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A new and short method for the synthesis of 2,4-methanoproline

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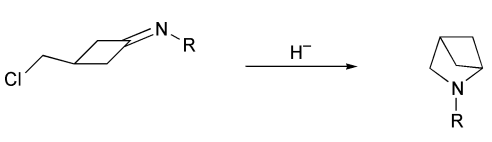
Received (in Cambridge, UK) 26th November 2001, Accepted 11th December 2001
First published as an Advance Article on the web 16th January 2002

2,4-Methanoproline, a supposed non-proteinogenic anti-feedant, was synthesised in 5 steps starting from allyl benzyl ether 3 in 10% overall yield with an intramolecular nucleophilic substitution as the key step for the formation of the bicyclic skeleton.

2,4-Methanoproline is a natural non-protein amino acid that was isolated from the seeds of *Ateleia herbert smithii* Pittier, a tree commonly growing at the coasts of Costa Rica.[1] The seeds of this legume species are ignored by at least 100 seed predators. It is thought that 2,4-methanoproline which is present in these seeds acts as an anti-feedant. Besides this interesting biological activity the amino acid is a proline analogue, which may be useful for polypeptide molecular design. Research has shown that this bicyclic proline analogue stabilizes the *trans* tertiary peptide bond.[2] Since its isolation in 1980, several syntheses of 2,4-methanoproline have been developed. Most of these syntheses are accomplished by an intramolecular [2 + 2] light induced cycloaddition of an appropriate diene.[3] Just one other approach, using an intramolecular cyclisation, was developed by Gaoni.[4] Not only the physiological activity of the amino acid, but also the rare 2-azabicyclo[2.1.1]hexane skeleton has drawn the attention of several groups, developing different strategies for the synthesis of the bicyclic skeleton. Most of the approaches to synthesize analogues containing the 2-azabicyclo[2.1.1]hexane skeleton use a [2 + 2] light induced cyclisation.[5] The synthesis of 5-hydroxy-2-azabicyclo[2.1.1]hexanes has been described by Krow *et al*. using a rearrangement of an appropriate bromohydrin.[6] Huet and co-workers recently reported an interesting synthesis of 5-substituted 2-azabicyclo-[2.1.1]hexanes using an intramolecular nucleophilic substitution of a cyclobutane derivative as the key step.[7]

Our approach to construct the 2-azabicyclic skeleton consists of an intramolecular ring closure of an amino acid which contains a four membered ring. This approach was inspired by our earlier work in which the skeleton was formed *via* a hydride induced intramolecular nucleophilic ring closure of a *N*-[3-(chloromethyl)-1-cyclobutylidene]amine (Scheme 1).[8] However, this method using 3-chloromethylcyclobutanone as precursor contained too many steps to be convenient for the synthesis of considerable amounts of azabicyclic compounds. Therefore, a more conveniently prepared precursor was needed.

Although the cyclobutanone **5** had been described before in the literature, the reaction conditions were not satisfactory. The literature method mentioned yields of ±50% for **4** on a small scale (~40 mmol) and about 35% on a large scale (~220 mmol).[9] Because of the low yield of this cycloaddition early in the synthesis strategy, a considerable improvement was needed to develop a realistic synthesis of the amino acid.



1 **2**

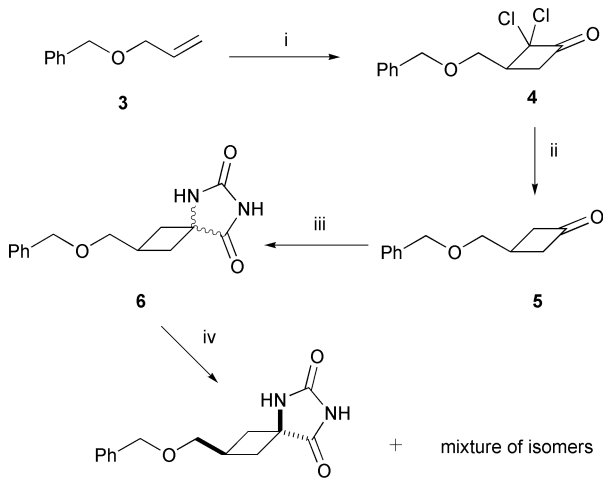
Scheme 1

Extensive research was performed on the optimisation of the reaction conditions in order to improve the yield of the reaction for quite a large scale production (~120 mmol). Using additional $POCl_3$ and careful monitoring of the reaction time, the yield could be improved up to 95% (crude yield, 75% after distillation). The cyclobutanone **5** was then easily converted to the corresponding hydantoin **6** using standard reaction conditions (NH_4Cl, $NH_4CO_3NH_4$, KCN, 50 °C, MeOH–H_2O) (Scheme 2).[10] The obtained hydantoin was purified by crystallisation (85% yield). The compound **6** was obtained in a 3:1 ratio of stereoisomers. The observed selectivity can be attributed to the steric interaction of the 3-benzyloxymethyl substituent on the cyclobutanone ring during the formation of the hydantoin, *i.e.* during the addition of cyanide onto the imino species. Since only the *cis*-isomer can lead to the desired amino acid a separation of the diastereoisomers was performed. This separation proved to be difficult and up to now only fractional crystallisation was successful. Although the yield dropped significantly (20%), the *cis*-isomer could be prepared in high purity. Further experiments will be performed in order to optimise the conditions for the separation of the *cis*-isomer.

