General Method for the Asymmetric Synthesis of α-Amino Acids *via* Alkylation of the Chiral Nickel(II) Schiff Base Complexes of Glycine and Alanine

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Nickel(II) complexes of Schiff bases derived from (*S*)-*o*-[(*N*-benzylprolyl)amino]benzaldehyde and alanine (**3**), or (*S*)-O-[(*N*-benzylpropyl)amino]benzophenone and alanine (**4**), or glycine (**5**) have been used for the asymmetric synthesis of α-amino acids under a variety of conditions. The method of choice consists of the reaction of the corresponding complex with the appropriate alkyl halide in DMF at 25 °C using solid NaOH as a catalyst. Low diastereoselective excess (d.e.) is observed for the alkylation of complex (**3**) with benzyl bromide and allyl bromide. Large selectivity (80%) is observed for the alkylation of complex (**4**). Optically pure (*R*)- and (*S*)-α-methyl-α-amino acids [(*S*)-α-methylphenylalanine, (*S*)-α-allylalanine and (*S*)-O-benzyl-α-methyltyrosine] were obtained (70—90%) after the alkylated diastereoisomeric complexes had been separated on SiO_2 and hydrolysed with aqueous HCl. The initial chiral reagents were recovered (80—92%). The alkylation of complex (**5**) gave (*S*)-alanine, (*S*)-valine, (*S*)-phenylalanine, (*S*)-tryptophan, (*S*)-isoleucine, (*S*)-2-aminohexanoic acid, and 3,4-dimethoxyphenylalanine with optical yields of 70—92%. The optically pure α-amino acids were obtained after the separation of the alkylated diastereoisomeric complexes on SiO_2. The stereochemical mechanism of the alkylation reaction is discussed.

α-Amino acids and their derivatives have numerous biological uses.[1] Non-proteinogenic amino acids are important both because of their pharmaceutical properties[1b] and their ability to serve as building blocks for physiologically active peptides.[1c] In recent years the application of α-amino acids in organic synthesis has grown.[2] In all these applications the enantiomerically pure amino acid is needed, and this is the underlying reason for recent progress in the field of asymmetric synthesis of α-amino acids.[3] The most significant results were achieved by Schöllkopf and his group who developed a general method for the efficient asymmetric synthesis of α-amino acids *via* alkylation of chiral bis-lactim ethers of dioxopiperazines.[3b] Unfortunately, the method has drawbacks including use of expensive reagents, multi-stage syntheses and, probably, difficulties in scale-up.

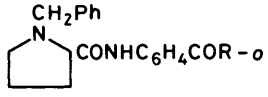
We believed that the important feature of the successful asymmetric synthesis *via* the bislactim ethers, *e.g.* rigid mutual arrangement of the chiral-inducing centre and the prochiral groups, could be realized in chiral α-amino acid complexes with transition metals. The advantages of such a system could be ready formation, the easy recovery of α-amino acids, and also, probably, greater CH acidity of the α-amino acid fragment allowing use of mild alkylation reaction conditions.

The application of simple chiral complexes of α-amino acids for the asymmetric synthesis of threonine,[4] asymmetric decarboxylation,[5] and asymmetric transformation of α-amino acids in cobalt(III) complexes[6] are well documented. Unfortunately the reaction with alkyl halides gave only very low yields of the described amino acids,[7] probably, because the α-amino group of the complexed α-amino acid is still susceptible to electrophilic attack.[8] The use of metal complexes formed from the Schiff bases of α-amino acids effectively protects the nitrogen atom.

Recently we employed (*S*)-o-(*N*-benzylprolylamino)benzaldehyde (**1**) and (*S*)-O-(*N*-benzylprolylamino)benzophenone (**2**) for the asymmetric synthesis of β-hydroxy-α-amino acids and retroracemization of α-amino acids[9a] *via* Schiff base complexes of nickel(II) and copper(II).

Enantio- and diastereo-isomerically pure β- and γ-substituted glutamic acids could also be obtained from the chiral nickel(II) complex of the Schiff base formed from glycine and compound (**2**).[9b] It seemed to us, therefore, that the use of such complexes was also a promising approach to the successful asymmetric synthesis of α-amino acids.

The present work describes a general method for the asymmetric synthesis of α-amino acids *via* alkyl halide alkylation of glycine and alanine in their chiral nickel(II) complexes with the Schiff bases formed from them with compounds (**1**) or (**2**).



(**1**) R = H
(**2**) R = Ph

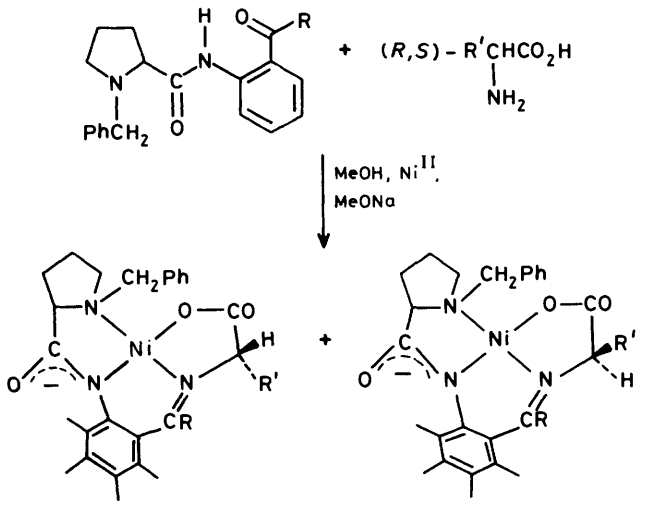
High chemical and optical yields, simplicity of the synthetic procedure, ease of recovery of the chiral auxiliary (**1**) or (**2**) and, finally, the possibility of obtaining optically pure α-amino acids *via* additional chromatographic separation of the diastereoisomeric complexes formed in the reaction make this method attractive. Preliminary results of this work were published earlier.[10]

Results

Synthesis and Structure of Nickel(II) *Complexes of the Schiff Bases Prepared from Compounds* (**1**) *or* (**2**) *and Alanine or Glycine.*—Compounds (**1**) and (**2**) interact with nickel(II) ions and glycine or alanine to give red complexes (see Scheme 1), as described earlier.[9,11a]

Diastereoisomeric complexes (**3a**) and (**3b**) and also (**4a**) and (**4b**) were separated on SiO_2 according to the published procedure.[11,12a]

Generation of Carbanions from Amino Acid Fragments of Complexes (**3a**) *and* (**3b**) *with* BuLi *in THF.*—The amino acid fragments in the complexes (**3**)—(**6**) have relatively high CH

