Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 6, pp. 1409-1418, 1995

0957-4166/95 $9.50+0.00

0957-4166(95)00174-3

Synthesis of a New Type of Conformationally Constrained α,α-Disubstituted-β-amino Acids and β-Lactams in Enantiomerically Pure Form.

Alberto Avenoza[a], Carlos Cativiela[b]*, Miguel París[a] and Jesús M. Peregrina[a]

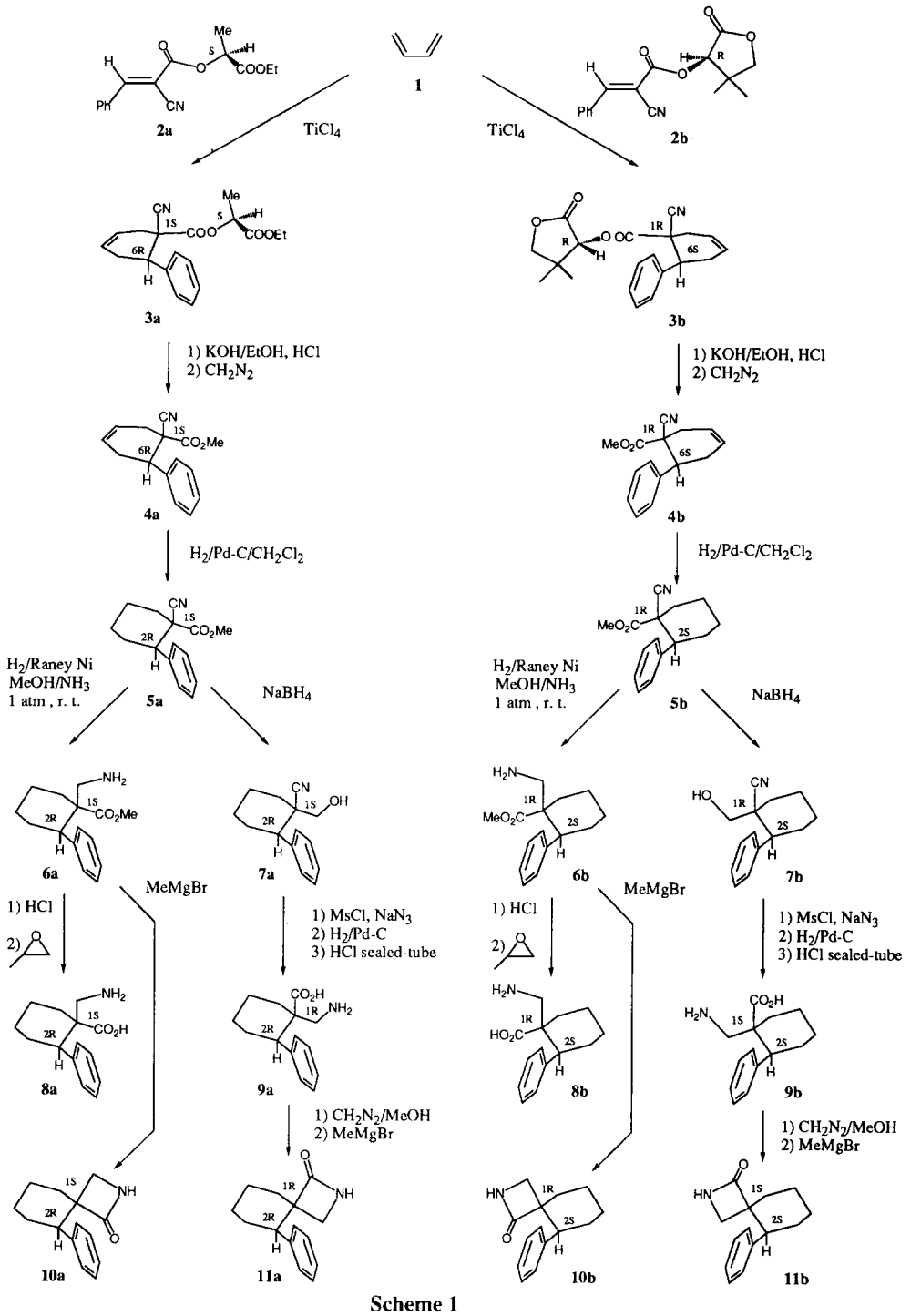
[a]Department of Chemistry (Organic Chemistry). Edificio Científico-Técnico. Sección Ciencias. Universidad de La Rioja. 26001 Logroño. Spain.

[b]Department of Organic Chemistry. Instituto de Ciencia de Materiales de Aragón. Universidad de Zaragoza-C.S.I.C. 50009 Zaragoza. Spain.

Abstract: Optically active *cis*- , **8a** and **8b**, and *trans*-1-aminomethyl-2-phenylcyclohexane-1-carboxylic acids, **9a** and **9b**, were obtained starting from 1,3-butadiene using Diels-Alder cycloadditions with chiral (E)-2-cyanocinnamates as key steps and following a protocol of stereocontrolled reactions. Subsequent cyclization of these conformationally constrained β-amino acids led to the corresponding α,α-disubstituted-β-lactams **10a**, **10b**, **11a** and **11b** in enantiomerically pure forms.

Interest in the synthesis of biologically active products containing quaternary carbon atoms has increased notably over the last decade[1]. The interesting properties of α- and β-amino acids with conformational rigidity, in particular for α,α-disubstituted series, have recently attracted the attention of numerous research groups[2] since the incorporation of these products into peptides can modify drastically their properties. Thus the description of new synthetic procedures or new products is a subject of continuous interest, especially when compounds can be prepared in an enantiomerically pure form. Whereas numerous papers have been recently published on α-amino acids, there are hardly any references to β-amino acids. As a consequence, the development of new methods providing a direct approach to β-constrained amino acids which can be cyclized to β-lactams constitutes an area of active research. We have previously reported that chiral (E)-2-cyanocinnamates are excellent dienophiles in asymmetric Diels-Alder reactions[3], allowing the synthesis of chiral products containing quaternary carbon atoms, and that (S)-ethyl lactate and (R)-pantolactone are excellent and complementary chiral auxiliaries. In this paper we wish to report that this methodology can be used for the synthesis of a new family of α,α-disubstituted-β-amino acids as well as for the synthesis of the corresponding cyclization products.

