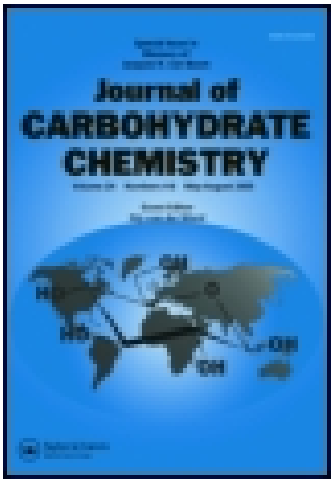

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Benzyl Ethers as Nucleophiles: From Hydroxy Cyclooctanes Toward Bridged C-Furanosides

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Attempted Lewis acid-mediated opening of a benzyloxy-functionalized eight-membered ring epoxide resulted in an intramolecular nucleophilic attack by a favorably disposed benzyloxy group to give a bridged furanose. A corresponding intramolecular nucleophilic attack of a benzyloxy group in a triflated cyclooctenol again gave a bridged furanose derivative.

Keywords Hydroxy cyclooctanes; Bridged C-furanosides

The protection of hydroxyl functionalities as benzyl ethers by means of deprotonation followed by reaction with a benzyl halide represents a widespread method particularly in carbohydrate chemistry and oligosaccharide synthesis.[1] The resulting benzyl ethers exhibit high stability under acidic, basic, and oxidative conditions and are readily removed employing catalytic hydrogenation. Since anionic benzyloxy groups have bad leaving group properties, they may undergo 1,2-eliminations only under strongly basic conditions if favorable steric and electronic prerequisites are met. The latter aspect relates particularly to acidic vicinal protons that enhance the elimination tendency of a benzyl ether substituent ultimately as benzyl alcohol.

Reactions in which the benzyl ether oxygen itself can act as a nucleophile leading to ring closures are rarely described. The nucleophilic opening of an iodonium ion intermediate **1** by the benzyl ether oxygen with concomitant

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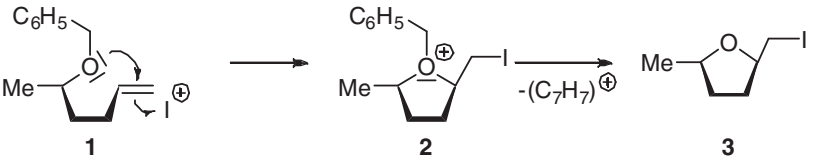
This paper is dedicated to Professor Robert V. Stick on the occasion of his 65th birthday.



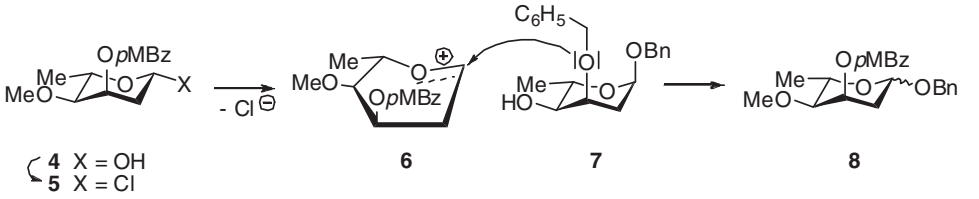
Scheme 1. Nucleophilic opening of an iodonium intermediate by the benzyl ether oxygen.

cleavage of the benzyl residue was observed and elaborated by Bartlett et al. as a ring closing reaction for the construction of *cis*-2,5 disubstituted tetrahydrofuran derivatives such as **3** (Sch. 1).[2]

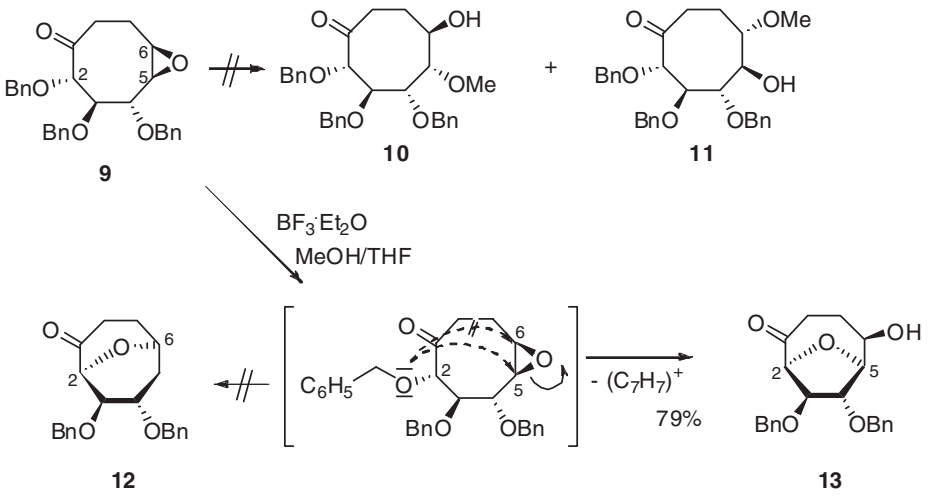
A corresponding transbenzylation of the 2,6-dideoxy glycopyranosyl chloride **5**, obtained from **4** and oxalyl chloride, in an attempted glycosylation reaction with the benzylated acceptor saccharide **7** was observed. This resulted in 63% of an anomeric mixture of benzyl glycosides **8** (α : 27%, ß: 39%) apparently via attack of the benzyloxy group at the intermediate oxocarbenium ion structure **6** (Sch. 2).[3]

