β-Oxy-α-diazo-carbonyl compounds. Part 5: An improved synthesis of β-hydroxy-α-diazo esters derived from monosaccharides and synthetic applications in the chemistry of 3-deoxy-2-ulosonic acids

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Abstract—Reactions of ethyl 2-diazoacetate with aldehydo sugars and monosaccharide derivatives in their hemiacetal form are reported. The use of diethyl zinc led to an improvement of yields and shorter reaction times compared with neutral conditions as previously described. The resulting products represent potentially useful substrates for the synthesis of 3-deoxy-2-keto-ulosonic acid derivatives. Thus, diazo derivatives from D-mannose were transformed into Ko and 3-epimer Ko derivatives in a straightforward process by reaction with *m*CPBA. © 2001 Published by Elsevier Science Ltd.

The chemistry of α-diazo carbonyl compounds has elicited great interest in the chemical community as evident by their long history of useful applications in organic chemistry[1] and, more recently, by the many efforts devoted to their reactions with transition metals.[2] The ease of preparation of these compounds[3] from readily accessible precursors, in conjunction with the wide variety of chemical transformations they effect, justifies the flurry of research activity in this field. Particularly, β-hydroxy-α-diazo carbonyl compounds, synthesized by reactions of diazo carbonyl compounds with aldehydes under basic conditions,[4] represent versatile and useful compounds whose chemistry has been widely explored.[5] Our interest for developing new synthetic strategies for the construction of complex sugar derivatives with potential biological interest, prompted us to study the synthesis and reactivity of β-hydroxy-α-diazo carbonyl compounds derived from monosaccharides,[6] finding interesting applications in the stereoselective synthesis of macrolide fragments,[7] 3-deoxy-2-ulosonic acids[8] and, more recently, in the synthesis of C-disaccharides.[9] We demonstrated that the use of base in these reactions produced the epimerization of the starting aldehydo-sugars at C-2.[10] As a consequence, β-oxy-α-diazo carbonyl compou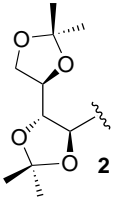nds were synthesized in t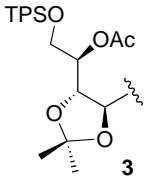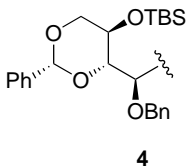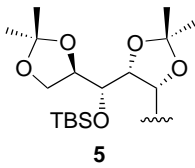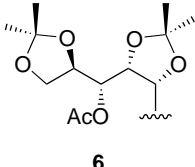he absence of base by a simple neat mixture of the corresponding aldehydo-sugar and ethyl diazoacetate. In general, the high reactivity of the employed starting aldehydo-sugars made it unnecessary to use base and products were obtained in good yield, however, in some cases, long reaction times were required resulting in a decrease of the yield (see Table 1). The use of organometallic derivatives of diazo carbonyl compounds as efficient reagents for reactions with carbonyl compounds is well known.[11] However, such derivatives have shown thermal instability and require the use of very low temperatures, which has limited their utility. Recently, a publication has appeared describing the use of commercially available diethyl zinc to form a more reactive zinc–diazo intermediate[12] which reacted smoothly with aldehydes. Therefore, in order to avoid the basic medium of other methods and enhance the reactivity of the diazo compounds, we decided to use diethyl zinc in equimolar amounts with respect to ethyl diazoacetate **1** (Scheme 1) and investigate its reaction with different aldehydo-sugars to improve yield and stereoselectivity.

Our interest in the chemistry and biology of natural 3-deoxy-2-ulosonic acids such as 3-deoxy-D-*arabino*-2-heptulosonic acid (DAH)[13] or 3-deoxy-D-*manno*-2-octulosonic acid (KDO)[14] led us to devise efficient and flexible syntheses of these compounds.[8] So, as a continuation of our research project engaged in the chemistry of these type of natural products, we considered D-*ara*-
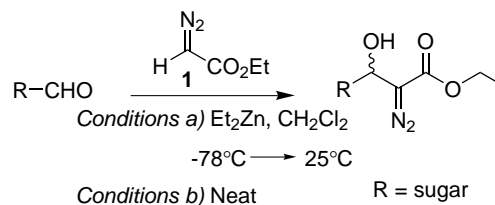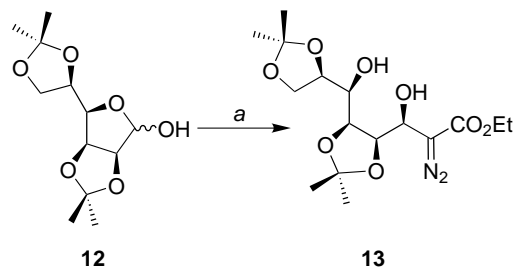
Table 1. Reactions of diazo compound **1** with aldehydo-sugars **2**, **3**, **4**, **5** and **6**

