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THE SYNTHESIS OF TROSPECTOMYCIN (6'-n-PROPYLSPECTINOMYCIN, U-63,366F) FROM SPECTINOMYCIN

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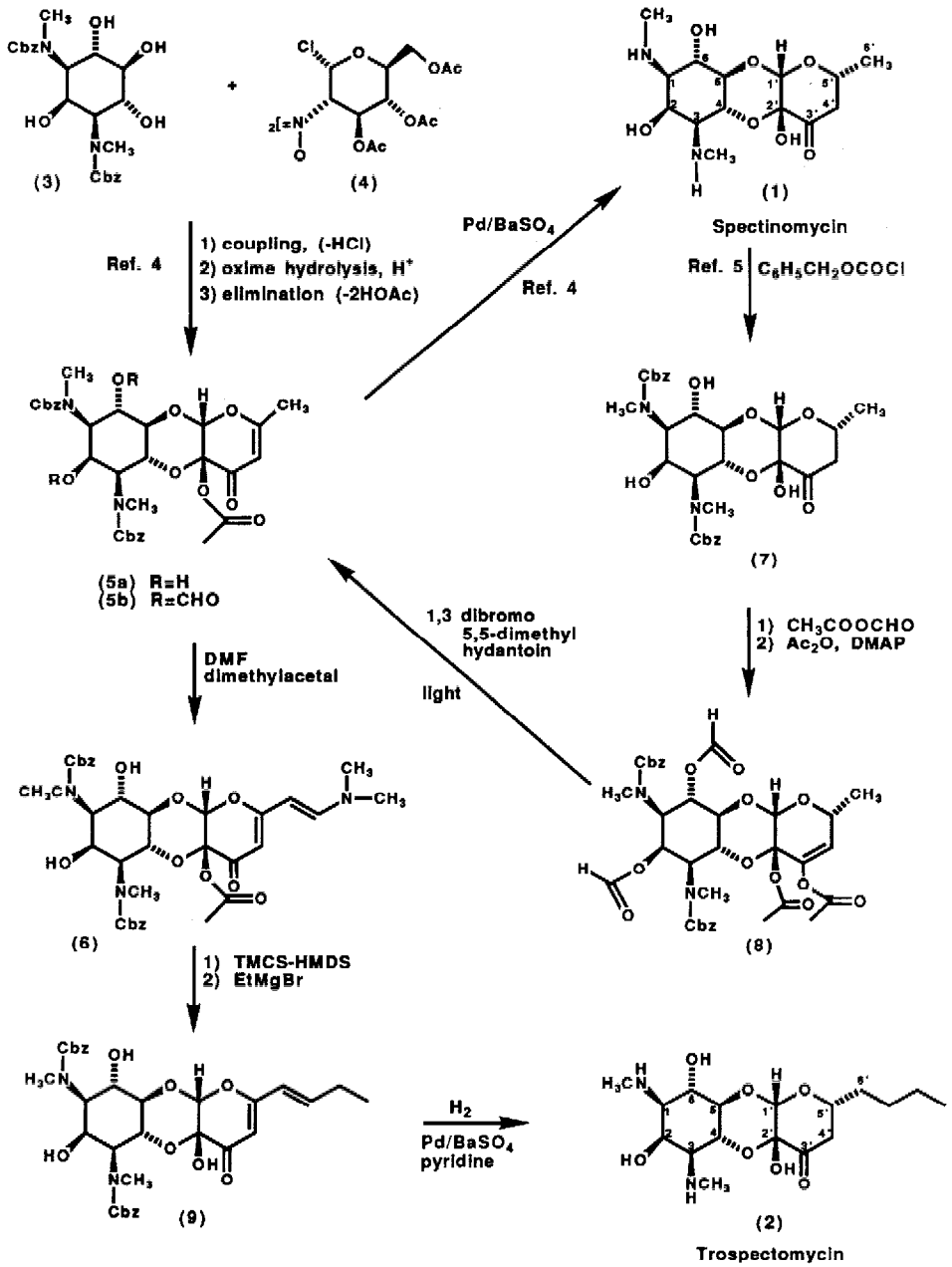
Abstract: *Spectinomycin (1) can, for the first time, be activated in the sensitive sugar ring and be carried on to trospectomycin, 6'-propylspectinomycin (2), in a simplified process.*

