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Preliminary communication

A general method for synthesis of alkyl 2-*N*-substituted and 2-*N*,*N*-disubstituted D-altrosamines

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Amino alcohols are widely used in asymmetric synthesis [1]. Their applications are very diverse: chiral catalysts, chiral adjuvants, etc. Some years ago, we started to use 2-amino sugar derivatives in several fields of our work [2–6]. Thus, 4,6-protected hexopyranoside derivatives from D-glucose and D-allose have been used in the synthesis of oxazolidines [2], while alkyl 2-amino sugar derivatives with D-*gluco*, D-*allo*, and D-*altro* configuration have been used as starting materials in the development of a novel method for 2-aminoglycal synthesis [3].

For this reason, we have developed some general methods for the synthesis of 2-alkylamino sugar derivatives with the above-mentioned configurations. The substances obtained by these methods had not been described previously. In previous work [4–6], we described the synthesis of benzyl 2-alkylamino- and 2-dialkylamino-D-glucopyranoside derivatives by opening of a sugar 2,3-fused oxazolidine ring, using various hydrides and organometallic reagents.

In this paper, we propose a general method for the synthesis of new 2-amino sugar derivatives with D-*altro* configuration by an opening reaction of the oxirane ring present in alkyl 2,3-anhydro-4,6-*O*-benzylidene-D-allopyranoside derivatives with several primary and secondary amines, and using lithium perchlorate as catalyst. This methodology has already been used on simpler oxiranes and simpler amines [7], but not on

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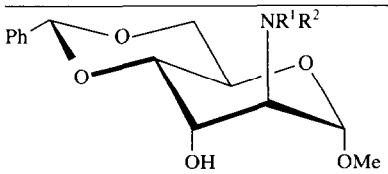
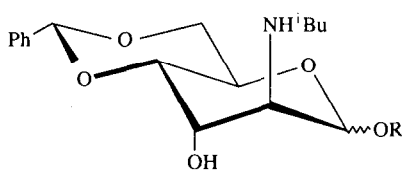
Table 1
New 2-alkylamino- and 2-dialkylamino-altrose derivatives

Product	R^1	R^2	Yield (%)	$[\alpha]_D^{25}$ (deg)	mp (°C)
					
1	*n*-Pr	H	90	+63.7 (*c* 1.8) [a]	166–167
2	*n*-Bu	H	92	+62.5 (*c* 1.2) [a]	154–155
3	*n*-$C_{12}H_{25}$	H	95	+42.3 (*c* 2.1) [a]	121–122
4	*n*-$C_{16}H_{33}$	H	94	+39.0 (*c* 1.6) [a]	98–99
5	*i*-Bu	H	96	+63.4 (*c* 1.5) [a]	156–167
6	Allyl	H	94	+59.8 (*c* 1.4) [a]	198–199
7	Bn	H	95	+43.0 (*c* 0.7) [a]	164–165
8	*i*-Pr	H	96	+74.5 (*c* 1.9) [a]	153–154
9	c-Hex	H	92	+125.3 (*c* 0.3) [a]	152–153
10	*t*-Bu	H	77	+70.3 (*c* 1.1) [a]	118–119
11	1-Adamantyl	H	75	+116.8 (*c* 0.6) [a]	148–149
12	Ph	H	78	+77.9 (*c* 1.7)) [a]	175–176
13	CH_2CH_2OH	H	89	+62.3 (*c* 2.1) [b]	163–164
14	$CH_2CH(OH)Me$	H	90 [c]	+52.6 (*c* 1.7) [b,d]	155–156 [d]
15	$CH_2CH(OH)Ph$	H	92 [c]	+33.5 (*c* 1.9) [b,d]	198–199 [d]
16	$CH(CH_2OH)CH(OH)Ph$	H	82	+87.6 (*c* 1.5) [b]	213–214
17	$CH_2CH_2CH_2NMe_2$	H	96	+38.1 (*c* 2.0) [a]	134–135
18	Et	Et	83	+99.3 (*c* 3.5) [a]	oil
19	$CH_2(CH_2)_2CH_2$		78	+59.8 (*c* 1.8) [a]	112–113
20	$CH_2(CH_2)_3CH_2$		82	+90.8 (*c* 1.3) [a]	117–118
21	$CH_2CH_2OCH_2CH_2$		89	+71.7 (*c* 1.2) [a]	118–119
22	$CH_2CH_2N{=}C(Me)$		76	+61.8 (*c* 0.7) [a]	117–118



23 R = αBn (86%) $[\alpha]_D^{25} = +324.6°$ (*c* 0.5) [a] mp = 96–97°C
24 R = βPh (77%) $[\alpha]_D^{25} = -208.0°$ (*c* 0.6) [a] mp = 212–213°C

[a] Dichloromethane as solvent.
[b] DMF as solvent.
[c] Before crystallization.
[d] For the diastereomer isolated by crystallization.

polyoxygenated oxiranes, as are sugar derivatives. Table 1 shows the substances obtained (**1–24**). The products were isolated in good yield (> 75%), even when very functionalized amines were used (**14–16** and **22**).

