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SYNTHESIS OF (+)-NEGAMYCIN FROM D-GLUCOSE

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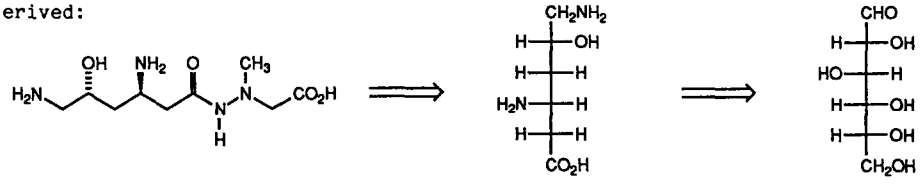
Summary: The broad spectrum antibiotic (+)-negamycin (1) was prepared from 1,2-O-isopropylidene-D-glucose (3) in nine steps.

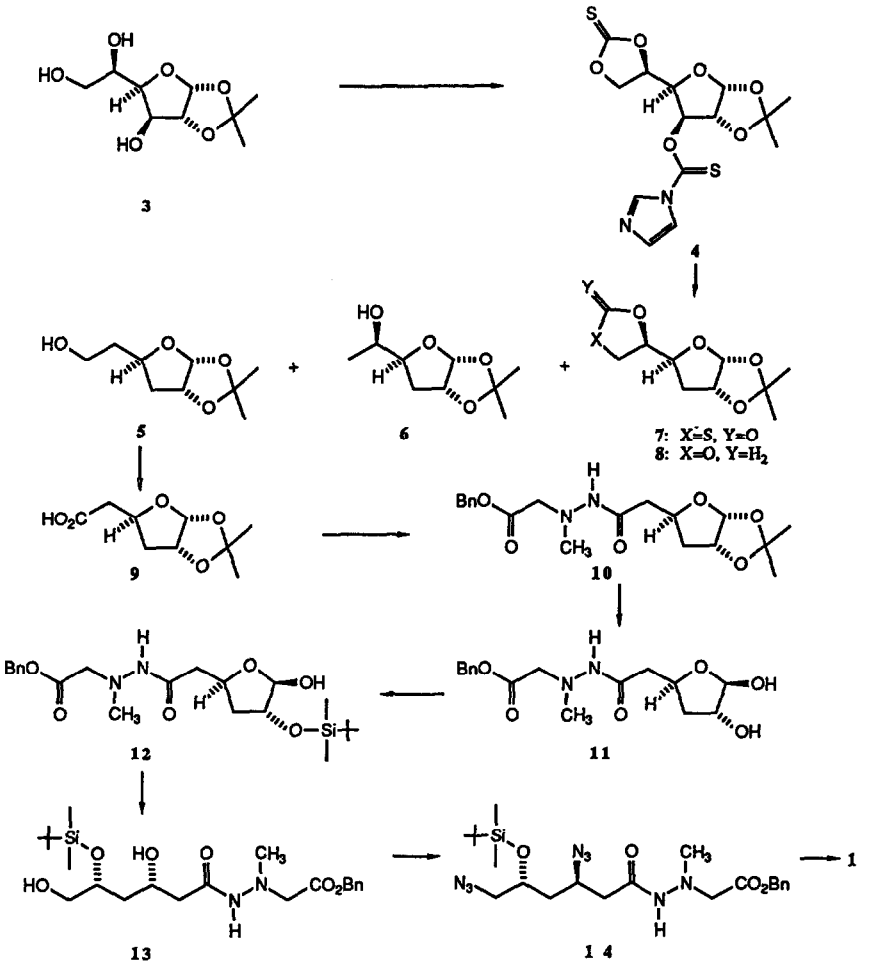
Negamycin (1) is a broad spectrum antibiotic elaborated by *Streptomyces purpeofuscus*.[1] The molecule exerts its biological activity by intervening in a number of specific phases of bacterial gene expression. Thus, negamycin was found to repress the initiation step of prokaryotic protein synthesis by inhibiting the binding of fmet-$tRNA_f$ to the ribosome-*m*RNA complex.[2] It has also been reported to cause misreading of *m*RNA codons, much like the aminoglycosides.[3] Moreover, the antibiotic was claimed to inhibit chain termination by blocking the release of completed peptide from the ribosome.[4]

