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ACID - CATALYZED REARRANGEMENT OF BUTYL 2-O-ACETYL-4,5-ANHYDRO-3,6-DIDEOXY-HEXALDONATE. SYNTHESIS OF RACEMIC EPIALLOMUSCARINE AND EPIMUSCARINE

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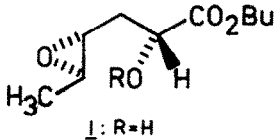
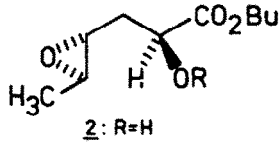
Abstract - Butyl 2-O-acetyl-4,5-anhydro-3,6-dideoxy-DL-*xylo*-hexaldonate (4) in the presence of $SnCl_4$ underwent an intramolecular rearrangement to give 2,5-anhydro ester 7. On the other hand the *lyxo* epimeric epoxide 5 under the same conditions afforded esters 7 and 8. Ester 7 was transformed into racemic epiallomuscarine (12), whereas the isomer 8 into racemic epimuscarine (13).

Butyl *trans* 4,5-anhydro-3,6-dideoxy-DL-*xylo*-hexaldonate (1) treated with a Lewis acid catalyst underwent the intramolecular opening of the oxirane ring and gave butyl 2,5-anhydro-3,6-dideoxy-DL-*arabino*-hexaldonate (3)[1]. On the other hand the epimeric epoxide 2 with *lyxo* configuration under the same conditions afforded an unidentified polymeric product[1,2]. The formation of 3 proceeds through the carbocationic 5-*endo* process which does not obey the Baldwin rules for ring closure[3].

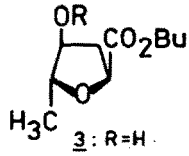
The intramolecular opening of the oxirane ring enabled a new synthesis of C-glycofuranoside type compounds. In order to demonstrate these new synthetic possibilities we have already reported a new simple preparation of racemic allomuscarine from 3[1,2].



1: R=H
4: R=Ac



2: R=H
5: R=Ac



3: R=H
6: R=Ac

C-glycofuranosides having 2,5-anhydro-3,6-dideoxyalditol skeleton occur in Nature as components or parts of numerous toxins such as muscarines, boromycin, palytoxin etc. Growing interest in the synthesis of C-glycosides prompted us to investigate further applications of β-hydroxyepoxides as potential substrates for the construction of 2,5-anhydroalditols.

A review of the literature revealed that *cis* and *trans* 1-acetoxy-3,4-epoxypentanes in the presence of BF_3 - etherate underwent a rearrangement leading to the migration of the acetyl group with the formation of a tetrahydrofuran ring[5]. The reaction proceeded with the overall retention of configuration at the epoxide ring carbon atoms with the intermediary orthoesters. Bearing in mind the mechanism of the rearrangement, we decided to examine the application of acetoxyepoxides 4 and 5 as the substrates for the formation of the C-glycofuranoside skeleton.