Trospectomycin (**2**) is an analog of spectinomycin[1a] having increased antimicrobial potency and spectrum.[1] Trospectomycin (**2**) is also the only aminocyclitol antibiotic (a group which includes gentamycin and neomycin) which has activity against anaerobic bacteria. It is currently being evaluated for efficacy in humans; it is uniquely useful among antibiotics evaluated in koalas[2] infected with *Chlamydia psittaci*. Thus an improved synthesis from spectinomycin (**1**), which is efficiently produced by fermentation, was sought.

Rosenbrook's review[3] points out that considerable effort was expended on modification of the functionalized, accessible parts of the molecule with little return in terms of antibacterial activity. The modification of the inaccessible 6'-center awaited the four step synthesis[4] of spectinomycin (**1**) from known compounds (**3**) and (**4**). In this synthesis, the penultimate intermediate (**5a**) has the 6'-center activated by an enone. In the original synthesis[1a] of trospectomycin (**2**) the enone (**5a**) was converted to enamine (**6**). Subsequent processing of enamine (**6**), which has been described,[1a] requires low temperature chemistry and five steps. This report addresses (a) the problematic and critical dehydrogenation of protected spectinomycin to obtain enone (**5b**); and (b) a simplified conversion of enamine (**6**) to trospectomycin.

Spectinomycin (**1**) nitrogens were protected with carbobenzyloxy groups as previously described.[5] The actinamine oxygens of (**7**) were protected with formyl groups by adding (**7**) to a cold solution of formic acid and acetic anhydride in ethyl acetate and pyridine (-40° → 25°, then 25° 16 hrs). The diformate of (**7**) ($[\alpha]_D$ -10 [c, 0.91 in $CHCl_3$], M+ calc. for $C_{32}H_{36}N_2O_{13}$ 656.2217, found 656.2222) was isolated in 96% yield after extraction. The diformate of (**7**) was acetylated with acetic anhydride and dimethylaminopyridine in ethyl acetate and pyridine at 55° for 10 hours to give enolacetate (**8**)[6] (M+-HOAc calc. for $C_{34}H_{36}N_2O_{13}$ 680.2217, found 680.2189) in 77% yield.


(3)
(4)
Ref. 4
1) coupling, (-HCl)
2) oxime hydrolysis, H+
3) elimination (-2HOAc)
Pd/BaSO4
Ref. 4
(1)
Spectinomycin
Ref. 5
C6H5CH2OCOCl
(5a) R=H
(5b) R=CHO
(7)
1,3 dibromo
5,5-dimethyl
hydantoin
light
1) CH3COOCHO
2) Ac2O, DMAP
DMF
dimethylacetal
(6)
(8)
1) TMCS-HMDS
2) EtMgBr
(9)
H2
Pd/BaSO4
pyridine
(2)
Trospectomycin

Classical methods of dehydrogenation based on elimination of α-bromo, α-sulfoxide or α-selenoxide intermediates were unsuccessful due to the sensitivity of the compounds. The spectinomycin carbonyl is very electrophilic due to surrounding oxygen atoms so that benzylic acid type of rearrangement occurs under mild conditions[5]; the addition of an additional heteroatom gives compounds which decompose rapidly at room temperature or below. Also $Pd(OAc)_2$ mediated dehydrogenation was unsuccessful. At this point, it was decided to take advantage of the unusual 5' pseudoaxial hydrogen which is highly activated toward radical reaction in enolacetate (**8**). Light initiated bromination with 1,3-dibromo-5,5-dimethyl hydantoin (CCl_4, ambient temperature, 20 minutes) gave the enone (**5b**) (UV in CH_3CN, 209 nm (19,500), 264 (8,800), 266 sh (8,750), $[\alpha]_D$ -8°, (C, .91 in $CHCl_3$) which was extracted for direct conversion to enamine (**6**). During enamine formation with dimethyl formamide dimethylacetal in dimethylformamide (55°, 3 hr) the methanol which is generated from dimethylformanide dimethylacetal served to hydrolyze the formyl protecting groups; added methanol toward the end of the reaction ensured complete hydrolysis (55°, 5 additional hours). Simple filtration through a silica gel column (10/1, w/w) served to separate the enamine from less basic impurities. The enamine (**6**) (M + calc. for diTMS $C_{41}H_{57}N_3O_{12}Si_2$, 839.3480, found 839.3466, UV (EtOH) 384 nm (64,300) was formed in 63% yield from (**8**).

