Total Synthesis of Hygromycin A

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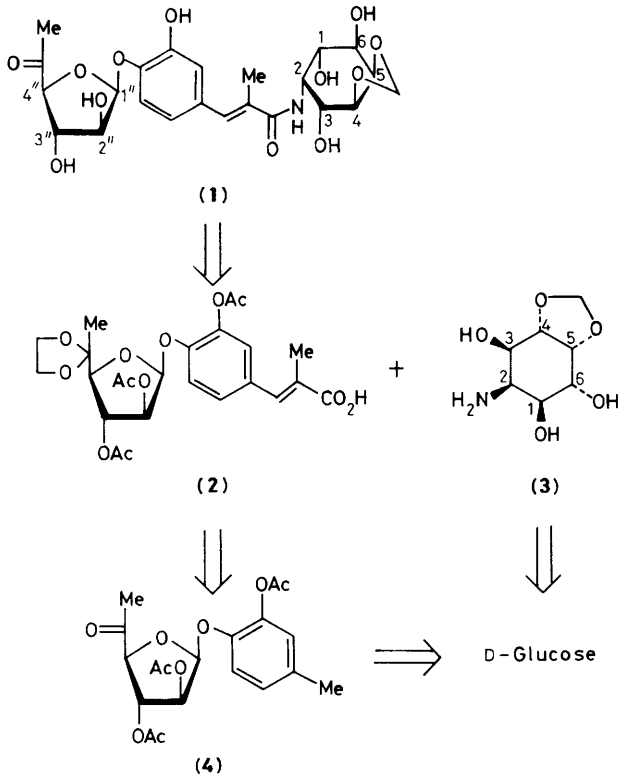
The first complete synthesis of antibiotic hygromycin A is reported; coupling of the protected sugar moiety (**2**) and the aminocyclitol (**3**) derived from D-glucose as the optically active form, followed by deprotection, gives the product (**1**) which was identified with an authentic sample by 400 MHz ^{1}H n.m.r. spectroscopy.

Hygromycin A (**1**) is an antibiotic first isolated[1] from the fermentation broth of *Streptomyces hygroscopicus* in 1953; it has attracted renewed interest due to the recent discovery of its hemagglutination inactivation activity[2] as well as its high antitreponemal activity.[3] The structure was tentatively assigned on the basis of a degradative method[4] and spectral analyses.[5] Although a few reports[6] have appeared so far on synthesis of the structure-components of (**1**), a total synthesis of the intact molecule has never been studied.

Recently, synthesis of 2-acetoxy-4-formylphenyl 2,3-di-*O*-

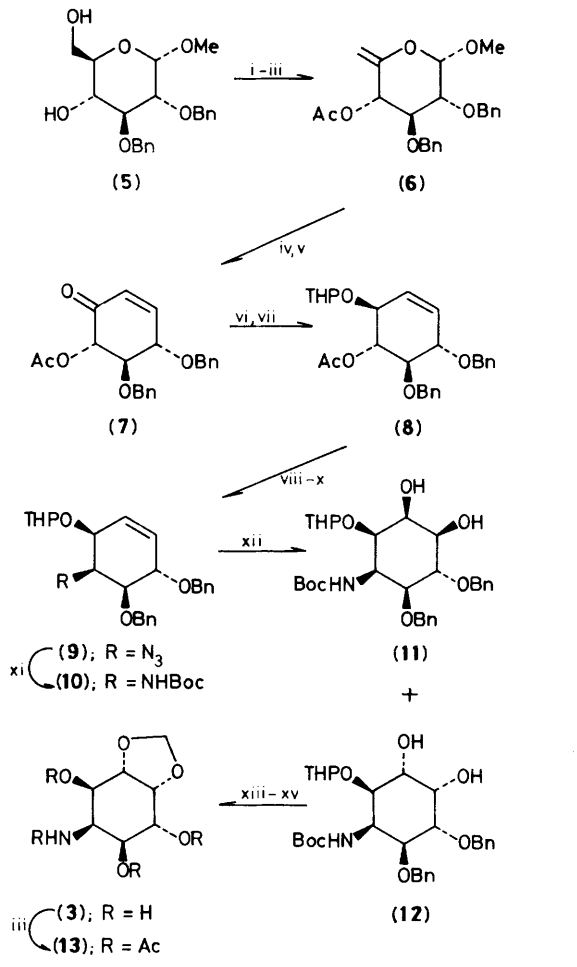


Scheme 1

acetyl-6-deoxy-α- and β-D-*arabino*-5-hexulofuranoside was carried out[7] to establish its anomeric configuration to be β. We now describe the first total synthesis of (**1**), thereby confirming the structure proposed.

Our strategy for elaboration of (**1**) is to condense the sugar moiety (**2**) with the aminocyclitol (**3**). The former was derived from 2-acetoxy-4-methylphenyl 2,3-di-*O*-acetyl-6-deoxy-β-D-*arabino*-5-hexulofuranoside (**4**)[7] by successive protection, oxidation, and Wittig olefination, and the latter was synthesised from D-glucose.

