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Chemical Transformation of Uronic Acids leading to Aminocyclitols. II.[1] Synthesis of Hexaacetyl-streptamine from N-Acetyl-D-glucosamine

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By employing the oxidative decarboxylation reaction using lead tetraacetate and successive nitromethane cyclization reaction in the reaction sequence, N-acetyl-D-glucosamine (**11a**) has been converted to hexaacetyl-streptamine (**20a**) in 8% overall yield. It has been also suggested that the present transformation would provide a versatile method for preparation of aminocyclitols from various types of uronic acids.

Keywords——N-acetyl-D-glucosamine; amino-uronic acid; lead tetraacetate oxidation; nitromethane cyclization; diaminocyclitol; hexaacetyl-streptamine

In recent years, we have demonstrated that the glucuronide linkage contained in oligoglycosides such as saponins is selectively cleaved by photolysis,[3,4] lead tetraacetate oxidation followed by alkali treatment,[1,3,5] acetic anhydride and pyridine treatment,[3,6] and anodic oxidation.[3] Among these cleavage methods, by employing the lead tetraacetate degradation, a glucuronide-saponin[1,3] is cleaved at the glucuronide moiety to liberate the sapogenol and the oligosaccharide portion in high yields.

In a continuing study for elucidation of the reaction pathway starting with methyl glucopyranosiduronic acid derivative (**1**) and terminating with formation of the diene (**4**), participation of a presumable dialdehydic intermediate (**3**) (or its equivalent) has been demonstrated by trapping **3** with nitromethane in the alkaline medium to furnish three nitrocyclitols (*myo* (**5**), *scyllo* (**6**), and *muco* (**7**)).[1] However, any effort for isolation of **3** has not yet been successful.

Since nitrocyclitols (**5**,**6**,**7**) are readily convertible to aminocyclitols (**8**,**9**,**10**),[7] it has become promising that uronic acids are chemically transformed to the corresponding aminocyclitols in general by employing the oxidative decarboxylation reaction with lead tetraacetate. On the other hand, although cyclitols including aminocyclitols are known to be biosynthesized from carbohydrates,[8] only a limited number of chemical studies have hitherto been reported on the syntheses of cyclitols starting with carbohydrates.[9] It seems quite interesting, there-

1) Part I: I. Kitagawa, M. Yoshikawa, and A. Kadota, *Chem. Pharm. Bull.* (Tokyo), **26**, 484 (1978), which simultaneously constituted Part XXIII in the series of "Saponin and Sapogenol" from this laboratory.
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3) I. Kitagawa and M. Yoshikawa, *Heterocycles*, **8**, 783 (1977).
4) *a*) I. Kitagawa, M. Yoshikawa, Y. Imakura, and I. Yosioka, *Chem. and Ind.*, **1973**, 276; *b*) I. Kitagawa, M. Yoshikawa, and I. Yosioka, *Tetrahedron Lett.*, **1973**, 3997; *c*) I. Kitagawa, M. Yoshikawa, Y. Imakura, and I. Yosioka, *Chem. Pharm. Bull.* (Tokyo), **22**, 1339 (1974).
5) *a*) I. Kitagawa, M. Yoshikawa, Y. Ikenishi, K.S. Im, and I. Yosioka, *Tetrahedron Lett.*, **1976**, 549; *b*) I. Kitagawa, M. Yoshikawa, K.S. Im, and Y. Ikenishi, *Chem. Pharm. Bull.* (Tokyo), **25**, 657 (1977).
6) I. Kitagawa, Y. Ikenishi, M. Yoshikawa, and K.S. Im, *Chem. Pharm. Bull.* (Tokyo), **25**, 1408 (1977).
7) I. Kitagawa, M. Yoshikawa, and H. Ohmori, presented at the 98th Annual Meeting of Pharmaceutical Society of Japan, Okayama, April 1978, Abstract Paper p. 344.
8) *a*) J.B. Walker, *Lloydia*, **34**, 363 (1971); *b*) K.L. Rinehart, Jr. and R.M. Stroshane, *J. Antibiot.*, **29**, 319 (1976); *c*) R.M. Stroshane, M. Taniguchi, K.L. Rinehart, Jr., J.P. Rolls, W.J. Haak, and B.A. Ruff, *J. Am. Chem. Soc.*, **98**, 3025 (1976).
9) *a*) J.M. Grosheintz and H.O.L. Fischer, *J. Am. Chem. Soc.*, **70**, 1479 (1948); *b*) F.W. Lichtenthaler, *Chem. Ber.*, **94**, 3071 (1961); *c*) H.H. Baer and J. Kovar, *Can. J. Chem.*, **54**, 2038 (1976).

