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Asymmetric Synthesis of Diethyl α-Amino-α-Alkyl-Phosphonates by Alkylation of the Chiral Schiff Base Derived from (+)-Ketopinic Acid and Diethylaminomethyl Phosphonate

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ASYMMETRIC SYNTHESIS OF DIETHYL α-AMINO-α-ALKYL-PHOSPHONATES BY ALKYLATION OF THE CHIRAL SCHIFF BASE DERIVED FROM (+)-KETOPINIC ACID AND DIETHYLAMINOMETHYL PHOSPHONATE.

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ABSTRACT: The alkylation of the chiral Schiff base derived from the condensation of (+)-ketopinic acid and diethyl aminomethylphosphonate followed by hydrolysis affords diethyl (S)-α-amino-α-alkyl phosphonates with high enantiomeric excesses when benzyl or allyl halides are used in the alkylation step. An improved procedure for the preparation of diethyl aminomethylphosphonate is also reported.

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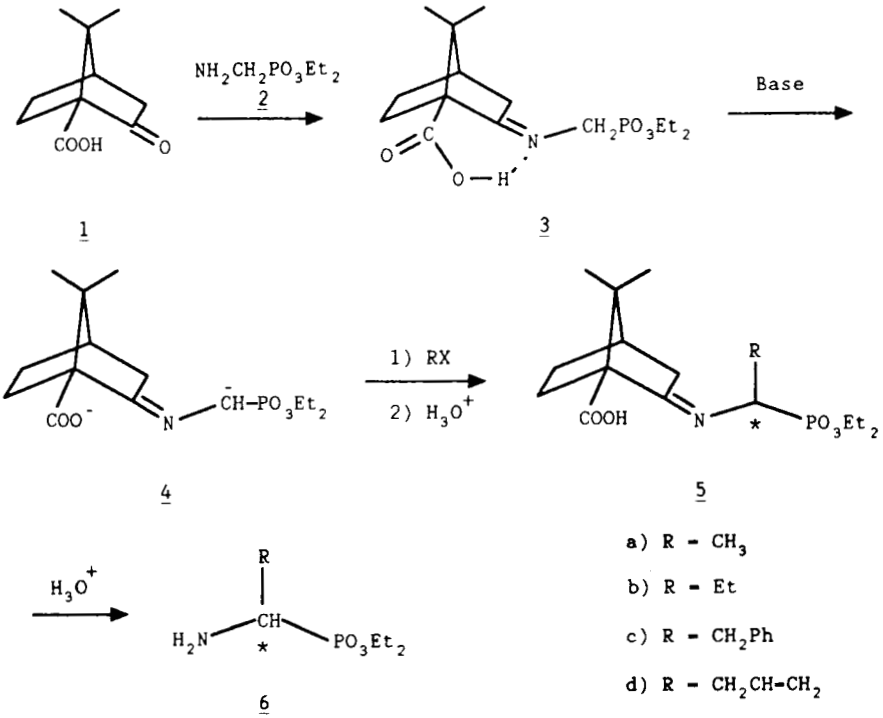
The phosphonic acid analogues of α-aminoacids, i.e. α-aminophosphonic acids, have attracted much attention in recent years for their biological activity [1]. These compounds and their derivatives, such as peptides [2], have found applications in antibiotics [3], enzyme inhibitors [4], herbicides [5].

The biological activity of α-aminophosphonic acids depends, in several cases, on their absolute stereochemistry [2a] but, despite the need to have optically active substances for biological assays, few methods are available for the asymmetric synthesis of α-aminophosphonic acids [6].

This communication reports our results in this field of synthesis [7]. The strategy we envisioned for the asymmetric synthesis of diethyl α-amino-α-alkyl-phosphonates 6 was based on the alkylation of the chiral Schiff base 3, which was derived from the condensation of (+)-ketopinic acid 1 and diethyl aminomethylphosphonate 2, followed by hydrolysis (scheme I).

