Asymmetric Synthesis of Phosphorus Analogues of Dicarboxylic α-Amino Acids

Vadim A. Soloshonok,[a,*] Yuri N. Belokon',[b,*] Nadezhda A. Kuzmina,[b] Victor I. Maleev,[b] Nataly Yu. Svistunova,[a] Vladimir A. Solodenko[a] and Valery P. Kukhar'[a]
[a] *Institute of Bioorganic Chemistry and Oil Chemistry, Ukrainian Academy of Sciences, Kiev, Ukraine*
[b] *Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow, Russia*

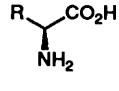
An efficient approach to the asymmetric synthesis of phosphorus analogues of dicarboxylic α-amino acids is described. The method of choice consists in the reaction of the nickel(II) complex (**4**) of the Schiff's base derived from (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone **3** and glycine with the appropriate alkyl halide, substituted with an alkylphosphonate group. The reactions were carried out in MeCN at 25 °C, with solid KOH as a catalyst. Michael-type base-catalysed addition of vinylphosphonate and vinylphosphinate to complex **4** in dimethylformamide (DMF) at 50–70 °C could also be employed. Significant diastereoselectivity (90% d.e.) was observed for the alkylation of complex **4**. Optically pure (*S*)-phosphinothricine, (*S*)-2-amino-3-phosphonopropanoic acid, (*S*)-2-amino-4-phosphonobutanoic acid and (*S*)-2-amino-5-phosphonopentanoic acid were obtained after the alkylated diastereoisomeric complexes had been separated on SiO_2 and hydrolysed with aq. HCl. The initial chiral reagent **3** was recovered (60–85%). Novel amino acids **9**, having free carboxy groups and esterified phosphonic and phosphinic groups, could also be obtained as intermediates due to the mild conditions of the decomposition of the alkylated diastereoisomeric complexes.

Phosphorus analogues of the α-amino acids are currently attracting considerable attention not only because they were the first compounds with a carbon-to-phosphorus bond to be isolated from living organisms,[1] but also because of their promising biological activities.[2] These compounds are able to act as false substrates and to interfere with biological mechanisms in a useful way. For example, the phosphonic analogue of glycine is a plant-growth regulator,[3] the phosphonic analogue of phenylalanine is a specific competitive inhibitor of phenylalanyl-5-RNA-synthetase,[4] and the phosphonodipeptide alafosfalin is a potent antimicrobial agent.[5]

Among the phosphorus analogues of dicarboxylic α-amino acids, phosphinothricin **1** and α-amino-ω-phosphonocarboxylic acids **2** seem to be the most interesting compounds from the biological point of view. (*S*)-Phosphinothricin **1** is a naturally occurring γ-phosphinic analogue of L-glutamic acid, isolated from cultures of *Streptomyces viridochromogenes*[1b] as the tripeptide phosphinothricyl-L-alanyl-L-alanine. Compound **1** exhibits strong herbicidal activity which is based on the inhibition of glutamine synthetase[1b,6] and is being developed as a contact herbicide for fruit and vine cultures.[7] The synthetic α-amino-ω-phosphonocarboxylic acids **2** are considered to be the most potent and selective antagonists known of certain excitatory amino acids, *e.g.* glutamate and *N*-methyl-D-aspartate (NMDA), and have found wide application in studies of the mechanisms of synaptic neurotransmission.[8]

The bioactivity of these compounds was shown to depend essentially on their stereochemical configuration. For example, the (*S*)-enantiomer of 2-amino-4-phosphonobutanoic acid **2a** is 20–40-times more active than the (*R*)-enantiomer in suppression of glutamate-mediated neurotransmission,[8h] and the activity of 2-amino-5-phosphonopentanoic acid **2b** as a NMDA antagonist has been attributed mainly to its (*R*)-enantiomer.[8d,8e] Similarly, the herbicidal activity of (*S*)-phosphinothricin **1** is twice as high as that of the racemic compound.[9]

In view of these findings, it became desirable to obtain the individual enantiomers of compounds **1** and **2** for biological evaluation. Although several methods for the synthesis of racemic phosphorus analogues of dicarboxylic amino acids have been reported,[10] only a few examples of a non-enzymatic