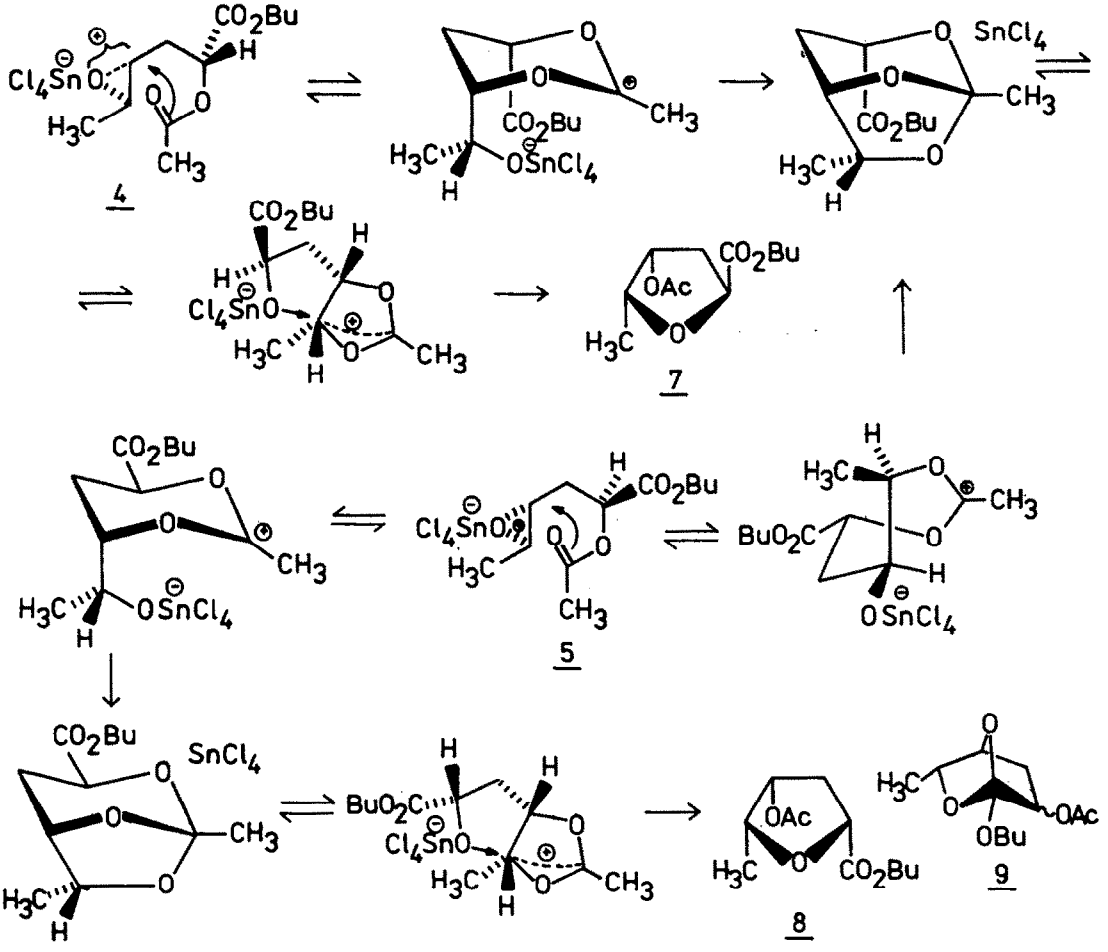
RESULTS AND DISCUSSION

A mixture of stereomeric epoxides 4 and 5 was prepared from the corresponding alcohols 1 and 2 using standard acetylation procedure. 4 and 5 can be separated into pure components by HPLC or by a multiple chromatography on a silica gel open tubular column. The rearrangement experiments were pe-

rformed using the mixture of 4 and 5. Reactions with pure epoxides were performed only on an analytical scale and were monitored by TLC.

The mixture of 4 and 5 when treated with 1 equiv. of tin tetrachloride in methylene chloride at -20°C gave three stereomeric products 6, 7 and 8 in the ratio of about 0.2 : 2.3 : 1 respectively. The products were separated into pure isomers by chromatography. Experiments performed on pure substrates revealed the stereochemical pathway of the reaction. The epoxide 4 afforded 7 as the sole product whereas the epoxide 5 gave 8 and 7. The formation of 6 from a mixture of 4 and 5 can be explained by the contamination of the starting material with epoxides of *arabino* and *ribo* configuration[2,6]. This contamination was removed when isomers 4 and 5 were separated and purified by HPLC.

Scheme 1[4]



The stereochemical pathway of the rearrangement confirmed our expectations based on literature data[5]. The reaction proceeds *via* the carbocationic mechanism involving the orthoester stage shown on Scheme 1. The reaction sequence leading from 4 to 7 and from 5 to 8 is initiated by the 6-*exo* opening of the oxirane ring. The formation of 7 from the epoxide 5 required the alternative way of rearrangement which proceeded with 7-*endo* ring closure at the first step of reaction (Scheme 1). The formation of orthoesters 9 which could result from a competitive intramolecular reaction involving oxirane ring opening by butyl ester carbonyl group was not detected. Such rearrangement was observed by us previously[2].

The configuration of the side product 6 was assigned by comparison of its spectral data with those found for a sample obtained on the other way[2]. The configuration of 7 and 8 was proved unequivocally *via* their transformation into epiallomuscarine (12) and epimuscarine (13) respectively (Scheme 2; Table 1).

Scheme 2[4]

