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Chiral 2-Cyano Esters as Synthetic Intermediates in the Synthesis of *R* and *S* α-Methylvaline

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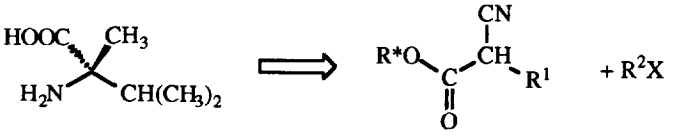
Abstract: *A divergent stereoselective synthesis of R and S α-methylvaline from (2RS) (1S,2R,4R)-10-dicyclohexylsulfamoylisobornyl 2-cyano-3-methylbutanoate has been developed.*

There has recently been considerable interest in non-proteinogenic naturally occurring amino acids[1] and in unnatural synthetic amino acids[2] for their enzyme inhibitory and antimetabolite properties and for their ability to impart protease resistance and unique conformational inducing properties when incorporated into proteins.[3]

α-Methylvaline is of particular interest because it is a strong type I/III turn and helix former[4] and an intermediate in the synthesis of the herbicide Arsenal.[5]

In the course of our research program we have been interested in the synthesis of both enantiomers of α-methylvaline and we have achieved their synthesis by extension of our previously described method of diastereoselective alkylation of chiral 2-cyano esters.[6]

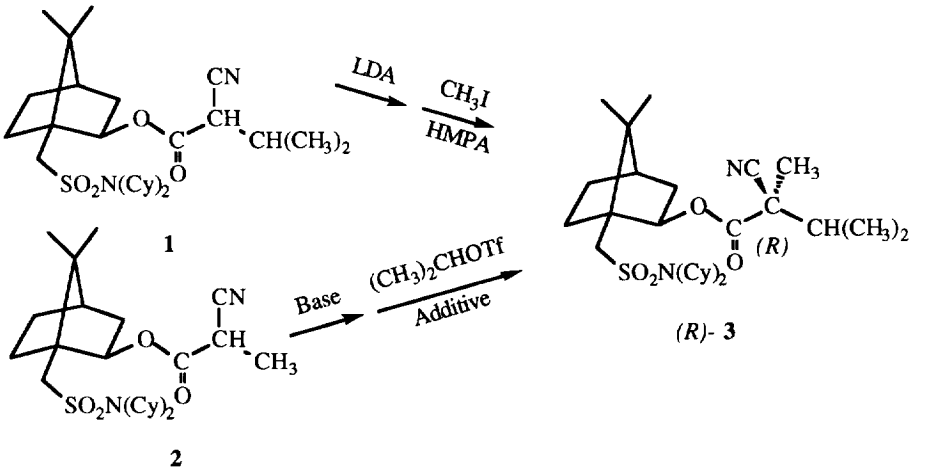


α-MeVal

By applying this method we may employ different strategies to obtain both enantiomers of the target molecule: i) by developing the synthesis of one enantiomer and using the antipode of the chiral auxiliary to obtain the other enantiomer, which is obvious, ii) by conveniently changing the alkyl chain in the substrate and electrophile and iii) by developing a divergent synthesis from the intermediate alkylated cyano ester as both functional groups can be transformed in the amino and the acid moiety.

First we tried the second option, bearing in mind that if we use an alkyl halide as the electrophile this must be a reactive one.[7] This discards the possibility of using isopropylhalides as reagents and we substituted them for the more reactive isopropyltriflate.[8] (Scheme 1)

Diastereoselective methylation of *(2RS) (1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3-methylbutanoate **1** was performed by generation of the enolate with lithium diisopropylamide for one hour in dry THF at -78 °C, followed by the addition of methyl iodide in the presence of hexamethylphosphoramide (HMPA) to yield *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2,3-dimethylbutanoate **3** as a mixture of diastereoisomers (d. r. = 82/18) in 96 % yield. The major diastereoisomer *(R)*-**3** was isolated in diastereomerically pure form by selective recrystallisation in hexane.



