Asymmetric Diels–Alder Reactions of Chiral (*E*)-2-Cyanocinnamates. 2. Synthesis of the Four 1-Amino-2-phenyl-1-cyclohexanecarboxylic Acids in Enantiomerically Pure Form

Carlos Cativiela*

Departamento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza, CSIC, 50009, Zaragoza, Spain

Alberto Avenoza, Miguel París, and Jesús M. Peregrina

Departamento de Química (Area: Orgánica); Sección: Ciencias; Universidad de La Rioja, 26001, Logroño, Spain

Received July 18, 1994[⊗]

High and complementary diastereoselectivities were obtained in the asymmetric Diels–Alder reactions of chiral (*E*)-2-cyanocinnamates with butadiene when (*S*)-ethyl lactate and (*R*)-pantolactone were used as chiral auxiliaries in the presence of $TiCl_4$. The most selective reactions allowed the synthesis of the cycloadducts **2a** and **3b**, whose absolute configurations were assigned by an X-ray diffraction study of diastereoisomer **3b**. The hydrolysis and subsequent hydrogenation of the stereoisomers gave the corresponding enantiomeric cyanocarboxylic acids. From these products the four 1-amino-2-phenyl-1-cyclohexanecarboxylic acids were synthesized in enantiomerically pure form following a protocol with stereocontrolled and stereodivergent transformations.

Introduction

The interest in synthesizing biologically active products containing quaternary carbon atoms has notably increased over the last decade.[1] The interesting properties of α-amino acids with conformational rigidity, in particular C_α methyl and α,α-disubstituted series, have recently attracted the attention of numerous research groups.[2] The description of new synthetic procedures and new products is a subject of recent interest, especially when compounds can be isolated in the enantiomerically pure form. In the course of our research on the asymmetric synthesis of new α-amino acids with conformational rigidity we have recently reported that unsaturated 5(4*H*)-oxazolones behave as excellent dienophiles in the synthesis of 2-substituted-1-aminocyclohexanecarboxylic acids in a racemic form;[3] although, so far, the use of different chiral catalysts has not allowed the synthesis of each stereoisomer. We have previously reported that chiral (*E*)-2-cyanocinnamates are excellent dienophiles in asymmetric Diels–Alder reactions,[4] allowing the synthesis of chiral products containing quaternary carbon atoms and also that (*S*)-ethyl lactate and (*R*)-pantolactone are excellent and complementary chiral auxiliaries. In this article we describe the use of this methodology to prepare the four stereoisomers of 1-amino-2-phenyl-1-cyclohexanecarboxylic acid using the appropriate degradation processes.

Results and Discussion

Chiral dienophiles **1a,b** were prepared according to the previously reported procedure[4] and were reacted with 1,3-butadiene (Scheme 1), under a variety of conditions. In the absence of a catalyst no reaction occurred and, although several catalysts were tried ($AlMe_3$, $AlClEt_2$, $AlCl_2Et$, $AlCl_3$, $SnCl_4$, $MgBr_2$, $ZnCl_2$, $BF_3{\cdot}Et_2O$, and Eu(tfc)$_3$), reaction was only observed when $TiCl_4$ was employed as the catalyst. In order to find suitable conditions for analyzing the results of the Diels–Alder reactions, the major cycloadducts **2a, 3b** were hydrolyzed with 10% KOH–ethanol, to give the corresponding enantiomeric carboxylic acids **4a,b**. These acids were transformed into the minor cycloadducts **2b**, **3a** by esterification with the chiral alcohols (*S*)-ethyl lactate and (*R*)-pantolactone in the presence of DCC and DMAP[5] (Scheme 2). In this way, the results of the Diels–Alder reactions could be analyzed by HPLC[6] and, in some cases, were

[⊗] Abstract published in *Advance ACS Abstracts,* November 15, 1994.

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(6) Entries 1–10: percentage conversion and diastereofacial selectivity (**2a/3a**) were determined by HPLC using a 90:10 hexane–*tert*-butyl methyl ether mixture as the mobile phase. Flow rate: 2.0 mL/min. Retention times: **3a** = 3.65 min, **2a** = 4.46 min, **1a** = 4.99 min. Detection: UV at 200 nm. Entries 11–13: Percentage conversion and diastereofacial selectivity (**2b/3b**) were determined by HPLC using a 65:35 hexane–*tert*-butyl methyl ether mixture as the mobile phase. Flow rate: 1.0 mL/min. Retention times: **2b** = 6.08 min, **3b** = 7.11 min, **1b** = 9.15 min. Detection: UV at 200 nm.

