C4 *Carbohydrate Research*, 80 (1980) C4–C7

Preliminary communication

Some aspects of the Knoevenagel–Doebner and Wittig reactions

F. J. LOPEZ APARICIO
Department of Organic Chemistry, University of Granada (Spain)
and F. J. LOPEZ HERRERA
Department of Organic Chemistry, University of Málaga (Spain)

(Received December 10th, 1979; accepted for publication, January 21st, 1980)

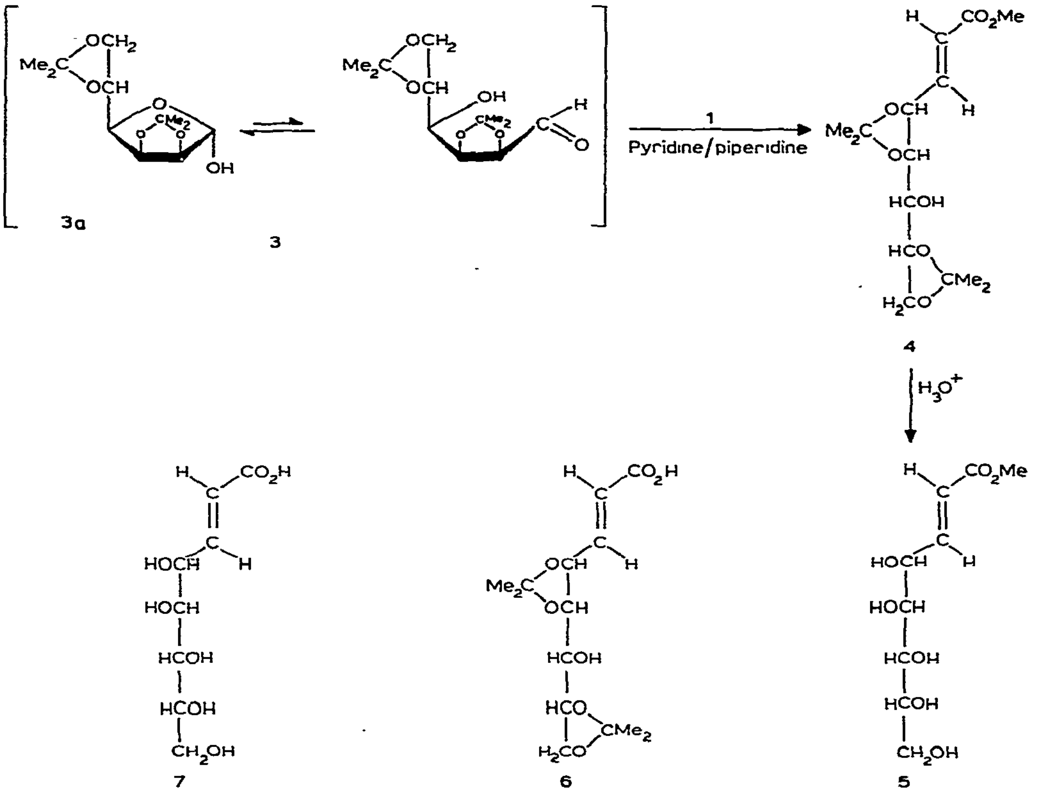
Both the Knoevenagel–Doebner[1] and the Wittig[2] reactions, when applied to a protected aldehydo sugar, can yield α,β-unsaturated esters when the appropriate reagents are used, for example, monomethyl malonate (1) for the Knoevenagel reaction and methoxycarbonylmethylenetriphenylphosphorane (2) for the Wittig reaction. The Knoevenagel reaction is more stereospecific and yields the *trans* product.

With partially protected reducing-sugars having HO-4 unsubstituted, an anomalous Wittig reaction[2,3] takes place. Recently[3a], derivatives of D-ribose, D-allose, and D-mannose have been treated with the ylid 2, showing that when a 2,3-*O*-isopropylidene group is present the products are the α and β anomers of the corresponding furanosyl *C*-glycosides. It was supposed that α,β-unsaturated esters were formed initially and subsequently underwent a spontaneous Michael-type ring-closure to give the furanosyl *C*-glycosides. The participation of this type of unsaturated ester as an intermediate in the anomalous Wittig reaction has been questioned[4], and the supposed intermediate 4 has been isolated[5].

