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Fragmentation of Carbohydrate Anomeric Alkoxy Radicals. A New Synthesis of Alduronic Acid Lactones

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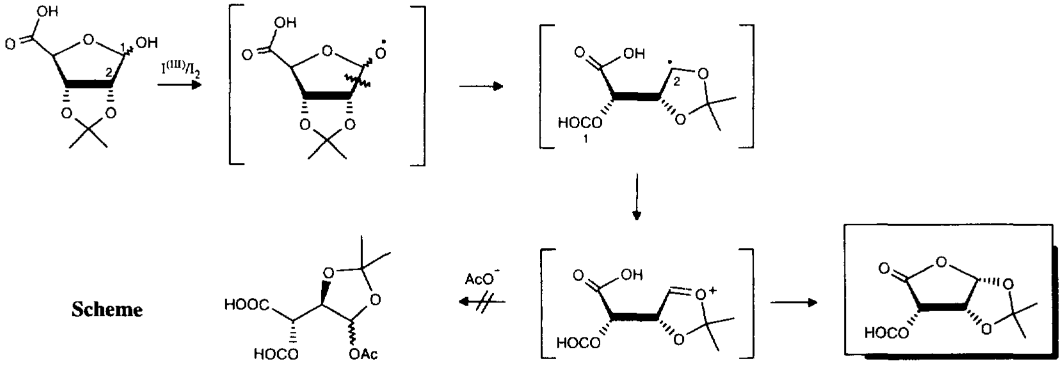
Abstract: Aldopyranosuronic and aldofuranosuronic acid lactones, with one carbon less, can be specifically obtained when hexuronic and penturonic acids in pyranose or furanose forms undergo a tandem β-fragmentation-cyclization reaction promoted by the system (diacetoxyiodo)benzene-iodine, under mild conditions. The lactones are formed via 1,5 and 1,6 intramolecular cyclization.

Carbohydrates are important synthetic precursors to enantiomerically pure molecules because of their ready availability, well defined stereochemistry, and highly functionalized structure. Hence, strategies for the translation of carbohydrate structural and stereochemical elements into intermediates for the construction of natural products are preparatively useful.[1] As part of our ongoing program on the β-fragmentation reaction of hemiacetals,[2] we have described the preparation of chiral building blocks by fragmentation of anomeric alkoxy radicals of carbohydrates,[3a] and more recently we communicated a novel strategy to obtain chiral furanose and pyranose derivatives.[3b] Alduronic acid 5,1- and 4,1-lactones (so-called pseudolactones) are interesting compounds because the former are intermediates in the synthesis of inositols and some glyoxylase inhibitors with cytotoxic and cancerostatic properties.[4] The 1,4-pseudolactones are also intermediates to the synthesis of carbocyclic nucleosides such as neplanocins that have attracted considerable chemical and



Scheme

biological interest because of their significant activities as antitumor and antiviral agents.[5] Some several step syntheses have been reported of these pseudolactones.[4, 5a]

With these considerations in mind we developed a tandem strategy for the synthesis of aldopyranosuronic and aldofuranosuronic acid lactones, illustrated in the Scheme, which is based on two different reactions: a) initial β-fragmentation reaction of the hemiacetal alcohol promoted by the formation of an anomeric alkoxy radical generated with the hypervalent iodine reagent/iodine system under mild conditions to yield a C-2 radical, and b) intramolecular trapping of this radical by a suitably positioned carboxyl group to yield a γ- or δ-lactone ring. This second reaction takes place, most probably, through the oxidation of the C-2 radical to an oxonium ion subsequently captured by the carboxyl group, or in an alternative possibility by the action of a carboxyl radical, formed from the acid group by an excess of reagent, on the C-2 radical to give the lactone. The rare 4,1-tetruronic and 5,1-penturonic acid lactones would be easily accessible using this methodology.

To this purpose the system (diacetoxyiodo)benzene (DIB)/I_2 at room temperature was used to generate the alkoxy radical. An additional mol/equiv of DIB was required to oxidize the C-2 radical intermediate to form the oxonium ion or in the alternative mechanism to promote the carboxyl radical formation. It should be noted that this latter intramolecular reaction must be very fast since acyclic side products, that could be originated by the intermolecular addition to C-2 of acetate anions from the reagent[3a,b] are not observed, as shown in the Scheme. Probably due to the mild reaction conditions the acid decarboxylation that could be expected has not been detected either.[6]