The synthesis of stereoisomeric chiral β-amino acids and β-lactams is shown in scheme 1 as a stereodivergent synthesis from 1,3-butadiene **1** as starting material, using as key steps Diels-Alder cycloadditions with the readily available chiral dienophiles[3b]: (E)-2-cyanocinnamate of (S)-ethyl lactate **2a** and (R)-pantolactone **2b**.


2a
1
2b
TiCl4
TiCl4
3a
3b
1) KOH/EtOH, HCl
2) CH2N2
1) KOH/EtOH, HCl
2) CH2N2
4a
4b
H2/Pd-C/CH2Cl2
H2/Pd-C/CH2Cl2
5a
5b
H2/Raney Ni
MeOH/NH3
1 atm , r. t.
NaBH4
H2/Raney Ni
MeOH/NH3
1 atm , r. t.
NaBH4
6a
7a
6b
7b
MeMgBr
MeMgBr
1) HCl
2)
1) MsCl, NaN3
2) H2/Pd-C
3) HCl sealed-tube
1) HCl
2)
1) MsCl, NaN3
2) H2/Pd-C
3) HCl sealed-tube
8a
9a
8b
9b
1) CH2N2/MeOH
2) MeMgBr
1) CH2N2/MeOH
2) MeMgBr
10a
11a
10b
11b

Scheme 1

After a typical purification procedure, the corresponding major cycloadducts **3a** and **3b** were obtained in enantiomerically pure forms. Their absolute configurations were previously determined by X-ray diffraction and reported in a recent paper[3a]. The alkaline hydrolysis with 10% KOH-ethanol of the cycloadducts **3a,b** gave the unsaturated cyano carboxylic acids, which were transformed, by the action of diazomethane, to the corresponding cyano methyl carboxylate enantiomers **4a** and **4b**, respectively.

Unsaturated compounds **4a,b** were hydrogenated over palladium-carbon to give saturated methyl carboxylates **5a,b**. The enantiomeric purity of these compounds was tested by means of ^{1}H-NMR, using an europium (III) chelate as a chiral shift reagent[3a]. From the saturated compounds **5a,b** and following a protocol of stereocontrolled transformations of the cyano and methoxycarbonyl substituents into aminomethyl and carboxylic acid groups, we have synthesised both enantiomers of *trans*- **8a,b** and *cis*-1-aminomethyl-2-phenylcyclohexane-1-carboxylic acids **9a,b**.

Nitriles can be easily reduced to primary amines with many reducing agents[4], but in the presence of an ester group a reducing agent comprising hydrogen and a catalyst[5] is most recommended. Whereas platinum, palladium and rhodium are described as good catalysts under mild conditions, in our case, when we attempted to hydrogenate the cyano group of the methyl esters **5a,b** with palladium-carbon or rhodium on alumine under elevated temperatures and pressures between 1 and 5 atmospheres, reaction did not occur. Only employing large amounts of palladium-carbon at 75 °C and 55 atmospheres and carrying out the hydrogenation of **5a,b** in the presence of ammonia, in order to minimize secondary amine formation[6] as a side product, we were able to obtain the aminomethyl derivatives **6a,b** in high yields. Nickel in the presence of ammonia is often used for this kind of hydrogenation with the reaction carried out at elevated temperatures and pressures, nevertheless in our case the use of Raney nickel in a solution of 10% ammonia-methanol at atmospheric pressure and room temperature gave the corresponding primary amines **6a,b** with excellent yields and secondary amine formation was not observed. Further hydrolysis of the methyl carboxylate group of aminomethyl derivatives **6a,b**, in 6N HCl under reflux, to give the β-amino acid hydrochlorides was followed by treatment with propylene oxide in ethanol to yield the desired optically active *trans*-β-amino acids **8a,b**.

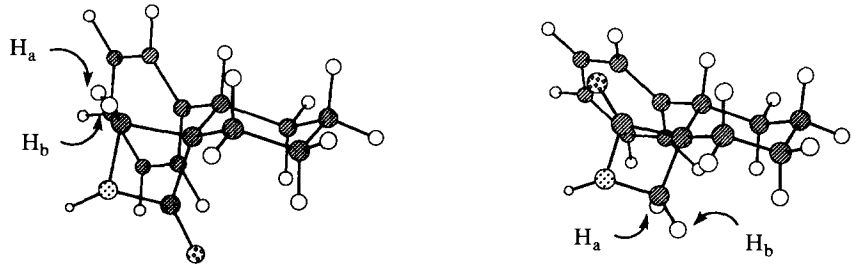
Treatment of aminomethyl derivatives **6a,b** with methylmagnesium bromide to deprotonate the amino group, allowed the formation of the β-lactam ring[7]. In this way, optically active *trans*-β-lactams **10a,b** were achieved in good yields, when the reactions were carried out in ethyl ether at room temperature.