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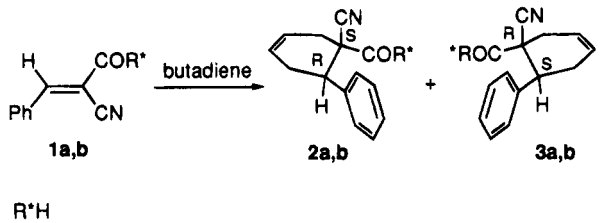
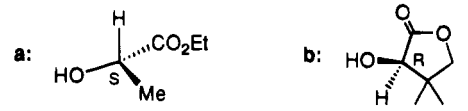
Scheme 1



R*H



Scheme 2

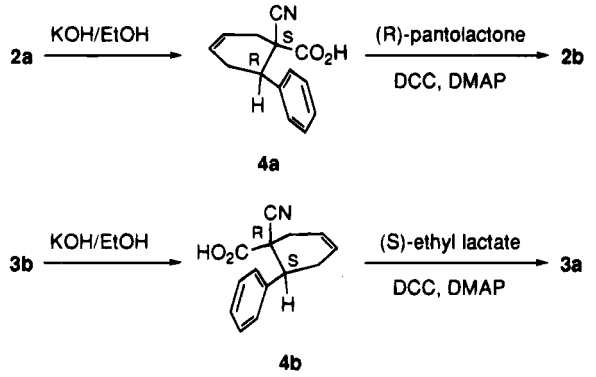


Table 1. Results Obtained from the Diels–Alder Cycloadditions between Dienophiles 1a,b and 1,3-Butadiene

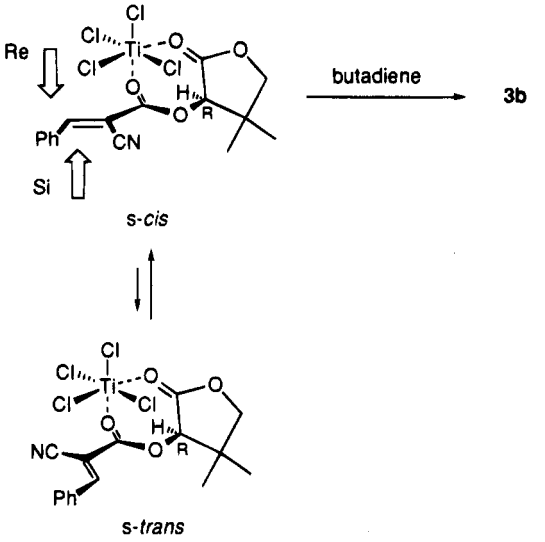
entry	dienophile (mmol/mL)[a]	$TiCl_4$ (equiv)	T (°C)	t (h)	convn (%)[b]	2a/3a[c]	2b/3b[c]
1	**1a** (0.03)	0.25	0	72	4	84:16	
2	**1a** (0.03)	0.50	0	72	14	91:9	
3	**1a** (0.03)	0.75	0	72	61	90:10	
4	**1a** (0.03)	1.00	0	72	91	90:10[d]	
5	**1a** (0.03)	1.50	0	72	83	86:14[d]	
6	**1a** (0.03)	1.00	20	72	89	89:11	
7	**1a** (0.03)	1.00	−25	72	44	93:7	
8	**1a** (0.06)	1.00	0	72	68	89:11	
9	**1a** (0.09)	1.00	0	48	96	92:8[d]	
10	**1a** (0.09)	1.00	−25	72	39	94:6	
11	**1b** (0.09)	1.00	−25	48	10		3:97[d]
12	**1b** (0.09)	1.00	0	60	95		2:98[d]
13	**1b** (0.09)	1.00	20	48	80		12:88[d]

[a] All reactions were carried out in CH_2Cl_2 with a ratio diene/dienophile = 10.0. [b] Determined by HPLC using a Hypersil Silica column (5 μm, 4.6 mm i.d. × 200 mm) and monitored, at 200 nm, using a diode array detector. [c] See ref 4. [d] Diastereofacial selectivity were confirmed by integration of the ^{1}H-NMR signals for the methine protons of the esters.

further confirmed by ^{1}H-NMR. In order to establish the stereochemistry of one of the diastereoisomers, the product of the most selective cycloaddition between dienophile **1b** and 1,3-butadiene (entry 12, Table 1) was purified by column chromatography and repeatedly recrystallized until constant optical rotation was obtained to give the pure diastereoisomer **3b**, and its absolute configuration was then determined by X-ray analysis.[17]

The results obtained in the Diels–Alder reaction, determined by HPLC, are summarized in Table 1 and show the influence of the reaction conditions on the conversion and diastereoselectivity (**2/3**). It can be seen in Table 1 that in catalyzed Diels–Alder reactions, using $TiCl_4$ as a catalyst, good conversions could be obtained using equimolar quantities of $TiCl_4$. Lesser amounts of catalyst made the reaction too slow to be useful and with higher amounts polymerization of the diene was observed. In all cases, diastereofacial selectivities were slightly improved working at lower temperatures, but under these conditions the cycloaddition rate is very low. The best results were obtained when the reaction was carried out at 0 °C with a catalyst ratio $TiCl_4$/dienophile = 1.00 and a dienophile concentration of 0.09 mmol/mL (entries 9 and 12). Under these conditions high conversions and very high diastereofacial selectivities can be obtained. The sense and degree of face selectivity is the same as that previously observed for cyclopentadiene.[4]

Scheme 3



These results, and the sense of the asymmetric induction, agree with the model of $TiCl_4$–dienophile chelate complexes, proposed and confirmed by Helmchen[7] to explain the results obtained in the cycloadditions of acrylates of (*S*)-ethyl lactate and (*R*)-pantolactone with 1,3-butadiene. It is expected that a similar, seven-membered chelate complex between the dienophile and the catalyst is formed. The absolute configuration of the pure diastereoisomer **3b**, determined by X-ray analysis, suggests that either in the s-*cis*/s-*trans* conformational equilibrium there is a great preference for the s-*cis* conformer or that this conformer is more reactive than the s-*trans* conformer. In this situation, the high diastereoselectivity observed when (*R*)-pantolactone is used as a chiral auxiliary (entries 11 and 12) can be explained by the preferential approach of the diene to the *si* face of the enoate moiety (Scheme 3).

