Synthesis of Enantio- and Diastereoiso-merically Pure Substituted Prolines *via* Condensation of Glycine with Olefins Activated by a Carbonyl Group

Yuri N. Belokon',* Aleksandr G. Bulychev, Viacheslav A. Pavlov, Eugenia B. Fedorova, Vladimir A. Tsyryapkin, Vladimir A. Bakhmutov, and Vasili M. Belikov
Nesmeyanov Institute of Organoelement Compounds, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R.

The glycine fragment in the nickel(II) complex (**1**) formed from the Schiff's base of glycine and (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone (**2**) undergoes base-catalysed Michael addition to acrylaldehyde, α-methylacrylaldehyde, (*E*)-crotonaldehyde, (*E*)-cinnamaldehyde, and methyl vinyl ketone. No products of 1,2-addition were found in the Et_3N-catalysed reactions. Addition followed by epimerization of the isomeric complexes proceeds with high diastereoselectivity at C_α (90%) and C_β of the corresponding amino acid side chains. After chromatographic separation, the diastereoisomerically pure complexes were decomposed and the resulting dihydropyrrole-2-carboxylic acids reduced with $NaBH_3CN$ to give (*S*)-proline, *trans*-3-methyl-(*S*)-proline, *trans*-5-phenyl-(*S*)-proline, and a mixture of *cis*- and *trans*-5-methyl-(*S*)-prolines. The chiral auxiliary (**2**) was recovered in 80—90% yield.

Non-proteinogenic α-amino acids attract ever-increasing interest as drugs or components of many therapeutic agents.[1] The specific activity is generally related to one stereoisomer or an enantiomer of a particular α-amino acid. Since the usual methods of enzymic synthesis are inapplicable to the preparation of optically pure uncommon α-amino acids, asymmetric chemical methods are required to solve the problem. This is the underlying reason for the recent progress in the field of asymmetric synthesis of uncommon α-amino acids.[2-5]

Among the uncommon α-amino acids, *C*-substituted prolines are unique because of their propensity, when incorporated into proteins, to induce strong conformational bias. Despite recent progress in stereoselective synthesis of *C*-substituted prolines,[6] versatile, convenient and general methods for their enantio- and diastereo-selective synthesis are not yet available.

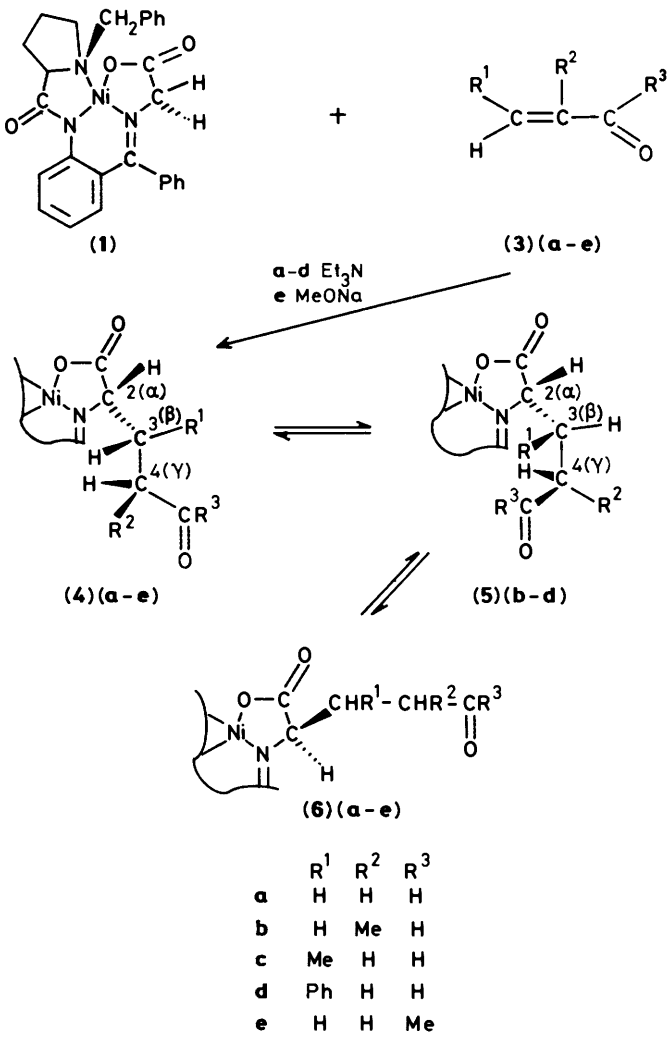
We set ourselves the task of developing such a method by elaboration of the Michael addition of a Ni^{II} complex (**1**) of the Schiff's base derived from (*S*)-*o*-[(*N*-benzylprolyl)-amino]benzophenone (**2**) and glycine to substituted acrylaldehydes.

Earlier we used the complex (**1**) to develop asymmetric general synthetic methods for β-hydroxy-α-amino acids,[5b] β- and γ-substituted glutamic acids,[5c] and α-methyl-α-amino acids.[5d,e] The general strategy and the connection of our work with the α-amino acid metal complexes are discussed in our previous paper.[5a,e]

Results

Synthesis of the Complex (**1**).—The complex (**1**) was obtained *via* condensation of (*S*)-*o*-[(*N*-benzylprolyl)amino]benzophenone with glycine in the presence of $Ni(NO_3)_2$ in methanol, as described earlier.[5b]

General Procedure for the Condensation of the Complex (**1**) *with Substituted Acrylaldehydes* (**3a—d**) *and Methyl Vinyl Ketone* (**3e**).—The complex (**1**) underwent addition to substituted acrylaldehydes and methyl vinyl ketone in methanol in the presence of Et_3N (MeONa in the case of methyl vinyl ketone) at 60 °C. Initially a complicated kinetically controlled mixture of products was formed. Under the experimental conditions the ratio of isomeric complexes changed (12—72 h) until equilibrium was reached, when only 1,4-addition products were detectable. The reaction sequence is outlined in Scheme 1.



	R^1	R^2	R^3
a	H	H	H
b	H	Me	H
c	Me	H	H
d	Ph	H	H
e	H	H	Me

Scheme 1.

Diastereoisomers were easily separated chromatographically on SiO_2 with the α*R*-isomers eluted first. As expected, they have the same set of proton signals, differing only in chemical shifts, and similar u.v.–visible and i.r. spectra. Their o.r.d. curves

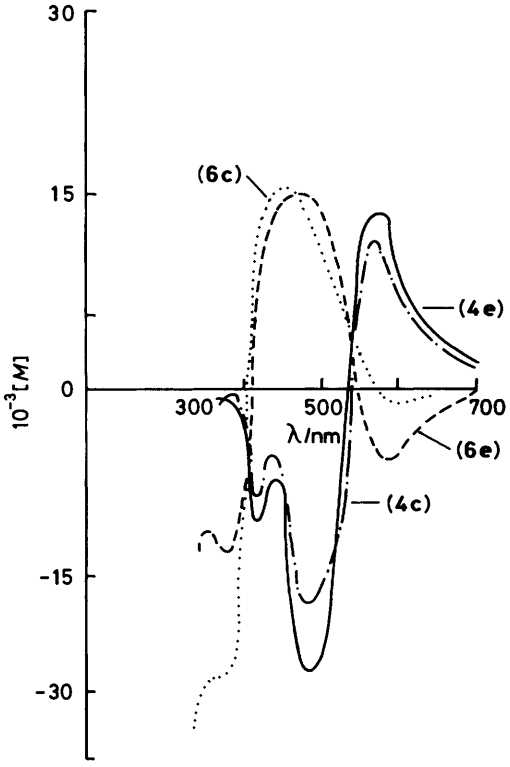


Figure 1. O.r.d. curves at 25 °C (MeOH)

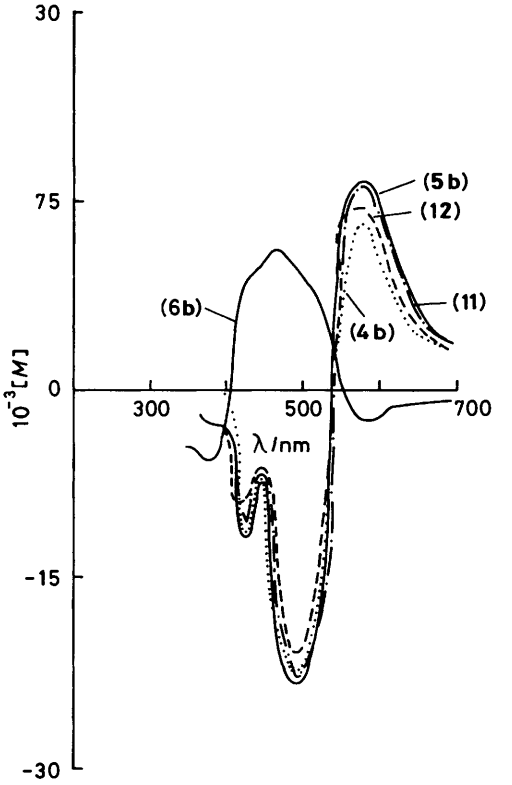


Figure 2. O.r.d. curves at 25 °C (MeOH); (**6b**) is a mixture of diastereoisomers

(Figures 1—3) could be used to assign the absolute configurations of the α-carbon atoms of the amino acid side chains, as discussed earlier;[5c] Cotton effects in the 400—500 nm regions were positive for α*R*- and negative for α*S*-forms. The

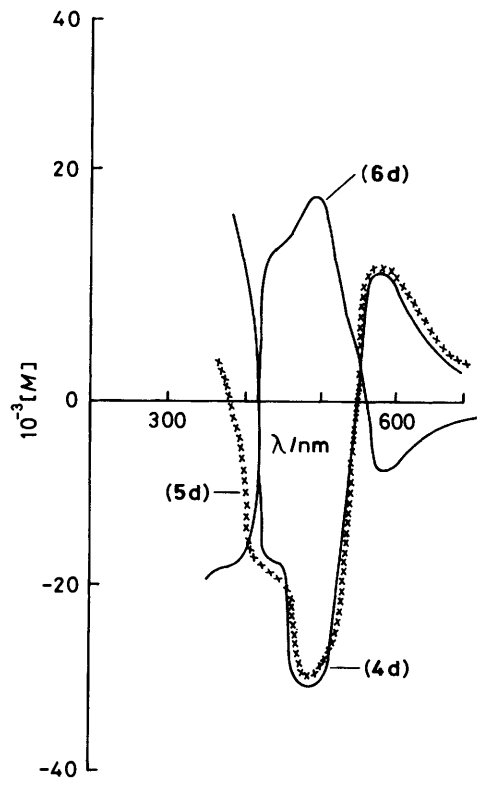


Figure 3. O.r.d. curves at 25 °C (MeOH)

equilibrium ratio α*S*:α*R* was greater than 95:5 for all the olefins studied. The configurations of the β- and γ-carbon atoms of the side chains in the case of diastereoisomeric complexes formed *via* condensation of (**1**) with (**3b—d**) were established by ^{1}H n.m.r.

