Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 1992, **2**(3), 89–91
Mendeleev Communications

Asymmetric Synthesis of (2*S*,3*R*)- and (2*S*,3*S*)-2-Aminomethyl-3-hydroxy-3-phenylpropanoic Acids *via* a Chiral Ni^{II} Complex of a Schiff Base Prepared from β-Alanine and (*S*)-2-[-*N*-(*N*′-benzyl)prolylamino]benzophenone

Yuri N. Belokon',* Snieguole M. Motsishkite, Viktor I. Maleev, Svetlana A. Orlova, Nikolai S. Ikonnikov, Ergash B. Shamuratov, Andrei S. Batsanov and Yurii T. Struchkov

A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 117813 Moscow, Russian Federation. Fax: +7 095 135 5085

A chiral Ni^{II} complex of a Schiff base derived from β-alanine and (*S*)-2-*N*-(*N*′-benzylprolyl)aminobenzophenone (BBP) undergoes an NaH-promoted reaction with benzaldehyde to produce a mixture of two diastereoisomeric complexes which, after chromatographic separation on SiO_2 and decomposition with acid, give optically pure (2*S*,3*R*)- and (2*S*,3*S*)-2-aminomethyl-3-hydroxy-3-phenylpropanoic acids.

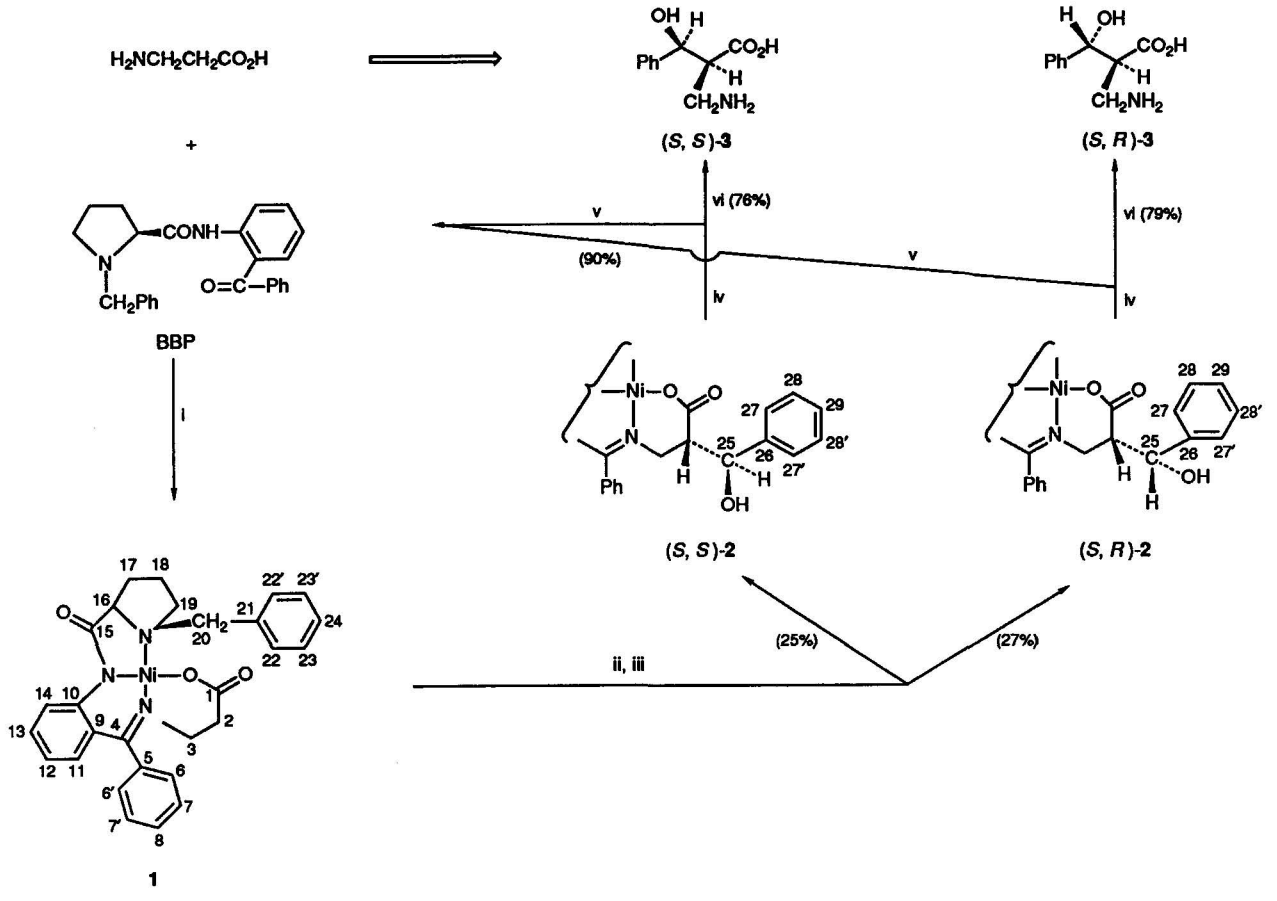
β-Amino acids are of major importance as components of physiologically active peptides, antibiotics or inhibitors of protolytic enzymes.[1] In addition, β-amino acids are used as starting materials for the synthesis of β-lactams[2] and other compounds.[3] At present, there are few methods available for asymmetric synthesis of chiral β-amino acids[4] and the elaboration of these methods has, therefore, become important.[5]

