Tetrahedron Letters,Vol.25,No.40,pp 4533-4536,1984 0030-4039/84 $3.00 + .00
Printed in Great Britain

SYNTHETIC APPROACH TOWARD ANTIBIOTIC TUNICAMYCINS --- VI
TOTAL SYNTHESIS OF TUNICAMYCINS

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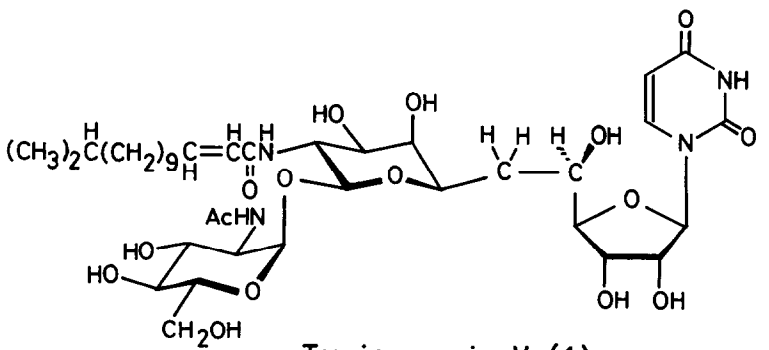
Summary: Tunicamycins and their eight analogs have been synthesized by condensation of a N-acetyl-D-glucosamine derivative and an anomeric chloride of tunicaminyl uracil, followed by deprotections and N-acylation.

Nucleoside antibiotic tunicamycins have been discovered in a fermentation broth of *Streptomyces lysosuperficus nov*, sp.[1] The antibiotics exhibit wide biological activities, such as antiviral and antimicrobial activities, a G_1 arrest of a cell culture, a higher susceptibility of transformed cells compared to that of normal cells, an alteration in a translocation of intracellar materials and modulation of cell differentiation.[2] Tunicamycin complex consists of at least sixteen homologs having different fatty acid residues.[3] The structures of tunicamycins have been established by a degradation study of the antibiotics, which are constituted of uracil, a fatty acid, N-acetyl-D-glucosamine and a C_{11} dialdose derivative named tunicamine.[4] A common component, tunicaminyl uracil has been synthesized in a preceding paper.[5]

In the present communication, we wish to report a total synthesis of tunicamycin V (u15iU)[6] (1), together with tunicamycin III (u14nU), VI (s15iU), VIII (u16nU), and eight analogs by a condensation of 2-acetamido-2-deoxy-4,6-O-isopropylidene-3-O-propionyl-α-D-glucopyranose (5) and 1-[2',3',5',8',9'-penta-



Tunicamycin V (1)

O-acetyl-10'-(benzyloxycarbonyl)amino-11'-chloro-1',6',10',11'-tetradeoxy-α-L-galacto-D-allo-undecodialdo-(11'R)-pyranose-(11',7')-furanosyl-(1',4')]-uracil (8), followed by deprotection and N-acylation with an appropriate fatty acid residue.

Compound 5 was prepared as follows. O-Isopropylidenation of allyl 2-acetamido-2-deoxy-α-D-glucopyranoside[7] (2) with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid afforded a 4,6-O-isopropylidene derivative (3)[14] in 87% yield. O-Acylation of 3 with propionic anhydride in pyridine gave a 3-O-propionyl derivative (4)[14] in 93% yield. Oxidative cleavage of the allyl group of 4 with selenium oxide in dioxane containing glacial acetic acid yielded 5[14] in 72% yield.

