Pergamon

Tetrahedron 56 (2000) 2577–2582

TETRAHEDRON

Convenient, Large-Scale Asymmetric Synthesis of Enantiomerically Pure *trans*-Cinnamylglycine and -α-Alanine

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Received 5 January 2000; revised 22 February 2000; accepted 23 February 2000

Abstract—Asymmetric syntheses of (*S*)-*trans*-cinnamylglycine and (*S*)-α-*trans*-cinnamyl-α-alanine via reactions of cinnamyl halides (Cl, Br) with Ni(II)-complexes of the chiral Schiff base of glycine or alanine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone were developed. Inexpensive and readily available reagents and solvents were used, including an easily recyclable chiral auxiliary. The simplicity of the experimental procedures and the high stereochemical outcome make this method synthetically attractive for preparing the target amino acids on multi-gram scales.

Introduction

Systematic studies conducted by our group into the chemical–physical basis for peptide-mediated biological information transfer, as a function of topographical properties and three-dimensional structure of peptides, has led to a uniquely fruitful approach to the de novo design of peptides via rational introduction of global and local constrains to the peptide's geometry.[1] Since phenylalanine (Phe) often plays a pivotal role as a pharmacophore element in biologically active peptides and proteins, much attention had been paid by us[2] and others[3,4] to the development of sterically constrained analogues of this essential amino acid and related tyrosine (Tyr) analogues to be used as building blocks in the rational design of peptide and proteins. Our efforts in this field resulted in the discovery of β-methyl-2′,6′-dimethyl tyrosine (TMT),[5] a unique amino acid, used as a key structural unit in the design and synthesis of numerous bioactive peptides, some of which have potential medicinal applications.[6] Thus, while the pattern of steric substitution on the Phe moiety in peptides have been extensively studied, little is known about the possibility of modifying biological activity of Phe-containing peptides by altering the distance between the pharmacophoric phenyl ring and the α-stereogenic carbon in the original Phe molecule. To pursue this opportunity we chose (*S*)-*trans*-cinnamylglycine (**1**) and -α-alanine (**2**) as the first, most interesting targets. In this paper we describe a convenient asymmetric method for preparing these amino acids on a multi-gram scale.

Results and Discussion

A literature search for enantiomerically pure *trans*-cinnamyl derivatives of glycine **1** and α-alanine **2** revealed that these amino acids have been prepared by traditional approaches such as biocatalytic resolution of the corresponding racemates[7] or elaboration of enantiomerically pure glutamic acid derivatives.[8] More recent and methodologically straightforward methods involved the asymmetric alkylation reaction of chiral equivalents of nucleophilic glycine and alanine, respectively. For instance, reactions between *trans*-cinnamyl bromide and lithium enolates of *c*-(*S*)-Val-Gly or Ala bis-lactim ethers,[9] or (2*S*,4*S*)-2-ferrocenyl-3-pivaloyl-4-methyl-1,3-oxazolidin-5-one[10] were shown to afford the corresponding derivatives of the target amino acids **1** and **2** in high chemical yield and excellent diastereoselectivity. In contrast, asymmetric cinnamylation of (6*S*)- or (6*R*)-6-methylmorpholine-2,5-dione derivatives was less successful, giving rise to the desired diastereomeric products in less than 75% de.[11] An efficient catalytic asymmetric hydrogenation of the corresponding enamide furnishing *trans*-cinnamylglycine (98.6% ee) also has been reported.[12] However, an apparent disadvantage of this method on a large scale would be the high pressure (90 psi) reduction protocol. One more approach to the stereochemically defined *trans*-cinnamylglycine (**1**) via asymmetric Claisen rearrangement of chelated enolates of chiral *N*-protected glycine allyl esters[13] should be mentioned in this short review.

Keywords: amino acids and derivatives; asymmetric synthesis; alkylation reactions; nickel complexes.

