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TRIMETHYLSILYL TRIFLUOROMETHANESULFONATE (TRIMETHYLSILYL TRIFLATE) AS AN EXCELLENT GLYCOSIDATION REAGENT FOR ANTHRACYCLINE SYNTHESIS. SIMPLE AND EFFICIENT SYNTHESIS OF OPTICALLY PURE 4-DEMETHOXYDAUNORUBICIN

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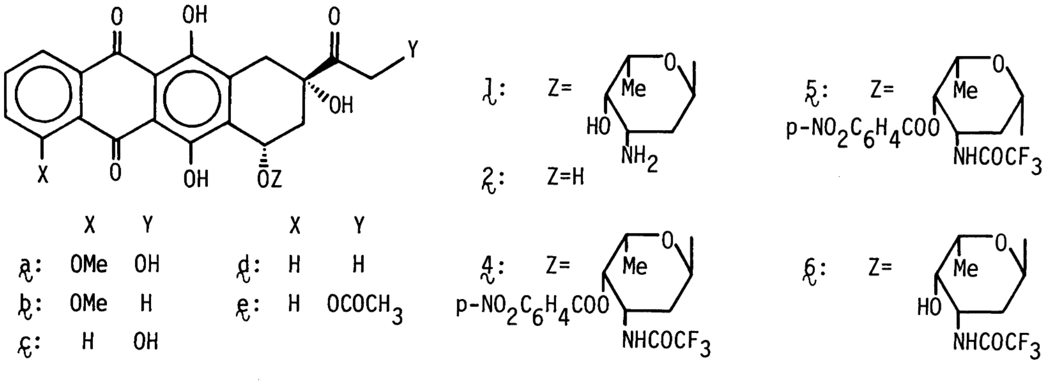
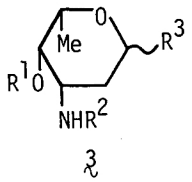
The title reagent was found to effect the glycosidation of (+)-4-demethoxyanthracyclinones with N-trifluoroacetyl-1,4-di-O-p-nitrobenzoyl-L-daunosamine, giving the α-glycosides in 99% yields. Sequential deprotections of the glycoside readily afforded optically pure (+)-4-demethoxydaunorubicin.

The anthracycline antibiotics, adriamycin(1a) and daunorubicin(1b), are of current interest because of their promising anticancer activity.[1)] While chemotherapy employing these natural antibiotics(1a,b) is hampered by a number of undesirable side effects including dose-related cardiotoxycity,[1)] the unnatural anthracyclines such as 4-demethoxyadriamycin(1c) and 4-demethoxydaunorubicin(1d) have been disclosed to exhibit more improved therapeutic indices than natural 1a,b.[1)]

Numerous synthetic efforts have been devoted to anthracycline chemistry for the past decade, culminating in the highly regio- or enantioselective preparations of natural and unnatural anthracyclinones(2a-d), the aglycones of anthracyclines (1a-d), as well as aminosugars including L-daunosamine(3a) and its epimeric congeners.[1,2)] However, probably due to difficulties which would be encountered for obtaining anthracyclinones and aminosugar derivatives in optically active forms, only a limited number of methods has been explored for the glycosidation reaction.

While the reported methods for glycoside formation generally consist of reactions of anthracyclinones 1) with 1-halo-aminosugar derivatives in the presence of





	R^1	R^2	R^3
a:	H	H	OH
b:	p-$NO_2C_6H_4CO$	$COCF_3$	$OCOC_6H_4NO_2$-p
c:	H	$COCF_3$	OH

	R^1	R^2	R^3
d:	CF_3CO	$COCF_3$	$OCOCF_3$
e:	p-$NO_2C_6H_4CO$	$COCF_3$	Cl

mercuric salt (Koenigs-Knorr reaction)[3] or silver triflate,[4] 2) with glycals derived from aminosugar derivatives in the presence of p-toluenesulfonic acid,[5] these reactions seem not to be applicable to the large scale preparation of anthracyclines due to rather low yields (usually 50-60%), uses of unstable 1-halo-aminosugar derivatives[3,4] and toxic[3] or expensive reagents,[4] and lack of stereoselectivity (formation of a mixture of α- and β-anomers).[1b,5]

Recently, we developed several efficient synthetic routes to optically pure 4-demethoxyanthracyclinones[(+)-2c,d] by employing asymmetric syntheses[6] and optical resolution.[7] Therefore, our attention was next focused on the exploitation of an efficient glycosidation method which might overcome the above-mentioned disadvantages because glycosidation reaction should be unavoidable especially in the synthesis of unnatural anthracyclines such as 1c,d.

