Pergamon

Tetrahedron Vol. 50, No. 32, pp. 9837-9846, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00568-0

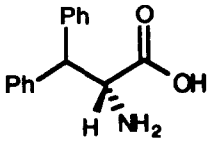
Asymmetric Synthesis of 3,3-Diphenyl-2-methylalanine, a New Unusual α-Amino Acid for Peptides of Biological Interest

Carlos Cativiela*, María D. Díaz-de-Villegas and José A. Gálvez

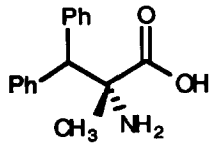
Instituto de Ciencia de Materiales de Aragón, Departamento de Química Orgánica, Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain

Abstract: A strategy of highly stereoselective enolate trapping of lithium *(1S,2R,4R)*- 10-dicyclohexylsulfamoylisobornyl-2-cyano-3,3-diphenylpropanoate combined with the appropriate rearrangement process allows the asymmetric synthesis of a novel α-methyl amino acid derived from 3,3-diphenylalanine (Dip).

The synthesis of non-proteinogenic, unnatural α-aminoacids has attracted the attention of numerous researchers[1] in connection with the design and synthesis of enzyme inhibitors[2] as potential constituents of pharmaceuticals,[3] as optically active starting materials for a variety of synthetic applications,[4] and for the study of enzymatic reaction mechanisms.[5] In particular, hydrophobic amino acids that incorporate a diphenylmethyl side chain, as in the case of 3,3-diphenylalanine (D-Dip), have proved to be a key substructural substitution in a potent peptidyl antagonist of the ET_A and ET_B endothelin receptors.[6] In this regard Goel *et al.* have recently reported the second chiral synthesis of D- and L-Dip[7] and the first of several cyclic derivatives of Dip.[8] Moreover, α,α-disubstituted α-amino acids have been the subject of considerable research during the last few years as the presence of α,α-disubstituted α-aminoacids in peptides is thought to play a crucial role in their ability to form *trans*-membrane helical ion channels. For example, it is known[9] that α,α-disubstituted α-aminoacids with a methyl group at the α-position tend to induce 3_{10}- or α-helical conformations when incorporated into peptides, and that the conformational consequences caused by the incorporation of asymmetrically α,α-dialkylsubstituted α-amino acids strongly depend on the chirality of these monomers.[10]



1



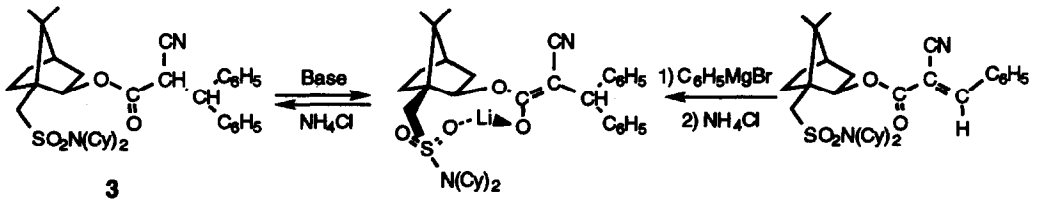
2

Bearing this point in mind, we undertook the chiral synthesis of 3,3-diphenylalanine (Dip) **1** and 3,3-diphenyl-2-methylalanine (MeDIP) **2** using an extension of our previously described methodologies[11] based on the asymmetric enolate trapping of lithium *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanoesters and the corresponding rearrangement process.

In order to obtain Dip asymmetrically, we tried deracemization by asymmetric protonation of the enolate derived from an equimolecular mixture of diastereoisomers of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenylpropanoate **3** under a variety of conditions. When compound **3** was treated with lithium diisopropylamide for one hour in dry THF at -78°C, followed by neutralization with saturated ammonium chloride solution, we obtained compound **3** as a mixture of diastereoisomers (d.r. = 75/25). Subsequently in order to improve diastereoselectivity, protonation of the enolates with magnesium, potassium and titanium as counter ions was studied and the results are listed in Table 1.

Table 1. Deracemization of Compound **3** with Different Bases.