Acid hydrolysis of the pure isomers liberated the initial benzophenones (**2**) in chemical yields of 80—90% and the intermediate (2*S*)-dihydropyrrole carboxylic acids. The latter, without isolation, were reduced with $NaBH_3CN$ in H_2O to the substituted prolines (60—90% yield) (Method A, Scheme 2). The structures of the α-amino acids were established by their ^{1}H n.m.r. and mass spectra. Enantiomeric purity was determined chiroptically or by chiral h.p.l.c. A detailed description of the condensation procedure for every olefin (**3**) is given separately.

Condensation with Acrylaldehyde; Synthesis of (R)- *and* (S)-*Prolines.*—The complex (**1**) underwent addition to (**3a**) according to Scheme 1 in 95% chemical yield. The ratios of the diastereoisomeric products of 1,4-addition are presented in the Table. Treatment of the diastereoisomers as outlined in Scheme 2 furnished (*R*)-Pro [from (**6a**)] and (*S*)-Pro [from (**4a**)] with enantiomeric excess (e.e.) >98%.

Addition catalysed by MeONa in MeOH at 25 °C produced a mixture of compounds, as shown in Scheme 3. Flash chromatography of the mixture produced, as well as the usual 1,4-addition products, compounds (**8**) and (**9**). The former was probably a product of the aldol condensation of (**1**) with (**4a**) and (**6a**); the latter (**9**) originated from the aldol condensation of (**1**) with the 1,4-addition product of MeOH and acrylaldehyde.

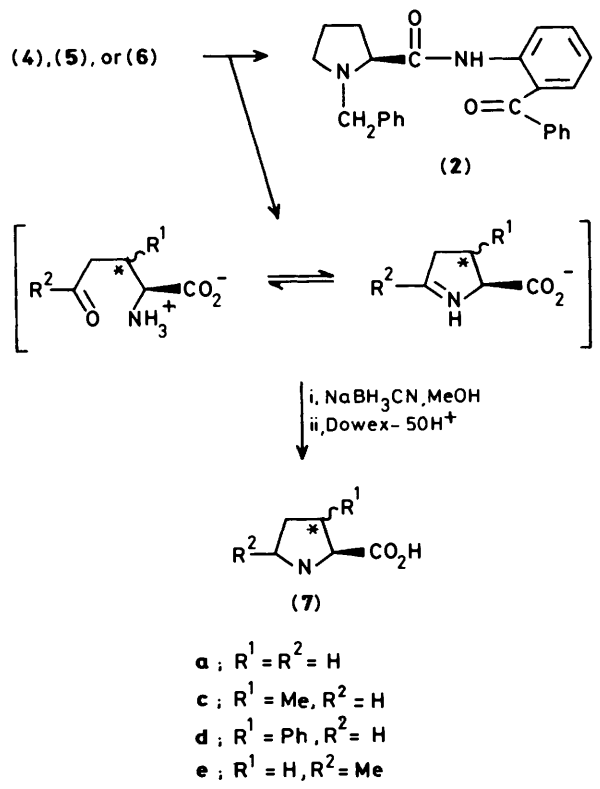
Condensation of (**1**) with (**3a**) catalysed by concentrated MeONa in MeOH at −78 °C gave, besides (**8**) and (**9**), an 18% yield of the product (**10**) of 1,2-addition of (**1**) to acrylaldehyde.

Condensation with (E)-*Crotonaldehyde* (**3c**); *Synthesis of* trans-3-*Methyl*-(S)-*proline.*—The complex (**1**) underwent

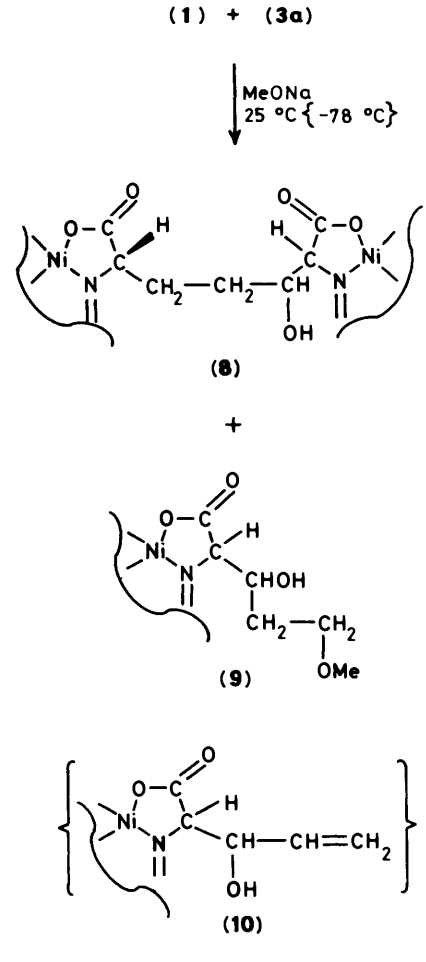
Table. Michael addition of the complex (**1**) to substituted acrylaldehydes and methyl vinyl ketone (Scheme 1)[a]

Olefin	Yield (%) of (**4**) + (**5**) + (**6**)	Yields (%) of individual diastereoisomeric complexes	Amino acids: Designation	Optical purity (% e.e.)	Chemical yield (%)[b]	Method
CH_2=CHCHO (**3a**)	73	(**4a**) 68.5 (58.4)[c]	(*S*)-Proline	>95	73	A
		(**6a**) 4.3 (14.6)[c]	(*R*)-Proline	>95	73	A
CH_2=CMeCHO (**3b**)	98	(**4b**) 29	*trans*-4-Methyl-(*S*)-proline	>95	70	B
		(**5b**) 61	*cis*-4-Methyl-(*S*)-proline	>95	74	B
		(**6b**) 8				
(*E*)-CH_3CH=CHCHO (**3c**)	96	(**4c**) 91.3	*trans*-3-Methyl-(*S*)-proline	>95	70	A
		(**6c**) 4.6	*trans*-3-Methyl-(*R*)-proline	>95	72	A
(*E*)-PhCH=CHCHO (**3d**)	100	(**4d**) 82 (73)[c]	*trans*-3-Phenyl-(*S*)-proline	>95	75	A
		(**5d**) 10 (10.7)[c]	*cis*-3-Phenyl-(*S*)-proline	>95	71	A
		(**6d**) 8 (16)[c]	*trans*-3-Phenyl-(*R*)-proline	>95	69	A
CH_2=CHC(O)Me (**3e**)	100	(**4e**) 96 (86)[c]	1:1 *cis*- and *trans*-5-methyl-(*S*)-proline	>95[c]	69	A
		(**6e**) 4 (14)[c]				

[a] Reaction conditions: MeOH solution, Et_3N [MeONa in the case of (**3e**)], 60 °C, under argon, ratio of olefin to (**1**) 1:1 to 1:4, 12—72 h. [b] Based on the initial pure diastereoisomer. [c] Kinetically controlled ratio of diastereoisomers (Et_3N as catalyst).



Scheme 2.



Scheme 3.

addition to (**3c**) in methanol in the presence of Et_3N. Isomers of types (**8**) and (**9**) were formed in the initial stages of the reaction, but after 72 h at 60 °C the mixture consisted mainly of two individual isomers (see Table). The absolute configurations of their side-chain α-carbon atoms were assigned from o.r.d. curves (Figure 1). The minor isomer (**6c**) (4.6%) was found to have the α*R*-configuration; the major isomer (91.4%) had the α*S*-configuration and could be designated either (**4c**) or (**5c**). Molecular models indicated that in the case of (**4c**) the most stable conformation of the side chain had its β-Me substituent under the Ni^{II} ion (see Figure 4). A similar conformation was observed earlier for analogously constructed complexes of (*S*)-Val.[7] The n.m.r. signal of the methyl protons of the major isomer (δ 2.07) testified to their strong deshielding, as observed in the case of other alkyl groups located above or under the Ni^{II} co-ordination plane.[7,8] Thus, the absolute configuration of the side chain could be assigned at (2*S*,3*S*), and the major isomer was (**4c**).

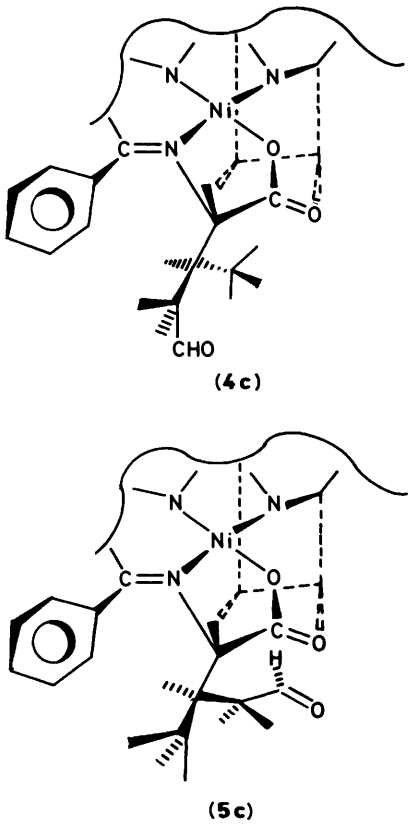


Figure 4. Conformations of the amino acid side chain in (**4c**) and (**5c**)

Treatment of (**4c**) as outlined in Scheme 2 gave initially benzophenone (**2**) and then pure (2*S*,3*S*)-isomer (**7c**) in 70% chemical yield and with more than 95% optical purity.