(*S*)-**1**, (*S*)-**2**

1; R = $CH_2CH_2P(Me)(O)OH$
2a; R = $CH_2CH_2P(O)(OH)_2$
2b; R = $CH_2CH_2CH_2P(O)(OH)_2$
2c; R = $CH_2P(O)(OH)_2$

asymmetric synthesis of compounds **1** and **2** have been described so far. (+)-2-Amino-3-phosphonopropanoic acid **2c** and (+)-2-amino-4-phosphonobutanoic acid **2a** were obtained from the optically active amino nitriles prepared by Strecker reaction of the corresponding ω-formylalkylphosphonates with hydrogen cyanide and (*S*)-(−)-α-methylbenzylamine. Acid hydrolysis, appropriate derivatization, enrichment of the diastereoisomers by fractional recrystallization, and deprotection led to the final compounds in 86–88% enantiomeric excess (e.e.).[11] An enantioselective synthesis of (*R*)-(−)- and (*S*)-(+)-2-amino-3-phosphonopropanoic acid **2c** with an optical purity of 97% was achieved by nucleophilic addition of trimethyl phosphite to (*R*)- and (*S*)-3-amino-*N*-(*tert*-butoxycarbonyl)-oxetan-2-one, respectively.[12] In a more general and practical approach a chiral glycine enolate equivalent has been employed for the synthesis either *via* alkylation with ω-halogenoalkylphosphonates (-phosphinates) or through the conjugate addition to vinyl-phosphonates (-phosphinates). Thus, both enantiomers of phosphinothricin **1** were prepared by employing Schollkopf's method[13] which entails alkylation of chiral bislactim ethers with isobutyl 2-chloroethyl(methyl)phosphinate (optical purity of the products was 93.5%).[14] An asymmetric synthesis of (*S*)-(+)-phosphinothricin [(*S*)-(+)-**1**] (optical purity 79%), (*S*)-(+)-2-amino-4-phosphonobutanoic acid [(*S*)-(+)-**2a**] (optical purity 50%) and their (*R*)-enantiomers (optical purity 73 and 45%, respectively) has been achieved by the Michael addition of vinylphosphorus compounds to chiral Schiff's bases obtained by the condensation of glycine ethyl ester and (1*S*,2*S*,5*S*)- or (1*R*,2*R*,5*R*)-2-hydroxypinan-3-ones.[15]

We report here a highly selective and experimentally simple procedure for the efficient asymmetric synthesis of homochiral phosphinothricin **1** and α-amino-ω-phosphonocarboxylic acids **2** by the alkylation of glycine in its chiral Schiff's base Ni^{II} complex with a chiral auxiliary, (*S*)-*o*-[(*N*-benzylprolyl)-

Table 1 Preparation of complexes **6a–d** and **7a–c** *via* alkylation of complex **4** and Michael addition esters of **9** and **10** to complex **4**

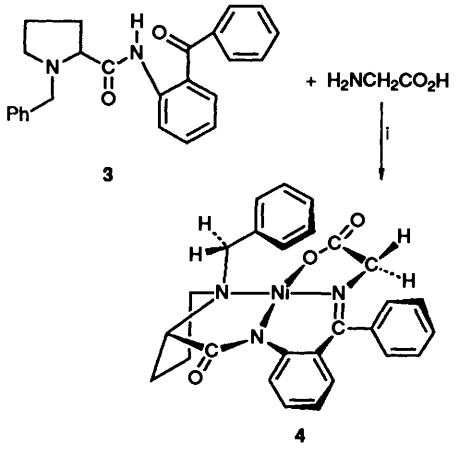
Reagent	Chemical yield (%)[a]	Relative proportions of isomers[b] **6a–d** (*S,S*)	**7a–c** (*S,R*)
$BrCH_2CH_2P(O)(Me)OEt$ **5a**	73.5	95	5
$BrCH_2CH_2P(O)(OEt)_2$ **5b**	69	93	7
$BrCH_2CH_2CH_2P(O)(OEt)_2$ **5c**	61	93.5	6.5
$ICH_2P(O)(OPr^i)_2$ **5d**	30	*c*	*c*
CH_2=CHP(O)(Me)OEt **9**	59	65; 94[d]	35; 6[d]
CH_2=CHP(O)$(OEt)_2$ **10**	61	68	32

[a] Based on initial amount of starting material **4**. [b] Percentage compositions of diastereoisomerically pure isomers. [c] (*S,R*)-Diastereoisomer hasn't been found among by-products. [d] After epimerization of reaction mixture in MeOH–MeONa.

amino]benzophenone (BPB) **3**.* Preliminary results of this work were published earlier.[16]

Results

Synthesis of Nickel(II) *Complex of the Schiff's Base Prepared from Compound* **3** *and Glycine.*—Compound **3** reacted with nickel(II) ions and glycine to give complex **4** (see Scheme 1), as described earlier.[17]



Scheme 1 *Reagents and conditions:* i, NaOMe, MeOH, $Ni(NO_3)_2$, 50 °C.

