General Method for the Asymmetric Synthesis of *anti*-Diastereoisomers of β-Substituted L-2-Aminobutanoic Acids *via* Chiral Nickel(II) Schiff's Base Complexes of Dehydroaminobutanoic Acid. X-Ray Crystal and Molecular Structure of the Nickel(II) Complex of the Schiff's Base from [(Benzylprolyl)amino]benzophenone and Dehydroaminobutanoic Acid

Yuri N. Belokon',* Ashot S. Sagyan, Silva A. Djamgaryan, Vladimir I. Bakhmutov, Sergei V. Vitt, Andrei S. Batsanov, Yuri T. Struchkov, and Vasili M. Belikov
Nesmeyanov Institute of Organoelement Compounds, USSR Academy of Sciences, Moscow, USSR

An efficient approach to the asymmetric synthesis of (L)-*allo*-isomers of β-substituted α-aminobutanoic acid is described. The chiral Ni^{II} complex of a Schiff's base derived from (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BBP) and glycine was treated with acetaldehyde in MeOH. The addition proceeds with high diastereoselectivity to give, if catalysed by MeONa, the corresponding complex of (*R*)-threonine, and, if catalysed by Et_3N, the corresponding complex of (*S*)-*allo*-threonine. The (*R*)-threonine complex was converted into the chiral Ni^{II} complex of dehydroaminobutanoic acid, and a X-ray diffraction structural study of its major isomer showed that the dehydroaminobutanoic acid moiety was in the *E*-configuration. The complex, in turn, entered into Michael addition reactions with nucleophiles, including MeOH, EtOH, PhSH, and $PhCH_2SH$. The reaction proceeded with high diastereoselectivity, producing predominantly complexes of the *allo*-threonine derivatives (d.e. > 90%). Diastereoisomerically and enantiomerically pure α-amino acids were obtained after chromatographic purification, decomposition of the complexes, and recovery of the initial chiral auxiliary, BBP. The thiol addition reaction is accompanied by a side reaction leading to the formation of sizeable amounts of the vinylglycine complex. An approach to the synthesis of optically active vinylglycine starting with racemic methionine is described.

Optically active non-proteinogenic α-amino acids are relatively abundant in nature, their number totalling about 700;[1,2] some occur free[1] with their function often being unknown. The best example of free α-amino acids serving as drugs is provided by L-3,4-dihydroxyphenylalanine and L-α-methyl-3,4-dihydroxyphenylalanine.[2] However, a greater number of the non-proteinogenic α-amino acids are constituents of polypeptide derivatives, including antibiotics.[1–3] Particularly important are β-functionally substituted α-amino acids. For example, L-α,β-diaminopropanoic acid is a constituent of tuberactinomycin,[3a] bleomycin,[3b] edeine,[3c] and A19003 antibiotics.[3d] L-*threo*-α-amino-β-mescantobutanoic acid is an essential part of nisin antibiotic[3e] and L-*threo*-α-amino-β-methoxybutanoic acid is found to be an essential part of a novel natural depsipeptide, FR900359, which may have potential therapeutic applications.[3f]

The utility of non-proteinogenic α-amino acids for the purpose of imparting novel conformational features and protease resistance to synthetic polypeptides is a rapidly developing avenue of research.[4]

Because there is a great variety of potential uses of homochiral α-amino acids with the diverse nature of their side chains, many different strategies for their asymmetric synthesis are being developed.[5,6] The methods used could be roughly divided into two groups; the first approach employs derivatives already containing carboxy- and α-amino-substituents,[5] the second relies on the introduction of the α-amino-substituent asymmetrically.[6] The first approach is based mainly on the use of chiral nucleophilic[5a] and electrophilic[5b] derivatives of glycine; the catalytic asymmetric reduction of achiral dehydroamino acids[5c] and catalytic asymmetric alkylation of achiral glycine derivatives[5d] with the use of transition metal complexes as catalysts being another possibility.

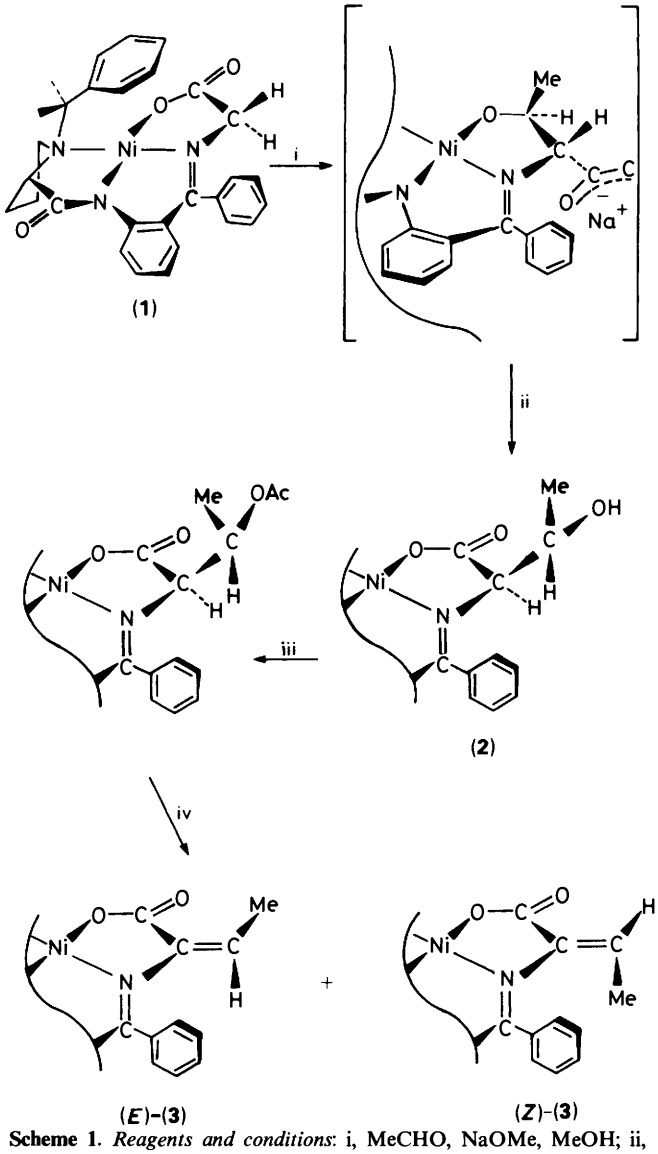
It should be mentioned that optically active β-functionally substituted α-amino acids (with the exception of α-amino-β-hydroxy acids) are usually produced *via* stereochemically unambiguous multistage substitution of the β-hydroxy group with a nucleophile in optically pure serine[7a] or threonine,[8] or from other L-amino acids by chemical transformations of their side chains.[7b] True asymmetric syntheses are rarely used for this particular purpose.[9]

Recently we developed a new approach to the synthesis of homochiral β-substituted α-aminopropanoic acids by employing a chiral Ni^{II} complex of a Schiff's base derived from (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BBP)† and dehydroalanine as an electrophile capable of asymmetric addition of different nucleophiles to the dehydroalanine moiety.[9a] It was the main goal of this work to broaden the scope of this reaction by including the dehydroaminobutanoic acid moiety as an electrophilic site for the nucleophilic attack. The nucleophilic addition would produce, in this case, a mixture of diastereoisomeric complexes, differing in the configurations of the α- and β-carbon atoms of the resulting amino acid. As was shown earlier, condensations of the Ni^{II} complex (**1**), derived from BBP and glycine, with aldehydes[10a] and vinyl aldehydes[10b] resulted in high diastereoselectivity at both α- and β-carbon atoms, and the reaction under study might be expected to be sufficiently stereoselective benefiting from the same kind of steric interactions inside the complex.

Results

Synthesis of the Ni^{II} Complex (**2**) *of the Schiff's Base formed from* (D)-*Threonine and BBP.*—The complex (**1**) was converted

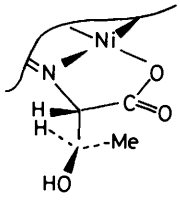
† Available from Merck (cat. no. 814473).



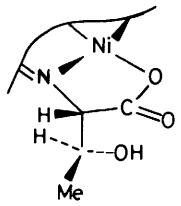
Scheme 1. *Reagents and conditions*: i, MeCHO, NaOMe, MeOH; ii, AcOH, MeOH; iii, Ac_2O, MeCN, 70–75 °C; iv, ACONa, DMF, 150 °C.

into complex (**2**) in MeOH by MeONa-catalysed addition of acetaldehyde to complex (**1**), as described earlier[10a] (Scheme 1).

Complex (**2**) was obtained in 90% yield by crystallization of the reaction mixture, the minor diastereoisomeric products of the addition reaction being the corresponding complexes of L-threonine (0.76%) and L-*allo*-threonine (2.1%), which were separated from the mother liquor by SiO_2 chromatography. The structure of the complexes was determined using the usual physical and chemical methods including quantitative and enantiomeric GLC analysis[11] of the amino acids recovered after the decomposition of the initial complexes. The significant difference between complexes of L-*threo*- and L-*allo*-threonine was found in their ^1H NMR spectra. The recurrence of the methyl protons of the L-*allo*-threonine moiety is at δ 1.08, whereas that of the group in the L-threonine moiety is at δ 1.9. The difference can be rationalized on the basis of the structure of the complex. As was shown earlier, the isopropyl group in related L-valine complexes was rigidly fixed in space with the *pro-S* methyl group located under the Ni^{II} co-ordination plane[12a] and its ^1H NMR signal shifted downfield (to δ 1.9) because of the deshielding influence of the Ni^{II} ions in their d^8 electronic configuration.[12] In the case of the L-threonine complexes, it is the methyl group which is situated under the metal ion, and it is the hydroxy group which occupies this position in the case of the *allo*-threonine complex.



threo-threonine



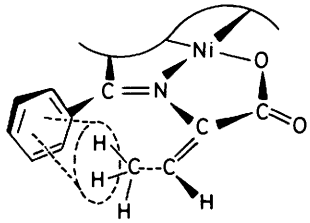
allo-threonine

Interestingly, the condensation of compound (**1**) with acetaldehyde, when catalysed by Et_3N and allowed to reach equilibration of the isomers (two months), led to a sizeable excess (7:1) of the L-*allo*-threonine diastereoisomer (>98% e.e. of the amino acid) over the *threo*-one.

Synthesis of Ni^{II} Complexes (**3**) *of the Schiff's Base derived from BBP and* Z- *or* E-α-*Aminodehydrobutanoic Acid.*—The synthetic sequence includes acetylation of complex (**2**) with Ac_2O in MeCN, followed by elimination of acetic acid from the complex, catalysed by MeCONa in dimethylformamide (DMF) at 150 °C (Scheme 1). The expected product (**3**) was obtained in 30% yield as a mixture of *E* and *Z* isomers in the ratio 5:1. The isomers were separated chromatographically on SiO_2 (benzene–acetone).

