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REVISION OF THE ASSIGNMENT OF RELATIVE STEREOCHEMISTRY IN SIBIROSAMINE: SYNTHESIS OF METHYL N-TOSYL α-D-SIBIROSAMINOPYRANOSIDE

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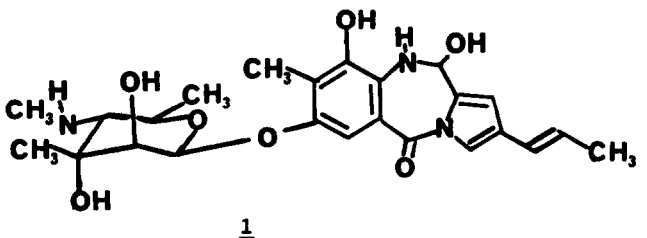
Abstract: A synthesis of the N-toluenesulfonamide of α-methyl D-sibirosaminopyranoside has resulted in a reassignment of the relative stereochemistry of sibirosamine, a rare sugar found as its glycoside in sibiromycin.

Of the benzodiazepinone antitumor antibiotics,[1] sibiromycin undergoes the most rapid reaction with DNA and forms the most stable adduct.[2] The relatively complex glycoside structure 1 was assigned to sibiromycin by Mesentsev et al. in 1974.[3] This assignment was made largely on the basis of spectroscopic and degradation studies on the methyl glycoside derived from acidic methanolysis of the antibiotic (believed to be the β-glycoside 2β).[4] Since that assignment, three groups have reported the preparation of derivatives of the α-methyl glycoside of sibirosamine (i.e. derivatives of 2α).[5] Apparently none of the synthetic products was compared with material derived from the natural product. Our own work[6] on the synthesis of sibiromycin has progressed to the synthesis of sibirosamine and now leads us to reassign the structure of sibirosamine as 3 (or its enantiomer),* epimeric at C-3 with the previously assigned structure.



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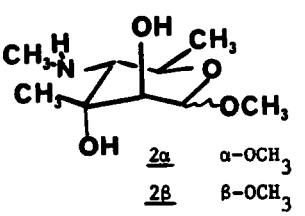
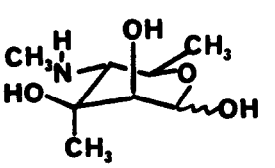