From the major cycloadducts **2a**, **3b** (entries 9 and 12) and following a protocol with stereocontrolled transformations, we have synthesized the four 1-amino-2-phenyl-1-cyclohexanecarboxylic acids, analogues of phenylalanine, in enantiomerically pure form. The synthesis of these chiral α-amino acids from cycloadducts **4a,b** obtained by alkaline hydrolysis of **2a** and **3b**, respectively, is outlined in Scheme 4. Unsaturated carboxylic acids **4a,b** were hydrogenated over palladium–carbon to give saturated carboxylic acids **5a,b**, which were repeatedly recrystallized until constant optical rotations were obtained. We have tested the enantiomeric purity of these carboxylic acids by means of ^{1}H-NMR, using a europium-

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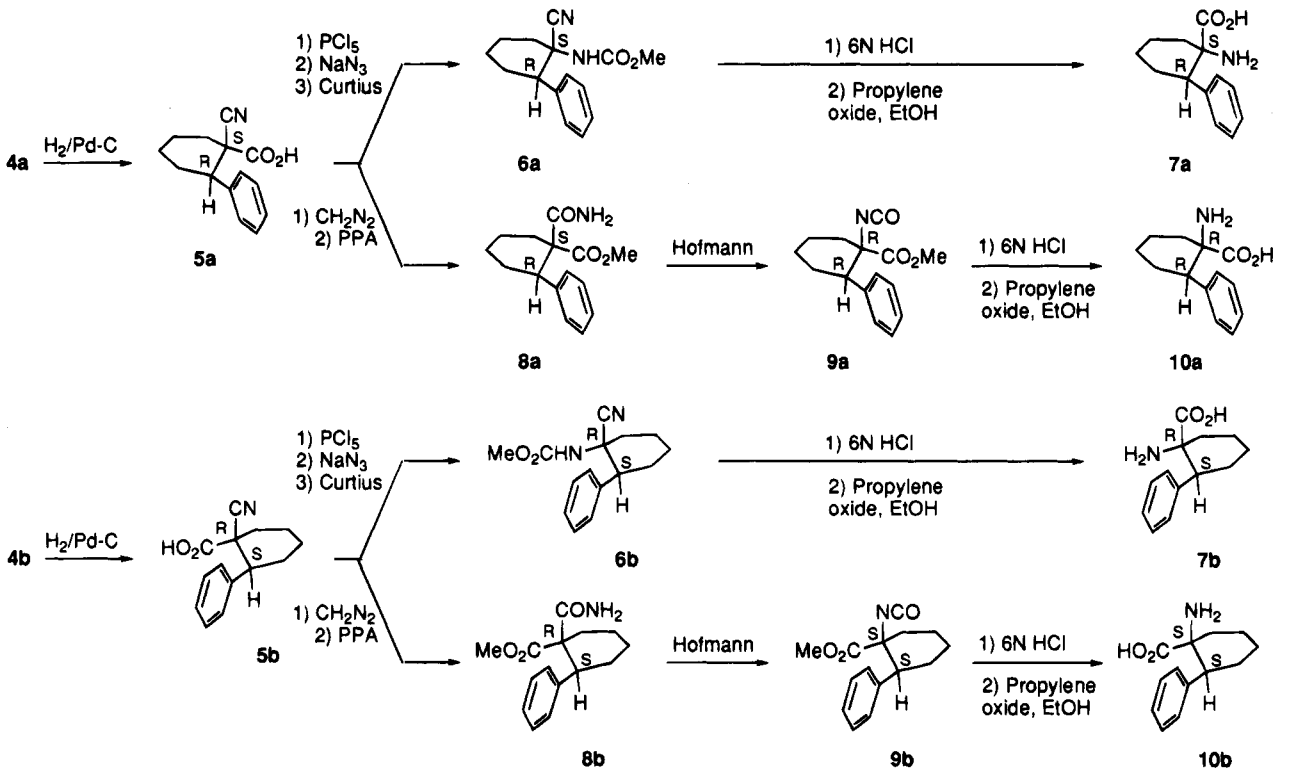
Scheme 4



(III) chelate as a chiral shift reagent[8] and the corresponding methyl esters, which were synthesized from carboxylic acids **5a,b** by addition of diazomethane in Et_2O at room temperature.

Treatment of both enantiomers **5a,b** with PCl_5 followed by NaN_3 gave the corresponding acyl azides, which were converted into carbamates **6a,b** by means of Curtius rearrangement. Further hydrolysis (in 6 N HCl) of the cyano and carbamate groups of compounds **6a,b** to give carboxyl and amino groups, respectively, was followed by treatment with propylene oxide in ethanol to yield optically active α-amino acids **7a,b**, which had identical optical rotation values, but were opposite in sign.

On the other hand, to synthesize the other α-amino acids, in which the phenyl and the amino groups adopt a *cis* configuration, we had to transform the cyano groups of compounds **5a,b** into amide groups, followed by selective transformation of these amides **8a,b** into the required amino acids **10a,b**.

