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Note

An unusual course of thioglycoside activation with bromine: synthesis and crystal structure of 4-*O*-acetyl-2-bromo-2,3,6-trideoxy-3-*C*-methyl-3-trifluroacetamido-α-L-altropyranosyl bromide

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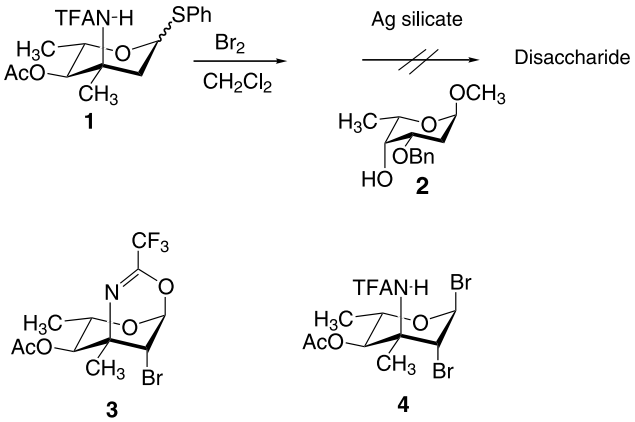
Abstract

Bromine activation of phenyl 4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-1-thio-α,β-L-*ribo*-hexopyranoside and attempted coupling with an acceptor in the presence of silver silicate gave an unusual bicyclic product, 2-trifluoromethyl-(4-*O*-acetyl-2-bromo-2,3,6-trideoxy-3-C-methyl-α-L-altrohexopyrano)-[3,2,1-*d*,*e*]-2-oxazine, instead of the expected disaccharide. Detailed investigation supported by X-ray crystallographic analysis showed that a trans dibromide is an intermediate in this reaction and that the dibromide is likely formed from a glycal that is generated by elimination during the coupling step.

Keywords: Bromodihydrooxazine; Bromine activation of thioglycosides; Cororubicin

Thioglycosides are among the most widely used glycosyl donors in carbohydrate chemistry.[1] Since the initial work of Ferrier and co-workers,[2] numerous methods for the synthesis and activation of thioglycosides for use in oligosaccharide synthesis have been developed.[3] During the course of our synthesis of the cororubicin trisaccharide,[4] we attempted the glycosylation of 3-*O*-benzyl-2,6-dideoxy-α-L-*lyxo*-hexopyranoside (**2**) with thioglycoside **1**, activated with bromine, a known method of thioglycoside activation (Scheme 1).[5] Instead of the expected disaccharide, the bicyclic bromodihydroxazine **3** was obtained. When the reaction was stopped after the bromination step, a product was isolated, and its structure was tentatively assigned as the 1,2-trans dibromide **4**. These unusual results prompted us to undertake a detailed study of the bromine activation of thioglycoside **1** in an effort to account for the formation of **3** and **4**. In this Note, we provide evidence for the formation of a glycal during the glycosylation depicted in Scheme 1 and confirmation by X-ray analysis of the structure of the dibromide **4**. We have also shown that the dibromide is converted to bicyclic oxazine **3** under conditions of glycosylation in the presence of silver silicate.



Scheme 1.

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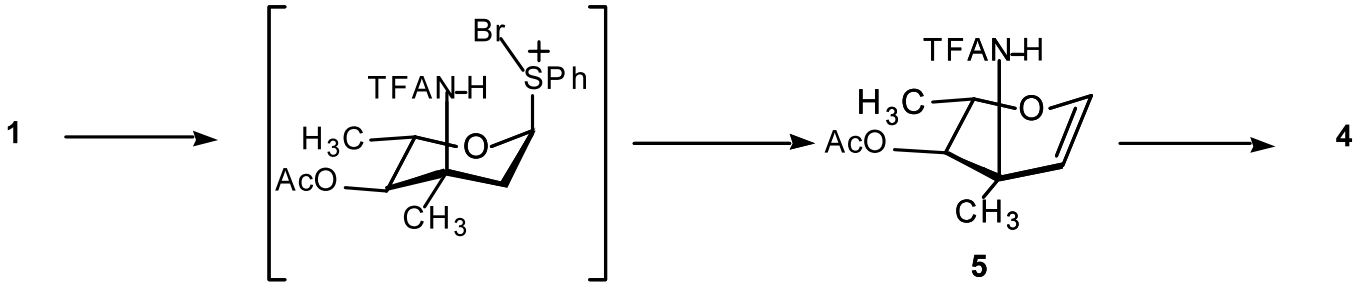


Scheme 2.

