Stereoselective Synthesis of the α-Allyl *C*-Glycoside of 3-Deoxy-D-*manno*-2-octulosonic Acid (KDO) by Use of Radical Chemistry

Tommy Wåglund[a] and Alf Claesson[b,*]

[a] Department of Organic Pharmaceutical Chemistry, Uppsala Biomedical Center, University of Uppsala, S-751 23 Uppsala, Sweden and [b] R & D Laboratories, Astra Alab AB, S-151 85 Södertälje, Sweden

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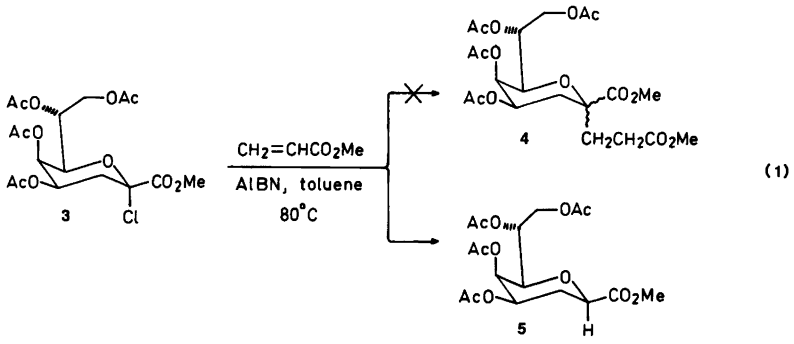
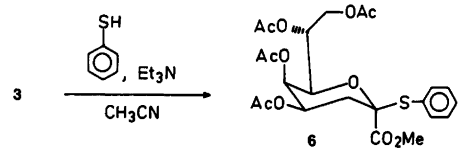
Methyl 2-*C*-allyl-2,6-anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*talo*-octonate (**9a**), the protected α-allyl *C*-glycoside of 3-deoxy-D-*manno*-2-octulosonic acid (KDO), has been synthesized using a photochemically initiated radical reaction. A phenyl thioglycoside (**8**) was used as the substrate and allyltributyltin as the acceptor. The stereoselectivity of the reaction was 90:10 in favour of the *talo*-isomer (α-).

We have been involved in the synthesis of derivatives of KDO (**1**, 3-deoxy-D-*manno*-2-octulosonic acid) in a search for agents which may be useful against infectious diseases caused by Gram-negative bacteria.[1] Many of these compounds were derived from KDO-β-pyranose by replacement of the anomeric hydroxy group with various substituents, in most cases resulting in the corresponding *C*-glycosides.[2] The preference for KDO-β-pyranose in the actual enzymatic reaction that we tried to influence has been demonstrated by ^{13}C NMR studies,[3] and was also indicated by the inhibitory activity of 2-deoxy-KDO-β-pyranose.[1c] In order to obtain β-*C*-glycosides of KDO we have already investigated an enolate alkylation reaction.[2] The lithium enolate of **2** was reacted with various electrophiles to give products (*C*-glycosides of KDO) with *galacto*:*talo* (β:α) ratios greater than 70:30, in most cases exceeding 90:10, i.e. fairly good stereoselectivity with predominantly the desired configuration.

In a different synthetic approach, the 2-chloro-2-deoxy-KDO derivative **3**[4] [eqn. (1)] was reacted with suitable nucleophiles, such as thiolates[5] or the enolate of dibenzyl malonate.[6] No products having the α-configuration were detected in these two reactions. In continuation of our investigations into new synthetic methods for *C*-glycosides of KDO we have explored the potential of C–C bond-forming radical reactions.[7] Glycosyl halides have been used



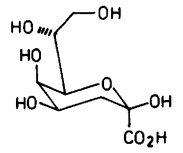
(1)



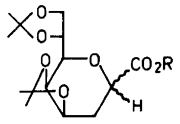
(2)

* To whom correspondence should be addressed at Astra Pain Control AB, S-151 85 Södertälje.

in such reactions with good results.[8] Particularly attractive was the potential application of this method to the readily available acetyl-protected compound **3** and the β-phenyl thioglycoside **6** [eqn. (2)]. Similar use of the isopropylidene-protected compound **8** [eqn. (4)] was expected to give indications of the influence of conformation on this reaction. By analogy with the corresponding *C*-glycosides compound **8** should prefer a skew-boat conformation,[9] which in turn should influence the stereoselectivity.



