SYNTHESES OF AMINOCYCLITOLS AND AMINOCYCLITOL-OLIGOGLYCOSIDES FROM URONIC ACIDS AND GLUCURONIDE-SAPONINS BY MEANS OF AN ELECTROLYTIC DECARBOXYLATION REACTION

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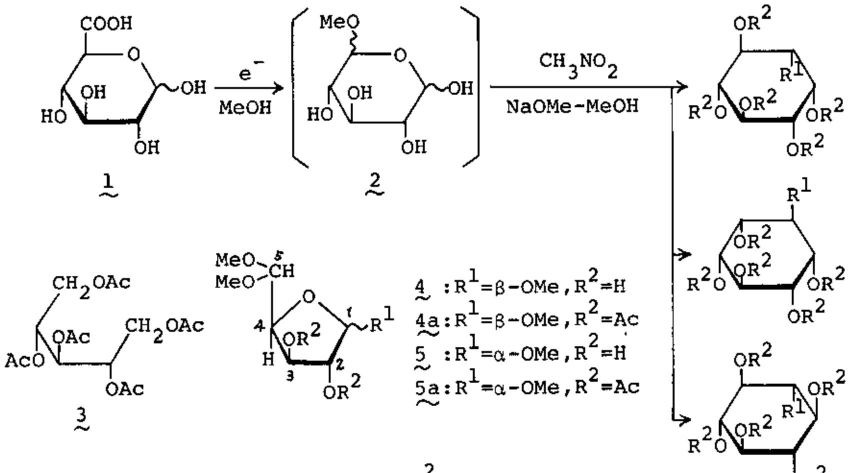
Abstract -- By use of the electrolytic decarboxylation reaction as the key step, aminocyclitols (6b, 7b, 8b, 10b, 14b) and aminocyclitol-oligoglycosides (*e.g.* 18) have been conveniently synthesized from uronic acids (1, 9, 12) and glucuronide-saponins (*e.g.* 15). The conversions include the first syntheses of optically active D-*neo*- and L-*neo*-nitrocyclitols (10, 14).

As an extension of our studies on four selective cleavage methods (photolysis,[1,2] lead tetraacetate degradation,[1,3] acetic anhydride-pyridine degradation,[1,4] and anodic oxidation[1,5]) for the glucuronide linkage in saponins, we have been working on the syntheses of natural products by use of the intermediates or the final products which are formed during or after these degradation reactions. Recently, we have utilized the aldehydic intermediate , which was produced in the lead tetraacetate degradation method, for the conversion from N-acetyl-D-glucosamine to hexaacetyl-streptamine.[6] In this paper, we describe our synthetic studies on aminocyclitols and their oligoglycosides starting with uronic acids and glucuronide-saponins[1] by means of the electrolytic decarboxylation reaction.[7]

When an ice-cooled methanolic solution of D-glucuronic acid (1) containing Et_2NH was subjected to constant current electrolysis for 3 h [glassy carbon electrode; 200 mA (10 mA/cm^2); *ca.* 40 V], a monomethyl cyclic acetal (2) was obtained. Since 2 was fairly unstable, the structure was confirmed by the following conversions. Reduction of 2 with $NaBH_4$ followed by acetylation (Ac_2O-pyridine) furnished the xylitol pentaacetate (3) in 65% yield, whereas heating a solution of 2



1

2

3

$\underset{\sim}{6}$: $R^1=NO_2, R^2=H$

$\underset{\sim}{6a}$: $R^1=NO_2, R^2=Ac$

$\underset{\sim}{6b}$: $R^1=NHAc, R^2=Ac$

$\underset{\sim}{7}$: $R^1=NO_2, R^2=H$

$\underset{\sim}{7a}$: $R^1=NO_2, R^2=Ac$

$\underset{\sim}{7b}$: $R^1=NHAc, R^2=Ac$

$\underset{\sim}{4}$: $R^1=\beta\text{-OMe}, R^2=H$

$\underset{\sim}{4a}$: $R^1=\beta\text{-OMe}, R^2=Ac$

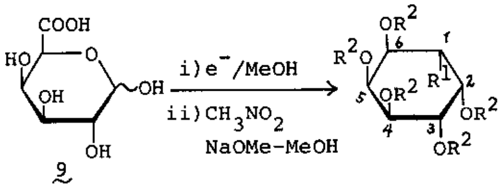
$\underset{\sim}{5}$: $R^1=\alpha\text{-OMe}, R^2=H$