1

2

Scheme 1

Table 1. Reaction of **3** with Isopropyl Triflate.

Base	Additive (mol)[a]	time [h]	yield [%]	*(R/S)*
LDA	-	4	30	65/35
LDA	HMPA (1.5)	4	37	48/52
LDA[b]	-	4	30	65/35
LDA	HMPA[c]	4	40	40/60
LDA	Et_2ClAl (1)	12	-	-
LDA	$TiCl_4/Ti(i\text{-}OPr)_4$ (1/0.5)	12	-	-
LDA	$MgCl_2$ (0.5)	4	20	60/40
LDA	$TfOBBu_2$ (1)	12	-	-
LDA[d]	-	12	-	-
LDA[d]	HMPA (0.5)	12	-	-
LiHMDS	-	4	55	65/35
NaHMDS	-	4	48	64/36
KHMDS	-	4	15	52/48

[a] per mol of substrate. [b] Inverse addition. [c] The enolate was generated in the presence of HMPA as cosolvent (THF/HMPA 9/1).

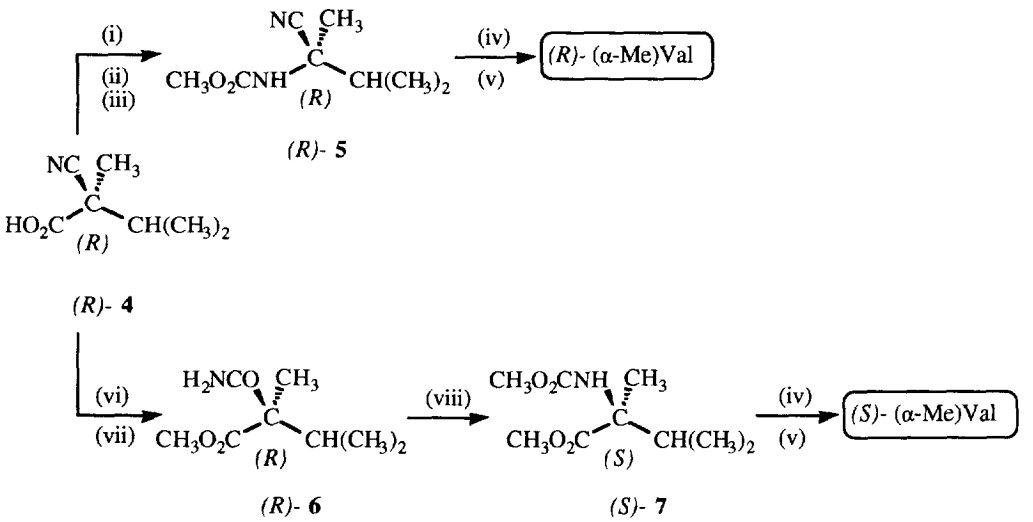
[d] The enolate was generated in the presence of the electrophile.

Diastereoselective isopropylation of *(2RS) (1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate **2** was carried out by generation of the enolate with base for one hour in dry THF at -78 °C, followed by the addition of isopropyl triflate under different conditions.

As shown in table 1 when LDA was used as the base we only obtained moderate yields of the alkylated product, with a very poor diastereomeric ratio in the presence or absence of HMPA. Moreover, the sense of induction was opposite to that observed when alkyl halides were used as electrophiles[7,9] which was attributed to the coordinating ability of the triflate and their competitive attack on the enolate from the coordination sphere of lithium. To prove this hypothesis we generated the enolate in the presence of a large amount of HMPA in order to occupy the coordination sphere of lithium with this coordinating agent before the addition of the electrophile and in this case we observed a reversal in the sense of asymmetric induction although the ratio of distereoisomers was only 60/40 in favour of the *S* compound. Substitution in the enolate of lithium for other metals did not improve the results as the reaction failed in all cases except when we used magnesium chloride. The reaction also failed when we tried to generate the enolate in the presence of the electrophile in order to improve the results by avoiding the formation of agregates.[10] With the use of hexamethyldisilazanes as bases we obtained slightly better yields but with the same diastereoselectivity and sense of induction.

