Letter

Synthesis of the new 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton as a constrained proline analogue

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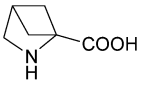
Received (in London, UK) 9th January 2003, Accepted 24th February 2003
First published as an Advance Article on the web 4th March 2003

The synthesis of the tricyclic amino ester 12 is described. This constrained proline analogue contains the formerly unknown 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton. A short 5 step sequence was developed allowing the production of 12 on a multi-gram scale. The key step consists of a stereoselective synthesis of a hydantoin that, after conversion to the amino ester, can be brominated and ring closed to the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton.

Introduction

Currently a lot of interest is being paid to the synthesis of natural products with interesting biological activities. Natural product analogues are continuously prepared to enhance activity and to suppress side effects. For several years our interest has been focused on 2,4-methanoproline **1**.



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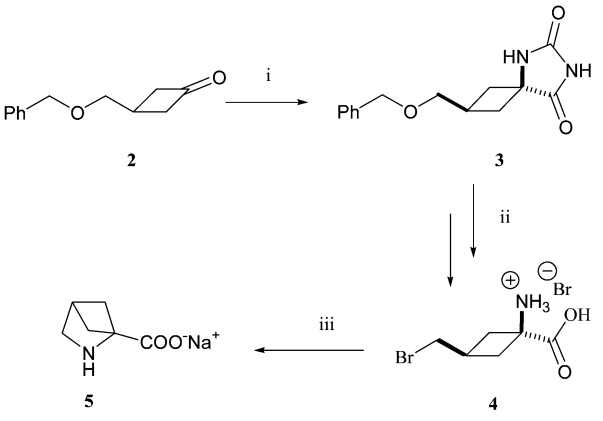
This natural amino acid was isolated in 1980 and is believed to act as an anti-feedant against seed predators.[1] In earlier work a short reaction pathway towards this constrained molecule was developed (Scheme 1).[2,3,4] Starting from the cyclobutanone **2** the hydantoin **3** was prepared and further transformed to the amino acid **4**, which could be converted to the natural 2,4-methanoproline **1**.

Constrained proline analogues play an important role in peptide design due to the selective stabilization of the *trans*- or the *cis*-amide bond when introduced into a peptide.[5] Since 2,4-methanoproline itself is a very constrained proline analogue, further elaboration of this methodology towards new heterocyclic skeletons seemed interesting.

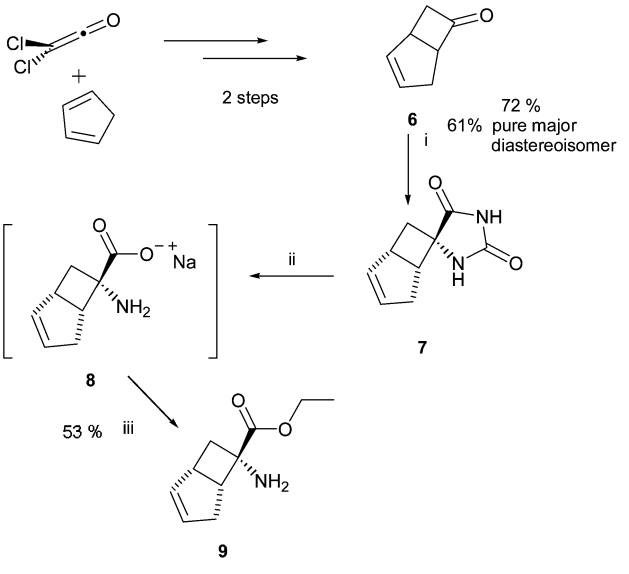
Results and discussion

Therefore, this new approach towards the 2-azabicyclo[2.1.1]-hexane skeleton was extended to make the even more constrained tricyclic amino ester **12**. Retrosynthetic analysis led to the bicyclic ketone **6** as the starting material which is known in the literature and can be synthesized on large scale by Diels–Alder reaction of cyclopentadiene and dichloroketene followed by radical dechlorination.[6,7] The ketone was first converted to the hydantoin **7** (Scheme 2) using potassium cyanide, ammonium chloride and ammonium carbonate. The reaction is diastereoselective and a mixture of isomers is formed. The



