Productive Asymmetric Synthesis of All Four Diastereomers of 3-(*trans*-2-Nitrocyclopropyl)alanine from Glycine with (*S*)- or (*R*)-2-[(*N*-Benzylprolyl)amino]benzophenone as a Reusable Chiral Auxiliary[‡]

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Dedicated to Professor Irina Beletskaya on the occasion of her 70th birthday

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All four diastereomers of 3-(*trans*-2-nitrocyclopropyl)alanine (**3**) were prepared by asymmetrically induced α-C alkylation of the glycine moiety in the [(*S*)- or (*R*)-Schiff base]Ni^{II} complex **7**, employing racemic *trans*-1-(iodomethyl)-2-nitrocyclopropane (**8**) as the alkylating agent. A notable difference in solubility between the two diastereomeric products **9a**/**9b** [when (*S*)-**7** was used as starting material] or **9d**/**9e** [when (*R*)-**7** was employed] allowed for their separation from the same reaction mixture. All the diastereomers of 3-(*trans*-2-nitrocyclopropyl)alanine (**3**) were produced upon brief exposure of the alkylation products **9** to dilute hydrochloric acid, with subsequent purification by ion-exchange chromatography and crystallization. The absolute configurations of the nickel complexes **9a**–**e** were established by X-ray crystallographic analyses. In addition, the X-ray crystal structure of (2*S*,1′*S*,2′*R*)-**3** was determined to confirm the convergence of the configurations of the parent nickel complexes **9** with those of the amino acids **3** derived from them.

Introduction

Nature makes use of cyclopropyl groups even in amino acids, and most of the over two dozens of known naturally occurring amino acids containing a cyclopropyl group as well as most of the cyclopropyl analogues of natural amino acids, are responsible for the observed biological activities of compounds containing them as constituents.[1] Among such natural products, the peptidolactone hormaomycin (**1**), which influences the secondary metabolite production of certain bacteria,[2] and the recently isolated belactosin A (**2**), which exhibits an antitumor activity,[3] are especially intriguing, as they contain the previously unknown 3-(*trans*-2-nitrocyclopropyl)alanine [(N*c*P)Ala, **3**] and 3-(*trans*-2-aminocyclopropyl)alanine [**4**, (A*c*P)Ala] as key constituents.

Feeding experiments with deuterium-labelled (N*c*P)Ala (**3**) as well as (A*c*P)Ala (**4**) have disclosed that the appropriate strain of *Streptomyces griseoflavus* incorporates the (2*S*,1′*S*,2′*R*) and (2*R*,1′*S*,2′*R*) diastereomers of 3-(*trans*-2-nitrocyclopropyl)alanine (**3**), but not **4** in hormaomycin.[4] Furthermore, it has recently been established that (2*S*,1′*S*,2′*R*)-**3** acquires the exocyclic position in **1**, while (2*R*,1′*S*,2′*R*)-**3** is incorporated in the hexapeptolide ring constituent of the pentapeptidic ring.[5] On the other hand, the 3-(*trans*-2-aminocyclopropyl)alanine (**4**) moiety in belactosin A (**2**) possesses the (2*S*,1′*R*,2′*S*) configuration.[3] Hence, there is an apparent need for a convergent and productive access to at least three diastereomers of the amino acid **3**, from which **4** can be prepared,[6] in enantiomerically pure form.

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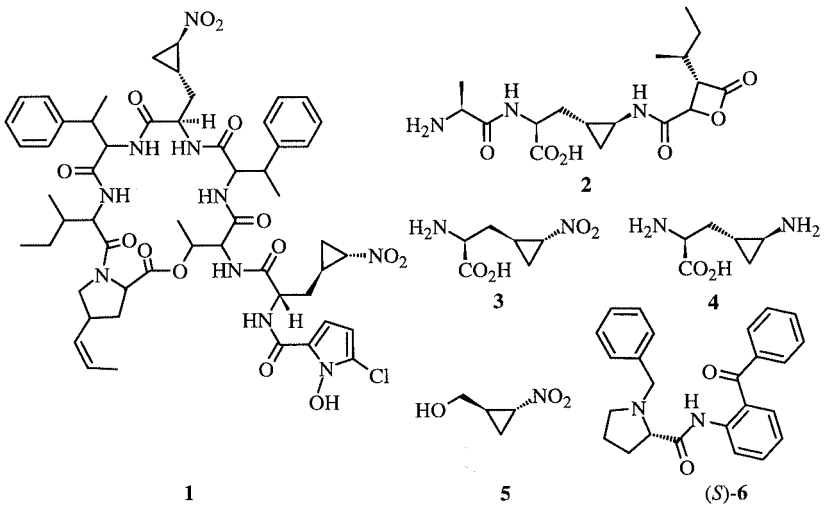


Both natural amino acids **3** and **4** can be prepared from the same precursor, (*trans*-2-nitrocyclopropyl)methanol (**5**), which was used in the previously reported syntheses of (2*RS*,1′*R*,2′*S*)- and (2*S*,1′*RS*,2′*RS*)-**3**.[6]

In an effort to elucidate the biosynthetic pathway leading to **1**, we have recently prepared a deuterium-labelled specimen of racemic **3**[4a,4c] and **4**.[4c,7] A procedure for the preparation of the enantiomerically enriched precursors (1*R*,2*R*)-**5** and (1*S*,2*S*)-**5** (*ee* 92%) had also been developed.[7] Since the naturally occurring amino acids **3** and **4** have not yet been synthesized in stereoisomerically pure form, we are prompted to report our results on the synthesis of all four diastereomers of **3**. With these in hand, the amino acid (2*S*,1′*R*,2′*S*)-**4** also becomes readily accessible by reduction of the nitro group.[6d]

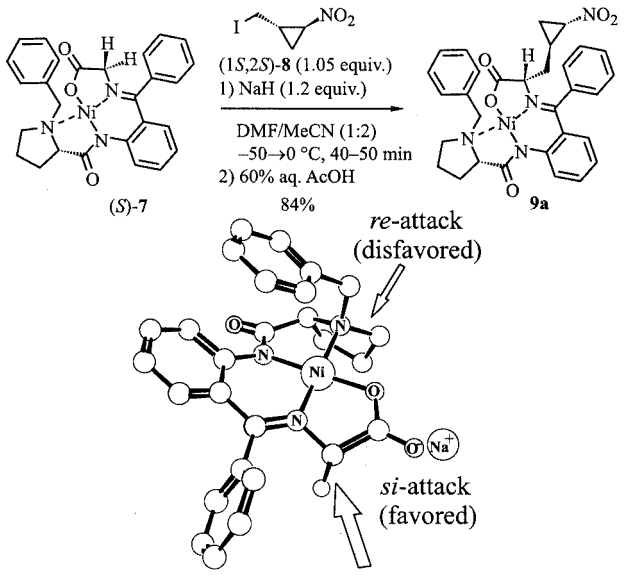
Among different synthetic approaches to enantiomerically pure α-amino acids,[8] the asymmetrically induced *C*-alkylation has shown its outstanding utility over the past decade, due to the simplicity of the experimental procedures and their general applicability.[9] 2-[(*N*-Benzylprolyl)amino]-benzophenone (BPB, **6**) has proved to be an efficient chiral auxiliary for the synthesis of more than 100 enantiomerically pure proteinogenic and non-proteinogenic α-amino acids.[10] The synthetic protocols make use of the Ni^{II} complexes of the Schiff bases derived from (*S*)- or (*R*)-**6** and simple amino acids (glycine or alanine). The amino acid moiety becomes a sufficiently strong C−H acid to undergo a set of electrophilic reactions in the presence of ordinary bases like NaH, NaOH, KOH, or K_2CO_3. This approach has also been successfully used by other research groups.[11]