Along studies toward functionalized cyclooctanoid natural product analogues,[4–6] several interesting and corresponding examples of intramolecular tetrahydrofuran formations could be observed. Eight-membered ring systems feature a considerably more flexible carbocyclic framework compared to their five- and six-membered counterparts.[7,8] Thus, a benzylether oxygen can interact much more easily with electrophilic centers provided sufficient spatial proximity is given and a thermodynamically stable ring system can be formed.

Upon treatment of epoxide **9**[5] with boron trifluoride in methanol/tetrahydrofuran, none of the expected regioisomeric methyl ethers **10** and **11** could be isolated. Instead, a bicyclic ether **system** resulted via epoxide opening by the 2-benzyloxy group of **9** to give exclusively one product in a good yield of 79%. It is assumed that the cleavage of the benzyl substituent occurred simultaneously and presumably released the mesomerically stabilized cation $(C_7H_7)^+$. Alternatively, intramolecular attack at C-6 would give the bridged six-membered ring system **12**, whereas opening at C-5 would result in formation of the bridged five-membered compound **13**. Since the ^{1}H NMR data (shifts and couplings) are ambiguous, there is evidence by the ^{13}C NMR data. In



Scheme 2. Transbenzylation instead of glycosylation of 2,6-dideoxy-ribohexopyranosides.

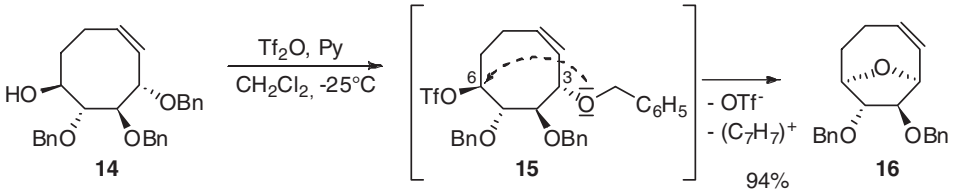


Scheme 3. Regioselective intramolecular opening of an epoxide by a benzyl ether oxygen.

keeping with findings in structurally related eight-membered derivatives,[4–6] the resonances of the ether carbons as well as the high field shift of the tertiary alcohol carbon C-6 (δ 71.44) give evidence for formation of the bridged furan structure **13**.

In another experiment alcohol **14**[4,5] was treated with triflic anhydride in pyridine/dichloromethane at –25°C to give the corresponding triflate. This highly reactive intermediate **15** could not be isolated. Again, intramolecular attack of the 3-O-benzyl group at C-6 from the bottom of the ring plane substituted the triflate. Under release of the benzyl cation $(C_7H_7)^+$, the bicyclic ether **16** was obtained in 94% yield (Sch. 4).

In summary, we have shown two examples of intramolecular ring closures based on the nucleophilicity of benzyloxy groups in conformationally flexible medium-sized ring systems. The novel bridged tetrahydrofuran compounds were obtained in good to excellent yields without detection of any byproducts. Apart from the interesting synthetic access to the isolated compounds and the potential applicability of this approach in natural product synthesis, they represent at the same time bridged C-furanoside derivatives due to their



Scheme 4. Intramolecular triflate substitution by a benzyl ether oxygen.

oxygenated substitution pattern and might therefore be useful building blocks for the construction of unnatural nucleotides.

For general methods cf. references 4–6.

