4-Fluoro-2,4-methanoproline

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4-Fluoro-2,4-methanoproline

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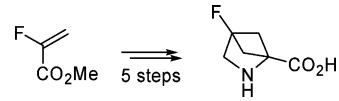
ABSTRACT



The first fluorinated analogue of the naturally occurring 2,4-methanoproline, 4-fluoro-2,4-methanoproline, has been synthesized in five steps from commercially available methyl 2-fluoroacrylate through a photochemical cyclization as a key step in generating a 2-azabicyclo[2.1.1]hexane skeleton.

2,4-Methanoproline (**1**) is a naturally occurring nonproteinogenic amino acid first isolated from the seeds of the legume *Ateleia herbert smithii* Pittier, growing in Costa Rica (Figure 1).[1,2] The seeds of this tree are ignored by more than 100 seed predators, and it was recently shown that derivatives of **1** have high insect antifeedant activity.[3] It is supposed that this biological activity is caused by the conformational rigidity of the 2-azabicyclo[2.1.1]hexane skeleton, which leads to the reduced metabolism of **1**, compared to proline. Since the first synthesis of 2,4-methanoproline in 1980,[4] a large number of different synthetic approaches to **1** have appeared,[5] thereby indicating an intense interest in this amino acid. For example, **1** was found to stabilize the peptide tertiary *trans*-amide bonds,[6] which is of great potential in peptide design, since the *cis*−*trans* isomerization of peptide bonds is closely related to biologically relevant processes, primarily to folding and unfolding.[7] In particular, **1** was used instead of proline to synthesize a conformationally constrained analogue of thyrotropin-releasing hormone (TRH) and to study the latter.[8] Moreover, **1** was also introduced into the oligopeptides bradykinin and angiotensin, which are neurotransmitters playing an important role in the regulation of blood pressure and heart function.[9] Last year, **1** was applied as a conformationally rigid building block to prepare new potential ligands of the nicotinic acetylcholine receptor.[10]

The substitution of fluorine for hydrogen in organic compounds is widely used to modify their physical, chemical, and biological characteristics.[11] Surprisingly, despite the great potential of 2,4-methanoproline (**1**), there are, to the best of our knowledge, no fluorinated analogues of **1** described in

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(2) Recently, **1** was also found in the legume *Bocoa alterna*: Kite, G. C.; Ireland, H. *Phytochemistry* **2002**, *59*, 163.

(3) Stevens, C. V.; Smagghe, G.; Rammeloo, T.; De Kimpe, N. *J. Agric. Food Chem.* **2005**, *53*, 1945.

(4) Pirrung, M. C. *Tetrahedron Lett.* **1980**, *21*, 4577.

(5) (a) Hughes, P.; Martin, M.; Clardy, J. *Tetrahedron Lett.* **1980**, *21*, 4579. (b) Hughes, P.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 4793. (c) Gaoni, Y. *Org. Prep. Proced. Int.* **1995**, *27*, 185. (d) Stevens, C.; De Kimpe, N. *J. Org. Chem.* **1996**, *61*, 2174. (e) Rammeloo, T.; Stevens, C. V.; De Kimpe, N. *J. Org. Chem.* **2002**, *67*, 6509. (f) Krow, G. R.; Herzon, S. B.; Lin, G.; Qiu, F.; Sonnet, P. E. *Org. Lett.* **2002**, *4*, 3151. (g) Rammeloo, T.; Stevens, C. V. *Chem. Commun.* **2002**, 250. (h) Grygorenko, O. O.; Artamonov, O. S.; Palamarchuk, G. V.; Zubatyuk, R. I.; Shishkin, O. V.; Komarov, I. V. *Tetrahedron: Asymmetry* **2006**, *17*, 252.

(6) (a) Montelione, G. T.; Hughes, P.; Scheraga, H. A. *J. Am. Chem. Soc.* **1986**, *108*, 6765. (b) Talluri, S.; Montelione, G. T.; van Duyne, G.; Piela, L.; Chardy, J.; Scheraga, H. A. *J. Am. Chem. Soc.* **1987**, *109*, 4473. (c) Piela, L.; Némethy, G.; Scheraga, H. A. *J. Am. Chem. Soc.* **1987**, *109*, 4477.

(7) (a) Bächinger, H. P.; Engel, J.; Bruckner, P.; Timpl, R. *Eur. J. Biochem.* **1978**, *90*, 605. (b) Salahuddin, A. *J. Biosci.* **1984**, *6*, 349. (c) *Cis-trans isomerization in biochemistry*; Dugave, C., Ed.; Wiley-VCH: Weinheim, 2006.

(8) Mapelli, C.; Van Halbeek, H.; Stammer, C. H. *Biopolymers* **1990**, *29*, 407.

