ASYMMETRIC SYNTHESIS OF DIETHYL α-AMINO- α-ALKYL-PHOSPHONATES BY ALKYLATION OF CHIRAL PHOSPHONOGLYCINE EQUIVALENTS: ROLE OF CHELATING EFFECTS

Giancarlo Jommi*, Giuliana Miglierini, Roberto Pagliarin, Guido Sello, Massimo Sisti

Università degli Studi di Milano – Dipartimento di Chimica Organica e Industriale - via G. Venezian, 21 – 20133 Milano - Italy

ABSTRACT: Diethyl α-amino-α-alkyl-phosphonates are obtained in good to high enantiomeric excesses by alkylation of chiral phosphonoglycine equivalents embodying the camphor skeleton. The chelating effects in the alkylation step play an important role in enhancing the diastereoselectivity of the reaction as substantiated by semiempirical calculations (AM1).

α-Aminophosphonic acids, the analogues of natural α-aminoacids, are of great interest due to their wide ranging biological activity.[1] The phosphonic moiety mimicks the transition-state or the intermediates of reactions involving nucleophilic attack to the carbonyl group of esters, amides, peptides and, as a consequence, α-aminophosphonic acids may function as related enzyme inhibitors.[2]
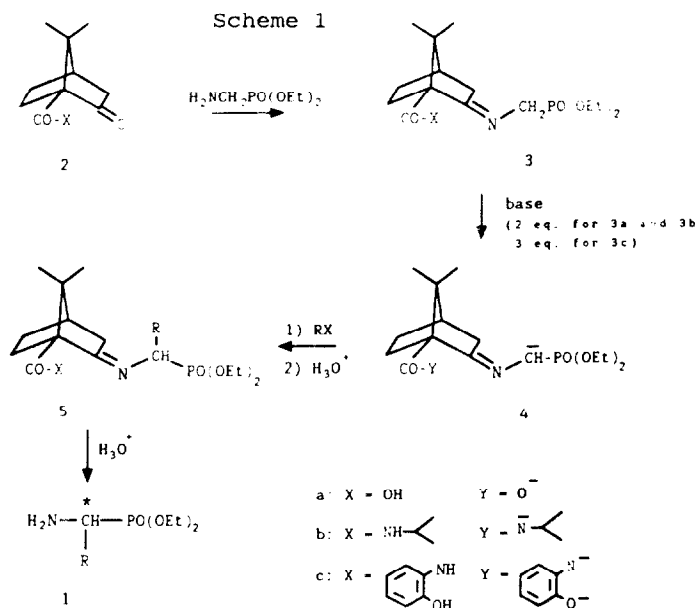
The biological activity of α-aminophosphonic acids depends on their absolute configuration, hence methods for asymmetric synthesis of these compounds constitute a main goal in this field.[3]

As previously reported by us [3a] the alkylation of the Schiff base derived from condensation of diethylaminomethylphosphonate and (+)-ketopinic acid, or natural camphor[4], proceeds with a very high endo-diasteroselectivity only when the electrophilic centre is adjacent to a π system[5]. Differently from camphor, (+)-ketopinic acid gives the possibility to tune the functionality of the substituent at carbon C-1 of the camphor skeleton and in this communication we study the effects influencing the diastereoselectivity of the alkylation step.

The Schiff bases 3b and 3c[6] were prepared by reacting a toluene solution of (+)-ketopinic acid amides 2b and 2c in the presence of boron trifluoride as Lewis catalyst and with azeotropic removal of water. Compound 3c was obtained in 90% yield after purification by flash chromatography while 3b was submitted to the following step without purification due to its instability to chromatographic systems. The absolute stereochemistry of 3b and 3c was ascertained by hydrolysis to

(+)-ketopinic acid with unchanged optical purity.[7] The Schiff bases **3b** and **3c** were assumed to have an E-configuration by analysis of their ^{1}H-NMR spectra where only one diastereoisomer is detectable.

The dianion **4b** and the trianion **4c** were generated at -78°C by treatment with two and three equivalents of lithium diisopropylamide respectively and alkylated with the appropriate electrophile at the same temperature.[8] Hydrolysis of compounds **5** with 2 N aqueous hydrochloric acid at 50°C afforded in good overall yields (40-50% from **3b** and 60-70% from **3c**) diethyl α-amino-α-alkyl-phosphonates **1**.

Scheme 1

$H_2NCH_2PO(OEt)_2$

base
(2 eq. for 3a and 3b
3 eq. for 3c)

1) RX
2) H_3O^+

2   3   4   5

$H_2N—CH—PO(OEt)_2$
R

1

a: X = OH   Y = O⁻
b: X = NH<   Y = N⁻<
c: X = ⬡NH/OH   Y = ⬡N⁻/O⁻

In table 1 the enantiomeric excesses of compounds **1** are reported[9].