fore, if the present transformation method for aminocyclitols could be applicable also for the uronic acids derived from neutral and amino carbohydrates. For example, when starting with an amino-sugar (*e.g.* D-glucosamine (**11**)), the conversion would end up with formation of a diaminocyclitol (*e.g.* streptamine (**20**)). In this cennection, the present paper reports in detail a facile conversion of N-acetyl-D-glucosamine (**11a**) through an amino-uronic acid derivative (**16**) leading to hexaacetyl-streptamine (**20a**).[10]

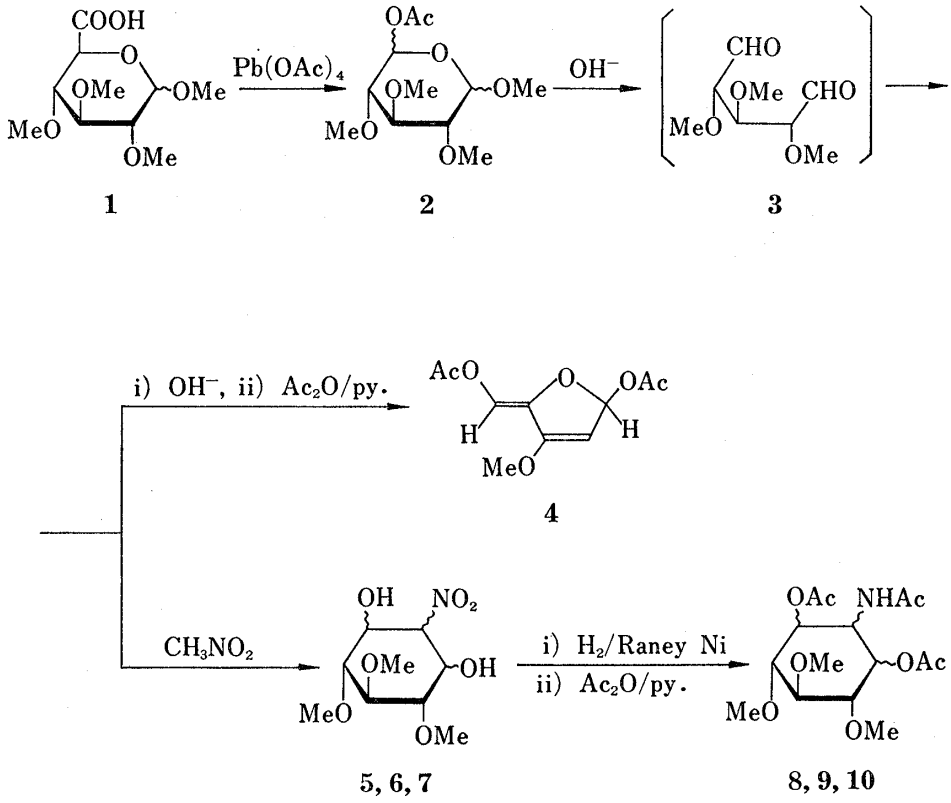


Chart 1

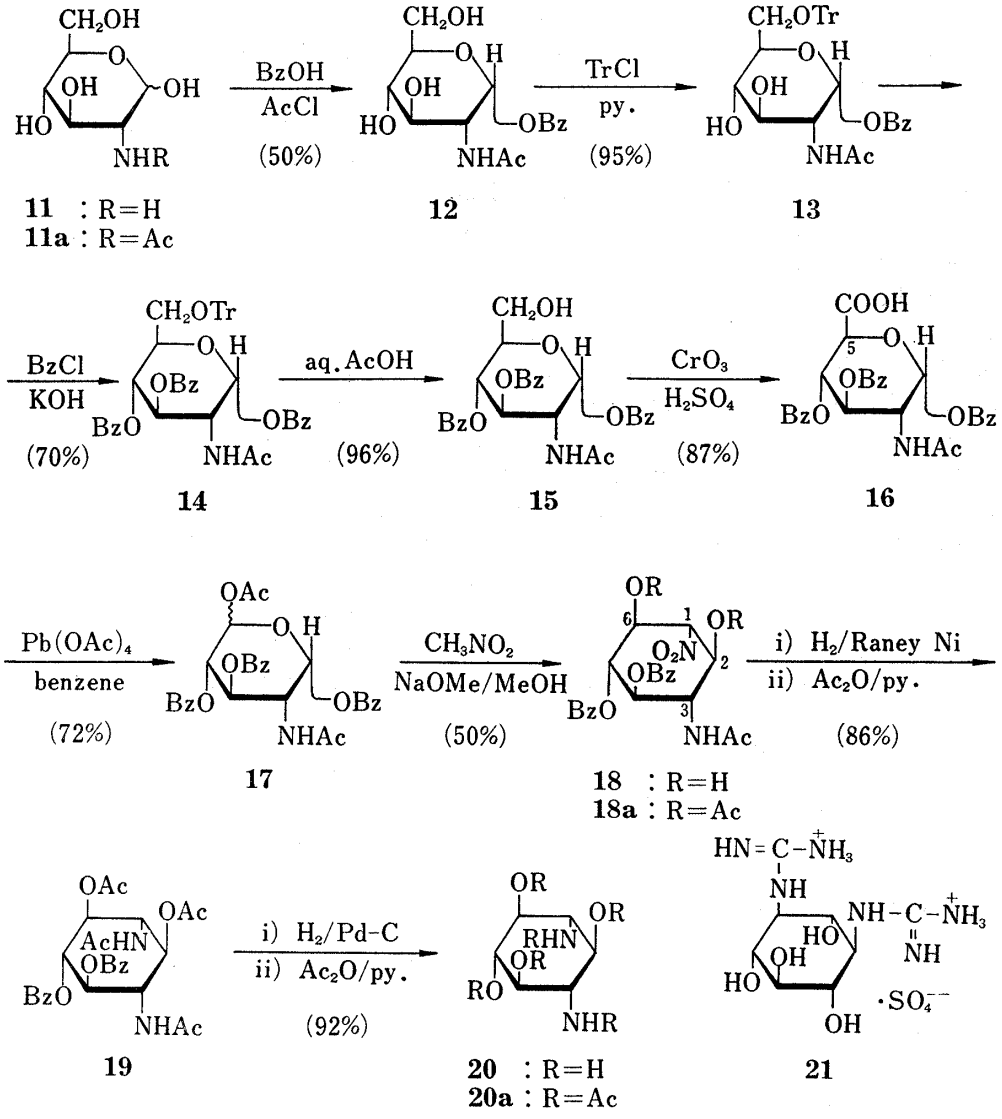
Amino-uronic Acid (16) from N-Acetyl-D-glucosamine (11a)

Benzyl 2-acetamido-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranoside (**15**)[11] was prepared from N-acetyl-D-glucosamine (**11a**) *via* **12**,[12] **13**,[13] and **14**.[11] Thus, treatment of **11a** with benzyl alcohol and acetyl chloride under reflux gave **12** in 50% yield. Tritylation of **12** furnished **13** in 95% yield. Successive benzylation of **13** with benzyl chloride and potassium hydroxide yielded **14** in 70% yield. Detritylation of **14** thus obtained gave **15** in 96% yield. The structures of **12**, **13**, **14**, and **15** have been substantiated by analysis of their physical properties and by comparison of their physical data with those reported previously (see Experimental).

Oxidation of **15** with chromium trioxide in aqueous sulfuric acid yielded desired amino-uronic acid: benzyl 2-acetamido-3,4-di-O-benzyl-2-deoxy-α-D-glucopyranosiduronic acid (**16**) in 87% yield. The infrared (IR) spectrum of **16** shows the presence of amide group and aromatic ring (1678, 1510, 1455 cm^{-1}), carboxyl (1733 cm^{-1}), and imino group (3435 cm^{-1}). The proton magnetic resonance (PMR) spectrum of **16** shows the signals ascribable to an aceta-

