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Stereoselective synthesis of both enantiomers of *N*-Boc-α-aryl-γ-aminobutyric acids

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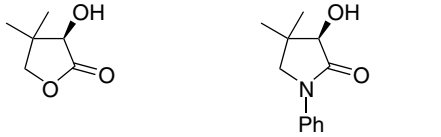
Abstract—Esterification of racemic α-aryl-β-cyanopropionic acid chlorides with either (*R*)- or (*S*)-*N*-phenylpantolactam as the chiral auxiliary in the presence of Et_3N resulted in the predominant formation of (α*R*,3′*R*)- or (α*S*,3′*S*)-configured pantolactam cyano ester, respectively, in nearly quantitative yields with diastereomeric ratios of up to 93:7. Column chromatography of the diastereoenriched cyano esters, followed by hydrolysis of the resulting diastereopure cyano esters under essentially nonracemizing conditions gave enantiopure α-aryl-β-cyanopropionic acids, which were readily converted in high yields into enantiopure (α*R*)- and (α*S*)-configured *N*-*tert*-butoxycarbonyl-α-aryl-γ-aminobutyric acid (GABA) derivatives of potential biological interest.

1. Introduction

(*R*)-Pantolactone, (*R*)-**1** (Fig. 1), is a known chiral auxiliary, which has been widely used in different asymmetric transformations. In particular, (*R*)-pantolactone has proven to be an efficient chiral auxiliary in the deracemization of α,α-disubstituted carboxylic acids, through a process, which usually implies: (i) conversion of the racemic mixture of the carboxylic acid into a racemic mixture of acid chlorides, (ii) the formation of the corresponding prochiral ketene, (iii) the diastereoselective amine-catalyzed nucleophilic addition of the chiral auxiliary, and (iv) controlled hydrolysis of the resulting diastereoenriched pantolactone esters. A wide range of carboxylic acids bearing different substituents at the α-position, including α-arylpropionic acids, α-haloalkanoic acids, as well as α-, β-, γ-, and δ-amino acids, have been deracemized with (*R*)-pantolactone, with diastereomeric ratios (dr) ranging from 85:15 to >98:2 in most cases.[1–13]



(*R*)-pantolactone, (*R*)-**1** (*R*)-*N*-phenylpantolactam, (*R*)-**2**

Figure 1. Structures of the chiral auxiliaries (*R*)-pantolactone and (*R*)-*N*-phenylpantolactam.

Several years ago we developed two alternative multigram syntheses of (*R*)- and (*S*)-*N*-phenylpantolactam, (*R*)- and (*S*)-**2** (Fig. 1),[14,15] as pantolactone analogues displaying several advantages as chiral auxiliaries relative to pantolactone: (1) easy availability of both enantiomers; (2) easy recovery as a consequence of their crystallizability, lipophilicity, and nonhygroscopic character; (3) easy detection by chiral HPLC with a UV detector, due to the presence of the aniline chromophore. Regarding their efficiency as chiral auxiliaries, (*R*)- and (*S*)-**2** were used in a series of asymmetric transformations such as Diels–Alder reactions,[16] nucleophilic substitution reactions on α-halo esters,[17–19] and deracemization of α-arylpropionic acids,[20] α-substituted α-arylacetic acids,[21] α-halo acids,[17,18] and α-amino acids,[19] leading to diastereoselectivities roughly parallel or even slightly superior to those obtained in similar cases using (*R*)-**1**.

In the most recent example of (*R*)-pantolactone's use as a chiral auxiliary in a deracemization reaction,

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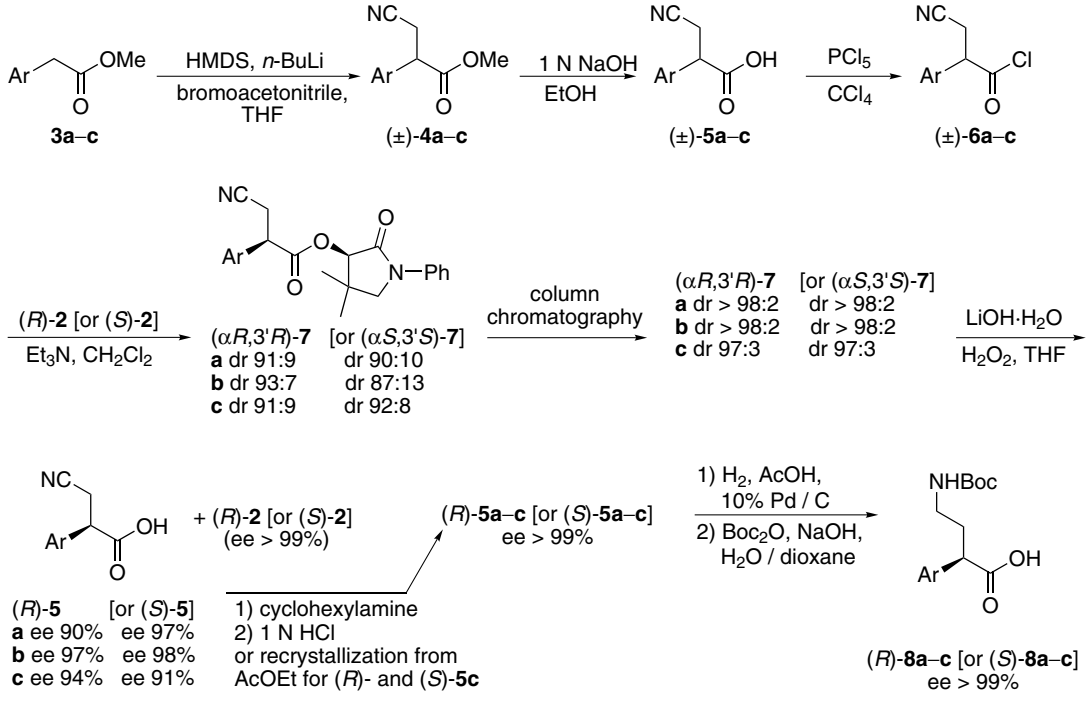
Calmès et al. reported the stereoselective synthesis of the (*R*)-enantiomer of *N*-*tert*-butoxycarbonyl-(*N*-Boc)-α-phenyl-γ-aminobutyric acid, (*R*)-**8a**, through an eight-step synthetic sequence in which the key step was the deracemization of the *N*-phthalyl derivative of α-phenyl-γ-aminobutyric acid, which was prepared in only 25% overall yield from racemic α-phenyl-β-cyanopropionic acid, (±)-**5a**.[12] Curiously, while deracemization of the *N*-phthalyl derivative of the desired γ-amino acid proceeded in 75% yield and 85:15 dr, the initially attempted deracemization of the cyano acid precursor (±)-**5a** also with (*R*)-**1**, which would have shortened the synthetic sequence and probably improved its overall yield, was reported to fail, leading in all attempts to a 1:1 mixture of the two diastereomeric (*R*)-pantolactone esters.[12] The good performance of (*R*)- and (*S*)-**2** as chiral auxiliaries in deracemization reactions relative to (*R*)-**1**, and the high biological interest of α-substituted derivatives of the major inhibitory neurotransmitter γ-aminobutyric acid (GABA),[22–27] prompted us to check the efficiency of (*R*)- and (*S*)-**2** as chiral auxiliaries in the deracemization system where (*R*)-pantolactone had failed. Herein we report the efficient use of (*R*)- and (*S*)-**2** as chiral auxiliaries in the deracemization of a series of α-aryl-β-cyano acids, (±)-**5a**–**c**, and the conversion of the resulting highly diastereoenriched *N*-phenylpantolactam esters into the corresponding enantiopure (*R*)- and (*S*)-*N*-(Boc)-α-aryl-γ-aminobutyric acids, (*R*)- and (*S*)-**8a**–**c**, as GABA derivatives with a potential affinity at the GABA receptors.

2. Results and discussion

The known α-aryl-β-cyano acid (±)-**5a**[12] and the new ones (±)-**5b**,**c** that were to be deracemized were prepared from the commercially available **3a** and the known methyl arylacetates **3b**[28] and **3c**,[29] respectively, following the procedure described for (±)-**5a**,[12] which implied an initial cyanomethylation with bromoacetonitrile of the lithium enolate of the esters **3a**–**c** in THF from −78 °C to room temperature, followed by saponification of the resulting cyano esters (±)-**4a**–**c** (Scheme 1). The initial deracemization studies were carried out with (±)-**5a** using racemic *N*-phenylpantolactam. In contrast with the usual one-pot deracemization methodologies using (*R*)-pantolactone as the chiral auxiliary, in which a prochiral ketene is preformed from the racemic acid chloride and a tertiary amine before the addition of the chiral auxiliary,[1–13] our methodology involves a rapid mixture of the acid chloride, the chiral auxiliary, and the tertiary amine usually in CH_2Cl_2 at 0 °C, therefore without preformation of the ketene, thus avoiding problems related to its hydrolysis or dimerization before reacting with the chiral auxiliary.[17–21] Under these conditions, a dynamic kinetic resolution process has also been proposed to explain the outcome of these reactions.[19] Thus, (±)-**5a** was reacted with PCl_5 in CCl_4 with the resulting crude acid chloride (±)-**6a** used directly in slight excess (1.5 equiv) in the subsequent reaction with (±)-**2** and excess of Et_3N (3.2 equiv) in anhydrous CH_2Cl_2 at 0 °C in the presence of 3 Å molecular sieves,



4–**8a**: Ar = phenyl; **4**–**8b**: Ar = 4-isobutylphenyl; **4**–**8c**: Ar = 6-methoxy-2-naphthyl

Scheme 1.

to afford a diastereomeric mixture of *N*-phenylpantolactam esters greatly enriched in one of the two possible diastereomeric racemic pairs (dr 93:7 as revealed from the integration in the ^{1}H NMR spectrum of the signals corresponding to the protons of the CH_3 group at the 4α-position of the pantolactam moiety). Regarding the sense of asymmetric induction of this transformation, it is known from deracemization reactions of α,α-disubstituted carboxylic acids using (*R*)-**1**, (*R*)-**2**, or (*S*)-**2** as chiral auxiliaries and Et_3N as the tertiary amine that the (α*R*)-configured pantolactone or pantolactam ester is preferentially formed from the (3′*R*)-configured auxiliary, and vice versa.[4,20,21] Accordingly, the racemic mixture (α*R*,3′*R*)-**7a**/(α*S*,3′*S*)-**7a** [(α*R**,3′*R**)-**7a**] was assumed to be the main product in this reaction.

