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Water soluble phosphines☆ Part XIII. Chiral phosphine ligands with amino acid moieties

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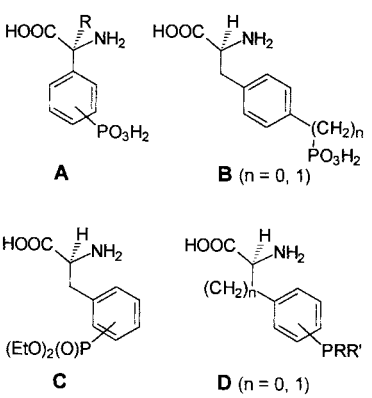
Abstract

Nucleophilic phosphination of the potassium or sodium salt of the fluorophenylalanines (**1a**, **2a**) or -glycines (**3a**, **4a**) with potassium phosphides Ph(R)PK (R = Me, Ph) yields chiral phosphine ligands (**1**–**7**) with amino acid moieties. The X-ray structure of **3**·2H_2O (space group *Pbca*) has been determined showing a betaine type structure for the amino acid moiety. The α-methyl derivatives of the phosphinophenylglycines (**10**, **11**) were obtained in an analogous manner as **1**–**7**. *ortho*- and *para*-Fluoroacetophenones have been employed as starting material for the syntheses of α-[4-fluorophenyl]-α-methylglycine (**9c**) and its *ortho*-isomer (**8c**), the X-ray structure of its monohydrate has been determined (space group $P\bar{1}$). The *N*-acetyl (**3b**, **8e**) and ester derivatives (**3d**, **8d**) of **3** and **8c** are accessible using standard procedures. Resolution of the diastereomeric salt **12** obtained from (*S*)-(+)-2-hydroxymethylpyrrolidine and *racem*-**8e** by fractionated crystallization yielded the (*S*,*R*)-isomer. The absolute configuration of (*S*,*R*)-**12** was determined by X-ray structural analysis (space group $P2_12_12_1$). Cleavage of (*S*,*R*)-**12** with hydrochloric acid gave enantiopure (*R*)-**8e** $[\alpha]_D^{20} = -30.9°$ ($c = 1$, CH_3OH). © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Nucleophilic phosphination; Fluorophenyl α-amino acids; α-Methylated; Phosphine derivatives; Resolution; X-ray structures

1. Introduction

Unnatural and non-proteinogenic α-amino acids containing functionalized aromatic substituents are of considerable interest as enzyme inhibitors [2a] and chiral synthons [2b]. They have been employed as building blocks for the syntheses and the design of new types of proteins and peptidomimetic drugs [2c] with unusual properties [2d]. Phosphono and phosphonomethyl derivatives of phenylglycine and alanine (**A** [3a], **B** [3c] and **C** [3d]) were tested as glutamate and aspartate antagonists. While compounds of type **A**–**C** have been known for more than 1 decade [3], preliminary reports on the analogous phosphino derivatives **D** appeared only very recently in the literature [4,5]. Due to their metal binding capacity these biologically based phosphine ligands are of potential use in medical imaging and in homogeneous catalysis.



Prior reports from this laboratory have documented the utility of nucleophilic phosphination of fluoroaromatic compounds as a straightforward synthetic strategy for the preparation of hydrophilic functionalized phosphine ligands [6]. The successful implementation of this nucleophilic phosphination strategy necessarily depends on the availability of suitable fluorophenyl derivatives of the amino acids. Some of them are commercially-

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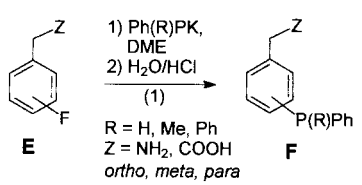
available (e.g. 2-, 3- or 4-fluorophenylalanine and 2-fluorophenylglycine) or may be prepared using standard synthetic procedures [7] as will be shown below.

In this paper we concentrate on the synthesis of phenylglycine and -alanine derivatives bearing phosphino substituents in the *ortho* or *para* position to the amino acid moieties ($CH(NH_2)COOH$ or $CH_2CH(NH_2)$-COOH) within the aromatic ring systems by nucleophilic phosphination. Preliminary results of this work have been published elsewhere [5]. The synthetic principle outlined here may be used for a modular approach [8] to a great variety of chiral mono- or bidentate (*P*- or *P*,*N*-donors) phosphine ligands which may find application in combinatorial catalysis [9].

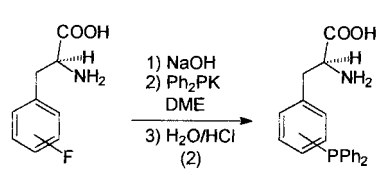
2. Synthesis of 2- and 4-diphenylphosphino derivatives of phenylalanine and -glycine

Nucleophilic phosphination of fluoroaromatic systems either with PH_3, primary or secondary phosphines in the superbasic medium [6a–c] or with alkali metal phosphides in anhydrous solvents normally requires activation of the C–F bond by electron withdrawing substituents like SO_3M, PO_3M_2, CN or COOM (M = Na, K) [6d,e]. This is, however, not a necessary prerequisite since it has been shown by us in previous work [6d] that phosphino derivatives of phenylacetic acid and benzylamine (**F**) are accessible by nucleophilic phosphination of the corresponding fluoroaromatic compounds **E** with CH_2–Z substituents (Z = NH_2, COOH) in high yields (Eq. (1)).



E **F**

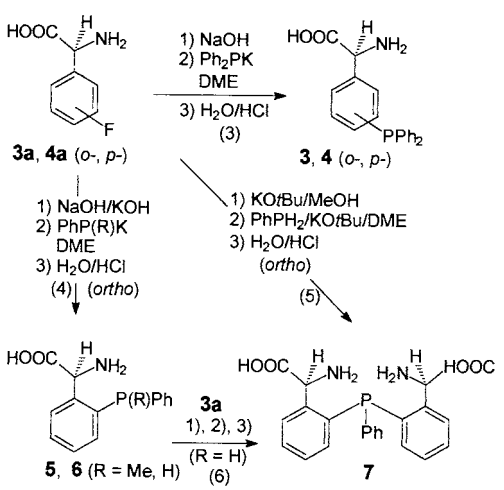
The extension of this synthetic strategy to fluorophenyl substituted amino acids was expected to yield the corresponding phosphino derivatives. Thus, when 2- or 4-fluorophenylalanine were reacted with potassium diphenylphosphide in DME at reflux temperature the phosphinophenyl amino acids **1** and **2** are formed in satisfying yields (Eq. (2)). Both isomers of fluorophenylalanine (**1a** (*ortho*) and **2a** (*para*)) [10a] are commercially available. **1a** was prepared from 2-fluorobenzyl chloride using the classical procedure first published by Marvel [10c].



1a, **2a** (*o*-, *p*-) **1**, **2** (*o*-, *p*-)

The phosphines **1** and **2** show singlets in the $^{31}P\{^1H\}$-NMR spectrum in a range typical for tertiary phosphines [11] with a high field shift of δP for the *ortho*-isomer **1** ($\delta P = -13.0$ ppm) as compared to that of **2** ($\delta P = -5.4$ ppm). The protons of the CH_2 units are inequivalent in both cases. Typical eightline patterns are obtained in the ^1H-NMR spectrum (AB part of an ABM spin system (A, B = CH_2, M = CH). Asymmetric substitution at the α-carbon atom of the amino acid moiety renders the phenyl groups of the Ph_2P unit in **1** inequivalent, two sets of resonances being observed for the aromatic carbon atoms in the $^{13}C\{^1H\}$-NMR spectrum.