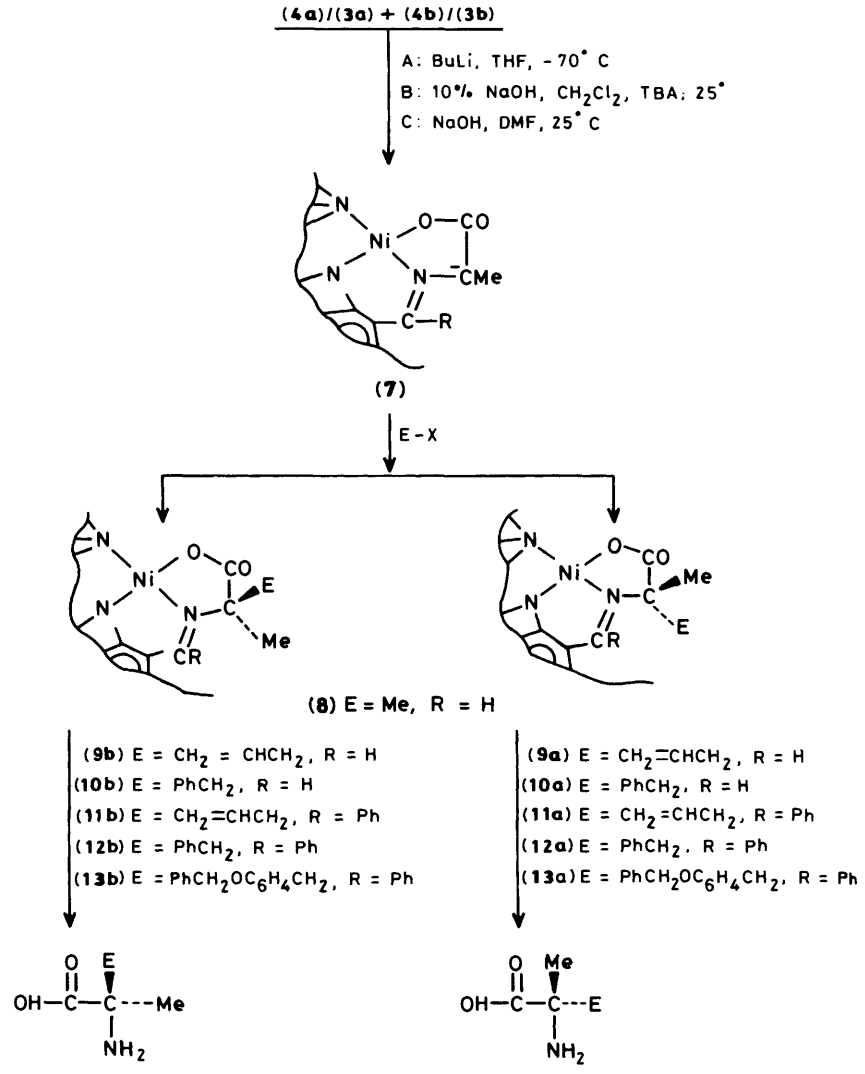


Scheme 1.

acidity.[13] When treated with BuLi in THF at −70 °C under argon these complexes ionized to giving intensely red solutions from which, after quenching with $^2H_2SO_4$ (^2H_2O solution), the initial complexes can be recovered with the α-proton of the amino acid fragment exchanged for deuterium. For example, treatment of either complex (**3a**) or (**3b**) with BuLi, followed by neutralization in ^2H_2O, gives a mixture of complexes consisting of 70% (*R*)-[α-^{2}H]alanine and 30% (*S*)-[α-^{2}H]alanine-containing isomers (Scheme 2).

The ratio was the same irrespective of whether the reactions were carried out with the separate isomer (**3a**) and (**3b**) or a mixture of them.

Synthesis of Enantioisomerically Pure α-Methyl-α-amino Acids via Alkylation of Complexes (**3**) *or* (**4**).—The carbanion generated from complex (**6**) (see Scheme 2) reacted with MeI producing, as the only isolable products, a complex of α-aminoisobutyric acid and/or starting material (**6**). Pure α-aminoisobutyric acid was obtained after decomposition of the reaction mixture. The same compound was produced by the MeI alkylation of the carbanion (**7**) generated from (**3a**) or (**3b**), or a mixture thereof (see Scheme 2). Alkylation of (**7**) by $PhCH_2Br$ or CH_2=$CHCH_2Br$ gave, in each case, two diastereoisomeric complexes, the ratio of which (see Table 1) was not influenced by the source of (**7**) [(**3a**), (**3b**) or a mixture thereof]. The



Scheme 2.

Table 1. Preparation of optically pure α-methyl-α-amino acids by alkylation of (*R*,*S*)-alanine in its Schiff base nickel(II) complexes[a]

		Method A			Method B			Method C		
			Ratio of isomers[d]			Ratio of isomers[d]			Ratio of isomers[d]	
Initial complex	RX	Chemical yield (%)[b]	(*S*,*S*)	(*S*,*R*)	Chemical yield (%)[b]	(*S*,*S*)	(*S*,*R*)	Chemical yield (%)[b]	(*S*,*S*)	(*S*,*R*)
(**3a**) + (**3b**)	MeI	92			90			90		
(**3a**)	$PhCH_2Br$	91	55	45						
(**3b**)	$PhCH_2Br$	92	55	45						
(**3a**) + (**3b**)	$PhCH_2Br$	94	56	44	94	66	34			
(**3a**) + (**3b**)	$CH_2{=}CHCH_2Br$	89	61	39	89	70	30	91	61	39
(**4a**) + (**4b**)	$PhCH_2Br$	84	90	10		No reaction		93	93	7
(**4a**) + (**4b**)	$CH_2{=}CHCH_2Br$[c]					No reaction		91	92	8
(**4a**) + (**4b**)	*p*-$PhCH_2OC_6H_4CH_2Cl$					No reaction		89	91	9

[a] α-Amino acids were obtained from the corresponding alkylated complexes (*S*,*S* or *S*,*R*), yield 77—90%. [b] Based on starting materials (**3**) and (**4**). [c] Alkylation with BuBr could also be successfully carried out, according to a preliminary experiment. [d] Ratio of diastereoisomerically pure alkylated isomers.

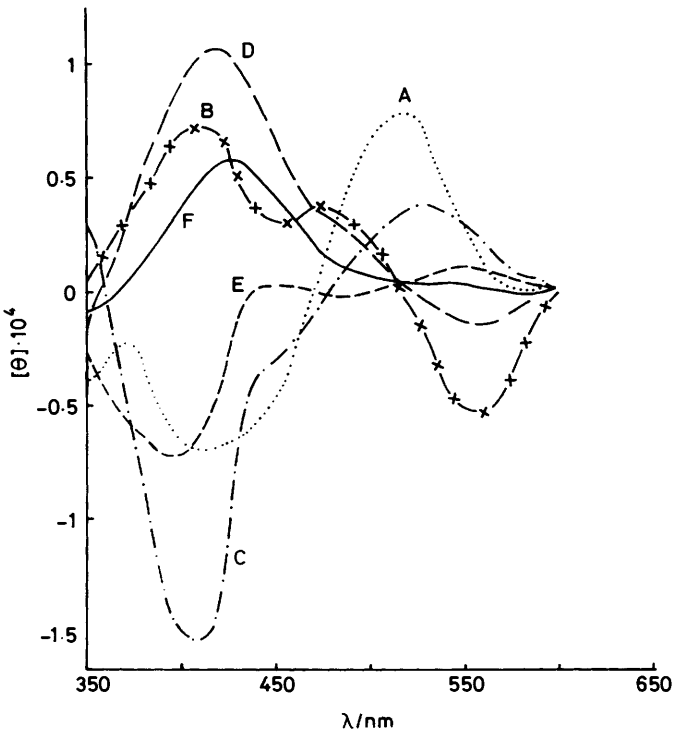


Figure 1. Vicinal contribution of the α-amino acid to the c.d. spectra of nickel(II) complexes formed from their Schiff bases with compound (**1**) (in MeOH): aa = (A) (*S*)-alanine, (B) (*R*)-alanine, (C) (*S*)-α-benzylalanine, (D) (*R*)-α-benzylalanine, (E) (*S*)-α-allylalanine, (F) (*R*)-α-allylalanine