Synthesis of Enantioisomerically Pure (S)-*Phosphinothricin,* (S)-2-*Amino*-3-*phosphonopropanoic Acid,* (S)-2-*Amino*-4-*phosphonobutanoic Acid and* (S)-2-*Amino*-5-*phosphonopentanoic Acid* via *Alkylation of Complex* **4**.—Alkylation of complex **4** with the appropriate alkyl halide was conducted according to Scheme 2 in MeCN solution at ambient temperature, and using powdered KOH as a base. Use of dimethylformamide (DMF) as a solvent or Na_2CO_3 as a base resulted in diminished yields either because of significant side-reactions or sluggishness of the main reaction. TLC (SiO_2) was used to monitor the progress of the reactions. Alkylation of complex **4** by halogeno phosphorus esters **5** gave, in each case, two diastereoisomeric complexes (**6** and **7**), the yields and ratios of which are given in Table 1. If the ratio **5**:**4** was kept in 1–1.5:1 region, there were no products of bis-alkylation. The mixture of alkylated diastereoisomers was separated on SiO_2, giving diastereoisomerically pure products **6a–c** and **7a–c**. The alkylation with $ICH_2P(O)(OPr^i)_2$ was an exception, the only isolable product found in the reaction mixture being the (*S*)-2-amino-3-phosphonopropanoic acid complex **6d**.

* Available from Merck (cat. no. 814473).

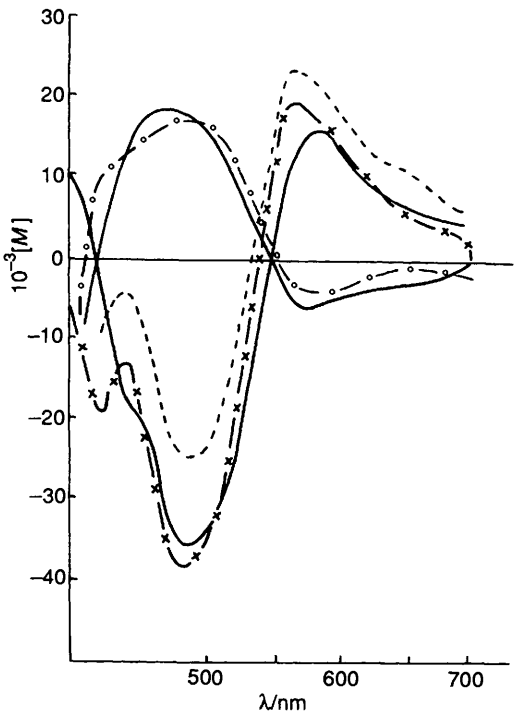
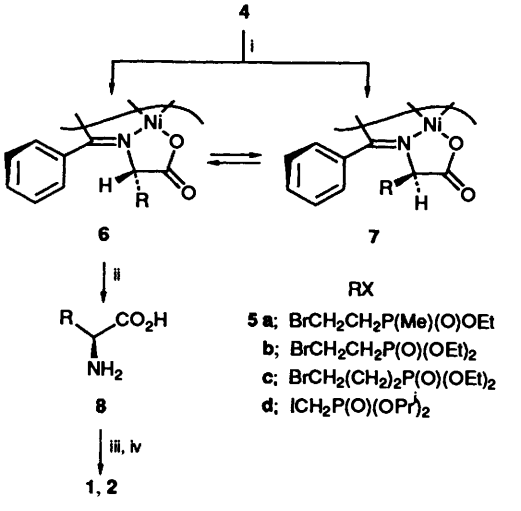


Fig. 1 ORD curves of the diastereoisomerically pure complexes **6** and **7** at 25 °C in $CHCl_3$. **6b**, ×—×; **6c**, – – –; **6d**, ——; **7b**, – – –; **7c**, o—o.



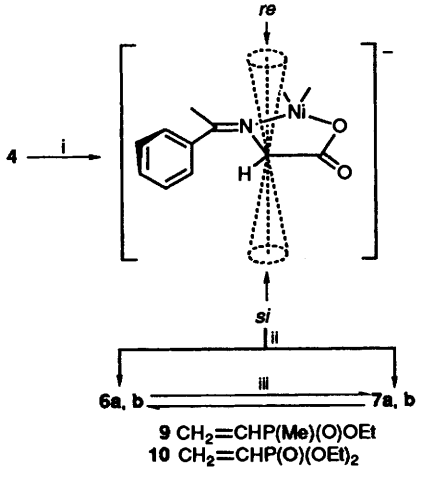
Scheme 2 *Reagents and conditions:* i, **5**, KOH, MeCN, TBAB, 25 °C; ii, MeOH, aq. HCl (2 mol dm^{-3}); iii, aq. HCl (6 mol dm^{-3}), reflux; iv, $MeCHCH_2O$

