REDUCTIVE ONE-STEP ELIMINATION OF AN ACETOXYL RESIDUE AT β-POSITION OF A NITRO GROUP: SYNTHESES OF (-)-SHIKIMIC ACID FROM D-MANNOSE AND 2-DEOXYSTREPTAMINE PENTAACETATE FROM N-ACETYL-D-GLUCOSAMINE

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Abstract -- By utilizing a reductive one-step elimination reaction of an acetoxyl residue at β-position of the nitro group in cyclitols, a synthesis of the ketocyclitol triacetate (15a), which was already converted to (-)-shikimic acid (16) and (-)-quinic acid (17), from D-mannose (4) and a conversion from N-acetyl-D-glucosamine (18) to 2-deoxystreptamine pentaacetate (22) have been accomplished.

During the course of chemical transformation studies on carbohydrates leading to cyclitols, we have found two convenient methods in which the oxidative decarboxylation reaction is the key step; i.e. i) lead tetraacetate oxidation[1] and ii) anodic oxidation[2] both followed by alkaline treatment. By virtue of these methods, the short-step conversions from triterpene-oligoglycosides to aminocyclitol-oligoglycosides and from sugars to cyclitols were effected. The transformation from N-acetyl-D-glucosamine to streptamine hexaacetate was also accomplished.[3,4]

All of these conversion pathways include the nitrocyclitol intermediates. During the examination of the chemical behavior of these nitrocyclitol derivatives, we have found that an acetoxyl residue at β-position of the nitro group is reductively eliminated by $NaBH_4$ treatment. This communication is a report on a synthesis of the ketocyclitol triacetate (15a), the key intermediate for the synthesis of (-)-shikimic acid (16) and (-)-quinic acid (17), from D-mannose (4) via the nitrocyclitols (12) and a synthesis of 2-deoxystreptamine pentaacetate (22) from N-acetyl-D-glucosamine (18) via the nitroaminocyclitol derivative (19). Both syntheses include the present reductive elimination reaction with $NaBH_4$.

It is known that various functions may be introduced to α and β positions of

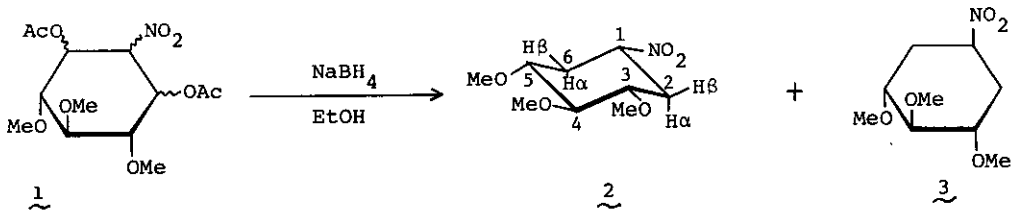
the nitro group in aliphatic nitro compounds[5] and nitro carbohydrates[6] through the nitro-olefin intermediates. In nitrocyclitols, the hydroxyl and acetoxyl residues at β-position of the nitro group are readily replaced by nucleophilic functions.[7,8] It was also reported that the elimination of the β-acetoxyl residue in nitro-sugars was effected stepwise via the nitro-olefin intermediate.[9] We have now found that $NaBH_4$ reduction effects the one-step elimination of the β-acetoxyl residue of the nitro group in nitrocyclitols.

Treatment of 1,[10] which was synthesized from D-glucuronic acid,[1] with $NaBH_4$ in EtOH at room temperature[11] for 1.5 h furnished two bisdeacetoxylated products, 2 (30%) and 3 (46%). The ir spectrum ($CHCl_3$) of 2, $C_9H_{17}O_5N$,[12] shows the preservation of the nitro residue (1552, 1377 cm^{-1}), while the ^1H nmr spectrum ($CDCl_3$) exhibits signals ascribable to three methoxyl groups at δ3.45 (6H, s) and δ3.60 (3H, s), a proton geminal to the nitro residue at δ4.32 (1H, t.t, J= 4, 12 Hz,1-H), and two methylene groups at δ1.79 (2H, d.d.d, J= 12, 12, 12 Hz, 2α-H, 6α-H) and δ2.58 (2H, d.d.d, J= 4, 4, 12 Hz, 2β-H, 6β-H). These spectral properties have defined the structure 2 having all equatorial substituents. The structure of 3, $C_9H_{17}O_5N$, has been elucidated by comparison of the physicochemical properties (ir, ms, ^1H nmr) with those of 2. 3 is the C-1 configurational isomer of 2.[13] Thus, the one-step reductive elimination of the β,β'-acetoxyl groups of the nitro group in 1 has been accomplished.