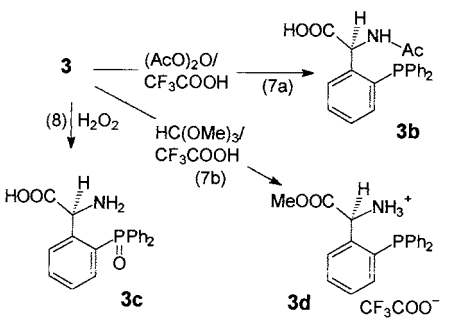
The phosphine ligands **3**–**5** with glycine moieties have been obtained by the same synthetic procedure as employed for **1** and **2** (Eqs. (3 and 4)). Due to the greater nucleophilicity of Ph(Me)PK [12] its reaction with **3a** (Eq. (4)) proceeds much faster than the corresponding reaction of **3a** with Ph_2PK. If enantiomerically pure **4a** (4-fluoro-D-α-phenylglycine, $[\alpha]_D^{20} = -138°$; $c = 1$, 1 m HCl) was employed for the nucleophilic phosphination according to Eq. (3), the product **4** obtained showed no optical activity. Under the reaction conditions obviously a complete racemization occurred via equilibrium deprotonation at the α-carbon atom of **4** [13]. Racemization of optically active amino acids is known to occur preferably in alkaline media and is accelerated by groups stabilizing the negative charge created in α-position [13c]. Racemization at the α-carbon atom was also observed during the phosphination of NH_2 and COOH protected (*S*)-β-bromoalanine with the less nucleophilic copper(I) phosphides [14].



The phosphine ligand **5** (R = Me) is obtained as a mixture of two diastereoisomers (*erytho* and *threo* isomer) as indicated by two $^{31}P\{^1H\}$-NMR resonances ($\delta P = -38.6$, -39.5 ppm, intensity ratio 1:1) and the observation of two sets of lines for the aromatic carbon atoms in the $^{13}C\{^1H\}$-NMR spectrum. One diastereoisomer ($\delta P = -39.5$ ppm) could be obtained almost pure by recrystallization of **5** from a 3:1 methanol–water

mixture. The solubility of **3**–**5** in water is very low. As for amino acids [15] it increases; however, significantly in the acid or basic range. The phenyl groups of the Ph_2P unit in **3** are inequivalent two sets of resonances being observed in the $^{13}C\{^1H\}$-NMR spectrum.

Attempts to synthesize the secondary phosphine derivative of phenylglycine **6** (R = H) selectively by reaction of the potassium salt of **3a** with PhPHK were not sucessful (Eq. (4)). A mixture of **6** and the tertiary phosphine **7** with two phenylglycine moieties was obtained (Eqs. (4 and 6)). If the potassium salt of **3a** is treated with a 2:1 molar ratio of $PhPH_2$–KO^{t}Bu, bifunctional **7** is formed as the main product. It is obtained as a mixture of three diastereoisomers (two meso forms, $\delta P = -24.7, -25.9$ ppm, and a racemate, $\delta P = -24.9$ ppm) (Eq. (5)), which could be separated by stepwise changing the pH value of the aqueous solution in the range between 0 and 7. The racemate shows two inequivalent CH groups as indicated by two resonances at 4.98 ppm ($^4J(PH) = 7.9$ Hz) and 4.88 ppm ($^4J(PH) = 7.6$ Hz).



The phosphine ligands **3**–**5** show reactions typical for amino acids and tervalent phosphorus compounds.

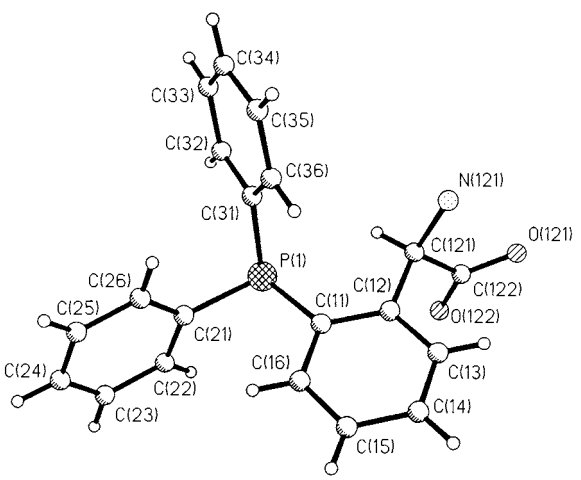


Fig. 1. Molecular structure of **3**·2H_2O. Selected bond lengths (Å) and angles (°): P(1)–C(11) 1.849(4), P(1)–C(21) 1.839(4), P(1)–C(31) 1.848(4), C(122)–O(121) 1.249(4), C(122)–O(122) 1.247(4), C(122)–C(121) 1.545(5), C(121)–N(121) 1.504(4); C(21)–P(1)–C(31) 100.6(2), C(21)–P(1)–C(11) 101.6(2), C(11)–P(1)–C(31) 104.4(2), O(121)–C(122)–O(122) 127.7(5), N(121)–C(121)–C(122) 108.8(3), O(122)–C(122)–C(121) 115.1(4), O(121)–C(122)–C(121) 117.2(4).

Thus on oxidation of **3** with H_2O_2 the phosphine oxide **3c** is formed (Eq. (8)). *N*-acetylation of **3** was achieved by reaction with acetic acid anhydride in the presence of a catalytic amount of CF_3COOH (Eq. (7a)). Esterification of **3** (Eq. (7b)) with orthoformate in methanol and equimolar amounts of trifluoro acetic acid gave the methyl ester **3d** as its trifluoro acetate salt. It shows a singlet in the ^{19}F-NMR spectrum at -73.1 ppm. The quartet at $\delta C = 118.1$ ppm ($^1J(CF) = 292.6$ Hz) in the $^{13}C\{^1H\}$-NMR spectrum may be assigned to the CF_3 group of the trifluoro acetate anion. For the two CO groups of **3b** separate resonances ($\delta C = 175.0$, 176.7 ppm) are observed in the $^{13}C\{^1H\}$-NMR spectrum in a δC range typical for carboxylic acids

3. X-ray structure of 3·2H_2O

In order to get detailed information about the influence of the amino acid moiety on the geometrical parameters of the triphenylphosphine skeleton of **3**, a crystal structure investigation was performed. The structure determination described in this paper is the first reported for a phosphino substituted amino acid.

Crystals of composition **3**·2H_2O suitable for X-ray structural analysis were obtained by recrystallization of **3** from water–methanol. The isolated molecule with the labeling scheme together with selected bond distances and bond angles is shown in Fig. 1. Crystallographic data are collected in Table 1.

The unit cell contains the *R*- and the *S*-enantiomer of **3** (space group *Pbca*). The amino acid substituent has a betaine type structure, the C–O distances within the CO_2 group being almost identical (O(121)–C(122) 1.249(4), O(122)–C(122) 1.247(4) Å) with a O(121)–C(122)–O(122) bond angle of 117.2(4)°. The C–N bond distance C(121)–N(121) (1.504(4) Å) is in a range typical for amino acids in their betaine form [16]. The molecules in **3**·2H_2O are held together by a hydrogen bonding network involving the NH_3^+, carboxylate groups and the water molecules. A detailed analysis of hydrogen bridging in the solid state of amino acids has been performed by Jönsson and Kvick [17] using neutron diffraction.

