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TOTAL SYNTHESIS OF APRAMYCIN

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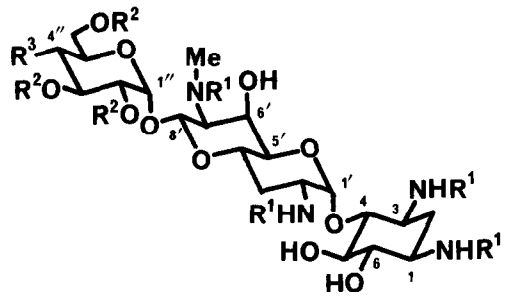
Summary: Apramycin has been stereoselectively synthesized from the previously synthesized aminoglycoside antibiotic, neamine, through the aminooctodiose derivative, aprosamine.

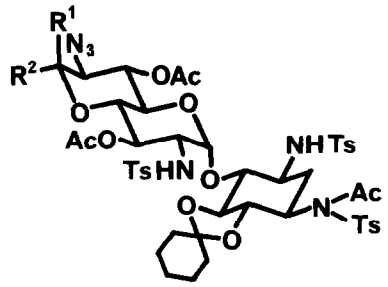
Apramycin (1),[1] a potent aminoglycoside antibiotic, contains the unusual aminooctodiose moiety. The significant antibiotic activity and unique structure have prompted substantial recent synthesis efforts.[2] We report herein the first total synthesis of apramycin (1) by a route that allows access to a wide variety of structural analogues as well. The synthesis begins with the preparation of the starting masked compound 2[3] (mp 142°, $[\alpha]_D$ -38°) in 79% overall yield from the previously synthesized aminoglycoside antibiotic, neamine[4], by the following sequence: (1) N-(benzyloxycarbonyloxy)-5-norbornene-2,3-dicarboximide (Z-ONB)[5]/Et_3N/aq. MeOH, 20°, 5h; (2) TsCl/Na_2CO_3/aq. dioxane, 20°, 5h; (3) 1,1-dimethoxycyclohexane[6]/TsOH/DMF, 50°, 25mmHg, 2 days. Saponification of 2 (KO-t-Bu/aq. t-BuOH/70°, 1h) followed by treatment with 30% HCHO and $NaBH_3CN$[7] (AcOH/MeCN/20°, 1h) afforded the 6'-N-dimethylamino compound, which after oxidation with m-chloroperbenzoic acid ($CHCl_3$/20°, 1h) gave the N-oxide (3·H_2O: 83%, mp 179°, $[\alpha]_D$ -23°). Treatment of 3 with benzoyl chloride (i-Pr_2EtN/Me_2CO/40°, 10min) produced the aldehyde (4·H_2O: 75%, mp 148°, $[\alpha]_D$ -15°), suggesting that the procedure would be useful for the preparation of aldehydes from the primary amines.[8] Addition of 15 equiv of allylmagnesium chloride (THF/60°, 0.5h) to 4 unexpectedly[2a,9] provided an approximately 1 : 1 mixture of 6'*S*-allylcabinol 5 [37%, mp 137°, $[\alpha]_D$ -20°, Rf 0.48 ($CHCl_3$-MeOH 20 : 1)] and 6'*R*-isomer 6 (41%, mp 133°, $[\alpha]_D$ -5°, Rf 0.43). The stereochemistry at C6' of 5 and 6 was clarified by ^{1}H-NMR of the derivatives 8a,b and 9 as described below. Oxidation of 5 (OsO_4/aq. dioxane, 20°, 0.5h and then $NaIO_4$, 1.5h) to give the aldehyde [^{1}H-NMR: 9.79 (CHO)] followed by selective removal of the cyclohexylidene group (50% AcOH in aq. dioxane, 20°, 1.5h) afforded the octodiose[2] derivative [7·H_2O: 60%, mp 183°, $[\alpha]_D$ -13° (MeOH)], which was acetylated (Ac_2O/Py, 40°, 16h) to a mixture of tetraacetates 8a [34%, mp 162°, $[\alpha]_D$ +18°, Rf 0.33 (PhH-EtOAc 2 : 1)] and 8b (37%, mp 168°, $[\alpha]_D$ +60°, Rf 0.38). Similarly, 6 was transformed into a single β-acetate 9 (mp 169°, $[\alpha]_D$ +30°). Their ^{1}H-NMR decoupling revealed the H-6' methine protons in 8a,b and 9 to be axial ($J_{5',6'}$=10) and equatorial ($J_{5',6'}$=2.5), respectively. Their 1-N-acetyl structures were deduced by the ^{1}H-NMR of the 1-N-acetyl-5,6,3',6',8'-penta-O-acetyl derivative 10 (mp 164°, $[\alpha]_D$ +58°), which was formed by removal (50% AcOH in aq. dioxane, 50°, 24h) of the cyclic acetal of 8b followed by acetylation (Ac_2O/Py, 40°, 12h): the significant downfield shift was observed for the H-1 signal (δ 4.34) in comparison with the H-3 signal (δ 3.40). The aforesaid intermediate 7 was converted by our method[10] (TsCl/Et_3N/MeCN, 20°, 12h and then Ac_2O/Py, 40°, 19h) into the acetyl glycal 11[11] (52%, mp 164°, $[\alpha]_D$ +98°).