Results and Discussion

The initial aim was to develop an efficient procedure for the alkylation of the chiral nickel complex (*S*)-**7** {[(*S*)-BPB/Gly]Ni^{II}} with enantiomerically enriched (*ee* = 92%) *trans*-1-(iodomethyl)-2-nitrocyclopropane (1*S*,2*S*)-**8**, which was derived from the corresponding alcohol (1*S*,2*S*)-**5** by treatment with iodine, triphenylphosphane and imidazole.[7]

The *C*-alkylation of (*S*)-**7** with (1*S*,2*S*)-**8** occurred fast and quantitatively in a dimethylformamide/acetonitrile (1:2) mixture, using NaH as a base (Scheme 1). As monitored by TLC, almost all (*S*)-**7** was consumed within 30 min to give the alkylation product **9a** in 84% yield after acidic workup and crystallization from a dimethylformamide/acetonitrile (1:2) mixture. As evidenced by an X-ray crystal structure analysis (Figure 1, **A**), the α-C atom bearing the *trans*-(2-nitrocyclopropyl)methylene moiety in **9a**, had an (*S*) configuration. Thus, the absolute configuration of the two chiral centers in the *trans*-2-nitrocyclopropyl group of **9a** is (1′*R*,2′*S*), which is the same as that of the initial iodide (1*S*,2*S*)-**8** (the perceived change of the configuration at C-1 of the cyclopropane ring in **9a** is only a change in the CIP nomenclature order of the substituents according to the sequence rules).

Trace amounts of other diastereomers of **9** were observed in the thin layer chromatogram (TLC) and ^1H NMR spec-



Scheme 1. Alkylation of the nickel complex (*S*)-**7** with (1*S*,2*S*)-**8**; structure **10** is derived from the X-ray crystallographic structure of **9c** (Figure 1, **C**)

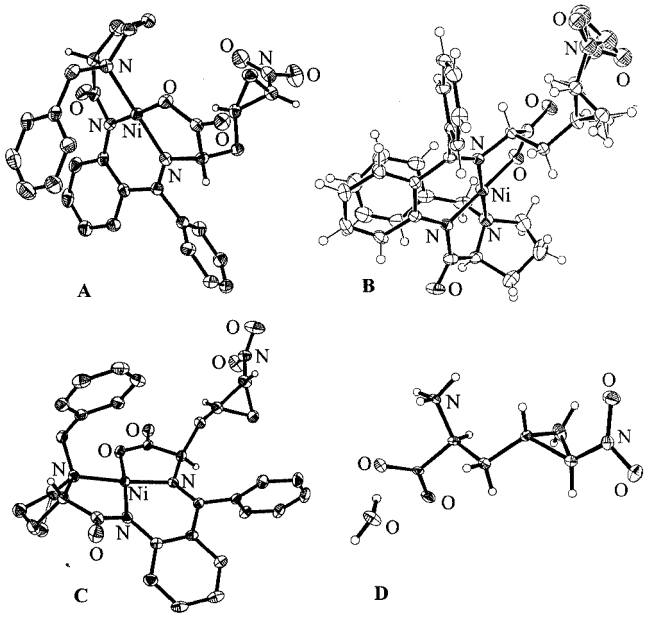
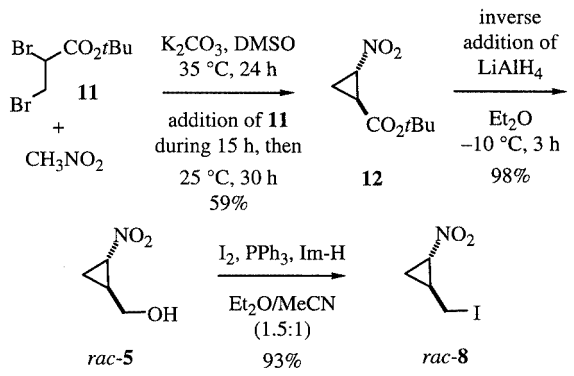


Figure 1. Molecular structures of the nickel complexes **9a** [**A**, (*S*) configuration in the proline and (2*S*,1′*R*,2′*S*) in the (N*c*P)Ala moiety], **9b** [**B**, (*S*) configuration in the proline and (2*S*,1′*S*,2′*R*) in the (N*c*P)Ala moiety], **9c** [**C**, (*S*) configuration in the proline and (2*R*,1′*S*,2′*R*) in the (N*c*P)Ala moiety], and (2*S*,1′*S*,2′*R*)-3-(*trans*-2-nitrocyclopropyl)alanine (**3**·0.5H_2O, **D**) in the crystal (displacement ellipsoids are shown at the 50% probability level)[15]

trum of the reaction mixture. These could have arisen from incomplete (*ee* = 92%) enantiomeric enrichment of the employed (1*S*,2*S*)-**8** and also from the competing electrophilic attack at the hindered *re* side of the anionic intermediate **10** (Scheme 1).

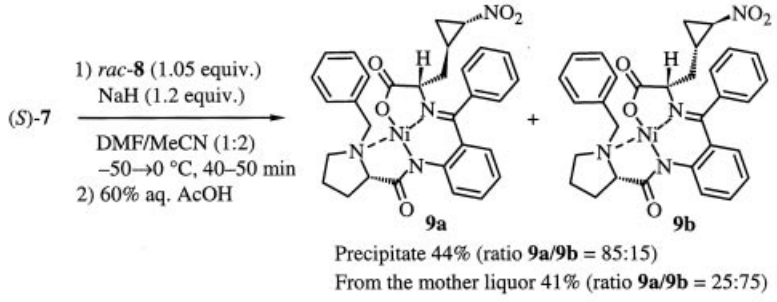
Although this procedure proved to be successful, it has the severe disadvantage of employing two chiral auxiliaries [i.e. a chiral oxazolidinone derivative[12] for the synthesis of (1*S*,2*S*)-**5**,[7] and the nickel complex (*S*)-**7** for the alkylation step] en route to the amino acid **3** with three stereogenic centers, and the synthetic sequence for the enantiomerically enriched alcohol **5** comprises several tedious and low-yielding steps. A better alternative appeared to be the alkylation of (*S*)-**7** with the racemic iodide **8** and subsequent separation of the diastereomeric products.

The racemic iodide **8** was prepared in three simple steps, starting from *tert*-butyl 2,3-dibromopropionate (**11**). First, the known synthesis of *tert*-butyl *trans*-2-nitrocyclopropanecarboxylate (**12**)[6c,6d] was significantly improved. (Scheme 2). The addition of the dibromo ester **11** to a mixture of nitromethane and potassium carbonate in DMSO increased the yield of **12** from 31 to 59%. Reduction of the ester **12** with lithium aluminum hydride (inverse addition of its solution in diethyl ether) afforded the racemic alcohol **5** in 98% yield. It is noteworthy, that the yield of the reduction product **5** drops drastically to a meager 25%, if the ester **12** is added to a solution of lithium aluminum hydride (the usual mode of addition). The alcohol **5** was converted into the iodide **8** in 93% yield by treatment with iodine, imidazole and triphenylphosphane.[13]



