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THE ABSOLUTE CONFIGURATION OF α-HYDROXYPHOSPHONATES

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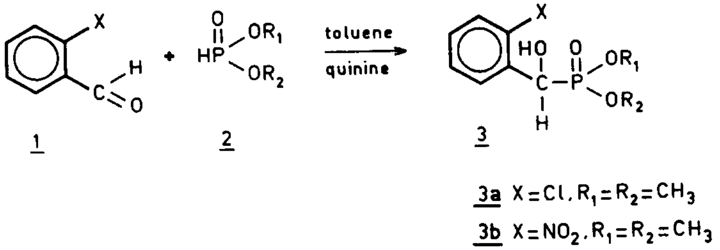
Summary: The absolute configuration and CD spectra of a series of chiral α-hydroxyphosphonates and phosphoric acids have been determinated. The hydroxyphosphonates were prepared via a quinine catalyzed 1,2-addition reaction of phosphite to aldehyde.

Recently we described a new example of a quinine catalyzed asymmetric synthesis, namely the condensation between aromatic aldehydes and phosphites.[1]

Scheme 1



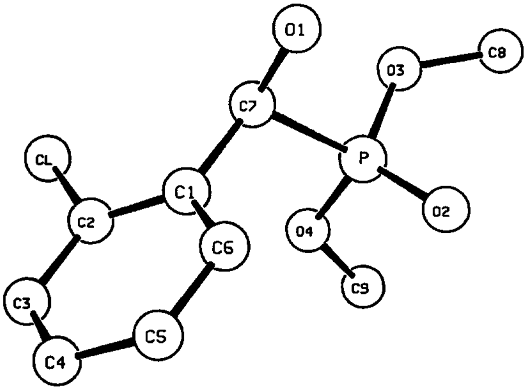
With X=NO_2 and R_1=R_2 = t-butyl, ee's of 80-85% were achieved. Furthermore conversion of 3 to its mono-acid (R_1=H, R_2=Me) or diacid (R_1=R_2=H) readily furnished a series of chiral acids, useful in resolutions.[2]

Finally diesters of 3 (R_1=R_2=Me or i-Pr) were found to be useful reagents for derivatization of chiral acids.[1] Using ^{31}P-NMR the enantiomeric excess of chiral acids could be determinated.

Here we describe the determination of the absolute configuration of products resulting from the reaction of 1 with 2. When X=Cl, the resulting α-hydroxyphosphonates are obtained optically active with ee's ranging from 10% (when R_1=R_2=Me) to 21% (when R_1=R_2=i-Pr). This trend towards higher ee's upon increasing the size of phosphite reactant appears to be general. Purification of 3a proved to be exceedingly simple, only one recrystallization of material (ee = 10% as checked via both the ^{19}F- and ^{31}P-NMR using the ester prepared with Moscher reagent[3]) from acetone is necessary to obtain 3a having ee's of better than 98%.

This unusual facility of purification by entrainment[4] is undoubtelly due to the fact that 3a as well as 3b exist as conglomerates.[5] Crystals of optically pure 3a $[\alpha]^{20}_{78}$ = -74 (c = 1, $CHCl_3$) were used for the determination of the absolute configuration using Bijvoet's method.[6]

Using Cu-radiation, we find that 3a $[\alpha]^{20}_{578}$= -74 (c = 1, $CHCl_3$) has the absolute configuration S(-) as shown in figure 1.

