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TOTAL SYNTHESIS OF SORBISTIN A_1 AND A POSITIONAL ISOMER[a,b]

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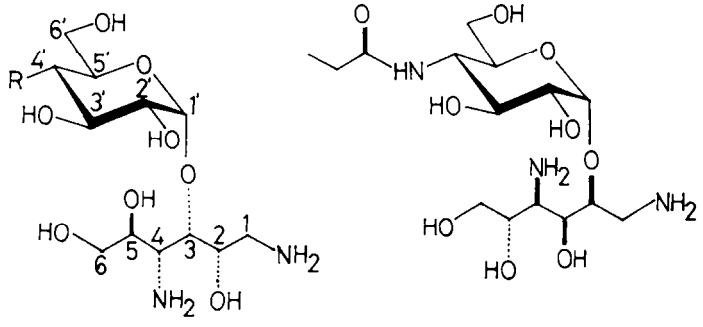
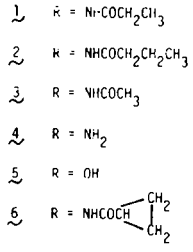
Abstract Total synthesis of sorbistin A_1 (**1**) and a positional isomer (**7**) is described for the first time in a regio- and stereo-controlled manner.

A new class of aminoglycoside antibiotics, sorbistins, were isolated in 1976 from the fermentation broth of *Pseudomonas*[1a,b,c] and *Streptovertillium*[2] species, and proved to have moderate but broad-spectrum activity against Gram-positive and Gram-negative bacteria, including some resistant bacteria carrying aminoglycoside-inactivating enzymes.[3] The unique structures (**1**–**5**) containing a 1,4-diamino-1,4-dideoxyalditol instead of an aminocyclitol moiety, were assigned to sorbistin A_1 (**1**) A_2 (**2**), B (**3**), D (**4**) and C (**5**), respectively, and ascertained through chemical correlations and X-ray crystallography.[2,4a,4b] Among them, sorbistin A_1 (**1**) was reported to be most active.[1a]

Various acyl analogues at C_4-NH_2 of sorbistin A_1 were prepared by Kawaguchi *et al.*[5] and a cyclopropane carboxylic acid analogue (**6**) was found to be as active as sorbistin A_1. A positional isomer of sorbistin A_1, having glycosidic linkage between C_1 and C_6 was also synthesized by Ponpipom *et al.* and found to be biologically inactive.[6]

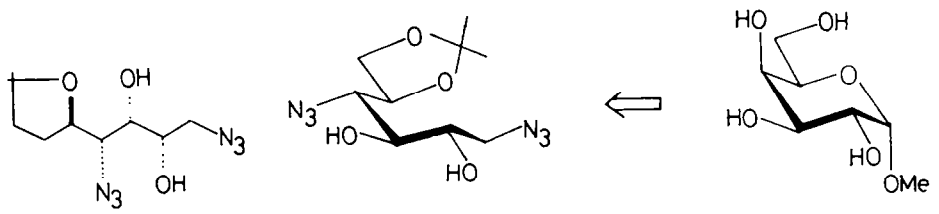
In this paper we describe the first total synthesis of **1** and the positional isomer **7** in a regio- and stereo-controlled manner. The key aspects considered in the synthesis of **1** and **7** are as follows: First, the α-glycosidic linkage is *syn* to the 2′-OH and 4′-NHCOEt, both of which may lead to the formation of a β-glycosidic linkage at C_1, through a neighbouring-group participation,[7] unless suitable protecting groups are employed. Second, regioselectivity is required for both glycosidation at OH and acylation of the NH_2 group. On this basis, diol **8** was chosen as a target molecule for the suitably protected aglycone part. Diol **8** may be rewritten as **9**, which indicates a possible transformation of **10** into **8** by introducing an azide function at C_4 with the inversion of stereochemistry. The glycosyl halide **11**





[a]Experimental part of this paper was taken from a part of the Ph.D. thesis of K.K. (The Univ of Tokyo, 1979).

[b]Preliminary communication; T. Ogawa, K. Katano and M. Matsui, *Carbohydr. Res.* **60**, C13 (1978).



8 9 10

was expected to afford the α-stereochemistry at the glycosidic linkage without any neighboring group participation from C_2 or C_4 to C_1 under appropriate conditions. Regioselective acylation at 4′-NH_2 was expected to be achieved by the intramolecular migration of the acyl group at $C_{6'}$ in the last step.

Synthesis of the suitably protected aglycon **8**

Acetylation of methyl 4,6-O-benzylidene-α-D-galactopyranoside **12**[8] afforded the diacetate **13**.[9] Debenzylidenation of **13** with 80% aq. acetic acid, tritylation at 6-OH and mesylation at 4-OH gave trityl mesylate **14**, m.p. 196–198°, $[\alpha]_D^{25}$ + 86.7°. The structure was confirmed by ^{1}H NMR which revealed three 3 H singlets at δ 2.05, 2.08 and 2.82. Treatment of **14** with sodium azide in DMF gave trityl azide **15**, ν_{max} 2100 cm^{-1}, which has D-*gluco* configuration according to the presence of the signal for C_3–H in the ^{1}H NMR at δ 5.45 ppm as 1 H triplet with J = 9 Hz.

Acetolysis of **15** in 1% H_2SO_4–Ac_2O afforded tetraacetate **16** as a mixture of α and β anomers in a ratio of 12:1. ^{1}H NMR revealed two anomeric protons at δ 6.29 (doublet, J = 4 Hz) for the α anomer and at δ 5.69 (doublet, J = 8 Hz) for the β anomer. The tetraacetate **16** had been synthesized in 1965 by Reist *et al.* by a different route.[10]

Saponification of **16** into tetraol **17**, $NaBH_4$ reduction of **17** into azide glucitol **18** and subsequent isopropylidenation of **18** with 2,2-dimethoxy-propane into diisopropylidene azide **19**, m.p. 88–89°, $[\alpha]_D^{25}$ + 11.0° was achieved in 50% yield without isolation of **17** and **18**. The crucial transformation of **19** into the target molecule **8** was achieved in 5 steps involving a regioselective intramolecular cyclization of the carbonate **20**.

