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THE STEREOSPECIFIC SYNTHESIS OF SPECTINOMYCIN

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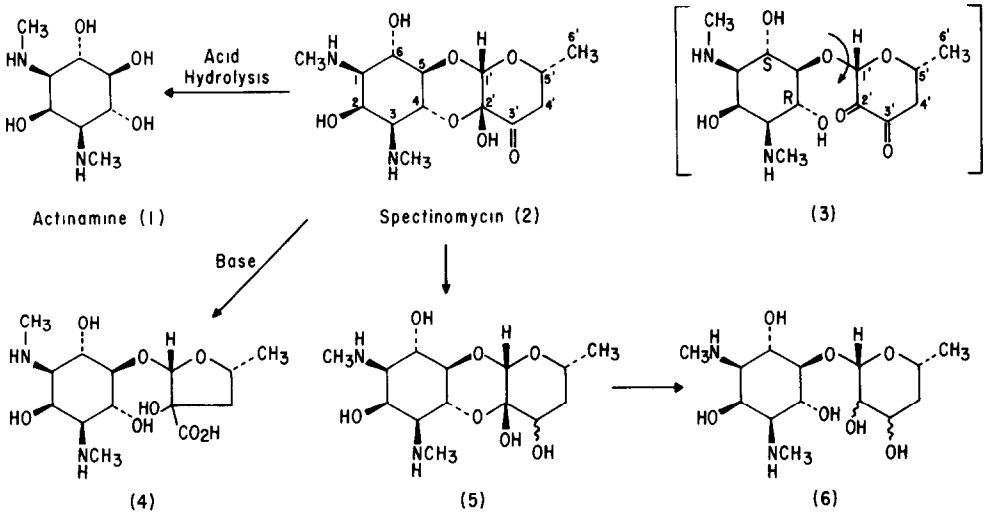
Summary: The first synthesis of spectinomycin, a complex and sensitive antibiotic, is described. The synthesis, which requires only four steps from known materials, has flexibility for modifying either half of the molecule.

Spectinomycin (2) is an aminocyclitol antibiotic having broad spectrum biological activity. It does not have the toxicity usually associated with the 2-deoxystreptamine containing aminocyclitols. The structure[1] of spectinomycin is unique among the aminocyclitols in that it contains a glycosylated actinamine ring which is cyclized to form a third ring by the formation of a hemiketal. Spectinomycin (2) has nine asymmetric centers; it contains a carbonyl at C-3'



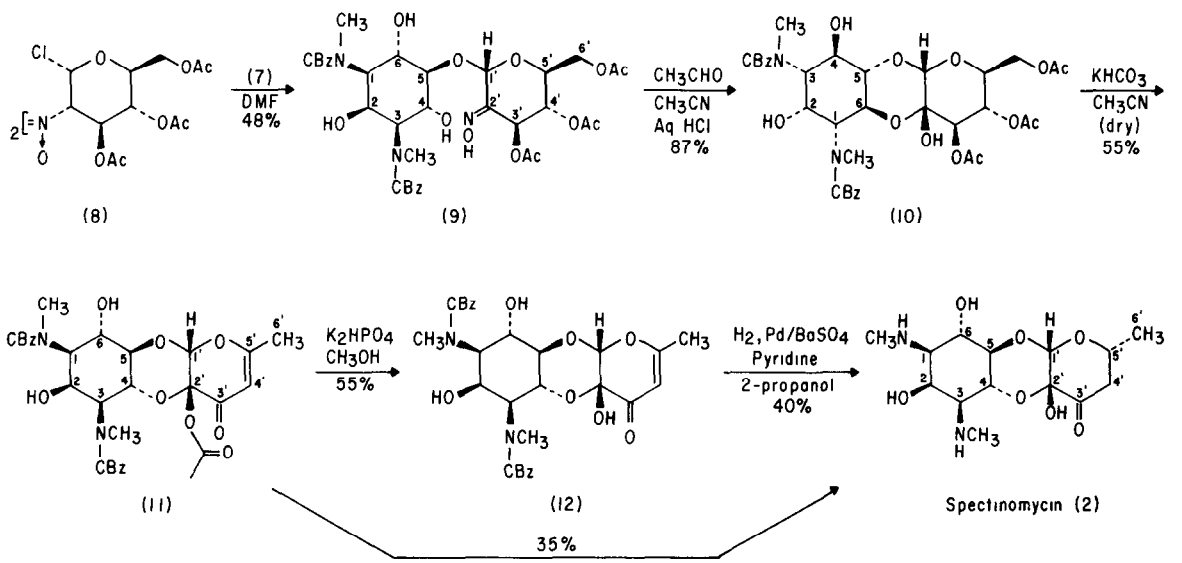
and two masked carbonyls at C-1' and C-2'.[2] This electrophilic portion of the molecule is sensitive to mild base which causes a benzylic acid type of rerrangement[1a] to give actinospectinoic acid (4). Acid hydrolysis gives actinamine (1)[1a] which has been synthesized from myoinositol[3] so that synthesis of spectinomycin from actinamine constitutes a formal total synthesis.