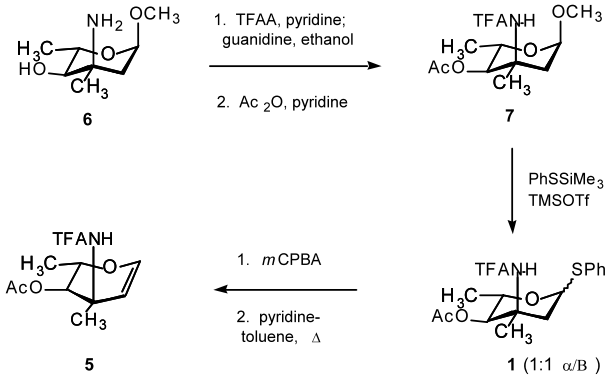
It occurred to us that a plausible pathway for the formation of the dibromide and oxazine products might consist of elimination from the Br-activated thioglycoside to give the glycal **5**, followed by the addition of bromine to give dibromide **4** (Scheme 2). Subsequent cyclization of **4** in the presence of silver silicate would provide the bicyclic dihydrooxazine **3**. In order to probe the formation of **3** and **4** in the attempted glycosylation with **1**, we first developed an independent synthesis of glycal **5**.

The synthesis of phenylthio glycoside **1** was carried out as described previously.[4,6] Methyl α-L-avidinosamine (**6**) was prepared by the procedure of Scharf and co-workers,[7] and the amino alcohol functionality in **6** was protected by selective N-trifluoroacetylation, followed by acetylation of the 4-hydroxyl group to give **7** in 68% overall yield (Scheme 3).[6] Conversion to the phenylthio glycoside **1** (1:1 mixture of anomers) was carried out by treatment of **7** with $PhSSiMe_3$ in the presence of TMS-triflate.[4] Glycal **5** was prepared from **1** by oxidation–sulfoxide elimination.

The reaction of both phenylthio glycoside **1** (either anomer separately or the mixture) and glycal **5** with bromine afforded the same product, assigned as the 1,2-trans dibromide **4**, in yields of 91 and 89%, respectively. Crystallization of the dibromide product and subsequent X-ray structural analysis confirmed our initial assignment of structure for **4**. The molecular structure of **4** (Fig. 1) clearly shows the *trans* orientation of the bromines with a Br-1–C-1–C-2–Br-2 dihedral angle of 154.51°. Selected crystal and structure refinement data is given in Table 1. Atomic coordinates and equivalent isotropic displacement parameters are shown in Table 2.

Having established the structure of dibromide **4**, we wished to attempt the cyclization of **4** to the bromodihydrooxazine **3** by treatment with silver silicate[8] in the absence of an acceptor. Treatment of **1** with bromine, followed by reaction of the resulting dibromide with silver silicate in toluene, gave **3** in 87% yield as a white solid that was characterized by NMR spectroscopy and elemental analysis.

Bicyclic oxazine derivatives of protected amino sugars have been previously reported by Nicolaou and co-workers in the total synthesis of amphotericin B[9] and by Dushin and Danishefsky in the synthesis of the carbohydrate domain of vancomycin.[10] An iodooxazine has been used as a key intermediate in the synthesis of a conformationally constrained 4-hydroxyproline analog.[11] In our studies of the synthesis of the cororu-



Scheme 3.