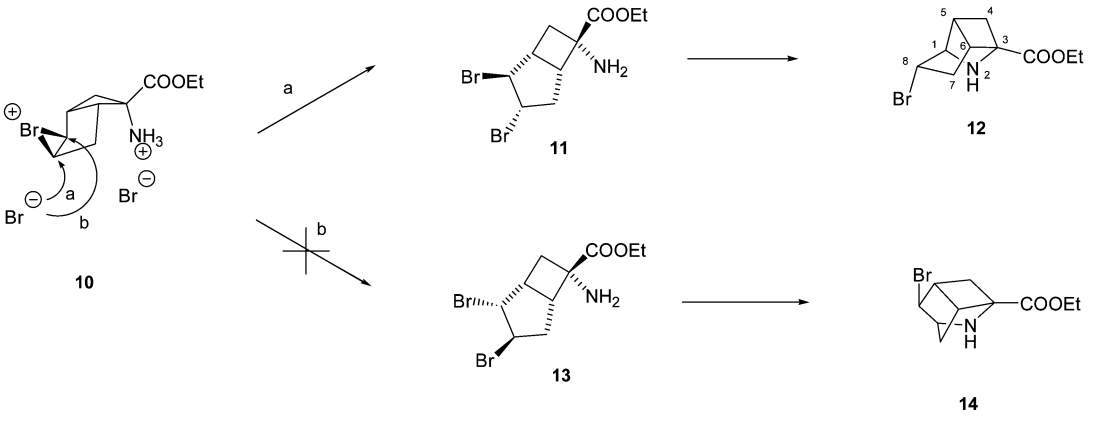
Scheme 1 Synthesis of the natural 2,4-methanoproline. Reagents and conditions: (i) NH_4Cl, $NH_4CO_3NH_4$, KCN, MeOH/H_2O 1:1, 50 °C, overnight, 85% (20% of *cis* isomer after fractional crystallization); (ii) 0.5 M NaOH, Δ 24 h then conc. HBr–H_2O, Δ 7 h, 73%; (iii) 3 equiv. NaOH, Δ 1.5 h, 91%.

major product was found to be the *endo* compound **7** through the preferential *exo* attack of cyanide on the *in situ* formed imine. The two diastereoisomers proved to have different solubilities, leading to selective crystallization during the reaction



Scheme 2 Reagents and conditions: (i) NH_4Cl, $NH_4CO_3NH_4$, KCN, MeOH/H_2O 1:1, 50 °C, overnight, 72% (61% of *cis* isomer after crystallization); (ii) 0.5 M NaOH, Δ 24 h then $SOCl_2$, EtOH, 53%.

 DOI: 10.1039/b300331k



Scheme 3 Diastereoselective bromination of **10**.

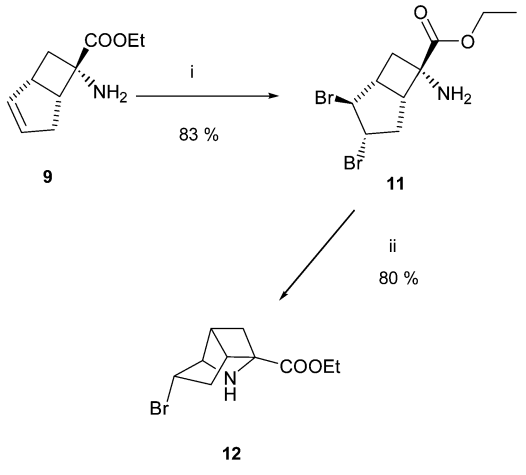
by good solvent choice. A straightforward filtration then leads to the isolation of the major diastereoisomer in 61% yield which is used in the further reactions. The hydantoin was then converted to the amino acid **8** by refluxing the molecule in a 0.5 M sodium hydroxide solution. The reaction proceeds quantitatively and the salt was converted to the amino ester so that the corresponding ester became soluble in organic solvents and could be isolated in 53% yield.