In order to synthesise the desired *cis*-isomers of β-amino acids and β-lactams, the methoxycarbonyl group of cyano esters **5a,b** was reduced to the hydroxymethyl group by means of sodium borohydride in THF at 50 °C, allowing the synthesis of cyano hydroxymethyl derivatives **7a,b** with excellent results. Further mesylation of the alcohols **7a,b** to afford the corresponding mesylate derivatives in near quantitative yield, followed by nucleophilic displacement, using sodium azide in DMF-water at 125 °C, gave the azidomethyl derivatives in 83-85% yield, which were subsequently hydrogenated with palladium-carbon as a catalyst to obtain quantitatively the cyano aminomethyl compounds. When we tried to hydrolyse the cyano group of these compounds in an acid medium, under several conditions, no reaction occurred. Hydrolysis was only observed when the reactions were performed in 6N HCl at 160 °C in a sealed-tube. The low reactivity of these nitriles, attached to a quaternary carbon, can be explained by the axial position that these groups adopt in the cyclohexane ring. In these conditions we obtained the corresponding *cis*-β-amino acid hydrochlorides, which were treated with propylene oxide in ethanol to yield the *cis*-β-amino acids **9a,b** in enantiomerically pure forms. These compounds were converted,

using diazomethane, into the β-amino methyl esters, which were cyclised to enantiopure *cis*-β-lactams **11a,b** according to the procedure previously described for the synthesis of the *trans*-β-lactams **10a, b**.

The proton NMR spectra of the final *cis* and *trans*-β-lactams showed several differences. For the *trans*-β-lactams **10a,b** the benzylic proton (H_{2a}) appeared as a doublet of doublets centred at 3.01 ppm, deshielded in comparison with the H_{2a} proton for the *cis*-β-lactams **11a,b** (doublet of doublets at 2.65 ppm with similar coupling constants). The rest of the protons attached to the cyclohexane ring of the *trans*-β-lactams are concentrated in the spectrum from 1.22 to 2.03 ppm, whereas for the *cis*-β-lactams the protons H_{3a} and H_{5a} exhibited chemical shifts at downfields (2.30 and 2.05 ppm, respectively). On the other hand, for both *cis*- and *trans*-isomers the methylene protons attached to the β-lactam ring showed a difference in their chemical shifts, the proton H_a (see Figure 1) appeared as a doublet, shielded with regard to proton H_b, but for the *trans*-β-lactams the protons H_a and H_b displayed a deshielding of the order of 0.2 ppm.

In order to explain these observations the conformers of lowest energy of both *cis* and *trans*-β-lactams were calculated by the AM1 semiempirical SCF-MO method[8] with standard parameters using the MOPAC 6.0 program, since it has been reported that standard AM1 SCF calculations predict quite well the geometry of the β-lactam ring[9]. The geometries of the most favorable conformers of **10** and **11** were the chair conformation, where the phenyl group adopts an equatorial position. These geometries with their corresponding calculated heats of formation are depicted in Figure 1.



cis-β-lactam
ΔH_f = -1.8 kcal/mol

trans-β-lactam
ΔH_f = -1.3 kcal/mol

Figure 1

From these geometries we have obtained the cartesian coordinates of protons H_{2a}, H_{3a}, H_{5a}, H_a and H_b, and have calculated the longe-range shielding effect of these protons due to the carbonyl and phenyl groups applying Pople's diagrams[10] and the values obtained are in agreement with those observed in the proton NMR spectra.

In conclusion, both enantiomers of conformationally constrained *cis* and *trans*-2-phenylcyclohexane-β-amino acids were obtained starting from the Diels-Alder cycloaddition between chiral (E)-2-cyanocinnamates and 1,3-butadiene, opening the way to a general procedure for the synthesis of 2-substituted cyclohexane-β-amino acids. Moreover, further cyclization of these amino acids led to the formation of the corresponding optically active β-lactams.

Acknowledgements: We are indebted to the *Dirección General de Investigación Científica y Técnica*, project PB91-0696 for its generous support. M. P. thanks the *Ministerio de Educación y Ciencia* for a FPI grant.

EXPERIMENTAL SECTION

Solvents were purified according to standard procedures. Analytical TLC was performed by using Polychrom SI F_{254} plates. Column chromatography was performed by using Silica gel 60 (230-400 mesh). ^1H and ^{13}C-NMR spectra were recorded on a Bruker ARX-300. Deuterated chloroform was used as a solvent with tetramethylsilane as the internal standard and in deuterated water with tetramethylsilane as the external standard using a coaxial microtube (the chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). The assignment of all separate signals in the ^1H-NMR spectra was made on the basis of coupling constants, selective proton-proton homonuclear decoupling experiments and proton-proton COSY experiments. Melting points were determined on a Büchi 530 and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240-C analyser and were in good agreement with the calculated values.

(1S, 6R)-Methyl 1-Cyano-6-phenyl-3-cyclohexene-1-carboxylate. 4a.

A solution of 1 M $TiCl_4$ in CH_2Cl_2 (10 mL, 10.0 mmol) was added to a solution of (E)-2-cyanocinnamate of (S)-ethyl lactate **2a** (2.73 g, 10.0 mmol) in dry CH_2Cl_2 (90 mL) kept under inert atmosphere. After stirring for 1 h at 0° C, a solution of 1,3-butadiene (5.40 g, 100 mmol) in dry CH_2Cl_2 (10 mL), at the same temperature, was added dropwise and the mixture was stirred for a further 72 h at 0° C. The reaction was quenched by the addition of solid $Na_2CO_3 \cdot 10H_2O$, the precipitate was filtered and the solution was evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with hexane-ethyl acetate (7:3) and the major cycloadduct **3a** was obtained in 85% yield, enantiomerically pure, as a white solid. Cycloadduct **3a** (2.77 g, 8.5 mmol) was refluxed with 10% KOH-EtOH (110 mL) for 15 h after which the solvent was removed. Water (50 mL) was added and the organic material extracted with CH_2Cl_2 (3 x 20 mL). The aqueous layer was acidified with 12 N HCl and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were evaporated *in vacuo* to yield 1.84 g (96%) of the corresponding carboxylic acid, which was esterified with a slight excess of a solution of diazomethane in Et_2O, at room temperature. After a few minutes, evaporation of the solvent afforded a residue, which was purified by silica gel column chromatography eluting with hexane-ethyl acetate (7:3) yielding quantitatively the required compound **4a** as an oil. Isolated yield, 1.95 g (81% from **2a**).