The partial hydrolysis of nitriles into amides has been widely described in the literature,[9] but in our case, when we attempted to hydrolyze the cyano group of the carboxylic acids **5a,b** in alkaline media[10] under various conditions (NaOH or KOH/H_2O_2 at 60 °C, NH_4OH/H_2O_2 at 60 °C, Na_2O_2/DMSO/nitrobenzene at room temperature, $Na_2CO_3/NaHCO_3/H_2O_2$ at 50 °C, and Na_2CO_3/DMSO/H_2O_2 at room temperature), reaction did not occur. Alternative methods investigated in acid media[11] or using a catalyst[12] such as $Hg(OAc)_2$, MnO_2, or $Bu_4N^+Br^-$ gave the same results. Only with PPA[13] at 110 °C did we detect the formation of the amide product in very low yield. The main products of this reaction arise from to the intramolecular Friedel–Crafts acylation[14] on the phenyl substituent attached to C_2 of the cyclohexane ring. Nevertheless, when we tried the hydrolysis in PPA with methyl carboxylates, quantitatively synthesized from carboxylic acids **5a,b** using diazomethane, the cyano groups were hydrated, allowing the synthesis of the amides **8a,b** in good yields.[15]

Selective Hofmann rearrangement of the amides **8a,b** by treatment with $Hg(OAc)_2$, methanol, and NBS in DMF

(8) Different shifts for the methoxycarbonyl groups of the methyl ester compounds arising from carboxylic acids **5a,b** have been observed when a molar ratio Eu(tfc)$_3$/substrate = 0.1 and [substrate] = 0.2 mmol/mL in $CDCl_3$ at 20 °C were used. (**5a,b**: without lanthanide δ(CO_2CH_3) = 3.51 ppm; **5a**: with lanthanide δ(CO_2CH_3) = 3.88 ppm; **5b**: with lanthanide δ(CO_2CH_3) = 3.93 ppm).

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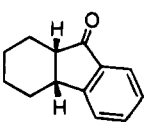
(15) The hydrolysis in PPA of the methyl carboxylates, starting from carboxylic acids **5a,b**, gave rise to the desired amides **8a,b** (62%) accompanied by the product **i**, arise from intramolecular Friedel–Crafts and further decarboxylation: 12% yield, oil. ^{1}H-NMR ($CDCl_3$) δ: 1.16–1.81(m, 6H); 2.04–2.17(m, 2H); 2.73–2.79(m, 1H); 3.34–3.42(m, 1H); 7.27–7.80(m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 22.4; 22.7; 23.1; 31.4; 38.8; 48.5; 123.9; 124.9; 127.3; 134.3; 135.6; 158.4; 208.0. Anal. Calcd for $C_{13}H_{14}O$ C: 83.82, H: 7.58. Found C: 83.99, H: 7.69. The structure assignment for **i** is supported by selective proton-proton homonuclear decoupling experiments and a proton–proton COSY experiment.



i

led to the formation of the isocyanates **9a,b**, instead of the corresponding carbamates. These isocyanates were subsequently converted into the optically active α-amino acids **10a,b** according to the hydrolysis procedure previously described for the synthesis of the other α-amino acids **7a,b**.

In summary, we have shown that the Diels–Alder reaction between 1,3-butadiene and (*E*)-2-cyanocinnamic chiral esters, using (*S*)-ethyl lactate and (*R*)-pantolactone as chiral auxiliaries, is the key step to the enantioselective synthesis of the corresponding cycloadducts **5a,b**. From these products, following a stereodivergent synthesis, the four conformationally restricted 1-amino-2-phenyl-1-carboxylic acids, analogues of phenylalanine, can be obtained in enantiomerically pure form.

Experimental Section

All manipulations with air-sensitive reagents were carried out under a dry argon atmosphere using standard Schlenk techniques. Solvents were purified according to standard procedures. Lewis acids and other chemical reagents were purchased from the Aldrich Chemical Co. Organic solutions were dried over anhydrous Na_2SO_4 and, when necessary, were concentrated under reduced pressure using a rotary evaporator. Analytical TLC was performed by using Polychrom SI F_{254} plates. Column chromatography was performed by using Kieselgel 60 (230–400 mesh). ^{1}H and ^{13}C-NMR spectra[16] were recorded in $CDCl_3$ with TMS as the internal standard and in D_2O–TFA with TMS as the external standard using a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in hertz). Melting points are uncorrected. Optical rotations were measured in 1 and 0.5 dm cells of 1 and 3.4 mL capacity, respectively. IR spectra were recorded on a Perkin Elmer 883 spectrometer; ν_{max} (cm^{-1}) is given for the main absorption bands.

Asymmetric Diels–Alder Cycloadditions. General Procedure. The catalyst was added, under an inert atmosphere, to a solution of chiral dienophile (1.0 mmol) in CH_2Cl_2 (7 mL). After being stirred for 1 h at room temperature, the solution was cooled to the reaction temperature (Table 1) and a solution of butadiene (540 mg, 10.0 mmol) in CH_2Cl_2 (3 mL) was added. The reaction was stirred for the time reported in Table 1 and then quenched by the addition of $Na_2CO_3 \cdot 10H_2O$. The mixture was filtered, and the filtrate analyzed by HPLC or ^{1}H-NMR following removal of the solvent.