Scheme 2. Preparation of the iodide *rac*-**8** from the dibromoester **11**

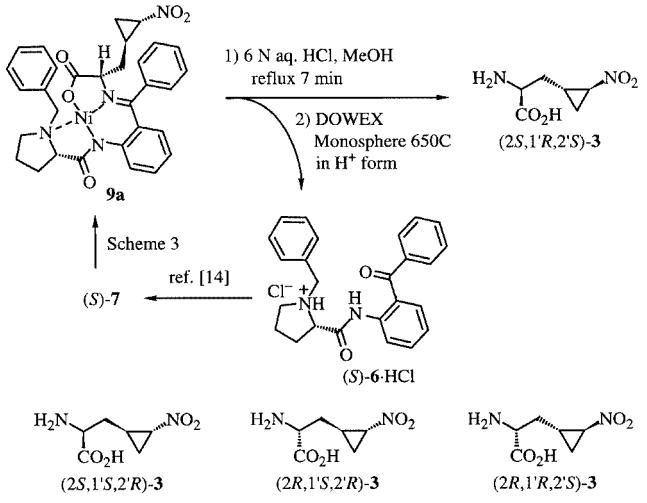
The racemic iodide **8** was employed in the alkylation of (*S*)-**7** (Scheme 3). After complete consumption (indicated by TLC) of (*S*)-**7** (ca. 40 min), the excess base was quenched with 60% aqueous acetic acid. This led to the formation of a precipitate that was composed of **9a** and **9b** in a ratio of 85:15 and weighed 44% of the total theoretically obtainable mixture of diastereomeric products. On the other hand, a mixture of the same **9a** and **9b** but in a ratio of 25:75 was secured from the liquid phase after an aqueous workup and column chromatography. This fraction accounted for 41% of the expected alkylation product. Thus, the combined yield of **9a** and **9b** was 85%, both readily available in diastereomerically enriched forms. The diastereomeric ratios of **9a** and **9b** varied to the extent of 2−4% for the obtained fractions, depending upon run and scale, with the average values of 85:15 and 25:75 (**9a/9b**) for the precipitate and the liquid phase fractions, respectively.



Scheme 3. Diastereomeric distribution of products after the alkylation of (*S*)-**7** with racemic iodide **8**

Recrystallization of the fraction enriched in **9a** from dimethylformamide/acetonitrile afforded **9a** with diastereomeric excesses varying between 95 and 98%. All physical data of this product are identical to those of **9a** obtained by alkylation of (*S*)-**7** with (1*S*,2*S*)-**8**. An X-ray crystal structural analysis was, however, performed to confirm the expected (2*S*,1′*R*,2′*S*) configuration of the (N*c*P)Ala moiety (Figure 1, **A**).

The complex **9a** with *de* = 95% was decomposed by treatment with 6 N hydrochloric acid (Scheme 4) to give the crude amino acid (2*S*,1′*R*,2′*S*)-**3**, $NiCl_2$, and the insoluble hydrochloride of (*S*)-**6**. The latter was recovered by filtration to the extent of 90−95%, and after brief drying in vacuo was reused for the preparation of (*S*)-**7**.[14] The crude amino acid (2*S*,1′*R*,2′*S*)-**3** was purified by eluting the resulting filtrate through a pad of DOWEX resin in H^+ form with 5−7% aqueous ammonia. A single crystallization from aqueous ethanol afforded the product (2*S*,1′*R*,2′*S*)-**3** ($[\alpha]_D^{20}$ = +72.7, *c* = 0.3 in H_2O) with *de* = 99% (chiral HPLC) and in 67% yield from **9a**.



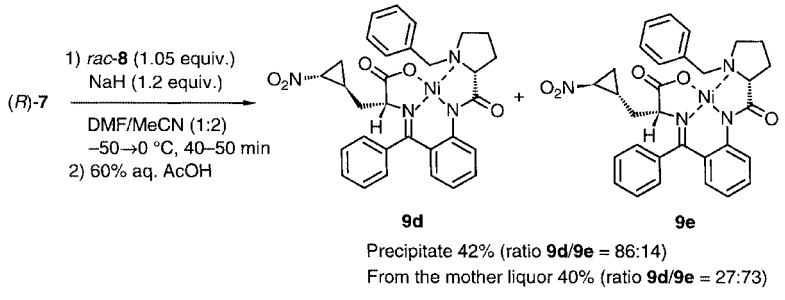
Scheme 4. Isolation of (N*c*P)Ala (**3**) from the corresponding nickel complexes **9**

The fraction enriched in **9b** (75:25) (Scheme 3), proved to be hardly separable by column chromatography. However, diastereomerically pure **9b** was obtained by slow crystallization of this 75:25 mixture of **9b** and **9a** from MeOH, albeit only in 30% yield. Interestingly, a minute amount (2−3%) of the diastereomer **9c** {[(*S*)-BPB/(2*R*,1′*S*,2′*R*)-(N*c*P)Ala]Ni^{II}} (Figure 1, **C**) was collected from a sample of **9b** with a spatula, due to a tremendous difference in crystal sizes of the two diastereomers. Therefore, this 75:25 mixture of **9b** and **9a** was decomposed without further purification with 6 N hydrochloric acid (Scheme 4) and the crude amino acid, after ion-exchange purification using DOWEX Monosphere 650C resin, was twice recrystallized from aqueous ethanol to give (2*S*,1′*S*,2′*R*)-**3** ($[\alpha]_D^{20}$ = −55.6, *c* = 0.32 in water) with diastereomeric and enantiomeric purity > 96% (chiral HPLC) and in 55% yield.

Similarly, (*R*)-**7** underwent smooth alkylation with *rac*-**8**, to give, after quenching with 60% aqueous acetic acid, 42% of a mixture of **9d** and **9e** (ca. 86:14 ratio) as a precipitate, while the workup of the reaction liquor afforded 40% of this diastereomeric mixture but in ca. 27:73 ratio (Scheme 5). The absolute configurations of the (N*c*P)Ala moiety in **9d** and **9e** were determined to be (2*R*,1′*S*,2′*R*) and (2*R*,1′*R*,2′*S*), respectively, by X-ray structural analyses (mirror images of **9a** and **9b**, Figure 1, **A**, **B**). Samples of **9d** and **9e** with diastereomeric purities > 95% were obtained as was described above for **9a** and **9b**.

(2*R*,1′*S*,2′*R*)-**3** and (2*R*,1′*R*,2′*S*)-**3** with *de* in the range of 95−99% were prepared from **9d** (*de*, 94−96%) and a **9d**/**9e** mixture (25:75), according to the same procedures as was outlined for (2*S*,1′*R*,2′*S*)-**3** and (2*S*,1′*S*,2′*R*)-**3** (Scheme 4).

The molecular geometries of the nickel complexes derived from the chiral auxiliary **6** have been studied intensively along with the development of this method for the synthesis of enantiomerically pure α-amino acids.[10,11] It was shown,[16] that the conformationally most labile parts of the molecule are the benzyl group and the five-membered ring of the proline moiety, while the coordination around the nickel atom is more constant. In all four cases of the diastereomers **9abde** the slightly distorted square coordination of Ni atoms remains virtually identical (Figure 2, **A**) and only the conformations of the side chains differ slightly. In all these molecules the phenyl rings of the benzyl groups adopt a *syn* orientation with respect to the Ni atom and are almost parallel to the coordination plane of the metal atom with the shortest intramolecular contacts between the *ipso*-C atom of the benzyl group and the Ni atom in the range of 2.91−3.10 Å. However, in the case of the molecule **9c**



Scheme 5. Diastereomeric distribution of products after the alkylation of (*R*)-**7** with racemic iodide **8**

