HETEROCYCLES, Vol. 63, No. 12, 2004, pp. 2797 - 2803
Received, 6th September, 2004, Accepted, 21st October, 2004, Published online, 26th October, 2004

SYNTHESIS OF 1,4:3,6-DIANHYDRO-D-MANNITOL 2,5-(HYDROGEN PHOSPHATE) AND ITS USAGE IN PALLADIUM-CATALYZED HYDROXYCARBONYLATION OF STYRENE

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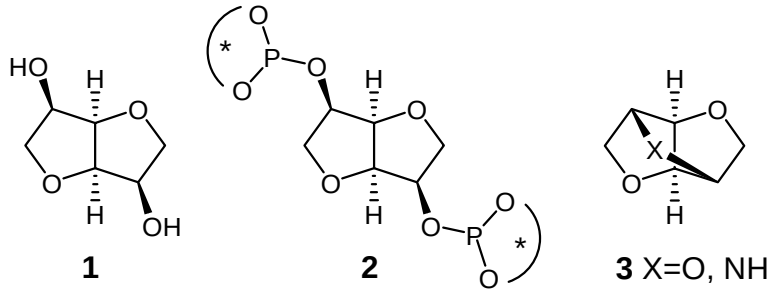
Abstract – Phosphorylation of 1,4:3,6-dianhydro-D-mannitol by phosphorus oxychloride in the presence of triethylamine followed by hydrolysis gave a cyclic hydrogen phosphate, which has the crystal structure of 6-hydroxy-6-oxo-2,5,7,10-tetraoxa-6-phospha-tricyclo[6.3.0.0^{4,11}]undecane. It was used as a chiral ligand in palladium-catalyzed hydroxycarbonylation of styrene. The regioselectivity was good, but the optical yield was limited.

INTRODUCTION

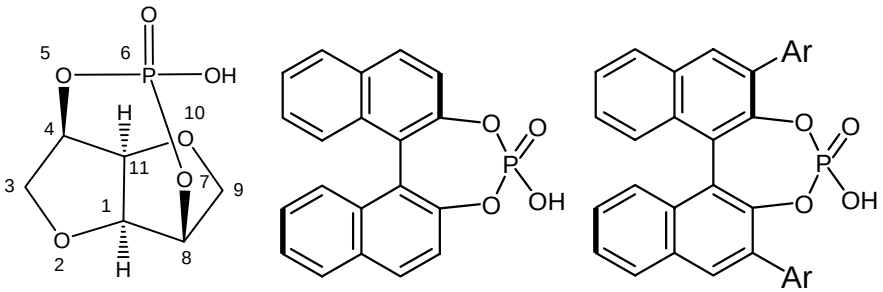
1,4:3,6-dianhydro-D-mannitol (**1**), also known as isomannide, is a *C-2* symmetric hexahydro[3,2-*b*]furan 3,6-diol with two *cis* hydroxyl groups located on the *endo* face of the *cis* fused bicyclic oxa five-membered rings. This skeleton might be utilized as a chiral platform for asymmetric synthesis and catalysis.[1]



1 **2** **3** X=O, NH

In 1999, Reetz *et al.* reported a highly enantioselective rhodium-catalyzed hydrogenation reaction using biphosphite (**2)** as the chiral ligand.[2] And we noticed with interest that two constrained tricyclic rings (**3)** (X = O, NH) were described by Cope *et al.* decades ago.[3] Thus, we envisioned a less constrained

1,4:3,6-dianhydro-D-mannitol 2,5-(hydrogen phosphate) (**4)** resembling the cyclic nature of 1,1'-binaphthlene-2,2'-diyl hydrogen phosphate (**5**), which is known as a resolving agent for many organic bases.[4]