The reaction of **19** with methyl chloroformate afforded the carbonate **20** $[\alpha]_D^{25}$ + 1.2°. ^{1}H NMR of **20** revealed a deshielded signal for C_3–H at δ 4.88 as 1 H triplet with J = 5 Hz which supports the assigned regiochemistry of two isopropylidene groups in **19** and **20**.

Hydrolysis of **20** in 80% aq. AcOH and evaporation of the solvent afforded the cyclic carbonate **21**. The structure of **21** was assigned from the IR data ν_{max} 1780 cm^{-1}. Subsequent isopropylidenation of **21** afforded monoisopropylidene carbonate **22** $[\alpha]_D^{25}$ − 55.0° in 79% yield from **20**. Tosylation of **22** gave **23**, m.p. 86.5–88°, $[\alpha]_D^{25}$ − 48.2°, ν_{max} 1800 cm^{-1}, δ_H 4.68–4.90 (2 H, multiplet, for C_2–H and C_3–H), which was transformed into diazide **24** by the reaction with NaN_3 in DMF. Then **24** was saponified into the target molecule **8** $[\alpha]_D^{25}$ − 14.6°. Over-all yield of **8** from **12** was 16%.

Synthesis of sorbistin A_1 *by employing the glycosyl halide* **11**

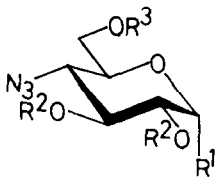
The diol **12** was converted into a 98% yield of dibenzyl ether **25**, m.p. 175–177°, $[\alpha]_D^{25}$ + 77.5°. Debenzylidenation of **25** to **26** which was converted into trityl ether **27**, $[\alpha]_D^{25}$ + 22.7° in 77% yield. Mesylation of **27** gave tritylmesylate **28**, $[\alpha]_D^{25}$ + 30.7°. Displacement of mesyl group by N_3^- afforded trityl azide **29**, $[\alpha]_D^{25}$ + 45.3°, in 85% yield from **27** and hydrolysis of trityl group of **29** gave a 95% yield of azide alcohol **30**, $[\alpha]_D^{25}$ + 102°, which was further treated with propionic anhydride to give **31**, $[\alpha]_D^{25}$ + 87.1°, in 98% yield.

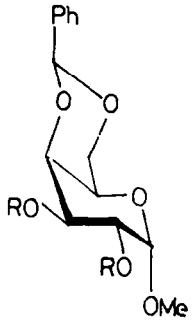
Acetolysis of **31** gave a 76% yield of propionyl acetate **32**, which was further treated to afford a 23% yield of glycosyl halide **11**, $[\alpha]_D^{25}$ + 147.5° and a 67% yield of **34** which was converted into **11** by treatment with thionyl chloride[12] in 72% yield. The combined yield of the glycosyl halide **11** from **32** was 71%. The α-stereochemistry at C_1 of **11** was assigned from ^{1}H NMR data which revealed C_1 H at δ 6.00 as a doublet with J = 4 Hz.

The desired intramolecular migration of acyl group at 6-O to the 4-NH_2 group was examined employing **34** as a model compound.

Reduction of the azide function of **31**[13] gave the amino propionate **34**, ν_{max} 1730 cm^{-1}, R_f 0.4 (toluene: EtOAc = 1:1). On keeping a $CHCl_3$ soln of **34** containing 1% of AcOH for 1.5 hr at 20°, the complete conversion of **34** into a new compound, R_f 0.2 (same solvent), presumably having the structure **35** was observed by tlc examination. Evaporation of the solvent effected a further transformation of **35** into the desired product **36**, R_f 0.05 (same solvent), m.p. 164–166°, $[\alpha]_D^{25}$ + 28.0°, ν_{max} 1640 cm^{-1} in 90% yield from **31**.

Since the expected intramolecular acyl migration could be performed under very mild conditions, the glycosidation of **8** with **11** was examined next employing Lemieux's method.[14] The reaction of **8** with **11** in the presence of Et_4NCl and i-Pr_2EtN in CH_2ClCH_2Cl gave a mixture of **37** and **38** in 55.5% yield. No separation could be effected for **37** and **38** on tlc. However, on hydrolysis of isopropylidene group of this mixture, **39** and **40** could be separated by chromatography on a column of silica gel. The ratio of **39** and **40** was 5:9. Anomeric stereochemistry in both





11 R^1 = Cl R^2 = Bn R^3 = COEt

15 R^1 = OMe R^2 = Ac R^3 = Tr

29 R^1 = OMe R^2 = Bn R^3 = Tr

30 R^1 = OMe R^2 = Bn R^3 = H

31 R^1 = OMe R^2 = Bn R^3 = COEt

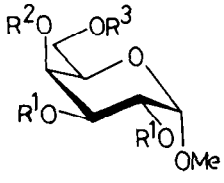
32 R^1 = OAc R^2 = Bn R^3 = COEt

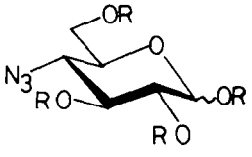
33 R^1 = OH R^2 = Bn R^3 = COEt

12 R = H

13 R = Ac

25 R = Bn





14 R^1 = Ac R^2 = Ms R^3 = Tr

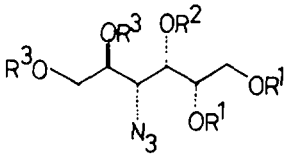
26 R^1 = Bn R^2 = R^3 = H

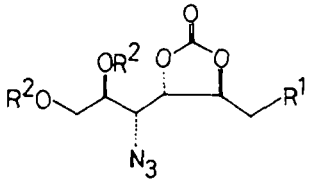
27 R^1 = Bn R^2 = H R^3 = Tr

28 R^1 = Bn R^2 = Ms R^3 = Tr

16 R = Ac

17 R = H





18 R^1 = R^2 = R^3 = H

19 $(R^1)_2$ = $(R^3)_2$ = CMe_2 R^2 = H

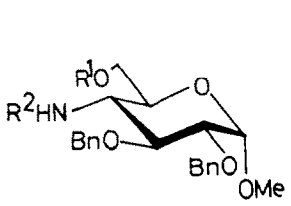
20 $(R^1)_2$ = $(R^3)_2$ = CMe_2 R^2 = CO_2Me