1 (β-KDO)



2 R = Me or Et

Results and discussion

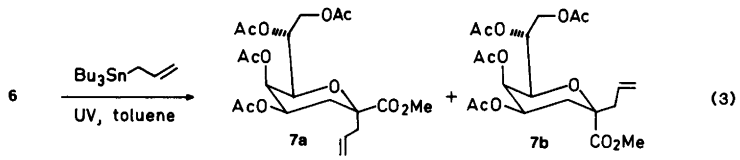
All attempts to transform **3** into **4** [eqn. (1)] failed. When AIBN was used as a radical initiator, methyl acrylate as an acceptor, and tributyltin hydride as a reducing agent, the main product was **5**.[2] Instead of reducing the intermediate radical formed after the addition step, tributyltin hydride reduced the original radical formed from **3**. Although the relative molar equivalents of tributyltin hydride and methyl acrylate were varied widely, compound **5** was always the main product. A minor amount of a glycal was also formed as a result of thermal elimination of HCl from **3**.

Reductive conditions were obviously not appropriate for our reaction system. Allyltributyltin may also be used as an acceptor in radical reactions.[10] In principle, this would eliminate the need for tributyltin hydride, since this avoids formation of an intermediate radical which must be reduced to give the product. However, in addition to acting as a reducing agent, tributyltin hydride also has an important function in the generation of radicals from the substrate.[7] It was therefore necessary also to change the method of radical initiation. Photochemical initiation has been reported for phenyl thioglycosides in this type of reaction,[10] and therefore we synthesized compound **6** [eqn. (2)] from benzenethiolate and **3**. Compound **6**, together with allyltributyltin, was then irradiated with UV light [eqn. (3)]. All phenyl thioglycoside was consumed within 10 h and compounds **7a** and **7b** were formed in moderate chemical yield (30%). The *talo*:*galacto* (α:β) ratio was found to be 50:50 by capillary gas chromatography.

Compound **8** was obtained from **6** by exchange of protecting groups [eqn. (4)].

The thioglycoside **8** was irradiated with UV light [eqn. (5)] under the same conditions as used for **6**, to give compounds **9a** and **9b** with a *talo*:*galacto* (α:β) ratio of 90:10. The determination of the absolute configuration of compounds **9a** and **9b** was based on spectral comparison with the corresponding ethyl ester **10** of known β-configuration, prepared by the enolate alkylation method mentioned previously.[2] The C-2 configuration of compounds **7a** and **7b** was assumed from their behaviour on TLC and GC, which was similar to that of analogous compounds synthesized in our laboratories.

In the above reactions we made the interesting observation that it was possible to increase the stereoselectivity by substituting isopropylidene groups for acetyl groups. This is clearly a conformational effect due to the probable locking of **8** into a skew-boat conformation ($B_{3,6}$ + $^{O}S_{3}$),[9] which might be maintained in the radical. The biologically desired β-configuration was, however, not favoured. Radical reactions reported[8,10,11] for carbohydrate-derived systems seem to have given predominantly the α-configuration. However, the substrates in such reactions usually did not have isopropylidene protecting groups, and a further difference



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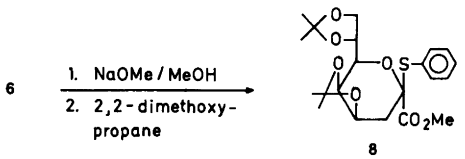
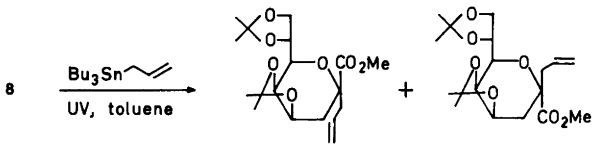


(4)



(5)

is the presence of a 2-hydroxy group in ordinary sugars. In addition, there are no reports involving carbohydrates with a carboxylic group attached to the radical (and anomeric) centre, hence direct comparisons may be misleading.

