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SYNTHESIS OF AMINOCYCLITOL PART OF 5-DE-O-METHYLSPORARICIN A

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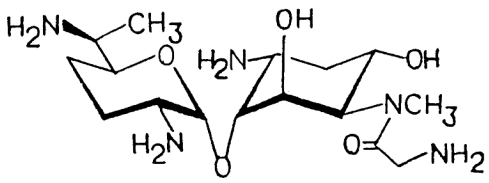
D,L-(1,2,4/5,6)-1,4,6-tri-O-acetyl-2,5-bis(benzyloxycarbonylamino)-5-N-methyl-1,4,6-cyclohexanetriol was synthesized from D,L-(1,2,3/4,5,6)-1,4-bis(benzyloxycarbonylamino)-2,3-O-isopropylidene-2,3,5,6-cyclohexanetetraol.

In the previous paper,[1] we reported a simple synthesis of 6-epi-purpurosamine B as a protected form, a sugar part of sporaricins,[2] from D-glucosamine. In relation to a total synthesis of sporaricins, we here wish to report a novel synthesis of a protected aminocyclitol part of 5-de-O-methylsporaricin A, which possesses the strongest antibacterial activity in sporaricins.[3]

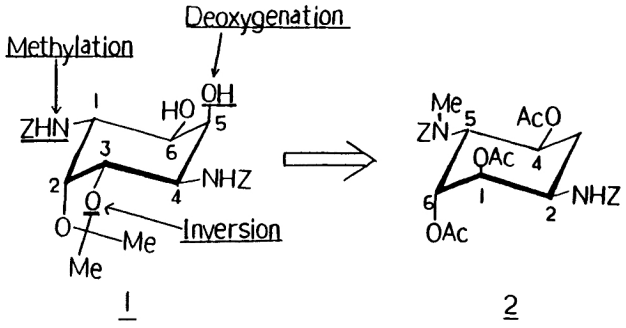


5-De-O-methylsporaricin A

We selected D,L-(1,2,3/4,5,6)-1,4-bis(benzyloxycarbonylamino)-2,3-O-isopropylidene-2,3,5,6-cyclohexanetetraol(1), which was easily obtained from nitromethane and glyoxal[4] as a starting material for the synthesis of D,L-(1,2,4/5,6)-1,4,6-tri-O-acetyl-2,5-bis(benzyloxycarbonylamino)-5-N-methyl-1,4,6-cyclohexanetriol(2). In order to transform 1 into 2, the three key-steps in Scheme 1 must be required; i) deoxygenation at the 5-position in 1, ii) inversion of the hydroxy group at the 3-position, iii) methylation of the amino group at the 1-position.

Regioselective benzoylation of the equatorial hydroxy group in 1 by 1.8 equivalent of benzoyl chloride in pyridine at room temperature for 21 h gave th corresponding 6-O-benzoate derivative(3) (mp 210-211 °C; FD-MS 591 (M^+)) in 84% yield. Mesylation of 3 afforded the corresponding 5-O-mesyl derivative(4) (^{1}H-NMR ($CDCl_3$) δ 1.36 and 1.56 (each s, $C(CH_3)_2$) and 3.02 (s, OMs); EI-MS 668 (M^+-1)) as syrup in 70% yield. Removal of the isopropylidene group in 4 with acetic acid and water (4:1) at 80 °C for 2 h gave the corresponding diol derivative(5) (mp 217-219 °C; ^{1}H-NMR (DMSO-d_6) δ 3.02 (s, OMs)) in 93% yield. Treatment of 5 with excess sodium

iodide in DMF at 100 °C for 8 h gave the corresponding 5-iodo derivative(6)[5] (FD-MS 660 (M^+)) as solid in 98% yield. Dehalogenation of 6 by tri-n-butyltin hydride in the presence of 2,2'-azobisisobutyronitrile in THF under reflux for 5.5 h gave D,L-(1,2,3/4,6)-4-O-benzoyl-3,6-bis(benzyloxycarbonylamino)-1,2,4-cyclohexanetriol(7) (mp 182 °C (decomp); ^{1}H-NMR (DMSO-d_6) δ 1.15-2.30 (m, CH_2); FD-MS 534 (M^+)) in 96% yield.