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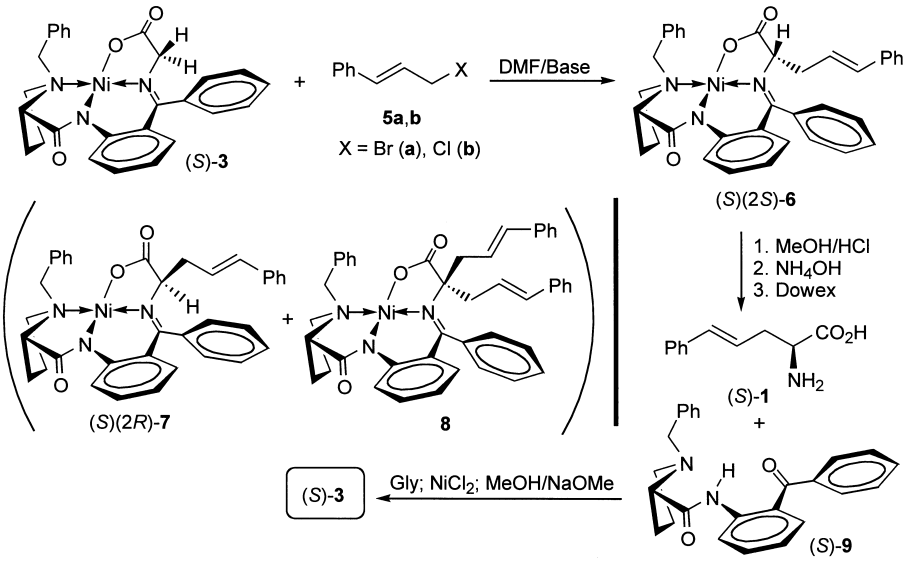
0040–4020/00/$ - see front matter
PII: S0040-4020(00)00176-9



Scheme 1.

In our experience, Ni(II)-complexes of the chiral Schiff bases of glycine or alanine[14,15] with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone (BPB), as chiral equivalents of nucleophilic glycine **3** and alanine **4**, provide a generally more practical solution for the asymmetric homologation of these simple amino acids than the above mentioned methods.[7–13] Apparent synthetic advantages of Ni(II)-complexes **3** and **4** over other known and well-tried chiral equivalents of nucleophilic glycine and alanine are the availability of **3** and **4** even on kilogram scales[16] and the extremely simple experimental procedure (vide infra) for the corresponding asymmetric alkylation step. Therefore, we decided to study the reactions of Ni(II)-complexes **3** and **4** with *trans*-cinnamyl halides to develop a practical large-scale asymmetric synthesis of the target amino acids.

Synthesis of (*S*)-*trans*-cinnamylglycine (1)

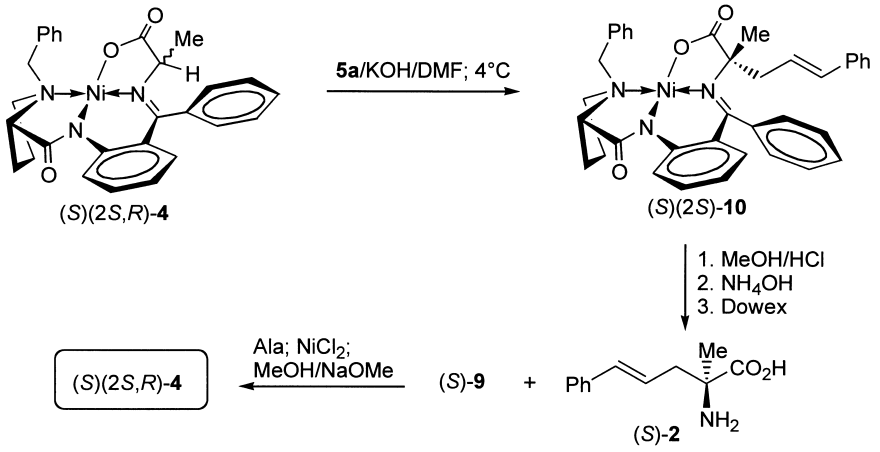
Since the reactivity of cinnamyl halides was expected to be similar to that of benzyl/allyl halides, we decided to use initially the conditions used previously for the corresponding benzylation/allylation of glycine complex (*S*)-**3**.[17] The reaction of complex (*S*)-**3** with *trans*-cinnamyl bromide **5a** was conducted in DMF solution at room temperature in oxygen-free[18] atmosphere (N_2) using powdered KOH as a base and 1/1.5 ratio of the starting (*S*)-**3** and **5a**, respectively (Scheme 1). The exothermic reaction was completed in less then 5 min, giving rise in high chemical yield to a mixture of products **6**, **7** and **8** in a ratio of 24.4/1.0/13.1, respectively (Table 1, entry 1). All three products were isolated in diastereomerically pure form by column chromatography and completely characterized. Based on the NMR spectra, compounds **6** and **7** were found to be the diastereomeric derivatives of *trans*-cinnamylglycine, while complex **8** showed data consistent with the corresponding bis-cinnamylation product. Investigation of the chiroptical properties[19] of complexes **6** and **7** allowed us to assign the absolute configuration of the corresponding *trans*-cinnamylglycine moieties as (*S*) and (*R*), respectively. The results obtained suggested that while the ratio of (*S*)-**6** and (*R*)-**7** diastereomers (92% de) is synthetically meaningful, the bis-cinnamylation side reaction would compromise a large preparative use of the method. Indeed, the bis-cinnamylation product **8** could be readily obtained as the major reaction product using 2.3 mol excess of bromide **5a** (entry 2). We reasoned that the unwanted bis-cinnamylation reaction could be suppressed by using a less powerful base or a less reactive cinnamyl halide.