Mild reduction of spectinomycin at the C-3' center gives the dihydrospectinomycins (5), which have markedly diminished antibiotic activity. Further reduction saturates the C-2' center giving the biologically inactive tetrahydrospectinomycins (6),[4] one isomer of which has been

synthesized by Suami.[5] Synthetic approaches to spectinomycin (2) based on tetrahydrospectinomycin intermediates would require considerable protecting group manipulation and mild, selective oxidations. Such transformations of tetrahydrospectinomycins have not been reported.

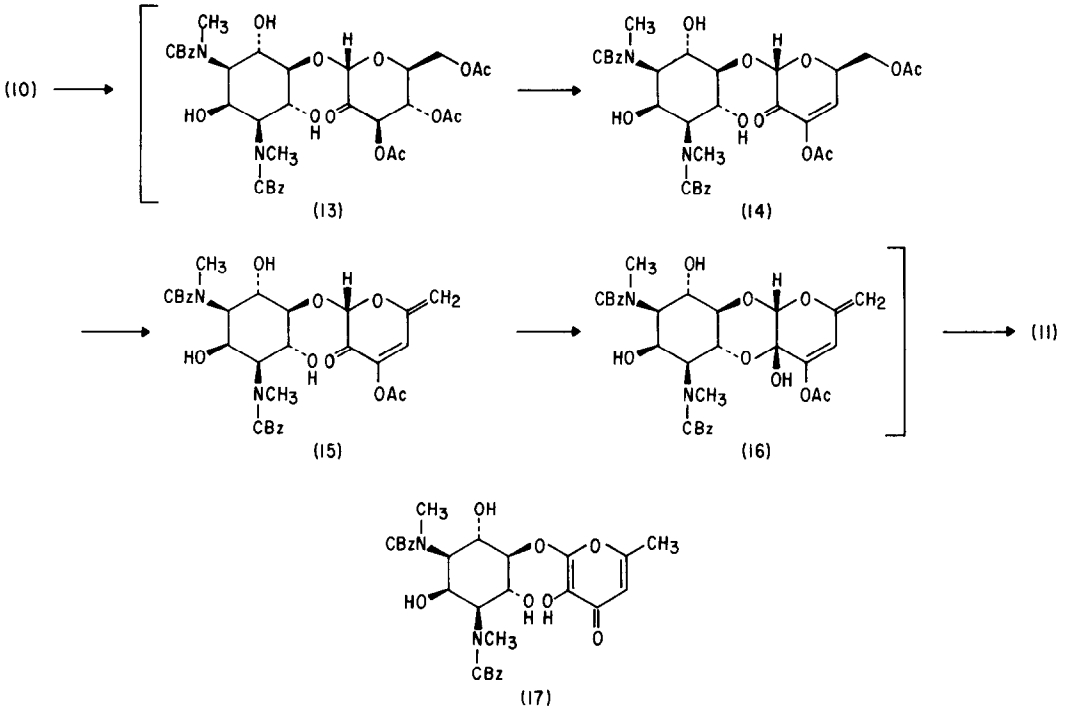
For synthetic analysis spectinomycin can be envisioned as its hypothetical functional equivalent, diketone (3). *A priori*, diketone (3) might cyclize to four possible products by involving the C-4 hydroxyl or the C-6 hydroxyl in *cis* or *trans* fused hemiketals. The occurance of one natural structure (2) and the apparent absence of the three alternatives may be understood by evaluation of anomeric effects at the C-1' and C-2' centers as well as the preference for chair rings and an equatorial C-5' methyl group. Natural hemiketal "folding" is the first of five major goals of spectinomycin synthesis and its favorable outcome would allow use of actinamine (1) as an achiral, stereochemically rich building block. Other key challenges of the synthetic problem are: (a) selective glycosylation at the C-5 hydroxyl, (b) control of anomeric stereochemistry, (c) use of a scheme which would allow generation of carbonyl groups at C-2' and C-3', preferably without introducing complex protecting group manipulation, (d) finally, the base sensitivity of spectinomycin must be respected. The synthesis to be described meets these challenges and offers an especially attractive method for generation of carbonyl equivalents at C-2' and C-3'.