Condensation with (E)-*Cinnamaldehyde* (**3d**); *Synthesis of* trans- *and* cis-3-*Phenyl*-(S)-*prolines*.—The addition catalysed by Et_3N in MeOH at 60 °C for 72 h gave a mixture of three major diastereoisomeric complexes in yields of 8, 80, and 10% in the order of their emergence from a chromatographic column. The α-configuration could be assigned to the first isomer (**6d**), and the α*S*-configuration to the second and third from their o.r.d. curves (Figure 3). The configuration at C_β of the latter two isomers could be easily established by the n.m.r. method as for the analogous complexes of (2*S*,3*R*)- and (2*S*,3*S*)-3-phenylglutamic acids.[5c] According to this analysis, the side-chain amino acid configuration of the major isomers was 2*S*,3*R*, as in (**4d**), while that of the last eluted was 2*S*,3*S*, as in (**5d**). Treatment of the pure isomers as shown in Scheme 2 gave (2*S*,3*R*)-3-phenylproline [*trans*-3-phenyl-(*S*)-proline] and (2*S*,3*S*)-3-phenylproline [*cis*-3-phenyl-(*S*)-proline], from (**4d**) and (**5d**), respectively. Compound (**6d**) after the usual treatment gave a sample of 3-phenylproline with R_F value on cellulose and n.m.r. spectrum identical with those of (2*S*,3*R*)-3-phenylproline. Hence, the configuration of the initial amino acid side chain in (**6d**) was 2*R*,3*S* and thus the resulting proline had the 2*R*,3*S*-configuration.

Condensation of (**1**) with (**3d**) is reversible. Under the experimental conditions (**6d**) was converted into an equilibrium mixture of all three isomers (**6d**), (**5d**), and (**4d**), and the complex (**1**) and cinnamaldehyde (*E*:*Z* 19:1) were also detected.

Condensation with Methyl Vinyl Ketone (**3e**); *Synthesis of a mixture of* cis- *and* trans-5-*Methyl*-(S)-*proline*.—The addition of the complex (**1**) to (**3e**) (catalysed by Et_3N) occurred readily in MeOH within 2 h. The diastereoisomeric complexes were separated as before and the side-chain absolute configurations (Figure 1) were determined in the usual manner. The initial kinetically controlled ratio of diastereoisomers (**4e**):(**6e**) (Scheme 1) was estimated as 5:1, and no products of side reactions were obtained. Equilibration of the isomers could be effected by keeping the mixture intact for another 72 h, but the reaction occurred more readily if catalysed by MeONa in MeOH. In this case the equilibrium ratio [(**4e**):(**6e**)] of 25:1 was reached within 20 min. Treatment of (**4e**) according to Scheme 2 gave a mixture of *cis*- and *trans*-5-methyl-(*S*)-prolines in the ratio 1:1. The ratio increased to 10:1 if the intermediate dihydropyrrole-2-carboxylic acid was catalytically hydrogenated over Pd–C.[6b,9]

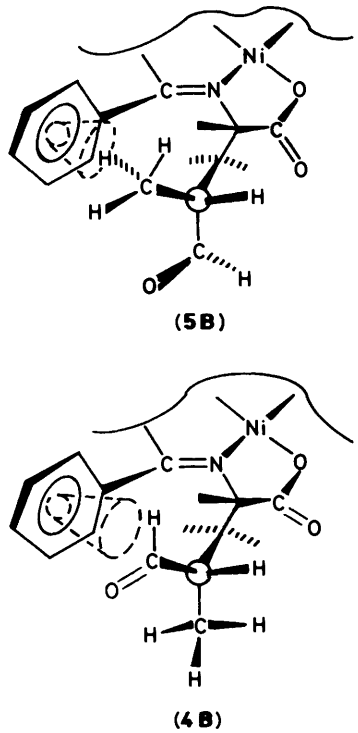
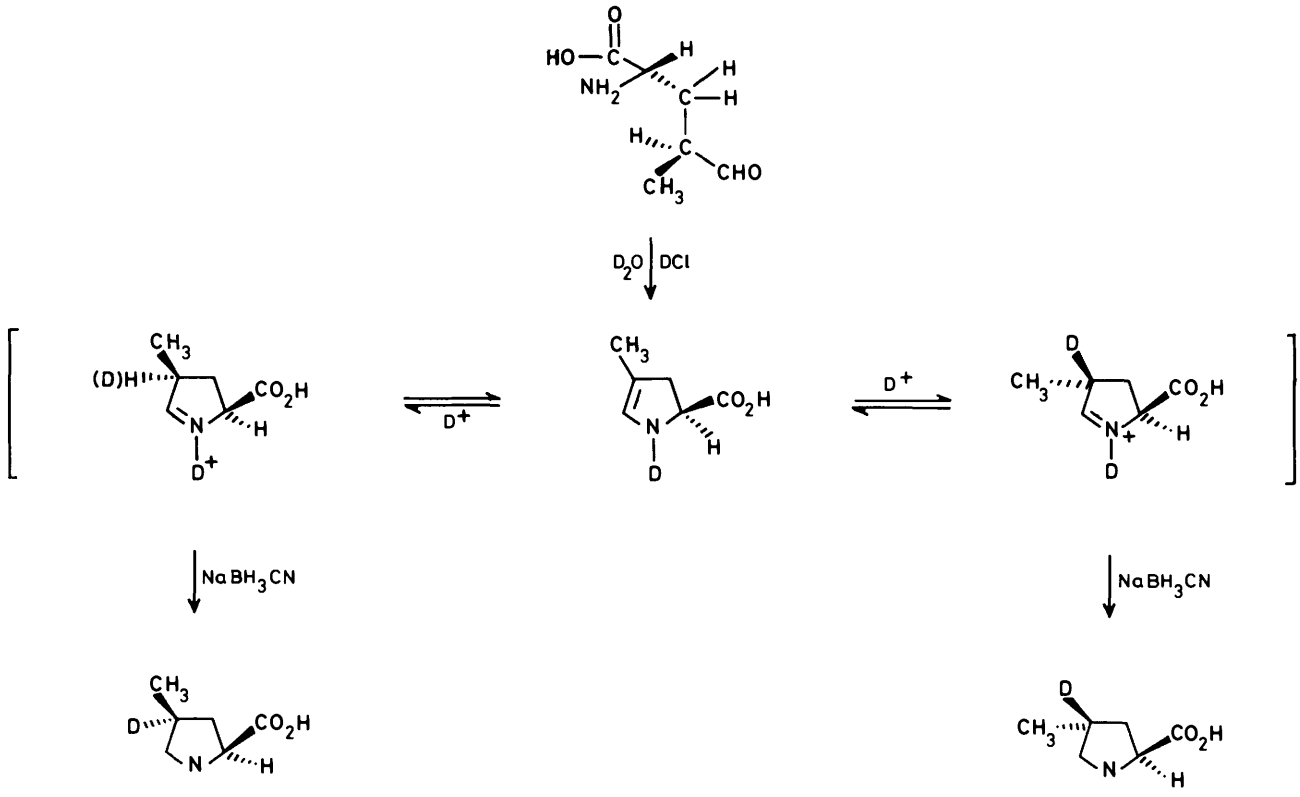


Figure 5. Conformations of the amino acid side chain in (**5b**) and (**4b**) and schematic representation of the shielding of the protons of the 3-methyl group in (**5b**), or the formyl proton in (**4b**) due to the diamagnetic ring current of the phenyl ring

Condensation with α-*Methylacrylaldehyde* (**3b**); *Synthesis of* cis- *and* trans-4-*Methyl*-(S)-*proline*.—Addition of the complex (**1**) to (**3b**) catalysed by Et_3N in MeOH gave after 36 h at 60 °C an equilibrium mixture of three isomers in yields of 11, 28, and 60.5% in order of their emergence from a chromatographic column. The α*R*-configuration could be assigned to the first isomer (**6b**), and the α*S*-configuration to the second and the third ones according to their o.r.d. curves (Figure 2). Analysis of the n.m.r. spectrum of (**6b**) suggested that the isomer was a mixture of two α*R*-isomers differing in their γ-configuration. The γ-configurations of the other two isomers could be established by n.m.r. as discussed later.

Molecular models of (**4b**) and (**5b**), as well as the *X*-ray crystal structure of the analogous Ni^{II} complex of the Schiff's base from (2*S*,4*R*)-4-methylglutamic acid and the benzophenone (**2**),[5c] indicate that the most favoured conformation of the amino acid side chain displaces the β,γ-bond outside the main co-ordination plane and positions the CH_3 and CHO groups as shown in Figure 5.



Scheme 4.

The 2*S*,4*R*-isomer (**5b**) has its side-chain γ-methyl substituent situated above the phenyl substituent on the C=N bond. Hence, one might expect the ^{1}H n.m.r. signals of the methyl protons in (**5b**) to be shifted upfield *vs.* (**4b**), owing to the diamagnetic current of the phenyl ring. On the other hand, (**4b**) (2*S*,4*S*) should have its aldehyde proton signal shifted upfield *vs.* (**5b**). Relative upfield shifts were observed for the resonances of the methyl group in the major isomer (60.5%) and the aldehyde proton in the second isomer (28%). The isomers could be thus designated (**5b**) and (**4b**), respectively. This assignment is additionally supported by the close similarity between the ^{1}H n.m.r. spectrum of (**5b**) and that of the previously studied complex of (2*S*,4*R*)-4-methylglutamic acid, unambiguously identified earlier.[5c]

Treatment of (**4b**) and or (**5b**) as indicated in Scheme 2 produced a 1:1 mixture of *cis*- and *trans*-4-methyl-(*S*)-prolines from either isomer. If the diastereoisomeric complexes were cleaved in DCl solution in D_2O, subsequent reduction with $NaBH_3CN$ produced a mixture of *cis*- and *trans*-4-methyl-(*S*)-[4-^{2}H]prolines. We assume that the formation of the intermediate dihydropyrrole-2-carboxylic acid is accompanied by racemization and hydrogen exchange at the 4-position according to Scheme 4.

