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Tricyclic Ortho Ester Formation from Trichloroethylidene Acetals of Sugars via Ketene Acetals

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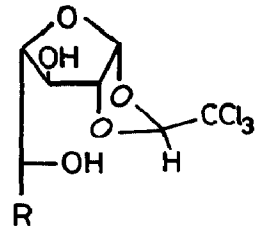
Abstract: *One step formation of the tricyclic dichloroethylidyne ortho esters from the reaction of trichloroethylidene acetals of* D-*galactose and* D-*arabinose with K tert-butoxide are described. The possible intermediate, i.e, ketene acetal was prepared separately, from the suitably protected 1,2-O-trichloroethylidene-α-*D-*galactofuranose. Stereoselective formation of an ortho ester anhydride, from the ketene acetal is also described.*

The reactivity of ketene acetals has recently attracted considerable attention. For example, reactions of some metal carbene complexes with ketene acetals afforded tricyclic ortho esters instead of the expected cyclopropanone acetals[1]. More work has been published on the reactions of silylketene acetals which have enhanced reactivity, and as such have been used in several reactions including carbon-carbon bond formation[2,3]. Formation of ketene acetals have been throughly investigated by McElvain *et.al*[4], but no reports have been found on the preparation of carbohydrate based ketene acetals. Formation of a bicyclic ortho ester, by the treatment of 2-chloromethyl-5-hydroxymethyl-1,3-dioxolane with K *tert*-butoxide has been mentioned in a patent and it has been suggested that the reaction proceeds via the ketene acetal[5].

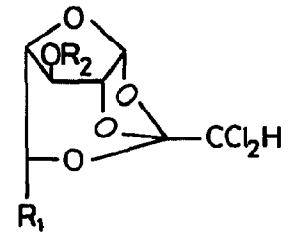
The ortho ester method of glycosylation has found a wide application in carbohydrate chemistry[6]. Tricyclic carbohydrate ortho esters such as 1,2,5-*O*-orthobenzoyl-α-D-arabinofuranose were also used[7]. However preparation of these ortho esters necessitates the initial preparation of bicyclic 1,2-ortho esters which undergo intramolecular transesterification or acylglycosyl halides, if a suitably situated free hydroxyl is available on the carbohydrate skeleton. Methods available for the preparation of 1,2-ortho esters are normally time consuming and laborious[6].

We have found that crystalline tricyclic dichloroethylidyne ortho esters of D-galactofuranose **3** and D-arabinofuranose **4** can be easily prepared in one step from the 1,2-*O*-trichloroethylidene acetals of these sugars (**1** and **2**), by their reaction with K*tert*-butoxide. Thus, (S) 1,2-*O*-(2,2,2-trichloroethylidene)-α-D-galactofuranose[8] **1** and 1,2-O-

(2,2,2-trichloroethylidene)-α-D-arabinofuranose[11] **2** (presumably S configuration) gave 1,2,5-*O*-(2,2-dichloroethylidyne)-α-D-galactofuranose **3** and 1,2,5-O-(2,2-dichloroethylidyne)-α-D-arabinofuranose **4** respectively. The acetals were simply refluxed with K *tert*-butoxide in *tert*-butanol. Only one product was detected by t.l.c (toluene-methanol, 9:1) in the reaction of **1**. Product **3** crystallised from the filtered *tert*-butanol solution(67%). An unidentified by product was observed in the reaction of **2**. The product **4** was crystallised from ethanol-H_2O(62%).

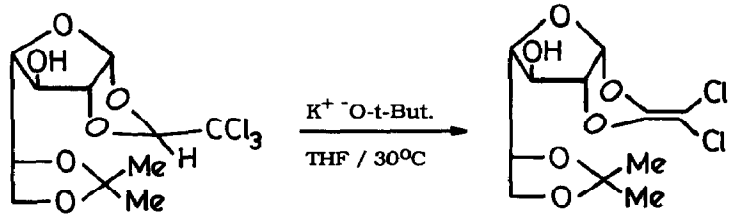


1 R = -CH_2OH
2 R = -H



3 R_1 = -CH_2OH ; R_2 = -H
4 R_1 = -H ; R_2 = -H
5 R_1 = -CH_2OAc ; R_2 = Ac
6 R_1 = -H ; R_2 = Ac

There is indirect evidence that these reactions proceed through the corresponding ketene acetals, although no intermediate could be detected. Reaction of 5,6-O-isopropylidene-1,2-*O*-(2,2,2-trichloroethylidene)-α-D-galactofuranose[8] **7** with K *tert*-butoxide, in which ortho ester formation is prevented gave the syrupy ketene acetal **8** (70%) which is characterised by its ^1H n.m.r spectrum, in which the characteristic acetal proton singlet has disappeared. The mass spectrum is also consistent with the proposed structure[11]. The i.r spectrumshowed a sharp line at 1713 cm^{-1} which is consistent with a double bond containing two oxygen substituents[9].