In previous papers we described the use of a reusable chiral reagent (*S*)-2-[*N*-(*N*′-benzylprolyl)amino]benzophenone (BBP) in Ni^{II} complexes of Schiff bases derived from BBP with glycine and alanine to obtain a number of nonproteinogenic α-amino acids in optically pure form.[6] In this work, we report the application of the same principle to the synthesis of optically active α-substituted β-amino acids, (2*S*,3*R*)- and (2*S*,3*S*)-2-aminomethyl-3-hydroxy-3-phenylpropanoic acid, *via* the reaction of benzaldehyde with the Ni^{II} complex of a Schiff base prepared from BBP and β-alanine (Scheme 1).

The starting complex **1**† was obtained by the interaction of β-alanine, BBP and a Ni^{II} salt in the presence of a base

† ^{13}C NMR spectra ($CHCl_3$) for **1**: δ 179.9 (C^1), 174.9 (C^{15}), 171.6 (C^4), 141.3 (C^{21}), 134.9 (C^{10}), 133.5 (C^5), 132.9–120.6 (C^6–C^8, C^{11}–C^{14}, C^{22}–C^{24}), 128.0 (C^9), 69.7 (C^{16}), 56.7 (C^{19}), 52.2 (C^3), 36.4 (C^2), 30.6 (C^{17}), 24.1 (C^{18}).

Mendeleev Commun., 1992, 2(3), 89–91



Scheme 1 *Reagents and conditions*: i, MeOH, $Ni(NO_3)_2$, MeONa, 65 °C, 24 h; ii, NaH, THF, PhCHO, −78→+20 °C; iii, chromatographic separation on SiO_2, $MeCO_2Et$–EtOH 5:1; iv, 3 mol dm^{-3} HCl, 100 °C, pH = 7 by aq. NH_3; v, extraction by $CHCl_3$; vi, DOWEX-50 × 8 in H^+ form, 1 mol dm^{-3} aq. NH_3

(MeONa). Then **1** was reacted with benzaldehyde in the presence of a very strong base NaH according to the following procedure: 2 equiv. of NaH were added to a solution of **1** (1 equiv.) in tetrahydrofuran (THF) at −78 °C in an argon atmosphere; the reaction mixture was stirred at −78 °C for 15 min, then benzaldehyde (10 equiv.) was added and the mixture was stirred at 20 °C for 102 h, then the reaction mixture was neutralized with 10% aqueous acetic acid, extracted with $CHCl_3$ and evaporated. The resulting mixture contained some starting complex **1** and equal amounts of two diastereoisomeric complexes **2**‡ which were separated by column chromatography on SiO_2. The reaction proceeds exclusively at the α-carbon atom of the amino acid moiety, as was established by comparison of the ^{13}C NMR spectra of the two diastereoisomeric complexes‡ with that of the initial complex **1**. Both isomers had almost identical ORD curves in the d–d transition region (380–700 nm). It is well documented[7] that the sign and magnitude of the Cotton effects in this region are predominantly determined by the chirality of the conformation of the chelate rings of the complexes. The chirality of the conformation in turn depends on the absolute configuration of the α-carbon atom of the amino acid fragments. Thus, the similarity of the ORD curves indicates the identify of the configuration of the α-carbon atoms of the amino acid moieties in both complexes. The difference in their structures evidently results from the opposite configurations of the β-carbon atoms of the amino acid side chain. A single crystal X-ray study of the second isomer (in order of its elution from the column) proves it to be

