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A Short Route to α-Chloro- and α-Azido-Ulosonic Esters

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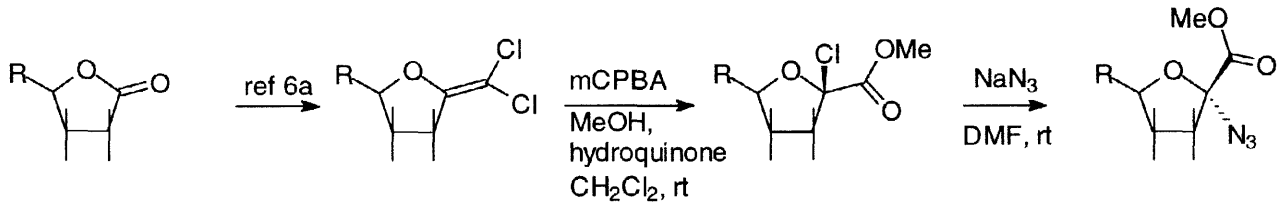
Abstract : A two step route to α-chloro-ulosonic esters from lactones involving the reaction of dichloroolefins with *m*-chloroperbenzoic acid in dichloromethane is described. Subsequent substitution of chlorine by the azide ion yields the corresponding anomeric azido-esters, which may be useful intermediates for the preparation of "anomeric amino-acids" and related compounds.

Carbohydrates having a quaternary anomeric centre are of high interest. Ulosonic acids such as sialic acid, KDO, KDN and their activated derivatives are among the most important representatives of this class of compounds.[1] Spiro-heterocycles derived from sugars such as hydantocidins are potent natural herbicides.[2] Such spiro-structures may also be regarded as carbohydrate mimics[3] and may show interesting biological properties as inhibitors of glycogen phosphorylase.[4] Anomeric amino esters are ideal precursors of this class of compounds and constitute a particular class of amino acids of interest, which has not been investigated in detail, because all these structures are prepared by multistep routes from furanose or lactones.[5]

We have introduced several years ago the olefination of sugar lactones as an efficient way for the functionalisation of the anomeric centre of sugars.[6] Dichloroolefins can be formed in high yield from lactones, and in an effort to explore the synthetic use of these compounds, we have investigated the reaction of the rather unreactive dichlorosubstituted double bond with *meta*-chloroperbenzoic acid (*m*-CPBA) (Scheme 1).[7] To our delight this reaction provides unexpected results towards the synthesis of chloro- and azido-esters of furanose derivatives.



Scheme 1

In preliminary experiments, treatment of dichloroolefin **1** with *m*-chloroperbenzoic acid in dichloromethane at room temperature for several hours led to a mixture of two products **6** and **7** in 41% and 35% yield respectively. The first product was identified as the tetrachloro derivative obtained by formal addition of chlorine on the double bond.[7] The second product was clearly a methyl ester as proved by IR, ^{1}H and ^{13}C

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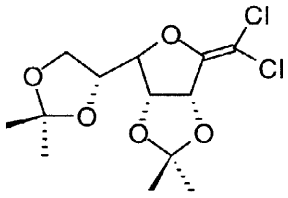
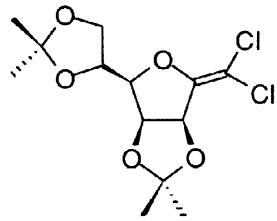
NMR spectra. Moreover mass spectrometry showed a m/z 321 $(M - CH_3)^+$ peak with an isotopic pattern in agreement with the presence of only one chlorine atom. The presence of this chlorine atom at the anomeric position was confirmed later on (*vide infra*). The formation of these two products was unexpected, in particular the origin of the methyl group in ester **7** remained unclear.