As a result of the steric interaction between the amino acid unit and the phenyl ring [C(3*n*)] ($n = 1$–6) the P–C distances P(1)–C(11) (1.849(4) Å) and P(1)–C(31) (1.848(4) Å) and the C(11)–P(1)–C(31) bond angle (104.4(2)°) are widened up. They are somewhat larger than the corresponding average values in Ph_3P (1.831 Å or 102.8°, respectively) [18]. The repulsion between Ph ring [C(3*n*)] ($n = 1$–6) and the amino acid moiety in **3** is also reflected by the extension of the bond length C(11)–C(12) (1.400(5) Å) and by the values obtained for the bond angles C(32)–C(31)–P(1) (114.6(4)°) or C(36)–C(31)–P(1) (125.1(4)°), respec-

Table 1
Crystal data

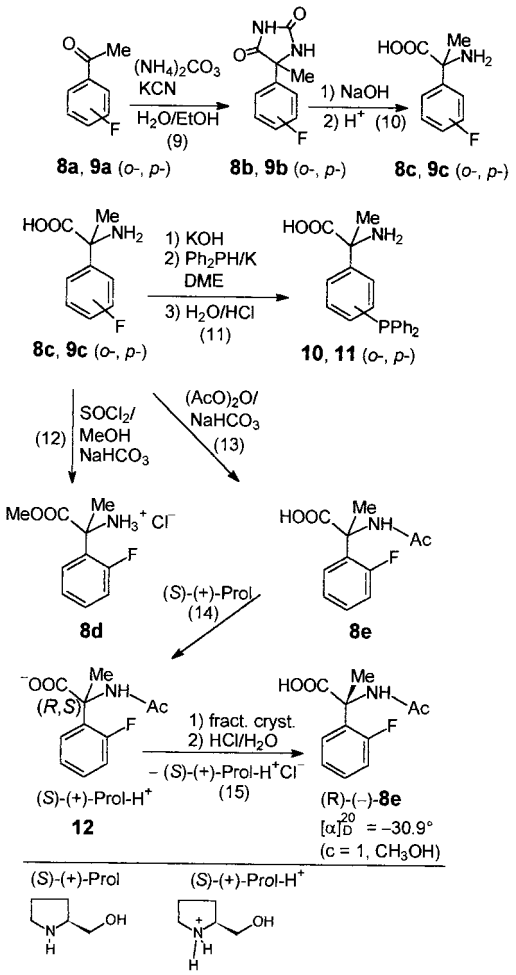
Compound	**3**·2H_2O	**8c**·H_2O	**12**·H_2O
Empirical formula	$C_{20}H_{22}NO_4P$	$C_9H_{12}FNO_3$	$C_{16}H_{25}FN_2O_5$
Formula weight	371.37	201.20	344.38
Crystal system	Orthorhombic	Triclinic	Orthorhombic
Space group	*Pbca*	$P\bar{1}$	$P2_12_12_1$
a (Å)	9.687(2)	6.0819(12)	6.8070(10)
b (Å)	10.629(3)	6.815(2)	10.647(2)
c (Å)	37.856(7)	11.645(3)	24.297(4)
α (°)	90	79.82(2)	90
β (°)	90	77.90(2)	90
γ (°)	90	86.50(2)	90
V (Å^3)	3898(2)	464.4(2)	1760.8(5)
Z	4	2	4
D_{calc} (g cm^{-3})	1.266	1.439	1.299
Radiation	Mo–K_α	Mo–K_α	Mo–K_α
Wavelength (Å)	0.71073	0.71073	0.71073
Temperature (K)	293(2)	293(2)	295(2)
Diffractometer	Siemens P4	Siemens P3	Siemens P3
Crystal size (mm)	$0.26\times0.40\times0.72$	$0.40\times0.40\times0.34$	$0.44\times0.40\times0.24$
μ (mm^{-1})	0.165	0.120	0.103
Transmission	–	0.9650–0.9547	0.9771–0.9605
θ Range (°)	$4\leq20\leq50$	2–30.06	2–27.50
Limiting indices	$0\leq h\leq11,\ 0\leq k\leq12,\ 0\leq l\leq45$	$0\leq h\leq8,\ -9\leq k\leq9,\ -16\leq l\leq16$	$-8\leq h\leq8,\ -13\leq k\leq13,\ -31\leq l\leq31$
Reflections	3463	4785	9350
Unique	3463	2736	4049
R_{int}	0.0	0.0164	0.0216
Observed ($I>2\sigma I$)	897	2182	3389
R_1 (obs)	0.045	0.048	0.034
wR_2 (all data)	0.126	0.1310	0.0896
Goodness-of-fit	0.803	0.961	1.001
Parameters	236	177	263
ΔF (e Å^{-3})	0.223 to −0.212	0.518 to −0.484	0.218 to −0.161
Flack parameter	None	None	−0.4(7)

tively. The triarylphosphine fragment has a propeller conformation with the three aromatic ring systems being rotated in the same sense.

4. Synthesis of α-methyl derivatives of phosphinophenylglycine

Amino acids are prone to racemization at the α-carbon atoms in acid and especially in basic media. The implication of this process for the syntheses of enantiopure phosphine ligands containing amino acid moieties according to Eqs. (2–5) has been shown above for **4**. In order to use this synthetic strategy for enantioselective syntheses of these ligands, the hydrogen at the C(α) carbon atom of the starting materials **3a**, **4a** had to be replaced by alkyl groups. The racemization process would also limit the application of optically pure ligands of type **3** or **4** as cocatalysts in enantioselective catalysis.

The starting materials **8c**, **9c** for the preparation of α-methyl derivatives of the *ortho*- and *para*-phosphinophenylglycines (**10**, **11**) have not yet been reported in the literature so far. They were obtained by hydrolysis of the hydantoines **8b**, **9b** obtained by the reaction of *ortho*- or *para*-fluoroacetophenone (**8a**, **9a**) with ammonium carbonate and potassium cyanide (Bucherer reaction [19,20]) (Eqs. (9 and 10)). For the hydantoines **8b**, **9b** and the α-methylfluorophenylglycines **8c**, **9c** singlets are observed in the $^{19}F\{^1H\}$-NMR spectrum in a range typical for δF (−110 to −115 ppm) of fluorophenyl compounds [21,22]. Two resonances at 156.5 and 177.3 or 156.8 and 177.4 ppm, respectively, are obtained in the $^{13}C\{^1H\}$-NMR spectrum for the carbonyl groups of the hydantoine system in **8b** or **9b**.



The methyl ester hydrochloride **8d** and the *N*-acetyl derivative **8e** have been obtained by reaction of **8c** with $SOCl_2$–MeOH or acetic acid anhydride in the presence of $NaHCO_3$, respectively, according to Eqs. (12 and 13) [20]. Both derivatives have been employed for the resolution of the racemate of **8c** by enzymatic methods or fractional crystallization of diastereoisomers formed with enantiopure organic bases (see below).

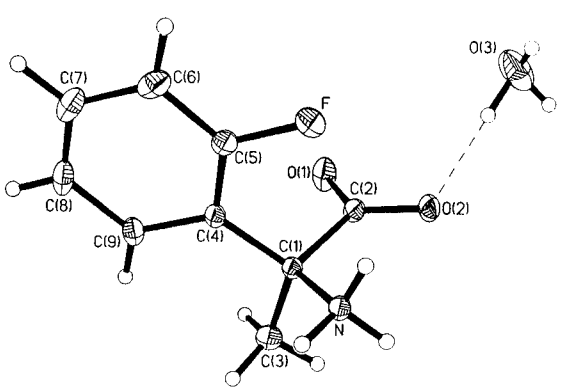


Fig. 2. Molecular structure of **8c**·H_2O. Selected bond lengths (Å) and angles (°): C(1)–C(2) 1.563(2), C(1)–C(3) 1.521(2), C(1)–C(4) 1.522(2), C(1)–N 1.502(2), C(2)–O(1) 1.235(2), C(2)–O(2) 1.249(2); N–C(1)–C(2) 108.1(1), N–C(1)–C(3) 107.1(1), N–C(1)–C(4) 109.0(1), C(2)–C(1)–C(3) 108.4(1), C(2)–C(1)–C(4) 109.9(1), C(3)–C(1)–C(4) 114.1(1).

Nucleophilic phosphination of the potassium salts of the α-methylfluorophenyl glycines with Ph_2PK in DME yields the phosphino derivatives **10** and **11** in satisfying yields (Eq. (11)). In the $^{31}P\{^1H\}$-NMR spectrum **10** and **11** show signals in the typical δP range found for tertiary aromatic phosphines [11] with a high field shift of δP for the *ortho* isomer (**10**: $\delta P = -13.7$; **11**: $\delta P = -1.7$ ppm). As in the case of **1** and **3** the Ph groups of the Ph_2P moieties are inequivalent, two sets of signals being observed in the $^{13}C\{^1H\}$-NMR spectrum for the *ipso* and *ortho* carbon atoms.