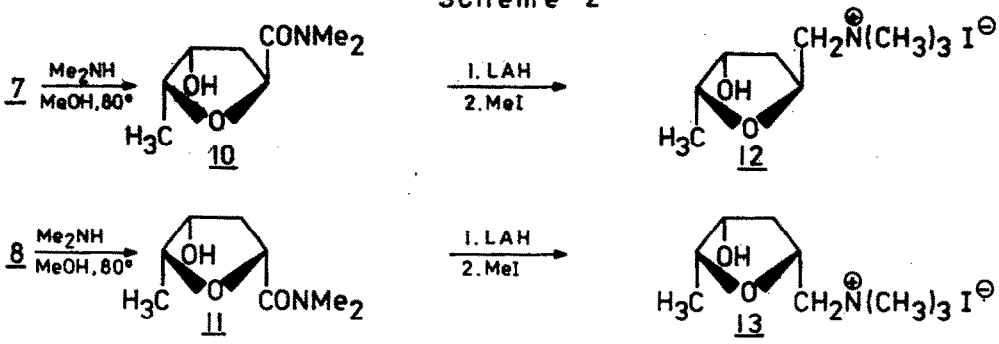


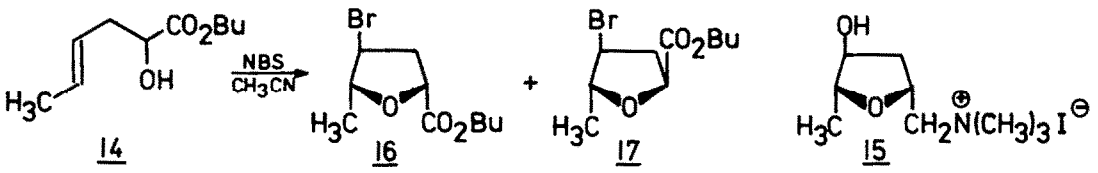
Table 1. Selected ^1H NMR chemical shifts and coupling constants of compounds 6 - 8, 10, 11, 16, 17 ($CDCl_3$) and 12, 13 (DMSO-d_6).

Comp.	H-1	H-2	H-3	H-3'	H-4	H-5	H-6	J_{23}	$J_{23'}$	$J_{33'}$	J_{34}	$J_{3'4}$	J_{45}
6	-	4.61	2.26	2.60	4.85	4.30	1.28	3.6	9.2	14.1	2.7	6.6	3.2
7	-	4.64	2.38		5.31	4.30	1.24	$\Sigma\|J\|$=16.0		*	$\Sigma\|J\|$=7.2		3.6
8	-	4.45	2.29	2.61	5.24	4.12	1.29	4.7	9.4	14.4	1.9	6.0	4.1
10	-	4.91	2.15	2.57	4.26	4.09	1.26	7.6	8.0	13.6	~0.7	5.2	3.2
11	-	4.90	2.26	2.34	4.05	3.98	1.32	1.8	9.3	13.8	~0	5.1	2.9
12	3.43	4.59	2.03	1.75	4.04	3.98	1.12	7.0	9.0	13.2	0.9	4.6	3.2
13	3.50	4.33	1.49	2.39	4.02	3.80	1.13	5.6	8.5	13.7	2.2	5.8	3.7
16	-	4.68	2.65		4.29	3.96	1.41	$\Sigma\|J\|$=14.0		*	$\Sigma\|J\|$=9.5		~0
17	-	4.60	2.41	2.98	~4.3	3.75	1.38	6.9	8.1	13.5	8.7	8.1	~0

* not visible

Transformation of epoxides 1, 4 and 5 either *via* direct opening of the oxirane ring in 1 or *via* the rearrangement and migration of the 2-O-acetyl group furnished a facile and stereocontrolled procedure for the preparation of DL-allomuscarine[1,2],(16), DL-epiallomuscarine (12) and DL-epimuscarine (13). These syntheses are based on ready available butyl E 2-hydroxy-hex-4-enoate (14)[6]. Although syntheses of allomuscarine (16), epiallomuscarine (12) and epimuscarine (13) have been already attempted[7,9,10] a simple stereocontrolled synthetic route to these biologically active compounds is still in demand. It is noteworthy that transformations attempted by us to obtain DL-muscarine failed.

Scheme 3[4]



As an alternative way for the formation of tetrahydrofuran ring from the adduct 14 we investigated the intramolecular bromoetherification using NBS in acetonitrile (Scheme 3). This process gave bromocompounds 16 and 17 with a relative low yield and poore stereoselectivity (1 : 2) and was not investigated further. Compounds 16 and 17 were separated into pure components by chromatography. The *arabino* configuration was assigned to the major product by analogy with the opening of the oxirane ring in 1 and 2.

EXPERIMENTAL

^1H NMR spectra were recorded in $CDCl_3$ solutions with a Jeol JNM-4H-100, a Varian - 300 and a Bruker - 500 spectrometers (TMS=0ppm). ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer in $CDCl_3$ solutions (TMS=0ppm). IR spectra were obtained on a Unicam SP-200 spectrophotometer. Melting

points are uncorrected. TLC was performed on Merck DC Alufolien (Kieselgel 60 F-254) and column chromatography using silica gel Merck (230-400mesh).

As the catalyst, stannic chloride solution in CH_2Cl_2 (1mmol/1mL) was employed.

The compounds 4 and 5 were separated by preparative HPLC using 5 3/8" x 30cm columns filled with 10μ Lichrosorb Si 60, which were eluted with hexane/ethyl acetate 80 : 20 solvent system. The chromatograph was home assembled and included, Orlita SDS, home made injector and Varian RI detector. The chromatography was repeated several times and 50mg samples were separated in each injection.

