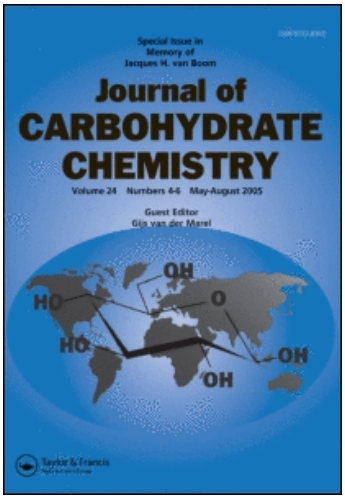

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Regioselective Alkylation and Acylation of Methyl, 2,6-Dideoxyhexo-Pyranosides Via Their Stannylene Acetals: Key Step for the Synthesis of Daunosamine and Related Amino-Sugars

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REGIOSELECTIVE ALKYLATION AND ACYLATION OF METHYL 2,6-DIDEOXYHEXOPYRANOSIDES VIA THEIR STANNYLENE ACETALS: KEY STEP FOR THE SYNTHESIS OF DAUNOSAMINE AND RELATED AMINO-SUGARS

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ABSTRACT

Synthetic intermediates for the preparation of 3-amino-2,3,6 (or 4-amino-2,4,6)-trideoxy-L-hexopyranosides, sugar moieties of anthracycline antibiotics, were selectively obtained from stannylene acetals of methyl 2,6-dideoxy-α- L-lyxo and arabino-hexopyranosides.

INTRODUCTION

The synthesis of new antitumour anthracyclines,[1] analogs of daunorubicin and doxorubicin modified in their sugar moiety, and of oligosaccharides,[2] natural constituents of class II anthracyclines, required in both cases selective acylation or alkylation of the 3-OH of methyl-2,6-dideoxy-L-hexopyranosides. This led us to synthesize for example 4-amino-2,4,6-trideoxy-L-hexopyranosides[3] from the corresponding L-arabino isomer (methyl 2-deoxy-L-rhamnopyranoside), while elaboration of the oligosaccharide of Aclacinomycin A was based upon selective O-benzylation of the corresponding L-lyxo-isomer (methyl-2-deoxy-L-fucoside).[4]

On the other hand, utility of organotin derivatives of alcohols in regioselective acylation, alkylation or oxidation reactions has been largely demonstrated[5] and the synthetic application of these stannylene acetals in the case of polyols such as carbohydrates is well documented.[6] The observed regioselectivity of those reactions seems to be usually determined by steric factors as demonstrated by substitution at the equatorial oxygen of vicinal axial-equatorial dibutylstannylene derivatized hydroxy groups.[7]

RESULTS AND DISCUSSION

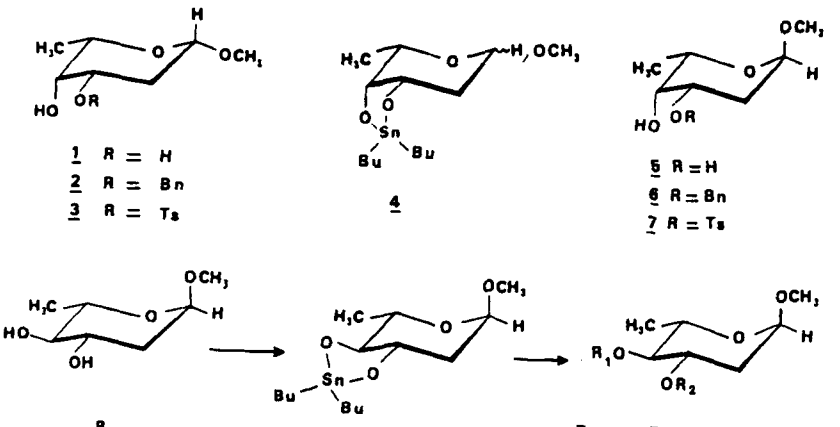
We previously reported[4] that treatment of methyl 2,6-dideoxy-β-L-lyxo-hexopyranoside (1) with dibutyltin oxide in benzene followed by alkylation (BnBr) catalyzed by tetrabutylammonium iodide[8] led regiospecifically, as might be expected, to the 3-O-benzyl compound 2 in 95 % yield after purification (lack of C-2 substituent and equatorial orientation of the 3 C-O bond).

