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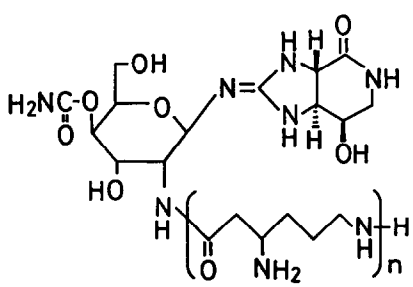
TOTAL SYNTHESIS OF ANTIBIOTIC STREPTOTHRICIN F [1)]

Shoichi Kusumoto, Susumu Imaoka, Yoshikazu Kambayashi, and Tetsuo Shiba
Department of Chemistry, Faculty of Science, Osaka University
Toyonaka, Osaka 560, Japan

ABSTRACT The first total synthesis of streptothricin F was achieved and its structure was unequivocally confirmed.

Streptothricin is a potent antibiotic which was isolated in very early time.[2)] Because of its inherent toxicity,[3)] however, little attention is paid to it now. We started synthetic studies on this antibiotic in order to elucidate the chemical structure and its relation to the antibiotic activity as well as the toxicity. Quite recently, we determined the structure of streptothricin as 1,[4,5)] extending the early proposal of van Tamelen et al.[6)] On the basis of this result, we now succeeded in the first total synthesis of streptothricin F (1, n=1) and consequently established the structure unequivocally. This work makes it possible, at the same time, to prepare various structural analogs of streptothricin which are necessary for our future study on the relationship between structure and activity.

In our previous synthesis of N^g-streptolidyl gulosaminide, a method was established to construct a β-glycosidic linkage between gulosamine and the exocyclic nitrogen atom of guanidine moiety in streptolidine [4)] Furthermore, it was shown that the 4-O-carbamoyl group can be smoothly introduced under a mild condition, and that this substituent and also a protected β-lysine moiety survive under the condition of the glycosyl guanidine formation [5)] Thus, in the following synthesis, β-lysine, carbamoyl and then streptolidine moieties were



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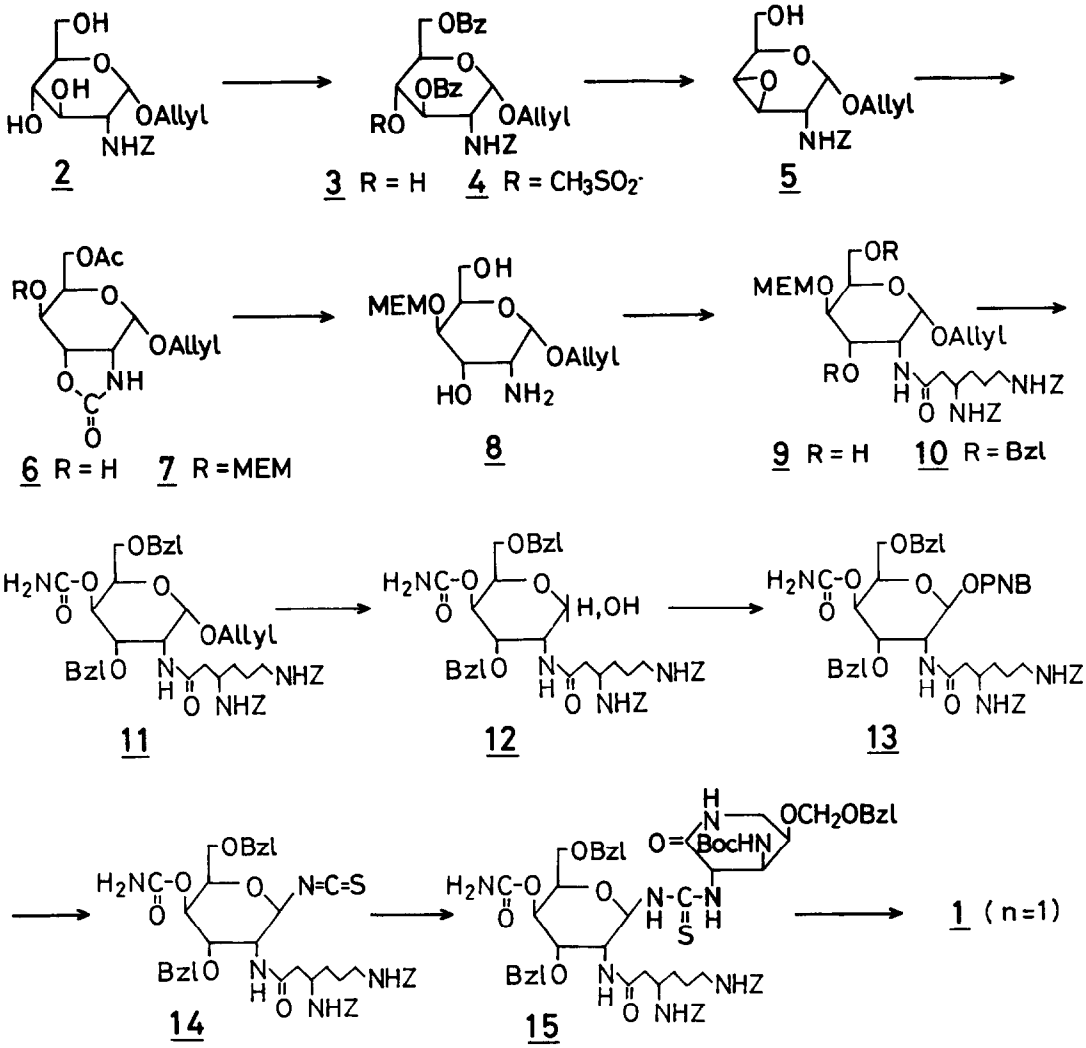
introduced in this order to the gulosamine molecule. The all persistent protecting groups employed were those which can be removed only by hydrogenolysis at the final synthetic stage.