The chemical yield was moderate, but in the same range as that often obtained in the enolate alkylation procedure.[2] If it proves possible to apply the radical reaction using more functionalized acceptors than allyltributyltin and still retain the chemical yield, this method may have some advantages in the synthesis of KDO analogues compared with the other methods previously mentioned. This is even true when the β-configuration is desired (using acetyl protecting groups). In the enolate reaction it proved necessary to use relatively reactive electrophiles for any reaction to occur at all[2] and in the route involving nucleophilic substitution of the KDO-chloride **3**, the competing elimination reaction limited the choice of suitable nucleophiles. Since the linking of a readily transformable allylic group to the anomeric carbon of sugars has proved to be an important tool in synthesis,[7] the radical method complements the enolate alkylating procedure in the synthesis of novel KDO derivatives.

Experimental

General. NMR spectra were recorded with a JEOL FX90Q instrument using $CDCl_3$ as the reference (δ_H 7.25 and δ_C 77.10 ppm). Coupling constants were measured in Hz. High resolution FAB-MS was performed with a JEOL DX-303 instrument. GC analyses were performed at 250 °C using a Carlo Erba Strumentazione GC 6000 Vega Series equipped with a 25 m SE 52 capillary column. TLC was performed on Merck silica gel 60 F_{254} aluminium sheets and spots were detected with UV light and/or by charring with sulfuric acid. Column chromatography was performed on Merck silica gel 60 (0.040–0.063 mm). A Hanovia 6515–34 photochemical immersion lamp (UV) was used in the photochemical radical initiations.

*Methyl 4,5,7,8,-tetra-*O*-acetyl-2,3-dideoxy-2-phenylthio-*β*-*D*-manno-octulosonate* (**6**). A mixture of compound **3** (1.41 g, 3.22 mmol), thiophenol (0.36 ml, 3.54 mmol), and Et_3N (0.54 ml, 3.87 mmol) was stirred in 50 ml of MeCN under a N_2 atmosphere for 1 h. After concentration, the residue was purified on a silica gel column (Et_2O–pentane 3:1) to give 1.13 g (69 %) of **6**: ^1H NMR ($CDCl_3$) δ 1.95–2.37 (m, 13 H, acetyl methyls, $H3_{ax}$), 2.60 (dd, 1 H, $^2J_{3eq,3ax}$ −12.3, $^3J_{3eq,4}$ 5.2, $H3_{eq}$), 3.53 (s, 3 H, OCH_3), 3.81–5.33 (m, 6 H, H4, H5, H6, H7, H8, H8′), 7.25–7.61 (m, 5 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 20.69 (acetyl methyls, overlapping signals), 32.05 (C3), 52.69 (OCH_3), 62.71 (C8), 63.76, 65.85, 67.30, 67.80 (C4–C7), 87.69 (C2), 128.57, 128.77, 130.01, 136.39 (aromatic), 168.00, 169.69, 169.84, 170.44, 170.54 (carbonyls); FAB-MS, $(M-H)^-$ at *m/z* 511.1269 (Calcd. 511.1274).

