# New synthesis of 7-azabicyclo[2.2.1]heptane-1-carboxylic acid 

Alberto Avenoza, ${ }^{\text {a,* }}$ Carlos Cativiela, ${ }^{\text {b }}$ Jesús H. Busto, ${ }^{\text {a }}$ Miguel A. Fernández-Recio, ${ }^{\text {a }}$ Jesús M. Peregrina ${ }^{\text {a }}$ and Fernando Rodríguez ${ }^{\text {a }}$<br>${ }^{\text {a}}$ Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, U.A.-C.S.I.C., 26006 Logroño, Spain<br>${ }^{\mathrm{b}}$ Departmento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza, Spain

Received 25 August 2000; revised 31 October 2000; accepted 2 November 2000


#### Abstract

This report describes a new synthetic route to 7-azabicyclo[2.2.1]heptane-1-carboxylic acid (Ahc), a constrained proline analogue, in which the key step is the Diels-Alder reaction using methyl 2-benzamidoacrylate as dienophile. © 2001 Elsevier Science Ltd. All rights reserved.


## 1. Introduction

The design and use of modified peptides in order to elucidate the spatial requirements for biologically active peptides and, consequently, to probe relationships between conformation and activity has attracted significant attention. ${ }^{1-3}$ One of the several ways to reach this goal is the use of conformationally constrained $\alpha$-amino acids, ${ }^{4,5}$ such as modified prolines, because of the high frequency of this amino acid at the central residues of the $\beta$-turn conformation. ${ }^{6,7}$

In this context, the 7-azabicyclo[2.2.1]heptane-1-carboxylic acid (Ahc) (1), an achiral compound, is particularly attractive as a rigid proline analogue. The only previous synthesis of $\mathbf{1}$ was carried out by Rapoport and co-workers from tert-butyl $N$-benzylthiopyroglutamate as a chiral substrate involving a transannular alkylation as a key step. ${ }^{8}$ Furthermore, Han, Hodge and co-workers have introduced this amino acid as a proline analogue in two bioactive molecules: a boroarginine thrombin inhibitor ${ }^{9}$ and a new class of HIV-1 protease inhibitor ${ }^{10}$ (Fig. 1).

## 2. Results and discussion

As part of our research project on the synthesis of new nonproteinogenic and unusual $\alpha$-amino acids, our interest in the amino acids with 7-azabicyclo[2.2.1]heptane skeleton as conformationally restricted proline analogues ${ }^{11-13}$ has prompted us to develop a new method to obtain the proline

[^0]analogue $\mathbf{1}$ in gram scale, using an achiral starting material. In the course of our research about hydroxy- $\alpha, \alpha$-disubsti-tuted- $\alpha$-amino acids and particularly in the synthesis of both stereoisomers of 1-amino-4-hydroxycyclohexane-1-carboxylic acid, the Diels-Alder cycloaddition of Danishefsky's diene to methyl 2-acetamidoacrylate was used as a key step. ${ }^{14}$

Our initial plan was to use the same precursor in the synthesis of amino acid 1, but we observed that this reaction worked with better results when the acetamide group was substituted by benzamide group. However, while methyl 2-acetamidoacrylate is easily obtained from commercially available 2-acetamidoacrylic acid, the corresponding 2-benzamide derivative must be synthesised. In this sense, we developed a new synthesis of methyl 2-benzamidoacrylate (4) starting from D,L-serine (2), and using a modified procedure described in the literature for different $\alpha, \beta$ dehydroamino acids. ${ }^{15,16}$ Initially, D,L-serine methyl ester hydrochloride (3) was obtained from D,L-serine, following the Mckillop's procedure. ${ }^{17}$ The $N$ - and $O$-benzoylation of this ester was achieved by the use of two equivalents of benzoyl chloride in the presence of triethylamine. Further elimination of benzoyl group by the action of DBU gave the required dienophile 4 in good yield (Scheme 1).