A starting material of gulosamine skeletone was prepared from D-glucosamine according to our recent modification of the Gross' procedure[7] for the corresponding benzyl glycoside[4] The structures and stereochemistries of the intermediates were confirmed in comparison with the benzyl derivatives Allyl 2-benzyloxycarbonylamino-2-deoxy-α-D-glucopyranoside (2) (mp 138.5-139 5°C, ^{1}H-NMR δ 4.92ppm, 1Hd, $J_{1,2}$=2Hz, H-1) was prepared from 2-benzyloxycarbonylamino-2-deoxy-D-glucose (3% dry HCl in allyl alcohol at 100°C for 30 min). Selective acylation of its 3- and 6-hydroxyl groups was effected by using 3 equivalents of benzoyl chloride at low temperature (in pyridine at -20°C for 3 hr and then at 0°C overnight) to give 3,6-dibenzoate (3).[8] It was then mesylated without further purification (mesyl chloride in pyridine) to give mesyl dibenzoate (4) (87% from 2, mp 102.5-105°C) Alkaline treatment of 4 (0.5N aqueous NaOH - dioxane 3 4 at room temperature overnight) afforded an 3,4-anhydro sugar of galacto-configuration (5) in a good yield (93%, mp 135-136°C). After acetylation of the 6-hydroxyl group of 5, the product was dissolved in acetic acid. On addition of water to this solution at 100°C, the epoxide ring was opened with participation of the neighboring benzyloxycarbonyl function[7] to afford an oxazolidone derivative of desired gulo-configuration, i e , allyl 6-O-acetyl-2-amino-2-N,3-O-carbonyl-2-deoxy-α-D-gulopyranoside (6) (78% from 5, mp 114-116°C).