*Methyl 4,5,7,8-tetra-*O*-acetyl-2-*C*-allyl-2,6-anhydro-3-deoxy-*D*-glycero-*D*-talo-* and *D*-galacto-*octonate* (**7a,b**). The thioglycoside **6** (0.08 g, 0.16 mmol), and allyltributyltin (0.10 ml, 0.32 mmol) were stirred in toluene (N_2) and irradiated overnight with UV light. The solution was then concentrated and the residue purified on a silica-gel column (Et_2O–pentane 3:1) to give **7a** and **7b** in equal amounts (chemical yield 33 %). **7a**: ^{1}NMR ($CDCl_3$) δ 1.87–2.28 (m, 14 H, acetyl methyls, $H3_{ax}$, $H3_{eq}$), 2.52 (dd, 1 H, H1′), 2.82 (dd, 1 H, H′1′), 3.75 (s, 3 H, OCH_3), 3.84–5.93 (m, 9 H, H4, H5, H6, H7, H8, H8′, vinylic); ^{13}C NMR ($CDCl_3$) δ 20.77, 20.87 (acetyl methyls, overlapping signals), 30.69 (C3), 36.55 (C1′), 52.57 (OCH_3), 62.49 (C8), 64.44, 66.78, 68.03, 68.68 (C4–C7), 80.94 (C2), 119.22 (C3′), 131.09 (C2′), 169.72, 170.17, 170.57 (carbonyls, overlapping signals); FAB-MS, $(M+H)^+$ at *m/z* 445.1696 (Calcd. 445.1710). **7b**: ^1H NMR ($CDCl_3$) δ 1.83–2.22 (m, 14 H, acetyl methyls, $H3_{ax}$, $H3_{eq}$), 2.38–2.57 (m, 2 H, allylic), 3.74 (s, 3 H, OCH_3), 3.90–6.00 (m, 9 H, H4–H8, H′8, vinylic); ^{13}C NMR ($CDCl_3$) δ 20.92 (acetyl methyls, overlapping signals), 31.64 (C3), 44.45 (C1′), 52.47 (OCH_3), 62.79 (C8), 64.59, 67.63, 68.13, 71.02 (C4–C7), 80.94 (C2), 119.32 (C3′), 131.14 (C3′), 169.77, 169.97, 170.07, 170.57, 170.82 (carbonyls); FAB-MS, $(M+H)^+$ at *m/z* 445.1689 (Calcd. 445.1710).

*Methyl 2,3-dideoxy-4,5:7,8-di-*O*-isopropylidene-2-*C*-phenylthio-*β*-*D*-manno-octulosonate* (**8**). Compound **6** was treated with NaOMe (from 0.15 g Na, 6.62 mmol) for 2 h. The mixture was neutralized with Dowex H^+ ion exchange resin, filtered, and concentrated. The residue was dissolved in acetone and 2,2-dimethoxypropane (0.76 g, 2.21 mmol) and *p*-toluenesulfonic acid (catalytic) were added to the solution, which was stirred for 1 h. The sulfonic acid was neutralized with Et_3N and the mixture was filtered through a short (2 cm) silica gel column (Et_2O), and concentrated. The residue was then chromatographed on a silica gel column (Et_2O–pentane 3:1) to give 0.81 g (86 %) of pure **8**: ^1H NMR ($CDCl_3$) δ 1.20–1.75 (m, 12 H, isopropyl methyls), 2.18 (dd, 1 H, $^2J_{3ax,3eq}$ −14.5, $^3J_{3ax,4}$ 6.4, $H3_{ax}$), 2.49 (dd, 1 H, $^3J_{3eq,4}$ 4.9, $H3_{eq}$), 3.48 (m, 4 H, methyl ester, H6), 4.00–4.55 (m, 5 H, H4, H5, H7, H8, H′8), 7.25–7.62 (m, 5 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 25.36, 26.00, 27.00, 27.40 (isopropyl methyls), 34.13 (C3), 52.32 (OCH_3), 67.13, 70.37, 70.72, 73.86, 74.81 (C4–C7), 86.32 (C2), 109.45, 109.85 [$C(CH_3)_2$], 128.45, 129.44, 130.34, 136.02 (aromatic), 169.48 (carbonyl); FAB-MS, $(M^+H)^+$ at *m/z* 425.1591 (Calcd. 425.1634).