5. X-ray structure of 8c·H_2O

In order to evaluate the structural effect of a methyl group introduced in the α-position of *ortho*-fluorophenylglycine, an X-ray structural analysis of **8c** was performed. Suitable crystals of composition **8c**·H_2O were obtained by recrystallization of **8c** from water–methanol mixtures. The results of the X-ray structural analysis are shown in Fig. 2, crystallographic data are collected in Table 1, selected bond lengths and angles are given in the caption to Fig. 2. The unit cell contains the *R*- and *S*-enantiomer of **8c** with a betaine type structure.

The plane of the fluorophenyl group is oriented roughly orthogonal to that of the C(1), C(2), O(1), O(2) fragment, the dihedral angle being 86.65(6)°. A similar orientation is found in *ortho*-fluorophenylglycine (**3a**), for which a dihedral angle of 105.5° was reported [23]. In **8c**, the methyl substituent (C(3)) lies in the plane of the fluorophenyl group, and this fact accounts for the relatively large C(3)–C(1)–C(4) angle (114.1(1)°). As shown by the C(5)–C(4)–C(1)–C(3) torsion angle of 179.0(1)°, the rotamer found in the crystal is that which avoids a short F···C(3) contact. Interestingly, a 28° value can be calculated for the corresponding torsion angle in **3a**, and this conformational difference between **8c** and **3a** is the most conspicuous effect attributable to quaternization of the α carbon of **3a**. The only other statistically significant substitution effects on the structure of **8c** are the elongation of the C(1)–C(2) bond length by 0.043(6) Å and the compression of the N–C(1)–C(2) and N–C(1)–C(4) bond angles on the average by 2.5°.

The conformation assumed by the fluorophenyl group in **8c** leads to a F···H(NC) contact of 2.17 Å[1], which

[1] In order to correct the hydrogen coordinates for the systematic shortening of X–H bonds as determined by X-ray diffraction, the hydrogen atoms were pushed along their X–H bond vector to a distance of 0.967 Å for X = O and 1.033 Å for X = N, which are typical values for such bonds as determined by neutron diffraction [24].

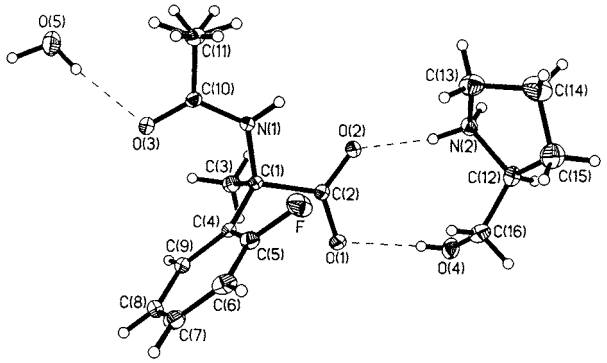


Fig. 3. Molecular structure of **12**·H_2O. Selected bond lengths (Å) and angles (°): C(1)–C(2) 1.555(2), C(1)–C(3) 1.535(2), C(1)–C(4) 1.524(2), C(1)–N(1) 1.471(2), C(2)–O(1) 1.255(2), C(2)–O(2) 1.236(2); N(1)–C(1)–C(2) 107.0(1), N(1)–C(1)–C(3) 110.3(1), N(1)–C(1)–C(4) 109.8(1), C(2)–C(1)–C(3) 106.0(1), C(2)–C(1)–C(4) 110.2(1), C(3)–C(1)–C(4) 113.3(1).

might be a weak, bent (F···H(NC)–N, 120°) intramolecular hydrogen bond [25]. Intermolecular hydrogen bonding is more important in **8c**. First, dimers with centrosymmetric ten-membered rings are formed, the H(NB)···O(2) $(-x, 1-y, 2-z)$ separation calculating to 1.79 Å. Second, a H(NA)···O(1) $(1+x, y, z)$ contact of 1.78 Å links the dimers to chains (Fig. 2). Third, the water oxygen atom O(3) donates its proton H(O3C) to the O(2) atom, and also acts as a weak acceptor [O(3)···H(NC) $(x-1, y, z)$, 2.27 Å], but these contacts are apparently not sufficient to prevent the disorder of the solvent.

6. Resolution of racemic derivatives of 8c

In contrast to the glycine derivative **3a** its α-methylated analog **8c** must be stable towards the racemization process [13] induced by strong bases like the nucleophilic phophido anions employed for the syntheses of the respective phosphino derivatives according to Eqs. (3–5 and 11). For the synthesis of optically active phosphine ligands with amino acid moieties enantiopure **8c** or its derivatives, e.g. **8d** or **8e**, were necessary.

Attempts to achieve the resolution of the ester hydrochloride **8d** by enzymatic ester hydrolysis [26,27] using lipases from different sources in two phase systems have been unsuccessful so far [28]. This may be due to the shielding of the COOMe group by the α-methyl group and the bulky *ortho*-fluorophenyl substituent.

Resolution of the *N*-acetylated derivative **8e** by salt formation and selective crystallization of the diastereomeric salts formed with cinchonin and cinchonidine in different solvents were not successful. Resolution of *racem*-**8e** could finally be achieved, however, using (*S*)-(+)-2-hydroxymethyl pyrrolidine as the chiral auxilliary base (Eq. (14)). Selective crystallization of diastereoisomeric salt **12** from acetone yielded one isomer $[\alpha]_D^{20} = +2.3°$ ($c = 1$, acetone), the absolute configuration (*S*,*R*) of which was determined by an X-ray structural analysis (see below). The chiral amine was cleaved from (*S*,*R*)-**12** with hydrochloric acid, optically active (*R*)-**8e** $[\alpha]_D^{20} = -30.9°$ ($c = 1$, CH_3OH) being obtained by extraction with ethylacetate (Eq. (15)).

The enantiomeric purity of (*R*)-**8e** was determined by derivatization with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetyl chloride ((*S*)-(+)-MTPACl) [29]. ^{19}F-NMR was employed for the detection of the diastereomeric derivatives. The amino acid derivative (*R*)-(−)-**8e** showed a negative Cotton effect at 260 and 215 nm [30]. The enantiomeric purity of the free acid **8c** was determined by liquid chromatography after derivatization with 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl isothiocyanate (BGIT) [31] to be better than 98%.

The (*S*)-(+)-2-hydroxymethyl pyrrolidine hydrochloride obtained on cleavage of diastereomeric **12** according to Eq. (15) was collected. On deprotonation with NaOH in the two-phase system water–CH_2Cl_2 the free base could be recovered in about 90% yield and reintroduced into the resolution process.

Parallel syntheses [9] of different enantiopure phosphine ligands of type **10** with amino acid moieties using (*R*)-(−)-**8e** as starting material are presently studied.

7. X-ray structure of 12·H_2O

The results of the X-ray determination are shown in Fig. 3. Since the structural solution was chosen to be consistent with the known *S*-conformation of the pyrrolidinium cation, the absolute configuration of the anion of **8e** in the crystal is found to be *R*. As in **8c**, the fluorophenyl group in **12** is oriented roughly perpendicular to the C(1), C(2), O(1), O(2) fragment, dihedral angle 80.02(6)°, and nearly parallel to the C(1)–C(3) bond with the fluorophenyl group again oriented so as to avoid a short C(3)···F contact, the C(5)–C(4)–C(1)–C(3) torsion angle being 175.4(1)°. While this rotamer might have been stabilized in **8c** by the F···H(NC) contact, we note that no F···H(N1) hydrogen bond is present in **12** as this separation is 3.00 Å.

