **11**. The stereochemistry of the pentynyl group was also indirectly confirmed by epimerization⁵ of **11** into the corresponding β -*C*-glucoside **14**. Treatment of **11** with dicobaltoctacarbonyl resulted in the dicobalthexacarbonyl complex **12**, which was epimerized into the β -complex **13**⁶ under the influence of a catalytic amount of triflic acid. Decomplexation of **13** with iodine led to the isolation of **14**, the β -configuration of which was unambiguously established by the ^1H -COSY data⁴ (e.g., $J_{1,2}$ 9.9 Hz) of its acetylated derivative. The validity of the stereoselective ring-opening is illustrated further (see Scheme 2) by the successful α -*C*-glycosidation of the fully benzylated epoxide **1** and 3,4-di-*O*-benzyl-6-*O*-trityl-epoxide **7**⁷ with the respective anions derived from trimethylsilylacetylene (**9**) and THP-protected propargyl alcohol (**10**) to give the functionalized α -*C*-glucosides **15** and **16**.

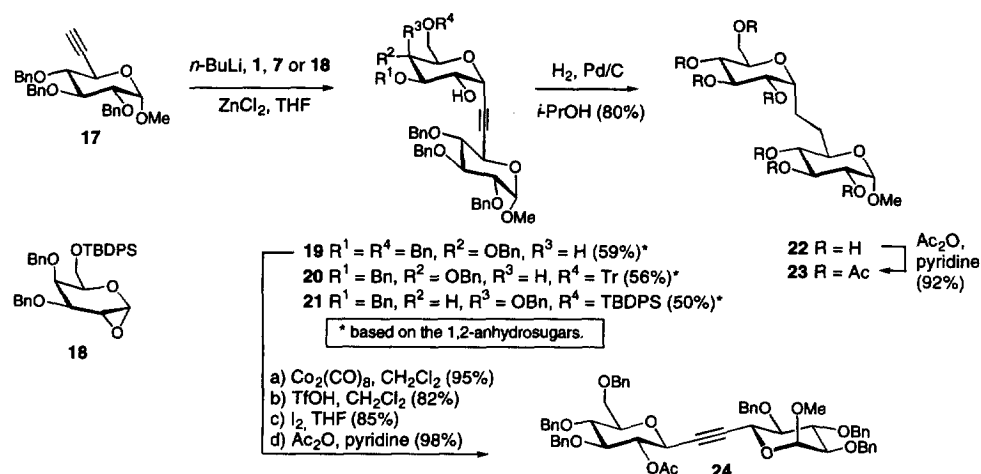
Scheme 2



Apart from this, it was gratifying to establish that the α -*C*-glycosidation procedure gave ready access⁸ (see Scheme 3) to the α -(1'-6)-*C*-disaccharide **22**, the carbon analog of methyl isomaltoside. Thus, ring-opening of the epoxide **1** with the anion derived from known⁹ fully benzylated methyl 6,7-

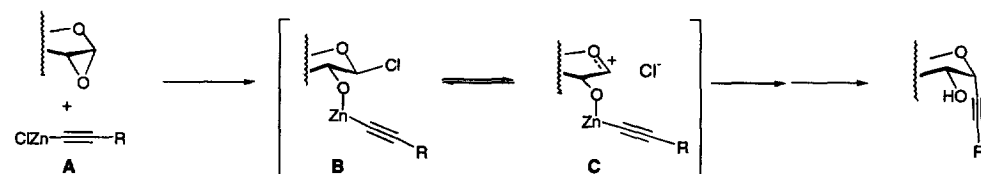
dideoxy- α -D-*gluco*-hept-6-ynopyranoside **17** led to isolation of partially protected dimer **19**, the α -(1'-6)-linkage of which was confirmed by NMR-spectroscopy ($J_{1,2}$ 6.0 Hz) of its 2'-OAc derivative. Removal of the benzyl groups and reduction of the acetylenic moiety in **19** with H_2 and catalytic palladium on carbon gave, after acetylation of **22**, homogeneous **23**, the 1H -COSY spectrum of which was in full accord with the proposed structure. In addition, epimerization of **19**, as mentioned earlier for the conversion of **11** into **14**, followed by acetylation gave the β -C-disaccharide **24** ($J_{1,2}$ 10.0 Hz) in an overall yield of 64%. Similarly, the 6'-O-trityl protected α -C-dimer **20** was readily obtained by ring-opening of **7** with **17**. Finally, glycosylation of **17** with the 6-O-*tert*-butyldiphenylsilyl protected D-*galacto* epoxide **18**, prepared by benzylation of 6-O-*tert*-butyldiphenylsilyl galactal¹⁰ and subsequent epoxidation with 3,3-dimethyldioxirane, proceeded also in a stereoselective fashion to give the α -C-dimer **21** in a comparable yield.