Entry	Base	M^{n+}	Yield [%]	Diastereomeric ratio
1	LDA	Li^+	96	75/25
2	KHDMS	K^+	95	80/20
3	CH_3MgBr	Mg^{2+}	96	86/14
4	$LDA/TiCl_4/Ti(^iPrO)_4$	Ti^{4+}	93	71/29



3

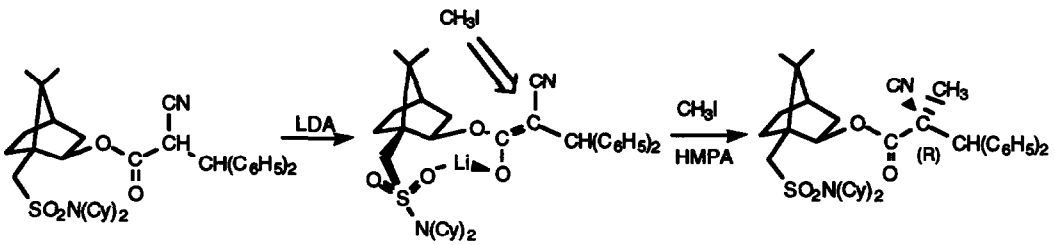
SCHEME 1

Among the four counter ions studied, the magnesium enolate gave the best results so we therefore tried an alternative method to generate the magnesiun enolate by conjugate addition of phenylmagnesiumbromide to *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl *(E)*-2-cyanocinnamate. However, subsequent enolate trapping did not improve the previous results and we obtained a mixture of diastereoisomers in a 70/30 diastereoisomeric ratio (Scheme 1).

The diastereoisomeric ratios of the products were determined in the crude reaction spectra by integration of the ^1H NMR (300 MHz) absorptions of the benzylic protons, as each diastereoisomer gave separate signals.

The minor diastereoisomer was eliminated by selective crystallization in hexane as it was the least soluble component of the mixture. Compound **3** was hydrolysed with a 10% solution of potassium hydroxide in methanol to the corresponding 2-cyano-3,3-diphenylpropanoic acid to be subjected to the corresponding rearrangement process. At this stage, the optical purity of this compound was measured *via* $Eu(hfc)_3$ ^1H-NMR after its esterification with diazomethane and we observed that almost total racemization had occurred. We tried acidic hydrolysis to obtain enantiomerically pure 2-cyano-3,3-diphenylpropanoic acid and acidic transesterification to obtain enantiomerically pure methyl 2-cyano-3,3-diphenylpropanoate, but unfortunately our attempts were unsuccessful, and we could not obtain enantiomerically pure DIP.

Subsequently, we attempted the asymmetric synthesis of 3,3-diphenyl-2-methylalanine (MeDIP) applying a similar methodology, as racemization is not possible for this compound because it does not contain an acidic hydrogen in the α-position. Conjugate addition of phenylmagnesiumbromide to *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl *(E)*-2-cyanocinnamate and subsequent enolate trapping with methyl iodide did not afford the *corresponding C-2 methyl derivative but instead gave compound* **3**. *In contrast,* diastereoselective methylation of the lithium enolate derived from *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenylpropanoate with methyl iodide in the presence of hexamethylphosphoramide (HMPA) afforded *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenyl-2-methylpropanoate **4** as a mixture of diastereoisomers (d.r. = 95/5, absolute configuration of the major diastereoisomer, 2R), from which the major diastereoisomer was isolated in diastereoisomerically pure form by selective crystallization in methanol (Scheme 2).



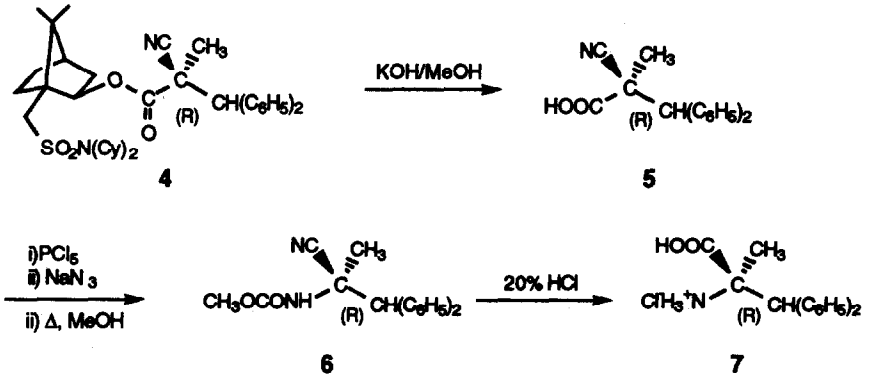
3 **4**

SCHEME 2

The diastereoisomeric ratio of the products was determined in the crude reaction spectrum by integration of the ^1H NMR (300 MHz) absorptions of the benzylic protons as each diastereoisomer gave separate signals.