The absolute configuration of the amino acid moiety was established according to the shapes of the ORD curves of the complexes **6** and **7**. The sign of the Cotton effect in the 500–700 nm region was always positive for (*S*)-amino acids and negative for their enantiomers. This general trend was not influenced by the structure of the α-amino acid's side-chain.[18] Fig. 1 indicates that the complexes **7**, having the greatest mobility on SiO_2, contain the amino acid moieties with the (*R*)-configuration at their α-carbon atoms and that the amino acids in complexes **6** have the (*S*)-configuration.

The mild conditions of the decomposition of the diastereoisomerically pure complexes **6** (see Scheme 2) furnished novel

amino acids **8** which have free carboxy groups and esterified phosphonic and phosphinic groups. Enantiomeric purity of the amino esters **8** could be determined *via* ligand-exchange HPLC on chiral phases.[19] Optically pure α-amino-ω-phosphonic and -phosphinic acids can be obtained from the corresponding esters **8** after hydrolysis of the latter with aq. HCl and treatment with propylene oxide.

Synthesis of Enantioisomerically Pure (S)-*Phosphinothricin and* (S)-2-*Amino-4-phosphonobutanoic Acid* via *Michael addition of Vinyl-phosphinate* **9** *and -phosphonate* **10** *to Complex* **4**.—The relatively high CH-acidity of the glycine fragment in the complex **4**[20] allowed us to conduct the Michael addition of substrates **9** and **10** to complex **4** under a variety of conditions by using diverse inorganic and organic bases, even such a weak base as 1,4-diazabicyclo[2.2.2]octane (DABCO). However, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was found to give the best results (see Scheme 3); the addition reactions were generally



Scheme 3 *Reagents and conditions:* i, DMF, DBU, 50–70 °C, 2–3 h; ii, **9** or **10**; iii, MeOH, MeONa, 25 °C

complete within 2–3 h at 50–70 °C and there were almost no side-reactions. The main experimental results are given in Table 1. The optical yield of (*S*)-phosphinothricine and (*S*)-2-amino-4-phosphonobutanoic acid prepared by this method may be increased from 30% to 90% after epimerization of the diastereoisomeric complexes in MeOH/MeONa prior to decomposition. Enantiomerically pure amino aicds could be obtained if additional purification steps, such as crystallization or flash chromatography of the mixture of the diastereoisomers, were introduced into the synthetic protocol. This is illustrated by the synthesis of homochiral (*S*)-phosphinothricine.

Discussion

As expected, and as shown earlier,[21] alkylation of complex **4** with alkyl halides in MeCN in the presence of powdered KOH produced a large d.e. of the (*S,S*)-diastereoisomers. The obvious reason for this is the equilibration of the (*S,R*)- and (*S,S*)-diastereoisomers being formed, catalysed by the strong base in the reaction mixture. The equilibrium is greatly shifted toward the (*S,S*)-*isomers*[17,18,21] and, thus, thermodynamics determine the stereochemical outcome of the reaction. The intramolecular non-bonding interaction of the amino acid side-chain with the phenyl substituent at the C–N bond (see Scheme 2) was suggested as the most important intramolecular non-bonding interaction which makes the (*S,R*)-diastereoisomers unstable relative to the (*S,S*)-isomers.[18c] In contrast, DBU-catalysed Michael addition to the activated C=C bonds produced a kinetically controlled ratio of (S,*R*)-/(*S,S*)-isomers with a d.e. of only 30–36% in favour of the (*S,S*)-isomer. As was shown by independent experiments, the base was too weak to effect epimerization of the diastereoisomeric mixture being formed under the experimental conditions. Such a low d.e. was also previously observed in the alkylation of complex **4** with alkyl halides under conditions of kinetic control[21] [BuLi; −70 °C; tetrahydrofuran (THF) and phase-transfer conditions].

The stereochemical model, based on the X-ray analytical data of the analogous complex of (*E*)-dehydroaminobutanoic acid,[18c] predicts much greater kinetic diastereoselectivity in the reaction because the carbanion should have been better shielded from the *re*-side by the phenyl substituent at the C=N bond. Molecular mechanics calculations made with the use of a 'PC-model' program (a modification of the MMX program from Serena Software) have predicted almost the same difference in the energies of the diastereoisomeric transition states of the alkylation of the intermediate carbanion of complex **4** with methyl iodide as the energy difference of the final alanine diastereoisomers. Clearly there are other effects, operating in the carbanion, which make kinetic stereoselectivity much less than thermodynamic stereoselectivity. The structure of the carbanion complex probably differs significantly from that of the neutral product and the stereochemical mechanistic speculations based on the structure of the latter are not valid in the case of the former. However, whatever the reasons for such low kinetic stereoselectivity, it has a bonus of allowing us to synthesize both enantiomers of the amino acids *via* a single alkylation of complex **4**, followed by chromatographic separation of diastereoisomeric complexes.

