Tetrahedron Letters, Vol.31, No.28, pp 4011-4014, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

THREE NOVEL MIMICS FOR THE CONSTRUCTION OF STERICALLY CONSTRAINED PROTEIN TURN MODELS

I. Ernest ,[a] J. Kalvoda,[b] G. Rihs,[c] and M. Mutter.*[d]

[a] Institut für Organische Chemie, Universität Basel, St. Johanns-Ring 19, CH-4056 Basel (Switzerland)

[b] Pharmazeutische Division, Ciba-Geigy AG, CH-4002 Basel (Switzerland)

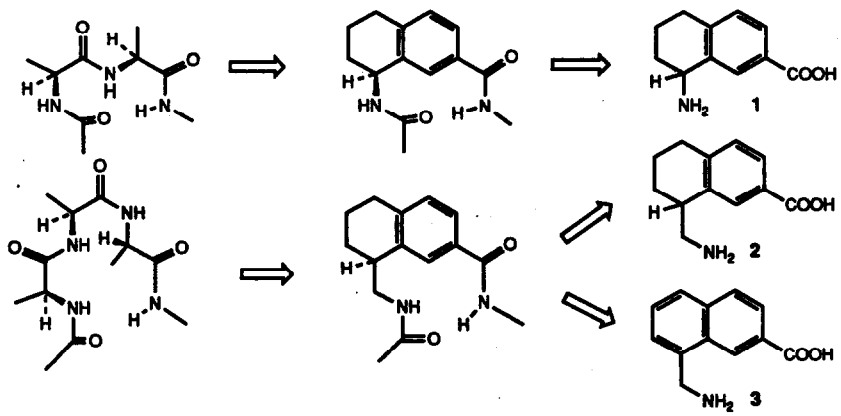
[c] Zentrale Forschung, Ciba-Geigy AG, CH-4002 Basel (Switzerland)

[d] Section de Chimie, Université de Lausanne, rue de la Barre 2, CH-1005 Lausanne (Switzerland)

Abstract: 8-Amino-5,6,7,8-tetrahydro-2-naphthoic acid (**1**), 8-aminomethyl-5,6,7,8-tetrahydro-2-naphthoic acid (**2**), and 8-aminomethyl-2-naphthoic acid (**3**) were synthesized in their protected forms for use in the construction of sterically constrained protein turn models.

The importance of various forms of turns in proteins and larger peptides as regular parts of the tertiary structure and often as binding and active sites in substrate-receptor and substrate-enzyme interactions[1] aroused recently the interest of chemists for the synthesis of artificial turn-inducing mimics[2]. The major purpose of such mimics, when incorporated in a peptide chain, is to constrain the chain in the otherwise preferred, but by no means rigid U-form conformation.

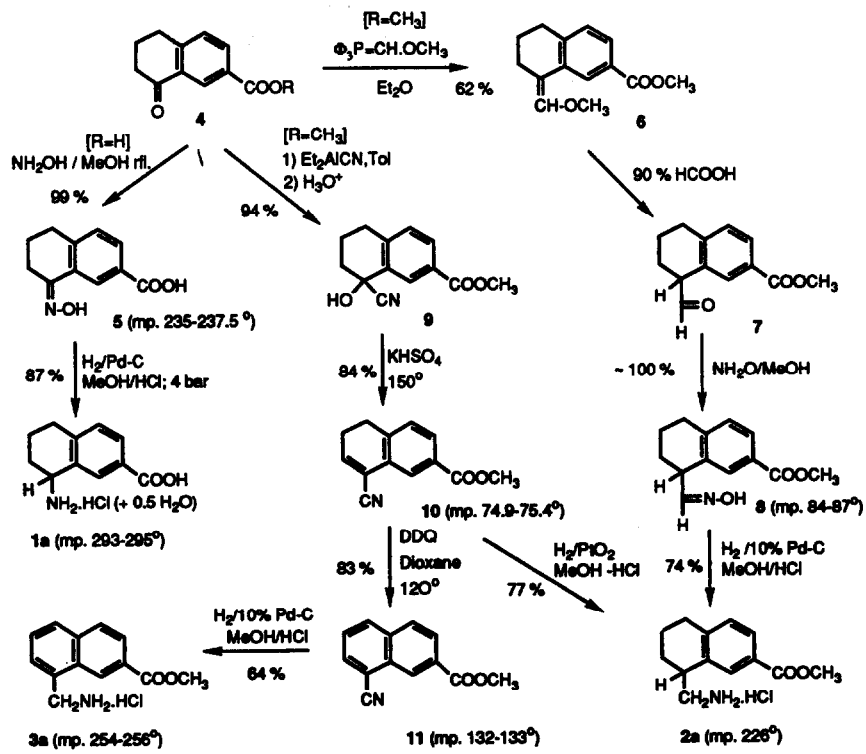
In the present paper, we describe the design and synthesis of three novel, simple, turn mimics of this type, *i.e.* compounds **1**, **2**, and **3** (Scheme 1).