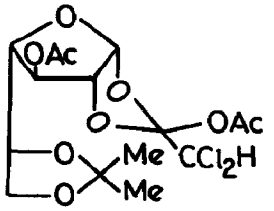


7 8

It is known that the acetal carbons of ketene acetals are sensitive to nucleophiles[3]. We have observed that the ketene acetal **8** is stable for several weeks if protected from atmospheric moisture. On contact with water however, it decomposes rapidly with development of acidity.

Ortho esters **3** and **4** gave crystalline di **5** and mono **6** acetate derivatives respectively. Attempted acetylation of **8** gave a crystalline diacetate derivative as the major product after three succesive acetylations with pyridine-acetic anhydride. This product is most likely an

ortho ester anhydride **9** formed by the attack of the acetate ion on the acetal carbon of **8**. After the first acetylation, the ^1H nmr spectrum of the crude product showed roughly 50% formation of **9**, based on the ratio of the H-1 doublets for monoacetylated ketene acetal (not isolated) and **9**. The propertion of **9** increased to ~90% after the third acetylation. The ^1H n.m.r spectrum showed the formation of only one stereoisomer which may be explained by consideration of the steric hindrance of the 5,6-*O*-isopropylidene ring[10] which may prevent the approach of the incoming nucleophile. The probable attack of the acetate ion on C-1 would have produced a β-D-galactofuranose derivative, but this possibility is eliminated as the observed J_{H_1,H_2} value (4Hz) is typical for α-D-galactofuranose derivatives[8,10]. Furthermore, ^{13}C nmr spectrum of **9** shows two carbonyl carbon signals at 169.7 and 166.0 ppm and a signal at 120.5 ppm can be assigned to the ortho ester carbon. Mass spectrum of **9** is also consistent with the proposed structure[11].



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Similar reactions of (R) 5,6-*O*-isopropylidene-1,2-*O*-(2,2,2-trichloroethylidene)-α-D-glucofuranose did not produce a significant amount of the ketene acetal even after prolonged reaction time. Reactions of other stereoisomeric trichloroethylidene acetals of sugars are currently being investigated.

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References and Notes

1. Wang, S.L.B.; Su, J.; and Wulff W.D. *J.Am.Chem.Soc.*, **1992**, *114*, 10665-10666.
2. Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P.G. *Tetrahedron Lett.*, **1990**, *31*, 6733-6736. Katritzky, A.R.; Shobana, N.; and Harris, P.A. *Tetrahedron Lett.*, **1990**, *31*, 3999-4002 . Dicker, I.B. *J.Org.Chem.*, **1993**, *58*, 2324-2327. Denmark, S.E.; Griedel, B.D.; and Coe, D.M. *J.Org.Chem.*, **1993**, *58*, 988-990. Collins, D.J.; Dosen, M.; and Jhingran, A.G. *Tetrahedron Lett.*, **1990**, *31*, 421-422. Boullet, F.T.; Latouche, R.; and Hamelin, J. *Tetrahedron Lett.*, **1993**, *34*, 2123-2126.
3. Eid, Jr, C.N.; Konopelski, J.P. *Tetrahedron Lett.*, **1990**, *31*, 305-306.
4. McElvain, S.M.; Curry, M.J. *J.Am.Chem.Soc.*, **1948**, *70*, 3781-3786.
5. DeWolfe, R.H.; *Carboxylic Ortho Acid Derivatives*, Academic Press, Inc. 1970, p.33.
6. Ernst, B.; DeMesmaeker, A.; Wagner, B.; Winkler, T. *Tetrahedron Lett.*, **1990**, *31*, 6167-6170.

