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Synthesis of new 2- or 3-deoxy carbapyranoses from furan

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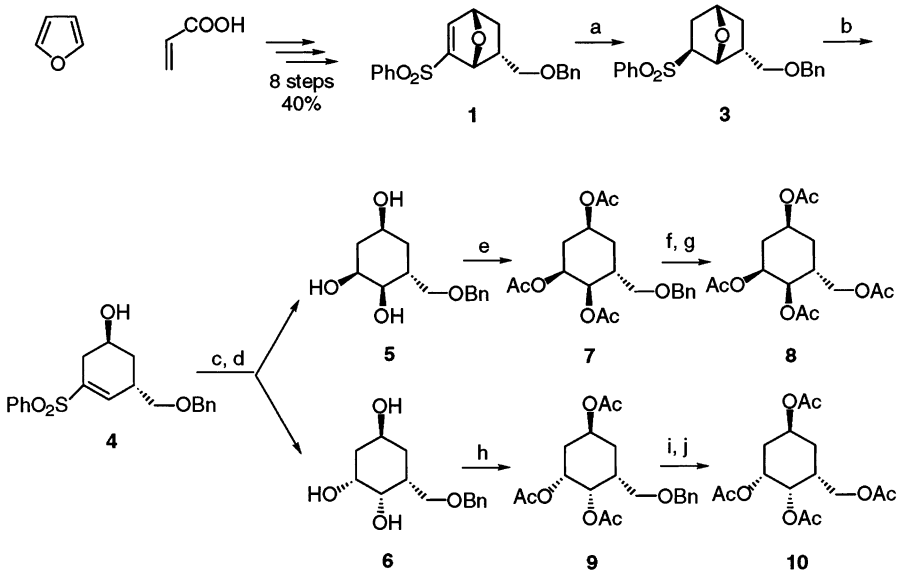
Abstract—The synthesis of new 2- or 3-deoxy carbapyranoses of the *allo*-, *galacto*-, *gluco*- and *manno*-series starting from furan are described. © 2001 Published by Elsevier Science Ltd.

Carbasugars are carbocyclic analogues of carbohydrates having a methylene group instead of the ring oxygen atom.[1] This family of carbohydrate mimics, currently attracts interest among chemists as well as biochemists due to the interesting biological activities which they exhibit.[2] Consequently several methodologies have been developed for the synthesis of both carbafuranoses and carbapyranoses[3] and today all 16 racemic carbapyranoses and most of the 32 enantiomeric carbapyranoses have already been prepared. This active research includes the deoxycarbafuranoses as component of carbocyclic nucleosides[2a] but the corresponding deoxy carbapyranoses have received less attention and, to the best of our knowledge, only three 6-deoxy carbapyranoses have been described.[4]

Following our interest in the development of synthetic methods to carbapyranoses and derivatives,[5] in this paper we report the synthesis of new 2- or 3-deoxy carbapyranoses, carbohydrate mimics of the corresponding deoxypyranoses which are components of many natural products.[6]



Scheme 1. *Reagents and conditions*: (a) $NaBH_4$, MeOH, 0°C, 78%; (b) *n*-BuLi, THF, –78°C, 93%; (c) Na-Hg, Na_2HPO_4, MeOH, –20°C to rt, 60%; (d) OsO_4, 4-methylmorpholine *N*-oxide, $NaHCO_3$, THF:*t*-BuOH:H_2O, rt, 92%; (e) Ac_2O, pyr, DMAP, 80%; (f) $BF_3{\cdot}OEt_2$, EtSH; (g) Ac_2O, pyr, DMAP, 60% (two steps); (h) Ac_2O, pyr, DMAP, 82%; (i) $BF_3{\cdot}OEt_2$, EtSH; (j) Ac_2O, pyr, DMAP, 65% (two steps).

