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Improved Protocol towards Isotopically Labelled 1-Deoxy-D-xylulose

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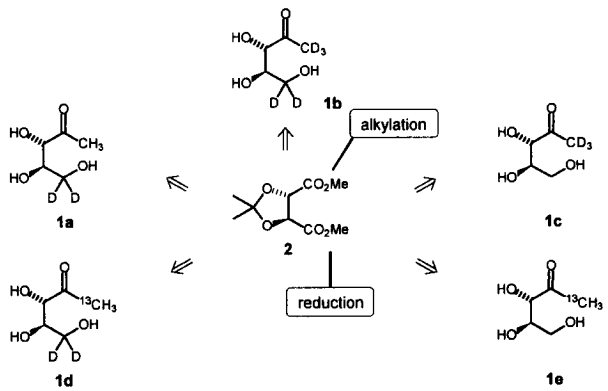
Abstract: An improved synthetic protocol towards 1-deoxy-[4,4-$^2H_2$]-D-xylulose (**1a**) (= 1-deoxy-[4,4-$^2H_2$]-D-*threo*pentulose) from dimethyl 2,3-*O*-isopropylidene-D-tartrate (**2**) (44% overall yield) is described. The key-operation is a novel one-pot reductive alkylation of the protected halfester **3**, by sequential treatment with superdeuteride(hydride) and methyl lithium, providing the protected 1-deoxy-D-xylulose (**5**) in high yield.

1-Deoxy-D-xylulose (DOX) and its 5-phosphate, first isolated in 1976 from *Streptomyces hygroscopicus*,[1] represent important intermediates within several biochemical pathways of pro- and eucaryotes. Following the recent discovery of a novel, mevalonate-independent pathway towards terpenoids,[2-5] the deoxysugar has gained particular attention as an alternate source for isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAP), the two principal building blocks of all terpenoids. In higher plants and bacteria isotopomers of DOX are readily incorporated into the terpenoids resulting in a degree of specific labelling far exceeding that known from administration of labelled mevalonates.[4,6,7] Due to the exceptional importance of the mevalonate-independent pathway in bacteria and plants, there is now a substantial demand for larger quantities of labelled 1-deoxy-D-xylulose, in particular that labelled with ^2H or ^{13}C for mass spectrometry or NMR studies. Accordingly, during the last two years several (semi)synthetic approaches have been published[7,8] but, to date, none of them matched all requirements for a simple and high yielding approach to selectively labelled isotopomers of 1-deoxy-D-xylulose like **1a-e**.



Scheme 1. Synthesis of isotopomers of 1-deoxy-D-xylulose **1a-e** from the protected tartaric diester **2**

Recently, we utilized the protected tartaric diester **2** as a highly versatile precursor towards various isotopically labelled deoxy-D-xyluloses **1a-e**.[9] The key step of this previously published sequence was alkylation of the isolated dilithio salt of the carboxylate-alcohol (corresponding to **4**, Scheme 2) with a large excess of methyl lithium (12.5 equiv.). The major drawback of this otherwise straightforward procedure was the extremely hygroscopic nature of the hydroxyacid, lithium salt, which required extensive drying and accounted for the large excess of methyl lithium. Larger scale preparations (> 0.5 g) were hampered for the same reason. Here we disclose that reduction and alkylation of the half ester **3** → **5**, can be achieved in a single

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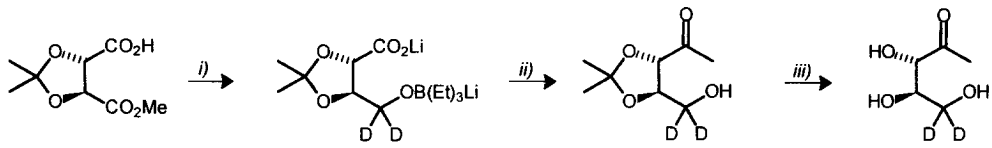
operation without isolation of intermediates. Moreover, the new approach requires only 4.0 equivalents of the organometallic reagent, thus allowing an economic use of $^{13}CH_3Li$ for the synthesis of 1-deoxy-[1-^{13}C]-D-xylulose **1e** or a doubly labelled 1-deoxy-[1-^{13}C, 5,5-$^{2}H_2$]-D-xylulose like, for example **1d**.