$\underset{\sim}{5a}$: $R^1=\alpha\text{-OMe}, R^2=Ac$

$\underset{\sim}{8}$: $R^1=NO_2, R^2=H$

$\underset{\sim}{8a}$: $R^1=NO_2, R^2=Ac$

$\underset{\sim}{8b}$: $R^1=NHAc, R^2=Ac$

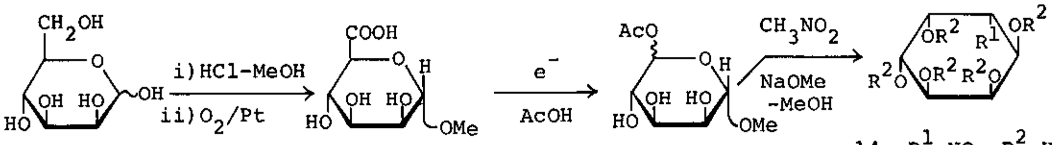


9

$\underset{\sim}{10}$: $R^1=NO_2, R^2=H$

$\underset{\sim}{10a}$: $R^1=NO_2, R^2=Ac$

$\underset{\sim}{10b}$: $R^1=NHAc, R^2=Ac$



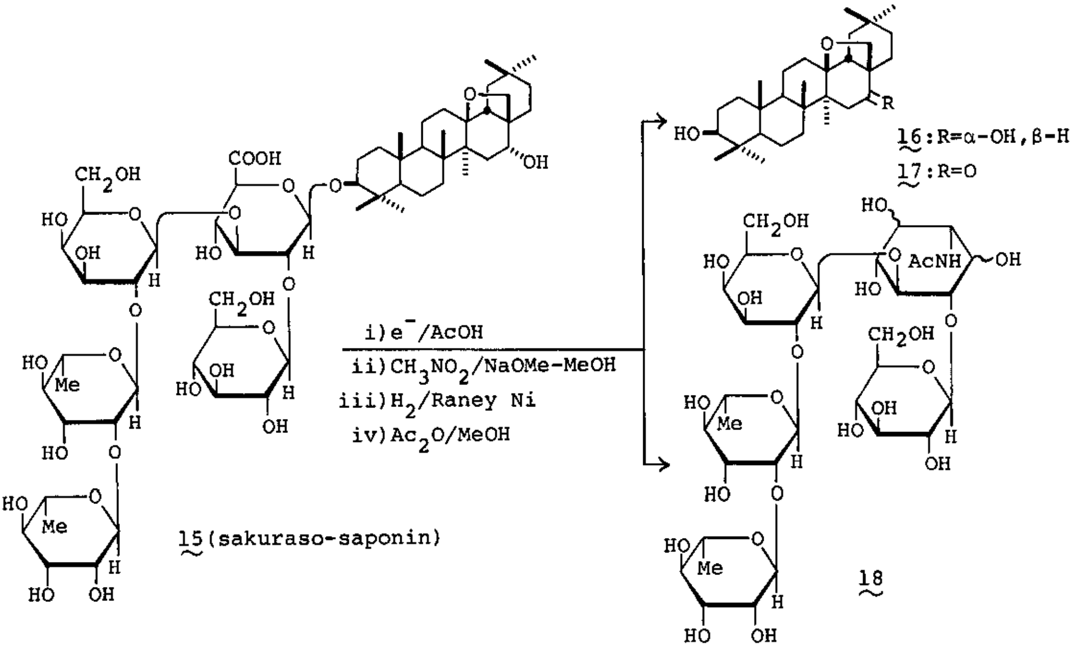
11

12

13

$\underset{\sim}{14}$: $R^1=NO_2, R^2=H$

$\underset{\sim}{14b}$: $R^1=NHAc, R^2=Ac$



$\underset{\sim}{15}$ (sakuraso-saponin)