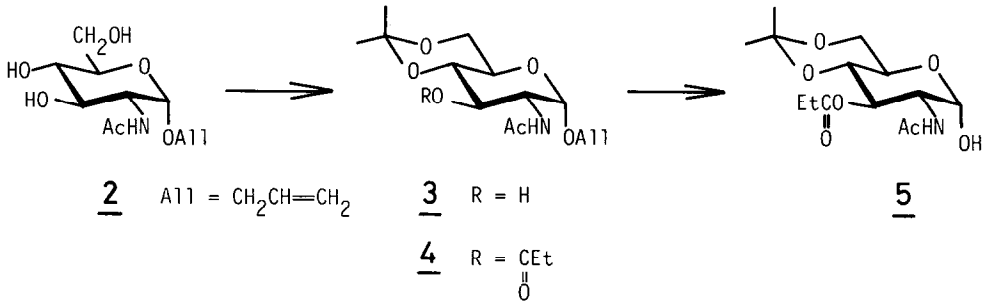
While, 8 was prepared from 1-[methyl 10'-(benzyloxycarbonyl)amino-2',3',5',8',9'-penta-O-acetyl-1',6',10'-trideoxy-α-L-galacto-D-allo-undecodialdo-(11'S)-pyranoside-(11',7')-furanosyl-(1',4')]-uracil[5] (6) as follows. Acetolysis of 6 in acetic anhydride containing sulfuric acid gave N-(benzyloxycarbonyl)-hexaacetate (7) in 68% yield. Chlorination of 7 in a mixture of acetyl chloride and dioxane containing dry hydrogen chloride afforded 8[14] in 73% yield.

Condensation of 5 and 8 in dichloromethane in the presence of silver carbonate, silver oxide and silver perchlorate under an argon atmosphere in the dark gave an aimed condensation product (9)[14] in 19% yield by a preparative chromatographic fractionation. O-Deacylation of 9 in methanolic sodium methoxide gave a compound (10) as a chromatographically homogeneous compound. Catalytic hydrogenolysis of 10 in methanol in the presence of palladium black and successive acylation with (E)-13-methyl-2-tetradecenoic acid[8] and dicyclohexylcarbodiimide gave a compound (11)[14] in 45% yield. Hydrolysis of 11 in aqueous acetic acid afforded 1,[14] in almost quantitative yield, which was identical with an authentic sample of tunicamycin V in the spectral (^{1}H NMR, IR)[9] and physical properties.[10] Tunicamycin V is a major component of tunicamycin complex, which was formerly designated tunicamycin A.[11] Also, 1 showed a similar ^{13}C NMR signal value for each carbon atom, except carbon atoms of the fatty acid residue, compared to that of streptovirudine A2 (u10iU),[12] which is a tunicamycin homolog having a short fatty acid chain.[13]

By an analogous reaction sequence, tunicamycin III (u14nU)(12), VI (s15iU)(13), VIII (u16nU)(14), and eight analogs: (0U)(15), (2U)(16), (s4nU)(17), (s8nU)(18), (s10nU)(19), (s12nU)(20), (s16nU)(21), (s20nU)(22) have been synthesized.[14] Compounds 1, 12, 13, 14, 18, 19, 20, 21 and 22 exhibited antiviral activity against Newcastle disease virus, and inhibitory activities for a glycoconjugate biosynthesis and a formation of lipid-linked intermediates.

Acknowledgment

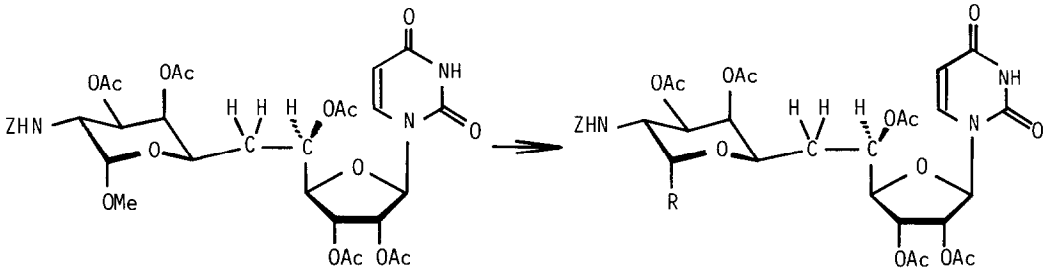
The authors wish to express their thanks to Prof. Gakuzo Tamura for his helpful advice and Meiji Seika Kaisha Ltd. for providing tunicamycins. Biological activities of the products have been determined by Dr. Akira



