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An efficient and versatile synthesis of apiose and some C-1-aldehyde- and/or 2,3-*O*-protected derivatives†

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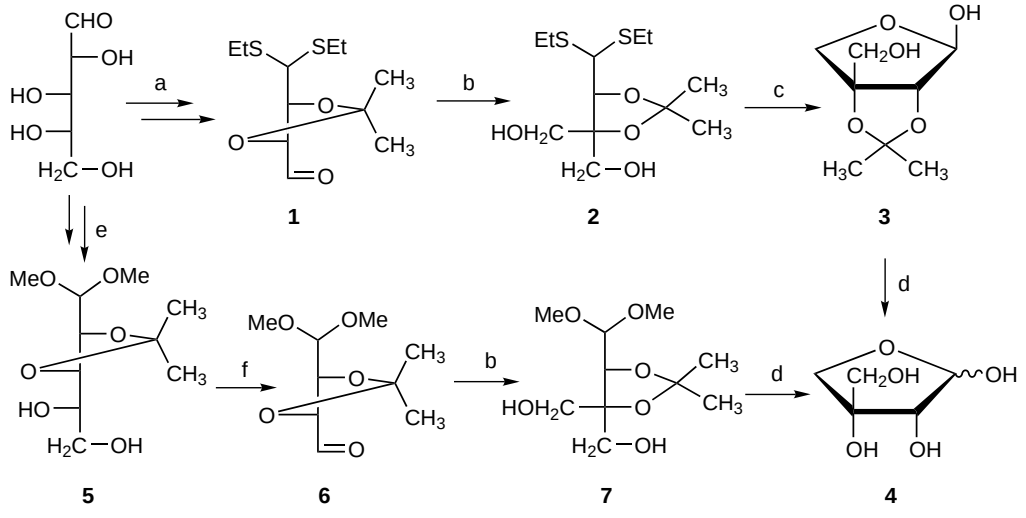
Abstract—The synthesis of 2,3-*O*-isopropylidene-β-D-apiofuranose (58% overall yield) from L-arabinose via 3-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-D-*glycero*-tetrose diethyl dithioacetal is reported. Starting from L-arabinose an alternative precursor of D-apiose, 3-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-D-*glycero*-tetrose dimethyl acetal, was prepared from 2,3-*O*-isopropylidene-L-*threo*-tetrodialdose dimethyl acetal and formaldehyde by the aldol-Cannizzaro reaction. Unprotected D-apiose is accessible from both precursors on acid hydrolysis.

A branched-chain sugar D-apiose [3-*C*-(hydroxymethyl)-D-*glycero*-tetrose, which can exist in two furanose forms, i.e. 3-*C*-(hydroxymethyl)-D-erythrofuranose and 3-*C*-(hydroxymethyl)-L-threofuranose][1] occurs widely in plants as a terminal residue of polysaccharides and glycosides, duckweed being a particularly rich source. It was first found in parsley in which it occurs as the flavinoid glycoside apiin.[2] D-Apiose-containing glycosides, such as saponins, flavinoids, phenolic or anthraquinone glycosides play an integral role in the biochemistry of plants.[3] Recently, some apionucleosides have been reported to be compatible with antiviral activities.[4,5]



Scheme 1. *Reagents and conditions*: (a) four steps, 74% overall (Ref. 18a,b); (b) aq. CH_2O, EtOH, NaOH, rt, 5 h, 83% of **2**, 80% of **7**; (c) HgO, $HgCl_2$, Me_2CO, H_2O, rt, 3 h, 95% (58% overall from arabinose); (d) Dowex-50 W (H^+), H_2O, 70°C, 5 h, 95%; (e) two steps, 40% overall (Ref. 19); (f) $NaIO_4$, MeOH, H_2O, 5°C to rt, 1 h, 90%.

Keywords: aldol-Cannizzaro reaction; acetals; dithioacetals.

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Numerous syntheses of apiose and its derivatives have been published,[6–17] most of which utilize the base-catalyzed condensation of an excess of formaldehyde with a suitably *O*-protected *aldehydo*-carbohydrate derivative.[9–14] All these procedures are multistep syntheses with rather low, at most moderate overall yields.

The submitted method is based on the protection of a C-1 aldehyde and all hydroxyl groups of an open chain pentose, generation of a C-4 aldehyde and its subsequent aldol-Cannizzaro reaction with formaldehyde to give apiose with protected functionality at C-1, C-2, and C-3 (Scheme 1). Unlike published methods where C-4 of the starting pentose becomes the C-1 aldehyde group of the final apiose derivative, in this approach the head and tail of the starting pentose chain do not become reversed. Due to the loss of chirality at C-3 in the product from the aldol-Cannizzaro step, only the stereochemistry at C-2 in the starting pentose determines whether D- or L-apiose will be formed. Thus, the choice of starting pentose is a matter of availability of the suitably protected *aldehydo*-pentose and whether the target is D- or L-apiose.

Considering these facts, D- or L-arabinose is the best choice and this method affords known[9–14] crystalline 2,3-*O*-isopropylidene-β-D- or L-apiofuranose in almost 60% overall yield (six steps from arabinose).

Thus, starting from L-arabinose, the corresponding 2,3-*O*-isopropylidene-L-*threo*-tetrodialdose diethyl dithioacetal (**1**) was prepared by a previously published four-step procedure[18] in 74% overall yield. The aldol-Cannizzaro reaction of protected dialdose **1** with a slight excess of formaldehyde gave 3-*C*-(hydroxymethyl)-2,3-*O*-isopropylidene-D-*glycero*-tetrose diethyl dithioacetal (**2**) in 83% yield. Conventional removal of the dithioacetal functionality afforded 2,3-*O*-isopropylidene-β-D-apiofuranose (**3**) in 95% yield (58% overall from L-arabinose).

An alternative precursor suitable for the aldol-Cannizzaro reaction, 2,3-*O*-isopropylidene-L-*threo*-tetrodialdose dimethyl acetal (**6**), was prepared from 2,3-*O*-isopropylidene-L-arabinose dimethyl acetal (**5**) (synthesized from L-arabinose in two steps according to the method published[19] for the D-isomer). 3-*C*-(Hydroxymethyl)-2,3-*O*-isopropylidene-D-*glycero*-tetrose dimethyl acetal (**7**) was obtained from **6** in 80% yield under the same reaction conditions[20] as applied to the preparation of **2**. Both **3** and **7**, when treated with Dowex 50 W(H^+) in water at 70°C, afforded free D-apiose (depicted as the 3-*C*-(hydroxymethyl)-D-erythrofuranose form **4**, Scheme 1) which was characterized as the corresponding *N*-benzylphenylhydrazone.[9,13]

In summary, we have described an alternative and efficient route to apiose and its new protected derivatives.[20] Especially, protection at C-1, O-2 and O-3 provides a potential for further modification at both hydroxymethyl groups giving rise to further new interesting apiose analogs. Moreover, this method affords the highest overall yields (58%) of the known 2,3-*O*-protected apiofuranose **3** presented up until now, which together with an inexpensive starting material and other chemicals, as well as routine synthetic procedures used throughout the synthesis, also makes this method interesting for large-scale preparations of apiose itself or it may be of more general utility in preparing suitably protected derivatives.

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20. Typical experimental procedure for aldol-Cannizzaro reaction is given in Ref. 13. CIMS: **2**: *m*/*z* 376.5 [M+C_5H_5NH]$^+$; **6**: *m*/*z* 284 [M+C_5H_5NH]$^+$; **7**: *m*/*z* 316 [M+C_5H_5NH]$^+$.