Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2329–2332

TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of (2*S*,3*R*,4*R*)-ethoxycarbonylcyclopropyl phosphonoglycine

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Received 24 April 1998; accepted 26 May 1998

Abstract

The synthesis of enantiomerically pure (2*S*,3*R*,4*R*)-ethoxycarbonylcyclopropyl phosphonoglycine is described, the key-step involving 1,4-addition of a chiral enolate to ethyl 4-bromo-crotonate.

1. Introduction

The synthesis of α-aminoacids in which the carbon skeleton has been constrained is an active research area.[1] In this regard[2] 2,3-methano aminoacids have attracted considerable attention. 3,4-Methano aminoacids[3] and particularly 3,4-methanoglutamic acid (or carboxy cyclopropyl glycine) an analog of the excitatory neurotransmitter L-glutamate with a restricted conformational side chain, gave rise to several publications. The isolation and structural characterization of (2*S*,3*S*,4*R*)-3,4-methanoglutamic acid from *Aesculas parviflora* and (2*S*,3*S*,4*S*)-3,4-methanoglutamic acid, from *Blighia sapida* were reported[4] in 1969. Several enantioselective syntheses using the diazoaddition method were published.[5]

2. Results

We describe here the first enantioselective synthesis of the phosphonic analogue of (2*S*)-ethoxycarbonylcyclopropylglycine using as a key-step the 1,4-addition reaction of the enolate of

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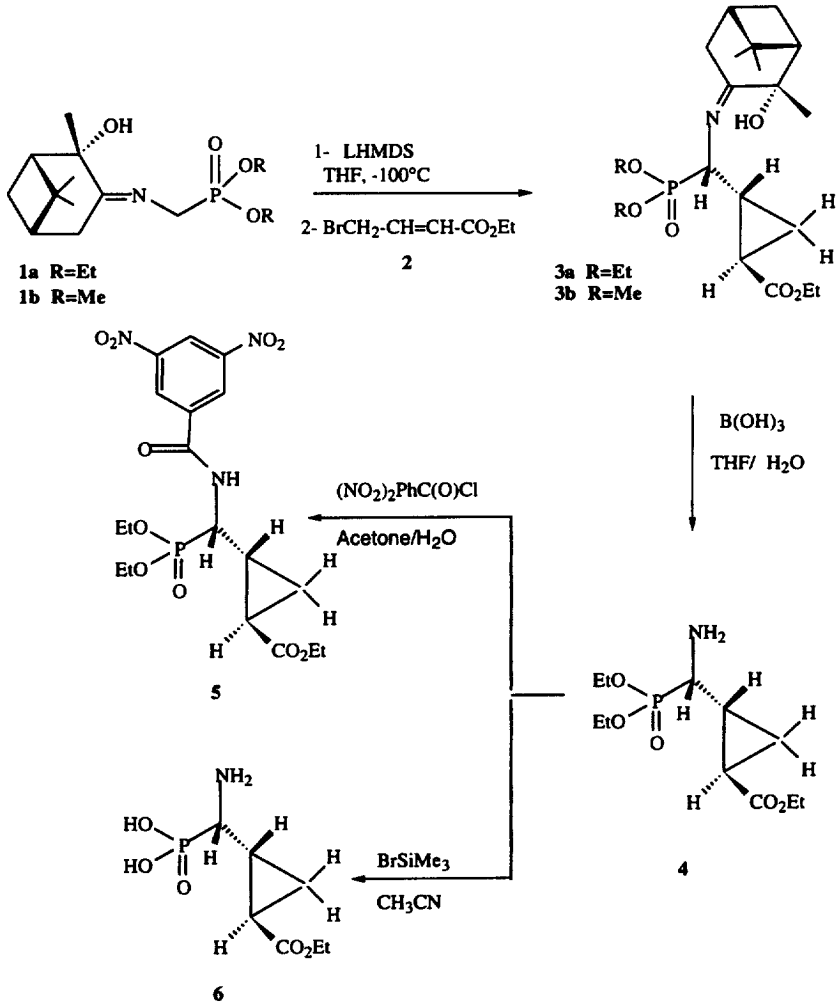
0957-4166/98/$ - see front matter
PII: S0957-4166(98)00216-X

the Schiff base[6] **1** prepared from dialkyl aminomethylphosphonate and (1*S*,2*S*,5*S*)-2-hydroxy pinan-3-one to ethyl 4-bromo crotonate **2**.