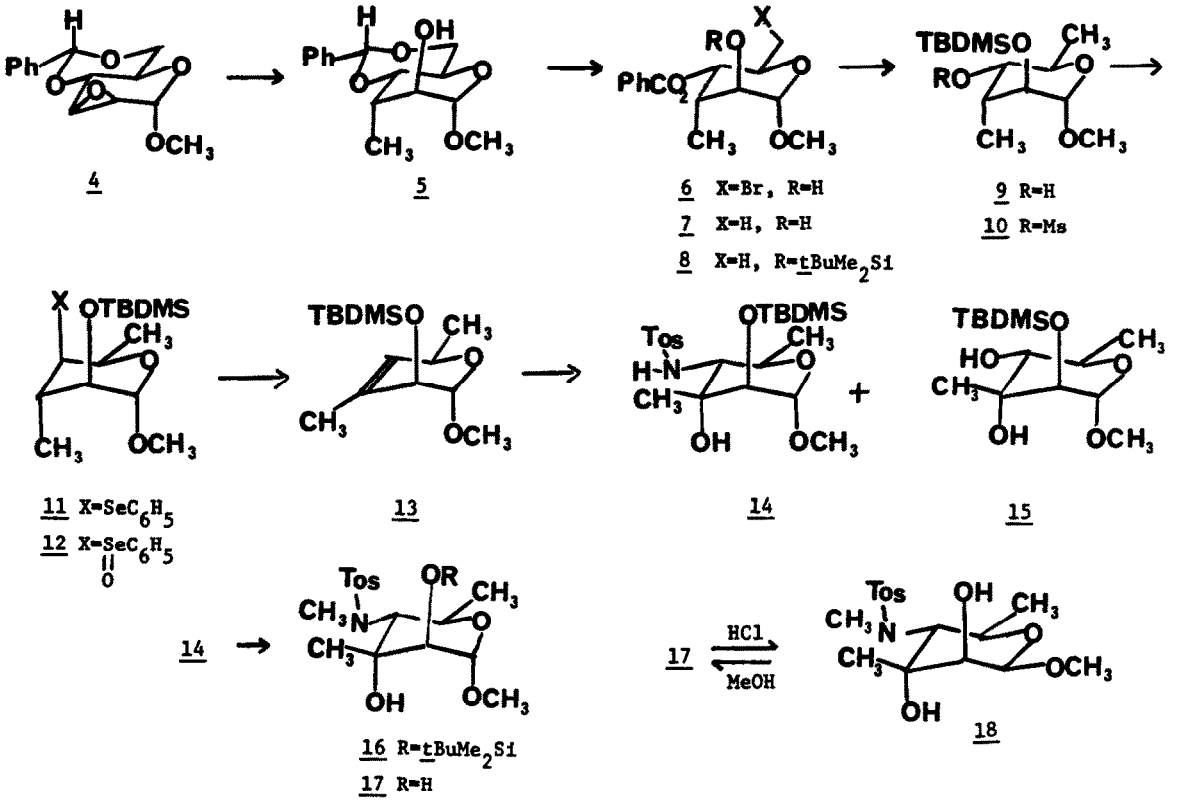
2α α-OCH_3
2β β-OCH_3



3 (or its enantiomer)

* Data obtained so far do not allow us to confirm or dispute the assignment of natural sibirosamine as a D-sugar.

Our initial efforts on the synthesis of sibirosamine, like those of other workers,[5] were aimed at derivatives of structure 2α. Our strategy resembled that of Dyong[5a] in that the key step utilized the OsO_4-catalyzed oxyamination[7] of a 3-C methyl hex-3-enopyranoside (see 13 → 14). Our synthesis of material to which we can confidently assign structure 17 is shown in Scheme 1.



Scheme 1

The readily prepared epoxide 4[8] was converted to the alcohol 5 by treatment with a large excess (20 equivalents) of dimethylmagnesium[9] in refluxing ether, THF (1:1) for 48 hr.[10] Deoxygenation at C-6 was readily accomplished by the Hanessian-Hullar reaction (NBS, refluxing CCl_4[11] to give 6, 88%) followed by hydrogenolysis of the bromo substituent (H_2, Ra-Ni, Et_3N)[11] to give 7 (97%). Protection of the C-2 hydroxyl (t-$BuMe_2SiCl$, imidazole, DMF) followed by removal of the benzoyl group from the C-4 hydroxyl (cat. NaOMe, MeOH) afforded 9 (85%, two steps).

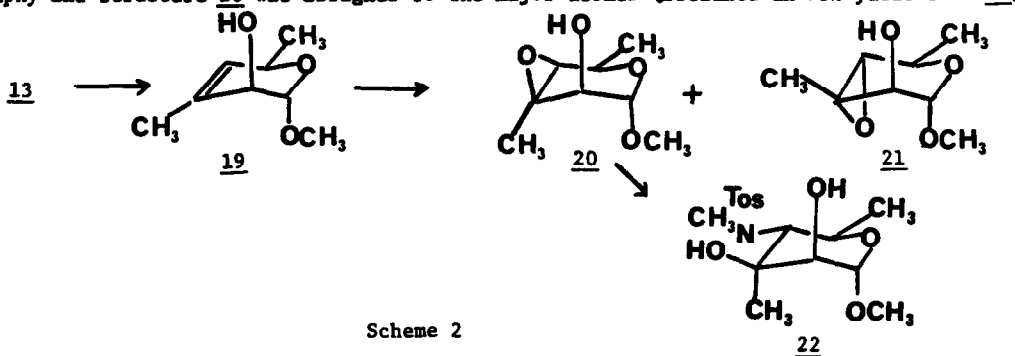
Regiospecific dehydration of 9 to 13 was accomplished in three steps: mesylation of the C-4 hydroxyl (to give 10), displacement with phenyl selenide (to give 11), and syn oxidative elimination ($NaIO_4$). The yield of 13 from 9 was 50%.