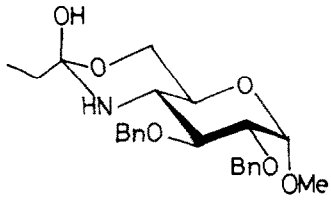
21 R^1 = OH R^2 = H

22 R^1 = OH $(R^2)_2$ = CMe_2

23 R^1 = OTs $(R^2)_2$ = CMe_2

24 R^1 = N_3 $(R^2)_2$ = CMe_2

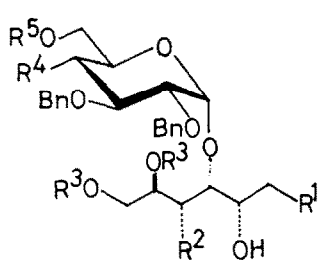


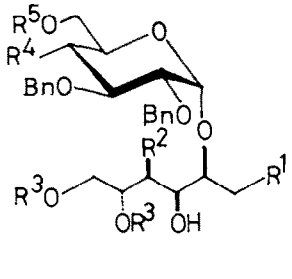


34 R^1 = COEt R^2 = H

35

36 R^1 = H R^2 = COEt





37 R^1 = R^2 = R^4 = N_3, $(R^3)_2$ = CMe_2, R^5 = COEt

38 R^1 = R^2 = R^4 = N_3, $(R^3)_2$ = CMe_2, R^5 = COEt

39 R^1 = R^2 = R^4 = N_3, R^3 = H, R^5 = COEt

40 R^1 = R^2 = R^4 = N_3, R^3 = H, R^5 = COEt

41 R^1 = R^2 = R^4 = NH_2, R^3 = H, R^5 = COEt

42 R^1 = R^2 = R^4 = NH_2, R^3 = H, R^5 = COEt

43 R^1 = R^2 = NH_2, R^3 = R^5 = H, R^4 = NHCOEt

44 R^1 = R^2 = NH_2, R^3 = R^5 = H, R^4 = NHCOEt

compounds was assigned as α by ^{1}H NMR data. C_1-H in **39** appeared at δ 4.90 as a doublet with J = 3 Hz and $C_{1'}$-H in **40** appeared at δ 4.96 as a doublet with J = 4 Hz. When the reactivity of the aglycon **8** was modified through tributylstannylation[15] the same sequence of reactions afforded **39** and **40** in a ratio of 3:4 in 25% yield.

Now partially protected pseudodisaccharides **39** and **40** were submitted to acyl-migration under the mild conditions established by model experiments. Thus, selective hydrogenation of the azide group in **39** in the presence of Lindlar catalyst to aminopropionate **41**, ν_{max} 1720 cm^{-1} and subsequent treatment of **41** in ethanol containing 1% AcOH afforded amide **43**, ν_{max} 1640 cm^{-1}, which was further hydrogenated using 10% Pd–C to afford a 61% yield of sorbistin A_1 HCl salt **1**, $[\alpha]_D^{25}$ + 50.2° (H_2O). The synthetic sample was identical with the authentic sample by tlc ($CHCl_3$: MeOH: NH_4OH = 1:3:2) examination and by comparison of ^{1}H NMR spectra.

The position isomer **7** was also obtained by submitting **40** to the same reaction sequence as described for **39** in 78% yield. The regio- and stereochemistry of **7** was confirmed by ^{1}H and ^{13}C NMR data as follows. ^{1}H NMR revealed $C_{1'}$-H at δ 5.17 as a doublet with J = 3 Hz. The α-stereochemistry of the glycosidic linkage in **7** was further supported by ^{13}C NMR, which showed $C_{1'}$ at δ 100.9 with $^1J_{CH}$ = 170.0 Hz in agreement with the empirical rule of Bock and Pedersen,[16] as in the case of sorbistin A_1, of which ^{13}C NMR showed $C_{1'}$ at δ 102.4 with $^1J_{CH}$ = 169.9 Hz. Migration of propionyl groups from $C_{6'}$-O to $C_{4'}$-NH_2 was confirmed by the following ^{13}C NMR data. In the case of sorbistin A_1, chemical shift of the C atoms carrying amino functions appeared at δ 56.4 for C_4, 52.0 for $C_{4'}$ and 43.1 for C_1 respectively, while, in the isomer **7**, they appeared at δ 56.3 for C_4, 52.0 for $C_{4'}$ and 41.5 for C_1. The presence of the glycosidic linkage at C_2-oxygen in the isomer **7** was also supported by the above ^{13}C NMR data which showed the β effect[17] on C_1 duc to glycosidation.

In conclusion, a new aminoglycoside antibiotic, sorbistin A_1 **1** and its positional isomer (**7**) could be synthesized with high regio- and streo-control, starting from methyl α-D-galactopyranoside.

EXPERIMENTAL

M.p's were determined with a Yanagimoto micro m.p. apparatus and were uncorrected. Optical rotations were determined with a Perkin Elmer Model 141 polarimeter for soln in $CHCl_3$, unless otherwise noted. IR spectra were recorded with an EPI-G2 Hitachi spectrophotometer, as KBr

discs for the crystalline samples and as neat films for the liquid samples. ^{1}H NMR spectra were recorded with a Varian HA-100 NMR spectrometer, using TMS as the internal standard. ^{13}C NMR spectra were recorded with a JNM-FX100FT NMR spectrometer operated at 25.05 MHz. The values of δ_C and δ_H are expressed in ppm downward from the internal standard for soln in $CDCl_3$, unless otherwise noted. Column chromatography was performed on columns of Silica Gel Merck (70–230 mesh; E. Merck, Darmstadt, West Germany). Tlc was performed on precoated plates (layer thickness, 0.25 mm; E. Merck, Darmstadt, West Germany) of Silica Gel $60F_{254}$.