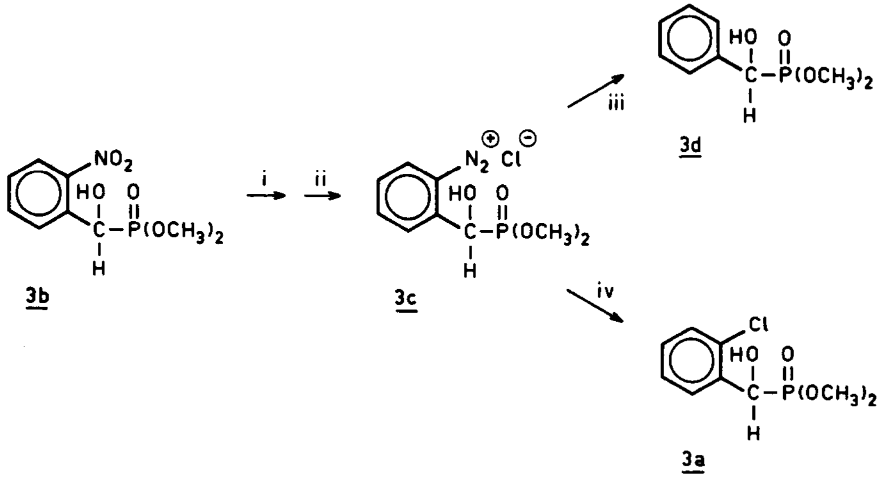


Relevant bond distances (A) and bond angles (degrees)[7].
C(1)-C(7) 1.515(7); C(7)-O(1) 1.437(6); C(7)-P 1.825(5); P-O(2) 1.459(4); P-O(3) 1.578(5); P-O(4) 1.579(4); C(6)-C(1)-C(7) 120.0(5); C(1)-C(7)-O(1) 111.7(4); C(1)-C(7)-P 105.3(3); C(7)-P-O(2) 116.5(3); C(7)-P-O(4) 101.6(2); C(7)-P-O(3) 103.3(3); O(3)-P-O(4) 105.0(3); O(4)-P-O(2) 113.8(3); O(2)-P-O(3) 115.0(3).

Figure 1 S(-) 3a

Correlation between dimethyl o-chloro-α-hydroxybenzylphosphonate 3a $[\alpha]^{20}_{578}$ -74 (c = 1, $CHCl_3$) having the S(-) configuration and other α-hydroxyphosphonates was made using the following series of reactions.[8]

Scheme 2



3b $[\alpha]^{20}_{578}$ = -417 (c = 1, $CHCl_3$), m.p. 108.5°-110°C[1]; 3d $[\alpha]^{20}_{578}$ = -46 (c = 1, acetone), m.p. 100°-101°C; 3a $[\alpha]^{20}_{578}$ = -76 (c = 1, $CHCl_3$) m.p. 114°-115°; i. 3 atm. H_2, 5% Pd/C, MeOH, 3 hrs, r.t.; ii. $NaNO_2$, HCl/H_2O, 0°C; iii. 20% H_3PO_2, 24 hrs, r.t.; iv. CuCl, 3 hrs; 3b→3d c.y. 85%; 3b→3a c.y. 86%.

Optically pure 3b is converted with 5% Pd/C and 3 atm. H_2 to the less stable amino compound 3 (X=NH_2, R_1=R_2=Me) $[\alpha]^{20}_{578}$ = +49 (c = 1, $CHCl_3$) which could be converted with $NaNO_2$ to the diazonium salt 3c. Treatment of 3c with a freshly prepared copper (I) chloride solution gives optically pure 3a which was shown to be identical with the optically pure compound we obtained after the recrystallization of the condensation product of o-chlorobenzaldehyde and dimethylphosphite using quinine as a catalyst.

Treatment of diazonium salt 3c with a 20% hypophosphoric acid solution leads to the optically pure compound 3d. We prepared 3d also by resolution of the mono-acid 3 (X=R_1=H, R_2=CH_3)[2] with quinine. The mono-acid 3 (X=R_1=H, R_2=CH_3) is converted to the diester 3d with diazomethane.[9] This diester was identical with the compound we obtained by the diazonium salt route (scheme 2).

This data indicates that:

(a) No racemization (at the potentially sensitive benzyl carbon in 3)[10] has taken place during the conversion of the $-NO_2$ group to the other groups.

(b) The absolute configuration of all of these compounds is now known based on the knowledge that 3a $[\alpha]^{20}_{578}$ = -74 (c = 1, $CHCl_3$) has the S(-)-configuration.

(c) Based on the CD spectra of 3 (X=H, NO_2, F, Cl, Br or NH_2, R_1=R_2=Me) the α-hydroxyphosphonates having the S configuration all show a negative Cotton effect at 225 nm. The CD spectrum of optically 3c is shown in fig. 2.

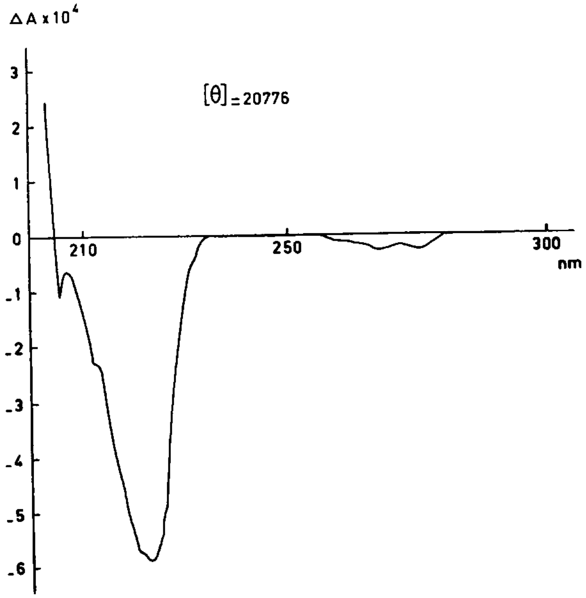


fig. 2: The CD spectrum of optically pure 3c, having the S(-) configuration

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