To avoid side reactions during the bromination of the double bond, the amino group was protected *in situ* as a hydrobromide salt. Again by good choice of solvent (and concentration), the formed brominated salt crystallizes and can be filtered from the reaction mixture. This hydrobromide salt is not hygroscopic and can be stored in a closed vessel for months without problems.

From similar brominations of the bicyclic ketone **6**, it is known that the bromonium ion is formed on the *exo* face.[8] In theory, the bromination of **9** can lead to the diastereoisomers **11** and **13** due to attack of bromide on the bromonium species **10** (route a or b in Scheme 3).

Ring closure could then lead to compounds **12** or **14**. However, the bromination reaction is diastereospecific and only compound **11** is obtained. This results from the attack of bromide from the less hindered side of the bromonium species **10** (route a in Scheme 3). Deprotecting the amine with $NaHCO_3$ and using an extra equivalent of triethylamine, the amino ester **11** can be cyclized to the new tricyclic skeleton (Scheme 4).

Since no other compounds containing the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton are known in the literature, the structure of **12** was proven by determining all the coupling constants (Fig. 1) and studying the H–H COSY and H–C HETCOR spectra. In these spectra, clear coupling between the H_8 and both H_{7a} and H_{7b} can be observed. Proton H_8 also couples with H_1. This means that the remaining C*H*Br couples with a CH and a CH_2. This can only be the case in compound **12**. Supplementary proof for the 2-azatricyclo[3.3.0.0^{3,6}]octane skeleton can be obtained by comparison of the coupling constants with predicted coupling constants. Since the molecule is very constrained, a good prediction of the torsion angles can be derived from a 3D-computer model (ACD/3D, version 4.02). Proton H_{7a} does not couple with proton H_6 due to a torsion angle of 88.4° which is in agreement with the Karplus equation stating that the coupling constant is then close to zero. Also proton H_{4a} does not couple with H_5. The prediction of the torsion angle is here around 73°.



Scheme 4 Reagents and conditions: (i) 1 equiv. HBr, 1 equiv. Br_2, sat. $NaHCO_3$, 83%; (ii) 1 equiv. NEt_3, Δ 24 h THF, 80%.

Experimental

General methods

^{1}H-NMR spectra were recorded at 270 MHz (JEOL EX270) with $CDCl_3$ as solvent (unless otherwise stated) and tetramethylsilane (TMS) as internal standard. ^{13}C-NMR spectra were recorded at 67.8 MHz. Mass spectra (MS) were obtained with a Varian MAT 112 mass spectrometer (70 eV). Diethyl ether and THF were dried and distilled over sodium (benzophenone ketyl control). Dichloromethane was dried and distilled over calcium hydride. The absolute value of the couplings constants (J) in Hz and assignments of ^{1}H and ^{13}C peaks were determined using COSY, HETCOR and DEPT experiments

cis-Cyclopentyl[1,2-*f*]-1,3-diazaspiro[3,4]octane-2,4-dione 7

To a solution of 40 ml of distilled water and 50 ml of methanol, 6 g of ketone 6, 2.97 g of ammonium chloride (1 equiv.),

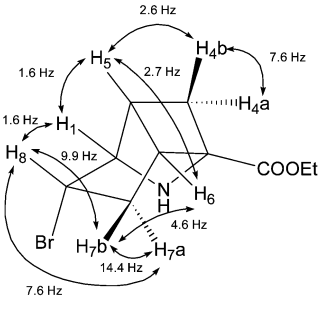


Fig. 1 Graphical representation of the coupling constants of ethyl 8-(*endo*)bromo-2-azatricyclo[3.3.0.0^{3,6}]octane-3-carboxylate **12**