Reaction of dienophile 4 with Danishefsky's diene in toluene gave a mixture of two cycloadducts: methyl


1
Figure 1. Structure of 7-azabicyclo[2.2.1]heptane-1-carboxylic acid (Ahc).




Scheme 2. Reagents and conditions: (a) Danishefsky's diene, toluene, reflux, 72 h ; (b) (i) $0.005 \mathrm{~N} \mathrm{HCl}-\mathrm{THF}(1: 4), 7 \mathrm{~h}$; (ii) $\mathrm{DBU}, \mathrm{MeOH}, 5^{\circ} \mathrm{C}, 12 \mathrm{~h}, 55 \%$; (c) $\mathrm{H}_{2}, \mathrm{Pd} / \mathrm{C}, \mathrm{CH}_{2} \mathrm{Cl}_{2}, 24 \mathrm{~h}, 95 \%$; (d) 2-trimethylsilyloxy-1,3-butadiene, $\mathrm{ZnI}_{2}, \mathrm{CH}_{2} \mathrm{Cl}_{2}$, reflux, 24 h ; (e) $0.005 \mathrm{~N} \mathrm{HCl}-\mathrm{THF}, 94 \%$.


Scheme 3. Reagents and conditions: (a) (i) L-selectride ${ }^{\circledR}$, THF, $-78^{\circ} \mathrm{C}$; (ii) $\mathrm{MsCl}, \mathrm{DIEA}, \mathrm{CH}_{2} \mathrm{Cl}_{2}, 68 \%$ two steps; (b) ${ }^{t} \mathrm{BuOK}, \mathrm{THF}, 81 \%$; (c) 6 N HCl, reflux, $99 \%$; (d) propylene oxide, EtOH , reflux, $89 \%$.

1-benzamido-c-2-methoxy-4-trimethylsilyloxy-3-cyclo-hexene- $r$-1-carboxylate and methyl 1-benzamido- $t$ - 2 -meth-oxy-4-trimethylsilyloxy-3-cyclohexene-r-1-carboxylate, corresponding to endo and exo attack respectively. This mixture of products was treated with a $0.005 \mathrm{~N} \mathrm{HCl}-\mathrm{THF}$ (1:4) solution and DBU in methanol at $5^{\circ} \mathrm{C}$ to give the corresponding enone 5. Hydrogenation of this product using $10 \%$ palladium-carbon as a catalyst in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ at room temperature, gave quantitatively ketone 6 (Scheme 2). The overall yield of this sequence was $52 \%$ on a multigram scale.

Our attention then focused on improving the yield of $\mathbf{6}$, using less steps and employing other dienes. Reaction of 4 with 2-trimethylsilyloxy-1,3-butadiene in the presence of $\mathrm{ZnI}_{2}$ as a catalyst, hydroquinone as a polymerisation inhibitor, using $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ as a solvent and further treatment of the reaction mixture with a $0.005 \mathrm{~N} \mathrm{HCl}-\mathrm{THF}(1: 4)$ solution, allowed to obtain directly ketone 6 with a $94 \%$ yield on the same scale ( 4 g ) as in the previous procedure (Scheme 2).

To obtain the constrained proline, we needed the compound in which the hydroxyl and benzamide groups adopt trans positions in the cyclohexane ring. Reduction of ketone 6 with L-selectride ${ }^{\circledR}$ at $-78^{\circ} \mathrm{C}$ in THF gave a mixture of alcohols in a ratio of $90 / 10$ in favour to the trans stereoisomer. Treatment of this mixture with methanesulphonyl chloride in diisopropylethylamine (DIEA) and further
purification by silica gel column chromatography furnished the corresponding methanesulphonate derivative 7. Basepromoted internal nucleophilic displacement of the methanesulphonate group, thereby yielding the 7-azabicyclo[2.2.1]heptane system of the constrained proline analogue, gave the desired compound $\mathbf{8}$ in high yield. The deprotected proline analogue 9 was obtained in $99 \%$ yield $^{18}$ from the hydrolysis of compound $\mathbf{8}$ and free amino acid $\mathbf{1}$ could be obtained from 9 by treatment with propylene oxide in ethanol ${ }^{18}$ (Scheme 3).