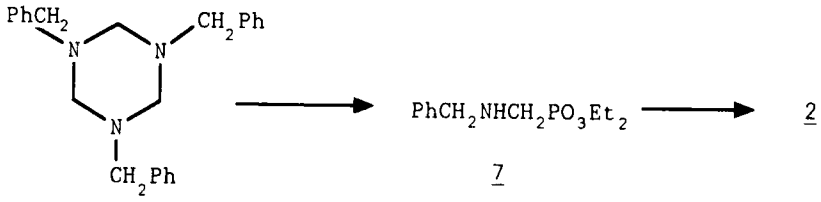
The chiral auxiliary (+)-ketopinic acid 1 was first employed by us [8], and subsequently by other authors



Scheme I

[9] to perform stereoselective aldolic condensations and alkylation reactions on the corresponding imines derived from glycine esters, or amines.

Besides its efficiency as a chiral auxiliary, it presents advantages, with respect to natural camphor [6d], in the imine bond formation which can be favoured by the hydrogen bond between the carboxylic



Scheme II

group and the nitrogen atom, and in the hydrolytic step which can be mild enough to avoid racemization.

Diethyl aminomethylphosphonate 2 was obtained by reaction of 1,3,5-tribenzylhexahydro-1,3,5-triazine with diethylphosphite at 100 °C and debenzylation of the resulting diethyl N-benzyl aminomethylphosphonate 7 [10]. We encountered some difficulties in performing the hydrogenolysis of 7 following the method described [10] which utilizes as catalyst 10% Pd on carbon in ethanol. Even different batches of catalyst required long reaction times with an average 20% conversion.

We found that the Pearlman catalyst [11], i.e. palladium hydroxide on carbon, allows a clean transformation of compound 7 into 2 in nearly quantitative yields (scheme II).

By reacting (+)-ketopinic acid 1 with 2 in ethanol at room temperature for 48h, the Schiff base 3 was isolated in quantitative yields. The classical methods of imine bond formation, i.e. Lewis catalyst and azeotropical removal of water, gave a reaction mixture which required further purification to obtain the pure compound 3. The Schiff base 3 was assumed to have an E configuration as the analysis of the resonances in the ^{1}H-NMR spectrum was consistent with the presence of one diastereoisomer.

The dianion 4 was generated at -78 °C with lithium diisopropylamide and alkylated with the appropriate electrophile at the same temperature. Compounds 5 were isolated in good yields (see experimental). Hydrolysis of 5 at room temperature with 0.25N aqueous hydrochloric acid afforded diethyl α-amino-α-alkyl-phosphonates 6, and the chiral auxiliary, with unchanged optical activity. These mild hydrolytic conditions may be due to the presence of the carboxylic group in the (+)-ketopinic acid as in fact, camphor imines [6d] require higher temperatures and more concentrated acids to react.

TABLE 1

Enantiomeric excesses of compounds 6 and total yields of the alkylation-hydrolysis sequence.

R	Yields %[a]	$[\alpha]_D^b$	ee%[b,c]	ee%[d]	Config.
CH_3	67	+ 2.63	18.0	15.1	S
CH_2CH_3	68	+ 4.98	69.3	62.2	S
$CH_2C_6H_5$	79	+ 17.66	97.7	93.0	S
CH_2-CH=CH_2	65	+ 4.17	96.8	92.2	S

a) Yields evaluated after bulb to bulb distillation of compounds 6
b) For the optical rotations of enantiomerically pure compounds 6 see ref. [6d] and [6f].
c) Enantiomeric excesses evaluated by optical rotations measured in $CHCl_3$.
d) Enantiomeric excesses evaluated by ^{19}F-NMR spectroscopy of the amides obtained by reacting compounds 6 with (+)-Mosher's acid chloride.

The enantiomeric excesses of compounds 6 were determined both by comparison of the reported optical rotations and by ^{19}F-NMR analysis of the corresponding amides obtained by reacting 6 with S(+)-α-methoxy-α-trifluoromethyl phenylacetic acid chloride [(+)-Mosher's acid chloride].

