Communications to the Editor

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SYNTHESIS OF DIBEKACIN (3',4'-DIDEOXYKANAMYCIN B) FROM D-GLUCOSAMINE AND D-GLUCOSE

Masayuki Yoshikawa, Masahiro Torihara, Takahiko Nakae, Bae Cheon Cha, and Isao Kitagawa*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565, Japan

An aminoglycoside antibiotic, dibekacin (=3',4'-dideoxykanamycin B) (22), has been synthesized from D-glucosamine and D-glucose using an oxidative decarboxylation reaction with lead tetraacetate and a reductive deacetoxylation reaction with sodium borohydride as key-reactions.

KEYWORDS —— dibekacin; 3',4'-dideoxykanamycin B; aminoglycoside antibiotic; aminocyclitol; D-glucosamine; D-glucose; nitromethane cyclization; oxidative decarboxylation; reductive deacetoxylation; selective glycosidation

Using an oxidative decarboxylation reaction with lead tetraacetate and a reductive deacetoxylation reaction with sodium borohydride as key-reactions, we have been developing a versatile new synthetic method for synthesizing aminocyclitols and their glycosides from monosaccharides.[1] As an application of this method, we reported a synthesis of ribostamycin, an aminoglycoside antibiotic, which comprises two monosaccharide residues attached one each to C-4 and C-5 hydroxyl groups of the central 2-deoxystreptamine moiety.[2] In this paper, we report a synthesis of dibekacin (=3',4'-dideoxykanamycin B) (22) using D-glucosamine and D-glucose as the starting materials.[3] Dibekacin is a clinically important aminoglycoside antibiotic prepared by the chemical modification of kanamycin B.[4] It comprises two monosaccharide residues attached to C-4 and C-6 hydroxyls of the 2-deoxystreptamine moiety.

N-Carbobenzyloxy(Cbz)-D-glucosamine (1)[5] was converted to 2 (an anomeric mixture in a 3:2 ratio) by successive treatment with *p*-anisylchlorodiphenylmethane (MMTrCl) and methanesulfonyl chloride, both in pyridine.[6] Two mesyloxy residues in 2 were removed with Zn-NaI and the resulting olefin was subjected to detritylation and benzoylation to provide 3 quantitatively from 2. 3 thus obtained was a 3:2 mixture of α-anomer, $C_{22}H_{23}NO_6$,[7] mp 152-154°C, $[\alpha]_D$ -18°, and β-anomer, $C_{22}H_{23}NO_6$, mp 149-151°C, $[\alpha]_D$ -40°. Catalytic hydrogenation (PtO_2, H_2 3.5 atm) of 3 and subsequent treatment of the product with 2,4-dinitrofluorobenzene (DNFB) and Na_2CO_3 furnished 4 (88%): a mixture of α-anomer, $C_{20}H_{27}N_3O_8$, yellow oil, $[\alpha]_D$ +53° and β-anomer, $C_{20}H_{27}N_3O_8$, yellow oil, $[\alpha]_D$ +14°. Alkaline deacylation of 4 followed by acidic hydrolysis (70°C), acetylation, and anomeric bromination (5°C, 5 min), provided α-bromide (5) (73% from 4).