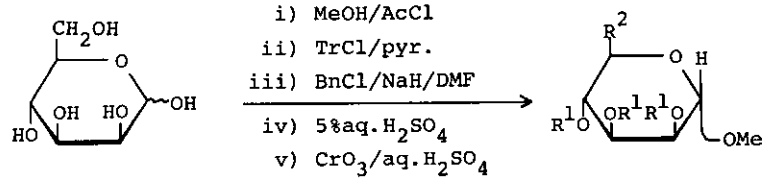
Next, we applied the reductive elimination reaction to a synthesis of the ketocyclitol triacetate (15a) from D-mannose (4). (-)-Shikimic acid (16) and (-)-quinic acid (17) are important biosynthetic precursors of many natural products and their chemical syntheses were reported several times.[14] However, to the best of our knowledge, a synthesis from D-arabinose is a sole example of a synthesis of optically active shikimic acid (16) and quinic acid (17),[15] in which 15a was the intermediate.

Methyl 2,3,4-tri-O-benzyl-α-D-mannosiduronic acid (9), which was prepared from D-mannose (4) via 5, 6, 7, and 8, was subjected to $Pb(OAc)_4$ oxidation[1] to furnish a mixture of 10 and 11. Nitromethane treatment of the mixture in MeONa-MeOH[1,2] yielded a nitrocyclitol mixture (12), which, without further separation, was acetylated with Ac_2O-BF_3 etherate to furnish the acetates (12a). $NaBH_4$ reduction of 12a in EtOH yielded two bisdeacetoxylated products, 13(27%) and 14(41%).

13, $C_{27}H_{29}O_5N$, $[\alpha]_D^{28}$ -28.6° ($CHCl_3$); ir (CCl_4): 3087, 3067, 3032, 1542, 1375 cm^{-1}; ^1H nmr ($CDCl_3$): δ3.53 (1H, d, J= 3, 8 Hz, 4-H), was converted to the

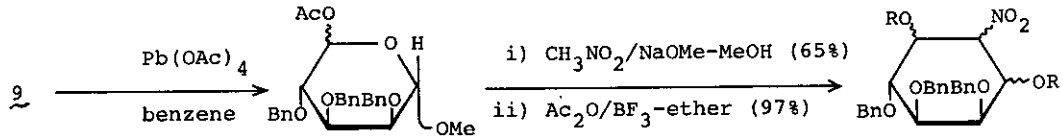


1 (myo, muco, scyllo) 2 3



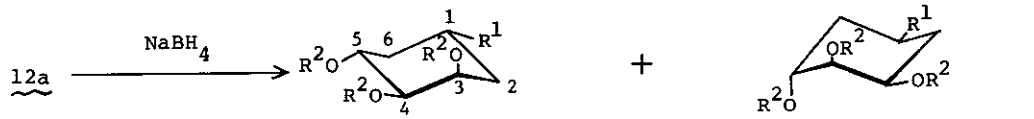
D-mannose (4)

5: R^1=H, R^2=CH_2OH
6: R^1=H, R^2=CH_2OTr
7: R^1=Bn, R^2=CH_2OTr
8: R^1=Bn, R^2=CH_2OH
9: R^1=Bn, R^2=COOH



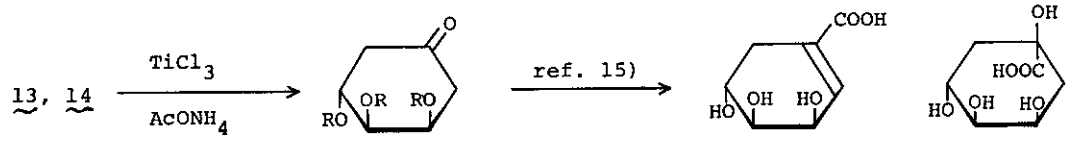
10 (α-OAc, 55%)
11 (β-OAc, 24%)