R	Product	Conditions **a** (reaction time/h, yield/%)	Conditions **b** (reaction time/h, yield/%)	Stereoselectivity at C-3 (3R:3S)
2	**7**	12, 85	12, 80	3:2
3	**8**	8, 80	2–4 days, 52	1:1
4	**9**	8, 84	7 days, 30	4:1
5	**10**	8, 94	7 days, 74	3.5:1
6	**11**	6, 85	8, 98	100:0

bino- and D-*manno*-aldehydes as starting materials for reactions with ethyl diazoacetate **1**. Table 1 summarizes the results obtained from these studies. Thus, D-*arabino*-aldehydo derivatives **2**, **3**,[15] **4** and D-*manno*-aldehydo sugars **5** and **6** were reacted with ethyl diazoacetate **1** in the presence of equimolar amounts of diethylzinc[16] at −78°C. After 6–12 h, reaction products **7**, **8**, **9**, **10** and **11**[17] were obtained in excellent yields and identical stereoselectivities as compared with reactions undertaken under neutral conditions. In particular, for the D-*arabino* series, the yields were widely improved when Et$_2$Zn was used in comparison with neutral conditions. In the case of the D-*manno* derivatives, the aldehyde **5** yielded the corresponding β-oxy-α-diazo ester **10** in better yield under neat conditions, while with aldehyde **6**, the yield decreased under conditions **a** versus conditions **b**.

These results prompted us to consider sugars in their hemiacetal forms for reactions with diazo compounds, which to our knowledge had not been attempted (Scheme 2). Thus, the mannofuranose derivative **12** was treated with **1** under similar conditions as above, and, after 12 h, just one isomer, the diazo **13** was obtained in a reasonably good yield (60%) together with starting sugar after flash column chromatography.
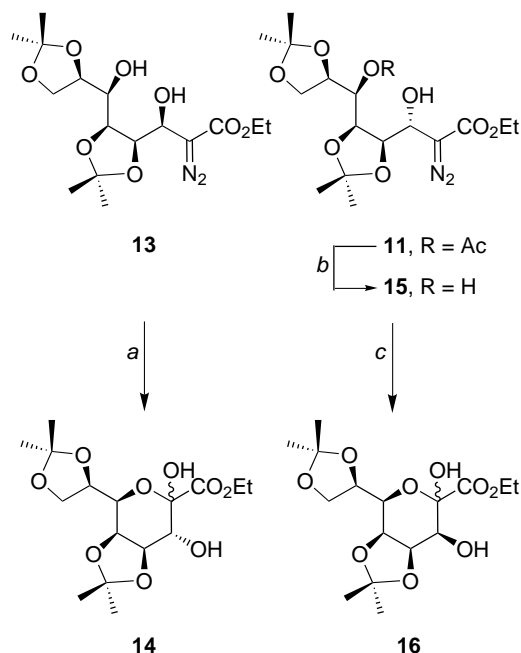
Scheme 1. General reaction of **1** with aldehydes.

Scheme 2. Synthesis of diazo derivative **13** from di-*O*-iso-propylidene-D-mannofuranose **12**. *Reagents and conditions*: (a) 1.5 equiv. HCN$_2$CO$_2$Et, 1.5 equiv. Et$_2$Zn, CH$_2$Cl$_2$, −78°C→−50°C→0°C, 8 h, 60%.

