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A STEREOCONTROLLED REARRANGEMENT OF SPECTINOMYCIN - THE STEREOCHEMICAL IDENTITY OF SPECTINOIC ACID

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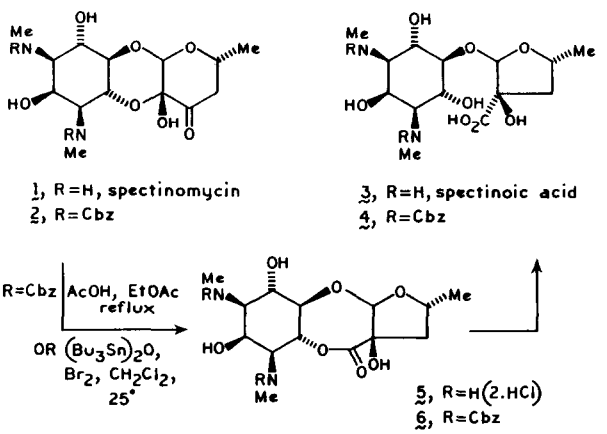
Abstract: Treatment of N-benzyloxycarbonylspectinomycin with weakly acidic catalysts or with bis(tri-n-butyltin)oxide and bromine leads to the formation of a lactone in high yield via a stereocontrolled tertiary α-ketol rearrangement. This product was chemically related to spectinoic acid which in turn was transformed into 5-deoxy-α-D-isosaccharino-1,4-lactone of known absolute configuration. The stereochemical identity of this acid is thus secured.

Spectinomycin 1, (Scheme 1) a broad spectrum antibiotic produced by several actinomycetes,[1] is a structurally[2] and biologically unique substance[3]. As such it occupies an unchallenged position in the large realm of aminocyclitol antibiotics in that it is the single representative of its kind. The unusual biological properties of spectinomycin[3,4] have stimulated a thrust of research activities in its chemical modification[1,5]. Although the final chapter in the chemistry of spectinomycin appears to have been written with two recently announced, independent and conceptually different syntheses[6,7], there still remains a stereochemical assignment to be unravelled concerning spectinoic acid[8], which is produced upon basic treatment of the antibiotic.

In this paper, we report on a unique stereocontrolled rearrangement undergone by N-benzyloxycarbonylspectinomycin 2, in mildly acidic media. The discovery of this process was preemted by our appreciation of the stereoelectronically unique opportunities offered by the structure in question for potential rearrangements, which made us all the more intrigued by a recurring bench-top observation[9]. We also present results that establish the complete stereochemical identity of spectinoic acid by an unambiguous chemical correlation.