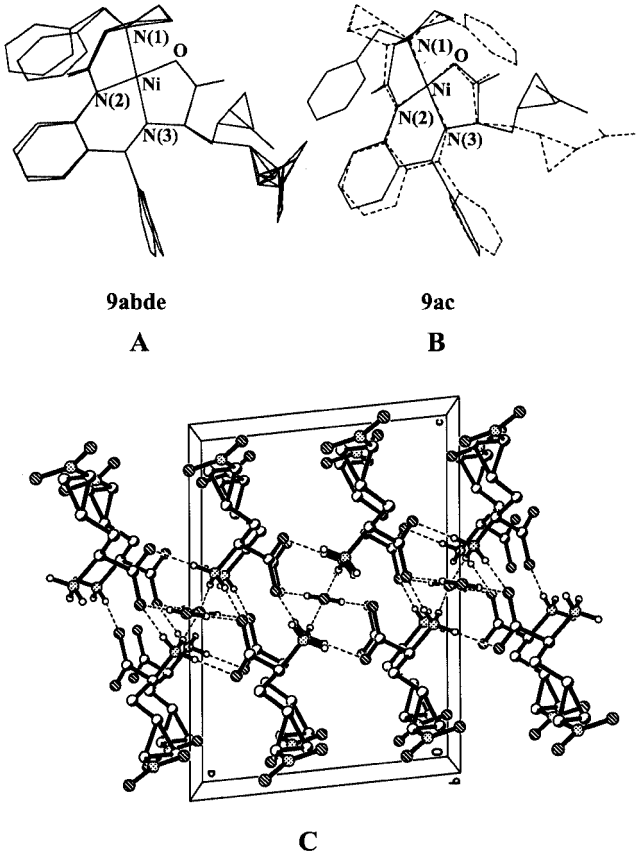


Figure 2. Graphical superposition of molecular structures of the Ni complexes **9abde** (**A**), **9ac** (**B**) and crystal packing of the amino acid (2*S*,1′*S*,2′*R*)-**3** (**C**) in the crystal

(Figure 1, **C**), in which the benzyl and the (2-nitrocyclopropyl)methylene groups are on the same side of the Ni atom, the conformation of the molecule is very different (Figure 2, **B**). The coordination polyhedron of the Ni atom is inverted in order to avoid close steric contacts between bulky side groups and there is no longer close contact between the benzyl group and the metal atom. The disordering of the proline ring in **9c** confirms the conformational flexibility of this part of the molecule.

Molecules of (2*S*,1′*S*,2′*R*)-**3** in the crystal are associated in sheets, parallel to the *x*0*y* plane, by an extensive network of N−H···O and O(water)−H···O hydrogen bonds (Figure 2, **C**). There are a number of relatively close C−H···O contacts between adjacent sheets. The directions of these contacts as well as the H···O distances (2.5−2.7 Å) correspond to the weak attractive C−H···O interactions of CH groups of cyclopropane rings.[17]

The diastereomeric amino acids **3** tend to form stable crystalline semihydrates, as was shown by the elemental analyses of (2*S*,1′*R*,2′*S*)-**3**, (2*R*,1′*S*,2′*R*)-**3**, and (2*R*,1′*R*,2′*S*)-**3**. This was also confirmed by an X-ray crystal structure elucidation of (2*S*,1′*S*,2′*R*)-**3** (Figure 1, **D**). The water can be removed, however, on drying in vacuo at 70 °C over a period of 3−4 d.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded at 250, 300, 600 (^{1}H), and 62.9, 75.5 [^{13}C, additional DEPT (Distortionless Enhancement by Polarization Transfer)] MHz on Bruker AM 250, AMX 300, and Inova 600 instruments in $CDCl_3$ solutions unless otherwise specified, δ in ppm, *J* in Hz. IR: Bruker IFS 66 (FT-IR) spectrometer, measured as KBr pellets or oils between KBr plates. MS (EI): Finnigan MAT 95 spectrometer. X-ray crystal structure analysis of **9a**−**e** and **3**: the X-ray single crystal data were collected at 120(1) K with a Bruker CCD SMART 1 K (**3**, **9b**, **c**, and **e**) and SMART 6000 (**9a** and **d**) diffractometers, equipped with Oxford Cryostream cooling devices, using graphite-monochromated Mo-K_α radiation. Crystallographic details and parameters of the data collection and refinement are given in Table 1. The structure solutions and refinements on F^2 were performed with the Bruker SHELXTL program suite. The hydrogen atoms in structures **3**, **9a**, and **9c** were located in difference Fourier syntheses and refined isotropically. The hydrogen atoms in the structures **9b**, **9d**, and **9e** were placed in calculated positions and refined in "riding mode" with a 1.2-fold isotropic displacement parameter of the corresponding C atom. Disordered parts of molecules **9c** and **9e** were refined with fixed site occupation factors of 0.5. CCDC-194678 [(2*S*,1′*R*,2′*S*)-**3**×0.5H_2O], -194679 (**9a**), -194680 (**9b**), -194681 (**9c**), -194682 (**9d**), and -194683 (**9e**) contain the supplementary crystallographic data for this paper.[15] Optical rotations: Perkin−Elmer 241 digital polarimeter, 1-dm cell. Diastereomeric purities of the nickel complexes **9** were determined by integration of the corresponding peaks in ^{1}H NMR spectra. Diastereomeric and enantiomeric purities of the amino acids **3** were determined by HPLC on a chiral column [Crownpak CR (+) or (−), eluent 2% aq. $HClO_4$ (5 mL $HClO_4$/1 L water) + 2% MeOH; UV detection at 210 nm]. M.p.: Büchi 540 capillary melting point apparatus, uncorrected values. TLC: Macherey−Nagel precoated sheets, 0.25 mm Sil G/UV_{254}. Column chromatography: Merck silica gel, grade 60, 230−240 mesh. Starting materials: Diethyl ether and THF were distilled from sodium benzophenone ketyl, CH_2Cl_2 and DMF from molecular sieves 4 Å, acetonitrile from P_4O_{10}. Compounds (*R*)- and (*S*)-**6**,[14] (*R*)- and (*S*)-**7**,[14] and **11**,[6c,6d] were prepared as described elsewhere. DOWEX Monosphere 650C ion-exchange resin was purchased from Fluka. All other chemicals were used as commercially available (Merck, Acrõs, BASF, Bayer, Hoechst, Degussa AG). All reactions were conducted under nitrogen. Organic extracts were dried with $MgSO_4$.

***tert*-Butyl *trans*-2-Nitrocyclopropanecarboxylate**[6c,6d] **(12):** A 4-L three-necked flask, equipped with a mechanical stirrer and a 500-mL dropping funnel, was charged with anhydrous K_2CO_3 (856 g, 6.2 mol), DMSO (2 L), and nitromethane (141.3 g, 125.3 mL, 2.31 mol). The mixture was stirred at ambient temperature for 20 min. The dropping funnel was filled with the dibromo ester **11** (617 g, 2.14 mol), which was then added dropwise within 15 h, maintaining the temperature of the contents at 30−35 °C. After the addition of **11** had been completed, the reaction mixture was vigorously stirred for 30 h. It was then poured into a 6-L separating funnel with ice-cold water (1.5 L), and the suspension was extracted with diethyl ether (5 × 500 mL). The combined organic layers were washed with water (3 × 500 mL), dried, concentrated under reduced pressure, and the residue was distilled bulb-to-bulb at 100−120 °C under reduced pressure (0.05 Torr). The distillate was fractionated at 0.5 Torr to give the ester **12** (236 g, 59%), as a waxy solid; b.p. 72−75 °C (0.5 Torr), m.p. 34 °C. ^{1}H NMR (250 MHz): δ = 1.46 (s, 9 H), 1.67 (ddd, *J* = 6.0, 7.5, 7.5 Hz, 1 H), 2.00 (ddd, *J* = 6.0, 10.5, 4.5 Hz, 1 H), 2.64 (ddd, *J* = 3.0, 7.5, 10.5 Hz, 1 H),

Table 1. Crystal and data collection parameters for compounds (2*S*,1′*S*,2′*R*)-**3** and **9a−e**