Diastereoenriched *N*-phenylpantolactam esters have been usually hydrolyzed to the corresponding enantioenriched carboxylic acids, recovering the chiral auxiliary without racemization, either under acidic conditions (mixture HOAc/aq HCl)[19–21] or under basic conditions ($LiOH{\cdot}H_2O$, or $LiOH{\cdot}H_2O/H_2O_2$).[17,18] In order to select the most appropriate hydrolysis methodology for esters **7**, the above-mentioned racemic (α*R**,3′*R**)-**7a** (dr 93:7) was used as a model compound. Reaction of (α*R**,3′*R**)-**7a** with a 2.5:1 mixture of AcOH and 2 M HCl at 120 °C afforded the cyano acid (±)-**5a** in only 51% yield, while its reaction with $LiOH{\cdot}H_2O$ in a 2:1 mixture THF/H_2O from 0 °C to room temperature afforded (±)-**5a** in 66% yield. The optimal results were obtained when the hydrolysis of (α*R**,3′*R**)-**7a** was carried out with $LiOH{\cdot}H_2O$ and 30% w/v H_2O_2 in dioxane at room temperature, in which cyano acid (±)-**5a** was obtained in 76% yield. It is worthy of note that in all cases, (±)-**2** was easily recovered in essentially quantitative yields through acid–base washings, and only in the reaction with $LiOH{\cdot}H_2O$ was a small amount of hydrolysis of the cyano group of (±)-**5a** to the corresponding amide observed.

Finally, following a reported procedure,[26] cyano acid (±)-**5a** was converted into the *N*-(Boc)-α-aryl-γ-amino acid (±)-**8a** in 66% yield by hydrogenation with 10% Pd/C in AcOH at 4 atm, followed by the reaction of the resulting crude γ-amino acid with di-*tert*-butyl dicarbonate (Boc_2O) and NaOH in a 1:2 mixture H_2O/dioxane at room temperature.

The good results obtained in these model studies prompted us to apply these methodologies to the conversion of cyano acids (±)-**5a**–**c** into enantiopure α-aryl-substituted GABA derivatives (*R*)- and (*S*)-**8a**–**c**, using (*R*)- and (*S*)-**2** as chiral auxiliaries. Thus, diastereoenriched *N*-phenylpantolactam esters (α*R*,3′*R*)-**7a**–**c** and (α*S*,3′*S*)-**7a**–**c** were obtained in essentially quantitative yields with diastereomeric ratios (dr 87:13 to 93:7) similar to that obtained in the model study, by the reaction of the acid chlorides (±)-**6a**–**c**, derived from cyano acids (±)-**5a**–**c**, with (*R*)- or (*S*)-**2**, respectively, under our standard reaction conditions (Scheme 1).

Interestingly, carefully conducted column chromatography of these diastereoenriched esters through silica gel allowed the isolation of (α*R*,3′*R*)-**7a**,**b** and (α*S*,3′*S*)-**7**a,**b** as single diastereomers by ^{1}H NMR (dr >98:2) in around 60% overall yield. In the **c** series, the chromatographic separation was slightly less efficient, producing (α*R*,3′*R*)-**7c** and (α*S*,3′*S*)-**7c** (dr >98:2 by ^{1}H NMR) in only 10% and 3% overall yield, respectively, and highly diastereoenriched (α*R*,3′*R*)-**7c** and (α*S*,3′*S*)-**7c** (dr 97:3 by ^{1}H NMR) in 27% and 43% yield, respectively. Hydrolysis of a sample of (α*R*,3′*R*)-**7a** (dr 90:10) with $LiOH{\cdot}H_2O$ in THF/H_2O from 0 °C to room temperature resulted in complete racemization of the resulting cyano acid **5a**, while the hydrolysis under the optimized conditions found in the model studies, that is, with $LiOH{\cdot}H_2O$/30% w/v H_2O_2 in dioxane at room temperature, proceeded in excellent yield (92%) but with a significant degree of racemization [40% enantiomeric excess of (*R*)-**5a**]. Fortunately, when the reaction of a sample of (α*R*,3′*R*)-**7a** (dr >98:2) was carried out in THF at 0 °C for 5 h, (*R*)-**5a** was obtained in 95% yield and 90% enantiomeric excess (ee), as determined by chiral HPLC, and the chiral auxiliary (*R*)-**2** was recovered in 76% yield in enantiopure form. Moreover, enantiopure (*R*)-**5a** (ee >99% by chiral HPLC) was obtained in 66% overall yield [from (α*R*,3′*R*)-**7a**] by precipitation of the cyclohexylammonium salt of the crude product (ee 90%), followed by recrystallization from isopropanol and reisolation of the acid after treatment with 1 M HCl. Comparison of the specific rotation of this enantiopure compound $\{[\alpha]_D^{20} = -155$ (*c* 0.94, $CH_2Cl_2)\}$ with that described for (*S*)-**5a** $\{[\alpha]_D^{28} = +154$ (*c* 1.04, $CH_2Cl_2)\}$[26] confirmed the (α*R*)-configuration assigned to this compound and to the ester precursor **7a**, and the sense of asymmetric induction predicted for the deracemization process with this kind of chiral auxiliaries. Hydrolysis of (α*S*,3′*S*)-**7a** (dr >98:2) under the best reaction conditions found for the hydrolysis of its enantiomer (α*R*,3′*R*)-**7a** proceeded in similar yield with respect to both (*S*)-**5a** and the chiral auxiliary (*S*)-**2**, but with a lower degree of racemization, obtaining cyano acid (*S*)-**5a** with 97% ee. Analogously, enantiopure (*S*)-**5a** (ee >99% by chiral HPLC) was obtained in 54% overall yield [from (α*S*,3′*S*)-**7a**] via the cyclohexylammonium salt of the crude product. The improved hydrolysis conditions were also applied to (α*R*,3′*R*)- and (α*S*,3′*S*)-**7b** (dr >98:2), and to (α*R*,3′*R*)- and (α*S*,3′*S*)-**7c** (dr 97:3), obtaining the corresponding cyano acids (*R*)- and (*S*)-**5b**,**c** in high yields (87–97%) and with essentially no racemization (Scheme 1). Enantiopure (*R*)- and (*S*)-**5b**,**c** (ee >99% by chiral HPLC) were obtained in 52–64% overall yield (from the corresponding diastereopure esters **7b**,**c**) via the cyclohexylammonium salt of the crude products [for (*R*)- and (*S*)-**5b**] or by direct recrystallization of the crude product [for (*R*)- and (*S*)-**5c**]. Worthy of note, in the hydrolysis of esters (α*R*,3′*R*)- and (α*S*,3′*S*)-**7b**,**c**, (*R*)- and (*S*)-**2** were recovered in 94–96% yield in enantiopure form. As previously described for (*S*)-**5a**,[26] hydrogenation of the enantiopure α-aryl-β-cyano acids (*R*)-**5a**–**c** and (*S*)-**5b**,**c**, followed by protection of the amino group of the resulting γ-amino acids led to the enantiopure *N*-(Boc)-α-aryl-γ-amino acids (*R*)-**8a**–**c** and (*S*)-**8b**,**c** (ee >99% by chiral HPLC) in 52–79% overall yield for the last two steps (Scheme 1). The sign of the optical rotations of

compounds (*R*)- and (*S*)-**5b**,**c** and **8b**,**c** coincide with those of the known (*R*)- and (*S*)-**5a** and **8a**, respectively, being in accord with their assigned configurations and those of (αR,3′*R*)- and (αS,3′*S*)-**7b**,**c** based on the asymmetric induction predicted for the deracemization process with these chiral auxiliaries, confirmed in this work in the phenyl (**a**) series.

3. Conclusion

Thus, α-aryl-substituted GABA derivatives (*R*)- and (*S*)-**8a**–**c** of potential biological interest have been prepared in enantiopure form (ee >99%) from the readily available methyl arylacetates **3a**–**c**, through a seven-step synthetic sequence, involving as the key step the deracemization of cyano acids (±)-**5a**–**c** using (*R*)- or (*S*)-*N*-phenylpantolactam as chiral auxiliaries. In sharp contrast with the reported absolute lack of efficiency of (*R*)-pantolactone as chiral auxiliary in the deracemization of this kind of cyano acids, the use of (*R*)- and (*S*)-*N*-phenylpantolactam led to the corresponding pantolactam esters in almost quantitative yields, with high levels of diastereoselectivity (dr up to 93:7), and with predictable sense of asymmetric induction [(αR)-configured esters are formed from (*R*)-**2**, and (αS)-configured esters are formed from (*S*)-**2**]. Moreover, (αR,3′*R*)- and (αS,3′*S*)-configured pantolactam esters in highly diastereoenriched form (dr >98:2 or 97:3) were obtained by column chromatography of the diastereoenriched crude materials resulting from the deracemization reactions. Hydrolysis of these esters under essentially nonracemizing conditions, followed by recrystallization of the resulting crude cyano acids or their cyclohexylammonium salts, and subsequent reisolation of the carboxylic acids in the last cases, led to enantiopure α-aryl-β-cyano acids (*R*)- and (*S*)-**5a**–**c**, which were transformed in good yields into the *N*-(Boc)-α-aryl-substituted GABA derivatives (*R*)- and (*S*)-**8a**–**c** through a standard procedure.

