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Inverse Klemer-Rodemeyer Fragmentation. Application to the Synthesis of Positional Isomers of Ristosamine and Acosamine

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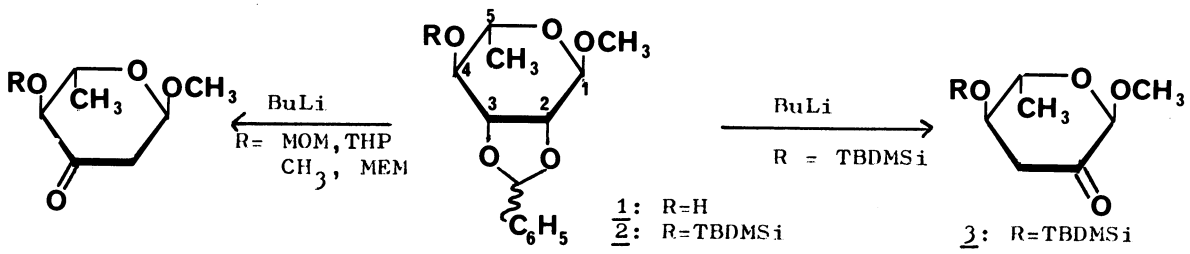
Application of the Klemer-Rodemeyer fragmentation to a 4-O-silicon substituted rhamnose benzylidene acetal leads to "inverse opening" of the dioxolane ring, thus opening a new route to 2-amino-2,3,6-trideoxy-L-hexoses.

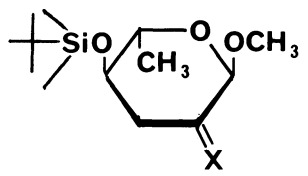
Base-induced decomposition of benzylidene acetals (the Klemer-Rodemeyer fragmentation) [1] has been shown in the L-rhamnose series to allow rapid access to various important nitrogen-containing carbohydrates such as daunosamine, evernitrose, ristosamine, vancosamine and acosamine. [2] It has been demonstrated [3] by enolate trapping experiments that proton abstraction at C-3 initiates this fragmentation. During the course of another project aimed at transferring L-rhamnose chirality to obtain optically active beta-lactams, [4] it turned out that protection of the alcohol at C-4 as a silyl ether resulted in deoxygenation at C-3, a result which is opposite to those on record, [1-3,5,6] and which is the subject of the present communication.

The exo/endo mixture of acetals 1 [5] was silylated (TBDMSiCl-imidazole-DMF)[7] to afford 2 [8] in 79% yield. When applied to 2, the Klemer-Rodemeyer fragmentation [1] (5 equiv. of n-BuLi in THF at -40 °C) produced deoxygenation at C-3 to

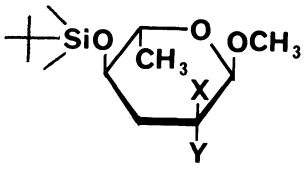


give 3, instead of the anticipated deoxygenation at C-2 which could not be detected. That in fact deoxygenation had occurred at C-3 was unambiguous : the ^{1}H NMR spectrum of the product showed a singlet for H-1 (δ = 4.55 ppm) instead of the doublet of doublet (or pseudo triplet) found for hexopyran-3-uloses. This was further confirmed when 3 was converted (NH_3OH^+, Cl^- ; 22% overall yield from 2) to a single easily purified oxime, 4 (δ_{H-1} = 4.85 ppm, singlet; ν_{OH} = 3380 and 3580 cm^{-1}; δ_{CH_2} = 33.5 ppm, $\delta_{C=NOH}$ = 158.7 ppm). Formation of such a 3-deoxy-rhamn-2-ulose, arising from deoxygenation at C-3, can be explained by proton abstraction at C-2. When compared with its carbon counterpart R_3C-O-, the lower

basicity of R_3Si-O- is certainly a factor; however the danger of deducing an overall effect from various components (inductive effect, hyperconjugation, d-orbitals participation) has been underlined as well. [9] It appears as if the bulkiness of the silyl moiety takes precedence over other considerations.



3: X=O
4: X=NOH
5: X=NOAc



6: X=NHCOCF$_3$, Y=H
7: X=H, Y=NHCOCF$_3$

The usefulness of this result can be demonstrated by the preparation of 2-amino-2,3,6-trideoxyhexopyranoses [10] as shown below. The oxime 4 was converted (Ac_2O-Pyr.; 84%) to its acetate 5 (δ_{COCH_3} = 2.15 ppm; δ_{CO} = 168.3 ppm), which was smoothly reduced with diborane [11] (10 equiv. at -70 °C for 2 h then RT for 20 h) to give compounds 6 and 7 in 54% overall yield after standard basic treatment and protection of the amine thus formed as its trifluoracetamide (ATFA-Pyr. at -20 °C). L-Ribo 6 (δ_{H-1} = 4.55 ppm, doublet J= 3.6 Hz) and L-Arabino 7 (δ_{H-1} = 4.44 ppm, singlet, $W_{1/2}$ = 3 Hz at 250 MHz) are formed in a 4 to 1 ratio; this outcome is intermediate between the enantiospecificity [12] and the non-discrimination [13] observed in similar reductions of 2-oximino carbohydrates.

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