It is noteworthy that diethyl (S)-(1-amino-2-phenylethyl)-phosphonate 6c and diethyl (S)-(1-amino-3-butenyl)-phosphonate 6d were obtained in good yields and with very high enantiomeric purity (ee ≧ 92%).

The results reported in Table 1 clearly indicate a preference for an endo-attack of the alkylating agents on the dianion 4 and an excellent diastereoselectivity in the alkylation step when the electrophylic center is adjacent to a π-system (R= CH_2-CH=CH_2, $CH_2C_6H_5$), as already observed for the alkylation of imines derived from natural camphor and glycine esters [13].

Work is in progress to improve the diastereoselectivity, when modest, by modifying the carboxylic group in the (+)-ketopinic acid.

Experimental section

IR spectra were recorded on a Perkin Elmer 457 spectrophotometer. ^{1}H-NMR spectra were measured in deuterochloroform with a Bruker AC 200 (200 MHz) and ^{19}F-NMR spectra with a Bruker AC 300 (282.4 MHz). Mass spectra were obtained with a VG 7070 EQ spectrometer. Optical rotations were measured at 25 °C using a 1dm

cell on a Perkin-Elmer 241 polarimeter. Microanalyses were carried out in the microanalytical laboratory of our Department using a Perkin-Elmer 240 instrument. Boiling points refer to bulb-to-bulb distillation using a Büchi GKR-50 apparatus. Analytical thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 F254. Tetrahydrofuran (THF) was distilled under nitrogen from lithium aluminum hydride. Organic solutions were dried over Na_2SO_4 and the product isolated by filtration and evaporation of the filtrate using a rotatory evaporator operating at 15 torr.

Diethyl aminomethylphosphonate 2. The diethyl-N-benzyl aminomethylphosphonate 7 (8.00 g, 31.1 mmol) was dissolved in absolute ethanol (200 ml) containing 10% $Pd(OH)_2$ on carbon (1.50 g) and hydrogenated at 25 °C and 1atm pressure until the uptake of hydrogen had ceased (24h; TLC MeOH/$CHCl_3$ 3/97). The catalyst was removed by filtration over celite and washed with ethanol (3 x 20ml). After evaporation of the solvent, diethyl aminomethylphosphonate 2 (5.15 g) was obtained in nearly quantitative yields and pure enough for the

following step. The physical and spectroscopical properties were identical to those already reported [10].

Schiff base 3. To a solution of (+)-ketopinic acid (1.82 g, 10.0 mmol) in ethanol (20 ml) a solution of diethyl aminomethylphosphonate (1.67 g, 10.0 mmol) in ethanol (20 ml) was added at room temperature. The mixture was allowed to stand at room temperature for two days. After removal of the solvent under vacuum, pure Schiff base 3 (3.30 g) was obtained in quantitative yields. An analytical sample was obtained by flash chromatography ($CHCl_3$/MeOH 95:5 as eluant).

3: oil; IR (neat) 3472, 1734, 1684, 1236, 1025 cm^{-1}; $[\alpha]_D^{20}$= + 48.9 (c = 2.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$)δ 0.98 (s, 3H), 1.27-1.45 (s + m, 9H), 1.61-1.82 (m, 1H), 2.00-2.24 (m, 4H), 2.33-2.80 (m, 2H), 3.88 (d, J=17.1 Hz, 2H), 4.07-4.25 (m, 4H); MS, m/z 331 (M^+), 316, 303, 287, 270, 256, 208, 194, 168, 150, 138, 111, 82. Anal. Calcd for $C_{15}H_{26}NO_5P$: C, 54.38; H, 7.85; N, 4.23. Found: C, 54.28; H, 7.76; N, 4.16.