4. Experimental

4.1. General

Melting points were determined in open capillary tubes with a MFB 595010M Gallenkamp melting point apparatus. 300 MHz ^{1}H NMR and 75.4 MHz ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer and 200 MHz ^{1}H NMR spectra on a Varian Gemini 200 spectrometer. The chemical shifts are reported in ppm (δ scale) relative to internal TMS, and coupling constants are reported in hertz (Hz). For the pantolactam esters **7**, the terms α or β are assigned to hydrogen atoms or methyl groups of the pantolactam moiety, which are *cis* or *trans* relative to the acyloxy substituent, respectively. For the assigment of the signals corresponding to the aromatic quaternary carbon atoms of compound **4b**, HETCOR long-range experiments were performed, while for the assigment of the signals corresponding to the aromatic hydrogen and carbon atoms of compounds **4c** and **5c**, COSY ^{1}H/^{1}H experiments using standard procedures and COSY ^{1}H/^{13}C experiments using the HMQC sequence with an indirect detection probe were performed. IR spectra were run on a FT/IR Perkin–Elmer model 1600 spectrophotometer. Absorption values are expressed as wave numbers (cm^{-1}); only significant absorption bands are given. Column chromatography was performed on silica gel 60 ACC (70–200 mesh, SDS, ref 2100027). Thin-layer chromatography (TLC) was performed with aluminum-backed sheets with silica gel 60 F_{254} (Merck, ref 1.05554), and spots were visualized with UV light and 1% aqueous solution of $KMnO_4$. Optical rotations were measured on a Perkin–Elmer model 241 polarimeter. Chiral HPLC analyses were performed on a Waters model 600 liquid chromatograph provided with a Waters model 486 variable λ detector using a Chiralcel OD-H column (25 × 0.46 cm) containing the chiral stationary phase cellulose tris(3,5-dimethylphenylcarbamate), with a flow of 0.8 mL/min and UV detection at $\lambda = 254$ nm. Condition A: mixture of hexane/isopropanol/trifluoroacetic acid in the ratio of 93:7:0.1 as eluent. Condition B: mixture of hexane/EtOH/trifluoroacetic acid in the ratio of 98:2:0.1 as eluent. Condition C: mixture of hexane/isopropanol/trifluoroacetic acid in the ratio of 95:5:0.1 as eluent. Condition D: mixture of hexane/EtOH/trifluoroacetic acid in the ratio of 99:1:0.1 as eluent. Condition E: mixture of hexane/EtOH/trifluoroacetic acid in the ratio of 90:10:0.1 as eluent. Condition F: mixture of hexane/EtOH/trifluoroacetic acid in the ratio of 95:5:0.1 as eluent. Analytical grade solvents were used for crystallization and chiral HPLC analyses, while pure for synthesis solvents were used in the reactions, extractions, and column chromatography. NMR spectra were performed at the Serveis Científico-Tècnics of the University of Barcelona, while elemental analyses were carried out at the Mycroanalysis Service of the IIQAB (CSIC, Barcelona, Spain).

4.2. (±)-3-Cyano-2-phenylpropionic acid (±)-5a[12]

Chiral HPLC, condition A: (*R*)-**5a**, $t_R = 20.6$ min, $k'_1 = 4.06$; (*S*)-**5a**, $t_R = 22.2$ min, $k'_2 = 4.46$; $\alpha = 1.10$; Res = 3.58.

4.3. (αR,3′*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 3-cyano-2-phenylpropionate (αR,3′*R*)-7a

A solution of cyano acid (±)-**5a** (1.00 g, 5.71 mmol) and PCl_5 (1.40 g, 6.72 mmol) in CCl_4 (9 mL) was stirred at 40 °C for 30 min. Evaporation of the volatile products from the reaction mixture gave the acid chloride (±)-**6a** (1.10 g, 99%), which was used in the following step without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.86 (dd, $J = 16.8$ Hz, $J' = 7.8$ Hz, 1H) and 3.09 (dd, $J = 16.8$ Hz, $J' = 7.0$ Hz, 1H) (3-H_2), 4.33 (pseudo t, $J \approx 7.3$ Hz, 1H, 2-H), 7.26–7.34 (m, 2H, Ar-H*ortho*), 7.42–7.50 (m, 3H, Ar-H*meta*, and Ar-H*para*).

To a cooled (0 °C) solution of (*R*)-**2** (0.82 g, 4.00 mmol) in anhydrous CH_2Cl_2 (12 mL) solution previously dried by stirring at 0 °C for 45 min with 4 g of 3 Å molecular sieves, a dried (6 g of 3 Å molecular sieves) solution of

acid chloride (±)-**6a** (1.10 g, 5.68 mmol) in anhydrous CH_2Cl_2 (18 mL), and a dried (12 g of 3 Å molecular sieves) solution of Et_3N (1.84 mL, 13.2 mmol) in anhydrous CH_2Cl_2 (24 mL) were successively added. The reaction mixture was stirred at 0 °C for 3 h, was washed with 1 N HCl (2×30 mL) and a saturated aqueous solution of $NaHCO_3$ (2×30 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo to give a diastereomeric mixture of (*R*)-pantolactam esters greatly enriched in the (α*R*,3′*R*)-**7a** diastereomer (1.43 g, 99%, dr 91:9 by ^{1}H NMR). An aliquot part of this residue (0.94 g) was submitted to column chromatography [silica gel (50 g), hexane/AcOEt mixtures]. On elution with hexane/AcOEt 75:25, (α*R*,3′*R*)-**7a** (570 mg, 60%, dr >98:2) and a mixture (α*R*,3′*R*)-**7a**/(α*S*,3′*R*)-**7a** (76 mg, dr 70:30) were successively isolated as a light brown oil and a light brown solid, respectively.

(α*R*,3′*R*)-**7a** (dr >98:2): $[\alpha]_D^{20} = -14.2$ (*c* 0.66, CH_2Cl_2). R_f 0.29 (SiO_2, hexane/AcOEt 75:25). IR (NaCl) *v*: 2214 (CN st), 1744 (C=O st ester), 1713 (C=O st lactam) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.11 (s, 3H, 4′α-CH_3), 1.30 (s, 3H, 4′β-CH_3), 2.90 (dd, $J = 17.0$ Hz, $J' = 7.4$ Hz, 1H) and 3.12 (dd, $J = 17.0$ Hz, $J' = 7.7$ Hz, 1H) (3-H_2), 3.50 (d, $J = 9.8$ Hz, 1H, 5′α-H), 3.60 (d, $J = 9.8$ Hz, 1H, 5′β-H), 4.12 (pseudo t, $J \approx 7.4$ Hz, 1H, 2-H), 7.16 (tdm, $J = 7.4$ Hz, $J' = 1.3$ Hz, 1H, H*para N*-phenyl), 7.30–7.43 (complex signal, 7H, Ar-H *C*-phenyl, and H*meta N*-phenyl), 7.54–7.60 (m, 2H, H*ortho N*-phenyl). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 21.1 (CH_3, 4′α-CH_3), 22.0 (CH_2, C3), 24.8 (CH_3, 4′β-CH_3), 37.3 (C, C4′), 47.8 (CH, C2), 57.7 (CH_2, C5′), 79.4 (CH, C3′), 117.4 (C, CN), 119.4 (CH, C*ortho N*-phenyl), 124.9 (CH, C*para N*-phenyl), 127.7 (CH, C*ortho C*-phenyl), 128.5 (CH, C*para* C-phenyl), 128.9 (CH, C*meta N*-phenyl), 129.1 (CH, C*meta C*-phenyl), 135.0 (C, C*ipso C*-phenyl), 138.8 (C, C*ipso N*-phenyl), 167.8 (C, C2′), 170.3 (C, C1). Anal. Calcd for $C_{22}H_{22}N_2O_3 \cdot 4/5H_2O$: C, 70.12; H, 6.32; N, 7.43. Found: C, 70.33; H, 6.40; N, 7.13.