10) I. Kitagawa, A. Kadota, and M. Yoshikawa, presented at the 98th Annual Meeting of Pharmaceutical Society of Japan, Okayama, April 1978, Abstract Paper p. 345.
11) J.C. Jacquinet, J.M. Petit, and P. Sinaÿ, *Carbohyd. Res.*, **38**, 305 (1974).
12) R. Kuhn, H.H. Baer, and A. Seeliger, *Ann.*, **611**, 236 (1958).
13) M. Shaban and R.W. Jeanloz, *Carbohyd. Res.*, **17**, 411 (1971).

mide group including an imino function (δ 5.48, 1H, d, J=9 Hz), three benzyls, an anomeric proton (δ 5.02, 1H, d, J=3 Hz), and a carboxyl (δ 6.49, 1H, br.s, $W_{h/2}$=16 Hz), among which two signals due to COOH and NH are exchangeable with deuterium oxide (D_2O).[14] Thus, the structure of **16** possessing a free carboxyl at C-5 has been substantiated.



(Bz=benzyl; Tr=trityl)

Chart 2

Hexaacetyl-streptamine (20a) from Amino-uronic Acid (16)

Treatment of **16** with lead tetraacetate in refluxing benzene furnished **17**, a mixture of two acetoxylated products (the ratio for 5α-acetoxyl: 5β-acetoxyl=*ca.* 1: 2), in 72% combined yield. The IR spectrum of **17** shows substitution of the acetoxyl group (1760 cm^{-1}) for the carboxyl group in **16**. The structure (**17**) ($^4C_1$ conformation)[15] has been further corroborated

14) The signals due to hydroxyl and carboxyl are readily exchangeable on D_2O treatment, however the signals due to the imino function is not so easily exchangeable. In order to make sure of the assignment for the carboxyl and the imino group, the PMR spectrum of **16** was also taken for the deuterochloroform ($CDCl_3$) solution which was kept at 35° for 12 hr after D_2O treatment.