To avoid racemization another approach (Method B) to the synthesis of 4-substituted prolines was developed as outlined in Scheme 5. The first stage is the reduction of the carbonyl group in (**5b**) or (**4b**) with MSA resin (BH_4^- form) in MeOH at 25 °C to give the complexes (**11**) and (**12**). The corresponding enantio- and diastereoiso-merically pure γ-hydroxy-α-amino acids could be recovered in the usual manner. Compounds (**11**) and (**12**) could be further treated with $MeSO_2Cl$ to give the corresponding *O*-Mes derivatives (**15**) and (**16**). Cleavage of the complexes with aq. HCl, followed by neutralization of the reaction mixture and extraction of the benzophenone (**2**), produced *cis*-4-methyl-(*S*)-proline from (**16**) and *trans*-4-methyl-(*S*)-proline from (**15**) in a chemical yield of 70% and with enantiomeric purity of 95%.

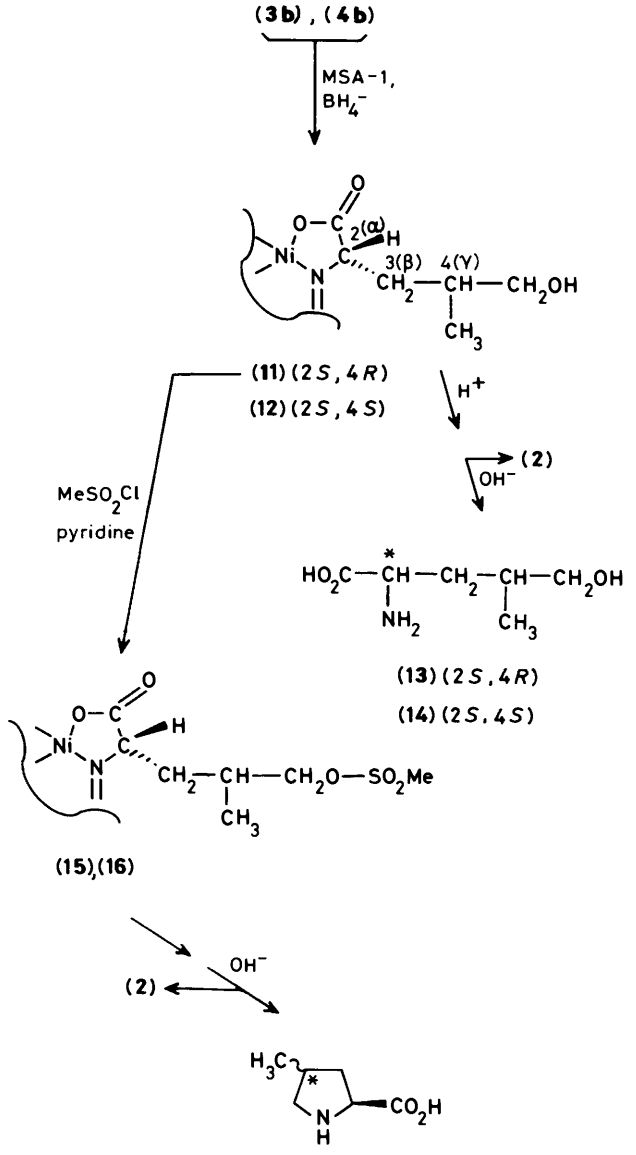
Discussion

The glycine fragment in the complex (**1**) has significant CH acidity, with pK_a 18.8 as measured in Me_2SO.[10] The carbanion generated in MeOH by Et_3N or MeONa is reactive enough to add to the activated C=C bonds of the olefins (**3**). The C=C bonds of the acrylaldehydes (**3**) constitute the only reactive sites of these bifunctional molecules even in the case of the sterically hindered crotonaldehyde and cinnamaldehyde, with catalysis by Et_3N. A large phenyl substituent on the C=N bond of (**1**) prevents intramolecular cyclization[11] or any bis-addition, as discussed earlier.[5e] The products of type (**8**) were probably formed *via* aldol condensation of (**4**), (**5**), or (**6**) with the complex (**1**). A significant amount (18%) of 1,2-addition product from acrylaldehyde and the complex (**1**) was detected only at low temperature (−78 °C) and with a high concentration of MeONa. Under these conditions the aldol products are stabilized by the formation of a new type of complex with a co-ordinated side-chain hydroxy group.[5b] However at low pH the 1,2-addition products are highly unstable thermodynamically, and in the presence of Et_3N rearrange to the corresponding 1,4-addition compounds, or in the case of (**8**) dissociate to (**1**) and a mixture of (**4**) and (**5**).

The stereochemical course of the Michael reaction is initially controlled by steric hindrance to the approach of an electrophile to the carbanion of (**1**).[5e] The kinetic stereoselectivity at C_α is relatively low. A similar observation was made for the alkylation of (**1**) with alkyl halides.[5d,e]

The Et_3N- (or MeONa-) catalysed equilibration of compounds (**4**)—(**6**) produces a much larger excess of (**4**) and (**5**) over (**6**) (see Table 1) than that initially observed.

We believe that the epimerization involves a series of α,β-



Scheme 5.

bond cleavage and formation steps. Conversion of (**6d**) into an equilibrium mixture of (**1**), (**4d**), (**5d**), (**6d**), and cinnamaldehyde supports this suggestion. Moreover, when the reaction was carried out in CH_3OD, deuterium was found in the γ-position of the side chain of the amino acid fragments in (**4d**), (**6d**), and (**5d**), and no deuterium was found in the α-position of the initial (**6d**). These results indicate that the initial base-catalysed cleavage of (**6d**) occurs *via* reversible formation of an intermediate γ-carbanion according to the $(E1cB)_R$ mechanism.[12]

Hence, the finally observed ratio of isomers reflects the relative thermodynamic stability not only of α-epimers but of β- and γ-epimers as well. A greater stability of the Ni^{II} complexes derived from (**2**), Ni^{II} and (*S*)-amino acids, as compared with (*R*)-amino acid-containing isomers, was discussed in previous papers.[7,13] Significant diastereoselectivity at C-β in the condensation of (**1**) with (**3c**), and a smaller but still sizable β-diastereoselectivity in the case of (**3d**) can be rationalized by molecular models of the isomers (**4c**) and (**5c**).

The most stable conformation of the amino acid side chain is that with the C_β–H bond oriented parallel to the C=N bond, with a *gauche* arrangement of the α- and β-protons (see Figure 4). This type of conformation was observed earlier for the closely related Ni^{II} complexes derived from the Schiff's base of (*S*)-*o*-[(*N*-benzylprolyl)amino]acetophenone and (*R*)- or (*S*)-Val.[7,13] As a consequence of this conformation (Figure 4), one of the β-alkyl substituents in each isomer is directed towards the proline *endo*-γ-hydrogen atom ($^{\gamma}H_{endo}$). Steric congestion, resulting from interaction of $^{\gamma}H_{endo}$ with either the CH_3 or the CH_2CHO group, is evidently smaller in the former case; hence (**4c**) is thermodynamically more stable than (**5c**). An increase in the volume of R (change from Me to Ph) brings the relative energies of (**4**) and (**5**) closer together. This may be the reason for a low β-diastereoselectivity in the condensation of (**1**) with (**3d**).

Conclusions

In this work we have elaborated a new approach to the synthesis of enantio- and diastereoiso-merically pure β-, γ-, or δ-substituted prolines based on a simple series of reactions and the use of relatively inexpensive reagents. The synthetic range is limited only by the availability of the corresponding substituted acrylaldehydes. Prolines bearing deuterium at the α- and/or γ-position can be prepared if either the condensation is carried out in CH_3OD (for α-labelled isomers) and/or if the decomposition of the final complex takes place in DCl solution in D_2O (for γ-labelling). Enantio- and diastereoiso-merically pure β- and γ-substituted δ-hydroxy-α-amino acids can also be obtained by this approach.

Experimental

General.—Reagents were purchased from Reakhim (U.S.S.R.), with the exception of *o*-aminobenzophenone, silica gel 60 F_{254}, and precoated silica gel 60 F_{254} plates (Merck) and Sephadex LH-20 (Pharmacia). Reagents and solvents were purified in the usual way. Sodium methoxide was prepared by dissolving metallic sodium in methanol under argon.

Spectra were recorded with the following instruments: u.v.–visible Specord UV-vis; ^1H n.m.r. Bruker WP-200 (200 MHz) and Tesla 467A; o.r.d. JASCO ORD/UV-5 (specific rotations measured with a Perkin-Elmer 241 polarimeter). M.p.s were measured with an Electrothermal apparatus. G.l.c.–mass spectra were obtained with a Nermag R10-10C–Girdel-32 system (ionizing voltage 70 eV; temperature of ion source 225 °C).

Enantiomeric and diastereoisomeric analyses of the α-amino acids were carried out by h.p.l.c. as described in ref. 14.

^1H N.m.r. spectra were obtained with use of the double resonance technique where necessary. Hexamethyldisiloxane (HMDS) was used as an internal reference in $CDCl_3$, and HMDS sealed in a glass capillary was used for D_2O solutions as an internal reference.

