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# Stereoselective Amination of Chiral Enolates: Synthesis of enantiomerically pure α,β-Diamino Acids, Chiral Key Compounds in the Synthesis of Conformationally Constrained Peptido- and Non-peptidomimetics.

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***Abstract:*** This work describes an efficient synthesis of enantiomerically pure *(R)*-2-aminomethylalanine, *(R)*-2-aminomethylnorvaline, *(R)*-2-aminomethylvaline, *(R)*-2-aminomethylleucine and *(R)*-2-aminomethylphenylalanine by electrophilic amination of chiral 2-cyanoesters with O-(diphenylphosphinyl)hydroxylamine followed by appropiate reduction and hydrolysis.

Of the growing number of non-coded synthetic and naturally occurring amino acids, α,β-diamino acids of type I play an important role due mainly to the following interesting features: 1) 2,3-diaminopropionic acid occurs naturally and is found to be a peptide residue present in a family of cyclopeptides which have antibiotic activity (capreomycin, viomycin, tuberactiomycin...),[1] 2) as open chain compounds, these amino acids can also be used to stabilize the specific conformations of peptides which contain them,[2] 3) they have been used to produce imidazolines, which have been employed as amide bond replacements in the design of peptidomimetics, thereby increasing the half-life of the parent peptide due to resistance to proteolysis,[3] 4) they can be cyclised to 3-amino-2-azetidinones,[4] giving rise to new clinically valuable β-lactam antibiotics.

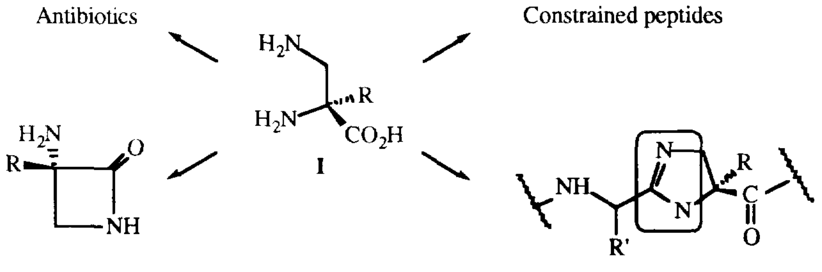
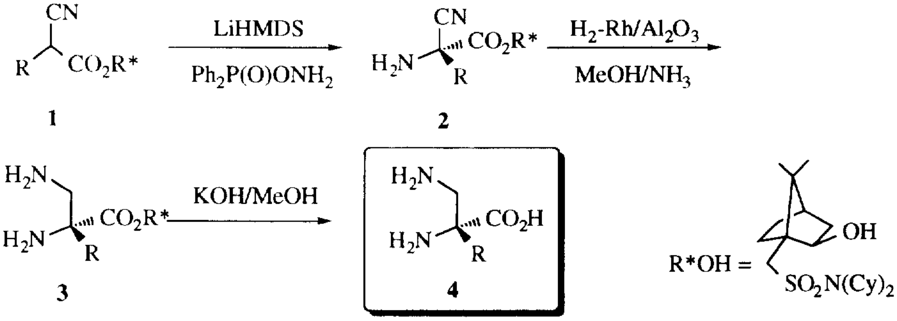


**Figure 1**

Several approaches to the preparation of chiral 2,3-diamino acids have been described. The resolution of racemic compounds derived from the alkylation of amino acid ester Schiff bases with N-bromomethylphthalimide[3c] or the Bucherer-Bergs reaction of α-aminoketones[2b] have been used in some cases. Most diastereoselective syntheses of these important amino acids are based on the alkylation of enolates derived from chiral bis-lactims,[5] oxazolodinones[6] and imidazolidinones.[7] To the best of our knowledge, there are no references on the synthesis of these compounds based on electrophilic amination.

In the course of our research program on the asymmetric synthesis of α,α-disubstituted amino acids we have developed[8] a simple and convenient route to the synthesis of *(2R)*-2-benzyl-2,3-diaminopropanonic acid based on the electrophilic amination of chiral *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl-2-cyano-3-phenylpropanoate and here, we detail our studies on the utility of this synthetic route in the preparation of a variety of 2-alkyl-2,3-diaminopropanoic acids.