Found C: 74.79, H: 6.20, N: 5.62

Anal. Calc. for $C_{15}H_{15}NO_2$ C: 74.65, H: 6.27, N: 5.81

^1H-NMR($CDCl_3$): δ= 2.40(brd, 1H, $J_{5e\text{-}5a}$=18.3, H_{5e}); 2.63(dd, 1H, $J_{2e\text{-}2a}$=17.5, $J_{2e\text{-}3}$=5.3, H_{2e}); 2.75-2.78(m, 1H, H_{5a}); 2.94(ddd, 1H, $J_{2a\text{-}2e}$=17.5, $J_{2a\text{-}3}$=4.4, $J_{2a\text{-}4}$=2.2, H_{2a}); 3.23(dd, 1H, $J_{6a\text{-}5a}$=11.9, $J_{6a\text{-}5e}$=5.1, H_{6a}); 3.43(s, 3H, COOMe); 5.71-5.79(m, 1H, H_4); 5.90-5.97(m, 1H, H_3); 7.23-7.41(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 29.8, 35.0(C_2, C_5); 45.7(C_6); 49.4(C_1); 53.1(COOMe); 118.1(CN); 121.6, 127.3, 127.9, 128.1, 128.6, 138.8(C_3, C_4, Arom.); 169.0(COOMe).

(1R, 6S)-Methyl 1-Cyano-6-phenyl-3-cyclohexene-1-carboxylate. 4b.

1.98 g of compound **4b** (82%) was obtained in a similar way to that described for **4a**, starting from (E)-2-cyanocinnamate of (R)-pantolactone **2b** (2.85 g, 10.0 mmol).

Found C: 74.77, H: 6.18, N: 5.66

Anal. Calc. for $C_{15}H_{15}NO_2$ C: 74.65, H: 6.27, N: 5.81

(1S, 2R)-Methyl 1-Cyano-2-phenyl-1-cyclohexanecarboxylate. 5a.

A solution of cycloadduct **4a** (1.95 g, 8.1 mmol) in CH_2Cl_2 (20 mL) was hydrogenated at room temperature for 16 h with 10% palladium-carbon (150 mg) as a catalyst. Removal of the catalyst and the solvent gave quantitatively the compound **5a** as a white solid. M.p.: 85-7 °C

Found C: 74.17, H: 6.91, N: 5.60

Anal. Calc. for $C_{15}H_{17}NO_2$ C: 74.04, H: 7.05, N: 5.76

^{1}H-NMR($CDCl_3$): δ= 1.50('q"t', 1H, J_{4a-5a}~J_{4a-4e}~J_{4a-3a}=12.6, J_{4a-5e}~J_{4a-3e}=3.9, H_{4a}); 1.79('q"t', 1H, J_{5a-6a}~J_{5a-5e}~J_{5a-4a}=12.6, J_{5a-6e}~J_{5a-4e}=3.6, H_{5a}); 1.87-1.99(m, 3H, H_{3a} + H_{4e} + H_{5e}); 2.03-2.15(m, 2H, H_{3e} + H_{6a}); 2.20(brd, 1H, J_{6e-6a}=12.0, H_{6e}); 3.08(dd, 1H, J_{2a-3a}=12.6, J_{2a-3e}=3.0, H_{2a}); 3.51(s, 3H, COOMe); 7.27-7.31(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 21.8, 25.4, 28.7, 34.8(C_3, C_4, C_5, C_6); 49.1(C_2); 52.9(COOMe); 53.2(C_1); 117.9(CN); 127.8, 127.9, 128.5, 139.8(Arom.); 169.4(COOMe).

(1R, 2S)-Methyl 1-Cyano-2-phenyl-1-cyclohexanecarboxylate. 5b.

In a similar way to that described for **5a**, compound **5b** was quantitatively obtained, starting from methyl ester **4b** (1.98 g, 8.2 mmol).

Found C: 74.13, H: 7.13, N: 5.62

Anal. Calc. for $C_{15}H_{17}NO_2$ C: 74.04, H: 7.05, N: 5.76

(1S, 2R)-Methyl 1-Aminomethyl-2-phenyl-1-cyclohexanecarboxylate. 6a.

Method A: Cycloadduct **5a** (486 mg, 2.0 mmol) was dissolved in a solution of 10% NH_3/MeOH and hydrogenated at 75 °C and 55 atmospheres for 20 h with 10% palladium-carbon (530 mg) as a catalyst. Removal of the catalyst and the solvent gave the required compound **6a** accompanied by the corresponding secondary amine. This mixture of products was dissolved in CH_2Cl_2 (30 mL) and extracted with 2 N HCl (3 x 15 mL). The aqueous solution was basified with 10% NaOH to pH ~ 12 and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic solutions were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to yield 394 mg (80%) of β-amino ester **6a** as a crude oil, which was used in the next step without purification.

Method B: Cycloadduct **5a** (486 mg, 2.0 mmol) was dissolved in a solution of 10% NH_3/MeOH and hydrogenated at room temperature and atmospheric pressure for 20 h with Raney nickel (2 mL) as a catalyst. Removal of the catalyst and the solvent gave the required compound **6a**, which was purified in a similar way to that described in the previous method. Isolated yield 453 mg (92%).

^{1}H-NMR($CDCl_3$): δ= 1.41-2.16(m, 8H, H_{3a} + H_{3e} + H_{4a} + H_{4e} + H_{5a} + H_{5e} + H_{6a} + H_{6e}); 2.96(brs, 4H, CH_2NH_2); 3.19(dd, 1H, J_{2a-3a}=12.3, J_{2a-3e}=3.3, H_{2a}); 3.59(s, 3H, COOMe); 7.04-7.26(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 20.6, 26.0, 26.9, 29.7(C_3, C_4, C_5, C_6); 39.0(CH_2NH_2); 48.8, 51.5(C_2, COOMe); 52.2(C_1); 126.7, 127.8, 128.4, 141.8(Arom.); 176.4(COOMe).