After the free 4-hydroxyl group of 6, to which the carbamoyl function is introduced later, had been tentatively protected (MEM chloride and ethyldiisopropylamine in dioxane at 70°C for 4 hr), the resultant MEM derivative 7 (73%, mp 80-82°C) was subjected to alkaline hydrolysis ($Ba(OH)_2$ in 50% EtOH under reflux for 1 hr) The product 8 was directly coupled with N^{β},N^{ε}-dibenzyloxycarbonyl-L-β-lysine[9] (EtOCOCl and triethylamine in dry THF) to give 9 (91%, mp 93-95°C), benzylation of which (benzyl bromide and BaO-$Ba(OH)_2$ in DMF at room temperature for 15 hr) yielded dibenzyl derivative 10 (66%, mp 94.5-95.5°C). The MEM group was now removed ($ZnBr_2$ in dry CH_2Cl_2) and the product was successively treated with chloroacetyl isocyanate (in CH_2Cl_2 at 0°C for 30 min) and with Zn-powder in methanol (at room temperature for 3 hr) to afford 4-carbamoyl derivative (11) (67% from 10, mp 122-124°C) Removal of glycosidic allyl group (isomerization with $RhCl(PPh_3)_3$ and cleavage with $HgCl_2$-HgO)[10] gave 12 (74%, mp 184.5-185.5°C), which was then treated with p-nitrobenzoyl chloride in pyridine to give 1-β-p-nitrobenzoate 13 (95%, mp 173-175°C, ^{1}H-NMR δ 5.91 ppm, 1Hd, $J_{1,2}$=9 0Hz, H-1) [11] This was then converted into β-glycosyl isothiocyanate 14 (22%, mp 158-159°C dec, ^{1}H-NMR δ 4.93 ppm, 1Hd, $J_{1,2}$=10Hz, H-1)[12] [i) dry HBr in CH_2Cl_2 at room temperature for 30 min, ii) KSCN and $CaSO_4$ in dry acetone]



Allyl = CH_2=CH CH_2- Boc = Bu^t-OCO- Bz = C_6H_5CO- Bzl = $C_6H_5CH_2$-

MEM = $CH_3OCH_2CH_2OCH_2$- PNB = *p*-O_2N-C_6H_4CO- Z = $C_6H_5CH_2OCO$-

Coupling of 14 with streptolidine part, i.e , 2,5-diamino-3-O-benzyloxymethyl-3-t-butoxycarbonylamino-2,3,5-trideoxy-D-arabinono-1,5-lactam,[4] to give syrupy thiourea derivative 15 (68%). It was subjected to the procedure for glycosyl guanidine formation [i) EtI in THF under reflux for 2 hr, ii) trifluoroacetic acid at room temperature for 15 min, iii) triethylamine in THF].[4] After hydrogenolytic removal of the protecting groups (Pd-black in acetic acid), the final product was subjected to column chromatography on Sephadex G-25 (BuOH-AcOH-

pyridine-H_2O 15 3 10 12) and then on Amberlite IRC50 (H^+form, 0.5 M pyridine-AcOH buffer pH 5.0). The purified product was converted into trihydrochloride [hygroscopic powder, $[\alpha]_D^{13}$ -49° (c 0.14, H_2O)] and identified with natural streptothricin F by means of TLC (cellulose, with several solvent systems including the same one as in the Sephadex G-25 column) and ^1H- as well as ^{13}C-NMR. The synthetic and natural samples showed identical antibiotic spectra

References and Footnotes

1) This work was presented at the 24th Symposium on the Chemistry of Natural Products, Osaka, Japan, October 1981.
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8) The positions of benzoyl groups in 3 was confirmed after conversion into propyl 2-acetamido-3,6-di-O-benzoyl-2-deoxy-α-D-glucopyranoside by catalytic reduction and N-acetylation. ^1H-NMR signals of H-3,4, and 6 appear at δ 5.39, near 3.9, and 4 6-4.8 ppm respectively, indicating that the 4-hydroxyl group is free.
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10) a) P. A Gent and R. Gigg, J Chem. Soc , Chem. Commun., 1974, 277.
b) R. Gigg and C D. Warren, J. Chem. Soc. (C), 1968, 1903.
11) Since gulosamine skeletone adopts a C1 conformation as judged from ^1H-NMR, the prefered formation of β-anomer can be explained by steric repulsion of the axial 3-O-benzyl function.
12) The low yield is due to the very unstable character of 14.

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