12 : R=H
12a: R=Ac



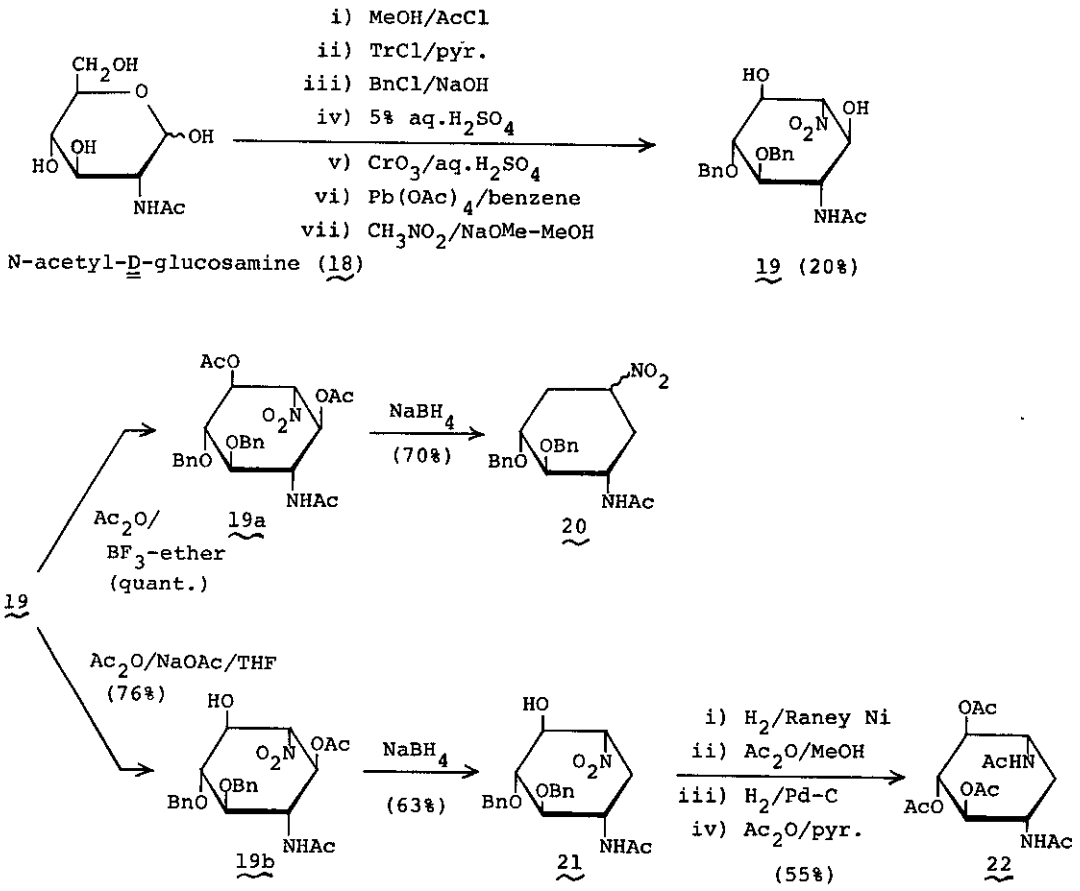
13 (27%): R^1=NO_2, R^2=Bn
13a : R^1=NHAc, R^2=Bn
13b : R^1=NHAc, R^2=Ac