Scheme 1

As shown in Scheme 1, one of the mimics, 8-amino-5,6,7,8-tetrahydro-2-naphthoic acid (ATA; **1**), was developed as a substitute for the central dipeptide part of a β-turn. The homologous 8-aminomethyl-5,6,7,8-tetrahydro-2-naphthoic acid (AMTA; **2**) - an extension of the preceding structure recommended by a CAMM analysis[3] - rather corresponds to the central tripeptide unit of a reverse turn. Finally, the achiral 8-aminomethyl-2-naphthoic acid (AMNA; **3**) resulted as a sterically acceptable and advantageous simplification of **2**.

The common starting point for the synthesis of all three mimics was the known 2-tetralon-7-carboxylic acid **4**, easily prepared in five simple steps from the commercially available 4-phenylbutyric acid[4] (Scheme 2). Hydrogenation of its oxime **5** (5 % Pd-C, HCl-MeOH) gave the crystalline hydrochloride of the racemic mimic **1a** in high yield. For the synthesis of the homologous mimic **2**, the methyl ester of **4** was first extended - in a two-step process involving the isomeric mixture of the enol-ethers **6** as intermediate - to the aldehyde **7**. In a similar way as in the case of **1**, the corresponding oxime **8** was hydrogenated to give the crystalline methyl ester hydrochloride **2a** in its racemic form. In an alternative synthesis of **2a**, the methyl ester of **4** was transformed (Et_2AlCN in toluene; H_3O^+) into an isomeric mixture of cyanohydrines **9** which on heating with $KHSO_4$ (150°C), was dehydrated to methyl 8-cyano-5,6-dihydro-2-naphthoate **10**. Hydrogenation of the latter, this time over platinum (PtO_2/H_2, HCl-MeOH), afforded **2a** in a high overall yield.

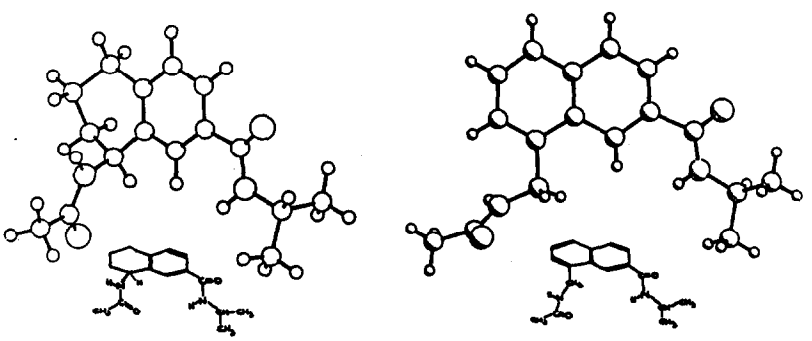


Scheme 2[5]

The dihydronaphthalene derivative **10** proved a suitable intermediate also for the synthesis of the AMNA mimic **3**. Dehydrogenation of **10** (DDQ in dioxane, 120°C) led smoothly to methyl 8-cyano-2-naphthoate **11** which, in its turn, was transformed - by hydrogenation on palladium (10% Pd-C, HCl-MeOH) - into the crystalline methyl ester-hydrochloride **3a** [5].

Finally, for their incorporation into peptide chains, the mimics were transformed to the corresponding N-Boc and N-Fmoc acids and/or activated esters[6].