## 3. Conclusion

In summary, we have developed a new and short methodology for the synthesis of a type of constrained proline (Ahc) with an excellent yield from an achiral starting material ( $51 \%$, five steps). In a future work, we will introduce this analogue in small peptides as a restricted proline analogue and we will conduct several structural studies.

## 4. Experimental

### 4.1. General procedure

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F ${ }_{254}$ plates. Column chromatography was performed using silica
gel 60 (230-400 mesh). ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra were recorded on a Bruker ARX-300 spectrometer at 300 MHz $\left({ }^{1} \mathrm{H}\right)$ and at $75 \mathrm{MHz}\left({ }^{13} \mathrm{C}\right)$, at $20^{\circ} \mathrm{C}$, and are reported in ppm downfield from TMS (chemical shifts are reported in ppm on the $\delta$ scale, coupling constants in Hz ). Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 341 polarimeter in an 1 dm cell of 1 mL capacity. Microanalyses were carried out on a CE Instruments EA-1110 analyser and were in good agreement with the calculated values. IR spectra were recorded on a PerkinElmer FT-IR Spectrum 1000 spectrometer.
4.1.1. Methyl 2-benzamidoacrylate (4). To a solution of D,L-serine methyl ester hydrochloride ( $4.5 \mathrm{~g}, 28.9 \mathrm{mmol}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ were added in portions $\mathrm{Et}_{3} \mathrm{~N}(9.6 \mathrm{~g}, 98.2 \mathrm{mmol})$ and $\mathrm{BzCl}(9.3 \mathrm{~g}, 66.7 \mathrm{mmol})$ kept under an inert atmosphere. The mixture was stirred for 7 h at room temperature and then was washed with a saturated solution of $\mathrm{NaHCO}_{3}$ $(2 \times 50 \mathrm{~mL})$, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated. The white solid was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$, kept under inert atmosphere, at $5^{\circ} \mathrm{C}$ and then $\mathrm{DBU}(5.2 \mathrm{~g}$, 33.9 mmol ) was added. After 3 h stirring at the same temperature, the reaction was washed with water ( 50 mL ) and a saturated solution of $\mathrm{NaHCO}_{3}(2 \times 50 \mathrm{~mL})$. The organic layer was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated to obtain 5.5 g of compound 4 as an oil (93\%). Anal. calcd for $\mathrm{C}_{11} \mathrm{H}_{11} \mathrm{NO}_{3} ; \mathrm{C}, 64.38 ; \mathrm{H}, 5.40 ; \mathrm{N}$, 6.83.; found C, 64.46; H, 5.32; N, 6.74; IR $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2}, \mathrm{~cm}^{-1}\right)$ : $3410(\mathrm{NH}), 1720(\mathrm{CO}), 1678(\mathrm{CON}) ;{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta$ $3.85\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3} \mathrm{O}\right) ; 5.95-6.02(\mathrm{~m}, 1 \mathrm{H}) ; 6.79(\mathrm{~s}, 1 \mathrm{H}), 7.43-$ 7.58 (m, 3H, Arom.); 7.79-7.88 (m, 2H, Arom.); 8.55 (br s, $1 \mathrm{H}, \mathrm{NH}) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 52.9\left(\mathrm{CH}_{3} \mathrm{O}\right) ; 108.6\left(\mathrm{C}_{3}\right)$; 126.7, 128.6 (Arom.); 130.8 (C2); 131.8, 134.0, (Arom.); 164.5, 165.5 (COO, CON).