(1R, 2S)-Methyl 1-Aminomethyl-2-phenyl-1-cyclohexanecarboxylate. 6b.

β-Amino ester **6b** was obtained as an oil in a similar way to that described for **6a**, starting from cycloadduct **5b** (483 mg, 2.0 mmol). Isolated yield, 409 mg (83%).

(1S, 2R)-1-Hydroxymethyl-2-phenyl-1-cyclohexanecarbonitrile. 7a.

A sodium borohydride solution (2.26 g, 40.0 mmol) in 9:1 THF-water (10 mL) was added to another solution of compound **5a** (972 mg, 4.0 mmol) in THF (15 mL). The reaction mixture was then heated at 50 °C for 3 h. Water (15 mL) was added and the excess of sodium borohydride was destroyed by the dropwise addition of 10% HCl solution. Tetrahydrofuran was eliminated under reduced pressure and the aqueous solution was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give 822 mg (95%) of compound **7a** as a crude oil, which was used in the next step without purification.

^{1}H-NMR($CDCl_3$): δ= 1.40('q''t', 1H, $J_{4a\text{-}5a}$~$J_{4a\text{-}4e}$~$J_{4a\text{-}3a}$=12.6, $J_{4a\text{-}5e}$~$J_{4a\text{-}3e}$=4.2, H_{4a}); 1.55-1.68(m, 2H, H_{6a} + OH); 1.73-1.96(m, 4H, H_{3e} + H_{4e} + H_{5a} + H_{5e}); 2.08('q'd, 1H, $J_{3a\text{-}4a}$~$J_{3a\text{-}3e}$~$J_{3a\text{-}2a}$=12.9, $J_{3a\text{-}4e}$=3.6, H_{3a}); 2.21(brd, 1H, $J_{6e\text{-}6a}$=12.9, H_{6e}); 2.61(dd, 1H, $J_{2a\text{-}3a}$=12.9, $J_{2a\text{-}3e}$=3.3, H_{2a}); 3.40(dd, 1H, $J_{a\text{-}b}$=10.8, $J_{a\text{-}OH}$=7.2, C$\underline{H_a}$$H_b$OH); 3.52(dd, 1H, $J_{b\text{-}a}$=10.8, $J_{b\text{-}OH}$=5.1, $CH_a\underline{H_b}$OH); 7.27-7.37(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 22.8, 25.9, 30.2, 33.5(C_3, C_4, C_5, C_6); 46.8(C_1); 47.8(C_2); 66.8(CH_2OH); 121.3(CN); 127.6, 128.0, 128.7, 140.6(Arom.).

(1R, 2S)-1-Hydroxymethyl-2-phenyl-1-cyclohexanecarbonitrile. 7b.

Compound **7b** was obtained as an oil in a similar way to that described for **7a**, starting from cycloadduct **5b** (975 mg, 4.0 mmol). Isolated yield, 805 mg (93%).

(1S, 2R)-1-Aminomethyl-2-phenyl-1-cyclohexanecarboxylic Acid. 8a.

Compound **6a** (124 mg, 0.5 mmol) was hydrolysed by refluxing for 16 h with 6 N HCl aqueous solution (15 mL). After filtration and extraction with CH_2Cl_2 (3 x 10 mL), the aqueous layer was evaporated *in vacuo* and EtOH (6 mL) and propylene oxide (2 mL) were added. The reaction mixture was refluxed for 2 h and the EtOH was removed *in vacuo*. The residue was suspended in CH_2Cl_2 (5 mL) and the white solid was filtered and dried to give 55 mg (46%) of β-amino acid **8a** as a white solid. $[\alpha]^{25}_D$(c = 1.6, 0.1 M TFA in H_2O) = +8.6 .

Found	C: 72.23, H: 8.21, N: 6.17
Anal. Calc. for $C_{14}H_{19}NO_2$	C: 72.10, H: 8.15, N: 6.00

^{1}H-NMR(D_2O-TFA): δ= 1.43-2.12(m, 8H, H_{3a} + H_{3e} + H_{4a} + H_{4e} + H_{5a} + H_{5e} + H_{6a} + H_{6e}); 3.08(d, 1H, $J_{a\text{-}b}$=12.0, C$\underline{H_a}$$H_b$$NH_2$); 3.29(dd, 1H, $J_{2a\text{-}3a}$=12.0, $J_{2a\text{-}3e}$=3.0, H_{2a}); 3.57(d, 1H, $J_{b\text{-}a}$=12.0, $CH_a\underline{H_b}NH_2$); 7.22-7.38(m, 5H, Arom.).

^{13}C-NMR(D_2O-TFA): δ= 19.8, 25.4, 26.0, 29.1(C_3, C_4, C_5, C_6); 37.5, 48.3, 49.7(C_1, C_2, CH_2NH_2); 127.5, 128.4, 128.6, 140.5(Arom.); 178.2(C$\underline{O}$OH).

(1R, 2S)-1-Aminomethyl-2-phenyl-1-cyclohexanecarboxylic Acid. 8b.

β-Amino acid **8b** was obtained as a white solid in a similar way to that described for **8a**, starting from β-Amino ester **6b** (126 mg, 0.5 mmol). Isolated yield, 51 mg (43%). $[\alpha]^{25}_D$(c = 2.0, 0.1 M TFA in H_2O) = -9.0

Found	C: 72.21, H: 8.23, N: 6.13
Anal. Calc. for $C_{14}H_{19}NO_2$	C: 72.10, H: 8.15, N: 6.00

(1R, 2R)-1-Aminomethyl-2-phenyl-1-cyclohexanecarboxylic Acid. 9a.