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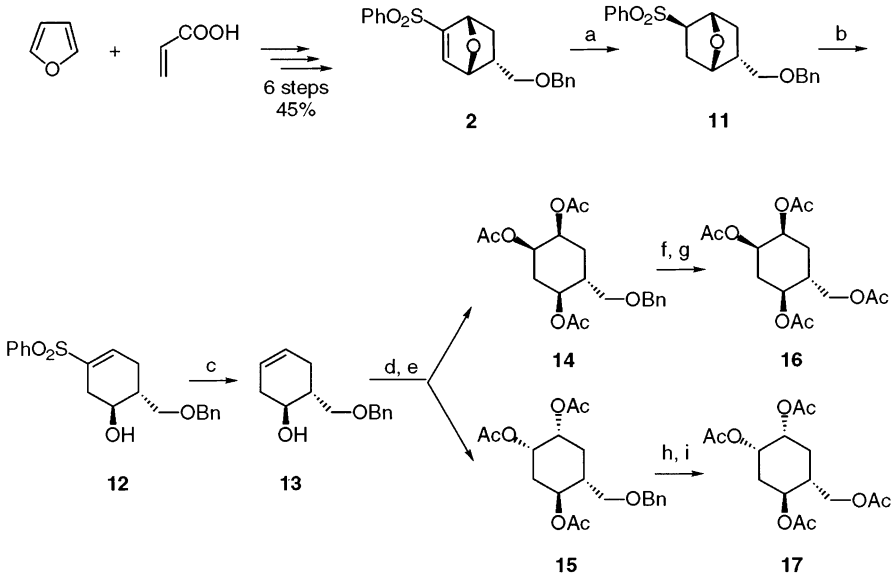

Scheme 2. *Reagents and conditions*: (a) $NaBH_4$, MeOH, 0°C, 71%; (b) *n*-BuLi, THF, −78°C, 72%; (c) Na-Hg, Na_2HPO_4, MeOH, −20°C to rt, 65%; (d) OsO_4, 4-methylmorpholine *N*-oxide, $NaHCO_3$, THF:*t*-BuOH:H_2O, rt, 70%; (e) Ac_2O, pyr, DMAP, 84%; (f) $BF_3{\cdot}OEt_2$, EtSH; (g) Ac_2O, pyr, DMAP, 55% (two steps); (h) $BF_3{\cdot}OEt_2$, EtSH; (i) Ac_2O, pyr, DMAP, 64% (two steps).

Our starting material was the oxabicyclic vinyl sulfones **1** and **2**, easily obtained from furan and acrylic acid[7] in 8 steps (40% overall yield) and 6 steps (45% overall yield), respectively.

Thus, reduction of the double bond in **1** ($NaBH_4$, MeOH, 0°C) led to *exo* sulfone **3**, which was transformed into the key intermediate **4** by α deprotonation of the sulfonyl group followed by β elimination of the bridged oxygen atom.[5d] Desulfonylation of the resulting cyclohexenol **4** with Na-Hg and further bishydroxylation with OsO_4 afforded the benzyl derivatives of 2-deoxy carbasugars **5** and **6** (ratio 1.2:1). After separation by column chromatography, treatment of **5** with Ac_2O in pyridine yielded **7**. Finally, deprotection of the benzylated hydroxy group with $BF_3{\cdot}OEt_2$ followed by acetylation gave 1,3,4,6-tetra-*O*-acetyl-2-deoxy-5a-carba-α-DL-allopyranose **8**[8] (Scheme 1).

On the other hand, the same three-step sequence for triol **6**, allowed us to obtain 1,3,4,6-tetra-*O*-acetyl-2-deoxy-5a-carba-α-DL-galactopyranose **10**.[9]

The synthesis of the 3-deoxy carbapyranoses was achieved following a similar procedure (Scheme 2). Reduction of **2** with $NaBH_4$ followed by ring opening reaction in **11** gave the cyclohexenyl sulfone **12**. Desulfonylation and bishydroxylation produced an inseparable 1.5:1 mixture of both isomers. We achieved the chromatographic separation of the two deoxy carbasugars derivatives after acetylation of the mixture of triols. At this stage, treatment of **14** and **15** with $BF_3{\cdot}OEt_2$ and further acetylation allowed us to obtain 1,2,4,6-tetra-*O*-acetyl-3-deoxy-5a-carba-α-DL-glucopyranose **16** and 1,2,4,6-tetra-*O*-acetyl-3-deoxy-5a-carba-β-DL-mannopyranose **17**.[10]

In summary, the synthesis of new 2-deoxy carbapyranoses of the *allo*- and *galacto*-series and new 3-deoxy carbapyranoses of the *gluco*- and *manno*-series has been achieved in a divergent fashion from furan via the readily available oxanorbornenic sulfones **1** and **2**. It should be pointed out that both compounds **1** and **2** are easily available in optically pure form since the starting Diels–Alder adduct of furan and acrylic acid has been obtained in both enantiomeric forms via optical resolution.[11] Studies are now underway to extend this strategy to the preparation of other carbasugars derivatives as well as carba-C-glycosides and carba-C-disaccharides and will be reported in due course.

