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LETTERS

General Syntheses of Ethyl 2-Ulosonates and 3-Deoxy-D-*manno*-oct-2-ulosonic Acid from Carbohydrate Lactones with 1-Ethoxyvinyllithium

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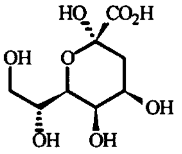
Abstract: Reactions of 1-ethoxyvinyllithium with isopropylidene or benzyl protected sugar lactones afforded the corresponding hemiacetals which, on ozonolysis, gave the ethyl 2-ulosonates. This allowed a rapid and efficient synthesis of 3-deoxy-D-*manno*-oct-2-ulosonic acid (KDO).

The 3-deoxy-D-*manno*-oct-2-ulosonic acid (KDO) **1** is an essential constituent of lipopolysaccharides (LPS) and acidic exopolysaccharides (K antigens) found in the cell surface of Gram-negative bacteria.[1] The incorporation of KDO is essential if cell growth is to occur in the bacteria. Thus the design and synthesis of potential inhibitors of lipopolysaccharide biosynthesis based upon analogues of KDO has attracted much attention, as has the synthesis of KDO itself.[2] Another ulosonic acid, 3-deoxy-D-*arabino*-hepta-2-ulosonic acid (DAH) **2**, plays an important role in the biosynthesis of amino acids in plants and micro-organisms as a key intermediate in the shikimate pathway.[3] It is therefore not surprising that these structures have invoked immense interests from both biological and synthetic standpoints.



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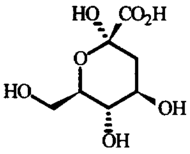

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As part of an ongoing programme to study the shikimate pathway, in particular, the syntheses of key biosynthetic intermediates and their analogues from carbohydrates,[4] we wished to develop a general strategy for the synthesis of a range of 2-ulosonic acids.

Since the first report on the alpha lithiation of ethyl vinyl ether,[5] the 1-alkoxyvinyllithium reagents have been employed in 1,2 and 1,4-addition reactions,[6] as well as for natural product syntheses.[7] As a result of this we were attracted to the use of 1-ethoxyvinyllithium,[8] because it is an ideal acyl anion equivalent that is easy to prepare and the precursor, ethyl vinyl ether, is available in commercial quantities. Combination of the reactivity of 1-ethoxyvinyllithium with readily available sugar lactones thus provides a concise and highly attractive approach to the synthesis of 2-ulosonic acids. In this letter we report on our findings employing this strategy.

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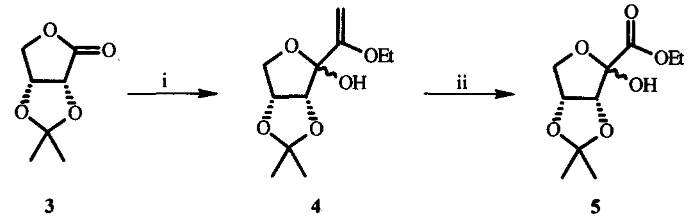
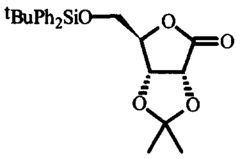
Our initial studies centred on the addition of 1-ethoxyvinyllithium to 2,3-*O*-isopropylidene-D-erythrono-1,4-lactone **3**[9] and the subsequent ozonolysis. The reaction of lactone **3** with 1-ethoxyvinyllithium proceeded smoothly in THF at −78 °C to furnish the hemiacetal **4** as an anomeric mixture in 83% yield.[10] Ozonolysis of lactol **4** in mixed solvents of dichloromethane and ethanol at −78 °C afforded the ethyl D-*erythro*-pent-2-ulosonate **5** in 88% yield (scheme 1).



