Pergamon

Tetrahedron Letters 43 (2002) 9411–9412

TETRAHEDRON LETTERS

A chiral tricyclic proline analogue obtained from camphor

Marian V. Gorichko, Oleksandr O. Grygorenko and Igor V. Komarov*

Department of Chemistry, Kiev Taras Shevchenko University, Vladimirskaya Street, 64, Kiev 01033, Ukraine

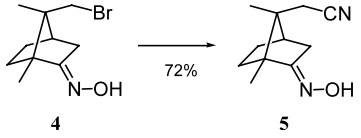
Received 27 August 2002; revised 26 September 2002; accepted 11 October 2002

Abstract—Synthesis of 3a,6a-dimethylhexahydro-1,4-methanocyclopenta[*c*]pyrrole-1(2*H*)-carboxylic acid, a new chiral constrained proline analogue is reported. The synthesis was accomplished in five steps from 8-bromocamphor, easily available in both enantiomeric forms. A key step in the synthesis is an intramolecular 'domino'-type cyclisation, initiated by a nucleophile attack at an activated C=N bond. © 2002 Published by Elsevier Science Ltd.

The last decade witnessed a growth of activity in the area of modified peptides. They have been found to possess many advantages in comparison to natural biologically active peptides in terms of activity, selectivity of the biological action, and in vivo stability.[1,2] One of the conceptual approaches towards the synthesis of modified peptides is incorporation of conformationally restricted α-amino acid analogues into the peptide backbone.[3] Of the α-amino acid analogues used, constrained proline analogues have attracted most attention.[4,5] This amino acid is frequently found in peptide β-turns which play an important role in peptide receptor recognition and antigen determination.[6] Here we report on the synthesis of a new chiral tricyclic proline analogue **1** starting from the natural terpenoid, camphor, available in both enantiomeric forms.

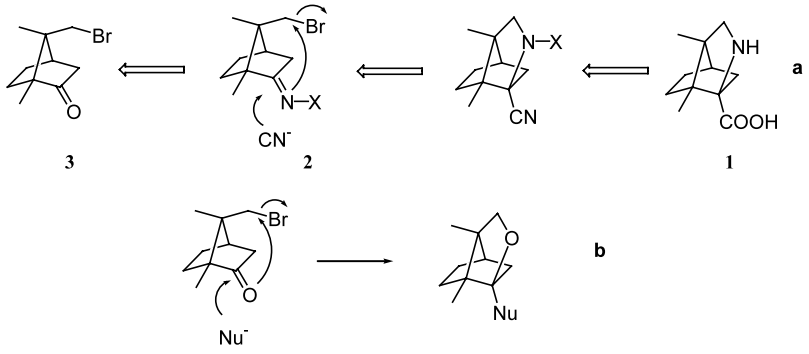
As the key step in the synthesis we planned to use the intramolecular 'domino'-type cyclisation of the 8-bromocamphor derivatives **2** which contain a C=N bond. 8-Bromocamphor **3** itself can be obtained stereospecifically from camphor in three steps which can be carried out on a large scale.[7] The cyclisation could be initiated by nucleophilic attack of the cyanide ion at the C=N bond, as shown in Scheme 1a. An analogous reaction (Scheme 1b) led to the formation of the 4-oxatricyclo[4.3.0.0^{3,7}]nonane skeleton.[8]

The success of the outlined synthetic plan depends crucially on the proper choice of the functional group X in compound **2**. First of all, it must be an electron-withdrawing group to increase the electrophilicity of the carbon atom in the azomethine group, otherwise simple nucleophilic substitution at C-8 will occur. For example, 8-bromocamphoroxime **4** reacts with the cyanide ion giving compound **5**—the product of nucleophilic substitution, not cyclisation (Scheme 2).



4 5

Scheme 2. *Reagents and conditions*: KCN/DMFA, reflux, 2 h.



3 2 1

Scheme 1.

* Corresponding author. E-mail: ik214@yahoo.com

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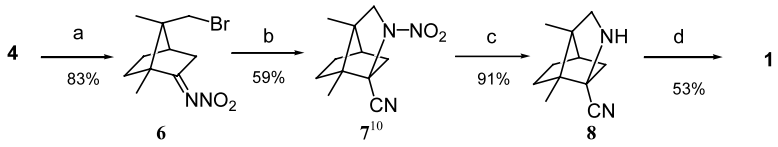
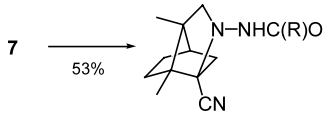
PII: S0040-4039(02)02325-0

