Available online at www.sciencedirect.com

ScienceDirect

*Mendeleev Commun.*, 2024, **34**, 11–12

Mendeleev Communications

# Enantioselective synthesis of 5-fluoro-L-DOPA *via* chemoenzymatic route

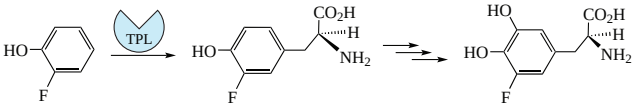
**Konstantin A. Kochetkov,*[a,b] Marina A. Tsvetikova,[a] Olga N. Gorunova,[a] Nataliya A. Bystrova[a] and Vyacheslav S. Yufriakov[a]**

[a] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119334 Moscow, Russian Federation. E-mail: const@ineos.ac.ru*

[b] *D. I. Mendeleev University of Chemical Technology of Russia, 125047 Moscow, Russian Federation*

DOI: 10.1016/j.mencom.2024.01.003

**The title compound, 5-fluoro-3,4-dihydroxy-L-phenylalanine, was prepared in four steps, with the key step having been the enantiospecific production of 5-fluoro-L-tyrosine by the chemoenzymatic reaction between 2-fluorophenol, potassium pyruvate and ammonia promoted by the live culture of *Citrobacter freundii* cells. 5-Fluoro-L-tyrosine was hydroxylated by sequential nitration, reduction and diazotization followed by hydrolysis.**



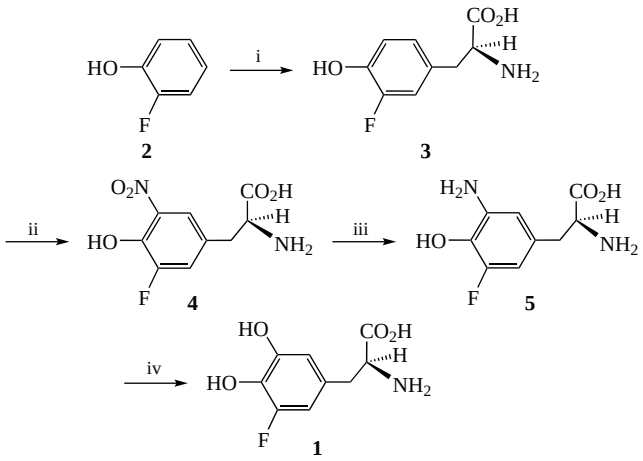

*Keywords*: 5-fluoro-L-DOPA, 5-fluoro-L-tyrosine, chemoenzymatic method, tyrosin phenol lyase, enantioselective synthesis, organofluorine compounds, amino acids.

Hydroxy amino compounds,[1–3] as well as various non-protein amino acids,[4,5] are of great practical importance due to their diverse physiological activities. On the other hand, the introduction of fluorine is widely used to modify the biological properties of various compounds.[4,6–9] Monofluorinated 3,4-dihydroxyphenylalanine (DOPA) derivatives are of interest for the diagnostic screening of Parkinson's disease using PET (Positron Emission Tomography).[1,4] Now 6-[$^{18}$F]-L-DOPA is a well-proven neurotracer with a wide range of applications.[4,10] Ecological biocatalysis,[11–17] cleavage of racemates into enantiomers,[5,18] and combined chemical-enzymatic methods[19,20] are currently used to obtain a variety of hydroxy amino compounds. The application of these environmentally friendly approaches to the production of amino acids and their derivatives,[5,21–23] in particular, L-DOPA,[24–26] L-Phe fluoro derivatives,[4,7] 6-fluoro-L-DOPA,[27] is well known; however, for obtaining 5-fluoro-L-DOPA **1**, these methods have not been used previously.

Syntheses of various fluorinated amino acids are multiply documented.[4] Monofluorinated DOPA derivatives are mainly obtained from the corresponding fluorine derivative of tyrosine and its subsequent oxidation to the target product. Previously,[28] 3-fluoro-L-tyrosine was obtained from 2-fluorophenol using tyrosine phenol lyase (TPL). It was found[29,30] that the presence of fluorine in position 3 of the aromatic fragment of tyrosine sharply decelerated its oxidation in the course of obtaining 5-fluoro-L-DOPA **1**. Moreover, fluorophenols themselves are oxidized with the release of fluoride ion, which leads to a side cyclization into 5,6-dihydroxy-2-carboxyindole. The further works were focused on obtaining 6-fluoro-L-DOPA, since the oxidation of 2-fluorotyrosine proceeded easier. 6-Fluorinated derivatives of L-DOPA were also obtained by direct fluorination of the amino acid,[31] however, this approach was unacceptable for the preparation of 5-fluoro-DOPA.[3] The asymmetric synthesis of 5-fluoro-L-DOPA[32] by stereoselective alkylation of a chiral glycine synthon under phase transfer conditions includes many steps with a total yield of 31%. Thus, the known methods for preparing the 5-fluoro-L-DOPA derivative are very limited. At the same time, the use of enzymes in the stereoselective preparation of compounds of various classes has become widespread.[33,34]

The aim of this work was to develop a chemical-enzymatic method for obtaining labile 5-fluoro-L-DOPA **1** under mild conditions, which makes it possible to exclude the use of toxic starting reactants and by-products of oxidation. The general transformations carried out to obtain enantiomerically pure 5-fluoro-L-DOPA **1** based on available 2-fluorophenol **2** are shown in Scheme 1.