The C(5)–F bond length of **12**·H_2O, 1.362(2) Å, compares well with that of **8c**, 1.364(2) Å, and neither differs significantly from that of the corresponding bond in **3a**, 1.354(6) Å. The endocyclic bond angles of the fluorophenyl groups in these three compounds exhibit deviations from the ideal 120° value which are typical for fluorine substitution [32–34]; thus the average C–C–C angle at the fluorinated carbon is spread to 124.3(2)° while the average endocyclic angles at the C(4) and C(6) atoms, which are in β position to the fluorine substituent, are compressed to 116.3(5) and

118.1(4)°, respectively. Another effect which might possibly be attributed to fluorine substitution is the asymmetry of the exocyclic bond angles of the C(4) atom. In **8c**, **12** and **3a**, the angle involving the fluorinated carbon atom (i.e. C(1)–C(4)–C(5)) is on the average 2.8(1)° smaller than the other angle.

With C(10)–N(1) and C(10)–O(3) bond lengths of 1.345(2) and 1.230(2) Å, respectively, the geometry of the amino acid group in **12** is unexceptional, and the 0.031(3) Å shortening of the C(1)–N(1) distance compared to that of the corresponding bond in **8c** is probably due to differences in the hybridization of the nitrogen atoms in these two compounds.

Fig. 3 shows how hydrogen bonding between anion and cation in the asymmetric unit of **12**·H_2O leads to formation of a nine-membered ring. The cation is also linked to a screw related anion by an H(N2B)···O(1) contact $(1-x, y-0.5, 1.5-z)$. The water oxygen atom O(5) donates not only a proton to the O(3) atom of the anion but also a proton to the O(4) atom of a screw-related cation. Since the O(1) atom participates in more hydrogen bonds than does the O(2) atom, it is not surprising that the C(2)–O(1) is somewhat longer (0.019(3) Å) than the C(2)–O(2) valency.

8. Experimental

For experimental details see Part XII of this series [1]. Phenylphosphine, diphenylphosphine [35a,b], phenylmethylphosphine [35c], 2- and 4-fluorophenylalanine as well as 2- and 4-fluorophenylglycine were purchased from Aldrich GmbH or synthesized by known methods [2a,27]. The sodium or potassium salts of the fluorophenyl amino acids have been prepared by addition of equivalent amounts of NaOH, KOH or KO^{t}Bu to the aqueous or methanol solutions, evaporating the solvent and drying the salts obtained in vacuo (20–60°C, 0.01 mbar). Starting materials were characterized by ^{1}H-, ^{13}C{^{1}H}- and ^{31}P{^{1}H}-NMR spectroscopy and mass spectrometry. ^{1}H-, ^{19}F-, ^{13}C{^{1}H}- and ^{31}P{^{1}H}-NMR spectra were recorded on a Bruker AC 400 or AM 250 and a Jeol FX90 Q Fourier transform spectrometer. Mass spectra were obtained on a Varian MAT 311A.

*8.1. Synthesis of the phosphino derivatives **1**, **2** of phenylalanine*

Solutions of Ph_2PK in DME were prepared by reaction of 1.13 g (29.0 mmol) or 0.59 g (15.0 mmol) of potassium with 5.40 g (29.0 mmol) or 2.79 g (15.0 mmol) of Ph_2PH dissolved in 60 or 100 ml of DME. To these solutions 6.00 g (27.1 mmol) of the potassium salt or 3.00 g (14.6 mmol) of the sodium salt of *ortho*- or *para*-fluorophenylalanine were added and the reaction mixtures were heated at reflux temperature for 18–24 h. Thereafter, the solvent was removed in vacuo (20°C, 0.01 mbar). The residue obtained was dissolved in water (50 or 20 ml) and conc. HCl was added until the solutions showed a pH value of 5. **1** was precipitated as a colorless solid, which was filtered off and washed with a 1:3 methanol–water mixture. For further purification it was recrystallized from 2:1 methanol–water mixture. On acidification, **2** was obtained as a viscous material, which after addition of 5 ml of methanol and heating to 60°C for 5 min gave a white solid, which was further purified by recrystallization from a 2:1 methanol–water mixture. Yields: 7.6 g (70%) **1**, 3.16 g (56%) **2**.

1. Anal. Calc. for $C_{21}H_{20}NO_2P{\cdot}CH_3OH{\cdot}H_2O$ (399.4): C, 66.15; H, 6.56; N, 3.51. Found: C, 66.05; H, 6.46; N, 3.67%. ^{1}H-NMR (CD_3OD, δ, ppm): 3.59, 3.18, 4.02, 6.8–7.5 (arom. H); ^{13}C{^{1}H}-NMR (CD_3OD, δ, ppm): 173.7, 141.9 ($J=25.5$), 137.9 ($J=13.6$), 137.4 ($J=9.5$), 137.3 ($J=9.4$), 135.1, 135.0 ($J=19.4$), 131.5 ($J=5.1$), 130.7, 130.1, 130.0, 129.8 ($J=7.0$), 129.7 ($J=6.9$), 128.7, 57.0 ($J=4.1$), 36.9 ($J=19.3$ Hz); ^{31}P{^{1}H}-NMR (CD_3OD, δ, ppm): −13.0.

2. Anal. Calc. for $C_{21}H_{20}NO_2P{\cdot}2H_2O$ (385.4): C, 65.45; H, 6.27; N, 3.63. Found: C, 64.80; H, 6.72; N, 3.37%. ^{1}H-NMR (CD_3OD, NH_3, δ, ppm): 3.31, 3.41 (CH_2), 3.86 (CH), 7.2–7.8 (arom. H); ^{13}C{^{1}H}-NMR (CD_3OD, NH_3, δ, ppm): 181.4, 141.1, 138.2 ($J=9.1$), 135.5 ($J=8.4$), 134.8 ($J=19.3$), 134.5 ($J=19.3$), 130.9 ($J=7.3$), 130.1, 129.7 ($J=7.1$ Hz), 58.7, 42.1; ^{31}P{^{1}H}-NMR (CD_3OD, NH_3, δ, ppm): −5.4.

*8.2. Synthesis of the phosphino derivatives **3**–**5** of phenylglycine*

To the solution of 3.07 g (16.5 mmol) or 4.90 g (26.3 mmol) Ph_2PH or 2.11 g (17.0 mmol) Ph(Me)PH, respectively, in 50 ml of DME, 0.64 g (16.5 mmol) or 1.02 g (26.2 mmol) or 0.66 g (17.0 mmol) of potassium metal was added. After completion of the metalation reactions the sodium salts of 3.0 g (17.7 mmol) 2-fluorophenylglycine or 4.67 g (27.6 mmol) 4-fluorophenylglycine were added. The reaction mixtures were heated at reflux for 3 h (**3**), 72 h (**4**) or 15 min (**5**), respectively. The residues obtained after removal of the solvent in vacuo (20–80°C, 0.02 mbar) were dissolved in 50 or 100 or 30 ml of water. To these solutions 10% HCl was added until a pH value in the range 4–5 was reached. The precipitates formed were filtered off and washed with three aliquots of a 1:3 methanol–water mixture. Further purification was achieved by recrystallization from water–methanol. Yields: 3.61 g (60%) **3**, 6.80 g (68%) **4**, 3.82 g (77%) **5**.

3. Anal. Calc. for $C_{20}H_{18}NO_2P{\cdot}2H_2O$ (371.4): C, 64.68; H, 5.97; N, 3.77. Found: C, 64.74; H, 5.95; N, 3.84%. ^{1}H-NMR (CD_3OD, δ, ppm): 5.72, 7.0–7.7

(arom. H); $^{13}C\{^1H\}$-NMR (CD_3OD, δ, ppm): 179.8, 142.4 ($J = 27.2$), 138.4 ($J = 13.7$), 137.8 ($J = 9.7$), 137.4 ($J = 8.9$), 136.1 ($J = 1.3$), 134.9 ($J = 19.2$), 134.6 ($J = 18.8$), 131.2, 130.1, 130.0, 129.8, 129.7 ($J = 6.8$), 129.6 ($J = 6.7$), 128.6 ($J = 4.7$), 57.6 ($J = 27.7$ Hz); $^{31}P\{^1H\}$-NMR (CD_3OD, δ, ppm): -9.6.