The diastereomeric ratio of the products was determined from the crude reaction spectra by integration of the ^1H NMR (300 MHz) absorptions of the methyne proton of the ester after the addition of the lanthanide shift reagent $Eu(fod)_3$ to observe separate signals for both diastereoisomers. The absolute configuration of the newly-formed chiral centre was assigned based on that of the final amino acid.

Next we tried a divergent synthesis of *R* and *S* α-methylvaline from the diastereomerically pure *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2,3-dimethylbutanoate *(R)*-**3** obtained by recrystallisation of the diastereomeric mixture in hexane.



(i) PCl_5, (ii) NaN_3, (iii) MeOH, Δ, (iv) 20 % HCl, (v) propylene oxide, EtOH, Δ, (vi) NaOH, H_2O_2, (vii) CH_2N_2, (viii) $Hg(OAc)_2$, NBS, MeOH

Scheme 2

Compound *(R)*-**3** was hydrolysed with 10 % potassium hydroxide in methanol to give the corresponding *(2R)* 2-cyano-2,3-dimethylbutanoic acid *(R)*-**4**, in 96 % yield. Curtius type rearrangement afforded *(2R)*-2-methoxycarbonylamino-2,3-dimethylbutyronitrile *(R)*-**5**. The cyanouretane *(R)*-**5**, obtained in 72 % yield, was deprotected with concomitant hydrolysis of the cyano group by treatment with 20 % hydrochloric acid to afford *(R)*-α-methylvaline hydrochloride from which we obtained the free amino acid in 94 % yield.

Conversely, Hoffman-type rearrangement of the amide *(R)*-**6**, obtained in 68 % yield from *(R)*-**4** by treatment with sodium hydroxide and hydrogen peroxide followed by esterification with diazomethane, afforded *(2S)*-methyl 2-methoxycarbonylamino-2,3-dimethylbutanoate *(S)*-**7** in 59 % yield. The uretane *(S)*-**7** was deprotected by treatment with 20 % hydrochloric acid to afford *(S)*-α-methylvaline hydrochloride from which enantiomerically pure *(S)*-α-methylvaline was obtained in 88 % yield.

To conclude, although the diastereoselective alkylation of chiral cyanoesters is a good method for the synthesis of α-methyl-α-alkylamino acids triflates are not good alternatives to poor electrophiles and it is better, therefore, to develop different degradation processes and obtain both enantiomers using the same chiral auxiliary.

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EXPERIMENTAL

Apparatus: ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity 300 MHz spectrometer in $CDCl_3$, DMSO-d_6 or D_2O, using the solvent signal as the internal standard, chemical shifts are expressed in ppm. 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. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Elemental analyses were determined on a Perkin-Elmer 2400 C, H, N, S analyser.

Chemicals: All reactions were carried out under Argon with magnetic stirring. Solvents were dried prior to use. Lithium diisopropylamide (LDA) was generated *in situ* from diisopropylamine and butyl lithium. Hexamethylphosphoramide, butyl lithium, lithium hexamethyldisilazane (LiHMDS), sodium hexamethyldisilazane (NaHMDS), potassium hexamethyldisilazane (KHMDS), diethylaluminum chloride, titanium (IV) chloride, titanium (IV) isopropoxide, magnesium chloride and dibutylboron triflate were purchased from Aldrich Chemical Co. and used as received. *(2RS) (1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl 2-cyano-3-methylbutanoate **1** and *(2RS) (1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate **2** were prepared following the method described in the literature.[9] TLC was performed on Merck precoated silicagel plates, which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Medium pressure chromatography was performed using 230-400 mesh (Merck) silicagel.

(2R) (1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl 2-cyano-2,3-dimethylbutanoate *(R)*- **3**.