Scheme 1 *Reagents and conditions:* i, 1-ethoxyvinyllithium, THF, −78 °C (83%); ii, O_3, CH_2Cl_2, EtOH, −78 °C; then Me_2S (88%)



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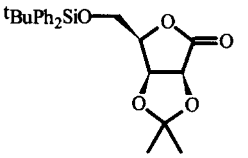

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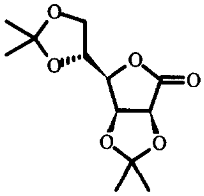

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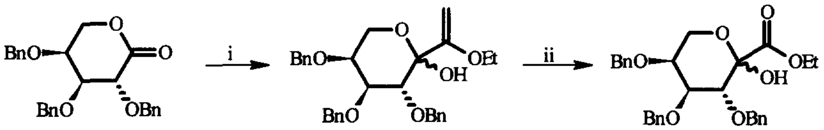
Following this success, we investigated the reactions of 1-ethoxyvinyllithium with isopropylidene protected furanonolactones **6**,[11] **7**[12] and **8**.[13] Thus 1-ethoxyvinyllithium readily added to the lactones **6**, **7**, and **8** and the resulting hemiacetals were converted to the corresponding ethyl ulosonates. The hemiacetals derived from these lactones proved somewhat labile towards chromatography on silica gel. However, in all cases they were successfully isolated when the silica gel was deactivated with triethylamine and the chromatography was conducted rapidly. Subsequent cleavage of the double bond in the hemiacetals with ozone furnished the corresponding ethyl ulosonates as anomeric mixtures (Table 1).



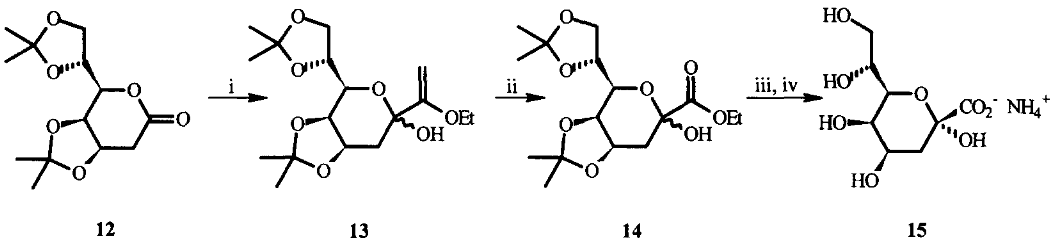
Scheme 2 *Reagents and conditions:* i, 1-ethoxyvinyllithium, THF, −78 °C (67%); ii, O_3, CH_2Cl_2, EtOH, −78 °C; then Me_2S (74%)

Attention was then turned to the six-membered pyranonolactones. Treatment of 2,3,4-tri-*O*-benzyl-L-arabinono-1,5-lactone **9**[14] with 1-ethoxyvinyllithium in THF at −78 °C afforded the hemiacetal **10** in 67% yield as a mixture of anomers. Ozonolysis of **10** proceeded uneventfully and gave the ethyl ulsonate **11** in 74% yield with the β-anomer as the major isomer.

Table 1

Lactone	Yield of hemiacetal (%)	Yield of ethyl 2-ulosonate (%)
3	D-*erythro* hemiacetal **4** (83)	D-*erythro* 2-ulosonate **5** (88)
6	D-*ribo* hemiacetal (84)	D-*ribo* 2-ulosonate (80)
7	D-*lyxo* hemiacetal (85)	D-*lyxo* 2-ulosonate (85)
8	D-*manno* hemiacetal (86)	D-*manno* 2-ulosonate (84)
9	L-*arabino* hemiacetal (67)	L-*arabino* 2-ulosonate (74)

Application of this strategy to the pyranonolactone **12**[2h] gave the corresponding hemiacetal **13** in 60% yield. Cleavage of the double bond in compound **13** with ozone afforded the ester **14**[2d] (84% yield), $[\alpha]_D$ +49.4 (c 0.57, $CHCl_3$). Deprotection of ethyl ulosonate **14** with aqueous trifluoroacetic acid, followed by treatment with aqueous ammonia gave the ammonium KDO **15**, the spectral and physical properties of which were in excellent agreement with those reported in the literature.[2g,2j,15]



Scheme 3 *Reagents and conditions:* i, 1-ethoxyvinyllithium, THF, −78 °C (60%); ii, O_3, CH_2Cl_2, EtOH, −78 °C; then Me_2S (84%); iii, aq. TFA (10%), 80 °C, 30 min; iv, aq. NH_3

In summary, we have demonstrated that 1-ethoxyvinyllithium adds to a wide range of sugar derived lactones in an efficient manner and this strategy provides ready access to ulosonic acids in a short number of steps.

