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New and Efficient Synthetic Routes to 1-Deoxy-D-xylulose

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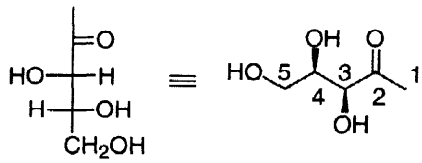
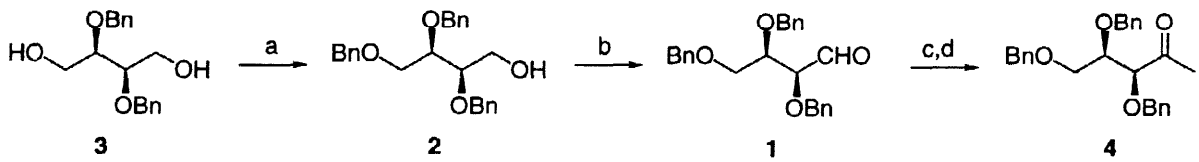
Abstract: The biochemically important deoxysugar 1-deoxy-D-xylulose was synthesized by improved methods. D-Tartaric acid is the starting material for a synthesis which proceeds via the intermediacy of 2,3,4-tribenzyl-D-threitol. Another, highly efficient route used the Sharpless asymmetric dihydroxylation of 5-benzyloxy-3-penten-2-one as its key step. These syntheses are especially useful for isotopic labeling. © 1998 Published by Elsevier Science Ltd. All rights reserved.

1-Deoxy-D-xylulose is a deoxyketopentose which is important as a biosynthetic precursor to vitamins B_1 and B_6 in bacteria.[1,2] It is also a precursor to isoprenoids in bacteria and higher plants[3-6] via a non-mevalonate pathway.[7] In connection with biosynthetic studies on this latter pathway, various forms of isotopically labeled 1-deoxy-D-xylulose needed to be prepared. The synthetic routes described in this paper were developed to allow the efficient synthesis of this sugar and to allow its synthesis in several isotopically labeled forms.



Various routes for the synthesis of 1-deoxy-D-xylulose have been published.[6,8-11] The reaction of a protected D-threose with an isotopically labeled methyl Grignard reagent seemed the most convenient method for labeling of the 1-position with ^{13}C or deuterium.[9,10] Benzyl ethers were chosen to be the sole protecting groups in order to avoid multiple deprotection steps and side reactions during the acidic deprotection of acetonides.[9] The required 2,3,4-tribenzyl-D-threose (**1**)[12] was prepared by Swern oxidation of 2,3,4-tribenzyl-D-threitol (**2**),[13] which was synthesized from diisopropyl-D-tartrate in three steps via the known 2,3-dibenzyl-D-threitol (**3**) (Scheme 1).[14] Quantitative deprotection of the resulting 3,4,5-tribenzyl-1-deoxy-D-xylulose (**4**)[15] was achieved by hydrogenation over 10% Pd/C in methanol at ambient temperature and pressure.



3 **2** **1** **4**

a. NaH, BnBr, THF, r.t. (75%); b. Swern (89%); c. MeMgBr, Et_2O, 0 °C (95% based on 10% recovery of starting material); d. Swern (88%).

Scheme 1

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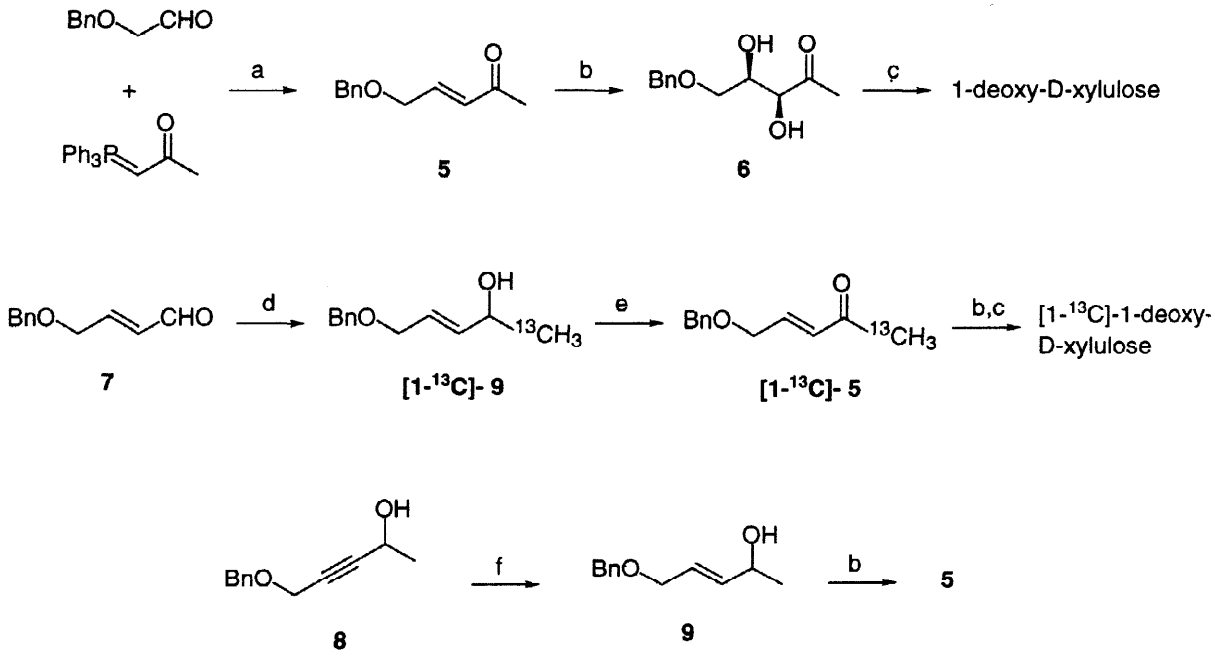
A more concise approach to 1-deoxy-D-xylulose was found using asymmetric dihydroxylation (AD) of (E)-5-benzyloxy-3-penten-2-one (**5**)[16] under the conditions specified by Walsh and Sharpless.[17] This reaction proceeds in high yield and with high stereoselectivity (Scheme 2). The product (5-benzyl-1-deoxy-D-xylulose, **6**)[18] consistently had a specific rotation $[\alpha]_D^{20}$ = +52.5 (CH_2Cl_2, c=1.17), which matched that reported for the same material derived from D-tartaric acid.[9] The product is easily purified by silica gel chromatography, and cleanly deprotected by catalytic dehydrogenation (10% Pd/C in methanol, quantitative).[9] Furthermore, protection at the 5-position prevents the formation of isomeric hemiketals which have been found to complicate the purification and analysis of 1-deoxy-D-xylulose derivatives when the 5-hydroxyl group is left unprotected.[10]