Application of K_2CO_3 in place of KOH dramatically decreased the reaction rate, taking more than 12 h at room temperature to reach 95% conversion of starting complex (*S*)-**3**. While our expectation was satisfied and not even a trace amount of bis-**8** was detected in the reaction mixture, the ratio of (*S*)-**6** and (*R*)-**7** diastereomers was disappointedly low (entry 3). The absence of bis-**8** in this

Table 1. The Reactions of Ni(II)-complex **3** with *trans*-cinnamyl halides **5a**,**b** (all reactions conducted in DMF in a nitrogen atmosphere)

Entry	**5a**,**b**	Ratio **3**/**5a**,**b**	Base	t, (°C)	Time	Ratio[a]			Yield[b] (%)
						6	**7**	**8**	
1	**a**	1.0/1.5	KOH	Room temperature	5 min	24.4	1.00	13.1	95.1
2	**a**	1.0/2.3	KOH	Room temperature	1 h	1.00	0.00	20.0	96.8
3	**a**	1.0/1.1	K_2CO_3	Room temperature	[c]	4.50	1.00	0.00	87.4
4	**b**	1.0/1.0	KOH	4	10 min	26.5	1.00	1.30	95.4

[a] Ratio of diastereomers determined by ^1H NMR analysis of crude reaction mixtures.
[b] Combined yield of all listed products.
[c] Overnight.



Scheme 2.

reaction might imply that K_2CO_3 as a base is ineffective in generating the corresponding enolates from the primary products (*S*)-**6** and (*R*)-**7**, and consequently, the observed stereochemical outcome is kinetically controlled. Indeed, treatment of the 4.5/1 mixture of (*S*)-**6** and (*R*)-**7**, with KOH in DMF solution resulted in a fast epimerization of the diastereomers to afford products (*S*)-**6** and (*R*)-**7** in thermodynamically controlled ratio of 27/1, respectively. After a series of additional experiments, we found that the less reactive cinnamyl chloride **5b** in combination with KOH as a base provides a synthetically acceptable solution. The reaction of complex (*S*)-**3** with **5b** conducted at 4°C gave a mixture of (*S*)-**6**, (*R*)-**7** and bis-**8** in a ratio of 26.5/1.0/1.3, respectively (entry 4). The same stereochemical outcome was reliably observed on gram and multi-gram scales.

Decomposition of the diastereomerically pure (*S*)-**6** under standard conditions[15] afforded the target amino acid (*S*)-**1** along with 94% recovery of the chiral ligand (*S*)-**9**, which was readily converted back to glycine complex (*S*)-**3** (Scheme 1). It is important to note that cinnamylglycine (*S*)-**1** was found to be extremely hydrophobic, necessitating the application of a mixture of NH_4OH/EtOH as an eluent to isolate (*S*)-**1** from a cation-exchange column.

Synthesis of (*S*)-α-*trans*-cinnamyl-α-alanine (1)