$\underset{\sim}{16}$: $R=\alpha\text{-OH}, \beta\text{-H}$

$\underset{\sim}{17}$: $R=O$

$\underset{\sim}{18}$

under reflux in 4.5% HCl-dry MeOH yielded two furanosides, 4 (27%) and 5 (15%), the structures of which were elucidated on the basis of the following properties including the mass spectra of their acetates, 4a and 5a. 4a, $C_{12}H_{20}O_8$,[8)] ir (CCl_4, cm^{-1}): no OH, 1760, 1240 (AcO), ^1H-nmr (d_5-pyr., δ)[9)]: 2.02, 2.05 (both 3H, s, AcO x 2), 3.34, 3.42, 3.45 (all 3H, s, MeO x 3), 4.54 (1H, d.d, J= 5.5, 8 Hz, 4-H), 4.75 (1H, d, J= 8 Hz, 5-H), 5.04 (1H, s, 1α-H), 5.26 (1H, br.s, $W_{h/2}$= 3 Hz, 2-H), 5.61 (1H, br.d, J= 5.5 Hz, 3-H). 5a, $C_{12}H_{20}O_8$,[8)] ^1H-nmr (CCl_4): 4.98 (1H, d, J= 4.5 Hz, 1β-H), and other spectral data suggest 5a to be the C-1 epimer of 4a.

It is evident that, under the electrolytic conditions described here, D-glucuronic acid is decarboxylated and a methoxyl group is introduced at C-5, but the oxidation of the hydroxyl group[5)] or the acetal moiety[10)] does not occur. Since the unstable monomethyl cyclic acetal (2) thus formed was expected to be the key intermediate for the nitromethane cyclization leading to the nitrocyclitol derivatives,[3c)] the direct conversion of D-glucuronic acid to nitrocyclitols was next carried out.

Thus, the reaction product obtained by constant current electrolysis of 1 was treated with CH_3NO_2/NaOMe-dry MeOH[3c)] under an Ar atmosphere to furnish three nitrocyclitols[11)]: 6 (*myo*, 37%), 7 (*muco*, 8%), and 8 (*scyllo*, 6%). The structures of these three nitrocyclitols were confirmed by their respective conversions to their pentaacetates: 6a, 7a, and 8a, with Ac_2O/BF_3-etherate. Furthermore, reduction of 6, 7, and 8 with H_2/Raney Ni (T-4)[12)] followed by acetylation, afforded the aminocyclitol hexaacetates (6b, 7b, 8b)[11)] in excellent yields, thus accomplishing syntheses of aminocyclitols from D-glucuronic acid without any previous protection of the hydroxyl functions in the starting compound. It should be noted here that the aminocyclitols thus obtained, preserve the configurations at C-2, C-3, and C-4 of the starting D-glucuronic acid. We then applied this conversion method to other isomeric uronic acids.

When D-galacturonic acid (9) was similarly subjected to electrolysis followed by cyclization with nitromethane, D-*neo*-nitrocyclitol (10), $C_6H_{11}O_7N$,[13)] mp 208-210°, $[\alpha]_D^{24}$ -31.8° (c= 1.0, H_2O),[14)] was obtained as the major product. The structure 10 was substantiated on the basis of ^1H-nmr analysis [with $Eu(fod)_3$ in $CDCl_3$] of its pentaacetate (10a): δ5.44, 6.13, 6.45, 6.66 (all 1H, d.d, J= 3, 11 Hz, four axial protons at C-1, C-3, C-4, C-6); 6.89, 7.18 (both 1H, t, J= 3 Hz, two equatorial protons at C-2, C-5). Reduction of 10 followed by acetylation, afforded an N-acetylaminocyclitol pentaacetate (10b), $C_{18}H_{25}O_{11}N$,[13] mp 281-282°, $[\alpha]_D^{25}$ -9.4° (c= 1.0, MeOH).

