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A NEW SYNTHETIC APPROACH TO AMINOGLYCOSIDE ANTIBIOTICS BY USE OF OXIDATIVE DECARBOXYLATION AND REDUCTIVE DEACETOXYLATION AS KEY-REACTIONS

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Summary: By use of a decarboxylation reaction with lead tetraacetate and a deacetoxylation reaction with sodium borohydride as key-reactions, paromamine (12) and tri-N-benzyloxycarbonylparomamine (12a) were synthesized from D-glucosamine.

Recently, by means of the oxidative decarboxylation reaction effected by lead tetraacetate or anodic oxidation, we developed two versatile conversion methods from carbohydrates leading to cyclitols.[1,2] Taking advantage of these chemical modification methods, several successful conversions from N-acetyl-D-glucosamine to streptamine hexaacetate[3,4] and from glucuronide-saponins to aminocyclitol-oligoglycosides[2] were accomplished. Furthermore, in the studies on the chemical behavior of nitrocyclitol derivatives, we found that $NaBH_4$ effected one-step reductive elimination of the acetoxyl function(s) located at β to the nitro group. By use of this reaction, deoxyaminocyclitols (*e.g.* 2-deoxystreptamine) were readily synthesized from N-acetyl-D-glucosamine and formal syntheses of (-)-shikimic acid and (-)-quinic acid from D-mannose were attained.[5]

As a continuing study on these chemical modifications of carbohydrates, a disaccharide (3), which was synthesized from D-glucosamine, was successfully converted to paromamine (12)[6] and its tri-N-benzyloxycarbonyl (Cbz) derivative (12a)[7] by utilizing $Pb(OAc)_4$ decarboxylation and $NaBH_4$ deacetoxylation as the key-reactions as described below. Since 12a was already converted to kanamycin C (13),[7] the present work constituted a formal synthesis of kanamycin C from D-glucosamine.[8]

Glycosidation under a N_2 atmosphere of 1[9] (1 mole) with 2[9] (2 mole) in benzene-dioxane (2:1) in the presence of *sym*-collidine and $AgClO_4$ (r.t., 30 min) furnished an α-disaccharide (3, 88%),[10] mp 164-165°C, $C_{40}H_{44}N_4O_{18}$,[11] $[\alpha]_D$ +8.3°, IR ($CHCl_3$, cm^{-1}): 3435, 3333 (NH), 1744 (br, Ac, Cbz), 1615, 1592 (arom.) 1503 (amide II, NO_2, arom.), 1338 (NO_2), FD-MS (*m/z*): 868 (M^+) and 4 (trace), mp 107-108°C, $C_{40}H_{44}N_4O_{18}$, $[\alpha]_D$ -17.8°, IR ($CHCl_3$): 3433, 3320, 1736 (br), 1621, 1595, 1506, 1337, FD-MS: 868 (M^+).[12]

The α-glycosidic linkage in the major disaccharide (3) was suggested from the glycosidation conditions[13] and was substantiated by ^{1}H NMR analysis (d_6-acetone)[14] of the deacetylated product (3a), mp 183-184°C, $C_{34}H_{38}N_4O_{15}$, IR ($CHCl_3$): 3580 (br, OH), 3440, 3347, 1700, FD-MS: 742 (M^+), which was quantitatively prepared from 3 with 0.01% NaOMe-dry MeOH (r.t., 2 hr). Signals due to two anomeric protons were observed at δ 4.72 (1H, d, J= 2 Hz) and 5.24 (1H, d, J= 3 Hz). The structure 3 was further supported from ^{13}C NMR data for 3a and physicochemical properties of 4a, mp 135-137°C, $C_{34}H_{38}N_4O_{15}\cdot 1/2H_2O$, which was prepared by deacetylation of the minor product 4.