14 (41%): R^1=NO_2, R^2=Bn
14a : R^1=NHAc, R^2=Bn
14b : R^1=NHAc, R^2=Ac



15 (72%): R=Bn
15a : R=Ac

16 17



N-acetylamino derivative (13a), $C_{29}H_{33}O_4N$, $[\alpha]_D^{28}$ -53.8° ($CHCl_3$) by reduction over Raney Ni T-4[16] followed by acetylation. Debenzylation of 13a (H_2/10% Pd-C) followed by acetylation gave 13b, $C_{14}H_{21}O_7N$, $[\alpha]_D^{28}$ -25.9° ($CHCl_3$); ir ($CHCl_3$): 3440, 1738, 1665, 1501 cm^{-1}; ^1H nmr ($CDCl_3$, δ): 1.93 (3H, s, eq. NHAc), 1.98, 2.00 (3H each, both s, eq. OAc x 2), 2.09 (3H, s, ax. OAc),[17] 4.86 (1H, d.d, J= 3.5, 10 Hz, 4-H), 5.22 (1H, d.d.d, J= 5, 10, 10 Hz, 5-H), 5.43 (1H, m, 3-H). Based on these findings, the structure 13 has been substantiated. The structure 14, $C_{27}H_{29}O_5N$, $[\alpha]_D^{28}$ -34.4° ($CHCl_3$), has been evidenced on the similar basis; i.e. the analysis of physical properties of 14a, $C_{29}H_{33}O_4N$, $[\alpha]_D^{28}$ -52.4° ($CHCl_3$) and the comparison of physical data of 14b with those reported for 14b.[18]

Treatment of 13 and 14 with $TiCl_3$-NH_4OAc[19] respectively yielded the same benzyl-ketocyclitol (15), $C_{27}H_{28}O_4$, $[\alpha]_D^{26}$ -59.0° ($CHCl_3$); ir (CCl_4): 1719, 1495 cm^{-1}, in 72% yield. Debenzylation followed by acetylation of 15 gave 15a which is identical with the authentic sample synthesized from (-)-quinic acid (17)[20] as judged

by ir, ^{1}H nmr, and $[\alpha]_D$ comparisons. Since 15a was already converted to 16 and 17 as mentioned above,[15] 16 and 17 have now been formally synthesized from D-mannose (4).

We next applied the reductive elimination reaction to a synthesis of 2-deoxystreptamine pentaacetate (22) from N-acetyl-D-glucosamine (18). The nitroaminocyclitol derivative (19),[3] which was synthesized from N-acetyl-D-glucosamine in 7 steps in improved overall yield (20%),[21] was quantitatively acetylated with Ac_2O-BF_3 etherate to give 19a.[3] $NaBH_4$ reduction of 19a in EtOH yielded a nitroaminocyclitol mixture (20, α-NO_2: β-NO_2= 2:3).[22] On the other hand, acetylation of 19 with Ac_2O-AcONa in THF[23] furnished the monoacetate (19b), $C_{24}H_{28}O_8N_2$, $[\alpha]_D^{28}$ +45.0° ($CHCl_3$); ir ($CHCl_3$): 3550, 3430, 1739, 1676, 1563, 1451, 1370 cm^{-1}, in 76% yield. $NaBH_4$ reduction of 19b in EtOH gave the monodeacetoxylated product (21), $C_{22}H_{26}O_6N_2$, $[\alpha]_D^{28}$ +20.0° ($CHCl_3$); ir ($CHCl_3$): 3420, 1674, 1552, 1503, 1452, 1373 cm^{-1}, in 63% yield. Successive treatment of 21 (reduction of the nitro group, N-acetylation, debenzylation, and O-acetylation) finally gave 2-deoxystreptamine pentaacetate (22), mp 322-323°, which is identical with the authentic sample by mixed mp, ir, and TLC, in 55% yield from 21.

We are currently working on the further application of this one-step reductive elimination reaction to the synthesis of other types of cyclitol derivatives.

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10) Since reduction of a configurationally specified nitrocyclitol (e.g. myo-isomer) gave a mixture of 2 and 3, the nitrocyclitol mixture (1) was used for the practical conversion.
11) It was found that the reduction may proceed similarly even under the chilled conditions (e.g. at -78°).
12) The molecular compositions were determined by high resolution mass spectrometry or elemental analyses. All compounds except 22 were obtained as colorless oils.
13) The ^{1}H nmr analysis shows that 3 is in a twist-boat conformation in solution. On alkaline treatment (aq. 5% NaOH, r.t.), 3 gave a mixture of 2 and 3, whereas 2 unchanged.
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21) Due to this improvement, the overall yield in the synthesis from N-acetyl-D-glucosamine (18) to streptamine hexaacetate has been increased from 8%[3] to 15%.
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