11.74 g ammonium carbonate (2.2 equiv.) and 4.34 g potassium cyanide (1.2 equiv.) is dissolved and heated for 24 h at 60 °C. During this period a white crystalline product precipitates from the reaction mixture. After 24 h the mixture is filtered and washed with 30 ml of distilled water. After drying, the white crystals are dried at high vacuum yielding 4.97 g (yield 50%) of **7** as a single diastereoisomer. The filtrate was evaporated and extracted with dichloromethane (2×50 ml) and water (50 ml). The organic phase was dried with $MgSO_4$, filtered and evaporated to give a mixture of the two diastereoisomers. This mixture was crystallized in a methanol:water (1:1) mixture and gave an extra 1.1 g of the desired diastereoisomer (11%). The total yield of the *cis* isomer is 61%. The supernatant contains still ~1.1 g (11%) of the mixture of isomers. *cis*-Isomer: ^{1}H-NMR (270 MHz, DMSO-d_6) 1.81 (1H, dd, $J = 12.2$ Hz, $J = 4.3$ Hz, CH_aH$_b$); 2.38–2.57 (2H, m, CH_2); 2.73 (1H, dd, $J = 12.4$ Hz, $J = 8.1$ Hz, CH$_a$$H_b$); 3.02 (1H, br s, CH); 3.18 (1H, br t, $J = 7.6$ Hz, CH); 5.75–5.82 (2H, m, C*H*=C*H*); ^{13}C-NMR (68 MHz, DMSO) 33.32 (CH_2), 38.24 (CH_2), 39.10 (CH), 43.85 (CH), 61.72 (Cquat), 131.97 (*C*H=), 133.31 (*C*H=), 156.89 (C=O), 178.81 (C=O); IR (NaCl): br 1721 cm^{-1} (C=O); MS (*m*/*z*): 178 (M$^+$, 7), 137 (6), 113 (9), 66 (100). (mp 247 °C). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66. Found: C, 60.67; H, 5.64%.

Ethyl 6-aminobicyclo[3.2.0]hept-2-ene-6-carboxylate 9

4.79 g of hydantoin **7** was dissolved in 160 ml of a 0.5 M NaOH solution and refluxed for 24 h. The solvent was evaporated, 50 ml of distilled water was added and the solution was again evaporated. The hydrochloride salt was prepared by adding 50 ml of a 2 M HCl solution followed by evaporation. Distilled water (50 ml) was added and evaporated. The resulting white powder was dried at high vacuum (0.05 mmHg). A solution of 6.08 g freshly distilled thionyl chloride was added at −15 °C to a stirred solution of 50 ml absolute ethanol. After 5 minutes the amino acid hydrochloride was added in one portion and kept at −15 °C for 10 minutes. The reaction mixture was allowed to warm to 0 °C and was kept at this temperature for 30 minutes. After this period, the solution was refluxed for an additional 2 h. Evaporation of the ethanol results in an oil which was dissolved in dichloromethane and extracted with a saturated $NaHCO_3$ solution until basic. The organic layer was washed with water and dried with $MgSO_4$. Filtration and evaporation gave 2.47 g ethyl 6-aminobicyclo[3.2.0]hept-2-ene-6-carboxylate (yield 53%; liquid). ^{1}H-NMR (270 MHz, $CDCl_3$) 1.31 (3H, t, $J = 7.1$ Hz, $COOCH_2CH_3$), 1.59 (1H, dd, $J = 12.5$ Hz, $J = 2.6$ Hz, CH$_{7a}$$H_{7b}$), 1.8 (2H, br s, NH_2), 2.41–2.46 (1H, m, CH$_{4a}$$H_{4b}$), 2.49–2.64 (1H, m, CH$_{4a}$$H_{4b}$), 3.02 (1H, ddd, $J = 12.4$ Hz, $J = 8.3$ Hz, $J = 1$ Hz, CH$_{7a}$$H_{7b}$), 3.14–3.21 (1H, m, H$_1$), 3.19–3.27 (1H, m, H$_5$), 4.21 (2H, q, $J = 7.1$ Hz, $COOCH_2CH_3$), 5.85 (2H, br s, C*H*=C*H*). ^{13}C-NMR (68 MHz, $CDCl_3$) 14.23 ($COOCH_2CH_3$), 32.88 (CH_2, 4), 39.98 (CH_2, 7), 40.20 (CH, 1), 44.02 (CH, 5), 58,58 (Cquat), 61.01 ($COOCH_2CH_3$), 131.91 (CH=), 135.29 (CH=), 175.86 (C=O); IR (NaCl) 1725 cm^{-1}; MS (*m*/*z*): no M$^+$, 152 (20), 135 (21), 115 (100), 108 (43), 71 (48). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34. Found: C, 60.35; H, 8.33%.