A number of total syntheses have been achieved of racemic negamycin,[5] as well as of the natural (+)-enantiomer.[6] We report here a new synthesis of (+)-negamycin which is distinguished from previous ones by its brevity, made feasible by utilizing D-glucose as chiral starting material from which the stereochemical content of the constituent (3*R*,5*R*)-δ-hydroxy-β-lysine (2) is readily derived:



1 2 D-Glucose

Our synthesis was begun with the commercially available 1,2-O-isopropylidene-D-glucose 3. Reaction of 3 with thiocarbonyldiimidazole in refluxing dichloroethane (20 min.) accomplished formation of a cyclic thiocarbonate involving the 5- and 6-oxygen functions, along with thiocarbamation of O-3, giving 4 (75%).[7] Reduction of 4 with Bu_3SnH[8] in refluxing toluene afforded as the major product the desired 3,5-dideoxy sugar derivative 5 (41%).[9] Minor by-products were the 3,6-dideoxygenated isomer 6 (18%), the thiolocarbonate 7 (9%), and the deoxygenation product 8 (14%), readily separable by silica gel chromatography. Oxidation of 5 with RuO_4 (catalytic) and $NaIO_4$ in CCl_4/MeCN/H_2O gave the corresponding hexuronic acid 9 (100%).[10]



(For conditions cf. text)

The hydrazide **10** (79%)[11] was then prepared from **9** with benzyl 2-hydrazinoacetate by the mixed anhydride method,[12] employing isobutyl chloroformate and N-methylmorpholine in THF (-10°C). Removal of the isopropylidene protecting group from **10** was accomplished by stirring its warm aqueous solution (30 min., 60°C) with acidic ion exchange resin (Dowex AG 50W X4, H^+-form), to yield **11**[13] (100%) as the β-anomer. When **11** was allowed to react (5d) with *t*-butyldimethylsilyl chloride in dichloroethane/pyridine (3:1) a good yield of the selectively 2-protected silyl-derivative **12** (50.4%)[14] was obtained, accompanied by only minor amounts of the isomeric 1-silylated (11.2%) and 1,2-disilylated (17.1%) by-products, all separable by silica gel chromatography.

The hemiacetal function of **12** was reduced with $NaBH_4$ in acetic acid buffered ethanol solution at 0°C to provide the diol **13** (80%).[15] Mitsunobu reaction[16] of **13** with 2.2 equiv. each of triphenylphosphine, hydrazoic acid (as a benzene solution), and diethyl azodicarboxylate in acetonitrile (in that order) afforded the diazide **14**[17] (70%). In a final step the azides were reduced to amino groups by catalytic hydrogenation over Pd/C in dioxane and aqueous HCl, with concomitant removal of the benzyl and silyl protecting groups.

Thus, enantiomerically pure (+)-negamycin (1), was obtained from 1,2-O-isopropylidene-D-glucose (3) by a diastereospecific synthesis sequence of nine linearly proceeding steps. The physical and antibacterial properties of our synthetic product were identical with those of material from natural sources.[18]