An attempt to utilize the diastereoisomeric complex of L-threonine instead of the D-threonine one (**2**) was unsuccessful. The corresponding *O*-acylated product failed to eliminate acetic acid under the experimental conditions of Scheme 1.

The isomer having the greatest R_f-value on SiO_2, and which was formed predominantly under the experimental conditions, had the chemical shift of its methyl protons at δ 1.65, which was typical for the shifts[13] of Me–C=C–. The peak for the methyl group in both *Z* and *E* isomers of bis-[(*N*-salicylidene)aminodehydrobutyrato]cobaltate(III) was at δ 2.15–2.20.[14] The minor isomer of complex (**3**) had the methyl signal at δ 0.84, which testified to a strong shielding of the protons by the diamagnetic ring current of the phenyl substituent at the C=N bond; this was a strong argument in favour of the *Z*-configuration of this isomer.



The final assignment of the configurations of the isomers came from the single-crystal X-ray structure analysis of the major isomer of complex (**3**). The atomic co-ordinates are given in Table 1; the bond lengths and angles are presented in Tables 2 and 3; the structure of the complex is shown in Figure 1. As can be seen from the data, the isomer has the *E*-configuration for the dehydroaminobutanoic acid moiety. The nickel atom has a slightly distorted square-planar co-ordination: the displacements from the O(1)N(1)N(2)N(3) mean plane are 0.10 Å for O(1) and N(2), −0.10 Å for N(1) and N(3), and 0.05 Å for Ni. The benzyl group adopts a common *endo* (towards Ni) orientation, and the proline moiety has a C_δ-envelope conformation. The metallocycle A adopts a chiral envelope λ-conformation with the N(1) atom tilted by 0.45 Å from the essentially planar NiO(1)C(1)C(2) moiety. A

Table 1. Atomic co-ordinates (× 10^4, Ni × 10^5) for complex (**3**).

Atom	*x*	*y*	*z*
Ni	32 737(22)	27 464(14)	32 653(6)
O(1)	3 809(9)	4 224(7)	3 134(3)
O(2)	3 912(10)	5 884(8)	3 506(3)
O(3)	3 490(11)	−510(7)	3 203(4)
N(1)	2 374(11)	3 270(8)	3 846(3)
N(2)	2 660(11)	1 291(8)	3 364(4)
N(3)	4 513(11)	2 207(9)	2 713(3)
C(1)	3 645(16)	4 896(11)	3 528(5)
C(2)	3 057(15)	4 280(10)	3 989(4)
C(3)	1 313(13)	2 818(12)	4 093(4)
C(4)	678(14)	1 742(10)	3 952(4)
C(5)	−627(15)	1 429(11)	4 175(5)
C(6)	−1 296(16)	438(12)	4 068(5)
C(7)	−638(16)	−287(12)	3 722(5)
C(8)	619(15)	−26(11)	3 500(5)
C(9)	1 362(15)	1 013(11)	3 605(4)
C(10)	3 507(16)	530(11)	3 143(5)
C(11)	4 791(16)	962(12)	2 832(5)
C(12)	6 244(16)	963(12)	3 108(5)
C(13)	6 737(18)	2 123(12)	3 163(5)
C(14)	5 986(15)	2 719(12)	2 729(5)
C(15)	3 806(15)	2 401(11)	2 216(4)
C(16)	2 323(16)	1 938(12)	2 157(5)
C(17)	1 080(16)	2 589(15)	2 283(5)
C(18)	−271(16)	2 108(24)	2 236(6)
C(19)	−514(23)	1 062(26)	2 064(8)
C(20)	730(23)	477(20)	1 974(7)
C(21)	2 108(20)	870(14)	1 990(6)
C(22)	3 605(16)	4 510(11)	4 451(5)
C(23)	4 525(22)	5 438(14)	4 628(6)
C(24)	653(15)	3 386(11)	4 550(5)
C(25)	746(16)	2 880(12)	5020(6)
C(26)	−12(19)	3 401(14)	5 426(5)
C(27)	−708(21)	4 353(14)	5 352(6)
C(28)	−850(22)	4 856(14)	4 899(7)
C(29)	−82(16)	4 347(13)	4 502(5)
O(W1)	3 542(14)	7 934(10)	3 965(4)
O(W2)	6 472(22)	8 068(16)	4 377(7)
O(W3)	1 251(22)	7 581(19)	4 652(7)
O(W4)	8 737(30)	7 164(24)	4 213(10)

Table 2. Bond lengths (Å) for complex (**3**).

Ni–O(1)	1.868(9)	C(6)–C(7)	1.40(2)
Ni–N(1)	1.856(9)	C(7)–C(8)	1.33(2)
Ni–N(2)	1.849(9)	C(8)–C(9)	1.45(2)
Ni–N(3)	1.961(9)	C(10)–C(11)	1.53(2)
O(1)–C(1)	1.33(2)	C(11)–C(12)	1.52(2)
O(2)–C(1)	1.21(2)	C(12)–C(13)	1.47(2)
O(3)–C(10)	1.26(2)	C(13)–C(14)	1.52(2)
N(1)–C(2)	1.41(2)	C(15)–C(16)	1.47(2)
N(1)–C(3)	1.29(2)	C(16)–C(17)	1.42(2)
N(2)–C(9)	1.39(2)	C(16)–C(21)	1.37(2)
N(2)–C(10)	1.33(2)	C(17)–C(18)	1.37(2)
N(3)–C(11)	1.54(2)	C(18)–C(19)	1.35(4)
N(3)–C(14)	1.48(2)	C(19)–C(20)	1.36(3)
N(3)–C(15)	1.49(2)	C(20)–C(21)	1.35(3)
C(1)–C(2)	1.53(2)	C(22)–C(23)	1.47(2)
C(2)–C(22)	1.35(2)	C(24)–C(25)	1.39(2)
C(3)–C(4)	1.46(2)	C(24)–C(29)	1.34(2)
C(3)–C(24)	1.52(2)	C(25)–C(26)	1.43(2)
C(4)–C(5)	1.38(2)	C(26)–C(27)	1.32(2)
C(4)–C(9)	1.41(2)	C(27)–C(28)	1.35(2)
C(5)–C(6)	1.37(2)	C(28)–C(29)	1.40(2)

Table 3. Bond angles for complex (**3**).

O(1)–Ni–N(1)	87.2(4)	C(6)–C(7)–C(8)	121(1)
O(1)–Ni–N(2)	176.5(4)	C(7)–C(8)–C(9)	122(1)
O(1)–Ni–N(3)	91.2(4)	N(2)–C(9)–C(4)	122(1)
N(1)–Ni–N(2)	93.8(4)	N(2)–C(9)–C(8)	121(1)
N(1)–Ni–N(3)	170.9(4)	C(4)–C(9)–C(8)	117(1)
N(2)–Ni–N(3)	88.3(4)	O(3)–C(10)–N(2)	128(1)
Ni–O(1)–C(1)	113.5(8)	O(3)–C(10)–C(11)	114(1)
Ni–N(1)–C(2)	108.4(8)	N(2)–C(10)–C(11)	117(1)
Ni–N(1)–C(3)	127.9(9)	N(3)–C(11)–C(10)	108(1)
C(2)–N(1)–C(3)	124(1)	N(3)–C(11)–C(12)	104(1)
Ni–N(2)–C(9)	123.4(8)	C(10)–C(11)–C(12)	115(1)
Ni–N(2)–C(10)	113.9(8)	C(11)–C(12)–C(13)	109(1)
C(9)–N(2)–C(10)	122(1)	C(12)–C(13)–C(14)	103(1)
Ni–N(3)–C(11)	105.1(7)	N(3)–C(14)–C(13)	104(1)
Ni–N(3)–C(14)	111.6(8)	N(3)–C(15)–C(16)	116(1)
Ni–N(3)–C(15)	111.1(7)	C(15)–C(16)–C(17)	120(1)
C(11)–N(3)–C(14)	104.1(9)	C(15)–C(16)–C(21)	121(1)
C(11)–N(3)–C(15)	113.8(9)	C(17)–C(16)–C(21)	118(1)
C(14)–N(3)–C(15)	110.8(9)	C(16)–C(17)–C(18)	118(2)
O(1)–C(1)–O(2)	122(1)	C(17)–C(18)–C(19)	125(2)
O(1)–C(1)–C(2)	112(1)	C(18)–C(19)–C(20)	113(2)
O(2)–C(1)–C(2)	126(1)	C(19)–C(20)–C(21)	127(2)
N(1)–C(2)–C(1)	111(1)	C(16)–C(21)–C(20)	118(2)
N(1)–C(2)–C(22)	126(1)	C(2)–C(22)–C(23)	131(1)
C(1)–C(2)–C(22)	120(1)	C(3)–C(24)–C(25)	120(1)
N(1)–C(3)–C(4)	122(1)	C(3)–C(24)–C(29)	121(1)
N(1)–C(3)–C(24)	121(1)	C(25)–C(24)–C(29)	119(1)
C(4)–C(3)–C(24)	116(1)	C(24)–C(25)–C(26)	117(1)
C(3)–C(4)–C(5)	118(1)	C(25)–C(26)–C(27)	120(1)
C(3)–C(4)–C(9)	122(1)	C(26)–C(27)–C(28)	124(2)
C(5)–C(4)–C(9)	120(1)	C(27)–C(28)–C(29)	115(2)
C(4)–C(5)–C(6)	122(1)	C(24)–C(29)–C(28)	124(1)
C(5)–C(6)–C(7)	119(1)		

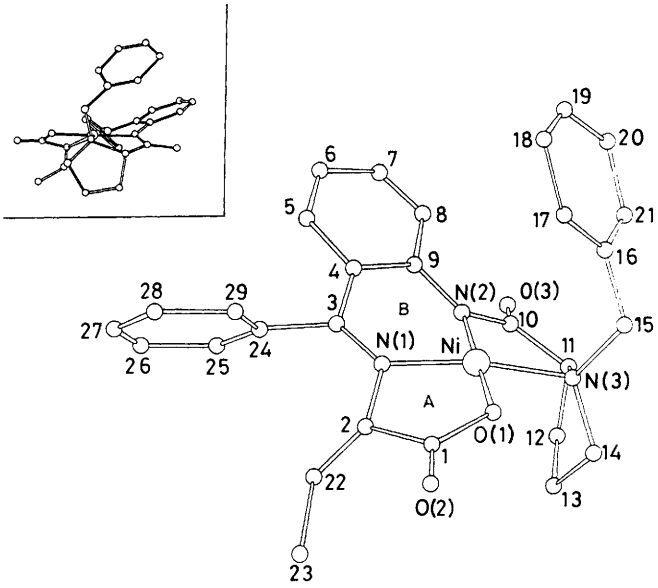


Figure 1. Structure of Ni^{II} complex of (*E*)-dehydroaminobutanoic acid Schiff's base with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone, (*E*)-(**3**). The insert is the view down the N(3)–Ni–N(1) axis of (*E*)-(**3**).

similar chiral conformation is found in the L-serine complex,[10a] and, probably, is responsible for the similarity of the ORD curves of (*E*)-(**3**) and other related complexes with an L-configuration of their α-amino acid moieties (Figure 2). The C=C bond of the dehydroaminobutanoic part of (*E*)-(**3**) is twisted, with a torsional angle C(1)C(2)C(22)C(23) of 11°, although the length of the bond, 1.35 Å, is not uncommon for this kind of bond.[15] The phenyl substituent at the C=N bond is skewed [the torsional angle N(1)C(3)C(24)C(29) is 66(4)°] relative to the plane of the bond and shields the *re-re* face of the C=C bond.

