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Short Note

(1*R*)-2,3,4,6-Tetra-*O*-benzyl-1-*C*-allyl-1-deoxy-1-*C*-(2-thiazolyl)-D-galactopyranose

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Abstract: We have previously reported that thiazolylketol acetates, synthesized by the addition of 2-lithiothiazole to sugar lactones followed by acetylation, are efficient glycosyl donors affording *O*-, *N*-, *P*-, and *C*-glycosides. After the first example of *C*-glycosidation recently described by us, we report here on the unexpected outcome of the reaction of a thiazolylketol acetate with allyltrimethylsilane in the presence of trimethylsilyl triflate. The obtained intermediate, an intramolecular *N*-thiazolium salt, could be stereoselectively converted into the desired allyl *C*-thiazolylketoside.

Keywords: carbohydrates; *C*-glycosides; glycosylation; thiazole

1. Introduction

The *C*-glycosides are the stable isosteres of the naturally occurring *O*-glycosides because the presence of a carbon instead of an oxygen atom at the anomeric position leads to glycosides that are not hydrolyzed by acids or glycosidases. Therefore, the *C*-glycosides can be used instead of the corresponding oxygen-linked glycoconjugates when more stable sugar derivatives are required for biological or pharmacological studies. To this end, a large number of synthetic methodologies were developed during the last forty years [1–19], although most of them were exploited only for the preparation of alkyl and aryl *C*-aldosides. In fact, the synthetic approaches to *C*-ketosides were barely explored, probably because the stereoselectivity at the anomeric position is difficult to predict and control.

The D-*galacto* configured thiazolylketol acetate **2** (Scheme 1), prepared from D-galactonolactone **1** as described [20], and the other pyranose and furanose analogues [21], allowed to efficiently synthesise *O*-, *N*-, and *P*-glycosides of the corresponding ulose (**3** and **5**) or ulosonic acid (**4** and **6**) derivatives through stereoselective glycosylation, thiazole-to-formyl conversion, and formyl reduction or oxidation [21]. Despite these good results, the first *C*-glycosylation of the thiazolylketol acetates—the reaction of **2** with trimethylsilyl cyanide in the presence of TMSOTf to give the *C*-uloside **7** (Scheme 1)—was reported by us three decades after the disclosure of the glycosyl donor **2** [22]. Aiming to gain access to more complex *C*-glycoside derivatives, we have envisaged the reaction of thiazolylketol acetate **2** with another well-known carbon nucleophile, namely the allyltrimethylsilane. However, contrary to the *C*-glycosidation carried out with more common glycosyl donors, i.e., lacking the thiazole moiety [23,24], we observed the formation of an intramolecular *N*-thiazolium salt from which the target allyl *C*-glycoside could be obtained upon treatment with tetrabutylammonium fluoride.

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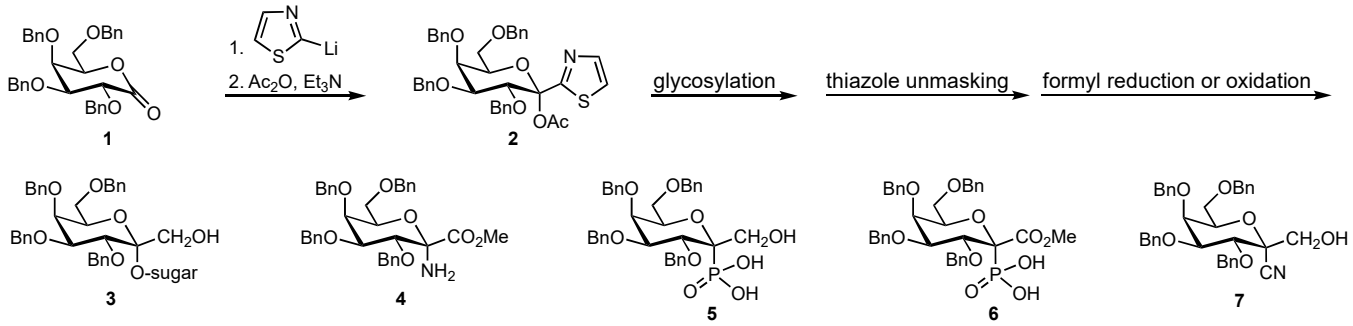
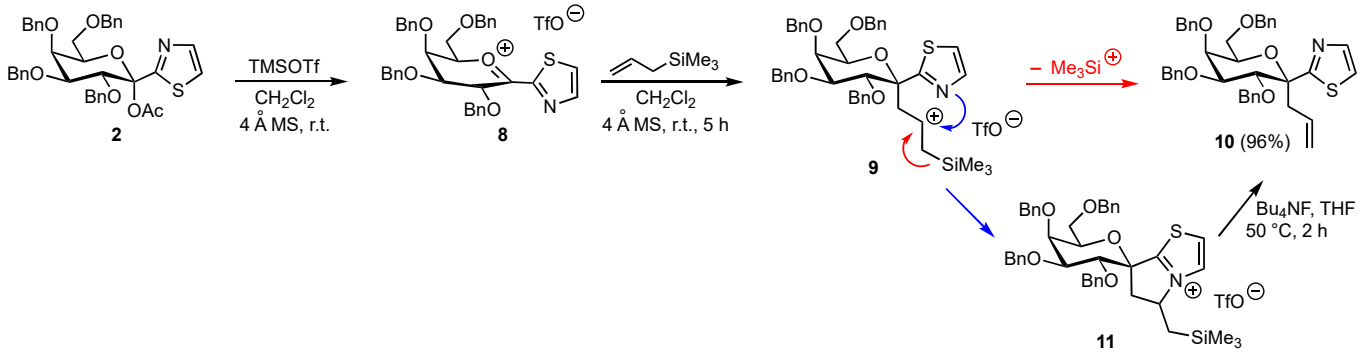