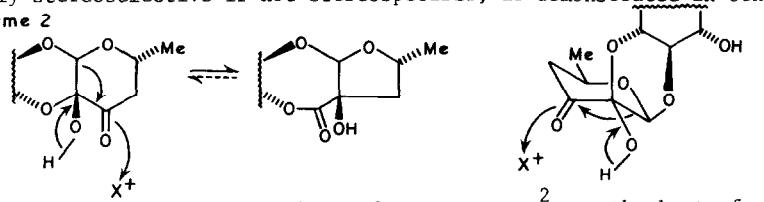
Scheme 1



Treatment of 2 with a mixture of bis(tri-n-butyltin)oxide (1.1 equiv.) and bromine (1.5 equiv.) in dry dichloromethane (25°, 4h) led to the lactone 6[10] in 84% yield, (amorph.solid); $[\alpha]_D$+ 6.7°;[11] λ_{max} 1750 cm^{-1}; n.m.r. data (p.p.m), 3.06 (NMe, broad s); 5.34 (anomeric H,s); M^+ 600. The same product could also be obtained (76%) by refluxing a solution of 2 in ethyl acetate containing 10% acetic acid for 18h. When treated with methanol containing K_2CO_3 (25°, 30 min), 6 gave the methyl ester of N-benzyloxycarbonylspectinoic acid, (~ quant.) λ_{max} 1720 cm^{-1};$[\alpha]_D$- 48.1°, M^+ 632. Alkaline hydrolysis of 6 (N NaOH, THF 1:10, 25°) gave N-benzyloxycarbonylspectinoic acid 4 (~ quant.); λ_{max} 1730 cm^{-1}; which upon hydrogenolysis (Pd/C, H_2, aq. MeOH, HCℓ) gave the known crystalline spectinoic acid (94%) identical with an authentic sample, mp 230-235° (dec.);$[\alpha]_D$- 89° ([13] C n.m.r.). Compound 4, and its methyl ester were also obtained individually by treatment of 2 with N NaOH-THF (1:10, 25°, 30 min., 95%) and NaOMe-MeOH (25°, 78%) respectively. Hydrogenolysis of 6 (10%, Pd/C, aq. MeOH, HCℓ) gave spectinoic acid lactone dihydrochloride 5 as an amorphous solid (83%);$[\alpha]_D$- 64.3° (H_2O); λ_{max} 1720 cm^{-1}; [13] C n.m.r.. This product, which is isomeric with spectinomycin, was devoid of antibacterial activity in vitro.

The formation of the lactone 6 can be attributed to an α-ketol rearrangement[12], well known in steroids[13], related natural products[14], and other cyclic systems[15] in which the prequisite functionalities are present. Most of these rearrangements take place under base catalysis and are in principle reversible processes, but there are also several reactions catalyzed by Lewis acids[16] and related reagents[17]. Spectinoic acid itself is a product of such a base-catalyzed rearrangement[2] and the present study has enabled us to isolate what could be construed as a transient intermediate, namely the corresponding lactone. The unique bonding arrangement and hetero-atom dispositions in spectinomycin[7,18] are ideally set up for stereoelectronically controlled rearrangements and fragmentations. Thus for the formation of the lactone 6, the favorable alignment of the migrating bond with the plane of the carbonyl group can be seen in two perspectives in Scheme 2. Unlike other cases however, this rearrangement was not reversible under the conditions studied[19]. The efficacy and mild conditions for the rearrangement in the presence of bis(tri-n-butyltin)oxide and bromine are worthy of note. The process may in fact be due to the formation of Bu_3SnOBr[20] which could activate the tertiary ketol unit by acid-base catalysis (Scheme 2, X=Br). No rearrangement takes place with bromine or the tin oxide individually. The formation of the lactone 6 as the only such product, and its stereochemical purity leads one to conclude that the rearrangement is highly stereoselective if not stereospecific, as demonstrated in other cases[15].

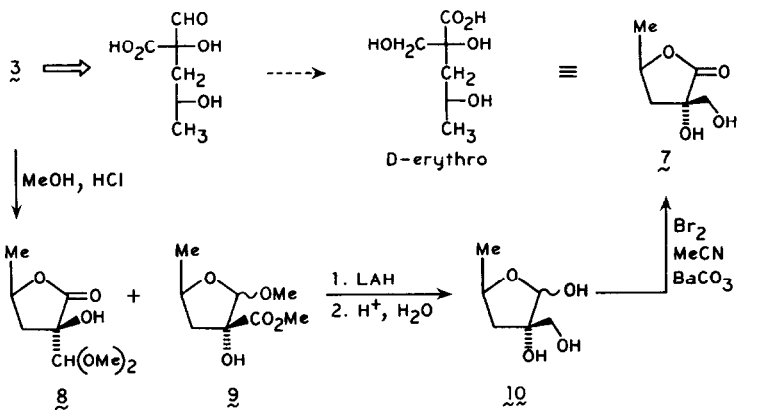
Scheme 2



Although spectinoic acid has been known for some years[2], to the best of our knowledge the stereochemical course of the rearrangement has not been clarified. As a consequence, the sense of chirality at the tertiary center has so far remained unassigned. We present herein definitive evidence for the stereochemical identity of this substance, hence of the precursor lactone 6, by direct chemical correlation with α-D-isosaccharino-1,4-lactone of known absolute configuration[21].