The other isomer **6** was also efficiently transformed into the glycal **11** through the inversion of the 6'-hydroxyl group. Mesylation of **6** (MsCl/Py, 20°, 2.5h) followed by displacement reaction (KOAc/DMSO, 80°, 18h) gave the acetate **12** (85%, mp 138°, $[\alpha]_D$ -33°). As described above, oxidation and selective hydrolysis of **12** afforded the octodiose derivative **13** (82%, mp 166°, $[\alpha]_D$ +2.5°), which was in turn led to **11** (55%). Azidonitration[12] of **11** [$NaN_3/(NH_4)_2Ce(NO_3)_6$, -17°, 2.5h, Ar) gave the 7'-azido compounds **14** [63%, mp 161°, $[\alpha]_D$ -13°, Rf 0.44 (PhH-EtOAc 3 : 1)] and **15** (14%, mp 157°, $[\alpha]_D$ +25°, Rf 0.50), the stereochemistry of which was ascertained by their ^{1}H-NMR. Alkaline treatment of either **14** or **15** in MeOH [$Ba(OH)_2 \cdot 8H_2O$, 60°, 25min] afforded the corresponding methyl β-glycoside **16** [mp 160°, $[\alpha]_D$ +5° (MeOH)] in 71% or 40% yield with the α-anomer. In a straightforward fashion **16** was transformed in 61% overall yield into the 7'-N-(benzyloxycarbonyl)-methylamino derivative **17** (mp 167°, $[\alpha]_D$ -44°) via a four-step process : (1) 3 atm H_2/Pt-black/MeOH, 20°, 2h; (2) Z-Cl/Na_2CO_3/aq. Me_2CO, 20°, 10min; (3) $LiAlH_4$/THF, 80°, 3h; (4) Z-Cl/Na_2CO_3/aq. Me_2CO, 20°, 10min. Mesylation of **17** (MsCl/Py, 8°, 11h; 20°, 5h) afforded quantitatively the labile dimesylate **18** (mp 164°, $[\alpha]_D$ +2.5°), which was selectively chlorinated[13] (LiCl/DMF, 100°, 2h, Ar) to form the 3'-chloro compound, followed by dechlorination (Bu_3SnH/α,α'-azobisisobutyronitrile/dioxane, 80°, 1.5h, Ar) to give the 3'-deoxy compound **19** (81%, mp 168°, $[\alpha]_D$ +13°). Epimerization[14] of the 6'-hydroxyl group was accomplished by treatment of **19** with AcONa ($MeOCH_2CH_2OH$, 130°, 2 days) to give the *cis*-7'-N,6'-O-carbonyl compound **20** (78%, mp 162°, $[\alpha]_D$ -25°), the stereochemistry of which was confirmed by the ^{1}H-NMR ($J_{5',6'}$=3.8, $J_{6',7'}$=7) and IR[14] (1750 cm^{-1}: *cis*-cyclic carbamate). Removal of the N-tosyl group of **20** (Na/liq. NH_3, -30°, 1h) followed by alkaline hydrolysis (2M NaOH, 100°, 5h) and subsequent acidic hydrolysis [Dowex 50WX2 (H