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7. ^{1}H NMR of 4 (DMSO-d_6): δ 1.29, 1.51 (s, 3H each, CMe_2), 4.83, 4.96 (AB of ABX, 2H, J_{gem}= 8 Hz, J_{vic}=8.5 and 7.5 Hz, 2 H-6), 4.88 (t, 1H, J=3.5 Hz, H-4), 4.89 (d, 1H, J=4 Hz, H-2), 5.55 (ddd, 1H, J=3.5, 7.5, and 8.5 Hz, H-5), 5.94 (d, 1H, J=3.5 Hz, H-3), 6.09 (d, 1H, J=4 Hz, H-1), 7.14, 7.82, 8.47 (ABX, 3H, J_{ortho}=1.5 Hz, J_{meta}=1 Hz, imidazole); $[\alpha]_D^{25}$ - 32.7° (c 1.083, DMF); mp 199°C (AcOEt).
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9. ^{1}H NMR of 5 (DMSO-d_6): δ 1.23, 1.39 (s, 3H each, CMe_2), 1.41 (ddd, 1H, J_{gem}=13.5 Hz, J_{vic}=5 and 11 Hz, one of 2 H-3), 1.66 (m, 2H, 2 H-5), 2.01 (dd, 1H, J_{gem}=13.5 Hz, J_{vic}=<1 and 4 Hz, one of 2 H-3), 3.48 (dt, 2H, J=5, 6.5 and 6.5 Hz, 2 H-6), 4.15 (m, 1H, H-4), 4.49 (t, 1H, J=5 Hz, OH), 4.71 (t, 1H, J=4 Hz, H-2), 5.72 (d, 1H, J=4 Hz, H-1); $[\alpha]_D^{25}$ - 8.2° (c 1.036, $CHCl_3$).
10. ^{1}H NMR of 9 (DMSO-d_6): δ 1.24, 1.40 (s, 3H each, CMe_2), 1.51 (ddd, 1H, J_{gem}=13.5 Hz, J_{vic}=4.5 and 11 Hz, one of 2 H-3), 2.06 (dd, 1H, J_{gem}=13.5 Hz, J_{vic}=<1 and 4 Hz, one of 2 H-3), 2.49 (m, 2H, 2 H-5), 4.36 (m, 1H, H-4), 4.73 (t, 1H, J=4 Hz, H-2), 5.73 (d, 1H, J=4 Hz, H-1), 12.31 (br s, 1H, COOH); $[\alpha]_D^{25}$ - 25.9° (c 1.047, $CHCl_3$).
11. ^{1}H NMR of 10 (DMSO-d_6): δ 1.24, 1.40 (s, 3H each, CMe_2), 1.34-1.49 (m, 1H, one of 2 H-3), 1.97 (dd, 3/5H, J_{gem}=13.5 Hz, J_{vic}=<1 and 4 Hz, one of 2 H-3 of major rotamer), 2.03 (br m, 2/5H, one of 2 H-3 of minor rotamer), 2.15, 2.29 (AB of ABX, 6/5H, J_{gem}=14 Hz, J_{vic}=6 and 6 Hz, 2 H-5 of major rotamer), 2.46-2.68 (br, 2/5H, one of 2 H-5 of minor rotamer), 2.53 (s, 6/5H, NMe of minor rotamer), 2.64 (s, 9/5H, NMe of major rotamer), 2.88 (dd, 2/5H, J_{gem}=16 Hz, J_{vic}=6 Hz, one of 2 H-5 of minor rotamer), 3.52, 3.68 (AB, 4/5H, J_{gem}=16 Hz, NCH_2 of minor rotamer), 3.72 (AB, 6/5H, J_{gem}=16 Hz, NCH_2 of major rotamer), 4.27 (m, 3/5H, H-4 of major rotamer), 4.32 (m, 2/5H, H-4 of minor rotamer),

4.68 (m, 1H, H-2), 5.16 (s, 2H, -CH_2Ø), 5.74 (d, 1H, J=4 Hz, H-1), 7.37 (m, 5H, Ø), 8.32 (s, 3/5H, NH of major rotamer), 9.14 (s, 2/5H, NH of minor rotamer); $[\alpha]_D^{25}$ - 14.7° (c 1.051, $CHCl_3$).

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13. ^{1}H NMR of 11 (DMSO-d_6): δ 1.58-1.96 (br m, 2H, 2 H-3), 2.13, 2.32 (AB of ABX, 6/5H, J_{gem}=14 Hz, J_{vic}=7 and 7 Hz, 2 H-5 of major rotamer), 2.40-2.70 (br, 2/5H, one of 2 H-5 of minor rotamer), 2.55 (s, 6/5H, NMe of minor rotamer, 2.64 (s, 9/5H, NMe of major rotamer), 2.92 (dd, 2/5H, J_{gem}=15.5 Hz, J_{vic}=6 Hz, one of 2 H-5 of minor rotamer), 3.56, 3.67 (AB, 4/5H, J_{gem}=16 Hz, NCH_2 of minor rotamer), 3.73 (AB, 6/5H, J_{gem}=16 Hz, NCH_2 of major rotamer), 3.89 (br s, 1H, H-2), 4.24-4.54 (br m, 1H, H-4), 4.82-4.99 (m, 2H, H-1 and OH-2), 5.15 (s, 2H, CH_2Ø), 5.96 (d, 2/5H, J=4.5 Hz, OH-1 of minor rotamer), 6.05 (d, 3/5H, J=4.5 Hz, OH-1 of major rotamer), 7.40 (s, 5H, Ø), 8.22 (s, 2/5H, NH of minor rotamer), 9.09 (s, 3/5H, NH of major rotamer); $[\alpha]_D^{25}$ - 5.2°, to +1.4° after 24 h (c 1.061, MeOH), mp 111-112°C (EtOH, -Et_2O).