Butyl 4-O-acetyl-2,5-anhydro-3,6-dideoxy-DL-*lyxo*, *xylo*, and *arabino*-hexaldonates (6, 7 and 8). A solution of the mixture of epoxides 4 and 5 (0.250g, 1mmol) in dry CH_2Cl_2 (10mL) was cooled to -20°C and treated under dry argon with $SnCl_4$ in CH_2Cl_2 (1mL). The solution was stirred for 2hr and then 20mL of CH_2Cl_2 was added. The mixture was washed with saturated $NaHCO_3$ and water, dried and the solvent evaporated. The oily residue was separated on a silica gel column using benzene - Et_2O 97:3 v/v as eluent. Three fractions were obtained:

7: (0.100g, 40%), colorless oil bp. 120°C/0.2Torr (air bath); IR (film): 1740, 1240cm^{-1}; ^{13}C NMR ($CDCl_3$): 13.68, 19.07, 30.62, 65.03 (butyl), 14.13 (C-6), 37.52 (C-3), 75.08, 75.18 (C-4, C-5), 78.47 (C-2), 173.06 (C-1).

6: (0.010g, 4%), colorless oil bp. 120°C/0.2Torr (air bath); IR (film): 1740, 1235cm^{-1}; ^{13}C NMR ($CDCl_3$): 13.66, 19.08, 30.67, 64.90 (butyl), 13.79 (C-6), 35.58 (C-3), 75.50, 77.11 (C-4, C-5), 78.69 (C-2), 172.60 (C-1) - data identical with those found for a sample obtained on the other way[2].

8: (0.043, 17%), colorless oil bp. 120°C/0.2Torr (air bath); IR (film): 1750, 1250cm^{-1};

(Anal. taken for a mixture of 6, 7 and 8; found: C, 58.8; H, 8.1. Calc. for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25)

2,5-Anhydro-3,6-dideoxy-N,N-dimethyl-DL-*lyxo*-hexaldonamide (10). A solution of 7 (0.20g, 1mmol) in 20% methanolic dimethylamine (5mL) was heated at 80°C in a steel bomb for 24hr. The solution was evaporated and purified by chromatography to give 10 (0.13g, 75%); mp. 62-64°C; IR (nujol): 3400, 1640cm^{-1}. (Found: C, 55.5; H, 8.9; N, 7.9. Calc. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09)

2,5-Anhydro-3,6-dideoxy-N,N-dimethyl-DL-*xylo*-hexaldonamide (11). 11 was prepared from 8 according to the procedure described above (70%); colorless syrup; IR (film): 3400, 1640cm^{-1}. (Found: C, 55.3; H, 8.8; N, 8.0. Calc. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09)

DL-Epiallomuscarine Iodide (12). Amide 10 (0.10g, 0.58mmol) was dissolved in THF (2mL) and slowly added to gently refluxing suspension of LAH (0.15g) in THF (3mL). After completion of the addition, the mixture was refluxed for 3hr. The excess of LAH was decomposed with water (0.2mL) and 10% NaOH aq. (0.2mL). The solution was filtered and the precipitate was washed with THF. The combined extract was dried and evaporated to dryness. The residue was dissolved in anhydrous ether (2mL), methyl iodide (2mL) was added and the mixture was left overnight. The colorless crystals were filtered and recrystallized from aceton - petroleum ether to give 12 (0.09g, 50%); mp. 160-161°C (lit.[7,8] mp. 159-160°C for DL-epiallomuscarine iodide); IR (nujol): 3400cm^{-1}; (Found: C, 35.7; H, 6.4; N, 4.5. Calc. for $C_9H_{20}INO_3$: C, 35.89; H, 6.69; N, 4.64)

DL-Epimuscarine Iodide (13). 13 was obtained from 11 according to the procedure described for 12. Colorless crystals mp. 133-135°C (aceton - petroleum ether) lit.[7] mp. 130-131°C. (Found: C, 35.6; H, 6.5; N, 4.6. Calc. for $C_9H_{20}INO_3$: C, 35.89; H, 6.69; N, 4.64)

Butyl 2,5-anhydro-4-bromo-3,4,6-trideoxy-DL-*ribo* and *arabino*-hexaldonates (16 and 17). A solution of 14 (0.36g, 2mmol) in dry acetonitrile (10mL) was cooled to 0°C and treated with NBS (0.7g, 4mmol) in four portions. The mixture was stirred at 0°C for 48hr. Subsequently the solvent was evaporated and the residue was separated on a silica gel column using hexane - Et_2O 9.5:0.5 v/v as eluent and gave two fractions:

16: (0.08g, 15%), colorless syrup bp. 130°C/0.2Torr (air bath); IR (film): 1750, 1240cm^{-1};

17: (0.12g, 23%), colorless syrup bp. 130°C/0.2Torr (air bath); IR (film):1740, 1240cm^{-1}.

(Anal. taken for a mixture of 16 and 17; found: C, 45.2; H, 6.7. Calc. for $C_{10}H_{17}BrO_3$: C, 45.28; H, 6.46)

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