Conclusions.—We report here a synthetic procedure by which various phosphorus analogues of dicarboxylic α-amino acids can be synthesized starting from glycine and a re-usable and commercially available chiral auxiliary (BPB). Preliminary experiments indicate that other homologues of aminophosphonic acids may be easily synthesized starting from the corresponding alkyl halides. High chemical and optical yields, the simplicity of the synthetic procedure, and the possibility of obtaining optically pure amino acids *via* additional chromatographic separation of the diastereoisomeric complexes formed in the reaction, make this method attractive.

Experimental

General.—Kieselgel 60 PF_{254} DC-plastikfolien (Merck) and silica gel L 40/100 (Chemapol, Praha) were used for TLC and column chromatography, respectively. DMF and MeCN were purified as described in ref. 22. (*S*)-2-[(*N*-Benzylprolyl)amino]-benzophenone (BPB) was available from Merck, catalogue 814473.0001, and compound **4** was synthesized according to ref. 17, starting from BPB and NiX_2.

^1H (198 MHz) and ^{31}P (80 MHz) NMR spectra were recorded on a Bruker WP-200 instrument with Me_4Si (TMS) as internal reference in $CDCl_3$ solution, and TMS sealed in a glass capillary for D_2O solution. Assignments of protons in the complexes under study were made by decoupling each separately observable proton multiplet and observing the collapse of the splitting thus produced. *J*-Values are given in Hz. ORD spectra were obtained with a JASCO ORD/UV-5 instrument. Optical rotations were measured on a Perkin-Elmer 241 polarimeter; [α] values are now given in units of 10^{-1} deg cm^2 g^{-1}. Molecular mechanics calculations were performed on a IBM-compatible 386-processor computer 'Graphite', using the 'PC-model'-program, available from Serena Software.

Synthesis of Alkylating Agents **5a–d** *and Compounds* **9** *and* **10**.—Alkyl halides **5a–d** were synthesized analogously to the

methods described in refs. 10, 23–25: ethyl 2-bromoethyl-(methyl)phosphinate **5a**, b.p. 90–93 °C (0.06 mmHg); n_D^{20} 1.4710; $\delta_H(CDCl_3)$ 1.28 (3 H, t, *J* 7, OCH_2Me), 1.48 (3 H, d, *J* 13.8, PMe) 2.40 (2 H, m, PCH_2), 3.50 (2 H, m, $BrCH_2$) and 4.03 (2 H, m, OCH_2); diethyl (2-bromoethyl)phosphonate **5b**, b.p. 85–90 °C (2 mmHg); n_D^{20} 1.4584; $\delta_H(CDCl_3)$ 1.34 (6 H, m, *J* 7, 2 × OCH_2Me), 2.39 (m, 2 H, m, PCH_2), 3.54 (2 H, m, $BrCH_2$) and 4.12 (4 H, d, *J* 7, 2 × OCH_2); diethyl (3-bromopropyl)-phosphonate **5c**, b.p. 110–116 °C (0.02 mmHg); n_D^{20} 1.4668; $\delta_H(CDCl_3)$ 1.25 (6 H, t, *J* 7, 2 × OCH_2Me), 1.6–2.4 (4 H, m, PCH_2CH_2), 3.45 (2 H, m, $BrCH_2$) and 4.00 (4 H, m, 2 × OCH_2); diisopropyl (iodomethyl)phosphonate **5d**, b.p. 70–72 °C (2 mmHg); n_D^{20} 1.4465; $\delta_H(CDCl_3)$ 1.1 (12 H, m, 4 × Me), 3.37 (m, 2 H, CH_2I) and 4.77 (2 H, m, 2 × $OCHMe_2$). Ethyl methyl(vinyl)phosphinate **9**, b.p. 64 °C (2 mmHg); n_D^{20} 1.4475; $\delta_H(C_6D_6)$ 1.06 (3 H, t, *J* 7.1, OCH_2Me), 1.43 (3 H, d, J_{PH} (13.8, PMe), 3.81–3.92 (2 H, m, OCH_2), 5.78 (1 H, ddd, J_{PH} 44, J_{HH} 5.6, 9.3, PCH=), 6.24 (1 H, dd, J_{PH} 23.1, J_{HH} 9.2, *E*-CH=) and 6.25 (1 H, dd, J_{PH} 23, J_{HH} 5.6, *Z*-CH=); diethyl vinylphosphonate **10**, b.p. 85 °C (9 mmHg); n_D^{20} 1.4252; $\delta_H(C_6D_6)$ 1.11 (6 H, t, *J* 7.0, 2 × Me), 3.85 (4 H, m, 2 × OCH_2), 5.74 (1 H, ddd, J_{PH} 44.1, J_{HH} 5.8, 9.2, PCH=), 6.22 (1 H, dd, J_{PH} 23.2, J_{HH} 9.2, *E*-CH=) and 6.25 (1 H, dd, J_{PH} 23.2, J_{HH} 5.8, *Z*-CH=).