1



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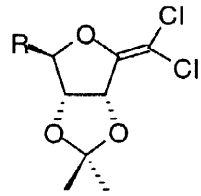
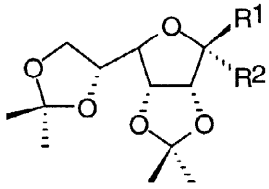
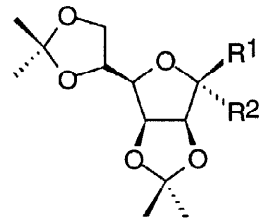


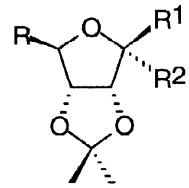
3 R = CH_2OAc
4 R = $CH_2OCH_2OCH_3$
5 R = H



6 R^1, R^2 = Cl, CCl_3
7 R^1 = Cl, R^2 =COOMe
8 R^1 = COOMe, R^2 = N_3



9 R^1 = Cl, R^2 =COOMe
10 R^1 = COOMe, R^2 = N_3



11 R= CH_2OAc, R^1 = Cl, R^2 =COOMe
12 R = CH_2OAc, R^1 = COOMe, R^2 = N_3
13 R = CH_2OMOM, R^1 = Cl, R^2 = COOMe
14 R = CH_2OMOM, R^1 = COOMe, R^2 = N_3
15 R = H, R^1 = Cl, R^2 = COOMe
16 R = H, R^1 = COOMe, R^2 = N_3

Table: Reaction times and yields for the synthesis of chloro- and azido-esters

Starting compound	Reaction time (h)[a]	Chloro-ester (yield)[a, b]	Reaction time (h)[c]	Azido-ester (yield)[b]
1	16	**7** (76)	0.5	**8** (88)
2	16	**9** (70)	1	**10** (78)
3	3	**11** (53)	4	**12** (70)
4	4	**13** (55)	2	**14** (72)
5	4	**15** (62)	4	**16** (76)

a) *m*-CPBA, MeOH, CH_2Cl_2, hydroquinone, rt.[8]

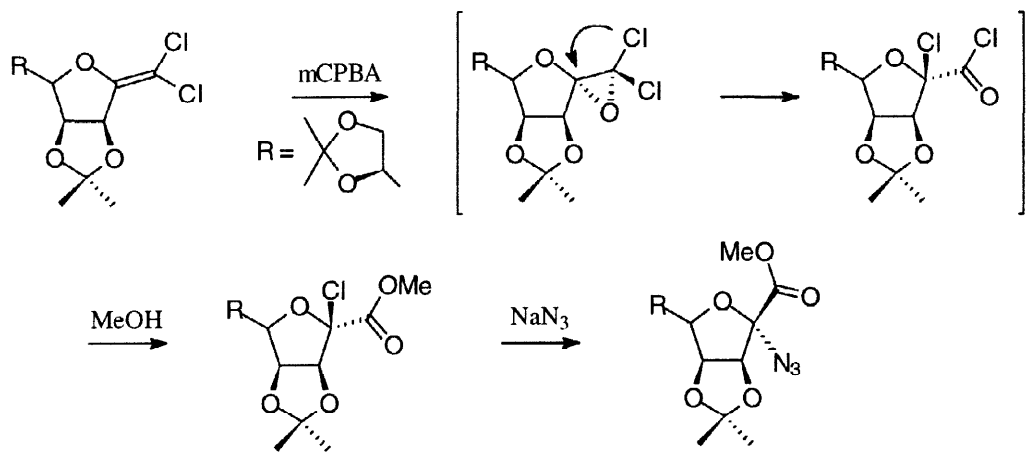
b) Yields refer to pure isolated products

c) NaN_3, DMF, rt.