4.1.2. Methyl 1-benzamido-4-oxo-2-cyclohexene-1-carboxylate (5). Danishefsky's diene ( $6.5 \mathrm{~mL}, 33.4 \mathrm{mmol}$ ) was added to a solution of methyl 2-benzamidoacrylate 4 $(1.7 \mathrm{~g}, 8.3 \mathrm{mmol})$ in dry toluene $(80 \mathrm{~mL})$ under an inert atmosphere. After stirring for 24 h , at reflux, another 8.3 mmol of 4 was added. After two days stirring at the same temperature, the solvent was evaporated in vacuo and a solution of $0.005 \mathrm{~N} \mathrm{HCl}-\mathrm{THF}(1: 4)(40 \mathrm{~mL})$ was added to the residue. The reaction mixture was stirred for 15 h at $20^{\circ} \mathrm{C}$, the solvent was evaporated and the residue was chromatographed on silica gel, eluting with hexane-ethyl acetate (2:8). The mixture was dissolved in $\mathrm{CH}_{2} \mathrm{Cl}_{2}(75 \mathrm{~mL})$ and DBU ( $2.7 \mathrm{~mL}, 18.2 \mathrm{mmol}$ ) was added. The reaction mixture was stirred for 24 h at $2^{\circ} \mathrm{C}$ and the solution was washed with $0.5 \mathrm{~N} \mathrm{HCl}(60 \mathrm{~mL})$. The aqueous phase was extracted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(5 \times 30 \mathrm{~mL})$ and the combined organic phases were dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered and evaporated. The residue was chromatographed on silica gel eluting with hexane-ethyl acetate (1:1), to yield 2.5 g of enone 5 as a white solid ( $55 \%$ ). Mp: $126-7^{\circ} \mathrm{C}$; Anal. calcd for $\mathrm{C}_{15} \mathrm{H}_{15} \mathrm{NO}_{4} ; \mathrm{C}, 65.92 ; \mathrm{H}, 5.53 ; \mathrm{N}, 5.13$.; found C, 65.84 ; H, 5.59; N, 5.05; IR $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2}, \mathrm{~cm}^{-1}\right): 3433(\mathrm{NH}), 1743$ (CO), $1685(\mathrm{CON}) ;{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 2.50-2.65(\mathrm{~m}$, $\left.4 \mathrm{H}, 2 \mathrm{H}_{5}+2 \mathrm{H}_{6}\right) ; 3.82\left(\mathrm{~s}, 3 \mathrm{H}, \quad \mathrm{CH}_{3} \mathrm{O}\right) ; 6.14(\mathrm{~d}, 1 \mathrm{H}$, $\left.J_{3-2}=10.0 \mathrm{~Hz}, \mathrm{H}_{3}\right) ; 7.10-7.20\left(\mathrm{~m}, 2 \mathrm{H}, \mathrm{NH}+\mathrm{H}_{2}\right) ; 7.41-$ 7.48 (m, 2H, Arom.); 7.50-7.58 (m, 1H, Arom.); 7.767.82 (m, 2H, Arom.); ${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 31.6,33.7\left(\mathrm{C}_{5}\right.$,
$\left.\mathrm{C}_{6}\right) ; 53.4\left(\mathrm{CH}_{3} \mathrm{O}\right) ; 58.5\left(\mathrm{C}_{1}\right) ; 127.1,128.6,130.5,132.2\left(\mathrm{C}_{3}\right.$, Arom.); 133.0 (Arom.); 146.9 ( $\mathrm{C}_{2}$ ); 167.0, 171.2 (COO, CON); 197.2 (CO).