The study of the electrophilic amination of chiral *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl-2-cyano-3-phenylpropanoate, previously comunicated,[8] showed that the presence of HMPA had no influence on the diastereoselectivity of the reaction and, moreover the optimun conditions for the amination reaction were the use of *O*-(diphenylphosphinyl)hydroxylamine as the amination reagent and lithium amides as the bases. We therefore proceeded to study the electrophilic amination of chiral 2-cyanopropanoates **1** under these conditions and we observed the formation of 2-amino-2-cyanopropanoates **2** in high yields and with acceptable diastereoselectivities. (Table 1)



**Scheme 1**

**Table 1.** Diastereoselective Electrophilic Amination of Chiral 2-Cyano Esters **1**

| Compound | R | Yield[a] (%) | Yield[b] (%) | Diastereomeric ratio | Absolute Configuration |
|---|---|---|---|---|---|
| **1a** | $CH_3$ | 87 | 67 | 78/22 | *(R)* |
| **1b** | $CH_3CH_2CH_2$ | 84 | 64 | 76/24 | *(R)* |
| **1c** | $(CH_3)_2CH$ | 78 | 60 | 70/30 | *(R)* |
| **1d** | $(CH_3)_2CHCH_2$ | 84 | 61 | 77/23 | *(R)* |
| **1e** | $C_6H_5CH_2$ | 91 | 70 | 80/20 | *(R)* |

[a] Crude. [b] Isolated major diastereoisomer.

In all cases the diastereomeric ratio of the products was determined from the crude reaction spectra by integration of the $^1$H-NMR (300 MHz) absorptions of the methine proton of esters **2**, as each diastereomer in the pair gave a doublet of doublets at about 5 ppm. Compounds **2** can be easily purified by flash chromatography ($SiO_2$; ether/hexane = 1/3) to afford diastereomerically pure compounds.

The absolute configuration of the newly-formed stereogenic center, when R = $C_6H_5CH_2$ was assigned by single crystal X-ray analysis[8] and showed the *R* configuration at C(2). The absolute configuration of the stereogenic center of compounds **1a** and **1d** was subsequently assigned on the basis of that of the final α,β-diamino acids as the sign and magnitude of their optical rotations corresponded to those recently described by Obrecht *et al.*[2b] for *(R)*-2-aminomethylalanine and *(R)*-2-aminomethyllleucine. The absolute configuration of the stereogenic center of compounds **1b** and **1c** was established by mechanistic considerations assuming that the attack of the electrophile had occurred from the same side that in the formation of compounds **1a**, **1d** and **1e**.

*(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-alkyl-2-amino-2-cyanoacetates **2** were converted into the corresponding diamino esters **3** in nearly quantitative yields by hydrogenation with rhodium on alumina by using a solution of the precursor in 1 % ethanol-ammonia at room temperature and atmospheric pressure with vigorous shaking to ensure the diffusion of the hydrogen into the solution. Hydrolysis of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-alkyl-2-amino-2-aminomethylacetates **2** with KOH/methanol furnished the corresponding potassium salts of the α,β-diamino acids **4** in enantiomerically pure form, from which we obtained the free amino acid by ion exchange chromatography. The results are summarised in Table 2.

**Table 2.** Synthesis of the α,β-Diaminoacids **4a-e**

| **Compound** | **R** | **Yield (%)** **3** | **Yield (%)** **4** |
|---|---|---|---|
| **a** | $CH_3$ | 83 | 94 |
| **b** | $CH_3CH_2CH_2$ | 93 | 90 |
| **c** | $(CH_3)_2CH$ | ≈ 100 | 92 |
| **d** | $(CH_3)_2CHCH_2$ | 92 | 97 |
| **e** | $C_6H_5CH_2$ | 85 | 95 |

In summary, the electrophilic amination of chiral enolates is a new route to enantiomerically pure *(R)*-2-aminomethylalanine **4a**, *(R)*-2-aminomethylnorvaline **4b**, *(R)*-2-aminomethylvaline **4c**, *(R)*-2-aminomethylleucine **4d** and *(R)*-2-aminomethylphenylalanine **4e**, useful intermediates in the synthesis of conformationally-constrained peptides, peptidomimetics in which the amide group has been substituted by hydrolitically stable subunits and β-lactams.

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## EXPERIMENTAL

Apparatus: Melting points were determined using a Büchi 510 capillary melting point apparatus and are uncorrected. Specific rotations were recorded using a Perkin-Elmer 241-C polarimeter with a thermally jacketed 10 cm cell at 25°C. IR spectra were obtained on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. $^{1}$H-NMR and $^{13}$C-NMR spectra were recorded in deuteriochloroform or deuterated water and referenced with respect to residual solvent signal on a Varian Unity 300 or a Bruker AMX300 spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane ($\delta$ 0.00 ppm), and coupling constants *(J)* are measured in Hertz. Mass spectra (MS) were recorded on a high-resolution VG-Autospec instrument. Elemental analyses were performed on a Perkin-Elmer 200 C,H,N,S elemental analyser.
Chemicals: All reactions were carried out under Ar with magnetic stirring. Solvents were dried prior to use. Lithium hexamethyldisilazane (LHMDS) and rhodium on alumina were purchased from the Aldrich Chemical Co. O-(diphenylphosphinyl)hydroxylamine was obtained according to the literature procedure.[9] TLC was performed on precoated silica gel plates which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Flash column chromatography was undertaken on silica gel (Kiesegel 60).