General Procedure for Michael Addition of the Complex (**1**) *to Acrylaldehydes and Methyl Vinyl Ketone.*—A mixture of the complex (**1**) (1.5 g, 3 mmol), Et_3N (0.6—1 ml), and the acrylaldehyde (or methyl vinyl ketone) (15 mmol) in MeOH (6 ml) was stirred at 60 °C under argon. The initial suspension of (**1**) eventually dissolved. The reaction was monitored by t.l.c. (SiO_2). Under the experimental conditions the complex (**1**) disappeared within 10 min—2 h, but equilibration amongst the diastereoisomers took up to 72 h. After the reaction had stopped the solvent was removed under reduced pressure. The residue was subjected to flash chromatography (2 × 100 cm column) on SiO_2. The fractions containing pure diastereoisomers could be further purified on Sephadex LH-20 to obtain analytically pure samples. If pure amino acids are the target the latter procedure can be discarded. Specific details are given for each addition separately.

General Procedure for the Synthesis of Substituted Prolines; Method A.—A solution of a pure diastereoisomer [(**4**)—(**6**)] (2 mmol) in EtOH (or MeOH) (7 ml) was slowly added with stirring to aqueous 3M HCl (10—15 ml) at 80 °C. After disappearance of the red colour of the complex, water was removed under reduced pressure, then water (10 ml) and $CHCl_3$ (30 ml) were added with stirring. The pH of the water layer was brought to 9.0 with aqueous NH_3, the organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 10 ml). The organic solutions were combined and evaporated under reduced pressure to yield the initial benzophenone (**2**) (80—90%). The aqueous solution was evaporated to dryness under reduced pressure, and MeOH (20 ml) was added, followed by $NaBH_3CN$ (0.5 g, 8 mmol). The mixture was stirred for 24 h at ambient temperature. T.l.c. on cellulose was used to monitor the reaction. After the reduction was complete the mixture was quenched with aqueous 3M HCl (pH brought to 5—6). The solution was subjected to cation exchange chromatography on Dowex 50 W resin (150 g). Elution with aqueous 4% NH_3 and subsequent removal of solvent under reduced pressure gave the α-amino acid in 60—80% yield. Specific details are given for each α-amino acid separately.

(S)-*Proline from* (**4a**). This was obtained as described earlier.[5c] Treatment of (**4a**) according to Method A produced (*S*)-Pro in a chemical yield of 73% and with optical purity 95%, according to h.p.l.c.

Mixture of cis- *and* trans-5-*Methyl*-(S)-*prolines from* (**4e**). Addition of (**1**) to methyl vinyl ketone (**3e**) gave two *diastereoisomers*: (**6e**) (0.08 g, 0.14 mmol) and (**4e**) (1.63 g, 2.85 mmol) in order of emergence from a chromatographic column (EtOAc–$CHCl_3$ 3:1); (**6e**), m.p. 189—191 °C (decomp.) (Found: C, 65.5; H, 5.6; N, 7.2. $C_{31}H_{31}N_3NiO_4$ requires C, 65.5; H, 5.5; N, 7.4%); o.r.d. *M* (25 °C; 8.3 × 10^{-4} mol dm^{-3} in MeOH; *l* 1 cm) −4 465 (578), +3 520 (546), +11 640 (436), and −10 300 (365 nm); $\lambda_{max.}$(MeOH) 550 (log ε 2.13), 418 (3.50), 333 (3.69), and 266 nm (4.22); $\nu_{max.}$(KBr) 1 720 cm^{-1} (ketone); δ($CDCl_3$; HMDS) 1.58—2.77 (m, 9 H, Pro 2 × β-H, 2 × γ-H, 1 δ-H; amino acid 2 × β-H, 2 × γ-H), 1.98 (s, 3 H, Me), 3.50, 4.32 (AB, 2 H, *J* 12 Hz, CH_2Ph), 3.62 (m, 2 H, amino acid α-H, Pro α-H), 4.12 (m, 1 H, Pro δ-H), and 6.60—8.50 (m, 14 H, ArH); (**4e**), m.p. 172—174 °C (decomp.) (Found: C, 65.4; H, 5.3; N, 7.3%); o.r.d. *M* (25 °C; 7.2 × 10^{-4} mol dm^{-3}; *l* 1 cm) +14 540 (578), +5 820 (546), −7 480 (436), and −970 (365 nm); $\lambda_{max.}$(MeOH) 540 (log ε 2.22) and 416 nm (3.48); $\nu_{max.}$(KBr) 1 720 cm^{-1} (ketone); δ($CDCl_3$) 1.67—3.55 (m, 10 H, amino acid 2 × β-H, 2 × γ-H; Pro 6 H), 2.0 (s, 3 H, Me), 3.52, 4.32 (AB, 2 H, *J* 12 Hz, CH_2Ph), 3.70 (m, Pro α-H, amino acid α-H), and 6.52—8.07 (m, 14 H, m, ArH). The mixture (1:1) of *cis*- and *trans*-5-methyl-(*S*)-proline was obtained from (**4e**) according to Method A in a yield of 69% (0.25 g, 1.96 mmol); δ(D_2O), 1.56 (d, 1.5 H, *J* 6.5 Hz, Me), 1.58 (d, 1.5 H, *J* 6.5 Hz, Me), 1.87 (m, 1 H, γ-H), 2.16—2.77 (m, 3 H, γ-H, 2 × β-H), 3.80 (m, 1 H, δ-H), and 4.40 (m, 1 H, α-H). The ethyl ester of *N*-trifluoroacetyl-*trans*- or *cis*-5-methylproline showed *m*/*z* 253 (M^+, 8%), 208 (1), and 180 (100).

trans-3-*Methyl*-(S)-*proline from* (**4c**). Addition of (**1**) to (*E*)-crotonaldehyde (**3c**) gave after 72 h two *diastereoisomers* (**6c**) 4.6% (0.08 g, 0.14 mmol) and (**4c**) (1.55 g, 2.74 mmol) in order of emergence from a chromatographic column (EtOAc–$CHCl_3$, 3:1).

Compound (**6c**) had m.p. 202 °C (decomp.) (Found: C, 66.0; H, 6.0; N, 7.8. $C_{31}H_{31}N_3NiO_4$ requires C, 65.5; H, 5.5; N, 7.4%); o.r.d. *M* (25 °C; 9.6 × 10^{-4} mol dm^{-3} in MeOH; *l* 1 cm) +630 (578), +6 250 (546), +11 700 (436), and −21 700 (365 nm); $\lambda_{max.}$(MeOH) 540 (log ε 2.41), 420 (3.49), 333 (3.68), and 265 nm (4.26); δ($CDCl_3$) 1.68—4.00 (m, 9 H, amino acid β-H, 2 × γ-H; Pro 2 × β-H, 2 × δ-H, 2 × γ-H), 1.83 (d, 3 H, *J* 7 Hz, CH_3), 4.12 and 4.89 (AB, 2 H, *J* 13 Hz, CH_2Ph), 3.59 (ABX, 1 H, J_{AX} 5, J_{BX} 10 Hz, Pro α-H), 3.92 (d, 1 H, *J* 3 Hz, amino acid α-H), 6.65—8.56 (m, 14 H, ArH), and 9.15 (s, 1 H, CHO). Compound (**6c**) was treated according to Method A, and *trans*-3-methyl-(*R*)-proline was obtained in 72% yield with enantiomeric purity >95% (h.p.l.c.). The ^1H n.m.r. spectrum was identical with that of *trans*-3-methyl-(*S*)-proline.

Compound (**4c**) had m.p. 227—230 °C (decomp.) (Found: C, 65.0; H, 5.5; N, 7.5%); o.r.d. *M* (25 °C; 6.43 × 10^{-4} mol dm^{-3} in MeOH; *l* 1 cm) +13 400 (578), +3 900 (546), +8 240 (436), and +310 (365 nm); $\lambda_{max.}$(MeOH) 540 (log ε 2.27), 420 (3.49), 333 (3.66), and 265 nm (4.16); δ($CDCl_3$) 1.97—3.50 (m, 8 H, amino acid β-H; Pro α-H, 2 × β-H, 2 × γ-H, 2 × δ-H), 2.06 (d, 3 H, *J* 7 Hz, CH_3), 2.36 (d, 2 H, *J* 7 Hz, amino acid γ-H), 3.09 4.42 (AB, 2 H, *J* 12 Hz, CH_2Ph), 3.97 (d, 1 H, *J* 3.5 Hz, amino acid α-H), 6.59—8.30 (m, 14 H, ArH), and 9.24 (s, 1 H, CHO). Compound (**4c**) was treated according to Method A and gave trans-3-*methyl*-(S)-*proline* in a yield of 70% (0.25 g, 1.91 mmol) with enantiomeric purity >95% as colourless prismatic crystals (from water–EtOH). The crystals turned into needles at 180—200 °C and melted at 242—247 °C (decomp.) (lit.,[15] m.p. 240—248 °C) (Found: C, 55.0; H, 8.95; N, 10.3. $C_6H_{11}NO_2$ requires C, 55.8; H, 8.6; N, 10.8%); $\alpha_{589}{}^{25}$ (*l* 1 dm, 6.0 g dm^{-3} in water) −31.0° [lit.,[15] −30.0° (1 g dm^{-3} in water)]; δ(D_2O) 1.40 (d, 3 H, *J* 6 Hz, CH_3), 1.90 (m, 1 H, γ-H), 2.40 (m, 1 H, γ-H), 2.60 (m, 1 H, β-H), 3.60 (m, 2 H, δ-H), and 3.82 (d, 1 H, *J* 8 Hz, α-H). Enantio- and diastereoiso-meric purity of the α-amino acid was higher than 95% according to h.p.l.c. The ethyl ester of the *N*-trifluoroacetyl *trans*- (or *cis*-) 3-methyl-(*S*)-proline showed *m*/*z* 253 (M^+, 8%), 208 (1), and 180 (100).

trans-3-*Phenyl*-(S)-*proline from* (**4d**), cis-3-*phenyl*-(S)-*proline from* (**5d**), *and* trans-3-*phenyl*-(R)-*proline from* (**6d**). Addition of (**1**) to (*E*)-cinnamaldehyde (1.98 g, 15 mmol) led to three major *diastereoisomers*: (**6d**) (0.15 g, 0.23 mmol), (**4d**) (1.52 g, 2.46 mmol), and (**5d**) (0.19 g, 0.30 mmol) in order of emergence from a chromatographic column (EtOAc–$CHCl_3$, 3:1).