Methyl 2,3-*di*-O-*acetyl*-4,6-O-*benzylidene*-α-D-*galactopyranoside* **13**. Compound **12** (11.4 g) in pyridine (50 ml) and Ac_2O (50 ml) was stirred for 15 hr at 20°. Evaporation of the solvent *in vacuo* afforded **13** (14.1 g, 95%). Recrystallization from EtOAc-i-Pr_2O gave pure **13**, mp. 117 119°, $[\alpha]_D^{25}$ + 205.1 (c = 0.59). (Found: C, 59.27; H, 6.04. $C_{18}H_{22}O_8$ requires: C, 59.01; H, 6.05%).

Methyl 2,3-*di*-O-*acetyl*-4-O-*mesyl*-6-O-*trityl*-α-D-*galactopyranoside* **14**. A soln of **13** (14 g) in 80% AcOH aq (450 ml) was stirred for 15 hr at 60–65°. AcOH was evaporated *in vacuo* by co-evaporation with toluene. To the residue dissolved in pyridine (100 ml) was added trityl chloride (13 g). The mixture was stirred for 15 hr at 20°. After further addition of trityl chloride (1 g), the mixture was stirred for 4 hr at 20°. To this mixture was added dropwise mesyl chloride (5.7 g) in pyridine (20 ml) at −5–0°. The mixture was stirred for 4 hr at 20°. Pyridine was evaporated *in vacuo*. The residue was poured into $NaHCO_3$ aq and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), and concentrated. The residue was triturated with ether to give crystalline **14** (11.3 g). The mother liquor was evaporated and chromatographed on silica gel (300 g). Elution with toluene–EtOAc (5:1) gave further **14** (4.5 g). Combined yield was 65.3%, m.p. 196–198°. $[\alpha]_D^{25}$ + 86.7° (c = 0.48). δ_H ($CDCl_3$); 2.05 and 2.08 (two 3 H, s, $COCH_3$), 2.82 (3 H, s, SO_2CH_3), 3.34 (3 H, s, OCH_3). (Found: C, 62.21; H, 5.81. $C_{31}H_{34}O_{10}S$ requires: C, 62.19; H, 5.72%).

1,2,3,6-*Tetra*-O-*acetyl*-4-*azido*-4-*deoxy*-α *and* β-D-*galactopyranoside* **16**. Compound **14** (15.7 g) and NaN_3 (15 g) in DMF (300 ml) was stirred for 7.5 hr at 130–140° (bath). The mixture was concentrated *in vacuo*. The residue was diluted with water and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to afford crude **15**, a small part of which was purified by chromatography on silica gel (toluene–EtOAc = 15:1). $[\alpha]_D^{25}$ + 90.0° (c = 0.47). δ_H ($CDCl_3$); 5.45 (1 H, t, J = 9 Hz, C_3-H). ν_{max}; 2100 cm^{-1} (N_3). (Found: C, 65.86; H, 5.72; N, 7.17. $C_{30}H_{31}O_7N_3$ requires: C, 66.04; H, 5.73; N, 7.70%). Crude **15** in Ac_2O (200 ml) containing conc H_2SO_4 (2 ml) was stirred for 7 hr at 20°. The mixture was diluted with ice-water and extracted by EtOAc. The organic layer was washed with $NaHCO_3$ aq and water, and dried ($MgSO_4$). The solvent was co-evaporated with toluene *in vacuo*. The residue was triturated with i-Pr_2O and the insoluble trityl alcohol was filtered off. The filtrate was concentrated and chromatographed on silica gel (350 g). Elution with toluene–EtOAc (4:1) afforded **16** (7.8 g, 79.7%), which was a mixture of α and β anomers in a ratio of 12:1. α-Anomer: $[\alpha]_D^{25}$ + 132° (c = 0.55). δ_H; 6.29 (1 H, d, J = 4 Hz, C_1-H). (Found: C, 44.69; H, 5.06; N, 11.49. $C_{14}H_{19}O_9N_3$ requires: C, 45.04; H, 5.13; N, 11.26%). β-Anomer: Recrystallization from i-Pr_2O, m.p. 98–99°. $[\alpha]_D^{25}$ + 38.1° (c = 0.54). δ_H; 5.69 (1 H, d, J = 8 Hz, C_1-H). (Found: C, 44.95; H, 5.11; N, 11.37. $C_{14}H_{19}O_9N_3$ requires: C, 45.04; H, 5.13; N, 11.26%).

4-*Azido*-4-*deoxy*-1,2; 5,6-*di*-O-*isopropylidene*-D-*glucitol* **19**. Compound **16** (7.8 g) in 0.05N NaOMe–MeOH (100 ml) was stirred for 15 hr at 20°. MeOH was evaporated *in vacuo*. To a soln of the residue in EtOH (100 ml) was added $NaBH_4$ (1 g) at 0°. The mixture was stirred for 6 hr at 20°. Excess $NaBH_4$ was destroyed with AcOH at −5–0°. Na^+ ion was removed by the treatment with Amberlist 15. The filtrate was evaporated *in vacuo* and the residue was co-evaporated with MeOH several times to remove boric acid. The residue **18** was dissolved in DMF (50 ml) and toluene (50 ml) and the soln was concentrated to a volume of 60 ml. To this soln was added 2,2-dimethoxypropane (10 ml) and *p*-TsOH (400 mg). The mixture was stirred for 3 hr at 70° and pyridine (5 ml) was added. The soln was evaporated *in vacuo* and the residue was diluted with $NaHCO_3$ aq and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), evaporated *in vacuo*, and chromatographed on silica gel (300 g). Elution with toluene–EtOAc–Et_3N (75:25:1) afforded **19**. Recrystallization (2.98 g, 50%) from i-Pr_2O, m.p. 88–89°, $[\alpha]_D^{25}$ + 11.0° (c = 0.82). δ_H; 1.25–1.55 (12 H, two isopropylidene groups). (Found: C, 50.33; H, 7.43; N, 14.64. $C_{12}H_{21}O_5N_3$ requires: C, 50.16; H, 7.37; N, 14.63%).