a. CH_2Cl_2, r.t. (82%); b. modified AD-reaction (86%); c. H_2, 10% Pd/C, MeOH, r.t. (quantitative); d. $^{13}CH_3MgI$, Et_2O, 0 °C (77%); e. Swern (79%); f. $LiAlH_4$

Scheme 2

The enone starting material (**5**) for the AD-route is readily synthesized, permitting isotopic labeling in various positions. A Wittig route to the enone[19] (E/Z product ratio 12:1) enables deuterium to be conveniently introduced into either the 3- or the 4 positon of 1-deoxy-D-xylulose.[20] A second route to the enone **5** enables labeling of the 1-position of 1-deoxy-D-xylulose via the reaction of isotopically labeled methyl Grignard reagents (e.g. [^{13}C]-MeMgI) with (E)-4-benzyloxy-2-butenal (**7**).[21] A third route starts from progargyl alcohol **8**,[22,23] available from benzyl propargyl ether[24] and acetaldehyde. Lithium aluminum hydride reduction of **8** gives the allylic alcohol **9**[21,25] in the E-configuration. Complete deuteration of the 3-position is obtained by using $LiAlD_4$, while the 4-position is cleanly deuterated by quenching the reduction reaction with D_2O.

1-Deoxy-D-xylulose could also be synthesized with deuterium in the 1-position by an exchange reaction. The methyl protons of 5-benzyl-1-deoxy-D-xylulose were readily exchanged in 20 mM NaOD in 90%

CH_3OD/D_2O. Under these conditions no exchange was detected by ^2H-NMR at the 3-position, although exchange at the 3-position (with epimerization) resulted when 0.5 M NaOD was used. Mild acidic conditions (20 mM DCl in 90% CH_3OD/D_2O) caused no detectable exchange.

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12. **1:** ^1H-NMR (300 MHz, $CDCl_3$): 9.708 (1H, d, J=1 Hz), 7.37-7.23 (15H, m), 4.753 (2H, d, J=11.8 Hz) coupled to 4.562 (2H, d, J=11.8 Hz), 4.636 (2H, d, J=11.8 Hz) coupled to 4.552 (2H, d, J=11.8 Hz), 4.462 (2H, s), 4.01-3.94 (2H, m), 3.71-3.61 (2H, m); ^{13}C-NMR (75 MHz, $CDCl_3$): 202.314 (s), 137.869 (s), 137.758 (s), 137.243 (s), 128.505 (d, 2C), 128.393 (d, 4C), 128.225 (d, 2C), 128.121 (d), 128.017 (d, 2C), 127.872 (d), 127.719 (d, 3C), 82.987 (d), 78.059 (d), 73.444 (t, 2C), 72.986 (t), 68.235 (t). MS (EI, 70 eV) m/z: 391 ($M+1^+$, 2%), 361 (2), 283 (10), 240 (11), 181 (31), 91 (100).
13. **2:** $[\alpha]_D^{20}$ = -10.7 (CH_2Cl_2, c=1.12); ^1H-NMR (300 MHz, $CDCl_3$): 7.39-7.25 (15H, m), 4.742 (2H, d, J=11.8 Hz) coupled to 4.631 (2H, d, J=11.8 Hz), 4.664 (2H, d, J=11.8 Hz) coupled to 4.615 (2H, d, J=11.8 Hz), 4.535 (2H, s), 3.85-3.61 (6H, m); ^{13}C-NMR (75 MHz, $CDCl_3$): 138.349 (s), 138.328 (s), 138.024 (s), 128.448 (d, 2C), 128.429 (d, 2C), 128.401 (d, 2C), 128.012 (d, 2C), 127.938 (d, 2C), 127.798 (d), 127.746 (d), 127.720 (d, 3C), 79.293 (d), 78.635 (d), 73.550 (t), 72.970 (t), 72.870 (t), 69.608 (t), 61.606 (t). MS (EI, 70 eV) m/z: 393 ($M+1^+$, 1%), 301 (3), 195 (9), 181 (9), 91 (100).
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15. **4:** $[\alpha]_D^{25}$ = -34.8 (CH_2Cl_2, c=1.35); ^1H-NMR (300 MHz, $CDCl_3$): 7.38-7.24 (15H, m), 4.686 (2H, d, J=11.7 Hz) coupled to 4.466 (2H, d, J=11.7 Hz), 4.658 (2H, d, J=11.7 Hz) coupled to 4.541 (2H,