Condensation of N,N'-dicarbobenzyloxyactinamine (7)[5] with nitrosodimer (8)[6] in dimethylformamide at room temperature gives a number of 1:1 adducts which are separated by silica gel chromatography. The major product (48%) is the desired oxime (9) [m/e (tetra TMS) 1063; anomeric proton at 6.2 δ; $[\alpha]_D^{25}$ -59° (C, 0.7, acetone)] in which α-glycosylation occurred on the C-5 hydroxyl group of the actinamine ring. In addition to the major product, 1-2% of the β-glycoside is formed (anomeric proton at 5.78 δ) as well as 10% of glycosides at C-4 or C-6 of the



actinamine. The latter compounds are reactive with periodate as expected. This antipode (8) derived from L-glucose was utilized because the known preference for α-glycosylation by the Lemieux method[7] ensures crucial natural chirality[1b] at the anomeric center.

Deoximation of the oxime triacetate (9) gives a single hemiketal triacetate (10)[8] [C-1' and C-2' at 99.7 and 94.6 ppm respectively (CD_3COCD_3 solvent), m/e (triTMS) 976 (M^+) 961 (M-15), $[\alpha]_D^{25}$ -65° (C, 0.9, chloroform)] which is isolated in 87% yield after column chromatography. The mode of hemiketal folding, which is destroyed in the next step, is assigned as being unnatural on the basis of spectral data. Further, consideration of anomeric effects and conformational analysis suggests the assigned structure (10), in which the C-6 hydroxyl has been involved in a *cis* hemiketal. The three other modes of folding would have axial substituents at C-3', C-4' and C-5'; conformational effects predominate in this situation. The next step accomplishes (a) removal of unwanted oxygen functionality at C-4' and C-6', (b) removal of unnatural stereochemistry at C-5', (c) generation of the sensitive carbonyl at C-3' as well as (d) introduction of natural folding of the hemiketal. This remarkable series of reactions is effected by stirring hemiketal triacetate (10) with a slurry of anhydrous potassium bicarbonate in acetonitrile at room temperature. Generation of the enoneacetate (11)[9] requires careful choice of conditions to avoid degradation of the enoneacetate (11) to the closely related 4-pyrone[10] (17). After completion of the reaction, the inorganic salts are filtered and the filtrate concentrated. Evaluation of the crude product (CMR and TLC) shows only one enoneacetate, product (11). This



enoneacetate (11) is crystallized directly and then chromatography of the mother liquor allows isolation of a total yield of 55%.

The first event in the conversion of hemiketal triacetate (10) is the base induced opening of the hemiketal to give an intermediate (13) which suffers β-elimination to give enolacetate (14). Under the specified conditions a second elimination of acetate occurs to give the α-acetoxydienone (15), having only one chiral center. This intermediate collapses to a new hemiketal (16) which undergoes acetyl migration to give the single enoneacetate (11). The

proper hemiketal folding has occurred (as judged by nmr) and establishes eight asymmetric centers with one remaining to be established at C-5'.

Careful hydrolysis of enoneacetate (11) with K_2HPO_4 in methanol gives 55% (76% conversion) of the free hemiketal (12) [$[\alpha]_D^{25}$ -56° (C, 1.0, CH_3OH), m/e (TriTMS) 814 (M^+), 749 (M-15)] in addition to pyrone (17).