4.4. (*R*)-3-Cyano-2-phenylpropionic acid (*R*)-5a

To a 0 °C-cooled solution of compound (α*R*,3′*R*)-**7a** (469 mg, 1.30 mmol, dr >98:2) in THF (21 mL) were added $LiOH \cdot H_2O$ (71 mg, 1.68 mmol) and 30% w/v H_2O_2 (0.3 mL, 2.65 mmol). The reaction mixture was stirred at 0 °C for 5 h and then treated with 1.5 N aqueous Na_2SO_3 (11.6 mL). The resulting mixture was extracted with CH_2Cl_2 (3×25 mL), and the combined organic extracts were dried with anhydrous Na_2SO_4 and evaporated at reduced pressure, recovering pantolactam (*R*)-**2** (202 mg, 76%, ee >99% by chiral HPLC). The aqueous phase was acidified with 1 N HCl and extracted with AcOEt (3×25 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and evaporated at reduced pressure to yield cyano acid (*R*)-**5a** (216 mg, 95%, ee 90%) as a white solid. An aliquot part of this crude product (199 mg, 1.14 mmol) was dissolved in Et_2O (5 mL) and treated with cyclohexylamine (0.13 mL, 1.14 mmol) and the precipitate thus formed was filtered in vacuo and crystallized from isopropanol (8 mL). The solid was treated with 1 M HCl and the resulting suspension was extracted with AcOEt (3×6 mL). The combined organic extracts were washed with H_2O (3×6 mL), dried with anhydrous Na_2SO_4, and evaporated at reduced pressure to give enantiopure (*R*)-**5a** (139 mg, 66% overall, ee >99% by chiral HPLC) as a white solid. $[\alpha]_D^{20} = -155$ (*c* 0.94, CH_2Cl_2) [lit.[26] $[\alpha]_D^{28} = +154$ (*c* 1.04, CH_2Cl_2) for (*S*)-**5a**]. Chiral HPLC, condition A: (*R*)-**5a**, $t_R = 20.7$ min. Mp: 84–85 °C (isopropanol). R_f 0.09 (SiO_2, hexane/AcOEt 1:1). IR (KBr) *v*: 3600–2500 (O–H st), 2261 (CN st), 1737 (C=O st) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.79 (dd, $J = 16.8$ Hz, $J' = 7.5$ Hz, 1H) and 3.00 (dd, $J = 16.8$ Hz, $J' = 7.5$ Hz, 1H) (3-H_2), 3.96 (dd, $J \approx J' \approx 7.5$ Hz, 1H, 2-H), 7.26–7.30 (m, 2H, H*ortho*), 7.30–7.42 (m, 3H, H*meta* and *para*), 11.10 (br s, 1H, COOH). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 21.2 (CH_2, C3), 47.4 (CH, C2), 117.2 (C, CN), 127.5 (CH, Ar-C*ortho*), 128.7 (CH, Ar-C*para*), 129.2 (CH, Ar-C*meta*), 134.8 (C, Ar-C*ipso*), 176.5 (C, C1). Anal. Calcd for $C_{10}H_9NO_2 \cdot 0.8H_2O$: C, 63.35; H, 5.64; N, 7.39. Found: C, 63.36; H, 5.75; N, 7.36.

4.5. (*R*)-4-(*tert*-Butoxycarbonylamino)-2-phenylbutanoic acid (*R*)-8a[12]

A mixture of (*R*)-**5a** (100 mg, 0.57 mmol, ee >99%), AcOH (15 mL) and 10% Pd/C (86 mg) was hydrogenated at 4 atm and at room temperature for 24 h. The catalyst was filtered off in vacuo through Celite®, and the filtrate was evaporated under reduced pressure to give crude (*R*)-4-amino-2-phenylbutanoic acid (135 mg) as a colorless oil, which was taken in H_2O (3 mL), cooled to 0 °C, and basified with 2 M NaOH (0.5 mL). To the cold basic solution, dioxane (6 mL) and Boc_2O (245 mg, 1.12 mmol) were successively added, and the reaction mixture was stirred at room temperature for 12 h. The organic solvent was evaporated at reduced pressure and the resulting mixture was diluted with H_2O (15 mL), washed with AcOEt (3×20 mL), acidified with 1 N HCl (4 mL), and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and evaporated at reduced pressure to yield (*R*)-**8a** (112 mg, 70% overall, ee >99% by chiral HPLC) as a pale yellow oil. The analytical sample of (*R*)-**8a** was obtained by precipitation of its cyclohexylammonium salt as described for (*R*)-**5a**. From a solution of crude (*R*)-**8a** (100 mg, 0.36 mmol) in Et_2O (5 mL) and cyclohexylamine (0.04 mL, 0.35 mmol), pure (*R*)-**8a** (60 mg) was obtained, after reisolation of the acid from its salt, as a colorless oil, which solidified on standing. $[\alpha]_D^{20} = -61$ (*c* 0.93, CH_2Cl_2) [lit.[12] $[\alpha]_D^{28} = -67$ (*c* 0.6, CH_2Cl_2)]. Chiral HPLC, condition B: (*R*)-**8a**, $t_R = 21.9$ min. Mp: 97–98 °C (CH_2Cl_2) [lit.[12] 98–100 °C (CH_2Cl_2)].

4.6. (α*S*,3′*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 3-cyano-2-phenylpropionate (α*S*, 3′*S*)-7a

It was prepared in a similar manner to that described for (α*R*,3′*R*)-**7a**. From (*S*)-**2** (820 mg, 4.00 mmol), acid chloride (±)-**6a** (1.10 g, 5.68 mmol), and Et_3N (1.84 mL,

13.2 mmol), a diastereomeric mixture of (*S*)-pantolactam esters greatly enriched in the (α*S*,3′*S*)-**7a** diastereomer (1.43 g, 99%, dr 90:10 by ^{1}H NMR) was obtained. An aliquot part of this residue (1.22 g) was submitted to column chromatography [silica gel (75 g), hexane/AcOEt mixtures]. On elution with hexane/AcOEt 75:25, (α*S*,3′*S*)-**7a** (715 mg, 58%, dr >98:2) and a mixture (α*S*,3′*S*)-**7a**/(α*R*,3′*S*)-**7a** (470 mg, dr 77:23) were successively isolated as a light brown oil and a brown solid, respectively.

(α*S*,3′*S*)-**7a** (dr >98:2): $[\alpha]_D^{20} = +17.5$ (*c* 0.71, CH_2Cl_2). R_f 0.30 (SiO_2, hexane/AcOEt 75:25). IR (NaCl) *v*: 2249 (CN st), 1744 (C=O st ester), 1712 (C=O st lactam) cm^{-1}. The NMR data coincide with those of (α*R*,3′*R*)-**7a**. Anal. Calcd for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73. Found: C, 72.97; H, 6.12; N, 7.69.

4.7. (*S*)-3-Cyano-2-phenylpropionic acid (*S*)-5a

It was prepared in a similar manner to that described for (*R*)-**5a**. From (α*S*, 3′*S*)-**7a** (596 mg, 1.65 mmol, dr >98:2), 30% w/v H_2O_2 (0.38 mL, 3.35 mmol), and $LiOH{\cdot}H_2O$ (90 mg, 2.15 mmol), pantolactam (*S*)-**2** (256 mg, 76%, ee >99% by chiral HPLC) and cyano acid (*S*)-**5a** (255 mg, 88%, ee 97%) were separately obtained. Enantiopure (*S*)-**5a** (127 mg, 54% overall, ee >99%) was obtained as a white solid from the crude product (208 mg, 1.19 mmol) via its cyclohexylammonium salt as described for (*R*)-**5a**. $[\alpha]_D^{20} = +153$ (*c* 0.72, CH_2Cl_2) [lit.[26] $[\alpha]_D^{28} = +154$ (*c* 1.04, CH_2Cl_2)]. Chiral HPLC, condition A: (*S*)-**5a**, $t_R = 22.2$ min. Mp: 87–88 °C (isopropanol) [lit.[26] 95–97 °C (Et_2O/petrol ether)].

4.8. (*S*)-4-(*tert*-Butoxycarbonylamino)-2-phenylbutanoic acid (*S*)-8a[26]

$[\alpha]_D^{20} = +68$ (*c* 0.92, CH_2Cl_2) [lit.[26] $[\alpha]_D^{28} = +62$ (*c* 0.7, CH_2Cl_2)]. Chiral HPLC, condition B: (*S*)-**8a**, $t_R = 23.2$ min. Mp: 108–109 °C (CH_2Cl_2) [lit.[26] 106–108 °C (CH_2Cl_2)].

4.9. (±)-Methyl 3-cyano-2-(4-isobutylphenyl)propionate (±)-4b

A 2.5 M solution of *n*-butyllithium in hexane (5.2 mL, 13.0 mmol) was added dropwise over 5 min to a stirred solution of hexamethyldisilazane (2.85 mL, 13.5 mmol) in anhydrous THF (27 mL) at −78 °C under argon, and the mixture was stirred at −78 °C for 1 h. To the resulting mixture, a solution of methyl (4-isobutylphenyl)acetate, **3b** (2.45 g, 11.9 mmol) in anhydrous THF (22 mL) was added at −78 °C over 10 min, and the mixture was stirred at the same temperature for 1 h, and then treated dropwise with a solution of bromoacetonitrile (1.45 mL, 20.8 mmol) in anhydrous THF (16 mL). The reaction mixture was stirred at −78 °C for 1 h, warmed slowly to room temperature, stirred at room temperature for an additional 16 h period, and quenched with 1 N HCl (60 mL). The organic solvent was evaporated at reduced pressure and the remaining aqueous layer was extracted with Et_2O (3 × 125 mL). The combined organic extracts were washed with H_2O (75 mL), dried with anhydrous Na_2SO_4, and evaporated at reduced pressure to give a brown oily residue (3.02 g), which was submitted to column chromatography [silica gel (150 g), hexane/Et_2O mixtures]. On elution with hexane/Et_2O 55:45, pure cyano ester (±)-**4b** was isolated as a colorless oil (2.22 g, 76%). R_f 0.37 (SiO_2, hexane/Et_2O 1:1). IR (NaCl) *v*: 2250 (CN st), 1737 (C=O st) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 0.90 [d, *J* = 6.6 Hz, 6H, $CH(CH_3)_2$], 1.85 [m, 1H, $CH(CH_3)_2$], 2.46 (d, *J* = 7.2 Hz, 2H, Ar-CH_2CH), 2.78 (dd, *J* ≈ 16.8 Hz, *J*′ ≈ 7.5 Hz, 1H) and 3.02 (dd, *J* ≈ 16.8 Hz, *J*′ ≈ 7.7 Hz, 1H) (3-H_2), 3.72 (s, 3H, OCH_3), 3.92 (pseudo t, *J* = 7.5 Hz, 1H, 2-H), 7.12–7.19 (complex signal, 4H, Ar-H). ^{13}C NMR (75.4 MHz, $CDCl_3$): 21.8 (CH_2, C3), 22.3 [CH_3, CH (CH_3)$_2$], 30.1 [CH, $CH(CH_3)_2$], 45.0 (CH_2, Ar-CH_2CH), 47.2 (CH, C2), 52.7 (CH_3, OCH_3), 117.6 (C, CN), 127.1 (CH) and 129.8 (CH) [Ar-C2(6) and Ar-C3(5)], 132.9 (C, Ar-C1), 142.0 (C, Ar-C4), 171.5 (C, C1). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.56; H, 7.80; N, 5.72.