15) Rules for conformation nomenclature for five- and six-membered rings in monosaccharides and their derivatives, *J. Chem. Soc. Chem. Commun.*, **1973**, 505.

by the PMR signals: δ 1.95 (1/3H, s) and δ 2.03 (2/3H, s) for the acetoxyl methyl and δ 6.25 (1/3H, d, J=3 Hz) and δ 6.00 (2/3H, d, J=8 Hz) for 5β-H and 5α-H, respectively. The acetate mixture (**17**), without further separation, was treated with nitromethane in 0.5 N sodium methoxide–methanol to furnish a mixture of several cyclitol derivatives, from which the major cyclitol (**18**) was isolated in 50% yield.

The IR spectrum of **18** shows the absorption bands due to hydroxyl (3620 cm^{-1}) and nitro group (1559 cm^{-1}) together with those ascribable to acetamide group and benzyl. The PMR spectrum of **18** shows the signals due to an acetamide methyl, two benzyl groups, and two hydroxyls (1H each at δ 4.99 and 5.15, both d, J=5 Hz, exchangeable with D_2O). In order to clarify the configuration of the cyclitol (**18**), **18** was acetylated with acetic anhydride and boron trifluoride etherate to give the diacetate (**18a**). The IR spectrum of **18a** lacks the hydroxyl absorption band but shows the prominent absorption band at 1755 cm^{-1} due to acetoxyl. The PMR spectrum of **18a** shows the signals due to two equatorial secondary acetoxyls at C-2 and C-6 (3H each, both s at δ 1.94 and 2.00[16]; 1H each, both d.d of J=10 and 10 Hz, at δ 5.48 and 5.59). It also shows the signals assignable to two protons at C-4 and C-5 which possess an equatorial benzyloxyl function (δ 3.59 and 3.89, 1H each, both d.d of J=10 and 10 Hz) and the signals due to one equatorial acetamide group at C-3 (δ 1.78, 3H, s[16]; δ 4.35, 1H, d.d.d, J=10, 10, and 10 Hz; δ 5.90, 1H, d, J=10 Hz, exchangeable with D_2O). The signal assignable to a proton on a carbon (C-3) bearing the acetamide group varies to a doublet of doublet upon D_2O treatment. These assignments have been further confirmed by taking the spectra in other solvents (hexadeutero(d_6)-acetone and hexadeutero(d_6)-benzene +$CDCl_3$) and by spin-decoupling experiments (Table I). Therefore, the structure of the diacetate has been clarified to be 1D-3-acetamido-2,6-di-O-acetyl-4,5-di-O-benzyl-1,3-dideoxy-1-nitro-*scyllo*-inositol (**18a**)[17] and the major cyclitol obtained in the above nitromethane cyclization to be 1D-3-acetamido-4,5-di-O-benzyl-1,3-dideoxy-1-nitro-*scyllo*-inositol (**18**).[17]

Table I. Spin-Decoupling Experiments of **18a**

Decoupled proton (δ)	Irradiated at δ		
	3.59	4.35	5.90
4-H (3.59, d.d, J=10,10 Hz)	—	t-like[a]	
3-H (4.35, d.d.d, J=10,10,10 Hz)	Deformed[a]	—	d.d (J=10,10 Hz)
N-H (5.90, d, J=10 Hz)		Singlet	

a) Due to close chemical shifts of both signals, well-defined results of spin-decoupling could not be obtained.

Catalytic hydrogenation of **18** over Raney nickel T-4[18] followed by acetylation with acetic anhydride and pyridine gave a diaminocyclitol derivative (**19**) in 86% yield. The IR spectrum of **19** shows the absorption bands due to acetoxyl and acetamide group (3280, 1741, 1658, and 1555 cm^{-1}). The PMR spectrum of **19** also supports the structure by the signals at δ 1.72 and 1.76 (3H each, both s, two equatorial acetamide methyls),[16] δ 1.89 (6H, s, two equatorial acetoxyls),[16] and δ 7.76 and 7.94 (1H each, both d, J=8 Hz, two imino groups). Removal of the benzyl group in **19** by catalytic hydrogenolysis over 5% palladium-carbon followed by acetylation furnished, in 92% yield, the final hexaacetate which has been found to be identical with authentic hexaacetyl-streptamine (**20a**) (see Experimental)[19] by mixed mp determina-