Compound (**6d**) had m.p. 124—126 °C (Found: C, 69.0; H, 5.5; N, 6.5. $C_{36}H_{33}N_3NiO_4$ requires C, 68.6; H, 5.3; N, 6.7%); o.r.d. *M* (25 °C, 1.0 × 10^{-3} mol dm^{-3} in MeOH; *l* 1 cm) −7 580 (578), +3 940 (546), +14 400 (436), and −1 980 (365 nm); $\lambda_{max.}$(MeOH) 530 (log ε 2.25), 420 (3.42), 333 (3.68), and 268 nm (4.17); δ($CDCl_3$) 1.75—3.67 (m, 7 H, Pro), 2.77 (m, 2 H, amino acid γ-H), 3.25 (m, 1 H, amino acid β-H), 3.29 and 3.49 (AB, 2 H, *J* 12 Hz, CH_2Ph), 4.17 (d, 1 H, *J* 4 Hz, amino acid α-H), 6.57—8.35 (m, 19 H, ArH), and 9.15 (s, 1 H, CHO). Compound (**6d**) was treated according to Method A, and *trans*-3-phenyl-(*R*)-proline was obtained in a yield of 70% (0.35 g, 1.72 mmol) with enantiomeric purity 95% (h.p.l.c.). ^1H N.m.r. and mass spectra of the amino acid were identical with those of *trans*-3-phenyl-(*S*)-proline (see later).

Compound (**4d**) had m.p. 118—122 °C (decomp.) (Found: C, 67.7; H, 5.4; N, 6.4. $C_{36}H_{33}N_3NiO_4{\cdot}0.5H_2O$ requires C, 67.6; H, 5.4; N, 5.6%); o.r.d. *M* (25 °C; 7.2 × 10^{-4} mol dm^{-3} in MeOH; *l* 1 cm) +13 900 (578), +554 (546), and −16 900 (436 nm); $\lambda_{max.}$(MeOH) 530 (log ε 2.36), 420 (3.49), 333 (3.71), and 265 nm (4.20); δ($CDCl_3$) 1.42 (m, Pro *endo*-γ-H), 1.66—3.31 (m, 6 H, Pro α-H, 2 × β-H, 2 × δ-H, *exo*-γ-H), 2.70 (ABX, 1 H, J_{AB} 16, J_{AX} 5 Hz, amino acid γ-H), 3.05 (ABX, 1 H, J_{AB} 16, J_{BX} 7 Hz, amino acid γ-H), 3.25 (m, 1 H, amino acid β-H), 3.40 and 4.21 (AB, 2 H, *J* 12 Hz, CH_2Ph), 4.22 (d, 1 H, *J* 4 Hz, amino acid α-H), 6.62—8.25 (m, 19 H, ArH), and 9.12 (s, 1 H, CHO). Compound (**4d**) was treated according to Method A, and trans-3-*phenyl*-(S)-*proline* was obtained in 75% yield with enantiomeric purity 95% (h.p.l.c.); m.p. 232—242 °C (decomp.) (Found: C, 69.0; H, 6.7; N, 7.0. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%); δ(D_2O) 2.50 (m, 1 H, γ-H), 2.73 (m, 1 H, γ-H), 3.80 (m, 3 H, β-H, 2 × δ-H), 4.37 (d, 1 H, *J* 9 Hz, α-H), 7.68 (m, 5 H, ArH). The ethyl ester *N*-trifluoroacetyl derivative showed

m/z 315 (M^+, 3.5%), 269 (12), 243 (14), and 242 (100); $\alpha_{589}{}^{25}$ (*l* 1 dm, 7.5 g dm^{-3} in 6M HCl) + 69.3°.

Compound (**5d**) had m.p. 154—169 °C (decomp.) (Found: C, 68.85; H, 5.5; N, 6.9%); o.r.d. *M* (25 °C; 6.3 × 10^{-4} mol dm^{-3} in MeOH; *l* 1 cm) +14 300 (578), +472 (546), −17 800 (436), and +8 080 (365 nm); $\lambda_{max.}$(MeOH) 560 (log ε 2.40), 420 (3.51), 333 (3.70), and 270 nm (4.24); δ($CDCl_3$) 2.0—3.81 (m, 7 H, Pro 2 × β-H, 2 × γ-H, δ-H, α-H; amino acid γ-H), 2.98 (ABX, 1 H, J_{AB} 18, J_{AX} 8 Hz; amino acid β-H), 3.42 and 4.30 (AB, 1 H, *J* 12 Hz, CH_2Ph), 3.93 (d, 1 H, *J* 7 Hz, amino acid α-H), 4.82 (m, 1 H, Pro δ-H), 5.57—8.21 (m, 19 H, ArH), and 9.60 (s, 1 H, CHO). Compound (**5d**) was treated according to Method A, and *cis*-3-phenyl-(*S*)-proline was obtained in a yield of 71% (0.35 g, 1.74 mmol) and enantiomeric purity 95% (h.p.l.c.); m.p. 214—220 °C (decomp.); δ(D_2O–DCl) 2.12 (m, 2 H, 2 × γ-H), 3.10 (m, 1 H, β-H), 3.43 (m, 1 H, δ-H), 3.61 (m, 1 H, δ-H), 4.42 (d, 1 H, *J* 9 Hz, α-H), and 7.23 (m, 5 H, ArH); $\alpha_{589}{}^{25}$ (4.5 g dm^{-3} in 6M HCl) +63.7°. The ethyl ester *N*-trifluoroacetyl derivative showed *m/z* 315 (M^+, 6.3%), 269 (7), 243 (14), and 242 (100).

1:1 *Mixture of* cis- *and* trans-4-*Methyl*[4-^{2}H]-(S)-*prolines from* (**4b**) [*or* (**5b**)].—Addition of (**1**) to α-methylacrylaldehyde (**3b**) led to three major diastereoisomers: (**6b**) (0.13 g, 0.24 mmol) as a 2:1 mixture of 2*R*,4*S*- and 2*R*,4*R*-isomers (**4b**) (0.5 g, 0.88 mmol), and (**5b**) (1.03 g, 1.82 mmol) in order of emergence from a chromatographic column ($CHCl_3$–hexane–methanol, 4.5:4.5:0.2).

Compound (**6b**) had m.p. 180—185 °C (decomp.) (Found: C, 65.4; H, 5.5; N, 6.7. $C_{31}H_{31}N_3NiO_4$ requires C, 65.5; H, 5.5; N, 7.4%); δ($CDCl_3$) 0.48 (d, 0.75 H, *J* 7 Hz, CH_3, 4*S*-diastereoisomer), 1.0 (d, 0.25 H, *J* 7 Hz, CH_3, 4*R*-diastereoisomer), 1.84—4.18 (m, 13 H, amino acid α-H, 2 × β-H, γ-H; Pro α-H, 2 × β-H, 2 × γ-H, 2 × δ-H), 3.50 and 4.36 (broadened AB, 2 H, *J* 12.5 Hz, CH_2Ph), 6.68—8.56 (m, 14 H, ArH), 9.06 (s, 0.25 H, CHO, 4*R*-diastereoisomer), and 9.54 (s, 0.75 H, CHO, 4*S*-diastereoisomer).

Compound (**4b**) had m.p. 188—191 °C (decomp.) (Found: C, 65.7; H, 5.4; N, 7.2%); o.r.d. *M* (25 °C; 1.7 × 10^{-4} mol dm^{-3} in MeOH; *l* 1 cm) +13 500 (578), +4 800 (546), −8 850 (436), and 0 (365 nm); $\lambda_{max.}$(MeOH) 540 (log ε 2.17), 416 (3.44), 333 (3.65), and 265 nm (4.10); δ($CDCl_3$) 1.07 (d, 3 H, *J* 7.5 Hz, CH_3), 1.94—4.18 (m, 6 H, Pro 2 × β-H, 2 × γ-H, 2 × δ-H), 2.03 (m, 2 H, amino acid β-H), 2.74 (m, 1 H, amino acid γ-H), 3.50 (m, 1 H, amino acid α-H), 3.51 and 4.39 (AB, 2 H, *J* 13 Hz, CH_2Ph), 3.97 (ABX, 1 H, J_{AX} 11, J_{BX} 5 Hz, Pro α-H), 6.62—8.15 (m, 14 H, ArH), and 9.15 (s, 1 H, CHO).

Compound (**5b**) had m.p. 210 °C (decomp.) (Found: C, 65.45; H, 5.5; N, 7.4%); o.r.d. *M* (25 °C; 1.7 × 10^{-3} mol dm^{-3} in MeOH; *l* 1 cm) +16 700 (578), +7 350 (546), −8 670 (436), and −3 290 (365 nm); $\lambda_{max.}$(MeOH) 540 (log ε 2.25), 416 (3.51), 333 (3.72), and 265 nm (4.23); δ($CDCl_3$) 0.53 (d, 3 H, *J* 7.5 Hz, CH_3), 1.97—3.06 (m, 7 H, Pro 2 × β-H, 2 × γ-H, δ-H; amino acid 2 × β-H), 2.80 (m, 1 H, amino acid γ-H), 3.49 (m, 1 H, amino acid α-H), 3.56 and 4.42 (AB, 2 H, *J* 12 Hz, CH_2Ph), 3.70 (m, 1 H, Pro δ-H), 3.86 (m, 1 H, Pro α-H), 6.62—8.09 (m, 14 H, ArH), and 9.56 (s, 1 H, CHO). Compound (**4b**) or (**5b**) was treated according to Method A, except that CH_3OD solutions of the complexes and solutions of DCl (instead of HCl) in D_2O (instead of water) were used when the complexes were decomposed. A mixture of *cis*- and *trans*-4-methyl-(*S*)-[4-^{2}H]proline was obtained in a yield of 71% (0.26 g, 1.29 mmol) and 1:1 ratio, according to g.l.c. and ^{1}H n.m.r.; δ(D_2O) 0.97 (s, 1.5 H, CH_3), 0.96 (s, 1.5 H, CH_3), 1.48—2.38 (m, 2 H, β-H), 2.75—3.35 (m, 2 H, β-H), and 3.9 (m, 1 H, α-H). The *cis*- and *trans*-ethyl ester *N*-trifluoroacetyl derivatives had almost identical mass spectra: *m/z* 254 (M^+, 3.3%), 253 (M^+, 1.4), 209 (0.6), 208 (0.7), 181 (100), 180 (47), 165 (1), and 164 (0.7).