2,3-Dibromo-6-(ethoxycarbonyl)bicyclo[3.2.0]heptan-6-yl ammonium bromide

Ethyl 6-aminobicyclo[3.2.0]hept-2-ene-6-carboxylate (0.5 g) was dissolved in 5 ml of dry dichloromethane and was cooled to 0 °C. Concentrated hydrogen bromide (0.48 g, 1.02 equiv., 48% in water) was added and the solution was stirred at this temperature for 15 minutes. Bromine (0.45 g, 1.02 equiv.) was dissolved in 5 ml of dichloromethane and added dropwise to the starting material at 0 °C. The reaction was allowed to warm to room temperature overnight while a white precipitate was formed. Dry ether was added and the mixture was filtered and washed with some additional ether. The filtrate was concentrated up to 20% of the original volume and the white powder was filtered and washed with ether. The powder was dried at high vacuum and 1.01 g (yield 87%) of 2,3-dibromo-6-(ethoxycarbonyl)bicyclo[3.2.0]-heptan-6-yl ammonium bromide was obtained. This product is not hygroscopic and is very stabile when kept in a closed vessel. (mp 187 °C) ^{1}H-NMR (270 MHz, DMSO-d_6) 1.28 (3H, t, $J = 7.1$ Hz, $COOCH_2CH_3$), 2.34–267 (2H, m, CH_2), 2.84–2.96 (3H, m, CH_2, CH), 3.13–3.21 (1H, m, CH), 4.27 (2H, q, $J = 7.1$ Hz, $COOCH_2CH_3$), 4.3–4.42 (2H, m, 2 × CHBr); ^{13}C-NMR (68 MHz, DMSO) 13.80 (CH_3); 34.59 (CH_2), 35.76 (CH_2), 40.81 (CH), 43.32 (CH), 54.05 (Cquat), 54.75 (CHBr), 59.73 (CHBr), 62.30 ($COOCH_2CH_3$), 170.42 (C=O); IR (KBr) 1738 cm^{-1}; MS (*m*/*z*): 344/342/340 (M$^+$ + H-HBr, 100).