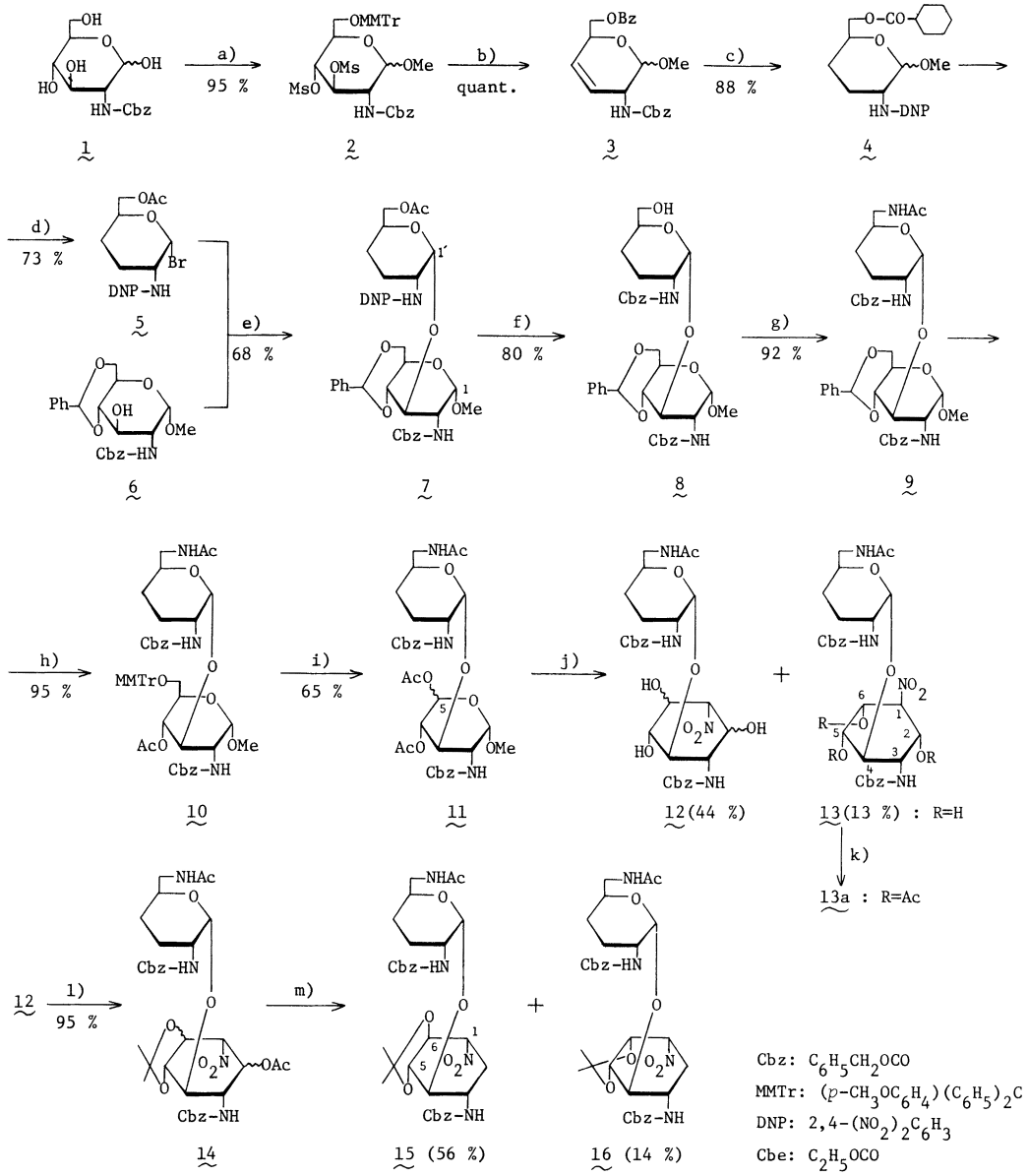
Glycosidation of 6 (0.9 mmole)[1b,5] with 5 (1.8 mmole) in the presence of $AgClO_4$ and *sym*-collidine in benzene-dioxane (2:1)(27°C, 15 min) furnished 7 (68%),[8] $C_{36}H_{40}N_4O_{14}$, yellow oil, $[\alpha]_D$ +22°, with a recovery of 6 (23%). The ^{13}C NMR spectrum (22.5 MHz, $CDCl_3$) of 7 showed signals due to two α-anomeric carbons [δc 100.3 (1-C), 97.9 (1'-C)]. Removal of the DNP and acetyl residues in 7 with Dowex 1x2 (OH^-)(25°C) and subsequent carbobenzyloxylation (2°C) yielded 8, $C_{36}H_{42}N_2O_{11}$, mp 182-183°C, $[\alpha]_D$ +26° (80% from 7). Tosylation of 8 followed by azide formation, reduction, and acetylation furnished 9, $C_{38}H_{45}N_3O_{11}$, mp 187-189°C, $[\alpha]_D$ +38° (93% from 8). Removal of the benzylidene group in 9 and subsequent treatment with MMTrCl and acetylation, gave 10, $C_{53}H_{59}N_3O_{13}$, colorless oil, $[\alpha]_D$ +33° (95% from 9).