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8. Data for: 1,3,4,6-tetra-*O*-acetyl-2-deoxy-5a-carba-α-DL-allopyranose, **8**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.70 (ddd, 1H, $J=3.4$, 11.2, 14.6 Hz, H-6), 1.85 (dt, 1H, $J=3.4$, 15.6 Hz, H-2), 2.04–2.00 (m, 1H, H-6), 2.04 (s, 3H, $COCH_3$), 2.07 (s, 6H, $2COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.27 (dd, 1H, $J=2.4$, 15.6 Hz, H-2), 2.63–2.54 (m, 1H, H-5), 4.01 (dd, 1H, $J=3.4$, 11.2 Hz, CH_2O), 4.20 (dd, 1H, $J=4.9$, 11.2 Hz, CH_2O), 4.90 (dd, 1H, $J=2.9$, 10.3 Hz, H-4), 5.05 (t, 1H, $J=3.4$ Hz, H-1), 5.30 (d, 1H, $J=3.4$ Hz, H-3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.8, 21.1, 21.3, 29.7, 31.5, 31.7, 63.7, 67.1, 68.0, 70.7, 170.2, 170.9. IR ($CHCl_3$): ν 2962, 2928, 1736, 1711 cm^{-1}. Anal. calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.67. Found: C, 54.70; H, 6.80.
9. Data for: 1,3,4,6-tetra-*O*-acetyl-2-deoxy-5a-carba-α-DL-galactopyranose, **10**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.63–1.58 (m, 1H, H-6), 1.73 (dt, 1H, $J=2.9$, 14.2 Hz, H-6), 1.95 (dd, 2H, $J=2.9$, 9.3 Hz, 2H-2), 2.00 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 2.41–2.38 (m, 1H, H-5), 3.87 (dd, 1H, $J=6.0$, 10.8 Hz, CH_2O), 3.96 (dd, 1H, $J=9.0$, 11.4 Hz, CH_2O), 5.12 (td, 1H, $J=3.0$, 10.2 Hz, H-3), 5.28 (t, 1H, $J=3.0$ Hz, H-1), 5.00 (bs, 1H, H-4). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.8, 20.9, 21.3, 26.7, 29.7, 33.6, 63.4, 67.5, 68.4, 68.5, 170.2, 170.2, 170.3, 170.9. IR ($CHCl_3$): ν 2960, 2928, 1736, 1647 cm^{-1}. Anal. calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.67. Found: C, 54.68; H, 6.82.
10. Data for: 1,2,4,6-tetra-*O*-acetyl-3-deoxy-5a-carba-α-DL-glucopyranose, **16**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.59 (ddd, 1H, $J=2.4$, 13.2, 15.6 Hz, H-6), 2.01 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.08–1.84 (m, 3H, 2 H-3 and H-5), 2.13 (s, 3H, $COCH_3$), 2.20–2.11 (m, 1H, H-6), 3.97 (dd, 1H, $J=3.0$, 11.1 Hz, CH_2O), 4.13 (dd, 1H, $J=4.8$, 11.1 Hz, CH_2O), 4.79 (td, 1H, $J=4.8$, 11.1 Hz, H-1), 4.86 (ddd, 1H, $J=3.0$, 4.5, 12.3 Hz, H-2), 5.35 (bs, H-1). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.8, 21.0, 21.1, 29.2, 29.7, 30.9, 35.3, 63.5, 67.6, 69.3, 170.0, 170.1, 170.9. IR ($CHCl_3$): ν 2926, 2854, 1740 cm^{-1}. Anal. calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.67. Found: C, 54.67; H, 6.80.

    Data for: 1,2,4,6-tetra-*O*-acetyl-3-deoxy-5a-carba-β-DL-mannopyranose, **17**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.66 (ddd, 1H, $J=2.7$, 10.8, 13.7 Hz, H-6), 2.03 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.11–1.77 (m, 3H, 2H-3 and H-5), 2.14 (s, 3H, $COCH_3$), 2.27 (dt, 1H, $J=4.5$, 13.9 Hz, H-6), 4.09 (m, 2H, CH_2O), 4.93 (ddd, 1H, $J=2.5$, 4.5, 11.1 Hz, H-1), 5.02–4.97 (m, 1H, H-4), 5.37 (bs, 1H, H-4). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.2, 21.4, 21.5, 27.8, 30.1, 33.6, 39.7, 64.8, 68.7, 68.9, 70.7, 170.5, 170.7, 171.3. IR ($CHCl_3$): ν 2930, 2854, 1739 cm^{-1}. Anal. calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.67. Found: C, 54.42; H, 6.79.
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