4. Anal. Calc. for $C_{20}H_{18}NO_2P \cdot C_2H_5OH$ (381.4): C, 69.28; H, 6.34; N, 3.67. Found: C, 69.58; H, 6.02; N, 3.99%. ^{1}H-NMR (CD_3OD, δ, ppm): 4.36, 7.1–7.6 (arom. H); $^{13}C\{^1H\}$-NMR (CD_3OD, δ, ppm): 179.6, 145.8, 138.8 ($J = 10.9$), 137.1 ($J = 10.5$), 135.0 ($J = 20.0$), 134.8 ($J = 19.6$), 130.1, 129.8 ($J = 6.9$), 128.6 ($J = 7.2$ Hz), 62.1; $^{31}P\{^1H\}$-NMR (CD_3OD, δ, ppm): -1.3.

5. Anal. Calc. for $C_{15}H_{16}NO_2P \cdot H_2O$ (291.3): C, 61.85; H, 6.23; N, 4.81. Found: C, 62.43; H, 6.55; N, 4.75%. ^{1}H-NMR (CD_3OD, δ, ppm): 1.64, 1.68, 5.37, 5.42; $^{13}C\{^1H\}$-NMR (CD_3OD, δ, ppm): 180.2, 179.9, 150.8 ($J = 26.4$), 150.6 ($J = 26.4$), 143.3 ($J = 11.2$), 142.9 ($J = 11.2$), 140.7 ($J = 13.2$), 140.6 ($J = 13.2$), 133.9 ($J = 2.1$), 133.2 ($J = 18.3$), 133.2 ($J = 2.0$), 132.8 ($J = 17.3$), 130.7, 130.5, 129.7 ($J = 5.1$), 129.5 ($J = 6.1$), 129.3, 128.8, 128.6, 128.5, 128.3 ($J = 6.1$), 127.8 ($J = 5.1$), 59.8 ($J = 22.4$), 59.2 ($J = 25.4$), 13.2 ($J = 14.2$), 13.1 ($J = 13.2$ Hz); $^{31}P\{^1H\}$-NMR (CD_3OD, δ, ppm): -38.6, -39.5.

8.3. Synthesis of the phosphine **7** with two amino acid moieties

A 9.86 g (58.3 mmol) sample of 2-fluorophenylglycine was dissolved in 50 ml of MeOH and 6.55 g (58.4 mmol) of KO^{t}Bu was added. After stirring for 2 h the solvent was removed in vacuo (20°C, 0.1 mbar). The residue obtained was suspended in 90 ml of DME. 6.87 g (61.2 mmol) of KO^{t}Bu and 3.3 g (30.6 mmol) of $PhPH_2$ was added to this suspension. The reaction mixture was stirred at 80°C for 7 days. After addition of 20 ml of water, all volatiles were removed in vacuo. The residue obtained was dissolved in 80 ml of water. Thereafter, conc. HCl was added to this solution until a pH value of 0 was reached. On addition of NaOH a precipitate was formed at pH 4.0 (4.95 g, racemate). It was filtered off and dried in vacuo. On addition of NaOH to the filtrate, until a pH value of 7 was reached, a further amount of **7** (3.84 g, *meso* forms) was obtained. Yield: 8.8 g (74%).

7. Anal. Calc. for $C_{22}H_{21}N_2O_4P \cdot 4H_2O$ (408.4): C, 55.00; H, 6.08; N, 5.83. Found: C, 55.62; H, 5.64; N, 5.96%. ^{1}H-NMR (D_2O, KOH, δ, ppm): racemate: 4.98 ($J = 7.9$), 4.88 ($J = 7.6$), 6.6–7.4 (arom. H); *meso* forms: 4.92 ($J = 7.4$), 4.87 ($J = 7.2$ Hz), 6.6–7.4 (arom. H); $^{13}C\{^1H\}$-NMR (D_2O, KOH, δ, ppm): racemate: 181.6, 181.5, 150.2 ($J = 18.1$), 150.0 ($J = 17.0$), 138.0 ($J = 9.0$), 137.0 ($J = 10.7$), 136.8 ($J = 9.4$), 136.3 ($J = 20.1$), 135.8, 135.5, 132.7, 132.3, 131.4, 131.0 ($J = 7.0$), 129.7, 129.6, 129.4 ($J = 5.1$), 129.4 ($J = 4.8$), 60.1 ($J = 23.7$), 59.9 ($J = 22.0$ Hz); $^{31}P\{^1H\}$-NMR (D_2O, KOH, δ, ppm): racemate: -24.9; *meso* forms: -24.7, -25.9.

8.4. Synthesis of derivatives of **3**

8.4.1. Synthesis of the N-acetyl derivative **3b**

A 1.00 g (2.86 mmol) sample of **3** was suspended in excess acetic acid anydride. After addition of a small quantity (ca. 0.01 g) of trifluoroacetic acid the reaction mixture was heated to 40°C for 30 min. The precipitate formed, on cooling the reaction mixture to 0°C, was collected on a suction funnel and washed with diethyl ether. After drying in vacuo (20°C, 0.01 mbar) **3b** was obtained as a colorless solid. Yield: 0.85 g (75%).

3b. Anal. Calc. for $C_{22}H_{20}NO_3P \cdot 0.5H_2O$ (386.4): C, 68.38; H, 5.48; N, 3.62. Found: C, 68.89; H, 5.60; N, 3.22%. ^{1}H-NMR (CD_3OD, δ, ppm): 1.58, 6.39; $^{13}C\{^1H\}$-NMR (CD_3OD, δ, ppm): 176.7 ($J = 1.7$), 175.0, 145.1 ($J = 27.4$), 141.2 ($J = 14.4$), 140.3 ($J = 10.0$), 140.1 ($J = 9.6$), 138.2, 137.7 ($J = 20.4$), 137.3 ($J = 19.5$), 133.2, 132.5, 132.3, 132.1 ($J = 7.3$), 132.1 ($J = 6.7$), 131.5 ($J = 4.6$), 58.6 ($J = 26.5$ Hz), 24.3; $^{31}P\{^1H\}$-NMR (CD_3OD, δ, ppm): -11.8.

8.4.2. Synthesis of the ester **3d**

To the solution of 0.86 g (2.6 mmol) of **3** and 0.53 g (5.0 mmol) of trimethylorthoformate in 5.0 ml of methanol, 0.30 g (2.6 mmol) of trifluoroacetic acid was added at 0°C. The reaction mixture was stirred at ambient temperature for 12 h. After removal of all volatiles in vacuo (20°C, 0.001 mbar) **3d** was obtained as a colorless solid. Yield: 1.10 g (93%).

3d. Anal. Calc. for $C_{23}H_{21}F_3NO_4P$ (463.4): C, 59.62; H, 4.57; N, 3.02. Found: C, 58.92; H, 4.65; N, 2.91%. ^{1}H-NMR (CD_3OD, δ, ppm): 3.34, 6.10; $^{13}C\{^1H\}$-NMR (CD_3OD, δ, ppm): 170.9, 163, 139.4 ($J = 27.6$), 137.7 ($J = 19.5$), 138.9 ($J = 14.8$), 137.3 ($J = 8.7$), 136.6 ($J = 1.2$), 136.5 ($J = 8.9$), 134.8 ($J = 19.6$), 131.5, 131.0, 130.2, 130.1, 129.8 ($J = 6.9$), 129.6 ($J = 7.1$), 128.1, 118.1 ($^1J(CF) = 292.6$), 54.6 ($J = 32.0$ Hz), 49.8; $^{31}P\{^1H\}$-NMR (CD_3OD, δ, ppm): -13.3; ^{19}F-NMR (CD_3OD, δ, ppm): -73.1.

8.4.3. Synthesis of the oxide **3c**

To a suspension of 0.50 g (1.43 mmol) of **3** in 1 ml of water, 0.16 ml 30% H_2O_2 (1.5 mmol) was added with cooling in an ice bath. For the isolation of the oxide all volatiles were evaporated from the clear solution leaving **3c** as a colorless solid. Yield: quantitative.

