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Synthesis of *(R)*- and *(S)*-2-amino-2-methylbutanoic acid (Iva) in enantiomerically pure form

Carlos Cativiela*, Maria D. Diaz-de-Villegas, and José A. Galvez

Instituto de Ciencia de Materiales de Aragón, Departamento de Química Orgánica, Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza, Spain

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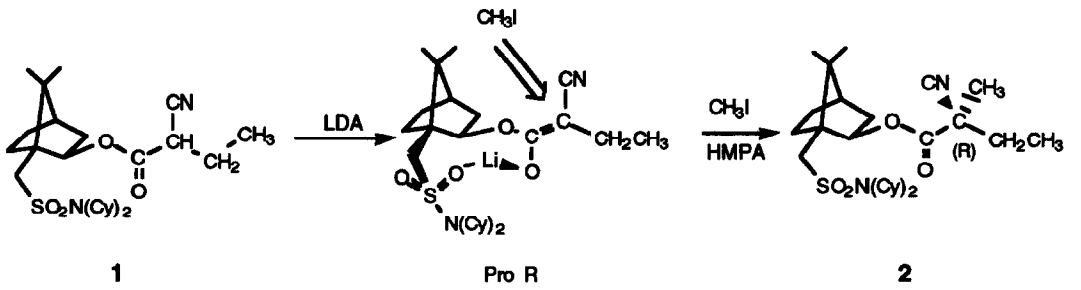
Abstract: A new strategy for the preparation of both enantiomers of 2-amino-2-methylbutanoic acid (Iva) based on diastereoselective alkylation of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanoesters and the corresponding degradation process is described.

Non-proteinogenic, unnatural α-aminoacids have attracted the attention of numerous researchers[1] in connection with the design and synthesis of enzyme inhibitors, as potential constituents of pharmaceuticals, as optically active starting materials for a variety of synthetic applications, and for the study of enzymatic reaction mechanisms. In particular, α,α-disubstituted α-amino acids have been the subject of considerable research in the last few years. A large number of these studies have focused on chiral (-)-*(2R)*-2-amino-2-methylbutanoic acid (D-Iva),[2] which is an important constituent of a class of microbial peptide antibiotics, known as the peptaibols.[3] The presence of α,α-disubstituted α-aminoacids in these peptides is thought to play a crucial role in their ability to form trans-membrane helical ion channels. Moreover, it is known[4] 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.[5]

In this paper, we present a very efficient strategy for the preparation of both enantiomers of 2-amino-2-methylbutanoic acid (Iva) based on the previously described[6] diastereoselective alkylation of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanoesters and the corresponding degradation process.

Diastereoselective methylation of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanobutanoate **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), as shown in Scheme 1. The reaction afforded *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methylbutanoate **2**[7] as a mixture of diastereomers

(d.r. = 80/20, absolute configuration of the major diastereomer, 2R) from which the major diastereomer was isolated in diastereomerically pure form by selective crystallization in diethyl ether.

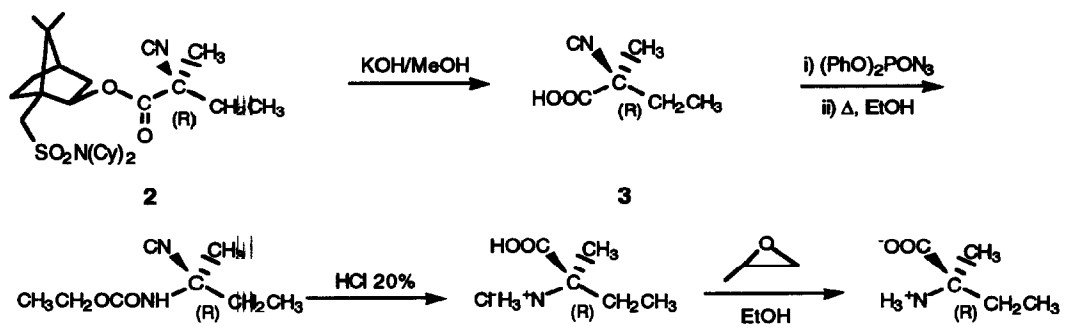


1 Pro R 2

SCHEME 1

The diastereomeric ratio of the products was determined in the crude reaction spectrum by integration of the ^{13}C NMR (75 MHz) absorptions of both the carbonyl and the cyano carbons of the cyano ester and the absolute configuration of the major diastereomer was assigned on the basis of that of the final product.

(2R)-(1S,2R,4R)-10-Dicyclohexylsulfamoylisobornyl 2-cyano-2-methylbutanoate **2** was hydrolysed with 10% potassium hydroxide in methanol to the corresponding *(2R)*-2-cyano-2-methylbutanoic acid **3**[8] which was subjected to Curtius-type rearrangement to afford *(2R)* 2-ethoxycarbonylamino-2-methylbutyronitrile **4**[9]. The cyanourethane **4**, obtained in 65% yield was deprotected with concomitant hydrolysis of the cyano group by treatment with 20% hydrochloric acid to afford *(2R)*-2-amino-2-methylbutanoic acid hydrochloride **5** from which enantiomerically pure *(2R)*-2-amino-2-methylbutanoic acid (D-Iva) **6**[10] was obtained in 93% overall yield for the two steps. (Scheme 2).



