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1-N-ACYLATION OF AMINOCYCLITOL ANTIBIOTICS VIA ZINC CHELATION AND REGIOSPECIFIC N-TRIFLUOROACETYLATION

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Summary: Amikacin and 1-N-[(S)-4-amino-2-hydroxybutyryl]-3',4'-dideoxykanamycin B have been prepared from kanamycin A and dibekacin by a novel, efficient sequence of reactions involving complex formation with Zn^{2+} and regiospecific N-trifluoroacetylation using ethyl trifluoroacetate.

Since butirosins[1] and amikacin,[2] which possess (S)-4-amino-2-hydroxybutyryl residue at the C-1-amino group of deoxystreptamine portion, have been found to be remarkably active against a variety of resistant bacteria, modification of aminocyclitol antibiotics by 1-N-acylation is of current interest.[2-7] However, the selective 1-N-acylation of aminocyclitol antibiotics has been hampered by difficulties in differentiating the reactivities of the functional groups. As an approach to this problem, transition metal chelation has recently been introduced to provide an efficient means. This method is based on the temporary protection of suitably disposed amino-hydroxy functions as metal chelates and subsequent acylation of the unbound amino group(s). Hanessian et al[5] described selective N-acylation of kanamycin A via chelation of vicinal amino-hydroxy group pair with Cu^{2+}. Nagabhushan et al[6] described N-acylation of sisomicin, gentamicins and kanamycin A via chelation of nonvicinal amino-hydroxy group pair (with Co^{2+}, Ni^{2+} and Cu^{2+}) between 1 and 2" positions as well as the chelation of vicinal amino-hydroxy group pair. In another report, Carney et al[7] utilized chelation of Cu^{2+} between vicinal amino groups in the selective N-acylation of seldomycin factor 5. We here report a novel, efficient method for the regiospecific 1-N-acylation of kanamycin-related antibiotics which involves zinc chelation followed by a regiospecific N-trifluoroacetylation.

We examined the complexing ability of a variety of metal ions for kanamycin A (KMA) and found that, among the metal ions tested (Ca^{2+}, Cr^{3+}, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Ru^{3+}, Ag^{+}, Sn^{4+}), Zn^{2+} gave the most satisfactory result. The remarkable stability of the zinc complexes

has been illustrated by the ability to stand benzyloxycarbonylation of the unbound amino groups without decomposition under normal conditions.

To a clear solution (after overnight stirring) of KMA and $Zn(OAc)_2 \cdot 2H_2O$ (2.5 - 5 mol equiv; washed[8] with THF before use) in DMSO (∿15 v/w parts for KMA), N-(benzyloxycarbonyloxy)-succinimide (NBES) (2.2 mol equiv.) was added and the solution was kept at room temperature for 1 h. Addition of ether gave a thick syrup. An aqueous-dioxane (1:1) solution of the syrup was charged on a column of Amberlite CG 50 (H^+ form, 100 - 200 mesh), and, after washing the column with aqueous dioxane, the column was developed with 0.5 - 1 M ammonia in aqueous dioxane (1:1). This procedure for removal of the zinc ion gave better yield than that by use of H_2S. Concentration of the solution (in the atmosphere of CO_2 at the last stage of concentration) gave 3,6'-bis-N-(benzyloxycarbonyl)kanamycin A (1) as monocarbonate,[9] y. 82%, $[\alpha]_D^{25}$ + 81° (c 1, H_2O-THF = 1:2). Found C, 51.95; H, 6.25; N, 6.68%. Calcd for $C_{34}H_{48}N_4O_{15} \cdot H_2CO_3$: C, 51.59; H, 6.19; N, 6.88%.

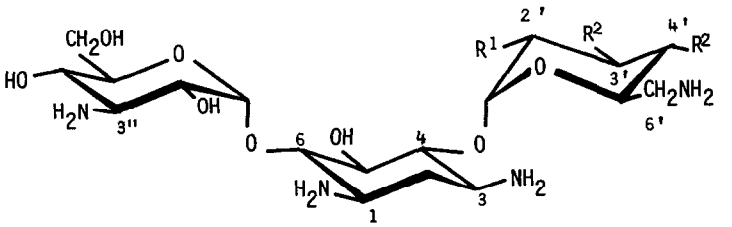
To prove the structure, 1 was tosylated to give di-N-tosyl derivative (pmr in pyridine-d_5: δ 2.12 and 2.24 for CH_3 of Ts). It afforded by hydrolysis 2-deoxy-1-N-tosylstreptamine and 3-deoxy-3-tosylamino-D-glucose which were characterized by pmr spectra.

