

A Comparison of the Wittig and Knoevenagel–Doebner Reactions for the Chain Extension of Aldoses

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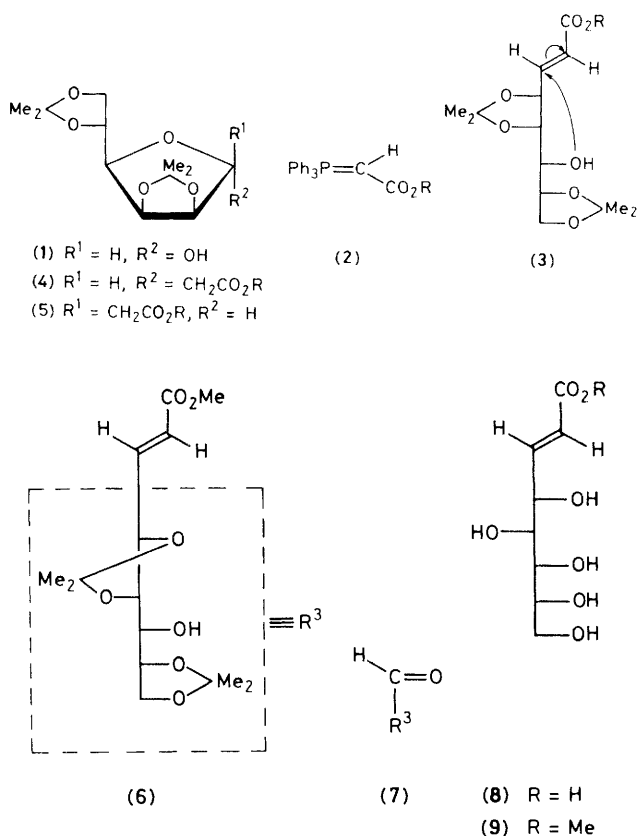
Reaction conditions are described for the chain extension of 2,3 : 5,6-di-*O*-isopropylidene-*D*-mannose (**1**) with a Wittig ylide (**2**) to give the acyclic *manno*-octenoate (**3**) or the *C*-glycofuranosides (**4** and **5**) and with the Knoevenagel–Doebner reaction to afford the isomeric *gluco*-octenoate (**6**); the isomerisation proved to occur in the latter reaction provides an explanation for an anomaly in the literature and indicates that the *C*-glycosides (**4** and **5**) are formed by a Michael-type ring closure rather than *via* a betaine intermediate.

Partially protected reducing aldose derivatives are known to undergo Wittig¹ and Knoevenagel–Doebner² reactions at the potential aldehyde group. Now, a comparative study is reported of the behaviour of 2,3 : 5,6-di-*O*-isopropylidene-*D*-mannose (**1**) in these reactions and it has been shown that the reactions involved are more complex than those which occur with simple aldehydes. We describe how the Wittig reaction can be employed to give preponderantly acyclic chain-extended sugar derivatives.

Treatment of the diacetonide (**1**) with the Wittig reagent (**2**, R = Me) in anhydrous benzene under reflux for 6 h gave a syrupy methyl *manno*-octenoate (**3**, R = Me) (55%),[†] { δ_{H} 6.21 (dd, $J_{2,3}$ 15.5, $J_{2,4}$ 1.2 Hz), 7.20 (dd, $J_{3,4}$ 6.5 Hz), 4.92 (ddd, $J_{4,5}$ 7.0 Hz), 4.53 (dd, $J_{5,6}$ 2.1 Hz), 3.80 (s, OMe), 2.45 (d, OH), and 1.36, 1.41, 1.42, and 1.57 (4 × Me); [α]_D²⁰ +16.9°, lit.,⁴ [α]_D¹⁷ +15.8°} together with a mixture of α - and β -*C*-furanosyl glycosides (**4** and **5**, R = Me). A more useful synthesis was achieved by similar treatment of compound (**1**) with the reagent (**2**, R = Et) which yielded the syrupy ethyl *manno*-octenoate (**3**, R = Et) as the sole product in 85% yield with [α]_D²⁰ +14.6°; δ_{H} 6.12 (dd, $J_{2,3}$ 16.0, $J_{2,4}$ 1.0 Hz), 7.11 (dd, $J_{3,4}$ 6.5 Hz), 4.86 (dt, $J_{4,5}$ 6.5 Hz), 4.48 (dd, $J_{5,6}$ 2.0 Hz), and 3.49 (m, 6-H).