(9) Juvvadi, P.; Dooley, D. J.; Humblet, C. C.; Lu, G. H.; Lunney, E. A.; Panek, R. L.; Skeean, R.; Marshall, G. R *Int. J. Pept. Protein Res* **1992**, *40*, 163.

(10) (a) Malpass, J. R.; Patel, A. B.; Davies, J. W.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 9348. (b) Patel, A. B.; Malpass, J. R. *J. Med. Chem.* **2008**, *51*, 7005.

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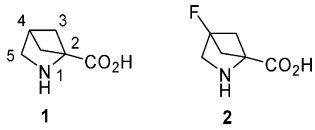
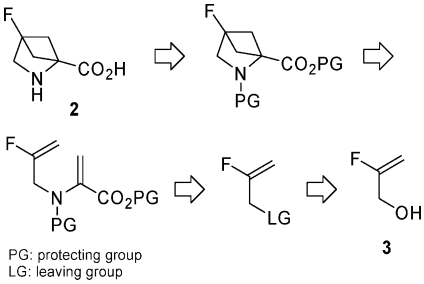


Figure 1. Natural nonproteinogenic amino acid 2,4-methanoproline (**1**) and its fluorinated analogue 4-fluoro-2,4-methanoproline (**2**). Proline numbering is shown.

the literature to date. Therefore, here we wish to report the synthesis of the first fluorine-containing analogue of 2,4-methanoproline (**1**): 4-fluoro-2,4-methanoproline (**2**) (Figure 1). The 4-C*H* position was selected for the labeling by a fluorine atom, since this is the only substitution which retains the nonchirality of **1**.

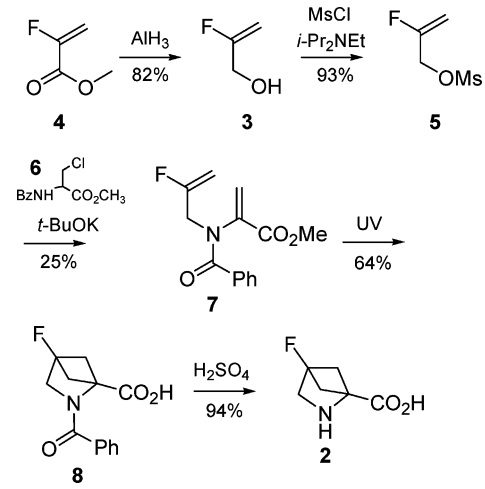
Among known approaches to construct the 2-azabicyclo-[2.1.1]hexane skeleton,[5,12] we chose a strategy based on an intramolecular light-induced [2 + 2] cycloaddition of the appropriate diene (Scheme 1).

Scheme 1. Retrosynthetic Approach to **2**



Recently, Piotrowski demonstrated the high efficiency of this reaction by synthesizing diverse potential ligands of the nicotinic acetylcholine receptor, the yields being good almost irrespective of the substituents in the starting dienes.[13] Our retrosynthetic approach to **2** was based on 2-fluoroallylic alcohol (**3**) as a starting material (Scheme 1). Surprisingly, although the compound **3** has already been described in the literature,[14] we found no efficient and straightforward method for its practical preparation from commercially available materials. Therefore, a procedure to obtain **3** directly from commercially available methyl 2-fluoroacrylate (**4**) was elaborated (Scheme 2).

Scheme 2. Synthesis of 4-Fluoro-2,4-methanoproline (**2**)



Reduction of **4** with AlH_3, generated in situ from $LiAlH_4$ and $AlCl_3$, at −5 °C smoothly afforded alcohol **3** in 82% yield (Scheme 2). Next, **3** was reacted with MsCl at room temperature using diisopropylethylamine as a base to produce mesylate **5** in 93% yield. Thereafter, alkylation of the readily available serine derivative BzNHCH(CH_2Cl)CO_2Me (**6**)[5a] with **5** was performed; however, the product **7** was obtained in only 25% yield.[15] The key step in the synthesis, the intramolecular light-induced [2 + 2] cycloaddition of diene **7**, smoothly afforded the target 2-azabicyclo[2.1.1]octane derivative (**8**) in 64% yield.

Finally, standard acidic cleavage of the *N*-Boc and COOMe groups in **8**, followed by ion-exchange chromatography on "Amberlite" resin, produced the fluorinated amino acid **2** in 94% yield.[16]

In summary, we have synthesized 4-fluoro-2,4-methanoproline (**2**): the first fluorinated analogue of a naturally occurring amino acid 2,4-methanoproline (**1**). The synthesis commences from commercially available methyl 2-fluoroacrylate (**4**) and involves five steps. The key synthetic step is a photochemical intramolecular [2 + 2] cyclization of

(11) (a) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645. (b) *Modern fluoroorganic chemistry*; Kirsch, P., Ed.; Wiley-VCH: Weinheim, 2004.