The same regiospecificity was again observed when the dibutyl stannylene derivatives[9] of methyl 2,6-dideoxy-β- and α-L-lyxo-hexopyranoside (1) and (5) (i.e. 4 on scheme) were treated with TsCl for 24 h at room temperature giving 3 and 7 in 90 and 98 % yields respectively after chromatography (dichloromethane-MeOH, 98:2). On the other hand, benzylation of the stannylene acetal of 5 gave regioselectively, as already reported[10], the 3-O-benzyl derivative 6 in 95 % yield after chromatography (hexane-EtOAc, 4:1). Consequently, the regioselectivity of these reactions is not influenced by the anomeric configuration.

The next question was : could any selectivity be observed during alkylation or acylation of the stannylene acetal of methyl 2,6-dideoxy-α-L-arabino-hexopyranoside (8) (e.g. 9 on scheme) where the two vicinal OH groups at C-3 and C-4 are trans diequatorial in the $^1C_4$ conformation of 8 ? If, as generally assumed, such regioselectivity depends on steric factors (or stereoelectronic effects), the lack of substituent at C-2 could be in favour of reaction at O-3. Actually, a noteworthy regioselectivity was observed when 9

was treated with BnBr under reflux in the presence of tetrabutylammonium iodide giving 10 in 70 % yield after chromatography (hexane-EtOAc, 7:3). Structural determination of 10 was based upon ^{1}H NMR data. The upfield shift of 4-H (dd at 3.19) in 10 with respect to the corresponding acetyl derivative 11 (dd at 4.77) was in agreement with the deshielding influence of esterification of the 4-OH.

Interestingly, when the stannylene complex 9 was stirred for 24 h at room temperature with TsCl, the 3-O-tosyl derivatives 12[11] was regioselectively obtained in 70 % yield after chromatography (dichloromethane-MeOH, 98:2).



	R_1	R_2
10	H	Bn
11	Ac	Bn
12	H	Ts
13	Bz	Bz
14	H	Bz

	R_1	R_2
15	pNBz	pNBz
16	H	pNBz
17	H	CH_3
18	CH_3	H

Although a little amount of 3,4-di-O-benzoyl derivative 13[12] ($\simeq$ 5 %) was obtained when 9 in toluene solution was stirred for 2 h at -45°C with benzoyl chloride (1.1 molar) and triethylamine (1.1 molar eq.), the 3-O-benzoyl derivative 14[12] was regioselectively obtained in 70 % yield after chromatography (hexane-EtOAc, 4:1). A similar result was obtained when p-nitrobenzoyl chloride was used instead of benzoyl chloride, 15 and 16 being isolated in 5 and 70 % yields respectively.

Compared with acylation and tosylation, alkylation of the tin intermediate 9 with methyl iodide required a large excess of alkylating agent, a longer reaction time and a higher temperature even in the presence of tetrabutylammonium iodide. Chromatography of the crude material with hexane-acetone (3:1) as the eluent afforded successively the 3-O-methyl derivative, methyl α-L-oleandroside[13] (17) and the 4-O-methyl derivative 18 in 52 % and 18 % yields respectively.

In conclusion selective preparation of 3-O-derivatives of methyl 2,6-dideoxy-α-L-lyxo and α-L-arabino hexopyranosides illustrates an extremely useful application of organotin alkoxides in carbohydrate chemistry. The orientation of attack could be due to the 3-oxygen atom preferentially binding apically in the dimeric structure which probably exists in benzene[14]. However, as regioselective tosylation[11] and acylation[12] of the 3-oxygen atom were already reported when the diol derivative 8 was treated with an equimolecular amount of appropriate reagent in pyridine at low temperature, both steric and electronic factors may play a deciding role and explain the present results.