*(2RS)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-alkylcyanoacetates **1**

**General procedure for the synthesis of cyanoesters 1a-d.** In a typical procedure the cyanoacyl chloride[10] (12 mmol) 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 successively with a 10% aqueous sodium hydrogen carbonate solution and water, dried with magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash chromatography on a silicagel column (eluent: ether/hexane 1/3) afforded the corresponding 2-alkyl-2-cyanoester **1a-d**.

***(2RS)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-cyanopropanoate 1a.** The general procedure was followed for the esterification of 1.386 g (12 mmol) of 2-cyanopropanoyl chloride to obtain 2.523 g (88% yield) of compound **1a** as an equimolar mixture of diastereomers whose physical and spectroscopical data have been previously described.[11]

***(2RS)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-cyanopentanoate 1b.** The general procedure was followed for the esterification of 1.746 g (10.8 mmol) of 2-cyanopentanoyl chloride to obtain 2.58 g (85% yield) of compound **1b** as an equimolar mixture of diastereomers. IR (Nujol) 2249, 1737 cm$^{-1}$; $^{1}$H-NMR ($CDCl_3$, 300 MHz) $\delta$ 0.86 (s, 3H), 0.95 (t, 3H, J = 6.6 Hz), 1.04 and 1.06 (s, 3H), 1.02-2.00 (m, 31H), 2.60 and 2.63 (d, 1H, J = 13.5 ), 3.20-3.35 (m, 2H), 3.35 (d, 1H, J = 13.5), 3.40-3.52 (m, 1H), 4.96-5.04 (m, 1H). $^{13}$C-NMR ($CDCl_3$, 75 MHz) $\delta$ 13.11, 13.14 and 13.19, 19.85, 20.02 and 20.21, 20.24 and 20.28, 25.11 and 25.17, 26.21 and 26.26, 26.33 and 26.38, 30.52 and 30.67, 31.62 and 31.67, 32.22 and 32.42, 33.04 and 33.21, 37.05 and 37.58, 39.09 and 39.17, 44.36 and 44.41, 49.24, 49.70 and 49.80, 53.64 and 53.84, 57.42 and 57.56, 80.35 and 80.37, 116.35 and 116.67, 164.67 and 166.64. Anal. Calcd for $C_{28}H_{46}N_2O_4S$: C, 66.36 %; H, 9.15 %; N, 5.53 %; S, 6.33 %. Found: C, 66.41 %; H, 9.09 %; N, 5.57 %; S, 6.27 %.

***(2RS)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-cyano-3-methylbutanoate 1c.** The general procedure was followed for the esterification of 1.746 g (10.8 mmol) of 2-cyano-3-methylbutanoyl chloride to obtain 2.702 g (89% yield) of compound **1c** as an equimolar mixture of diastereomers whose physical and spectroscopical data have been previously described.[11]

***(2RS)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-cyano-4-methylpentanoate 1d.** The general procedure was followed for the esterification of 1.914 g (10.9 mmol) of 2-cyano-4-methylpentanoyl chloride to obtain 2.65 g (85% yield) of compound **1d** as an equimolar mixture of diastereomers. IR (Nujol) 2245, 1744 cm$^{-1}$; $^{1}$H-NMR (CDCl$_3$, 300 MHz) δ 0.86 (s, 3H), 0.93 (d, 3H, J = 6.3 Hz), 0.97 and 0.98 (d, 3H, J = 6.3 Hz), 1.05 and 1.06 (s, 3H), 1.15-2.03 (m, 29H), 2.62 and 2.65 (d, 1H, J = 13.5 Hz and J = 13.2 Hz), 3.20-3.32 (m, 3H), 3.34 and 3.86 (d, 1H, J = 13.5 Hz and J = 13.2 Hz), 3.43-3.54 (m, 1H), 4.96-5.01 (m, 1H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 19.95, 20.32, 20.88 and 21.08, 22.58, 25.21, 26.08 and 26.10, 26.35 and 26.46, 26.99, 30.63 and 30.77, 32.34 and 32.53, 33.12 and 33.29, 35.71 and 36.20, 37.67 and 38.36, 39.05 and 39.21, 44.48, 49.35, 49.87 and 49.89, 53.78 and 53.94, 57.58, 80.47, 116.86, 164.99. Anal. Calcd for $C_{29}H_{48}N_2O_4S$: C, 66.88 %; H, 9.29 %; N, 5.38 %; S, 6.16 %. Found: C, 66.81 %; H, 9.38 %; N, 5.41 %; S, 6.23 %.

***(2RS)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 3-phenyl-2-cyanopropanoate 1e.** (Prepared according to the procedure previously described by ourselves[12]).