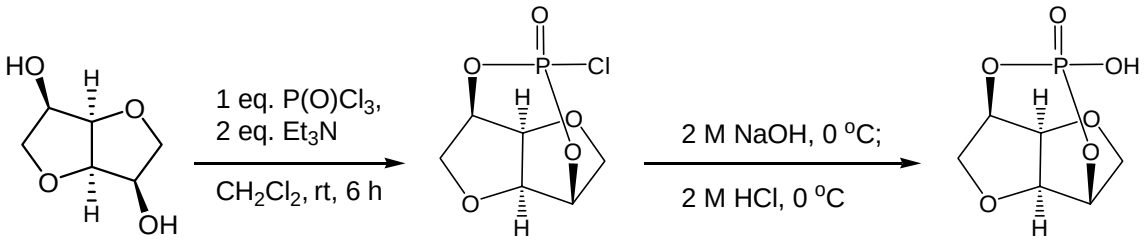


4 **5** **6**

In 1983, Alper *et al.* developed a palladium-catalyzed regiospecific hydroxycarbonylation of alkenes under mild conditions.[5] Later, they used **5** as a chiral ligand for the enantioselective synthesis of 2-arylpropionic acid and claimed a quite high optical yield of 91% based on optical rotation measurement.[6] Recently, renewed interest in asymmetric catalysis by chiral Brønsted acid (**6)** was reported.[7] Nifant'ev *et al.* extensively examined the phosphorylation of alcohols and phenols including many carbohydrates by trivalent phosphorus chlorides and amides.[8] The preparation and purification of some phosphites and phosphoramides based on 1,4:3,6-dianhydro-D-mannitol were also described. Herein, we report the synthesis of the free monophosphoric acid (**4)** through direct phosphorylation of **1** by phosphorus oxychloride and following hydrolysis. Its usage in Alper's catalytic system was examined.

RESULTS AND DISCUSSION

Scheme 1



1 **7** **4**

As illustrated in Scheme 1, phosphorylation of **1** with phosphorus oxychloride in the presence of triethylamine followed by hydrolysis gave the cyclic hydrogen phosphate (**4)**. However, the solubility of **1** in aprotic solvent such as benzene, THF and dichloromethane was not good. Addition of triethylamine ruptured the hydrogen bonding, thus improving the solubility of the substrate. The reaction was monitored by ^{31}P NMR sampling. As can be expected, monophosphorylation, bisphosphorylation, and intermolecular or intramolecular phosphorylation made the ^{31}P NMR spectrum somewhat complicated.

After optimization including searching for the solvent, changing the reaction temperature from -78 ^{o}C to reflux, varying the reactants ratio and employing a slow addition procedure or reverse addition protocol, the intramolecular bisphosphorylated **7** became the major intermediate as indicated by ^{31}P NMR spectrum. Phosphorus oxychloride was added slowly by syringe into the solution of **1** and two equivalents of triethylamine in dichloromethane at room temperature. After filtration and evaporation, the residue was hydrolyzed in 2 M aqueous sodium hydroxide at 0 ^{o}C and then neutralized by 2 M hydrochloric acid. Recrystallization from water provided the desired product (**4)**. Its X-Ray structure is illustrated in Figure 1 with selected bond lengths and bond angles listed in Table 1.[9]

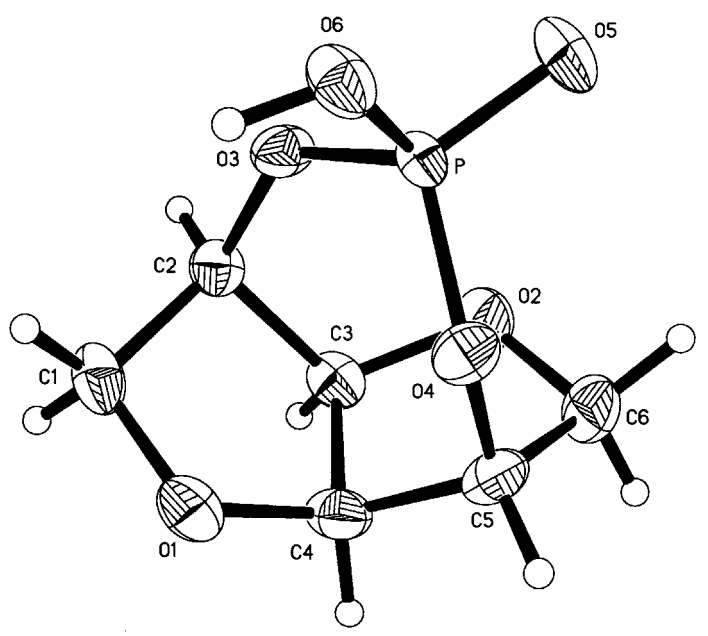


Figure 1 Molecular Structure of Compound (**4)**

Table 1 Selected bond lengths (×10^{-1} nm) and bond angles (^{o}) for **4**

P—O(5)	1.4680(11)	O(5)-P-O(6)	109.55(7)
P—O(6)	1.5360(12)	O(5)-P-O(3)	110.51(8)
P—O(3)	1.5560(11)	O(6)-P-O(3)	106.27(7)
P—O(4)	1.5657(11)	O(5)-P-O(4)	115.06(8)
O(3)—C(2)	1.4406(18)	O(6)-P-O(4)	104.35(6)
O(4)—C(5)	1.447(2)	O(3)-P-O(4)	110.57(6)
O(6)—H(9)	0.871(18)	P-O(6)-H(9)	112(2)