The final step is hydrogenation of the olefin from the convex side of the molecule and concommitant hydrogenolysis of the carbobenzyloxy groups. At the conclusion of the reaction GLC/MS shows only the natural isomer. The product is isolated in 40% yield by crystallization as its dihydrochloride salt. It has identical physical and biological properties with the natural antibiotic. A more direct alternative is hydrogenation of the enoneacetate (11) itself, since the acetyl group is reactive enough to be removed under the hydrogenation conditions. In this case the crystalline yield is 35% from enoneacetate (11). This synthetic scheme has the flexibility for modifying either half of the molecule by choice of different starting materials. The preparation of modified antibacterial agents using this approach will be reported.

FOOTNOTES AND REFERENCES

(1) a) P. F. Wiley, A. D. Argoudelis and H. Hoeksema, *J. Amer. Chem. Soc., 85,* 2652 (1963).
b) T. G. Cochran, D. J. Abraham and L. L. Morton, *J. Chem. Soc., Chem. Comm.,* 494 (1972).

(2) The aminoglycoside numbering system has been used so that numbering of the intermediates is consistent with that of the antibiotic.

(3) T. Suami, S. Ogawa and H. Sano, *Bull. Chem. Soc. Japan, 43,* 1843 (1970).

(4) J. C. Knight and H. Hoeksema, *J. Antibiotics, 28,* 136 (1975).

(5) T. Suami, J. Nishiyama, H. Ishikawa, H. Okada and T. Kinoshita, *Bull. Chem. Soc. Japan, 50,* 2754 (1977).

(6) H. Paulsen, P. Stadler and F. Tödter, *Chem. Ber., 110,* 1925 (1977).

(7) R. U. Lemieux, T. L. Nagabhushan and I. K. O'Neill, *Can. J. Chem., 43,* 4136 (1968).

(8) NMR data for (10); PMR (CD_3COCD_3, 100 Hz); 2.06 (9H, s), 2.88 (3H, s), 3.12 (3H, s), 4.20 (8H, m), 5.08 (2H, s), 5.14 (2H, s), 5.82 (1H, d), 6.21 (1H, s), 7.38 δ (10H, s). CMR (CD_3COCD_3): 170.8, 170.7, 170.0, 138.0, 129.2, 128.5, 99.7, 94.6, 82.7, 74.5, 71.2, 69.2, 68.5, 67.4, 66.2, 62.8, 60.5, 57.8, 31.8, 31.6, 20.6 ppm.

(9) The enoneacetate (11) has the following physical properties: mp 151-154°, UV (C_2H_5OH): 204 (20,950), 206, sh, (20,650), 267 nm (11,550), [$[\alpha]_D^{25}$ -43° (C, 1.0, acetone). PMR ($CDCl_3$, 270 Hz): 2.07 (3H, s), 2.15 (3H, s), 3.05 (3H, s), 3.07 (3H, s), 3.50 (1H, d, J=9.4), 3.97 (1H, d, J=11.4), 4.05 (1H, d of d, J=9.4, 9.4), 4.40 (1H, br, s), 4.63 (1H, J=9.7, 7.5), 4.78 (1H, d of d, J=10.5, 10.3), 5.05 (1H, m), 5.14 (2H, s), 5.15 (2H, s), 5.18 (1H, m), 5.42 (1H, s) 5.98 (1H, s), 7.32 δ (10H). CMR (CD_3COCD_3): 182.5, 172.9, 169.5, 137.6, 137.5, 128.6, 127.8, 102.7, 95.5, 93.1, 75.0, 74.0, 66.8, 65.6, 60.3, 59.6, 56.7, 31.1, 20.4 ppm. m/e calcd. for $C_{38}H_{52}N_2O_{12}Si_2$, 784.3058. Found 784.3097.

(10) 2-Ketosugar derivatives are known to give 4-pyrones under mild conditions. By loss of acetate from C-4 and C-1, Kojic acid derivatives are produced, R. W. Binkley, *J. Org. Chem., 42,* 1216 (1977). Loss of benzoate from C-4 and from C-6 has led to allomaltols, F. W. Lichtenthaler, K. Strobel and G. Rendel, *Carb. Res., 49,* 57 (1976). The ferric chloride reactive pyrone (17) was characterized as its tetraacetate.

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