Both isomers of complex (**3**) could be easily equilibrated with

Table 4. Michael addition of nucleophiles to complex (3).[a]

Entry	Initial (3)	Nucleophile	Solvent	t/°C	Catalyst	Chemical yield (%)[b]	Amino acid enantiomeric purity (%)[c] (configuration)
1	(*E*)-(3)	MeO^-	MeOH	50–55	MeONa (0.2M)	78	>98 (2*S*,3*S*)
2	(*Z*)-(3)	MeO^-	MeOH	50–55	MeONa (0.2M)	80	>98 (2*S*,3*S*)
3	(*E*)-(3)	EtO^-	EtOH	50–55	EtONa (0.04M)	79[d]	>98 (2*S*,3*S*)
4	(*Z*)-(3)	EtO^-	EtOH	50–55	EtONa (0.04M)	76[d]	>98 (2*S*,3*S*)
5	(*E*)-(3)	PhS^-	MeCN	25	NaOH[e]	65[d]	>98 (2*R*,3*S*)
6	(*E*)-(3)	$BzlS^-$	MeCN	25	NaOH[e]	67	>98 (2*R*,3*S*)

[a] Concentration of (3) was 0.5M. [b] Isolated yield of the diastereoisomerically pure complex based on initial complex (3) used; the amino acids were recovered from the complex in 75–80% yield. [c] GLC enantiomeric analysis. [d] The initial reaction mixture contained 3–5% of other addition diastereoisomers. [e] Powdered NaOH was used.

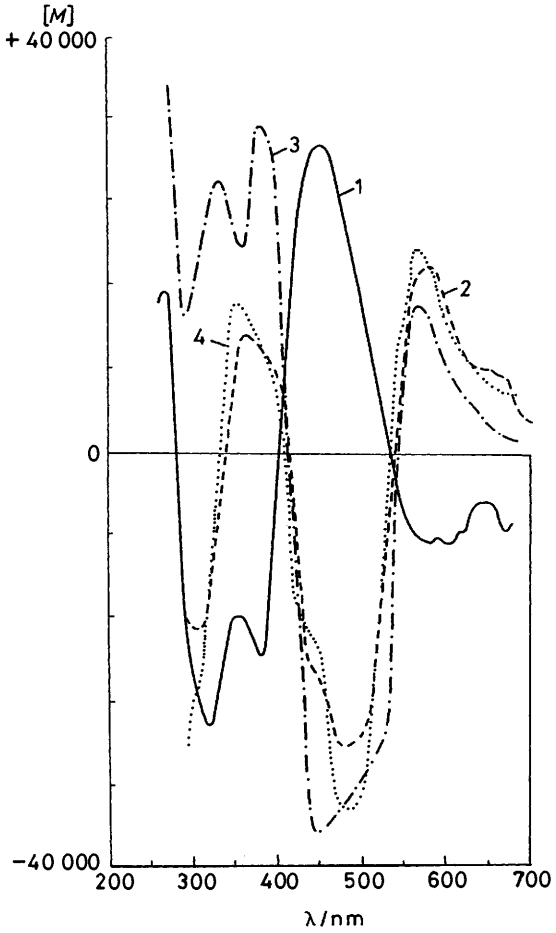
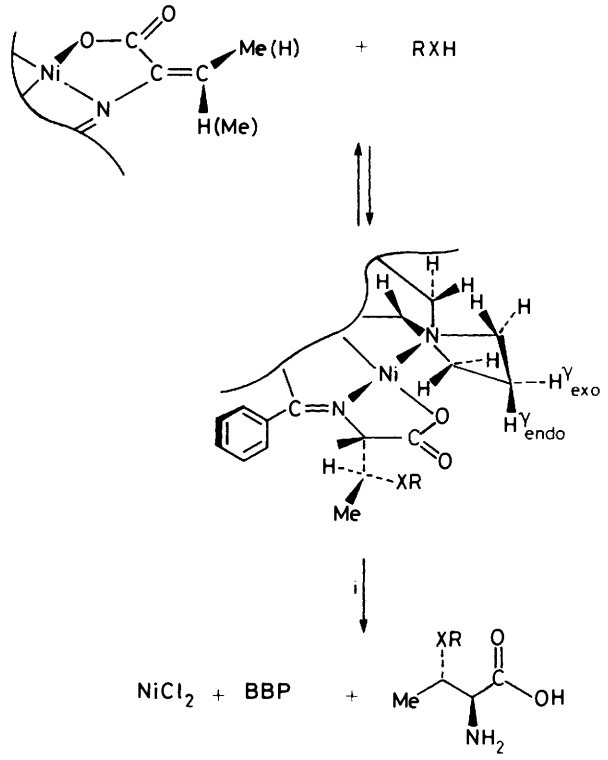


Figure 2. ORD curves (25 °C; MeCN) of the Ni^{II} complexes:
1 (*R*)-threonine
2 (2*R*,3*S*)-2-amino-3-(benzylthio)butanoic acid
3 (*E*)-dehydroaminobutanoic acid
4 (2*S*,3*S*)-2-amino-3-methoxybutanoic acid.

diazabicyclo-octane (DABCO) in MeCN to give the same 1:1 ratio of *E* and *Z* isomers.

Synthesis of Enantiomerically and Diastereoisomerically Pure β-Substituted α-Aminobutanoic Acids.—As expected, the double bond of complex (3) was sufficiently electrophilic to add



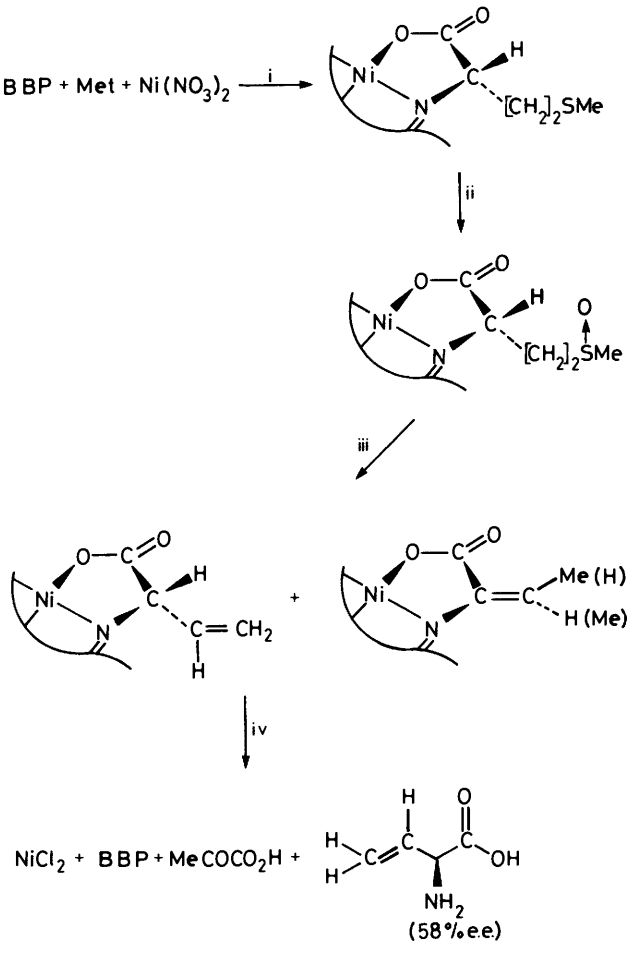
Scheme 2. RXH = MeOH, EtOH, PhSH, BzlSH. *Reagent*: i, aq. HCl.

nucleophiles such as thiolate and alcoholate ions (Scheme 2), whereas benzylamine and dimethylamine did not give sizeable amounts of the addition products.

Chromatographic purification or crystallization provided diastereoisomerically pure complexes. The ORD curves of the complexes could be used to assign L-absolute configurations to the α-carbon atoms of the amino acid side chains; as discussed earlier,[9a,10b] Cotton effects in the 500–700 nm region were positive for α-L- and negative for α-D-amino acids (Figure 2). The absolute configuration of the β-carbon atoms was assigned using ^1H NMR shifts of the methyl protons which were found in the region δ 1.07–1.1 for all the major addition products. Thus, by employing the arguments put forward to understand the difference in the chemical shifts of threonine and *allo*-threonine moieties in the complexes, the mutual arrangement of the two asymmetric carbon atoms in the amino acid moiety

of the reaction products could be assigned as *allo*. The result did not depend on which of the two isomers of complex (3) was used as the initial compound (Table 4, entries 1,3 and 2,4). The minor isomers, obtained usually as admixtures with other side products, were found in quantities not exceeding 5% and their amount strongly depended on the type of the nucleophile used (Table 4). A side reaction, producing threonine complexes, consumed *ca.* 4% of the initial complex (3) in the case of addition of ethanol. The additions of thiols were also accompanied by some threonine complex accumulation and by substantial formation of a vinylglycine complex [as a mixture with (3) in the rates 1.2:1–2:1; up to 18%]. Attempts to prepare the vinylglycine derivative by treatment of complex (3) with powdered NaOH or sodium phenolate in boiling MeCN were unsuccessful.

The synthesis of the L-vinylglycine complex was completed as shown in Scheme 3, starting with racemic methionine. The first stage of the reaction was the formation of the corresponding L-Met complex *via* the enantioselection of the L-enantiomers of the amino acid by BBP and Ni^{II} ions accompanied by simultaneous racemization of the remaining D-enantiomer in the solution. The transfer of the Met complex into the vinylglycine one followed the same principle that was developed earlier by the Rapoport's[16a] and Seebach's[16b] groups. The L-vinylglycine complex has been obtained together with some complex (3), and its ^1H NMR spectrum was identical with that of the sample of the side product from addition of the thiol.



