A Short Route to 2-*C*-Alkyl-2-deoxy-sugars from D-Mannose

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The lithium enolate (**2**), readily obtained from the D-mannose derivative (**1**) at low temperature, reacts with electrophilic reagents in a tetrahydrofuran–hexamethylphosphoric triamide mixture, providing a short route to 2-*C*-alkyl sugars; the subsequent enolization–alkylation creates a chiral quaternary carbon centre.

In recent years, there has been intense interest in the synthesis of natural products using carbohydrates as a chiral source.[1] For such purposes new synthetic routes leading to stereospecific carbon–carbon bond formation in a sugar moiety have been developed.[2,3] Ketone enolate alkylation has been widely used in organic synthesis,[4] and appears to be a useful route. Nevertheless, owing to their instability, ketone enolates of carbohydrates have not been extensively studied from this view point. To the best of our knowledge, Butterworth, Overend, and Williams[5] described the first α-methylation of a sugar ketone using a barium oxide–methyl iodide system. The use of sodium hydride led to decomposition. We report here our preliminary results in the alkylation of a ketone lithioenolate derived from D-mannose.

Table 1. 2-Deoxy-2-*C*-alkyl sugars obtained from (**2**)

Product	Reaction time/h	Yield (%)[a]	M.p./°C	[α]D (*c* 0.1,$CHCl_3$)
(**3a**)	1	41	203—205[b]	+129°[b]
(**3b**)	10	38	216	+85°
(**3c**)	8	44	156—158	+81°
(**3d**)	2	47	206—208	+136°
(**3e**)	0.5	55	163—165	+109°
(**4**)	18	49	124—126	+104°

[a] Yield of isolated pure products. [b] Lit.[8] m.p. 199—200 °C; [α]D +143.6°.

When the dibenzylidene sugar (**1**) was allowed to react with butyl-lithium at −30 °C, the lithium enolate (**2**) was formed.[6] We found that (**2**) reacted with some electrophiles at low temperature in the presence of hexamethylphosphoric triamide (HMPA), to give the expected alkylated derivatives (**3**).† The ^1H n.m.r. spectra of these compounds clearly established the equatorial position of the introduced chain. In addition a few dialkylated derivatives at C(2) have been isolated (<5%). Our

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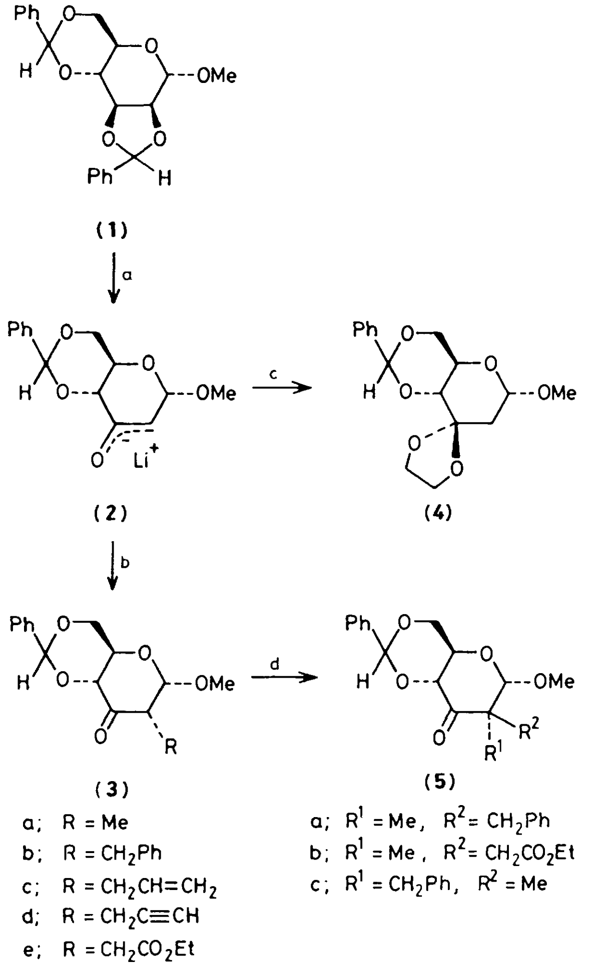
† Typically (**1**) (3 mM) in 50 ml of dry tetrahydrofuran was treated with butyl-lithium (6.6 mM) at −30 °C under argon. After 10 min hexamethylphosphoric triamide (5 ml) was added followed by the alkylating agent (3.6 mM). The mixture was stirred until the corresponding ketone had completely disappeared (monitored by t.l.c., AcOEt–hexane 1/3). The compounds (**3**) were isolated after hydrolysis with a saturated ammonium chloride solution and extracted with methylene chloride. Direct crystallization of the crude mixture afforded (**3a**) and (**3d**). Further purification was achieved by silica gel column chromatography.



Scheme 1. i; BuLi, THF, −30 °C. ii; RBr, HMPA–THF, −30 °C. iii; $BrCH_2CH_2OAc$, HMPA–THF, 0 °C. iv; LDA, THF, then R^2Br, HMPA–THF, −20 °C.

results are summarized in Table 1. When 2-bromoethyl acetate was used as the electrophilic reagent, reaction occurred only at 0 °C and led to the formation of (**4**). Spectral analysis and mass spectrometry confirmed the proposed structure. This represents a rare example of the formation of a dioxolan ring in a basic medium.[7]

We also investigated the alkylation of the ketone (**3**). For example deprotonation of (**3a**) with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −20 °C followed by reaction with an excess of benzyl bromide or ethyl bromoacetate led to the expected derivatives (**5a**) and (**5b**) in moderate yields together with some recovered starting material. In both cases a single isomer was isolated (see Table 2). The α-methylation of ketone (**3b**) was then studied. We were able to isolate, albeit in low yield, (**5c**), the C(2) epimer of (**5a**) (Scheme 1).‡ Spectral analyses were consistent with an equatorial orientation of the methyl group in (**5a**) and (**5b**) based on a comparison of the chemical shift of the methyl group in (**3a**) with its C(2) epimer.[8] This is a result of electrophilic attack from the less hindered β-face of the enolate. Only a few examples of such *gem*-dialkyl carbohydrates have been reported to date.[3,9]

Table 2. Results of the alkylation of (**3a**) and (**3b**).

Product	Starting ketone	Reaction time/ h	Yield (%)[a]	M.p./ °C	$[\alpha]_D$ (c 0.1, $CHCl_3$)
(**5a**)	(**3a**)	5	47	gum	+17°
(**5b**)	(**3a**)	2	44	128—30	+52°
(**5c**)	(**3b**)	5	28	gum	+35°

[a] Yield of pure product based on the starting ketone.

This application of ketone enolate alkylation to carbohydrates provides a new route to 2-*C*-alkyl-2-deoxy- and *gem*-dialkyl-sugars.

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‡ Alkylation at C(4) was also observed.