Our simplification of the original five step[1a] conversion of enamine (**6**) to trospectomycin (**2**) is as follows. The enamine (**6**) was silylated (THF, hexamethyldisilazane, trimethylsilylchloride, 55°, 2.5 hr) and concentrated to a foam. The foam was taken up in toluene (THF gave a poor yield) and treated with five equivalents of ethylmagnesium bromide at 0° → 25°. It appears that magnesium complexation is important since removal of the 2'-0-acetyl group could be observed before conjugate addition occurred. Following extractive workup, the product was desilylated (0° in 10:1 CH_3CN-48% aqueous HF for 5 hours). Extraction and a simple chromatography (10:1) gave dienone (**9**) [M + H] + calc for $C_{33}H_{39}N_2O_{11}$, 639.2554, found 639.2576. UV in EtOH, 207 nm (21,000), 247 (690), 259 sh (6600), 300 (17,450). $[\alpha]_D$ + 27° (C, 0.88 in EtOH). in 60% yield from enamine (**6**).

The final step of the sequence is saturation of the olefinic bonds and hydrogenolysis of the carbobenzyloxy groups without reduction of the carbonyl group. This was done under 1 atmosphere of hydrogen using $Pd/BaSO_4$ in 2-propanol and catalytic pyridine with vigorous stirring (2.3 hr). After concentration under vacuum the residue was taken up in water and neutralized with one equivalent of sulfuric acid; the solution was lyophilized, taken up in water and acetone was added to yield crystalline trospectomycin sulfate (59% yield). $[\alpha]_D$ + 20° (.90 g/100 ml H_2O), MS (FAB) M + 375.

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6. C-13 Spectra:

Enolacetate (**8**), d_6-acetone: 168.9, 167.7, 161.4, 161.0, 157.1, 139.8, 137.6, 129.0, 128.4, 128.1, 122.8, 94.7, 92.2, 74.0, 71.3, 69.1, 67.6, 67.2, 55.9, 55.4, 31.4, 30.5, 21.1, 21.0, 20.7 ppm.

Enone (**5b**), d_6-acetone: 182.4, 173.2, 169.9, 161.5, 160.9, 157.0, 137.6, 129.1, 128.5, 128.2, 103.5, 95.6, 93.2, 74.0, 72.0, 67.8, 66.8, 56.0, 55.4, 31.5, 30.6, 20.9 ppm.

Enamine **6**, d_6-acetone: 180.3, 171.2, 169.8, 163.3, 157.7, 157.2, 150.3, 138.0, 137.9, 129.1, 128.3, 95.5, 95.1, 95.0, 94.9, 88.7, 75.4, 74.6, 67.3, 66.2, 59.6, 36.3, 30.44 br, 31.5, 31.2, 20.9 ppm.

Dienone **9**, d_6-acetone: 188.4, 145.8, 137.7, 129.1, 128.7, 128.3, 123.5, 101.3, 99.1, 88.1, 76.3, 74.6, 67.3, 66.3, 65.2, 60.1, 57.3, 31.7, 31.5, 26.3, 12.6 ppm.

Trospectomycin (**2**), D_2O (CH_3CN as internal standard): 92.8 (1' + 2'), 91.1 (3'), 71.8 (5), 69.0 (5'), 65.1 (6), 64.7 (4), 60.8 (1), 59.1 (2), 57.7 (3), 38.7 (4'), 32.7 (6'), 30.3 (NCH_3), 29.7 (NCH_3), 25.7 (7'), 21.1 (8'), 12.4 (9') ppm.

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