d, J=11.7 Hz), 4.447 (2H, s), 4.03-3.97 (2H, m), 3.67-3.61 (2H, m), 2.168 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$): 210.587 (s), 137.936 (s), 137.876 (s), 137.253 (s), 128.508 (d, 2C), 128.427 (d, 2C), 128.371 (d, 2C), 128.343 (d, 2C), 128.177 (d, 2C), 128.109 (d), 127.859 (d), 127.742 (d, 3C), 84.763 (d), 78.823 (d), 73.704 (t), 73.389 (t), 73.375 (t), 68.868 (t), 27.846 (q). MS (EI, 70 eV) m/z: 405 ($M+1^+$, 4%), 297 (5), 254 (9), 240 (11), 181 (25), 91 (100).

16. **5:** ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40-7.26 (5H, m), 6.802 (1H, dt, J=16.1, 4.5 Hz, H-4), 6.351 (1H, dt, J=16.1, 1.9 Hz, H-3), 4.573 (2H, s, Bn CH_2), 4.204 (2H, dd, J=1.9, 4.5 Hz, H-5), 2.265 (3H, s, H-1); ^{13}C-NMR (75 MHz, $CDCl_3$): 198.025 (s), 142.873 (d, C-4), 137.639 (s), 130.407 (d, C-3), 128.477 (d, 2C), 127.875 (d), 127.670 (d, 2C), 72.943 (t), 68.822 (t), 27.230 (q).
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18. **6:** ^{1}H-NMR (300 MHz, CD_3OD): 7.37-7.22 (5H, m), 4.543 (2H, s, Bn CH_2), 4.181 (1H, d, J=2.4 Hz, H-3), 4.130 (1H, dt, J=2.4, 6.3 Hz, H-4), 3.629 (1H, dd, J=6.3, 9.6 Hz, H-5), 3.534 (1H, dd, J=6.3, 9.6 Hz, H-5), 2.214 (3H, s); ^{1}H-NMR (300 MHz, $CDCl_3$): 7.41-7.17 (5H, m), 4.573 (2H, s, Bn CH_2), 4.26-4.17 (2H, m, H-3,4), 3.714 (1H, d, J=4.4, OH), 3.644 (1H, s, H-5), 3.623 (1H, d, J=0.8 Hz, H-5), 2.372 (1H, d, J=7.5 Hz, OH), 2.279 (3H, s); ^{13}C-NMR (75 MHz, $CDCl_3$): 208.068 (s), 137.599 (s), 128.528 (d, 2C), 127.973 (d), 127.881 (d, 2C), 77.150 (d, C-3), 73.664 (t), 71.013 (t, C-5), 70.459 (d, C-4), 25.565 (q).
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23. **8:** ^{1}H-NMR (300 MHz, $CDCl_3$): 7.39-7.26 (5H, m), 4.593 (2H, s), 4.582 (1H, m), 4.026 (2H, d, J=1.6 Hz), 1.473 (3H, s, J=6.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): 137.432 (s), 128.416 (d, 2C), 128.042 (d, 2C), 128.856 (d), 88.460 (s), 79.984 (s), 71.723 (t), 58.398 (d), 57.408 (t), 24.271 (q). MS (EI, 70 eV) m/z: 190 (M^+, 6%), 145 (40), 117 (15), 107 (24), 105 (15), 91 (100).
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25. **9:** ^{1}H-NMR (300 MHz, $CDCl_3$): 7.39-7.24 (5H, m), 5.803 (2H, m), 4.528 (2H, s), 4.338 (1H, m), 4.028 (2H, m), 1.531 (1H, br. s), 1.287 (3H, d, J=6.4 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): 138.250 (s), 137.084 (d, C-3), 128.369 (d, 2C), 127.733 (d, 2C), 127.611 (d), 126.276 (d, C-4), 72.330 (t), 70.102 (t), 68.212 (d), 23.190 (q).