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SPECTINOMYCIN CHEMISTRY II[1].
THE SYNTHESIS OF 6'-SUBSTITUTED SPECTINOMYCIN ANALOGS

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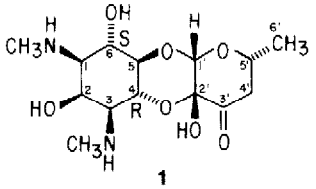
Summary: 6'-Hydroxyspectinomycin is made from known materials in five steps. This chemistry gives access for modification at the C-4' and C-6' positions; the syntheses of 6'-bromospectinomycin and 6'-chlorospectinomycin are also described.

Spectinomycin (1) is an aminocyclitol antibiotic having broad spectrum activity. Previous reports from these laboratories describe the first chemical synthesis of spectinomycin[1] as well as compounds having modified sugar rings.[2] The crucial step of our approach to this complex and sensitive system is exemplified by the conversion of (2) to (3) and (4) to (5) by the intermediacy of non-isolable enol acetates (6) and (7) respectively. The approach greatly simplifies the synthetic task by avoiding the use of oxidative reagents to generate the C-3' carbonyl; protecting group manipulation is thus minimized. The method also takes advantage of the natural oxidation



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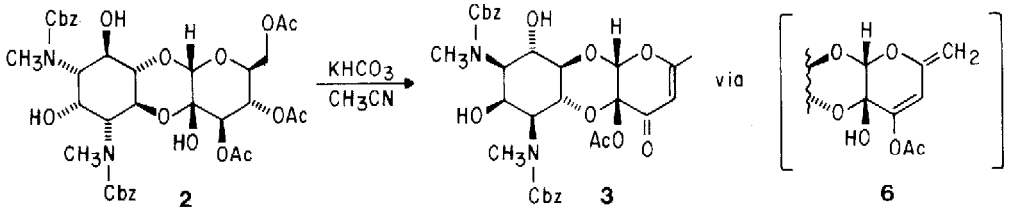

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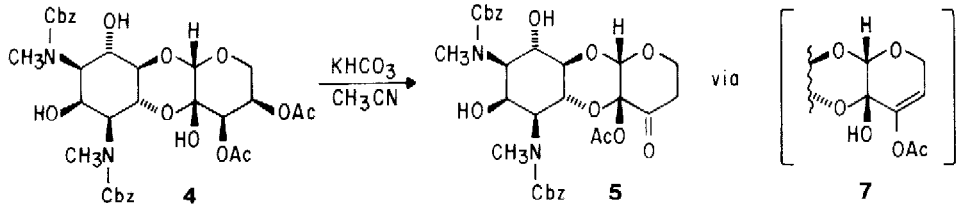

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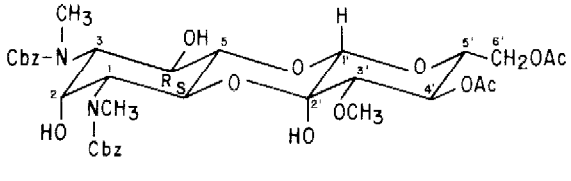
pattern of available sugars. The fundamental, interesting question of the mode of hemiketal "folding" in these molecules has also been addressed previously.[1,2] Either the C-4 hydroxyl or the C-6 hydroxyl can be involved in hemiketal formation and the ring fusion can be *cis* or *trans*. The equilibrium composition of the four possible "folding" modes can be understood in terms of anomeric effects at C-1' and C-2' in addition to conformational effects. For example, the parent antibiotic (1) and 5'-demethylspectinomycin, derived from (5), exist only in the natural "folding" mode.[2] However, inversion of the C-5' center in (1) leads to profound reorganization of the folding structure to relieve the C-5' methyl from an axial position.[2]

Enol derivatives such as (6) and (7), if isolable, would be of high interest for synthesis of analogs. This paper describes the use of a sugar which has been methylated on the C-3' oxygen so that acetate migration of the type (6)→(3) or (7)→(5) is precluded. Consequent generation and isolation of an enol ether allows activation of C-4' toward modification and imparts stability to the system relative to the rearrangement prone C-3' carbonyl. Furthermore, the activated sugar of interest, (9), is a known compound which has been found to give a favorable β/α glycosylation ratio in a Lemieux glycosylation reaction.[3]