2 All = $CH_2CH{=}CH_2$ **3** R = H

4 R = CEt (=O)

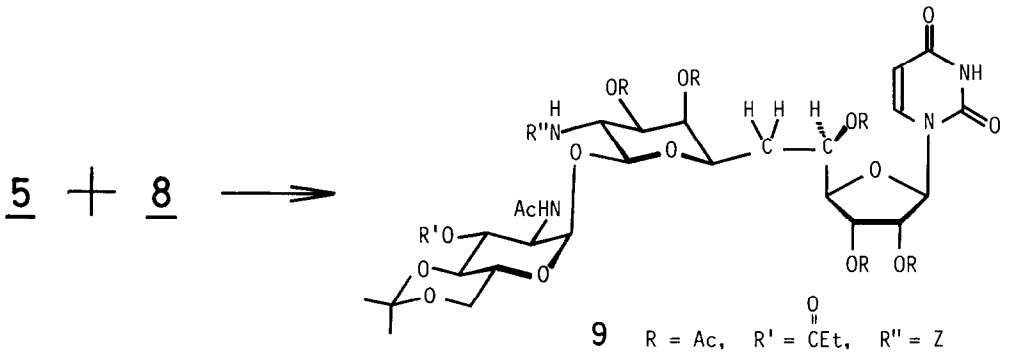
5



6

7 R = OAc

8 R = Cl



9 R = Ac, R' = CEt (=O), R'' = Z

10 R = H, R' = H, R'' = Z

11 R = H, R' = H,

R'' = $CC(=O)C{=}C(H)-(CH_2)_9-CH(CH_3)_2$

1

Takatsuki, to whom their thanks are due.

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8. The α,β-unsaturated isoacid was synthesized as follows. (cf. B. M. Trost, N. Salzman and Kunio Hiroi, *J. Am. Chem. Soc.*, 98, 4887 (1976)).

$$(CH_3)_2CH(CH_2)_2ZnBr + ClCO(CH_2)_8COOEt \longrightarrow (CH_3)_2CH(CH_2)_{11}COOEt$$

$$\longrightarrow (CH_3)_2CH(CH_2)_9C(H) = C(H)COOEt \xrightarrow{HCOOH,\ H_2SO_4} (CH_3)_2CH(CH_2)_9C(H) = C(H)COOH$$

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12. D. Tresselt, K. Eckardt, W. Ihn, and D. Krebs, *J. Nat. Products*, 46, 483 (1983).
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14. All new compounds gave satisfactory elemental analysis. Selected spectral and physical data are as follows. 3; mp 107°C, 4; 104°C, $[\alpha]_D^{26}$ +85.1° (c 1.1, $CHCl_3$), 5; mp 159°C, ^1H NMR (90 MHz, $CDCl_3$) δ 5.19 (d, 1H, $J_{1,2}$=3.8 Hz, H-1), IR (KBr) 3420 cm^{-1} (NH and OH), 8; mp 105°C (dec), $[\alpha]_D^{19}$ +97.4° (c 0.6, $CHCl_3$), ^1H NMR (90 MHz, $CDCl_3$) δ 6.27 (d, 1H, $J_{10',11'}$=5 Hz, H-11'), 9; mp 150°C, $[\alpha]_D^{21}$ +60.7° (c 0.53, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$) δ 4.65 (d, 1H, $J_{10',11'}$=8.1 Hz, H-11'), 5.02 (d, 1H, $J_{1'',2''}$=3.7 Hz, H-1''), 11; mp 226-232°C (dec), $[\alpha]_D^{23}$ +58.0° (c 1.2, MeOH), 1; mp 242-244°C (dec), $[\alpha]_D^{20}$ +50° (c. 0.2, MeOH), SIMS *m/e* 831 ($M+H^+$), ^1H NMR (200 MHz, CD_3OD) δ 4.60 (d, 1H, $J_{10',11'}$=8.5 Hz, H-11'), 4.93 (d, 1H, $J_{1'',2''}$=3.4 Hz, H-1''), ^{13}C NMR δ 88.3, 98.7, 100.9 (anomeric carbons), 12; mp 234-242°C (dec), 13; mp 248-250°C (dec), 14; mp 241-250°C (dec), 15; mp 166-178°C (dec), 16; mp 185-193°C (dec), 17; mp 191-200°C (dec), 18; mp 200-208°C (dec), 19; mp 214-228°C (dec), 20; mp 236-241°C (dec), 21; mp 245-247°C (dec), 22; mp 245-251°C (dec).

(Received in Japan 8 June 1984)