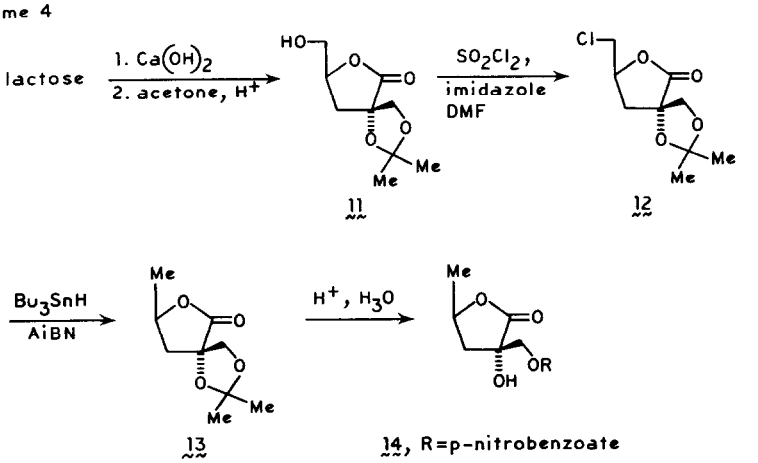
Methanolysis[22] of 3 (3% MeOH, HCℓ) gave a 1:3 mixture of the lactone 8 (Scheme 3) and the mixture of glycosides 9 (~ quant.) which could be separated by column chromatography of the corresponding p-nitrobenzoates (DMAP, pyr.). The crystalline p-nitrobenzoate derived from 8 showed mp 123.5 - 125°; $[\alpha]_D$ - 20°. Sequential reduction of 9 (LAH, ether, 93%) and hydrolysis of the resulting diol (aq. HCℓ, reflux, 90 min. 83%) gave the lactol 10 as a mixture of anomers, which upon oxidation with bromine in acetonitrile containing suspended barium carbonate gave the corresponding lactone 7 characterized as its crystalline mono-p-nitrobenzoate ester (58% overall), mp 123.5 - 125°; $[\alpha]_D$ - 10.9°.

Scheme 3



Lactone 7 was in turn prepared from the known α-D-isosaccharino-1,4-lactone[23,24] by the sequence of reactions shown in Scheme 4. Thus, the readily available isopropylidene derivative 11[24] was chlorinated with sulfuryl chloride in DMF with added imidazole[25] (25°, 6h), to give the chloride 12 (84%, syrup), $[\alpha]_D$ + 28.8°. Reduction with tri-n-butyltin hydride/AIBN[26] in toluene (reflux, 4h), gave the deoxy derivative 13 as a syrup (95%); $[\alpha]_D$ + 31.7°. Finally, acid hydrolysis (aq. 80% AcOH, 80°, 30 min) followed by selective p-nitrobenzoylation (Et_3N, CH_2Cl_2, 25°) gave the crystalline p-nitrobenzoate 14 identical with material obtained from spectinomycin.

Scheme 4



Acknowledgements

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References and notes

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8. Originally named actinospectinoic acid[2] after the parent antibiotic actinospectacin, now known as spectinomycin. For consistency we therefore propose the name, spectinoic acid.
9. It was observed by one of us (R.R.) that storing solutions of 2 in organic solvents such as ethyl acetate or chromatography over silica gel resulted in the progressive formation of a new, less polar product.
10. This product was initially encountered in the oxidation of N-benzyloxycarbonyl-4(R)-dihydrospectinomycin under essentially the same conditions, as cited in ref. 30 in our original paper[7] .
11. Yields are for isolated pure products. Rotations were measured in chloroform unless otherwise stated. ^{1}H n.m.r. and ^{13}C n.m.r spectra were recorded at 90 MHz and 80 or 100 MHz respectively.
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19. Inspection of molecular models reveals that the alignment of the migrating bond with the plane of the lactone carbonyl group in a least one of several possible conformations of 6 may not be as favored as in 2. Differences in non-bonded interactions and in the electrophilicities of the carbonyl carbon atoms in 2 and 6 may also play a role (referee's suggestion)
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