Cyclopropane ring formation by anionic Michael addition to alkenes such as **2** has been previously reported as an efficient method.[7] In this report we have studied the influence of two esters (dimethyl and diethyl) and three bases (potassium *tert*-butoxide, lithium diisopropylamide, lithium hexamethyl disilazide) on the yield and diastereoselectivity of the 1,4-addition reaction. Among the bases tested, LHMDS prepared from BuLi in ether yielded the best results. Reaction of the enolates of the Schiff bases **1a** (R=Et) and **1b** (R=Me) with **2** in THF at −100°C led respectively to **3a** (85% yield, one isomer, detected by ^{1}H and ^{31}P NMR) and **3b** (50% yield, two inseparable isomers 90/10). Three stereogenic centres are generated in the sequence of Michael addition of the lithiated phosphonoglycine equivalent to ethyl 4-bromocrotonate and subsequent cyclisation; only one isomer **3a** was obtained starting from **1a**. Hydrolysis of the imine **3a** with boric acid (pH=6 to 6.2) produced the oily aminoester **4** in 92% yield.



To assign unambiguously the configurations of the cyclopropanic carbons, **4** was transformed into the crystalline N-p-nitrobenzoyl and N-dinitrobenzoyl derivatives. Only the N-(3,5-dinitrobenzoyl) aminoester **5** was suitable for X-ray study which allowed assignment of the (3*R*,4*R*)-configurations. Treatment of **4** with $BrSiMe_3$ in CH_3CN led to the aminophosphonic acid **6** in 80% yield.

In conclusion we have described an efficient synthesis of enantiomerically pure (2*S*,3*R*,4*R*)-ethoxycarbonylcyclopropyl phosphonoglycine in three steps and in 62% overall yield.

3. Experimental

Thin layer chromatography was performed on Merck precoated silica gel $60F_{254}$ plates and spots were visualized by ultraviolet light or/and by iodine vapour. Melting points were obtained on a Büchi 510 apparatus and were not corrected. Optical rotations were determined with a Perkin–Elmer 141 polarimeter. ^1H and ^{31}P NMR spectra were recorded on a Brucker spectrometer AC 250. Mass spectra were measured on Jeol JMS DX 100 and DX 300 apparatus.

*3.1. Schiff bases of ethoxycarbonylcyclopropyl phosphonoglycine diethyl and dimethyl ester: **3a, 3b***

n-BuLi (13 ml, 20.82 mmol) in ether was added under N_2 with stirring to hexamethyldisilazane (4.39 ml, 20.82 mmol) dissolved in anhydrous THF at 0°C. The mixture was cooled to −100°C and the Schiff base **1a** or **1b** dissolved in anhydrous THF (2 ml) was added. After 15 min ethyl 4-bromocrotonate (3.4 ml, 18.92 mmol) in anhydrous THF (2.5 ml) was added and the solution was stirred (15 h), until completion of the reaction (TLC) (temperature was allowed to slowly reach −20°C).

