ACES Asian Chemical Editorial Society

doi.org/10.1002/ajoc.202400818

ASIAN JOURNAL OF ORGANIC CHEMISTRY
Research Article

www.asianjoc.org

Studies on the Synthesis of Some Functionalized Azaheterocycles through Oxidative Ring Opening/Ring Closing by Reductive Amination

Melinda Nonn,[a, b] Róbert Berkecz,[c, d] Santos Fustero,[e] Ágnes Lackfi,[f, g] Gábor Hornyánszky,[f] and Loránd Kiss*[g]

Selected functionalized saturated azaheterocycles have been prepared by ring expansion from various cycloalkene derivatives involving oxidative ring opening/ring closing by reductive amination. Studies have been conducted regarding the outcome of the transformations, the effect of the ring strain, and stereocontrol. The synthesized amino acid derivatives possessing either an aryl or fluorine element in their structure might be relevant building blocks for foldamer chemistry.

Introduction

Functionalized saturated azaheterocycles are considered to be highly relevant moieties as being key elements of molecular entities relevant in drug research and natural product chemistry. Therefore, they have a major interest in synthetic organic and medicinal chemistry. Examples containing azaheterocyclic frameworks include alkaloids, antitumoral agents, antibiotics, antiviral agents, and many drugs. The stereochemical architecture, along with the nature and the stereochemical characteristics of the substituents, is essential in determining their pharmaceutical properties.[1]

Azaheterocyclic amino acids with an extra nitrogen atom in their structure possess a wide range of biological and pharmaceutical potentials. Some of them are known as antiviral agents or they are present in various pharmacologically important bioactive products (anticancer agents, antineuralgics, cardioprotective or anti-inflammatory agents). In addition, they may function as building blocks in foldamer chemistry (Figure 1).[2]

Reductive amination is known as a common and effective method for the construction of saturated *N*-heterocyclic frameworks, involving an oxidative ring opening step of various cycloakenes, followed by cyclization under treatment with primary amines of the formed dialdehydes.[3]

Results and Discussion

Our current aim during this work was to extend our protocol developed earlier [3 h] and to perform further studies utilizing the synthetic method applied earlier. It was based on the oxidative transformation of some unsaturated bicyclic β-lactams or β-amino acids with a cycloalkene skeleton, leading to functionalized piperidines.

Highly strained unsaturated cyclic frameworks are valuable starting compounds for the creation of versatile and useful structural elements through transformations driven by strain release. Accordingly, these approaches give rise to attractive molecular scaffolds, which are highly interesting for pharmaceutical chemistry and drug design.[4] Taking into consideration the very attractive chemical behavior of the restricted ring systems, our main goal was the investigation and comparison of the reactivity of various β-lactam scaffolds as bicyclic strained systems in view of ring opening transformations followed by cyclization under double reductive amination.

The first starting material used in this investigation was racemic unsaturated bicyclic γ-lactam (±)-**7**, the so-called Vince

[a] *M. Nonn*
MTA TTK Lendület Artificial Transporter Research Group, Institute of Materials and Environmental Chemistry, HUN-REN Research Center for Natural Sciences, H-1117 Budapest, Magyar tudósok krt. 2, Hungary

[b] *M. Nonn*
National Drug Research and Development Laboratory, HUN-REN Research Centre for Natural Sciences, Magyar tudósok krt. 2, H-1117 Budapest, Hungary

[c] *R. Berkecz*
Institute of Pharmaceutical Analysis, University of Szeged, Somogyi u. 4, H-6720, Szeged, Hungary

[d] *R. Berkecz*
Department of Forensic Medicine, Albert Szent-Györgyi Health Centre, Kossuth Lajos sgt. 40 H-6724, Szeged, Hungary

[e] *S. Fustero*
Department of Organic Chemistry, University of Valencia, Pharmacy Faculty, 46100, Burjassot, Valencia, Spain

[f] *Á. Lackfi, G. Hornyánszky*
Department of Organic Chemistry and Technology, Faculty of Chemical Technology and Biotechnology, Budapest University of Technology and Economics, Műegyetem rkp. 3., H-1111 Budapest, Hungary