The absolute configuration of compound **4** was assigned by ^1H NMR spectroscopy as we have observed a correlation between the absolute configuration of chiral 2-cyanoesters derived from *(1S,2R,4R)*-10-dicyclohexylsulfamoylisoborneol of known configuration[12] and NMR chemical shifts. In these compounds the signal due to the methine proton always appears at higher field in the *S* isomers than in the *R* isomers. This stereochemical assignement was later supported by circular dichroism measurements on the final amino acid.

(1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenyl-2-methylpropanoate **4** was hydrolysed with 10% potassium hydroxide in methanol to the corresponding *(2R)*-2-cyano-3,3-diphenyl-2-methylpropanoic acid **5** which was subjected to the corresponding rearrangement process (Scheme 3).



SCHEME 3

Curtius type rearrangement afforded *(2R)*-2-methoxycarbonylamino-3,3-diphenyl-2-methylpropanonitrile **6**. The cyanourethane **6**, obtained in 95% yield, was deprotected with concomitant hydrolysis of the cyano group by treatment with 20% hydrochloric acid to afford *(2R)*-3,3-diphenyl-2-methylalanine hydrochloride **7** in 77% yield.

The absolute configuration of 3,3-diphenyl-2-methylalanine was made on the basis of the characteristic circular dichroism (CD) spectral pattern of its 1:1 metal to ligand complex with $Eu(fod)_3$ in chloroform in the 350-250 nm region (Figure 1). It has been described previously[13] that 1:1 complexes between $Eu(fod)_3$ and L series amino acids exhibit a positive CD band at around 310 nm and a negative band in the 290-280 nm region. First of all we confirmed this spectral pattern for α-methylamino acids by using L-methylphenylalanine and D-methylvaline. The CD spectrum of the 1:1 $Eu(fod)_3$-MeDIP complex (Figure 1) showed a negative CD band at 316 nm and a positive band at 290 nm confirming that MeDIP had an *R* configuration, which is in accordance with the absolute configuration of compound **4** at C(2) assigned by NMR correlation.

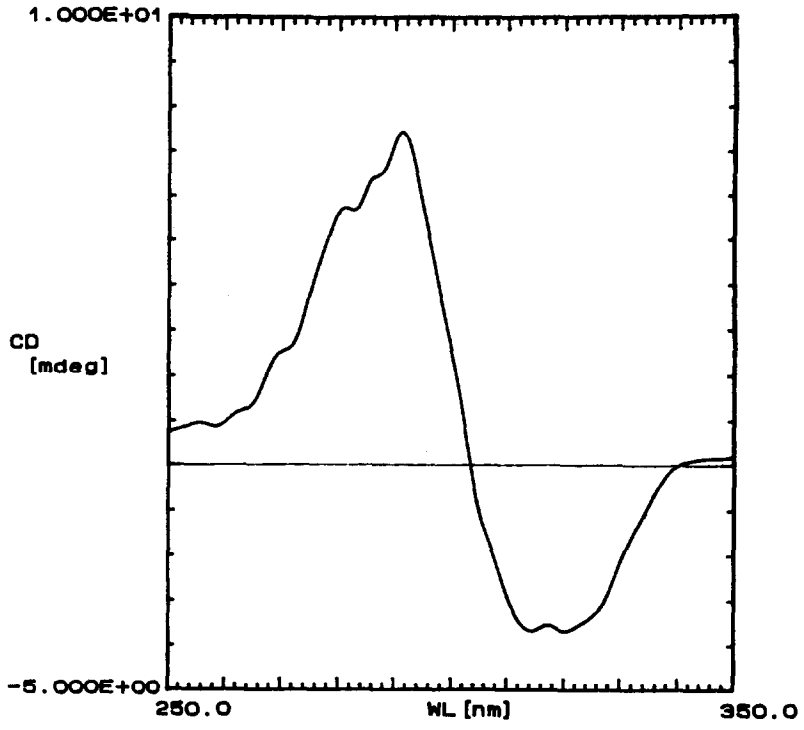


FIGURE 1. CD spectrum of 1:1 Eu(fod)$_3$-MeDIP complex in chloroform.

