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β-Oxy-α-diazo-carbonyl compounds. Part 6: Synthesis and reactivity of 3-deoxy-2-diazo-esters derived from monosaccharides. Applications in the synthesis of 2-*C*-alkyl-KDO analogues and related compounds

Francisco Sarabia and Fidel Jorge López-Herrera*

Departamento de Bioquímica, Biología Molecular y Química Orgánica, Facultad de Ciencias, Universidad de Málaga, 29071 Málaga, Spain

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Abstract—Reactions of 6-*O*-protected diazo derivatives **8**, **9** and **10** with transition metals Rh(II) and Cu(II) under a variety of different conditions of solvents and temperatures, were studied in order to obtain 2-*C*-alkyl analogues of KDO. In fact, these types of products (**11**, **12**) were obtained in good yields when Rh(II) was used as a catalyst in benzene. The interesting seven-membered ring products (**13**) were obtained only for **8** and **9**, as single diastereoisomers and their formations were favored when Cu(II) catalysts were used.

The biological importance of 3-deoxy-D-*manno*-2-octulosonic acid (KDO, **1**) as an essential component of the LPS (lipopolysaccharides) contained in the outer membrane of Gram-negative bacteria[1] has led to important biological and synthetic efforts in recent decades, including the identification of the enzymes involved in the biosynthetic pathway of LPS[2] and efficient and convergent syntheses of KDO[3] and KDO-conjugates.[4] From these studies, the potential inhibition against CMP-KDO or KDO-8-phosphate synthetases, the enzymes responsible for incorporation of KDO into the LPS, has been deemed to be important for the design of a new emerging class of novel antibiotics against Gram-negative bacteria. Two important factors draw attention to the consideration of KDO analogues as potential new antibiotics. Firstly, the increase of resistant Gram-negative bacteria strains towards conventional antibiotics,[5] which in turn have directed clinicians and pharmaceutical companies towards the discovery of new antibiotics with different mechanisms of action. Secondly, the recent disclosure of the 3D structure of the protein KDO-8-phosphate synthetase[6] provides access to the rational design of potent and efficient inhibitors, and consequently, to new leads for the fighting against Gram-negative bacteria.[7] Not surprisingly, intense activity in this direction has been achieved in recent years with the synthesis of variety of analogues including deoxy-derivatives,[3r,8] aza-[9] or carba-cyclic analogues,[10] side or terminal chain modified derivatives[11] and *C*-glycoside analogues.[3r,12] Among the wide variety of modified KDO structures, 2-deoxy-KDO (**2**) appears to be the most potent inhibitor of CMP-KDO synthetase identified to date.[13]

Our research program has been directed towards the synthesis of complex sugar derivatives of biological importance and has led us to convergent syntheses of KDO and 2-deoxy-KDO based on the chemistry of β-oxy-α-diazo esters derived from monosaccharides.[14] In the preceding paper,[15] we reported an efficient and high yielding synthesis of these types of products, by using diethyl zinc as a promoter for enhancing the reactivity of ethyl diazoacetate. These products represent common precursors for the synthesis of KDO (**1**), 2-deoxy-KDO (**2**), KO (**3a**) and its epimer at C-3 (**3b**) as is depicted in Scheme 1. In the present paper, we wish to report the syntheses of 2-deoxy-2-*C*-alkyl analogues of KDO via diazo chemistry.[16] Thus, based on our previous work, the diazo ester **7**,[14] used for the synthesis of **2**, represented an interesting synthetic intermediate for the synthesis of the above mentioned 2-*C*-alkyl analogues of KDO.

Keywords: KDO analogues; CMP-KDO synthetase inhibitors; diazo; carbenoids; monosaccharides.

* Corresponding author.