[g] *Á. Lackfi, L. Kiss*
Institute of Organic Chemistry, Stereochemistry Research Group, HUN-REN Research Center for Natural Sciences, H-1117 Budapest, Magyar tudósok krt. 2, Hungary
Tel: +36-30-1600354
E-mail: kiss.lorand@ttk.hu
kiss.lorand00@gmail.com

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ajoc.202400818

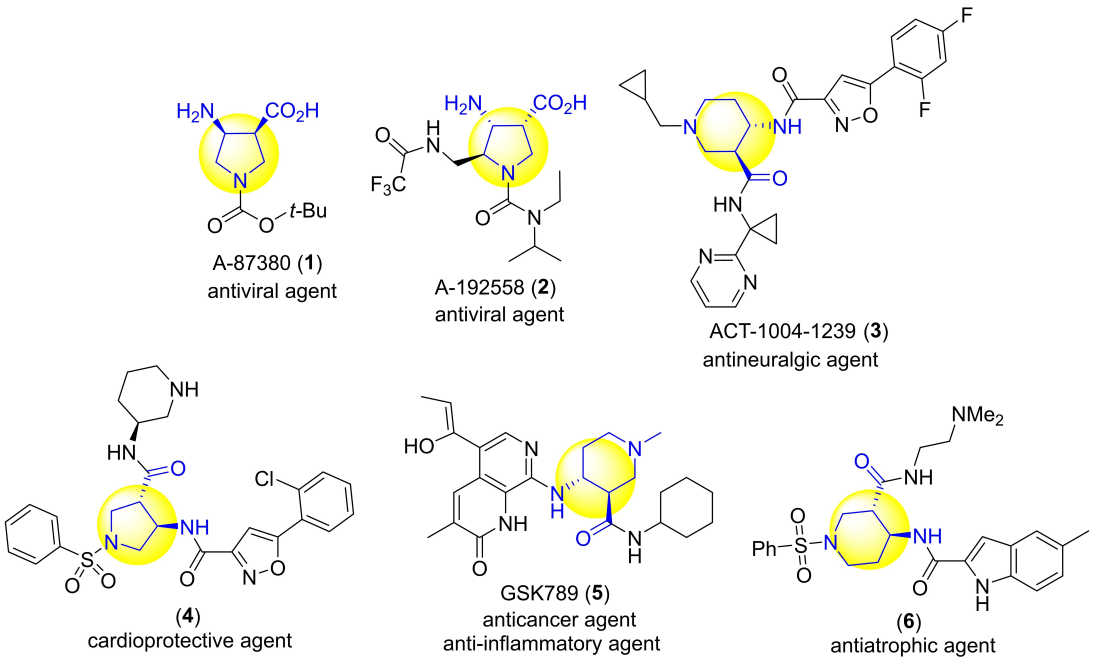
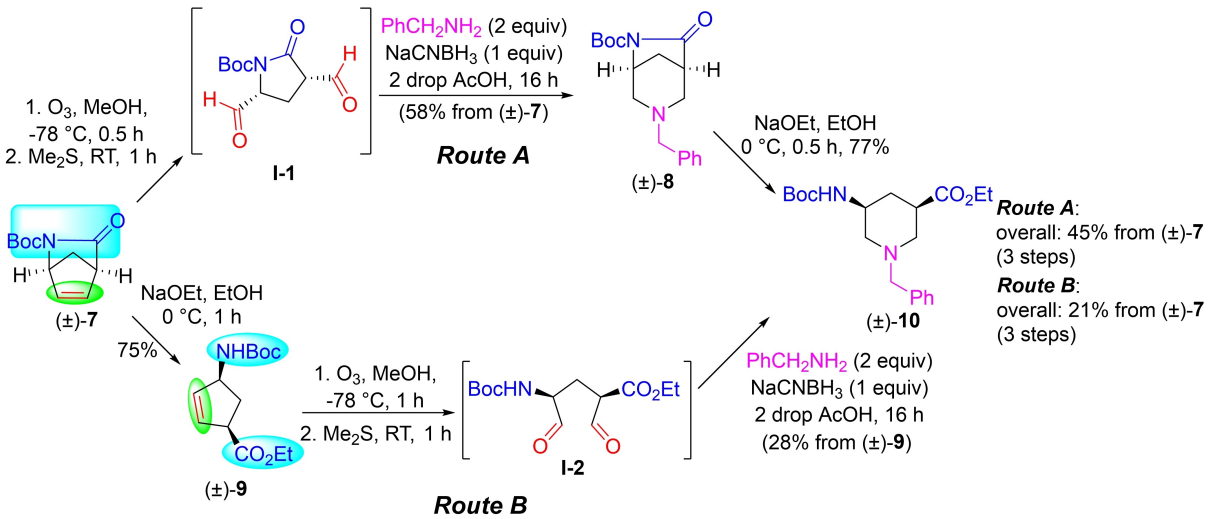