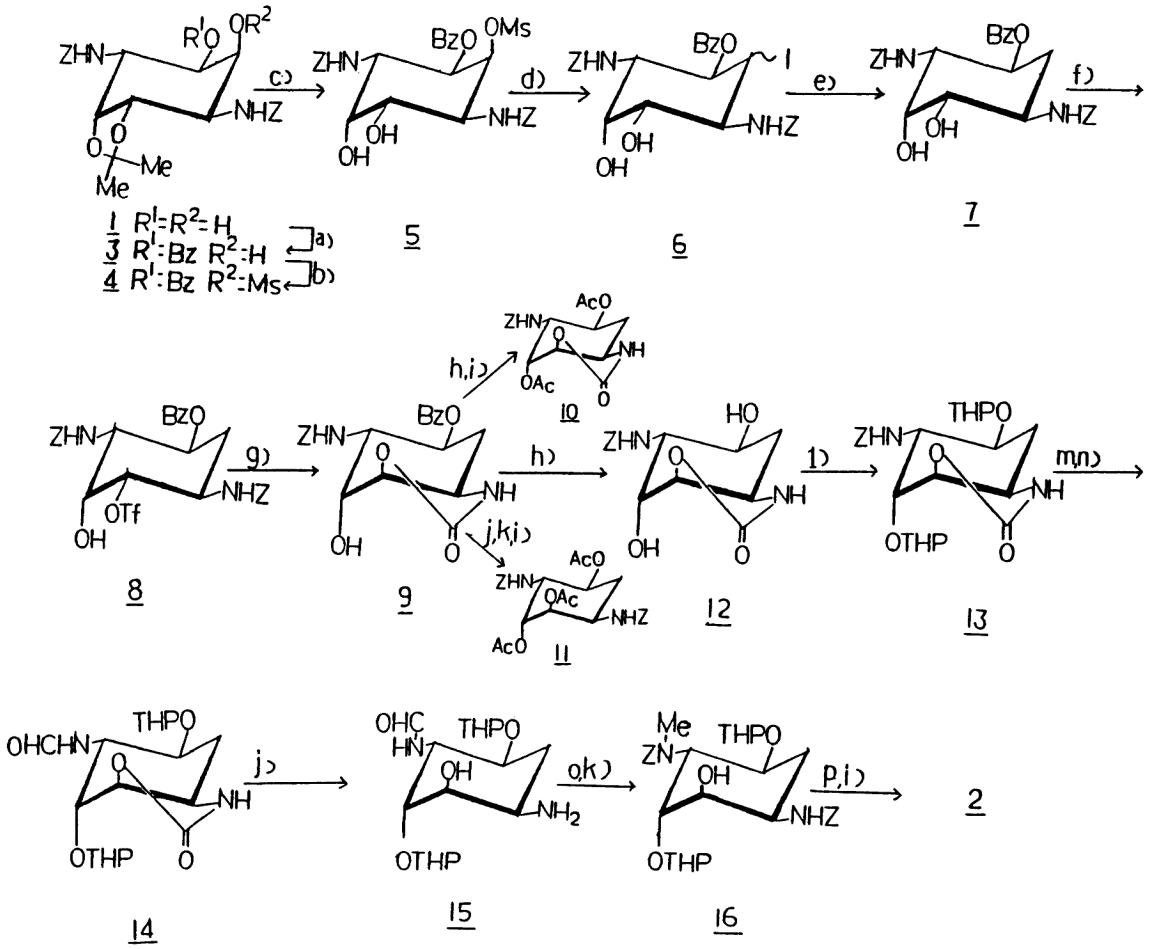


Scheme 1.

Regioselective trifluoromethanesulfonylation of the equatorial hydroxy group in 7 by 1.2 equivalent of trifluoromethanesulfonic anhydride in pyridine at 0 °C for 3 h gave the corresponding 3-O-trifluoromethanesulfonate derivative(8) (mp 138-139 °C) in 95% yield. Formation of a cyclic carbamate accompanied by inversion of the hydroxy group at the 3-position in 8 was achieved by heating 8 at 60-65 °C in DMF for 2.5 h to give D,L-(1,2,4/5,6)-2-amino-4-O-benzoyl-5-benzyloxycarbonylamino-1-O,2-N-carbonyl-1,4,6-cyclohexanetriol(9) (mp 77-78 °C; IR (Nujol) 1740, 1710, and 1520 cm^{-1}; EI-MS 426 (M^+)) in 60% yield. The structure of 9 was confirmed as follows; i) the compound(10), obtained by removal of the benzoyl group in 9 followed by acetylation, showed one equatorial acetyl group (δ 1.96) and one axial acetyl group (δ 2.11) in ^{1}H-NMR ($CDCl_3$), ii) the compound(11), obtained by removal of the benzoyl group and the cyclic carbamate group in 9 followed by protection of the amino function with benzyloxycarbonyl group and finally acetylation of the hydroxy functions, showed one equatorial acetyl group (δ 1.90) and two axial acetyl groups (δ 2.05) in ^{1}H-NMR ($CDCl_3$).