2 3 4 5 6

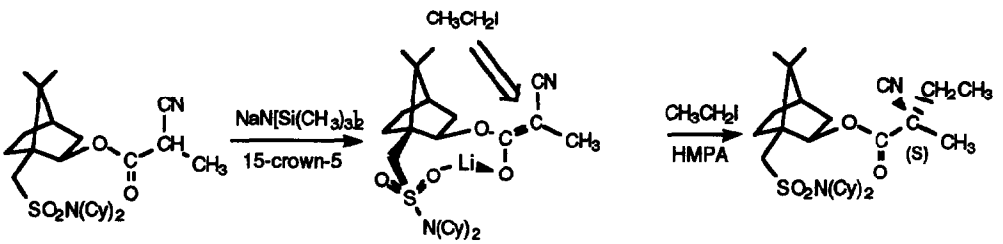
SCHEME 2

The $[\alpha]_D$ value ($[\alpha]_D$ = -11.28 c = 5% in H_2O)[11] of compound **6** confirmed its chiral purity as well as the absolute configuration assigned to all compounds.

The stereochemical results are consistent with the model proposed for the alkylation of the enolate generated by 1,4-addition of hydride to E *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanocinnamate.[12]

In order to obtain enantiomerically pure *(2S)*-2-amino-2-methylbutanoic acid (L-Iva) we have tested diastereoselecive ethylation of the enolate generated from *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyanopropanoate **7**. Using the previously described protocol a substantial decrease in yield and the level of diastereoselectivity (d.r. = 70/30) was observed. In this case the major diastereoisomer was *(2S)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methylbutanoate as expected.

In our case the addition of ethyl iodide to a preformed solution of the enolate generated by the addition of sodium bis(trimethylsilyl)amide to **7** in the presence of 15-crown-5-ether at -78 °C, as recently described by Baldwin and associates,[13] did not improve the results since we obtained *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methylbutanoate as a mixture of diastereomers (d.r. = 60/40, absolute configuration of the major diastereomer, 2S) in 70% yield. (Scheme 3)



7 Pro R **2**

SCHEME 3

So in order to obtain enantiomerically pure 2-amino-2-methylbutanoic acid **6** of S configuration the best strategy would be to use the enantiomer of the chiral alcohol. The use of this method for the general synthesis of α,α-disubstituted α-amino acids is now in progress.

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(7) *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-cyano-2-methylbutanoate **2.** M.p. = 133°C. $[\alpha]_D$ = -55.6 (c = 1 in $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 0.86 (s, 3H), 1.05 (s, 3H), 1.14 (t, 3H, J = 7.2 Hz), 1,53 (s, 3H), 1.00-2.20 (m, 29H), 2.59 (d, 1H, J = 13.5 Hz), 3.18-3.32 (m, 2H), 3.37 (d, 1H, J = 13.5 Hz), 4.97 (dd, 1H, J = 7.8 Hz, J = 2.7 Hz). ^{13}C NMR ($CDCl_3$) δ 9.5, 19.8, 20.2, 22.9, 25.0, 26.1, 26.2, 26.8, 30.5, 30.5, 31.9, 33.3, 39.3, 44.2, 44.3, 49.2, 49.5, 53.4, 57.3, 80.0, 119.95, 167.9. IR (nujol) ν = 2253, 1739 cm $^{-1}$.

(8) *(2R)*-2-cyano-2-methylbutanoic acid **3.** Oil. $[\alpha]_D$ = + 3.1 (c = 1 in $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1,08 (t, 3H, J = 7.2 Hz), 1.59 (s, 3H), 1.76-2.05 (m, 2H), 8.36 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 9.6, 22.7, 31.4, 44.9, 119.3, 174.0. IR (nujol) ν = 3500-2500, 2250, 1725 cm $^{-1}$.

(9) *(2R)*-2-ethoxycarbonylamino-2-methylbutyronitrile **4.** Oil. $[\alpha]_D$ = -1.7 (c = 0.8 in $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ 1.03 (t, 3H, J = 7.5 Hz), 1.24 (t, 3H, J = 6.9 Hz), 1,62 (s, 3H), 1.79-2.02 (m, 2H), 4.14 (c, 2H, J = 6.9 Hz), 4.92 (brs, 1H). ^{13}C NMR ($CDCl_3$) δ 8.3, 114.4, 24.6, 32.6, 51.4, 61.5, 120,2, 154.5. IR (nujol) ν = 3326, 2240, 1717 cm $^{-1}$.

(10) *(2R)*-2-amino-2-methylbutanoic acid **6.** M.p. = >300°C. $[\alpha]_D$ = -11.28 (c = 5% in H_2O). ^{1}H-NMR (D_2O) δ 0.76 (t, 3H, J = 7.8 Hz), 1.32 (s, 3H), 1.54-1.83 (m, 2H). IR (nujol) ν = 3300-2250, 1600, cm $^{-1}$.

(11) $[\alpha]_D$ = -11.28, c = 5% in H_2O for D-isovaline,.Bake, C.G.; Fu, S.C.J.; Birnbaum, S.M.; Sober, H.A., Greenstein, J.P.; *J. Am. Chem. Soc.*, **1952**, *74*, 4701.

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