An Effective Method to Incorporate Phosphorus Atoms into the Secondary Carbons of Pyranosides[1]

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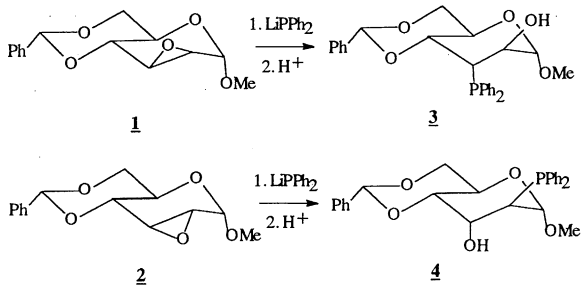
Two new chiral phosphines, methyl 3-deoxy-3-(diphenylphosphino)-4,6-O-benzylidene-α-D-altropyranoside (3) and methyl 2-deoxy-2-(diphenylphosphino)-4,6-O-benzylidene-α-D-altropyranoside (4), have been prepared in high yields from D-glucose via regioselective and stereospecific ring-opening of epoxides. 3 and 4 have been characterized by ^{1}H, ^{13}C, ^{31}P NMR and MS spectra. Crystal structure of 3 has been determined by the single-crystal X-ray diffraction analysis.

Chiral phosphines are the most useful ligands in enantioselective catalysis with transition metal complexes.[2] Much attention has been paid to synthesize chiral phosphines by the transformation of precursors from the chiral pool which can omit resolution steps.[3] Particularly, it is very attractive to synthesize chiral phosphines from cheap D-sugars since these sugars are the richest not only in stereochemistry but also in amount in the chiral pool and possess many hydroxyl groups as synthetic starting points. However, the types of chiral phosphines in which the phosphorus atoms attach directly to the secondary carbons of D-sugars are few. It may be more effective to transfer chirality from chiral carbon backbones to the substituents on achiral phosphorus atoms which link to the secondary chiral carbons rather than to the primary carbons. By nucleophilic replacement reaction, it is difficult to link phosphorus atoms to the secondary carbons of pyrano-, or furano-sugar derivatives because of competing elimination reaction.[4] Nakamura et al[5] and Yamashita et al[6] have synthesized chiral phosphines in which the phosphorus atoms are attached to the secondary carbons of sugar derivatives through glucosid-4-ulose derivatives as key intermediates reacting with secondary phosphines. In present paper we describe a new synthetic method to link phosphorus atoms directly to the secondary carbons of pyranosides.

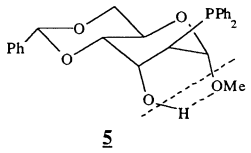
To a stirred solution of $LiPPh_2$ (1.06 mmol, 0.106 N) in THF (10 cm^3) at -10°C was added a solution of methyl 2,3-anhydro-4,6-O-benzylidene-α-D-mannopyranoside (1) or methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside (2) (0.264 g, 1.0 mmol) in DMF (20 cm^3) over 20 min under N_2 atmosphere. After continuous stirring for 2 h., the red solution discoloured indicating that $LiPPh_2$ had disappeared. Then NH_4Cl (0.08 g, 1.5 mmol) was added and stirred for 30 min. The salt formed was filtered off and the filtrate concentrated under reduced pressure. Flash chromatography (ethyl acetate-petroleum ether, v:v, 1:2) of the residue gave methyl 3-deoxy-3-(diphenylphosphino)-4,6-O-benzylidene-α-D-altropyranoside (3, 0.42 g, 91%) or methyl 2-deoxy-2-(diphenylphosphino)-4,6-O-benzylidene-α-D-altropyranoside (4, 0.36 g, 80%), respectively (see scheme 1).



Scheme 1.

These two new chiral phosphines 3 and 4 were characterized by ^{1}H, ^{13}C, ^{31}P NMR, MS, IR spectra and elemental analyses.[7] Assignment of pyrano-ring protons of 3 and 4 was carried out with the aid of 2D ^{1}H-^{1}H COSY and ^{1}H-^{13}C HMQC spectra. The ^{1}H and ^{13}C NMR studies demonstrate that the phosphorus atom of 3 links to C_3 and that of 4 to C_2. $^{31}P\{^{1}H\}$ NMR signal of 3 appears at -21.7 ppm and that of 4 at -16.9 ppm. The result of ^{31}P NMR spectra, shifting about 5 ppm from 4 to 3, is consistent with the assignment of the position of phosphorus atoms by ^{1}H NMR.

Mass spectra of 3 and 4 showed obvious differences in the range 350-460 u. The abundance of $[M^+-1]$ ion of 3 is 40%, while that of 4 is only 3%. The losses of H_2O and $CH_3\cdot$ are common processes in the fragmention of organic compounds having hydroxyl and methoxy groups. It is indeed observed in the spectrum of 3 but not in the spectrum of 4. The extent and ease of formation of the $[M^+-CH_3OH]$ ion (30%, and only 5% for 3) for 4 together with the fact mentioned above suggest that the decomposition process of M^+ for 4 contains a transient state 5. In addition, the abundance of $[M^+ -77]$ ion is 33% for 3 and only 2% for 4, suggesting that the crowded space around the phosphorus atom in 3 makes one of the attached phenyl groups easy to lose.