4.10. (±)-3-Cyano-2-(4-isobutylphenyl)propionic acid (±)-5b

To a solution of cyano ester (±)-**4b** (1.51 g, 6.16 mmol) in EtOH (50 mL) was added 1 N NaOH (7.3 mL, 7.3 mmol), and the reaction mixture was stirred at room temperature for 3 h, and concentrated in vacuo. The resulting residue was partitioned between H_2O (35 mL) and AcOEt (60 mL). The aqueous phase was acidified with 1 N HCl (pH 2–3) and extracted with AcOEt (3 × 60 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated at reduced pressure to afford the cyano acid (±)-**5b** as a white solid (1.36 g, 96%). Chiral HPLC, condition C: (*S*)-**5b**, $t_R = 16.1$ min, $k'_1 = 3.36$; (*R*)-**5b**, $t_R = 19.6$ min, $k'_2 = 4.32$; $\alpha = 1.29$; Res = 7.87. Mp: 122–123 °C (AcOEt). R_f 0.14 (SiO_2, hexane/Et_2O 1:1). IR (KBr) *v*: 3300–2500 (O–H st), 2251 (CN st), 1705 (C=O st) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 0.89 [d, *J* = 6.6 Hz, 6H, $CH(CH_3)_2$)], 1.85 [m, 1H, $CH(CH_3)_2$], 2.46 (d, *J* = 6.9 Hz, 2H, Ar-CH_2CH), 2.78 (dd, *J* ≈ 16.8 Hz, *J*′ ≈ 7.4 Hz, 1H) and 3.00 (dd, *J* = 16.8 Hz, *J*′ = 7.5 Hz, 1H) (3-H_2), 3.94 (pseudo t, *J* = 7.5 Hz, 1H, 2-H), 7.13–7.21 (br signal, 4H, Ar-H), 10.48 (br signal, 1H, COOH). ^{13}C NMR (75.4 MHz, $CDCl_3$) *δ*: 21.3 (CH_2, C3), 22.4 [CH_3, $CH(CH_3)_2$], 30.1 [CH, $CH(CH_3)_2$], 45.0 (CH_2, Ar-CH_2CH), 47.2 (CH, C2), 117.3 (C, CN), 127.2 (CH) and 129.9 (CH) [Ar-C2(6) and Ar-C3(5)], 132.1 (C, Ar-C1), 142.4 (C, Ar-C4), 176.7 (C, C1). Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.60; H, 7.66; N, 5.97.

4.11. (α*R*,3′*R*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 3-cyano-2-(4-isobutylphenyl)propionate (α*R*,3′*R*)-7b

(±)-3-Cyano-2-(4-isobutylphenyl)propionyl chloride (±)-**6b** was prepared in a similar manner to that

described for (±)-**6a**. From (±)-**5b** (1.01 g, 4.37 mmol), PCl_5 (1.02 g, 4.90 mmol), and CCl_4 (6.5 mL), (±)-**6b** (1.07 g, quantitative yield) was obtained as a brown solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.91 [d, $J = 6.6$ Hz, 6H, $CH(CH_3)_2$], 1.88 [m, 1H, $CH(CH_3)_2$], 2.50 (d, $J = 7.0$ Hz, 2H, Ar-CH_2CH), 2.84 (dd, $J = 16.8$ Hz, $J' = 7.6$ Hz, 1H) and 3.07 (dd, $J = 16.8$ Hz, $J' = 7.6$ Hz, 1H) (3-H_2), 4.30 (t, $J = 7.6$ Hz, 1H, 2-H), 7.16–7.27 (br signal, 4H, Ar-H).

The (*R*)-pantolactam ester (α*R*,3′*R*)-**7b** was prepared in a similar manner to that described for (α*R*,3′*R*)-**7a**. From (*R*)-**2** (609 mg, 2.97 mmol), acid chloride (±)-**6b** (1.07 g, 4.29 mmol), and Et_3N (1.33 mL, 9.54 mmol), a diastereomeric mixture of (*R*)-pantolactam esters greatly enriched in the (α*R*,3′*R*)-**7b** diastereomer (1.22 g, 98%, dr 93:7 by ^{1}H NMR) was obtained, and submitted to column chromatography [silica gel (65 g), hexane/AcOEt mixtures]. On elution with hexane/AcOEt 75:25, pure (α*R*,3′*R*)-**7b** (784 mg, 63%, dr >98:2) and a mixture (α*R*,3′*R*)-**7b**/(α*S*,3′*R*)-**7b** (148 mg, dr 76:24) were successively isolated as light brown oils.

(α*R*,3′*R*)-**7b** (dr >98:2): $[\alpha]_D^{20} = -29.4$ (*c* 0.36, CH_2Cl_2). R_f 0.38 (SiO_2, hexane/AcOEt 75:25). IR (NaCl) *v*: 2250 (CN st), 1747 (C=O st ester), 1716 (C=O st lactam) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 [d, $J = 6.6$ Hz, 6H, $CH(CH_3)_2$], 1.11 (s, 3H, 4′α-CH_3), 1.30 (s, 3H, 4′β-CH_3), 1.85 [m, 1H, $CH(CH_3)_2$], 2.45 (d, $J = 6.9$ Hz, 2H, Ar-CH_2CH), 2.89 (dd, $J = 16.8$ Hz, $J' = 7.2$ Hz, 1H) and 3.11 (dd, $J = 16.8$ Hz, $J' = 7.8$ Hz, 1H) (3-H_2), 3.50 (d, $J = 9.9$ Hz, 1H, 5′α-H), 3.60 (d, $J = 9.9$ Hz, 1H, 5′β-H), 4.10 (pseudo t, $J = 7.5$ Hz, 1H, 2-H), 5.42 (s, 3′-H), 7.14–7.38 (complex signal, 7H, Ar-H *C*-phenyl and H*para* and H*meta N*-phenyl), 7.55–7.59 (m, 2H, H*ortho N*-phenyl). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 21.1 (CH_3, 4′α-CH_3), 22.0 (CH_2, C3), 22.4 [CH_3, $CH(CH_3)_2$], 24.8 (CH_3, 4′β-CH_3), 30.1 [CH, $CH(CH_3)_2$], 37.3 (C, C4′), 45.0 (CH_2, Ar-CH_2CH), 47.5 (CH, C2), 57.7 (CH_2, C5′), 79.3 (CH, C3′), 117.5 (C, CN), 119.4 (CH, C*ortho N*-phenyl), 124.9 (CH, C*para N*-phenyl), 127.3 [CH, C2(6) *C*-phenyl], 128.9 (CH, C*meta N*-phenyl), 129.8 [CH, C3(5) *C*-phenyl], 132.2 (C, C1 *C*-phenyl), 138.8 (C, C*ipso N*-phenyl), 140.0 (C, C4 *C*-phenyl), 167.8 (C, C2′), 170.4 (C, C1). Anal. Calcd for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.23; N, 6.69. Found: C, 74.37; H, 7.46; N, 6.55.

4.12. (*R*)-3-Cyano-2-(4-isobutylphenyl)propionic acid (*R*)-5b

It was prepared in a similar manner to that described for (*R*)-**5a**. From (α*R*,3′*R*)-**7b** (719 mg, 1.72 mmol, dr >98:2), 30% w/v H_2O_2 (0.43 mL, 3.79 mmol), and $LiOH{\cdot}H_2O$ (94 mg, 2.24 mmol), pantolactam (*R*)-**2** (337 mg, 96%, ee >99% by chiral HPLC) and cyano acid (*R*)-**5b** (351 mg, 88%, ee 97%) were separately obtained as white solids. Enantiopure (*R*)-**5b** (207 mg, 52% overall, ee >99%) was obtained as a white solid from the crude product (351 mg, 1.52 mmol) via its cyclohexylammonium salt as described for (*R*)-**5a**. $[\alpha]_D^{20} = -131$ (*c* 0.83, CH_2Cl_2). Chiral HPLC, condition C: (*R*)-**5b**, $t_R = 19.3$ min. Mp: 100–101 °C (isopropanol). R_f 0.14 (SiO_2, hexane/Et_2O 1:1). IR (KBr) *v*: 3500–2800 (O–H st), 2238 (CN st), 1728 and 1683 (C=O st) cm^{-1}. The ^{1}H and ^{13}C NMR spectra are coincidental with those of (±)-**5b**. Anal. Calcd for $C_{14}H_{17}NO_2{\cdot}0.1H_2O$: C, 72.14; H, 7.44; N, 6.01. Found: C, 71.94; H, 7.65; N, 5.93.