Since cinnamylation of alanine complex **4** cannot be accompanied by the problematic side reactions encountered in the case of glycine complex (*S*)-**3**, we used the more reactive *trans*-cinnamyl bromide and KOH as a base. Alanine complex **4** was prepared and used as a mixture of (*S*)(2*S*) and (*S*)(2*R*) diastereomers in a ratio of 10/1, respectively. As one can assume, the homologation of complex **4** occurs via formation of the corresponding enolate, and thus the initial diastereomeric composition of starting **4** does not influence the stereochemical outcome of the corresponding alkylation/benzylation/allylation reactions.[14,15] Having conducted a series of reactions between alanine complex (*S*)(2*S*,*R*)-**4** and **5a** varying the reaction temperature and ratio of the starting compounds, we found that the best synthetic result could be obtained using 1/1.1 ratio of (*S*)(2*S*,*R*)-**4** and **5a**, respectively, at 4°C (Scheme 2). Under these reaction conditions the cinnamylation of complex (*S*)(2*S*,*R*)-**4** was completed in 30 min affording the product **10** in high chemical yield. Analysis of the crude reaction mixture by ^{1}H NMR revealed trace amounts of some byproducts formed in a ratio to **10** less than 1/50. Based on its spectral data and chiroptical properties, the absolute configuration of **10** was determined to be (*S*)(2*S*). Attempts to isolate the corresponding (2*R*)-diastereomer among the minor products were not successful. It is interesting to note that the diastereoselectivity obtained in this reaction (>98% de) is better than that reported for the benzylation/allylation (90–92% de) of complex **4**.[14,15]

Decomposition of product (*S*)(2*S*)-**10** (Scheme 2) afforded the target (*S*)-α-*trans*-cinnamyl-α-alanine (**2**) as well as chiral ligand (*S*)-**9** which was recycled to give the starting alanine complex (*S*)(2*S*,*R*)-**4**. As with the glycine derivative (*S*)-**1**, the amino acid (*S*)-**2** was found to be highly hydrophobic. However, its purification to the analytically pure state was readily achieved by recrystallization from H_2O/ethanol.

In conclusion, we have demonstrated that enantiomerically pure (*S*)-*trans*-cinnamylglycine (**1**) and (*S*)-α-*trans*-cinnamyl-α-alanine (**2**) can be readily prepared via reaction of Ni(II)-complexes of glycine and alanine, respectively, with cinnamyl halides (Cl, Br). Inexpensive and readily available reagents and solvents are used, including a recyclable chiral ligand, (*S*)-**9**. The simplicity of the experimental procedures and high stereochemical outcome make this method synthetically attractive for preparing the target amino acids on multi-gram scales.

Experimental

General

^{1}H and ^{13}C NMR were performed on a Bruker DRX-500 (500.130 MHz) spectrometer and a Bruker AM-250 (250.133 MHz) spectrometer using TMS and $CDCl_3$ as internal standards. High Resolution Mass Spectra (HRMS) were recorded on a JEOL HX110A instrument. Optical rotations were measured on a JASCO P-1020 polarimeter.

Melting points (mp) are uncorrected and were obtained on a Thomas–Hoover apparatus in open capillaries. All reagents and solvents, unless otherwise stated, are commercially available and were used as received. Synthesis of the Ni(II)-complex of the Schiff base of (*S*)-BPB and glycine (*S*)-**1** was accomplished by literature procedure.[17] Unless otherwise stated, R_f values were taken using ethyl acetate/acetone (20/1) as an eluting system. Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H and ^{13}C NMR spectroscopy. All new compounds were characterized by ^{1}H, ^{13}C NMR and HRMS.

General procedure for the reactions of complexes (*S*)-3 and (*S*)(2*S*,*R*)-4 with cinnamyl halides 5a,b

To a solution of complex **3** or **4** (10 mmol) in DMF (45 mL) at 4°C (ice water) under oxygen-free atmosphere, KOH powder (100 mmol) was added with stirring. The mixture was warmed to room temperature, and *trans*-cinnamyl halide **5a**,**b** in DMF (4 mL) was added dropwise. The course of the reaction was monitored by TLC (SiO_2). Each sample was quenched with 5% aqueous acetic acid and the products were extracted with chloroform before being applied to the TLC plate. Upon disappearance of the starting **3** or **4**, the reaction mixture was poured into icy 5% acetic acid aqueous solution (200 mL) and stirred with a glass bar to initiate crystallization. The crystalline product was filtered off, thoroughly washed with water and dried in vacuo to afford the corresponding diastereomeric products. In the case of complex (*S*)-**3**, resulting complexes **6**, **7**, and **8** were isolated by flash chromatography on silica gel using acetone/ethyl acetate (1/20) as an eluent, to afford diastereomerically pure **8** (emerges first), **6** (emerges second), and **7** (emerges last). For yields, ratios of starting compounds (*S*)-**3** and **5a**,**b**, and products **6**, **7**, and **8** see Table 1. Alanine derivative (*S*)(2*S*)-**10** was purified prior to decomposition on a short silica gel column using acetone/ethyl acetate (1/20) as an eluent.