Scheme 1. Previous syntheses of glycosides **3**–**7** from the thiazolylketol acetate **2**.

2. Results and Discussion

The thiazolylketol acetate **2** was treated with 10 equiv. of commercially available allyltrimethylsilane in the presence of trimethylsilyl triflate (TMSOTf) and 4 Å powdered molecular sieves for 5 h at room temperature. Then, the reaction mixture was neutralized by adding triethylamine and filtered through a pad of Celite to give the intramolecular *N*-thiazolium salt **11** in almost quantitative yield instead of the expected allyl *C*-glycoside **10** (Scheme 2). The structure of **11** could be established by NMR analysis since its proton spectrum showed the signal of the trimethylsilyl group at 0.18 ppm (singlet, 9 H) while the signals of the thiazole hydrogens were significantly shifted downfield (doublets, 8.52 and 8.04 ppm) due to the positive charge onto the heterocycle (Figure S1). Moreover, in the ^{13}C-NMR spectrum was present a quartet at 120.8 ppm with a large coupling constant (320 Hz) typical of the trifluoromethanesulfonate (triflate) anion (Figures S2 and S3). The presence of the triflate anion was confirmed by the signal at 78.7 ppm in its ^{19}F-NMR spectrum (Figure S4). Therefore, after the addition of the anomeric oxycarbenium ion **8** to the alkene leading to the carbocation **9**, the latter did not form the new double bond through release of the trimethylsilyl cation as expected (Scheme 2, red arrows) but underwent the intramolecular attack of the thiazole nitrogen to form **11**, a rather stable salt featuring a fused five-member ring (Scheme 2, blue arrows).



Scheme 2. *C*-glycosidation of the thiazolylketol acetate **2** with allyltrimethylsilane followed by desilylation with tetrabutylammonium fluoride.

Fortunately, we found that upon reaction of the crude *N*-thiazolium salt **11** with tetrabutylammonium fluoride in THF at 50 °C for 2 h, compound **10** could be recovered in 96% overall yield after column chromatography. As already observed for the *O*-, *N*-, *P*-, and *C*-glycosidation of the D-*galacto*-configured thiazolylketol acetate **2** [21,22], the allyl *C*-glycoside **10** was obtained as a single α-D (axial) anomer. The anomeric configuration was proved by the positive nuclear Overhauser effect (nOe) between one of the -CH_2- hydrogens of the allyl group and the axially oriented H-3 and H-5 protons of the pyranose ring, which adopts the usual $^4C_1$ conformation (Figure S5). Irradiation of the signal at

2.85 ppm showed a significant increase of the signals at 3.88 ppm (H-3) and 3.93 ppm (H-5), besides the obvious effect on the geminal hydrogen at 3.60 ppm.

3. Materials and Methods

Anhydrous CH_2Cl_2 (99.8%), anhydrous THF (99.9%), allyltrimethylsilane (98%), trimethylsilyl triflate (99%), triethylamine (99%), tetrabutylammonium fluoride trihydrate (98%), acetic acid (99.99%), powdered 4 Å molecular sieves (5 μm average particle size), and Celite were purchased from Sigma-Aldrich (Saint-Quentin-Fallavier, France). The reactions were monitored by TLC on silica gel 60 F_{254} (Merck, Molsheim, France) with detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel 60 (40–63 μm, Merck). Optical rotations were measured at 20 ± 2 °C in the stated solvent; $[\alpha]_D$ values are given in deg mL g^{-1} dm^{-1}. ^{1}H NMR (300 and 400 MHz), ^{13}C NMR (75 and 100 MHz), and ^{19}F NMR (282 MHz) spectra were recorded in $CDCl_3$ at room temperature with a Varian Gemini 300 MHz and a Bruker Avance 400 MHz spectrometer. In the ^{1}H NMR spectra reported below, the n and m values quoted in geminal or vicinal proton–proton coupling constants $J_{n,m}$ refer to the number of the corresponding sugar protons. FT-IR spectra were recorded using a Perkin Elmer Spectrum 3 instrument equipped with an ATR accessory. High-resolution mass spectrometry (Waters Micromass Q-TOF, Waters Corp., Milford, MS, USA) analyses were carried out at the "Laboratoire de Mesures Physiques" (University of Montpellier).