4.1.3. Methyl 1-benzamido-4-oxocyclohexane-1-carboxylate (6). Method A: A solution of enone $5(4 \mathrm{~g}, 14.63 \mathrm{mmol})$ in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(200 \mathrm{~mL})$ was hydrogenated at atmospheric pressure for 24 h at room temperature, using $10 \%$ palladium-carbon ( 1 g ) as a catalyst. After the removal of the catalyst and the solvent, the residue was chromatographed on silica gel eluting with hexane-ethyl acetate (6:4), to yield 3.8 g of compound 6 as a white solid. (95\%). Method B: 2-Trimethylsilyloxy-1,3-butadiene $(8.3 \mathrm{~g}, 58.5 \mathrm{mmol})$ was added to a solution of methyl 2-benzamidoacrylate $4(4.0 \mathrm{~g}, 19.5 \mathrm{mmol})$ and $\mathrm{ZnI}_{2}(6.3 \mathrm{~g}$, 19.5 mmol ) in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(90 \mathrm{~mL})$ kept under an inert atmosphere. After stirring for 24 h , at reflux, the solution was filtered and washed with water $(1 \times 20 \mathrm{~mL})$, the organic phase was dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. Then, a solution of $0.005 \mathrm{~N} \mathrm{HCl}-\mathrm{THF}(1: 4)(40 \mathrm{~mL})$ was added to the residue and the reaction mixture was stirred for 5 h at room temperature. The solvent was evaporated and the mixture was diluted with $\mathrm{CH}_{2} \mathrm{Cl}_{2}(75 \mathrm{~mL})$ and washed with brine $(2 \times 20 \mathrm{~mL})$. The combined organic phases were dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$, filtered, and evaporated. The residue was chromatographed on silica gel eluting with hexane-ethyl acetate (6:4) to yield 5.0 g of compound 6 as a white solid. $(94 \%) . \mathrm{Mp}$ : $133-4^{\circ} \mathrm{C}$; Anal. calcd for $\mathrm{C}_{15} \mathrm{H}_{17} \mathrm{NO}_{4} ; \mathrm{C}, 65.44 ; \mathrm{H}, 6.22$; N, 5.09; found C, 65.67; $\mathrm{H}, 6.27 ; \mathrm{N}, 5.25$; IR $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2}, \mathrm{~cm}^{-1}\right): 3430(\mathrm{NH}), 1743$ (COO), 1716 (CO), 1673 (CON); ${ }^{1} \mathrm{H}$ NMR ( $\mathrm{CDCl}_{3}$ ): $\delta$ $2.40-2.58(\mathrm{~m}, 8 \mathrm{H}) ; 3.77\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3} \mathrm{O}\right) ; 6.67(\mathrm{br} \mathrm{s}, 1 \mathrm{H}$, NH ); 7.24-7.54 (m, 3H, Arom.); 7.60-7.81 (m, 2H, Arom.) ; ${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 32.3,36.7\left(\mathrm{C}_{2}, \mathrm{C}_{3}, \mathrm{C}_{5}, \mathrm{C}_{6}\right)$; $52.8\left(\mathrm{CH}_{3} \mathrm{O}\right) ; 58.0\left(\mathrm{C}_{1}\right) ; 127.1,128.6,132.0,133.6$ (Arom.); 167.9, 173.2 (COO, CON); 209.1 (CO).
4.1.4. Methyl 1-benzamido-c-4-methanesulfonyloxycyclo-hexane-r-1-carboxylate (7). Compound 6 ( 4.0 g , 14.5 mmol ) was dissolved in dry THF ( 80 mL ) and L-selectride ${ }^{\circledR}(17.3 \mathrm{~mL}$ of 1 M sol. in THF, 17.3 mmol$)$ was added dropwise at $-78^{\circ} \mathrm{C}$ under an inert atmosphere. After 20 h stirring at the same temperature, the reaction was quenched by the addition of a saturated $\mathrm{NH}_{4} \mathrm{Cl}$ solution $(20 \mathrm{~mL})$. The resulting mixture was allowed to warm up to room temperature, the solvent evaporated and the residue