Ni(II) complex of Schiff base of (*S*)-BPB and (*S*)-*trans*-cinnamylglycine (6). R_f=0.30. Mp 129–130°C. $[\alpha]_D^{25}$=2695° (*c* 0.0302, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.52–1.58 (1H, m), 1.97 (1H, ddd, *J*=17.0, 10.5, 6.5 Hz), 2.13–2.21 (1H, m), 2.24–2.30 (1H, m), 2.48, 2.64 (2H, ABXY, J_{AB}=14.0 Hz, J_{AX}=7.0 Hz, J_{AY}=4.0 Hz, J_{BX}=7.0 Hz, J_{BY}=6.0 Hz), 2.82–2.91 (1H, m), 3.31 (1H, dd, *J*=10.5, 7.0 Hz), 3.43 (1H, ddd, *J*=10.0, 6.5, 3.0 Hz), 3.51, 4.35 (2H, AB, *J*=12.5 Hz), 4.14 (1H, dd, *J*=6.0, 4.0 Hz), 6.54, 6.72 (2H, ABXY, J_{AB}=15.5 Hz, J_{AX}=J_{AY}=7.5 Hz), 6.65–6.69 (2H, m), 6.99 (1H, m), 7.13–7.19 (2H, m), 7.23–7.34 (6H, m), 7.43–7.48 (3H, m), 7.50–7.57 (2H, m), 8.02–8.03 (2H, m), 8.20 (1H, part of AB, *J*=9.0 Hz). ^{13}C NMR ($CDCl_3$) δ 23.2, 30.7, 37.7, 57.2, 63.2, 70.3, 70.6, 120.6, 123.5, 123.5, 126.3, 126.6, 127.1, 127.7, 127.9, 128.5, 128.8, 128.9, 129.0, 129.8, 131.5, 132.3, 133.2, 133.3, 134.1, 134.7, 137.0, 139.2, 142.7, 171.0, 178.9, 180.4. HRMS (FAB) $[M+H]^+$ calcd for $C_{36}H_{33}N_3NiO_3$ 614.1954, found 614.1964.

Ni(II) complex of Schiff base of (*S*)-BPB and (*R*)-*trans*-cinnamylglycine (7). R_f=0.25. Mp 202.0–202.5°C. $[\alpha]_D^{25}$=−1329° (*c* 0.0256, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.20–1.32 (1H, m), 1.58–1.69 (2H, m), 2.01–2.04 (1H, m), 2.35–2.42 (1H, m), 2.57–2.63 (1H, m), 3.40 (1H, dd, *J*=9.5, 3.5 Hz), 3.81, 4.37 (2H, AB, *J*=13.5 Hz), 3.99–4.02 (1H, m), 4.05–4.14 (2H, m), 6.55, 6.74 (2H, ABXY, J_{AB}=15.8 Hz, J_{AX}=J_{AY}=7.6 Hz), 6.74, 6.80 (2H, AB, *J*=8.0 Hz), 7.06–7.11 (1H, m), 7.18–7.36 (7H, m), 7.44–7.45 (3H, m), 7.48–7.52 (5H, m), 8.52 (1H, d, *J*=8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 23.5, 31.1, 37.9, 56.5, 61.1, 68.7, 70.8, 120.7, 123.6, 124.1, 126.1, 126.5, 127.0, 127.6, 128.0, 128.6, 128.8, 129.2, 129.8, 131.8, 132.1, 132.6, 133.7, 134.2, 134.7, 137.2, 143.1, 171.1, 178.9, 182.2. HRMS (FAB) $[M+H]^+$ calcd for $C_{36}H_{33}N_3NiO_3$ 614.1954, found 614.1948.