In order to obtain more information about the supposed Michael-type cyclisation, we have reacted 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (3) and 1 in pyridine–piperidine at 90°. An excess of 1 was gradually added to provide for its loss by decarboxylation. The only product that was isolated in good yield was methyl *trans*-2,3-dideoxy-4,5:7,8-di-*O*-isopropylidene-D-*manno*-oct-2-enonate (4, 70%), m.p. 75–76°, $[\alpha]_D^{20}$ $-9°$ (*c* 1.3, methanol), λ_{max}^{MeOH} 215 nm (ϵ 6×10^{-3}). ^{1}H-N.m.r. data (CDCl$_3$): δ 6.85 (dd, 1 H, *J* 5 and 15 Hz, H-3), 6.08 (dd, 1 H, *J* 1 and 15 Hz, H-2), 4.56 (ddd, 1 H, *J* 1, 5, and 8 Hz, H-4), 3.7 (s, 3 H, MeO), and 2.3 (d, 1 H, *J* 7 Hz, exchangeable with D$_2$O, OH). Mass spectrum: *m/e* 301 (M$^+$ – Me).

Hydrolysis of 4 with 20% aqueous acetic acid yielded methyl *trans*-2,3-dideoxy-D-*manno*-oct-2-enonate (5), m.p. 119–120°, $[\alpha]_D^{20}$ $-28°$ (*c* 1, ethanol). ^{1}H-N.m.r. data (D$_2$O): δ 6.86 (dd, 1 H, *J* 5.5 and 16 Hz, H-3), 6.05 (dd, 1 H, *J* 1.8 and 16 Hz, H-2), and 3.7 (s, 3 H, MeO).

Hydrolysis of 4 with 5% aqueous KOH yielded the monohydrate of *trans*-2,3-dideoxy-4,5:7,8-di-*O*-isopropylidene-D-*manno*-oct-2-enonic acid (6), m.p. 117–118°, $[\alpha]_D^{20}$ $-19°$ (*c* 1, ethanol). ^{1}H-N.m.r. data (CDCl$_3$): δ 6.92 (dd, 1 H, *J* 6 and 16 Hz, H-3), 6.07 (dd, 1 H, *J* 1.5 and 16 Hz, H-2), 4.55 (ddd, *J* 1.5 and 6 Hz, H-4), and 1.3–1.5 (m, 12 H, 2 CMe$_2$).



Acid hydrolysis of **6** gave *trans*-2,3-dideoxy-D-*manno*-oct-2-enonic acid (**7**), m.p. 140–141°, $[\alpha]_D^{20}$ −24.5° (c 1, water). ^{1}H-N.m.r. data (D_2O): δ 7.15 (dd, 1 H, J 5 and 16 Hz, H-3) and 6.31 (dd, 1 H, J 1 and 16 Hz, H-2). On oxidation (sodium metaperiodate and Ag_2O), **7** gave only fumaric acid, in accord with the *trans* configuration of the 2,3-double-bond.

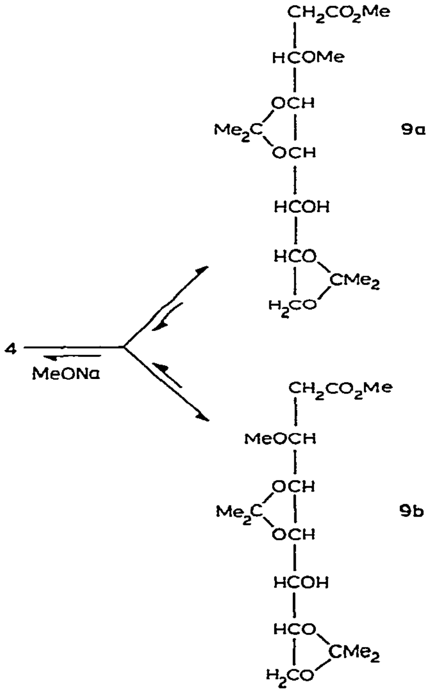
The accepted mechanism for the Knoevenagel–Doebner reaction does not suggest the possibility of the formation of cyclic products by any competing process, previously to, or simultaneously with, the formation of the double bond.

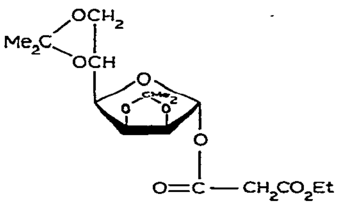
The isolation of **4**, the supposed intermediate in the ring-closure[3a] reaction, allows this supposition to be tested. However, **4** was stable under the conditions (the action of two mol of **2** under reflux in acetonitrile) reported for the anomalous Wittig reaction.