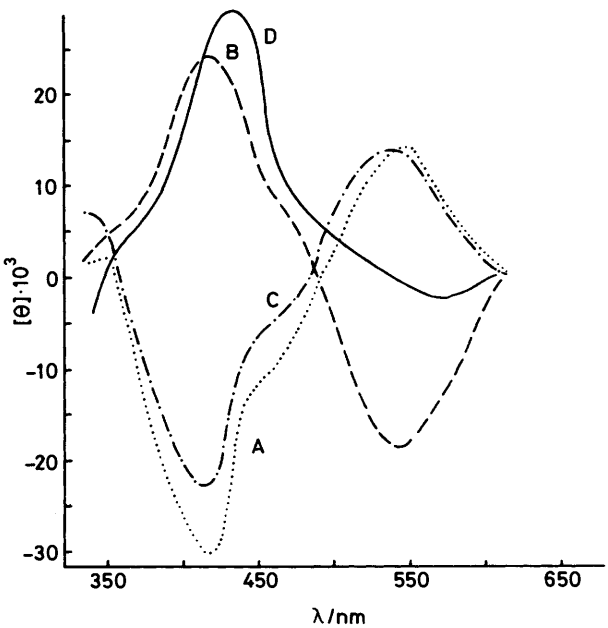


Figure 2. Vicinal contribution of α-amino acid to the c.d. spectra of nickel(II) complexes formed from their Schiff bases with compound (**2**) (in MeOH): (A) (*S*)-phenylalanine, (B) (*R*)-phenylalanine, (C) (*S*)-α-benzylalanine, (D) (*R*)-α-benzylalanine

alkylation reaction could also be conducted under phase-transfer conditions (P.T.C.) in CH_2Cl_2–10% aqueous NaOH (Method B) or DMF–solid NaOH (Method C). The results summarized in Table 1 indicate that the ratio of the isomers is not influenced by the experimental conditions. The mixture of alkylated diastereoisomers was separated on SiO_2 giving diastereoisomerically pure (**9a**) and (**9b**) and (**10a**) and (**10b**).

Optically pure α-amino acids (yield 77—88%) can be easily obtained from the complexes after decomposition of the latter with aqueous HCl, while the initial compound (**1**) was recovered (yield 80—98%). The absolute configuration of the α-methyl-α-amino acids was assigned using vicinal contributions[9] of the amino acid chiral fragments to the c.d. spectra of the diastereoisomers. Figure 1 shows the corresponding vicinal contributions in the spectra of (**9a**) and (**9b**) and (**10a**) and (**10b**). Also included for the purpose of comparison were the contributions of (*S*)-alanine and (*R*)-alanine fragments to the c.d. spectra of (**3a**) and (**3b**), respectively. It is seen from this Figure that Cotton effects in the region of 400—500 nm are positive for the (*R*)-amino acid-containing isomers and negative for the complexes of (*S*)-amino acids. (−)-α-Methyl-β-phenylalanine was found to have the (*S*)-configuration, this being in complete agreement with the previous indirect assignments.[15]

Alkylation of (**4a**) or (**4b**) with $PhCH_2Br$ ($CH_2{=}CHCH_2Br$ or $PhCH_2OC_6H_4CH_2Cl$) was successfully carried out by method C using a significant excess of the alkylating agent (1.5—5 equiv.). Method A could also be used, but no reaction was observed under phase-transfer conditions (Method B).

The ratio of the diastereoisomers formed (**11a**, **b**)—(**13a**, **b**)

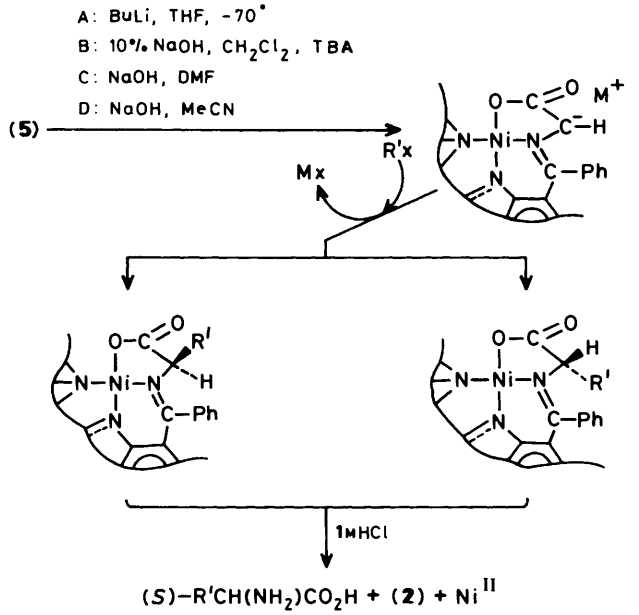
Table 2. Enantioisomeric purity and chemical yields of α-amino acids derived *via* alkylation of (5)

RX	α-Amino acid	Enantioisomeric purity (e.e)[a] (%) Method A	B	C	D	Chemical yield[b] (%) Method A	B	C	D
MeI	Alanine	42	41	70	84	77	69	82	75
$PhCH_2Br$	Phenylalanine	56	58	92	86 (>99[d])	71	83	83	79
BuBr	α-Aminohexanoic acid				>98				77
Me_2CHBr	Valine			92	79			81	73
$IndCH_2NMe_3I$	Tryptophan				>95[c]				69[e]
$3,4\text{-}(MeO)_2C_6H_3CH_2Cl$	3,4-Dimethoxyphenylalanine			94[c]				77[e]	
Bu^sBr	Isoleucine			74[f]					

[a] G.l.c. analysis, unless otherwise stated. [b] Based on initial quantity of (5). [c] Polarimetry was used for e.e. determination. [d] Amino acid was obtained from a pure diastereoisomer. [e] ^1H n.m.r. method[16] was used. [f] Ratio of *threo*/*erythro* is 2.5.

was not sensitive to the diastereoisomeric purity of the starting material (4) and was greatly in favour of an (*S*)-amino acid-containing isomer (with diastereoisomeric excess, d.e. >80%), than in the case of (3) alkylation (d.e. = 10—40%). Optically pure α-amino acids could be obtained after the separation of the alkylated isomers on SiO_2. The absolute configuration of the α-amino acids was established on the basis of the c.d. spectra of the corresponding complexes (see Figure 2).

Asymmetric Synthesis of (S)-*Alanine*, (S)-*Valine*, (S)-*Phenylalanine*, (S)-*Tryptophan*, (S)-*Isoleucine*, (S)-3,4-*Dimethoxyphenylalanine and* (S)-*Aminohexanoic Acid* via *Alkylation of Complex* (5).—Alkyl halide alkylation of complex (5) was conducted under a variety of conditions (see Scheme 3).



Scheme 3. R′ = MeI, $PhCH_2Br$, $Me(CH_2)_3Br$, Me_2CHBr, $C_8H_6NCH_2NMe_3$, and $3,4\text{-}(MeO)_2C_6H_3CH_2Cl$

If the ratio of the alkyl halide: complex (5) was not greater than 1.0—1.5, there were no bisalkylation products: MeI alkylation was an exception to this in that, an α-aminoisobutyric acid complex was found if MeI was used in ratios greater than 1:1.