16) *a*) F.W. Lichtenthaler and P. Emig, *Tetrahedron Lett.*, **1967**, 577; *b*) *Idem*, *Carbohyd. Res.*, **7**, 121 (1968).
17) IUPAC commission on the nomenclature of organic chemistry and IUPAC-IUB commission of biochemical nomenclature, *European J. Biochem.*, **5**, 1 (1968).
18) S. Nishimura, *Bull. Chem. Soc. Japan*, **32**, 61 (1959).
19) The authentic sample was prepared from streptidine sulfate (**21**) by hydrolysis followed by acetylation.[20] Streptidine sulfate was kindly provided by Dr. T. Kishi of Takeda Chem. Ind. to whom the authors deepest thanks are due.
20) R.L. Peck, C.E. Hoffhine, Jr., E.W. Peel, R.P. Graber, F.W. Holly, R. Mozingo, and K. Folkers, *J. Am. Chem. Soc.*, **68**, 776 (1946).

tion, IR (KBr), and PMR (d_6-dimethyl sulfoxide (DMSO)).[21] The overall yield from N-acetyl-D-glucosamine (**11a**) to hexaacetyl-streptamine (**20a**) is 8% (28.5% from **16** to **20a**), improvement of which, especially from **11a** to **14**, will be the subject of future study.

Although several synthetic methods of streptamine (**20**) starting with inositols,[21] conduritols,[22] *cis*-trioxatris-*σ*-homobenzene,[23] and N-acetyl-D-glucosamine (*via* different synthetic pathway),[24] have hitherto been reported, the present conversion seems to be significant due to not only its simplicity throughout the procedure but also the overall yield as compared to most of these previous methods.

Remarks should be added again as that the present transformation would provide a versatile transformation method starting with various types of uronic acids (including oilgo- and polysaccharides) leading to the corresponding aminocyclitol derivatives. Works in these aspects are in progress in this laboratory.

Experimental[25]

Benzyl 2-Acetamido-2-deoxy-α-D-glucopyranoside (12) from N-Acetyl-D-glucosamine (11a)——A solution of **11a** (24 g) in a mixture of dry benzyl alcohol (100 ml) and acetyl chloride (1 ml) was heated under reflux for 30 min. After cooling, the reaction mixture was diluted with ether to yield the brown precipitate which was collected by filtration and crystallized from EtOH to furnish **12** as colorless needles (14 g, 50% yield). **12**, mp 184.0° $[\alpha]_D^{21}$ +164.2° (c=0.9, H_2O). (lit.[12] mp 183—184° (EtOH), $[\alpha]_D^{23}$ +168.5° (c=1, H_2O)). IR ν_{max}^{KBr} cm^{-1}: 3300 (br, OH, NH), 1645 (amide I), 1550 (amide II), 1120, 1050 (C–O–C), 778, 730, 695 (phenyl).

Tritylation of 12 giving 13——To a solution of **12** (12 g) in dry pyridine (90 ml) was added trityl chloride (20 g) and the total solution was left standing at 35° for 12 hr. The reaction mixture was poured into ice-water and extracted with AcOEt. The AcOEt solution was washed with water, dried over $MgSO_4$, and evaporated under reduced pressure to yield a slightly yellowish oily product. Purification of the product by column chromatography (silica gel 400 g; $CHCl_3$–MeOH=50: 1→10: 1) furnished **13** (20.5 g, 95% yield). **13**, mp 97.0° (colorless fine crystals from ether–hexane), $[\alpha]_D^{17}$ +51.0° (c=1.9, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3330 (br, OH, NH), 1658 (amide I), 1546 (amide II), 1050 (C–O–C), 1450, 700 (phenyl). PMR ($CDCl_3$, δ): 1.73 (3H, s, >NAc), 3.96 (m,[26] 2-H, deformed upon irradiation at δ 4.78 and 6.36), 4.78 (1H, d, J=3 Hz, 1-H, varied to a singlet upon irradiation at δ 3.96), 6.36 (1H, d, J=9 Hz, exchangeable with D_2O, >NH, varied to a singlet upon irradiation at δ 3.96), 7.02—7.46 (20H, m, phenyl×4). Lit.[13] mp 101—102° (ether–hexane), $[\alpha]_D^{20}$ +39° (c=1.3, $CHCl_3$), IR ν_{max}^{KBr} cm^{-1}: 3350 (br), 1655, PMR ($CDCl_3$, δ): 1.87 (3H, s), 6.34 (1H, d, J=9 Hz), 7.34 (20H, m).

