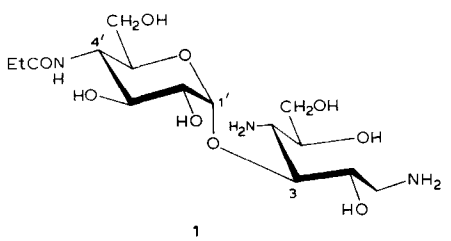
Carbohydrate Research, 60 (1978) C13–C17

Preliminary communication

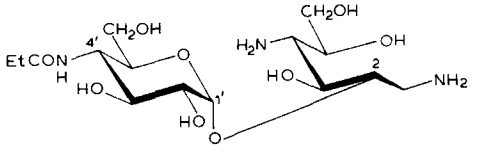
A synthesis of sorbistin A_1 and a position isomer thereof

TOMOYA OGAWA*, KIYOAKI KATANO, and MASANAO MATSUI
The Institute of Physical and Chemical Research, Wako-shi, Saitama 351 (Japan)
(Received November 28th, 1977; accepted for publication, December 8th, 1977)

A new aminoglycoside antibiotic, sorbistin A_1 (**1**), was first isolated[1] in 1976 from the fermentation broth of Pseudomonas species, and proved to have moderate but broad-spectrum activities against Gram-positive and Gram-negative bacteria, including some resistant bacteria carrying aminoglycoside-inactivating enzymes[2]. The unique structure **1**, containing a 1,4-diamino-1,4-dideoxyalditol instead of an aminocyclitol moiety, was ascertained through chemical correlations and by X-ray crystallography[3].



1

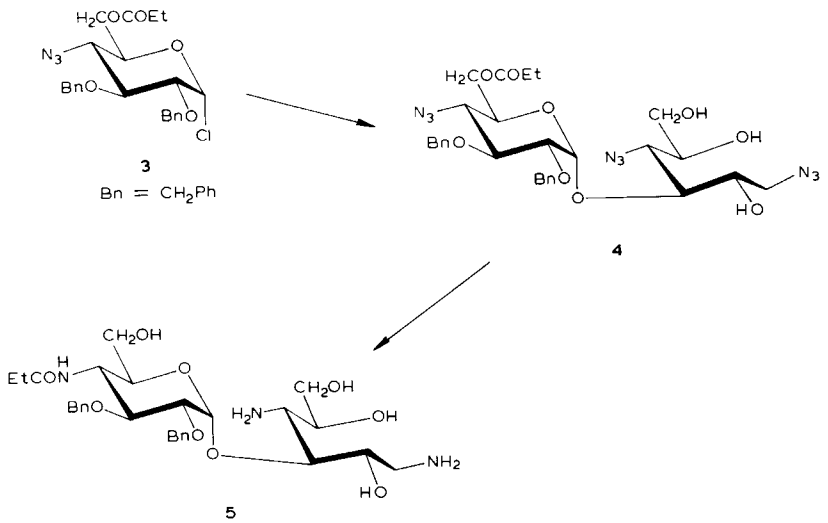


2

We report here the first synthesis of **1** and its isomer **2** in a regio- and stereocontrolled way. The important aspect to be taken into account for the synthesis of **1** is that the α stereochemistry of the glycoside linkage is *syn* to the 2′-hydroxyl group and the 4′-amide group, both of which might lead to the formation of a β-glycoside linkage through neighboring-group participation[4], unless suitable protective groups are employed. From this point of view, intermediate **3**, specifically protected by benzyl and azide groups, should be most promising for the stereocontrolled synthesis of the pseudodisaccharide **4**, which, in turn, by hydrogenation and subsequent acyl migration, might lead to the desired compound **5**, an immediate precursor to **1**.

In order to achieve an efficient synthesis of **4**, both the aglycon and the glycosyl moiety were synthesized from the same starting material, methyl 4,6-*O*-benzylidene-α-D-

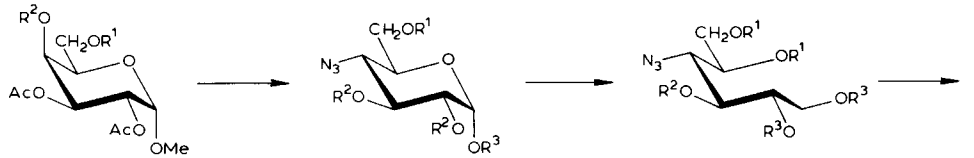
*To whom enquiries should be addressed.