The methyl and ethyl octenoates (**3**) could be cyclised to the glycosides (**4** and **5**) in base according to the conditions described by Moffatt and his co-workers.⁵ Moreover, when the diacetonide (**1**) was treated with 3 equivalents of the ylide (**2**, R = Me or Et) in acetonitrile under reflux, the *C*-glycofuranosides (**4** and **5**, R = Me or Et) were formed in reactions in which the intermediate u.v.-active enoate could be detected, thereby providing support for the proposal by Moffatt *et al.*⁵ that the *C*-glycosides are formed *via* enoates which undergo a Michael-type ring closure as indicated (**3**).

Treatment of compound (**1**) in a Knoevenagel–Doebner reaction with monomethyl malonate in pyridine and piperidine for 72 h at 90 °C gave, as anticipated, a methyl 4,5 : 7,8-di-*O*-isopropylidene-octenoate [72% yield after allowance is made for unchanged (**1**)] with m.p. 79 °C, [α]_D –22.2° (in MeOH), which Aparicio and his co-worker⁶ had similarly prepared and claimed had the *D* *manno* configuration. This configurational assignment must be incorrect since the physical constants for their compound differ from those reported here for compound (**3**) (R = Me) as do the ¹H and ¹³C n.m.r. spectra [δ_{H} 6.37 (dd, $J_{2,3}$ 16.0, $J_{2,4}$ 1.5 Hz), 7.16 (dd, $J_{3,4}$ 5.5 Hz), 4.79 (ddd, $J_{4,5}$ 8.0 Hz), 3.89 (OMe), 2.55 (d, OH), and 1.41, 1.46, 1.51, and 1.52 (4 × Me)]. Also, the chemical behaviour of the compound obtained by Aparicio and Herrera⁶ is different from that of our compound (**3**) since it could not be induced to cyclise, an observation interpreted by the Spanish workers as refuting Moffatt's mechanism for *C*-glycofuranoside formation; instead they proposed a betaine intermediate.



It occurred to us that the basic conditions employed in the Knoevenagel–Doebner reaction had caused epimerisation at C-4 to give an octenoate with the *D*-*gluco* configuration (**6**). This was shown to be so by synthesising compound (**6**) from 2,3 : 5,6-di-*O*-isopropylidene-*D*-glucose (**7**) by a Wittig reaction with the ylide (**2**, R = Me). Compound (**6**) was found to be identical with the compound described by Aparicio and Herrera⁶ and obtained by us from the Knoevenagel–Doebner reaction with the diacetonide (**1**). It could be converted, without concomitant cyclisation, into the acid (**8**) and ester (**9**) both of which had physical constants and n.m.r. spectral characteristics in close agreement with the compounds described by the Spanish workers.⁶ Consequently, they were handling *D*-*gluco* compounds rather than the *D*-*manno* isomers as they described. Also, it is now clear why they failed to induce cyclisation, since an intramolecular Michael reaction with compound (**6**) would produce a *C*-glycofuranoside with a highly strained *trans*-fused 4,5-*O*-isopropylidene ring system which is not the case with compound (**3**).

Attempts to isomerise compound (**1**) with base failed to yield 2,3 : 5,6-di-*O*-isopropylidene-*D*-glucose and one such experiment gave only *N*-(2,3 : 5,6-di-*O*-isopropylidene- α -*D*-mannofuranosyl)-piperidine in good yield.

[†] The configuration is defined since the octenoate has been converted into the known ammonium 3-deoxy-*manno*-oct-2-ulosonate.³

Satisfactory elemental analyses and spectral characteristics have been obtained for all compounds described. Unless stated otherwise optical rotations were measured for solutions in chloroform.

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