Figure 1. Some biologically relevant azaheterocyclic amino acid derivatives with an extra *N*-atom in their structure.

lactam.[5,6] The initial synthetic approach was based on the direct transformation of the ring olefin bond in lactam (±)-**7** across ozonolysis, followed by treatment of the resulting diformyl intermediate (I-1) with benzylamine and $NaCNBH_3$ under reductive amination conditions and provided through cyclization of the corresponding bicyclic lactam derivative (±)-**8**[7] (*Route A*, Scheme 1). Next, applying a new procedure, this compound on treatment with NaOEt at 0 °C for 30 min readily underwent lactam ring opening affording compound (±)-**10**. It is a new γ-amino ester derivative with a piperidine ring in 45% overall isolated yield from (±)-**7** (*Route A*). We were interested in synthesizing compound (±)-**10** on an alternative route. This consisted of a new synthetic step, involving the lactam opening of (±)-**7** in the presence of NaOEt at 0 °C in 1 h, followed by ozonolysis of the resulting cyclopentene amino ester (±)-**9**.[5,6] This treatment gave, across the non-isolable acyclic diformyl intermediate **I-2** under reductive amination with benzylamine, amino ester (±)-**10** with an overall isolated yield of 21% from (±)-**7** (*Route B*).

Although common synthetic steps are involved in both routes presented on Scheme 1, it was curious to find the difference in overall yields (45% *Route A* vs. 21% *Route B*). A plausible explanation of this observation might be attributed to the higher susceptibility in reactivity in ring opening of strained bicyclic γ-lactams (±)-**7** and (±)-**8**.

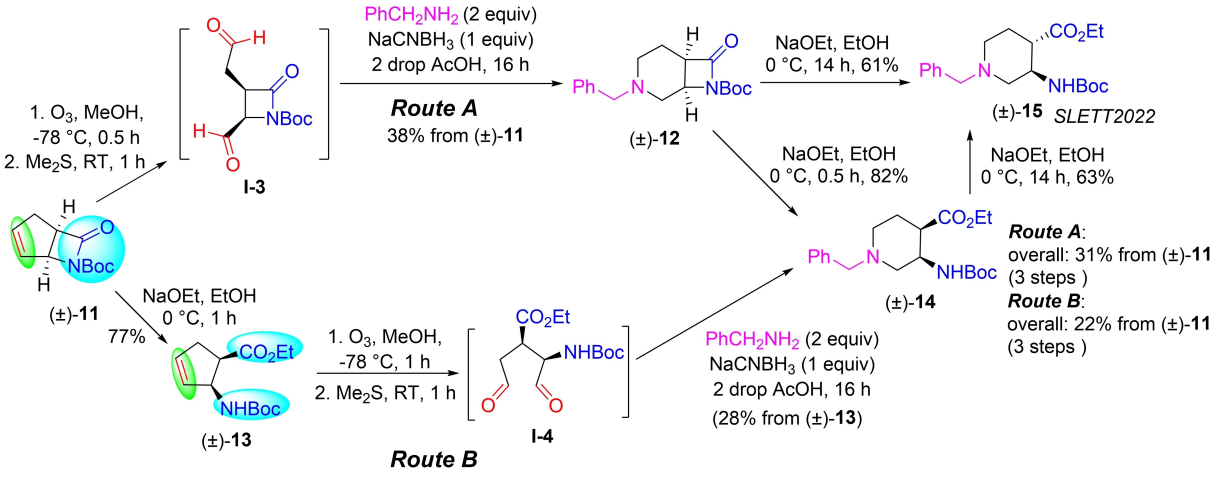


Scheme 1. Transformation of unsaturated bicyclic γ-lactam (Vince lactam) (±)-**7** into piperidine γ-amino ester (±)-**10** through olefin bond oxidative cleavage followed by double reductive amination.