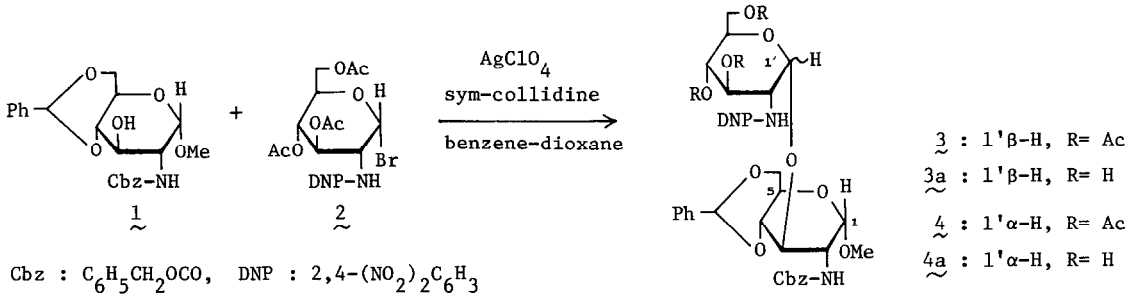
Removal of the benzylidene group from 3 ($HClO_4$-acetone, r.t., 4 hr) and subsequent reaction with *p*-anisylchlorodiphenylmethane (MMTrCl)-pyridine (r.t., 2 hr) quantitatively yielded 5, mp 102-104°C, $C_{53}H_{56}N_4O_{19}\cdot H_2O$. The monoMMTr derivative (5) was then converted to 6 (82%), colorless oil, $C_{57}H_{62}N_2O_{18}$, *via* successive three reactions: i) removal of the DNP group with Dowex 1x2 (OH^-) in acetone (r.t., 12 hr), ii) treatment with CbzCl-aq.sat. $NaHCO_3$ in dioxane (r.t., 80 min) and iii) acetylation with Ac_2O-pyridine in the presence of 4-dimethylaminopyridine (r.t., 12 hr).

After removing the MMTr group from 6 with BF_3-etherate in dry THF-ether (1:2)(r.t., 1 hr), the alcohol (5-CH_2OH) was oxidized with the Jones reagent (r.t., 3 hr) and the resulting uronic acid (5-COOH) was subjected to $Pb(OAc)_4$ degradation in benzene-pyridine (50:1)(reflux, 3.5 hr)[1,3] to furnish 7 (a mixture of 5β- and 5α-OAc derivatives, 71% from 6), colorless oil, IR ($CHCl_3$): no OH, 3439 (NH), 1745, 1232 (OAc).

Treatment of this 5-acetoxylated mixture with CH_3NO_2 in 1% NaOMe-dry MeOH (r.t., 36 hr) furnished the *scyllo*-nitrocyclitol glycoside (8, 22%), very hygroscopic white powder, IR (KBr): 3369 (br), 1554, 1382 (NO_2), FD-MS: 638 (M^+ +1), 660 (M^++Na), together with a mixture of nitrocyclitol glycosides of other types (29%). The *scyllo* glycoside (8) was then treated with benzaldehyde and $ZnCl_2$ under a N_2 atmosphere (r.t., 2.5 hr) to furnish the monobenzylidene derivative (9, 84%), mp 223-226°C, $C_{35}H_{39}N_3O_{14}$, FD-MS: 725 (M^+). Cyclohexylidenation of 9 with 1,1-dimethoxycyclohexane and *p*-TsOH·H_2O in DMF (80°C, 2.5 hr) and subsequent acetylation with Ac_2O-AcONa (r.t., 30 hr) yielded 10 (52%), colorless oil, $C_{45}H_{51}N_3O_{16}$, IR (CCl_4): no OH, 1742, 1727, FD-MS: 889 (M^+).

The *scyllo* configuration of the cyclitol moiety in 10 was shown by its ^{1}H NMR spectrum.[14] Thus, in addition to proton signals due to the D-glucosamine moiety [*e.g.* δ 4.14 (1H, dd, J= 9, 9 Hz, 4'-H), 5.17 (1H, d, J= 2 Hz, 1'-H), and 5.40 (1H, dd, J= 9, 9 Hz, 3'-H)], signals assignable to the cyclitol-protons were observed at δ 4.02 (1H, dd, J= 10, 10 Hz, 6-H), 4.74 (1H, dd, J= 10, 10 Hz, 1-H), and 5.68 (1H, dd, J= 10, 10 Hz, 2-H), which were in good accord with the *scyllo* configuration.