Synthesis of Complexes **6a–d** *and* **7a–c** via *Alkylation of Complex* **4**.—Alkyl halide (13 mmol) was added to compound **4** (5 g, 1 × 10^{-2} mol) in carefully purified, vigorously stirred MeCN (13 cm^3) under argon, followed by addition of finely ground KOH (2.8 g, 5.0 × 10^{-2} mol) and tetrabutylammonium bromide (TBAB) (0.1 g, 3 × 10^{-4} mol). The mixture was stirred for 2–3 h at 20–25 °C until compound **4** was consumed (as monitored by TLC) after which the reaction mixture was added slowly to a stirred solution of AcOH (0.1 mol) in water (200 cm^3). The precipitated thick, red suspension of diastereoisomeric complexes was filtered off, washed with water several times, and dried *in vacuo* (filtration could be substituted with extraction $CHCl_3$, followed by evaporation of the solvent) to give a mixture of complexes **6a–d** and **7a–c**. The diastereoisomers were separated on SiO_2 (100 g SiO_2 for 1 g of mixture), with $CHCl_3$–Me_2CO (4:1) as eluent, *R*-complexes **7a–c** being eluted first.

Complex **6a** had m.p. 198–205 °C (Found: C, 60.5; H, 5.7; N, 6.6. $C_{32}H_{36}N_3NiO_5P$ requires C, 60.78; H, 5.74; N, 6.65%); $[\alpha]_{589}^{25}$ (0.4 g dm^{-3} in $CHCl_3$; *l* 5 cm) +2490; $\delta_H(CDCl_3)$ 1.29 and 1.33 (3 H, t, *J* 7.2, Me), 1.36 and 1.42 (3 H, d, *J* 13.6, PMe), 1.60–2.95 (9 H, m, amino acid 2 × CH_2 and Pro β-, γ-, δ-H), 3.40–3.60 (2 H, m, Pro α-, δ-H), 3.85 (1 H, m, amino acid α-H), 4.02 (2 H, m, CH_2), 3.58 and 4.35 (2 H, AB, *J* 12.8, CH_2Ph) and 6.60–8.21 (14 H, m, ArH); $\delta_P(CDCl_3)$ 53.0 [m, $CH_2P(Me)(O)OEt$].

Complex **7a** had m.p. 84–90 °C (Found: C, 60.3; H, 5.5; N, 6.3%); $[\alpha]_{589}^{25}$ (0.4 g dm^{-3} in $CHCl_3$; *l* 5 cm) −795; $\delta_H(CDCl_3)$ 1.18 and 1.29 (3 H, t, *J* 7.1, Me), 1.34 and 1.40 (3 H, d, *J* 13.5, Me), 1.60–3.68 (9 H, m, amino acid 2 × CH_2 and Pro α-, β-, γ, δ-H), 3.81 (1 H, m, amino acid α-H), 4.01 (2 H, m, CH_2), 3.55 and 4.43 (2 H, AB, *J* 12.6, CH_2Ph) and 6.60–8.60 (14 H, m, ArH); $\delta_P(CDCl_3)$ 53.2 [m, $CH_2P(Me)(O)OEt$].

Complex **6b** had m.p. 70–78 °C (Found: C, 60.1; H, 5.8; N, 6.7. $C_{33}H_{38}N_3NiO_6P$ requires C, 59.84; H, 5.78; N, 6.34%); $[\alpha]_{589}^{26}$ (0.5 g dm^{-3} in $CHCl_3$; *l* 5 cm) +2608; $\delta_H(CDCl_3)$ 1.27 (3 H, t, *J* 7.5, Me), 1.28 (3 H, t, *J* 7.5, Me), 1.60–2.80 (8 H, m, amino acid CH_2, Pro β-, γ-, δ-H), 3.50–3.80 (2 H, m, amino acid CH_2), 3.45 (1 H, m, Pro α-H), 3.55 and 4.45 (2 H, AB, *J* 12.6, CH_2Ph), 4.10 (5 H, m, 2 × CH_2, amino acid α-H) and 6.55–8.20 (14 H, m, ArH).