### *(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-alkyl-2-aminocyanoacetates **2**

**General procedure for the electrophilic amination of cyanoesters 1a-e.** In a typical procedure lithium hexamethyldisilylamide 1M in hexane (1.65 ml, 3.3 mmol) was added by means of a syringe to a stirred mixture of the corresponding *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-alkylcyanoacetate **1** (3 mmol) in dry THF (50 ml) under argon at -78 °C. After 1h *O*-(diphenylphosphinyl)hydroxylamine (1.049 g, 4.5 mmol) was added and the resulting mixture was vigorously stirred for 12 h at room temperature and the mixture was then quenched with a saturated aqueous ammonium chloride solution (60 ml). Ether extraction, washing with water, drying with magnesium sulfate and concentration *in vacuo* yielded a mixture of diastereomers of the corresponding *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-alkyl-2-aminocyanoacetate **2.** The crude product was chromatographed on a silica gel columm (eluent: ether/hexane 1/3) to afford diastereomerically pure compounds.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-amino-2-cyanopropanoate *(R)*-2a.** The general procedure was followed for the amination of 1.43 g (3 mmol) of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate **1a** to obtain 988 mg (67% yield) of diastereomerically pure ***(R)*-2a.** M. p. 151 °C; IR (Nujol) 3378, 3306, 2242, 1757 cm$^{-1}$; $[\alpha]^{D}$ = - 48.0 (c 1, in chloroform); $^{1}$H-NMR (CDCl$_3$, 300 MHz) δ 0.86 (s, 3H), 1.06 (s, 3H), 1.10-2.03 (m, 27H), 1.67 (s, 3H), 2.15 (sbr, 2H), 2.62 (d, 1H, J = 13.5 Hz), 3.20-3.40 (m, 2H), 3.44 (d, 1H, J = 13.5 Hz), 5.03 (dd, 1H, J = 8.1 Hz, J = 2.7 Hz). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 19.9, 20.2, 25.2, 25.7, 26.2, 26.4, 27.0, 31.0, 32.1, 33.5, 38.9, 44.4, 49.4, 50.3, 53.6, 54.2, 57.5, 80.5, 120.2, 168.8. Anal. Calcd for $C_{26}H_{43}N_3O_4S$: C, 63.26 %; H, 8.78 %; N, 8.51 %; S, 6.49 %. Found: C, 63.35 %; H, 8.85 %; N, 8.45 %; S, 6.53 %.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-amino-2-cyanopentanoate *(R)*-2b.** The general procedure was followed for the amination of 1.52 g (3 mmol) of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopentanoate **1b** to obtain 1 g (64% yield) of diastereomerically pure ***(R)*-2b**. M. p. 163 °C; IR (Nujol) 3401, 3381, 3321, 2244, 1738 cm$^{-1}$; $[\alpha]^D$ = - 47.2 (c 1, in chloroform); $^1$H-NMR (CDCl$_3$, 300 MHz) δ 0.86 (s, 3H), 0.95 (t, 3H, 7.5 Hz), 1.07 (s, 3H), 1.10-2.03 (m, 31H), 2.10 (sbr, 2H), 2.61 (d, 1H, J = 13.5 Hz), 3.20-3.40 (m, 2H), 3.47 (d, 1H, J = 13.5 Hz), 5.04 (dd, 1H, J = 8.1 Hz, J = 2.4 Hz). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 13.6, 17.8, 19.9, 20.2, 25.2, 26.1, 26.3, 27.0, 31.0, 32.1, 33.5, 38.9, 41.1, 44.4, 49.4, 50.3, 54.2, 57.5, 58.3, 80.3, 119.6, 169.0. Anal. Calcd for $C_{28}H_{47}N_3O_4S$: C, 64.45 %; H, 9.08 %; N, 8.05 %; S, 6.15 %. Found: C, 64.50 %; H, 9.01 %; N, 8.11 %; S, 6.09 %.