This stereochemical result is also consistent with the model proposed for the enolate trapping of lithium enolates generated from *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3-alkylpropanoates with alkyl halides,[12] which provides additional support for the stereochemical assignment.

In summary, we have developed a highly stereoselective route that allows the asymmetric synthesis of *(2R)*-3,3-diphenyl-2-methylalanine, a novel and unusual α-methyl amino acid that can be considered as a sterically demanding and conformationally fixed analogue of phenylalanine, which can be used in the development of new peptidomimetics.

Acknowledgement: This work was supported by the Dirección General de Investigación Científica y Técnica, project number PB91-0696.

EXPERIMENTAL

Apparatus: ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity 300 MHz spectrometer in deuterochloroform using the solvent signal as internal standard. Chemical shifts (δ) are expressed in parts per million and the coupling constants (J) are given in hertz. IR spectra

were recorded on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter at 25°C. Circular dichroism spectra were measured on a Jasco 710 spectropolarimeter. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Mass spectra (MS) were determined on a high-resolution VG-Autospec spectrometer.

Chemicals: All reactions were carried out under an atmosphere of argon with magnetic stirring. Solvents were dried prior to use. Lithium diisopropylamide (LDA) was generated *in situ* from diisopropylamine and *n*-butyllithium. Hexamethylphosphotriamide and 3.0 M solution of phenylmagnesium bromide in ether were purchased from the Aldrich Chemical Co. *(2RS)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 3-phenyl-2-cyanopropenoate was prepared following the method described in the literature.[14] TLC was performed on Merck precoated silica-gel plates which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Flash column chromatography was performed using 230-400 mesh (Merck) silica-gel.

Synthesis of *(2RS)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenylpropanoate 3

(2-RS)-Ethyl 2-cyano-3,3-diphenylpropanoate

A stirred slurry of CuI (540 mg. 2.8 mmol) in dry diethyl ether (100 mL) under an argon atmosphere was cooled to 0 °C in an ice bath. A solution of 3.0 M phenylmagnesium bromide in dry diethyl ether (18.6 mL, 56 mmol) was added and after 10 min a solution of ethyl 2-cyanocinnamate (5.63 g, 28 mmol) in dry diethyl ether (150 mL) was added dropwise. The stirring was continued for further 1 h at 0 °C , the reaction mixture was then cooled to - 80°C and quenched with saturated aqueous NH_4Cl solution. The cooling bath was removed after 5 min and the mixture was allowed to warm up to room temperature. Ether extraction, washing with water, drying ($MgSO_4$), concentration *in vacuo* and purification of the residue by flash chromatography on a silica-gel column (eluent ether/hexane 1/3) afforded *(2-RS)*-ethyl 2-cyano-3,3-diphenylpropanoate in 96% yield.

Oil ; IR 2246, 1736 cm^{-1}; HRMS (FAB): m/z = 279.1247 (M^+ calc for $C_{18}H_{17}NO_2$ 279.1259); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.07 (t, 3H, J = 7.2 Hz), 4.08 (c, 1H, J = 7.2 Hz), 4.22 (d, 1H, J = 8.4 Hz), 4.71 (d, 1H, J = 8.4 Hz), 7.20-7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.6, 43.5, 51.0, 62.8, 115.2, 127.6, 127.7, 127.8, 128.2, 128.8, 128.9, 138.7, 139.3, 165.0.

(2-RS)-2-Cyano-3,3-diphenylpropanoic acid

(2-RS)-Ethyl 2-cyano-3,3-diphenylpropanoate (5.58 g, 20 mmol) was added to a solution of KOH 10 % in methanol (40 mL) and the reaction mixture was refluxed for 5 h. The resulting solution was cooled and the solvent evaporated. The residue was diluted with water (15 mL) and washed with ether. The aqueous layer was then acidified and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford *(2-RS)*-2-cyano-3,3-diphenylpropanoic acid as a white solid in 92% yield.