Synthesis of cis- *and* trans-4-*Methyl*-(S)-*prolines; Method B.*—A reaction mixture (2 g) obtained from compounds (**1**) and (**3b**) as already described was dissolved in MeOH (20 ml) and added dropwise to a stirred suspension of MSA-1 resin (10 ml; BH_4^- form)[16] in a minimal volume of MeOH. The reduction was monitored by t.l.c. After the initial complexes had disappeared the resin was filtered off and washed with MeOH. The filtrate and washings were combined and evaporated under reduced pressure. The residue was chromatographed on SiO_2 ($CHCl_3$–Me_2CO 5:1), and three major fractions were separated. A 2:1 mixture of 2*R*,4*S*- and 2*R*,4*R*-isomers of the Ni^{II} complex of the Schiff's base derived from (**2**) and 2-amino-4-hydroxymethylpentanoic acid was eluted first as a single fraction (8%) (0.13 g, 0.24 mmol); δ($CDCl_3$) 0.33 (d, 1 H, *J* 7 Hz, CH_3, 4*R*-isomer), 0.83 (d, 2 H, *J* 7 Hz, CH_3, 4*S*-isomer), 1.42—4.33 (m, 15 H, Pro 7 H, amino acid 6 H, CH_2Ph), and 6.52—8.50 (m, 14 H, ArH). The second band contained the *complex* (**12**) (0.4 g, 0.69 mmol, 23%); m.p. 195 °C (decomp.) (Found: C, 64.8; H, 5.5; N, 6.7. $C_{31}H_{33}N_3NiO_4$ requires C, 65.3; H, 5.8; N, 7.4%); o.r.d. *M* (25 °C; 7.83 × 10^{-4} mol dm^{-3} in MeOH; *l* 1 cm) +13 500 (578), +4 900 (546), and −8 900 (436 nm); $\lambda_{max.}$(MeOH) 540 (log ε 2.32), 4.18 (3.48), 333 (3.69), and 265 nm (4.20); δ($CDCl_3$) 0.85 (d, 3 H, *J* 7.5 Hz, CH_3), 1.46—4.30 (m, 13 H, Pro 7 H, amino acid 6 H), 3.51 and 4.36 (AB, *J* 12 Hz, CH_2Ph), and 6.56—8.10 (m, 14 H, ArH). The third band contained the complex (**11**) (1.07 g, 1.89 mmol, 63%); m.p. 204—212 °C (decomp.) (Found: C, 65.0; H, 5.6; N, 6.9%); o.r.d. *M* (25 °C; 1.37 × 10^{-3} mol dm^{-3} in MeOH; *l* 1 cm) +16 700 (578), +7 450 (546), −8 760 (436), and −3 100 (365 nm); $\lambda_{max.}$(MeOH) 540 (log ε 2.16), 418 (3.46), 333 (3.65), and 265 nm (4.16); δ($CDCl_3$) 0.38 (d, 3 H, *J* 7.5 Hz, CH_3), 1.27—3.80 (m, 12 H, Pro 2 × β-H, 2 × δ-H, 2 × γ-H; amino acid α-H, γ-H, 2 × β-H, 2 × δ-H), 3.99 (m, 1 H, Pro α-H), 3.97 and 4.40 (AB, *J* 12 Hz, CH_2Ph), and 6.60—8.12 (m, 14 H, ArH). To a solution of (**11**) [or (**12**)] (0.8 mmol) and pyridine (0.5 ml) in CH_2Cl_2 (10 ml) was added $MeSO_2Cl$ (1 ml) with vigorous stirring. The reaction was monitored by t.l.c. (SiO_2; $CHCl_3$–Me_2CO 5:1). After the initial complex had disappeared the mixture was transferred to the top of a chromatographic column and purified on SiO_2 (1.5 × 40 cm; $CHCl_3$–Me_2CO, 5:1). The purified diastereoisomeric complex was decomposed in the usual manner with aqueous HCl, and the pH of the solution was brought to 9.0 by adding dry Na_2CO_3; the benzophenone (**2**) was recovered by extraction with $CHCl_3$. The amino acid was obtained by the ion-exchange technique as before. *cis*-4-Methyl-(*S*)-proline was obtained in 74% yield (0.08 g, 0.59 mmol) from (**12**); m.p. 229—231 °C (lit.,[6a] 230—231 °C); $\alpha_{589}{}^{25}$ (3.5 g dm^{-3} in water) −78 °C [lit.,[6a] (1.0 g dm^{-3} in water) −82 °C]; δ(D_2O) 0.86 (d, 3 H, *J* 7 Hz, CH_3), 1.51 (m, 1 H, β-H), 2.27 (m, 2 H, β-H, γ-H), 2.67 (m, 1 H, δ-H), 3.25 (m, 1 H, δ-H), and 3.92 (m, 1 H, α-H); *m/z* 253 (M^+, 5.4%), 208 (1), 180 (100), and 179 (0.7). *trans*-4-Methyl-(*S*)-proline was obtained in 70% yield (0.07 g, 0.57 mmol) from (**11**), m.p. 230—238 °C (lit.,[6a] 231—239 °C); $\alpha_{589}{}^{25}$ (1.0 g dm^{-3} in water) −56 °C [lit.,[6a] α_{589} (1.0 g dm^{-3} in water) −57 °C]; δ(D_2O) 0.86 (d, 3 H, *J* 7.5 Hz, CH_3), 1.76 (m, 1 H, β-H), 2.15 (m, 2 H, β-H, γ-H), 2.66 (ABX, 1 H, J_{AB} 16, J_{AX} 8 Hz, δ-H), 3.35 (AB, 1 H, J_{AB} 11, J_{BX} 6 Hz, δ-H), and 4.01 (ABX, 1 H, J_{AX} 1.0, J_{BX} 4 Hz, α-H); *m/z* 253 (M^+, 8.5%), 208 (0.5), 180 (100), and 179 (0.9).

(2S,4S)- *or* (2S,4R)-2-*Amino*-4-*hydroxymethylpentanoic Acid*, (**14**) *or* (**13**).—Compound (**12**) was decomposed as already described to give the acid (**14**), obtained in the usual manner by ion exchange in 70% yield (0.07 g, 0.48 mmol); δ(D_2O) 0.75 (d, 3 H, *J* 7 Hz, CH_3), 1.50 (m, 3 H, 2 × β-H, γ-H), 3.25 (d, 2 H, *J* 7 Hz, CH_2O) 3.25 (m, 1 H, α-H); *m/z* (ethyl ester *N*-trifluoroacetyl derivative) 294 ($M - CO_2Et$, 62%). Compound (**13**) was obtained from (**11**) in 50% yield (0.14 g, 0.94 mmol); δ(D_2O) 0.77 (d, 3 H, *J* 7 Hz, CH_3), 1.40—1.75 (m, 3 H, 2 × β-H, γ-H), 3.25

(m, 2 H, CH_2O), and 3.55 (m, 1 H, α-H); *m/z* (ethyl ester *N*-trifluoroacetyl derivative) 294 ($M - CO_2Et$, 33%).

Condensation of the Complex (**1**) *with Acrylaldehyde in the Presence of Sodium Methoxide at* 25 °C.—To the complex (**1**) (0.25 g, 0.25 mmol) in NaOMe (2 ml; 1.2 mol dm^{-3}), a solution of acrylaldehyde (0.03 ml, 0.45 mmol) in MeOH (1 ml) was added. After the complex (**1**) had been consumed (t.l.c.), the reaction was quenched with aqueous acetic acid. The resulting mixture was partitioned between water and $CHCl_3$. The organic layer was evaporated under reduced pressure, and the residue chromatographed on SiO_2 ($CHCl_3$–Me_2CO, 5:1). More than seven fractions separated as orange-red bands on the column (or the preparative t.l.c. plates); the major fractions were the second, fifth, and sixth. The second fraction (0.05 g, 0.02 mmol, 11%) was a Ni^{II} complex of a Schiff's base derived from (**2**) and 2-amino-3-hydroxy-4-methoxybutanoic acid (**9**); δ($CDCl_3$) 1.65—3.67 (m, 10 H, Pro 2 × β-H, 2 × γ-H, 2 × δ-H; amino acid β-H, 2 × γ-H, 2 × δ-H), 3.25 (s, 3 H, MeO), 4.0 (m, 2 H, Pro α-H, amino acid α-H), 3.80 and 4.54 (AB, *J* 12 Hz, CH_2Ph), and 6.62—8.50 (m, 14 H, ArH). When treated with MeONa (1 mol dm^{-3}) compound (**9**) underwent changes in o.r.d. (or c.d.) curves, and u.v.–visible spectra were typical of β-hydroxy-α-amino acid complexes. The fifth fraction (**8**) was an isomer of a Ni^{II} complex of a Schiff's base derived from (**2**) and 2,6-diamino-3-hydroxyheptanedioic acid (0.08 g, 0.08 mmol, 32%); δ($CDCl_3$) 1.52—3.98 (m, 21 H, Pro 14 H, amino acid 7-H), 3.50 and 4.46 (AB, 2 H, *J* 12 Hz, CH_2Ph), and 3.92 and 5.02 (AB, 2 H, *J* 12 Hz, CH_2Ph). Acid hydrolysis of this isomer of (**8**) produced the benzophenone (**2**) and 2,6-diamino-3-hydroxyheptanedioic acid (74%); δ(D_2O) 1.35—2.00 (m, 4 H, 2 × δ-H, 2 × γ-H), 3.48 (d, 1 H, *J* 5 Hz, β-H), 3.60 (d, 1 H, *J* 5 Hz, α-H), and 3.85 (m, 1 H, ε-H). The sixth fraction was another diastereoisomer of (**8**) (35%); δ($CDCl_3$) 1.46—4.50 (m, 21 H, Pro 14 H, amino acid 7 H), 3.46 (one part of two AB systems, 2 H, CH_2Ph), 4.25 and 4.37 (the other part of two AB systems, *J* 12 Hz, 2 H, CH_2Ph), and 6.52—8.42 (m, 28 H, ArH). Acid hydrolysis of the isomer produced the benzophenone (**2**) and 2,6-diamino-3-hydroxyheptanedioic acid (81%); δ(D_2O) 1.50—1.75 (m, 4 H, 2 × δ-H, 2 × γ-H), 3.50 (d, 1 H, *J* 5 Hz, α-H), 3.65 (m, 1 H, ε-H), and 3.90 (m, 1 H, β-H); *m/z* (ethyl ester *N*-trifluoroacetyl derivative) 551 ($M + H^+$, <0.1%) and 477 ($M - CO_2Et$).