galactopyranoside. First, regioselective synthesis of the precursor **18** of the aglycon moiety was developed as follows. Methyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-α-D-galactopyranoside[5] (**6**), m.p. 117–119°, $[\alpha]_D$ +205.1°, was* successively treated with (*i*) 80% aq. acetic acid for 15 h at 60–65°, (*ii*) trityl chloride–pyridine, and (*iii*) mesyl chloride–pyridine, to give a 70% yield of the trityl mesylate **7**, m.p. 196–198°, $[\alpha]_D$ +86.7°. Reaction of **7** with sodium azide in $HCONMe_2$ (7.5 h at 130–140°) gave the trityl azide **8**, $[\alpha]_D$ +90.0°, which, on treatment with 100:1 acetic anhydride–conc. sulfuric acid for 7 h at 20°, afforded (in 80% yield from **7**), a mixture of triacetate** **9**, $[\alpha]_D$ +132.0°, and the β anomer, m.p. 98–99°, $[\alpha]_D$ +38.1°, in the ratio of 12:1. This mixture was submitted to saponification in 0.1M sodium methoxide in methanol during 15 h at 20°, and subsequent reduction of **10** by sodium borohydride in ethanol gave azido alcohol **11**, which was further converted into diisopropylidene azide **12**, m.p. 88–89°, $[\alpha]_D$ +11.0°, (in 50% yield from **9**) on treatment with 2,2-dimethoxypropane in $HCONMe_2$ in the presence of a catalytic amount of *p*-toluenesulfonic acid (3 h at 70°). Introduction of a second azide group was performed as follows. Reaction of **12** with an excess of methyl chloroformate in 1:1 pyridine–dichloroethane during 15 h at –15 to –20° gave a quantitative yield of the methyl carbonate **13**, $[\alpha]_D$ +1.2°; δ 4.88 (t, 1 H, *J* 5 Hz, H-3). Hydrolysis of the isopropylidene group of **13** in 80% aq. acetic acid during 2 h at 80°, and subsequent isopropylidenation with 2,2-dimethoxypropane in $HCONMe_2$ in the presence of a catalytic amount of *p*-TsOH during 3 h at 50–60° gave a 79% yield of cyclic carbonate **15**, $[\alpha]_D$ –55.0°. Tosylation of **15** to give **16**, m.p. 86.5–88°, $[\alpha]_D$ –48.2°, and treatment of tosylate **16** with sodium azide in $HCONMe_2$ during 2 h at 85–90°, afforded a 76% yield of diazide **17**, $[\alpha]_D$ –89.1°. Saponification of **17** with 0.1M

*Values of $[\alpha]_D$ are for solutions in chloroform, unless otherwise noted. All compounds for which an $[\alpha]_D$ value is reported gave satisfactory elemental analyses, and reasonable ^{1}H-n.m.r. (in $CDCl_3$) and i.r. data.

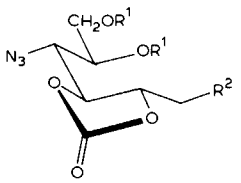
A mixture of **9 and the β anomer had been obtained[6] by a different route, but in a lower, overall yield.

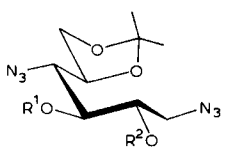


6 R^1 , R^2 = CHPh
7 R^1 = Tr, R^2 = Ms

8 R^1 = Tr, R^2 = Ac, R^3 = Me
9 R^1 = R^2 = R^3 = Ac
10 R^1 = R^2 = R^3 = H

11 R^1 = R^2 = R^3 = H
12 R^1, R^1 = R^3, R^3 = CMe_2, R^2 = H
13 R^1, R^1 = R^3, R^3 = CMe_2, R^2 = CO_2Me





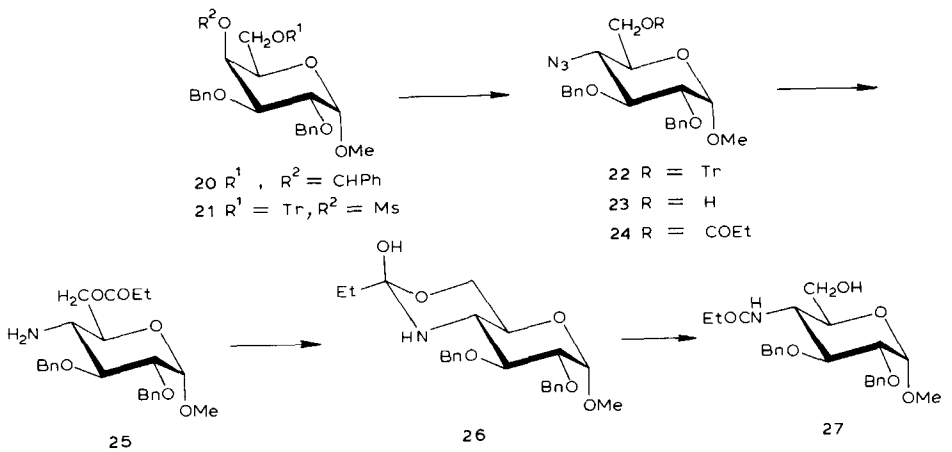
14 R^1 = H, R^2 = OH
15 R^1 , R^1 = CMe_2, R^2 = OH
16 R^1 , R^1 = CMe_2, R^2 = OTs
17 R^1 , R^1 = CMe_2, R^2 = N_3