Scheme 3. *Reagents and conditions*: i, MeOH, NaOMe; ii, KIO_4; iii, DMSO, 180 °C; iv, aq. HCl.

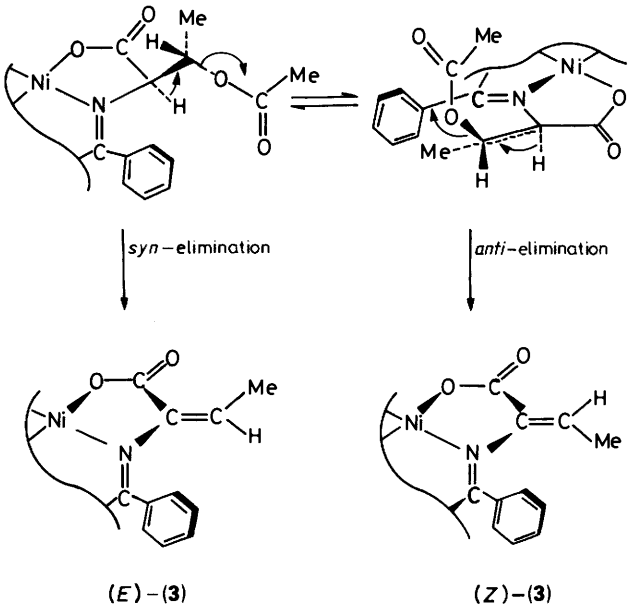
The α-amino acids were recovered from the diastereoisomerically pure complexes by treatment of the latter with aq. HCl (Schemes 2 and 3), followed by neutralization of the reaction mixture and extraction of BBP. Purification of the α-amino acids has been achieved using the usual ion-exchange technique and crystallization. All the amino acids were enantiomerically and diastereoisomerically pure, L-vinylglycine being the only exception (58% e.e.). In the latter case it is the racemization of this optically labile amino acid during the recovery operation which might be responsible for the observed low enantiomeric purity of the compound. At least, BBP, recovered from the mixture of the diastereoisomerically pure vinylglycine complex and complex (3), was enantiomerically pure, according to the polarimetric data.

Discussion

Condensation of compound (1) with acetaldehyde catalysed by MeONa produced complexes of D-threonine because, at high pH, substitution of the ionized carboxy group for the ionized hydroxy group in the main co-ordination plane of Ni^{II} occurred[10a] (Scheme 1) and the rearranged complex was thermodynamically more stable with its α-amino acid moiety in the D-*threo*-form.[10a] However, as soon as the reaction mixture had been neutralized, the complex returned to the carboxy-co-ordinated form in which the α-amino acid of *R* (or D)-configuration is thermodynamically unfavourable.[9a,10,12a] Dehydration of complex (2), carried out according to Scheme 1, relieves the steric strain. The structure of (*E*)-(3) may shed some light on the origin of nonbonding interactions causing the strain. As can be seen from Figure 1, the amino acid α-carbon atom has sp^2 electronic configuration. Therefore, the chiral λ-conformation of the amino acid chelate ring might only be induced by the chiral proline moiety *via* the system of interconnected chirally distorted chelate rings. The chiral puckering of metallocycle B, in turn, causes the phenyl substituent at the C=N bond to shield the *re*-side of the amino acid moiety (see the inset, Figure 1). Substitution of the achiral dehydroaminobutanoate moiety for a D-amino acid would, undoubtedly, result in severe steric congestion originating from the nonbonding interactions of the alkyl group of the amino acid side chain with the phenyl substituent. Steric interaction of the side chain of the D-amino acid with the *N*-benzyl substituent, as postulated earlier,[12a] may also provide part of the strain energy in the complex. On the other hand, an L-amino acid would have its alkyl side chain further removed from the phenyl substituents, and any change from sp^3 configuration at the α-carbon atom to sp^2 in this case would be energetically unfavourable. The failure to induce dehydration of the L-threonine complex may stem from this.

Whatever the mechanism of the elimination reaction, the ratio of *E* and *Z* isomers (5:1) was determined by kinetic effects, the relative ease of *syn*- relative to *anti*-elimination (Scheme 4), and not by the thermodynamic stability of the final products (1:1 ratio). Steric congestion in the transition state of *anti*-elimination (probably *E*1cB)[14] might result from the nonbonding interaction between the phenyl substituent at the N=C bond and the methyl group of the threonine moiety. Interaction of the phenyl substituent with the proton of the threonine moiety in the case of *syn*-elimination could be expected to be less severe. The energy difference between the two transition states might be responsible for the greater proportion of *E*-isomer in the final product.

Strong nucleophile addition to the C=C bond of complex (3) proceeds smoothly to give predominantly complexes of L-*allo*-threonine derivatives. Since both isomers of complex (3) afforded the same mixture of addition products, the diastereoisomeric ratio of the amino acid moieties was clearly

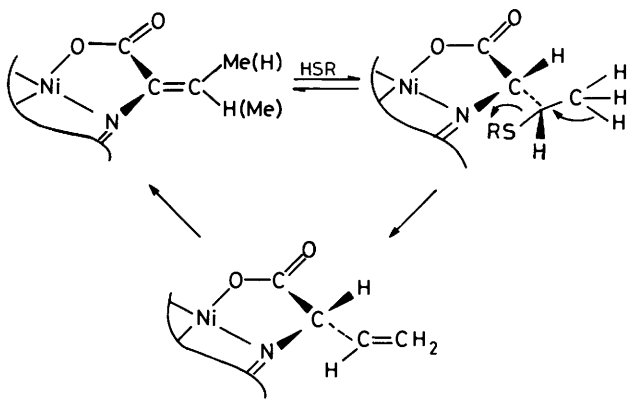


Scheme 4.

thermodynamically controlled. The equilibrium between the isomers was, probably, established *via* a series of addition–elimination steps of RXH and the concomitant epimerization of the final product *via* the intermediate carbanion of the α-amino acid moiety. Addition of acetaldehyde to complex (**1**) under thermodynamic control at low pH also furnished the complex of L-*allo*-threonine predominantly.

The only difference which distinguishes between complexes of *allo*- and *threo*-isomers is the orientation of the heteroatom (oxygen atom in the case of threonines) either under the metal ion (*allo*), or outside the co-ordination sphere (*threo*) (see above). Steric congestion, resulting from interaction of the proline *endo*-γ-hydrogen atom with either the Me or the RX group (Scheme 2) is, evidently, smaller in the latter case. Some support for this notion may be derived from the relative conformational energies of methyl, alkoxy, and alkylthio groups, as determined for substituted cyclohexanes.[17] In the case of MeOH addition, the *threo*-isomer was not found among the reaction products, but with increasing size of the entering group its proportion became greater, never, however, exceeding 5%. Some kind of apical co-ordination of the heteroatom to the central metal ion might also contribute to the thermodynamic predominance of the L-*allo*-isomers. The energy of such co-ordination might not be great; 1–2 kcal mol^{-1}* values would be sufficient to shift the equilibrium towards the *allo*-isomer. The conformation of the L-serine side chain in a related complex, according to the X-ray crystal-structure analysis data, puts the hydroxy group under the metal ion at a distance of 3.3 Å,[10a] which may be considered as an indirect indication of some kind of interaction.

Formation of the vinylglycine complex in the addition of thiol cannot be rationalized on the basis of the usual mechanism of allylic rearrangement because treatment of complex (**3**) with powdered NaOH in MeCN furnished no complex of vinylglycine even after prolonged heating in MeCN. We believe that the complex originated from the thiol addition compound, as shown in Scheme 5. Base-catalysed elimination of the thiol gives rise to the vinylglycine complex which, *via* allylic rearrangement and a series of addition–elimination steps, is



Scheme 5.

at equilibrium with complex (**3**) and the thiol addition complex.

The side reaction of formation of the threonine complex may come from addition of hydroxide ion to complex (**3**) and its significance may be determined by the relative rates of addition of water and of nucleophile to complex (**3**) and the relative concentrations of the corresponding products.

Conclusions

The method elaborated in this work is suitable for the production of enantiomerically and diastereoisomerically pure derivatives of *allo*-threonine and is based on a simple series of reactions and the use of relatively inexpensive reagents. The range of nucleophiles capable of addition to complex (**3**) is probably not limited to the conjugated bases of alcohols or thiols. There are other candidates including organometallic compounds, and carbanions of CH-acids. The disadvantage of the method consists of a relatively low chemical yield of complex (**3**), but the yield was not optimized and might be capable of being further increased.

Experimental

General.—Reagents were purchased from Reakhim (USSR), with the exception of *o*-aminobenzophenone, silica gel 60 F_{254}, and precoated silica gel 60 F_{254} plates (Merck), Sephadex LH-20 (Pharmacia), and silica gel for column chromatography L 40/100 (Lachema). 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: UV-visible, Specord M-40; ^{1}H NMR, Bruker WP-200 (200 MHz) and Tesla 467A; ORD, JASCO ORD/UV-5 (specific rotations measured with a Perkin-Elmer 241 polarimeter). M.p.s were measured with an Electrothermal apparatus. GC-MS spectra were obtained with a Nermag R 10-10C-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 GLC as described in ref. 11*a*. The method is a modification of the published procedure based on the use of Chirasil-L-Val.[11b]

^{1}H NMR spectra were obtained with use of the double-resonance technique where necessary. Hexamethyldisiloxane (HMDS) was used as internal reference in $CDCl_3$, and sodium 3-trimethylsilylpropane-1-sulphonate (DSS) was used as internal reference for D_2O solutions.

X-*Ray Analysis.*—Red crystals of (*E*)-(**3**)·4H_2O were obtained from aqueous EtOH. Crystal data: $C_{29}H_{27}N_3NiO_3$·4H_2O, M = 596.3, orthorhombic, a = 9.153(2), b = 11.975(1),

* 1 cal = 4.184 J.