(1*S*,6*R*)-1-Cyano-6-phenyl-3-cyclohexene-1-carboxylate of (*S*)-Ethyl Lactate. 2a. This compound was obtained from the (*E*)-2-cyanocinnamate of (*S*)-ethyl lactate **1a** (2.73 g, 10.0 mmol) following the general procedure described above for the asymmetric Diels–Alder reaction (1 equiv of $TiCl_4$, 0 °C, 3 days). The reaction mixture was treated with $Na_2CO_3 \cdot 10H_2O$ and filtered, and the solvent was removed. The major cycloadduct **2a** was purified by silica gel column chromatography, eluting with hexane–EtOAc (6:4). Compound **2a** was obtained as a white solid in 92% yield. Mp: 53–5 °C. IR: 2247(CN); 1739(2CO). ^{1}H-NMR ($CDCl_3$) δ: 1.18(t, 3H, J = 7.1); 1.36(d, 3H, J = 7.1); 2.45(brd, 1H, J = 18.4); 2.63–2.75(m, 2H); 3.01(brd, 1H, J = 17.8); 3.35(dd, 1H, J = 11.3, J = 5.5); 4.02–4.14(m, 2H); 4.89(q, 1H, J = 7.1); 5.73–5.78(m, 1H); 5.92–5.96(m, 1H); 7.24–7.42(m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 14.0; 16.5; 30.8; 35.4; 44.6; 49.7; 61.5; 70.2; 117.9; 121.7; 127.5; 127.9; 128.0; 128.6; 139.2; 167.5; 169.4. Anal. Calcd for $C_{19}H_{21}NO_4$ C: 69.69, H: 6.47, N: 4.28. Found C: 69.56, H: 6.36, N: 4.33.

(1*R*,6*S*)-1-Cyano-6-phenyl-3-cyclohexene-1-carboxylate of (*R*)-Pantolactone. 3b. Starting from the (*E*)-2-cyanocinnamate of (*R*)-pantolactone **1b** (2.85 g, 10.0 mmol) and following the same procedure as described for **2a**, the major cycloadduct **3b** was obtained, after purification and recrystallization from cyclohexane–$CHCl_3$, as a white solid in 88% yield. Mp: 116–8 °C. IR: 2247(CN); 1744(CO); 1734(CO). ^{1}H-NMR ($CDCl_3$) δ: 0.90(s, 6H); 2.48(brd, 1H, J = 18.3); 2.57–2.69(dddd, 1H, J = 18.3, J = 11.4, J = 4.2, J = 2.4); 2.75(dd, 1H, J = 17.7, J = 5.1); 3.00(ddd, 1H, J = 17.7, J = 4.2, J = 2.4); 3.34(dd, 1H, J = 11.4, J = 5.4); 3.89(brs, 2H); 5.09(s, 1H); 5.74–5.79(m, 1H); 5.92–5.96(m, 1H); 7.24–7.43(m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 19.4; 22.4; 31.7; 35.7; 39.9; 44.9; 49.2; 76.0; 76.6; 117.8; 121.6; 127.5; 127.6; 128.0; 128.9; 139.2; 167.6; 170.6. Anal. Calcd for $C_{20}H_{21}NO_4$ C: 70.77, H: 6.24, N: 4.13. Found C: 70.62, H: 6.15, N: 4.07.

(1*S*,6*R*)-1-Cyano-6-phenyl-3-cyclohexene-1-carboxylic Acid. 4a. Cycloadduct **2a** (3.00 g, 9.2 mmol) was refluxed with 10% KOH–EtOH (110 mL) for 15 h and the solvent was removed. Water (50 mL) was added and the organic material extracted with CH_2Cl_2 (3 × 20 mL). The aqueous layer was acidified with 12 N HCl and extracted with CH_2Cl_2 (3 × 20 mL). The organic solution was evaporated *in vacuo* to yield 2.01 g (96%) of carboxylic acid **4a** as a white solid. Mp: 104–6 °C. IR: 2242(CN); 1710(CO). ^{1}H-NMR ($CDCl_3$) δ: 2.39(brd, 1H, J = 18.1); 2.63–2.70(m, 2H); 2.85(brd, 1H, J = 15.4); 3.22-(dd, 1H, J = 11.7, J = 5.1); 5.71–5.76(m, 1H); 5.92–5.97(m, 1H); 7.24–7.37(m, 5H); 8.65(brs, 1H). ^{13}C-NMR ($CDCl_3$) δ: 30.1; 35.1; 45.1; 49.5; 117.6; 121.3; 127.5; 128.0; 128.1; 128.7; 138.6; 173.3. Anal. Calcd for $C_{14}H_{13}NO_2$ C: 73.98, H: 5.77, N: 6.17. Found C: 73.87, H: 5.66, N: 6.06.

(1*R*,6*S*)-1-Cyano-6-phenyl-3-cyclohexene-1-carboxylic Acid. 4b. Carboxylic acid **4b** was obtained as a white solid in a similar way to that described for **4a**, starting from cycloadduct **3b** (2.98 g, 8.8 mmol). Isolated yield, 1.91 g (95%). Anal. Calcd for $C_{14}H_{13}NO_2$ C: 73.98, H: 5.77, N: 6.17. Found C: 73.90, H: 5.68, N: 6.03.