4.13. (*R*)-4-(*tert*-Butoxycarbonylamino)-2-(4- isobutylphenyl)butanoic acid (*R*)-8b

It was prepared in a similar manner to that described for (*R*)-**8a**. From (*R*)-**5b** (136 mg, 0.59 mmol, ee >99%), AcOH (15 mL), and 10% Pd/C (90 mg), followed by treatment of a solution of the intermediate crude amino acid (211 mg) in H_2O (3 mL) with 2 N NaOH (2.4 mL), dioxane (6 mL), and Boc_2O (258 mg, 1.17 mmol), (*R*)-**8b** (103 mg, 52% overall, ee >99% by chiral HPLC) was obtained as a pale yellow oil. The analytical sample of (*R*)-**8b** was obtained via its cyclohexylammonium salt as described for (*R*)-**5a**. From a solution of crude (*R*)-**8b** (100 mg, 0.30 mmol) in Et_2O (5 mL) and cyclohexylamine (0.05 mL, 0.44 mmol), pure (*R*)-**8b** (65 mg) was obtained, after reisolation of the acid from its salt, as a colorless oil. $[\alpha]_D^{20} = -63$ (*c* 1.19, CH_2Cl_2). Chiral HPLC, condition D: (*R*)-**8b**, $t_R = 18.1$ min. R_f 0.21 (SiO_2, hexane/AcOEt 1:1). IR (NaCl) *v*: 3500–2750 (O–H st and N–H st), 1707 (C=O st) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 [d, $J = 6.6$ Hz, 6H, $CH(CH_3)_2$], 1.41 [s, 9H, $C(CH_3)_3$], 1.83 [m, 1H, $CH(CH_3)_2$], 1.92 (m, 1H) and 2.27 (m, 1H) (3-H_2), 2.43 (d, $J = 7.2$ Hz, 2H, Ar-CH_2CH), 3.11 (m, 2H, 4-H_2), 3.58 (dd, $J = J' = 7.5$ Hz, 1H, 2-H), 4.60 (br s, 0.6H, NH, main rotamer), 6.10 (br signal, 0.4H, NH, minor rotamer), 7.08 (d, $J = 8.1$ Hz, 2H) and 7.20 (d, $J = 8.1$ Hz, 2H) (Ar-H). The signal corresponding to COO–H was not observed. ^{13}C NMR (75.4 MHz, $CDCl_3$), main rotamer, δ: 22.4 [CH_3, $C(CH_3)_3$], 28.4 [CH_3, $CH(CH_3)_2$], 30.2 [CH, $CH(CH_3)_2$], 33.2 (CH_2, C3), 38.8 (CH_2, C4), 45.0 (CH_2, Ar-CH_2CH), 48.7 (CH, C2), 79.4 [C, $C(CH_3)_3$], 127.6 (CH) and 129.4 (CH) [Ar-C2(6) and Ar-C3(5)], 135.2 (C, Ar-C1), 141.0 (C, Ar-C4), 155.9 (C, OCONH), 178.6 (C, C1). ^{13}C NMR (75.4 MHz, $CDCl_3$), differentiated signals of the minor rotamer, δ: 40.0 (CH_2, C4), 81.0 [C, $C(CH_3)_3$], 158.0 (C, OCONH). Anal. Calcd for $C_{19}H_{29}NO_4{\cdot}0.1H_2O$: C, 67.67; H, 8.73; N, 4.15. Found: C, 67.50; H, 8.80; N, 4.10.

4.14. (α*S*,3′*S*)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 3-cyano-2-(4-isobutylphenyl)propionate (α*S*,3′*S*)-7b

It was prepared in a similar manner to that described for (α*R*,3′*R*)-**7a**. From (*S*)-**2** (900 mg, 4.39 mmol), acid chloride (±)-**6b** (1.61 g, 6.45 mmol), and Et_3N (1.99 mL, 1.44 mmol), a diastereomeric mixture of (*S*)-pantolactam esters greatly enriched in the (α*S*,3′*S*)-**7b** diastereomer (1.82 g, 99%, dr 87:13 by ^{1}H NMR) was obtained, and submitted to column chromatography [silica gel (100 g), hexane/AcOEt mixtures]. On elution with hexane/AcOEt 75:25, (α*S*,3′*S*)-**7b** (1.14 g, 62%, dr >98:2) and a mixture (α*S*,3′*S*)-**7b**/(α*R*,3′*S*)-**7b** (240 mg, dr 76:24) were successively isolated as light brown oils.

(αS,3′S)-**7b** (dr >98:2): $[\alpha]_D^{20} = +25.6$ (*c* 0.39, CH_2Cl_2). R_f 0.38 (SiO_2, hexane/AcOEt 75:25). IR (NaCl) *v*: 2242 (CN st), 1745 (C=O st ester), 1716 (C=O st lactam) cm^{-1}. The NMR data coincide with those of (αR,3′R)-**7b**. Anal. Calcd for $C_{26}H_{30}N_2O_3$: C, 74.61; H, 7.23; N, 6.69. Found: C, 74.44; H, 7.25; N, 6.60.

4.15. (*S*)-3-Cyano-2-(4-isobutylphenyl)propionic acid (*S*)-5b

It was prepared in a similar manner to that described for (*R*)-**5a**. From (αS,3′S)-**7b** (979 mg, 2.34 mmol, dr >98:2), 30% w/v H_2O_2 (0.60 mL, 5.29 mmol), and $LiOH{\cdot}H_2O$ (131 mg, 3.12 mmol), pantolactam (*S*)-**2** (459 mg, 96%, ee >99% by chiral HPLC) and cyano acid (*S*)-**5b** (525 mg, 97%, ee 98%) were separately obtained as white solids. Enantiopure (*S*)-**5b** (310 mg, 57% overall, ee >99%) was obtained from the crude product (525 mg, 2.27 mmol) via its cyclohexylammonium salt as described for (*R*)-**5a**. $[\alpha]_D^{20} = +125$ (*c* 0.89, CH_2Cl_2). Chiral HPLC, condition C: (*S*)-**5b**, $t_R = 16.4$ min. Mp: 98–99 °C (isopropanol). R_f 0.14 (SiO_2, hexane/Et_2O 1:1). IR (KBr) *v*: 3500–2800 (O–H st), 2248 (CN st), 1727 and 1683 (C=O st) cm^{-1}. The ^1H and ^{13}C NMR spectra are coincidental with those of (±)-**5b**. Anal. Calcd for $C_{14}H_{17}NO_2{\cdot}0.1H_2O$: C, 72.14; H, 7.44; N, 6.01. Found: C, 72.19; H, 7.49; N, 6.01.

4.16. (*S*)-4-(*tert*-Butoxycarbonylamino)-2-(4-isobutylphenyl)butanoic acid (*S*)-8b

It was prepared in a similar manner to that described for (*R*)-**8a**. From (*S*)-**5b** (428 mg, 1.85 mmol, ee >99%), AcOH (50 mL), and 10% Pd/C (268 mg), followed by treatment of a solution of the intermediate crude amino acid (664 mg) in H_2O (10 mL) with 2 N NaOH (5 mL), dioxane (19 mL), and Boc_2O (795 mg, 3.64 mmol), (*S*)-**8b** (423 mg, 68% overall, ee >99% by chiral HPLC) was obtained as a pale yellow oil. The analytical sample of (*S*)-**8b** was obtained via its cyclohexylammonium salt as described for (*R*)-**5a**. From a solution of crude (*S*)-**8b** (423 mg, 1.26 mmol) in Et_2O (10 mL) and cyclohexylamine (0.15 mL, 1.31 mmol), pure (*S*)-**8b** (274 mg) was obtained, after reisolation of the acid from its salt, as a colorless oil. $[\alpha]_D^{20} = +61$ (*c* 0.65, CH_2Cl_2). Chiral HPLC, condition D: (*S*)-**8b**, $t_R = 16.1$ min. R_f 0.23 (SiO_2, hexane/AcOEt 1:1). IR (NaCl) *v*: 3500–2750 (O–H st and N–H st), 1708 (C=O st) cm^{-1}. The ^1H and ^{13}C NMR spectra are coincidental with those of (*R*)-**8b**. Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.14; H, 8.72; N, 4.09.

4.17. (±)-Methyl 3-cyano-2-(6-methoxy-2-naphthyl)propionate (±)-4c

It was prepared in a similar manner to that described for (±)-**4b**. From a solution of hexamethyldisilazane (1.92 mL, 9.10 mmol) in anhydrous THF (18 mL), a 2.5 M solution of *n*-butyllithium in hexane (3.5 mL, 8.75 mmol), a solution of ester **3c** (1.84 g, 8.00 mmol) in anhydrous THF (11 mL), and a solution of bromoacetonitrile (0.98 mL, 14.1 mmol) in anhydrous THF (11 mL), followed by column chromatography [silica gel (65 g), hexane/AcOEt mixtures] of the crude product (1.94 g), (±)-**4c** (1.58 g, 73%) was obtained as a white solid. Mp: 150–151 °C (sublimed at 160 °C/0.5 Torr). R_f 0.51 (SiO_2, hexane/AcOEt 1:1). IR (KBr) *v*: 2244 (CN st), 1734 (C=O st) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.89 (dd, $J = 16.8$ Hz, $J' = 7.5$ Hz, 1H) and 3.12 (dd, $J = 16.8$ Hz, $J' = 7.5$ Hz, 1H) (3-H_2), 3.73 (s, 3H, CO-OCH_3), 3.92 (s, 3H, Ar-OCH_3), 4.08 (dd, $J = J' = 7.5$ Hz, 1H, 2-H), 7.12 (d, $J = 2.7$ Hz, 1H, Ar-5-H), 7.18 (dd, $J = 9.0$ Hz, $J' = 2.7$ Hz, 1H, Ar-7-H), 7.33 (dd, $J = 8.4$ Hz, $J' = 1.8$ Hz, 1H, Ar-3-H), 7.67 (d, $J \approx 1.8$ Hz, 1H, Ar-1-H), 7.72 (d, $J \approx 9.0$ Hz, 1H, Ar-8-H), superimposed in part 7.75 (d, $J \approx 8.4$ Hz, 1H, Ar-4-H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 21.8 (CH_2, C3), 47.6 (CH, C2), 52.8 (CH_3, $COOCH_3$), 55.3 (CH_3, Ar-OCH_3), 105.5 (CH, Ar-C5), 117.6 (C, CN), 119.5 (CH, Ar-C7), 125.1 (CH, Ar-C3), 126.7 (CH, Ar-C1), 127.9 (CH, Ar-C4), 128.7 (C, Ar-C8a), 129.3 (CH, Ar-C8), 130.6 (C, Ar-C2), 134.2 (C, Ar-C4a), 158.1 (C, Ar-C6), 171.5 (C, C1). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.50; H, 5.66; N, 5.31.