The stereochemistry of product **13** was determined by transformation of diazo **13** to the epimer-Ko derivative **14**, reported in the literature,[18] by reaction with *m*CPBA. On the other hand, diazo compound **11**, whose stereochemistry at C-3 was already known,[8c] was transformed into the diol **15**, whose NMR spectra was not identical to that of **13**.[19] Similarly for **13**, **15** was transformed into the Ko derivative **16** by treatment with *m*CPBA in 92% yield (Scheme 3). Both Ko derivatives **14** and **16**[20] represent versatile and useful intermediates for the synthesis of oligosaccharides containing Ko units,[21] which have recently been isolated from the exopolysaccharides of bacteria.[22]

In conclusion, an efficient and high yielding synthesis of β-hydroxy-α-diazo esters derived from monosaccharides is reported by reaction of ethyl 2-diazoacetate **1** in the presence of equimolar amounts of diethyl zinc. These reactions proved to be highly efficient even in large

scale (∼10 g scale of starting aldehydes). The resulting products are of interest as intermediates for the synthesis of natural DAH and KDO, for the synthesis of Ko derivatives and for the synthesis of other analogues as is reported in the following publication.[23]

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Scheme 3. Syntheses of Ko derivatives **14** and **16**. *Reagents and conditions:* (a) 1.5 equiv. *m*CPBA, CH$_2$Cl$_2$, 0°C→25°C, 1 h, 94%; (b) 1.2 equiv. NaMeO, MeOH, 25°C, 0.5 h, 95%; (c) 1.5 equiv. *m*CPBA, CH$_2$Cl$_2$, 0°C→25°C, 1 h, 92%.

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16. Diethyl zinc (1 M) in hexanes is commercially available from ALDRICH.

17. Diazo compounds **7**, **10** and **11** have already been described in the literature (see Ref. 10 for **7** and Ref. 8c for **10** and **11**). Product **8** (more polar isomer): $R_f = 0.75$ (silica gel, 25% EtOAc in hexanes); IR (thin film) v_{max} (cm^{-1}) 3430, 3050, 2957, 2865, 2109, 1737, 1653, 1390, 1256; ^{1}H NMR (400 MHz, CDCl$_3$) δ more polar isomer: 7.65–7.50 (m, 4H, SiPh$_2$), 7.45–7.30 (m, 6H, SiPh$_2$), 4.66 (d, $J = 4.5$ Hz, 1H, CH(OH)CN$_2$), 4.20–4.05 (m, 4H), 3.83–3.77 (m, 2H), 3.72 (dd, $J = 6.0$, 3.5 Hz, 1H), 3.60 (bs, 1H, OH), 3.05 (bs, 1H, OH), 1.30 (s, 3H, C(CH$_3$)$_2$), 1.24 (s, 3H, C(CH$_3$)$_2$), 1.19 (t, $J = 7.5$ Hz, 3H, CO$_2$CH$_2$CH_3), 0.99 (s, 9H, SiC(CH$_3$)$_3$); ^{13}C NMR (50.3 MHz, CDCl$_3$) δ 167.3, 135.4, 129.8, 127.6, 109.8, 81.6, 78.2, 72.9, 67.9, 65.8, 64.8, 60.8, 29.7, 26.7, 25.4, 19.1, 14.3; (less polar isomer): 7.71–7.62 (m, 4H, SiPh$_2$), 7.38–7.28 (m, 6H, SiPh$_2$), 4.51 (d, $J = 6.3$ Hz, 1H, CH(OH)CN$_2$), 4.25–4.14 (m, 2H), 4.12 (c, $J = 7.5$ Hz, 2H, CO$_2$CH_2CH$_3$), 3.80–3.71 (m, 3H), 3.65 (bs, 1H, OH), 2.81 (d, $J = 3.8$ Hz, 1H, OH), 1.32 (s, 3H, C(CH$_3$)$_2$), 1.28 (s, 3H, C(CH$_3$)$_2$), 1.18 (t, $J = 7.5$ Hz, 3H, CO$_2$CH$_2$CH_3), 0.98 (s, 9H, SiC(CH$_3$)$_3$); ^{13}C NMR (50.3 MHz, CDCl$_3$) δ 168.3, 135.9, 130.3, 128.2, 128.1, 109.7, 83.4, 76.9, 73.2, 64.9, 61.8, 46.3, 29.8, 26.9, 26.7, 26.1, 19.7, 14.6; FAB HRMS (NBA) m/e 585.2635, M+1 calcd for C$_{30}$H$_{40}$N$_2$O$_8$Si: 585.2632. Product **9** (mixture of stereoisomers at C-3): $R_f = 0.32$ (silica gel, 25% EtOAc in hexanes); IR (thin film) v_{max} 3462, 3043, 2936, 2864, 2103, 1735, 1685, 1653, 1383, 1256 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70–7.64 (m, 2H, Ph), 7.56–7.30 (m, 8H, Ph), 5.48 (s, 1H, CHPh, major isomer), 5.47 (s, 1H, CHPh, minor isomer), 5.02 (dd, 1H, $J = 6.7$, 4.9 Hz, 1H, CH(OR), major isomer), 4.93 (dd, 1H, $J = 6.0$, 4.7 Hz, 1H, CH(OR), minor iso-