Benzylation of 13 giving 14——A solution of **13** (5 g) in benzyl chloride (30 ml) was treated with potassium hydroxide (5 g) and kept stirring at 160° for 12 hr. After cooling, the reaction mixture was diluted with AcOEt and washed with water to remove the inorganic material. Working up of the AcOEt solution as for **12** gave a slightly yellowish oily product which was purified by column chromatography (silica gel 200 g; hexane–AcOEt=10: 1) to furnish **14** (4.0 g, 70%). **14**, mp 164.0—165.5° (colorless needles from ether–light petroleum), $[\alpha]_D^{17}$ +97.1° (c=0.9, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: no OH, 3250 (NH), 1640 (amide I), 1550 (amide II), 1450, 745, 695 (phenyl). PMR (CCl_4, δ): 1.70 (3H, s, >NAc), 4.22 (m,[26] 2-H, deformed upon irradiation at δ 4.90 and 5.66), 4.90 (1H, d, J=3 Hz, 1-H, varied to a singlet upon irradiation at δ 4.22), 5.66 (1H, d, J=9 Hz, exchangeable with D_2O, >NH, varied to a singlet upon irradiation at δ 4.22), 6.66—7.48 (30H, m, phenyl×6). Lit.[11] mp 161—162.5° (ether-light petroleum), $[\alpha]_D^{20}$ +82° (c=0.65, $CHCl_3$), IR ν_{max}^{Nujol} cm^{-1}: 3240, 1640, 1550, 740, 695.

Detritylation of 14 giving 15——A solution of **14** (2 g) in AcOH (10 ml) was added with H_2O (3 ml) and heated at 75—80° for 1 hr. After neutralization with aq. 10% K_2CO_3, the white precipitate was collected

21) *a*) K. Heyns and H. Paulsen, *Chem. Ber.*, **89**, 1152 (1956); *b*) T. Suami and S. Ogawa, *Bull. Chem. Soc. Japan*, **40**, 1925 (1967); *c*) S. Ogawa, T. Abe, H. Sano, K. Kotera, and T. Suami, *Bull. Chem. Soc. Japan*, **40**, 2405 (1967); *d*) F.W. Lichtenthaler, H. Leinert, and T. Suami, *Chem. Ber.*, **100**, 2383 (1967); *e*) T. Suami, S. Ogawa, H. Sano, and N. Kato, *Bull. Chem. Soc. Japan*, **44**, 1992 (1971).

22) N. Kurihara, T. Kurokawa, and M. Nakajima, *Agric. Biol. Chem.*, **31**, 1166 (1967).

23) R. Schwesinger and H. Prinzbach, *Angew. Chem. Int. Ed. Engl.*, **14**, 630 (1975).

24) *a*) M.L. Wolfrom, S.M. Olin, and W.J. Polglase, *J. Am. Chem. Soc.*, **72**, 1724 (1950); *b*) S. Ogawa, K.L. Reinhart, Jr., G. Kimura, and R.P. Johnson, *J. Org. Chem.*, **39**, 812 (1974).

25) The instruments used for obtaining the physical data and the experimental conditions for chromatography were same as in Part I.[1]

26) The coupling pattern is obscure due to the overlapping with the other signals.

by filtration. The filtrate was extracted with AcOEt and the AcOEt extract was treated as for **12** to give the residue. The above precipitate and the residue were combined and crystallized from EtOH to furnish **15** (1.46 g, 96%) as colorless needles. **15**, mp 207.0°, $[\alpha]_D^{17}$ +131.7° (c=0.8, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 3450 (OH), 3290 (NH), 1650 (amide I), 1555 (amide II), 1455, 730, 692 (phenyl). PMR ($CDCl_3$, δ): 1.78 (3H, s, >NAc), 4.25 (m,[26] 2-H, deformed upon irradiation at δ 4.85 and 5.35), 4.85 (1H, d, J=3 Hz, 1-H, varied to a singlet upon irradiation at δ 4.25), 5.35 (1H, d, J=9 Hz, exchangeable with D_2O, >NH, varied to a singlet upon irradiation at δ 4.25), 7.12—7.33 (15H, m, phenyl×3). Lit.[11] mp 204—205° (EtOH), $[\alpha]_D^{20}$ +121° (c=0.73, $CHCl_3$), IR ν_{max}^{Nujol} cm^{-1}: 3480, 3320, 1650, 1550, 720, 690.