Mp = 162 °C ; IR 2251, 1730 cm^{-1}; HRMS (FAB): m/z = 251.0949 (M^+ calc for $C_{16}H_{13}NO_2$ 251.0946); ^1H NMR ($CDCl_3$, 300 MHz) δ) 4.25 (d, 1H, J = 7.8 Hz), 4.72 (d, 1H, J = 7.8 Hz), 7.20-7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 43.5, 50.6, 115.3, 127.7, 127.8, 127.9, 128.2, 128.9, 138.4, 139.2, 169.0.

(2RS)-(1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenylpropanoate **3**
(2-RS)-2-Cyano-3,3-diphenylpropanoyl chloride (3.23 g, 12 mmol) [obtained from *(2-RS)*-2-cyano-3,3-diphenylpropanoic acid according to the literature procedure][15] was added by means of a syringe to a stirred mixture of silver cyanide (1.206 g, 9 mmol) and *(1S,2R,4R)*-10-dicyclohexylsulfamoylisoborneol (2.382 g, 6 mmol) in toluene (60 mL) under argon and the mixture was heated at 80 °C for 4 h. The reaction mixture was then filtered, washed succesively with a 10 % aqueous sodium hydrogen carbonate solution and water, dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash chromatography on a silica-gel column (eluent ether/hexane 1/3) afforded 3.6 g (95% yield) of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenylpropanoate **3** as an equimolecular mixture of diastereoisomers.
Spectroscopic data for the mixture: IR 2248, 1746, cm^{-1}; HRMS (FAB): m/z = 630.3501 (M^+ calc for $C_{38}H_{50}N_2O_4S$ 630.3491); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 and 0.79 (s, 3H), 0.79 and 0.82 (s, 3H), 1.00-2.00 (m, 27H), 2.58 and 2.62 (d, 1H, J = 13.5 Hz), 3.24 and 3.33 (d, 1H, J = 13.5 Hz), 3.18-3.36 (m, 2H), 4.01 (J = 7.8 Hz) and 4.26 (J = 4.5 Hz) (d, 1H), 4.78 (J = 7.8 Hz) and 4.84 (J = 4.5 Hz) (d, 1H), 4.92-5.02 (m, 1H), 7.20-7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.67 and 19.84, 20.24 and 20.27, 25.10 and 25.20, 26.29 and 26.31, 26.36 and 26.44, 26.85 and 26.95, 30.58 and 30.62, 32.39 and 32.52, 33.08 and 33.25, 38.51 and 38.84, 43.51 and 43.59, 44.28 and 44.40, 49.10 and 49.23, 49.58 and 49.82, 49.90 and 50.58, 53.83 and 53.89, 57.52 and 57.54, 80.57 and 81.12, 115.53 and 116.08, 127.42 and 127.52, 127.63 and 127.84, 127.74 and 127.92, 128.23 and 128.61, 128.79, 128.83 and 129.14, 138.51 and 138.81, 139.77 and 139.97, 163.73 and 163.82.

General procedure for deracemization
A solution of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenyl propanoate **3** (650 mg, 1 mmol) in dry THF (5 mL) was added to a solutionof base (1.2 mmol) in dry THF (25 mL), under argon at -78 °C (Li, K and Ti enolates) or 0 °C (Mg enolate). The resulting mixture was stirred for 1h at the same temperature. In the case of the titanium enolate, titanium (IV) isopropoxide (142 mg, 0.5 mmol) and titanium (IV) chloride (190 mg, 1 mmol) were added dropwise to a solution of the lithium enolate and the resulting mixture was stirred for an aditional 1h at - 78 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (5 mL). Ether extraction, washing with water, drying ($MgSO_4$), concentration *in vacuo* and flash chromatography (eluent ether/hexane 1/2) afforded *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenylpropanoate **3** as a mixture of diastereoisomers (see table 1). Recrystallization from hexane afforded the major compound in diastereoisomerically pure form.