In order to keep the synthesis as short as possible, the deprotection of the ether function, the conversion of the formed alcohol to the halogenide and the liberation of the amino acid were performed in a one-pot reaction by treatment of **7** with hydrobromic acid (48% solution in water) under reflux for seven hours.

Because of the quite harsh reaction conditions during these conversions, some unidentified side reactions occurred. Nevertheless, the amino acid **8** could be isolated in moderate yields (55%)(Scheme 3). Performing the reaction in two steps could prevent the formation of side products.

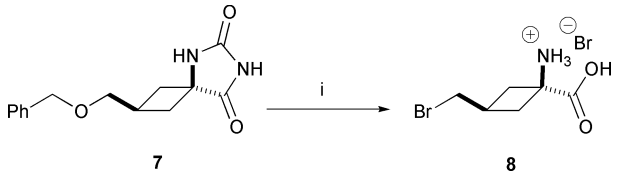
Firstly, the hydantoin **7** was hydrolysed with a sodium hydroxide solution (0.5 N, Δ 24 h, quantitatively)(Scheme 4).



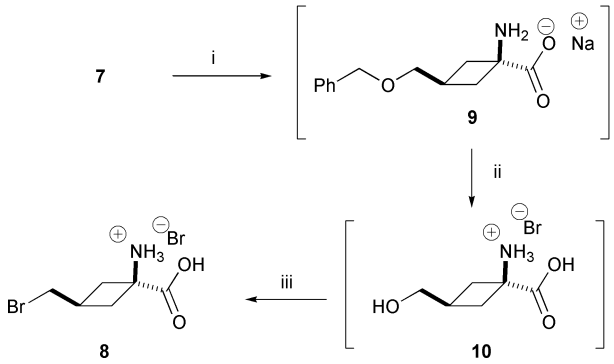
3 **4** **5** **6** **7**

Scheme 2 *Reagents and conditions*: i, Cl_3CCOCl, $POCl_3$, Et_2O reflux, 1 d, 95% crude; ii, Zn, HOAc, Δ 4 h, 75%; iii, NH_4Cl, $NH_4CO_3NH_4$, KCN, MeOH–H_2O 1:1, 50 °C, overnight, 85%; iv, fractional crystallisation, 20%.

DOI: 10.1039/b110765h



Scheme 3 *Reagents and conditions*: i, conc. HBr–H_2O, Δ 7 h, 55%.

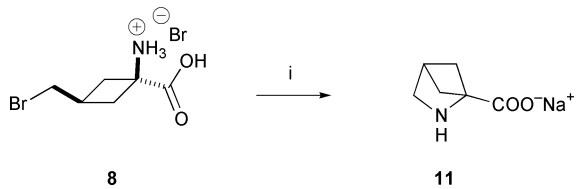


Scheme 4 *Reagents and conditions*: i, 0.5 N NaOH, Δ 24 h, 100%; ii, conc. HBr–H_2O, Δ 1 h; iii, conc. HBr–H_2O, Δ 6 h, 73%.

The ether functionality was subsequently converted to the 3-bromomethylcyclobutanyl amino acid **8**.[11] Interrupting the reaction after one hour of reflux showed that the ether function was almost completely converted to the alcohol **10** and benzyl bromide. An additional period of reflux of six hours was needed yielding **8** in 73%.

In order to build the azabicyclic ring system, the amino acid **8** was refluxed in a sodium hydroxide solution and was quantitatively converted to 2,4-methanoproline (Scheme 5). After recrystallisation this amino acid could be obtained in 91% yield.

In conclusion, the synthesis of 2,4-methanoproline was performed in 5 steps in an overall yield of 10%. The advantage of this procedure lays in the possibility to perform it on quite a large scale which can be problematic using known procedures. This approach might also be more suitable for the synthesis of 2,4-methanoproline analogues. Futher elaboration of this methodology is currently under investigation for the preparation of analogues containing the azabicyclic skeleton in order to evaluate the assumed anti-feedant properties of the analogues.



Scheme 5 *Reagents and conditions*: i, 3 equiv. NaOH, Δ 1.5 h.

This work was supported by the Belgian IWT (Instituut ter bevordering van het Wetenschappelijk en Technologisch Onderzoek in Vlaanderen) (Institute for the Promotion of Innovation by Science and Technology in Flanders).

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10 Hydantoin **7**: δ_H (270 MHz, $CDCl_3$) 2.19–2.25 (m, 2H), 2.59–2.75 (m, 3H), 3.46 (d, J = 4.0 Hz, 2H), 4.56 (s, 2H), 6.61 (s, br, 1H), 7.28–7.40 (m, 5H), 8.92 (s, br, 1H); δ_C (68 MHz; $CDCl_3$) 27.14, 34.86, 59.41, 72.06, 73.13, 127.74, 127.85, 128.52, 137.99, 156.48, 177.95.
11 Amino acid **8**: δ_H (270 MHz, D_2O) 2.0 (CH_3CN, ref.), 2.18–2.27 (m, 2H), 2.67–2.76 (m, 2H), 2.94 (sept, 1H), 3.53 (d, J = 10.3 Hz, 2H); δ_C (68 MHz; D_2O) 2.0 (CH_3CN, ref) 29.94, 35.26, 38.46, 52.60, 173.70.