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TRIMETHYLSILYL BROMIDE AS A MILD, STEREOSELECTIVE ANOMERIC BROMINATING AGENT[1]

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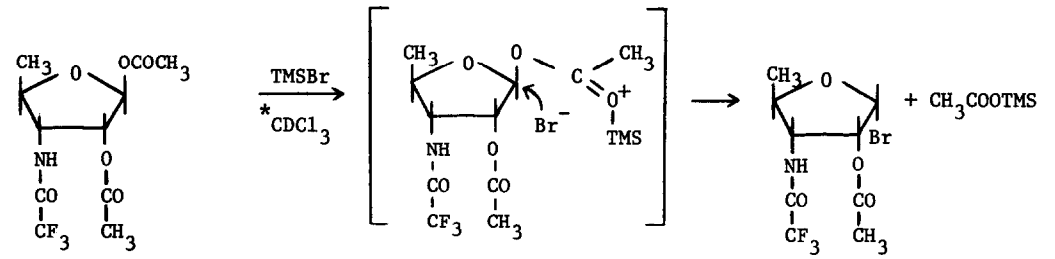
Summary: Stereoselective bromination of anomeric glycosyl acetates was achieved with trimethylsilyl bromide under mild conditions and in the presence of various protecting groups commonly employed in carbohydrate chemistry.

For some time these laboratories have been involved with the preparation and biological evaluation of analogs of the antitumor antibiotics adriamycin and daunorubicin, including analogs in which the naturally-occurring daunosaminyl moiety has been replaced by "fraudulent" furanose and pyranose glycosides. In this regard, the need has been accentuated for a general, high-yielding synthesis of glycosyl halides for use in coupling reactions. Glycosyl bromides, which in particular allow greater reactivity at the anomeric center, have proven in many cases to be available in poor yield, or to be inaccessible, by the traditional procedure which involves anhydrous HBr, usually in CH_2Cl_2 or CH_3CO_2H solvent, acting upon an anomeric acetate.[3] For example, in connection with the synthesis of novel aminofuranose glycosides of anthracyclines as daunorubicin analogs,[4,5] we found that the preparation of the bromo-derivatives 2a and 2b from the acetates 1a and/or 1b by conventional means could be realized only in crude yields of <20%, and the significant impurities present could not be separated due to the instability of the product. Such complications at the end of a multistep carbohydrate synthesis were inacceptable and led us to investigate a new methodology.

The possible value of trimethylsilyl bromide (TMSBr) for the preparation of anomeric bromides[6] was suggested by the recent publications of Jung and Lyster[7,8] concerning the use of trimethylsilyl iodide (TMSI) for the non-aqueous hydrolysis of esters and acetals. The choice of TMSBr was motivated by considerations of the greater strength of the Si-Br bond relative to Si-I, and the lower nucleophilicity of Br^- relative to I^-, each of which was taken as an indication of the greater potential selectivity of TMSBr for an anomeric center. TMSI has an indiscriminate range of reactivity: in addition to alcohol cleavage, it is found that ethers, esters, and acetals, each a useful protecting group in carbohydrate chemistry, are also cleaved by TMSI.[9] In contrast, TMSBr shows, in the examples studied to date, complete selectivity for

esters at the anomeric center. Thus, as monitored by NMR spectrometry, when a solution of 3-amino-3,5-dideoxy-3-N-trifluoroacetyl-1-O-acetyl-α-D-ribopentofuranose (1b) in $CDCl_3$ solution was treated with 1.5 equivalents of TMSBr at 0° and allowed to come to room temperature, a rapid diminution of the anomeric proton signal was observed. This signal, a doublet at δ6.40 (J=4.0 Hz), was concomitantly replaced, predominantly by a singlet at δ6.32, corresponding to the inverted β-bromo derivative, and, to a much lesser extent, by a doublet at δ6.80 (J=4.0 Hz), corresponding to the α-bromo derivative. The reaction was complete in 40 min. After 80 min, the product distribution had equilibrated to a ratio of α:β=3:5. The volatile byproduct, trimethylsilyl acetate, and excess TMSBr were easily removed by vacuum distillation.



1a (β anomer)
1b (α anomer)

2a (α anomer)
2b (β anomer)

*or CH_2Cl_2; CH_2Cl-CH_2Cl; $CHCl_3$ (ethanol free).

The pure β-compound (1a), when similarly treated and monitored by NMR, underwent much less rapid conversion to the inverted α-bromide. The anomeric proton signal, a singlet at δ6.20, was replaced over 180 min by signals which had equilibrated on completion of the reaction (180 min) to a ratio of α:β=3:5.