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A single-crystal X-ray diffraction analysis of 3 was carried out. Crystal data: monoclinic (from 2-propanol), space group $P2_1$, a=9.294(1), b=7.999(1), c=15.925(2)Å, β=96.17(5)°, V=1176.9Å^3, Z=2, Dc=1.271 g/cm^3. A total of 1971 independent reflections was collected on an Enraf-Nonius CAD-4 automatic four-circle diffractometer with graphite monochromatized Cu-Kα radiation. The structure was solved by direct methods. The final R-factor is 4.5%. Figure 1 shows a computer-generated perspective drawing of the molecular structure of 3. The bond lengths of P-C_3 and P-C(aromatic) are 1.888(5), 1.851(5) and 1.845(5)Å, respectively. These data are all slightly longer than those of P-C (aliphatic) and P-C

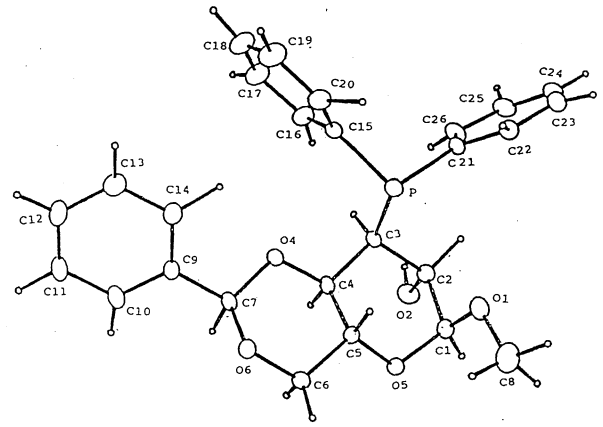

Figure 1. The crystal structure of 3.

(aromatic) bonds.[8] It supports the conclusion deduced from MS that the space around P atom of 3 is crowded.

The ring-opening of 2,3-anhydro-pyranosides with strong base occurs stereospecifically with configuration inversion. However, it may take place at carbon atoms C_2 or/and C_3, resulting in a mixture of products. The site of nucleophilic attack can be controlled by steric and electronic effects. It was found that diphenylphosphino anions attack the secondary carbons of α-D-pyranosides with high regioselectivity in our experiment. For compound 1, the phosphorus anion attacks mainly C_3; for compound 2, C_2. This methodology of linking phosphorus atoms to the secondary carbons of pyranosides directly, combined with other methods such as derivatizing the hydroxyl group formed from epoxide ring-opening with chlorodiphenylphosphine or tosylating the primary hydroxyl group at C_6, then substituted by phosphorus anion to introduce another phosphorus atom, can prepare many new bidentate chiral phosphines from sugars. Further studies of this aspect are in progress.

It is well known that increasing steric bulk of monodentate phosphine ligands leads to higher regioselectivity in hydroformylation.[9] The new phosphines 3 and 4 with such bulkiness thus should improve the *n/iso* ratio and have potentiality in application in this type of reactions. Furthermore, we have also found that 3 and 4 are easily hydrolytically cleaved to obtain a type of water-soluble phosphines which can be used for biphasic catalysis.

References and Notes

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7 Selected physical data. For 3: mp 204-206°C, $[\alpha]_D^{20}$ = +6.0° (C = 2, $CHCl_3$). $^{31}P\{^1H\}$ NMR($CDCl_3$), δ -21.7. ^1H NMR ($CDCl_3$, Bruker AM-400 spectrometer), δ 7.70-6.72(m, 15H), 5.45(s, 1H, PhCH), 4.57(m, 1H, H_5), 4.48(s, 1H, H_1), 4.43 (m, 1H, H_4), 4.25(dd, 1H, H_6), 3.78(dt, 1H, $H_{6'}$), 3.51(m, 1H, H_3), 3.49(m, 1H, H_3), 3.43(s, 3H, CH_2). $^{13}C\{^1H\}$, δ 101.3 (C_7), 101.1(C_1), 76.9(d, C_4, ^2J(P-C) = 9.9 Hz), 69.7(d, C_2, ^2J(P-C) = 5.2 Hz), 69.1(C_6), 60.8(d, C_5, ^3J(P-C) = 12.2 Hz), 54.7(CH_3), 41.2(C_3, ^1J(P-C) = 24.3 Hz). For 4: mp 190-192°C, $[\alpha]_D^{20}$ = +1.4° (C = 4, $CHCl_3$). $^{31}P\{^1H\}$ NMR ($CDCl_3$), δ -16.9. ^1H NMR($CDCl_3$), δ 7.58-7.33(m 15H), 5.64(s, 1H, PhCH), 4.46(d, 1H, H_1), 4.35(m, 1H, H_6), 4.30(m, 1H, H_5), 4.17(q, 1H, H_4), 4.00(m, 1H, H_3), 3.90(t, 1H, $H_{6'}$), 3.30(s, 3H, CH_3), 3.24(m, 1H, H_2). $^{13}C\{^1H\}$, δ 102.2(C_7), 100.1(d, C_1, ^2J(p-C) = 21.0 Hz), 77.3(d, C_4, ^3J(P-C) = 12.4 Hz), 69.4(C_6), 67.2(d, C_3, ^2J(P-C) = 18.0 Hz), 58.6(C_5), 55.6(CH_3), 44.8(d, C_2, ^1J(P-C) = 14.2Hz).
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