(2S, 3R, 4S, 5S, 6R)-2,5-Anhydro-3,4-dibenzyloxy-cyclooctan-2,5,6-triol-1-one (13)

A solution of (2*S*, 3*R*, 4*S*, 5*R*, 6*R*)-2,3,4-tribenzyloxy-5,6-epoxy-cyclooctane **9**[5] (7.9 mg, 17 μmol) in tetrahydrofuran (0.8 mL) was treated with $BF_3 \cdot Et_2O$ (3.3 μL, 3.7 mg, 26 μmol) and methanol (0.1 mL) for 3 h at 70°C. Addition of some drops of triethylamine and dilution with dichloromethane (1 mL) resulted in the raw material. This was purified by column chromatography on silica gel with EtOAc/pet. ether 1:2 to give **13** (5 mg, 14 μmol, 79%) as a colorless syrup. $[\alpha]_{546}^{20}$ 82.7 (*c* 0.36 in $CHCl_3$). δ_H (400 MHz; $CDCl_3$) 1.87–1.92 (2H, m H7a,b), 2.34–2.40 (1H, m, H8b), 4.24 (1H, broad s, H4), 4.42, 4.43 (2 × 1H, 2 × d, OCH_2), 4.46 (1H, dd, $J_{4,5} = 0.5$, $J_{5,6} = 5.1$, H5), 4.50 (1H, ddd, $J_{2,3} = 8.9$, $J_{3,4} = 2.0$, H3), 4.54, 4.62 (2 × 1H, 2 × d, OCH_2), 4.69 (1H, d, $J_{2,3} = 8.9$, H2), 7.27–7.38 (10H, m, Ar). δ_C (100 MHz; $CDCl_3$) 27.41 (1C, C7), 37.72 (1C, C8), 71.44 (1C, C6), 71.67, 73.12 (2C, OCH_2), 84.13 (1C, C4), 85.97 (1C, C2), 87.23 (1C, C5), 87.28 (1C, C3), 127.97, 128.04, 128.59 (10C, Ar), 137.32, 137.67 (2C, Ar), 211.79 (1C, C1). Maldi-Tof calc. for $C_{22}H_{24}O_5$ 368.46, found $[M+Na]^+$ 391 $[M+K]^+$ 407. ν_{max}(thin-film)/cm^{-1} 1716 (C=O).

cis-(3S, 4R, 5R, 6R)-3,6-Anhydro-4,5-dibenzyloxy-cycloocten (16)

A solution of cis-(1*S*, 2*R*, 3*R*, 4*S*)-2,3,4-tribenzyloxy-cyclooct-5-en-1-ol **14**[4,5] (55 mg, 124 μmol) in dichloromethane (2 mL), and pyridine (40 μL, 40 mg, 495 μmol) was cooled to –25°C. After addition of triflic anhydride (25 μL, 42 mg, 148 μmol) and stirring at –20°C for 1 h, the mixture was slowly warmed to rt and the solvents evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with EtOAc/pet. ether 1:10 to give **16** (39 mg, 116 μmol, 94%) as a colorless syrup. $[\alpha]_{546}^{20}$ –129.6 (*c* 1 in $CHCl_3$). δ_H (500 MHz, C_6D_6) 1.55–1.61 (1H, m, H7b), 1.85–1.99 (2H, m, H8b, 7a), 2.28–2.34 (1H, m, H8a), 4.01 (1H, dd, $J_{4,5} = 4.3$, $J_{5,6} = 2.5$, H5), 4.23, 4.26 (2 × 1H, 2 × d, OCH_2), 4.33 (1H, dd, $J_{3,4} = 6.8$, $J_{4,5}$ 4.3 H4), 4.37, 4.41 (2 × 1H, 2 × d, OCH_2), 4.45 (1H, dd, $J_{5,6} = 2.5$, H6), 4.69 (1H, dd ~ t, $J_{2,3} = 5.7$, $J_{3,4} = 6.8$, H3), 5.63–5.66 (1H, dd, $J_{1,2} = 11.7$, $J_{2,3} = 5.7$, H2), 5.75 (1H, ddd, $J_{1,2} = 11.7$, H1), 7.07–7.32 (1OH, m, Ar). δ_C (100 MHz; C_6D_6) 25.35 (1C, C8), 33.32 (1C, C7), 71.93, 72.64 (2C, OCH_2), 78.26 (1C, C3), 81.91(1C, C6), 88.36 (1C, C5), 89.00 (1C, C4), 127.95, 127.99, 128.55, 128.58 (10C, Ar), 130.32 (1C, C2), 132.01 (1C, C1), 138.81, 138.92 (2C, Ar). Maldi-Tof calc. for $C_{22}H_{24}O_3$ 336.46, found $[M+Na]^+$ 359, $[M+K]^+$ 375.

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