Reaction of the Complex (**8**) *with Triethylamine in Methanol.*—A solution of (**8**) (0.015 g, 0.01 mmol) in a solution of Et_3N in MeOH (1 ml; 0.2 mol dm^{-3}) was kept at 25 °C for 2 h to give a 1:1 mixture of (**1**) and (**4a**) according to t.l.c. and ^1H n.m.r. spectra.

Condensation of the Complex (**1**) *with Acrylaldehyde in the Presence of Sodium Methoxide at* −78 °C.—The ratios of the reagents were the same as in the experiment at 25 °C. Eight fractions were observed. The third (18%) was a Ni^{II} complex (**10**) of a Schiff's base derived from the benzophenone (**2**) and vinylserine; m.p. 170—172 °C; δ($CDCl_3$) 1.88—4.23 (m, 9 H, Pro 7 H, amino acid α-H, β-H), 3.57 and 4.30 (AB, 2 H, *J* 12 Hz, CH_2Ph), and 5.57 (m, 2 H, CH_2=C). Acid hydrolysis of (**10**) produced (**2**) and vinylserine in 58% yield; δ(D_2O) 3.76 (d, 1 H, *J* 5 Hz, α-H), 4.70 (m, 1 H, β-H), 5.60 (m, 2 H, δ-H), and 5.98 (m, 1 H, γ-H); *m/z* (ethyl ester *N*-trifluoroacetyl derivative) 351 (M^+), 278 ($M - CO_2Et$), 237 ($M - CF_3CO_2H$), and 1.64 ($M - CO_2Et - CF_3CO_2H$).

Epimerization of the Complex (**6d**) *by Triethylamine in Methanol* (*or Methan*[^{2}H]*ol*).—A mixture of (**6d**) (0.3 g, 0.06 mmol), (*E*)-cinnamaldehyde (0.08 ml, 0.07 mmol) Et_3N (0.12 ml) in anhydrous MeOH (1.2 ml) was kept at 60 °C for 48 h to give compounds (**4d**), (**5d**), and (**6d**) in ratios 0.8:8:1 (t.l.c.). Reaction in CH_3OD without the addition of cinnamaldehyde produced after 8 h some (*Z*)- and (*E*)-α-deuteriocinnamaldehyde (*Z*:*E* 1:8, according to g.l.c. and mass spectrometry), 4-deuterio-(**6d**), 4-deuterio-(**5d**), and 2-deuterio-(**1**), according to ^1H n.m.r. data.

References

1 J. Martens, *Top. Curr. Chem.*, 1984, **125**, 165; G. Nass and K. Poralla, *Naturwissenschaften*, 1971, **58**, 603; G. C. Barret, 'Chemistry and Biochemistry of the Amino Acids,' Chapman and Hall, London and New York, 1985.

2 U. Schöllkopf, *Top. Curr. Chem.*, 1983, **109**, 65; *Pure Appl. Chem.*, 1983, **55**, 1799; *Chem. Scr.*, 1985, **25**, 105; D. Seebach, E. Jurasti, D. Miller, C. Schickli, and T. Weber, *Helv. Chim. Acta*, 1987, **70**, 237; Y. Yamamoto, M. Kirihata, J. Ichimoto, and H. Ueda, *Agric. Biol. Chem.*, 1985, **49**, 1761; J. Bajgrowicz, B. Cossec, Ch. Pigiere, R. Jacquier, and Ph. Viallefount, *Tetrahedron Lett.*, 1983, **24**, 3721.

3 Y. Yamamoto, W. Ito, and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 1985, 1131; L. Duhamel, S. Fonquay, and J.-Ch. Plaquevent, *Tetrahedron Lett.*, 1986, **27**, 4975; P. J. Sinclair, D. Zhai, J. Reibenspics, and R. M. Williams, *J. Am. Chem. Soc.*, 1986, **108**, 1103.

4 L. A. Trimble and J. C. Vederas, *J. Am. Chem. Soc.*, 1986, **108**, 6397; D. A. Evans, Th. C. Britton, R. L. Dorow, and J. F. Dellaria, *ibid.*, p. 6395; C. Gennari, L. Colombo, and G. Bertolini, *ibid.*, p. 6394; D. A. Evans and A. E. Weber, *ibid.*, p. 6757; W. Oppolzer and R. Moretti, *Helv. Chim. Acta*, 1986, **69**, 8.

5 (*a*) Yu. N. Belokon, I. E. Zeltzer, V. I. Bakhmutov, M. B. Saporovskaya, M. G. Ryzhov, A. I. Yanovsky, Yu. T. Struchkov, and V. M. Belikov, *J. Am. Chem. Soc.*, 1983, **105**, 2010; (*b*) Yu. N. Belokon, A. G. Bulychev, S. V. Vitt, Yu. T. Struchkov, A. S. Batsanov, T. V. Timofeeva, V. A. Tsyryapkin, M. G. Ryzhov, L. A. Lysova, V. I. Bakhmutov, and V. M. Belikov, *ibid.*, 1985, **107**, 4252; (*c*) Yu. N. Belokon, A. G. Bulychev, M. G. Ryzhov, S. V. Vitt, A. S. Batsanov, Yu. T. Struchkov, V. I. Bakhmutov, and V. M. Belikov, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1865; (*d*) Yu. N. Belokon, N. I. Chernoglazova, K. A. Kochetkov, N. S. Garbalinksya, and V. M. Belikov, *J. Chem. Soc., Chem. Commun.*, 1985, 171; (*e*) Yu. N. Belokon, V. I. Bakhmutov, N. I. Chernoglazova, K. A. Kochetkov, S. V. Vitt, N. S. Garbalinskaya, and V. M. Belikov, *J. Chem. Soc., Perkin Trans. 1*, 1988, 305.

6 (*a*) S. L. Titouani, J. P. Lavergne, and P. Viallefont, *Tetrahedron*, 1980, **36**, 2961; (*b*) L. T. Ho, B. Gopalan, and J. J. Nestor, *J. Org. Chem.*, 1986, **51**, 2405; (*c*) J. K. Thottathil, J. L. Moniot, R. H. Mueller, M. K. Y. Wong, and T. P. Kissick, *ibid.*, p. 3140; (*d*) K. Drauz, A. Kleeman, J. Martens, and S. Scherbreich, *ibid.*, p. 3494; (*e*) J. K. Thottathil and J. L. Moniot, *Tetrahedron Lett.*, 1986, **27**, 151; (*f*) U. Schöllkopf, R. Hinrichs, and R. Lonsky, *Angew. Chem., Int. Ed. Engl.*, 1987, **26**, 143.

7 Yu. N. Belokon, V. I. Maleyev, S. V. Vitt, M. G. Ryzhov, Yu. D. Kondrashov, S. N. Golubev, Yu. P. Vauchskii, A. I. Kazika, M. I. Novikova, P. A. Krasutskii, A. G. Yurchenko, I. L. Dubchak, V. E. Shklover, Yu. T. Struchkov, V. I. Bakhmutov, and V. I. Belikov, *J. Chem. Soc., Dalton Trans.*, 1985, 17.

8 L. G. Warner, N. J. Rose, and D. H. Busch, *J. Am. Chem. Soc.*, 1968, **90**, 6938; T. Ito and D. H. Busch, *ibid.*, 1973, **95**, 7528.

9 A. C. Coda, G. G. Desimoni, A. G. Invernizzi, P. P. Righetti, P. F. Seneci, and G. Tacconi, *Gazz. Chim. Ital.*, 1985, **115**, 111.

10 M. I. Terekhova, Yu. N. Belokon, V. I. Maleev, N. I. Chernoglazova, K. A. Kochetkov, V. M. Belikov, and E. S. Petrov, *Izv. Akad Nauk SSSR, Ser. Khim.*, 1986, 905.

11 L. Casella, M. Gullotti, A. Pasini, G. Giani, M. Manassero, M. Sansoni, and A. Sironi, *Inorg. Chim. Acta*, 1976, **20**, 31; L. Casella, M. Gullotti, and E. Melani, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1827.

12 R. A. Bartsch and J. Zavada, *Chem. Rev.*, 1980, **80**, 453.

13 S. V. Lindeman, T. V. Timofeeva, V. I. Maleyev, Yu. N. Belokon, M. G. Ryzhov, V. M. Belikov, Yu. T. Struchkov, *Acta Crystallogr., Ser C*, 1985, **41**, 1290.

14 V. A. Shirokov, V. A. Tsyryapkin, L. V. Nedospasova, A. A. Kurganov, and V. A. Davankov, *Bioorg. Khim.*, 1983, **9**, 878.

15 J. Kollonitsch, A. N. Scott, and G. A. Doldouras, *J. Am. Chem. Soc.*, 1966, **88**, 3624.

16 H. W. Gibson and F. C. Bailey, *J. Chem. Soc., Chem. Commun.*, 1977, 815.

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