Treatment of 10 with BF_3-etherate followed by Jones oxidation provided a uronide, which, by decarboxylative acetoxylation with $Pb(OAc)_4$ in benzene-pyridine (5:1)(reflux for 1.5 h),[1] was converted to 11, a 1:3 mixture of 5α- and 5β-OAc isomers (65% from 10). Treatment of 11 with 1.7% NaOMe-MeOH / CH_3NO_2 (1:1)(26°C, 48 h) furnished 12 (44%)(a mixture of *scyllo* and *myo* isomers) and 13 (13%, *muco*), $C_{30}H_{38}N_4O_{12}$, white powder, $[\alpha]_D$ +15°, which, on acetylation with Ac_2O-BF_3 etherate, was converted to the acetate (13a). The ^1H NMR spectrum (500 MHz, $CDCl_3$) of 13a substantiated the structure with signals due to three O-acetyl groups [δ 1.93 (6H), 1.98(3H)] and protons attached to the nitrocyclitol moiety: δ 4.82 (dd, J=9.5, 9.5 Hz, 1-H), 5.31 (dd, J=4.8, 9.5 Hz, 2-H), 3.99 (ddd, J=4.5, 4.8, 10.0 Hz, 3-H), 3.92 (dd, J=4.3, 4.5 Hz, 4-H), 5.52 (dd, J=4.3, 4.8 Hz, 5-H), 5.26 (dd, J=4.8, 9.5 Hz, 6-H). Thus, the *muco* configuration of 13 was ascertained.

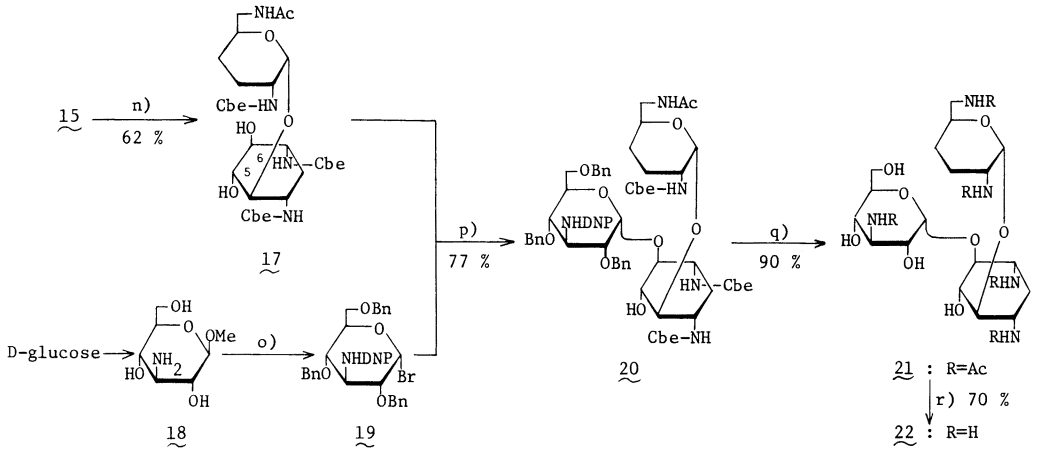
Treatment of 12 with isopropenyl methyl ether in DMF in the presence of *d*-10-camphorsulfonic acid (CSA) and subsequent acetylation, afforded 14. $NaBH_4$ reduction of 14 in 95% EtOH (5°C, 30 min) yielded 15 (56%), $C_{33}H_{42}N_4O_{11}$, colorless oil, $[\alpha]_D$ +32°, and 16 (14%), $C_{33}H_{42}N_4O_{11}$, colorless oil, $[\alpha]_D$ +19°. The ^1H NMR spectrum (500 MHz, $CDCl_3$) of 15 corroborated the structure with signals due to protons on the cyclitol moiety: δ 4.63 (ddd, J=4.3, 9.8, 9.8 Hz, 1-H), 3.92 (dd, J=9.8, 9.8 Hz, 6-H), and 3.47 (dd, J=9.8, 9.8 Hz, 5-H). Comparison in detail of the ^1H and ^{13}C NMR data for 15 and 16 revealed that 16 was a 6-epimer of 15. Catalytic hydrogenation [Raney Ni (T-4), H_2 1 atm] of 15 followed by carboethoxylation and removal of the isopropylidene group, furnished 17 (62%), $C_{23}H_{40}N_4O_{11}$, white powder, $[\alpha]_D$ +33°.