A solution of *(2RS) (1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-3-methylbutanoate **1** (2.02 g, 4 mmol) in dry THF (20 ml) was added to a dry THF solution (100 ml) of lithium diisopropylamide, generated *in situ* from diisopropylamine (480 mg, 4.8 mmol) and butyl lithium (4.4 mmol), under argon at -78 °C. After 1h a solution of methyl iodide (5.68 g, 40 mmol) and HMPA (1.08 g, 6 mmol) in dry THF (20 ml) was added by syringe. The reaction mixture was allowed to warm to room temperature and stirring was continued overnight. The mixture was then quenched with a saturated aqueous NH_4Cl solution (20 ml). Ether extraction, washing with water, drying over $MgSO_4$ and concentration *in vacuo* yielded a mixture of diastereoisomers of *(R)*-**3** as a crude oil in 96 % yield. Purification of the crude product by flash chromatography and recrystallisation from hexane afforded diastereomerically pure *(2R) (1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2,3-dimethylbutanoate *(R)*- **3**.

M.p. 138 °C; $[\alpha]_D$ = - 52.3 (c = 1 in $CHCl_3$); IR 2253, 1742 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.87 (s, 3H), 1.03 (s, 3H), 1.05 (d, 3H, J = 6.9 Hz), 1.12 (d, 3H, J = 6.9 Hz), 1.49 (s, 3H), 1.00-2.10 (m, 27H), 2.24 (m, 1H, J = 6.9 Hz), 2.58 (d, 1H, J = 13.2 Hz), 3.20-3.38 (m, 2H), 3.36 (d, 1H, 13.2 Hz), 4.95 (dd, 1H, J = 7.5 Hz, J = 3.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.9, 19.5, 19.9, 20.3, 21.5, 25.0, 26.1, 26.3, 26.9, 30.5, 31.9, 33.4, 34.1, 39.4, 44.1, 49.2, 49.3, 49.4, 53.3, 57.2, 80.2, 118.9, 168.1. Anal. Calcd. for $C_{29}H_{48}N_2O_4S$: C, 66.88; H, 9.29; N, 5.38; S, 6.16. Found: C, 67.02; H, 9.36; N, 5.47; S, 6.04.

General procedure for isopropyltriflate alkylations

A typical experiment was carried out as follows: A solution of *(2RS) (1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate **2** (478 mg, 1 mmol) in dry THF (5 ml) was added to a dry THF solution (25 ml) of base (1.2 mmol), under argon at -78 °C. After 1h a solution of an organometallic compound was added ocasionally and stirring was continued for 1h at -78 °C. Then isopropyltriflate (2 mmol), and when necessary HMPA (270 mg, 1.5 mmol), in dry THF (10 ml) was added by syringe. The reaction mixture was allowed to warm to room temperature and stirring was continued for the time indicated in table 1. The mixture was then quenched with a saturated aqueous NH_4Cl solution (20 ml). Ether extraction, washing with water, drying over $MgSO_4$ and concentration *in vacuo* yielded a mixture of diastereoisomers of **3** as a crude oil.

(2R) 2-Cyano-2,3-dimethylbutanoic acid *(R)*- **4**.

(2R) (1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl 2-cyano-2,3-dimethylbutanoate *(R)*- **3** (2.08 g, 4 mmol) was added to a solution of 10% 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 by water (15 ml) and washed with ether. The aqueous layer was then acidified and extracted with ether. The organic layer was dried over $MgSO_4$ and concentration *in vacuo* yielded *(2R)* 2-cyano-2,3-dimethylbutanoic acid *(R)*- **4** as a white solid in 96 % yield.

M.p. 53 °C; $[\alpha]_D$ = + 1.7 (c = 1 in $CHCl_3$); IR 2247, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.09 (d, 6H, J = 6.9 Hz), 1.58 (s, 3H), 2.18 (m, 1H, J = 6.9 Hz), 8.68 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.2, 18.9, 20.9, 35.0, 49.8, 118.2, 175.0. Anal. Calcd. for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.21; H, 7.92; N, 10.01.