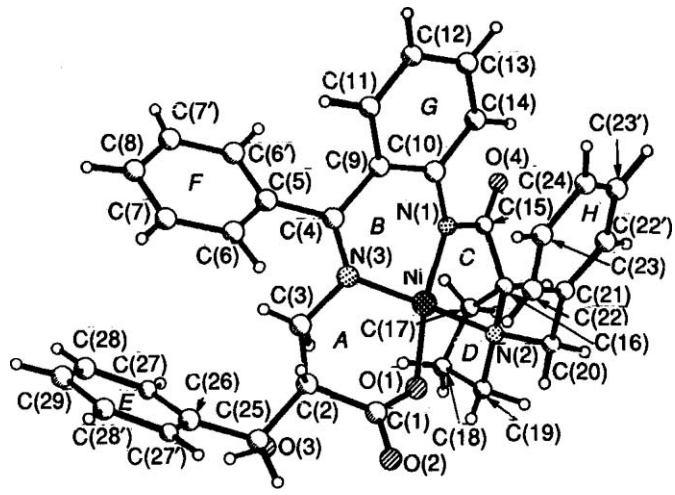


Fig. 1 The molecular structure of (*S,S*)-**2**. Main geometrical parameters: bond lengths (Å): Ni—O(1) 1.878(4), Ni—N(1) 1.849(5), Ni—N(2) 1.951(5), Ni—N(3) 1.871(5), N(3)=C(4) 1.301(7), N(3)—C(3) 1.479(7); bond angles (°): O(1)—Ni—N(1) 168.7(2), O(1)—Ni—N(2) 87.8(2), O(1)—Ni—N(3) 93.6(2), N(1)—Ni—N(2) 86.7(2), N(1)—Ni—N(3) 93.1(2), N(2)—Ni—N(3) 172.6(2)

‡ The complexes have the same elemental analyses and the same set of NMR resonances, differing in their chemical shifts.

^{13}C NMR spectra ($CHCl_3$) (*S,R*)-**2**: δ 179.8 (C^1), 177.8 (C^{15}), 172.3 (C^4), 140.9 (C^{26}), 140.7 (C^{21}), 133.9–133.3 (C^5, C^9), 132.8–120.5 (C^6–C^8, C^{11}–C^{14}, C^{22}–C^{24}, C^{27}–C^{29}), 128.4 (C^{10}), 73.5 (C^{25}), 69.7 (C^{16}), 62.0 (C^{20}), 56.7 (C^{19}), 54.0 (C^3), 51.8 (C^2), 30.5 (C^{17}), 24.1 (C^{18}).

(*S,S*)-**2**: δ 179.8 (C^1), 171.8 (C^{15}), 171.7 (C^4), 141.6 (C^{26}), 140.9 (C^{21}), 133.8–133.6 (C^5, C^9), 128.0 (C^{10}), 132.6–120.4 (C^6–C^8, C^{11}–C^{14}, C^{22}–C^{24}, C^{27}–C^{29}), 72.1 (C^{25}), 69.9 (C^{16}), 61.8 (C^{20}), 56.9 (C^{19}), 52.4 (C^3), 52.2 (C^2), 30.5 (C^{17}), 23.9 (C^{18}).

Mendeleev Commun., 1992, 2(3), 89–91

(2*S*,3*S*)-**2**§ and its structure is shown in Fig. 1. Clearly, the complex containing the (2*S*,3*R*)-isomer of the amino acid, and was the first to be eluted.

The diastereoisomerically pure complexes were decomposed with 3 mol dm^{-3} HCl, enantiomerically pure (2*S*,3*R*)- and (2*S*,3*S*)-2-aminomethyl-3-hydroxy-3-phenylpropanoic acids [(*S*,*R*)-**3** and (*S*,*S*)-**3**] were obtained (75–80%) and BBP recovered (90%), as described for the decomposition of the α-amino acid complexes.[6] According to GLC analysis,¶ the enantiomeric excess (e.e.) of (*S*,*R*)-**3**‖ is 97% and 98% for (*S*,*S*)-**3**.‖

The important feature of the reactivity of **1** is the regioselectivity of the benzaldehyde attack at the α-position of the β-alanine moiety, which may be rationalized by the greater CH-acidity of its α- relative to the β-protons. The very significant α-carbon atom asymmetric induction may be derived from the thermodynamic stability of the (*S*)-α-configuration in which the side chain assumes an equatorial orientation with the least possible repulsion between the chain and the phenyl group at the C=N bond. Molecular mechanics calculations** generally support this notion.

We hope that the described approach may eventually lead to the development of a general method for the asymmetric synthesis of α-substituted β-amino acids.