On the other hand, a bromide (19) was prepared from 18[9] *via* DNP protection, O-benzylation, acidic hydrolysis, and anomeric bromination. Glycosidation of 17 (0.08 mmole) with 19 (0.16 mmole) in the presence of $AgClO_4$ and *sym*-collidine in benzene-dioxane (2:1)(24°C, 30 min) furnished 20 (77%), $C_{56}H_{71}N_7O_{19}$, yellow powder, $[\alpha]_D$ +75°. The ^{13}C NMR spectrum (22.5 MHz, d_5-pyridine) of 20 showed the presence of two α-linkages with signals due to anomeric carbons (δc 97.9, 97.0). Furthermore, comparison of the ^{13}C NMR data for 17 and 20 indicated a glycosidation shift of the C-6 signal of 20. Thus, it became clear that selective glycosidation at the C-6-OH of 17 probably occurred due to the steric congestion on the C-5-OH of 17 caused by the neighboring C-4 glycosyloxy moiety.

Removal of the DNP group and the Cbe group (100°C, 4 h) of 20 and subsequent N-acetylation and catalytic hydrogenation (5% Pd-C, H_2 2.5 atm), yielded penta-N-acetyldibekacin (21, 90%), which was found to be identical with the authentic



(a) MMTrCl / Py.; MsCl / Py. (b) Zn / NaI / DMF (100°C,4.5 h); *p*-TsOH·H_2O / Et_2O; BzCl / Py. (c) H_2 / PtO_2 / AcOH; 2,4-dinitrofluorobenzene / Na_2CO_3 / H_2O-acetone (1:2) (d) 1% NaOMe-MeOH; 6N.aq.HCl-AcOH (1:4,70°C); Ac_2O / Py.; 25% HBr-AcOH / $CHCl_3$ (5°C) (e) $AgClO_4$ / *sym*-collidine / benzene-dioxane (2:1) (f) Dowex 1x2 (OH^-form) / acetone-H_2O (10:1); carbobenzoxy chloride / $NaHCO_3$ / dioxane-H_2O (2:1) (g) *p*-TsCl / Py.; NaN_3 / DMF (80°C); Zn / 90% aq.AcOH / DMF (2°C); Ac_2O / Py. (h) 60% $HClO_4$-acetone (1:60); MMTrCl / Py.; Ac_2O / 4-dimethylaminopyridine / Py. (i) BF_3-Et_2O / THF; Jones oxid.; $Pb(OAc)_4$ / benzene-Py. (5:1) (j) CH_3NO_2 / 1.7% NaOMe-MeOH (k) Ac_2O / BF_3-Et_2O (l) isopropenyl methyl ether / CSA / DMF; Ac_2O / NaOAc (m) $NaBH_4$ / 95% EtOH (5°C)



(n) H_2 / Raney Ni (T-4); ethyl chloroformate / Na_2CO_3 / H_2O-dioxane; 80% aq.AcOH (60°C) (o) 2,4-dinitrofluorobenzene / Na_2CO_3 / H_2O-acetone (4:1); BnBr / BaO / $Ba(OH)_2 \cdot 8H_2O$ / DMF; 6N.aq.HCl-AcOH (90°C); 25% HBr-AcOH / $CHCl_3$ (5°C) (p) $AgClO_4$ / *sym*-collidine / benzene-dioxane (2:1) (q) Dowex 1x2 (OH^-form) / acetone-H_2O (10:1); $Ba(OH)_2 \cdot 8H_2O$ / dioxane-H_2O (2:1); Ac_2O / MeOH; H_2 / Pd-C / AcOH (r) 80% aq.$NH_2NH_2 \cdot H_2O$

sample[10] by mixed mp determination and by $[\alpha]_D$, TLC, IR (KBr), and ^{13}C NMR (CD_3OD) comparisons. Finally, deacetylation of 21 with 80% aq. NH_2NH_2 in a sealed tube (100°C, 72 h) furnished dibekacin (22, 70%) identical with the authentic sample[4] [TLC, IR (KBr), $[\alpha]_D$].

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6) All reactions were carried out under an N_2 atmosphere with stirring unless stated otherwise.
7) The molecular composition of the new compounds and their chemical formulae were determined by elemental analysis.
8) The yield was calculated on the basis of 6.
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