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-amino-2-cyano-3-methylbutanoate *(R)*-(2c).** The general procedure was followed for the amination of 1.52 g (3 mmol) of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3-methylbutanoate **1c** to obtain 939 mg (60% yield) of diastereomerically pure ***(R)*-2c**. M. p. 117 °C; IR (Nujol) 3396, 3330, 2244, 1737 cm$^{-1}$; $[\alpha]^D$ = - 36.5 (c 1, in chloroform); $^1$H-NMR (CDCl$_3$, 300 MHz) δ 0.86 (s, 3H), 1.02 (d, 3H, 6.8 Hz), 1.07 (s, 3H), 1.13 (d, 3H, J = 6.8 Hz), 1.20-2.05 (m, 30H), 2.60 (d, 1H, J = 13.4 Hz), 3.22-3.40 (m, 2H), 3.48 (d, 1H, J = 13.4 Hz), 5.06 (dd, 1H, J = 7.8 Hz, J = 2.9 Hz). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 16.7, 17.9, 19.9, 20.2, 25.2, 26.1, 26.4, 27.0, 31.1, 32.1, 33.5, 36.6, 38.9, 44.5, 49.4, 50.4, 54.3, 57.5, 63.3, 80.1, 118.5, 169.2. Anal. Calcd for $C_{28}H_{47}N_3O_4S$: C, 64.45 %; H, 9.08 %; N, 8.05 %; S, 6.15 %. Found: C, 64.39 %; H, 9.03 %; N, 8.12 %; S, 6.08 %.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-amino-2-cyano-4-methylpentanoate *(R)*-2d.** The general procedure was followed for the amination of 1.56 g (3 mmol) of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-4-methylpentanoate **1d** to obtain 980 mg (61% yield) of diastereomerically pure ***(R)*-2d**. M. p. 151 °C; IR (Nujol) 3397, 3372, 2238, 1745 cm$^{-1}$; $[\alpha]^D$ = - 54.0 (c 1, in chloroform); $^1$H-NMR (CDCl$_3$, 300 MHz) δ 0.86 (s, 3H), 0.92 (d, 3H, 6.3 Hz), 1.02 (d, 3H, J = 6.3 Hz), 1.07 (s, 3H), 1.10-2.00 (m, 30H), 2.08 (sbr, 2H), 2.61 (d, 1H, J = 13.5 Hz), 3.18-3.40 (m, 2H), 3.49 (d, 1H, J = 13.5 Hz), 5.00 (dd, 1H, J = 8.1 Hz, J = 2.7 Hz). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 19.9, 20.2, 22.7, 23.4, 25.1, 25.2, 26.1, 26.4, 27.0, 31.1, 32.1, 33.5, 38.5, 44.5, 46.7, 49.4, 50.3, 54.3, 57.5, 80.5, 119.7, 169.3. Anal. Calcd for $C_{29}H_{49}N_3O_4S$: C, 65.01 %; H, 9.22 %; N, 7.84 %; S, 5.98 %. Found: C, 65.11 %; H, 9.17 %; N, 7.79 %; S, 5.91 %.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-amino-2-cyano-3-phenylpropanoate *(R)*-2e.** The general procedure was followed for the amination of 1.66 g (3 mmol) of *(2RS)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3-phenylpropanoate **1e** to obtain 1.19 g (70% yield) of diastereomerically pure ***(R)*-2e**. M. p. 199 °C; IR (Nujol) 3393, 3371, 2920, 2248, 1744 cm$^{-1}$; $[\alpha]^D$ = - 44.6 (c 1, in chloroform); $^1$H-NMR (CDCl$_3$, 300 MHz) δ 0.60 (s, 3H), 1.75 (s, 3H), 1.02-2.03 (m, 27H), 2.12 (sbr, 2H), 2.52 (d, 1H, J = 13.5 Hz), 3.12 (d, 1H, J = 13.2 Hz), 3.18 (d, 1H, J = 13.2 Hz), 3.20-3.38 (m, 2H), 3.32 (d, 1H, J = 13.5 Hz), 4.96 (dd, 1H, J = 7.8 Hz, J = 3 Hz), 7.28 (s, 5H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 19.4, 20.1, 25.2, 26.1, 26.4, 27.0, 30.9, 32.0, 33.6, 38.2, 44.4, 45.1, 49.3, 50.3, 54.3, 57.5, 59.8, 80.0, 119.4, 127.9, 128.5, 130.3, 132.9, 168.3. Anal. Calcd for $C_{32}H_{47}N_3O_4S$: C, 67.46 %; H, 8.31 %; N, 7.37 %; S, 5.63 %. Found: C, 67.41 %; H, 8.26 %; N, 7.45 %; S, 5.67 %.