With this unique cyclic hydrogen phosphate in hand, we examined its usage as a chiral ligand in Alper's catalytic system[5, 6] (Scheme 2). As it was stated, 10% mol palladium(II) chloride, 5% mol hydrogen phosphate combined with 20% mol cupric chloride and oxygen constituted the catalyst and additive

system. The reaction was conducted in THF under acidic condition at room temperature with a mixed carbon monoxide and oxygen atmosphere.

Scheme 2

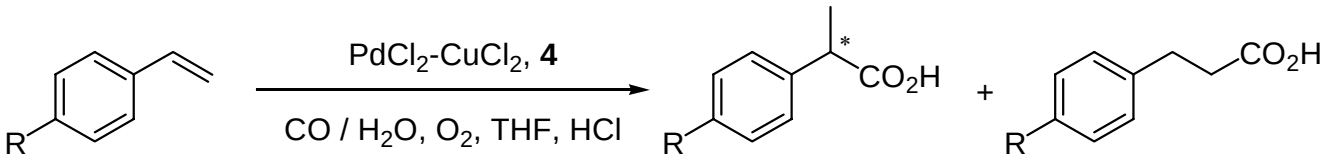


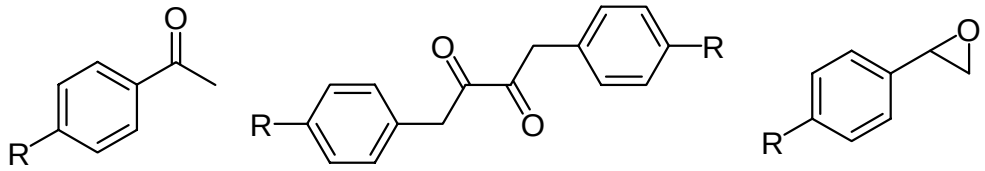
Table 2 Palladium-catalyzed asymmetric hydroxycarbonylation of styrenes

Entry	Substrate	Additive	Yield[a] / %	Iso : linear[b]	Ee[c] / %
1[d]	R = H	$CuCl_2$	40	89/11	9
2			48	91/9	11
3		$CoCl_2$	21	97/3	2
4		$NiCl_2$	34	91/9	11
5		$SnCl_2$	40	97/3	2
6		$LaCl_3$	39	98/2	2
7[d]	CH_3	$CuCl_2$	20	91/9	23
8			43	88/12	22
9[e]			32	95/5	24
10[f]			45	85/15	13
11	OCH_3		50	94/6	4
12	Cl		28	71/29	-
13	$C(CH_3)_3$		40	77/23	7
14	$CH_2CH(CH_3)_2$		56	91/9	4

(a) isolated yields; (b) based on ^{1}H NMR spectrometry; (c) determined by chiral HPLC: KROMASIL KR100-5CHI- TBB, hexane/*i*-propanol/HOAc = 100/1/0.05 or 0.1, 1.0 mL/min, retention time: 10-15 min or 20-30 min; (d) CO/O_2 (1/1) was bubbled through the mixture; (e) 10% mol **4**; (f) 5% mol $PdCl_2$, 10% mol $CuCl_2$.