Even when the above reaction was carried out with 1 mol equiv of $Zn(OAc)_2 \cdot 2H_2O$ and 2.2 mol equiv of NBES, the major product was 1 with slight formation of 6'-N-benzyloxycarbonylkanamycin A, a tris-N-(benzyloxycarbonyl)kanamycin A and tetrakis-N-(benzyloxycarbonyl)kanamycin A. On the other hand, when the analogous reaction was carried out with 1 mol equiv of $Ni(OAc)_2 \cdot 4H_2O$ and 2.2 (or 3.2) mol equiv of NBES, another bis-N-(benzyloxycarbonyl)kanamycin A different from 1 and several other products were formed. This result showed that the feature of Zn^{2+} chelation is different from that of Ni^{2+} chelation described by Nagabhushan et al.[6]

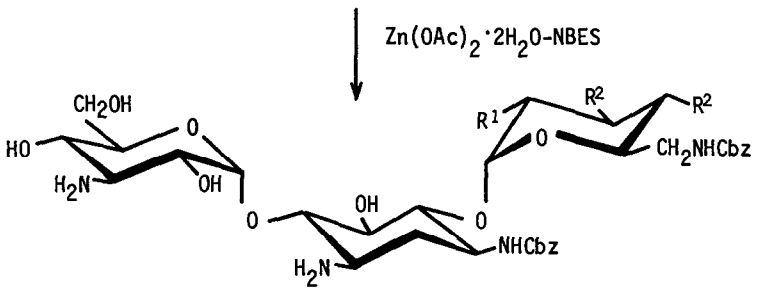
Application of the above reaction sequence to 3',4'-dideoxykanamycin B[10] (dibekacin) gave 3,2',6'-tris-N-(benzyloxycarbonyl)-3',4'-dideoxykanamycin B (2), which was easily purified by washing the resulting thick syrup obtained by addition of ether with 3 M aqueous ammonia until Zn^{2+} disappeared[11] (checked[12] by color reaction with diphenylcarbazide and NH_3), y. 85%, $[\alpha]_D^{25}$ + 77° (c 1, H_2O-THF = 1:2). Found C, 56.64; H, 6.43; N, 7.77%. Calcd for $C_{42}H_{55}N_5O_{14} \cdot H_2CO_3$: C, 56.39; H, 6.27; N, 7.65%.

The regiospecific 3"-protection of 1 and 2 was successfully achived by treating 1 or 2 carbonate with ethyl trifluoroacetate (∿1.3 mol equiv) in DMSO (∿5 v/w parts for the starting m.). The 3"-N-trifluoroacetylation was almost completed within 10 min at room temperature. 3,6'-Bis-N-(benzyloxycarbonyl)-3"-N-(trifluoroacetyl)kanamycin A[13] (3), $[\alpha]_D^{25}$ + 98° (c 1, pyridine), and 3,2',6'-tris-N-(benzyloxycarbonyl)-3',4'-dideoxy-3"-N-(trifluoroacetyl)kanamycin B[14] (4), $[\alpha]_D^{25}$ + 67° (c 1, pyridine), were obtained in ∿95% yields respectively. Even after 1 hour, the trifluoroacetylation gave almost no other product. A plausible mechanism for the fast and selective reaction may involve participation of vicinal 2" or 4"-hydroxyl group or both. This regiospecific N-trifluoroacetylation seems to find wide application in selective amino-protection adjacent to hydroxyl group(s). Investigation of the scope of this reaction is under study.