2,3-Dibromo-6-(ethoxycarbonyl)bicyclo[3.2.0]heptan-6-yl amine 11

1.5 g 2,3-Dibromo-6-(ethoxycarbonyl)bicyclo[3.2.0]-heptan-6-yl ammonium bromide was dissolved in 20 ml of dichloromethane and was extracted with a saturated $NaHCO_3$ solution until basic. The water phase was extracted twice with 20 ml dichloromethane. The organic layers were combined and dried with $MgSO_4$, filtered and evaporated to give 1.15 g 2,3-dibromo-6-(ethoxycarbonyl)bicyclo[3.2.0]heptan-6-yl amine (yield 95%; liquid). The product obtained has a purity > 95% and was used as such in the next step without purification.^{1}H-NMR (270 MHz, $CDCl_3$) 1.33 (3H, t, $J = 7.1$ Hz, $COOCH_2CH_3$), 2.16 (2H, br s, NH_2), 2.44 (1H, dd, $J = 13.4$ Hz, $J = 7.1$ Hz, CH_aH$_b$), 2.61 (1H, dt, $J = 16.5$ Hz, $J = 2.5$ Hz, CH_cH$_d$), 2.80–2.93 (2H, m, CH$_a$$H_b$and CH$_c$$H_d$), 3.20 (1H, br q, $J = 8.1$ Hz, CH), 3.30–3.37 (1H, m, CH), 4.25 (2H, q, $J = 7.1$ Hz, $COOCH_2CH_3$), 4.60 (1H, s, CHBr), 4.72 (1H, br d, $J = 2.6$ Hz, CHBr),^{13}C-NMR (68 MHz, $CDCl_3$) 14.18 (CH_3), 34.23 (CH_2), 39.35 (CH_2), 43.67 (CH), 49.22 (CH), 55.24 (Cquat), 56.48 (CHBr), 60.02 (CHBr), 61.20 ($COOCH_2CH_3$), 175.77 (C=O); IR (NaCl) 1729 cm^{-1}; MS (*m*/*z*): no M$^+$, 314/312/310 (11), 270/268/266 (36), 180 (26), 140 (38), 115 (100), 106 (34), 80 (34).

Ethyl 8-(*endo*)bromo-2-azatricyclo[3.3.0.0^{3,6}]octan-3-yl carboxylate 12

2,3-Dibromo-6-(ethoxycarbonyl)-bicyclo[3.2.0]heptan-6-yl amine (1.12 g) was dissolved in 115 ml of dry THF and 0.36 g (1.1 equiv.) of triethylamine was added. The resulting solution was refluxed for 24 h. The solution was concentrated up to 20% of its original volume and 50 ml of dry ether was added so that a white powder was formed that was filtered off. The filtrate was evaporated and the resulting oil was purified by flash chromatography and gave 0.68 g ethyl-8-(*endo*)bromo-2-azatricyclo[3.3.0.0^{3,6}]octan-3-yl carboxylate. (solvent: CH_2Cl_2/EtOAc 1/1; $R_f = 0.34$; yield 80%; liquid) .^{1}H-NMR (270 MHz, $CDCl_3$) 1.29 (3H, t, $J = 7.3$ Hz, $COOCH_2CH_3$), 1.83 (1H, dd, $J = 14.5$ Hz, $J = 7.6$ Hz, CH$_{7a}$), 1.92 (1H, d, $J = 7.6$ Hz, CH$_{4a}$), 2.24 (1H, ddd, $J = 14.4$ Hz, $J = 9.9$ Hz, $J = 4.6$ Hz, CH$_{7b}$), 2.34 (1H, dd, $J = 7.6$ Hz, $J = 2.6$ Hz, CH$_{4b}$), 2.66 (1H, ddd, $J = 2.6$ Hz, $J = 2.6$ Hz, $J = 1.6$ Hz, H$_5$), 2.70 (1H, dd, $J = 4.6$ Hz, $J = 2.9$ Hz, H$_6$), 3.57 (1H, br s, H$_1$), 4.19 (2H, q, $J = 7.2$ Hz, $COOCH_2CH_3$), 4.29 (1H, ddd, $J = 9.8$ Hz, $J = 7.6$ Hz, $J = 1.6$ Hz, CH$_8$Br); ^{13}C-NMR (68 MHz, $CDCl_3$) 14.20 ($COOCH_2CH_3$), 32.97 (CH_2, 7), 39.01 (CH_2, 4), 43.47 (CH, 5), 54.00 (CH, 6), 55.38 (CH, 8), 60.93 (CH_2, $COOCH_2CH_3$), 63.18 (CH, 1), 70.26 (Cquat, 3), 169.00 (C=O); IR (NaCl) 1732 cm^{-1} (C=O); MS (*m*/*z*): 261/259 (M$^+$, 8), 194/192 (40), 180 (79), 106 (64), 99 (100). Anal. Calcd for $C_{10}H_{14}BrNO_2$: C, 46.17; H, 5.42. Found: C, 46.16; H, 5.40%.

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