### *(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-alkyl-2-amino-2-aminomethylacetates 3

**General procedure for the catalytic hydrogenation of cyanoesters 2a-e.** In a typical procedure a solution of the corresponding *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-alkyl-2-aminocyanoacetate **2** (1 mmol) in 1 % ammonia-ethanol (50 ml) was hydrogenated with rhodium on alumina (200 mg) at 25 °C and atmospheric pressure with vigorous shaking. The reaction was followed by TLC and when it was finished (16 h), the catalyst was removed by filtration and the filtrate evaporated to dryness. Purification of the residue by flash chromatography (eluent: ether/ethanol 9/1) afforded diastereomerically pure compounds.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-amino-2-aminomethylpropanoate *(R)*-(3a).** The general procedure was followed for the hydrogenation of 987 mg (2 mmol) of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-amino-2-cyanopropanoate ***(R)*-2a** to obtain 826 mg (83% yield) of diastereomerically pure ***(R)*-3a**. M. p. 153 °C; IR (Nujol) 3382, 1732 cm$^{-1}$; $[\alpha]^D$ = - 50.4 (c 1, in chloroform); $^1$H-NMR (CDCl$_3$, 300 MHz) δ 0.85 (s, 3H), 0.98 (s, 3H), 1.10-2.03 (m, 31H), 1.24 (s, 3H), 2.59 (d, 1H, J = 12.9 Hz), 2.62 (d, 1H, J = 13.5 Hz), 3.04 (d, 1H, J = 12.9 Hz), 3.21 (d, 1H, J = 13.5 Hz), 3.18-3.32 (m, 2H), 4.85 (dd, 1H, J = 7.8 Hz, J = 3 Hz). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 20.1, 20.4, 23.8, 25.2, 26.4, 26.5, 27.0, 30.9, 32.3, 33.4, 40.0, 44.3, 49.2, 49.4, 51.4, 54.0, 57.5, 59.1, 79.2, 175.6. Anal. Calcd for $C_{26}H_{47}N_3O_4S$: C, 62.74 %; H, 9.52 %; N, 8.44 %; S, 6.44 %. Found: C, 62.69 %; H, 9.59 %; N, 8.36 %; S, 6.50 %.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-amino-2-aminomethylpentanoate *(R)*-3b.** The general procedure was followed for the hydrogenation of 1.04 g (2 mmol) of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-amino-2-cyanopentanoate ***(R)*-2b** to obtain 978 mg (93% yield) of diastereomerically pure ***(R)*-3b**. Oil; IR (Nujol) 3320, 1769 cm$^{-1}$; $[\alpha]^D$ = - 27.7 (c 1, in chloroform); $^1$H-NMR (CDCl$_3$, 300 MHz) δ 0.84 (s, 3H), 0.86 (t, 3H, J = 6.9 Hz), 0.95 (s, 3H), 1.02-2.03 (m, 31H), 2.50 (sbr, 4H), 2.63 (d, 1H, J = 13.5 Hz), 2.74 (d, 1H, J = 12.9 Hz), 3.11 (d, 1H, J = 12.9 Hz), 3.22 (d, 1H, J = 13.5 Hz), 3.18-3.32 (m, 2H), 4.85 (dd, 1H, J = 7.8 Hz, J = 3 Hz). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 14.1, 17.1, 18.3, 19.8, 20.3, 25.1, 26.3, 26.4, 27.0, 31.0, 32.2, 33.4, 44.3, 49.2, 49.3, 49.5, 54.3, 57.6, 58.2, 62.4, 79.7, 174.0. Anal. Calcd for $C_{28}H_{51}N_3O_4S$: C, 63.96 %; H, 9.78 %; N, 7.99 %; S, 6.10 %. Found: C, 63.91 %; H, 9.85 %; N, 7.89 %; S, 6.17 %.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-amino-2-aminomethyl-3-methylbutanoate *(R)*-3c.** The general procedure was followed for the hydrogenation of 1.04 g (2 mmol) of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-amino-2-cyano-3-methylbutanoate ***(R)*-(2c)** to obtain 1.05 g (≈ 100% yield) of diastereomerically pure ***(R)*-3c**. M. p. 161 °C; IR (Nujol) 3389, 1731 cm$^{-1}$; $[\alpha]^D$ = - 27.0 (c 1, in chloroform); $^1$H-NMR (CDCl$_3$, 300 MHz) δ 0.82 (d, 3H, J = 6.8 Hz), 0.85 (s, 3H), 0.89 (d, 3H, J = 6.8 Hz), 0.95 (s, 3H), 1.02-2.03 (m, 32H), 2.61 (d, 1H, J = 13.4 Hz), 2.67 (d, 1H, J = 12.7 Hz), 3.00 (d, 1H, J = 12.7 Hz), 3.23 (d, 1H, J = 13.4 Hz), 3.18-3.32 (m, 2H), 4.80 (dd, 1H, J = 7.6 Hz, J = 2.7 Hz). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ 16.0, 17.7, 19.8, 20.4, 25.1, 26.3, 26.4, 26.9, 30.7, 32.0, 32.8, 33.4, 39.9, 44.1, 48.8, 49.1, 49.3, 53.7, 57.3, 65.9, 79.7, 176.1. Anal. Calcd for $C_{28}H_{51}N_3O_4S$: C, 63.96 %; H, 9.78 %; N, 7.99 %; S, 6.10 %. Found: C, 63.89 %; H, 9.71 %; N, 7.88 %; S, 6.01 %.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-amino-2-aminomethyl-4-methylpentanoate *(R)*-3d**. The general procedure was followed for the hydrogenation of 1.07 g (2 mmol) of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-amino-2-cyano-4-methylpentanoate ***(R)*-2d** to obtain 993 mg (92% yield) of diastereomerically pure ***(R)*-3d**. M. p. 160 °C; IR (Nujol) 3378, 1732 $cm^{-1}$; $[\alpha]^D$ = - 31.5 (c 1, in chloroform); $^1$H-NMR ($CDCl_3$, 300 MHz) δ 0.86 (d, 3H, J = 6.6 Hz), 0.88 (s, 3H), 0.95 (d, 3H, J = 6.6 Hz), 1.00 (s, 3H), 1.02-2.03 (m, 34H), 2.56 (d, 1H, J = 12.7 Hz), 2.64 (d, 1H, J = 13.4 Hz), 3.07 (d, 1H, J = 12.7 Hz), 3.25 (d, 1H, J = 13.4 Hz), 3.20-3.36 (m, 2H), 4.84 (dd, 1H, J = 8.2 Hz, J = 3 Hz). $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 20.0, 20.4, 23.7, 24.3, 24.5, 25.1, 26.4, 26.5, 27.0, 30.9, 32.1, 33.5, 39.7, 44.3, 45.4, 49.2, 49.5, 51.6, 53.9, 57.4, 62.5, 79.8, 176.0. Anal. Calcd for $C_{29}H_{53}N_3O_4S$: C, 64.52 %; H, 9.90 %; N, 7.78 %; S, 5.94 %. Found: C, 64.59 %; H, 9.95 %; N, 7.71 %; S, 5.98 %.