The mixture was quenched with a NH_4Cl saturated solution (60 ml) and extracted with ether (3×20 ml). The organic layer was dried ($MgSO_4$), concentrated in vacuo and the residue chromatographed on silica gel to yield **3a** (85%) R_f: 0.75 (ether/MeOH=95/5). ^1H NMR ($CDCl_3$) δ: 0.7 (m, 1H); 0.78 (s, 3H); 1.1 (m, 1H); 1.27 (s, 3H); 1.2 (t, 3H, J=6.9 Hz); 1.3 (t, 6H, J=7 Hz); 1.37 (s, 3H); 1.5 (d, 1H, J=10.5 Hz); 1.83 (m, 1H); 1.98 (m, 2H); 2.25 (m, 2H); 2.4 (m, 2H); 2.68 (m, 1H); 3.9 (d×d, 1H, J=5 Hz, J_{P-H}=9.5 Hz); 4.1 (m, 6H). ^{31}P NMR ($CDCl_3$): 22.78. $[M+H]^+$ 430 (FAB). **3b** (Major isomer): ^1H NMR ($CDCl_3$) δ: 0.75 (m, 1H); 0.85 (s, 3H); 1.2 (m, 1H); 1.22 (t, 3H, J=7 Hz); 1.27 (s, 3H); 1.3 (m, 1H); 1.4 (s, 3H); 1.57 (d, 1H, J=10 Hz); 1.83 (m, 1H); 1.95–2.08 (m, 2H); 2.32 (m, 1H); 2.47 (m, 1H); 2.6 (m, 2H); 3.7 (2×d, 6H, J_{P-H}=11 Hz); 3.9 (d×d, 1H, J=5.3 Hz, J_{P-H}=14 Hz); 4.15 (m, 2H). ^{31}P NMR ($CDCl_3$): 25.28. $[M+H]^+$ 402 (FAB).

*3.2. Ethoxycarbonylcyclopropyl phosphonoglycine diethyl ester: **4***

To a solution of the Schiff base **3a** (2 g, 4.66 mmol) in THF (3 ml) was added a 1 M aqueous solution of boric acid at pH=6.2 (with phosphate buffer). The mixture was stirred at 45°C for 3 h. THF was concentrated in vacuo, the aqueous layer extracted with ether, neutralised ($NaHCO_3$) and extracted with CH_2Cl_2 (3×25 ml). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Yield: 92% $[\alpha]_D^{20}=-29$ (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.95 (m, 1H); 1.21 (t, 3H, J=7 Hz); 1.31 (t, 6H, J=6 Hz); 1.6 (m, 4H); 1.9 (m, 1H); 2.45 (d×d, 1H, J=6 Hz, J_{P-H}=12 Hz); 4.1 (m, 6H). $[M+H]^+$ 280 (FAB).

*3.3. N-(3,5-Dinitrobenzoyl) ethoxycarbonylcyclopropyl phosphonoglycine diethyl ester: **5***

To a solution of **4** (0.6 g, 2.15 mmol) in acetone (7.5 ml) and $NaHCO_3$ (0.315 g, 6.15 mmol) in H_2O (2.5 ml) at −5°C was added dinitro-3,5-benzoyl chloride (0.643 g, 2.8 mmol) in acetone (2 ml) over 10 min. The mixture was stirred for 2 h at −5°C and 1 h at room temperature. Acetone was concentrated in vacuo, the aqueous layer was acidified with 1 N HCl (pH=2) and extracted with ether (3×20 ml). The

organic layer was evaporated and the residue chromatographed on silica gel. Yield=85%, R_f=0.47 (ether), m.p.=132–134°C (ether), $[\alpha]_D^{20}$=−60 (c=1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.1 (m, 1H); 1.15 (t, 3H, J=6.9 Hz); 1.22 (t, 3H, J=6.9 Hz); 1.25 (m, 3H); 1.3 (t, 3H, J=6.9 Hz); 4.1 (m, 6H); 7.7 (1H, NH); 8 (d, 2H, J=8.7 Hz); 8.21 (d, 2H, J=8.7 Hz). ^{31}P NMR ($CDCl_3$) δ=20.8. $[M+H]^+$=474 (FAB). $C_{18}H_{24}N_3O_{10}P$ calc: C 45.67, H 5.11, N 8.88, found: C 46.09, H 5.15, N 8.91.