According to this approach, several partially alkylated or acylated monosaccharides of high synthetic potential have been prepared in good yield : compounds 3 which has been previously used as a precursor of methyl 3-amino-2,3,6-trideoxy-L-xylo-hexopyranoside or 3-epi-L-daunosamine,[10] and 12, which has been widely synthesized as a key intermediate in the preparation of L-daunosamine,[11] L-acosamine,[15] L-ristosamine[16] and L-megosamine.[17] Other derivatives have been involved in syntheses of 4-amino-2,4,6-trideoxy-L-hexopyranoses (14 as precursor of the L-lyxo isomer[12] and 17 as precursor of the 3-O-methyl derivative of the L-arabino isomer or L-holantosamine[13]) or of branched-chain sugars (6 as precursor of L-rubranitrose[10]).

EXPERIMENTAL

General Methods and Material. Melting points were determined on a Hofler hot-stage microscope and are uncorrected. IR spectra

were recorded on a Perkin-Elmer Model 257 spectrophotometer, calibrated against polystyrene film and are expressed in cm^{-1}. ^1H NMR spectra were obtained on a Bruker HX 270 in $CDCl_3$ (s, singlet ; d, doublet ; m ; multiplet ; q, quadruplet) (TMS refer. 0 and coupling constants in Hertz).Silica gel for column chromatography or flash chromatography was Merck silica gel H.60 n°7736. Microanalyses were performed by the "Laboratoire de Microanalyse du CNRS" Gif-sur-Yvette.

General procedures for benzylation, tosylation and methylation. A mixture of hexopyranoside (1 mmol) and dibutyltin oxide (1.2 mmol) in benzene (50 ml) was refluxed for 4-6 h with continuous removal of water. After concentration to half-volume, tetrabutylammonium iodide (0.5 mmol) was added and the following procedures used : Procedure A : BnBr (1.5 mmol) was added and the mixture stirred under reflux for 18-24 h ; Procedure B : TsCl (1.5 mmol) was added and the mixture was stirred at room temperature for 6-8 h ; Procedure C : MeI (15 mmol) was added in several portions while the mixture was stirred under reflux for 72 h.

General procedure for benzoylation and p-nitrobenzoylation, Procedure D : A mixture of hexopyranoside (1 mmol) and dibutyltin oxide (1.2 mmol) in toluene (50 ml) was refluxed for 4 h with continuous removal of water and then concentrated to half volume. After cooling at -45°C, Et_3N (1.1 mmol) and p-NBzCl or BzCl (1.1 mmol) were added. The mixture was stirred at the same temperature for 2 h and then, methanol (2-5 ml) was added before the reaction mixture was allowed to reach room temperature.

General work-up. Silica gel (≅ 1 g/mmol of starting material) was added to the reaction mixture and the solvent removed in vacuo. The resulting powder was flash chromatographied with eluent as indicated for each compound.

Methyl 2,6-dideoxy-3-O-tosyl-β-L-lyxo-hexopyranoside (3). Treatment of methyl 2,6-dideoxy-β-L-lyxo-hexopyranoside (1) (290 mg) according to procedure B afforded 550 mg (90 %) of 3 after flash chromato-

graphy (dichloromethane-methanol, 98:2). Constants and spectroscopic data of 3 were in full agreement with those previously reported.[9]

Methyl 3-O-benzyl-2,6-dideoxy-α-L-lyxo-hexopyranoside (6). Treatment of methyl 2,6-dideoxy-α-L-lyxo-hexopyranoside (5) (500 mg) following procedure A led to 500 mg (95 %) of 5 after flash chromatography (hexane-ethyl acetate, 4:1) : syrup, $|\alpha|_D^{20}$ -125° (c 1.8, chloroform) ; lit.[10]: syrup, $|\alpha|_D^{20}$-127° (c 1, chloroform).