3 **4** **5** **1a**

Scheme 2. *i)* 3.2 eq. $LiBEt_3D$/THF, 0 °C , 1h; *ii)* 4.0 eq. CH_3Li/THF, 0 °C, 2 h then CO_2; *iii)* 2N HCl/H_2O/CH_3CN, 25 °C, 24h.

Thus, the readily available[9] half ester **3** is reduced with 3.2 eq. $LiBEt_3D$ and the resulting dilithio salt of trialkylalkoxyboronate-complex **4** is directly alkylated with 4.0 equiv. of CH_3Li yielding the hydroxyketone **5** after non-protic work-up with CO_2 as described (68 % yield).[9] Removal of the isopropylidene group was achieved in 73% yield with 2 N HCl using a solvent mixture of H_2O and CH_3CN.[10,11] The overall yield from **2** to the deuterium labelled sugar **1a** was 44%, illustrating the high efficiency of the sequence.

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References

1. Slechta, L.;Johnson, L.F. *J. Antibiot.* **1976**, *29*, 685.
2. Flesch, G.; Rohmer, M. *Eur. J. Biochem.* **1988**, *175*, 405.
3. Rohmer, M.; Knani, M.; Simonin, P.; Sutter, B.; Sahm, H. *Biochem. J.* **1993**, *295*, 517.
4. Arigoni, D.; Sagner, S.; Latzel, C.; Eisenreich, W.; Bacher, A.; Zenk, M. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 10600-10605 and references cited therein.; Eisenreich, W.; Schwarz, M.; Cartayrade A.; Arigoni D.; Zenk MH.; Bacher A. *Chem. Biol.* **1998**, *5*, 221.
5. Lichtenthaler, H.K. *Fett/Lipids* **1998**, *100*, 128.
6. Piel, J.; Donath, J.; Bandemer, K.; Boland, W. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2478.
7. Adam K.P.; Zapp J., *Phytochemistry* **1998**, *48*, 953.
8. Blagg B.S.J.; Poulter C.D., *J. Org. Chem.* **1999**, 64, 1508, and references cited therein.
9. Piel, J.; Boland, W. *Tetrahedron Lett.* **1997**, *38*, 6387.
10. Kennedy, I.A.; Hemscheidt, T.; Britten, J.F.; Spenser, I.D. *Can. J. Chem.* **1995**, *73*, 1329.
11. *One Pot Reduction and Alkylation of 3.* A chilled and well stirred solution of **3** (1,02 g, 5 mmol) in dry THF (15 ml) was gradually treated within 10 min with $LiBEt_3D$ in THF (1M solution, 16 ml, 1.6 mmol). Stirring was continued for 1h at 0°C and then cold THF (30 ml, 0°) was added, followed after 5 min by a solution of methyl lithium in diethyl ether (5%-soln., 13 ml, 20,0 mmol). After stirring for 2h at 0° dry CO_2 was quickly sparkled through the mixture to quench remaining methyl lithium. The yellow, slightly clouded mixture was slowly poured into conc. aq. NH_4Cl (500 ml) and the pH was adjusted at 3.5 with 2N HCl. After vigorous stirring for 30 min to hydrolyze BEt_3-complexes the mixture was neutralized with 2 N NaOH, saturated with NaCl and extracted with EtOAc (3 x 200 ml). The combined organic layers were dried (Na_2SO_4), the solvent evaporated and the product purified by column chromatography on Florisil using pentane/ethyl acetate (1:1) for elution. Colorless oil (0.60 g, 68 % from **3**).