4.18. (±)-3-Cyano-2-(6-methoxy-2-naphthyl)propionic acid (±)-5c

It was prepared in a similar manner to that described for (±)-**5b**. From (±)-**4c** (1.10 g, 4.09 mmol), 1 N NaOH (4.3 mL, 4.30 mmol), and EtOH (28 mL), cyano acid (±)-**5c** (0.93 g, 89%) was obtained as a white solid. Chiral HPLC, condition E: (*R*)-**5c**, $t_R = 21.5$ min, $k'_1 = 4.52$; (*S*)-**5c**, $t_R = 24.4$ min, $k'_2 = 5.26$; $\alpha = 1.16$; Res = 6.47. Mp: 160–161 °C (AcOEt). R_f 0.12 (SiO_2, hexane/AcOEt 1:1). IR (KBr) *v*: 3500–2700 (O–H st), 2268 (CN st), 1732 (C=O st) cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ: 2.97 (dd, $J = 16.8$ Hz, $J' = 7.5$ Hz, 1H) and 3.12 (dd, $J = 16.8$ Hz, $J' = 7.5$ Hz, 1H) (3-H_2), 3.88 (s, 3H, OCH_3), 4.11 (dd, $J = J' = 7.5$ Hz, 1H, 2-H), 4.89 (s, COOH), 7.13 (dd, $J = 8.7$ Hz, $J' = 2.7$ Hz, 1H, Ar-7-H), 7.21 (d, $J \approx 2.7$ Hz, 1H, Ar-5-H), 7.39 (dd, $J = 8.4$ Hz, $J' = 1.8$ Hz, 1H, Ar-3-H), 7.728 (d, J 8.7 Hz, 1H, Ar-8-H), 7.732 (br s, 1H, Ar-1-H), 7.76 (d, $J \approx 8.4$ Hz, 1H, Ar-4-H). ^{13}C NMR (75.4 MHz, CD_3OD) δ: 22.0 (CH_2, C3), 48.7 (CH, C2), 55.7 (CH_3,OCH_3), 106.6 (CH, Ar-C5), 119.5 (C, CN), 120.3 (CH, Ar-C7), 126.7 (CH, Ar-C3), 127.8 (CH, Ar-C1), 128.6 (CH, Ar-C4), 130.2 (C, Ar-C8a), 130.3 (CH, Ar-C8), 133.2 (C, Ar-C2), 135.6 (C, Ar-C4a), 159.4 (C, Ar-C6), 174.5 (C, C1). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.43; H, 5.25; N, 5.44.

4.19. (αR,3′R)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 3-cyano-2-(6-methoxy-2-naphthyl)propionate (αR,3′R)-7c

(±)-3-Cyano-2-(6-methoxy-2-naphthyl)propionyl chloride (±)-**6c** was prepared in a similar manner to that described for (±)-**6a**. From (±)-**5c** (707 mg, 2.77 mmol), PCl_5 (686 mg, 3.29 mmol), and CCl_4 (4.5 mL), (±)-**6c**

(762 mg, quantitative yield) was obtained as a brown solid. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.94 (dd, $J = 17.0$ Hz, $J' = 7.8$ Hz, 1H) and 3.16 (dd, $J = 17.0$ Hz, $J' = 6.8$ Hz, 1H) (3-H_2), 3.94 (s, 3H, OCH_3), 4.46 (dd, $J \approx J' \approx 7.4$ Hz, 1H, 2-H), 7.15 (d, $J = 2.6$ Hz, 1H, Ar-5-H), 7.22 (dd, $J = 8.8$ Hz, $J' = 2.6$ Hz, 1H, Ar-7-H), 7.30 (dd, $J \approx 8.4$ Hz, $J' = 1.8$ Hz, 1H, Ar-3-H), 7.71 (d, $J = 1.8$ Hz, 1H, Ar-1-H), 7.76 (d, $J \approx 8.8$ Hz, 1H, Ar-8-H), 7.82 (d, $J = 8.4$ Hz, 1H, Ar-4-H).

The pantolactam ester (αR, $3'R$)-**7c** was prepared in a similar manner to that described for (αR,$3'R$)-**7a**. From (*R*)-**2** (402 mg, 1.96 mmol), acid chloride (±)-**6c** (762 mg, 2.79 mmol), and Et_3N (0.90 mL, 6.46 mmol), a diastereomeric mixture of (*R*)-pantolactam esters greatly enriched in the (αR, $3'R$)-**7c** diastereomer (860 mg, 99%, dr 91:9 by ^{1}H NMR) was obtained, and submitted to column chromatography [silica gel (45 g), hexane/AcOEt mixtures]. On elution with hexane/AcOEt 75:25, (αR,$3'R$)-**7c** (88 mg, 10%, dr >98:2) and diastereoenriched (αR,$3'R$)-**7c** [(232 mg, 27%, dr 97:3) and (400 mg, dr 90:10)] were successively isolated as light brown solids.

(αR,$3'R$)-**7c** (dr >98:2): $[\alpha]_D^{20} = -14.3$ (*c* 1.02, CH_2Cl_2). Mp: 60–61 °C (hexane/AcOEt 75:25). R_f 0.20 (SiO_2, hexane/AcOEt 75:25). IR (KBr) *v*: 2249 (CN st), 1745 (C=O st ester), 1712 (C=O st lactam) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.11 (s, 3H, 4′α-CH_3), 1.30 (s, 3H, 4′β-CH_3), 2.97 (dd, $J = 16.8$ Hz, $J' \approx 7.5$ Hz, 1H) and 3.20 (dd, $J = 16.8$ Hz, $J' = 7.5$ Hz, 1H) (3-H_2), 3.49 (d, $J = 9.6$ Hz, 1H, 5′α-H), 3.58 (d, $J = 9.6$ Hz, 1H, 5′β-H), 3.91 (s, 3H, OCH_3), 4.25 (dd, $J \approx J' \approx 7.5$ Hz, 1H, 2-H), 5.44 (s, 3′-H), 7.11–7.18 [complex signal, 3H, 5-H and 7-H naphthyl, and H*para N*-phenyl], 7.34 (m, 2H, H*meta N*-phenyl), 7.44 (dd, $J = 8.7$ Hz, $J' = 1.8$ Hz, 1H, 3-H naphthyl), 7.55 (m, 2H, H*ortho N*-phenyl), 7.74 (d, $J = 8.7$ Hz, 1H, 8-H naphthyl), 7.76 (d, $J \approx 8.7$ Hz, 1H, 4-H naphthyl), 7.78 (br s, 1H, 1-H naphthyl). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 21.2 (CH_3, 4′α-CH_3), 22.1 (CH_2, C3), 24.8 (CH_3, 4′β-CH_3), 37.3 (C, C4′), 47.8 (CH, C2), 55.3 (CH_3, OCH_3), 57.7 (CH_2, C5′), 79.4 (CH, C3′), 105.6 (CH, C5 naphthyl), 117.5 (C, CN), 119.4 (3CH, C7 naphthyl, and C*ortho N*-phenyl), 124.9 (CH, C*para N*-phenyl), 125.4 (CH, C3 naphthyl), 127.0 (CH, C1 naphthyl), 127.9 (CH, C4 naphthyl), 128.7 (C, C8a naphthyl), 128.9 (CH, C*meta N*-phenyl), 129.5 (CH, C8 naphthyl), 130.0 (C, C2 naphthyl), 134.3 (C) (C2, C4a naphthyl), 138.8 (C, C*ipso N*-phenyl), 158.0 (C, C6 naphthyl), 167.8 (C, C2′), 170.4 (C, C1). Anal. Calcd for $C_{27}H_{26}N_2O_4 \cdot 0.6H_2O$: C, 71.54; H, 6.05; N, 6.18. Found: C, 71.45; H, 5.75; N, 5.96.