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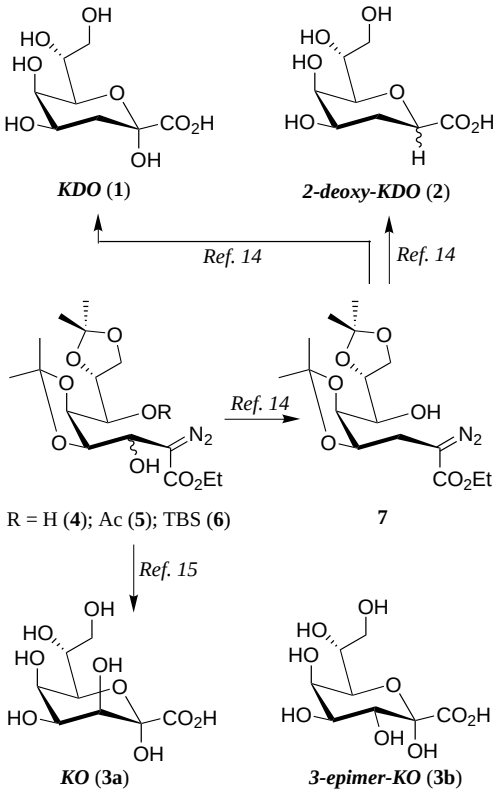
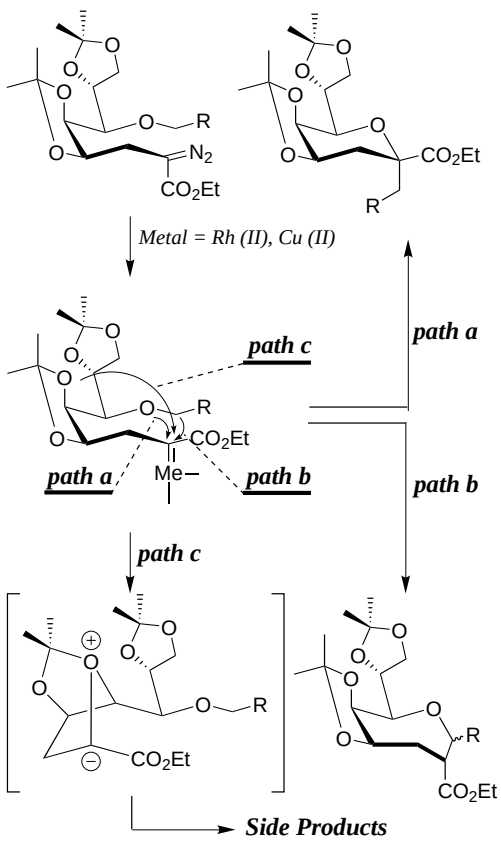


Scheme 1. Syntheses of KDO (**1**), 2-deoxy-KDO (**2**) and KO (**3**).

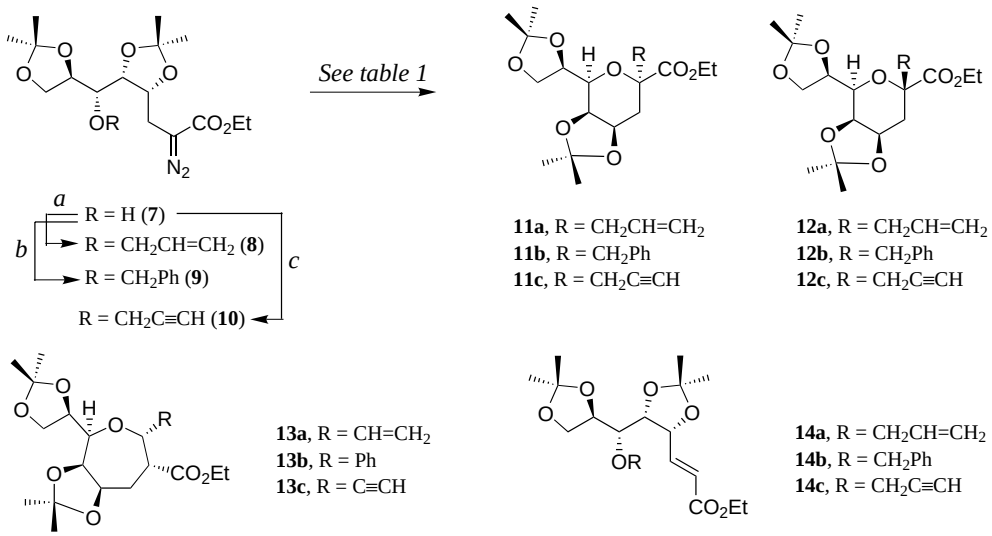
The protection of the free hydroxyl group at C-6 of **7** as an ether, followed by exposure of the resulting diazo compound to the action of metals such as Rh(II) or Cu(II), should lead to the desired 2-*C*-alkyl KDO derivatives. This insertion reaction involves initial formation of an oxonium ylide, followed by a [1,2] or [2,3] sigmatropic rearrangement resulting in the migration of the alkyl group to the diazo carbon (path a).[17] In fact, one can find prominent examples of this reaction applied towards the synthesis of natural products in the literature.[18] Nevertheless, the polyfunctional substrate offers other reaction pathways from the highly reactive carbenoid species such as CH insertion (path b), oxonium ylide formation from different oxygen atoms and subsequent rearrangements (path c) (Scheme 2).

