Multigram-scale Synthesis of Enantiopure 3,3-Difluoroproline

Christelle Doebelin, Yuanjun He, Theodore M. Kamenecka

PII: S0040-4039(16)31468-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.11.012
Reference: TETL 48298

To appear in: *Tetrahedron Letters*

Received Date: 20 October 2016
Revised Date: 31 October 2016
Accepted Date: 2 November 2016

Please cite this article as: Doebelin, C., He, Y., Kamenecka, T.M., Multigram-scale Synthesis of Enantiopure 3,3-Difluoroproline, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.11.012

Tetrahedron Letters
journal homepage: www.elsevier.com

Multigram-scale Synthesis of Enantiopure 3,3-Difluoroproline

Christelle Doebelin, Yuanjun He, and Theodore M. Kamenecka*

Department of Molecular Therapeutics, The Scripps Research Institute, Scripps Florida, 130 Scripps Way #A2A, Jupiter, FL 33458, USA

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
3,3-dilfuoroproline
Chiral resolution
Gram-scale synthesis

ABSTRACT

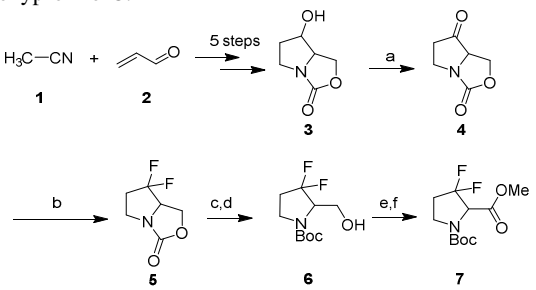
An efficient route for the synthesis of enantiopure 3,3-difluoroproline on multigram-scale is described herein. The deoxofluorination can be achieved with DAST on the corresponding racemic pyrrolidinone in good yield. Resolution of the racemate by crystallization with D- and L-tyrosine hydrazide provides both enantiomers of 3,3-difluoroproline in high yield and ee%.

For 60 years, the replacement of hydrogen by fluorine has been used in medicinal chemistry to modulate properties of druglike compounds.[1–5] A fluorine atom is regarded as a bioisostere of hydrogen. The substitution of a hydrogen atom by fluorine can block undesirable metabolism at a specific site, can increase lypophilicity and/or binding affinity and can modulate ADME parameters. Countless drugs and clinical candidates take advantage of fluorine atoms for these reasons. More recently, fluorinated amino acids have been incorporated in proteins to study stability, configuration, protein folding, and protein-protein interactions.[6–9] Optically pure 4,4-difluoroproline was synthesized over 30 years ago. It has shown is usefulness especially in medicinal chemistry to significantly improve potency, selectivity and/or solubility.[10–13] We were in need of enantiomerically pure 3,3-difluoroproline in gram quantities, and were surprised by the lack of suitable methods to synthesize it. Hence, we devised a synthetic route that could deliver optically pure material in just a few steps with minimal purifications. Herein we describe our approach.

Two major synthetics pathways have been described for the synthesis of 3,3-difluoroproline derivatives. In 1993, Hart and Coward, described the synthesis of racemic 3,3-difluoroproline from the masked 3-hydroxyprolinol **3** (Scheme 1).[14] Compound **3** can be obtained in five steps following the procedure describe by Tamaru et al.[15] In 1995, Shi et al. reported a synthetic pathway providing racemic β,β-difluoroproline starting from β,β-difluoro-α-keto-esters.[16]

This process was then optimized to allow the synthesis of chiral β,β-difluoroproline derivatives (Scheme 2).[17] The number of steps in these routes and the use of specific reagents (ie. allyltributyltin/AIBN, ozone) make these synthetic pathways time-consuming and difficult to scale up. We envisioned an alternate strategy to 3,3-difluoroproline starting from a commercially available β-ketoproline derivative that was both fast and scalable. For larger scale synthesis (> 30 g), we synthesized the β-ketoproline and adjusted the protecting groups to suit our needs.