The Lemieux coupling of N,N'-dicarbobenzyloxyactinamine (8) with the known nitroso dimer (9)[3] gave a 40% yield of glycosides (10) at the C-5 oxygen. The ratio of α/β anomers is about 9/1 which differs from the result obtained[3] in the glycosylation of a garamine derivative with (9) (α/β ratio of about 2/3). The β-anomer (10b)[4] was deoximated using dilute acid to give a mixture of two hemiketals (11)[4] and (12)[4] in 15% and 61% yield, respectively. The less stable hemiketal, (11), in which the S-hydroxyl is involved in the hemiketal can be converted to the more stable, naturally folded, hemiketal (12) by equilibration ($KHCO_3/CH_3CN$, 25°C, 5 hr). The preference for hemiketal (12) over (11) is illustrated in perspective drawings. Both structures have (a) all chair rings (b) equivalent equatorial substituents and (c) equivalent anomeric effects at the C-2' center. Hemiketal (11), however, has an additional (destabilizing) anomeric effect at the C-1' center. Prolonged treatment of (12), and/or (11), with base ($KHCO_3/CH_3CN$, 25°C, 5 days; causes the desired β-elimination of acetate from a transient C-2' carbonyl giving the enol ether (13)[4] in 91% yield. Mild methanolic base serves to remove the 6'-O-acetyl group



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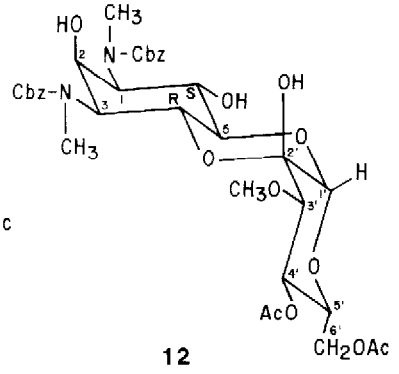

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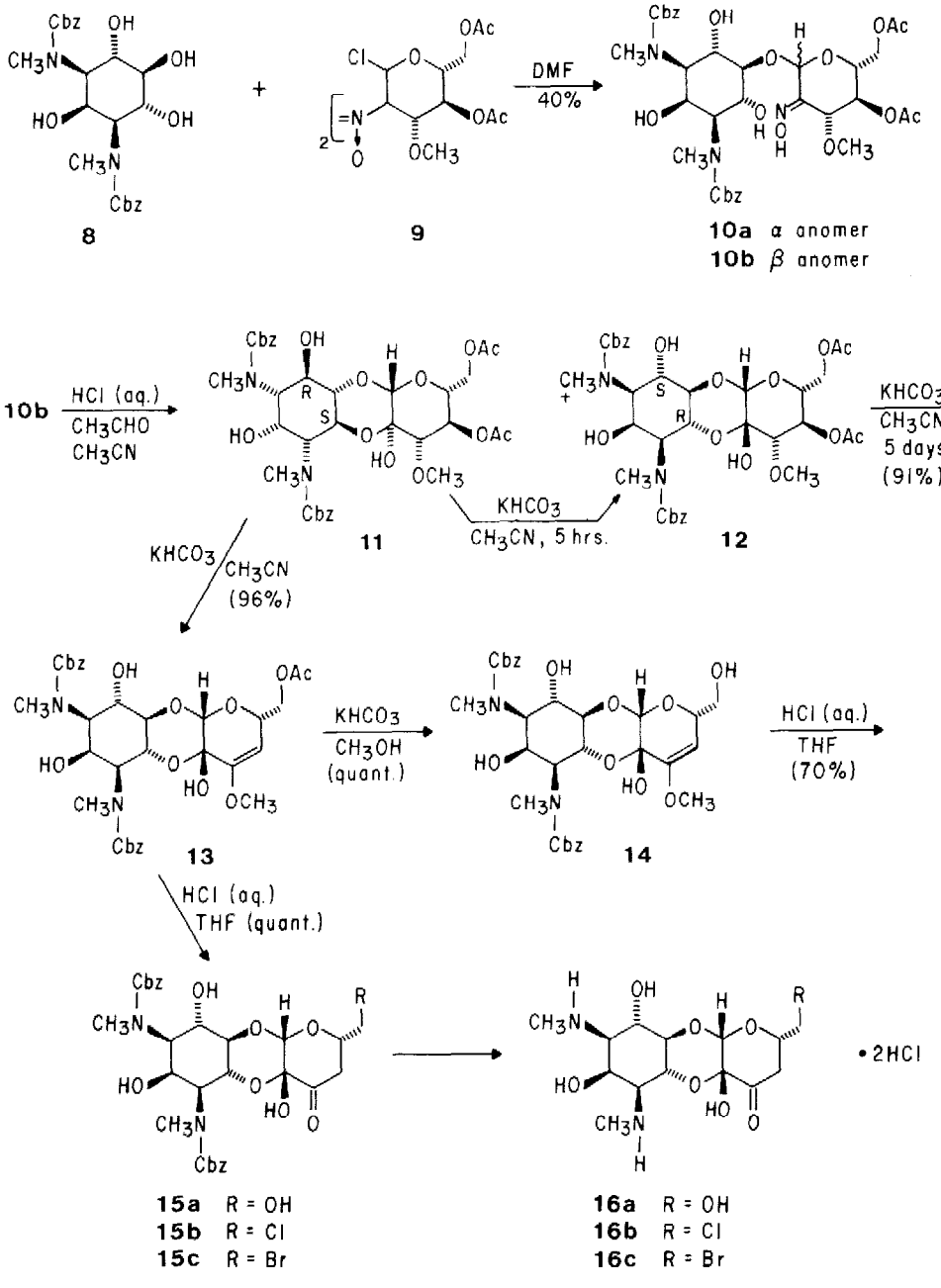