Oxidation of 15 giving 16——To a solution of **15** (2 g) in acetone (150 ml) was added Jones reagent (20 ml) (prepared from CrO_3 7 g, H_2O 30 ml, and conc. H_2SO_4 11.2 g) and the total mixture was kept stirring at 21° for 30 min. The reaction mixture was then poured into ice-water and extracted with AcOEt. Working up of the AcOEt extract as for **12** yielded white powder which was crystallized from hexane–acetone to furnish **16** (1.8 g, 87% yield) as colorless needles. **16**, mp 210.0—212.5°, $[\alpha]_D^{18}$ +80.4° (c=1.3, acetone). *Anal.* Calcd. for $C_{29}H_{31}NO_7$: C, 68.91; H, 6.18; N, 2.77. Found: C, 68.85; H, 6.11; N, 2.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3435 (NH), 1733 (COOH), 1678 (amide I), 1510 (amide II), 1455, 693 (phenyl). PMR ($CDCl_3$, δ): 1.78 (3H, s, >NAc), 4.25 (m,[26] deformed upon irradiation at δ 5.02 and 5.48), 5.02 (1H, d, J=3 Hz, 1-H, varied to a singlet upon irradiation at δ 4.25), 5.48 (1H, d, J=9 Hz, exchangeable with D_2O, >NH, varied to a singlet upon irradiation at δ 4.25), 6.49 (1H, br.s, $W_{h/2}$=16 Hz, readily exchangeable with D_2O, COOH), 7.15—7.30 (15H, m, phenyl×3).

Acetoxylation *via* Oxidative Decarboxylation of 16 giving 17——To a solution of **16** (8 g, 0.02 mol) in dry benzene (150 ml) was added $Pb(OAc)_4$ (23 g, 0.05 mol), and the total mixture was heated under reflux for 2 hr. After cooling, the reaction mixture was diluted with AcOEt and washed with water to remove inorganic material. Working up of the AcOEt extract as for **12** yielded a syrup product which was treated with hexane to furnish **17** (5.9 g, 72% yield) as white powder. **17** (a mixture of two epimers at C-5), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (NH), 1760 (OAc), 1679 (amide I), 1502 (amide II), 1458, 696 (phenyl), 1071, 1040 (C–O–C). PMR ($CDCl_3$, δ): 1.77 (3H, s, >NAc), 1.95 (1/3H, s, 5α-OAc), 2.03 (2/3H, s, 5β-OAc), 4.76 (1H, d-like, J=*ca.* 3 Hz, 1-H), 5.79 (1H, d, J=9 Hz, exchangeable with D_2O, >NH), 6.00 (2/3H, d, J=8 Hz, 5α-H), 6.25 (1/3H, d, J=3 Hz, 5β-H), 6.92—7.56 (15H, m, phenyl×3).

Nitromethane Cyclization of 17 giving 18——To a stirred solution of **17** (5 g) in nitromethane (27 ml) was added dropwise 0.5 N NaOMe–MeOH (40 ml) at 30° and the total mixture was kept stirring for 6 hr. The reaction mixture was made weakly acidic (pH 6) with AcOH and evaporated under reduced pressure to give a syrupy product. Column chromatography (silica gel 250 g, $CHCl_3$→$CHCl_3$–MeOH) of the product furnished **18** (2.06 g, 50% yield). **18**, mp 180.0—183.0° (colorless needles from EtOH), $[\alpha]_D^{18}$ −12.6° (c=0.9, acetone). *Anal.* Calcd. for $C_{22}H_{26}N_2O_7$: C, 61.38; H, 6.09; N, 6.51. Found: C, 61.21; H, 5.98; N, 6.26. IR ν_{max}^{KBr} cm^{-1}: 3620 (OH), 3480 (NH), 1644 (amide I), 1559 (amide II, NO_2), 721, 700 (phenyl). PMR (d_6-acetone, δ): 1.87 (3H, s, >NAc), 4.99, 5.15 (1H each, both d, J=5 Hz, exchangeable with D_2O, OH×2), 7.26 (10H, br.s, $W_{h/2}$=4 Hz, phenyl×2).

Acetylation of 18 giving 18a——To a stirred solution of **18** (42 mg) in Ac_2O (1.5 ml) was added BF_3-etherate (0.03 ml) at 15°. After stirring for 30 min, the reaction mixture was poured into ice-water. The white precipitate was collected by filtration and crystallized from $CHCl_3$–CCl_4 to furnish **18a** (49 mg, 98% yield) as colorless needles. **19**, mp 182.0—184.0°, $[\alpha]_D^{18}$ +13.0° (c=0.6, acetone). *Anal.* Calcd. for $C_{26}H_{30}N_2O_7$: C, 60.69; H, 5.88; N, 5.45. Found: C, 60.28; H, 5.79; N, 5.17. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: no OH, 3420 (NH), 1755 (OAc), 1680 (amide I), 1566 (amide II, NO_2), 1030 (C–O–C). PMR ($CDCl_3$, δ): 1.78 (3H, s, >NAc), 1.94, 2.00 (3H each, both s, OAc×2), 3.59 (1H, d.d, J=10, 10 Hz, 4-H), 3.89 (1H, d.d, J=10, 10 Hz, 5-H), 4.35 (1H, d.d.d, J=10, 10, 10 Hz, varied to d.d, J=10, 10 Hz on D_2O treatment), 4.57—4.94 (5H, m, 1-H, benzyl CH_2×2), 5.48, 5.59 (1H each, both d.d, J=10, 10 Hz, 2-H, 6-H), 5.90 (1H, d, J=10 Hz, exchangeable with D_2O, >NH), 7.29 (10H, s, phenyl×2). Decoupling experiments were as given in Table I. PMR (d_6-acetone, δ): 1.83 (3H, s, >NAc), 1.95, 1.97 (3H each, both s, OAc×2), 3.93, 3.99 (1H each, both d.d, J=9, 9 Hz, 4-H, 5-H), 4.35 (1H, m, 3-H), 5.16 (1H, t, J=10 Hz, 1-H), 5.61 (2H, t-like, J=*ca.* 10 Hz, 2-H, 6-H), 7.30 (10H, s, phenyl×2). PMR (d_6-benzene+$CDCl_3$ (1:1), δ): 1.67, 1.71, 1.80 (3H each, all s, >NAc, OAc×2), 3.44, 3.68 (1H each, both d.d, J=9, 9 Hz, 4-H, 5-H), 5.51, 5.66 (1H each, both d.d, J=9, 9 Hz, 2-H, 6-H), 6.09 (1H, d, J=10 Hz, >NH), 7.20 (10H, s, phenyl×2).