4-*Azido*-4-*deoxy*-1,2;5,6-*di*-O-*isopropylidene*-3-O-*methoxycarbonyl*-D-*glucitol* **20**. To a soln of **19** (2.88 g) in pyridine (60 ml) and $ClCH_2ClCH_2$ (60 ml) was added dropwise $ClCO_2Me$ (10 ml) at −10 to −5°. The mixture was stirred for 4 hr at −5° and allowed to stand at −20° overnight. The mixture was further stirred at −5° for 6 hr, and further $ClCO_2Me$ (5 ml) was added to the mixture at 2 hr intervals. The mixture was poured into $NaHCO_3$ aq and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (100 g). Elution with toluene–EtOAc–Et_3N (80:20:1) gave **20** (3.0 g, 86.7%). $[\alpha]_D^{25}$ + 1.2° (c = 0.41). δ_H; 1.3–1.5 (12 H, two isopropylidene groups), 3.82 (3 H, s, OMe), 4.88 (1 H, t, J = 5 Hz, C_3-H). ν_{max}; 1750 (CO), 2100 cm^{-1} (N_3). (Found: C, 48.81; H, 6.79; N, 12.12. $C_{14}H_{23}O_7N_3$ requires: C, 48.69; H, 6.71; N, 12.17%).

4-*Azido*-2,3-O-*carbonyl*-4-*deoxy*-5,6-O-*isopropylidene*-D-*glucitol* **22**. A soln of **20** (1.7 g) in 80% AcOH aq (50 ml) was stirred for 2 hr at 80°. The mixture was concentrated *in vacuo* and co-evaporated 3 times with toluene. The residual oil **21** was dissolved in DMF (25 ml) and toluene (25 ml). The soln was again evaporated *in vacuo* and to the residue in DMF (30 ml) was added 2,2-dimethoxypropane (1 ml) and *p*-TsOH (100 mg). The mixture was stirred at 50–60° for 3 hr. Pyridine (2 ml) was added. The solvent was evaporated *in vacuo*. The residue was diluted with $NaHCO_3$ aq and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (100 g). Elution with toluene–EtOAc (2:3) afforded **22** (1.06 g, 78.5%). $[\alpha]_D^{25}$ − 55.0° (c = 0.28). δ_H; 1.36, 1.45 (two 3 H, s, isopropylidene group), 2.92 (1 H, m, OH), 4.65–4.85 (2 H, m, C_2-H and C_3-H).

4-*Azido*-2,3-O-*carbonyl*-4-*deoxy*-5,6-O-*isopropylidene*-1-O-*tosyl*-D-*glucitol* **23**. A soln of **22** (1.06 g) in pyridine (20 ml) was treated with TsCl (900 mg). The mixture was stirred for 22 hr at 20° and then for 2 hr at 55°. Pyridine was evaporated and the residue was diluted with $NaHCO_3$ aq and extracted with EtOAc. The organic layer was washed with $NaHCO_3$ aq and water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel (100 g). Elution with toluene–EtOAc (2:1) afforded **23** (1.13 g, 68%). Recrystallization from EtOAc–i-Pr_2O–n-hexane. M.p. 86.5–88°. $[\alpha]_D^{25}$ − 48.2° (c = 0.69). δ_H; 1.36, 1.45 (two 3 H, s, isopropylidene group), 2.48 (3 H, s, aromatic Me), 4.68–4.90 (2 H, m, C_2-H and C_3-H). ν_{max} (cm^{-1}) 2100 (N_3), 1800 (CO). (Found: C, 47.69; H, 4.96; N, 9.85. $C_{17}H_{21}O_8N_3S$ requires: C, 47.77; H, 4.95; N, 9.83%).

1,4-*Di*-*azido*-2,3-O-*carbonyl*-1,4-*dideoxy*-5,6-O-*isopropylidene*-D-*glucitol* **24**. A soln of **23** (621 mg) and NaN_3 (621 mg) in DMF (6 ml) was stirred for 2 hr at 85–90°. DMF was evaporated *in vacuo* and the residue diluted with $NaHCO_3$ aq and extracted with EtOAc. The organic layer was washed successively with $NaHCO_4$ aq and water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue (449 mg, quantitative yield) was enough pure for the next step. A small amount of crude **24** (69 mg) was purified by chromatography on silica gel (10 g). Elution with toluene–EtOAc (2:1) afforded an anlytical sample of **24** $[\alpha]_D^{25}$ − 89.1 (c = 0.51. δ_H; 1.36, 1.45 (two 3 H, s, isopropylidene group), 4.62–4.84 (2 H,

m, C_2–H and C_3–H). (Found: C, 40.22; H, 4.72; N, 28.21. $C_{10}H_{14}O_5N_6$ requires: C, 40.27; H, 4.73; N, 28.18%).

1,4-*Di-azido*-1,4-*di-deoxy*-5,6-O-*isopropylidene*-D-*glucitol* **8**. A soln of **24** (380 mg) in 0.25 N NaOMe–MeOH (5 ml) was stirred for 4 hr at 20°. MeOH was evaporated *in vacuo* and the residue was chromatographed on silica gel (20 g). Elution with toluene–EtOAc (2:1) afforded **8** (330 mg, 95%). $[\alpha]_D^{25}$ − 14.6 (c = 0.61). δ_H: 1.36, 1.46 (two 3H, s, isopropylidene group), 2.90–3.10 (2H, m, two OH, disappeared upon the addition of D_2O). ν_{max} (cm^{-1}): 2100 (N_3), 3400 (OH). (Found: C, 39.74; H, 5.99; N, 31.08. $C_9H_{16}O_4N_6$ requires: C, 39.70; H, 5.92; N, 30.87%).