It the first enzymatic step, 2-fluorophenol **2** was coupled with potassium pyruvate and ammonia to produce 3-fluoro-L-tyrosine **3**[29,30] by analogy with data[12] using a live cell culture. Cells of bacteria *Citrobacter freundii* containing the enzyme tyrosine phenol lyase were used immediately after cultivation in a nutrient




**Scheme 1** *Reagents and conditions*: i, $NH_3$, $Me(CO)CO_2K$, lipase TPL; ii, $HNO_3$; iii, Sn, HCl; iv, $Ba(NO_2)_2$, $CuSO_4$, boiling.

medium. The isolated 3-fluoro-L-tyrosine **3** was further nitrated to 3-fluoro-5-nitro-L-tyrosine **4** in the usual way,[35] and subsequent reduction gave 3-amino-5-fluoro-L-tyrosine **5**. The last step consisted in the diazotization of amine **5** followed by hydrolysis of the diazonium compound without isolation with the formation of the target 5-fluoro-L-DOPA **1** with 68% yield and high stereoselectivity under mild process conditions. The overall yield for all steps was 53%. DOPA and its derivatives are easily oxidized under the action of atmospheric oxygen into DOPA-quinones.[29,30] The use of 5-fluoro-3-tyrosine **5** in the last step and an inert atmosphere allowed us to avoid the side reaction of a quinone formation. The results of the $^{1}$H and $^{19}$F NMR study showed the absence of an impurity of oxidized compounds. To generate nitrous acid, barium dinitrite that formed an insoluble precipitate of barium sulfate with sulfate anion in a solution was used, which simplified the isolation of the product **1**. Nitrous acid was taken in an equimolar amount to aminotyrosine **5**, while diazotization proceeded selectively at the aromatic amino group.

In conclusion, an environmentally friendly chemical-enzymatic method for obtaining 5-fluoro-L-DOPA based on 2-fluorophenol was proposed and implemented. The characteristic features of the transformations carried out were mild reaction conditions under inert atmosphere, high stereoselectivity of the process and yields of the target product, elimination of the oxidation of the intermediate product leading to side compounds, and simplification of the isolation of pure products.

This work was supported by the Ministry of Science and Higher Education of the Russian Federation (contract no. 075-03-2023-642) and was performed employing the equipment of Center for molecular composition studies of INEOS RAS.

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.01.003.