(1S,2R,4R)-10-dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenylpropanoate **3**
Physical and spectroscopic data for the major compound: Mp 204 °C; $[\alpha]_D$ = -22.4 (c = 1 in $CHCl_3$); IR 2248, 1746, cm^{-1}; HRMS (FAB): m/z = 630.3501 (M^+ calc for $C_{38}H_{50}N_2O_4S$ 630.3491); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.77 (s, 3H), 0.79 (s, 3H), 1.00-2.00 (m, 27H), 2.58 (d, 1H, J = 13.5 Hz), 3.33 (d, 1H, J = 13.5 Hz), 3.18-3.36 (m, 2H), 4.26 (d, 1H, J = 4.5 Hz), 4.84 (d, 1H, J = 4.5 Hz) , 4.98 (dd, 1H, J = 7.5 Hz, J = 3 Hz), 7.20-7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.7, 20.2, 25.2, 26.3, 26.4, 26.9, 30.6, 32.4, 33.2, 38.5, 43.6, 44.4, 49.2, 49.8, 49.9, 53.9, 57.5, 80.6, 116.1, 127.4, 127.7, 127.8, 128.6, 128.8, 129.1, 138.5, 139.8, 163.8.

(2R)-(1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenyl-2-methylpropanoate **4**
A solution of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenylpropanoate **3** (2.52 g, 4 mmol) in dry THF (10 mL) was added to a solution of lithium diisopropylamide in dry THF (100 mL), [generated *in situ* from diisopropylamine (480 mg, 4.8 mmol) and butyl lithium (4.4. mmol)], under argon at -78 °C was added . After 1 h a solution of methyl iodide (5.68 g, 40 mmol) and HMPA (1.08 g, 6 mmol) in dry THF (10 mL) was added by means of a syringe and the resulting mixture was stirred for 12 h at room temperature. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (10 mL). Ether extraction, washing with water, drying ($MgSO_4$), concentration *in vacuo* and purification of the residue by flash chromatography (eluent ether/hexane 1/3) afforded *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenyl-2-methylpropanoate **4** as a mixture of diastereoisomers (d.r. = 95/5) in 92 % yield. Recrystallization from methanol afforded the diastereoisomerically pure compound *(R)*-**4** in 71 % yield.
Mp 189 °C; $[\alpha]_D$ = +44.5 (c = 2 in $CHCl_3$); IR 2240, 1739, cm^{-1}; HRMS (FAB): m/z = 644.3661 (M^+ calc for $C_{39}H_{52}N_2O_4S$ 644.3647); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 3H), 0.90 (s, 3H), 1.00-2.00 (m, 27H), 1.55 (s, 3H), 2.64 (d, 1H, J = 13.5 Hz), 3.40 (d, 1H, J = 13.5 Hz), 3.28-3.44 (m, 2H), 4.47 (s, 1H), 4.89 (dd, 1H, J = 7.5 Hz, J = 3 Hz), 7.20-7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.9, 20.4, 25.2, 25.4, 26.2, 26.4, 26.9, 30.6, 32.0, 33.7, 39.1, 44.2, 47.4, 49.2, 49.6, 53.5, 55.5, 57.4, 81.3, 119.3, 126.9, 127.7, 128.1, 128.5, 128.6, 130.1, 138.9, 139.4, 167.8.

(2R)-2-Cyano-3,3-diphenyl-2-methylpropanoic acid **5**
(2R)-(1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl 2-cyano-3,3-diphenyl-2-methylpropanoate **4** (2.57 g, 4 mmol) was added to a 10 % solution of KOH in methanol (20 mL) and the reaction mixture was refluxed for 5 h. The resulting solution was cooled and the solvent evaporated. The residue was diluted with water (15 mL) and washed with ether. The aqueous layer was then acidified and extracted with ether. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to afford *(2R)*-2-cyano-3,3,-diphenyl-2-methylpropanoic acid **5** as a white solid in 89 % yield.
Mp = 140 °C ; $[\alpha]_D$ = +78.5 (c = 2 in $CHCl_3$) ; IR 2246, 1732 cm^{-1}; HRMS (FAB): m/z = 265.1119 (M^+ calc for $C_{17}H_{15}NO_2$ 265.1102); ^1H NMR ($CDCl_3$, 300 MHz) δ) 1.60 (s, 3H), 4.32 (s, 1H), 7.20-7.40 (m, 6H), 7.40-7.50 (m, 4H), 8.38 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.5, 48.8, 56.8, 119.0, 127.6, 128.0, 128.1, 128.7, 128.8, 129.5, 137.5, 138.9, 174.4.

