The Synthesis of (2*R*,3*S*,4*R*)-4-Benzyloxy-2-benzyloxymethyl-3-hydroxy-*N*-toluene-*p*-sulphonylpyrrolidine

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Summary The synthesis of a pyrrolidine ring system has been achieved from D-ribono-1,4-lactone.

IN connection with our synthetic work[1] on pyrrolidine derivatives, we report the synthesis of the title compound by a new approach, using as starting material D-ribono-1,4-lactone (**1**).

(2*R*,3*S*,4*R*)-4-Benzyloxy-2-benzyloxymethyl-3-hydroxypyrrolidine and related diastereoisomeric heterocyclic derivatives are of interest as skeletal analogues of the antitumour antibiotic, anisomycin.[2]

Treatment of 2,3-*O*-cyclohexylidene-D-ribono-1,4-lactone[3] (**2**) with toluene-*p*-sulphonyl chloride in pyridine yielded the 2,3-*O*-cyclohexylidene-5-*O*-toluene-*p*-sulphonyl-D-ribono-1,4-lactone (**3**). The sulphonate (**3**) was converted into 5-azido-2,3-*O*-cyclohexylidene-5-deoxy-D-ribono-1,4-lactone (**4**), m.p. 81—82°, $[\alpha]_D$ + 20·9° (*c* 0·91;$CHCl_3$) in 78% yield, by a displacement reaction with sodium azide in dimethylformamide. Selective reduction of (**4**), using sodium borohydride in propan-2-ol at 0° afforded 5-azido-2,3-*O*-cyclohexylidene-5-deoxy-D-ribitol (**5**), characterised as crystalline di-*p*-nitrobenzoate (**6**), m.p. 117—118°, $[\alpha]_D$ −26·7° (*c* 1·61; $CHCl_3$). Benzylation of 5-azido-2,3-*O*-cyclohexylidene-5-deoxy-D-ribitol (**5**), with benzyl chloride–sodium hydride in dimethyl sulphoxide gave 5-azido-1,4-di-*O*-benzyl-2,3-*O*-cyclohexylidene-5-deoxy-D-ribitol (**7**). Mild acidic hydrolysis of the cyclohexylidene group in (**7**) using Amberlite IR 120(H^+) afforded 5-azido-1,4-di-*O*-benzyl-5-deoxy-D-ribitol (**8**), m.p. 95—96°, $[\alpha]_D$ −36·7° (*c* 0·9;$CHCl_3$).

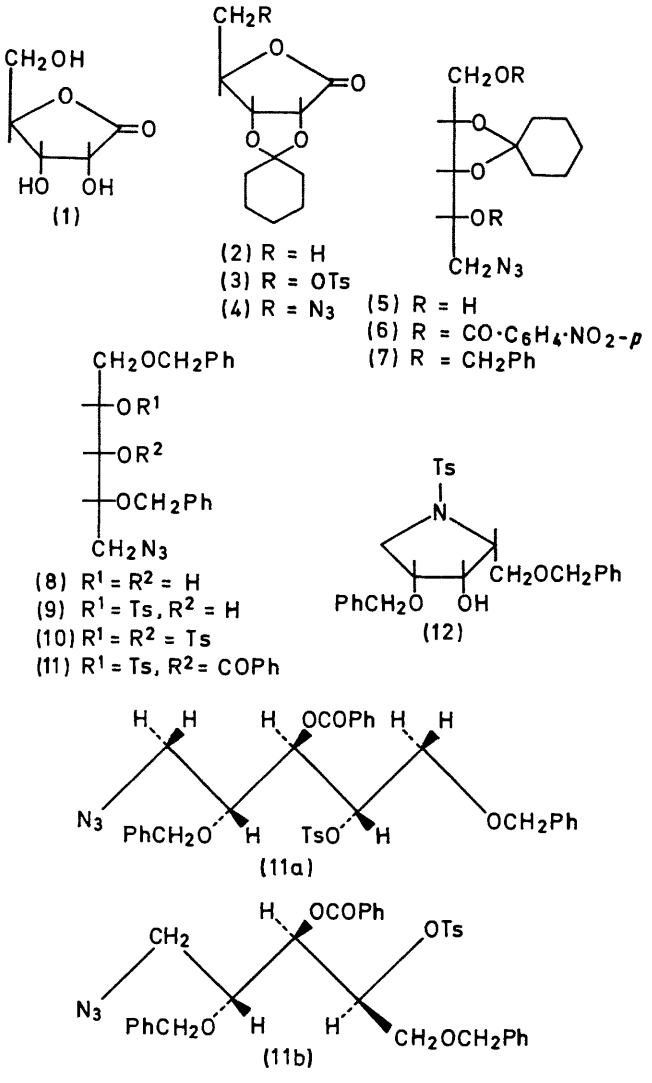
Since the purpose of this study was to obtain the pyrrolidine derivatives by intramolecular cyclization, we decided to introduce a leaving group at C-2 of the diol (**8**). Reaction of 5-azido-1,4-di-*O*-benzyl-5-deoxy-D-ribitol (**8**) with 3 molar equivalents of toluene-*p*-sulphonyl chloride in pyridine gave a mixture of two products. From this mixture a crystalline di-sulphonate (**10**), m.p. 77—79°, $[\alpha]_D$ −22° (*c* 0·91; $CHCl_3$) and a crystalline mono-sulphonate, m.p. 82—83°, $[\alpha]_D$ + 11·7° (*c* 1·37; $CHCl_3$) were isolated in the ratio 1 to 9. The n.m.r. spectrum of the mono-sulphonate did not provide clear-cut evidence of the location of the sulphonate ester group. After treatment of the mono-sulphonate with benzoyl chloride, it was readily converted into its syrupy mono-benzoate.