Scheme 3



The results obtained by the α -C-glycosidation method presented in this paper may be rationalized by the course of events depicted in Scheme 4. The alkynyl-zinc complex **A**, readily formed by reaction of a lithium alkynylide with zinc chloride, interacts with a 1,2-anhydrosugar derivative to

Scheme 4



give the β -chloride complex **B** which is in equilibrium with the ion-pair **C**. Intramolecular α -directed delivery of the alkynyl moiety in **C** will eventually result in the formation of α -C-glycosides.

In conclusion, the stereoselective ring-opening described in this paper presents an attractive route to the synthesis of versatile sugar synthons. A detailed study on the scope and mechanism of this α -C-glycosidation approach will be published in due course.

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3. The possible occurrence of intermediate **4** or its ion-pair (*cf.* complex **C** in scheme 4) may be surmised (see: C.M. Timmers, G.A. van der Marel, J.H. van Boom, *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 609) by the fact that ZnCl_2 -mediated condensation of epoxide **1** with primary alcohols affords a mixture of α and β anomers.
4. Relevant analytical data: **11** R_f 0.31 (25% EtOAc/light petroleum), MS (ESI): $m/z=523$ ($\text{M}+\text{Na}$) $^+$, 539($\text{M}+\text{K}$) $^+$. Acetylated **11** $^1\text{H-COSY}$ (CDCl_3): δ 7.35-7.12 (m, 15H, CH_{arom}); 4.98 (dt, 1H, H-1, $J_{1,2}$ 5.8 Hz, $J_{1,9}$ 2.1 Hz); 4.87 (dd, 1H, H-2, $J_{2,3}$ 9.7 Hz); 4.90-4.49 (m, 6H, CH_2 Bn); 3.98 (t, 1H, H-3); 3.80-3.65 (m, 4H, H-4, H-5, 2x H-6); 2.21 (dt, 2H, H-9); 2.01 (s, CH_3 Ac); 1.53(m, 2H, H-10); 1.01 (t, 3H, H-11); Acetylated **14** $^1\text{H-COSY}$ (CDCl_3): 7.40-7.10(m, 15H, CH_{arom}); 5.11 (dd, 1H, H-2, $J_{2,1}$ 9.8 Hz, $J_{2,3}$ 9.3 Hz); 4.81-4.50 (m, 6H, CH_2 Bn); 4.03 (dt, 1H, H-1, $J_{1,9}$ 2.0 Hz); 3.77-3.66 (m, 3H, H-4, 2x H-6); 3.61 (t, 1H, H-3); 3.45 (m, 1H, H-5); 2.15 (dt, 2H, H-9); 2.03 (s, CH_3 Ac); 1.48 (m, 2H, H-10); 0.93 (t, 3H, H-11). **19**: R_f 0.57 (50% EtOAc/light petroleum), MS (ESI): $m/z=909$ ($\text{M}+\text{NH}_4$) $^+$, 914 ($\text{M}+\text{Na}$) $^+$. Acetylated **19** $^1\text{H-COSY}$ (CDCl_3): δ 7.37-7.10 (m, 30H, CH_{arom}); 5.07 (dd, 1H, H-1', $J_{1,2}$ 6.0 Hz, $J_{1,5}$ 1.6 Hz); 5.00-4.44 (m, 12H, CH_2 Bn); 4.92 (dd, 1H, H-2', $J_{2,3}$ 9.9 Hz); 4.54 (d, 1H, H-1, $J_{1,2}$ 3.1 Hz); 4.42 (dd, 1H, H-5, $J_{5,4}$ 9.8 Hz); 3.98 (m, 1H, H-5'); 3.90 (t, 1H, H-3'); 3.89 (t, 1H, H-3); 3.74 (dd, 1H, H-6 $_{\text{A}}$); 3.68 (dd, 1H, H-4'); 3.64 (dd, 1H, H-6 $_{\text{B}}$); 3.51 (m, 2H, H-2, H-4); 3.41 (s, 3H, OCH_3); 1.91 (s, 3H, CH_3 Ac).
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6. R_f values (10% EtOAc/light petroleum) of the cobalt complexes **12** and **13** are 0.38 and 0.54, respectively.
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