We have now found that the glycosidation of optically pure 4-demethoxyanthracyclinones with N-trifluoroacetyl-1,4-di-O-acyl-L-daunosamine derivatives can be efficiently achieved by using trimethylsilyl triflate,[8] to give the desired α-glycoside in almost quantitative yields.

After several preliminary experiments, N-trifluoroacetyl-1,4-di-O-p-nitrobenzoyl-L-daunosamine(3b),[10b,c] mp 201-202 °C, $[\alpha]_D^{20}$ -117°(c 0.029, Me_2CO) [lit.,[3a] mp 202-203 °C, $[\alpha]_D^{20}$ -125°(c 0.03, EtOH)], was chosen as the most promising aminosugar counterpart for the glycosidation because of its larger stability under the air, and of its good feasibility (82%) from N-trifluoroacetyl-L-daunosamine(3c)[10a,c] according to the reported procedure.[3a]

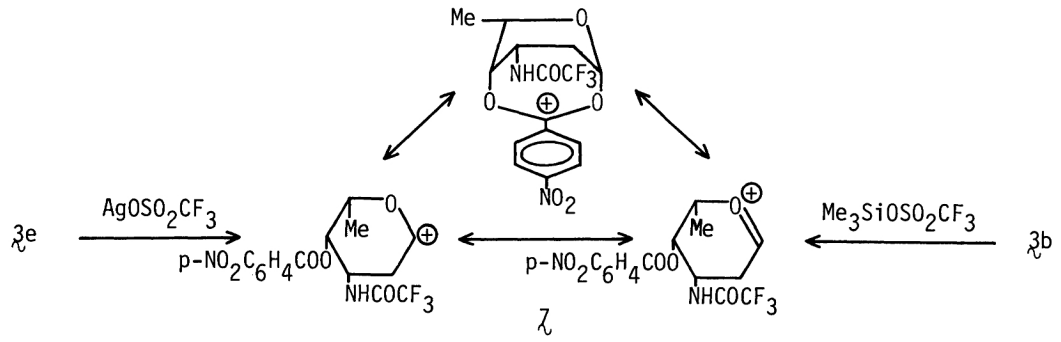
The glycosidation reaction of optically pure (+)-4-demethoxydaunomycinone [(+)-2d],[10a] with 3b was carried out as follows: Trimethylsilyl triflate (2.6 equiv.) was gradually added to a solution of 3b (1.3 equiv.) in CH_2Cl_2-Et_2O (3:1) cooled at -40 °C in the presence of molecular sieves 4A. The whole mixture was stirred at -3~-5 °C for 1 h, then cooled to -15 °C. A solution of (+)-2d (1.0 equiv.) in CH_2Cl_2 was added to the reaction mixture. After being stirred at -15 °C for 2.5 h, the mixture was poured onto a two layer mixture of satd. $NaHCO_3$ and EtOAc to quench the glycosidation reaction. Usual extractive isolation followed by simple filtration through a short silica gel column (EtOAc-C_6H_6 1:4) gave the almost pure α-glycoside, (-)-4'-O-p-nitrobenzoyl-N-trifluoroacetyl-4-demethoxydaunorubicin[(-)-4d][11] in 99% yield. No formation of the undesired β-glycoside(5d) was definitely ascertained by TLC and NMR analyses of this sample. Trituration (C_6H_{14}-$CHCl_3$) of the isolated α-glycoside afforded pure (-)-4d[10a,c] as a bright orange powder in 92% yield, mp 171-173 °C, $[\alpha]_D^{20}$ -78.0°(c 0.11, dioxane)[lit.,[4b] mp 171-175 °C, $[\alpha]_D^{20}$ -89.0 °(c 0.1, dioxane)].

The α-glycoside[(-)-4d] was readily converted to (+)-1d according to the reported reaction scheme.[3a,4b] Mild alkaline hydrolysis (0.1 mol dm^{-3} NaOH in MeOH-CH_2Cl_2, 0 °C, 0.5 h) of (-)-4d afforded (+)-N-trifluoroacetyl-4-demethoxy-

daunorubicin[(+)-6d] as a red crystalline powder,[10a] mp 150-154 °C, $[\alpha]_D^{20}$ +190° (c 0.10, dioxane)[lit.,[4b] mp 155-156 °C, $[\alpha]_D^{20}$ +190°(c 0.1, dioxane)], in an almost quantitative yield. Further treatment of (+)-6d with aqueous alkaline condition (0.1 mol dm^{-3} NaOH, rt, 0.5 h), gave rise to cleavage of the N-trifluoroacetyl group, furnishing (+)-1d (isolated as its hydrochloride)[10a] as an orange crystalline powder in 77% yield, mp 184-187 °C (decomp), $[\alpha]_D^{20}$ +188°(c 0.10, MeOH)[lit., mp 183-185 °C,[3b] $[\alpha]_D^{20}$ +187°(c 0.1, MeOH)[4b]].