T.l.c. (SiO_2) was used to monitor the progress of the reactions which, when complete (10—180 min), were quenched with aqueous HCl to give recovery of the initial compound (2) and the amino acids (yield 70—90%). Structural assignments were made on the basis of chromatographic data (t.l.c. and g.l.c.) and ^1H n.m.r. spectroscopy; the optical purity was checked by g.l.c.[11a] For tryptophan and 3,4-dimethoxyphenylalanine polarimetry was used (see Table 2). As can be seen from the data of Table 2, the optical yields of amino acids depend on the experimental conditions, the greatest enantiomeric excess (e.e.) being achieved using Methods C and D. Method C allows the use of greater concentrations of reagents and reactions are complete within 10—30 min at 25 °C. The optical yield of (*S*)-alanine prepared by method C increased from 70 to 90% after epimerization of the diastereoisomeric complexes in MeOH. Enantioisomerically pure α-amino acids could be obtained if a small amount of the diastereoisomer-containing (*R*)-α-amino acid was separated by preparative flash chromatography (SiO_2 $CHCl_3$—Me_2CO, 5:1); this is illustrated by the (*S*)-phenylalanine synthesis (Table 2).

Discussion

Since the pK_a values of complexes (3), (5), and (6) in DMSO were 19.2, 18.8, and 19.5, respectively,[13] their CH acidity is greater than that of fluorene (pK_a = 22.6[17]) and acetophenone (pK_a = 24.7[17]) and approaches that of mononitro compounds ($pK_a \approx 17$[17]).

The carbanions formed from complexes (3), (5), and (6) under the effect of BuLi react as expected with electrophiles. Because of their relatively high thermodynamic acidity and great kinetic stability it was possible to alkylate the complexes not only under strongly basic conditions (−70 °C, BuLi, THF), but also using solid NaOH in aprotic solvents (MeCN or DMF) at 25 °C.

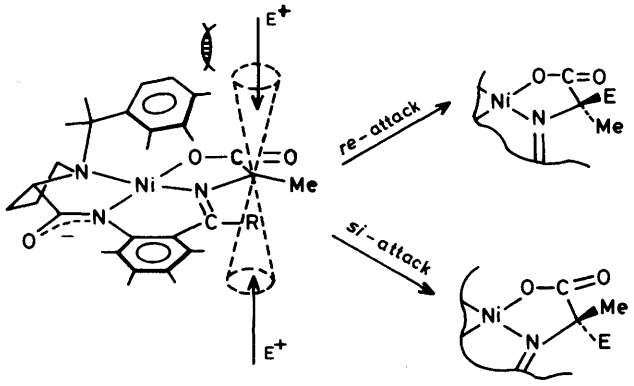
To make the reaction synthetically useful the following problems had to be solved: (i) bisalkylation, where possible, had to be eliminated by the choice of appropriate reagents and experimental conditions; (ii) the method had to give easy access to α-methyl-α-amino acids; (iii) then optically pure α-amino acids would have to be the final products of the synthesis.

With small and reactive alkyl halides bisalkylation of the glycine fragment in the complexes was expected to be an important side reaction. In fact, alkylation of complex (6) with MeI yielded no alanine complex, even if a single equivalent of MeI was used. Clearly, the intermediate product of monoalkylation (complex of alanine) reacted faster than the initial complex (6) with an additional MeI molecule to produce the α-aminoisobutyric acid complex. In contrast to complex (6), alanine was synthesized by MeI alkylation of the glycine fragment of complex (5) in good yields (Table 2). Apparently, the phenyl substituent at the carbon atom of the C=N bond makes the addition of the second Me group to the glycine frag-

ment of complex (**5**) sterically less favourable. Similar effects were observed earlier on addition of formaldehyde[12a] and acrylonitrile[9b] to complex (**5**). The use of all the other alkyl halides resulted in monoalkylation of complex (**5**) in good yields (Table 2).

α-Methyl-α-amino acids were synthesized effectively by alkylation of complex (**3**), but their e.e. values (Table 1) were low. The alanine fragment of complex (**4**) retains its ability to enter alkylations, although the reaction was sluggish and a greater excess of the alkylating agent was needed. Nevertheless, the d.e. of the reaction is relatively large (Table 1).

In the case of α-methyl-α-amino acid synthesis and deuteriation, it is the larger rates of the *si* as compared to the *re* attack that underlie the stereochemical outcome of the reactions of the intermediate carbanions (Scheme 4).



Scheme 4.

Steric shielding of the carbanion's *re*-side by the benzyl group [for both complexes (**3**) and (**4**)], attenuated by the phenyl substituent at the C=N bond in the case of complex (**4**), is, probably, responsible for the excess of (*S*)-α-methyl-α-amino acids and (*R*)-[2-^{2}H]alanine in the alkylation and deuteriation reactions, respectively.

The alkylation of the glycine fragment of complex (**5**) gives rise to the α-amino acid complexes containing a labile α-proton. Under the experimental conditions of Methods A and B (Scheme 3 and Table 2) there is no epimerization of the alkylated complexes and the stereochemical outcome of the reaction is still kinetically controlled. In contrast, Methods C and D give a mixture of diastereoisomers, epimerization of which proceeds effectively under the experimental conditions, the stereochemical results being thermodynamically controlled. In complete agreement with the previous results,[9,11] the diastereoisomer with an (*S*)-amino acid is energetically favoured.

Conclusion.—We report here a synthetic procedure by which a broad range of α-amino acids can be synthesized starting from glycine and alanine and re-usable reagents. Because of the high concentration of the reaction mixtures, and the use of NaOH as a catalyst for the room-temperature reactions the method is convenient for producing relatively large quantities of optically active α-amino acids of both proteinogenic and non-proteinogenic α-amino acids. Additional effective chromatographic separation of diastereoisomeric complexes ensures 100% optical purity of the α-amino acids prepared.

Experimental

Materials.—(*S*)-Alanine and Gly were supplied by Reanal (Budapest) and Reakhim (Moscow). Kieselgel 60 PF_{254} DC-plastikfolien (Merck) and silicagel L 40/100 (Chemapol, Praha) were used for t.l.c. and column chromatography, respectively. Sephadex LH-20 was the product of Pharmacia, Sweden. DMF and MeCN were purified as described in ref. 18. (*S*)-2-[*N*-*N*′-Benzylpropyl)amino]benzaldehyde (**1**), (*S*)-2-[N-(*N*′-benzylprolyl)amino]benzophenone (**2**), and also compounds (**5**) and (**6**) were available from previous work.[9a,11a] ^{1}H N.m.r. spectra were recorded on a Tesla-NMR-BS-467A and Bruker WP-200 instruments using $Me_3SiOSiMe_3$ (HMDS) as an internal reference in $CDCl_3$ and CF_3CO_2H solutions and HMDS sealed in a glass capillary for D_2O solutions. Assignments of protons in the complexes under study were made by decoupling each, separately observable proton multiplet and observing the collapse of the splitting produced. U.v.-vis spectra were obtained with a Specord-u.v.-vis spectrophotometer and c.d. spectra with a Jasco-J-20 instrument. Optical rotations were measured on a Perkin-Elmer-241 polarimeter.