The result is shown in Table 2. In general, the regioselectivity was good (up to 98/2), but both the yield and enantioselectivity were poor. *p*-Methylstyrene gave better optical yield (*S* configuration by comparing with reported optical rotation). Cupric chloride was a superior additive. The difference between bubbling carbon monoxide and oxygen or a closed balloon atmosphere was small (Entries 1, 7). The reaction became very sluggish with insufficient oxygen supply. Increasing the amount of chiral ligand gave only similar results (Entry 9). Decreasing the amounts of catalyst and additive led to poorer regioselectivity and enantioselectivity (Entry 10). The yield and regioselectivity were poor for substrate

with chlorine in the *para* position (Entry 12). Bulky substituent *t*-Bu also decreased the branch to linear ratio (Entry 13). Ibuprofen was obtained in 56% yield, but the enantioselectivity was only 4% ee (Entry 14). For all substrates, several undesired side products were isolated and identified as acetophenone (**8**), 1,4-diphenylbutane-2,3-dione (**9**) and styrene oxide (**10**), which hampered improvement and limited the scope in this reaction.



8 **9** **10**

To conclude, some informative aspects of the phosphorylation of 1,4:3,6-dianhydro-D-mannitol by phosphorus oxychloride were described. The crystal structure of a new cyclic hydrogen phosphate is reported. And the preliminary results of its usage in palladium-catalyzed hydroxycarbonylation of styrene are presented.

EXPERIMENTAL

Melting points were uncorrected. Specific rotation was recorded on a PERKIN-ELMER 341 polarimeter. ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were obtained on a VARIAN MERCURY 300 spectrometer. IR spectrum was recorded on a BIO-RAD FTS-185 spectrometer. EIMS and HRMS were obtained on an AGILENT 5973N MSD and an IONSPEC 4.7 TESLA FTMS spectrometer.

1,4:3,6-Dianhydro-D-mannitol 2,5-(hydrogen phosphate) (**4**):

2.0 mL (20 mmol) of phosphorus oxychloride was added by syringe into a solution of 2.92 g (20 mmol) of **1** and 7.0 mL (50 mmol) of triethylamine in 50 mL of dichloromethane over 1 h at rt. The stirring was continued for 5 h (^{31}P NMR spectrum indicating a major peak δ -0.8 ppm). After filtration and evaporation, the residue was taken up by aqueous NaOH (2 M, 50 mL) at 0 ^{o}C, and then neutralized with 2 M HCl. White solid was collected after concentrated at temperature below 20 ^{o}C. Recrystallization from water and MeOH provided 1.0 g of the product (25%). mp: 283 ^{o}C (decomp); $[\alpha]_D^{20}$ +8.1^{o} (*c* 0.5, H_2O); IR (KBr): ν 2565, 2297, 1725, 1251, 1218, 1127, 1057, 1015, 938, 765 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.84-4.83 (m, 2H), 4.62-4.60 (m, 1H), 4.52-4.50 (m, 1H), 4.40-4.36 (d, *J* = 11.7 Hz, 2H), 4.02-4.01 (d, *J* = 3.3 Hz, 1H), 3.98-3.97 (d, *J* = 3.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 79.9, 77.1-77.0 (d, *J* = 8.7 Hz), 74.2-74.1 (d, *J* = 2.9 Hz); ^{31}P NMR (121 MHz, DMSO-d_6): δ -3.4; EIMS: *m/z* 209 ([M+H]$^{+}$, 2%); HRMS: calcd for $C_6H_{10}O_6P$ ([M+H]$^{+}$) 209.0209, found 209.0206.

Typical procedure for the hydroxycarbonylation (also see refs. 5 and 6):

1.0 mL of HCl (37%) and 1.0 mL of water were added into a solution of 35 mg of $PdCl_2$ in 10 mL of THF. Carbon monoxide was bubbled through the mixture for 5 min before 0.4 mmol of $CuCl_2$ and 0.1 or 0.2 mmol of **4** were added. Oxygen was bubbled for 10 min, and then *p*-methylstyrene (1.9 mmol) was introduced. The reaction was kept under 1 atm of CO/O_2 (1/1) at rt for 12 h with stirring. The mixture was diluted with water (25 mL) and extracted with ether (3 × 30 mL). The combined organic layer was washed with 2 M NaOH (3 × 30 mL). The aqueous phase was acidified to pH 2 by 2 M HCl and extracted with ether (3 × 30 mL). The ether layer was dried over $MgSO_4$, filtrated and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether / ethyl acetate = 4/1 to 1/1) and the product was obtained as a colorless oil.

ACKNOWLEDGEMENTS

We thank National Natural Science Foundation of China and Shanghai Municipal Committee of Science and Technology for financial support.

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9. Crystallographic data for the structural analysis has been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 241796 for compound (**4**). Copies of this information may be obtained free of charge from: www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.