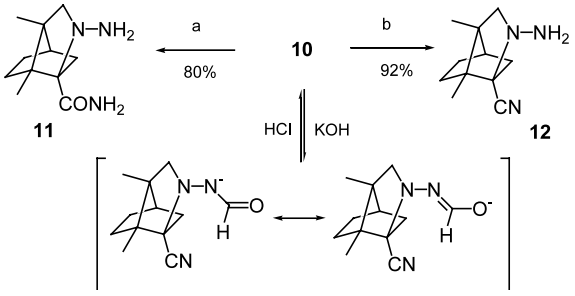


Scheme 3. *Reagents and conditions*: (a) aqueous $NaNO_2/H_2SO_4$, 1 h; (b) $(CH_3)_2C(OH)CN$/KOH/ethanol, reflux, 1 h; (c) H_2/Pd–C/MeOH, 60°C, 2 days; (d) conc. aq. HCl, reflux, 1.5 days.



9, R= CH_3; **10**, R = H

Scheme 4. *Reagents and conditions*: Zn/RCOOH, 60°C, 2.5 h.



Scheme 5. *Reagents and conditions*: (a) 10% aq. KOH, reflux, 2 h; (b) 10% aq. HCl, heating, 15 min.

Another important feature of the group X should be its ease of removal. We found that the nitro group meets these requirements. Nitroimine **6** is easily available from the oxime **4.** The carbon atom of the C=N bond in **6** is electrophilic enough for the compound to undergo the desired cyclisation to yield **7**. Subsequent Pd-catalysed hydrogenolysis of the nitro group and hydrolysis of the nitrile accomplishes the synthesis of **1**[9](Scheme 3).

We also explored the possibility of reducing the nitro group in **7** without cleavage of the N–N bond. The reduction could be performed by Zn in acetic or formic acid yielding the acylated derivatives **9** or **10**[11] (Scheme 4).

The latter compound dissolves in dilute aqueous potassium hydroxide, most likely because of reversible deprotonation; addition of hydrochloric acid regenerates the starting material. Heating results in hydrolysis in both alkaline and acidic media to yield **11**[12] and **12**,[13] respectively (Scheme 5).

Acknowledgements

Financial support from Du Pont de Nemours International S.A. is gratefully acknowledged.

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9. For **1**, ^{1}H NMR (400 MHz, DMSO-d_6, δ) (for hydrochloride): 10.33 (br. s, 1H), 9.16 (br. s, 1H), 3.21 (m, 1H), 2.90 (m, 1H), 2.20 (m, 1H), 2.05 (m, 2H), 1.78 (m, 1H), 1.59 (d, J=13.2 Hz, 1H), 1.43 (m, 1H), 1.33 (m, 1H), 0.93 (s, 6H).
10. For **7**, ^{1}H NMR (400 MHz, DMSO-d_6, δ): 3.95 (d, J=11.4 Hz, 1H, 5-CH_2), 3.68 (d, J=11.4 Hz, 1H, 5-CH_2), 2.12 (m, 1H), 2.03 (m, 1H), 1.55–1.78 (m, 4H), 1.37 (m, 1H), 1.08 (s, 3H), 0.95 (s, 3H). IR (KBr, cm^{-1}): 1530 (N–NO_2, N–O as), 2240 (C≡N).
11. For **10**, The product is a mixture of isomers; ^{1}H NMR (400 MHz, DMSO-d_6, δ) (for major): 9.29 (d, J=9.6 Hz, 1H, NH), 8.09 (d, J=9.6 Hz, 1H, CHO), 2.97 (d, J=9.6 Hz, 1H, 5-CH_2), 2.73 (d, J=9.6 Hz, 1H, 5-CH_2), 2.47 (m, 1H), 1.94 (s, 1H), 1.64–1.75 (m, 2H), 1.49 (m, 1H), 1.30 (m, 1H) 1.15–1.22 (m, 4H), 0.86 (s, 3H).
12. For **11**, ^{1}H NMR (400 MHz, DMSO-d_6, δ): 7.01 (br. s, 1H, $CONH_2$), 6.82 (br. s, 1H, $CONH_2$), 3.44 (br. s, 2H, N–NH_2), 2.97 (d, J=9.6 Hz, 5-CH_2), 2.33 (d, J=9.6 Hz, 5-CH_2), 1.86 (m, 2H), 1.76 (m, 1H), 1.65 (m, 1H), 1.31 (d, J=12.4 Hz, 1H), 1.17 (m, 2H), 0.88 (s, 3H), 0.75 (s, 3H).
13. For **12**, ^{1}H NMR (400 MHz, DMSO-d_6, δ): 3.74 (br. s, 2H, NH_2), 2.90 (d, J=9.6 Hz, 1H, 5-CH_2), 2.34 (m, 2H), 1.86 (m, 1H), 1.66–1.73 (m, 2H), 1.56 (m, 1H), 1.41 (m, 1H), 1.26 (m, 1H), 1.04 (s, 3H), 0.77 (s, 3H).