Triethylamine (366 mg, 3.6 mmol) was added to a solution of the alcohol **7a** (649 mg, 3.0 mmol) in CH_2Cl_2 (25 mL) cooled in ice. Methanesulphonyl chloride (413 mg, 3.6 mmol) was added dropwise and the solution stirred

at 0 °C for 30 min. Water (20 mL) was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give 851 mg (96%) of the corresponding mesylate as a white solid. M.p.: 74-6 °C

^{1}H-NMR($CDCl_3$): δ= 1.43('q''t', 1H, J_{4a-5a}~J_{4a-4e}~J_{4a-3a}=12.6, J_{4a-5e}~J_{4a-3e}=3.9, H_{4a}); 1.63('t'd, 1H, J_{6a-6e}~J_{6a-5a}=12.6, J_{6a-5e}=3.6, H_{6a}); 1.74-1.98(m, 4H, H_{3e} + H_{4e} + H_{5a} + H_{5e}); 2.11('q'd, 1H, J_{3a-4a}~J_{3a-3e}~J_{3a-2a}=12.6, J_{3a-4e}=3.3, H_{3a}); 2.28(brd, 1H, J_{6e-6a}=12.6, H_{6e}); 2.62(dd, 1H, J_{2a-3a}=12.6, J_{2a-3e}=3.0, H_{2a}); 2.96(s, 3H, $MeSO_2$); 3.97(s, 2H, CH_2O); 7.31-7.35(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 22.4, 25.6, 30.2, 33.8(C_3, C_4, C_5, C_6); 37.5($MeSO_2$); 44.7(C_1); 48.1(C_2); 71.4(CH_2O); 119.4(CN); 128.1, 128.2, 128.9, 139.3(Arom.).

This compound (851 mg, 2.9 mmol) was dissolved in 16:1 DMF-water (8 mL) and sodium azide (377 mg, 5.8 mmol) was added with stirring. After 24 h at 125 °C, DMF was evaporated *in vacuo*, Et_2O (25 mL) was added to the crude product, and the solution was filtered through a short silica gel column using Et_2O as eluent. After evaporation of the solvent, 686 mg of an oil was obtained, which was chromatographed on a silica gel column eluting with hexane-ethyl acetate (8:2) to afford 594 mg (85%) of the corresponding azidomethyl derivative. M.p.: 57-9 °C.

^{1}H-NMR($CDCl_3$): δ= 1.42('q''t', 1H, J_{4a-5a}~J_{4a-4e}~J_{4a-3a}=12.9, J_{4a-5e}~J_{4a-3e}=3.9, H_{4a}); 1.61('t'd, 1H, J_{6a-6e}~J_{6a-5a}=12.9, J_{6a-5e}=3.9, H_{6a}); 1.78-1.97(m, 4H, H_{3e} + H_{4e} + H_{5a} + H_{5e}); 2.07('q'd, 1H, J_{3a-4a}~J_{3a-3e}~J_{3a-2a}=12.6, J_{3a-4e}=3.6, H_{3a}); 2.17(brd, 1H, J_{6e-6a}=12.9, H_{6e}); 2.62(dd, 1H, J_{2a-3a}=12.6, J_{2a-3e}=3.0, H_{2a}); 3.18(d, 1H, J_{a-b}=12.3, $C\underline{H}_aH_bN_3$); 3.33(d, 1H, J_{b-a}=12.3, $CH_a\underline{H}_bN_3$); 7.32-7.37(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 22.8, 25.8, 30.2, 34.2(C_3, C_4, C_5, C_6); 45.2(C_1); 48.3(C_2); 56.6(CH_2N_3); 120.4(CN); 127.8, 128.2, 128.7, 139.8(Arom.).

This azide (594 mg, 2.5 mmol) was dissolved in MeOH (25 mL) and hydrogenated at 35 °C for 4 h with 10% palladium-carbon (102 mg) as a catalyst. Removal of the catalyst and the solvent gave 513 mg (97%) of the required compound (1R,2S)-1-aminomethyl-2-phenyl-1-cyclohexanecarbonitrile as a white solid. M.p.: 64-6 °C.

^{1}H-NMR($CDCl_3$): δ= 1.07(brs, 2H, NH_2); 1.33-1.48(m, 2H, H_{4a} + H_{6a}); 1.73-1.96(m, 4H, H_{3e} + H_{4e} + H_{5a} + H_{5e}); 2.06('q'd, 1H, J_{3a-4a}~J_{3a-3e}~J_{3a-2a}=12.6, J_{3a-4e}=3.3, H_{3a}); 2.19(brd, 1H, J_{6e-6a}=12.9, H_{6e}); 2.52(dd, 1H, J_{2a-3a}=12.6, J_{2a-3e}=3.0, H_{2a}); 2.54(d, 1H, J_{a-b}=13.5, $C\underline{H}_aH_bNH_2$); 2.73(d, 1H, J_{b-a}=13.5, $CH_a\underline{H}_bNH_2$); 7.27-7.37(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 23.1, 26.0, 30.8, 34.3(C_3, C_4, C_5, C_6); 47.4(C_1); 49.2, 49.6(C_2, CH_2NH_2); 122.0(CN); 127.5, 128.2, 128.6, 141.0(Arom.).

A solution of 6 N HCl (10 mL) and β-aminonitrile (513 mg, 2.4 mmol) was placed in a sealed-tube and the reaction was heated at 160 °C for 20 h. After filtration and extraction with Et_2O (3 x 10 mL), the aqueous layer was evaporated *in vacuo* and EtOH (9 mL) and propylene oxide (3 mL) were added. The reaction mixture was refluxed for 1 h and the precipitate was filtered and dried to give 389 mg (68%) of β-amino acid **9a** as a white solid. (54% from **7a**). $[\alpha]^{25}_D$(c = 2.3, 0.1 M TFA in H_2O) = -41.7 .

