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

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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 α-amino acids,[4,5] such as modified prolines, because of the high frequency of this amino acid at the central residues of the β-turn conformation.[6,7]

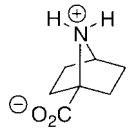
In this context, the 7-azabicyclo[2.2.1]heptane-1-carboxylic acid (Ahc) (**1**), an achiral compound, is particularly attractive as a rigid proline analogue. The only previous synthesis of **1** was carried out by Rapoport and co-workers from *tert*-butyl *N*-benzylthiopyroglutamate as a chiral substrate 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 non-proteinogenic and unusual α-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 analogue **1** in gram scale, using an achiral starting material. In the course of our research about hydroxy-α,α-disubstituted-α-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 α,β-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).

Keywords: Diels–Alder reactions; aza compounds; bicyclic heterocyclic compounds; amino acids and derivatives.

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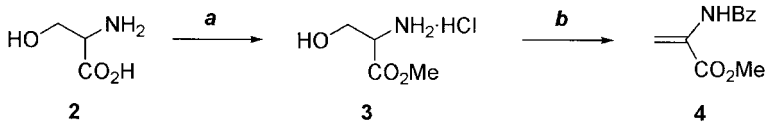
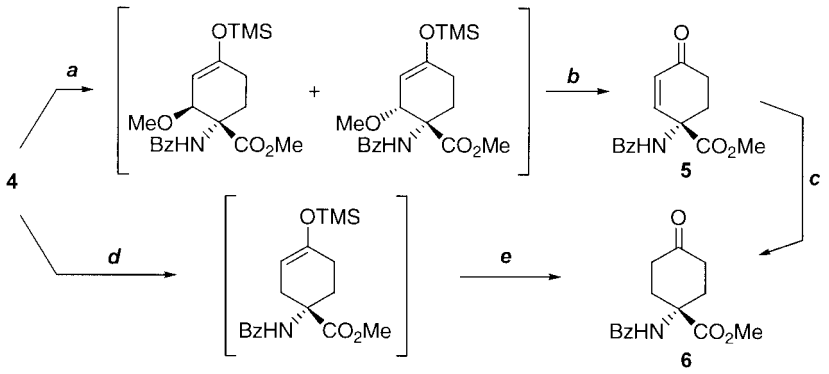
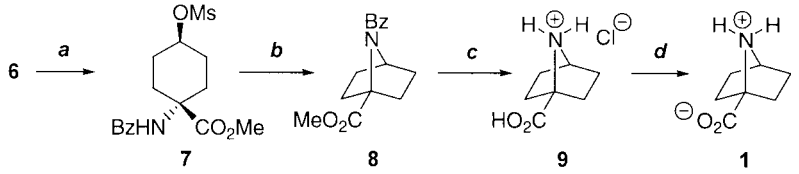


2 3 4

Scheme 1. *Reagents and conditions*: (a) Ref. 17; (b) (i) BzCl, Et_3N, CH_2Cl_2, room temperature, 7 h,; (ii) DBU, MeOH, 3 h, 94%.



Scheme 2. *Reagents and conditions*: (a) Danishefsky's diene, toluene, reflux, 72 h; (b) (i) 0.005N HCl–THF (1:4), 7 h; (ii) DBU, MeOH, 5°C, 12 h, 55%; (c) H_2, Pd/C, CH_2Cl_2, 24 h, 95%; (d) 2-trimethylsilyloxy-1,3-butadiene, ZnI_2, CH_2Cl_2, reflux, 24 h; (e) 0.005N HCl–THF, 94%.



Scheme 3. *Reagents and conditions*: (a) (i) L-selectride®, THF, −78°C; (ii) MsCl, DIEA, CH_2Cl_2, 68% two steps; (b) ^{t}BuOK, THF, 81%; (c) 6N HCl, reflux, 99%; (d) propylene oxide, EtOH, reflux, 89%.

1-benzamido-*c*-2-methoxy-4-trimethylsilyloxy-3-cyclohexene-*r*-1-carboxylate and methyl 1-benzamido-*t*-2-methoxy-4-trimethylsilyloxy-3-cyclohexene-*r*-1-carboxylate, corresponding to *endo* and *exo* attack respectively. This mixture of products was treated with a 0.005N HCl–THF (1:4) solution and DBU in methanol at 5°C to give the corresponding enone **5**. Hydrogenation of this product using 10% palladium–carbon as a catalyst in CH_2Cl_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 **6**, using less steps and employing other dienes. Reaction of **4** with 2-trimethylsilyloxy-1,3-butadiene in the presence of ZnI_2 as a catalyst, hydroquinone as a polymerisation inhibitor, using CH_2Cl_2 as a solvent and further treatment of the reaction mixture with a 0.005N HCl–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® at −78°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**. Base-promoted 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 **8** in high yield. The deprotected proline analogue **9** was obtained in 99% yield[18] from the hydrolysis of compound **8** and free amino acid **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}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer at 300 MHz (^{1}H) and at 75 MHz (^{13}C), at 20°C, and are reported in ppm downfield from TMS (chemical shifts are reported in ppm on the δ 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 Perkin–Elmer FT-IR Spectrum 1000 spectrometer.