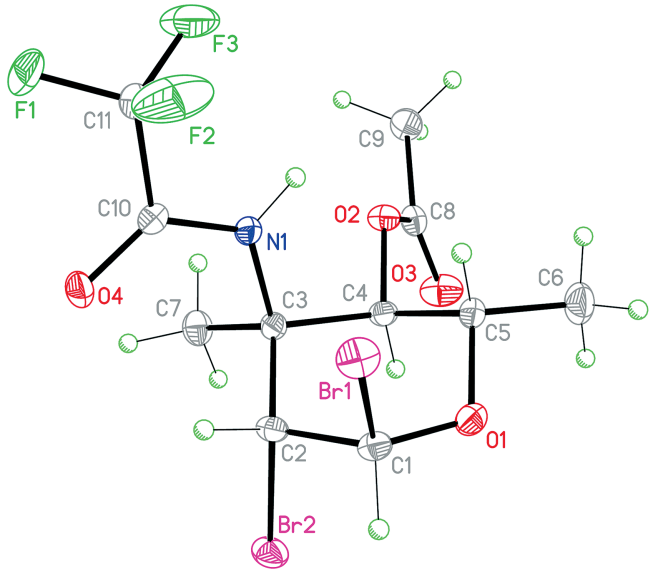
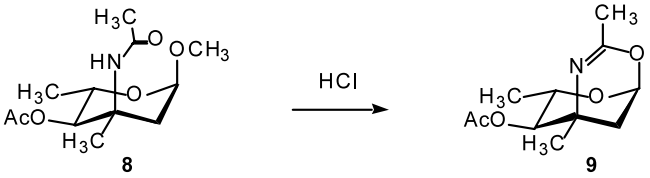


Fig. 1. ORTEP diagram of **4** showing the atomic numbering scheme. The Br-1–C-1–C-2–Br-2 dihedral angle is 154.51°. Thermal ellipsoids are drawn at the 30% probability level.

Table 1
Crystal data and structure refinement for **4**

Empirical formula	$C_{11}H_{14}Br_2F_3NO_4$
Formula weight	441.05
Temperature (K)	173(2)
Radiation	Mo K_α ($\lambda = 0.71073$ Å)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a (Å)	9.6326(5)
b (Å)	10.2540(6)
c (Å)	16.0234(9)
Volume (Å^3)	1582.67(15)
Z	4
ρ (calculated) (g cm^{-3})	1.851
Absorption coefficient (mm^{-1})	5.166
$F(000)$	864
Crystal size (mm^3)	$0.4 \times 0.4 \times 0.3$
θ Range for data collection (°)	2.36–28.28
Index ranges	$-12 \le h \le 12$, $-10 \le k \le 13$, $-20 \le l \le 20$
Reflections collected	7624
Independent reflections	3487 [$R_{int} = 0.0288$]
Completeness to $\theta = 28.28°$	96.3%
Absorption correction	SADABS
Max/min transmission	0.3063 and 0.2318
Refinement method	Full-matrix least-squares on F^2
Refined parameters	193
Goodness-of-fit on F^2	0.990
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0248$, $wR_2 = 0.0560$
R indices (all data)	$R_1 = 0.0282$, $wR_2 = 0.0572$
Absolute structure parameter	0.047(9)
Flack parameter	0.0466
Largest difference peak and hole (e Å^{-3})	0.362 and −0.431

bicin trisaccharide, a dihydrooxazine **9** was obtained by treatment of methyl glycoside **8** with HCl.[4] While compounds such as **9** and **3** might be expected to undergo β-glycosylation stereoselectively, we have thus far been unable to find suitable conditions for their activation.



The formation of dibromide **4** during the bromine-activation of thioglycoside **1** observed in this study suggests a tendency of 2-deoxy thioglycosides to undergo elimination to glycals in the presence of a thiophilic reagent and an even weakly basic counterion. It is interesting to note that other methods of thioglycoside activation, such as NIS–triflic acid or NBS, or conversion of **1** to the glycosyl fluoride and activation with Cp_2ZrCl_2, did not result in the formation of the dihydrooxazine.[4]

1. Experimental

1.1. 1,5-Anhydro-4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-L-*ribo*-hex-1-enitol (5)

To a solution of phenyl 4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-1-thio-α,β-L-*ribo*-hexopyranoside (**1**, 1.03 g, 2.63 mmol) in anhydrous dichloromethane (50 mL) under nitrogen was added MCPBA (0.857 g of 70–75%, 4.96 mmol). After 2 h, aq 10% sodium thiosulfate solution was added, and the mixture was poured into a separatory funnel. The aqueous phase was extracted with dichloromethane (3×10 mL), and the combined organic phases were dried (sodium sulfate) and concentrated under reduced pressure. Purification by flash chromatography (75:25 hexane–EtOAc; R_f 0.16) gave 0.67 g (62%) of syrupy sulfoxide as a mixture of diastereomers. HREIMS Calcd for $C_{17}H_{19}F_3NO_5S$ $[M-H]^+$ 406.0936. Found 406.0878. Without further separation, the sulfoxide (0.34 g, 0.82 mmol) was heated in anhyd toluene (13 mL) in a pressure tube at 140 °C for 36 h. Concentration under reduced pressure gave a syrup that was