Found	C: 72.25, H: 8.23, N: 6.19
Anal. Calc. for $C_{14}H_{19}NO_2$	C: 72.10, H: 8.15, N: 6.00

^{1}H-NMR(D_2O-TFA): δ= 1.46-2.37(m, 8H, H_{3a} + H_{3e} + H_{4a} + H_{4e} + H_{5a} + H_{5e} + H_{6a} + H_{6e}); 2.76(dd, 1H, J_{2a-3a}=12.0, J_{2a-3e}=3.0, H_{2a}); 3.01(d, 1H, J_{a-b}=12.0, $C\underline{H}_aH_bNH_2$); 3.24(d, 1H, J_{b-a}=12.0, $CH_a\underline{H}_bNH_2$); 7.26-7.46(m, 5H, Arom.).

^{13}C-NMR(D_2O-TFA): δ= 21.2, 25.1, 28.3, 31.5(C_3, C_4, C_5, C_6); 47.6, 47.8, 50.2(C_1, C_2, CH_2NH_2); 127.6, 128.7, 128.8, 141.3(Arom.); 176.6($\underline{C}OOH$).

(1S, 2S)-1-Aminomethyl-2-phenyl-1-cyclohexanecarboxylic Acid. 9b.

β-Amino acid **9b** was obtained as a white solid in a similar way to that described for **9a**, starting from alcohol **7b** (645 mg, 3.0 mmol). Isolated yield, 391 mg (56%). $[\alpha]^{25}_D$(c = 2.6, 0.1 M TFA in H_2O) = +42.2

Found	C: 72.22, H: 8.26, N: 6.14
Anal. Calc. for $C_{14}H_{19}NO_2$	C: 72.10, H: 8.15, N: 6.00

(1S, 2R)-2-Phenylcyclohexanespiro-3'-(2'-azetidinone). 10a.

To a stirred solution of methylmagnesium bromide (0.5 mL of 3.0 M solution in Et_2O, 1.5 mmol) in Et_2O (20 mL) was added dropwise compound **6a** (122 mg, 0.5 mmol) in Et_2O (5 mL) and the mixture was stirred for 2 h at room temperature, in an inert atmosphere. When the reaction was finished an aqueous solution of 10% NH_4Cl (25 mL) was added and the mixture was stirred until the two layers became clear. The aqueous layer was separated and extracted with Et_2O (2 x 10 mL). The combined Et_2O solutions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to yield the corresponding β-lactam **10a** as a crude oil, which was chromatographed on a silica gel column eluting with hexane-ethyl acetate (6:4) to afford 95 mg (90%) of enantiomerically pure β-lactam **10a** as a white solid. $[\alpha]^{25}_D$(c = 1.8, $CHCl_3$) = +45.0 . M.p.: 145-7 °C

Found	C: 78.22, H: 7.81, N: 6.63
Anal. Calc. for $C_{14}H_{17}NO$	C: 78.14, H: 7.90, N: 6.51

^{1}H-NMR($CDCl_3$): δ= 1.23-1.50(m, 2H, H_{4a} + H_{6a}); 1.66('q'd, 1H, $J_{3a\text{-}4a}$~$J_{3a\text{-}3e}$~$J_{3a\text{-}2a}$=12.6, $J_{3a\text{-}4e}$=3.3, H_{3a}); 1.82-2.03(m, 5H, H_{3e} + H_{4e} + H_{5a} + H_{5e} + H_{6e}); 2.95(d, 1H, $J_{a\text{-}b}$=5.7, CH_aH_bNH); 3.01(dd, 1H, $J_{2a\text{-}3a}$=12.6, $J_{2a\text{-}3e}$=3.0, H_{2a}); 3.11(d, 1H, $J_{b\text{-}a}$=5.7, CH_aH_bNH); 5.36(brs, 1H, NH); 7.18-7.39(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 23.4, 25.8, 28.3, 32.6(C_3, C_4, C_5, C_6); 43.9(CH_2NH); 44.2(C_2); 63.2(C_1); 126.6, 128.1, 128.6, 141.1(Arom.); 173.7(CONH).

(1R, 2S)-2-Phenylcyclohexanespiro-3'-(2'-azetidinone). 10b.

In a similar way to that described for **10a**, starting from β-amino ester **6b** (123 mg, 0.5 mmol), enantiomerically pure β-lactam **10b** was obtained as a white solid in 92% yield. $[\alpha]^{25}_D$(c = 1.9, $CHCl_3$) = -46.3

Found	C: 78.20, H: 8.01, N: 6.60
Anal. Calc. for $C_{14}H_{17}NO$	C: 78.14, H: 7.90, N: 6.51

(1R, 2R)-2-Phenylcyclohexanespiro-3'-(2'-azetidinone). 11a.

Solid β-amino acid **9a** (233 mg, 1.0 mmol) was dissolved in 4:1 THF-2N HCl (5 mL) and the reaction mixture was evaporated *in vacuo* to obtain the amino acid hydrochloride, which was dissolved in MeOH (10 mL) and a solution of diazomethane in Et_2O was added, at 0 °C. After a few minutes, evaporation of the solvent afforded a residue of methyl ester hydrochloride, which was dissolved in 1 N HCl (10 mL), basified with an aqueous 2N NaOH solution and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give 238 mg (96%) of the corresponding (1R, 2R)-methyl 1-aminomethyl-2-phenyl-1-cyclohexanecarboxylate as an oil.

^{1}H-NMR($CDCl_3$): δ= 1.31-1.98(m, 8H, NH_2 + H_{3e} + H_{4a} + H_{4e} + H_{5a} + H_{5e} + H_{6a}); 2.15-2.27(m, 2H, H_{3a} + H_{6e}); 2.56(dd, 1H, $J_{2a\text{-}3a}$=12.3, $J_{2a\text{-}3e}$=3.3, H_{2a}); 2.58(d, 1H, $J_{a\text{-}b}$=13.2, $CH_aH_bNH_2$); 2.99(d, 1H, $J_{b\text{-}a}$=13.2, $CH_aH_bNH_2$); 3.59(s, 3H, COOMe); 7.17-7.28(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 22.6, 26.1, 29.3, 33.1(C_3, C_4, C_5, C_6); 50.5, 50.8, 51.0(C_2, CH_2NH_2, COOMe); 52.3(C_1); 126.8, 128.3, 128.7, 142.2(Arom.); 173.9(COOMe).