Scheme 1.
Synthesis of DL-3,3-difluoroproline derivative from masked 3-hydroxyprolinol **3**.[a]



1 2 3 4 5 6 7

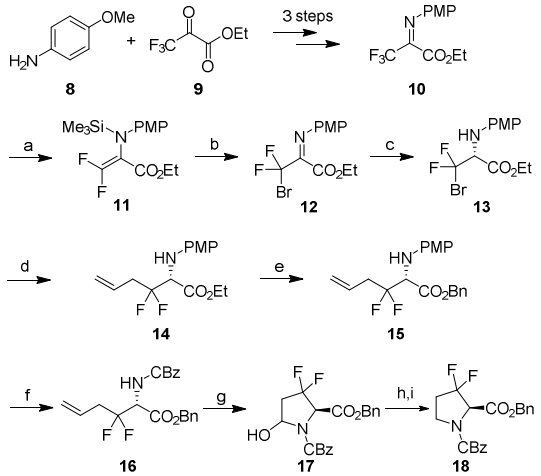
[a]Reagents: a) $(CF_3CO)_2O$, DMSO, Et_3N, CH_2Cl_2, 73%; b) DAST, CH_2Cl_2, -78°C to rt, 64%; c) 6N HCl, reflux; d) $(Boc)_2O$, $NaHCO_3$, $CHCl_3$, H_2O, 92% from **5**; e) $RuO_2.xH_2O$, 10%$NaIO_4$, EtOAc; f) CH_2N_2, Et_2O, 93% from **6**.

* Corresponding author.
E-mail address: kameneck@scripps.edu

We initiated our synthetic investigations from commercially available ethyl N-Boc-3-oxopyrrolidine-2-carboxylate **19**. The key step is the deoxofluorination of the β-oxo group.[18] Literature data as well as our own in-house studies confirm that the use of nucleophilic fluorination agents like DAST and its relatives on acyclic 3-keto esters fails to provide the desired 3,3-difluoro ester.

Scheme 2.

Initial synthesis of enantiopure 3,3-difluoroproline derivative.[a]

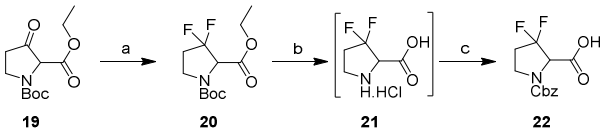


[a]Reagents: a) Mg, NaI, Me_3SiCl, DMF, 50%; b) NBS, CH_2Cl_2, rt, 97%; c) H_2, $Pd(OCOCF_3)_2$, (R)-BINAP, rt; d) allyltributyltin, AIBN, toluene, 90°C, 87% from **10**; e) CHTD, BnOH, toluene, reflux, 89%; f) *i* CAN, CH_3CN, 0°C, *ii* $Na_2S_2O_3$, CBzCl, $NaHCO_3$, 0°C, 39%; g) *i* O_3/O_2, CH_2Cl_2, -78°C, *ii* Me_2S, -78°C to rt, 77%; h) $PPh_3.Cl_2$, DMF, 0°C to rt; i) H_2 (1 atm), $RhCl(PPh_3)_3$, benzene, rt, 87%, > 99%ee.

These reactions lead to the formation of difluoro olefin esters and the occurrence of several side products.[19] To our knowledge, the fluorination of an α-amino β-keto esters had only been described in the patent literature.[20–22] With this in mind, we tested three different fluorination agents (Deoxo-Fluor®[23], DAST[24] and XtalFluor-E®[25]) with ketone **19** in CH_2Cl_2 (Scheme 3). In all reactions conditions tested, desired product **20** was detected, however despite using six equivalents of fluorination agent, the reactions failed to go to conversion. The reaction was ultimately improved by using 3 equivalents of DAST *without* solvent. Under these reaction conditions, 80% conversion of ketone **19** was observed by ^{1}H-NMR. The 3,3-difluoro ester **20** was isolated in 64% yield on multigram scale (5-6 g) starting with ketone **19**. Surprisingly, the reaction was quite clean, affording none of the by-products observed when using acyclic β-ketoesters. The hydrolysis of the Boc protecting group and the ester was achieved in a single step using aqueous 6N HCl at 60°C for 5h. We observed significant degradation of desired compound **21** at higher temperature (> 70°C) likely through competing β-elimination pathways. After removing excess HCl, the obtained amino acid was directly protected with benzyl chloroformate for easier isolation producing racemic Cbz-3,3-difluoroproline derivate **22** in 81% yield over three steps from **20**.

