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Preliminary communication

The reaction of derivatives of methyl 2,3-*O*-benzylidene-α-L-rhamnopyranoside with butyl-lithium

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Retrosynthetic analysis of a number of rare sugars currently of interest in our laboratory indicated that methyl 2,6-dideoxy-α-L-*erythro*-hexopyranosid-3-ulose bearing a temporary protecting-group at position 4 would serve as a common precursor. Literature precedents[1,2] suggested that such a compound might be derived from a suitably protected methyl 2,3-*O*-benzylidene-α-L-rhamnopyranoside by expulsion of benzaldehyde through the action of organolithium compounds (formally as shown in **1**). The diastereoisomeric methyl 2,3-*O*-benzylidene-4-*O*-methyl-α-L-rhamnopyranosides (**2**), for example, react[1,2] with butyl-lithium in tetrahydrofuran at −30° to give an acceptable yield of **3**, which has been transformed[3] into L-evernitrose (**4**) by way of cyanomesylation. However, Horton and co-workers[2] have demonstrated that neither the hydroxylated compound **5** nor the benzyl ether **6** is suitable for the reaction, because either formation of the 4-oxyanion or abstraction of a proton from the benzyl group impedes the removal of a proton from the dioxolane ring. Although the transformation **7**→**8** (40% yield) has been accomplished[4] with *sec*-butyl-lithium in tetrahydrofuran at −30°, the use of tetrahydropyran-2-yl as a protecting group introduces a new centre of asymmetry, which is generally undesirable.

Our own efforts to secure a temporarily protected methyl 2,6-dideoxy-α-L-*erythro*-hexopyranosid-3-ulose have focused on the reaction of butyl-lithium with **9** and **10** at low temperatures. Each of the derivatives **9** and **10** was obtained as a distillable mixture of diastereoisomers when **5**[2] was allowed to react overnight at room temperature with either 2-methoxyethoxymethyl chloride[5] or methoxymethyl chloride in dichloromethane containing ethyldi-isopropylamine. The acetal groups at O-4 of **9** and **10** should withstand the strongly basic conditions of the elimination reaction, furnishing products having an acid-labile group at this position*.

Butyl-lithium reacted with **9** in tetrahydrofuran at −40° to give, after chromatography, the ketone **11** {m.p. 42–44°, $[\alpha]_D$ −235° (*c* 1, chloroform)} in 41% yield,

*Although cleavage of 2-methoxyethoxymethyl ethers occurs on prolonged treatment with butyl-lithium at *room temperature*, this reaction does not appear to be pre-eminent at lower temperatures[6]. The cleavage of ethers by alkyl-lithium reagents is well known[7].

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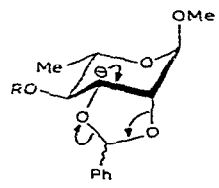

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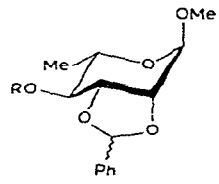
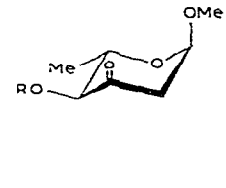
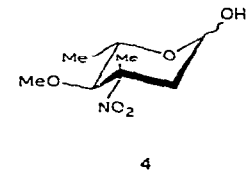


2 R = Me
5 R = H
6 R = Bzl
7 R = tetrahydropyran-2-yl (THP)
9 R = $CH_2OCH_2CH_2OMe$ (MEM)
10 R = CH_2OMe



3 R = Me
8 R = THP
11 R = MEM
12 R = CH_2OMe



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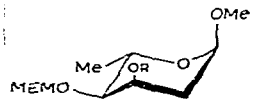
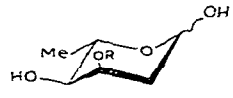


13 R = H
15 R = Me



14 R = H
16 R = Me

17

and with **10** at −30° to afford **12** {m.p. 73–74.5°, $[\alpha]_D$ −344° (*c* 1, chloroform)} in 38% yield. The somewhat moderate yields of **11** and **12**, which are comparable to those obtained in similar reactions[2,4], are recompensed by the directness of the route.