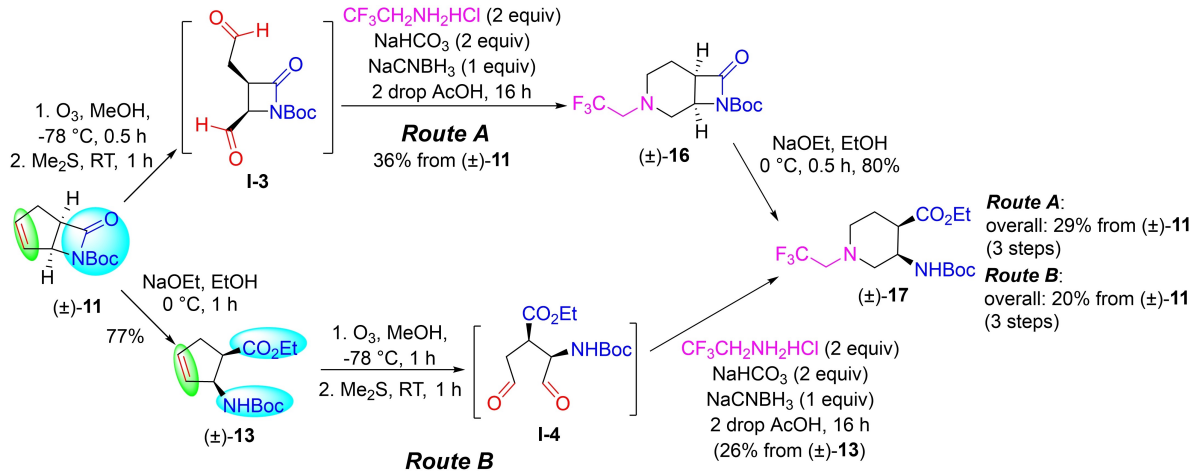
In continuation, we explored the behavior of an isomer, racemic unsaturated bicyclic β-lactam (±)-**11** utilizing a method analogous to that applied with γ-lactam (±)-**7**.[8] We investigated again two alternative synthetic paths. First, lactam (±)-**11** was subjected to ozonolysis of the ring olefin bond. It furnished the corresponding piperidine-fused β-lactam (±)-**12** [3 h] through the non-isolable, unstable dialdehyde intermediate **I-3** under reductive amination with benzylamine. Compound (±)-**12**, when submitted to NaOEt-mediated lactam ring opening, depending on the reaction conditions, furnished amino ester (±)-**14** [3 h] (0 °C, 0.5 h, 31 % overall yield from (±)-**11**, *Route A*) and its epimer (±)-**15** (0 °C, 14 h) (Scheme 2). Amino ester (±)-**15** could also be accessed through epimerization of (±)-**14**.

Next, to perform a comparative study, an alternative route was followed, based on the transformation of amino ester (±)-**13**[8] (derived from lactam (±)-**11**) by ozonolysis/reductive amination protocol to afford piperidine derivative (±)-**14** in 22 % overall yield (from (±)-**11**) (*Route B*). Again, it might be concluded that *Route A*, involving the ring opening step of two strained systems ((±)-**11** and (±)-**12**)), is favored in view of the overall yield related to target molecule (±)-**14**.

Our further intention was to analyze the ring cleavage/ring closing sequences of both routes by changing the nature of the primary amine used in the reductive amination step. Accordingly, we selected 2,2,2-trifluoroethylamine as the functional group with a high electron-withdrawing property. The starting lactam (±)-**11** was first converted by ozonolysis followed by treatment with trifluoroethylamine into the corresponding piperidine-fused lactam (±)-**16**.[7b] Applying a novel synthetic approach, the opening of the azetidinone ring with NaOEt in compound (±)-**16** provided new amino ester (±)-**17** in 29 % overall yield from (±)-**11** (*Route A*, Scheme 3). Following alternative *Route B*, amino ester (±)-**17** was obtained in 20 % yield from (±)-**11**. A difference in the yields of the two alternative pathways could be detected. While this difference is not significant, it indicates again the preferred outcome, when



Scheme 2. Transformation of unsaturated bicyclic β-lactam (±)-**11** into piperidine β-amino ester (±)-**14** through oxidative cleavage of the olefin bond followed by double reductive amination.