*(1R)-2,3,4,6-Tetra-O-benzyl-1-C-allyl-1-deoxy-1-C-(2-thiazolyl)-*D*-galactopyranose (***10***)*

A mixture of **2** (500 mg, 0.75 mmol), activated 4 Å powdered molecular sieves (0.50 g), and anhydrous CH_2Cl_2 (7.5 mL) was stirred at room temperature under a nitrogen atmosphere for 10 min, then allyltrimethylsilane (1.20 mL, 7.50 mmol) and trimethylsilyl triflate (140 μL, 0.75 mmol) were added. The mixture was stirred at room temperature for 5 h, then diluted with triethylamine (0.30 mL) and CH_2Cl_2 (50 mL), filtered through a pad of Celite, and concentrated to afford crude **11**. A solution of the latter and nBu$_4$NF·3H$_2$O (2.37 g, 7.50 mmol) in anhydrous THF (7.5 mL) was stirred at 50 °C for 2 h, then cooled to room temperature, diluted with acetic acid (2 mL), and concentrated. The residue was eluted from a column of silica gel with 8:1 cyclohexane-AcOEt to give **10** (467 mg, 96%) as a colorless syrup; $[\alpha]_D = -7.9$ (c = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz): δ 7.77 (d, 1H, J = 4.0 Hz, Th), 7.40–7.26 (m, 21H, 4 Ph, Th), 5.69 (dddd, 1H, J = 5.6, 8.0, 10.2, 17.2 Hz, C*H*=CH$_2$), 5.17 (dddd, 1H, J = 1.0, 1.5, 2.0, 17.2 Hz, 1 H of CH=C*H*$_2$), 5.08 and 4.67 (2 d, 2H, J = 12.0 Hz, PhC*H*$_2$), 5.02 (dddd, 1H, J = 1.0, 1.0, 2.0, 10.2 Hz, 1 H of CH=C*H*$_2$), 4.77 (s, 2H, PhC*H*$_2$), 4.54 and 4.48 (2 d, 2H, J = 11.6 Hz, PhC*H*$_2$), 4.54 and 4.25 (2 d, 2H, J = 10.4 Hz, PhC*H*$_2$), 4.10 (dd, 1H, $J_{3,4}$ = 2.8, $J_{4,5}$ = 0.8 Hz, H-4), 4.06 (d, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 3.93 (ddd, 1H, $J_{5,6a}$ = 7.6, $J_{5,6b}$ = 5.2 Hz, H-5), 3.88 (dd, 1H, H-3), 3.77 (dd, 1H, $J_{6a,6b}$ = 9.2 Hz, H-6a), 3.63 (dd, 1H, H-6b), 3.60 (dddd, 1H, J = 1.0, 1.5, 5.6, 14.8 Hz, 1 H of C*H*$_2$-CH=), and 2.85 (dddd, 1H, J = 1.0, 1.0, 8.0, 14.8 Hz, 1 H of C*H*$_2$-CH=). ^{13}C NMR (100 MHz): δ 174.7 (C), 141.9 (CH), 139.3 (C), 138.6 (C), 138.5 (C), 138.1 (C), 132.8 (CH), 128.45 (CH), 128.42 (CH), 128.3 (CH), 128.23 (CH), 128.20 (CH), 127.83 (CH), 127.77 (CH), 127.6 (CH), 127.51 (CH), 127.47 (CH), 127.35 (CH), 127.29 (CH), 119.9 (CH), 118.0 (CH_2), 82.2 (CH), 82.1 (C), 81.0 (CH), 75.9 (CH_2), 74.6 (CH), 74.4 (CH_2), 73.6 (CH_2), 72.8 (CH_2), 71.6 (CH), 68.8 (CH_2), and 33.4 (CH_2). FT-IR (cm^{-1}): 3088, 3064, 3030, 2917, 2868, 1496, 1453, 1361, 1093, 992, 913, 731, and 694. HRMS (ESI/Q-TOF): m/z calcd. for $C_{40}H_{42}NO_5S$ $[M+H]^+$ 648.2778, found 648.2780.

4. Conclusions

The allyl *C*-thiazolylketoside **10** constitutes a versatile building block since it is bearing two orthogonal functional groups. In fact, while the thiazole ring can be easily converted

into a formyl group, which is then reduced or oxidized, the allyl moiety is a suitable substrate for the well-known dihydroxylation (leading to a vicinal diol) [25–27] or cross-metathesis (affording longer chain derivatives) reactions [28,29]. Moreover, it is expected that all the above-mentioned transformations will take place, leaving unaltered the configuration of the starting material **10** due to the quaternary nature of the anomeric carbon.

Supplementary Materials: The following supporting information can be downloaded at ^{1}H- and ^{13}C-NMR spectra of **11** (Figures S1−S3); ^{19}F-NMR spectrum of **11** (Figure S4); NOEDIF NMR spectrum of **10** (Figure S5); ^{1}H- and ^{13}C-NMR spectra of **10** (Figures S6 and S7); and HRMS and IR spectra of **10** (Figures S8 and S9).

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Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflicts of interest.

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