type) resin/H_2O, 20°, 12h and then elution with aq. ammonia] provided the aminooctodiose derivative, methyl β-aprosaminide[1a] [**21**·H_2O: 65%, mp ∿145°, $[\alpha]_D$ +109° (H_2O)], which was further hydrolyzed (4N HCl, 95°, 72h) to give aprosamine[1a] [**22**·4HCl: 70%, mp 180° (dec.), $[\alpha]_D$ +44° (H_2O)]. Both **21** and **22** were identical in all respects with the naturally derived products, thus setting the stage for introduction of the 4-amino-4-deoxy-D-glucose unit. N-benzyloxycarbonylation of **22** (Z-Cl/Na_2CO_3/NaOH/aq. Me_2CO, 20°, 2h) generated the key intermediate [**23**·H_2O: 71%, mp 195° (dec.), $[\alpha]_D$ +43° (MeOH)]. Methanolysis (1.2% HCl gas in MeOH, 70°, 5h) or methylation (MeI/Ag_2O/MeCN, 20°, 1h) of **23**, followed by reduction (3 atm H_2/Pd-black/aq. dioxane, 20°, 5h) gave methyl β-aprosaminide **21** in a fairly good yield (81% or 70%). The findings suggested that the 1,3-diaxial interaction between C6'- and C8'-substituents favored the exclusive formation of the β-glycoside even under acidic conditions.[15] On the other hand, reaction of O-benzylglycosyl halides with alcohols are known to yield predominantly the corresponding α-glycosides.[16] Consequently, it was anticipated that reaction of O-benzylglycosyl halide with **23** would produce the desired α-glycosyl-β-aprosaminide in a reasonable yield. Then, the glycosidation was realized under modified Mukaiyama conditions[16a] (PhH/dioxane/$SnCl_2$/$AgClO_4$/MS 4A, 0°, 2 days) by using 1 equiv of the alcohol **23** and 2 equiv of 4-azido-2,3,6-tri-O-benzyl-4-deoxy-β-D-glucopyranosyl fluoride [oil, $[\alpha]_D$ +108°, ^{1}H-NMR: 5.19 (dd, $J_{1,2}$=6.4, $J_{1,F}$=52, H-1)], the latter of which was prepared from the corresponding α-D-glycosyl chloride,[16] to give the desired glycoside **24** [mp 92°, $[\alpha]_D$ +63°, Rf 0.41 ($CHCl_3$-MeOH 12 : 1); **23**: Rf 0.35] in 21% yield (37% yield based on unrecovered alcohol **23**. Hydrogenolysis of **24** [3 atm H_2/Pd-black/dioxane-AcOH-H_2O (3 : 1 : 1), 20°, 2h] followed by column chromatography on Amberlite CG-50 (NH_4 type) resin with aq. ammonia (0 → 0.1M) completed the synthesis, giving apramycin [1·H_2CO_3·H_2O: 74%, mp 240° (dec.), $[\alpha]_D$ +162°