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10. All new compounds gave satisfactory spectral and microanalytical data. Selected data: **5**: Anomeric mixture (4:1); $[\alpha]_D$ −80.5 (c 3.18, $CHCl_3$); ν_{max}(neat film) 3432, 1743 cm^{-1}; δ_H (270 MHz) 1.34 (3H, t, *J* 7.25 Hz, major), 1.35 (3H, appt, *J* 7.25 Hz, minor), 1.30(3H, s, major), 1.40 (3H, s, minor), 1.45 (3H, s, major), 1.58 (3H, s, minor), 4.11 (1H, appdd, minor), 4.14 (1H, dd, *J* 10.56, 3.3 Hz, major), 4.30 (2H, q, *J* 7.26 Hz, major), 4.32 (2H, q, *J* 7.25 Hz, minor), 4.39 (1H, d, 1.98 Hz, minor, OH), 4.43 (1H, bs, OH), 4.68 (1H, d, *J* 5.94 Hz, major), 4.79 (1H, d, *J* 5.93 Hz, minor), 4.90 (1H, ddd, *J* 5.92, 3.93, 3.3 Hz, major, minor); δ_C (67.8 MHz) *major anomer* 13.94, 24.82, 25.81, 62.04, 72.17, 79.81, 86.69, 103.95, 113.15, 168.31; *minor anomer* 13.86, 24.74, 25.92, 61.96, 70.03, 80.01, 80.18, 103.95, 113.96, 168.45; m/z HRMS (CI, NH_3), Found MNH_4^+, 250.1291, $C_{10}H_{20}NO_6$ requires *MNH_4*, 250.1291. **13**: mixture of anomers; ν_{max}(neat film) 3498, 1612 cm^{-1}; δ_H (270 MHz) 1.14-1.57 (15H, m), 2.03-2.26 (2H, m), 3.09-3.39 (1.7H, m), 3.40-3.53 (0.3H, m), 3.60-3.80 (2H, m), 3.81-4.07 (3H, m), 4.08-4.22 (0.4H, m), 4.23-4.54 (2H, m), 4.56-4.77 (1H, m), 5.03-5.20 (0.6H, m); δ_C (67.8 MHz) *major anomer* 157.14, 109.07, 109.01, 95.60, 76.33, 75.55, 72.87, 69.95, 66.42, 63.60, 31.91, 26.56, 26.27, 25.14, 24.21, 14.04; *minor anomer* 162.00, 109.01, 107.43, 95.60, 74.05, 73.50, 72.54, 71.33, 67.05, 62.95, 33.59, 26.88, 25.92, 25.05, 24.07, 14.18; m/z HRMS (CI, NH_3), Found MH^+,.345.1913 $C_{17}H_{29}O_7$ requires *MH*, 345.1913. **14**: $[\alpha]_D$ +49.4 (c 0.57, $CHCl_3$); ν_{max}(neat film) 3397, 1743 cm^{-1}; δ_C (67.8 MHz) *major anomer* 13.92, 25.29, 26.82, 26.96, 32.31, 66.19, 66.74, 69.86, 70.50, 71.25, 73.90, 94.32, 109.11, 109.28, 169.62; *minor anomer* 14.03, 24.18, 25.00, 25.29, 25.98, 30.89, 61.88, 67.07, 70.61, 72.28, 73.27, 73.81, 95.48, 109.28, 109.48, 169.62; m/z HRMS (CI, NH_3), Found MNH_4^+, 364.1971, $C_{16}H_{30}NO_8$ requires *MNH_4*, 364.1971.
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