	9a	**9b**	**9c**	**9d**	**9e**	(2*S*,1′*S*,2′*R*)-**3**
Empirical formula			$C_{31}H_{30}N_4NiO_5$			$C_6H_{10}N_2O_4\times0.5H_2O$
Formula mass			597.30			183.17
Crystal size [mm]	0.18 × 0.16 × 0.04	0.46 × 0.20 × 0.06	0.37 × 0.20 × 0.14	0.20 × 0.12 × 0.12	0.18 × 0.08 × 0.07	0.26 × 0.18 × 0.03
Crystals	tetragonal	monoclinic	orthorhombic	tetragonal	monoclinic	monoclinic
Space group	$P4_12_12$	$P2_1$	$P2_12_12_1$	$P4_32_12$	$P2_1$	$C2$
a [Å]	9.9924(3)	10.4310(4)	9.7686(4)	9.9946(1)	10.4309(4)	9.8099(6)
b [Å]	9.9924(3)	8.8255(3)	14.8822(6)	9.9946(1)	8.8239(3)	6.3597(4)
c [Å]	55.176(2)	14.9390(6)	18.3546(8)	55.195(1)	14.9327(5)	13.6047(8)
α [°]	90	90	90	90	90	90
β [°]	90	92.04(2)	90	90	91.98(2)	96.05(3)
γ [°]	90	90	90	90	90	90
V [Å^3]	5509.2(3)	1374.39(9)	2668.4(2)	5513.5(1)	1373.60(8)	844.04(9)
Z	8	2	4	8	2	4
D [calculated, g·cm^{-3}]	1.440	1.443	1.487	1.439	1.444	1.441
μ [mm^{-1}]	0.753	0.755	0.777	0.752	0.755	0.124
F(000)	2496	624	1248	2496	624	388
θ range [°]	2.07−29.00	1.95−28.00	2.22−30.31	2.07−27.50	1.95−29.00	3.01−26.00
Refl. collected	60595	12337	23087	29979	15515	3100
Refl. independent	7343	6476	7229	6306	7016	1550
R_{int}	0.0818	0.0318	0.0234	0.0370	0.0442	0.0404
Absorption correction	numerical	semi-empirical from equivalents				
Parameters refined	490	376	466	490	376	158
GOOF	0.935	1.056	1.090	1.145	1.020	1.091
R_1 [$I > 2\sigma(I)$]	0.0369	0.0553	0.0295	0.0291	0.0443	0.0512
wR_2	0.0731	0.1372	0.0722	0.0709	0.0866	0.1213
$R_1(F)$	0.0684	0.0629	0.0326	0.0345	0.0612	0.0605
$wR_2(F^2)$	0.0819	0.1426	0.0735	0.0733	0.0930	0.1262
Absolute structure parameter	−0.04(1)	−0.01(1)	0.011(8)	−0.02(1)	0.01(1)	could not be determined
Largest diff. peak, hole [e·Å^{-3}]	0.395, −0.293	0.452, −0.322	0.499, −0.307	0.268, −0.216	0.405, −0.313	0.246, −0.258

4.53 (ddd, *J* = 3.0, 4.5, 7.5 Hz, 1 H) ppm. ^{13}C NMR: (62.9 MHz): δ = 17.06 (CH_3), 26.07 (CH_2), 27.9 (CH_2), 59.1 (CH_2), 82.64 (C), 167.9 (C) ppm. IR: ṽ = 3115, 2908, 1776, 1558, 1361, 1000 cm^{-1}. MS (EI): *m*/*z* = 187 (1) [M$^+$], 114 (100), 100 (23), 71 (7), 67 (36), 55 (8), 41 (4).

***rac*-(*trans*-2-Nitrocyclopropyl)methanol**[6c,6d] **(*rac*-5) from the Ester 12:** A 1 M solution of $LiAlH_4$ in diethyl ether (110 mmol, 110 mL) was added dropwise at −10 °C over 3 h to a stirred solution of the ester **12** (37.44 g, 0.20 mol) in anhydrous diethyl ether (350 mL). The reaction mixture was stirred at ambient temperature for 1 h, whereafter a saturated aqueous solution of Na_2SO_4 (84 mL) was added dropwise at −5 °C. The resulting slurry was stirred at ambient temperature for 1.5 h. The liquid organic layer was separated, and the solids were suspended in water (200 mL), and extracted with diethyl ether (5 × 100 mL). The organic phases were combined with the reaction liquid layer, dried, and concentrated at reduced pressure. The residue was purified by column chromatography (silica gel; hexane/diethyl ether, 1:1; R_f = 0.17) to give 22.97 g (98%) of the alcohol *rac*-**5** as a colorless oil. ^{1}H NMR (250 MHz): δ = 1.21 (ddd, *J* = 5.9, 6.9, 8.1 Hz, 1 H), 2.02−2.09 (m, 1 H), 2.12 (br. s), 2.39−2.45 (m, 1 H), 3.15 (dd, *J* = 4.2, 4.9 Hz, 2 H), 4.17 (ddd, *J* = 4.2, 4.2, 6.9 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 3.6 (CH_2), 22.0 (CH_2), 26.1 (CH), 62.9 (CH) ppm. MS (DCI): *m*/*z* = 135 (100) [M + NH_4^+].

***rac-trans*-1-(Iodomethyl)-2-nitrocyclopropane (*rac*-8):** Solid iodine (96.14 g, 0.378 mol) was added in small portions at −5 °C over a period of 40 min to a solution of the alcohol **5** (22.9 g, 0.196 mol), PPh_3 (89.53 g, 0.34 mol), and imidazole (24.1 g, 0.357 mol) in a mixture of Et_2O (580 mL) and MeCN (390 mL), and the reaction mixture was stirred at ambient temperature for 3 h. It was then poured into a 4-L separating funnel containing diethyl ether (1 L). The resulting suspension was washed with 20% aq. $Na_2S_2O_3$ (3 × 0.8 L) and water (0.5 L). The organic fraction was dried with $MgSO_4$ and concentrated under reduced pressure. The residue was covered with a hexane/diethyl ether (1:1) mixture (1.5 L) and stirred at ambient temperature for 1 h. The precipitate was filtered off and discarded. The filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; hexane/diethyl ether, 12:1; R_f = 0.11) to give 42.3 g (93%) of *rac*-**8** as a colorless oil. ^{1}H NMR (250 MHz): δ = 1.21 (ddd, *J* = 5.9, 6.9, 8.1 Hz, 1 H), 2.02−2.09 (m, 1 H), 2.39−2.45 (m, 1 H), 3.15 (dd, *J* = 4.2, 4.9 Hz, 2 H), 4.17 (ddd, *J* = 4.2, 4.2, 6.9 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 3.6 (CH_2), 22.0 (CH_2), 26.1 (CH), 62.9 (CH) ppm. IR: ṽ = 3098, 2961, 2897, 1547, 1435, 1369, 571 cm^{-1}. MS (EI): *m*/*z* = 227 (8) [M$^+$], 181 (18), 100 (22), 86 (27), 54 (91).