(1*S*,6*R*)-1-Cyano-6-phenyl-3-cyclohexene-1-carboxylate of (*R*)-Pantolactone. 2b. (*R*)-Pantolactone (65 mg, 0.5 mmol) and DMAP (11 mg, 0.1 mmol) were added to a solution of carboxylic acid **4a** (113 mg, 0.5 mmol) in CH_2Cl_2 (5 mL). DCC (113 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (5 mL) and added dropwise to the above solution at 0 °C. After 1 h at 0 °C the mixture was allowed to warm to room temperature and stirred for 20 h. The *N,N'*-dicyclohexylurea was filtered off and washed with CH_2Cl_2. The combined filtrate and washings were evaporated and the residual oil was purified by silica gel column chromatography using hexane–EtOAc (7:3) as eluent to afford 73 mg (43%) of compound **2b** as a white solid. Mp: 119–121 °C. IR: 2242(CN); 1792(CO); 1757(CO). ^{1}H-NMR ($CDCl_3$) δ: 0.62(s, 3H); 0.80(s, 3H); 2.43(brd, 1H, J = 18.3); 2.75–2.82(m, 2H); 2.94(brd, 1H, J = 17.8); 3.30(dd, 1H, J = 12.0, J = 5.1); 3.84(d, 1H, J = 3.0); 3.84(d, 1H, J = 3.0); 4.99-(s, 1H); 5.74–5.79(m, 1H); 5.93–5.96(m, 1H); 7.27–7.44(m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 19.2; 22.0; 31.0; 35.0; 39.8; 45.5; 49.4; 76.0; 76.6; 117.3; 121.5; 127.3; 128.2; 128.4; 128.7; 138.9; 167.7; 170.8. Anal. Calcd for $C_{20}H_{21}NO_4$ C: 70.77, H: 6.24, N: 4.13. Found C: 70.67, H: 6.13, N: 4.03.

(1*R*,6*S*)-1-Cyano-6-phenyl-3-cyclohexene-1-carboxylate of (*S*)-Ethyl Lactate. 3a. In a similar way to that described for **2b**, starting from carboxylic acid **4b** (200 mg, 0.9 mmol) and (*S*)-ethyl lactate (104 mg, 0.9 mmol), compound **3a** was obtained as an oil in 47% yield. IR: 2245(CN); 1747(2CO). ^{1}H-NMR ($CDCl_3$) δ: 1.07(d, 3H, J = 7.0); 1.22(t, 3H, J = 7.1); 2.41(brd, 1H, J = 18.3); 2.69–2.83(m, 2H); 2.93(brd, 1H, J = 15.6); 3.23(dd, 1H, J = 11.9, J = 5.1); 4.09–4.16(m, 2H); 4.67-(q, 1H, J = 7.0); 5.74–5.78(m, 1H); 5.91–5.93(m, 1H); 7.23–7.39(m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 14.0; 16.1; 30.0; 35.2; 45.7; 48.9; 61.5; 70.1; 117.8; 121.7; 127.2; 128.0; 128.2; 128.6; 139.0; 168.0; 169.4. Anal. Calcd for $C_{19}H_{21}NO_4$ C: 69.69, H: 6.47, N: 4.28. Found C: 69.58, H: 6.33, N: 4.17.

(1*S*,2*R*)-1-Cyano-2-phenyl-1-cyclohexanecarboxylic Acid. 5a. A solution of compound **4a** (2.01 g, 8.8 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 required compound **5a** as a white solid, which was successively recrystallized until a constant α was recorded. Mp: 135–7 °C. IR: 2258(CN); 1748(CO) ^{1}H-NMR ($CDCl_3$) δ:

(16) The assignment of all separate signals in the ^{1}H-NMR spectra was made on the basis of coupling constants, selective proton–proton homonuclear decoupling experiments, and proton–proton COSY experiments.

(17) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

1.50('q"t', 1H, J = 12.9, J = 3.6); 1.80('q"t', 1H, J = 13.5, J = 3.3); 1.85–2.17(m, 5H); 2.27(brd, 1H, J = 12.9); 3.06(dd, 1H, J = 12.6, J = 3.0); 7.19–7.38(m, 5H); 9.37(brs, 1H). ^{13}C-NMR ($CDCl_3$) δ: 21.8; 25.3; 28.8; 34.9; 48.4; 53.4; 117.3; 128.0; 128.6; 128.7; 139.3; 174.7. $[\alpha]^{25}_D$(c = 2.3, $CHCl_3$) = −11.1°. Anal. Calcd for $C_{14}H_{15}NO_2$ C: 73.33, H: 6.60, N: 6.11. Found C: 73.45, H: 6.73, N: 6.00.

(1*R*,2*S*)-1-Cyano-2-phenyl-1-cyclohexanecarboxylic Acid. 5b. In a similar way to that described for **5a**, compound **5b** was quantitatively obtained, starting from carboxylic acid **4b** (1.91 g, 8.4 mmol). $[\alpha]^{25}_D$(c = 2.1, $CHCl_3$) = +11.1°. Anal. Calcd for $C_{14}H_{15}NO_2$ C: 73.33, H: 6.60, N: 6.11. Found C: 73.40, H: 6.71, N: 6.18.