(2R) 2-Methoxycarbonylamino-2,3-dimethylbutyronitrile *(R)*- **5**.

Phosphorus pentachloride (625 mg, 3 mmol) was added to a solution of *(2R)* 2-cyano-2,3-dimethylbutanoic acid *(R)*- **4** (423 mg, 3 mmol) in dry ether (20 ml) and the reaction mixture was stirred at room temperature for 1h. The ether and most of the phosphorus oxychloride was removed at reduced pressure. The oily residue was dissolved in toluene (20 ml) and the solvent and the residual phosphorus oxychloride distilled under *vacuo*. This operation was repeated to ensure complete removal of the phosphorus oxychloride. The acid chloride was then cooled and dissolved in dry acetone (6 ml). Then a solution of sodium azide (292 mg, 4.5 mmol) in water (2 ml) was added and stirring was continued for 1h. Concentration *in vacuo* yielded a white solid which was extracted with toluene. The organic layer was dried over $MgSO_4$ 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 (hexane/ether 1:2 as eluent) afforded 367 mg of *(2R)* 2-methoxycarbonylamino-2,3-dimethylbutyronitrile *(R)*- **5** as an oil in 72 % yield.

Oil; $[\alpha]_D$ = + 10.5 (c = 2 in $CHCl_3$); IR 3332, 2239, 1713 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.01 (d, 3H, J = 6.9 Hz), 1.09 (d, 3H, J = 6.9 Hz), 1.56 (s, 3H), 2.23 (m, 1H, J = 6.9 Hz), 3.68 (s, 3H), 4.99 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.3, 17.5, 21.4, 35.1, 52.4, 55.2, 119.8, 154.9. Anal. Calcd. for $C_8H_{14}N_2O_2$: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.22; H, 8.36; N, 16.67.

(R) -α-Methylvaline

(2R) 2-Methoxycarbonylamino-2,3-dimethylbutyronitrile *(R)*- **5** (340 mg, 2 mmol) was hydrolysed by refluxing for 12 h with 20 % aqueous hydrochloric acid (30 ml). After filtration and extraction with ether the solution was evaporated under *vacuo*. The residue was dissolved in water and evaporated under reduced pressure to expel the excess hydrochloric acid. Then ethanol (6 ml) and propylene oxide (2 ml) were added and the mixture was refluxed for 30 min. After removal of ethanol the white residue was dissolved in distilled water and eluted through a C18 reverse-phase sep-pak cartridge. Removal of water afforded 246 mg of *(R)*-α-methylvaline in 94 % yield.

M.p. 215 °C (dec); $[\alpha]_D$ = + 3.9 (c = 1.3 in water); IR 3550-2500, 1683 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 0.78 (d, 3H, J = 6.9 Hz), 0.82 (d, 3H, J = 6.9 Hz), 1.27 (s, 3H), 1.96 (m, 1H, J = 6.9 Hz). ^{13}C NMR (D_2O-DMSO-d_6, 75 MHz) δ 15.3, 16.6, 20.1, 33.5, 79.94, 176.8. Anal. Calcd. for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 55.02; H, 9.76; N, 10.82.

(2R) Methyl 2-carbamoyl-2,3-dimethylbutanoate *(R)*- **6**.

(2R) 2-Cyano-2,3-dimethylbutanoic acid *(R)*- **4** (423 mg, 3 mmol) was dissolved in a 1N aqueous solution of NaOH (3.5 ml). To this stirred solution were added successively 30 % hydrogen peroxide (10 ml) and a 10 % aqueous solution of NaOH (5 ml) and stirring was continued for another 12 h. The resulting mixture was acidified and extracted with ether. The organic layer was dried over $MgSO_4$ and after filtration diazomethane was added. The solvent was removed under reduced pressure and the resulting residue purified by flash chromatography (ether as eluent) to afford 353 mg of *(2R)* methyl 2-carbamoyl-2,3-dimethylbutanoate *(R)*- **6** as a white solid in 68 % yield.

