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β-Oxy-α-Diazo Carbonyl Compounds. III. $Rh_2(AcO)_4$ Mediated Decomposition of β-Acetoxy-α-Diazo Esters. Application to the Synthesis of Natural 3-Deoxy-2-keto Aldonic Acids (KDO and DAH).

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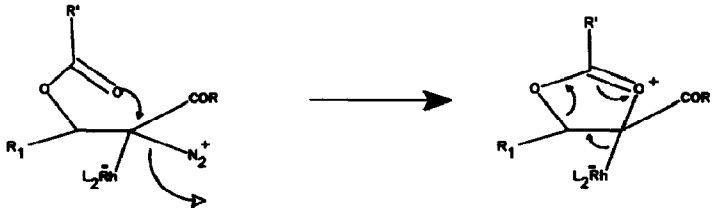
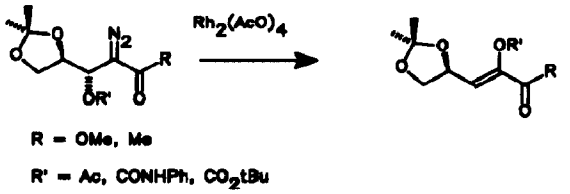
Abstract: β-Acetoxy-α-diazo esters yield α-enol acetate esters quantitatively by reaction with dirhodium tetraacetate. The reaction was used to prepare the major natural compounds 3-Deoxy-D-arabino-2-Heptulosonic acid (DAH, **1**) and 3-Deoxy-D-manno-2-Octulosonic acid (KDO, **2**) by conversion of the enol acetate function to the corresponding ketone.

β-Hydroxy-α-diazo carbonyl derivatives, readily available by aldol-like condensation of aldehydes or ketones with diazocarbonyl compounds in basic[1] or neutral media[2], allow attractive functionalization. Nevertheless, the primary synthetic application of these compounds is their conversion into the corresponding β-keto carbonyl compounds by photolysis[3] or rhodium catalysed decomposition[4]. Following previous studies on the chemistry of β-oxy-α-diazo carbonyl compounds[5] aimed at exploring the synthetic potential of these interesting derivatives, in this work we used the well-known Rhodium II- mediated rearrangement of β-acetoxy-α-diazo esters[6] to synthesize the significant natural products 3-deoxy-D-manno-2-octulosonic acid (KDO) **2**, an essential component of the outer lipopolysaccharide membrane of all Gram-negative bacteria[7], and 3-deoxy-D-arabino-2-heptulosonic acid (DAH)[8] **1**, the first intermediate in the biosynthesis of aromatic aminoacids by the shikimate pathway in plants and bacteria. The synthesis of these products, particularly that of KDO, **2**, has aroused much interest in the last few decades[9] as a means for developing a new class of antibiotics against Gram-negative bacteria.

A plausible mechanism for the Rhodium II-catalysed decomposition of β-acyloxy-α-diazo carbonyl compounds, proposed by Ikota et al. for methyl 3-phenyl-3-benzoyloxy-2-diazo propionate[6], starts with the attack of the carbonyl group to the electrophilic metal-stabilized carbenoid to form a 5-member cyclic intermediate that is finally converted into enol carboxylate by carboxylate migration (Scheme 1). We extended this reaction to different carboxyl derivatives (acetates, carbonates and carbamates) and obtained a quantitative yield of the carboxyl rearranged compound in all cases.