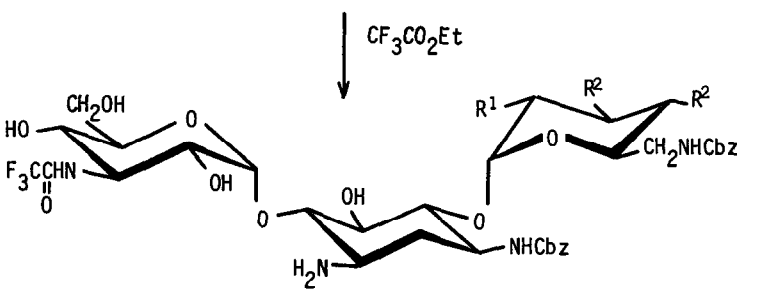
Finally, compound 3 and 4 were treated with N-hydroxysuccinimide ester of (S)-4-(benzyloxycarbonylamino)-2-hydroxybutyric acid in the usual manner[2] to give 5 and 6, respectively.



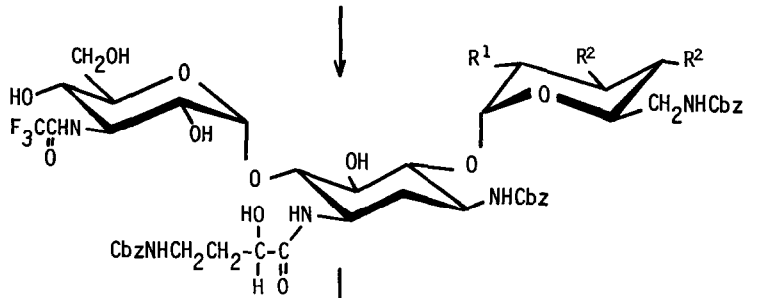
	R^1	R^2
Kanamycin A	OH	OH
Dibekacin	NH_2	H



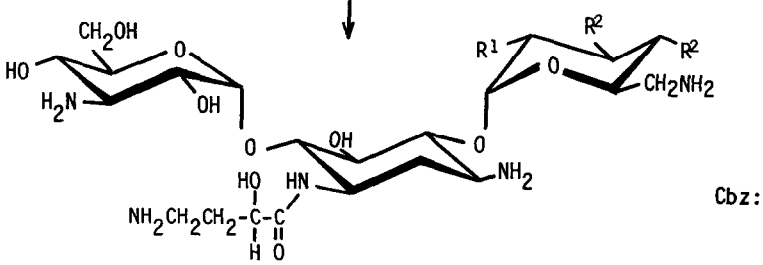
	R^1	R^2
1	OH	OH
2	NHCbz	H



	R^1	R^2
3	OH	OH
4	NHCbz	H



	R^1	R^2
5	OH	OH
6	NHCbz	H



	R^1	R^2
7	OH	OH
8	NH_2	H

Cbz: $CO_2CH_2C_6H_5$

Hydrolysis with 1 M ammonia in aqueous THF (1:1 - 1:2) at room temperature overnight followed by hydrogenolysis with palladium black gave the desired products amikacin (7) and 1-N-[(S)-4-amino-2-(hydroxybutyryl)]dibekacin (8) identical with authentic specimens[2,15] in every respect, respectively. Overall yields from KMA and dibekacin were >60%.

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References and Notes

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8. Direct use of commercial zinc acetate should be avoided because it contains some free acetic acid which interfered with the formation of zinc chelates.
9. Concentration without contact of CO_2 is prone to cause intermolecular transacylation to give a mixture of randomly N-benzyloxycarbonylated products.
10. H. Umezawa, S. Umezawa, T. Tsuchiya and Y. Okazaki, J. Antibiot., 24, 485 (1971); S. Umezawa, H. Umezawa, Y. Okazaki and T. Tsuchiya, Bull. Chem. Soc. Jpn., 45, 3624 (1972)
11. Since 2 was insoluble in water, most of Zn^{2+} was removed by washing the syrup with water, however, further washing with aqueous ammonia was necessary to remove the remaining Zn^{2+}.
12. J. C. Touchstone and M. F. Dobbins, "Practice of Thin Layer Chromatography", p. 193, John Wiley & Sons, Inc., 1978.
13. Ether was added to the reaction mixture to give a crude solid of 3 containing DMSO which could be used for the next reaction without purification to give excellent yield of 5. For purification, the solid was washed with water saturated with $KHCO_3$ and then with water to give pure 3 as hemicarbonate.
14. The solid obtained after addition of ether was treated as described above for 3 to give a hemicarbonate.
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