The n.m.r. spectrum of the mono-benzoate (Table) was entirely consistent with structure (**11**). Consequently, the mono-sulphonate must be 5-azido-1,4-di-*O*-benzyl-5-deoxy-2-*O*-toluene-*p*-sulphonyl-D-ribitol (**9**), the desired product for subsequent cyclization.

The final step in the sequence for the preparation of the pyrrolidine ring was accomplished by a reductive cyclisation. Hydrogenation of the azide (**9**) with Adams's catalyst, followed by toluene-*p*-sulphonylation, gave a crystalline compound, m.p. 63—64°, $[\alpha]_D$ −46° (*c* 1; $CHCl_3$). Its elemental analyses and mass and n.m.r. spectral data were compatible only with structure (**12**). The formation of the pyrrolidine ring can be rationalized in

N.m.r. data of 5-*azido*-3-O-*benzoyl*-1,4-*di*-O-*benzyl*-5-*deoxy*-2-O-*toluene*-p-*sulphonyl*-D-*ribitol* (**11**) *in* $CDCl_3$ *at* 100 *MHz*

	1-H	1′-H	2-H	3-H	4-H	5-H	5′-H	
Chemical shifts (δ p.p.m.)	3·54	3·63	4·96	5·34	3·92	3·15	3·36	
Coupling constants (Hz)	$\lvert J_{1,1'}\rvert$ 10·80	$J_{1,2'}$ 6·25	$J_{1',2}$ 4·75	$J_{2,3}$ 3·20	$J_{3,4}$ 6·0	$J_{4,5}$ 6·15	$J_{4,5'}$ 2·50	$\lvert J_{5,5'}\rvert$ 13·40



terms of an intramolecular nucleophilic displacement. The presence of the free hydroxy-group in (**12**) due to a selective *N*-sulphonylation, provides further possibilities for structural modification.

Recently,[4,5] it was shown, using n.m.r. spectroscopy, that the conformation of acyclic carbohydrate derivatives is not a planar zigzag arrangement, when they contain eclipsed β-interaction. In the light of these results, it seemed interesting to examine the molecular shape of 5-azido-3-*O*-benzoyl-1,4-di-*O*-benzyl-5-deoxy-2-*O*-toluene-*p*-sulphonyl-D-ribitol (**11**) by n.m.r. spectroscopy.

The planar zigzag arrangement of (**11a**) contains an eclipsed β-interaction between tosyloxy- and benzoyloxy-groups at C-2 and C-4. The observed values of $J_{2,3}$ (3·2 Hz) and $J_{3,4}$ (6 Hz) (Table) are consistent with a predominant conformer (**11b**), in which 2-H and 3-H are gauche related.

Satisfactory elemental analyses have been obtained for all the compounds described.

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