3c. Anal. Calc. for $C_{20}H_{18}NO_3P \cdot H_2O$ (369.4): C, 65.03; H, 5.46; N, 3.79. Found: C, 64.63; H, 5.34; N, 3.59%. ^{1}H-NMR (CD_3OD, δ, ppm): 5.12, 7.0–7.8 (arom. H); $^{13}C\{^1H\}$-NMR (CD_3OD, δ, ppm): 174.3 ($J = 0.9$), 141.4 ($J = 6.9$), 135.3 ($J = 12.8$), 134.6 ($J = 2.5$), 134.2 ($J = 3.2$), 133.5 ($J = 10.1$), 133.1 ($J = 10.5$), 132.8 ($J = 108.1$), 132.7 ($J = 100.7$), 132.6 ($J = 9.1$),

131.8 ($J = 104.5$), 130.3 ($J = 12.6$), 130.1 ($J = 12.7$), 130.1 ($J = 12.6$), 57.8 ($J = 4.9$ Hz); $^{31}P\{^1H\}$-NMR (CD_3OD, δ, ppm): 42.7.

8.5. Synthesis of 2- and 4-fluoro-α-methylphenylglycine (**8c**, **9c**)

8.5.1. 5-(2-fluorophenyl)-5-methylhydantoine and 5-(4-fluorophenyl)-5-methylhydantoine (**8b**, **9b**)

An 80.1 g (1.23 mol) or a 13.0 g (0.20 mol) sample of potassium cyanide and 237.3 g (2.47 mol) or 38.4 g (0.40 mol) of $(NH_4)_2CO_3$ were dissolved in a 1.5 l or 0.4 l of a 1:1 mixture of water–ethanol. To this solution, 85.5 g (0.62 mol) or 13.8 g (0.1 mol) of 2- or 4-fluoroacetophenone, respectively, was added. After heating the reaction mixture to 40°C for 2 h its volume was reduced to about one-half by evaporation in vacuo (20°C, 0.1 mbar). The precipitate formed was filtered off and dried in vacuo. A further charge may be obtained on acidification of the filtrate with HCl until the solution shows a pH value of 5. Yields: 98.5 g (77%) **8b**, 14.2 g (68%) **9b**.

8b. Anal. Calc. for $C_{10}H_9FN_2O_2$ (208.2): C, 57.69; H, 4.36; N, 13.46. Found: C, 57.90; H, 4.48; N, 13.52%. ^1H-NMR (DMSO-d_6, δ, ppm): 1.74, 7.2–7.6 (arom. H), 8.32, 10.9; $^{13}C\{^1H\}$-NMR (DMSO-d_6, δ, ppm): 177.3, 160.6 ($J = 248.0$), 156.5, 130.8 ($J = 8.9$), 128.6 ($J = 3.3$), 126.5 ($J = 11.6$), 124.5 ($J = 3.3$ Hz), 116.2 ($J = 21.9$), 61.4, 23.2; ^{19}F-NMR (DMSO-d_6, δ, ppm): −113.1.

9b. ^1H-NMR (DMSO-d_6, δ, ppm): 1.74, 7.2–7.6 (arom. H), 8.7; $^{13}C\{^1H\}$-NMR (DMSO-d_6, δ, ppm): 177.4 ($J = 0.7$), 162.2 ($J = 244.7$), 156.8, 136.4 ($J = 3.1$), 127.9 ($J = 8.4$), 115.6 ($J = 21.5$ Hz), 64.1, 25.4; ^{19}F-NMR (DMSO-d_6, δ, ppm): −110.3.

8.5.2. Syntheses of **8c** and **9c**

A 95.8 g (0.46 mol) sample of **8b** or 14.2 g (0.068 mol) of **9b** was suspended in 250 or 150 ml of water. On addition of 76.8 g (1.165 mol) of KOH (85%) or 6.0 g (0.15 mol) of NaOH clear solutions were obtained which were heated for 2 days under reflux. For the isolation of the amino acids, conc. HCl was added until the solutions showed a pH of 5. After cooling of the reaction mixtures to 20°C the precipitate was filtered off using a Buchner funnel. The products thus obtained were recrystallized from water. Yields: 64.1 g (72%) **8c**, 8.9 g (71%) **9c**.

8c. Anal. Calc. for $C_9H_{10}FNO_2 \cdot 0.5H_2O$ (192.2): C, 56.24; H, 5.77; N, 7.29. Found: C, 56.68; H, 5.19; N, 8.14%. ^1H-NMR (CD_3OD–D_2O, δ, ppm): 1.71, 7.0–7.7 (arom. H); $^{13}C\{^1H\}$-NMR (CD_3OD–D_2O, δ, ppm): 185.2, 164.9 ($J = 244.5$), 138.9 ($J = 12.9$), 131.9 ($J = 8.8$), 131.0 ($J = 5.0$), 127.4 ($J = 3.2$), 118.9 ($J = 22.8$ Hz), 63.0, 28.9; ^{19}F-NMR (CD_3OD–D_2O, δ, ppm): −111.2.

9c. Anal. Calc. for $C_9H_{10}FNO_2$ (183.2): C, 59.01; H, 5.50; N, 7.64. Found: C, 59.25; H, 5.56; N, 7.72%. ^1H-NMR (D_2O, δ, ppm): 1.45, 6.7–7.4 (arom. H); $^{13}C\{^1H\}$-NMR (D_2O, δ, ppm): 169.1, 163.7 ($J = 242.0$), 144.3, 129.4 ($J = 8.2$), 117.3 ($J = 21.3$ Hz), 63 (br), 28.6; ^{19}F-NMR (D_2O, δ, ppm): −114.2.

8.6. Syntheses of α-(2-diphenylphosphinophenyl)-α-methylglycine (**10**) and α-(4-diphenylphosphinophenyl)-α-methylglycine (**11**)

To a solution of 23.0 mmol of Ph_2PK prepared by reaction of 4.28 g (23.0 mmol) of Ph_2PH with 0.90 g (23.0 mmol) of potassium in 40 ml of dimethoxyethane, 4.03 g (22.0 mmol) of **8c** or 4.14 g (22.6 mmol) of **9c**, respectively, were added and the reaction mixtures were heated for 24 or 48 h. The residue obtained after all volatiles had been removed in vacuo was dissolved in 40 ml of water, and conc. HCl was added until the pH of the solution reached a value of 4.5. The precipitate formed was filtered off, washed with three aliquots of water–methanol mixtures and was finally recrystallized from a 5:1 methanol–water mixture. Yields: 4.4 g (55%) **10**, 6.2 g (75%) **11**.

10. Anal. Calc for $C_{21}H_{20}NO_2P \cdot H_2O$ (367.4): C, 68.65; H, 6.04; N, 3.81. Found: C, 67.94; H, 5.99; N, 3.59%. ^1H-NMR (D_2O, δ, ppm): 6.3–7.4 (arom. H), 1.45 (CH_3); $^{13}C\{^1H\}$-NMR (D_2O, δ, ppm): 186.0 ($J = 1.4$), 154.2 ($J = 25.8$), 139.8 ($J = 10.6$), 139.8 ($J = 10.1$), 139.5, 136.5 ($J = 16.6$), 135.3 ($J = 18.8$), 135.3 ($J = 18.4$), 132.0, 130.7 ($J = 6.1$), 130.6, 129.2, 128.7 ($J = 7.2$), 65.3 ($J = 7.0$), 30.5 ($J = 4.4$ Hz); $^{31}P\{^1H\}$-NMR (D_2O, δ, ppm): −13.7.

11. Anal. Calc. for $C_{21}H_{20}NO_2P \cdot H_2O$ (367.4): C, 68.65; H, 6.04; N, 3.81. Found: C, 68.54; H, 6.09; N, 3.84%. ^1H-NMR (DMSO-d_6, δ, ppm): 7.1–7.6 (arom. H), 1.71 (CH_3); $^{13}C\{^1H\}$-NMR (DMSO-d_6, δ, ppm): 170.4, 142.3, 136.7 ($J = 11.4$), 136.7 ($J = 11.3$), 135.2 ($J = 11.1$), 133.2 ($J = 19.5$), 133.2 ($J = 19.4$), 132.9 ($J = 19.9$), 129.0, 128.8 ($J = 6.9$), 126.2 ($J = 7.1$ Hz), 61.9, 23.4; $^{31}P\{^1H\}$-NMR (DMSO-d_6, δ, ppm): −1.7.