*Methyl 2-*C*-allyl-2,6-anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-*D*-glycero-*D*-talo-* and *D*-galacto-*octonate* (**9a,b**). The thioglycoside **6** (0.33 g, 0.79 mmol) and allyltributyltin (0.49 ml, 1.58 mmol) were stirred in toluene (N_2) and irradiated with UV light overnight. The mixture was concentrated and the residue was purified on a silica gel

column (Et_2O–pentane 3:1) giving **9a** as the major product (chemical yield 30%). **9a**: ^1H NMR ($CDCl_3$) δ 1.18–1.50 (m, 12 H, isopropylidene methyls), 1.75 (dd, 1 H, $^2J_{3ax,3eq}$ −15.4, $^3J_{3ax,4}$ 2.1, $H3_{ax}$), 2.21–2.50 (m, 2 H, 2-methylene), 2.70 (dd, 1 H, $^3J_{3eq,4}$ 3.3, $H3_{eq}$), 3.32 (dd, 1 H, $^3J_{6,5}$ 1.7, $^3J_{6,7}$ 7.9, H6), 3.68 (s, 3 H, methyl ester), 3.89–4.59 (m, 6 H, H4, H5, H7, H8, H'8), 4.90–6.00 (vinylic); ^{13}C NMR ($CDCl_3$) δ 24.66, 25.01, 25.21, 27.15 (isopropylidene methyls), 31.69 (C3), 43.60 (C1'), 52.08 (OCH_3), 67.28 (C8), 69.97, 72.32, 72.46, 74.01 (C4–C7), 109.25, 109.50 [$C(CH_3)_2$], 80.54 (C2), 119.22 (C3'), 131.68 (C2'), 174.06 (carbonyl); FAB-MS, $(M+H)^+$ at *m/z* 357.1930 (Calcd. 357.1913). **9b**: mixture together with analogous glycal; FAB-MS, $(M^+H)^+$ at *m/z* 357.1923 (Calcd. 357.1913).

*Ethyl 2-*C*-allyl-2,6-anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-*D*-glycero-*D*-galacto-octonate* (**10**). This reference compound was prepared using the enolate alkylating method described in Ref. 3: ^1H NMR: ($CDCl_3$) δ 1.11–1.56 (m, 15 H, isopropylidene methyls, ethyl ester methyl), 1.93–2.09 (m, 2 H, $H3_{ax}$, $H3_{eq}$), 2.45 (ddt, 1 H, $^2J_{H1',H'1'}$ −13.8, $^3J_{H1',H2'}$ 7.9, $^4J_{H1',H-H'3'}$ 1.0, H1'), 2.77 (ddt, 1 H, $^3J_{H'1',H2'}$ 6.3, $^4J_{H'1',H-H'3'}$ 1.2, H'1'), 3.35 (dd, 1 H, $^3J_{6,5}$ 1.8, $^3J_{6,7}$ 7.9, H6), 3.98–4.60 (m, 7 H, H4, H5, H7, H8, H'8, ethyl ester methylene), 4.85–6.00 (m, 3 H, vinylic); ^{13}C NMR ($CDCl_3$) δ 14.39 (ethyl ester methyl), 25.31, 25.45, 26.95, 27.15 (isopropylidene methyls), 31.19 (C3), 44.90 (C1'), 61.10 (ethyl ester methylene), 67.03 (C8), 70.87, 71.67, 73.76, 73.91 (C4–C7), 80.54 (C2), 109.25 [$C(CH_3)_2$, overlapping signals], 118.43 (C3'), 132.34 (C2'), 173.26 (carbonyl); FAB-MS: it was not possible to separate the molecular ion from the matrix (PEG).

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