***(2R)-(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-amino-2-aminomethyl-3-phenylpropanoate *(R)*-3e**. The general procedure was followed for the hydrogenation of 1.14 g (2 mmol) of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-amino-2-cyano-3-phenylpropanoate ***(R)*-2e** to obtain 973 mg (85% yield) of diastereomerically pure ***(R)*-3e**. Oil; IR (Nujol) 3373, 1731 $cm^{-1}$; $[\alpha]^D$ = - 47.0 (c 0.8, in chloroform); $^1$H-NMR ($CDCl_3$, 300 MHz) δ 0.86 (s, 3H), 0.98 (s, 3H), 1.02-2.03 (m, 31H), 2.58 (d, 1H, J = 12.6 Hz), 2.64 (d, 1H, J = 13.2 Hz), 2.84 (d, 1H, J = 13.5 Hz), 3.01 (d, 1H, J = 13.5 Hz), 3.11 (d, 1H, J = 12.6 Hz), 3.25 (d, 1H, J = 13.2 Hz), 3.18-3.32 (m, 2H), 4.88 (dd, 1H, J = 7.8 Hz, J = 3 Hz), 7.10-7.27 (m, 5H). $^{13}$C-NMR ($CDCl_3$, 75 MHz) δ 20.1, 20.4, 25.1, 26.3, 26.4, 27.0, 30.8, 32.2, 33.4, 39.8, 42.8, 44.4, 49.2, 49.6, 49.9, 54.0, 57.4, 62.8, 79.7, 126.8, 128.3, 130.1, 136.0, 174.9. Anal. Calcd for $C_{32}H_{51}N_3O_4S$: C, 66.97 %; H, 8.97 %; N, 7.32 %; S, 5.59 %. Found: C, 66.91 %; H, 8.93 %; N, 7.39 %; S, 5.66 %.

*(2R)*-2-alkyl-2-amino-2-aminomethylacetic acids **4**

**General procedure for the acidic hydrolysis of diaminoesters 3a-e.** In a typical procedure the corresponding *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-alkyl-2-amino-2-aminomethylacetate **3** (1.5 mmol) was added to a 10 % solution of potassium hydroxide in methanol (25 ml) and the mixture was refluxed for 5h. After completion the resulting solution was cooled and the solvent evaporated. The residue was diluted in water (15 ml) and washed with ether. The aqueous layer was then acidified and poured through an ion exchange column (DOWEX® 50 x 8-200, H+ form, 100 ml). The column was washed with water until the eluate became neutral and then eluted with diluted ammonium hydroxide until the ninhydrin test became negative. The combined eluates were evaporated to dryness giving the corresponding 2-alkyl-2-amino-2-aminomethylacetic acid **4** as a white solid.

***(2R)*-2-Amino-2-aminomethylpropanoic acid *(R)*-4a.** The general procedure was followed for the hydrolysis of 750 mg (1.5 mmol) of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-amino-2-aminomethylpropanoate ***(R)*-3a** to obtain 166 mg (94% yield) of enantiomerically pure ***(R)*-4a**. M. p. 200 °C (dec) [lit.[2b] m. p. >202-204 °C (dec)]; $[\alpha]^D$ = - 4.2 (c 0.2, in methanol) [lit.[2b] $[\alpha]^D$ = - 4.5 (c 0.2, in methanol)]; $^1$H-NMR ($D_2O$, 300 MHz) δ 1.24 (s, 3H), 2.79 (d, 1H, J = 13.5 Hz), 2.94 (d, 1H, J = 13.5 Hz). $^{13}$C-NMR ($D_2O$, 75 MHz) δ 20.2, 45.3, 57.9, 176.7.