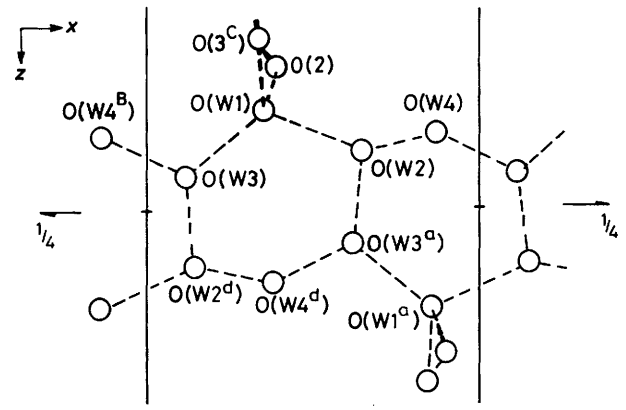


Figure 3. Hydrogen bonds in the structure of (*E*)-(3)-4H_2O. Atoms generated from the references ones by symmetry operations: [a] $x + \frac{1}{2}, \frac{3}{2} - y, 1 - z$; [b] $x - 1, y, z$; [c] $x, y + 1, z$; [d] $x - \frac{1}{2}, \frac{3}{2} - y, 1 - z$.

c = 26.533(3) Å, V = 2 908.2(7) Å^3, Z = 4, D_c = 1.36 g cm^{-3}, space group $P2_12_12_1$, $F(000)$ = 1 160. The unit-cell parameters and reflection intensities from a plate-like crystal of dimensions *ca.* 0.4 × 0.2 × 0.1 mm were measured with a four-circle automated Hilger & Watts diffractometer (T 20 °C, Mo-K_α radiation, λ 0.710 69 Å, θ/2θ scan, 2θ < 50°, scan speed 2–10 deg min^{-1}, scan width of 1.6°, no cystal decay was observed, 1 118 independent observed reflections with $F^2 > 2\sigma$). The structure was solved by Patterson and Fourier methods. No absorption correction was applied. Owing to an insufficient number of reflections in the least-squares refinement only the Ni and 11 peripheral carbon atoms were refined in anisotropic approximation, whereas other non-hydrogen atoms were refined isotropically. Hydrogen atoms of complex (**3**) were included as fixed contributions in calculated positions (C–H bond distances of 1.0 Å; B_{iso} 1 Å^2 larger than B_{eq} of the corresponding carbon atoms), and water hydrogens were not located. The weighting scheme $w = [\sigma^2(F) + 0.0001\,F_o^2]^{-1}$ was used. The refinement converged to R = 0.056 (R_w = 0.050) for the absolute structure corresponding to the known (*S*)-proline, and to R = 0.064 (R_w = 0.060) for the inverted structure, thus confirming the former structure with a 99.5% probability according to Hamilton's test.[18] Atomic co-ordinates are listed in Table 1. The calculations were carried out with an Eclipse S/200 minicomputer using the INEXTL (modified EXTL) programs.[19] The crystal packing of molecules of complex (*E*)-(**3**) leaves infinite channels along the 2_1 axes [x, 3/4, 1/2], [x, 1/4, 0], *etc.*, occupied by double ribbons of molecules of water of crystallization. In the ribbons the contacts O(W1)···O(W2) 2.90(2), O(W1)···O(W3) 2.81(2), O(W2)···O(W3[a]) 2.70(3), O(W2)···O(W4) 2.38(3), and O(W3)···O(W4[b]) 2.63(3) Å evidently correspond to hydrogen bonds. The ribbons are linked to the host structure *via* the hydrogen bonds O(W1)···O(2) 2.76(2) and O(W1)···O(3[c]) 2.75(2) Å (Figure 3). The large thermal factors of O(W2), O(W3), and O(W4) [17.9(7), 20.6(8), and 30(1) Å^2, *vs.* 8.8(4) Å^2 for O(W1)] and somewhat shortened contacts involving O(W4) may reflect some disorder or non-stoicheiometric occupancy of water positions.*

Syntheses of (S)-2-[N-(N-*Benzylprolyl*)*amino*]*benzophenone* (*BBP*) *and the Initial Complex* (**1**).—These were carried out as described in ref. 10*a*. The improvement on the synthesis of complex (**1**) consisted in the neutralization of the reaction mixture (with aq. HCl) after it had been stirred for 4–5 h at 50–60 °C, evaporation of the solution, and addition of water. The resulting precipitate was separated, dissolved in $CHCl_3$, and the solution was washed several times with water. The solution was evaporated and the residue was recrystallized from acetone. An additional portion of complex (**3**) was obtained from the mother liquor by chromatography on SiO_2 as described in ref. 10*a*.

General Procedure for the Recovery of BBP and the α-Amino Acids from the Ni^{II} *Complexes.*—To a solution of the complex in MeOH (or EtOH) (1 g in 10 ml) was added 2M-aq. HCl (8–10 mol equiv.), and the mixture was refluxed until the red colour of the solution disappeared (3–10 min). The solution was evaporated, a small volume of cold water was added to the residue, and the resultant precipitate of BBP hydrochloride was collected and washed several times with small portions of cold water. The aqueous solutions were combined, the pH was brought to 8–9 with aq. NH_3, and the remaining BBP was extracted with several portions of $CHCl_3$. The aqueous phase was adsorbed onto strongly acidic ion-exchange resin Dowex 50 × 8 (or a similar type of resin). The resin was washed with distilled water till the washings became neutral, and then the amino acid was removed from the column with 5% aq. NH_3. The solution was evaporated and the residue was recrystallized. Enantiomeric analysis of the amino acids was performed before the crystallization.

Ni^{II} *Complex* (**2**) *of the Schiff's Base of* (R)-*Threonine and BBP.*—To a solution of complex (**1**) (18.3 g, 3.67 × 10^{-2} mol) in 0.2M-MeONa in MeOH (150 ml) under argon was added acetaldehyde (12.1 ml, 2.1 × 10^{-1} mol). The mixture was stirred at room temperature. The reaction was monitored by TLC [SiO_2; $CHCl_3$–acetone (5:1)] with the initial neutralization of an aliquot. After the ratio of the isomers ceased changing (less than 2 h), the reaction mixture was neutralized with conc. AcOH (27 ml) and evaporated to dryness. $CHCl_3$ (150 ml) and water (20 ml) were added to the stirred residue; the organic layer was separated, washed several times with water, and evaporated. A portion of heptane was added to the residue and the mixture was evaporated to remove traces of acetic acid. To the residue was added a portion of boiling acetone (the minimum amount necessary to dissolve the mixture). After cooling overnight, the resultant precipitate was collected and dried *in vacuo* to give complex (**2**) (17.0 g, 85%) as red crystals. The mother liquor was additionally purified on a SiO_2 column [30 × 5 cm; $CHCl_3$–acetone (5:1)].

Four additional fractions were obtained (as red bands); the first fraction, in the order of its emergence from the chromatographic column, was complex (**2**) (1 g, 5%) which was combined with the portion obtained by crystallization; complex (**2**) had m.p. 165–167 °C (Found: C, 64.6; H, 5.4; N, 8.3. $C_{29}H_{29}N_3NiO_4$ requires C, 64.23; H, 5.39; N, 7.74%); λ_{max}(MeCN) 266 (log ε 4.24), 328 (3.72), 423 (3.52), and 525 nm (3.27); $[\alpha]_{589}^{25}$ (2 g dm^{-3} in MeCN; *l* 1 cm) −609°; δ($CDCl_3$) 1.62 (3 H, d, *J* 7 Hz, Me), 3.7 (1 H, m, *J* 5 and 6 Hz, amino acid β-H), 1.62–3.9 (7 H, m, Pro α-, β-, γ-, δ-H) 4.0 (1 H, d, *J* 5 Hz, amino acid α-H), 3.77 and 4.46 (2 H, AB, *J* 12 Hz, CH_2Ph), and 6.8–8.5 (14 H, m, ArH). Threonine recovered from complex (**2**) was enantiomerically pure and had the D- or *R*-configuration according to GLC.

The second fraction according to ^{1}H NMR data was unchanged complex (**1**) (0.36 g recovery, 2%).

The third fraction, the *Ni*^{II} *complex of the Schiff's base of* (S)-*threonine and BBP*, was obtained as red crystals (0.15 g, 0.76%) (Found: C, 64.45; H, 5.5; N, 7.85. $C_{29}H_{29}N_3NiO_4$ requires C, 64.23; H, 5.39; N, 7.74%); λ_{max}(MeCN) 336 (3.81),

* *Supplementary data* (see section 5.6.3 of the Instructions for Authors, in the January issue). H-Atom co-ordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

419 (3.65), and 532 nm (2.53); $[\alpha]_{589}^{25}$ (1.27 g dm^{-3} in MeCN; *l* 0.5 cm) +3 244°; δ($CDCl_3$) 1.91 (3 H, d, *J* 7 Hz, Me), 1.95–4.0 (8 H, m, amino acid β-H, and Pro α-, β-, γ-, δ-H), 4.05 (1 H, d, *J* 5 Hz, amino acid α-H), 3.58 and 4.38 (2 H, AB, *J* 12 Hz, CH_2Ph), and 6.61–8.2 (m, ArH). Threonine recovered from the fraction was enantiomerically pure and had the L-or *S*-configuration according to GLC.

The fourth fraction was the *Ni^{II} complex of the Schiff's base of* (S)-allo-*threonine and BBP* (0.38 g, 2.1%) (Found: C, 64.4; H, 5.4; N, 7.8. $C_{29}H_{29}N_3NiO_4$ requires C, 64.23; H, 5.39; N, 7.74%); λ_{max}(MeCN) 337 (3.67), 422 (3.28), and 520 nm (2.82); $[\alpha]_{589}^{25}$ (0.73 g dm^{-3} in MeCN; *l* 0.5 cm) +2990°; δ($CDCl_3$) 1.06 (3 H, d, *J* 7 Hz, Me), 2.02–3.08 (8 H, m, amino acid β-H, and Pro α-, β-, γ-, δ-H), 3.88 (1 H, d, amino acid α-H), and 6.85–8.1 (m, ArH). allo-*Threonine* recovered from the fraction was enantiomerically pure and had the L or *S*-configuration according to GLC.

Synthesis of L-allo-*Threonine*.—To a stirred solution of complex (**1**) (5 g 1.0 × 10^{-2} mol) in MeOH (42 ml) was added acetaldehyde (16.5 ml, 0.3 mol) followed by Et_3N (3.2 ml, 2.3 × 10^{-2} mol). The reaction mixture was left in a stopped flask for 2 months at ambient temperature. The reaction was monitored by TLC. The initial complex was converted within one hour into a mixture of threonine diastereoisomeric complexes but it took at least 2 months for the equilibrium between the isomers to be established. Decomposition of the reaction mixture gave (*S*)-*allo*-threonine and (*S*)-threonine (according to GLC) in a 7:1 ratio and of enantiomeric purity 100 and 57%, respectively.