High-yielding (73%) Koenigs-Knorr glycosidations ($HgBr_2$, HgO, 4A Sieves, CH_2Cl-CH_2Cl) were achieved with glycosyl bromides derived from both 1a and 1b, affording the β- and α-glycosides of daunomycinone in identical ratios of 3.8:1.[10]

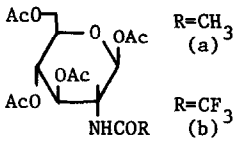
An anomeric center is an ambiguous substrate for mechanistic interpretations based on the inversion of configuration. Although continuous analysis by NMR indicated apparent inversion of the anomeric center, the predisposition for subsequent anomerization to produce the thermodynamically-stable bromo-products was observed when using TMSBr in place HBr. The likely chemical intermediate involved in the reaction is shown in the scheme.

The great practical advantage of TMSBr over HBr in the preparation of anomeric bromides appears to lie in its generality, high yield, and capacity to be continuously monitored by NMR techniques. A number of examples have been investigated, for which data are summarized in Table 1. Examples 3 through 10 show the structural diversity and functional sensitivity compatible with the reagent, with compounds 3a and 5 being particularly noteworthy examples.

Among other anomeric protecting groups, methyl glycosides and 1,2-O-isopropylidenes play a predominant role. The methyl glycoside 12 was found to be completely stable to the reaction conditions normally employed. The 1,2-O-isopropylidene in 11 was observed to undergo a very

Table 1

Reactivity of Anomeric Substrates with TMSBr[a]



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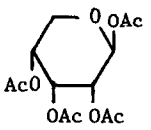

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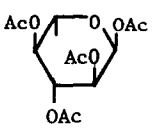

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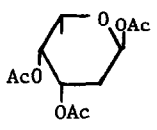

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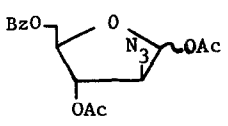

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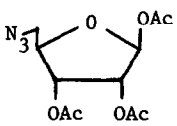

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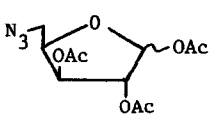

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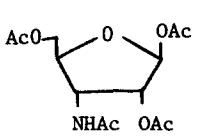

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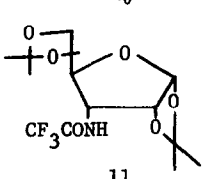

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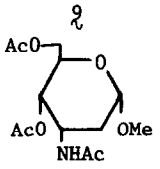

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	Acetate		Bromide		
Cpd	Configuration	δ[b]	Configuration	δ[c]	Yield, Conditions
3a	100% β	5.7(d) J=9Hz	100% α	6.52(d) J=4.2Hz	Quant., 2 hr
3b	100% β	5.8(d) J=9Hz	100% α	6.62(d) J=4.2Hz	Quant., 3 hr
4	100% β	6.0(d) J=6Hz	90% α 10% β	6.35(s) J=1Hz 6.40(d) J=6H	Quant., 1 hr
5[d]	70% β 30% α	6.2(d) J=6Hz	100% α	6.25(d) J=1.8Hz	85%, 24 hr
6	100% α	6.20(t) J=2Hz	100% α	6.60(t) J=1.8Hz	Quant., 20 min
7[d]	70% α 30% β	6.20(s) 6.16(d) J=3Hz	88% β 12% α	6.35(s) 6.50(d) J=4Hz	88%, 36 hr
8	100% β	6.16(s)	62% β 38% α	6.28(s) 6.72(d) J=2.5Hz	100%, 18 hr
9[d]	33% β 67% α	5.10(s) 5.32(d) J=4.5	27% β 73% α	5.92(s) 6.22(d) J=4.8Hz	Quant., 24 hr
10	100% β	6.05(s)	81% β 18% α	6.35(s) 6.70(d) J=4.6Hz	Quant., 24 hr
11	100% α	5.70(d) J=3Hz	100% β	6.00(s)	40%, 72 hr
12	100% α	4.80(t) J=3Hz	—	--	No reaction, 72 hr

(a) 100 mg glycosyl acetate substrate was dissolved in 0.5 ml dry, acid-free $CDCl_3$, cooled to 0° C, and 150 µl TMSBr added via a microsyringe. Reactions continued at room temperature.
(b) Acetate anomeric proton resonance, ppm.
(c) Bromide anomeric proton resonance, ppm.
(d) Anomeric mixture.

slow conversion to the corresponding β-D-ribo-hexofuranosyl bromide, while the 5,6-O-isopropylidene function remained stable throughout the 72 hr reaction period. Current studies include the possibility of selectively functionalizing the anomeric position of such a sugar in the presence of an intrinsically less-stable protecting group at the 5,6-position.

Acknowledgment

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