Methyl 2,3-*di*-O-*benzyl*-4,6-O-*benzylidene*-α-D-*galactopyranoside* **25**. Compound **12** (6 g) was dissolved in DMF (30 ml) and toluene (30 ml) and was evaporated *in vacuo*. To the residue redissolved in DMF (60 ml) was added NaH (60%, 2.13 g). The mixture was stirred for 1.5 hr at 20° and then cooled to − 5°. To this mixture was added dropwise benzylbromide (8.17 g) for 10 min. The mixture was stirred for 3 hr at 20° and poured into ice–water (1000 ml) carefully and left at 5° for two days. The precipitated crystals were collected, washed successively with cold water and ether and dried to give **25** (9.62 g, 98%). Recrystallization from EtOAc-i-Pr_2O, m.p. 175–177°. $[\alpha]_D^{25}$ + 77.5° (c = 0.56). (Found: C, 72.49; H, 6.50. $C_{28}H_{30}O_6$ requires: C, 72.71; 6.54%).

Methyl 2,3-*di*-O-*benzyl*-6-O-*trityl*-α-D-*galactopyranoside* **27**. Compound **25** (9 g) suspended in 80% AcOH aq (200 ml), was stirred for 3 hr at 80–85°. AcOH was co-evaporated with toluene. The residue **26** in pyridine (100 ml) was treated with trityl chloride (6.0 g) and the mixture was stirred for 20 hr at 20°. Pyridine was evaporated *in vacuo* and the residue was diluted with $NaHCO_3$ aq and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on silica gel (350 g). Elution with toluene–Et_3N (100:1) afforded trityl alcohol. Further elution with toluene–EtOAC–Et_3N (100:10:1) gave **27** (9.2 g, 76.7%). $[\alpha]_D^{25}$ + 22.7° (c = 0.48). (Found: C, 77.94; H, 6.53. $C_{40}H_{40}O_6$ requires: C, 77.90; H, 6.53%).

Methyl 2,3-*di*-O-*benzyl*-4-O-*mesyl*-6-O-*trityl*-α-D-*galacto-pyranoside* **28**. To a soln of **27** (5.5 g) in pyridine (50 ml) was added dropwise mesyl chloride (1.3 g) in pyridine (10 ml) for 10 min at − 5°–0°. The mixture was stirred for 17 hr at 20°, concentrated *in vacuo* to a volume of about 20 ml, poured into ice-water (4 l), and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give **28** (5.6 g, 91%). An analytical sample was obtained by chromatography on silica gel (toluene–EtOAc–Et_3N = 100:10:1). $[\alpha]_D^{25}$ + 30.7° (c = 0.53). δ_H: 2.83 (3H, s, SO_2Me), 3.32 (3H, s, OMe), 5.16 (1H, d, J = 3 Hz, C_1–H). (Found: C, 70.98; H, 6.15. $C_{41}H_{31}O_8S$ requires: C, 70.88; H, 6.09%).

Methyl 4-*azido*-2,3-*di*-O-*benzyl*-4-*deoxy*-6-O-*trityl*-α-D-*glucopyranoside* **29**. A soln of **28** (5.62 g) and NaN_3 (5 g) in DMF (100 ml) was stirred for 25 hr at 140–160°. The mixture was concentrated *in vacuo* to a volume of about 20 ml, diluted with water and extracted with EtOAc. Organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on a column of silica gel (200 g, toluene–EtOAc–Et_3N = 100:10:1) gave **29** (4.85 g, 93.4%). $[\alpha]_D^{25}$ + 45.3° (c = 0.34). ν_{max} (cm^{-1}): 2100 (N_3). (Found: C, 74.93; H, 6.22; N, 6.49. $C_{40}H_{39}O_5N_3$ requires: C, 74.86; H, 6.13; N, 6.55%).

Methyl 4-*azido*-2,3-*di*-O-*benzyl*-4-*deoxy*-α-D-*glucopyranoside* **30**. A soln of **29** (8.63 g) in 80% AcOH aq (200 ml) was stirred during 3 hr at 80°. The mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel (170 g). Elution with toluene–EtOAc (2:1) afforded **30** (5.1 g, 95%). $[\alpha]_D^{25}$ + 102° (c = 0.53). (Found: C, 62.92; H, 6.31; N, 10.41. $C_{21}H_{25}O_5N_3$ requires: C, 63.14; H, 6.31; N, 10.52%).

Methyl 4-*azido*-2,3-*di*-O-*benzyl*-4-*deoxy*-6-O-*propionyl*-α-D-*glucopyranoside* **31**. To a soln of **30** (1 g) in pyridine (10 ml) was added propionic anhydride (2 ml). The mixture was stirred for 15 hr at 20°. Pyridine and excess proionic anhydride was evaporated *in vacuo*. The residue was chromatographed on a silica gel (30 g). Elution with toluene–EtOAc (3:1) afforded **31** (1.12 g, 98%). $[\alpha]_D^{25}$ + 87.1 (c = 0.48). δ_H: 1.14 (3H, t, J = 7 Hz, $CH_2\underline{CH}_3$), 2.36 (2H, q, J = 7 Hz, $CO\underline{CH}_2CH_3$). ν_{max} (cm^{-1}): 1740 (CO), 2120 (N_3). (Found: C, 62.99; H, 6.37; N, 9.21. $C_{24}H_{29}O_6N_3$ requires: C, 63.28; H, 6.42; N, 9.23%).

1-O-*Acetyl*-4-*azido*-2,3-*di*-O-*benzyl*-4-*deoxy*-6-O-*propionyl*-α-D-*glucopyranose* **32**. A soln of **31** (2.0 g) in Ac_2O (20 ml) containing conc H_2SO_4 (0.2 ml) was stirred for 30 min at 20°. The mixture was poured into ice–$NaHCO_3$ aq (500 ml) and extracted with EtOAc. The organic layer was washed successively by $NaHCO_3$ aq, H_2O, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (200 g). Elution with toluene–EtOAc (7:1) gave **32** (1.6 g, 75.5%) which was used directly for the next step. δ_H: 1.15 (3H, t, J = 7 Hz, $CH_2\underline{CH}_3$), 2.16 (3H, s, $COCH_3$), 2.36 (2H, q, J = 7 Hz, $CO\underline{CH}_2CH_3$), 6.32 (1H, d, J = 3 Hz, C_1–H).

