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Camphor-based oxazaphospholanes as chiral templates for the enantioselective synthesis of α-chlorophosphonic acids

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Abstract

Constrained camphor-derived oxazaphospholanes have provided an efficient entry for the preparation of enantiomerically enriched α-chlorophosphonic acids.

Phosphonic acids and their derivatives play an important role in medicinal chemistry as mimics of the tetrahedral transition state of sp^2 S_N reactions and as non-hydrolyzable surrogates for the corresponding carboxylic acids and phosphates. These compounds exhibit interesting and unique properties as antiviral agents, haptens to elicit catalytic antibodies, peptide analogues, enzyme inhibitors and antibiotics.[1]

In contrast to the extensively investigated amino phosphoryl compounds, α-halophosphonic acids have received less attention even though it has been reported that they may function as inhibitors of some viral and human DNA polymerases.[2] A synthetic approach to α-halophosphonic acids with high enantiomeric excesses would be of significant value considering that the absolute configuration at the α-position in substituted phosphonic acids has been shown to be important for the biological activity.[2,3] To the best of our knowledge, few methods have been reported to date for the asymmetric synthesis of α-chlorophosphonic acids.[4]

We describe here a straightforward entry to enantiomerically enriched α-chlorophosphonic acids **1** based on diastereoselective alkylation of a chiral non-racemic chloromethyl phosphonic acid equivalent (Scheme 1).

We elected to use the camphor derivative **2** as a highly defined template considering its ready availability in either enantiomeric form. Furthermore, related rigid aminoalcohol backbones have been widely employed in diastereoselective syntheses.[5]

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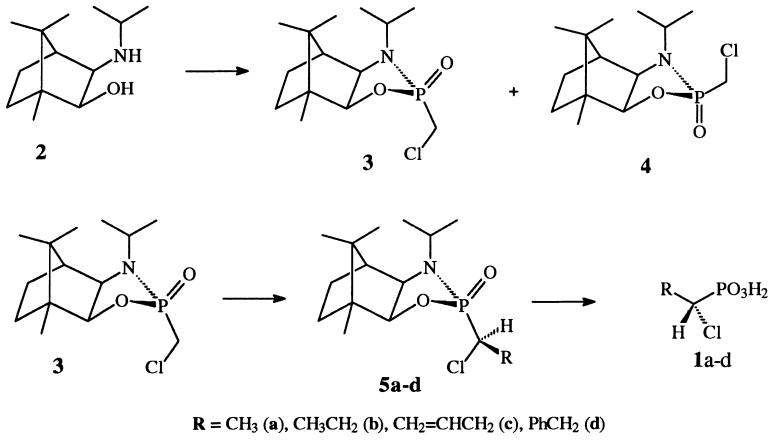

Scheme 1.

The β-aminoalcohol **2** was obtained according to literature methods[5b,c] starting from (1*R*)-(−)-camphorquinone. By reacting compound **2** (24 mmol) with chlorophosphonic acid dichloride (28 mmol) in anhydrous toluene and in the presence of triethylamine (56 mmol) at 60°C for 6 h, the two diastereoisomeric 2-chloromethyl-1,3,2-oxazaphospholanes **3**[6] and **4** were obtained in the ratio 10:1 as judged from the intensity of the ^{31}P NMR signals (δ_P=35.99 and 37.79 ppm, respectively). The two diastereoisomers could be cleanly separated by flash silica gel chromatography with light petroleum:ethyl acetate 9:1→3:7 as eluant (75% overall yields). It has been reported[7] that the absolute stereochemistry of 1,3,2-oxazaphospholanes derived from ephedrine could be assigned by the deshielding of the proton *H*C-O-P=O *cis* to the phosphoryl oxygen in the ^{1}H NMR spectrum. In our case, the proton at C2 (monoterpene numbering) resonates at 4.37 and 4.47 ppm for the diastereoisomers **3** and **4**, respectively.

The major 2-chloromethyl-1,3,2-oxazaphospholane **3** was treated with LDA (1.1 equiv.) at −90°C in THF to generate the Li^+-**3**$^-$, followed, after 2 h, by addition of benzyl bromide (1.0 equiv.). After standing at −90°C for 5 h, the reaction mixture was quenched with methanol.