Synthesis of the Ni^{II} Complex (**3**) *of the Schiff's Base of* E- *and* Z-*Dehydroaminobutanoic Acid and BBP*.—To a solution of complex (**2**) (6.9 g, 1.27 × 10^{-2} mol) in anhydrous MeCN (20 ml) was added acetic anhydride (23 ml, 0.24 mol) and the mixture was heated to 70–75 °C for 2 h. The reaction was monitored by TLC [SiO_2; $CHCl_3$–acetone (5:1)]. After disappearance of the initial complex (**2**), the solvent was removed under reduced pressure and DMF (20 ml) and anhydrous $MeCO_2Na$ (5.36 g) were added to the residue. After several evacuations and purges with Ar, the mixture was heated to 150 °C for 1 h under argon and then poured into a stirred, cooled solution of 1% aq. acetic acid (2 l). The resultant precipitate was separated, and dissolved in $CHCl_3$. The organic layer was washed with water, and evaporated. The residue was chromatographed on a SiO_2 column [30 × 5 cm; benzene–acetone (1:1)]. Complex (*E*)-(**3**) was obtained as the first fraction (1.69 g, 25.4%). The second fraction contained complex (*Z*)-(**3**) (0.29 g, 4.4%). Complex (*E*)-(**3**) had m.p. 128–130 °C (Found: C, 67.1; H, 5.6; N, 8.1. $C_{29}H_{27}N_3NiO_3$ requires C, 66.44; H, 5.19; N, 8.01%); λ_{max}(MeOH) 270 (4.19), 339 (3.84), 430 (3.47), and 531 nm (2.65); $[\alpha]_{589}^{25}$ (2 g dm^{-3} in MeOH; *l* 1 cm) +2 500°; δ($CDCl_3$) 1.65 (3 H, d, *J* 6 Hz, Me), 1.95–3.75 (7 H, m, Pro α-, β-, γ-, δ-H), 3.35 and 4.3 (2 H, AB, *J* 12 Hz, CH_2Ph), 5.05 (1 H, q, *J* 6 Hz, *H*C=C), and 6.65–8.0 (14 H, m, Ar*H*).

Complex (*Z*)-(**3**) (Found: C, 65.7; H, 5.8; N, 7.9%); $[\alpha]^{25}$ (2 g dm^{-3} in MeOH; *l* 0.2 cm) +2 400° (589), +2 070° (578), −1 980° (546), −1 030° (436), and +250° (365 nm); λ_{max}(MeOH) 268 (4.18), 335 (3.75), 428 (3.47), and 542 nm (2.62), δ($CDCl_3$) 0.84 (3 H, d, *J* 6 Hz, Me), 1.9–4.0 (7 H, m, Pro α-, β-, γ-, δ-H), 3.32 and 4.28 (2 H, AB, *J* 12 Hz, CH_2Ph), 5.8 (1 H, q, *J* 6 Hz, HC=C), and 6.81–8.18 (14 H, m, ArH).

(2S,3S)-2-*Amino*-3-*methoxybutanoic Acid*.—Complex (*E*)-(**3**) or (*Z*)-(**3**) (2.5 g 4.8 × 10^{-3} mol) was dissolved in a 0.2M-solution of MeONa in MeOH (25 ml). The reaction mixture was stirred at 50–55 °C under argon. The reaction was monitored by ^1H NMR spectroscopy, by recording the disappearance of the vinyl proton signal at δ 5.05 (or δ 5.8), or by using the shift of the UV maximum from 430 nm in the initial compound to 420 nm in the addition product. After the disappearance of complex (**3**), the reaction mixture was neutralized with conc. acetic acid (or aq. HCl) and evaporated; the residue was chromatographed on a SiO_2 column [3.5 × 30 cm; benzene–acetone (1:1)] and additionally purified on a Sephadex LH-20 column [benzene–EtOH (3:1)]. The *complex of* (2S,3S)-2-*amino*-3-*methoxybutanoic acid* was obtained as a single orange band (2.08 g, 78%), m.p. 134–135 °C decomp.) (Found: C, 64.85; H, 5.7; N, 7.4. $C_{30}H_{31}N_3NiO_4$ requires C, 64.77; H, 5.61; N, 7.55%); $[\alpha]^{25}$ (7 × 10^{-4} mol in MeCN; *l* 1 cm) +2 830° (589), +30 000° (578), +323° (546), and −1 934° (436 nm); λ_{max}(MeCN) 265 (4.18), 338 (3.68), 420 (3.5), and 529 nm (2.39); δ($CDCl_3$) 1.05 (3 H, d, *J* 6 Hz, Me-C), 1.8–3.5 (7 H, m, Pro α-, β-, γ-, δ-H), 3.26 (1 H, m, *J* 2 and 6 Hz, amino acid β-H), 3.49 (3 H, s, MeO), 3.85 (1 H, d, *J* 2 Hz, amino acid α-H), 3.37 and 4.35 (2 H, AB, *J* 12 Hz, CH_2Ph), and 6.8–8.07 (14 H, m, ArH).

The complex (1.8 g, 3.2 × 10^{-2} mol) was decomposed in the usual manner, and the amino acid was recovered and recrystallized from EtOH to yield (2S, 3S)-2-*amino*-3-*methoxybutanoic acid* as white crystals (0.34 g, 80%), m.p. 220–224 °C (decomp.) (Found: C, 45.1; H, 8.3; N, 10.5. $C_5H_{11}NO_3$ requires C, 45.12; H, 7.99; N, 10.51%); $[\alpha]_{589}^{25}$ (6.1 g dm^{-3} in aq. 6M-HCl) +29.1°. Enantio- and diastereoiso-meric purity of the α-amino acid was higher than 98% according to GLC; δ(D_2O–DCl) 1.59 (3 H, d, *J* 6.8 Hz, Me-C), 3.71 (3 H, s, MeO), 4.33 (1 H, m, *J* 3.5, and 6.8 Hz, β-H), and 4.62 (1 H, d, *J* 3.5 Hz, α-H). The amino acid samples obtained from (*E*)-(**3**) and (*Z*)-(**3**) were identical.

(2S,3S)-2-*Amino*-3-*ethoxybutanoic Acid*.—Complex (*E*)-(**3**) or (*Z*)-(**3**) (2 g, 3.8 × 10^{-3} mol) was dissolved in 0.04M-EtONa in EtOH (25 ml) and the mixture was further treated as described above for the case of addition of MeOH. The reaction product was purified on a SiO_2 column [5 × 35 cm; benzene–acetone (1:1)]. Two orange bands separated in order of emergence from the column; yields 1.72 g (79%) and 0.114 g respectively. To obtain analytically pure samples of the complexes the compounds were additionally purified on a Sephadex LH-20 column [benzene–EtOH (2:1)]. The first fraction was the diastereoisomerically pure *product of addition of EtOH complex to* (**3**); m.p. 118–119 °C (Found: C, 65.5; H, 5.9; N, 7.5. $C_{31}H_{33}N_3NiO_4$ requires C, 65.28; H, 5.83; N, 7.36%); $[\alpha]_{589}^{25}$ (2 g dm^{-3} in MeCN; *l* 2 cm) +2 750°; λ_{max}(MeCN) 264 (4.3), 338 (3.8), 423 (3.6), and 528 nm (2.43); δ($CDCl_3$) 1.1 (3 H, d, *J* 6.6 Hz, *Me*CH), 1.41 (3 H, t, *J* 7.1 Hz, *Me*CH_2), 1.42–3.7 (7 H, m, Pro α-, β-, γ-, δ-H), 3.38 (1 H, m, *J* 2.5 and 6.6 Hz, MeC*H*), 3.55 and 4.44 (2 H, AB, *J* 12.7 Hz, CH_2Ph), 3.75 (2 H, m, *J* 10.1, 7.1, and 1.5 Hz, MeCH_2), 3.93 (1 H, d, *J* 2.5 Hz, amino acid α-H), and 6.58–8.27 (14 H, m, ArH).

The complex (1.4 g, 2.45 × 10^{-3} mol) furnished (2S,3S)-2-*amino*-3-*ethoxybutanoic acid* (0.28 g, 78%), which was recrystallized from EtOH; m.p. 215 °C (decomp.) (Found: C, 48.8; H, 8.9; N, 9.5. $C_6H_{13}NO_3$ requires C, 48.96; H, 8.9; N, 9.51%); $[\alpha]_{589}^{25}$ (11 g dm^{-3} in 6M-HCl; *l* 5 cm) +22.4°. Enantio- and diastereoiso-meric purity of the α-amino acid was higher than 98% according to GLC; δ(D_2O) 1.31 (3 H, t, *J* 7 Hz, *Me*CH_2), 1.42 (3 H, d, *J* 6.5 Hz, *Me*CH), 3.7 (2 H, ABX_3, *J* 10 and 7.1 Hz, MeCH_2), 4.2 (1 H, q, *J* 6.5 and 3.6 Hz, MeC*H*), and 4.33 (1 H, d, *J* 3.6 Hz, amino acid α-H). The amino acid samples obtained from (*E*)-(**3**) and (*Z*)-(**3**) were identical.

The second fraction, according to the GC-MS spectra of the

trimethylsilyl derivatives of the amino acids recovered from it, consisted of complexes containing glycine, two diastereoisomers of 2-amino-3-ethoxybutanoic acid, and two diastereoisomers of threonine in the proportions 1:1.25:2.2:1.5:1, respectively.

(2R,3S)-2-*Amino*-3-(*phenylthio*)*butanoic Acid.**—To a solution of complex (*E*)-(**3**) or (*Z*)-(**3**) (2.5 g, 4.8 × 10^{-3} mol) in MeCN (8 ml) were added NaOH (0.02 g, 5 × 10^{-4} mol) and PhSH (0.98 ml, 9.6 × 10^{-3} mol) with careful exclusion of oxygen by several freeze–pump–thaw cycles under argon. The mixture was stirred at 25 °C until the initial complex (**3**) had disappeared, as monitored by TLC [SiO_2; $CHCl_3$–acetone (5:1)]. Then conc. acetic acid (0.03 ml) (or aq. HCl, the same no. of equiv.) was added to the reaction mixture to neutralize the NaOH, the solution was evaporated, and the residue was chromatographed on a SiO_2 column [3.5 × 35 cm; CH_2Cl_2–acetone (5:1)]. Four fractions separated in order of emergence from the chromatographic column in yields of 1.98 g, 0.1 g, 0.08 g, and 0.35 g. The first fraction was the diastereoisomerically pure *product of the addition of thiophenol to* (**3**) (1.98 g, 65%); m.p. 118–120 °C (Found: C, 65.6; H, 5.2; N, 6.8. $C_{35}H_{33}N_3NiO_3S$ requires C, 66.26; H, 5.24; N, 6.62%); λ_{max}(MeCN) 259 (4.3), 339 (3.72), 428 (3.51), and 530 nm (2.39); $[\alpha]_{589}^{25}$ (1.52 g dm^{-3} in MeCN; *l* 2 cm) +1 680; δ($CDCl_3$) 1.07 (3 H, d, *J* 6.5 Hz, Me), 2.93 (1 H, m, *J* 6.5 and 3.5 Hz, amino acid β-H), 1.85–3.7 (7 H, m, Pro α-, β-, γ-, δ-H), 3.5 and 4.55 (2 H, AB, *J* 12.5 Hz, C*H*$_2$Ph), and 6.45–8.2 (19 H, m, ArH).