Scheme 3.

Difluorination of N-Boc-3-oxopyrrolidine-2-carboxylate.[a]

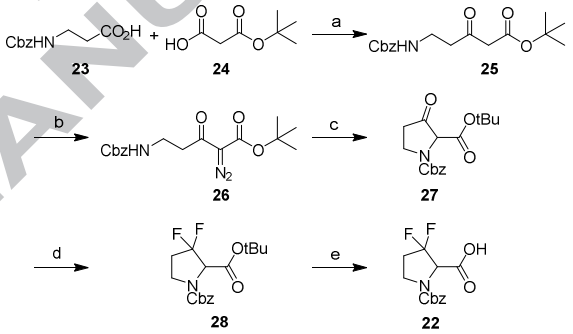


[a]Reagents: a) DAST, neat, 0°C-rt, 18h, 64%; b) HCl 6N, 60°C, 5h; c) CbzCl, $NaHCO_3$, H_2O, THF, rt, 24h, 81% over two steps.

This synthetic pathway was useful to prepare several grams of 3,3-difluoroproline, but for larger batches, we used Moyer et al.'s[26] synthesis of cyclic α-amino-β-keto ester **27** (Scheme 4), but modified the protecting groups to simplify the chemistry. The *tert*-butyl ester could be cleaved at room temperature, leaving the Cbz-group needed for the resolution step. The key step of the synthetic pathway is the cyclization of α-diazo-β-keto ester in presence of $Rh_2(OAc)_4$.

Scheme 4.

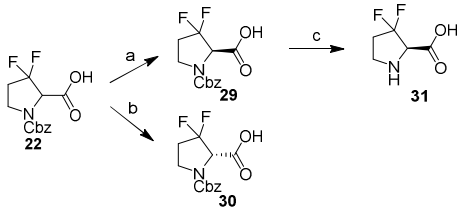
Preparation and fluorination of N-Cbz-3-oxopyrrolidine-2-carboxylate.[a]



[a]Reagents: a) (i) CDI, THF, rt, 18h; (ii) *i*PrMgBr, 0°C-rt, 5h, 95%; b) m-carboxybenzenesulfonyl azide, CH_3CN, Et_3N, rt, 2h, 95%; c) $Rh_2(OAc)_4$, toluene, 90°C, 1h, 91%; d) DAST, DCM, rt, 18h, 71%; e) TFA, DCM, rt, 5h, qt.

β-keto ester **25** was obtained by a Masamune-Claisen condensation between the two commercially available carboxylic acids **23** and **24** in presence of 1,1'-carbonyldiimidazole (CDI) and isopropylmagnesium bromide. The diazo group was introduced by diazo transfer from the 3-carboxybenzenesulfonyl azide[27] in 95% yield. The resulting *m*-carboxybenzenesulfonamide can be easily removed from desired compound **26** by an alkaline wash. Cyclization of the α-diazo β-keto ester **26** in the presence of $Rh_2(OAc)_4$ gave **27** in 91% yield. Deoxofluorination was performed in the presence of DAST to afford the β,β-difluoroproline derivate **28** in 71% yield. Prior to the fluorination step, no silica gel chromatography was needed which was advantageous on multi-gram scale (> 30 g). Moreover, the presence of the Cbz protecting group from the beginning of the synthesis facilitated reaction monitoring by UV and was desired for the resolution step. Another advantage of this synthetic pathway was the presence of the *t*-butyl ester which was cleaved under milder conditions than the ethyl ester. The use of TFA/DCM at rt, during the hydrolysis instead of 6N HCl at 60°C reduced the risk of formation of undesired side products.