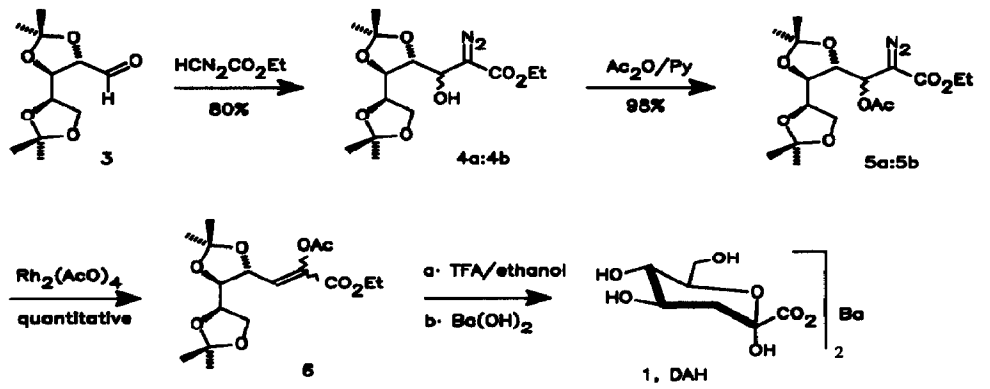
Scheme 1





This reaction was applied to the synthesis of the 3-deoxy-2-keto aldonic acids KDO and DAH. Firstly, reaction of 2,3:4,5-di-O-isopropylidene-D-arabino aldehyde **3**[10] with ethyl diazoacetate in the absence of solvent and catalyst provided the 3:2 diastereoisomer mixture of the corresponding β-hydroxy-α-diazo esters **4a:4b** in a 80%yield. The two diastereoisomers were separated by flash chromatography, which allowed structural assignment of the NMR spectra and elucidation of the absolute configuration at C-3 for each diastereoisomer[11]. Acetylation of the diastereoisomers (**4a:4b**) gave the acetyl derivatives (**5a:5b**). Rhodium-catalysed decomposition of **5a** gave the Z enol acetate **6** quantitatively and stereospecifically. The other diastereoisomer, **5b**, gave the corresponding E-**6** isomer. Acid hydrolysis of either Z-**6** or E-**6** with TFA led to DAH in a quantitative yield; the product was identified as its barium salt[12] (Scheme 2).