Methyl 2,6-dideoxy-3-O-tosyl-α-L-lyxo-hexopyranoside (7). Treatment of 5 (300 mg) according to procedure B afforded 585 mg (98 %) of 7 after flash chromatography (hexane-ethyl acetate 2:1) : mp 95-96° (hexane-acetone 1:1), $|\alpha|_D^{20}$ -140° (c 1.1, chloroform) ; IR_{max}^{film} : 3420(OH) and 1600 cm^{-1}(Ar). ^1H NMR : δ 7.72(d, J = 6) and 7.26 (d, J = 6)(AB, Aromat.), 4.82 (m, 3-H), 4.70 (d, J = 3, 1-H), 3.82 (q, J = 7, 5-H) ; 3.75 (broad s, 4-H), 3.25 (s, OCH_3), 2.44 (s, tosyl), 2.09 (m, J = 13, J' = 9, J" = 3, 2a-H) and 1.70 (m, J = 13, J' = 5, 2e-H), 1.25 (d, J = 7, 6-CH_3).

Anal. Calcd for $C_{14}H_{20}O_6S$ (316.31) : C, 53.15, H, 6.37, O, 30.34, S, 10.11 ; Found : C, 53.28, H, 6.45, O, 30.20, S, 10.02.

Methyl 3-O-benzyl-2,6-dideoxy-α-L-arabino-hexopyranoside (10). Treatment of 8 (1.6 g, 10 mmol) according to procedure A gave 1.75 g (70 %) after flash chromatography (hexane-ethyl acetate, 7:3) : syrup, $|\alpha|_D^{20}$ -40° (c 1.2, chloroform) ; IR_{max}^{film} 3440(OH) and 1500 cm^{-1} (Ar) ; ^1H NMR : δ 4.73 (d, J = 4, 1-H), 3.74-3.59 (m, 3-H, and 5-H), 4.62 (d, J = 12) and 4.44 (d, J = 12) (CH_2 benzyl), 3.30 (s, OCH_3), 3.19 (dd, J = J' = 10, 4-H), 2.27 (dd, J = 13, J' = 4, 2e-H) and 1.61 (m, J = 13, J' = 10, J" = 3, 2a-H), 1.29 (d, J = 7, 6-CH_3).

Anal. Calcd for $C_{14}H_{20}O_4$ (252.30) : C, 66.64, H, 7.99, O, 25.37 ; Found : C, 66.75, H, 8.03, O, 25.50.

Methyl 4-O-acetyl-3-O-benzyl-2,6-dideoxy-α-L-arabino-hexopyranoside (11). To a solution of 10 (150 mg, 0.6 mmol) in pyridine (15 ml) was added acetic anhydride (3 ml). After stirring at r.t. for 2 h, extraction with ether afforded 160 mg (89 %) of 11 : syrup, $|\alpha|_D^{20}$-84° (c 1, chloroform) ; IR_{max}^{film} : 1740, 1230 and 1040 cm^{-1} (OAc) ; ^1H NMR : δ 4.77 (d, J = 4, 1-H), 4.77 (dd, J = J' = 10, 4-H), 4.61 (d, J = 12) and 4.48 (d, J = 12)(CH_2 benzyl), 3.90-3.68 (m, 3-H and 5-H), 3.27 (s, OCH_3), 2.24 (dd, J = 13, J' = 5, 2e-H), 2.02 (s, OAc), 1.67 (m, J = 13, J' = 12, J" = 4, 2a-H), 1.14 (d, J = 7, 6-CH_3).

Anal. Calcd for $C_{16}H_{22}O_5$ (294.35) : C, 65.28, H, 7.54, O, 27.17 ; Found : C, 65.35, H, 7.60, O, 27.30.