3.4. (2S,3R,4R)-Ethoxycarbonylcyclopropyl phosphonoglycine: 6

To phosphonic aminoester **4** (1 g, 3.58 mmol) in CH_3CN (12 ml) was added dropwise $BrSiMe_3$ (1.9 ml, 14.33 mmol). The mixture was stirred under argon at 60°C for 10 h. The solution was concentrated under reduced pressure, the residue treated with H_2O and the aqueous solution concentrated in vacuo. Ethyl acetate (20 ml) was added, the solution was filtered and the product dried under vacuum. Yield=80%, $[\alpha]_D^{20}$=−35 (c=1.1, MeOH). ^1H NMR (CD_3COCD_3) δ: 1.2 (t, 3H, J=7 Hz); 1.3 (m, 2H); 1.5 (m, 1H); 1.85 (m, 1H); 2.2 (m, 3H); 4.05 (m, 2H); 4.55 (m, 1H). $[M+H]^+$=224 [FAB].

3.5. Crystal structure of 5

Crystal data: $C_{18}H_{24}N_3O_{10}P$ M_W=473.37, orthorhombic, space group $P2_12_12_1$, Z=8, a=9.975(5), b=18.932(4), c=24.885(9) Å, V=4699(3) Å^3, d_{calc}=1.34 g cm^{-3}, λ (Cu-Kα)=1.5418 Å, μ=1.54 mm^{-1}.

Intensity data were measured on a Enraf–Nonius CAD-4 diffractometer using graphite-monochromated Cu-Kα radiation and the (θ–2θ) scan technique up to θ=69°. There were 6382 collected reflections, 4865 unique (R_{int}=0.039) of which 2356 were considered as observed, having I>2σ (I). Three ethyl chains were disordered occupying two positions. Hydrogens are in theoretical positions. Refinement minimizing the function $\Sigma w(Fo^2-|Fc|^2)^2$, R=0.071 and wR_2=0.201, goodness of fit 1.05. The residual electron density in the final difference map was located between −0.25 and 0.24 e Å^3. The two molecules in the asymmetric unit form a dimer linked by two hydrogen bonds N–H..O=P [2.831(10) and 2.825(9) Å]. Computer-programs: SHELXS86, SHELX93.

Supplementary materials for X-ray crystallography: lists of coordinates, bond distances, bond angles, torsional angles have been deposited at the Cambridge Crystallographic Data Center.

References

1. Giannis, A.; Kolter, T. Angew. Chem. Int. Ed. Engl. **1993**, 32, 1244; Kahn, M. *Synlett* **1993**, 821.
2. For reviews see Alami, A.; Calmes, M.; Daunis, J.; Jacquier, R. *Bull. Soc. Chim. Fr.* **1993**, 130, 5; Burgess, K.; Ho, K. K.; Moye-Sherman, D. *Synlett* **1994**, 575.
3. Stammer, C. H. *Tetrahedron* **1990**, 46, 2231.
4. Fowden, L.; Smith, A.; Millington, D. S.; Sheppard, R. C. *Phytochemistry* **1969**, 8, 437.
5. Kurokawa, N.; Ohfune, Y. *Tetrahedron Lett.* **1985**, 26, 83; Yamanoi, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, 29, 1181.
6. Ouazzani, F.; Roumestant M. L.; Viallefont Ph.; El Hallaoui A. *Tetrahedron: Asymmetry* **1991**, 2, 913; Ryglowski A.; Lazaro R.; Roumestant M. L.; Viallefont Ph. *Synthetic Commun.* **1996**, 26, 1739.
7. Kolsaker, P.; Storesund, H. J. *J. Chem. Soc., Chem. Comm.* **1972**, 375; Joucla, M.; El Goumzili, M.; Fouchet, B. *Tetrahedron Lett.* **1986**, 1677; Zindel, J.; De Meijere A. *Synthesis* **1994**, 190.