4.1.1. Methyl 2-benzamidoacrylate (4). To a solution of D,L-serine methyl ester hydrochloride (4.5 g, 28.9 mmol) in CH_2Cl_2 were added in portions Et_3N (9.6 g, 98.2 mmol) and BzCl (9.3 g, 66.7 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 $NaHCO_3$ (2×50 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The white solid was dissolved in CH_2Cl_2, kept under inert atmosphere, at 5°C and then DBU (5.2 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 $NaHCO_3$ (2×50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to obtain 5.5 g of compound **4** as an oil (93%). Anal. calcd for $C_{11}H_{11}NO_3$; C, 64.38; H, 5.40; N, 6.83.; found C, 64.46; H, 5.32; N, 6.74; IR (CH_2Cl_2, cm^{-1}): 3410 (NH), 1720 (CO), 1678 (CON); ^{1}H NMR ($CDCl_3$): δ 3.85 (s, 3H, CH_3O); 5.95–6.02 (m, 1H); 6.79 (s, 1H), 7.43–7.58 (m, 3H, Arom.); 7.79–7.88 (m, 2H, Arom.); 8.55 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 52.9 (CH_3O); 108.6 (C_3); 126.7, 128.6 (Arom.); 130.8 (C_2); 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 mL, 33.4 mmol) was added to a solution of methyl 2-benzamidoacrylate **4** (1.7 g, 8.3 mmol) in dry toluene (80 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 0.005N HCl–THF (1:4) (40 mL) was added to the residue. The reaction mixture was stirred for 15 h at 20°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 CH_2Cl_2 (75 mL) and DBU (2.7 mL, 18.2 mmol) was added. The reaction mixture was stirred for 24 h at 2°C and the solution was washed with 0.5N HCl (60 mL). The aqueous phase was extracted with CH_2Cl_2 (5×30 mL) and the combined organic phases were dried over anhydrous Na_2SO_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°C; Anal. calcd for $C_{15}H_{15}NO_4$; C, 65.92; H, 5.53; N, 5.13.; found C, 65.84; H, 5.59; N, 5.05; IR (CH_2Cl_2, cm^{-1}): 3433 (NH), 1743 (CO), 1685 (CON); ^{1}H NMR ($CDCl_3$): δ 2.50–2.65 (m, 4H, $2H_5$+$2H_6$); 3.82 (s, 3H, CH_3O); 6.14 (d, 1H, J_{3-2}=10.0 Hz, H_3); 7.10–7.20 (m, 2H, NH+H_2); 7.41–7.48 (m, 2H, Arom.); 7.50–7.58 (m, 1H, Arom.); 7.76–7.82 (m, 2H, Arom.); ^{13}C NMR ($CDCl_3$): δ 31.6, 33.7 (C_5, C_6); 53.4 (CH_3O); 58.5 (C_1); 127.1, 128.6, 130.5, 132.2 (C_3, Arom.); 133.0 (Arom.); 146.9 (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 g, 14.63 mmol) in dry CH_2Cl_2 (200 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 g, 58.5 mmol) was added to a solution of methyl 2-benzamidoacrylate **4** (4.0 g, 19.5 mmol) and ZnI_2 (6.3 g, 19.5 mmol) in dry CH_2Cl_2 (90 mL) kept under an inert atmosphere. After stirring for 24 h, at reflux, the solution was filtered and washed with water (1×20 mL), the organic phase was dried over anhydrous Na_2SO_4 and filtered. Then, a solution of 0.005N HCl–THF (1:4) (40 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 CH_2Cl_2 (75 mL) and washed with brine (2×20 mL). The combined organic phases were dried over anhydrous Na_2SO_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%). Mp: 133–4°C; Anal. calcd for $C_{15}H_{17}NO_4$; C, 65.44; H, 6.22; N, 5.09; found C, 65.67; H, 6.27; N, 5.25; IR (CH_2Cl_2, cm^{-1}): 3430 (NH), 1743 (COO), 1716 (CO), 1673 (CON); ^{1}H NMR ($CDCl_3$): δ 2.40–2.58 (m, 8H); 3.77 (s, 3H, CH_3O); 6.67 (br s, 1H, NH); 7.24–7.54 (m, 3H, Arom.); 7.60–7.81 (m, 2H, Arom.); ^{13}C NMR ($CDCl_3$): δ 32.3, 36.7 (C_2, C_3, C_5, C_6); 52.8 (CH_3O); 58.0 (C_1); 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-methanesulfonyloxycyclohexane-*r*-1-carboxylate (7). Compound **6** (4.0 g, 14.5 mmol) was dissolved in dry THF (80 mL) and L-selectride® (17.3 mL of 1 M sol. in THF, 17.3 mmol) was added dropwise at −78°C under an inert atmosphere. After 20 h stirring at the same temperature, the reaction was quenched by the addition of a saturated NH_4Cl solution (20 mL). The resulting mixture was allowed to warm up to room temperature, the solvent evaporated and the residue washed with ethyl acetate (1×50 mL) and $CHCl_3$/2-propanol (3:1) (2×30 mL). Evaporation of the solvent gave a residue that was chromatographed on silica gel eluting with hexane–ethyl 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}H NMR signals). The mixture of alcohols was dissolved in dry CH_2Cl_2 (70 mL) under an inert atmosphere and diisopropylethylamine (4.5 mL, 26.2 mmol) and methanesulfonyl chloride (2.0 mL, 26.2 mmol) were then added to this solution at 0°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% $NaHCO_3$, dried over anhydrous Na_2SO_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°C; Anal. calcd for $C_{16}H_{21}NO_6S$; 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 (CH_2Cl_2, cm^{-1}): 3437 (NH), 1741 (CO), 1672 (CON); ^1H NMR ($CDCl_3$): δ 1.84–1.96 (m, 2H); 2.02–2.18 (m, 4H); 2.30–2.43 (m, 2H); 3.06 (s, 3H, CH_3SO_2); 3.77 (s, 3H, CH_3O); 4.95–5.00 (m, 1H, H_4); 6.24 (br s, 1H, NH); 7.40–7.58 (m, 3H, Arom.), 7.73–7.80 (m, 2H, Arom.); ^{13}C NMR ($CDCl_3$): δ 27.1, 27.5 (C_2, C_3, C_5, C_6); 38.8 (CH_3SO_2); 52.7 (CH_3O); 58.1 (C_1); 77.0 (C_4); 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-1-carboxylate (8). To a solution of **7** (2.4 g, 6.7 mmol) in dry THF (70 mL) an 1 M solution of ^{t}BuOK in THF (7.4 mL, 7.4 mmol) was added under an inert atmosphere, at −78°C. After stirring for 1 h at −78°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 2N HCl solution (8 mL) and the resulting mixture was extracted with ethyl acetate (1×30 mL) and CH_2Cl_2 (2×30 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 g (81%) of **8** as a white solid. Mp: 100–2°C; Anal. calcd for $C_{15}H_{17}NO_3$; C, 69.48; H, 6.61; N, 5.40; found C, 69.39; H, 6.78; N, 5.47; IR (CH_2Cl_2, cm^{-1}): 1740 (CO), 1646 (CON); ^1H NMR ($CDCl_3$): δ 1.43–1.55 (m, 2H); 1.67–1.97 (m, 4H); 2.22–2.35 (m, 2H); 3.73 (s, 3H, CH_3O); 4.14–4.24 (m, 1H, H_4); 7.27–7.46 (m, 3H, Arom.), 7.57–7.64 (m, 2H, Arom.); ^{13}C NMR ($CDCl_3$): δ 30.0, 31.7 (C_2, C_3, C_5, C_6); 52.0, 61.7, 67.2 (CH_3O, C_1, C_4); 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 g, 3.85 mmol) was suspended in an aqueous 6N 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 (2×10 mL) and the aqueous layer evaporated to give 678 mg of the salt **9** (99%). ^1H NMR (CD_3OD): δ 1.52–1.80 (m, 2H); 1.82–2.02 (m, 6H); 3.97–4.06 (m, 1H, H_4); ^{13}C NMR (CD_3OD): δ 28.9, 31.9 (C_2, C_3, C_5, C_6); 60.0, 73.1 (C_1, C_4); 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 C_{18} reverse-phase Sep-pak cartridge which, after the removal of the water, gave 41 mg (89%) of α-amino acid **1** as a white solid. ^1H NMR (D_2O): δ 1.83–1.92 (m, 2H); 2.02–2.10 (m, 6H); 4.15–4.20 (m, 1H, H_4); ^{13}C NMR (D_2O): δ 27.5, 30.6 (C_2, C_3, C_5, C_6); 58.1, 74.5 (C_1, C_4); 175.4 (COO).

Acknowledgements

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18. Spectroscopic data for **9** and **1** are in agreement with the data reported by Rapoport (Ref. 8).