Ni(II) complex of Schiff base of (*S*)-BPB and bis-(*trans*-cinnamyl)glycine (8). R_f=0.52. Mp 194–195°C. $[\alpha]_D^{25}$=2102° (*c* 0.0245, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.40–1.43 (1H, m), 1.90 (1H, ddd, *J*=17.0, 11.0, 6.5 Hz), 2.12–2.17 (2H, m), 2.42, 2.63 (2H, ABX, J_{AB}=14.5 Hz, J_{AX}=9.0 Hz, J_{BX}=5.5 Hz), 2.57, 2.72 (2H, ABX, J_{AB}=15.5 Hz, J_{AX}=6.5 Hz, J_{BX}=7.0 Hz), 2.60–2.70 (1H, m), 3.24–3.70 (1H, t, *J*=8.5 Hz), 3.31, 4.30 (2H, AB, *J*=12.5 Hz), 3.54–3.57 (1H, m), 6.19, 6.56 (2H, ABXY, J_{AB}=15.0 Hz, J_{AX}=J_{AY}=7.0 Hz), 6.63, 6.73 (2H, ABXY, J_{AB}=15.0 Hz, J_{AX}=J_{AY}=8.0 Hz), 6.97 (1H, ddd, *J*=15.5, 8.5, 6.0 Hz), 7.06–7.17 (5H, m), 7.23–7.29 (2H, m), 7.33–7.37 (3H, m), 7.46–7.58 (7H, m), 7.81 (1H, d, *J*=8.5 Hz), 8.12 (2H, d, *J*=7.5 Hz). ^{13}C NMR ($CDCl_3$) δ 22.8, 30.7, 41.4, 43.3, 58.4, 64.2, 70.6, 82.3, 120.6, 123.4, 124.1, 126.3, 126.5, 127.2, 127.5, 127.6, 127.7, 128.1, 128.6, 128.7, 128.8, 129.8, 131.3, 131.4, 133.0, 133.9, 134.2, 134.6, 136.5, 137.1, 137.2, 141.6, 172.8, 180.6, 180.8. HRMS (FAB) $[M+H]^+$ calcd for $C_{45}H_{41}N_3NiO_3$ 730.2580, found 730.2601.

Ni(II) complex of Schiff base of (*S*)-BPB and (*S*)-α-*trans*-cinnamyl-α-alanine (10). Starting from 5.0 g of (*S*)(2S,R)-**4**, 5.80 g (94.6%) of **10** was obtained. R_f=0.40. Mp 123–124°C. $[\alpha]_D^{25}$=2192° (*c* 0.0262, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, s), 1.41–1.47 (1H, m), 1.89–1.95 (1H, ddd, *J*=17.2, 10.7, 6.5 Hz), 2.07–2.23 (2H, m), 2.57–2.68 (3H, m), 3.27 (1H, dd, *J*=10.0, 7.0 Hz), 3.49 (1H, ddd, *J*=10.0, 6.5, 2.5 Hz), 3.61, 4.39 (2H, AB, *J*=13.0 Hz), 6.61–6.68 (3H, m), 6.92 (1H, ddd, *J*=15.5, 9.0, 6.5 Hz), 7.09–7.14 (2H, m), 7.23–7.26 (2H, m), 7.31–7.38 (5H, m), 7.41–7.45 (1H, m), 7.48–7.53 (4H, m), 8.04 (2H, t, *J*=7.0 Hz). ^{13}C NMR ($CDCl_3$) δ 22.9, 29.4, 30.5, 43.7, 57.3, 63.4, 70.1, 78.5, 120.6, 123.8, 124.0, 126.5, 127.0, 127.5, 127.7, 128.0, 128.5, 128.6, 128.8, 128.9, 129.5, 130.6, 131.6, 133.3, 133.4, 134.5, 136.6, 137.1, 141.9, 172.6, 180.4, 181.7. HRMS (FAB) $[M+H]^+$ calcd for $C_{37}H_{35}N_3NiO_3$ 628.2110, found 628.2096.

General procedure for decomposition of complexes (*S*)(2*S*)-(6) and (*S*)(2*S*)-(10)

Isolation of (*S*)-*trans*-cinnamylglycine (1) and (*S*)-α-*trans*-cinnamyl-α-alanine (2) and recovery of chiral ligand (*S*)-9. A solution of diastereo- and enantiomerically pure complex (*S*)(2*S*)-(**6**) or (*S*)(2*S*)-(**10**) (10 mmol) in MeOH (15 mL) was added dropwise to a mixture of aqueous 3N HCl and MeOH (1/1) (70 mL) at 70°C with stirring. Upon disappearance of the red color of the starting complex, the reaction mixture was evaporated and dried in vacuo to dryness. Conc. $NH_3{\cdot}H_2O$ (45 mL) was added,

followed by extraction with $CHCl_3$ (40 mL). The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated and dried in vacuo to afford (94.8–97.3%) of free (*S*)-**9**. The aqueous solution was evaporated and dried in vacuo, dissolved in water/EtOH (1/1) and loaded on Dowex 50X2 100 cation-exchange resin. Elution of the column with 10% $NH_3 \cdot H_2O$/EtOH (1/1) and subsequent evaporation gave the target amino acids (*S*)-**1** and (*S*)-**2**.