7. Kochetkov, N.K.; Bochkov, A.F.; and Yazlovetsky, I.G. *Carbohyd. Res.*, **1969**, *9*, 49-60.
8. Anıl, H.; Yüceer, L.; Yüceer, T. *Carbohyd. Res.*, **1983**, *123*, 153-156.
9. Miller, J.B. *J.Org.Chem.*, **1960**, *25*, 1279-1285.
10. Anıl, H.; Yüceer, L. *Carbohyd. Res.*, **1983**, *123*, 315-319.
11. Physical data for key compounds:
All optical rotation values were obtained at 28 ± 2°C.
2: m.p. 184-186°C (methanol); $[\alpha]_D$ + 30.2 (c 1.7, CH_3OH). Diacetate of **2** : m.p. 42-44°C (pet-ether); $[\alpha]_D$-18.5 (c 1.0, Pet.ether); ^1H NMR (60 MHz, $CDCl_3$): δ 5.66 (s,$CHCCl_3$), 6.25 (d, $J_{1,2}$ 4Hz, H-1), 4.98 (d, $J_{2,3}$ ~0 Hz, H-2), 5.13 (bs, H-3), 3.80-4.50 (m, H-4,5,5'), 2.10, 2.15 (2s, 2xAc).
3: m.p. 159-161°C(CH_3OH); $[\alpha]_D$ +26.1(c 4.9, CH_3OH); ^1H NMR(400 MHz, CD_3OD): δ 5.99(s, -CCl_2H), 6.03(d, $J_{1,2}$ 4Hz, H-1), 4.58(q, $J_{2,4}$ ~1Hz, H-2), 4.28(s, $J_{2,3}$ ~0Hz, H-3), 4.50(m, H-4), 4.00(m, H-5), 3.67(m, H-6,6'); Mass spec.:241[M^+-(CH_2OH), 75%].
4: m.p. 117-119°C(EtOH-H_2O); $[\alpha]_D$-41.0(c 1.26, CH_3OH); ^1H NMR(60 MHz, CD_3OD): δ 5.98(s, -CCl_2H), 6.05(d, $J_{1,2}$ 4Hz, H-1), 4.63(q, $J_{2,4}$ ~1Hz, H-2), 4.13(m, H-3,4), 3.80 (m, H-5,5').
5: m.p. 123-124°C(Pet.ether); $[\alpha]_D$+41.0(c 2.13, CH_3OH); ^1H NMR(400 MHz, $CDCl_3$): δ 5.75 (s, -CCl_2H), 6.09(d, $J_{1,2}$ 4Hz, H-1), 4.81(q, $J_{2,4}$ ~1Hz, H-2), 5.24(s, $J_{2,3}$ ~0Hz, H-3), 4.60(bs, H-4), 4.37(m, H-6,6'), 4.25(m, H-5), 2.11, 2.16(2s, 2xAc); Mass spec.:283 [M^+-(CH_2OAc), 13%].
6: m.p.130-132°C($CHCl_3$); $[\alpha]_D$-60.89(c 0.77, $CHCl_3$); ^1H NMR(60 MHz, $CDCl_3$): δ 5.78(s, -CCl_2H), 6.08(d, $J_{1,2}$ 4Hz, H-1), 4.80(q, $J_{2,4}$ ~1Hz, H-2), 5.25(s, $J_{2,3}$ ~0Hz, H-3), 4.52 (m, H-4), 4.08, 4.12(bs, s, H-5,5'), 2.12(s, Ac).
8: $[\alpha]_D$-4.11(c 4, CCl_4); ^1H NMR(200 MHz, $CDCl_3$); δ 6.35(d, $J_{1,2}$ 4Hz, H-1), 5.00(d, $J_{2,3}$ ~0Hz, H-2), 4.45(bs, H-3), 3.80-4.15(m, H-4,5,6,6'), 1.26, 1.33(2s, 2xMe), 2.77(bs, OH); Mass spec.: 312(M^+, 33%), 297(M^+-Me, 20%), 254(M^+-Acetone, 28%), 236 (M^+-Acetone-H_2O, 15%).
9: m.p.103-105°C (CCl_4-Pet.ether); $[\alpha]_D$+9.50(c 1.42, $CHCl_3$); ^1H NMR(60 MHz, CCl_4): δ 5.98(s, -CCl_2H), 6.05(d, $J_{1,2}$ 4Hz, H-1), 5.13(m, H-2,3), 3.5-4.5(m, H-4,5,6,6'), 2.12, 2.16(2s, 2xAc), 1.43, 1.46(2s, 2xMe). ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.7, 166.0 (2xCH_3-C=O), 120.5 (C-orthoester), 110.1 (C-acetal), 107.2 (C-1), 89.3, 84.3, 77.1, 75.2, 71.2 (C-2 to C-5 and CCl_2H), 65.7 (C-6), 26.2, 25.6 (2xMe), 20.6, 21.6 (2xCH3-C=O); Mass spec.: 415(M^++1, 18%), 355 (415-AcOH, 75%), 356 (415-OAc, 20%), 101 (from C-4, C-5 bond fission, 100%).
12. All new compounds gave satisfactory elemental analyses except **8** which gave varying results in four consequtive analyses, two of which conformed with the K salt of **8**. We presume that this product is a partial K salt.

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