Methyl 2,6-dideoxy-3-O-tosyl-α-L-arabino-hexopyranoside (12). Treatment of 8 (10 g, 62 mmol) according to procedure B gave 14.3 g (75 %) of 12 after flash chromatography (hexane-ethyl acetate, 3:1). M.p., IR and spectroscopic data were identical in all respects with literature data.[11,17]

Methyl 3,4-di-O-benzoyl-2,6-dideoxy- and Methyl 3-O-benzoyl-2,6-dideoxy-α-L-arabino-hexopyranoside (13 and 14). Treatment of 8 (1 g, 6.16 mmol) according to procedure D with benzoyl chloride led to 78 mg (5 %) of 13 and 1.15 g (70 %) of 14 separated by flash chromatography (hexane-ethyl acetate, 4:1). 13 and 14 were identical in all respects with the literature data.[12]

Methyl 2,6-dideoxy-3,4-di-O-p-nitrobenzoyl and methyl 2,6-dideoxy 3-O-p-nitrobenzoyl-α-L-arabino-hexopyranoside (15 and 16). Treatment of 8 (1g, 6.16 mmol) according to procedure D (with p-nitrobenzoyl chloride) afforded 95 mg (5 %) of 15 and 1.98 g (70 %) of 16 easily separated by flash chromatography (hexane-ethyl acetate 3:1).

15 : m.p. 78°C (hexane) ; $|\alpha|_D^{20}$ +9° (c 1.93, chloroform) ; IR_{max}^{Nujol} : 1720, 1280, 1050 (ester), 1610, 1595 cm^{-1} (Ar). ^1H NMR : δ 8.30-8.10 (m, 8H, aromat.), 5.69 (m, 3-H), 5.19 (dd,

J = J' = 10, 4-H), 4.85 (d, J = 3, 1-H), 4.09 (m, 5-H), 2.48 (dd, J = 13, J' = 5, 2e-H), 2.02 (m, J = 13, J' = 10, J" = 3, 2a-H), 1.30 (d, J = 7, 6-CH_3).

Anal. Calcd for $C_{21}H_{20}N_2O_{10}$ (460.41) : c, 54.78, H, 4.38 ; Found : C, 54.92, H, 4.29

16 : m.p. 164°C (hexane-acetone) ; $|\alpha|_D^{20}$= -76° (c 1.13, chloroform) ; IR : 3700 (OH), 1720, 1275, 1050, 1040 (ester), 1610 cm^{-1} (Ar). ^1H NMR : δ 8.30 (d, J = 9) and 8.24 (d, J = 9)(AB, 4H, aromat.), 5.33 (m, 3-H), 4.77 (d, J = 3, 1-H), 3.74 (m, 5-H), 3.41 (dd, J = J' = 10, 4-H), 3.33 (s, OCH_3), 2.31 (dd, J = 13, J' = 5, 2e-H), 1.89 (m, J = 13, J' = 10, J" = 3, 2a-H), 1.36 (d, J = 7, 6-CH_3).

Anal. Calcd for $C_{14}H_{17}NO_7$ (311.30) : C, 54.01, H, 5.50, O, 35.97 ; Found : C, 54.15, H, 5.60 ; O, 36.01.

Methyl 2,6-dideoxy-3-O-methyl and methyl 2,6-dideoxy-4-O-methyl α-L-arabino-hexopyranosides (17 and 18). Treatment of 8 (500 mg, 3 mmol) according to procedure C gave 255 mg (52 %) of 17 and 100 mg (≃18 %) of 18 separated by column chromatography (hexane-ethyl acetate, 3:1). Physical and spectroscopic data were in agreement with the literature[13] for 17 while 18 could be crystallized from hexane-acetone.

18 : m.p. 75-77°C, $|\alpha|_D^{20}$ -105° ; ^1H NMR : δ 4.68 (d, J = 3, 1-H), 3.90 (m, 3-H), 3.60-3.48 (m, 5-H), 3.54 (s, OMe), 3.28 (s, OMe), 2.67 (dd, J = J' = 9, 4-H), 2.07 (m, J = 13, J' = 5, 2e-H) and 1.65 (m, J = 13, J' = 9, J" = 3, 2a-H), 1.32 (d, J = 7, 6-CH_3).

Anal. Calcd for $C_8H_{16}O_4$ (176.21) : C, 54.53 H, 9.15, O, 36.32 ; Found : C, 54.65 H, 9.32 O, 36.25.

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