mer), 4.85 (d, $J = 11.5$ Hz, 1H, PhCH_2O, major isomer), 4.82 (d, $J = 11.4$ Hz, 1H, PhCH_2O, minor isomer), 4.78 (d, $J = 11.4$ Hz, 1H, PhCH_2O, minor isomer), 4.62 (d, $J = 11.5$ Hz, 1H, PhCH_2O, major isomer), 4.29–4.04 (m, both isomers), 3.95 (dd, 1H, $J = 9.0$, 1.5 Hz, 1H, CH(OR), major isomer), 3.84 (dd, 1H, $J = 9.2$, 2.7 Hz, 1H, CH(OR), minor isomer), 3.61 (dd, 1H, $J = 10.3$ Hz, 1H, CH(OR), major isomer), 3.39 (d, $J = 6.8$ Hz, 1H, major isomer), 1.25 (t, $J = 7.3$ Hz, 3H, CO$_2$CH$_2$CH_3, minor isomer), 1.23 (t, $J = 7.0$ Hz, 3H, CO$_2$CH$_2$CH_3, mayor isomer), 0.89 (s, 9H, SiC(CH$_3$)$_3$, minor isomer), 0.87 (s, 9H, SiC(CH$_3$)$_3$, mayor isomer), 0.09, 0.05, 0.04 (3s, Si(CH$_3$)$_2$, both isomers); ^{13}C NMR (50.3 MHz, CDCl$_3$) (major isomer) δ 166.3, 138.1, 137.3, 128.9, 128.4, 128.2, 127.9, 127.7, 126.1, 101.3, 82.3, 76.5, 74.2, 72.3, 71.9, 66.9, 61.9, 25.7, 17.9, 14.4, −3.8, −4.8; FAB HRMS (NBA) m/e 557.2931, M+1 calcd for C$_{29}$H$_{40}$N$_2$O$_7$Si: 557.2934.

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19. Diazo **15**: $R_f = 0.42$ (silica gel, 50% EtOAc in hexanes); IR (thin film) v_{max} 3465, 2995, 2945, 2103, 1734, 1684, 1458, 1371, 1067 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.99 (dd, 1H, $J = 9.6$, 6.2 Hz, 1H, CH(OH)CN$_2$CO$_2$Et), 4.45 (dd, 1H, $J = 6.5$, 0.9 Hz, 1H, CH(OR)), 4.25 (c, $J = 7.2$ Hz, 2H, CO$_2$CH_2CH$_3$), 4.23 (dd, $J = 6.5$, 2.6 Hz, 1H, CH(OR)), 4.15–3.99 (m, 4H), 2.78 (bs, 1H, OH), 1.46, 1.42, 1.38 and 1.36 (4s, 12H, 2×C(CH$_3$)$_2$), 1.29 (t, $J = 7.2$ Hz, 3H, CO$_2$CH$_2$CH_3); ^{13}C NMR (50.3 MHz, CDCl$_3$) δ 166.8, 109.3, 108.6, 76.6, 76.4, 75.4, 69.0, 67.0, 66.4, 60.9, 26.9, 26.7, 25.3, 24.8, 14.4; FAB HRMS (NBA) m/e 375.2019, M+1 calcd for C$_{16}$H$_{26}$N$_2$O$_8$: 375.2018.

20. All new compounds exhibited satisfactory spectroscopic and analytical and/or accurate mass data.

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