18 R^1 = R^2 = H
19 R^1 , R^2 = H, $SnBu_3$

sodium methoxide in methanol during 4 h at 20° gave, in 95% yield, the specifically protected alditol **18**, $[\alpha]_D$ −14.6°, which is suitable for the glycosidation affording **1** and **2**. The overall transformation of **6** into **18** was achieved in 16% yield.

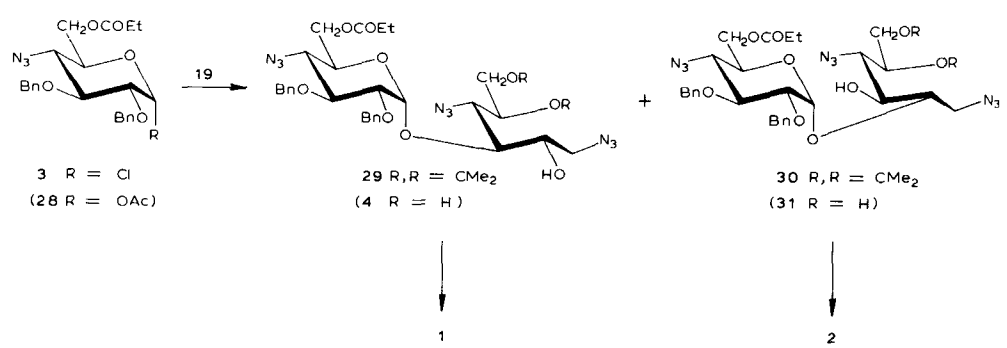
Next, a synthetic route to glycosyl chloride **3** was developed as follows. Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside[7] (**20**), m.p. 175–177°, $[\alpha]_D$ +77.5°, was hydrolyzed in 80% aq. acetic acid during 3 h at 60–85°, the product treated with trityl chloride in pyridine, and the ether mesylated in the usual way, to afford the trityl mesylate **21**, $[\alpha]_D$ +30.7°, in 72% yield. Treatment of mesylate **21** with sodium azide in $HCONMe_2$ during 2.5 h at 140–150° gave trityl azide **22**, $[\alpha]_D$ +45.3°, in 94% yield. Removal of the trityl group with 80% aq. acetic acid during 3 h at 80° gave azide alcohol **23**, $[\alpha]_D$ +102°, in 95% yield; on reaction with propionic anhydride in pyridine (15 h at 20°), this afforded a 98% yield of propionate **24**, $[\alpha]_D$ +87.1°.

In order to test the expected intramolecular, acyl migration of **4** to give **5** (as depicted), a model experiment was performed by using **24**. Hydrogenation of **24** in ethanol with Lindlar catalyst[8] gave the unstable amino propionate **25**, ν_{max} 1750 cm^{-1}, in quantitative yield. Acyl migration was effected in two ways. Heating of neat **25** during 12 h at 150–160°/66.6 Pa afforded an 80% yield of **27**, m.p. 164–166°, $[\alpha]_D$ +28.0°; ν_{max} 1640 cm^{-1}. The propionyl amide **27** could also be obtained under much milder conditions; on keeping a chloroform solution of **25** containing 1% of acetic acid during 1.5 h at 20°, a 70% yield of **27** was isolated by direct crystallization, presumably *via* the intermediacy of **26**, which could be detected by t.l.c.



Acetolysis of **24** in 1% sulfuric acid–acetic anhydride during 30 min at 20° gave a 76% yield of α-acetate **28**, δ 6.32 (d, 1 H, *J* 3 Hz, H-1),which, by treatment with hydrogen chloride in dichloromethane during 15 h at 20°, was converted into the desired chloride **3**, $[\alpha]_D$ +147.5°; δ 6.0 (d, 1 H, *J* 4 Hz, H-1), in 67% yield. Transformation of **20** into **3** was achieved in 32% overall yield.