(2R)- 2-Methoxycarbonylamino-3-3-diphenyl-2-methylpropanonitrile **6**

Phosphorous pentachloride (625 mg, 3 mmol) was added to a solution of *(2R)*-2-cyano-3,3-diphenyl-2-methylpropanoic acid **5** (795 mg, 3 mmol) in dry diethyl ether (20 mL) and the reaction mixture was stirred at room temperature for 1h. The ether and most of the phosphorous oxychloride were removed under reduced pressure. The oily residue was dissolved in toluene (20 mL) and the solvent and the residual phosphorous oxychloride distilled *in vacuo*. This operation was repeated to ensure complete removal of the phosphorous oxychloride. The acid chloride was then cooled to room temperature and dissolved in dry acetone (6 mL). A solution of sodium azide (292 mg, 4.5 mmol) in water (2 mL) was then added and stirring was continued for 1h. Concentration *in vacuo* yielded a white solid which was extracted into toluene (20 mL). The organic layer was dried ($MgSO_4$) and, after filtration, dry methanol (10 mL) was added. The solution was stirred at 80 °C for 2 h and the toluene was removed under reduced pressure. Purification of the residue by flash chromatography (eluent hexane/ether 1/2) afforded 837 mg (95 % yield) of *(2R)*- 2-methoxycarbonylamino-3,3-diphenyl-2-methylpropanonitrile **6** as a white solid.

Mp = 77 °C ; $[\alpha]_D$ = +119.6 (c = 2 in $CHCl_3$) ; IR 3305, 2238, 1705, 1694 cm^{-1}; HRMS (FAB): m/z = 295.1458 (MH^+ calc for $C_{18}H_{19}N_2O_2$ 295.1446); ^1H NMR ($CDCl_3$, 300 MHz) δ) 1.79 (s, 3H), 3.64 (s, 3H), 4.17 (s, 1H), 4.99 (brs, 1H), 7.20-7.40 (m, 6H), 7.45-7.60 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.5, 52.4, 53.9, , 59.6, 120.0, 128.0, 128.1, 128.8, 129.1, 129.3, 129.4, 137.4, 137.5, 154.7.

(2R)- 2-Amino-3,3-diphenyl-2-methylpropanoic acid hydrochloride **7**

(2R)- 2-Methoxycarbonylamino-3-3-diphenyl-2-methylpropanonitrile **6** (588 mg, 2 mmol) was hydrolysed by refluxing for 3 d with 20 % aqueous hydrochloric acid (20 mL). After filtration and extraction with ether, the solvent was evaporated *in vacuo*. The residue was dissolved in water and evaporated under reduced pressure to expel the excess hydrochloric acid. Removal of water afforded 449 mg (77 % yield) of *(2R)*- 2-amino-3,3-diphenyl-2-methylpropanoic acid hydrochloride **7**.

Mp = 271 °C (desc) ; $[\alpha]_D$ = +8.2 (c = 1 in HCl_{aq} 1N) ; IR 1729 cm^{-1}; HRMS (FAB): m/z = 256.1349 (MH^+-HCl calc for $C_{16}H_{18}NO_2$ 256.1252); ^1H NMR (D_2O, 300 MHz) δ) 1.53 (s, 3H), 4.38 (s, 1H), 7.20-7.35 (m, 6H), 7.35-7.45 (m, 4H). ^{13}C NMR (D_2O/CD_3COCD_3, 75 MHz) δ 21.2, 57.7, 63.3, 128.0, 128.3, 128.8, 129.2, 129.6, 136.8, 137.3, 173.4.

REFERENCES

(1) For reviews see: (a) O'Donnell, M. J. Ed. '*α-Amino Acid Synthesis*' *Tetrahedron Symposia-in-print* **1988**, *44*, 5253. (b) Williams, R. M. '*Synthesis of Optically Active α-Amino Acids*' Pergamon Press: Oxford **1989.** (c) Duthaler, R. O. *Tetrahedron*, **1994**, *50*, 1539.