Removal of the benzoyl group in 9 by alkaline hydrolysis gave D,L-(1,2,4/5,6)-2-amino-5-benzyloxycarbonylamino-1-O,2-N-carbonyl-1,4,6-cyclohexanetriol(12) (mp 213-214 °C; IR (Nujol) 1730 and 1675 cm^{-1}; EI-MS 322 (M^+)) in 64% yield. Protection of the hydroxy groups in 12 with dihydropyran gave the corresponding 4,6-bis-O-tetrahydropyranyl derivative(13) (IR (Nujol+EtOH) 1750 and 1700 cm^{-1}) as syrup in 74% yield. Hydrogenation of 13 in the presence of 10% palladium on carbon, followed by treatment with p-nitrophenyl formate and triethylamine in 50%

aqueous methanol at room temperature for 3.5 h, gave D,L-(1,2,4/5,6)-2-amino-1-O, 2-N-carbonyl-5-formamido-4,6-bis-O-tetrahydropyranyl-1,4,6-cyclohexanetriol(14) (IR (Nujol+$CHCl_3$) 1740 and 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.20 (s, CHO); FD-MS 385 (M^++1)) as glass in 67% yield. Selective removal of the cyclic carbamate group in 14 with 1 equivalent of barium hydroxide octahydrate in 50% aqueous 1,4-dioxane at 55-60 °C for 7 h gave D,L-(1,2,4/5,6)-2-amino-5-formamido-4,6-bis-O-tetrahydropyranyl-1,4,6-cyclohexanetriol(15) (IR (Nujol) 1650 cm^{-1}; ^{1}H-NMR (D_2O) δ 8.15



Z:$CO_2CH_2C_6H_5$ Ms:SO_2CH_3 Bz:COC_6H_5 Tf:SO_2CF_3 THP:tetrahydropyranyl

a) BzCl/Py b) MsCl/Py c) AcOH-H_2O (4:1) d) NaI/DMF e) $(n\text{-}Bu)_3SnH$-AIBN/THF f) Tf_2O/Py g) Δ/DMF h) concd NH_4OH/MeOH i) Ac_2O/Py j) $Ba(OH)_2$/aq Dioxane k) ZCl l) DHP-TsOH/DMF m) H_2-10% Pd-C n) p-$O_2NC_6H_4OCHO$-Et_3N o) $LiAlH_4$/THF p) TsOH·Py/EtOH

Scheme 2. Synthetic route for protected aminocyclitol part of 5-de-O-methylsporaricin A.

(s, CHO); FD-MS 358 (M^+)) as glass in 47% yield. Treatment of 15 with lithium aluminium hydride in THF under reflux for 1.5 h, followed by protection of the amino groups with benzyloxycarbonyl function, gave D,L-(1,2,4/5,6)-2,5-bis(benzyloxycarbonylamino)-5-N-methyl-4,6-bis-O-tetrahydropyranyl-1,4,6-cyclohexanetriol(16) (IR (Nujol+EtOH) 1680, 1500, 1320, and 1200 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.97 (s, NCH_3) and 7.25 (s, 2 X Ph); FD-MS 613 (M^+)) as syrup in 46% yield. The compound 16 is suitable for glycosidation with the 6-epi-purpurosamine B derivative to lead to 5-de-O-methylsporaricins. The compound 16 was converted into D,L-(1,2,4/5,6)-1,4,6-tri-O-acetyl-2,5-bis(benzyloxycarbonylamino)-5-N-methyl-1,4,6-cyclohexanetriol(2) (IR (Nujol) 1740-1710 and 1680 cm^{-1}; ^{13}C-NMR ($CDCl_3$) δ 20.9, 30.3, 32.2, 45.8, 54.1, 65.3, 65.8, 67.1, 67.4, 68.0, 70.7, 71.3, 127.7, 128.2, 128.6, 136.0, 136.4, 155.9, 156.7, 168.7, 169.3, and 169.8; EI-MS 571 (M^+)) as glass in 51% yield by removal of the tetrahydropyranyl groups subsequent acetylation. The sample prepared above was identical in every respect (TLC, IR, ^{1}H-NMR, ^{13}C-NMR, and Mass) with the sample prepared from tetra-N-acetylsporaricin B by successive methanolysis,[2] de-O-methylation by 56% hydriodic acid,[3] protection of the amino groups with benzyloxycarbonyl function and subsequent acetylation of the hydroxy groups.

References

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4) F.W.Lichtenthaler and H.O.L.Fischer, J. Am. Chem. Soc., 83, 2005 (1961).

5) Configuration at the 5-position in 6 was not determined.

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