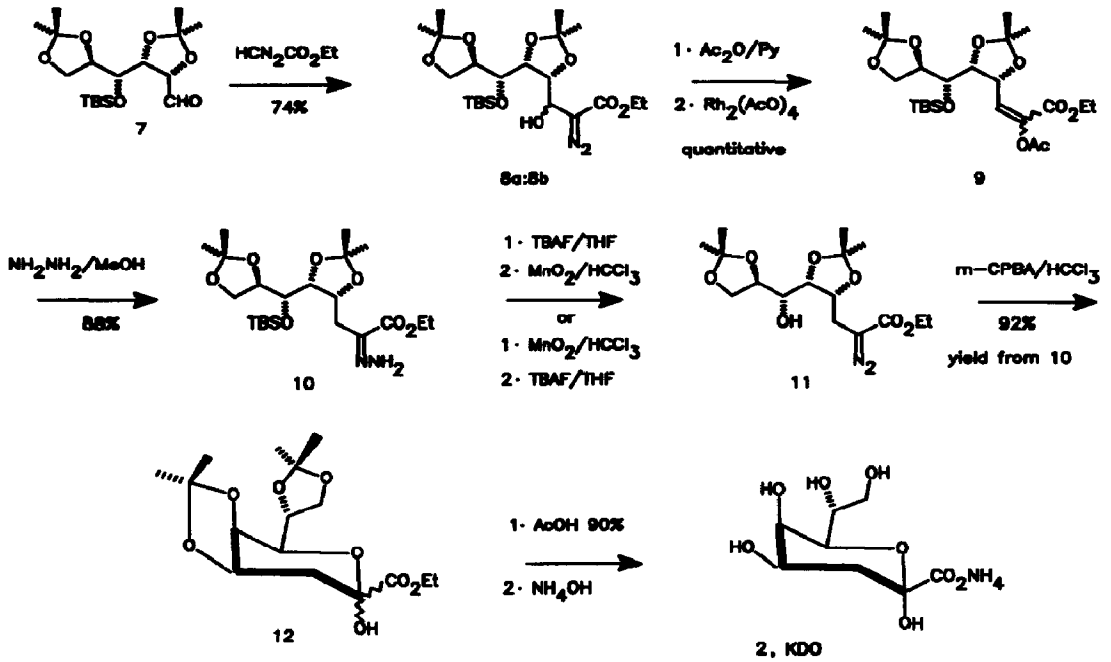
Scheme 2



For synthesizing KDO **2**, 2,3:5,6-di-O-isopropylidene-4-*tert*-Butyldimethylsilyl-D-manno aldehyde **7**[13] was condensed with ethyl diazoacetate as described above to obtain the 3.5:1 diastereoisomer mixture of β-hydroxy-α-diazo esters **8a:8b** in a 74% yield. Acetylation and rhodium decomposition afforded the Z:E enol acetates **9** in a quantitative yield. Conversion of the enol acetate to the corresponding ketone was accomplished by acid hydrolysis with TFA (as with **6**); however, a complex mixture was obtained from which KDO could not be detected by comparison with an authentic KDO sample[14]. This was ascribed to the well-known instability of KDO in acid media[15]. Also, conversion of the enol acetate to ketone by basic treatment (MeOH/KOH 0.1N) was similarly unsuccessful, probably due to the lack of stability of the ketone under the basic reaction conditions. Inclusion of an additional step allowed KDO to be prepared. Thus, treatment of **9** with 1M hydrazine in methanol gave the hydrazone **10**[16] (88% after purification), which was stable under the basic conditions used. This stability can be ascribed to the less marked acid character of the α-hydrogens to the hydrazone group relative to the ketone group, which avoids the side undesirable reactions observed in treating **9** with MeOH-KOH . Hydrolysis of *tert*-Butyldimethylsilane with TBAF in THF provided the corresponding 4-O-unprotected hydrazone in a quantitative yield . Cleavage of the hydrazone group by ozonolysis[17] gave a complex mixture of products including 50% of the pyranose **12**. Alternatively, the hydrazone was quantitatively oxidized to the 2-diazo ester **11** by activated manganese dioxide. This diazo compound was treated with m-CPBA in chloroform to give a high yield (92% from

10) of the anomeric mixture of the pyranose 12 . Similarly, the deprotection-oxidation reaction sequence (from 10 to 11) could be reversed with no yield loss. Finally, cleavage of acetals 12 (AcOH 90%, 90 ºC, 15 min.) and treatment with 30% ammonia of the resulting ester provided the ammonium salt of KDO[18] in quantitative yield (Scheme 3).

Scheme 3



In conclusion, the proposed synthetic method allows expeditious, ready synthesis of KDO and DAH . The yields of both 3-deoxy-2-keto aldonic acids are quite high and the reactions involved proceed under very mild conditions. Moreover, the condensation products 3-hydroxy-2-diazo esters 4, 8 and the 3-deoxy-2-diazo ester 11 are valuable compounds for the synthesis of KDO or DAH analogues.