The key oxyamination reaction gave 70%[12] of sulfonamide 14 and 20% of diol 15 (separated by flash chromatography[13] on silica gel, eluent CH_2Cl_2: acetone, 20:1). N-Methylation of amide 14 (CH_3I, tBuOK, 89%)[7c] followed by desilylation of 16 gave 17, the N-tosyl derivative of the

α-methyl glycoside of the target sugar. Equilibration of this material (9% HCl in methanol) afforded a mixture of α- and β- anomers (1.4:1); no attempt was made to separate the components of this mixture which exhibited a single spot on tlc (silica). Rather, the nmr spectrum (H^1, 250 MHz) of the mixture was compared with that of the N-tosyl methyl glycoside obtained from degradation[4] of sibiromycin (9% HCl, reflux; TsCl, aq NaOH). This comparison (Table I, columns 1 and 2) clearly indicated that the N-tosyl glycoside derived from sibiromycin was neither the α-anomer 17 (a derivative of 2α) nor the β-anomer 18 (a derivative of 2β); therefore, the methyl glycoside which was obtained from the natural product can be neither 2α nor 2β.

Inspection of the evidence used for the original structure assignment led us to believe that the most likely source of error was in the designation of stereochemistry at C-3. We therefore directed our efforts toward the synthesis of the C-3 epi glycoside 22.

The α-methyl glycoside 22 was obtained from our previously prepared intermediate 13 in three steps. Desilylation to give 19 ($Bu_4N^+F^-$, 91%) followed by treatment with m-chloroperoxybenzoic acid gave a mixture of epoxy alcohols. The components were separated by flash chromatography and structure 20 was assigned to the major isomer (obtained in 75% yield from 19).[14]



Scheme 2

Treatment of epoxide 20 with the sodium salt of N-methyl toluenesulfonamide in DMF gave the target glycoside 22. This material had ir and nmr (H^1, 250 MHz) spectra which were identical to those of the single glycoside which had been obtained from the degradation of sibiromycin (Table I). An attempt to equilibrate the anomeric methoxyl (9% HCl, MeOH) resulted in

Table I. ^1H NMR Signals for Nonexchangeable Hydrogens of 17, 17+18, and 22. (Chemical shift (δ), multiplicity, coupling constants (Hz), integration)

17 (synthetic)	17+18 (synthetic)	22 (synthetic and from natural product)*
1.06 d,J=6.3 Hz,3H	0.86 d,J=6.0 Hz; 1.06 d,J=6.3 Hz	0.55 d,J=5.8 Hz,3H
1.20 d,J=0.8 Hz,3H	1.20 s; 1.41 s	1.38 s,3H
2.41 s,3H	2.41 s	2.44 s,3H
2.91 s,3H	2.89 s; 2.91 s	2.89 s,3H
3.43 s,3H	3.43 s; 3.52 s	3.34 s,3H
3.47 br s,1H	3.36 br s; 3.47 br s	3.55 br s,1H
3.92 d,J=10.2 Hz,1H	3.78 d,J=11.0 Hz; 3.92 d,J=10.4	3.67 d,J=9.6 Hz,1H
4.08 dq,J=10.2, 6.3 Hz,1H	3.95 (approx) m, 4.08 m	3.78 dq,J=9.6, 5.8 Hz,1H
4.68 d,J=1.1 Hz, 1H	4.68 d,J=1.1 Hz; 4.80 d,J=1.1 Hz	4.68 d,J=1.4 Hz,1H
7.30 d,J=8.1 Hz,2H	7.30 d,J=8.1 Hz	7.33 d,J=7.9 Hz,2H
7.72 d,J=8.1 Hz,2H	7.72 d,J=8.1 Hz	7.74 d,J=7.9 Hz,2H

*Coupling constants were determined on the synthetic material.

recovery of only the starting anomer. An NOE experiment on this synthetic material confirmed the cis relationship of the C-3 methyl and H-2 and H-5.

$$\text{Sibiromycin} \xrightarrow[2)\ \text{TsCl, NaOH}]{1)\ 9\%\ \text{HCl/MeOH}} \underline{22}\ \text{(or its enantiomer)}$$

Additional work on the structure and synthesis of sibiromycin is in progress.

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12. The use of 2.5% OsO_4 (rather than 1%, references 5a,7) resulted in a significant improvement in the yield of sulfonamide 14. Reaction time in both cases was 8 days at 60°C.
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