Stereoselective Route to a New Class of Phosphasugars. Novel Analogues of 2-Deoxyglucose and 2-Deoxyallose

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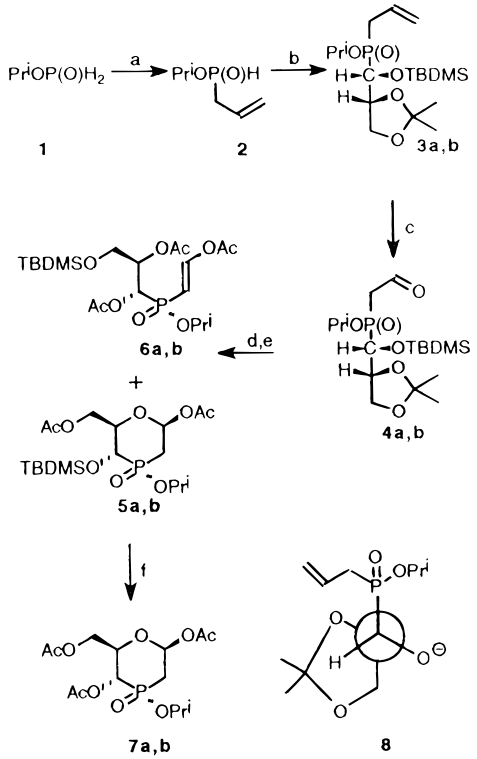
Heterosugars are inherently interesting substances because of the ubiquity of carbohydrates in living systems, but the stereochemical complexity of the pentoses and hexoses has ensured that only restricted ranges of heteroatom analogues have been made. To avoid tedious separation of a multiplicity of stereoisomers, the preferred approach has been to insert a heteroatom into an existing sugar framework. In the area of phosphasugars,[1] this has meant either replacement of the hemiacetal oxygen, or of C(1), by phosphorus. Synthetic convenience dictates that the phosphorus atom frequently carries an alkyl or an aryl group, and this would be expected to detract from the isosteric nature of the resultant heterosugar. We wished to develop more general routes to phosphasugars where the phosphorus atom replaced a carbon atom and carried no other carbon substituents. Ideally, this would involve replacing CH(OH) with PH(O), but it is synthetically simpler to use P(O)OAlk since this group is convertible to PH(O).[2]

We have briefly described in a conference report[4] a successful but impractical (poor yield, no stereoselectivity) route to the 3-phosphapentopyranoses in which C(3) is replaced by $P(O)OCH_3$. We now describe a practical route to 2-deoxy-3-phosphahexoses made feasible by the stereoselective addition of a phosphinate to (*R*)-2,3-*O*-isopropylideneglyceraldehyde.

Alkylation of isopropyl phosphinate,[3] **1**, with allyl bromide affords isopropyl allylphosphinate, **2** (65%), which, in the presence of triethylamine and *tert*-butyldimethylchlorosilane, adds smoothly to (*R*)-2,3-*O*-isopropylideneglyceraldehyde to give the dialkyl phosphinates **3a,b**, a 1:1 mixture of *only two* (^{31}P NMR, TLC) diastereomers (81%), readily separable by chromatography (Scheme 1). No other stereoisomers were detectable, indicating a de of >95%. No selectivity was observed at phosphorus, and the configuration generated at carbon is *S* [X-ray of final product]. From a study of models, and assuming a preferred conformation for the D-glyceraldehyde acetonide in which the 2-oxygen is antiperiplanar to the carbonyl oxygen, **8**, Cram-type analysis suggests that attack on the *si* face of the carbonyl by the (nucleophilic) phosphorus atom to give the *S*-isomer would be much less sterically hindered than attack on the *re* face.

Scheme 1[a]



[a] Key: (a) Et_3N,CH_2=$CHCH_2Br$; (b) Et_3N, (*R*)-glyceraldehyde acetonide, Bu^t Me_2SiCl; (c) O_3, Me_2S; (d) CF_3CO_2H, H_2O, THF; (e) Ac_2O, Py, DMAP; (f) KF, 18-crown-6, Ac_2O.

However, this unusually high stereoselectivity may also be thermodynamically driven since, for example, the stereoselectivity is reduced if Me_3SiCl is used in place of the *tert*-butyl analogue.[5] Ozonolysis of either **3a** or **3b** generated the formyl compounds **4a** (83%) or **4b** (80%),

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(5) Initial studies with model compounds (PhCHO and MeOP(O)H_2) suggest that the reaction is controlled by both the ready reversibility of the addition and the bulk of the silane. We will report on a detailed study of these factors at a later date.