A ^{31}P NMR spectrum of the crude reaction mixture indicated the formation of a 24:1 mixture of the monoalkylation products of **3**. The major diastereoisomer **5d**[6] was obtained by a two-fold crystallization step from *n*-hexane–diethyl ether affording a single product (δ_P=38.18 ppm) in 60% yield. This was submitted to X-ray single-crystal structural analysis in order to ascertain the stereochemical outcome of the alkylation step and to further confirm the absolute stereochemistry at the phosphorus stereocentre (Fig. 1).

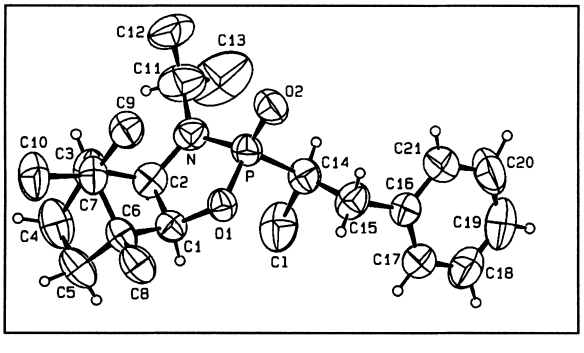

Figure 1. ORTEP II[8] plot of **5d** with arbitrary numbering. Thermal ellipsoid at 50% probability level; H atoms of methyl groups are omitted for clarity

In light of the highly diastereoselective alkylation of Li^+-**3**$^-$, we decided to test the generality of this behaviour. The results obtained in the alkylation of Li^+-**3**$^-$ with a variety of alkyl halides are reported in Table 1.

Table 1
Diastereoselective alkylation of Li^+-**3**$^-$

	RX	Yield%[a]	d.e.%[b]	δ (^{31}P-NMR)[c]
a	CH_3I	70	71	39.31; 38.02
b	C_2H_5I	65	76	38.87; 37.47
c	CH_2=$CHCH_2Br$	75	86	38.26; 36.94
d	$PhCH_2Br$	80	92	38.18; 36.77

[a] Yields of isolated compounds **5** as a diastereomeric mixture after silica gel chromatography.
[b] Diastereomeric excesses of compounds **5** evaluated by ^{31}P-NMR spectroscopy.
[c] ^{31}P chemical shift ($CDCl_3$) of the major and minor diastereomer, respectively.

The diastereofacial selectivity to give the major *R*-isomer at the newly created stereogenic centre is probably due to efficient steric hindrance by the *N*-isopropyl moiety in **3**, thereby directing the electrophile to the less hindered side of Li^+-**3**$^-$.

Treatment of compounds **5a**–**d** in THF with 4N HCl at 60°C promoted removal of the chiral auxiliary[9] and the reaction mixture was purified by Dowex® 50W-X8 (H^+-form) chromatography to afford the required α-chlorophosphonic acids **1a**–**d** in good to excellent yields. Comparison of specific rotations of **1a**–**d** with those of the literature[4a] gave ee values in very good agreement with the de values found for **5a**–**d**.

In summary, we have shown that alkylation of the anion derived from 2-chloromethyl-1,3,2-oxazaphospholane **3** gives rise to α-chlorophosphonic acids in a straightforward and highly stereoselective fashion. Finally, the chlorine atom present in **3** represents a useful handle for further manipulation. Work is in progress in our laboratories to establish the synthetic potential of this novel chiral non-racemic chloromethyl phosphonic acid equivalent.