while maintaining the enol ether; the product, (14)[4] is a highly versatile intermediate for modification at the C-4' and C-6' centers of spectinomycin. The enol ether (14) can be hydrolyzed to N,N'-dicarbobenzyloxy-6'-hydroxyspectinomycin (15a)[4] in 70% yield by using dilute HCl in aqueous tetrahydrofuran. Alternatively, acidic hydrolysis converts (13) to (15a) directly. Hydrogenolysis of (15a) with palladium black gives 6'-hydroxyspectinomycin in 70% crude yield; it can be crystallized as the dihydrochloride salt (16a)[4] (mp 201-205° dec.).

Treatment of 6'-hydroxyspectinomycin derivative (15a) with $P(C_6H_5)_3/CCl_4$ or $P(C_6H_5)_3/CBr_4$ gives 6'-chlorospectinomycin derivative (15b)[4] in 42% yield and 6'-bromospectinomycin derivative (15c)[4] in 37% yield respectively. Hydrogenolysis using $Pd/BaSO_4$ in 2-propanol followed by acidification with HCl converts (15b) to 6'-chlorospectinomycin dihydrochloride (16b).[4] In similar fashion (15c) is deprotected to give 6'-bromospectinomycin dihydrochloride (16c).[4]

All of these analogs modified at the 6' position (R = OH, Cl, Br) have good *in vitro* antibacterial activity when tested against Gram positive and Gram negative bacteria.