In order to evaluate the different possible pathways and others not indicated in Scheme 2 and to optimize the formation of the desired 2-*C*-alkyl derivatives for biological evaluations as CMP-KDO synthetase inhibitors, we prepared the 6-*O*-allyl, benzyl and propargyl derivatives by conventional procedures (Scheme 3). With the products **8**, **9** and **10** in hand, and taking into account that factors such as the nature of the transition metal, solvent and temperature can influence the ratio of the possible products, we carried out an extensive study of the insertion reaction by modification of these factors. The results from these studies are summarized in Table 1.

From these results, we concluded that the most suitable transition metal to obtain the six-membered ring derivatives (**11** and **12**) was Rh(II), using benzene as a solvent under reflux conditions. The use of methylene chloride and Cu(II) as the catalyst in the form of $Cu(acac)_2$ or $Cu(hfacac)_2$ favored the formation of the seven-membered ring derivative (**13**) by a stereoselective intramolecular CH insertion. The elimination products **14a**, **14b** and **14c** were formed in different proportions depending on the reaction conditions; however, when Cu(II) was employed using CH_2Cl_2 as solvent they were the main products. In the particular case of the allyl derivative **8**, the resulting six-membered ring derivative **11a**/**12a** was obtained as a 1:1 mixture of isomers at C-2. These structures were confirmed by comparison with the NMR data reported in the literature.[12a] For the six-membered ring products **11b**/**12b** and **11c**/**12c**, their structures were also confirmed by comparison with the literature NMR data reported by Claesson et al.[11a] As we mentioned above, the corresponding oxepanes **13a** and **13b**, were obtained as single isomers. The configurational assignments were established according to NMR information and two-dimensional COSY and NOESY experiments.[19] Similarly, the comparison of the coupling constants $J_{1,2}$ values for **13a** and **13b**, with those of related oxepane systems[20] led us to establish the *cis* relationship of the system contained in **13**. In addition, for a final tentative absolute configuration assignment, conformational analysis of the four possible diastereoisomers revealed an agreement between the theoretical and experimental $J_{1,2}$ values for the *cis* stereoisomer.[21] Finally, in the case of the *O*-propargyl derivative **10**, it was found out that neither



Scheme 2. Formation of carbenoids species from *O*-protected derivatives of **7** and possible reactions.



Scheme 3. Reactions of *O*-protected diazo derivatives with transition metals. *Reagents and conditions*: (a) 1.5 equiv. NaH, 2.0 equiv. $BrCH_2CH{=}CH_2$, THF, 0°C, 12 h, 68%; (b) 1.5 equiv. NaH, 3.0 equiv. $BrCH_2Ph$, THF, 0°C, 12 h, 75%; (c) 2.5 equiv. NaH, 3.0 equiv. $BrCH_2CCH$, THF, 0°C, 2 h, 88%.

Table 1. Reactions of diazo compounds **8**, **9** and **10** with Rh(II) and Cu(II) catalysts

Diazo	Catalyst	Solvent	Conditions	Time (h)	**11**/**12** (%)	**13** (%)	**14** (%)
8	$Rh_2(OAc)_4$	CH_2Cl_2	rt	0.5	30	65	5
8	$Rh_2(OAc)_4$	Benzene	rt	0.5	40	50	10
8	$Rh_2(OAc)_4$	Benzene	Reflux	0.5	35	65	0
8	$Cu(acac)_2$	CH_2Cl_2	rt	1.0	0	10	90
8	$Cu(acac)_2$	CH_2Cl_2	Reflux	1.0	0	30	70
8	$Cu(acac)_2$	Benzene	rt	12	0	95	5
8	$Cu(acac)_2$	Benzene	Reflux	1.0	10	80	10
8	$Cu(hfacac)_2$	Benzene	rt	24	0	90	10
8	$Cu(hfacac)_2$	Benzene	Reflux	1.0	0	100	0
9	$Rh_2(OAc)_4$	Benzene	Reflux	1.0	35	55	10
9	$Cu(acac)_2$	Benzene	Reflux	1.0	5	85	10
10	$Rh_2(OAc)_4$	Benzene	Reflux	1.0	85	0	15

solvent nor temperature affected the ratio of the products when Rh(II) was used as catalyst. On the other hand, the expected allene, which would be formed after a sigmatropic rearrangement of the corresponding oxonium ylide intermediate, was not detected, indicating a different mechanism of the alkyl group migration. Recently, these allenes have been synthesized using a similar reaction by use of a ruthenium catalyst.[22]

In conclusion, insertion reactions of *O*-alkyl diazo derivatives of D-mannose, promoted by transition metals, were investigated in order to synthesize 2-deoxy-2-*C*-alkyl analogues of KDO. Specific reaction conditions and catalysts favored the formation of the desired analogues in reasonably good yields, although with a no stereoselectivity. However, the seven-membered ring products, formed by a CH insertion showed complete stereoselectivity. All the synthesized products provide access to complex analogues of KDO via chemical modifications of the pendant groups at C-2 and will be tested as inhibitors of CMP-KDO synthetase.