(6) The reaction mixture after deprotection but before acetylation shows the presence of two anomeric protons (δ 5.25, 5.43) Under basic conditions, rapid epimerization at C_1 would be expected with the resultant predominant formation of the less hindered equatorial acetate. The enol acetate formation presumably occurs with the acyclic form since **5a,b** are stable under the acetylation conditions.

(7) **7A**: yield 75%, an oil; ^{31}P NMR ($CDCl_3$) δ 33.97; ^1H NMR ($CDCl_3$) δ 5.82 (m, 1H), 5.24 (d, J = 10.55 Hz, 1H), 4.85 (m, 1H), 4.25 (dd, J = 4.9, 12.35 Hz, 1H), 4.0 (bd, J = 11.7 Hz, 1H), 3.91 (m, 1H), 2.31−2.24 (m, 2H), 2.08 (s, 3H), 2.06 (s, 3H), 2.017 (s, 3H), 1.36−1.33 (2d, J = 6.18 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 173.32, 168.6, 168.4, 91.8, 73.1, 65.3 (d, J = 99 Hz), 61.6 (d, J = 12.13 Hz), 35.42 (d, J = 82.9 Hz), 24.43, 23.62, 20.6, 20.4, 20.14, 13.9; MS (EI^+) m/e 367 (M + 1, 2), 307 (25), 264 (30), 239, 222 (90), 180, 43 (100); $[\alpha]_D$ +7.24 (CH_3OH). **7B**: a felt-like mass of white needles (84%); mp 153−154 °C; ^{31}P NMR ($CDCl_3$) δ 35.66; ^1H NMR ($CDCl_3$) δ 6.06 (dt, J = 3.09, 10.26 Hz, 1H), 5.16 (dd, J = 3.06, 10.23 Hz, 1H), 4.80 (m, 1H), 4.38 (dd, J = 4.09, 12.3 Hz, 1H), 4.23 (m, 1H), 4.08 (dt, J = 2.0, 10.23 Hz, 1H), 2.48−2.0 (m, 2H), 2.16 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 1.35−1.25 (2d, J = 6.15 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 170.5, 169.3 (d, J = 3.0 Hz), 168.2, 91.8 (d, J = 4.04 Hz), 73.0 (d, J = 4.04 Hz), 72.1 (d, J = 7.02 Hz), 65.3 (d, J = 102 Hz), 61.9 (d, J = 12.1 Hz), 35.8 (d, J = 81.9 Hz), 24.3, 23.9, 20.8, 20.6, 20.4; MS (EI^+) m/e 367 (M + 1, 10), 341 (5), 324 (20), 307, 281, 264, 222 (50), 180 (50), 167, 125 (75), 115, 107, 70, 43 (100); $[\alpha]_D$ +9.30 (CH_3OH). Anal. Calcd for $C_{14}H_{23}O_9P$: C, 45.88; H, 6.33; found: C, 45.63; H, 6.48.

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which on deprotection of the diol functionality followed by acetylation afforded the two 2-deoxyphosphahexose acetates **5a** (70%) and **5b** (53%) together with variable amounts of the acyclic enol acetates **6a,b**.[6] Finally, removal of the silyl group and acetylation of the resultant alcohols afforded the two 3-phosphasugar acetates epimeric at phosphorus, **7a** (75%, mp 153−154 °C) and **7b** (84%).[7] We tentatively identified **7b** as the isomer with the isopropoxy axial on the basis of ^{1}H NOE measurements, and this assignment was subsequently confirmed by a single-crystal X-ray structure determination on **7a**, the only compound in this series to be obtained crystalline.[8] Since the absolute stereochemistry of the starting aldehyde is known, this structure serves to establish absolute stereochemistry throughout the series.

The sequence provides access to reasonable amounts of these phosphasugars in fair yields (ca. 30% overall based on the glyceraldehyde acetonide) and excellent stereochemical purity. We are currently exploring the generality of the stereoselective addition of phosphorus nucleophiles to aldehydes and the extension of this approach to the synthesis of other hexoses and pentoses.

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Supporting Information Available: Procedures and characterization data (18 pages).

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