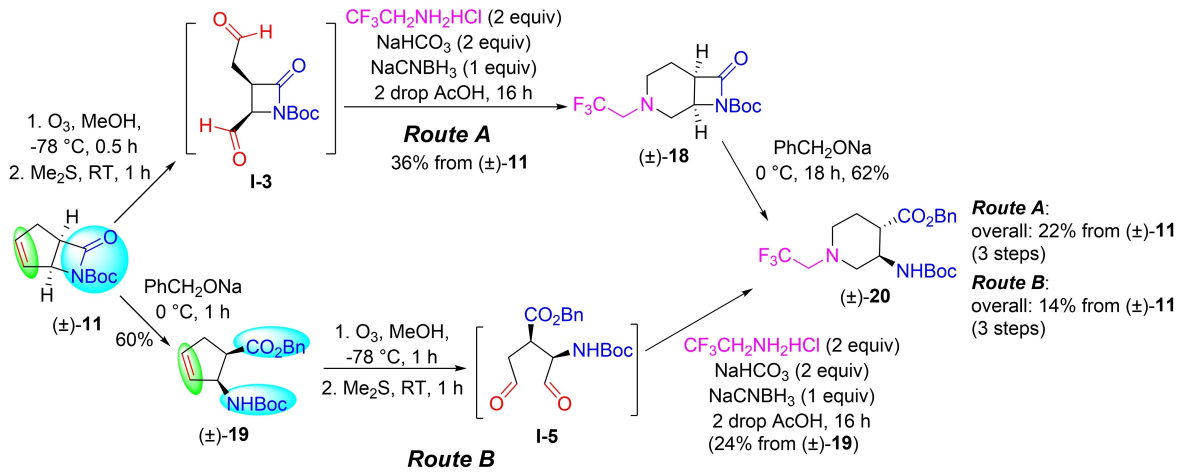
Scheme 3. Transformation of unsaturated bicyclic β-lactam (±)-**11** into piperidine β-amino ester (±)-**17** through olefin bond oxidative cleavage followed by double reductive amination.

bicyclic strained systems ((±)-**11** and (±)-**16**) were subjected to olefin bond cleavage and lactam opening.

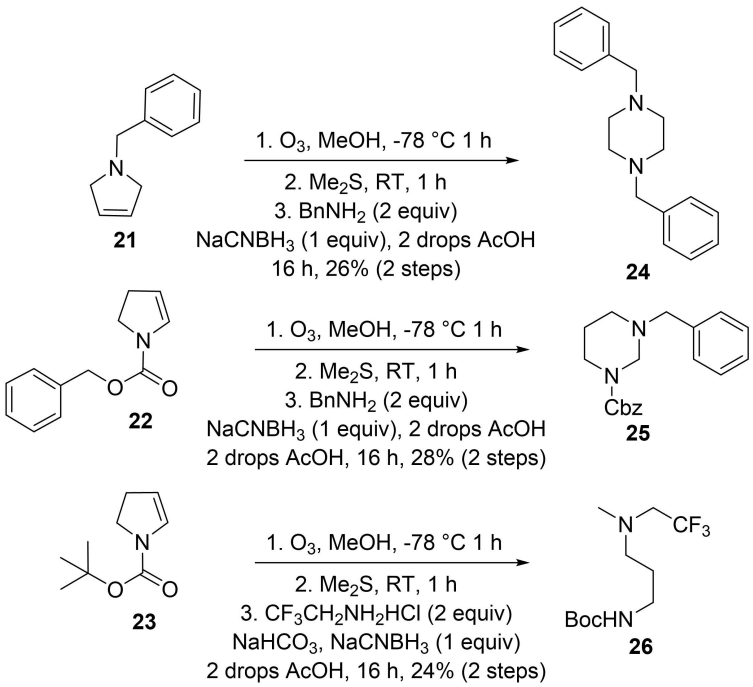
We continued our investigation with respect to the reactivity of the ring olefin bond by analyzing the nature of the ester group. Thus, fluorine-containing piperidine derivative (±)-**20**[7b,9] was prepared on two alternative ways again. When opening the cyclopentene ring in (±)-**11**, cyclization of dialdehyde **I-3** afforded across the bicyclic lactam (±)-**18**[7b] target amino ester (±)-**20** in 22% overall yield (from (±)-**11**) (Scheme 4).