Table 2
Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters (Å$^2 \times 10^3$) for **4**

	x	y	z	U(eq)
Br(1)	4503(1)	12,319(1)	814(1)	34(1)
Br(2)	8916(1)	11,043(1)	1538(1)	34(1)
C(1)	6485(3)	11,706(3)	696(2)	26(1)
C(2)	6879(3)	10,885(3)	1453(2)	23(1)
C(3)	6455(3)	9424(3)	1398(2)	21(1)
C(4)	6747(3)	8971(3)	505(2)	23(1)
C(5)	6084(3)	9841(3)	−158(2)	26(1)
C(6)	6394(4)	9424(4)	−1043(2)	41(1)
C(7)	7175(3)	8536(3)	2030(2)	31(1)
C(8)	6998(3)	6717(3)	135(2)	27(1)
C(9)	6239(4)	5449(3)	127(2)	34(1)
C(10)	4320(3)	9772(3)	2242(2)	24(1)
C(11)	2753(3)	9513(3)	2293(2)	33(1)
F(1)	2347(2)	9370(3)	3061(1)	73(1)
F(2)	2065(2)	10,508(3)	1986(2)	85(1)
F(3)	2342(3)	8478(3)	1875(2)	79(1)
N(1)	4941(2)	9334(2)	1544(1)	22(1)
O(1)	6695(2)	11,129(2)	−63(1)	30(1)
O(2)	6174(2)	7669(2)	429(1)	25(1)
O(3)	8173(2)	6888(2)	−94(2)	42(1)
O(4)	4869(2)	10,364(2)	2814(1)	32(1)

U(eq) is defined as one-third of the trace of the orthogonalized U_{ij} tensor.

purified by flash chromatography with 75:25 hexane–EtOAc (R_f 0.52) to give 0.98 g (42%) of glycal **5**: $[\alpha]_D$ −20.5° (*c*, 0.08, $CHCl_3$), ^{1}H NMR: δ 6.56 (bs, 1 H, NH), 6.31 (d, $J_{1,2}$ 5.99 Hz, H-1), 5,23 (d, 1 H H-2), 4.89 (d, 1 H, $J_{4,5}$ 10.43 Hz, H-4), 3.95 (m, 1 H, H-5), 2.15 (s, 3 H, CH_3CO), 1.45 (s, 3 H, 3-CH_3), 1.32 (d, $J_{5,6}$ 6.2 Hz, H-6); ^{13}C NMR: δ 131.1 (C1), 115.4 (C2), 68.7 (C4), 34.5 (C5), 23.2 (C2), 21.1 (3-CH_3) 18.0 (C6); IR (film) 3100, 1650, 1300, 1200 cm^{-1}; HREIMS Calcd for $C_{11}H_{15}F_3NO_4$ $[M+H]^+$ 282.0953. Found 282.0943.

1.2. 4-*O*-Acetyl-2-bromo-2,3,6-trideoxy-3-*C*-methyl-3-trifluroacetamido-L-altropyranosyl bromide (4)