(2) See for example: (a) Maycock, A. L.; Aster, S. D.; Patchett, A. A. '*Enzyme-Activated Irreversible Inhibitors*' Seiler, N.; Jung, M. J.; Koch-Weser, J. Eds., Elsevier: New York **1978.** (b) Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.*, **1990**, *112*, 770. (c) Enders, D.; Jegelka,

U.; Dücker, B. *Angew. Chem., Int. Ed. Engl.*, **1993**, *32*, 423;. (d) Wittenberger, S. J.; Baker, W. R.; Donner, B. G. *Tetrahedron*, **1993**, *49*, 1547.

(3) See for example: (a) Kleeman, A.; Leuchtenberger, W.; Hoppe, B.; Tanner, H. '*Ullmann's Encyclopedia of Industrial Chemistry*' Vol A2, VCH: Weinheim **1985**. (b) Koskinen, A. M. P.; Rapoport, H. *J. Org. Chem.*, **1989**, *54*, 1859. (c) Shuman, R. T.; Ornstein, P. L.; Paschal, J. W.; Gesellchen, P. D. *J. Org. Chem.*, **1990**, *55*, 738. (d) Kessler, H. *Angew. Chem., Int.Ed.Engl.*, **1993**, *32*, 543.

(4) For a review see: Coppola, G. M.; Schuster, H. F. "*Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*' John Wiley and Sons: New York **1987**.

(5) See for example: (a) Chung, J. Y. L.; Wasicak, J. T.; Arnold, W. A.; May, C. S.; Nadzan, A. M.; Holladay, M. W. *J. Org. Chem.*, **1990**, *55*, 270. (b) Pellicciari, R.; Natalini, B.; Marinozzi, M. *Tetrahedron Lett.*, **1990**, *31*, 139. (c) Holladay, M. W.; Lin, C. W.; May, C. S.; Garvey, D. S.; Witte, D. G.; Miller, T. R.; Wolfram, C. A. W.; Nadzan, A. M. *J. Med. Chem.*, **1991**, *34*, 455. (d) Bruncko, M.; Crich, D. *Tetrahedron Lett.*, **1992**, *33*, 6251.

(6) (a) Doherty, A. M.; Cody, W. L.; Leitz, N. L.; DePue, P. L.; Taylor, M. D.; Rapundalo, S. T.; Hingorani, G. P.; Major, T. C.; Panek, R. L.; Taylor, D. G. *J. Cardiovasc. Pharmacol.*, **1991**, 17 (suppl. 7) S59. (b) Cody, W. L.; Doherty, A. M.; He, J. X.; DePue, P. L.; Rapundalo, S. T.; Hingorani, G. P.; Major, T. C.; Panek, R. L.; Dudley, D. T.; Haleen, S. J.; LaDouceur, D.; Hill, K. E.; Flynn, M. A.; Reynolds, E. E. *J. Med. Chem.*, **1992**, *35*, 3301.

(7) Chen, H. G.; Beylin, V. G.; Marlatt, M.; Leja, B.; Goel, O. P. *Tetrahedron Lett.*, **1992**, *33*, 3293.

(8) Beylin, V. G.; Chen, H. G.; Dunbar, J.;Goel, O. P.; Harter, W.; Marlatt, M.; Topliss, J. G. *Tetrahedron Lett.*, **1993**, *34*, 953.

(9) (a) Mutter, M. *Angew.Chem.*, **1985**, *97*, 639. (b) Toniolo, C. CRC *Critical. Rev. Biochem.*, **1980**, *9*, 1. (c) Prasad, B.V.V.; Balaram, P. CRC *Critical. Rev. Biochem.*, **1984**, *16*, 307. (d) Karle, I.L.; Balaram, P. CRC *Critical. Rev. Biochem.*, **1990**, *29*, 6747.

(10) Altmann, K.H.; Altmann, E.; Mutter, M. *Helv.Chim.Acta*, **1992**, *75*, 1198.

(11) (a) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry*, **1993**, *4*, 1145. (b) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry*, **1994**, *5*, 261. (c) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Synlett*, **1993**, 302.

(12) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *J. Org. Chem.*, **1994**, *54*, 2497.

(13) Toome, V., Wegrzynski, B. *Amino Acids* **1991**, *1*, 176.

(14) Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron: Asymmetry*, **1993**, *4*, 229.

(15) Ireland, E.; Chaykwsky, M. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 171.

(*Received in UK* 10 *June* 1994; *accepted* 24 *June* 1994)