(1*S*,2*R*)-1-[(Methoxycarbonyl)amino]-2-phenyl-1-cyclohexanecarbonitrile. 6a. PCl_5 (0.83 g, 4.0 mmol) was added to a solution of compound **5a** (0.91 g, 4.0 mmol) in Et_2O (40 mL) and the reaction mixture was stirred at room temperature for 90 min. The solvent and most of the PCl_5 was removed under reduced pressure. The oily residue was dissolved in toluene (20 mL) and the solvent and the residual PCl_5 distilled off *in vacuo*. This operation was repeated to ensure complete removal of the PCl_5. The acid chloride was dissolved in acetone (12 mL) and a solution of NaN_3 (0.46 g, 7.0 mmol) in water (4 mL) was added. The reaction was stirred for 90 min and evaporation of the solvent gave a white solid which was extracted with toluene. The organic solution was dried and after filtration, MeOH (16 mL) was added. The solution was stirred at 80 °C for 2 h and the solvent was removed under reduced pressure. Purification of the residue by silica gel column chromatography, eluting with hexane–EtOAc (6:4) afforded 0.78 g (76%) of compound **6a** as a white solid. Mp: 146–8 °C. IR: 3389(NH); 2241(CN); 1728(CO). ^{1}H-NMR ($CDCl_3$) δ: 1.43('q"t', 1H, J = 12.9, J = 4.2); 1.63('t'd, 1H, J = 12.9, J = 3.0); 1.82('q"t', 1H, J = 14.4, J = 3.3); 1.84–1.94(m, 3H); 2.16('q'd, 1H, J = 12.9, J = 3.0); 2.73(dd, 1H, J = 12.9, J = 3.0); 3.09(brd, 1H, J = 12.9); 3.60(s, 3H); 4.87(brs, 1H); 7.37–7.42(m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 22.6; 25.4; 30.1; 36.7; 51.4; 52.2; 57.0; 118.5; 128.3; 128.4; 129.2; 138.3; 154.7. Anal. Calcd for $C_{15}H_{18}N_2O_2$ C: 69.73, H: 7.03, N: 10.85. Found C: 69.60, H: 6.91, N: 10.76.

(1*R*,2*S*)-1-[(Methoxycarbonyl)amino]-2-phenyl-1-cyclohexanecarbonitrile. 6b. A 1.49 g amount of compound **6b** was obtained in a similar way to that described for **6a**, starting from carboxylic acid **5b** (1.66 g, 8.0 mmol). Anal. Calcd for $C_{15}H_{18}N_2O_2$ C: 69.73, H: 7.03, N: 10.85. Found C: 69.65, H: 6.93, N: 10.79.

(1*S*,2*R*)-1-Amino-2-phenyl-1-cyclohexanecarboxylic Acid. 7a. Carbamate **6a** (0.78 g, 3.0 mmol) was hydrolyzed by refluxing for 3 days with 20% aqueous HCl (30 mL). After filtration and extraction with Et_2O (3 × 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 1 h and after removal of the EtOH, the white residue was dissolved in distilled water and eluted through a C_{18} reverse-phase sep-pak cartridge. Removal of the water afforded 0.47 g (71%) of α-amino acid **7a** as a white solid. IR: 1717(CO). ^{1}H-NMR (D_2O–TFA) δ: 1.44–1.57(m, 1H); 1.74–2.52(m, 7H); 2.96(brd, 1H, J = 12.9); 7.33–7.45(m, 5H). ^{13}C-NMR (D_2O–TFA) δ: 21.2; 24.5; 28.4; 33.6; 50.3; 63.4; 128.4; 128.5; 129.2; 138.3; 172.3. $[\alpha]^{25}_D$(c = 2.3, 0.1 M TFA in H_2O) = −31.6°. Anal. Calcd for $C_{13}H_{17}NO_2$ C: 71.19, H: 7.82, N: 6.39. Found C: 71.08, H: 7.89, N: 6.28.

(1*R*,2*S*)-1-Amino-2-phenyl-1-cyclohexanecarboxylic Acid. 7b. In a similar way to that described for **7a**, starting from carbamate **6b** (0.91, 4.0 mmol), α-amino acid **7b** was obtained as a white solid in 73% yield. $[\alpha]^{25}_D$(c = 2.0, 0.1 M TFA in H_2O) = +32.5°. Anal. Calcd for $C_{13}H_{17}NO_2$ C: 71.19, H: 7.82, N: 6.39. Found C: 71.10, H: 7.84, N: 6.30.

Methyl (1*S*,2*R*)-1-(Aminocarbonyl)-2-phenyl-1-cyclohexanecarboxylate. 8a. A slight excess of a solution of diazomethane in Et_2O was added dropwise, at room temperature, to a solution of carboxylic acid **5a** (0.91 g, 4.0 mmol) in Et_2O (20 mL). After a few minutes, evaporation of the solvent quantitatively afforded the methyl (1*S*,6*R*)-1-cyano-2-phenyl-1-cyclohexanecarboxylate. A mixture of this compound (0.97 g, 4.0 mmol) and PPA (14 mL) was refluxed for 60 h. The solution was then cooled and poured onto crushed ice, and the corresponding amide was extracted with CH_2Cl_2 (3 × 30 mL). After evaporation of the solvent, the residue was chromatographed, eluting with hexane–EtOAc (6:4) to give 0.65 g (62%) of compound **8a** as an oil. IR: 3500, 3300(NH_2); 1717(CO); 1660(CO). ^{1}H-NMR ($CDCl_3$) δ: 1.39–1.62(m, 2H); 1.70–1.92(m, 3H); 2.09–2.23(m, 2H); 2.32(ddd, 1H, J = 13.5, J = 6.3, J = 4.2); 3.50(dd, 1H, J = 12.9, J = 3.0); 3.72(s, 3H); 5.50(brs, 1H); 5.94(brs, 1H); 7.18–7.35(m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 22.3; 24.1; 29.0; 40.9; 47.1; 52.6; 59.3; 126.9; 128.2; 129.0; 142.3; 172.2; 174.2. Anal. Calcd for $C_{15}H_{19}NO_3$ C: 68.93, H: 7.33, N: 5.36. Found C: 68.99, H: 7.45, N: 5.43.