washed with ethyl acetate $(1 \times 50 \mathrm{~mL})$ and $\mathrm{CHCl}_{3} / 2$-propanol (3:1) $(2 \times 30 \mathrm{~mL})$. Evaporation of the solvent gave a residue that was chromatographed on silica gel eluting with hexaneethyl acetate (1:9), obtaining 3.63 g as a mixture of alcohols trans/cis, in a 10:90 ratio (determined by the integration of ${ }^{1} \mathrm{H}$ NMR signals). The mixture of alcohols was dissolved in dry $\mathrm{CH}_{2} \mathrm{Cl}_{2}(70 \mathrm{~mL})$ under an inert atmosphere and diisopropylethylamine ( $4.5 \mathrm{~mL}, 26.2 \mathrm{mmol}$ ) and methanesulfonyl chloride ( $2.0 \mathrm{~mL}, 26.2 \mathrm{mmol}$ ) were then added to this solution at $0^{\circ} \mathrm{C}$. The solution was left to reach room temperature and, after 36 h stirring at room temperature, the mixture was washed with an aqueous solution of $5 \%$ $\mathrm{NaHCO}_{3}$, dried over anhydrous $\mathrm{Na}_{2} \mathrm{SO}_{4}$ and filtered. After the evaporation of the solvent, the residue was chromatographed on a silica gel column, eluting with hexane-ethyl acetate (1:1), to obtain 3.5 g of compound 7 ( $68 \%$ from ketone 6). Mp: $140-2^{\circ} \mathrm{C}$; Anal. calcd for $\mathrm{C}_{16} \mathrm{H}_{21} \mathrm{NO}_{6} \mathrm{~S}$; C,
54.07; H, 5.96; N, 3.94; S, 9.02; found C, 53.98; H, 6.18; N, 3.80; S, 8.84; IR ( $\left.\mathrm{CH}_{2} \mathrm{Cl}_{2}, \mathrm{~cm}^{-1}\right): 3437$ (NH), 1741 (CO), $1672(\mathrm{CON}) ;{ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 1.84-1.96(\mathrm{~m}, 2 \mathrm{H})$; 2.02-2.18 (m, 4H); 2.30-2.43 (m, 2H); 3.06 (s, 3H, $\mathrm{CH}_{3} \mathrm{SO}_{2}$ ); 3.77 (s, $3 \mathrm{H}, \mathrm{CH}_{3} \mathrm{O}$ ); 4.95-5.00 (m, $1 \mathrm{H}, \mathrm{H}_{4}$ ); 6.24 (br s, $1 \mathrm{H}, \mathrm{NH}$ ); 7.40-7.58 (m, 3H, Arom.), 7.737.80 (m, 2H, Arom.); ${ }^{13} \mathrm{C}$ NMR ( $\mathrm{CDCl}_{3}$ ): $\delta 27.1,27.5\left(\mathrm{C}_{2}\right.$, $\left.\mathrm{C}_{3}, \mathrm{C}_{5}, \mathrm{C}_{6}\right) ; 38.8\left(\mathrm{CH}_{3} \mathrm{SO}_{2}\right) ; 52.7\left(\mathrm{CH}_{3} \mathrm{O}\right) ; 58.1\left(\mathrm{C}_{1}\right) ; 77.0$ $\left(\mathrm{C}_{4}\right) ; 127.0,128.6,132.0,133.8$ (Arom.); 167.6; 173.6 (COO, CON).
4.1.5. Methyl $N$-benzoyl-7-azabicyclo[2.2.1]heptane-1carboxylate (8). To a solution of $7(2.4 \mathrm{~g}, 6.7 \mathrm{mmol})$ in dry THF ( 70 mL ) an 1 M solution of ${ }^{t} \mathrm{BuOK}$ in THF $(7.4 \mathrm{~mL}, 7.4 \mathrm{mmol})$ was added under an inert atmosphere, at $-78^{\circ} \mathrm{C}$. After stirring for 1 h at $-78^{\circ} \mathrm{C}$, the reaction was warmed to room temperature and allowed to stand at this temperature for 16 h . The reaction was quenched by the addition of an aqueous 2 N HCl solution ( 8 mL ) and the resulting mixture was extracted with ethyl acetate $(1 \times 30 \mathrm{~mL})$ and $\mathrm{CH}_{2} \mathrm{Cl}_{2}(2 \times 30 \mathrm{~mL})$. The organic layer was dried, filtered and