The complex (1.98 g, 3.12 × 10^{-3} mol) was decomposed in the usual manner, the only difference being that some EtOH (10%) was added to the aq. NH_3 to recover the amino acid from the resin. The amino acid was recrystallized from aqueous EtOH to yield (2R,3S)-2-*amino*-3-(*phenylthio*)*butanoic acid* (0.51 g, 76%); m.p. 175–176 °C (decomp.) (Found: C, 57.1; H, 6.0; N, 6.9. $C_{10}H_{13}NO_2S$ requires C, 56.84; H, 6.20; N, 6.62%); $[\alpha]_{589}^{25}$ [4.8 g dm^{-3}; 6M-aq. HCl–EtOH (21:1); *l* 5 cm] −14.6°. Enantio- and diastereoiso-meric purity of the α-amino acid was higher than 98% according to GLC; δ(CD_3OD) 1.37 (3 H, d, *J* 7.1 Hz, Me), 3.9 (1 H, m, *J* 7.1 Hz, β-H), 3.97 (1 H, d, *J* 3.25, α-H), 7.3–7.6 (5 H, m, Ph).

The second fraction was the complex of (2*R*,3*R*)-2-amino-3-(phenylthio)butanoic acid† (0.11 g, 3.6%), δ($CDCl_3$) 2.1 (3 H, d, *J* 7 Hz, Me), 1.85–3.7 (7 H, m, Pro α-, β-, γ-, δ-H, and amino acid β-H), 4.4 (1 H, d, *J* 4 Hz, amino acid α-H), 4.47 and 3.55 (2 H, AB, *J* 12 Hz, C*H*$_2$Ph), and 6.8–8.2 (m, ArH). Additional support for the structure came from the GC-MS analysis of the amino acid recovered from the complex.

The third fraction was a mixture of mainly threonine complexes.

The fourth fraction was a mixture of (*S*)-vinylgycine complex and complex (**3**) (1.2–2:1 ratio according to ^{1}H NMR data). The former had the same set of physical and chemical properties as the vinylglycine complex obtained from methionine as described below.

(2R,3S)-2-*Amino*-3-(*benzylthio*)*butanoic Acid.*†—Complex (**3**) (2.5 g, 4.77 × 10^{-3} mol) and phenylmethanethiol (1.1 ml, 9.4 × 10^{-3} mol) reacted under the same conditions as described for the addition of thiophenol to complex (**3**); the reaction mixture was chromatographed on a SiO_2 column [3 × 35 cm; CH_2Cl_2–acetone (5:1)]. Two fractions were collected in order of emergence from the chromatographic column. The first fraction consisted of the diastereoisomerically pure *complex of* (2R,3S)-2-*amino*-3-(*benzylthio*)*butanoic acid* (2.08 g, 67.0%); m.p. 108–114 °C (Found: C, 67.0; H, 5.4; N, 6.8. $C_{36}H_{35}N_3NiO_3S$ requires C, 66.67; H, 5.44; N, 6.47%); λ_{max}(MeCN) 264 (4.17), 338 (3.66), 425 (3.48), and 535 nm (2.32); $[\alpha]_{589}^{25}$ (2 g dm^{-3} in MeCN; *l* 1 cm) +1 940°; δ($CDCl_3$) 1.07 (3 H, d, *J* 7 Hz, Me), 2.32 (1 H, m, *J* 3.6 and 7 Hz amino acid β-H), 1.75–3.27 (7 H, m, Pro α-, β-, γ-, δ-H), 3.42 (1 H, d, *J* 3.6 Hz, amino acid α-H), 3.77 and 4.13 (2 H, AB, *J* 12 Hz, SCH_2), 3.53 and 4.4 (AB, *J* 12 Hz, C*H*$_2$Ph), and 5.6–8.3 (19 H, m, ArH). The amino acid was recovered as described above.

The complex (1.6 g, 2.5 × 10^{-3} mol) produced (2R,3S)-2-*amino*-3-(*benzylthio*)*butanoic acid* (0.5 g, 88%); m.p. 175 °C (decomp.) (Found: C, 58.0; H, 6.4; N, 6.5. $C_{11}H_{15}NO_2S$ requires C, 58.63; H, 6.71; N, 6.21%); $[\alpha]_{589}^{25}$ [2.3 g dm^{-3} in 6M-aq. HCl–EtOH (2:1) *l* 5 cm] −84.1°. Enantio- and diastereoisomeric purity of the α-amino acid was higher than 98% according to GLC; δ(CD_3OD) 1.17 (3 H, d, *J* 7.2 Hz, Me), 3.35 (1 H, m, *J* 7.2 and 3 Hz, β-H), 3.8 (2 H, s, SCH_2), 4.09 (1 H, d, *J* 3 Hz, α-H), and 7.2–7.4 (5 H, m, Ph).

The second fraction was found to consist of vinylglycine complex (**3**), and some amino acids of unknown structure according to GC-MS analysis.

(S)-*Vinylglycine.*—To a stirred solution of (*S*)-BBP (6.2 g, 1.6 × 10^{-2} mol) and $Ni(NO_3)_2 \cdot 6H_2O$ (8.34 g, 2.8 × 10^{-2} mol) in MeOH (90 ml) was added a solution of (±)-methionine (10 g, 6.7 × 10^{-2} mol) in 1.5M-NeONa (90 ml). After being stirred at 50 °C for 2 h, the reaction mixture was quenched with acetic acid (9.0 ml) and evaporated. Water (2 l) was added to the mixture and the precipitate was collected, dissolved in $CHCl_3$, and the organic layer was washed with water and evaporated to give the almost diastereoisomerically pure *red complex of* L-*methionine* (8.55 g, 92.9%) (recrystallized from acetone), m.p. 213–214 °C (Found: C, 62.5; H, 5.45; N, 7.1. $C_{30}H_{31}N_3NiO_3S$ requires C, 62.95; H, 5.45; N, 7.34%); λ_{max}(MeCN) 268 (4.46), 333 (3.74), 421 (3.49), and 527.5 nm (3.35); $[\alpha]_{589}^{25}$ (2.7 g dm^{-3} in MeCN; *l* 2 cm +2 437°; δ($CDCl_3$) 1.86 (3 H, s, Me), 1.85–3.4 (11 H, m, Pro α-, β-, γ-, δ-H, and amino acid β-, γ-H), 3.44 and 4.35 (2 H, AB, *J* 12 Hz, C*H*$_2$Ph), 3.94 (1 H, m, amino acid α-H), and 6.58–8.08 (m, ArH).

To a stirred solution of the complex (8.45 g, 1.48 × 10^{-2} mol) in MeOH (41.5 ml) was added a solution of KIO_4 (3.46 g, 1.50 × 10^{-2} mol) in water (14 ml), and the mixture was stirred for 2 h at 50–52 °C. The reaction was monitored by TLC [SiO_2; $CHCl_3$–acetone (3:1)]. After disappearance of the initial complex, the reaction mixture was filtered, the filtrate was evaporated, and the residue was purifed on a SiO_2 column [45 × 5 cm; $CHCl_3$–acetone (3:1)]. The corresponding *sulphoxide complex* (8.14 g, 94%) was obtained as a mixture of two diastereoisomers (because of chirality at the sulphur atom) in the ratio 2:1, m.p. 121–123 °C (Found: C, 60.8; H, 5.3; N, 7.0. $C_{30}H_{31}N_3NiO_4S$ requires C, 61.24; H, 5.31; N, 7.13%); $[\alpha]_{589}^{25}$ (1.8 g dm^{-3} in MeCN; *l* 0.5 cm) +2 583°; δ($CDCl_3$) 2.0–3.5 (11 H, m, Pro α-, β-, γ-, δ-H, and amino acid β-, γ-H), 2.43 (1.92 H, s, Me), 2.5 (1.08 H, s, Me), 3.53 and 4.44 (2 H, AB, *J* 12.8 Hz, C*H*$_2$Ph), 3.86 (0.64 H, dd, *J* 4 Hz, amino acid α-H), 3.96 (0.36 H, dd, *J* 4 Hz, amino acid α-H), and 6.65–8.08 (14 H, m, ArH).

The sulphoxide complexes (8.04 g, 1.37 × 10^{-2} mol) were stirred at 180 °C in dimethyl sulphoxide (DMSO) (40 ml) under argon for 4 h (longer heating resulted in diminished yields). The reaction mixture [50% of the initial complexes and 50% of the vinylglycine complex and complex (**3**)] was poured into water (3 l). After 24 h the precipitate was collected, washed

* The configuration of the amino acid α-carbon atom is L according to the ORD curve of the addition product. The usual *S*-designation for L-amino acids becomes *R* for the β-thio-substituted α-amino acids (R. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 567).