Synthesis of Compounds (**4a**) *and* (**4b**).—A solution of (*R,S*)-alanine (1.74 g, 19.5 mmol) in 1.2M MeONa in MeOH (23 ml) was added to a stirred solution of compound (**2**) (1.5 g, 3.9 mmol) and $Ni(NO_3)_2{\cdot}6H_2O$ (2.25 g, 7.78 mmol) in MeOH (23 ml). Stirring was continued for 2 h at 50 °C under argon (Ar) after which the reaction mixture was cooled, neutralized with an appropriate amount of AcOH, and added to a mixture of water (75 ml) and $CHCl_3$ (25 ml) with vigorous agitation; the aqueous layer was then separated and extracted several times with $CHCl_3$ (3 × 25 ml). The organic layer and the extracts were combined and evaporated under reduced pressure and the residue was chromatographed on SiO_2 (150 g)/$CHCl_3$–Me_2CO, 5:1, giving the first, minor orange-coloured band (**4b**) followed by a major orange band (**4a**). Each fraction was additionally purified on 'Sephadex' LH-20 (PhH–EtOH, 2:1). The purification of Sephadex is necessary to obtain analytical samples of the complexes but if the synthesis of the α-amino acid is the target, the procedure may be discarded. To avoid possible explosion, caution should be exercised in avoiding addition of any basic admixtures to the solvent system used for the chromatographic separation. Toluene could be used instead of benzene for the Sephadex chromatography. (**4b**) (0.127 g, 6.3%), m.p. 190—196 °C (Found: C, 65.95; H, 5.35; N, 7.9. $C_{28}H_{27}N_3NiO_3$ requires C, 65.65; H, 5.31; N, 8.20%); $\lambda_{max.}$(MeOH) 267 (log ε 4.20), 332 (3.69), 419 (3.55), and 540 nm (2.20); δ($CDCl_3$) 1.33 (d, 3 H, Me, *J* 7.5 Hz), 1.91—4.19 (m, 7 H, Pro), 3.85 (q, 1 H, *J* 7.5 Hz α-H Ala), 6.62—8.45 (m, 14 H, Ar), 3.38, and 4.30 (AB, 2 H, CH_2Ph, *J* 12.5 Hz). (**4a**) (1.69 g, 84.5%), m.p. 147—154 °C (Found: C, 65.45; H, 5.4; N, 8.0. $C_{28}H_{27}N_3NiO_3$ requires C, 65.65; H, 5.31; N, 8.20%); $\lambda_{max.}$(MeOH) 266 (log ε 4.21), 332 (3.62), 417 (3.52), and 531 (2.27); δ($CDCl_3$) 1.51 (d, 3 H, Me Ala, *J* 7.5 Hz), 1.93—3.77 (m, 7 H, Pro), 3.85 (q, 1 H, α-H Ala), 6.50—8.07 (m, 14 H, Ar), and 3.50 and 4.38 (AB, 2 H, CH_2Ph, *J* 12.5 Hz).

Synthesis of Compounds (**3a**) *and* (**3b**).—$Ni(NO_3)_2{\cdot}6H_2O$ (3.05 g, 12 mmol) followed by 1M MeONa in MeOH (20 ml) was added with stirring to a solution of compound (**1**) (3.08 g, 10 mmol) in MeOH (160 ml) under argon. Stirring was continued for 15 min and then a solution of (*R,S*)-alanine (4.46 g, 50 mmol) in 1M MeONa (60 ml) was added. Stirring was continued for 2 h at 40 °C under argon. The disappearance of the starting material (**1**) was monitored by t.l.c. On completion of the reaction [< 10% of starting material (**1**) remained in the solution], water (150 ml) and $CHCl_3$ (20 ml) were added to the mixture and the aqueous layer was extracted with $CHCl_3$ (3 × 50 ml). The extracts were combined and evaporated under reduced pressure to give a mixture of (**3a**) and (**3b**) (3.92 g, 90%). The diastereoisomers were separated on SiO_2 (300 g)/$CHCl_3$–Me_2O (5:1) as orange bands of equal intensity, (**3a**) being eluted first. Each diastereoisomer was additionally purified on a LH-

20 column using PhH–EtOH (3:1) and dried over P_2O_5 *in vacuo*: (**3a**) (2.47 g, 57%), m.p. 203—210 °C (Found: C, 60.6; H, 5.35; N, 9.65. $C_{22}H_{23}N_3NiO_3$ requires C, 60.6; H, 5.3; N, 9.65%); $\lambda_{max.}$(MeOH) 521 (log ε 2.17), 411 (3.51), 329 (3.69), and 261 (4.09); δ($CDCl_3$) 1.66 (d, 3 H, Me, *J* 7.5 Hz), 2.11—3.65 (m, 7 H, Pro), 3.98 (q, 1 H, α-H Ala, *J* 7.5 Hz), 6.91—8.64 (m, 9 H, Ar), 7.50 (s, 1 H, HC=N), and 3.51 and 4.43 (AB, 2 H, CH_2Ph, *J* 12.5 Hz); (**3b**) (1.43 g, 33%), m.p. 181—187 °C (Found: C, 60.25; H, 5.4; N, 9.6. $C_{22}H_{23}N_3NiO_3$ requires C, 60.59; H, 5.31; N, 9.63%); $\lambda_{max.}$(MeOH) 520 (log ε 2.03), 409 (3.39), 333 (3.67), and 264 (4.12); δ($CDCl_3$) 1.58 (d, 3 H, CH_3, *J* 7.5 Hz), 1.90—3.76 (m, 7 H, Pro), 4.11 (q, 1 H, α-H Ala), 6.88—8.58 (m, 9 H, Ar), 7.57 (s, 1 H, HC=N), and 3.50 and 4.23 (AB, 2 H, CH_2Ph, *J* 12.5 Hz).

Generation of Compound (**7**) *and Substitution of Deuterium for Hydrogen in the Alanine Fragment of Compounds* (**3a**) *and* (**3b**).—BuLi (0.44M solution in hexane; 0.1 mmol, 0.25 ml) was added to (**3a**) or (**3b**) (0.044 g, 0.11 mmol) in THF (3 ml) at −75 °C under argon, with stirring. The solution immediately turned deep red indicating the formation of the carbanion (**7**). After 15 min the mixture was added to a soluton of $^2H_2SO_4$ (0.015 g, 0.15 mmol) in ^2H_2O (1 ml). The solution was extracted several times with $CHCl_3$ and the combined extracts were evaporated to provide a residue which was purified on Sephadex LH-20 using PhH–EtOH (2:1) as eluant. The ^1H n.m.r. spectrum of the mixture of deuteriated diastereoisomers so obtained (90%) contained no signals assignable for the α-protons of the Ala fragments whilst the doublets of their Me groups had collapsed to singlets. Integration of the appropriate signals of the mixture gave the same diastereoisomer ratio as did quantitative t.l.c. analysis.