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Footnotes & References

1) D.R. White, R.D. Birkenmeyer, R.C. Thomas, S.A. Mizsak and V.H. Wiley, Tet. Lett., 30, 2737 (1979). D.R. White, R.D. Birkenmeyer, R.C. Thomas, S.A. Mizsak and V.H. Wiley, Aminocyclitol Antibiotics, ACS Symp. Ser. #125; American Chemical Society; Washington, D.C., 1980, p. 111. For a second synthesis see: S. Hanessian and R. Roy, J. Am. Chem. Soc. 101:5839 (1979).
2) R.C. Thomas, D.R. White, V.H. Wiley & D.A. Forster, Aminocyclitol Antibiotics, ACS Symposium Ser. #125:American Chemical Society; Washington, D.C., 1980, p. 121.
3) M. Kugelman, A.K. Mallams and H.F. Vernay, J.C.S. Perkin I, 1118 (1976).
4) (10b): m.p. 214-216°C. Mass spectrum, m/e (tetra-TMS): 1035 (M+), 1020, 946, 747, 689, 673, 645, 629, 493, 393, 380. CMR ($CDCl_3$): 170.6, 169.6, 157.7, 156.5, 150.4, 136.5, 128.6, 128.1, 127.8, 95.7, 92.7, 78.7, 73.8, 73.2, 71.2, 70.1, 67.5, 66.8, 64.1, 60.0, 56.8, 29.7, 20.8, 20.6 ppm.
(11): Mass spectrum (tri-TMS): 948 (M+), 933, 889, 745, 629, 618. CMR (d_6-acetone): 170.9, 170.2, 157.8, 157.7, 138.3, 128.4, 129.2, 99.3, 94.4, 83.5, 83.1, 74.6, 74, 70.4, 67.3, 66.2, 64.8, 63.5, 61.1, 60.6, 57.3, 31.8, 20.7, 20.8 ppm.
(12): Mass spectrum (tri-TMS): 948 (M+), 933, 889, 858, 813, 745, 618. Exact mass (tri-TMS) calc'd for $C_{44}H_{88}N_2O_{15}Si_3$: 948.3927. Found: 948.3931. CMR (d_6-acetone): 170.3, 157, 138.2, 129.1, 128.4, 95.8, 93.8, 84.4, 75.1, 74, 73.0, 69.8, 67.2, 67.4, 66.4, 65.1, 63.7, 61.1, 60.8, 60.2, 57.4, 31.8, 20.9, 20.7 ppm. The structures of folding isomers are assigned on the basis of CMR gamma (γ) effects across the dioxane ring [for references and a discussion of the γ effect, which is highly dependent on angles and distances between a carbon and a γ electronegative substituent, see S.A. Mizsak and G. Slomp, Prostaglandins 10:807 (1975)]. The naturally folded isomer (12) shows two γ effects which are characteristic of spectinomycin itself. C-5 (75.1 ppm) is shielded by the γ effect between C-5 and the pyrone ring oxygen, and C-4 (66.4 ppm) is shielded by the γ effect between C-4 and C-2'-OH. Compound (11) shows only one of these γ effects, that due to the orientation of C-6 (66.2 ppm) and the C-2'-OH. The chemical shift of C-5 in (11) is now (83.1 ppm). These structures (11) and (12) are readily distinguished from other possibilities by the observation of these effects.
(13): Mass spectrum (tri-TMS): 888 (M+), 873, 828, 815, 709, 653, 629. CMR (d_6-acetone): 171.1, 157.7, 154.2, 138.2, 129.2, 128.5, 95.7, 95.6, 89.2, 75.3, 74.7, 71.7, 67.4, 67.0, 66.5, 65.2, 60.2, 60.8, 57.6, 57.8, 55.6, 31.8, 20.8.
(14): Mass spectrum (tetra-TMS): 918 (M+), 903, 888, 815, 762, 742, 692, 624, 493, CMR (d_6-acetone) 157, 153.6, 138.2, 129.2, 96.7, 95.9, 89.5, 75.2, 73.8, 74.1, 74.5, 67.2, 67.4, 66.4, 65.3, 60.5, 57.8, 55.4, 31.8 ppm.
(15a): Mass spectrum (tetra-TMS): 904 (M+), 889, 629, 493, 449, 369, 305. CMR (d_6-acetone) 201.4, 157.7, 138.1, 129.2, 128.4, 97.6, 92.3, 71.7, 73.9, 72.8, 67.3, 66.3, 65.7, 64.7, 61.0, 60.1, 57.3, 40.6, 31.5.
(16a): Exact Mass calc'd for $C_{26}H_{56}N_2O_8Si_4$: 636.3114; found: 636.3081. CMR (D_2O) 94.9, 93.1, 73.4, 70.9, 67.2, 66.8, 64.5, 62.8, 60.8, 59.8, 37.1, 31.9, 31.4 ppm.
(15b): Mass spectrum (tri-TMS): 850 (M+), 835, 822, 814, 745, 629. CMR (d_6-acetone) 192, 157, 138.0, 129.2, 128.4, 97.3, 92.1, 75.2, 74.7, 71.5, 67.3, 66.4, 65.7, 60.2, 60.9, 57.4, 47.0, 41.6, 31.5 ppm.
(16b): Mass spectrum (tri-TMS): 581 (M-1), 566, 551, 545. CMR (D_2O) 94.7. 94.5, 92.9, 72.3, 71.0, 67.0, 66.8, 62.7, 60.7, 59.8, 47.5, 38.3, 31.9, 31.4 ppm.
(15c): Mass Spectrum (tri-TMS): 896 894 (M+), 881 879 (M-15), 814 (M-HBr), 745, 629, (CMR (d_6-acetone) 192, 157, 138.1, 129.2, 128.4, 97.2, 92.0, 75.2, 74.5, 70.9, 67.3, 66.3, 65.6, 60.5, 57.5, 42.5, 35.5, 31.5 ppm.
(16c): CMR (D_2O) 94.7, 94.6, 92.8, 71.6, 71.0, 67.1, 66.8, 62.8, 60.8, 59.8, 39.3, 36.3, 31.9, 31.5 ppm.

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