† The α-carbon absolute configuration is L according to the ORD curve of the complex.

with water, and chromatographed on a SiO_2 column [$CHCl_3$–acetone (3:1)] to give a mixture (3.22 g, 45%) of (*S*)-vinylglycine complex and (**3**) (4:1 assessed from the peak heights of the corresponding olefinic signals) as a single band; m.p. 237–239 °C (Found: C, 66.1; H, 5.0; N, 7.9. $C_{29}H_{27}N_3NiO_3$ requires C, 66.44; H, 5.19; N, 8.01%); λ_{max}(MeCN) 268 (4.39), 333 (3.72), 428 (3.51), and 529 nm (2.40); $[\alpha]_{589}^{25}$ (2 g dm^{-3} in MeCN; *l* 2 cm) +2 640°; δ($CDCl_3$) 1.9–3.8 (7 H, m, Pro α-, β-, γ-, δ-H), 3.52 and 4.4 (2 H, AB, *J* 12 Hz, CH_2Ph), 4.37 (1 H, d, *J* 5 Hz, amino acid α-H), 5.35 (1 H, d, J_{gem} 0.75, J_{cis} 10.8 Hz, amino acid γ-H_{cis}), 5.54 (1 H, d, J_{gem} 0.75, J_{trans} 17.3 Hz, amino acid γ-H_{trans}), 6.0 (1 H, m, *J* 5, 10.8, and 17.3 Hz, amino acid β-H), and 6.6–8.13 (14 H, m, ArH). (*S*)-Vinylglycine was recovered by the general procedure, the only alteration of the protocol being that Ni^{II} ions were removed by filtration of the solution through chelating Dowex A-1 resin before adsorption onto Dowex 50 × 8 resin. From the initial complex (0.28 g, 5.3 × 10^{-4} mol) was obtained (*S*)-vinylglycine (0.04 g, 75%); m.p. 181 °C; $[\alpha]_{589}^{25}$ (5.2 g dm^{-3} in 6M-HCl; *l* 5 cm) +61.5°; $[\alpha]_{589}^{25}$(4 g dm^{-3} in water; *l* 5 cm) +48.9° [lit.,[16b] +89° (0.1–1 g dm^{-3} water)], the enantiomeric purity of the amino acid was 58% according to GLC data; δ(D_2O) 4.26 (1 H, d, *J* 7 Hz, α-H), 5.48 (2 H, m, *J* 9.5 and 16.6 Hz, γ-H), and 5.97 (m, *J* 7, 9.5, and 16.6 Hz). BBP, recovered after the decomposition of the complex, was optically pure as indicated by polarimetric data.

Epimerization of Complexes (E)- *and* (Z)-(**3**).—To a solution of complex (*E*)-(**3**) or (*Z*)-(**3**) (2.1 × 10^{-2} g, 1.84 × 10^{-4} mol) in MeCN (2 ml) was added DABCO (2 × 10^{-3} g, 1.85 × 10^{-5} mol) and the mixture was kept for 160 h at ambient temperature. The equilibrium ratio of isomers was 1:1 according to ^{1}H NMR and TLC data.

References

1 L. Fowden and P. Lea, *Adv. Enzymol.*, 1979, **50**, 117; I. Wagner and H. Musso, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 816.

2 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.

3 (*a*) H. Yoshioka, T. Aoki, H. Goko, K. Nakatsu, T. Noda, H. Sakikibara, T. Take, A. Nagata, J. Abe, T. Wakamiya, T. Shiba, and T. Kaneko, *Tetrahedron Lett.*, 1971, 2043; (*b*) T. Takita, Y. Muraoka, T. Yoshioka, A. Fuji, K. Maeda, and H. Umezawa, *J. Antibiot.*, 1972, **25**, 755; (*c*) T. Hetinger and L. Craig, *Biochemistry*, 1970, **9**, 1224; (*d*) J. Van Der Baan, J. Barnik, and F. Bickelhaupt, *J. Antibiot.*, 1983, **36**, 784; (*e*) J. Gross and J. Morell, *J. Am. Chem. Soc.*, 1971, **93**, 4634; (*f*) A. Miyamae, M. Fujioka, S. Koda, and Y. Morimoto, *J. Chem. Soc., Perkin Trans. 1*, 1989, 873.

4 A. Spatola in 'Chemistry and Biochemistry of Amino Acids, Peptides and Proteins,' ed. B. Weinstein, Marcel Dekker, New York and Basel, 1983, vol. 7, p. 267.

5 (*a*) R. Fitzi and D. Seebach, *Tetrahedron*, 1988, **44**, 5277; U. Schollkopf, Th. Tiller, and J. Bardenhagen, *ibid.*, p. 5293; I. Ojima, H. Chen, and X. Qiu, *ibid.*, p. 5307; A. Achqar, M. Boumzebra, M. Roumestant, and P. Viallefont, *ibid.*, p. 5319; S. Ikegami, H. Uchiyama, T. Hayama, T. Katsuki, and M. Yamaguchi, *ibid.*, p. 5333; D. Evans and A. Weber, *J. Am. Chem. Soc.*, 1986, **108**, 6757; H. Kuzuhara, N. Watanabe, and M. Ando, *J. Chem. Soc., Chem. Commun.*, 1987, 95; T. Oguri, N. Kawai, T. Shiori, and S. Yamada, *Chem. Pharm. Bull.*, 1978, **26**, 803; T. Nakatsuka, T. Miwa, and T. Mukaiyama, *Chem. Lett.*, 1981, 279; Yu. Belokon, V. Bakhmutov, N. Chernoglazova, K. Kochetkov, S. Vitt, N. Garbalinskaya, and V. Belikov, *J. Chem. Soc., Perkin Trans. 1*, 1988, 305; G. Bold, R. Duthaler, and M. Riediker, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 497; (*b*) R. Williams and W. Zhai, *Tetrahedron*, 1988, **44**, 5425; Y. Yamamoto and W. Ito, *ibid.*, p. 5415; U. Schollkopf, S. Gruettner, R. Anderskewitz, G. Egert, and M. Dyrbusch, *Angew. Chem.*, 1987, **99**, 717; Y. Belokon, A. Popkov, N. Chernoglazova, M. Saporovskaya, V. Bakhmutov, and V. Belikov, *J. Chem. Soc., Chem. Commun.*, 1988, 1336; (*c*) H. Brunner and W. Leitner, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1180; B. Vineyard, W. Knowles, M. Sabacky, G. Bachman, and D. Weinkauff, *J. Am. Chem. Soc.*, 1977, **99**, 5946; A. Chan and J. Halpern, *ibid.*, p. 1980, **102**, 838; (*d*) Y. Ito, M. Sawamura, E. Shirakawa, K. Hayashizaki, and T. Hayashi, *Tetrahedron*, 1988, **44**, 5253; J. Genet, S. Juge, S. Achi, S. Mallart, J. Montes, and G. Levif, *ibid.*, p. 5263, and cited references.

6 D. Evans, T. Britton, R. Dorow, and J. Dellaria, *Tetrahedron*, 1988, **44**, 5525; W. Oppolzer and R. Moretti, *ibid.*, p. 5541; G. Guanti, L. Banfi, and E. Narizano, *ibid.*, p. 5553; S. Cardani, A. Bernardi, L. Colombo, C. Gennari, C. Scolastico, and I. Venturini, *ibid.*, p. 5563, and cited references.

7 (*a*) J. Baldwin, R. Adlington, and D. Birch, *J. Chem. Soc., Chem. Commun.*, 1985, 256; L. Arnold, T. Kalantar, and J. Vederas, *J. Am. Chem. Soc.*, 1985, **107**, 7105; J. Baldwin, R. Adlington, D. Birch, J. Crawford, and J. Sweeney, *J. Chem. Soc., Chem. Commun.*, 1986, 1339; J. Baldwin, R. Adlington, A. Basak, P. Imming, K. Ponnamperuma, H. Ronneberg, C. Schofield, H. Ting, and N. Turner, *ibid.*, 1989, 802; L. Arnold, J. Drover, and J. Vederas, *J. Am. Chem. Soc.*, 1987, **109**, 4649; (*b*) J. Scholtz and P. Bartlett, *Synthesis*, 1989, 542; S. Kano, T. Yokomatsu, H. Iwasawa, and S. Shibuya, *Chem. Pharm. Bull.*, 1988, **36**, 3341.

8 J. Morell, P. Fleckenstein, and E. Gross, *J. Org. Chem.*, 1977, **42**, 355; K. Nakajima, M. Neya, S. Yamada, and K. Okawa, *Bull. Chem. Soc. Jpn.*, 1982, **55**, 3049; S. Ponsare and J. Vederas, *J. Org. Chem.*, 1989, **54**, 2311.

9 (*a*) Yu. Belokon, A. Sagyan, S. Djamgaryan, V. Bakhmutov, and V. Belikov, *Tetrahedron*, 1988, **44**, 5507; (*b*) U. Groth, U. Schollkopf, and Y. Chiang, *Synthesis*, 1982, 864; U. Schollkopf, K. Westphalen, J. Schroder, and K. Horn, *Liebigs Ann. Chem.*, 1988, 781.

10 (*a*) Yu. Belokon, A. Bulychev, S. Vitt, Yu. Struchkov, A. Batsanov, T. Timofeeva, V. Tsyryapkin, M. Ryzhov, L. Lysova, V. Bakhmutov, and V. Belikov, *J. Am. Chem. Soc.*, 1985, **107**, 4252; (*b*) Yu. Belokon, A. Bulychev, V. Pavlov, E. Fedorova, V. Tsyryapkin, V. Bakhmutov, and V. Belikov, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2075.

11 (*a*) M. Saporovskaya, V. Pavlov, and L. Volkova, *Zh. Anal. Khim.*, 1989, 525; (*b*) H. Frank, G. Nicolson, and E. Bayer, *J. Chromatogr. Sci.*, 1977, **15**, 174.

12 (*a*) Yu. Belokin, A. Bulychev, S. Vitt, Yu. Struchkov, A. Batsanov, T. Timofeeva, V. Tsyryapkin, M. Ryzhov, Yu. Kondrashov, S. Golubev, Yu. Vauchskii, A. Kasika, M. Novikova, P. Krasutskii, A. Yurchenko, I. Dubchak, V. Schklover, Yu. Struchkov, V. Bakhmutov, and V. Belikov, *J. Chem. Soc., Dalton Trans.*, 1985, 17; (*b*) L. Warner, N. Rose, and D. Busch, *J. Am. Chem. Soc.*, 1968, **90**, 6938; T. Ito and D. Busch, *ibid.*, 1973, **95**, 7528.

13 R. Silverstein, G. Bassler, and T. Morrill, 'Spectrometric Identification of Organic Compounds,' 4th edn., Wiley, New York, Chichester, Brisbane, Toronto, and Singapore.

14 Yu. Belokon, A. Sagiyan, I. Ponomarenko, V. Bakhmutov, and V. Belikov, *J. Chem. Soc., Perkin Trans. 2*, 1985, 21; *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 395.

15 'Progress in Stereochemistry,' eds. W. Klyne and P. B. D. la Mare, Butterworths Scientific, London, 1954, vol. 1.

16 (*a*) A. Ardakani and H. Rapoport, *J. Org. Chem.*, 1980, **45**, 4817; (*b*) Th. Weber, R. Aeschiman, Th. Maetzke, and D. Seebach, *Helv. Chim. Acta*, 1986, **69**, 1365.

17 E. Eliel, N. Allinger, S. Angyal, and G. Morrison, 'Conformational Analysis,' Interscience, New York, London, and Sydney, 1985.

18 W. Hamilton, *Acta Crystallogr.*, 1965, **18**, 502.

19 R. Gerr, A. Yanovskii, and Yu. Struchkov, *Kristallografia*, 1983, **28**, 1029.

Paper 9/04280F
Received 6th *October* 1989
Accepted 3rd *January* 1990