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11. Epimer **4a**: $[\alpha]_D^{20}$ +3.6° ($CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ ppm: 4.72 (dd, 1H, $J_{3,4}$ = 4.5 Hz and $J_{3,OH}$= 6.1 Hz, H-3); 4.20 (q, 2H, J= 7.0 Hz, $-OCH_2-$); 4.13-4.02 (m, 2H, H-4, H-6); 4.00 (dd, 1H, J = 5.4 Hz, J = 8.5 Hz; H-5); 3.90 (dd, 1H, $J_{6,7}$= 4.2 Hz and $J_{7,7'}$= 8.1 Hz, H-7); 3.88 (dd, 1H, $J_{6,7'}$= 6.5 Hz and $J_{7,7'}$= 8.1 Hz, H-7'); 2.80 (d, 1H, $J_{3,OH}$= 6.1 Hz, -OH); 1.41 and 1.31 (2s, 6H, CMe_2); 1.36 (s, 6H, CMe_2); 1.24 (t, 3H, J = 7.0 Hz, $-CO_2CH_2\underline{CH_3}$). Epimer **4b**: $[\alpha]_D^{20}$ +6.6° ($CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ ppm: 4.67 (dd, 1H, $J_{3,4}$ = 6.3 Hz and $J_{3,OH}$= 2.5 Hz, H-3); 4.20 (q, 2H, J= 7.2 Hz, $-OCH_2-$); 4.19-4.03 (m, 3H, H-4, H-5, H-6); 3.96 (dd, 1H, $J_{6,7}$= 4.2 Hz and $J_{7,7'}$= 7.5 Hz, H-7); 3.74 (t, 1H, $J_{6,7'}$= 7.5 Hz and $J_{7,7'}$= 7.5 Hz, H-7'); 3.45 (d, 1H, $J_{3,OH}$= 2.5 Hz, -OH); 1.42, 1.37, 1.35 and 1.33 (4s, 12H, CMe_2); 1.25 (t, 3H, J = 7.2 Hz, $-CO_2CH_2\underline{CH_3}$). Elemental Analysis: Calcd for $C_{15}H_{24}O_7N_2$, 52.94% C, 7.05% H, 8.23% N; found: 52.64% C, 7.25% H, 7.63% N.
12. ^{1}H-NMR data of **1** (D_2O) δ ppm: 4.02-3.75 (m, 4H); 3.47 (m, 1H); 2.23 (dd, 1H, $J_{3e,3a}$= 13.1 Hz and $J_{3e,4}$=5.0 Hz, H-3e); 1.82 (dd, 1H, $J_{3a,3e}$= 13.1Hz and $J_{3a,4}$= 12.2 Hz, H-3a); ^{13}C-NMR (D_2O) δ ppm: 177.4 (C-1); 97.3 (C-2); 74.5, 71.4, 69.7 (C-4, 5, 6); 61.2 (C-7) and 40.0 (C-3). m. p. = 182 °C, $[\alpha]_D^{20}$ +33.3° (c 0.55, H_2O); lit[9a] m. p. = 185 °C, $[\alpha]_D^{20}$ +33.0° (c 1.0, H_2O).
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16. Product **10**: $[\alpha]_D^{20}$ -35.71° ($CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ ppm: 6.42 (w s, 2H, $=NNH_2$); 4.40 (ddd, 1H, $J_{4,3}$ = 1.6 Hz, $J_{4,5}$= 11.0 Hz and $J_{4,5}$ = 4.9 Hz, H-4); 4.25 (q, 2H, J = 7.1 Hz, $-OCH_2-$); 4.14 (dd, 1H, $J_{8,7}$ = 6.1 Hz and $J_{8,8'}$= 7.8 Hz , H-8); 4.08 (dt, 1H, $J_{7,6}$ = 6.1 Hz, $J_{7,8}$= 6.1 Hz and $J_{7,8'}$ = 7.8 Hz, H-7); 3.97 (dd, 1H, $J_{5,4}$ = 4.9 Hz and $J_{5,6}$= 8.9 Hz, H-5); 3.94 (dd, 1H, $J_{6,7}$ = 6.1 Hz and $J_{6,5}$= 8.9 Hz, H-6); 3.87 (t, 1H, $J_{8',7}$ and $J_{8,8'}$= 7.8 Hz, H-8'); 2.85 (dd, 1H, $J_{3,4}$ = 11.0 Hz and $J_{3,3'}$= 14.0 Hz, H-3); 2.74 (dd, 1H, $J_{3',4}$ = 1.6 Hz and $J_{3,3'}$= 14.0 Hz, H-3'); 1.56, 1.43, 1.37 and 1.29 (4s, 12H, CMe_2); 1.34 (t, 3H, J = 7.1 Hz, $-CO_2CH_2\underline{CH_3}$); 0.90 (s, 9H, $-OSi-C(CH_3)_3$); 0.12 (s, 6H, $-OSi(CH_3)_2$). Exact mass calcd for $C_{22}H_{42}O_7N_2Si$: 474.2761; found: 474.2824.
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18. NMR data were identical with commercially available KDO[14]. ^{1}H-NMR data of **2** (D_2O) δ ppm: 4.50-4.40 (m); 4.20 -3.97 (m); 3.94-3.76 (m); 3.73-3.55 (m); 2.60 (dd, J = 14.2 Hz and J = 6.7 Hz); 2.33 (m); 2.09-1.81 (m); ^{13}C-NMR (D_2O) δ ppm: 176.8 (C-1); 96.3 (C-2); 71.2, 69.3, 66.7, 66.3 (C-4, 5, 6,7); 63.1 (C-8) and 33.7 (C-3). m. p. = 121 °C, $[\alpha]_D^{20}$ +40.3° (c 0.57, H_2O); lit[15a] m. p. = 121-124 °C, $[\alpha]_D^{20}$ +40.3° (c 1.9, H_2O); lit.[9f] m. p. = 120-122 °C, $[\alpha]_D^{20}$ +38.7° (c 1.0, H_2O).

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