M.p. 69 °C; $[\alpha]_D$ = - 45.8 (c = 1 in $CHCl_3$); IR 3418, 1720, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (d, 3H, J = 6.6 Hz), 0.87 (d, 3H, J = 6.6 Hz), 1.24 (s, 3H), 2.40 (m, 1H, J = 6.6 Hz), 3.70 (s, 3H), 5.93

(brs, 1H), 6.73 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.9, 17.3, 18.3, 35.7, 52.5, 58.3, 173.2, 175.1. Anal. Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.61; H, 8.59; N, 7.96.

(2S) Methyl 2-methoxycarbonylamino-2,3-dimethylbutanoate *(S)*- **7**.

Dry methanol (1.92 g, 60 mmol) and a solution of NBS (463 mg, 2.6 mmol) in dry DMF (3 ml) were added at room temperature to a solution of *(2R)* methyl 2-carbamoyl-2,3-dimethylbutanoate *(R)*- **6** (346 mg, 2 mmol) and $Hg(OAc)_2$ (765 mg, 2.4 mmol) in dry DMF (10 ml). The reaction was stirred for 12 h at room temperature and the resulting mixture was evaporated under *vacuo*. The solid residue was extracted with ether washed successively with water, 5 % hydrochloric acid and saturated aqueous $NaHCO_3$ solution, the organic layer dried over $MgSO_4$, the solvent removed under reduced pressure and the resulting product purified by flash chromatography (ether as eluent) to afford 239 mg of *(2S)* methyl 2-methoxycarbonylamino-2,3-dimethylbutanoate *(S)*- **7** as an oil in 59 % yield.

Oil; $[\alpha]_D$ = - 2.2 (c = 1 in $CHCl_3$); IR 3356, 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.85 (d, 3H, J = 6.9 Hz), 0.90 (d, 3H, J = 6.9 Hz), 1.38 (s, 3H), 2.08 (m, 1H, J = 6.6 Hz), 3.59 (s, 3H), 3.69 (s, 3H), 5.23 (brs, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 17.1, 17.3, 18.8, 35.2, 51.8, 52.2, 62.9, 155.7, 174.2. Anal. Calcd. for $C_9H_{17}NO_4$: C, 53.19; H, 8.43; N, 6.89. Found: C, 52.98; H, 8.41; N, 6.96.

(S) -α-Methylvaline

(2S) Methyl 2-methoxycarbonylamino-2,3-dimethylbutanoate *(S)*- **7** (340 mg, 2 mmol) was hydrolysed by refluxing for 12 h with 20 % aqueous hydrochloric acid (30 ml). After filtration and extraction with ether the solution was evaporated under *vacuo*. The residue was dissolved in water and evaporated under reduced pressure to expel the excess hydrochloric acid. Then ethanol (6 ml) and propylene oxide (2 ml) were added and the mixture was refluxed for 30 min. After removal of ethanol the white residue was dissolved in distilled water and eluted through a C18 reverse-phase sep-pak cartridge. Removal of water afforded 230 mg of *(S)*-α-methylvaline in 88 % yield.

M.p. 215 °C (dec); $[\alpha]_D$ = - 4 (c = 1.3 in water) [lit.[11] $[\alpha]_D$ = - 4 (c = 1.3 in water)]; IR 3550-2500, 1683 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 0.78 (d, 3H, J = 6.9 Hz), 0.82 (d, 3H, J = 6.9 Hz), 1.27 (s, 3H), 1.96 (m, 1H, J = 6.9 Hz). ^{13}C NMR (D_2O-DMSO-d_6, 75 MHz) δ 15.3, 16.6, 20.1, 33.5, 79.94, 176.8.

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