Alkylation of (*S*)-7 with (1*S*,2*S*)-8. Preparation of 9a: A suspension of (*S*)-**7** (3.45 g, 6.92 mmol) in a mixture of DMF (3.4 mL) and MeCN (6.9 mL) was degassed with two freeze-pump-thaw cycles at −50 °C. NaH (0.33 g, 60% in oil, 8.30 mmol) and (1*S*,2*S*)-**8** (1.65 g, 7.27 mmol) were then added. The cooling bath was removed, and the reaction mixture was vigorously stirred for 40−50 min. When the temperature rose to 0 °C, the reaction flask was immersed into an ice/water bath to maintain the low temperature. Upon consumption of all (*S*)-**7** (TLC monitoring; $CHCl_3$/acetone, 7:1; R_f = 0.12), 60% aqueous AcOH (3.40 mL) was added slowly to avoid much foaming. After an additional 5 min of stirring, the reaction mixture was poured into a 100-mL separating funnel, containing water

(40 mL). The resulting slurry was extracted with $CHCl_3$ (3 × 25 mL). The combined organic fractions were dried and concentrated under reduced pressure. The crude product was dissolved in hot DMF (27 mL) and precipitated with MeCN (47.5 mL). The mother liquor was concentrated under reduced pressure and the residue was triturated with a mixture of DMF (1.8 mL) and MeCN (2.1 mL) over a period of 1 h. The precipitate of **9a** (*de* = 95−98%) was filtered off, combined with the first crop and dried in vacuo at 50 °C to give 3.47 g (84%) of **9a** (*de* = 96%). A second crystallization afforded **9a** with *de* > 98% as a light red solid, m.p. 270 °C (decomp.), $[\alpha]_D^{20}$ = +2401 (*c* = 0.1, MeOH). ^{1}H NMR (250 MHz): δ = 0.49−0.58 (m, 1 H), 1.05−1.20 (m, 1 H), 1.7−1.84 (m, 1 H), 2.04−2.31 (m, 2 H), 2.42−2.58 (m, 2 H), 2.59−2.79 (m, 2 H), 3.46−3.60 (m, 3 H), 3.57 (d, *J* = 12.5 Hz, 1 H), 3.90−3.99 (m, 2 H), 4.42 (d, *J* = 12.7 Hz, 1 H), 6.60−6.67 (m, 2 H), 6.88−6.92 (m, 1 H), 7.10−7.21 (m, 2 H), 7.25−7.41 (m, 3 H), 7.42−7.61 (m, 3 H), 8.05−8.16 (m, 3 H) ppm. ^{13}C NMR: δ = 18.5 (CH_2), 21.9 (CH), 24.0 (CH_2), 30.8 (CH_2), 36.8 (CH_2), 57.4 (CH_2), 58.7 (CH), 63.4 (CH), 68.9 (CH), 70.2 (CH_2), 120.8 (CH), 123.7 (CH), 126.0 (C), 127.3 (CH), 127.4 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 129.5 (CH), 130.2 (CH), 131.5 (CH), 132.5 (CH), 133.3 (CH), 133.4 (C), 133.6 (C), 142.5 (C), 171.1 (C), 178.5 (C), 180.6 (C) ppm. IR: $\tilde{\nu}$ = 3072, 3028, 2968, 2877, 1666, 1625, 1589, 1537, 1437, 1368, 1341, 1257, 1165, 1080, 1060, 1016, 965, 897, 756, 702, 682, 570, 486 cm^{-1}. MS (EI): *m*/*z* = 596.2 (28) [M^+], 552.2 (32), 497.2 (3), 453.2 (6), 439.2 (12), 347.1 (7), 217.1 (17), 161.1 (14), 160.1 (100), 91.1 (21), 44 (5). $C_{31}H_{30}N_4NiO_5$ (597.3): calcd. C 62.34, H 5.06, N 9.38; found C 62.26, H 5.29, N 9.25.

Alkylation of the Nickel Complex (*S*)-7 with *rac-trans*-1-(Iodomethyl)-2-nitrocyclopropane (8). Preparation of 9a and 9b: The reaction was carried out with (*S*)-**7** (32.85 g, 65.94 mmol), NaH (3.16 g, 60% in mineral oil, 79.1 mmol), and *rac*-**8** (15.71 g, 69.23 mmol) in a mixture of DMF (32 mL) and MeCN (65 mL) as described above for the alkylation with (1*S*,2*S*)-**8**. Upon consumption of all (*S*)-**7** (TLC monitoring; $CHCl_3$/acetone, 7:1; R_f = 0.12), 60% aqueous AcOH (7 mL) was added slowly to avoid foaming. After an additional 5 min of stirring, the reaction mixture was filtered through a G4 fritted glass filter. The solid fraction (17.33 g, 44%, *dr* = 85:15) was dissolved in hot DMF (205 mL) and precipitated with MeCN (236 mL) to give 10.16 g of **9a** (*de* = 95−98%). The mother liquor was concentrated under reduced pressure, and the residue (7.02 g) was triturated with a mixture of DMF (13 mL) and MeCN (15.8 mL) over a period of 1 h. The precipitate of **9a** (3.85 g, *de* = 94−96%) was filtered off, combined with the first crop and dried in vacuo at 50 °C to give 14.01 g of **9a** (*de* = 95−97%) (36% based on **7**). The filtrate obtained after the trituration, was combined with the liquid phase of the reaction mixture, and poured into a 1-L separating funnel with water (350 mL). The resulting slurry was extracted with $CHCl_3$ (3 × 300 mL). The combined organic fractions were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; $CHCl_3$/acetone, 7:1; R_f = 0.25) to give 16.15 g (41%) of a mixture of **9b** and **9a** in a 75:25 ratio. This was used for the preparation of (2*S*,1′*S*,2′*R*)-**3** without further diastereomeric enrichment. A sample of the alkylation product **9b** (0.392 g) with *de* > 98% was isolated after slow concentration of the saturated solution of the **9b**/**9a** mixture (*dr* = 75:25, 1.12 g) in MeOH (ca. 4 mL). **9b**: Dark red solid, m.p. 263 °C (decomp.), $[\alpha]_D^{20}$ = +2340 (*c* = 0.1, MeOH). ^{1}H NMR: δ = 0.92 (ddd, *J* = 6.7, 6.7, 7.4 Hz, 1 H), 1.41−1.49 (m, 1 H), 1.86−1.94 (m, 1 H), 2.08−2.24 (m, 3 H), 2.39−2.57 (m, 2 H), 2.58−2.71 (m, 1 H), 3.32−3.37 (m, 1 H) 3.44−3.58 (m, 3 H), 3.53 (d, *J* = 12.7 Hz, 1 H), 3.99 (dd, *J* = 3.5, 8.6 Hz, 1 H), 4.41 (d, *J* = 12.5 Hz, 1 H), 6.85 (d, 7.5 Hz, 2 H), 7.10−7.20 (m, 1 H), 7.25−7.37 (m, 2 H), 7.45−7.51 (m, 3 H), 7.58−7.62 (m, 1 H), 7.63−7.68 (m, 2 H), 8.02−8.12 (m, 3 H) ppm. ^{13}C NMR: δ = 17.9 (CH_2), 21.6 (CH), 23.9 (CH_2), 30.6 (CH_2), 36.3 (CH_2), 57.2 (CH_2), 59.4 (CH), 63.2 (CH_2), 68.6 (CH), 70.0 (CH_2), 120.8 (CH), 123.7 (CH), 126.0 (C), 127.3 (CH), 127.4 (CH), 128.8 (CH) 129.0 (CH), 129.1 (CH), 129.5 (CH), 130.2 (CH), 131.5 (CH), 132.5 (CH), 133.3 (CH), 133.4 (C), 133.6 (C), 142.5 (C), 171.1 (C), 178.5 (C), 180.6 (C) ppm. IR: $\tilde{\nu}$ = 3097, 3069, 2969, 2928, 2876, 1668, 1655, 1583, 1539, 1436, 1362, 1339, 1256, 1165, 1079, 1059, 1028, 970, 895, 755, 702, 668, 570, 480 cm^{-1}. MS (EI): *m*/*z* = 596.2 (31) [M^+], 552.2 (35), 537.6 (2), 497.2 (3), 453.2 (7), 439.2 (12), 347.1 (7), 320.1 (1), 217.1 (17), 161.1 (14), 160.1 (100), 91.1 (21), 44 (5).