4.20. (*R*)-3-Cyano-2-(6-methoxy-2-naphthyl)propionic acid (*R*)-5c

It was prepared in a similar manner to that described for (*R*)-**5a**. From (αR,$3'R$)-**7c** (200 mg, 0.45 mmol, dr 97:3), 30% w/v H_2O_2 (0.11 mL, 0.97 mmol), and $LiOH \cdot H_2O$ (25 mg, 0.59 mmol), pantolactam (*R*)-**2** (88 mg, 95%, ee >99% by chiral HPLC) and cyano acid (*R*)-**5c** (100 mg, 87%, ee 94%) were separately obtained as white solids. Recrystallization of the crude cyano acid from AcOEt (1.5 mL) afforded enantiopure (*R*)-**5c** (73 mg, 64%, ee >99%) as a white solid. $[\alpha]_D^{20} = -124$ (*c* 0.20, THF). Chiral HPLC, condition E: (*R*)-**5c**, $t_R = 21.5$ min. Mp: 161–162 °C (AcOEt). R_f 0.12 (SiO_2, hexane/AcOEt 1:1). IR (KBr) *v*: 3400–2700 (O–H st), 2269 (CN st), 1733 (C=O st) cm^{-1}. The ^{1}H and ^{13}C NMR spectra are coincidental with those of (±)-**5c**. Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.43; H, 5.09; N, 5.38.

4.21. (*R*)-4-(*tert*-Butoxycarbonylamino)-2-(6-methoxy-2-naphthyl)butanoic acid (*R*)-8c

It was prepared in a similar manner to that described for (*R*)-**8a**. From (*R*)-**5c** (105 mg, 0.41 mmol, ee >99%), AcOH (15 mL), and 10% Pd/C (68 mg), followed by treatment of a solution of the intermediate crude amino acid (124 mg) in H_2O (2 mL) with 2 N NaOH (1.7 mL), dioxane (4 mL), and Boc_2O (168 mg, 0.77 mmol), (*R*)-**8c** (91 mg, 62% overall, ee >99% by chiral HPLC) was obtained as a pale yellow oil. The analytical sample of (*R*)-**8c** was obtained via its cyclohexylammonium salt as described for (*R*)-**5a**. From a solution of crude (*R*)-**8c** (91 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) and cyclohexylamine (0.03 mL, 0.26 mmol), pure (*R*)-**8c** (65 mg) was obtained, after reisolation of the acid from its salt, as a colorless oil. $[\alpha]_D^{20} = -57$ (*c* 0.70, CH_2Cl_2). Chiral HPLC, condition F: (*R*)-**8c**, $t_R = 16.9$ min. R_f 0.15 (SiO_2, hexane/AcOEt 1:1). IR (NaCl) *v*: 3600–2600 (O–H st and N–H st), 1706 (C=O st) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 [s, 9H, $C(CH_3)_3$], 1.92–2.08 (m, 1H) and 2.24–2.44 (m, 1H) (3-H_2), 2.97–3.19 (m, 2H, 4-H_2), 3.74 (dd, $J \approx J' \approx 7.6$ Hz, 1H, 2-H), 3.90 (s, 3H, OCH_3), 4.63 (br signal, 0.6H, NH, main rotamer), 6.12 (br signal, 0.4H, NH, minor rotamer), 7.08 (d, $J \approx 2.4$ Hz, 1H, Ar-5-H), 7.12 (dd, $J = 8.7$ Hz, $J' = 2.4$ Hz, 1H, Ar-7-H), 7.38 (d, $J = 8.4$ Hz, 1H, Ar-3-H), superimposed 7.659 (br s, 1H, Ar-1-H), 7.665 (d, $J = 8.7$ Hz, 1H, Ar-8-H), 7.672 (d, $J \approx 8.4$ Hz, 1H, Ar-4-H). The signal corresponding to COO–H was not observed. ^{13}C NMR (75.4 MHz, $CDCl_3$), main rotamer, δ: 28.4 [CH_3, $C(CH_3)_3$], 33.2 (CH_2, C3), 38.8 (CH_2, C4), 48.9 (CH, C2), 55.3 (CH_3, OCH_3), 79.5 [C, $C(CH_3)_3$], 105.5 (CH, Ar-C5), 119.0 (CH, Ar-C7), 126.2 (CH, Ar-C3), 126.7 (CH, Ar-C1), 127.3 (CH, Ar-C4), 128.8 (C, Ar-C8a), 129.2 (CH, Ar-C8), 133.1 (C, Ar-C2), 133.8 (C, Ar-C4a), 157.6 (2C, Ar-C6, and OCONH), 178.3 (C, C1). ^{13}C NMR (75.4 MHz, $CDCl_3$), differentiated signals of the minor rotamer, δ: 39.8 (CH_2, C4), 80.8 [C, $C(CH_3)_3$], 155.9 (C, OCONH). Anal. Calcd for $C_{20}H_{25}NO_5 \cdot 1/5H_2O$: C, 66.17; H, 7.05; N, 3.86. Found: C, 66.27; H, 7.38; N, 3.53.

4.22. (αS,$3'S$)-4,4-Dimethyl-2-oxo-1-phenylpyrrolidin-3-yl 3-cyano-2-(6-methoxy-2-naphthyl)propionate (αS,$3'S$)-7c

It was prepared in a similar manner to that described for (αR,$3'R$)-**7a**. From (*S*)-**2** (631 mg, 3.08 mmol), acid chloride (±)-**6c** (1.16 g, 4.24 mmol), and Et_3N (1.4 mL,

10.1 mmol), a diastereomeric mixture of (*S*)-pantolactam esters greatly enriched in the (α*S*,3′*S*)-**7c** diastereomer (1.35 g, 99%, dr 92:8 by ^{1}H NMR) was obtained, and submitted to column chromatography [silica gel (90 g), hexane/AcOEt mixtures]. On elution with hexane/AcOEt 75:25, (α*S*,3′*S*)-**7c** (36 mg, 3%, dr >98:2) and diastereoenriched (α*S*,3′*S*)-**7c** [(592 mg, 43%, dr 97:3) and (282 mg, dr 90:10)] were successively isolated as light brown solids.

(α*S*,3′*S*)-**7c** (dr >98:2): $[\alpha]_D^{20} = +16.5$ (*c* 1.01, CH_2Cl_2). Mp: 58–59 °C (hexane/AcOEt 75:25). R_f 0.18 (SiO_2, hexane/AcOEt 75:25). IR (KBr) *v*: 2249 (CN st), 1745 (C=O st ester), 1714 (C=O st lactam) cm^{-1}. The ^{1}H and ^{13}C NMR spectra are coincidental with those of (α*R*,3′*R*)-**7c**. Anal. Calcd for $C_{27}H_{26}N_2O_4$: C, 73.28; H, 5.93; N, 6.33. Found: C, 73.23; H, 6.02; N, 6.15.

4.23. (*S*)-3-Cyano-2-(6-methoxy-2-naphthyl)propionic acid (*S*)-5c

It was prepared in a similar manner to that described for (*R*)-**5a**. From (α*S*,3′*S*)-**7c** (550 mg, 1.24 mmol, dr 97:3), 30% w/v H_2O_2 (0.30 mL, 2.65 mmol), and $LiOH{\cdot}H_2O$ (67.6 mg, 1.61 mmol), pantolactam (*S*)-**2** (240 mg, 94%, ee >99% by chiral HPLC) and cyano acid (*S*)-**5c** (285 mg, 90%, ee 91%) were separately obtained as white solids. Enantiopure (*S*)-**5c** (169 mg, 53%, ee >99%) was obtained as a white solid by recrystallization of the crude product from AcOEt (5 mL). $[\alpha]_D^{20} = +129$ (*c* 0.62, THF). Chiral HPLC, condition E: (*S*)-**5c**, $t_R = 24.4$ min. Mp: 154–155 °C (AcOEt). R_f 0.12 (SiO_2, hexane/AcOEt 1:1). IR (KBr) *v*: 3400–2700 (O–H st), 2270 (CN st), 1732 (C=O st) cm^{-1}. The ^{1}H and ^{13}C NMR spectra are coincidental with those of (±)-**5c**. Anal. Calcd for $C_{15}H_{13}NO_3{\cdot}0.1H_2O$: C, 70.08; H, 5.18; N, 5.45. Found: C, 70.04; H, 5.08; N, 5.40.

4.24. (*S*)-4-(*tert*-Butoxycarbonylamino)-2-(6-methoxy-2- naphthyl)butanoic acid (*S*)-8c

It was prepared in a similar manner to that described for (*R*)-**8a**. From (*S*)-**5c** (126 mg, 0.49 mmol, ee >99%), AcOH (15 mL), and 10% Pd/C (83 mg), followed by treatment of a solution of the intermediate crude amino acid (150 mg) in H_2O (3 mL) with 2 N NaOH (2 mL), dioxane (5 mL), and Boc_2O (212 mg, 0.97 mmol), (*S*)-**8c** (104 mg, 59% overall, ee >99% by chiral HPLC) was obtained as a pale yellow oil. The analytical sample of (*S*)-**8c** was obtained via its cyclohexylammonium salt as described for (*R*)-**5a**. From a solution of crude (*S*)-**8c** (104 mg, 0.29 mmol) in CH_2Cl_2 (5 mL) and cyclohexylamine (0.03 mL, 0.26 mmol), pure (*S*)-**8c** (63 mg) was obtained, after reisolation of the acid from its salt, as a colorless oil. $[\alpha]_D^{20} = +61$ (*c* 0.99, CH_2Cl_2). Chiral HPLC, condition F: (*S*)-**8c**, $t_R = 21.2$ min. R_f 0.15 (SiO_2, hexane/AcOEt 1:1). IR (NaCl) *v*: 3500–2700 (O–H st and N–H st), 1707 (C=O st) cm^{-1}. The ^{1}H and ^{13}C NMR spectra are coincidental with those of (*R*)-**8c**. Anal. Calcd for $C_{20}H_{25}NO_5{\cdot}1/5H_2O$: C, 66.17; H, 7.05; N, 3.86. Found: C, 66.19; H, 6.82; N, 3.64.

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