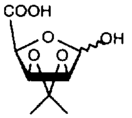
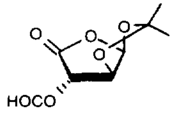
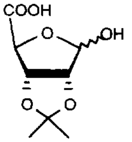
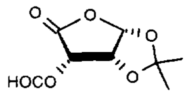
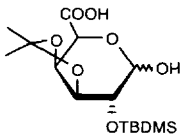
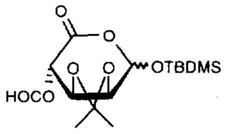
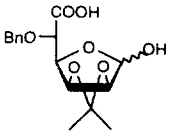
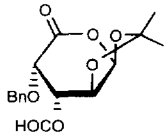
With the aim of testing the reaction and its scope we prepared substrates from the D-threose (entries 1 and 3 in the Table) and D-erythrose carbohydrate series (entries 2 and 4), and they were treated with DIB and I_2 under the conditions displayed in the Table. The 2,3-*O*-isopropylidene-D-lyxuronic acid (**1**), obtained from D-mannose,[7] undergoes reaction to give the threuronic acid 4,1-lactone derivative **2**[8] as a crystalline compound, that shows an IR absorption at 1805 cm^{-1}. As observed in the NMR spectrum, only one isomer at C-1 was obtained and the expected *cis*-stereochemistry between H-1 and H-2 was confirmed by the coupling constant, $J_{1,2}$ = 3.9 Hz, displayed.

The erythruronic acid lactone derivative **4**[9] was similarly formed as an oily compound (IR absorption 1774 cm^{-1}) from 2,3-*O*-isopropylidene-D-riburonic acid (**3**) as the sole product obtained. The *cis*-stereochemistry of the 1,2-isopropylidene group is consistent with the coupling constant $J_{1,2}$ = 4.6 Hz observed.

The 5,1-penturonic acid lactones were synthesized from hexuronic acids in pyranose or furanose forms (entries 3 and 4); in these cases, from the intermediate proposed in the mechanism shown in the Scheme, a mixture of isomers at C-1 was expected, since the steric hindrance observed for the butyrolactones is lacking. Accordingly, the 2-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-galactopyranosuronic acid (**5**) underwent cleavage and cyclization to afford in good yield the lyxopyranosuronic acid 5,1-lactone derivatives **6**[10] and **7**[11](α:β = 2.7), in a separable mixture. Contrarily, the 2,3-*O*-isopropylidene-5-*O*-benzyl-D-mannofuranosuronic acid (**8**) gave only the β-isomer of the arabinopyranosuronic acid 5,1-lactone **9**[12] (confirmed by the $J_{1,2}$ = 4.3 Hz for a *cis* configuration), probably due to the additional hindrance exerted by the isopropylidene group on the formation of the α-isomer.

The procedure that is developed under mild conditions is compatible with the protective groups commonly used in carbohydrate chemistry. This reaction may be a very valuable procedure for descending the alduronic acid series for preparing specific 4,1-tetruronic and 5,1-penturonic acid lactones which are sometimes difficult to achieve by other methods. The obtained products display different protective groups that

Table. Synthesis of 4,1-tetruronic and 5,1-penturonic acid lactones.

Entry	Substrate	Solvent	Conditions[a]			Products	Yield
			DIB (mmol)	I_2 (mmol)	time (h)		%
1	 **1**	CH_2Cl_2	2	1	1	 **2**	51
2	 **3**	CH_2Cl_2	2	1	1	 **4**	43
3	 **5**	CH_2Cl_2	2.5	1	1	 **6** α **7** β	70
4	 **8**	CH_2Cl_2	2	1	3	 **9**	52

[a] Per mmol of substrate. DIB = (diacetoxyiodo)benzene; TBDMS = *tert*-butyldimethylsilyl

may be of interest when these lactones are to be employed as chiral sources and further chemical transformations are needed.

Representative Experimental Procedure: A solution of 2-*O*-(*tert*-butyldimethylsilyl)-3,4-*O*-isopropylidene-D-galacturonic acid (**5**) (54 mg, 0.16 mmol) in dry CH_2Cl_2 (7 ml) containing (diacetoxyiodo)benzene (129 mg, 0.4 mmol) and iodine (41 mg, 0.16 mmol) was stirred at room temperature (20 °C) for 1 h. The reaction mixture was then poured into aqueous sodium thiosulphate and extracted with diethyl ether. The residue was separated by column chromatography (*n*-hexane-ethyl acetate 8:2 v/v) to give the lactones **6** and **7** (37.5 mg, 70%, α:β = 2.7). Alternatively, the reaction mixture was filtered over Celite and then submitted to flash chromatography (Merck silica gel 60).