Alkylation of (*R*)-7 with *rac*-8. Preparation of 9d and 9e: The reaction was carried out with (*R*)-**7** (5.80 g, 11.64 mmol), NaH (0.558 g, 60% in mineral oil, 13.97 mmol), and *rac*-**8** (2.77 g, 12.22 mmol) in a mixture of DMF (5.8 mL) and MeCN (11.6 mL) as described above for the alkylation with (1*S*,2*S*)-**8**. When all (*R*)-**7** had been consumed (TLC monitoring; $CHCl_3$/acetone, 7:1; R_f = 0.12), 60% aqueous AcOH (1.3 mL) was added slowly. After an additional 5 min of stirring, the reaction mixture was filtered through a G4 fritted glass filter. The solid fraction (2.96 g, *dr* ≈ 86:14) was dissolved in hot DMF (36 mL) and precipitated with MeCN (42 mL) to give 2.23 g of **9d** (*de* = 97%). The mother liquor was concentrated under reduced pressure, and the residue was triturated with a mixture of DMF (2.3 mL) and MeCN (2.8 mL) over a period of 1 h. The precipitate of **9d** (*de* = 94−96%) was filtered off, combined with the first crop, and dried in vacuo at 50 °C to give 2.40 g of **9d** (*de* = 94%) [35% based on (*R*)-**7**]. The filtrate obtained after the trituration was combined with the liquid phase of the reaction mixture, and poured into a 250-mL separating funnel, containing water (60 mL). The resulting slurry was extracted with $CHCl_3$ (3 × 50 mL). The combined organic fractions were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; $CHCl_3$/acetone, 7:1; R_f = 0.25) to give 2.77 g (40%) of a mixture of **9e** and **9d** in a ca. 77:23 ratio. This was used for the preparation of (2*R*,1′*R*,2′*S*)-**3** without further diastereomeric enrichment. A sample of the alkylation product **9e** (0.12 g) with *de* > 98% was obtained as described for **9b**. **9d**: Light red solid, m.p. 270 °C (decomp.), $[\alpha]_D^{20}$ = −2406 (*c* = 0.1, MeOH). ^{1}H NMR (250 MHz): δ = 0.49−0.57 (m, 1 H), 1.05−1.20 (m, 1 H), 1.71−1.84 (m, 1 H), 2.04−2.33 (m, 2 H), 2.42−2.58 (m, 2 H), 2.59−2.79 (m, 2 H), 3.46−3.60 (m, 3 H), 3.57 (d, *J* = 12.5 Hz, 1 H), 3.91−3.99 (m, 2 H), 4.42 (d, *J* = 12.7 Hz, 1 H), 6.60−6.67 (m, 2 H), 6.88−6.92 (m, 1 H), 7.10−7.21 (m, 2 H), 7.24−7.40 (m, 3 H), 7.42−7.61 (m, 3 H), 8.02−8.15 (m, 3 H) ppm. ^{13}C NMR: δ = 18.5 (CH_2), 21.9 (CH), 24.0 (CH_2), 30.8 (CH_2), 36.8 (CH_2), 57.4 (CH_2), 58.7 (CH), 63.4 (CH_2), 68.9 (CH), 70.2 (CH_2), 120.8 (CH), 123.7 (CH), 126.0 (C), 127.3 (CH), 127.4 (CH), 128.8 (CH) 128.9 (CH), 129.0 (CH), 129.5 (CH), 130.2 (CH), 131.5 (CH), 132.5 (CH), 133.3 (CH), 133.4 (C), 133.6 (C), 142.5 (C), 171.1 (C), 178.5 (C), 180.6 (C) ppm. IR: $\tilde{\nu}$ = 3072, 3028, 2968, 2878, 1666, 1625, 1589, 1537, 1437, 1368, 1341, 1257, 1165, 1080, 1060, 1015, 965, 897, 756, 702, 682, 570, 486 cm^{-1}. MS (EI): *m*/*z* = 596.2 (28) [M^+], 552.2 (32), 497.2 (3), 453.2 (6), 439.2 (12), 347.1 (7), 217.1 (17), 161.1 (14), 160.1 (100), 91.1 (21), 44 (5). **9e**: Dark red solid, m.p. 260 °C (decomp.), $[\alpha]_D^{20}$ = −2329 (*c* = 0.1, MeOH). ^{1}H NMR: δ = 0.92 (ddd, *J* = 6.7, 6.7, 7.4 Hz, 1 H), 1.41−1.49 (m, 1 H), 1.86−1.94 (m, 1 H), 2.08−2.24 (m, 3 H), 2.39−2.57 (m, 2 H), 2.58−2.71 (m, 1 H), 3.32−3.37 (m, 1 H) 3.44−3.58 (m, 3 H), 3.53 (d, *J* = 12.7 Hz, 1 H), 3.99 (dd, *J* = 3.5, 8.6 Hz, 1 H), 4.41 (d, *J* = 12.5 Hz, 1 H), 6.85 (d, *J* = 7.5 Hz, 2 H), 7.10−7.20 (m, 1 H), 7.25−7.37 (m, 2 H), 7.45−7.51 (m, 3 H), 7.58−7.62 (m, 1 H), 7.63−7.68 (m, 2 H), 8.02−8.12 (m, 3 H) ppm.

^{13}C NMR: δ = 17.9 (CH_2), 21.6 (CH), 23.9 (CH_2), 30.6 (CH_2), 36.3 (CH_2), 57.2 (CH_2), 59.4 (CH), 63.2 (CH_2), 68.6 (CH), 70.0 (CH_2), 120.8 (CH), 123.7 (CH), 126.0 (CH_2), 127.3 (CH), 127.4 (CH), 128.8 (CH) 129.0 (CH), 129.1 (CH_2), 129.5 (CH), 130.2 (CH), 131.5 (CH), 132.5 (CH), 133.3 (CH), 133.4 (C), 133.6 (C), 142.5 (C), 171.1 (C), 178.5 (C), 180.6 (C) ppm. IR: ṽ = 3097, 3067, 2969, 2927, 2876, 1668, 1654, 1583, 1539, 1436, 1362, 1339, 1256, 1165, 1078, 1059, 1028, 970, 895, 755, 702, 668, 570, 480 cm^{-1}. MS (EI): *m*/*z* = 596.2 (31) [M^+], 552.2 (35), 537.6 (2), 497.2 (3), 453.2 (7), 439.2 (12), 347.1 (7), 320.1 (1), 217.1 (17), 161.1 (14), 160.1 (100), 91.1 (21), 44 (5).

General Procedure (GP1) for the Decomposition of the Nickel Complexes 9 and Isolation of the Amino Acids 3: 6 N aq. HCl (175 mL) was added to a vigorously stirred suspension of **9** (21.0 g, 35.16 mmol) in refluxing methanol (90 mL). The mixture was gently heated under reflux for 7−10 min. The resulting green syrup was concentrated under reduced pressure at 40 °C. The solid residue was taken up with hot water (260 mL). The precipitate was filtered off, washed with water (70 mL), and dried to give **6**·HCl (13.32 g, 90% recovery) as a colorless solid. The filtrate was combined with the washings, neutralized to pH = 6.0 with 25% aqueous ammonia (ca. 6 mL), and extracted with $CHCl_3$ (3 × 300 mL). The combined organic layers were dried and concentrated under reduced pressure to give another portion of **6** (0.54 g, overall 94% recovery). The aqueous fraction was concentrated to ca. 60 mL and neutralized with 25% ammonia to pH = 6.5. The amino acid **3** was separated from the nickel salts by elution of the neutralized concentrate through an H^+-form DOWEX ion-exchange resin (type as above) column (ca. 150 g of resin) with 5−7% aqueous ammonia. The fraction of the eluate that showed red pigmentation on developing with ninhydrin, was collected. This was concentrated under reduced pressure at 40−45 °C. The crude amino acid **3** was dissolved in hot water (17 mL). The hot turbid solution was filtered and diluted with ethanol (28 mL). The precipitate, formed after storing at 0 °C for 1 h, was filtered off, washed with cold ethanol (10 mL), and dried in vacuo at 40 °C to give 3.9−4.0 g (64−65%) of the amino acid **3**.