evaporated to give a residue, which was purified by silica gel column chromatography eluting with hexane-ethyl acetate (7:3), to give $1.4 \mathrm{~g}(81 \%)$ of $\mathbf{8}$ as a white solid. Mp: $100-2^{\circ} \mathrm{C}$; Anal. calcd for $\mathrm{C}_{15} \mathrm{H}_{17} \mathrm{NO}_{3} ; \mathrm{C}$, 69.48; H, 6.61; N, 5.40; found C, 69.39; H, 6.78; N, 5.47; IR $\left(\mathrm{CH}_{2} \mathrm{Cl}_{2}, \mathrm{~cm}^{-1}\right): 1740(\mathrm{CO}), 1646$ (CON); ${ }^{1} \mathrm{H}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 1.43-1.55(\mathrm{~m}, 2 \mathrm{H}) ; 1.67-1.97(\mathrm{~m}, 4 \mathrm{H}) ; 2.22-$ $2.35(\mathrm{~m}, 2 \mathrm{H}) ; 3.73\left(\mathrm{~s}, 3 \mathrm{H}, \mathrm{CH}_{3} \mathrm{O}\right) ; 4.14-4.24\left(\mathrm{~m}, 1 \mathrm{H}, \mathrm{H}_{4}\right)$; 7.27-7.46 (m, 3H, Arom.), 7.57-7.64 (m, 2H, Arom.); ${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CDCl}_{3}\right): \delta 30.0,31.7\left(\mathrm{C}_{2}, \mathrm{C}_{3}, \mathrm{C}_{5}, \mathrm{C}_{6}\right) ; 52.0,61.7,67.2$ $\left(\mathrm{CH}_{3} \mathrm{O}, \mathrm{C}_{1}, \mathrm{C}_{4}\right) ; 128.0,128.3,131.1,134.1$ (Arom.); 171.2; 173.9 (COO, CON).
4.1.6. 7-Azabicyclo[2.2.1]heptane-1-carboxylic acid hydrochloride (9). Compound 8 ( $1.0 \mathrm{~g}, 3.85 \mathrm{mmol}$ ) was suspended in an aqueous 6 N HCl solution ( 30 mL ) and heated under reflux for 24 h . The solvent was evaporated in vacuo, the residue was dissolved in water, washed with diethyl ether $(2 \times 10 \mathrm{~mL})$ and the aqueous layer evaporated to give 678 mg of the salt $9(99 \%)$. ${ }^{1} \mathrm{H}$ NMR ( $\left.\mathrm{CD}_{3} \mathrm{OD}\right): \delta$ $1.52-1.80(\mathrm{~m}, 2 \mathrm{H}) ; 1.82-2.02(\mathrm{~m}, 6 \mathrm{H}) ; 3.97-4.06(\mathrm{~m}, 1 \mathrm{H}$, $\left.\mathrm{H}_{4}\right) ;{ }^{13} \mathrm{C}$ NMR $\left(\mathrm{CD}_{3} \mathrm{OD}\right): \delta 28.9,31.9\left(\mathrm{C}_{2}, \mathrm{C}_{3}, \mathrm{C}_{5}, \mathrm{C}_{6}\right) ; 60.0$, $73.1\left(\mathrm{C}_{1}, \mathrm{C}_{4}\right)$; 171.4 (COO).
4.1.7. 7-Azabicyclo[2.2.1]heptane-1-carboxylic acid, Ahc (1). The residue of amino acid hydrochloride 9 ( 58 mg , 0.33 mmol ) was dissolved in ethanol ( 3 mL ) and propylene oxide ( 1 mL ) was added. The mixture was heated under reflux for 2 h and after the removal of the solvent, the residue was dissolved in distilled water ( 2 mL ) and eluted through a $\mathrm{C}_{18}$ reverse-phase Sep-pak cartridge which, after the removal of the water, gave $41 \mathrm{mg}(89 \%)$ of $\alpha$-amino
acid 1 as a white solid. ${ }^{1} \mathrm{H} \operatorname{NMR}\left(\mathrm{D}_{2} \mathrm{O}\right): \delta 1.83-1.92(\mathrm{~m}$, 2H); 2.02-2.10 (m, 6H); 4.15-4.20 (m, 1H, H $)_{4}$; ${ }^{13} \mathrm{C}$ NMR $\left(\mathrm{D}_{2} \mathrm{O}\right): \delta 27.5,30.6\left(\mathrm{C}_{2}, \mathrm{C}_{3}, \mathrm{C}_{5}, \mathrm{C}_{6}\right) ; 58.1,74.5\left(\mathrm{C}_{1}, \mathrm{C}_{4}\right)$; 175.4 (COO).