The usefulness of **11** and **12** in synthesis is illustrated by the following examples. L-Digitoxose (**14**) is available by reduction of **11** with sodium borohydride to give **13** {81%, b.p. 95–100° (bath)/0.2 mmHg, $[\alpha]_D$ −128° (*c* 1, chloroform)}, which yielded the free sugar {71%, m.p. 105–107°, $[\alpha]_D$ −47° (equil., *c* 1, water)**} on hydrolysis with boiling, aqueous acetic acid. Methylation[9] of **13** in anhydrous tetrahydrofuran gave **15** {92%, b.p. 75–80° (bath)/0.05 mmHg, $[\alpha]_D$ −158° (*c* 1, chloroform)}, which liberated L-cymarose*** (**16**) on acidic hydrolysis (0.05M sulphuric acid at 65–70° for 2 h). *Hydrogenation of the oxime* {83%, m.p. 78–81°, $[\alpha]_D$ −320° (*c* 1, chloroform)} derived from **11** over Adams' catalyst in methanol containing acetic anhydride furnished the acetamido derivative **17** {b.p. 128–132° (bath)/~0.1 mmHg, $[\alpha]_D$ −166° (*c* 1.3, chloroform)} in virtually quantitative yield. Hydrolysis of **17** with boiling, aqueous acetic acid gave *N*-acetyl-L-ristosamine {72%, m.p. 133–135°, $[\alpha]_D$ −38° (equil., *c* 0.7, water)†}. This synthesis of an L-ristosamine derivative compares favourably with others in the literature[13].

In connection with synthetic work on methyl-branched amino and nitro sugars, we have found that **12** can be converted by the Bourgeois procedure[14] into the cyano-

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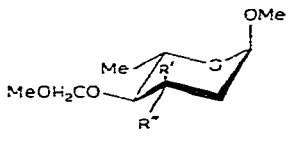
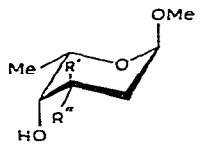
**D-Digitoxose has m.p. 105–108°, $[\alpha]_D$ +47.8° (equil., *c* 1.06, water)[8].

***This sugar, which was required in connection with structural studies of variose[10], was identified by comparison with the D enantiomer[11].

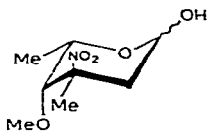
†The D enantiomer has m.p. 134°, $[\alpha]_D$ +39° (equil., *c* 0.5, water)[12].



18 R′ = OH, R″ = CN
19 R′ = CN, R″ = OH
20 R′ = OMs, R″ = CN
21 R′ = CN, R″ = OMs



22 R′ = Me, R″ = NHAc
23 R′ = NHAc, R″ = Me



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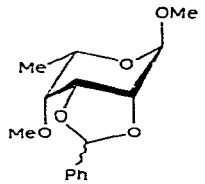

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hydrins **18** {m.p. 74.5–76.5°, $[\alpha]_D$ −146° (*c* 0.85, chloroform)} or **19** {m.p. 84.5–86°, $[\alpha]_D$ −81° (*c* 1, chloroform)}. Equilibration studies established that **18** is the kinetic product, whose configuration at C-3 was assigned by analogy[3] and chemical correlation[15]. Mesylation of **18** and **19** gave **20** {m.p. 112–114°, $[\alpha]_D$ −126° (*c* 0.6, chloroform)} and **21** {m.p. 127–128.5° (dec.), $[\alpha]_D$ −155° (*c* 1.15, chloroform)}, respectively, in good yield. Current work, based on literature precedents[3,14,16], is directed towards the synthesis of the L-vancosaminide **22**[17], its stereoisomer **23**[18], and L-rubranitrose[19] (**24**) [a stereoisomer of L-evernitrose[20] (**4**)] from **20** and **21**. Since these transformations involve manipulation of the configuration at C-4, they require temporary protection of the hydroxyl group at this position*. This approach to L-rubranitrose (**24**), for example, was prescribed by the failure of the benzylidene-L-talopyranoside **25** to eliminate benzaldehyde on treatment with butyl-lithium[15] (*cf.* **2**→**3**[2]).

New compounds had elemental analyses and spectroscopic properties in agreement with the structures assigned.

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*We have recently reported[21] an alternative synthesis of the L-vancosaminide **22**, in which an oxidation–reduction sequence was used to invert the configuration at C-4 of the equatorial isomer.

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