Reductive deacetoxylation of 10 with $NaBH_4$ in 95% EtOH (r.t., 3.5 hr)[5] furnished 11 (89%), mp 139-141°C, $C_{41}H_{47}N_3O_{13}$, IR ($CHCl_3$): 3600, 3424, 1722,

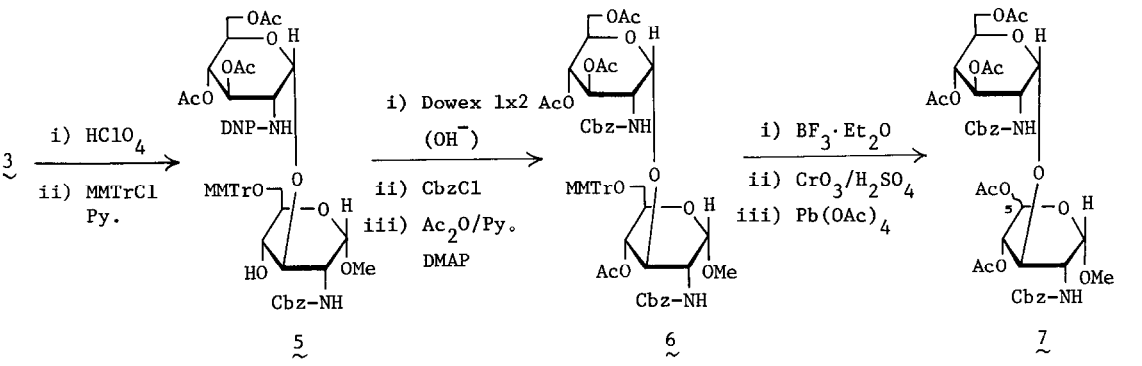


1 ~ 2 ~

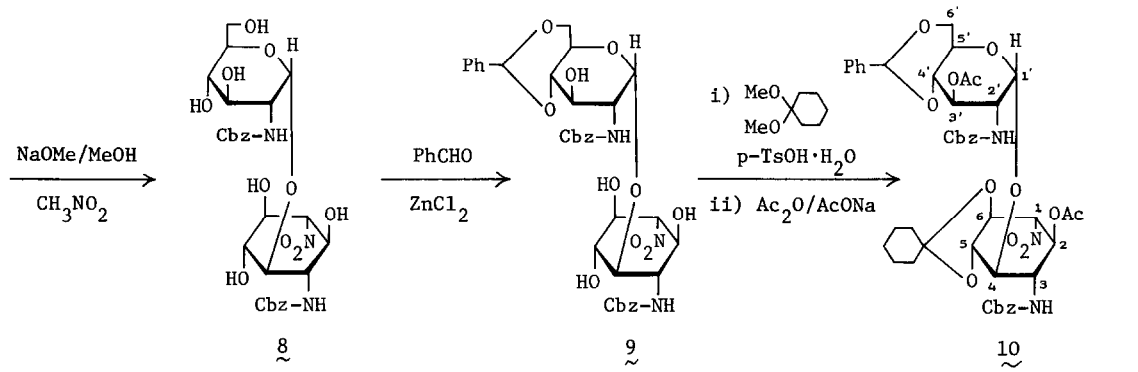
3 ~ : 1'β-H, R= Ac
3a ~ : 1'β-H, R= H
4 ~ : 1'α-H, R= Ac
4a ~ : 1'α-H, R= H

Cbz : $C_6H_5CH_2OCO$, DNP : $2,4\text{-}(NO_2)_2C_6H_3$

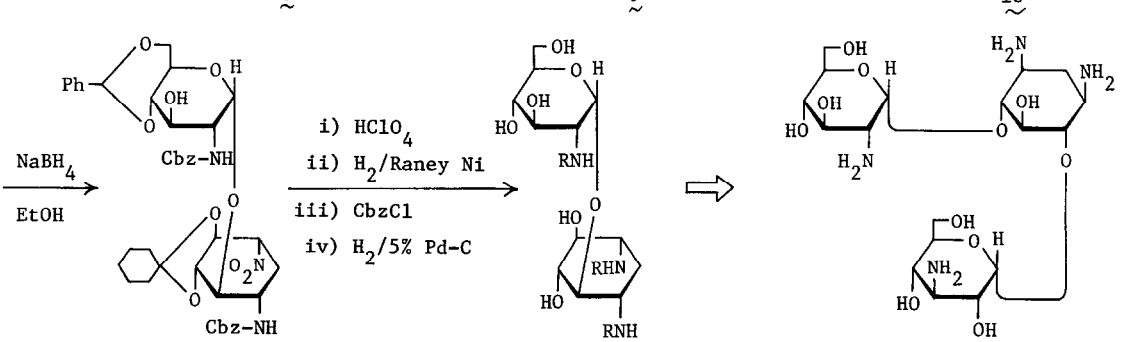
MMTr : $(p\text{-}CH_3OC_6H_4)(C_6H_5)_2C$