In order to examine generality of the explored glycosidation reaction, the reaction of (+)-14-acetoxy-4-demethoxydaunomycinone[(+)-2e] and 3b was next attempted. The aglycone[(+)-2e][10b,c], mp 187-188.5 °C, $[\alpha]_D^{20}$ +181°(c 0.10, dioxane), was prepared from (+)-2d in 70% overall yield by simultaneous bromination (pyridinium bromide perbromide in THF, 2.5 h) and substitution (KOAc in Me_2CO, 1.5 h). Successive treatments of 3b (1.2 equiv.) with trimethylsilyl triflate (2.7 equiv.) and (+)-2e (1.0 equiv.) in a manner similar to that for (+)-2d were found to give the desired α-glycoside[(-)-4e][10b,c] as an orange crystalline solid, mp 167-170 °C, $[\alpha]_D^{20}$ -53.5°(c 0.10, dioxane), in 99% yield after filtration through a short silica gel column. On the other hand, (+)-2d was subjected to the glycosidation with (-)-N-1,4-O-tri-trifluoroacetyl-L-daunosamine [(-)-3d],[10b,c] mp 133.5-135 °C, $[\alpha]_D^{20}$ -69.5°(c 0.12, Me_2CO)(lit.,[3c] mp 132-134 °C), prepared [$(CF_3CO)_2O$ in Et_2O] from 3c in 51% yield, under the same condition as that described above. Obtained unstable 4'-O-trifluoroacetyl-α-glycoside was immediately hydrolyzed (0.1 mol dm^{-3} NaOH in MeOH-CH_2Cl_2, 0 °C, 0.5 h), giving (+)-6d[10a] in 61% yield after chromatographic separation (SiO_2, $CHCl_3$-Me_2CO 19:1). These results definitely disclose that the developed glycosidation reaction might have a general applicability, and that p-nitrobenzoyl group might be considered the best acyloxy group which should be introduced at the C_1-position of L-daunosamine derivatives prior to the glycosidation.

Precise mechanism of the novel glycosidation reaction is presently obscure. However, we have already observed that the glycosidation of (+)-2d with N-trifluoroacetyl-4-O-p-nitrobenzoyl-L-daunosamyl chloride(3e) by the use of silver triflate according to the reported procedure[4] exclusively gave (+)-4d[10a] in 51% yield with a 47% recovery of (+)-2d. This glycosidation reaction has been best explained to proceed through the cationic species(7).[3a] Since formation of the same cationic species(7) could be reasonably expected for the exploited glycosidation reaction, the observed higher yield of (+)-4d might be elucidated by the assumption that the reactivity of 7 derived from 3b and trimethylsilyl triflate



is amplified more than that from 3e and silver triflate.

Due to its high chemical yield, operational simplicity, and uses of inexpensive reagent and stable L-daunosamine derivative, the developed glycosidation reaction might be considered to be one of the best preparation method of anthracyclines, especially unnatural anthracyclines, among those hitherto reported.[3,4]

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8) Although trimethylsilyl triflate has been successfully utilized in the synthesis of nucleosides and disaccharides, [H. Vorbüggen, K. Krolikiewicz, and B. Bennua, Chem. Ber., 114, 1234(1981); T. Ogawa, K. Beppu, and S. Nakabayashi, Carbohydr. Res., 93, C6(1981).] anthracycline synthesis has never been attempted using this novel reagent.[9]

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10) a) IR and NMR spectra were identical with those reported; b) IR, NMR and Mass spectra were in agreement with the assigned structure; c) Satisfactory analytical data were obtained for this compound.

11) This sample showed a completely single spot on TLC analysis [SiO_2, R_f=0.53 (EtOAc-C_6H_6 1:4)]. The NMR spectrum of this sample also exhibited a single anomeric proton at 5.70 ppm as a broad singlet (W_H=6.0 Hz) corresponding to the assigned α-glycoside structure.[3d,4b]

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