(12) Some representative examples: (a) Lescop, C.; Mévellec, L.; Huet, F. *J. Org. Chem.* **2001**, *66*, 4187. (b) Krow, G. R.; Lin, G.; Herzon, S. B.; Thomas, A. M.; Moore, K. P.; Huang, Q.; Carroll, P. J. *J. Org. Chem.* **2003**, *68*, 7562. (c) Jenkins, C. L.; Lin, G.; Duo, J.; Rapolu, D.; Guzei, I. A.; Raines, R. T.; Krow, G. R. *J. Org. Chem.* **2006**, *71*, 1754. (d) Esslinger, S.; Koch, H. P.; Kavanaugh, M. P.; Philips, D. P.; Chamberlin, A. R.; Thompson, C. M.; Bridges, R. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3101.

(13) Piotrowski, D. W. *Synlett* **1999**, *7*, 1091.

(14) (a) Laue, K. W.; Haufe, G. *Synthesis* **1998**, 1453. (b) Nagakura, I.; Savary, D. N.-H.; Schlosser, M. *Helv. Chim. Acta* **1980**, *63*, 1257.

(15) A similar transformation using allyl bromide is described in ref 5. The corresponding product was obtained in 94% yield. However, in that work a 20-fold excess of allyl bromide was used.

(16) Spectral and analytical data for the key compounds: **Methyl 2-benzoyl-4-fluoro-2-azabicyclo[2.1.1]hexane-1-carboxylate (8)**: colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ 2.34 (2 H, br s, 2 × C*H*H), 2.44 (2 H, br s, 2 × CH*H*), 3.61 (2 H, s, NCH_2), 3.81 (3 H, s, CH_3), 7.43 (2 H, t, $^3J_{H-H}$ = 7.5 Hz, Ph), 7.51 (1 H, t, $^3J_{H-H}$ = 7.5 Hz, Ph), 7.73 (2 H, d,$^3J_{H-H}$ = 7.0 Hz, Ph); ^{13}C NMR (125 MHz, $CDCl_3$, Me_4Si) δ 47.0 (d, $^2J_{C-F}$ = 10.1 Hz, 2 × CH_2), 52.6 (s, OCH_3), 53.9 (d, $^2J_{C-F}$ = 27.7 Hz, NCH_2), 60.4 (d, $^3J_{C-F}$ = 22.6 Hz, CCO_2CH_3), 87.8 (d, $^1J_{C-F}$ = 265.4 Hz, *C*F), 127.1 (s, *C*H, Ph), 128.6 (s, *C*H, Ph), 132.1 (s, *C*H, Ph), 133.2 (s, tert-*C*, Ph), 167.7 (d, $^4J_{C-F}$ = 11.3 Hz, N*C*OPh), 173.5 (s, CO_2CH_3); ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$) δ −173.1 (s, *F*); MS *m*/*z* (CI) 264 (M + 1, 100). **4-Fluoro-2-azabicyclo[2.1.1]hexane-1-carboxylic Acid (2)**: white solid; mp > 220 °C; ^{1}H NMR (500 MHz, $CDCl_3$, Me_4Si) δ 2.34 (2 H, d, *J* = 5.5 Hz, 2 × C*H*H), 2.58 (2 H, br s, 2 × CH*H*), 3.50 (2 H, s, NCH_2); ^{13}C NMR (125 MHz, $CDCl_3$, Me_4Si) δ 44.5 (d, $^2J_{C-F}$ = 20.1 Hz, 2 × CH_2), 46.4 (d, $^2J_{C-F}$ = 30.2 Hz, NCH_2), 62.3 (d, $^4J_{C-F}$ = 17.6 Hz, NCH_2C), 87.8 (d, $^1J_{C-F}$ = 264.2 Hz, *C*F), 170.4 (d, $^4J_{C-F}$ = 8.8 Hz, *C*OOH); ^{19}F NMR (470 MHz, $CDCl_3$, $CFCl_3$) δ −170.4 (s, *F*). Anal. Calcd for $C_6H_8FNO_2$: C, 49.66; H, 5.56; N, 9.65. Found: C, 49.78; H, 5.42; N, 9.83.

diene **7** to obtain the 2-azabicyclo[2.1.1]hexane skeleton (**8**). During the synthesis, an easy and efficient one-step procedure to prepare a valuable building block, 2-fluoroallylic alcohol (**3**), from **4** was elaborated.

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Supporting Information Available: Experimental precedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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