A New Approach to the Stereospecific Synthesis of Branched-chain Sugars

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Darzens condensation of two readily available carbohydrate ketones with chloromethyl *p*-tolyl sulphone gave stereospecifically α,β-epoxy sulphones, in the presence of azide ion the latter afforded branched-chain functionalized azido-sugars.

The natural occurrence of branched-chain amino-sugars in various antibiotics has stimulated a considerable amount of research towards their synthesis.[1] We report a new approach to these compounds, based on the stereospecific formation from uloses of α, β-epoxy sulphones, followed by opening of their three-membered ring in the presence of azide ions. The method proposed has great versatility since it allows the generation of α-azido aldehydes which may be subsequently transformed into almost any type of functionalized branched-chain amino-sugars.

Vogt and Tavares have reported that aldehydes and ketones undergo Darzens condensation with α-halogeno sulphones in the presence of potassium t-butoxide as base.[2] By an appropriate modification of the experimental conditions,† we have succeeded, with chloromethyl *p*-tolyl sulphone, in forming stereospecifically α,β-epoxy sulphones (**3**) and (**4**),‡ with the expected stereochemistry at the quaternary centres, in good yields (75%) from the two readily available carbohydrate ketones (**1**) and (**2**).§ In the presence of sodium azide, α,β-epoxy sulphones (**3**) and (**4**) furnished α-azido aldehydes (**5**) and (**6**) respectively (75—78%). Sodium borohydride treatment of aldehydes (**5**) and (**6**) followed by exposure of the trifluoromethanesulphonates of the resulting primary alcohols (**7**) and (**8**) to tetrabutylammonium fluoride afforded the α-fluoromethyl azido-sugars (**15**) and (**16**) respectively in

† In a typical experiment, to a solution of chloromethyl *p*-tolyl sulphone (10 mM) and ulose (10 mM) in a mixture of tetrahydrofuran (75 ml) and t-butyl alcohol (2 ml) at 5 °C was added in small portions potassium t-butoxide (10 mM). The mixture was then stirred for 3 h at room temperature. Usual workup followed by chromatography gave pure α,β-epoxy sulphone.

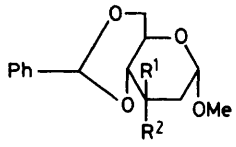
‡ Although only one isomer is formed, the stereochemistry at the epoxymethine carbon is unknown.

§ The reaction was also investigated with a number of other carbohydrate derived ketones. However, the absence of stereoselectivity and modest yields in the generation of the corresponding α,β-epoxy sulphones diminish the synthetic utility of the Darzens condensation on these uloses.

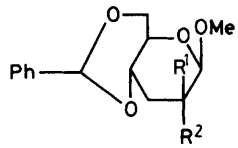
Table 1. ^{13}C Chemical shifts (δ values).[a]

Carbon	(3)	(5)	(7)	(9)	(10)	(11)	(12)	(4)	(6)	(8)	(13)	(14)
C-1	98.1	97.5	98.1	99.0	99.0	98.9	99.0	99.2	106.1	106.7	105.6	105.4
C-2	33.1	38.4	36.2	42.6	41.8	43.4	41.6	69.3	68.4	64.5	55.0	53.6
C-3	66.6	66.7	63.1	69.5	68.5	49.9	49.2	31.1	34.5	34.6	39.1	39.1
C-4	75.3	83.0	83.9	85.5	83.3	86.6	84.1	75.7	74.1	74.6	74.9	72.3
C-5	61.6	61.0	61.3	61.8	59.7	61.2	59.4	71.0	71.1	71.4	71.6	71.4
C-6	69.9	69.6	69.5	69.5	69.4	69.5	69.3	68.8	68.6	68.8	68.8	68.7
C-7	102.3	102.3	102.2	101.8	101.7	101.9	101.7	101.8	102.1	102.1	102.1	102.4
OMe	55.4	55.3	55.3	55.1	55.4	55.0	55.1	57.3	57.4	57.4	57.6	57.8
	SO_2CH	CHO	CH_2OH	3-Me	3-Me	3-Me	3-Me	SO_2CH	CHO	CH_2OH	CN	CN
	63.5	196.5	64.6	22.8	25.3	22.9	28.0	64.6	197.9	62.7	120.9	121.1

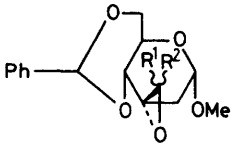
[a] Chemical shifts for aromatic carbons are not given; (3) and (4) exhibit Me signals at δ 21.8. Spectra were measured in $DCCl_3$ solution at 50.31 MHz.