(*S*)-*trans*-Cinnamylglycine (1). Yield: (90.2%); mp 238–239°C (dec.). $[\alpha]_D^{25}=-30.7°$ (*c*0.11, MeOH), −18.3° (*c*0.57, 1 N HCl); lit.[20] mp 197–200°C. $[\alpha]_D^{25}=-18.7°$, (*c*1, 1 N HCl). ^1H NMR (CD_3OD/D_2O) δ 2.75, 2.83 (2H, ABXY, J_{AB}=15.0 Hz, $J_{AX}=J_{AY}$=7.5 Hz, $J_{BX}=J_{BY}$=6.0 Hz), 3.78 (1H, dd, *J*=7.5 Hz, 5.0 Hz), 6.21, 6.62 (2H, ABXY, J_{AB}=15.0 Hz, $J_{AX}=J_{AY}$=7.5 Hz), 7.24–7.27 (1H, m), 7.32–7.35 (2H, m), 7.43–7.44 (2H, m). ^{13}C NMR (CD_3OD/D_2O) δ 35.4, 55.5, 123.9, 127.3, 128.8, 129.7, 135.8, 137.8, 174.4. HRMS(FAB) $[M+H]^+$ calcd for $C_{11}H_{13}NO_2$ 192.1025, found 192.1032.

(*S*)-α-*trans*-Cinnamyl-α-alanine (2). Yield: (90.6%); mp 249–250°C (dec.). $[\alpha]_D^{25}=-12.9°$ (*c* 0.51, MeOH); lit.[10] mp 241–245°C. $[\alpha]_D^{21}=13.1°$ (*R* enantiomer, *c*0.4, MeOH). ^1H NMR (CD_3COCD_3/D2O) δ 1.49 (3H, s), 2.61, 2.77 (2H, ABX, J_{AB}=14.5 Hz, J_{AX}=8.5 Hz, J_{BX}=6.5 Hz), 6.19, 6.54 (2H, ABX, J_{AB}=15.5 Hz, $J_{AX}=J_{AY}$=7.5 Hz), 7.13–7.16 (1H, m), 7.22–7.25 (2H, m), 7.35–7.36 (2H, m). ^{13}C NMR (CD_3OD/D_2O) δ 22.6, 41.3, 61.7, 123.6, 127.0, 128.1, 129.1, 135.6, 137.6, 175.6. HRMS(FAB) $[M+H]^+$ calcd for $C_{12}H_{15}NO_2$ 206.1181, found 206.1181.

Acknowledgements

This work was supported by the grants from US Public Health Service Grant and the National Institute of Drug Abuse DA 06284, DA 04248 and DK 17420. The views expressed are those of the authors and not necessarily of the USPHS.

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18. Presence of oxygen in the reaction mixture can result in the corresponding oxidation products of the Ni-complexes.
19. It has been demonstrated[14,15] that CD and ORD spectra of Ni(II)-complexes of this type in neutral solutions exhibit two maxima in the region of metal d–d transition (Cotton effects at 450 and 550 nm). In the ORD spectra, the sign of Cotton effects in this region strictly depends upon the conformation of the polycyclic system of chelate rings. Thus, in the case of complexes containing α-monosubstituted α-amino acid, the pseudoaxial orientation of the amino acid side chain, corresponding to an α-(L) configuration of an α-amino acid, causes a Cotton effect with a positive sign at the 500–700 nm region and a negative sign at 400–450 nm. On the other hand, a pseudoequatorial orientation of the amino acid side chain brings about opposite signs of the Cotton effects at 400–450 (positive) and at the 500–700 nm (negative) region. As established in numerous studies, this general trend is not influenced by the structure and nature of the α-amino acid side chain, and the configuration of other stereogenic centers that may be within it. ^{1}H NMR spectra of the complexes containing α-(L)- and α-(D)-amino acids are also very characteristic, featuring a substantial difference in chemical shifts of aromatic and methylene protons of the (*N*-benzyl)proline moiety.
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