Catalytic Hydrogenation followed by Acetylation of 18 giving 19——A solution of **18** (100 ml) in AcOH (1 ml) was treated with Raney Ni T-4-EtOH solution[18] (1 ml) and was shaken under hydrogen atmosphere at 18° for 3 hr. After filtration for removing the catalyst, the filtrate was evaporated under reduced pressure. The residue thus obtained was dried and acetylated with Ac_2O (1 ml) and pyridine (1 ml) for 12 hr in the usual manner. A syrupy product, obtained by evaporation of the solvent under reduced pressure, was crystallized from EtOH to afford **19** (105 mg, 86% yield) as colorless needles. **19**, mp 291.0—293.0° (in a sealed capillary), $[\alpha]_D^{19}$ +33.5° (c=0.4, dioxane). *Anal.* Calcd. for $C_{28}H_{34}N_2O_8$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.46; H, 6.44; N, 5.09. IR ν_{max}^{KBr} cm^{-1}: 3280 (NH), 1741 (OAc), 1658 (amide I), 1555 (amide II). PMR (d_6-DMSO, δ): 1.72, 1.76 (3H each, both s, >NAc×2), 1.86 (6H, s, OAc×2), 3.78—4.23 (2H, m, 4-H, 5-H), 4.55—5.10 (8H, m, 1-H, 2-H, 3-H, 6-H, $>CH_2$×2), 7.27 (10H, s, phenyl×2), 7.76, 7.94 (1H each, both d, J=8 Hz, >NH×2).

Catalytic Hydrogenolysis followed by Acetylation of 19 giving Hexaacetyl-streptamine (20a)——To a solution of **19** (48 mg) in EtOH (50 ml) and AcOH (1 ml) was added 5% Pd-C (100 mg) and the total mixture was kept stirring under hydrogen atmosphere at 35° for 5 hr. After filtration for removing the catalyst, the filtrate was evaporated under reduced pressure. The residue thus obtained was acetylated with Ac_2O (1 ml) and pyridine (1 ml) for 12 hr. Evaporation of the solvent under reduced pressure yielded a syrupy product which was crystallized from EtOH to furnish **20a** (37 mg, 92% yield). **20a** was identified with the authentic sample[20] by IR (KBr), PMR (d_6-DMSO), and mixed mp (330.0° in a sealed capillary with transition point between 239—247°).[21]

Preparation of 20a from Streptidine Sulfate (21)——A solution of **21** (100 mg) in H_2O (10 ml) was added with aq. saturated $Ba(OH)_2$ (10 ml) and heated under reflux under nitrogen atmosphere for 26 hr. The reaction mixture was neutralized with aq. 0.8N H_2SO_4 and the inorganic precipitate was removed by filtration. Evaporation of the filtrate under reduced pressure gave a residue which was acetylated with Ac_2O (2.5 ml) and NaOAc (25 mg) by heating under reflux for 1 hr. The reaction mixture was then evaporated under reduced pressure and the residue was extracted with $CHCl_3$. The $CHCl_3$ soluble portion was evaporated under reduced pressure to give a product. Crystallization of the product from EtOH furnished **20a** (15 mg) as colorless needles. **20a**, mp 330.0° (in a sealed capillary with transition point between 239—247°). IR ν_{max}^{KBr} cm^{-1}: 3370 (NH), 1756 (OAc), 1660 (amide I), 1558 (amide II), 1219, 1030 (C–O–C). PMR (d_6-DMSO, δ): 1.72 (6H, s, >NAc), 1.91 (12H, s, OAc×4), 7.82 (2H, d, J=10 Hz, >NH×2).

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