General procedure for alkylation of the Schiff base 3. To a solution of lithium diisopropylamide (2.1 mmol) in anhydrous THF (6 ml) a solution of the Schiff base 3 (1.0 mmol) was added at -78 °C under argon atmosphere. After stirring for 30 min (the solution becomes intensely red-coloured) a solution of the alkylating agent (2.1 mmol) in anhydrous THF (2 ml) was added. The mixture was allowed to react at -78 °C for 3h. After evaporation of the solvent under vacuum, aqueous 0.1N hydrochloric acid (15 ml) was added and the mixture extracted with ethyl acetate (4 x 10ml). The combined organic extracts were washed with water (2 x 15ml), dried and evaporated under vacuum. Compounds 5a, 5b, 5d were pure enough for the following step. Compound 5c was chromatographed on silica gel (AcOEt/MeOH 95:5 as eluant) to remove the excess of benzylbromide. All attempts to separate the two diastereoisomers derived from the alkylation of 3 were unsuccessful, therefore ^{1}H-NMR spectra were run on the diastereoisomeric mixtures.

5a: 90% yields; oil; ^{1}H-NMR ($CDCl_3$) δ 0.95 (s), 1.05

(s), 1.13 (s), 1.25 (s), 1.26-1.42 (m, 6H), 1.44(dd, J=7.1 , 1.8), 1.55 (dd, J=6.8, 1.8), 1.62-2.92 (m, 7H), 3.78-3.99 (m, 1H), 4.05-4.38 (m, 4H); MS, m/z 346 (M^+ +1), 328, 317, 301, 286, 208, 190, 164, 136, 121, 109, 95, 84, 67.

5b: 87% yields; oil; ^{1}H-NMR ($CDCl_3$) δ 0.91 (t, J=7.1 Hz, 3H), 1.04 (s, 3H), 1.11 (s, 3H), 1.20-1.43 (m, 6H), 1.59-2.87 (m, 9H), 3.54-3.71 (m, 1H), 4.03-4.26 (m, 4H); MS, m/z 359 (M^+), 331, 315, 222, 204, 178, 162, 149, 136, 123, 109, 91, 81, 69.

5c: 95% yields; oil; ^{1}H-NMR ($CDCl_3$) δ 0.88 (s, 3H), 1.08-1.48 (s + m, 9H), 1.55-2.62 (m, 7H), 2.89-3.12 (m, 1H), 3.27-3.42 (m, 1H), 3.80-3.99 (m, 1H), 4.00-4.30 (m, 4H), 7.02-7.39 (m, 5H); MS, m/z 422 (M^+ +1), 404, 393, 377, 330, 312, 302, 284, 266, 192, 181, 148, 139, 120, 109, 91, 81, 77, 67.

5d: 85% yields; oil; ^{1}H-NMR ($CDCl_3$) δ 0.91 (s), 1.03 (s), 1.11 (s), 1.25 (s), 1.28-1.43 (m, 6H), 1.48-2.85 (m, 9H), 3.69-3.85 (m, 1H), 4.05-4.28 (m, 4H), 5.04-5.22 (m, 2H), 5.52-5.76 (m, 1H); MS, m/z 371 (M^+),

356, 343, 330, 326, 312, 302, 234, 230, 216, 190, 139, 121, 109, 91, 81, 65.

General procedure for hydrolysis of alkylated Schiff bases 5. A mixture of alkylated Schiff base 5 (0.1 mmol), aqueous 0.25N hydrochloric acid (2 ml) and tetrahydrofuran (1 ml) was stirred at room temperature for 48h. The organic solvent was evaporated under vacuum and the aqueous layer extracted with ethylacetate (3 x 5ml).After evaporation of the organic extracts, (+)-ketopinic acid was recovered in quantitative yields and unchanged optical activity. The aqueous layer was alkalinized to pH=8.5 with a saturated aqueous sodium carbonate solution (5 ml) and extracted with ethyl acetate (3 x 10ml). The combined extracts were dried over Na_2SO_4 and evaporated to yield compounds 6 which were purified by bulb-to-bulb distillation under reduced pressure.