Methyl (1*R*,2*S*)-1-(Aminocarbonyl)-2-phenyl-1-cyclohexanecarboxylate. 8b. In a similar way to that described for **8a**, starting from carboxylic acid **5b** (0.91 g, 4.0 mmol), compound **8b** was obtained as an oil in 59% yield. Anal. Calcd for $C_{15}H_{19}NO_3$ C: 68.93, H: 7.33, N: 5.36. Found C: 68.02, H: 7.46, N: 5.41.

Methyl (1*R*,2*R*)-1-Isocyanato-2-phenyl-1-cyclohexanecarboxylate. 9a. MeOH (2.40 g, 75.0 mmol) and a solution of NBS (0.59 g, 3.3 mmol) in DMF (4 mL) were added, at room temperature, to a solution of compound **8a** (0.65 g, 2.5 mmol) and $Hg(OAc)_2$ (0.96 g, 3.0 mmol) in DMF (12 mL). The reaction was stirred for 12 h at room temperature and the resulting mixture was evaporated *in vacuo*. The solid residue was extracted with Et_2O (3 × 20 mL), the solvent removed, and the residue purified by silica gel column chromatography, eluting with hexane–EtOAc (6:4) to afford 0.61 g (95%) of compound **9a** as a white solid. Mp: 98–100 °C. IR: 2250(NCO); 1717(CO). ^{1}H-NMR ($CDCl_3$) δ: 1.37–1.53(m, 1H); 1.65–2.11(m, 7H); 3.10(dd, 1H, J = 12.9, J = 3.3); 3.66(s, 3H); 7.14–7.32(m, 5H). ^{13}C-NMR ($CDCl_3$) δ: 21.1; 25.7; 27.7; 36.7; 49.5; 53.0; 69.9; 125.9; 127.5; 128.2; 128.3; 140.3; 173.2. Anal. Calcd for $C_{15}H_{17}NO_3$ C: 69.47, H: 6.61, N: 5.40. Found C: 69.55, H: 6.50, N: 5.49.

Methyl (1*S*,2*S*)-1-Isocyanato-2-phenyl-1-cyclohexanecarboxylate. 9b. In a similar way to that described for **9a**, starting from compound **8b** (0.62 g, 2.4 mmol), isocyanate **9b** was obtained as a white solid in 94% yield. Anal. Calcd for $C_{15}H_{17}NO_3$ C: 69.47, H: 6.61, N: 5.40. Found C: 69.55, H: 6.50, N: 5.49.

(1*R*,2*R*)-1-Amino-2-phenyl-1-cyclohexanecarboxylic Acid. 10a. Starting from isocyanate **9a** (0.61, 2.4 mmol) and following the hydrolysis procedure described above for compound **7a**, α-amino acid **10a** was obtained as a white solid in 79% yield. IR: 1698(CO). ^{1}H-NMR (D_2O–TFA) δ: 1.40–1.69(m, 2H); 1.87–2.16(m, 5H); 2.32('t'd, 1H, J = 14.1, J = 4.5); 3.50(dd, 1H, J = 12.9, J = 3.6); 7.25–7.47(m, 5H). ^{13}C-NMR (D_2O–TFA) δ: 19.4; 24.5; 25.3; 32.7; 45.7; 65.0; 128.1; 128.2; 129.2; 138.1; 173.2. $[\alpha]^{25}_D$(c = 1.1, 0.1 M TFA in H_2O) = −21.6°. Anal. Calcd for $C_{13}H_{17}NO_2$ C: 71.19, H: 7.82, N: 6.39. Found C: 71.08, H: 7.77, N: 6.28.

(1*S*,2*S*)-1-Amino-2-phenyl-1-cyclohexanecarboxylic Acid. 10b. In a similar way to that described for **10a**, starting from isocyanate **9b** (0.58 g, 2.2 mmol), α-amino acid **10b** was obtained as a white solid in 80% yield. $[\alpha]^{25}_D$(c = 1.6, 0.1 M TFA in H_2O) = +22.5°. Anal. Calcd for $C_{13}H_{17}NO_2$ C: 71.19, H: 7.82, N: 6.39. Found C: 71.10, H: 7.75, N: 6.30.

Acknowledgment. This research was supported by the Dirección General de Investigación Científica y Técnica (project number PB91-0696). M.P. thanks the Ministerio de Educación y Ciencia for a doctoral fellowship.

Supplementary Material Available: A full listing of ^{1}H and ^{13}C-NMR data, of all new compounds, complete with peak assignments; copies of ^{1}H and ^{13}C-NMR spectra for oily compounds **3a** and **8a** (9 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.