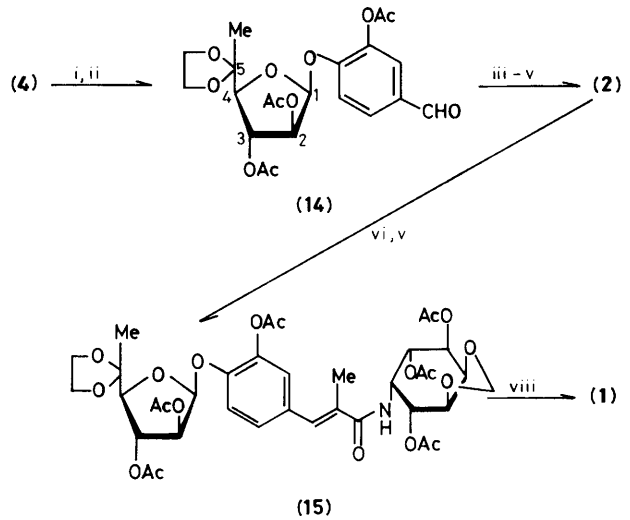
Methyl 2,3-di-*O*-benzyl-α-D-glucopyranoside (**5**)[8] was chosen as the starting material for a chiral synthesis of (**3**). The primary hydroxyl of (**5**) was displaced with iodide, and the product was dehydroiodinated and successively acetylated to give the 5-enopyranoside (**6**) (60% overall yield). Ferrier reaction[9] of (**6**) followed by dehydration afforded the cyclohexene derivative (**7**) (77%). Reduction of the carbonyl group of (**7**) with sodium borohydride–$CeCl_3$ proceeded stereoselectively to give a single alcohol, which was isolated as the tetrahydropyranyl ether (**8**) (96%). *O*-Deacetylation of (**8**) followed by treatment with methanesulphonyl chloride gave the mesylate, azidolysis of which in hexamethylphosphoric triamide (HMPA) gave the azide (**9**) (59%) *via* a direct S_N2 reaction. The azide (**9**) was reduced with $LiAlH_4$ and the amine was converted into the *N*-t-butoxycarbonyl derivative (**10**). Oxidation of (**10**) with OsO_4 in aqueous *N*,*N*-dimethylformamide (DMF) gave a 1 : 2 mixture of the *epi*-inosamine-2 derivative (**11**) and desired *neo*-inosamine-2 derivative (**12**) in 66% combined yield. Introduction of the methylene acetal group between the 4,5-hydroxyls of (**12**) was conducted with methylene bromide and NaH in DMF, and, then, the product was deprotected to give (**3**), which was characterised as the tetra-*N*,*O*-acetyl derivative (**13**) {36% overall yield, $[\alpha]_D^{27}$ −46° ($CHCl_3$)}, identical with an authentic sample† {$[\alpha]_D^{27}$ −49° ($CHCl_3$)} in all respects. The present synthesis confirmed its absolute configuration, deduced previously by the spectral analyses.[5]



Scheme 2. i, I_2, Ph_3P, imidazole, PhMe, 50 °C; ii, Bu^{t}OK, tetrahydrofuran (THF), 0 °C → room temp.; iii, Ac_2O, pyridine; iv, $HgCl_2$, acetone–H_2O (1 : 2), reflux; v, $MeSO_2Cl$, Et_3N, CH_2Cl_2; vi, $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C; vii, dihydropyran, pyridinium *p*-toluenesulphonate (PPTS), CH_2Cl_2; viii, MeONa, MeOH; ix, $MeSO_2Cl$, pyridine, 50 °C; x, NaN_3, hexamethylphosphoric triamide (HMPA), 100 °C; xi, $LiAlH_4$, Et_2O, 0 °C, then $(Boc)_2O$, Et_3N, CH_2Cl_2; xii, OsO_4, 4-methylmorpholine *N*-oxide, *N*,*N*-dimethylformamide (DMF)–H_2O (4 : 1), 75 °C; xiii, NaH, CH_2Br_2, DMF, 0 °C → room temp.; xiv, H_2, $Pd(OH)_2$, EtOH; xv, CF_3CO_2H, $CHCl_3$, room temp.

The methyl ketone function of (**4**) was initially protected[10] by the acetal group, in order to suppress β-elimination of the 3-OAc and ready epimerisation at C-4. The acetal was then oxidised with cerium(IV) ammonium nitrate (CAN) to give the aldehyde (**14**) (63% overall yield), which was subjected to Wittig reaction with $Ph_3P{=}C(Me)CO_2Et$, followed by saponification and acetylation, affording (**2**) (66%).

† The authentic sample was prepared from hygromycin A by the following sequence: (1) alkaline hydrolysis, (2) acetylation, and (3) purification by a silica gel column.



Scheme 3. i, $(CH_2OMe_3Si)_2$, $Me_3SiOSO_2CF_3$, CH_2Cl_2, −5 °C; ii, CAN, MeCN–H_2O (1:2), 5 °C; iii, $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, room temp.; iv, 1 M NaOH, MeOH, 50 °C; v, Ac_2O, pyridine; vi, (**3**), $(EtO)_2P(O)CN$, Et_3N, DMF, 0 °C; vii, MeONa, then CF_3CO_2H–H_2O (3:2), room temp.

Coupling of (**2**) and (**3**) was conducted under conditions of Shioiri's protocol[11] and the condensate (**15**) was obtained as the acetate (50%), *O*-deacetylation and acid hydrolysis of which gave hygromycin A (**1**) {55%, m.p. 110—112 °C (decomp.), $[\alpha]_D^{28}$ −148° (H_2O)}, identical with an authentic sample‡ {m.p. 113—115 °C, $[\alpha]_D^{23}$ −136° (H_2O)} in all respects.

‡ Physical data were provided by Dr. S. Harada.

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