1.2.1. Method A. From **1**. To a solution of phenyl 4-*O*-acetyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-1-thio-α,β-L-*ribo*-hexopyranoside (**1**, 0.138 g, 0.35 mmol) in anhyd dichloromethane (8 mL) under was added bromine (23 μL, 0.46 mmol) while stirring at 0 °C under nitrogen. The reaction was quenched after 2 h by the addition of 5% aq sodium thiosulfate solution (20 mL), and the organic phase was dried (sodium sulfate) and concentrated to give 0.142 g (91%) of dibromide as a syrup that crystallized after storage for several days at −10 °C: mp 40–45 °C; R_f 0.58 (75:25 hexane–EtOAc); $[\alpha]_D$ −35.4° (*c*, 0.8, $CHCl_3$); ^{1}H NMR: δ 6.74 (bs, 1 H, NH), 6.65 (t, 1 H, $J_{1,2}$ 1.2 Hz, $J_{1,5}$ 0.8 Hz, H-1), 5.60 (d, 1 H, H-2), 5.33 (d, 1 H, $J_{4,5}$ 10.1 Hz, H-4), 4.24 (m, 1 H, $J_{5,6}$ 6.2 Hz, H-5), 2.20 (s, 3 H, CH_3CO), 1.67 (s, 3 H, 3-CH_3), 1.31 (d, 3 H, H-6); ^{13}C NMR: δ 168.7, 156.8 (q, *J* 38 Hz), 115.1 (q, *J* 289 Hz), 84.6 (C1), 72.6 (C4), 67.1 (C5), 57.8 (C3), 51.1 (C2), 24.2 (3-CH_3), 20.4 (CH_3CO), 17.0 (C6).

1.2.2. Method B. From **5**. To a stirred solution of **5** (0.062 g, 0.219 mmol) in anhyd dichloromethane (3.5 mL) was added bromine (14 μL, 0.135 mmol) at 0 °C under nitrogen. The reaction was quenched after 3.5 h as in Section 1.2.1, to give 0.86 g (89%) of dibromide.

1.3. 2-Trifluoromethyl-(4-*O*-acetyl-2-bromo-2,3,6-trideoxy-3-*C*-methyl-α-L-altropyrano)-[3,2,1-*d*,*e*]-2-oxazine (3)

To a solution of thioglycoside **1** (1:1 α/β, 0.152 g, 0.39 mmol) in anhydrous dichloromethane was added a solution of bromine (40 μL) in dichloromethane (3.5 mL) at 0 °C under nitrogen. After stirring for 15 min, the reaction mixture was concentrated under reduced pressure at room temperature and anhyd toluene (18 mL) was added. The reaction was again concentrated to remove additional traces of bromine. Toluene (7.5 mL) was added, followed by silver silicate (2.14 g).[8] After stirring for 30 min at room temperature, the reaction mixture was filtered through a pad of Celite and concentrated to yield bromooxazine **3** as a white solid; yield, 0.122 g, 87%: mp 62 °C; R_f 0.65 (75:25 hexane–EtOAc); $[\alpha]_D$ +33.6° (*c*, 1.7, $CHCl_3$), ^{1}H NMR: δ 5.60 (d, 1 H, $J_{1,2}$ 1.9 Hz, H-1), 5.37 (d, 1 H, $J_{4,5}$ 9.8 Hz, H-4), 4.06 (d, 1 H, H2), 3.65 (dq, 1 H, H-5), 2.15 (s, 3 H, CH_3CO), 1.44 (s, 3 H, 3-CH_3), 1.25 (d, 3 H, $J_{5,6}$ 6.1 Hz, H-6); ^{13}C NMR: δ 170.7, 147.5 (*J* 39.6 Hz), 116.0 (*J* 277.5 Hz), 94.4 (C1), 73.3 (C4), 67.7 (C5), 54.8 (C3), 48.7 (C2), 23.1 (3-CH_3), 20.6 (CH_3CO), 17.1 (C6). Anal. Calcd for $C_{11}H_{13}BrF_3NO_4$: C, 36.68; H, 3.64; N, 3.89. Found: C, 36.61; H, 3.67; N, 3.77.

1.4. Crystallographic structure determmination

Compound **4** crystallized from a neat syrup at −10 °C. The single-crystal X-ray diffraction experiment was performed on a Bruker P4/CCD diffractometer. Crystal and structure refinement data are summarized in Table 1. Systematic absences uniquely defined the space group as $P2_12_12_1$. The structure was solved using direct methods and subsequent difference Fourier syntheses. Final structure refinement was made using full-matrix, least-squares procedures. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were calculated in idealized positions and refined isotropically. The correct absolute structure was unambiguously determined; a Flack parameter of 0.0466 was obtained. All software used in the structure determination and sources of the scattering factors are contained in the SHELXTL (5.10) program library (G. Sheldrick, Siemens XRD, Madison, WI).

2. Supplementary material

Complete crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 261532. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336-033, e-mail: deposit@ccdc.cam.ac.uk; Web: http://www.ccdc.cam.ac.uk).

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