Isolation of Amino Acids from the Complexes and Recovery of Compounds (**1**) *and* (**2**). The complexes were decomposed, the amino acids obtained, and compounds (**1**) and (**2**) recovered, according to the general method outlined in the literature.[9,12] The optical purity of the amino acids was determined by g.l.c.[9,12] or polarimetry [12a] (for tryptophan and 3,4-dimethoxyphenylalanine), or ^1H n.m.r. using water-soluble europium(III)-(*R*)-propylenediaminetetra-acetate.[16]

Asymmetric Synthesis of (S)-*Alanine*, (S)-*Phenylalanine*, (S)-*Valine*, (S)-*Tryptophan*, 3,4-*Dimethoxyphenylalanine*, *and* (S)-2-*Aminohexanoic Acid*.—Four methods were used to alkylate compound (**5**) with alkyl halides. For the alanine synthesis a 1:1 ratio of MeI to (**5**) was used throughout.

Method A. BuLi (1.1 mmol in hexane) was added to compound (**5**) (0.5 g, 1 mmol) in THF (30 ml) at −70 °C under argon, with stirring. After 15 min, a THF solution (5 ml) of the alkyl halide (1.5 mmol) was added dropwise, and during 1 h the temperature was allowed to rise to 20 °C. Quenching with dilute HCl and extraction with $CHCl_3$ followed by evaporation of the solvent gave a mixture of the diastereoisomeric complexes.

Method B. A solution of compound (**5**) (0.5 g, 1 mmol), and the alkyl halide (3 mmol) in CH_2Cl_2 (15 ml) was stirred under argon with 10% aqueous NaOH (1 ml) to which tetrabutylammonium iodide (0.4 g, 1.1 mmol) had been added. Stirring was continued for 5—7 h at 20—25 °C until compound (**5**) had been consumed [as monitored by t.l.c. (SiO_2, $CHCl_3$–Me_2CO, 5:1)]. Quenching with dilute HCl, extraction with $CHCl_3$, and work-up of the extract gave a mixture of diastereoisomers.

Method C. Alkyl halide (20 mmol) was added to compound (**5**) (10 g, 20 mmol) in DMF (15 ml) followed by addition of finely ground NaOH (2 g, 50 mmol) with vigorous stirring under argon. Stirring was continued for 15—30 min after which the reaction mixture was added slowly, with stirring, to a solution of AcOH (0.1 mol) in water (200 ml). 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 $CHCl_3$ extraction followed by evaporation of the solvent).

Method D. Alkyl halide (1.5 mmol) was added to compound (**5**) (0.5 g, 1 mmol) dissolved in carefully purified MeCN (20 ml) followed by addition of finely ground NaOH (0.1 g, 2.5 mmol) with vigorous stirring under argon. Stirring was continued for 2—3 h at 20—25 °C until compound (**5**) was consumed (as monitored by t.l.c.). Quenching with dilute HCl, extraction with $CHCl_3$, followed by work-up of the extract gave the mixture of diastereoisomers.

The diastereoisomers obtained according to methods A, B, C, and D were decomposed, as described above. The chemical and optical yields of the α-amino acids prepared are presented in Table 2. Compound (**2**) was recovered (yield 70—92%).

Synthesis of Optically Pure (S)-*Phenylalanine*.—The mixture of diastereoisomeric complexes obtained after alkylation of compound (**5**) with benzyl bromide was chromatographed on SiO_2 ($CHCl_3$–Me_2CO 5:1) using 100 g of SiO_2 for 1 g of the distereoisomeric mixture. The first, minor, fraction (7%) contained the diastereoisomeric complex of (*R*)-phenylalanine, m.p. 197—202 °C (Found: C, 69.65; H, 5.6; N, 7.5. $C_{34}H_{31}N_3NiO_3$ requires C, 69.41; H, 5.31; N, 7.13%); $\lambda_{max.}$(MeOH) 263 (log ε 4.37), 335 (3.91), 419 (3.54), and 533 (2.21); δ($CDCl_3$) 1.85—3.85 (m, 7 H, Pro), 2.83 and 2.97 (ABX, 2 H, CH_2Phe, J_{AB} 14 Hz, J_{AX} 6.2 Hz, J_{BX} 5.8 Hz), 3.40 and 3.68 (AB, 2 H, CH_2Ph, *J* 12.5 Hz), 4.15 (m, 1 H, α-H Phe), and 6.65—8.40 (m, 19 H, Ar).

The second, major fraction (93 %) contained the diastereoisomeric complex of (*S*)-phenylalanine, m.p. 241—246 °C (Found: C, 69.6; H, 5.45; N, 7.55. $C_{34}H_{31}N_3NiO_3$ requires C, 69.41; H, 5.31; N, 7.13%); $\lambda_{max.}$(MeOH) 265 (log ε 4.32), 338 (3.73), 420 (3.54), and 538 (2.48); δ($CDCl_3$) 1.82—3.85 (m, 7 H, Pro), 2.82 and 3.07 (ABX, 2 H, CH_2Phe, J_{AB} 14 Hz, J_{AX} 6.0 Hz, J_{BX} 6.2 Hz), 3.43 and 4.25 (AB, 2 H, CH_2Ph, *J* 12.5 Hz), 4.25 (m, 1 H, α-H, Phe), and 6.63—8.20 (m, 19 H, Ar). (*S*)-Phenylalanine was obtained and compound (**2**) recovered from the complex, as described above.

Synthesis of α-Aminoisobutyric Acid.—This compound could be obtained from compound (**3**) or (**6**) by alkylation with MeI. In the case of (**6**), 2 equiv. of MeI were required to bring the reaction to completion. Methods A, B, C, and D could be successfully employed. Compound (**8**) (yield 90%) was purified by chromatography on SiO_2 ($CHCl_3$–Me_2CO, 1:1) and, additionally, on Sephadex LH-20. (**8**), m.p. 203—209 °C (Found: C, 61.25; H, 5.51; N, 9.3. $C_{23}H_{25}N_3NiO_3$ requires C, 61.36; H, 5.59; N, 9.33%); $\lambda_{max.}$(MeOH) 519 (log ε 2.17), 409 (3.57), 329 (3.75), and 264 (4.25); δ($CDCl_3$) 1.52 (s, 3 H, CH_3), 1.56 (s, 3 H, CH_3), 1.95—3.75 (m, 7 H, Pro), 6.74—8.28 (m, 9 H, Ar), 7.58 (s, 1 H, HC=N), and 3.48 and 4.52 (AB, 2 H, CH_2Bzl, *J* 12 Hz).

α-Aminoisobutyric acid was obtained from compound (**8**), as described above; δ(D_2O) 1.51 (s, 2 Me).

Synthesis of α-Methyl-α-amino Acids.—These compounds were prepared from compound (**3**) (A, B, and C methods) and compound (**4**) (A and C methods). In both cases an excess (1.5—5 equiv.) of alkyl halide was used in the reaction.