8.7. Synthesis of N-acetyl-α-(2-fluorophenyl)-α-methylglycine (**8e**)

To a suspension of 9.17 g (109.2 mmol) of $NaHCO_3$ in 300 ml of a 1:1 water–dioxane mixture, 10.0 g (54.6 mmol) of **8c** and 1.3 equivalents of acetic anhydride were added. The reaction mixture was stirred at 50°C for 4 h. Thereafter, all volatile materials were removed in vacuo using a rotary evaporator. The residue obtained was dissolved in 200 ml of water. Half concentrated hydrochloric acid was added until a pH value of 1.5 was reached. The *N*-acetyl derivative **8e** precipitated was filtered off and recrystallized from ethanol. Yield: 10.8 g (88%).

8e. Anal. Calc. for $C_{11}H_{12}FNO_3$ (225.2): C, 58.66; H, 5.37; N, 6.22. Found: C, 58.49; H, 5.65; N, 6.11%. ^{1}H-NMR (DMSO-d_6, δ, ppm): 6.94–7.57 (arom. H), 1.94 (CH_3), 1.89 (CH_3); $^{13}C\{^1H\}$-NMR (DMSO-d_6, δ, ppm): 173.1, 168.9, 160.1 ($J = 247.2$), 129.4 ($J = 9.2$), 128.8 ($J = 4.1$), 128.6 ($J = 11.2$), 123.7 ($J = 3.1$), 115.8 ($J = 23.4$ Hz), 59.6, 23.2, 23.0; ^{19}F-NMR (DMSO-d_6, δ, ppm): -111.4.

8.8. Synthesis of α-(2-fluorophenyl)-α-methylglycine-methyl ester hydrochloride (8d)

A 30.2 g (0.254 mol) sample of thionylchloride was added to 100 ml of methanol at 0°C within a period of 30 min and the reaction mixture was stirred for another 30 min at this temperature. A 15.5 g (84.6 mmol) sample of the amino acid **8c** was dissolved in this solution and the reaction mixture was stirred for 4 days. After completion of the reaction (control by ^{19}F-NMR spectroscopy) all volatiles were removed in vacuo using a rotary evaporator (20°C, 20 mbar). The solid obtained was washed with 300 ml of ether and dried in vacuo. Yield: 19.4 g (95%).

8d. Anal. Calc. for $C_{10}H_{13}ClFNO_2 \cdot 0.5H_2O$ (242.7): C, 49.49; H, 5.81; N, 5.77. Found: C, 49.25; H, 5.42; N, 5.64%. ^{1}H-NMR (D_2O, δ, ppm): 7.2–7.65 (arom. H), 3.79 (CH_3), 2.02 (CH_3); $^{13}C\{^1H\}$-NMR (D_2O, δ, ppm): 174.2, 162.2 ($J = 246.2$), 135.2 ($J = 9.2$), 130.4 ($J = 2.0$), 127.7 ($J = 3.0$), 124.4 ($J = 12.2$), 118.6 ($J = 21.4$ Hz), 60.9, 56.7, 23.3; ^{19}F-NMR (D_2O, δ, ppm): -114.1.

8.9. Syntheses and resolution of diastereomeric 12, preparation of (R)-(−)-8e

To a suspension of 16.53 g (73.4 mmol) of racemic **8e** in 110 ml of acetone, 7.42 g (73.4 mmol) of (*S*)-(+)-2-hydroxymethylpyrrolidine was added. The reaction mixture was heated at reflux until all **8e** had been dissolved. On cooling the solution to ambient temperature, **12** was precipitated as colorless needles which were collected by filtration through a suction funnel. A further crop of **12** was obtained on concentration of the filtrate to 50 ml and cooling to −10°C. Yield: 8.41 g (35%).

12. Anal. Calc. for $C_{16}H_{23}FN_2O_4$ (326.4): C, 58.89; H, 7.10; N, 8.58. Found: C, 58.89; H, 7.06; N, 8.47%. ^{1}H-NMR (D_2O, δ, ppm): 6.94–7.58 (arom. H), 3.52–3.73, 3.11–3.16, 1.95, 1.89; $^{13}C\{^1H\}$-NMR (D_2O, δ, ppm): 178.9, 170.9, 162.0 ($J = 247.2$), 132.1 ($J = 11.2$), 130.7 ($J = 5.1$), 129.4 ($J = 9.2$), 124.3 ($J = 3.1$), 116.2 ($J = 22.4$ Hz), 62.6, 61.5, 46.3, 27.1, 24.8, 23.6, 22.7; ^{19}F-NMR (D_2O, δ, ppm): -114.7.

The crystals obtained above were suspended in 20 ml of water. Half concentrated hydrochloric acid was added until a pH value of 1.5 was reached. The reaction mixture was extracted with three aliquots of 30 ml of ethylacetate. The collected organic phases were dried over magnesium sulfate. After evaporation of the extracts in vacuo, **8e** was obtained as a colorless solid. Yield: 5.57 g (96%). $[\alpha]_D^{20} = -30.9°$ ($c = 1$, CH_3OH).

8.10. X-ray structure analyses of 3·2H2O, 8c·H2O and 12·H2O

8.10.1. X-ray structure of 3·2H2O

A crystal (0.26 × 0.40 × 0.72 mm) was sealed in a capillary. X-ray data were measured with a Siemens P4 diffractometer equipped with a graphite monochromator and employing Mo–K_α radiation. The structure was solved by direct methods using SHELXS-86 and refined against F^2 with SHELXL-93.

8.10.2. X-ray structure of 8c·H2O

A block-shaped crystal (0.34 × 0.40 × 0.40 mm) was glued to a glass fiber. X-ray data were measured with a Siemens P3 diffractometer equipped with a graphite monochromator and employing Mo–K_α radiation. A hemisphere of data ($4° \le 2\theta \le 60°$) was collected with the θ–2θ scan technique, reflections with 2θ below 50° being measured twice. Intensities were derived by profile analysis and were corrected for absorption and the drift of the three standards. The positions of the non-hydrogen atoms were located by direct methods. Subsequently the hydrogen atoms were revealed by a difference Fourier synthesis, which showed that the hydrogen atoms of the water molecule were disordered over three sites. The structure was refined with a SHELXTL program package (version 5.03) with non-hydrogen atoms anisotropic and hydrogen atoms isotropic, and crystal data are given in Table 1.

8.10.3. X-ray structure of 12·H2O

A crystal (0.24 × 0.40 × 0.44 mm) was glued to a glass fiber, and intensity data ($4° \le 2\theta \le 55°$) comprising two octants and their Friedel equivalents were measured with a Siemens P3 diffractometer using the ω-scan technique. Intensities were derived by profile fitting, and they were corrected for absorption and the fluctuations of the three standard reflections. The structure was solved by direct methods with the hydrogen atoms being located by a difference Fourier calculation. This showed that the methyl group of C(11) is disordered. While the hydrogen atoms which are bonded to the nitrogen and oxygen atoms were refined isotropically, those bonded to the carbon atoms were placed in idealized positions. The refinement converged, and crystal data are given in Table 1.

9. Supplementary material

Further details of the crystal structure investigation on **3** are available from the Fachinformationszentrum Karls-

ruhe, D-76344 Eggenstein-Leopoldshafen, Germany, on quoting the depository number CSD 405956. Details of the crystal structures of **8c**·H_2O and **12**·H_2O may be obtained from the Cambridge Crystallographic Data Centre, 12 Union Rd, Cambridge CB2 1EZ, UK, by quoting the respective depository numbers CCDC 134136 and 134137, the authors and the literature reference.

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