Acknowledgements

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19. Compound **13a**: $R_f = 0.42$ (silica gel, 50% EtOAc in hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (ddd, $J = 17.2$, 10.4, 6.8 Hz, 1H, C*H*=CH$_2$), 5.29 (d, $J = 17.2$ Hz, 1H, CH=C*H*$_2$), 5.19 (d, $J = 10.4$ Hz, 1H, CH=C*H*$_2$), 4.37–4.32 (m, 2H, H-1, H-8), 4.30 (dd, $J = 6.2$, 4.6 Hz, 1H, H-6), 4.19 (m, 1H, H-5), 4.16–4.07 (m, 3H, H-9, $CO_2CH_2CH_3$),

3.98 (dd, $J=8.9$, 4.7 Hz, 1H, H-10), 3.50 (dd, $J=7.6$, 0.8 Hz, 1H, H-7), 2.80 (ddd, $J=8.0$, 6.1, 1.2 Hz, 1H, H-2), 2.32–2.26 (m, 1H, H-3), 2.08 (ddd, $J=13.1$, 4.1, 1.0 Hz, 1H, H-4), 1.55, 1.46, 1.38 and 1.36 (4s, 12H, $2\times C(CH_3)_2$), 1.25 (t, $J=7.2$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.3, 134.9, 117.8, 109.4, 108.3, 76.2, 76.1, 75.2, 66.9, 60.6, 43.5, 27.8, 27.5, 27.1, 25.6, 25.4, 14.1; FAB HRMS (NBA) m/e 393.1891, M+Na calcd for $C_{19}H_{30}O_7$: 393.1884. Compound **13b**: $R_f=0.42$ (silica gel, 50% EtOAc in hexanes); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.30 (m, 5H, Ph), 4.97 (d, $J=6.3$ Hz, 1H, H-1), 4.40 (dd, $J=6.0$, 0.8 Hz, 1H, H-6), 4.36 (ddd, $J=7.4$, 6.2, 4.7 Hz, 1H, H-8), 4.27 (ddd, $J=10.0$, 6.0, 4.3 Hz, 1H, H-5), 4.10 (dd, $J=8.8$, 6.4 Hz, 1H, H-9), 4.00 (dd, $J=8.9$, 4.6 Hz, 1H, H-10), 3.93–3.77 (m, 2H, $CO_2CH_2CH_3$), 3.63 (dd, $J=7.6$, 1.1 Hz, 1H, H-7), 3.09 (ddd, $J=8.2$, 6.4, 1.5 Hz, 1H, H-2), 2.57 (ddd, $J=14.4$, 9.3, 8.2 Hz, 1H, H-3), 2.09 (ddd, $J=14.4$, 4.0, 1.4 Hz, 1H, H-4), 1.57, 1.41, 1.39 and 1.37 (4s, 12H, $2\times C(CH_3)_2$), 1.04 (t, $J=7.1$ Hz, 3H, $CO_2CH_2CH_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 171.1, 139.4, 127.9, 127.7, 126.5, 109.4, 108.4, 81.9, 76.4, 76.3, 75.2, 66.9, 60.4, 44.9, 29.7, 28.0, 27.7, 27.0, 25.7, 25.3, 13.7; FAB HRMS (NBA) m/e 443.2025, M+Na calcd for $C_{23}H_{32}O_7$: 443.2038.

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21. Theoretical studies based on conformational studies of **13a** and **13b** revealed a concordance between theoretical $J_{1,2}$ values for the minimized conformers and experimental $J_{1,2}$. Thus, theoretical coupling constants $J_{1,2}$ were of 4.0 and 5.0 Hz for **13a** and **13b**, respectively, finding 6.1 and 6.3 Hz for experimental values, respectively. On the other hand, a similar analysis carried out on the other three possible diastereoisomers showed $J_{1,2}$ values quite different respect to the experimental ones.
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