Although methyl *cis*- and *trans*-4,5,7-tri-*O*-benzyl-2,3-dideoxy-D-*ribo*-hept-2-enonate (**8**) cyclise under mild, basic conditions (0.1M MeONa in MeOH, 10 min at room temperature)[3a], **4** was stable to such treatment. However, after 12 h, a mixture of methyl 2-deoxy-4,5 : 7,8-di-*O*-isopropylidene-3-*O*-methyl-D-*glycero*-D-*galacto*- (**9a**) and -D-*glycero*-D-*talo*-octonate (**9b**) was produced in almost quantitative yield, and in the ratio 2:1 (by g.l.c.). These structures were assigned on the basis of elemental analysis, mass spectrum [m/e 333 ($M^+ - Me$)], i.r. spectrum [3500 cm^{-1} (OH; no absorptions for C=C and

=C–H)], and ^{1}H-n.m.r. data ($CDCl_3$) [δ 3.7 and 3.41 (2 MeO in **9a**) and 3.7 and 3.44 (2 MeO in **9b**)]. Absolute configurations at C-3 were shown when acid hydrolysis in the presence of periodic acid, followed by Ag_2O-oxidation and alkaline hydrolysis, gave a levorotatory (in water or acetone) mixture of methoxysuccinic acids. Thus, the preponderant isomer had the D-*glycero*-D-*galacto* configuration[6].

The failure of **4** to cyclise is probably due to steric hindrance at the β-face in the transition state[7].

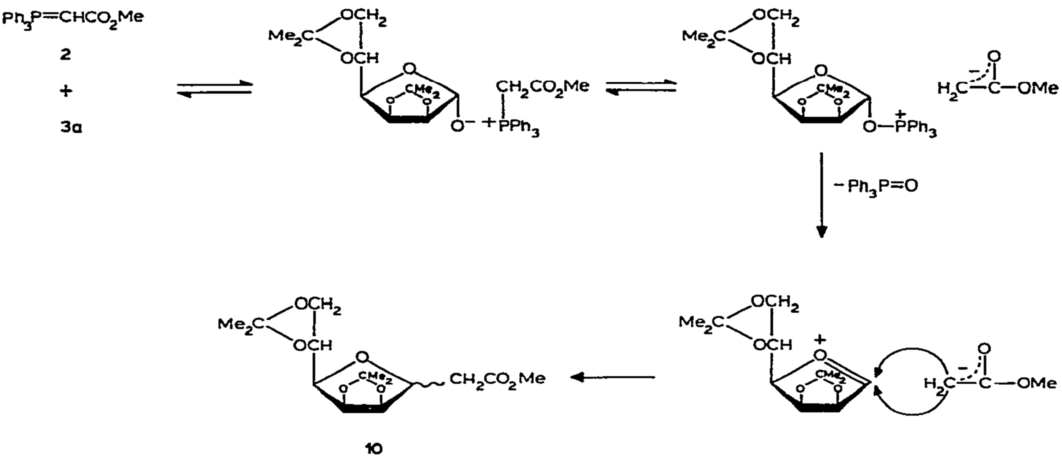




11

The above results show that the unsaturated ester **4** cannot be an intermediate in the anomalous Wittig reaction that leads to **10**. The annexed mechanism is proposed, which involves a betaine structure[8].

In an attempt to trap the intermediates in this reaction, an experiment was performed in diethyl malonate. In addition to **10**, the only new product appeared to be **11**, which could have been formed by the action of the anion of **3a** on the malonic ester.



REFERENCES

1 N. K. Kochetkov and B. I. Dmitriev, *Chem. Ind. (London)*, (1962) 2147–2148; *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1962) 1262–1263; F. Alonso Cermeño, A. M. Gonzalez Nogal, and F. J. Lopez Aparicio, *An. Quim.*, 68 (1972) 285–292; F. J. Lopez Aparicio and F. J. Lopez Herrera, *ibid.*, 72 (1976) 931–937; F. J. Lopez Aparicio, M. Gomez Guillen, and I. Izquierdo Cubero, *ibid.*, 72 (1976) 938–945; 73 (1977) 1168–1176.

2 Yu. A. Zhdanov, Yu. E. Alexeev, and V. G. Alexeeva, *Adv. Carbohydr. Chem. Biochem.*, 27 (1972) 227–299.

3 (*a*) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, 97 (1975) 4602–4613; (*b*) J. Cosineau and J. A. Secrist, III, *J. Carbohydr. Nucleos. Nucleot.*, 3 (1976) 185–189.

4 V. A. Polenov, Dissertation, Rostov-on-Don, cited in ref. 2, pp. 290–292.

5 Yu. A. Zhdanov and L. A. Uzlova, *Zh. Obshch. Khim.*, 41 (1971) 1396–1399.

6 T. Purdie and S. Williamson, *J. Chem. Soc.*, 67 (1895) 957–982; T. Purdie and H. W. Bolam, *ibid.*, 67 (1895) 944–956.

7 J. Defaye and D. Horton, *Carbohydr. Res.*, 14 (1970) 128–132.

8 M. Grayson, *J. Am. Chem. Soc.*, 82 (1960) 3919–3924.