(*S*)- and (*R*)-α-Allyl-α-alanine was derived from compound (**3**). The diastereoisomeric complexes (**9a**) and (**9b**) were separated on a SiO_2 (100 g of the adsorbent for 1 g of the mixture) column ($CHCl_3$–Me_2CO, 5:1) and each was additionally purified on Sephadex LH-20. Compound (**9a**) (the first, major band), m.p. 212—217 °C (Found: C, 63.25; H, 5.75; N, 8.6. $C_{25}H_{27}N_3NiO_3$ requires C, 63.05; H, 5.71; N, 8.82%); $\lambda_{max.}$(MeOH) 524 (log ε 2.44), 412 (3.53), 331 (3.74), and 263 nm (4.29); δ($CDCl_3$) 1.47 (s, 3 H, Me), 2.01—3.57 (m, 7 H, Pro), 2.32 and 2.69 (ABX, 2 H, CH_2CH=, J_{AX} 7 Hz, J_{BX} 8 Hz, J_{AB} 13.7 Hz), 5.12 and 5.28 (m, 2 H, CH_2=, J_{trans} 17 Hz, J_{cis} 9 Hz, J_{gem} 1 Hz),

6.04 (ABXKL, 1 H, CH=, J_{KX} 17 Hz, J_{LX} 9 Hz, J_{AX} 7 Hz, J_{BX} 8 Hz), 4.38 and 4.54 (AB, 2 H, CH_2Ph, J 12.5 Hz), 6.8—8.5 (m, 9 H, Ar), and 7.46 (s, 1 H, HC=N). Compound (**9b**) (the second, minor band), m.p. 201—207 °C (Found: C, 63.4; H, 5.8; N, 8.95. $C_{25}H_{27}N_3NiO_3$ requires C, 63.05; H, 5.71; N, 8.82%); $\lambda_{max.}$(MeOH) 522 (log ε 2.20), 411 (3.54), 330 (3.69), and 261 (4.21); δ($CDCl_3$) 1.52 (s, 3 H, Me), 1.90—3.75 (m, 7 H, Pro), 2.44 and 2.74 (ABX, 2 H, CH_2CH=, J_{AX} 6.5 Hz, J_{BX} 8 Hz; J_{AB} 14.5 Hz), 5.05 and 5.25 (m, 2 H, CH_2=, J_{trans} 17.5 Hz; J_{cis} 10 Hz, J_{gem} 1 Hz), 5.80 (ABXKL, 1 H, CH=, J_{KX} 17.5 Hz, J_{LX} 10 Hz, J_{AX} 6.5 Hz, J_{BX} 8 Hz), 3.42 and 4.35 (AB, 2 H, CH_2Ph, J 12.5 Hz), 6.81—8.42 (m, 9 H, Ar), and 7.45 (s, 1 H, CH=N).

(*S*)-α-Allyl-α-alanine was obtained from compound (**9a**), as described above, and recrystallized from EtOH; it had m.p. 308 °C (Found: C, 55.45; H, 8.65; N, 10.6. $C_6H_{11}NO_2$ requires C, 55.80; H, 8.59; N, 10.84%); δ(D_2O) 1.60 (s, 3 H, Me), 2.73 (m, 2 H, CH_2), 5.33 (m, 2 H, CH_2=), and 5.76 (m, 1 H, CH=); α (589 nm, 25 °C, 13 g dm^{-3} in 1M HCl, *l* 10 cm) −14.4°, α (589 nm, 25 °C, 13 g dm^{-3}, H_2O, *l* 10 cm) −28.5°; (*R*)-α-Allyl-α-alanine was obtained from compound (**9b**), α (589 nm, 25 °C, 9.6 g dm^{-3}, 1M HCl, *l* 10 cm) +14.2°.

(S)- *and* (R)-α-*Allyl-α-alanine Derived from Compound* (**4**).—The diasteroisomeric complexes (**11a**) and (**11b**) obtained from compound (**4**) using Method C were separated on SiO_2 $CHCl_3$–Me_2CO, 5:1) using 100 g of the adsorbent for 1 g of the mixture, and each was additionally purified on LH-20 (PhH–EtOH, 2:1). Compound (**11a**) (the first, major fraction, 92%), m.p. 218—223 °C (Found: C, 67.0; H, 5.6; N, 7.55. $C_{31}H_{31}N_3NiO_3$ requires C, 67.40; H, 5.65; N, 7.60%); $\lambda_{max.}$(MeOH) 264 (log ε 4.21), 332 (3.74), 418 (3.48), and 531 nm (2.27); δ($CDCl_3$) 1.13 (s, 3 H, Me), 1.87—3.51 [m, 7 H, Pro], 2.43 (d, 2 H, CH_2, J 7 Hz), 3.65 and 4.43 (AB, 2 H, CH_2Ph, J 12.5 Hz), 5.38 (m, 2 H, CH_2=, J_{trans} 14 Hz, J_{cis} 9 Hz, J_{gem} 1 Hz), 6.63 (m, 1 H, CH=), and 6.43—8.19 (m, 14 H, Ar). Compound (**11b**) (the second, minor fraction, 8%) had m.p. 189—196 °C (Found: C, 67.25; H, 5.45; N, 7.85. $C_{31}H_{31}N_3NiO_3$ requires C, 67.40; H, 5.65; N, 7.60%); $\lambda_{max.}$(MeOH) 262 (log ε 4.40), 330 (3.60), 417 (3.41), and 5.21 nm (2.12); δ($CDCl_3$) 1.47 (s, 3 H, CH_3), 1.93—3.76 (m, 7 H, Pro), 2.18 and 2.43 (ABX, 2 H, CH_2, J_{AB} 14.5 Hz, J_{AX} 7 Hz, J_{BX} 6 Hz), 3.47 and 4.38 (AB, 2 H, CH_2Ph, J 12.5 Hz), 5.21 (m, 2 H, CH_2=, J_{trans} 16 Hz, J_{cis} 11 Hz, J_{gem} 1 Hz), 5.75 (m, 1 H, HC=), and 6.45—8.17 (m, 14 H, Ar); (*S*)-α-Allyl-α-alanine and (*R*)-α-allyl-α-alanine were obtained from compounds (**11a**) and (**11b**), respectively, as described above.

(S)- *and* (R)-α-*Benzyl-α-alanine Derived from Compound* (**3**).—The diastereoisomeric complexes (**10a**) and (**10b**) were separated on a SiO_2 column (50 g of the adsorbent for 1 g of the mixture $CHCl_3$–Me_2CO, 5:1) and each was additionally purified on Sephadex LH-20. Compound (**10a**) (the first, major band), m.p. 199—204 °C (Found: C, 66.3; H, 5.5; N, 7.65. $C_{28}H_{27}N_3NiO_3$ requires C, 66.19; H, 5.56; N, 7.98%); $\lambda_{max.}$(MeOH) 521 (log ε 2.24), 411 (3.51), 329 (3.69), and 264 nm (4.21); δ($CDCl_3$) 1.54 (s, 3 H, CH_3), 1.86—3.63 (m, 7 H, Pro), 2.75 and 3.20 (AB, 2 H, CH_2Ph, J 12 Hz), 3.38 and 4.18 (AB, 2 H, CH_2Ph, J 12 Hz), 6.82—8.50 (m, 14 H, Ar), and 7.50 (s, 1 H, HC=N).