The reaction occurs by addition of the amine to a solution of the starting oxirane and

the catalyst in acetonitrile at 90 °C. The general procedure is given below. The shortest reaction times (12–24 h) were obtained when primary (RCH_2NH_2) or secondary (RCH_2NHCH_2R) amines without branching in the α-position were used. The reaction rate slowed (36–48 h) when amines with branching in the α-position (*i*-$PrNH_2$, cyclohexylamine, *t*-$BuNH_2$, adamantylamine) or an aromatic amine ($PhNH_2$) were used. The longest reaction times (3–4 days) were observed when the reagent also had one or two oxygen atoms, as these could also competitively coordinate with the lithium cations.

Besides the good yield obtained, the reactions were accomplished with very high regio- and stereo-selectivity, 2-Alkylamino- or 2-dialkylamino-altrose derivatives were always obtained (NMR data), in agreement with the general rule in ring-opening reactions of an oxirane fused to rigid systems. However, compound **18** (83%) and an isomer (3%) were obtained when diethylamine was used. They were characterized by NMR data [1], the latter being identified as methyl 4,6-*O*-benzylidene-3-deoxy-3-diethylamino-α-D-glucopyranoside (**25**).

When the ring-opening reaction was carried out with racemic 3-amino-2-propanol or 2-amino-1-phenylethanol, a diastereomeric mixture (ca. 1 : 1, as detected by ^{1}H NMR) was obtained. Crystallization from ethanol led to a pure diastereomer in each case. Both diastereomers could be isolated by chromatography on silica gel. We are currently using these compounds (**14** and **15**) as a source of new chiral oxazolidines not fused to the sugar ring.

In addition, the acetyl derivatives of all the amino alcohols obtained were prepared for characterization. It is noteworthy that in substances with α-ramification in R^1, such as **8–12** and **16**, only *O*-acetylation was observed. *N*-Acetylation did not occur with either longer reaction time or higher temperature. This could be explained by the nitrogen atom's being strongly hindered by both its axial position on the sugar ring and the group in the α-position in R^1, which prevent its reaction with electrophilic reagents.

The products obtained were characterized by their elemental analyses, MS (CI and EI) data, and NMR (DEPT, COSY, and CHCORR experiments) data. We have recently reported [8] the analysis of the mass spectra of all the products described in this paper.

General procedure.—A solution of the oxirane (10 mmol) and $LiClO_4$ (20 mmol) in MeCN (40 mL) was heated under stirring at 90 °C, and the corresponding amine (40 mmol) was added. The mixture was stirred until completion of the reaction (TLC) (time indicated above). It was then left to cool to room temperature and poured into ice–water with stirring. In most cases, the precipitate obtained was filtered off and crystallized from EtOH or EtOH–water. In some cases (**18**, **19**, and **20**), the reaction mixture was soluble in ice–water. The aqueous solution was extracted with CH_2Cl_2 and the combined extracts were washed with water. The organic phase was dried (Na_2SO_4) and

[1] For **18**: Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.29; H, 7.78; N, 3.99. Mass spectrum (CI): *m/z* 338 (20%) $[M+H]^+$. ^{1}H NMR data (200 MHz, $CDCl_3$, 25 °C): δ 4.67 (s, 1 H, H-1), 3.08 (d, 1 H, $J_{2,3}$ 1.8 Hz, H-2), 4.14 (dd, 1 H, $J_{3,4}$ 3.0 Hz, H-3).

For **25**: Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 63.95; H, 7.96; N, 4.02. Mass spectrum (CI): *m/z* 338 (100%) $[M+H]^+$. ^{1}H NMR data (200 MHz, $CDCl_3$, 25 °C): δ 4.92 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 3.52 (dd, 1 H, $J_{2,3}$ 10.2 Hz, H-2), 3.24 (t, 1 H, $J_{3,4}$ 10.2 Hz, H-3).

evaporated in vacuo to dryness. The solid obtained was crystallized (**19** and **20**) or fractionated by chromatography on a silica gel column (**18** and **25**).

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