Complex **7b** had m.p. 88–93 °C (Found: C, 60.1; H, 6.1; N, 6.5%); $[\alpha]_{589}^{26}$ (0.2 g dm^{-3} in $CHCl_3$; *l* 5 cm) −873; $\delta_H(CDCl_3)$ 1.25 (3 H, t, *J* 7.5, Me), 1.26 (3 H, t, *J* 7.5, Me), 1.40–2.75 (8 H, m, amino acid CH_2 and Pro β-, γ-, δ-H), 3.60–3.75 (2 H, m, CH_2), 3.50 (1 H, m, Pro α-H), 3.50 and 4.43 (2 H, AB, *J* 12.5, CH_2Ph), 4.15 (5 H, m, 2 × CH_2 and amino acid α-H) and 6.60–8.50 (14 H, m, ArH).

Complex **6c** had m.p. 82–87 °C (Found: C, 60.2; H, 6.0; N, 6.3. $C_{34}H_{40}N_3NiO_6P$ requires C, 60.37; H, 5.96; N, 6.21%); $[\alpha]_{589}^{28}$ (0.2 g dm^{-3} in $CHCl_3$; *l* 5 cm) +2282; $\delta_H(CDCl_3)$ 1.29 (3 H, t, *J* 7.8, Me), 1.30 (3 H, t, *J* 7.7, Me), 1.62–2.80 (10 H, m, amino acid 2 × CH_2 and Pro β-, γ-, δ-H), 3.47 (1 H, m, Pro α-H), 3.46–3.56 (2 H, m, CH_2), 3.56 and 4.41 (2 H, AB, *J* 12.5, CH_2Ph), 3.83 (1 H, m, amino acid α-H), 4.05 (4 H, m, 2 × CH_2) and 6.60–8.18 (14 H, m, ArH); $\delta_P(CDCl_3)$ 30.44 [m, $CH_2P(O)(OEt)_2$].

Complex **7c** had m.p. 89–93 °C (Found: C, 60.3; H, 5.9; N, 6.1%); $[\alpha]_{589}^{28}$ (0.3 g dm^{-3} in $CHCl_3$; *l* 5 cm) −782; $\delta_H(CDCl_3)$ 1.23 (3 H, t, *J* 7.6, Me), 1.27 (3 H, t, *J* 7.6, Me), 1.24–2.75 (10 H, m, amino acid 2 × CH_2 and Pro β-, γ-, δ-H), 3.64–3.74 (2 H, m, CH_2), 3.54 (1 H, m, Pro α-H), 3.53 and 4.43 (2 H, AB, *J* 12.5, CH_2Ph), 4.20 (5 H, m, 2 × OCH_2, and amino acid α-H) and 6.64–8.37 (14 H, m, ArH); $\delta_P[(CD_3)_2CO]$ 30.57 [m, $CH_2P(O)(OEt)_2$].

Complex **6d** had m.p. 73–80 °C (Found: C, 57.45; H, 5.95; N, 6.0. $C_{34}H_{40}N_3NiO_6P{\cdot}2H_2O$ requires C, 57.32; H, 6.23; N, 5.90%); $[\alpha]_{589}^{25}$ (0.5 g dm^3 in $CHCl_3$; *l* 5 cm) +1700; $\delta_H(CDCl_3)$ 1.07 (3 H, d, *J* 7.5, Me), 1.15 (3 H, d, *J* 7.4, Me), 1.26 (3 H, d, *J* 7.5, Me), 1.32 (3 H, d, *J* 7.5, Me), 1.90–2.80 (6 H, m, Pro β-, γ-, α-H), 3.47 (1 H, m, Pro α-H), 3.57 and 4.46 (2 H, AB, *J* 12.5, CH_2Ph), 3.65–3.86 (2 H, m, CH_2), 4.10 (1 H, m, amino acid α-H), 4.78 (2 H, m, 2 × CH) and 6.63–8.35 (14 H, m, ArH); $\delta_P(CDCl_3)$ 24 [m, $CH_2P(O)(OPr^i)_2$].