TABLE 1 - Enantiomeric excesses of compounds **1**

Chiral auxiliary	R=CH$_3$	R=CH$_2$CH$_3$	R=CH$_2$-CH=CH$_2$	R=CH$_2$Ph	Config.
2a	15.1%[a]	62.2%[a]	92.2%[a]	93.0%[a]	S
	18.0%[b]	69.3%[b]	96.8%[b]	97.7%[b]	
2b	22.0%[a]	56.0%[a]	92.0%[a]	93.0%[a]	S
	25.0%[b]	58.0%[b]	97.0%[b]	96.0%[b]	
2c	47.6%[a]	81.0%[a]	94.0%[a]	>99.0%[a]	S
	50.0%[b]	82.0%[b]	96.7%[b]	95.2%[b]	
Camphor[4]	11%	69%	>95%	>95%	S

a) Enantiomeric excesses evaluated by ^{19}F-NMR spectroscopy of the amides obtained by reacting compounds **1** with (+)-Mosher's acid chloride
b) Enantiomeric excesses evaluated by optical rotations measured in CHCl$_3$

While the results in terms of enantiomeric excesses are comparable employing benzyl or allyl halides, a major improvement is obtained with 2c as chiral auxiliary in the alkylation step with methyl or ethyl iodides.

In order to rationalize the experimental results, a modelling study was undertaken utilizing a semiempirical approach (AM1).[10]

TABLE 2 - Calculated distances between potentially coordinating atoms

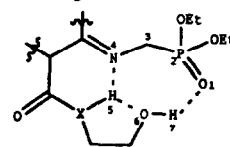| Compound	Dist. 4-5	Dist. 1-5	Dist. 5-6	Dist. 1-7
3a	2.14	3.77	-	-
3b	2.45	4.69	-	-
3c	2.43	4.71	2.50	3.79
camphor	-	-	-	-

Figure 1

Table 2 reports the distances between the hydrogen atoms and the possible coordinating atoms (figure 1). Only in the case of 3c[11] are two hydrogen bonds present, giving a greater rigidity to the structure. We can hypothesize that a similar chelation of lithium cations takes place in the trianion 4c and this chelation tends to hinder the exo-approach of the electrophile. While an explanation of the behaviour of benzyl and allyl halides(which does not appear to depend on the chiral auxiliaries and needs further investigations[12]) the model proposed can partly justify the experimental results. The modelling study also suggests possible structural modifications of the chiral auxiliary in order to improve the diastereoselectivity of the alkylation step of imines derived from the camphor skeleton.

Further studies are in progress.

References and Notes

1. (a) Dhawan, B.; Redmore, D., Phosphorous and Sulfur, 1987, 32, 119 and references cited therein. (b) Nenzil, E.; Cassaigne, A., Exp. Am. Biochim. Med., 1980, 34, 165.

2. (a) Giannousis, P.P.; Bartlett, R.W., J. Med. Chem., **1987**, 30, 1603. (b) Logush, E.W.; Walker, D.M.; McDonald, J.F.; Leo, G.C.; Franz, J.E., J. Org. Chem., **1988**, 53, 4069. (c) Allen, M.C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J.M., J. Med. Chem., **1989**, 32, 1652.

3. (a) Ferrari, M.; Jommi, G.; Miglierini, G.; Pagliarin, R.; Sisti, M., Synthetic Commun., **1992**, 22, 107. (b) Benmark, S.E.; Chatani, N.; Pansare, S.V., Tetrahedron, **1992**, 48, 2191. (c) Laschat, S.; Kunz, H., Syntesis, **1992**, 90. (d) Groth, U.; Richter, L.; Schöllkopf, U., Tetrahedron, **1992**, 48, 117 and references cited in ref. 3a-3d.

4. Schöllkopf, U.; Schütze, R., Liebigs Am. Chem., **1987**, 45.

5. The imines derived from natural camphor and glycine esters exhibit a similar behaviour: McIntosh, J.M.; Mishra, P., Can. J. Chem., **1986**, 64, 726.

6. 3b: ^{1}H-NMR (CDCl$_3$) δ 4.28-4.05 (m, 5H), 3.88-3.76 (d, $^2J_{CH_2-P}$ = 16.6Hz, 2H), 2.68-2.43 (m, 2H), 2.24-1.91 (m, 3H), 1.65-1.10 (m, 17H), 0.98 (s, 3H). 3c: ^{1}H-NMR (CDCl$_3$) δ 7.13-6.77 (m, 4H), 4.27-4.08 (m, 4H), 3.87 (d, $^2J_{CH-P}$ = 17.1Hz, 2H), 2.73-2.55 (m, 2H), 2.25-2.02 (m, 4H), 1.78-1.62 (m, 1H), 1.38-1.25 (m + s, 9H), 0.98 (s, 3H).

7. Kokke, W.C.M.; Varkevisser, F.A., J. Org. Chem., **1974**, 39, 1653.

8. We employed the same procedure as reported in ref. 3a for the alkylation of the Schiff bases 3b and 3c.

9. The enantiomeric excess obtained utilizing (+)-camphor and (+)-ketopinic acid as chiral auxiliaries are also reported in table 1 for comparison purposes.

10. (a) Dewar, M.J.S.; Zoebish, E.G.; Healy, E.F.; Stewart, J.P., J. Am. Chem. Soc., **1985**, 107, 3902. (b) Quantum Chemistry Program Exchange n. 527, Indiana University, Indiane, U.S.A.

11. Yaozhong, J.; Peng, G.; Guilan, L., Synthetic Commun., **1990**, 20, 15.

12. Preliminary studies indicate a stabilizing interaction between filled π-orbitals of the alkylating agent and the empty phosphorous orbitals.