Compound (**10b**) (the second, minor band), m.p. 187—188 °C (Found: C, 66.3; H, 5.7; N, 8.0. $C_{28}H_{27}N_3O_3Ni$ requires C, 66.19; H, 5.56; N, 7.98%); $\lambda_{max.}$(MeOH) 519 (log ε 2.21), 413 (3.47), 332 (3.69), and 261 nm (4.27); δ($CDCl_3$) 1.58 (s, 3 H, Me), 1.88—3.68 (m, 7 H, Pro), 2.93 and 3.33 (AB, 2 H, CH_2Ph, J 12 Hz), 3.18 and 4.20 (AB, 2 H, CH_2Ph, J 12 Hz), 6.38—8.33 (m, 14 H, Ar), and 7.35 (s, 1 H, HC=N). (*S*)-α-Benzyl-α-alanine was obtained from (**10a**), as described above, m.p. 298—299 °C (Found: C, 66.2; H, 6.95; N, 7.7. $C_{10}H_{13}NO_2$ requires C, 67.02; H, 7.31; N, 7.81%); δ (0.1M DCl in D_2O) 1.65 (s, 3 H, CH_3), 3.03 and 3.49 (AB, 2 H, CH_2, J 14 Hz), and 7.47 (m, 5 H, Ar); α (589 nm, 25 °C, 10.4 g dm^{-3}, 1M HCl, *l* 10 cm) −4.5° [lit.,[19] α (589, 20 °C, 1M HCl) −4.7°]. (*R*)-α-Benzyl-α-alanine obtained from (**10b**) had the same elemental analysis and the ^{1}H n.m.r. spectrum as the *S*-enantiomer, α (589 nm, 25 °C, 5 g dm^{-3}, 1M HCl, *l* 10 cm) +4.2°.

(S)- *and* (R)-α-*Benzyl-α-alanine from Compound* (**4**).—Diasteroisomeric complexes (**12a**) and (**12b**) obtained from compound (**4**) using Method C were separated on SiO_2 (50 g of the adsorbent for 1 g of the mixture $CHCl_3$–Me_2CO, 5:1) and each was additionally purified on LH-20 (PhH–EtOH, 2:1). Compound (**12a**) (the first, major, fraction, 93%), m.p. 120—124 °C (Found: C, 69.65; H, 5.35; N, 7.1. $C_{35}H_{33}N_3NiO_3$ requires C, 69.78; H, 5.52; N, 6.96%); $\lambda_{max.}$(MeOH) 262 (log ε 4.23), 335 (3.68), 421 (3.49), and 524 nm (2.37); δ($CDCl_3$) 1.11 (s, 3 H, Me), 1.65—3.20 (m, 7 H, Pro), 3.13 (m, 2 H, CH_2), 3.48 and 4.25 (AB, 2 H, CH_2Bzl, J 12.5 Hz), and 6.50—8.13 (m, 19 H, Ar).

Compound (**12b**) (the second, minor fraction, 7%), m.p. 107—113 °C (Found: C, 69.45; H, 5.65; N, 7.25. $C_{35}H_{33}N_3NiO_3$ requires C, 69.78; H, 5.52; N, 6.96%); $\lambda_{max.}$(MeOH) 263 (log ε 4.14), 331 (3.65), 419 (3.45), and 521 nm (2.18); δ($CDCl_3$) 1.51 (s, 3 H, Me), 1.93—3.70 (m, 7 H, Pro), 2.82 and 3.08 (AB, 2 H, CH_2Ph, J 14.5 Hz), 3.35 and 4.18 (AB, 2 H, CH_2Ph, J 12.5 Hz), and 6.58—7.90 (m, 19 H, Ar).

(*S*)-α-Benzyl-α-alanine and (*R*)-α-benzyl-α-alanine were obtained from compounds (**12a**) and (**12b**), respectively, as described above.

(S)- *and* (R)-O-*Benzyl-α-methyltyrosine from Compound* (**4**).—The diastereoisomeric complexes (**13a**) and (**13b**) obtained from compound (**4**) using Method C were separated on SiO_2 ($CHCl_3$–Me_2CO, 5:1) using 30 g of the adsorbent for 1 g of the diastereoisomeric mixture and each was additionally purified on LH-20 (PhH–EtOH, 2:1). Compound (**13a**) (the first, major fraction, 91%), m.p. 99—104 °C (Found: C, 71.0; H, 5.35; N, 5.9. $C_{42}H_{39}N_3NiO_4$ requires C, 71.20; H, 5.54; N, 5.92%); $\lambda_{max.}$(MeOH) 267 (log ε 4.10), 337 (3.60), 421 (3.40), and 523 nm (2.35); δ($CDCl_3$) 1.15 (s, 3 H, Me), 1.72—3.33 (m, 7 H, Pro), 3.12 (s, 2 H, CH_2 Tyr), 3.55 and 4.31 (AB, 2 H, CH_2Ph, J 12.5 Hz), 5.08 (s, 2 H, CH_2O), and 6.85—8.13 (m, 23 H, Ar).

Compound (**13b**) (the second, minor fraction, 9%), m.p. 124—130 °C (Found: C, 70.95; H, 5.25; N, 6.05. $C_{42}H_{39}N_3NiO_4$ requires C, 71.20; H, 5.54; N, 5.92%); $\lambda_{max.}$(MeOH) 263 (log ε 4.08), 339 (3.66), 418 (3.46), and 519 nm (2.16); δ($CDCl_3$) 1.45 (s, 3 H, Me), 1.78—3.75 (m, 7 H, Pro), 2.75 and 3.01 (AB, 2 H, CH_2 Tyr, J 16 Hz), 3.40 and 4.15 (AB, 2 H, CH_2Ph, J 12.5 Hz), 4.90 and 5.00 (AB, 2 H, CH_2O, J 12.5 Hz), and 6.60—7.89 (m, 23 H, Ar).

(S)- *and* (R)-O-*Benzyl-α-methyltyrosine*.—These were obtained from compounds (**13a**) and (**13b**), respectively, as described below.

2M Aqueous HCl (150 ml) was added to a solution of the diastereoisomer (20 g, 28 mmol) in MeOH (110 ml) and the mixture was stirred and refluxed until the red colour had disappeared (10—40 min). The solution was then evaporated almost to dryness under reduced pressure when water (50 ml) and a 10% solution of NH_3 in water (100 ml) were added with stirring to the residue; $CHCl_3$ (30 ml) was then added to the thick slurry, with vigorous agitation. The mixture was then filtered and the precipitate washed with $CHCl_3$. The $CHCl_3$ layer and washings were combined and evaporated to give recovery of compound (**2**). The precipitate was transferred to a flask containing EDTA (0.5 g) in 5% aqueous NH_3 solution (150 ml). The suspension was stirred under reflux for 30 min after which the amino acid was filtered off and recrystallized

from EtOH–water (2:1) to give *O*-benzyl-α-methyltyrosine (5.5 g, 73%). (*S*)-*O*-Benzyl-α-methyltyrosine, m.p. 270—272 °C, α [589 nm, 17 °C, 21 g dm^{-3} in CF_3CO_2H–H_2O (3:2), *l* 10 cm] −3.39° (Found: C, 71.8; H, 6.9; N, 4.9. $C_{17}H_{19}NO_3$ requires C, 71.56; H, 6.71; N, 4.91%); δ(CF_3CO_2H) 1.46 (s, 3 H, Me), 2.85 and 3.13 (AB, 2 H, CH_2, *J* 14 Hz), 4.73 (s, 2 H CH_2O), and 6.45—6.96 (m, 9 H, Ar).

(*R*)-*O*-Benzyl-α-methyltyrosine, m.p. 272—274 °C, α [589 nm, 17 °C, 17 g dm^{-3} in CF_3CO_2H–H_2O (3:2), *l* 10 cm] +3.36°. The ^1H n.m.r. spectrum of the *R*-enantiomer is indistinguishable from that of the *S*-isomer.

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Received 27*th May* 1986; *Paper* 6/1027