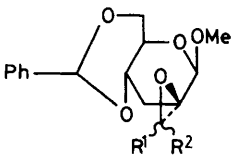
(1) $R^1R^2 = O$
(5) $R^1 = N_3$; $R^2 = CHO$
(7) $R^1 = N_3$; $R^2 = CH_2OH$
(9) $R^1 = OH$; $R^2 = Me$
(10) $R^1 = Me$; $R^2 = OH$
(11) $R^1 = NH_2$; $R^2 = Me$
(12) $R^1 = Me$; $R^2 = NH_2$
(15) $R^1 = N_3$; $R^2 = CH_2F$
(17) $R^1 = H$; $R^2 = CH_2OH$



(2) $R^1R^2 = O$
(6) $R^1 = CHO$; $R^2 = N_3$
(8) $R^1 = CH_2OH$; $R^2 = N_3$
(13) $R^1 = CN$; $R^2 = NH_2$
(14) $R^1 = NH_2$; $R^2 = CN$
(16) $R^1 = CH_2F$; $R^2 = N_3$
(18) $R^1 = OH$;
$R^2 = CH_2SO_2C_6H_4p\text{-}Me$

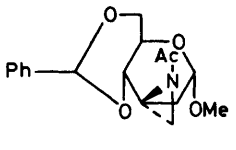


(3)

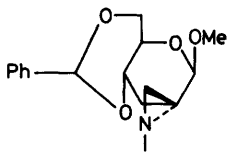


(4)

$R^1 = H, R^2 = SO_2C_6H_4Me\text{-}p$



(19)



(20)

quantitative yields. The latter appear to be excellent optically active synthons for the preparation of α-fluoromethyl α-amino acids which exhibit enzyme inhibitor properties.[3]

The stereochemistry at the quaternary centres of α,β-epoxy sulphones (3) and (4) was established by a ^{13}C n.m.r. study (Table 1) of the azido aldehydes (5) and (6) and azido hydroxymethyl compounds (7) and (8) which they respectively furnished. ^{13}C n.m.r. spectroscopy has been shown to be useful for the determination of the configuration of substituents on quaternary centres.[4] Thus, a greater steric compression effect is experienced by C-5 in (10) and (12) than in their epimers (9) and (11). In the former pair of models the axial H-5 interacts 1,3-diaxially with a C-3/heteroatom linkage and not as in (9) and (11) with a C-3/carbon bond [C-5 Δδ (9)–(10) 2.1; (11)–(12) 1.8 p.p.m.] (Table 1). The chemical shift of C-5 in the spectrum of (5) and (7) is characteristic of compounds having axially disposed carbon–carbon bonds at C-3. Similarly, C-4 in model (14) is shielded by 2.6 p.p.m. relative to its epimer (13). The chemical shift of C-4 in the spectrum of (6) and (8) indicates that these compounds have axially oriented carbon–carbon linkages at C-2.

The stereochemistry at the quaternary centres was also established by direct chemical correlation. Thus, lithium aluminium hydride treatment of the methanesulphonate of (7) and (8) gave, after acetylation of the reaction products, the *N*-acetyl aziridines (19)[5] and (20)[6] respectively.

Thus, ring opening with the azide nucleophile of the α,β-epoxy sulphones studied is shown to occur with complete regiospecificity at the β-carbon with respect to the sulphone group and according to an S_N2 reaction. The nucleophilic attack of ketones (1) and (2) took place as expected, from the less hindered β and α face, respectively.

The behaviour of the α,β-epoxy sulphones (3) and (4) was also investigated in the presence of hydride ion. Although lithium triethylborohydride treatment of (3) afforded the branched-chain sugar (17) in about 60% yield, α,β-epoxy sulphone (4) furnished only the tertiary alcohol (18) with various reagents. Access to (17) by this method is of synthetic utiltity in view of the complex mixture obtained upon hydroboration of the Wittig product from (1).[7]

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6 Compound prepared by the cyanohydrine route,[4] unpublished results.
7 Unpublished observation.