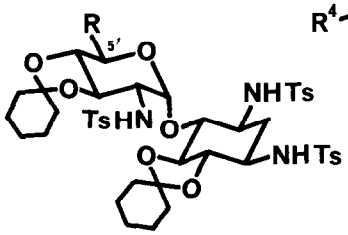
1 (Apramycin): $R^1 = R^2 = H$, $R^3 = NH_2$

24: $R^1 = Z$, $R^2 = Bzl$, $R^3 = N_3$



14: $R^1 = ONO_2$, $R^2 = H$

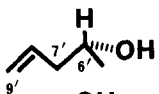
15: $R^1 = H$, $R^2 = ONO_2$

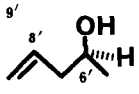


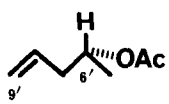
2: $R = {}^{6'}CH_2NHZ$

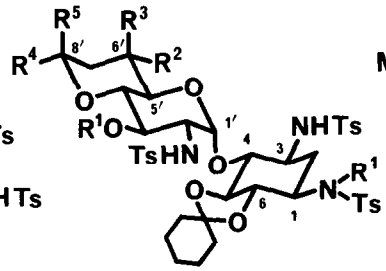
3: $R = CH_2N(O)Me_2$

4: $R = CHO$

5: $R =$ 

6: $R =$ 

12: $R =$ 



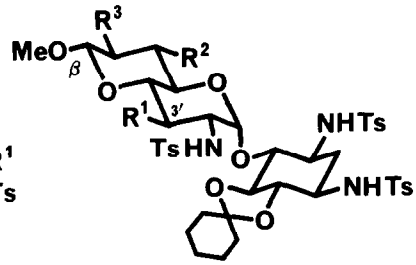
7: $R^1 = R^3 = H$, $R^2 = OH$
$R^4, R^5 = H, OH$

8a: $R^1 = Ac$, $R^2 = R^5 = OAc$
$R^3 = R^4 = H$

8b: $R^1 = Ac$, $R^2 = R^4 = OAc$
$R^3 = R^5 = H$

9: $R^1 = Ac$, $R^2 = R^5 = H$
$R^3 = R^4 = OAc$

13: $R^1 = R^3 = H$, $R^2 = OAc$
$R^4, R^5 = H, OH$

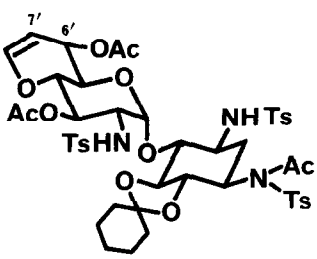


16: $R^1 = R^2 = OH$, $R^3 = N_3$

17: $R^1 = R^2 = OH$, $R^3 = N\langle^{Z}_{Me}$

18: $R^1 = R^2 = OMs$, $R^3 = N\langle^{Z}_{Me}$

19: $R^1 = H$, $R^2 = OMs$,
$R^3 = N\langle^{Z}_{Me}$



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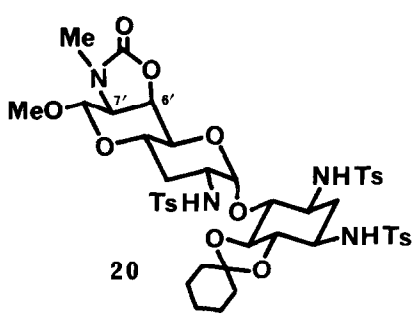
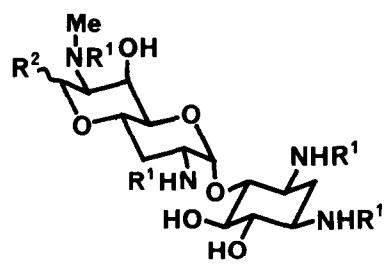


20



21: $R^1 = H$, $R^2 = \beta$-OMe

22 (Aprosamine):
$R^1 = H$, $R^2 = OH$

23: $R^1 = Z$, $R^2 = OH$

(H_2O)] which was identical in all respects (TLC, IR, ^{1}H-NMR and antibacterial activity) with the authentic sample.