***(2R)*-2-Amino-2-aminomethylpentanoic acid *(R)*-4b.** The general procedure was followed for the hydrolysis of 780 mg (1.5 mmol) of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-amino-2-aminomethylpentanoate ***(R)*-3b** to obtain 197 mg (90% yield) of enantiomerically pure ***(R)*-4b**. M. p. 265 °C (dec); $[\alpha]^D$ = + 10.6 (c 1, in water); $^1$H-NMR ($D_2O$, 300 MHz) δ 0.73 (t, 3H, J = 7.2 Hz), 0.97-1.28 (m, 2H), 1.35-1.65 (m, 2H), 2.75 (d, 1H, J = 13.5 Hz), 2.96 (d, 1H, J = 13.5 Hz). $^{13}$C-NMR ($D_2O$, 75 MHz) δ 13.4, 16.6, 37.4, 45.8, 62.9, 177.0. Anal. Calcd for $C_6H_{14}N_2O_2$: C, 49.30 %; H, 9.65 %; N, 19.16 %. Found: C, 49.21 %; H, 9.73 %; N, 19.20 %.

***(2R)*-2-Amino-2-aminomethyl-3-methylbutanoic acid *(R)*-4c.** The general procedure was followed for the hydrolysis of 780 mg (1.5 mmol) of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-amino-2-aminomethyl-3-methylbutanoate ***(R)*-3c** to obtain 202 mg (92% yield) of enantiomerically pure ***(R)*-4c**. M. p. 255 °C; $[\alpha]^D$ = + 1.0 (c 0.9, in water); $^1$H-NMR ($D_2O$, 300 MHz) δ 0.77 (d, 3H, J = 6.6 Hz), 0.79 (d, 3H, J = 6.6 Hz) 1.92 (m, 1H, J = 6.6 Hz), 2.77 (d, 1H, J = 13.5 Hz), 3.03 (d, 1H, J = 13.5 Hz). $^{13}$C-NMR ($D_2O$, 75 MHz) δ 14.1, 15.2, 30.8, 43.1, 64.2, 176.4. Anal. Calcd for $C_6H_{14}N_2O_2$: C, 49.30 %; H, 9.65 %; N, 19.16 %. Found: C, 49.23 %; H, 9.73 %; N, 19.21 %.

***(2R)*-2-Amino-2-aminomethyl-4-methylpentanoic acid *(R)*-4d.** The general procedure was followed for the hydrolysis of 810 mg (1.5 mmol) of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-amino-2-aminomethyl-4-methylpentanoate ***(R)*-3d** to obtain 233 mg (97% yield) of enantiomerically pure ***(R)*-4d**. M. p. 243 °C [lit.[2b] m. p. >220 °C (dec)]; $[\alpha]^D$ = + 28.2 (c 0.2, in water) [lit.[2b] $[\alpha]^D$ = + 32.0 (c, 0.2 in water)]; $^1$H-NMR ($D_2O$, 300 MHz) δ 0.74 (d, 3H, J = 5.7 Hz), 0.79 (d, 3H, J = 5.7 Hz), 1.39-1.46 (m, 1H), 1.51-1.64 (m, 2H), 2.69 (d, 1H, J = 13.5 Hz), 2.96 (d, 1H, J = 13.5 Hz). $^{13}$C-NMR ($D_2O$, 75 MHz) δ 20.6, 22.1, 22.3, 42.4, 45.8, 61.4, 175.9.

***(2R)*-2-Amino-2-aminomethyl-3-phenylpropanoic acid *(R)*-4e.** The general procedure was followed for the hydrolysis of 860 mg (1.5 mmol) of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-amino-2-aminomethyl-3-phenylpropanoate ***(R)*-3e** to obtain 276 mg (95% yield) of enantiomerically pure ***(R)*-4e**. M. p. 222 °C; $[\alpha]^D$ = - 8.25 (c 0.8, in water); $^1$H-NMR ($D_2O$, 300 MHz) δ 2.72 (d, 1H, J = 13.5 Hz), 2.87 (d, 1H, J = 13.2 Hz), 3.02 (d, 1H, J = 13.5 Hz), 3.13 (d, 1H, J = 13.2 Hz), 7.10-7.30 (m, 5H). $^{13}$C-NMR ($D_2O$, 75 MHz) δ 42.1, 45.9, 62.5, 127.5, 128.7, 130.0, 134.7, 176.9. Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84 %; H, 7.26 %; N, 14.42 %. Found: C, 61.77 %; H, 7.33 %; N, 14.49 %.

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