14. ^{1}H NMR of 12 (DMSO-d_6): δ 0.03 (s, 6H, $SiMe_2$), 0.84 (s, 9H, Si-*t*-Bu), 1.74 (m, 2H, 2 H-3), 2.14, 2.31 (AB of ABX, 6/5H, 2 H-5 of major rotamer), 2.42-2.66 (br, 2/5H, one of 2 H-5 of minor rotamer), 2.54 (s, 6/5H, NMe of minor rotamer), 2.62 (s, 9/5H, NMe of major rotamer), 2.91 (dd, 2/5H, J_{gem}=16 Hz, J_{vic}=6 Hz, one of 2 H-5 of minor rotamer), 3.54, 3.66 (AB, 4/5H, J_{gem}=16 Hz, NCH_2 of minor rotamer), 3.72 (AB, 6/5H, J_{gem}=16 Hz, NCH_2 of major rotamer), 4.02 (br m, 1H, H-2), 4.34 (m, 3/5H, H-4 of major rotamer), 4.38 (m, 2/5H, H-4 of minor rotamer), 4.89 (d, 2/5H, J=5 Hz, H-1 of minor rotamer), 4.91 (d, 3/5H, J=4 Hz, H-1 of major rotamer), 5.13 (s, 2H, CH_2Ø), 6.11 (d, 2/5H, J=5 Hz, OH-1 of minor rotamer), 6.20 (d, 3/5H, J=4 Hz, OH-1 of major rotamer), 7.39 (s, 5H, Ø), 8.26 (s, 2/5H, NH of minor rotamer), 9.11 (s, 3/5H, NH of major rotamer); $[\alpha]_D^{25}$ + 0.7° (c 1.109, $CHCl_3$).

15. ^{1}H-NMR of 13 (DMSO-d_6): δ 0.03 (s, 6H, $SiMe_2$), 0.84 (s, 9H, SitBu), 1.34-1.64 (m, 2H, 2 H-4), 2.04 (m, 6/5H, 2 H-2 of major rotamer), 2.26-2.80 (br, 4/5H, 2 H-2 of minor rotamer), 2.56 (s, 6/5H, NMe of minor rotamer), 2.63 (s, 9/5H, NMe of major rotamer), 3.34 (m, 2H, 2 H-6), 3.60 (br AB, 4/5H, NCH_2 of minor rotamer), 3.74 (s, 6/5H, NCH_2 of major rotamer), 3.76 (m, 1H, H-5), 3.85-4.06 (br m, 1H, H-3), 4.36-4.80 (br, 2H, 2 OH), 5.14 (s, 2H, CH_2Ø), 7.40 (s, 5H, Ø), 8.27 (s, 2/5H, NH of minor rotamer), 9.04 (s, 3/5H, NH of major rotamer); $[\alpha]_D^{25}$ + 6.0 (c 0.980, $CHCl_3$).

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17. ^{1}H NMR of 14 (DMSO-d_6, 1:1 rotamers): δ 0.11 (s, 3/2 H, SiMe), 0.12 (s, 3H, $SiMe_2$), 0.13 (s, 3/2 H, SiMe), 0.89 (s, 9H Si-*t*-Bu), 1.40-1.54 (m, 1H, one of 2 H-4), 1.54-1.72 (m, 1H, one of 2 H-4), 2.31 (d, 1H, J= 7 Hz, 2 H-2), 2.42-2.73 (br m, 1H, 2 H-2), 2.55 (s, 3/2 H, NMe), 2.66 (s, 3/2 H, NMe), 3.17 (dt, 1H, J_{gem}=13 Hz, J_{vic}=5 and 5 Hz, one of 2 H-6), 3.48 (dt, 1H, J_{gem}=13 Hz, J_{vic}=4 and 4 Hz, one of 2 H-6), 3.53 and 3.71 (br AB, 1H, NCH_2), 3.74 (AB, 1H, J_{gem}=18.5 Hz, NCH_2), 3.87-4.04 (br m, 2H, H-3 and H-5), 5.12 (s, 1H, CH_2Ø), 5.13 (br s, 1H, CH_2Ø), 7.26-7.44 (m, 5H, Ø), 8.46 (br s, 1/2 H, NH), 9.33 (s, 1/2 H, NH); $[\alpha]_D^{25}$+ 11.9° (c 1.156, $CHCl_3$).

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