Scheme 5.
Chiral resolution [a]



[a]Reagents: a) (i) D-tyrosine hydrazide, iPrOH, MeOH, 90°C-rt, 18h; (ii) HCl 1N, 80%, 99%ee; b) L-tyrosine hydrazide, iPrOH, MeOH, 90°C-rt, 18h; (ii) HCl 1N, 80%, 99%ee; c) Pd/C, H_2, EtOAc, rt, 18h, 99%.

We next tackled the resolution of our racemic material. Tyrosine hydrazide (Tyr-$NHNH_2$) has been shown to efficiently resolve several amino acid derivatives.[28–30] Vogler and Lanz.[28] reported that L-tyrosine hydrazide could resolve DL-amino acids to provide the D-antipodes with high efficiency and enantiomeric excess. Fortunately, in this case, the 3,3-bis-fluorine substitution did not interfere with the resolution, and using D-tyrosine hydrazide, we isolated the salt of acid **29** after filtration, with 99%ee and 80% yield after the first crystallization (Scheme 5). D-tyrosine hydrazide was easily prepared from D-tyrosine ($0.50/gram) in two steps (93% yield on 3 kg scale) following the same method as described for the L-tyrosine hydrazide after recrystallization.[31] An acidic wash removed the hydrazide, which could be recovered and recycled.[28] A second crystallization of the mother liquor with L-tyrosine hydrazide afforded the opposite enantiomer, (S)-3,3-difluoro-Cbz-proline **30** with 99%ee and 80% yield following acidic work-up. The same yield and enantiomeric excess were observed during the resolution of acid **22** on milligram scale (20 mg) as well as on 70 g scale. Enantiomeric excess was determined using chiral HPLC (see supporting information). The deprotection of the Cbz group by hydrogenation (99% yield) afforded enantiopure 3,3-difluoroproline in 5 steps from commercially available starting materials.

In summary, the synthetic pathway described herein gives access to optically pure (S)- and (R)-3,3-difluoroproline with good yields at each step. Purification by flash chromatography was only necessary after the key fluorination step, allowing for the easy production of gram quantities of the desired compound. 3,3-difluoroproline could be used as a scaffold in medicinal chemistry or in non-natural peptide synthesis.

Acknowledgments

Supported by the National Institute on Drug Abuse (DA033622 to T.M.K.).

Supplementary data

Supplementary data (experimental protocols and spectroscopic data) associated with this article can be found in the online version.