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8. Compound (**2**): m.p. 71-72.5 °C (*n*-hexane); $[\alpha]_D$ -12° ($CHCl_3$, *c*, 0.14); IR (CCl_4) ν_{max} 1805, 1736 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.45 (3H, s, CH_3), 1.53 (3H, s, CH_3), 4.75 (1H, d, *J* 3.9 Hz, 2-H), 5.15 (1H, s, 3-H), 6.28 (1H, d, *J* 3.9 Hz, 1-H), 8.09 (1H, s, OCOH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 159.1 (OCOH), 115.6 ($C(CH_3)_2$), 103.9 (1-C), 80.5 (3-C), 73.4 (2-C), 27.9 (CH_3), 26.9 (CH_3); EIMS *m/z* 203.05780 ($[M+1]^+$, 2%), 187 ($[M-CH_3]^+$, 77%), 159 (21%).
9. Compound (**4**): IR (CCl_4) ν_{max} 1774, 1752 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.47 (3H, s, CH_3), 1.56 (3H, s, CH_3), 5.02 (1H, dd, *J* 4.6, 3.1 Hz, 2-H), 5.57 (1H, d, *J* 4.6 Hz, 1-H), 6.1 (1H, d, *J* 3.1 Hz, 3-H), 8.22 (1H, s, OCOH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 168.2 (C), 158.9 (CH), 116.9 (C), 101.2 (CH), 76.1 (CH), 69.2 (CH), 27.8 (CH_3), 26.8 (CH_3); EIMS *m/z* 187.02437 ($[M-CH_3]^+$, 24%), 173 (3).
10. Compound (**6**): IR ($CHCl_3$) ν_{max} 1774, 1739 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 0.21 (6H, s, OSi^tBuMe_2), 0.95 (9H, s, OSi^tBuMe_2), 1.38 (3H, s, CH_3), 1.52 (3H, s, CH_3), 4.24 (1H, dd, *J* 8.1, 6.8 Hz, 2-H), 4.50 (1H, dd, *J* 8.0, 7.9 Hz, 3-H), 5.45 (1H, d, *J* 6.7 Hz, 1-H), 5.46 (1H, dd, *J* 8.1, 0.5 Hz, 4-H), 8.21 (3H, s, OCOH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 163.8 (C), 159.1 (CH), 112.4 (C), 96.9 (CH), 77.3 (CH), 73.1 (CH), 70.5 (CH), 26.7 (CH_3), 25.4 (3 x CH_3), 24.6 (CH_3), 17.9 (C), -4.7 (CH_3), -5.2 (CH_3); EIMS *m/z* 331.12148 ($[M-CH_3]^+$, 8%), 289 (18%), 215 (9%).
11. Compound (**7**): IR ($CHCl_3$) ν_{max} 1777, 1739 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 0.21 (3H, s, OSi^tBuMe_2), 0.23 (3H, s, OSi^tBuMe_2), 0.96 (9H, s, OSi^tBuMe_2), 1.39 (3H, s, CH_3), 1.55 (3H, s, CH_3), 4.44 (1H, dd, *J* 3.4, 8.3 Hz, 2-H), 4.60 (1H, dd, *J* 7.4, 8.3 Hz, 3-H), 5.67 (1H, d, *J* 3.4 Hz, 1-H), 6.02 (1H, dd, *J* 7.4, 0.7 Hz, 4-H), 8.21 (1H, s, OCOH); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 165.8 (C), 159.1 (CH), 113.5 (C), 94.4 (CH), 73.4 (CH), 72.8 (CH), 70.4 (CH), 26.1 (CH_3), 25.4 (3 x CH_3), 24.9 (CH_3), 17.8 (C), -5.1 (CH_3), -5.2 (CH_3); EIMS *m/z* 331.12139 ($[M-CH_3]^+$, 19%), 289 (18%), 215 (9%).
12. Compound (**9**): IR (CCl_4) ν_{max} 1742 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.37 (3H, s, CH_3), 1.40 (3H, s, CH_3), 4.34 (1H, d, *J* 2.8, 4-H), 4.44 (1H, dd, *J* 4.3, 3.5 Hz, 2-H), 4.72 (1H, d, *J* 11.9 Hz, CH_2Ph), 4.93 (1H, d, *J* 11.9 Hz, CH_2Ph), 5.58 (1H, ddd, *J* 0.9, 3.5, 2.8 Hz, 3-H), 5.97 (1H, d, *J* 4.3 Hz, 1-H), 7.30-7.37 (5H, Ar), 8.08 (1H, d, *J* 0.9 Hz, OCOH). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ_C 166.3 (C), 159.1 (CH), 136.1 (C, Ar), 128.6 (2 x CH, Ar), 128.4 (CH, Ar), 128.3 (2 x CH, Ar), 112.6 (C), 99.5 (CH), 74.4 (CH), 73.1 (CH_2), 70.9 (CH), 69.8 (CH), 26.9 (CH_3), 25.7 (CH_3); EIMS *m/z* 307.08191 ($[M-CH_3]^+$, 4%), 231 (28%), 187 (97%).

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