## Acknowledgements

We are indebted to the Dirección General de Investigación Científica y Técnica, project PB97-0998, and to the Universidad de La Rioja, project API-99-B02, for its generous support. M. A. F.-R. and F. R. thank the Ministerio de Educación y Ciencia for FPI grants.

## References

1. Giannis, A.; Kolter, T. Angew. Chem., Int. Ed. Engl. 1993, 32, 1244-1267.
2. Gante, J. Angew. Chem., Int. Ed. Engl. 1994, 33, 1699-1720.
3. Abell, A. Advances in Amino Acid Mimetics and Peptidomimetics; JAI: Greenwich, 1999; Vol. 2.
4. Cativiela, C.; Díaz-de-Villegas, M. D. Tetrahedron: Asymmetry 1998, 9, 3517-3599.
5. Cativiela, C.; Díaz-de-Villegas, M. D. Tetrahedron: Asymmetry 2000, 11, 645-732.
6. Halab, L.; Lubell, W. D. J. Org. Chem. 1999, 64, 3312-3321.
7. Hanessian, S.; McNaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. Tetrahedron 1997, 53, 12789-12854.
8. Campbell, J. A.; Rapoport, H. J. Org. Chem. 1996, 61, 63136325.
9. Han, W.; Pelletier, J. C.; Hodge, C. N. Bioorg. Med. Chem. Lett. 1998, 8, 3615-3620.
10. Han, W.; Pelletier, J. C.; Mersinger, L. J.; Kettner, C. A.; Hodge, C. N. Org. Lett. 1999, 1, 1875-1877.
11. Avenoza, A.; Cativiela, C.; Busto, J. H.; Peregrina, J. M. Tetrahedron Lett. 1995, 36, 7123-7126.
12. Avenoza, A.; Cativiela, C.; Busto, J. H.; Peregrina, J. M. Synthesis 1998, 1335-1338.
13. Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. Tetrahedron: Asymmetry 1999, 10, 39994007.
14. Avenoza, A.; Cativiela, C.; Fernández-Recio, M. A.; Peregrina, J. M. J. Chem. Soc., Perkin Trans. 1 1999, 33753379.
15. Goodall, K.; Parsons, A. F. Tetrahedron Lett. 1995, 36, 32593260.
16. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. J. Chem. Soc., Perkin Trans. 1 1999, 3697-3703.
17. Mckillop, A.; Taylor, R. J. K.; Watson, R. J. Synthesis 1994, 31.
18. Spectroscopic data for $\mathbf{9}$ and $\mathbf{1}$ are in agreement with the data reported by Rapoport (Ref. 8).

[^0]:    Keywords: Diels-Alder reactions; aza compounds; bicyclic heterocyclic compounds; amino acids and derivatives.

    * Corresponding author. Tel.: +34-941-299655; fax: +34-941-299621;
    e-mail: alberto.avenoza@dq.unirioja.es