References

1. Swallow, S. *Prog. Med. Chem.* **2015**, *54* (2), 65–133.
2. Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37* (2), 267–432.
3. Hagmann, W. K. *J. Med. Chem.* **2008**, *51* (15), 4359–4369.
4. Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317* (317), 1881–1886.
5. Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58* (21), 8315–8359.
6. Hodgest, J. A.; Raines, R. T. *J. Am. Chem. Soc.* **2003**, *125* (31), 9262–9263.
7. Jäckel, C.; Salwiczek, M.; Koksch, B. *Angew. Chemie - Int. Ed.* **2006**, *45* (25), 4198–4203.
8. Cornilescu, G.; Hadley, E. B.; Woll, M. G.; Markley, J. L.; Gellman, S. H.; Cornilescu, C. C. *Protein Sci.* **2007**, *16* (9), 14–19.
9. Marsh, E. N. G. *Acc. Chem. Res.* **2014**, *47* (10), 2878–2886.
10. Qiu, Z.; Lin, X.; Zhou, M.; Liu, Y.; Zhu, W.; Chen, W.; Zhang, W.; Guo, L.; Liu, H.; Wu, G.; Huang, M.; Jiang, M.; Xu, Z.; Zhou, Z.; Qin, N.; Ren, S.; Qiu, H.; Zhong, S.; Zhang, Y.; Zhang, Y.; Wu, X.; Shi, L.; Shen, F.; Mao, Y.; Zhou, X.; Yang, W.; Zhen Wu, J.; Yang, G.; Mayweg, A. V; Shen, H. C.; Tang, G. *J. Med. Chem.* **2016**, *59* (16), 7651–7666.
11. Jansen, K.; Heirbaut, L.; Verkerk, R.; Cheng, J. D.; Joossens, J.; Cos, P.; Maes, L.; Lambeir, A.; Meester, I. De; Augustyns, K.; Van Der Veken, P. *J. Med. Chem.* **2014**, *57* (7), 3053–3074.
12. Gardelli, C.; Nizi, E.; Muraglia, E.; Crescenzi, B.; Ferrara, M.; Orvieto, F.; Pace, P.; Pescatore, G.; Poma, M.; Ferreira, M. D. R. R.; Scarpelli, R.; Homnick, C. F.; Ikemoto, N.; Alfieri, A.; Verdirame, M.; Bonelli, F.; Paz, O. G.; Taliani, M.; Monteagudo, E.; Pesci, S.; Laufer, R.; Felock, P.; Stillmock, K. A.; Hazuda, D.; Rowley, M.; Summa, V. *J. Med. Chem.* **2007**, *50* (20), 4953–4975.
13. De Bruin, G.; Huber, E. M.; Xin, B. T.; Van Rooden, E. J.; Al-Ayed, K.; Kim, K. B.; Kisselev, A. F.; Driessen, C.; Van Der Stelt, M.; Van Der Marel, G. A.; Groll, M.; Overkleeft, H. S. *J. Med. Chem.* **2014**, *57* (14), 6197–6209.
14. Hart, B. P.; Coward, J. K. *Tetrahedron Lett.* **1993**, *34* (31), 4917–4920.
15. Tamaru, Y.; Kawamura, S.; Bando, T.; Tanaka, K.; Yoshida, Z. *J. Org. Chem.* **1988**, *53* (2), 5491–5501.
16. Shi, G.-Q.; Cai, W.-L. *J. Org. Chem.* **1995**, *60* (20), 6289–6295.
17. Suzuki, A.; Mae, M.; Amii, H.; Uneyama, K. *J. Org. Chem.* **2004**, *69* (15), 5132–5134.
18. Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12* (2), 305–321.
19. Bildstein, S.; Ducep, J.-B.; Jacobi, D.; Zimmermann, P. *Tetrahedron Lett.* **1995**, *36* (28), 5007–5010.
20. Li, W.; Oliver, E.; Rojas, C.; Kalish, V.; Belyakov, S. WO 2004/071454.
21. Burnett, D.; Bursavich, M. G.; Mcriner, A. WO 2015/109109.
22. Kamenecka, T. M.; He, Y. WO 2016/025669.
23. Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64* (19), 7048–7054.
24. Hudlicky, M. *Org. React.* **1988**, *35*, 513–637.
25. L'heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; Laflamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M. *J. Org. Chem.* **2010**, *75* (10), 3401–3411.
26. Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem* **1985**, *50* (12), 5223–5230.
27. Moreau, R. J.; Sorensen, E. J. *Tetrahedron* **2007**, *63* (28), 6446–6453.
28. Vogler, K.; Lanz, P. *Helv. Chim. Acta* **1966**, *49* (4), 1348–1354.
29. Rodebaugh, R. M.; Cromwell, N. H. *J. Heterocycl. Chem* **1969**, *6* (6), 993–994.
30. Jaen, J. C. *e-Eros Encycl. Reagents Org. Synth. John Wiley Sons, LTd, Ed. Chichester, UK* **2011**.
31. Kudelko, A.; Zielinski, W.; Ejsmont, K. *Tetrahedron* **2011**, *67* (40), 7838–7845.

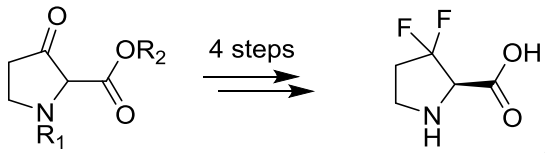
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Multigram-scale Synthesis of Enantiopure 3,3-Difluoroproline

Christelle Doebelin, Yuanjun He, Theodore M. Kamenecka

Leave this area blank for abstract info.



***Highlights**

- Enantioselective synthesis of 3,3-difluoroproline
- Short scalable synthesis
- Resolution provided both enantiomer in high ee and yield