Synthesis of Complexes **6a/b** *and* **7a/b** via *Michael Addition of Compounds* **9** *and* **10** *to Complex* **4**.—Compounds **9** or **10** (3 × 10^{-3} mol) was added to complex **4** (1 g, 2 × 10^{-3} mol) in vigorously stirred DMF (1.5 cm^3), followed by addition of DBU (0.1 cm^3), under argon. The mixture was stirred for 2–3 h at 50–70 °C, after which the reaction mixture was added slowly to a stirred solution of AcOH (10 mmol) in water (20 cm^3). The precipitated thick, red suspension of diastereoisomeric complexes was filtered off, washed with water several times, and dried *in vacuo*. The diastereoisomers **6a** or **6b** and **7a** or **7b** were separated on SiO_2 as described above.

Epimerization of Complexes **6** *and* **7**.—A mixture (1 g) of the diastereoisomeric complexes, recovered from the Michael addition reaction, was dissolved in a 2 molar methanolic solution of sodium methoxide (2 cm^3) at ambient temperature. After the epimerization had been completed, as monitored by TLC, the solution was neutralized, and further treatment of the reaction mixture was carried out as described above. No epimerization of complexes **6** and **7** was observed under the effect of DBU for (at least) 4 h at 50–70 °C.

Isolation of Amino Acids from the Complexes, and Recovery of Compound **3**.—The complexes were decomposed, the amino acids **8a**, **b**, **1** and **2a–c** were obtained, and chiral auxiliary **3** was recovered, according to the general methods outlined in the literature.[18–21]

The optical purity (>99% e.e. from the diastereoisomerically pure complexes **6a–d**) of the amino acids was determined by ligand-exchange HPLC (**8a–d**)[19] and polarimetry (**1**, **2a–c**).[12–15]

Compound **8a**: yield 83.5%; m.p. 143–148 °C (Found: C, 39.8; H, 7.7; N, 6.7. $C_7H_{16}NO_4P$ requires C, 40.19; H, 7.71; N, 6.69%); $[\alpha]_{589}^{25}$ (1 g dm^{-3} in water; *l* 1 cm) +7.89; δ_H (D_2O) 1.13 (3 H, t, *J* 7.0, Me), 1.43 (3 H, d, *J* 13.8, Me), 2.50–3.50 (4 H, m, amino acid 2 × CH_2), 3.62 (1 H, t, *J* 6.9, amino acid α-H) and 3.90 (2 H, q, *J* 7.5, CH_2).

Compound **8b**: yield 69%; m.p. 155–161 °C (Found: C, 39.8; H,

7.6; N, 5.7. $C_8H_{18}NO_5P$ requires C, 40.16; H, 7.58; N, 5.86%); $[\alpha]_{589}^{25}$ (0.5 g dm^{-3} in water; *l* 1 cm) +9.22; $\delta_H(D_2O)$ 1.53 (6 H, t, *J* 7.0, 2 × Me), 2.05–2.40 (4 H, m, amino acid 2 × CH_2), 4.00 (1 H, t, *J* 5.5, amino acid α-H) and 4.35 (4 H, m, 2 × CH_2); $\delta_P(D_2O)$ 33.99 [m, $CH_2P(O)(OEt)_2$].

Compound **1**: yield 91%; m.p. 215–218 °C; $[\alpha]_{589}^{25}$ (0.5 g dm^{-3} in water; *l* 1 cm) +16.8; $\delta_H(D_2O)$ 1.99 (3 H, d, *J* 14.2, Me), 2.27–3.15– (4 H, m, amino acid 2 × CH_2) and 4.60 (1 H, t, *J* 6.5, amino acid α-H).

Compound **2a**: yield 64%; m.p. 227–232 °C; $[\alpha]_{589}^{25}$ (0.3 g dm^{-3} in 6 mol dm^{-3} HCl; *l* 1 cm) +27.6; $\delta_H(D_2O)$ 1.7 (2 H, m, CH_2), 2.1 (2 H, m, CH_2) and 4.0 (1 H, t, *J* 6.1, α-H); $\delta_P(D_2O)$ 25.7 [m, $CH_2P(O)(OH)_2$].

Compound **2b**: yield 51%; m.p. 225–229 °C; $[\alpha]_{589}^{25}$ (0.1 g dm^{-3} in 6 mol dm^{-3} HCl; *l* 1 cm) +25.8; $\delta_H(D_2O)$ 1.5–2.3 (6 H, m, 3 × CH_2) and 4.1 (1 H, t, *J* 6.1, α-H); $\delta_P(D_2O)$ 25.5 [m, $CH_2P(O)(OH)_2$].

Compound **2c**: yield 84%; m.p. 223–226 °C; $[\alpha]_{589}^{25}$ (0.5 g dm^{-3} in water; *l* 1 cm) +8.0; $\delta_H(D_2O)$ 2.14–2.35 (2 H, m, CH_2) and 4.21 (1 H, m, α-H).

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