§ *Crystal data* for (*S*,*S*)-**2**: $C_{35}H_{33}N_3O_4Ni$, $M=618$, orthorhombic, space group $P2_12_12_1$, $a=9.733(2)$, $b=10.093(3)$ Å, $c=29.704(4)$, $V=2918(2)$ Å^3, $\rho_c=1.401$ g cm^{-3}, for $Z=4$. Experimental data were measured at 298 K on a Siemens P3/PC automatic diffractometer using Mo–Kα radiation ($\lambda=0.71069$ Å, graphite monochromator θ–2θ scan, $\theta\leq25°$). The structure was solved by the heavy-atom technique and refined by full-matrix least-squares in the anisotropic approximation. All H atoms (with the exception of benzene H atoms which were placed geometrically) were located in the difference Fourier synthesis and included in the final refinement in the isotropic approximation (benzene H atoms were refined using the 'riding model' procedure). The refinement converged to $R=0.041$ ($R_w=0.040$) for 2403 independent reflections with $F^2\geq3\sigma$. All calculations were carried out on an IBM PC AT by means of the SHELXTL PC program package. Atomic coordinates, bond lengths and angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, see Notice to Authors, *J. Chem. Soc., Chem. Commun.*, 1992, Issue No. 1.

¶ Pyrex column, $L=41$ m, i.d. = 0.22 mm, $l=0.12$ mkm, diamide–polysiloxane chiral phase 'Chirasil-Val' type.

‖ *Characterization data* for (*S*,*R*)-**3**: $[\alpha]_D^{25}+44.6$ (*c* 0.47, 2 mol dm^{-3} HCl); ^{1}H NMR (D_2O, DCl) δ 2.90–3.20 (m, 4H, CH_2, CHOH, CHO_2H), 7.20–7.38 (m, 5H, Ph); ^{13}C NMR (H_2O, HCl) δ 173.9 (CO_2H), 139.4 (*i*-Ph), 128.6 (*p*-Ph), 128.4 (*o*-Ph), 125.9 (*m*-Ph), 72.5 (*C*HOH).

For (*S*,*S*)-**3**: $[\alpha]_D^{25}-16.8$ (*c* 0.53, 2 mol dm^{-3} HCl); ^{1}H NMR (D_2O, DCl) δ 2.96–3.23 (m, 4H, CH_2, CHOH, $CHCO_2H$), 7.15–7.31 (m, 5H, Ph); ^{13}C NMR (H_2O, HCl) δ 174.1 (CO_2H), 140.1 (*i*-Ph), 128.6 (*p*-Ph), 128.1 (*o*-Ph), 125.6 (*m*-Ph), 72.7 (*C*HOH), 49.7 ($CHCO_2H$), 37.1 (CH_2).

** We used the program PCMODEL from Serena Software.

References

1 *Dictionary of Antibiotics and Related Substances*, Chapman and Hall, London, New York, 1988.

2 S. Kim, S. B. Chang and P. H. Lee, *Tetrahedron Lett.*, 1987, **28**, 2735; C. Gennari, I. Venturini, G. Gislon and G. Schimperna, *Tetrahedron Lett.*, 1987, **28**, 227; G. Cainelli, D. Giacomini, M. Panunzio, G. Martelli and G. Spunta, *Tetrahedron Lett.*, 1987, **28**, 3593; T. Kunieda, T. Nagamatsu, T. Higuchi and M. Hirobe, *Tetrahedron Lett.*, 1987, **29**, 2203.

3 H. H. Wasserman, R. K. Brunner, J. D. Buynak, C. G. Cartner, T. Oku and P. R. Robinson, *J. Am. Chem. Soc.*, 1985, **107**, 519.

4 C. N. C. Drey, in *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall, New York, 1985, pp. 25–54; O. W. Griffith, *Annu. Rev. Biochem.*, 1986, **55**, 855.

5 H. Esterman and D. Seebach, *Helv. Chim. Acta*, 1988, **71**, 1824; H. Kunz, D. Schanzenbach, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 1068; R. Herranz, J. Castro-Pichel and T. Garcia-Lopez, *Synthesis*, 1989, 703; P. Gmeiner, *Tetrahedron Lett.*, 1990, **31**, 5717; E. Juaristi, D. Quintana, B. Lamatsch and D. Seebach, *J. Org. Chem.*, 1991, **56**, 2553; J. P. Konopelski, K. C. Chu and G. R. Negrete, *J. Org. Chem.*, 1991, **56**, 1355.

6 Y. N. Belokon', A. S. Sagiyan, S. M. Djamgaryan, V. I. Bakhmutov, S. V. Vitt, A. S. Batsanov, Y. T. Struchkov and V. M. Belikov, *J. Chem. Soc., Perkin Trans. 1*, 1990, 2301 and references cited therein.

7 C. J. Hawkins, *Absolute Configuration of Metal Complexes*, Wiley Interscience, New York, 1971; 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. M. Belikov, *J. Chem. Soc., Dalton Trans.*, 1985, 17.

Received: Moscow, 29th December 1991
Cambridge, 3rd March 1992; Com. 2/00274D