4-*Azido*-2,3-*di*-O-*benzyl*-4-*deoxy*-6-O-*propionyl*-α-D-*glucopyranosyl chloride* **11**. A soln of **32** (1.62 g) in CH_2Cl_2 (100 ml) was saturated with dry HCl at − 5°. The mixture was kept at 20° for 15 hr and the solvent was evaporated *in vacuo*. The residue was co-evaporated *in vacuo* with toluene and chromatographed on silica gel (100 g). Elution with toluene–EtOAc (10:1) gave **11** (327 mg, 22.4%). $[\alpha]_D^{25}$ + 147.5 (c = 0.48). δ_H: 6.00 (1H, d, J = 4 Hz, C_1–H). Elution with toluene–EtOAc (2:1) gave **33** (940 mg, 66.7%). **33** (360 mg) was dissolved in $SOCl_2$ (5 ml) and left at 20° for 15 hr. Co-evaporation of $SOCl_2$ with toluene and chromatography on silica gel (5 g, toluene–EtOAc = 10:1) afforded **11** (272 mg 72%). Combined yield of **11** from **32** was 70.6%. **11** was used directly for the next step.

Methyl 4-*amino*-2,3-*d*-O-*benzyl*-4-*deoxy*-N-*propionyl*-α-D-*glucopyranoside* **36**. Compound **31** (103 mg) and Lindlar catalyst (50 mg) in EtOH (5 ml) was stirred under H_2 for 4 hr at 20°. The catalyst was filtered off (celite) and the filtrate was concentrated *in vacuo* to the residue **34**. ν_{max} (cm^{-1}) 1730 (CO_2). A soln of **34** (80 mg) in $CHCl_3$ (2 ml) containing AcOH (0.002 ml) was kept at 20° for 1.5 hr, when tlc (toluene–EtOAc = 1:1) showed the disappearance of **34** (R_f 0.4) and the formation of a new spot (**35**, R_f 0.2). Evaporation of the solvent *in vacuo* and the trituration of the residue with i-Pr_2O afforded crystalline **36** (72 mg, 90%, R_f 0.05), m.p. 164–166°. $[\alpha]_D^{25}$ + 28.0 (c = 0.59). δ_H: 1.06 (3H, t, J = 7 Hz, $CH_2\underline{CH}_3$), 1.96 (2H, q, J = 7 Hz, $CO\underline{CH}_2CH_3$). ν_{max} (cm^{-1}): 1640 (CON), 3280 (NH). (Found: C, 66.99; H, 7.28; N, 3.23. $C_{24}H_{31}NO_6$ requires: C, 67.11; H, 7.28; N, 3.26%).

1,4-*Diazido*-1,4-*dideoxy*-3(*or* 2)-O-(4′-*azido*-2′,3′-*di*-O-*benzyl*-4′-*deoxy*-6′-O-*propionyl*-α-D-*glucopyranosyl*)-D-*glucitol* **39** (for **40**). (a) A mixture of **11** (419 mg), **8** (300 mg) and Et_4NCl (181 mg) was dried *in vacuo*. To this mixture was added Et(i-Pr)$_2$N (240 mg) in $ClCH_2CHCl_2$ (10 ml) and the mixture was stirred under reflux for 3 days. After cooling to room temp, the mixture was diluted with CH_2Cl_2 (30 ml). The organic layer was successively washed with $NaHCO_3$ aq and water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (60 g). Elution with toluene–EtOAc–Et_3N (50:10:0.6) gave 4-azido-2,3-di-O-benzyl-4-deoxy-6-O-propionyl-D-glucal (243 mg) and the mixture of **37** and **38** (81 mg, 55.5%). Further elution with toluene–EtOAc (2:1) recovered diol **8** (243 mg). A soln of the mixture of **37** and **38** (95 mg) in 80% AcOH aq (10 ml) was left at 20° for 2 days. The solvent was co-evaporated with toluene. The residue was chromatographed on silica gel (7 g). Elution with $CHCl_3$–MeOH (100:1) gave **39** (25 mg, 28%) and **40** (41 mg, 45.8%). **39**: $[\alpha]_D^{25}$ + 57.4° (c = 0.94). δ_H ($CDCl_3$): 1.16 (3H, t, J = 7 Hz, $CH_2\underline{CH}_3$), 2.40 (2H, q, J = 7 Hz, $\underline{CH}_2CH_3$), 4.90 (1H, d, J = 3 Hz, C_1–H). **40**: $[\alpha]_D^{25}$ + 57.2° (c = 0.29). δ_H: 1.14 (3H, t, J = 7 Hz, $CH_2\underline{CH}_3$), 2.37 (2H, q, J = 7 Hz, $\underline{CH}_2CH_3$), 4.96 (1H, d, J = 4 Hz, C_1–H).

(b) Compound **8** (189 mg) and bis(tri-n-butyltin)oxide

(210 mg) in toluene (20 ml) was refluxed for 2 hr with continuous azeotropic removal of water. Evaporation of toluene afforded 2-O or 3-O-tributyltin derivative of **8**, which was further reacted with **11** (282 mg) in the presence of Et_4NCl (102 mg) in $ClCH_2ClCH_2$ (3 ml) for 2 days at 50° and then for 15 hr under reflux. The mixture was concentrated *in vacuo* and chromatographed on silica gel (30 g). Elution with toluene EtOAc Et_3N (50:10:0.6) gave a mixture of **37** and **38** (65 mg, 25%). Treatment of this mixture as described in (a) afforded **39** (19 mg, 31%) and **40** (25 mg, 41%). **39** and **40** were used for the next step without further characterization.