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3) All compounds have been fully characterized by spectroscopic means and elemental analyses. Rf-values were measured on silica gel Merck TLC 60F-254. Melting points were uncorrected. Optical rotations were done in $CHCl_3$ at *c* 1.00 (23°) and ^{1}H-NMR spectra (250MHz; δ, ppm from TMS, and J in Hz) were in $CDCl_3$ (with or without D_2O) solution, unless stated otherwise. Significant ^{1}H-NMR spectral data are the following. **1**: (5% ND_3-D_2O) 4.29(broad s, 1H, H-6'), 4.92(d, J=8.5, H-8'), 5.15 (d, J=3.5, H-1'), 5.37(d, J=3.5, H-1"). **2**: 5.12(s, CH_2Ph), 5.26(d, H-1'). **3**: 3.24 & 3.31(s, Me_2N), 5.45(d, J=3, H-1'). **4**: 2.41(s, Ts), 9.67(s, CHO). **5**: 3.97(dd, J=9.5 & 7, H-5'), 5.11(dd, J=10 & 2, H-9'), 5.14(dd, J=17.5 & 2, H-9'), 5.90(m, H-8'). **6**: 4.12(dd, J=10 & 3.5, H-5'), 5.09(dd, J=8 & 1.5, H-9'), 5.14(dd, J=15 & 2, H-9'), 5.88(m, H-8'). **7**: (CD_3CN+D_2O) 4.69(dd, J=10 & 2, H-8'ax), 5.08 & 5.09(d, J≅4, H-1'), 5.21 (dull d, J=3, H-8'eq). **8a**: 3.48(dt, J=10, 10 & 3.8, H-2'), 3.95(t, J=10, H-5'), 4.53(dt, J= 10.5, 10.5 & 4.5, H-1), 6.07(dull d, H-8'). **8b**: 3.83(t, J=10, H-5'), 4.54(dt, J=10.5, 10.5 & 4, H-1), 4.95(m, H-6'), 5.28(d, J=3.5, H-1'), 5.60(dd, J=10 & 2, H-8'). **9**: 4.36(dd, J=10 & 2.5, H-5'), 5.59(m, H-6'), 5.85(dd, J=9.5 & 3, H-8'). **10**: 3.40(m, H-3), 3.80(t, J=9.5, H-4), 4.34(m, H-1), 5.22(t, J=9.5, H-5), 5.56(dd, J=10.5 & 2.5, H-8'), 5.65(t, J≅10, H-6). **11**: 4.84(dd, J=6 & 2.3, H-7'), 5.32(m, H-6'), 6.29(dd, J=6 & 1.5, H-8'). **12**: 3.77(dd, J=11 & 8.5, H-5'), 5.07(dd, J=10 & 2, H-9'), 5.12(dd, J=16 & 2, H-9'). **13**: 1.98(s, Ac), 2.35 & 2.41 (s, Ts). **14**: 3.94(dd, J=10.5 & 4, H-7'), 5.40(t, J≅10, H-6'), 6.20(d, J=4, H-8'). **15**: 3.50 (dd, J=10 & 9, H-7'), 5.13(t, J=10, H-6'), 5.43(d, J=9, H-8'). **16**: [(CD_3)$_2$CO+D_2O] 3.47(t, J=9.5, H-6'), 3.53(s, OMe), 4.21(d, J=8, H-8'), 5.34(d, J=3.5, H-1'). **17**: 3.03(t, J=9.5, H-7'). 3.22(s, NMe). **18**: 2.80 & 2.96(s, Ms), 3.00(s, NMe). **19**: (50°) 2.76(s, Ms), 3.00(s, NMe). **20**: (CD_3CN+D_2O) 3.52(dd, J=7 & 6, H-7'), 4.22(dd, J=10.5 & 3.8, H-5'), 4.42(d, J=6, H-8'), 4.71(dd, J=7 & 3.8, H-6'), 4.93(d, J=3.5, H-1'). **21**: (5% ND_3-D_2O) 2.46(dd, J=8.5 & 3, H-7'), 3.64(dd, J=10 & 2.5, H-5'), 4.26(t, J≅3, H-6'), 4.52(d, J=8.5, H-8'). **22**·4HCl: (D_2O) 4.51 & 4.58(t, J≅3, H-6'), 5.20(d, J=9, H-8'ax), 5.47(d, J=4, H-8'eq), 5.75(d, J=3, H-1') & 5.77(d, J=3.5, H-1'). **23**: (CD_3CN+D_2O) 3.00(s, NMe), 4.21(broad s, H-6'). **24**: (CD_3CN+D_2O, 50°) 3.73(dt, J=13, 4 & 4, H-2'), 5.24(d, J=4, H-1'), 5.27(d, J=9.5, H-8'), 5.41(d, J=3, H-1").
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11) The glycal **11** was treated with 1% HCl in aq. dioxane (50°, 2 days), followed by acetylation (Ac_2O/Py, 40°, 12h) to give **10** as one of the anomeric acetates, supporting the 1-N-acetyl structure.
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