X-Ray crystallography of **5d**: formula $C_{21}H_{31}ClNO_2P$, F_w=540.30, four-circle Syntex P4 diffractometer, graphite monochromator, Mo-Kα radiation, λ=0.71073 Å, crystal dimensions=0.58×0.48×0.44 mm^3, orthorhombic, space group $P2_12_12_1$, a=7.2301(6), b=10.3394(8), c=28.739(3) Å, V=2148.4(3) Å^3, Z=4, D_c=1.224 g cm^{-3}, μ(Mo-Kα)=0.267 mm^{-1}, F(000)=848 electrons. Intensity data (5584) collected in the range $4<2\theta<55°$ with limits h=0, 9; k=0, 13; l=−37, 37; merging R=0.0134, total number of reflections=4945, observed [$I>2\sigma(I)$] 3851. Data reduction with Lorentz and polarization corrections was carried out by XSCANS;[10] no absorption correction was applied. The structure was solved by direct methods (SIR92[11]) and refined (SHELX97[12]) by full-matrix least-squares based on 4945 F_o^2; all reflections used with weights $w=1/[\sigma(F_o^2)+(0.0583P)^2]$ were $P=(F_o^2+2F_c^2)/3$. Non-H atoms were refined anisotropically; H atoms of the isopropyl moiety were in calculated positions, the others were refined isotropically. The isopropyl group may be affected by partial rotational disorder; in fact it presents large displacement parameters (mainly for methyl C13, see Fig. 1), the distance C11–C13 [1.413(5) Å] is very short and it was impossible to refine H atoms of the group. Neutral atomic scattering factors and anomalous dispersion effects were those included in SHELX97. The absolute configuration of the molecule was determined without ambiguity by Flack's[13] method whose value converged to 0.03(6). Final agreement indices (based on F^2) were R=0.0581, R_w=0.1031 (R=0.0381, R_w=0.0951 on observed reflections) and goodness-of-fit 1.028.

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6. Selected data. Compound **3**: m.p. 115°C (hexane–Et_2O); $[\alpha]_D^{25}$=−29.5 (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.37 dd [1H] (^3J=7.6 Hz, $^3J_{H-P}$=5.2 Hz), 3.89 dd [1H] ($^2J_{AB}$=14.5 Hz, $^2J_{H-P}$=11.8 Hz), 3.70 dd [1H] ($^2J_{AB}$=14.5 Hz, $^2J_{H-P}$=6.4 Hz), 3.59 dd [1H] (^3J=7.6 Hz, $^3J_{H-P}$=4.9 Hz), 3.55 m [1H], 2.02 d [1H] (^3J=4.5 Hz), 1.85–1.45 m [3H], 1.40 d [3H] (^3J=6.5 Hz), 1.36 d [3H] (^3J=6.5 Hz), 1.34 s [3H], 1.05 s [3H], 0.97 m [1H], 0.88 s [3H]; ^{31}P NMR ($CDCl_3$, 81.0 M Hz) δ 35.99; Elem. anal.: C, 54.85; H, 8.20; N, 4.50; calcd for $C_{14}H_{25}ClNO_2P$: C, 54.99; H, 8.24; N, 4.58. Compound **5d**: m.p. 108°C (hexane–Et_2O); $[\alpha]_D^{25}$=+8.45 (*c* 1.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.32 m [5H], 4.39 dd [1H] (^3J=7.5 Hz, $^3J_{H-P}$=5.3 Hz), 4.23 ddd [1H] ($^2J_{H-P}$=11.9 Hz, ^3J=6.2 Hz, ^3J=2.4 Hz), 3.74 ddd [1H] ($^2J_{AB}$=14.7 Hz, $^3J_{H-P}$=5.3 Hz, ^3J=2.4 Hz), 3.57 dd [1H] (^3J=7.5 Hz, $^3J_{H-P}$=4.6 Hz), 3.56 m [1H], 3.05 ddd [1H] ($^2J_{AB}$=14.7 Hz, $^3J_{H-P}$=5.7 Hz, ^3J=11.9 Hz), 2.04 d [1H] (^3J=5.0 Hz), 1.77–1.55 m [3H], 1.39 d [3H] (^3J=6.7 Hz), 1.37 s [3H], 1.34 d [3H] (^3J=6.6 Hz), 1.08 s [3H], 0.97 m [1H], 0.90 s [3H]; ^{31}P NMR ($CDCl_3$) δ 38.18; Elem. anal.: C, 63.65; H, 7.97; N, 3.50; calcd for $C_{21}H_{31}ClNO_2P$: C, 63.71; H, 7.89; N, 3.54.
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