It was assumed that the methyl group should come from methanol probably present in minute amount in the solvent as a stabilizer. Indeed no methyl ester **7** was formed when performing the reaction in carefully purified dichloromethane. However, no reaction occurred in pure methanol (*m*-CPBA, MeOH), except the clean removal of the 5,6-O-isopropylidene group due to the acidic medium. The use of a stocchiometric amount of methanol improved the yield of ester **7** but the chloro derivative **6** was always formed. We have shown that this

reaction probably arose from the decomposition of *m*-CPBA which reacts with dichloromethane to produce a powerful chlorinating reagent with a reactivity close to that of molecular chlorine.[7] The radical nature of the decomposition of *m*-CPBA at elevated temperature has been reported by Lefort et al..[9] Thus, the reaction was performed in the presence of a radical inhibitor.[10] Treatment of olefin **1** with *m*-CPBA (2eq.), MeOH (10 eq.) and hydroquinone (2 eq.) gave the chloroester **7** in 76% yield. A series of substrates was thus transformed accordingly (see Table). In all cases a single isomer was formed based on ^{13}C nmr data. The yields are good for substrates **1, 2** and **5** in which all substituents on the furanose ring are on the same side. The yields are slightly lower in the *ribo* series, compounds **3** and **4**, in which both sides of the ring are substituted. The reaction conditions are compatible with the presence of an ester group and the presence of acetals.

Introduction of the azide function was carried out by treatment of the chloro-ester with sodium azide in dry dimethylformamide. Yields were good in each case and again a single isomer was formed. This is in favour of a nucleophilic substitution at the tertiary anomeric centre occurring with net inversion.[5b] The α anomeric configuration of the azido group was firmly established on compound **10** [11] by comparison with literature data,[5b] both anomers being known compounds.[5] The α orientation of the azido group indicates a β configuration of the chloro derivative **9**. This shed some light on a possible mechanism of chloroester formation which could be rationalized as depicted in the manno series on Scheme 2



Scheme 2

The first step could be the expected formation of an epoxide. This reaction is probably very slow because of the poor reactivity of dichloroolefins. This accounts for the need for a radical scavenger which prevent induced decomposition of *m*-CPBA. The isopropylidene ring favours the *anti* attack and the formation of a single isomer. The dichloroepoxide should rearrange quickly to the corresponding chloroacylchloride which reacts immediatly with methanol.[12] As a consequence of the rearrangement, the chlorine atom is *cis* to the isopropylidene ring. Net inversion of configuration during azide substitution led to the azido ester having the azide group *trans* to the isopropylidene as firmly established in the *manno* series (*vide supra*). An alternative route could be the opening of the epoxide by assistance of the ring oxygen doublet, followed by trapping of the resulting oxenium ion by chloride ion from both faces of the sugar ring. This would give a mixture of isomers in which the *trans* chloro derivative would be preponderant and the azide would be *cis* to the isopropylidene ring in contrast to the observed configuration of compound **10**. The whole reaction seems to be very fast as no intermediate product can be detected by tlc analysis.

In conclusion, we have opened a short and efficient route to stereochemically defined chloro- and azido-esters of ulosonic acids. This reaction proceeds with high stereocontrol, likely via dichloroepoxide formation followed by fast rearrangement to acyl chloride and esterification. Sugar-derived aminoacids of interest in the peptidomimetics field can be obtained in a few steps from readily available lactones.

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11. Spectra data of compound **10**: mp 110°C, $[\alpha]_D$ +110 (c 0.1, $CHCl_3$); lit.[5b] mp 112-113°C, $[\alpha]_D$ +119 (c 0.6, $CHCl_3$); ^1H nmr (250 MHz) δ: 1.33 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 4.03 (dd, 1H, $J_{5,6}$ 8Hz, H-5), 4.13 (m, 2H, H-7, H-7'), 4.52 (ddd, 1H, $J_{6,7}$ 6, $J_{6,7'}$ 4 Hz, H-6), 4.63 (d, 1H, $J_{3,4}$ 5.5 Hz, H-3), 4.86 (dd, 1H, $J_{4,5}$ 3.5 Hz, H-4); ^{13}C nmr δ: 25.6, 25.8, 26.1, 26.5, CH_3, 55.3, OCH_3, 68.1, 71.8, 78.6, 85.1, 87.3, (C-3-C-6), 98.8 C-2, 11.2, 114.8, C-CH_3, 164.4, C=O.
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