Methyl α-D-mannopyranosiduronic acid (12), which was prepared from D-mannose by methyl glycosidation followed by catalytic oxidation,[15] was subjected to electrolysis for 7 h [Pt electrode; 100 mA (20 mA/cm^2); 50-60 V] in AcOH containing Et_3N to afford 13 in good yield. Nitromethane cyclization of 13 furnished, as the major product, L-neo-nitrocyclitol (14), $C_6H_{11}O_7N$,[13] mp 209-210.5°, $[\alpha]_D^{14}$ +30.2° (c= 0.54, H_2O),[14,16] which was readily converted to the N-acetylaminocyclitol pentaacetate (14b), $C_{18}H_{25}O_{11}N$,[13] mp 281-282°, $[\alpha]_D^{25}$ +8.9° (c= 1.0, MeOH), by reduction and subsequent acetylation.

The electrolytic conversion from a uronic acid to an aminocyclitol was then applied to glucuronide-saponins in anticipation of the preparation of aminocyclitol oligoglycosides from the oligosaccharide moiety of saponins.

Sakuraso-saponin (15),[17] a glucuronide-saponin from the root of Primula sieboldi, was subjected to electrolysis (Pt electrode) in AcOH containing Et_3N as described above and the product was subsequently subjected to cyclization with nitromethane. Protoprimulagenin A (16, 22%)[18] and aegicerin (17, 16%)[5,18] were liberated from the sapogenol moiety. Reduction followed by N-acetylation (Ac_2O/MeOH) of the oligosaccharide fraction, resulted in the formation of an *N-acetylaminocyclitol oligoglycoside* (18, myo, 20%, very hygroscopic).

The ir spectrum (KBr) of the oligoglycoside (18) showed the absorption bands due to hydroxyls and an amide group (1640, 1563 cm^{-1}), whereas the ^1H-nmr spectrum ($CDCl_3$-CD_3OD-D_2O)[19] showed signals at δ1.30 (6H, br.d, J= 5 Hz, Me in rhamnose moiety x 2) and 2.03 (3H, s, NAc). Methanolysis (9% HCl-dry MeOH) of 18 liberated methyl glucopyranoside, methyl galactopyranoside, methyl rhamnopyranoside, and N-acetyl-myo-inosamine-(1) (= 1-acetamido-1-deoxy-myo-inositol)(GLC, TLC).

As a result of this data together with the structure of sakuraso-saponin (15), the structure 18 has been assigned to the N-acetylaminocyclitol oligoglycoside, in which the configuration of two hydroxyls in the myo-inosamine moiety are not yet specified and are currently under study.

In order to extend the scope of the present conversion method, desacyl-jegosaponin,[17] another glucuronide-saponin from the pericarps of Styrax japonica, was subjected to the same procedrue and a corresponding N-acetylaminocyclitol oligoglycoside was successfully obtained from its oligosaccharide moiety.

As mentioned above, we have previously accomplished the conversion from uronic acids to aminocyclitols by means of the lead tetraacetate degradation method.[3c,6] In these cases, however, the hydroxyl functions in the starting uronic acid must be protected during the procedure so that the conversion requires more reaction steps. On the other hand, in the present electrolytic conversion procedure, no previous protection of the hydroxyl functions in the starting uronic acid derivatives is needed although the overall yields are as yet unsatisfactory in some cases. Since amino sugars are readily convertible to their corresponding amino uronic acid derivatives, the present method seems to be suitable for the conversion of sugars to aminocyclitols and of glucuronide-saponins to aminocyclitol-oligoglycosides. Work on these subjects is in progress.

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