## References

1 R. Chirakal, N. Vasdev, M.-C. Asselin, G. J. Schrobilgen and C. Nahmias, *J. Fluorine Chem.*, 2002, **115**, 339.
2 L. A. Sviridova, G. A. Golubeva, A. N. Tavtorkin and K. A. Kochetkov, *Amino Acids*, 2012, **43**, 1225.
3 C. Lamberth, *Amino Acids*, 2016, **48**, 929.
4 J. Moschner, V. Stulberg, R. Fernandes, S. Huhmann, J. Leppkes and B. Koksch, *Chem. Rev*., 2019, **119**, 10718.
5 J. B. Hedges and K. S. Ryan, *Chem. Rev*., 2020, **120**, 3161.
6 S. Sengupta and S. Chandrasekaran, *Org. Biomol. Chem*., 2019, **17**, 8308.
7 K. Pałka, K. Podsadni and M. Pająk, *J. Label. Compd. Radiopharm*., 2023, **66**, 362.
8 L. V. Politanskaya, G. A. Selivanova, E. V. Panteleeva, E. V. Tretyakov, V. E. Platonov, P. V. Nikul'shin, A. S. Vinogradov, Ya. V. Zonov, V. M. Karpov, T. V. Mezhenkova, A. V. Vasilyev, A. B. Koldobskii, O. S. Shilova, S. M. Morozova, Ya. V. Burgart, E. V. Shchegolkov, V. I. Saloutin, V. B. Sokolov, A. Yu. Aksinenko, V. G. Nenajdenko, M. Yu. Moskalik, V. V. Astakhova, B. A. Shainyan, A. A. Tabolin, S. L. Ioffe, V. M. Muzalevskiy, E. S. Balenkova, A. V. Shastin, A. A. Tyutyunov, V. E. Boiko, S. M. Igumnov, A. D. Dilman, N. Yu. Adonin, V. V. Bardin, S. M. Masoud, D. V. Vorobyeva, S. N. Osipov, E. V. Nosova, G. N. Lipunova, V. N. Charushin, D. O. Prima, A. G. Makarov, A. V. Zibarev, B. A. Trofimov, L. N. Sobenina, K. V. Belyaeva, V. Ya. Sosnovskikh, D. L. Obydennov and S. A. Usachev, *Russ. Chem. Rev*., 2019, **88**, 425.
9 E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315.
10 M. Pretze, C. Wängler and B. Wängler, *BioMed Res. Int*., 2014, Article ID 674063.
11 *Applied Biocatalysis: The Chemist's Enzyme Toolbox*, eds. J. Whittall and P. W. Sutton, Wiley, 2020.
12 Q. Do, G. T. Nguyen and R. S. Phillips, *Amino Acids*, 2016, **48**, 2243.
13 D. L. Obydennov, A. I. El-Tantawy and V. Ya. Sosnovskikh, *Mendeleev Commun.*, 2019, **29**, 1.
14 O. A. Mostovaya, Yu. A. Valiullina, C. T. Chan, O. S. Potrekeeva, P. L. Padnya, Yu. F. Zuev and I. I. Stoikov, *Mendeleev Commun.*, 2019, **29**, 520.
15 B. L. Grigorenko, E. D. Kots, A. I. Krylov and A. V. Nemukhin, *Mendeleev Commun.*, 2019, **29**, 187.
16 S. Wu, R. Snajdrova, J. C. Moore, K. Baldenius and U. T. Bornscheuer, *Angew. Chem., Int. Ed*., 2021, **60**, 88.
17 M. K. F. Mohr, R. Saleem-Batcha, N. V. Cornelissen and J. N. Andexer, *Chem. – Eur. J*., 2023, **29**, e202301503.
18 K. A. Kochetkov, M. A. Galkina and O. M. Galkin, *Mendeleev Commun.*, 2010, **20**, 314.
19 K. I. Galkin, *Mendeleev Commun.*, 2022, **32**, 399.
20 V. S. Yufryakov, M. A. Tsvetikova, N. A. Bystrova and K. A. Kochetkov, *Russ. Chem. Bull*., 2023, **72**, 1268.
21 E. A. Markvicheva, S. V. Kuptsova, T. Yu. Mareeva, A. A. Vikhrov, T. N. Dugina, S. M. Strukova, Y. N. Belokon, K. A. Kochetkov, E. N. Baranova, D. Poncelet, V. Parmar, R. Kumar, V. P. Zubov and D. Rumsh, *Appl. Biochem. Biotechnol*., 2000, **88**, 145.
22 F. M. Plieva, K. A. Kochetkov, I. Singh, V. S. Parmar, Yu. N. Belokon' and V. I. Lozinsky, *Biotechnol. Lett*., 2000, **22**, 551.
23 K. V. Alferov, Y. N. Zhukov, E. N. Khurs and R. M. Khomutov, *Mendeleev. Commun.*, 2003, **13**, 243.
24 T. Koyanagi, T. Katayama, H. Suzuki, H. Nakazawa, K. Yokozeki and H. Kumagai, *J. Biotech*., 2005, **115**, 303.
25 S. Ates, E. Cortenlioglu, E. Bayraktar and U. Mehmetoglu, *Enzyme Microb. Technol*., 2007, **40**, 683.
26 S. F. Rahman, S. Gobikhrisnan, M. Gozan, G. T. Jong and D.-H. Park, *Korean Chem. Eng. Res*., 2016, **54**, 817.
27 S. Kaneko, K. Ishiwata, K. Hatano, H. Omura, K. Ito and M. Senda, *Appl. Radiat. Isot*., 1999, **50**, 1025.
28 T. Nagasawa**,** T. Utagawa, J. Goto, C.-J. Kim, Y. Tani, H. Kumagai and H. Yamada, *Eur. J. Biochem*., 1981, **117**, 33.
29 R. S. Phillips, K. Ravichandran and R. L. von Tersch, *Enzyme Microb. Technol*., 1989, **11**, 80.
30 R. S. Phillips, R. L. von Tersch, J. G. Fletcher and A. H. Lai, in *Amino Acids*, eds. G. Lubec and G. A. Rosenthal, Springer, Dordrecht, 1990, pp. 166–172.
31 F. Füchtner and J. Steinbach, *Appl. Radiat. Isot*., 2003, **58**, 575.
32 W.-P. Deng, K. A. Wong and K. L. Kirk, *Tetrahedron: Asymmetry*, 2002, **13**, 1135.
33 A. Patti and C. Sanfilippo, *Int. J. Mol. Sci*., 2022, **23**, 2675.
34 B. P. Dwivedee, S. Soni, M. Sharma, J. Bhaumik, J. K. Laha and U. C. Banerjee, *ChemistrySelect*, 2018, **3**, 2441.
35 C. Niemann and M. M. Rapport, *J. Am. Chem. Soc*., 1946, **68**, 1671.

*Received: 25th September 2023; Com. 23/7258*