5 ~ 6 ~ 7 ~



8 ~ 9 ~ 10 ~



11 ~

12a ~ : R= Cbz (i,ii,iii)
12 ~ : R= H (i,ii,iv)

13 ~

1564, 1513, 1367, FD-MS: 789 (M^+). The ^{1}H NMR spectrum of 11 clearly indicated correctness of the structure: δ 1.90-2.23 (2H, m, 2-H_2) and δ 4.53 (1H, ddd, J= 5, 11, 11 Hz, 1-H).

Finally, removal of the benzylidene and cyclohexylidene protecting groups from 11 with $HClO_4$-acetone (r.t., 10 min) and subsequent reduction (Raney Ni T-4 in AcOH-EtOH) and benzyloxycarbonylation (CbzCl-5% aq. Na_2CO_3 in acetone) furnished tri-N-Cbz-paromamine (12a)[7] (55% from 11). On the other hand, treatment of 11 with $HClO_4$-acetone followed by reduction of the nitro group and removal of the Cbz group by catalytic hydrogenation (H_2/5% Pd-C) afforded paromamine (12) in 56% yield.

The present approach to the construction of the aminocyclitol glycoside (*e.g.* 12) is characteristic, since the conversion starts with an initial synthesis of an appropriate disaccharide and is followed by modification of one of two monosaccharide moieties into an aminocyclitol counterpart (*e.g.* the 2-deoxystreptamine moiety in 12). We are currently exploring this approach to the synthesis of other aminoglycoside antibiotics comprising more monosaccharide moieties.

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References and Notes

1) T. Kitagawa, M. Yoshikawa, and A. Kadota, Chem. Pharm. Bull.(Tokyo), 26, 484 (1978).
2) a) I. Kitagawa, T. Kamigauchi, K. Shirakawa, Y. Ikeda, H. Ohmori, and M. Yoshikawa, Heterocycles, 15, 349 (1981); b) I. Kitagawa, M. Yoshikawa, T. Kamigauchi, K. Shirakawa, and Y. Ikeda, Chem. Pharm. Bull.(Tokyo), 29, 2571 (1981).
3) I. Kitagawa, A. Kadota, and M. Yoshikawa, Chem. Pharm. Bull.(Tokyo), 26, 3825 (1978).
4) M. Yoshikawa, T. Kamigauchi, Y. Ikeda, and I. Kitagawa, Chem. Pharm. Bull. (Tokyo), 29, 2582 (1981).
5) M. Yoshikawa, Y. Ikeda, H. Kayakiri, and I. Kitagawa, Heterocycles, 17, 209 (1982).
6) S. Umezawa, T. Miyazawa, and T. Tsuchiya, J. Antibiot.(Tokyo), 25, 530 (1972).
7) S. Umezawa, S. Koto, K. Tatsuta, and T. Tsumura, Bull. Chem. Soc. Jpn., 42, 529 (1969).
8) M. Yoshikawa, Y. Ikeda, H. Kayakiri, K. Takenaka, and I. Kitagawa, presented at the 8th Symposium on the Progress in Organic Reactions and Syntheses. Symposium Papers p. 31 (Oct. 1981, Toyama).
9) P. F. Lloyd and M. Stacey, Tetrahedron, 9, 116 (1960).
10) The yield was calculated on the basis of 1.
11) The molecular compositions of compounds given with the chemical formulae were determined by elemental analyses.
12) When the glycosidation of 1 (1 mole) with 2 (2 mole) was undertaken in benzene-$CHCl_3$ (1:1) in the presence of same reagents, 3 (65%) and 4 (26%) were obtained.
13) a) A. Hasegawa, N. Kurihara, D. Nishimura, and M. Nakajima, Agric. Biol. Chem.(Tokyo), 32, 1123 (1968); b) K. Igarashi, J. Irisawa, and T. Honma, Carbohyd. Res., 39, 213 (1975).
14) The ^{1}H NMR spectra were taken on a JEOL FX-200 (200 MHz) spectrometer and the assignments were made on the basis of decoupling experiments in detail.

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