To test the ability of our mimics as turn-inducing entities, their N-acetyl-N'-isopropyl amides (derivatives **1b**, **2b** and **3b**, respectively) were prepared as simple models of β-turn peptides (the acetyl group simulating the i, the iPr-NH grouping the i+3-amino acid). The X-ray analysis of **1b** and **3b** showed lacking intramolecular H-bonds (Figure 1). Also, the ^{1}H-NMR spectra of **2b** and **3b** in DMSO did not show any evidence for internal H-bonding; the temperature coefficients for the chemical shifts of the N-H protons were indicative of exposure to solvent, with values between 6 and 7 ppb·K^{-1}, well above the value expected for hydrogens involved in an internal H-bond (< 3 ppb·K^{-1})[7,8]. However, the general geometry of mimics **1** and **3**, as evidenced by the X-ray analysis of **1b** and **3b**, makes them well-suited for building up compounds with the characteristics of an open U-turn. A similar conclusion could be drawn for the mimic **2**, based on CAMM and spectroscopical studies of **2b**.



1b **3b**

Figure 1. PLUTO drawings of mimic derivatives **1b** and **3b**. Crystal data and atomic parameters have been submitted to the Cambridge Crystal Data Bank.

Full details on the synthesis of the novel three mimics and their incorporation into peptide chains will be published elsewhere. An example for the successful use of one of them in the synthesis of a cyclic peptide carrier for use in the construction of a template-assembled synthetic protein (TASP) is described in the accompanying publication[9].

Acknowledgements: We thank the Analytical Services of Ciba-Geigy AG (Dr. W. Padowetz) for the elemental analyses, Mr. S. Moss and Prof. H. Fritz (both Central Function Research, Ciba-Geigy AG, Basel) for the IR spectra and for the NMR studies of our compounds, respectively. M. M. thanks the Swiss National Research Foundation for financial support.

References and Notes:

1. G. D. Rose, L. M. Gierasch, J. A. Smith (1985) *Adv. Protein Chem.* **37**, 1.
2. See *e.g.*, G. L. Olson, M. E. Voss, D. E. Hill, M. Kahn, V. S. Madison, Ch. M. Cook (1990) *J. Am. Chem. Soc.* **112**, 323 and references therein.
3. We thank here Dr. C.N. Cohen, Pharmaceuticals Division, Ciba-Geigy Limited, Basel, for the CAMM analysis. Full details will be published elsewhere.
4. G. Baddeley, R. Williamson (1956) *J. Chem. Soc.* 4647; a substantial technical improvement was achieved in the last step of the synthesis, *i.e.* in the cyclization of 4-p-carboxyphenyl-butyric acid to the ketoacid **4**, by using polyphosphoric acid instead of $AlCl_3$/NaCl.
5. All compounds of Scheme 2 as well as the N-acetyl-N'-isopropyl-amides of **1** - **3** were fully characterized by elemental analyses and IR and NMR spectroscopy. A full paper including all data is in preparation.
6. Derivatives of **1**: N-Boc-acid: mp. 209-210.5°; N-Fmoc-acid: mp. 234-235.5°; N-acetyl-N'-isopropylamide (**1b**): mp. 227-228°.
   Derivatives of **2**: Free acid **2**: mp. 256.7-258.5°; N-acetyl-acid: mp. 222.5-224°; N-acetyl-N'-isopropylamide (**2b**): mp. 150.5-151.5°.
   Derivatives of **3**: N-Boc-methyl ester ester: mp.109.5-110.5°; N-Boc-acid: mp.196-197°; N-Fmoc-acid: mp. 256°; N-Fmoc-acid chloride: mp. 180-181°; N-Fmoc-2,4,5-trichlorophenyl ester: mp. 182-184°; N-acetyl-methyl ester: mp. 143-144°; N-acetyl-N'-isopropyl-amide (**3b**): mp.198-199°.
7. H. Kessler (1982) *Angew. Chem.* **94**, 509; *Angew. Chem. Int. Ed. Engl.* **21**, 512.
8. Full details of the NMR studies (Prof. H. Fritz, Zentrale Forschung, Ciba-Geigy AG, Basel) will be published elsewhere.
9. I. Ernest, S. Vuilleumier, H. Fritz and M. Mutter (1990) *Tetrahedron Letters* (accompanying paper).

(Received in Germany 19 April 1990)