Finally, the four crucial steps of the synthesis were performed in the following way. Tributylstannylation[9] of diol **18** to give the tributyltin alkoxide[10] **19**, and reaction of **19** with an equimolar amount of **3** in dichloroethane in the presence of tetraethylammonium chloride during 15 h at 90°, gave a mixture of pseudodisaccharides **29** and **30** in 50% yield; this was hydrolyzed with 80% aq. acetic acid (2 days at 20°), to give triol **4**, $[\alpha]_D$ +57.4°; δ 4.90 (d, 1 H, *J* 3 Hz, H-1′), and triol **31**, $[\alpha]_D$ +57.2°; δ 4.96 (d, 1 H, *J* 4 Hz, H-1′) in the ratio of 3:4, in 66% yield after separation by column chromatography on silica gel with 100:1 $CHCl_3$–MeOH. Direct glycosidation of **18** with **3** by the halide ion-catalyzed method[11], and subsequent hydrolysis, however, afforded **4** and **31** in the ratio of 1:2 (in 36% yield). Thus, the regioselectivity in glycosidation could be modified by stannylation of diol **18**, although no significant improvement in the yield was observed.



Partially protected pseudodisaccharide **4** was submitted to the acyl-migration reaction under the mild conditions established by the model experiment. Thus, selective hydrogenation of **4** by Lindlar catalyst in ethanol, subsequent treatment of the product in ethanol containing 1% of acetic acid during 15 h at 20°, and hydrogenolysis of the benzyl groups in the presence of 10% Pd–C and the stoichiometric amount of hydrogen chloride, gave a 70% yield of sorbistin A_1 (**1**) as the hydrochloride, an amorphous solid, $[\alpha]_D$ +50.2° (*c* 0.5, H_2O), which was identical with an authentic sample (by ^{1}H-n.m.r. data).

The same sequence of reactions applied to **31** gave the position isomer (**2**) of sorbistin A_1, as the hydrochloride, in 69% yield; $[\alpha]_D$ +50.8° (*c* 1.03, H_2O); δ 5.17 (d, 1 H, *J* 3 Hz, H-1′) in D_2O.

ACKNOWLEDGMENTS

A generous gift of authentic sorbistin A_1 by Meiji Seika Kaisha, Ltd., is greatly appreciated. We also thank Dr. H. Homma and his staff for the elemental analyses, and Dr. J. Uzawa and Mrs. T. Chijimatsu for recording and measuring the n.m.r. spectra.

REFERENCES

1 H. Tsukiura, M. Hanada, K. Saito, K. Fujisawa, T. Miyaki, H. Koshiyama, and H. Kawaguchi, *J. Antibiot.*, 29 (1976) 1137–1146; K. Nara, Y. Sumino, K. Katamoto, S. Akiyama, and M. Asai, *Chem. Lett.*, (1977) 33–36.
2 T. Naito, S. Nakagawa, Y. Narita, and H. Kawaguchi, *J. Antibiot.*, 29 (1976) 1286–1296.
3 M. Konishi, S. Kamata, T. Tsuno, K. Numata, H. Tsukiura, T. Naito, and H. Kawaguchi, *J. Antibiot.*, 29 (1976) 1152–1162; K. Nara, K. Katamoto, S. Suzuki, S. Akiyama, and E. Mizuta, *Chem. Lett.*, (1977) 229–234; J. P. Kirby, G. E. Van Lear, G. O. Morton, W. E. Gore, W. V. Curran, and D. B. Borders, *J. Antibiot.*, 30 (1977) 344–347.
4 D. Nishimura, A. Hasegawa, and M. Nakajima, *Agric. Biol. Chem.*, 36 (1972) 1767–1772; P. J. L. Daniels, A. K. Mallams, and J. J. Wright, *J. Chem. Soc., Chem. Commun.*, (1973) 675–676.
5 D. J. Bell and G. D. Greville, *J. Chem. Soc.*, (1955) 1136–1140.
6 E. J. Reist, R. R. Spencer, D. F. Calkins, B. R. Baker, and L. Goodman, *J. Org. Chem.*, 30 (1965) 2312–2317.
7 T. Ogawa, M. Akatsu, and M. Matsui, *Abstr. Kakusan Kagaku Symp., 3rd, Sapporo, Japan*, (1975) 30–33.
8 E. J. Corey, K. C. Nicolaou, R. D. Balanson, and Y. Machida, *Synthesis*, (1975) 590–591.
9 A. G. Davies, *Synthesis*, (1969) 56–64.
10 T. Ogawa and M. Matsui, *Carbohydr. Res.*, 51 (1976) C13–C18.
11 R. U. Lemieux, K. B. Hendriks, R. V. Stick, and K. James, *J. Am. Chem. Soc.*, 97 (1975) 4056–4062.