(2*S*,1′*R*,2′*S*)-2-Amino-3-(2-nitrocyclopropyl)propionic Acid [(2*S*,1′*R*,2′*S*)-3-(2-Nitrocyclopropyl)alanine, 3] from 9a: The amino acid (2*S*,1′*R*,2′*S*)-**3** (5.5 g, 67%) was prepared from **9a** (28.5 g, 47.18 mmol) according to GP1. A single crystallization of the crude amino acid, obtained after elution from the DOWEX ion-exchange column, afforded (2*S*,1′*R*,2′*S*)-**3** with *de* = 99% as a colorless solid, m.p. 200−202 °C (decomp.), $[\alpha]_D^{20}$ = +72.7 (*c* = 0.3, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 1.31 (ddd, *J* = 6.4, 6.4, 7.3 Hz, 1 H), 1.84−1.99 (m, 2 H), 2.08−2.20 (m, 2 H), 3.84 (dd, *J* = 6.5, 6.5 Hz, 1 H), 4.38 (ddd, *J* = 3.0, 3.9, 6.9 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 21.3 (CH_2), 25.2 (CH), 34.4 (CH_2), 56.8 (CH), 62.1 (CH_2), 173.9 (C) ppm. IR: ṽ = 3335, 3095, 2604, 1589, 1536, 1441, 1398, 1371, 1309, 878, 683, 540, 503 cm^{-1}. MS (DCI): *m*/*z* = 366.1 (11) [2 M + NH_4^+], 349.1 (2) [2 M + H^+], 319.1 (3), 209.0 (23) [M + NH_3 + NH_4^+], 192.0 (100) [M + NH_4^+], 175.0 (5) [M + H^+], 145.0 (19), 128.0 (3). $C_6H_{10}N_2O_4$ (174.1) calcd. C 41.38, H 5.79, N 16.09; found C 41.17, H 5.67, N 16.04.

(2*S*,1′*S*,2′*R*)-2-Amino-3-(2-nitrocyclopropyl)propionic Acid [(2*S*,1′*S*,2′*R*)-3-(2-Nitrocyclopropyl)alanine, 3] from a 9b/9a (75:25) Mixture: The amino acid (2*S*,1′*S*,2′*R*)-**3** (3.29 g, 55%) was prepared from a **9b**/**9a** (75:25) mixture (20.69 g, 34.65 mmol) according to GP1. Twofold crystallization of the crude amino acid, isolated after elution from the DOWEX ion-exchange column, gave (2*S*,1′*S*,2′*R*)-**3** with *de* = 96% as a colorless solid, m.p. 200−203 °C (decomp.), $[\alpha]_D^{20}$ = −55.6 (*c* = 0.3, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 1.37 (ddd, *J* = 6.8, 6.8, 7.4 Hz, 1 H), 1.81−1.99 (m, 3 H), 2.01−2.18 (m, 1 H), 3.84 (dd, *J* = 6.0, 6.0 Hz, 1 H), 4.38 (ddd, *J* = 3.0, 3.9, 6.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 20.5 (CH_2), 24.4 (CH), 33.8 (CH_2), 56.3 (CH), 61.7 (CH), 174.1 (C) ppm. IR: ṽ = 3345, 3103, 2923, 1542, 1443, 1368, 1301, 1252, 882, 671, 567, 505 cm^{-1}. MS (DCI): *m*/*z* = 366.1 (11) [2 M + NH_4^+], 349.1 (2) [2 M + H^+], 319.1 (3), 209.0 (24) [M + NH_3 + NH_4^+], 192.0 (100) [M + NH_4^+], 175.0 (5) [M + H^+], 145.0 (20), 128.0 (3).

(2*R*,1′*S*,2′*R*)-2-Amino-3-(2-nitrocyclopropyl)propionic Acid [(2*R*,1′*S*,2′*R*)-3-(2-Nitrocyclopropyl)alanine, 3] from 9d: The amino acid (2*R*,1′*S*,2′*R*)-**3** (0.28 g, 61%) was prepared from **9d** (1.6 g, 2.68 mmol) according to GP1. A single crystallization of the crude amino acid, isolated after elution from the DOWEX ion-exchange column, afforded (2*R*,1′*S*,2′*R*)-**3** with *de* = 96% as a colorless solid, m.p. 198−200 °C (decomp.), $[\alpha]_D^{20}$ = −72.2 (*c* = 0.32, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 1.37 (ddd, *J* = 6.8, 6.8, 7.4 Hz, 1 H), 1.84−1.99 (m, 2 H), 2.08−2.20 (m, 2 H), 3.84 (dd, *J* = 6.5, 6.5 Hz, 1 H), 4.38 (ddd, *J* = 3.0, 3.9, 6.9 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz): δ = 21.3 (CH_2), 25.2 (CH), 34.4 (CH_2), 56.8 (CH), 62.1 (CH), 173.9 (C) ppm. IR: ṽ = 3335, 3093, 2595, 1589, 1536, 1441, 1398, 1371, 1309, 878, 683, 539, 503 cm^{-1}. MS (DCI): *m*/*z* = 366.1 (11) [2 M + NH_4^+], 349.1 (2) [2 M + H^+], 319.1 (3), 209.0 (23) [M + NH_3 + NH_4^+], 192.0 (100) [M + NH_4^+], 175.0 (5) [M + H^+], 145.0 (19), 128.0 (3). $C_6H_{10}N_2O_4$·0.5H_2O (183.2) calcd. C 39.34, H 6.04, N 15.29; found C 39.14, H 5.84, N 15.12.

(2*R*,1′*R*,2′*S*)-2-Amino-3-(2-nitrocyclopropyl)propionic Acid [(2*R*,1′*R*,2′*S*)-3-(2-Nitrocyclopropyl)alanine, 3] from a 9e/9d (77:23) Mixture: The amino acid (2*R*,1′*R*,2′*S*)-**3** (0.32 g, 42%) was prepared from a **9e**/**9d** (75:25) mixture (2.60 g, 4.35 mmol) according to GP1. Twofold crystallization of the crude amino acid, isolated after elution from the DOWEX ion-exchange column, gave (2*R*,1′*R*,2′*S*)-**3** with *de* = 96% as a colorless solid, m.p. 199−202 °C (decomp.), $[\alpha]_D^{20}$ = +56.3 (*c* = 0.3, H_2O). ^{1}H NMR (300 MHz, D_2O): δ = 1.37 (ddd, *J* = 6.8, 6.8, 7.4 Hz, 1 H), 1.80−1.99 (m, 3 H), 2.01−2.18 (m, 1 H), 3.84 (dd, *J* = 6.0, 6.0 Hz, 1 H), 4.38 (ddd, *J* = 3.0, 3.9, 6.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 20.5 (CH_2), 24.4 (CH), 33.8 (CH_2), 56.3 (CH), 61.7 (CH), 174.1 (C) ppm. IR: ṽ = 3345, 3103, 2923, 1541, 1443, 1368, 1301, 1252, 882, 671, 567, 505 cm^{-1}. MS (DCI): *m*/*z* = 366.1 (11) [2 M + NH_4^+], 349.1 (2) [2 M + H^+], 319.1 (3), 209.0 (24) [M + NH_3 + NH_4^+], 192.0 (100) [M + NH_4^+], 175.0 (5) [M + H^+], 145.0 (20), 128.0 (3). $C_6H_{10}N_2O_4$·0.25H_2O (178.7) calcd. C 40.34, H 5.92, N 15.68; found C 40.29, H 5.90, N 15.38.

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