Sorbistin A_1 **1**. **39** (20 mg) and Lindlar catalyst (40 mg) in EtOH (2 ml) was stirred under H_2 for 4 hr at 50°. The catalyst was filtered off (celite). The filtrate was evaporated to the residue **41** (no absorption due to N_3 in IR). A soln of **41** in EtOH (2 ml) containing AcOH (0.2 ml) was kept at 20° for 15 hr. Solvent was evaporated to the residue **43**, of which IR showed a shift of the CO band from 1720 cm^{-1} (**41**) to 1640 cm^{-1}. The residue **43** was further hydrogenolyzed in EtOH (1 ml) containing 0.1 N HCl (0.62 ml) by 10% Pd C (30 mg) for 6 hr at 20°. The catalyst was filtered off (celite). The filtrate was concentrated and submitted to a column of CG50 (Type I, NH_4^+ form, 3 ml). Elution with 0.5N NH_4OH and evaporation of the solvent *in vacuo* gave the residue which was dissolved in 0.1N HCl (0.66 ml) and evaporated to give Sorbistin A_1 hydrogen chloride (10 mg, 61.4%). $[\alpha]_D^{25}$ + 50.2° (*c* = 0.5, H_2O). δ_C (D_2O): 179.2 (C-1″), 102.4 (C-1′), 78.9 (C-3), 73.0 (C-2, C-2′), 70.8 (C-5′), 69.7 (C-3′), 68.6 (C-5), 63.0 (C-6), 61.7 (C-6′), 56.4 (C-4), 52.0 (C-4′), 43.1 (C-1), 30.2 (C-2″), 10.4 (C-3″). δ_H (D_2O): 5.21 (1 H, d, J = 3 Hz), 2.28 (2 H, q, J = 7 Hz), 1.09 (3 H, t, J = 7 Hz).

1,4-*Diamino*-1,4-*dideoxy*-2-O-(4′-*amino*-4′-*deoxy*-N-*propionyl*-α-D-*glucopyranosyl*)-D-*glucitol* **7**. **40** (41 mg) and Lindlar catalyst (50 mg) in EtOH (3 ml) was stirred for 6 hr at 20° and worked up as described above to give **42**. A soln of **42** in EtOH (2 ml) containing AcOH (0.12 ml) was kept at 20° for 15 hr and processed as described above to afford **44**. Hydrogenolysis of **44** in EtOH by 10% Pd-C afforded **7** as HCl salt (26 mg, 78%). $[\alpha]_D^{25}$ + 50.8° (*c* = 1.03, H_2O). δ_C (D_2O): 179.1 (C-1″), 100.9 (C-1′), 77.5 (C-2), 73.2 (C-2′), 72.7 (C-5), 70.8 (C-5′), 69.5 (C-3′), 68.3 (C-3), 62.7 (C-6), 61.8 (C-6′), 56.3 (C-4), 52.0 (C-4′), 41.5 (C-1), 30.2 (C-2″), 10.5 (C-3″). δ_H (D_2O): 5.17 (1 H, d, J = 3 Hz), 2.28 (2 H, q, J = 8 Hz), 1.09 (3 H, t, J = 8 Hz).

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REFERENCES

[1a]H. Tsukiura, M. Hanada, K. Saito, K. Fujisawa, T. Miyaki, H. Koshiyama and H. Kawaguchi, *J. Antibiotics*, **29**, 1137 (1976).
[1b]K. Tomita, Y. Hoshino, Y. Uenoyama, K. Fujisawa, H. Tsukiura and H. Kawaguchi, *Ibid.* **29**, 1147 (1976):
[1c]K. Nara, Y. Sumino, S. Akiyama and M. Asai, *Chem. Lett.* **33** (1977).
[2]J. P. Kirby, G. E. Van Lear, G. O. Morton, W. E. Gove, W. V. Curran and D. B. Borders, *J. Antibiotics* **30**, 344 (1977).
[3]T. Naito, S. Nakagawa, Y. Narita and H. Kawaguchi, *Ibid.* **29**, 1286 (1976).
[4a]M. Konishi, S. Kamata, T. Tsuno, K. Numata, H. Tsukiura, T. Naito and H. Kawaguchi, *Ibid.* **29**, 1152 (1976).
[4b]K. Nara, K. Katamoto, S. Suzuki, S. Akiyama and E. Mizuta, *Chem. Lett.* 229 (1977).
[5]T. Naito, S. Nakagawa, Y. Narita and H. Kawaguchi, *J. Antibiotics* **29**, 1286 (1976).
[6]M. M. Ponpipom, R. Bugianesi, E. Walton and T. Y. Shen, *Carbohydr. Res.* **65**, 121 (1978).
[7]D. Nishimura, A. Hasegawa and M. Nakajima, *Agr. Biol. Chem.* **36**, 1767 (1972); P. J. L. Daniels, A. K. Mallams and J. J. Wright, *J. Chem. Soc.* Chem. Commun. 675 (1973).
[8]A. Muller, M. Moricz and G. Verner, *Chem. Ber.* **72B** 745 (1939).
[9]D. J. Bell and G. D. Greville, *J. Chem. Soc.* 1136 (1955).
[10]E. J. Reist, R. R. Spencer, D. F. Calkins, B. R. Bakers and L. Goodman, *J. Org. Chem.* **30**, 2312 (1965).
[11]J. S. Brimacombe, *Methods Carbohydr. Chem.* **6**, 376 (1972).
[12]V. D. Grob, T. G. Squires and J. R. Vercellotti, *Carbohydr. Res.* **10**, 595 (1969).
[13]E. J. Corey, K. C. Nicolaou, R. B. Balanson and Y. Machida, *Synthesis* 590 (1975).
[14]R. U. Lemieux, K. B. Hendricks, R. V. Stick and K. James, *J. Am. Chem. Soc.* **97**, 4056 (1975).
[15]T. Ogawa and M. Matsui, *Carbohydr. Res.* **51**, C13 (1976).
[16]K. Bock, I. Lundt and C. Pedersen, *Tetrahedron Letters* 1037 (1973); K. Bock and C. Pedersen, *J. Chem. Soc.* Perkin Trans. II, 293 (1974); *Acta. Chem. Scand.* Ser. B, **29**, 258 (1975).
[17]R. Kasai, M. Suzuo, J. Asakawa and O. Tanaka, *Tetrahedron Letters* 175 (1977); K. Tori, S. Seo, Y. Yoshimura, H. Arita and Y. Tomita, *Ibid.* 179 (1977).