In a similar way to that described for **10a**, starting from this β-amino ester (238 mg, 0.9 mmol), enantiomerically pure β-lactam **11a** was obtained as a white solid in 92% (88% from **9a**) yield. $[\alpha]^{25}_D$(c = 1.0, $CHCl_3$) = -131.1 . M.p.: 144-6 °C

Found C: 78.20, H: 7.85, N: 6.62

Anal. Calc. for $C_{14}H_{17}NO$ C: 78.14, H: 7.90, N: 6.51

^{1}H-NMR($CDCl_3$): δ= 1.36('q''t', 1H, $J_{4a\text{-}5a}$~$J_{4a\text{-}4e}$~$J_{4a\text{-}3a}$=12.9, $J_{4a\text{-}5e}$~$J_{4a\text{-}3e}$=3.6, H_{4a}); 1.71-1.815(m, 3H, H_{3e} + H_{5e} + H_{6a}); 1.93(brd, 1H, $J_{4e\text{-}4a}$=12.9, H_{4e}); 2.05('q''t', 1H, $J_{5a\text{-}6a}$~$J_{5a\text{-}5e}$~$J_{5a\text{-}4a}$=12.9, $J_{5a\text{-}6e}$~$J_{5a\text{-}4e}$=3.6, H_{5a}); 2.20(brd, 1H, $J_{6e\text{-}6a}$=14.2, H_{6e}); 2.30('q'd, 1H, $J_{3a\text{-}4a}$~$J_{3a\text{-}3e}$~$J_{3a\text{-}2a}$=12.9, $J_{3a\text{-}4e}$=3.6, H_{3a}); 2.65(dd, 1H, $J_{2a\text{-}3a}$=12.9, $J_{2a\text{-}3e}$=3.3, H_{2a}); 2.74(d, 1H, $J_{a\text{-}b}$=5.4, $C\underline{H_a}H_bNH$); 2.89(d, 1H, $J_{b\text{-}a}$=5.4, $CH_a\underline{H_b}NH$); 5.39(brs, 1H, NH); 7.23-7.34(m, 5H, Arom.).

^{13}C-NMR($CDCl_3$): δ= 23.1, 26.5, 30.2, 34.6(C_3, C_4, C_5, C_6); 46.1(CH_2NH); 49.3(C_2); 61.5(C_1); 126.8, 128.3, 128.7, 142.2(Arom.); 173.9(CONH).

(1S, 2S)-2-Phenylcyclohexanespiro-3'-(2'-azetidinone). 11b.

In a similar way to that described for **11a**, starting from β-amino acid **9b** (232 mg, 1.0 mmol), enantiomerically pure β-lactam **11b** was obtained as a white solid in 84% yield. $[\alpha]^{25}_D$(c = 1.4, $CHCl_3$) = +132.7 .

Found C: 78.24, H: 8.03, N: 6.65

Anal. Calc. for $C_{14}H_{17}NO$ C: 78.14, H: 7.90, N: 6.51

REFERENCES AND NOTES

1. Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.
2. (a) Recent reviews on the asymmetric synthesis of α-amino acids: Williams, R. M. *Synthesis of Optically Active α-Amino Acids* Pergamon Press: Oxford 1989. Williams, R. M. *Aldrichimica Acta* **1992**, *25*, 11. Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.
   (b) Recent reviews on the asymmetric synthesis of β-amino acids: Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3. Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.
   (c) Recent reviews on the asymmetric synthesis of constrained amino acids: Gante, J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699. Liskamp, R. M. J. *Recl. Trav. Chim. Pays-Bas* **1994**, *1*, 113.
3. (a) Avenoza, A.; Cativiela, C.; París, M.; Peregrina, J. M. *J. Org. Chem.* **1994**, *59*, 7774. (b) Avenoza, A.; Cativiela, C.; Gimeno, S.; Lahoz, F. J.; Mayoral, J. A.; Peregrina, J. M. *J. Org. Chem.* **1992**, *57*, 4664. (c) Avenoza, A.; Cativiela, C.; Mayoral, J. A.; Peregrina, J. M. *Tetrahedron: Asymmetry* **1992**, *3*, 913. (d) Avenoza, A.; Cativiela, C.; Mayoral, J. A.; Peregrina, J. M.; Sinou, D. *Tetrahedron: Asymmetry* **1990**, *1*, 765.
4. Rabinovitz, M., in Rappoport, Z. *The Chemistry of the Cyano Group* Interscience: New York 1970. pp 307-340.
5. Rylander, P. N. *Hydrogenation Methods* Academic Press: London 1985. pp 94-103.
6. (a) Freifelder, M. *J. Am. Chem. Soc.* **1960**, *82*, 2386. (b) Freifelder, M.; Ng, Y. H. *J. Pharm. Sci.* **1965**, *54*, 1204. (c) Freifelder, M. *J. Am. Chem. Soc.* **1944**, *66*, 876.
7. (a) Ed. Georg, G. I. *The Organic Chemistry of β-Lactams* VCH: New York 1993. (b) Mukerjee, A. K.; Srivastava, R. C. *Synthesis* **1973**, 327.
8. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
9. Cossio, F. P.; Ugalde, J. M.; López, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995.
10. (a) Pople, J. A. *J. Chem. Phys.* **1962**, *37*, 60. (b) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* Pergamon Press: Oxford 1972. pp 88-92. (c) Günter, H. *NMR Spectroscopy* Wiley: New York 1987.

(*Received in UK* 1 *May* 1995)