Diethyl (S)-(1-aminoethyl)phosphonate 6a: 75% yields; b.p. 110 °C/7.5 10-3torr; $[\alpha]_D^{20}$ = + 2,63 (c=2.0, $CHCl_3$) (lit [6f] $[\alpha]_D$ = + 14.6) ; ^{1}H-NMR ($CDCl_3$) δ

1.31 (dd, J_{H-H} =7.3Hz, J_{P-H}=17.4 Hz, 3H), 1.32 (t, J=7.2Hz, 6H), 1.53 (m, 2H), 3.10 (m, 1H), 4.12 (dq, $J_{H-H}=J_{P-H}$=7.2Hz, 4H); MS, m/z 181 (M^+), 166, 152, 138, 111, 93, 84, 82, 65.

Anal. Calcd for $C_6H_{16}NO_3P$: C, 39.78; H, 8.84; N, 7.73. Found: C, 39.70; H, 8.78; N, 7.69.

Mosher's amide of 6a: ^{19}F-NMR ($CDCl_3$) δ - 118.84; - 118.47.

Diethyl (S)-(1-aminopropyl)phosphonate 6b: 78% yields; b.p. 125 °C/7.5 10-3torr; $[\alpha]_D^{20}$= + 4.98 (c = 1.8, $CHCl_3$) (lit [6d] $[\alpha]_D^{20}$ = + 7.18); ^{1}H-NMR ($CDCl_3$) δ 1.09 (t, J=7.2 Hz, 3H), 1.36 (t, J=7.1 Hz, 6H), 1.45-1.77 (m, 4H), 2.89 (m, 1H), 4.28 (dq, $J_{H-H}=J_{P-H}$ =7.1 Hz, 4H); MS, m/z 196 (M^+ +1), 178, 165, 149, 139, 123, 109, 91.

Anal. Calcd for $C_7H_{18}NO_3P$: C, 43.07; H, 9.23; N, 7.18. Found: C, 42.95; H, 9.15; N, 7.12.

Mosher's amide of 6b: ^{19}F-NMR ($CDCl_3$) δ -118.81; - 118.43

Diethyl (S)-(1-amino-2-phenylethyl)phosphonate 6c: 83% yields; b.p. 160°C/10-2torr; $[\alpha]_D^{20}$ = + 17.66 (c =

1.0, $CHCl_3$) (lit [6f] $[\alpha]_D$ = - 18.07 for the opposite enantiomer); ^{1}H-NMR ($CDCl_3$) δ 1.35 (t, J=6.6 Hz, 6H), 1.63 (m, 2H), 2.58-2.79 (m, 1H), 3.15-3.37 (m, 2H), 4.10 (dq, $J_{H-H}=J_{P-H}$=6.6Hz, 4H), 7.12-7.40 (m, 5H); MS, m/z 258 (M^+ +1), 180, 166, 138, 120, 110, 103, 91, 81, 77, 65.

Anal. Calcd for $C_{12}H_{20}NO_3P$: C, 56.03; H, 7.78; N, 5.45. Found: C, 55,90; H, 7.85; N, 5.38.

Mosher's amide of 6c: ^{19}F-NMR ($CDCl_3$) δ - 118.84; - 118.72

Diethyl (S)-(1-amino-3-butenyl)phosphonate 6d: 76% yields; b.p. 120 °C/7.5 10-3torr; $[\alpha]_D^{20}$= +4.17 (c = 1.6, $CHCl_3$) (lit [6f] $[\alpha]_D$ = + 4.31): ^{1}H-NMR ($CDCl_3$) δ 1.32 (t, J=6.6 Hz, 6H); 1.49 (m, 2H), 2.09-2.32 (m, 1H), 2.49-2.70 (m, 1H), 2.94-3.11 (m, 1H), 4.12 (dq, $J_{H-H}=J_{P-H}$ = 6.6 Hz, 4H), 5.05-5.23 (m, 2H), 5.69-5.93 (m, 1H); MS, m/z 208 (M^+ +1), 183, 165, 149, 139, 70.

Anal. Calcd for $C_8H_{18}NO_3P$: C, 46.37; H, 8.69; N, 6.76. Found. C, 46.22; H, 8.60; N, 6.66.

Mosher's amide of 6d: ^{19}F-NMR ($CDCl_3$) δ - 118.67; -118.59

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