Our next aim during this work was to demonstrate the high utility of the above synthetic protocol, based on the oxidative olefin bond cleavage of unsaturated cyclic systems, followed by cyclization with double reductive amination. For this purpose, we selected three commercial unsaturated azaheterocycles (**21**–**23**) as starting materials. All three compounds were submitted to ozonolysis and then treated with benzylamine in the presence of $NaCNBH_3$. Pyrroline derivatives **21** and **22**, after ozonolysis and reductive amination with benzylamine, produced as expected, the corresponding azaheterocycles **24** and **25** (Scheme 5).

Surprisingly, when pyrroline derivative **23** was subjected to the oxidative ring opening/reductive amination sequence with benzylamine, only an unidentifiable product mixture was formed. However, changing the amine source to 2,2,2-trifluroethylamine, the same reaction resulted in an acyclic derivative, which was isolated and identified as compound **26** (Scheme 5).



Scheme 4. Transformation of unsaturated bicyclicβ β-lactam (±)-**11** into piperidine β-amino ester (±)-**20** through olefin bond oxidative cleavage followed by double reductive amination.



Scheme 5. Transformation of some unsaturated azaheterocycles (**21**–**23**) through olefin bond oxidative cleavage followed by reductive amination.

This unexpected outcome might be explained according to the protocol depicted on Scheme 6.

Thus, starting compound **23** under ozonolysis, through dialdehyde **I-6**, in rection with trifluoroethylamine gave imine **I-7**, which under reductive conditions afforded **I-10** through cyclization and ring reopening. Next, the reductive procedure along H_2O elimination furnished structure **26**. It should be noted, that a similar procedure by reacting **21** and **22** under similar conditions with trifluoroethylamine failed, which is quite unexplainable.

Conclusions

The current work is intended to give an insight into the chemical behavior of some bicyclic strained ring systems (unsaturated bicyclic β- and γ-lactams vs. unsaturated monocyclic β- and γ-amino esters) and it provides a comparative analysis regarding the ring cleavage/cyclization with ring expansion of these structures. It was found that the ring strain release may facilitate the ring-opening process. The target azaheterocyclic compounds have been prepared via alternative synthetic routes. Furthermore, the synthesized amino acid derivatives possessing either an aryl moiety or a fluorine-containing element in their structure, in view of the influence on the secondary structures of peptides,[10] might be considered as highly interesting building blocks in foldamer chemistry. Further studies related to the transformation under various experimental conditions of the above systems as well as of other analogue bicyclic strained systems are under investigation in our laboratory.

Experimental Part

General Experimental Procedure for the Ozonolysis/Reductive Amination of Unsaturated Compounds

The alkene compound (500 mg) and 50 ml of MeOH were added to a 3-necked round-bottom flask equipped with a magnetic stirring bar. The reaction mixture was cooled with a dry ice/acetone bath (−78 °C). With the help of an ozone generator the oxygen was transformed into ozone and it flowed into the reaction mixture. The reaction mixture was stirred until completion of the reaction (monitoring by TLC). Then, after the cooling bath was removed, 0.5 ml of dimethyl sulfide was added into the reaction mixture. This mixture was stirred while warming to room temperature for 1 h. Next, amine hydrochloride (2 equiv), $NaHCO_3$ (2 equiv), $NaCNBH_3$ (1 equiv), and one drop of acetic acid were added to the reaction mixture followed by stirring overnight. Then, the solvent was removed by rotatory evaporation, the crude residue was diluted with EtOAc (30 ml) and washed 3×15 ml of water. The organic phase was dried with Na_2SO_4 and then concentrated under reduced pressure. The products were purified by column chromatography (*n*-hexane/EtOAc) giving the corresponding nitrogen-containing compounds.

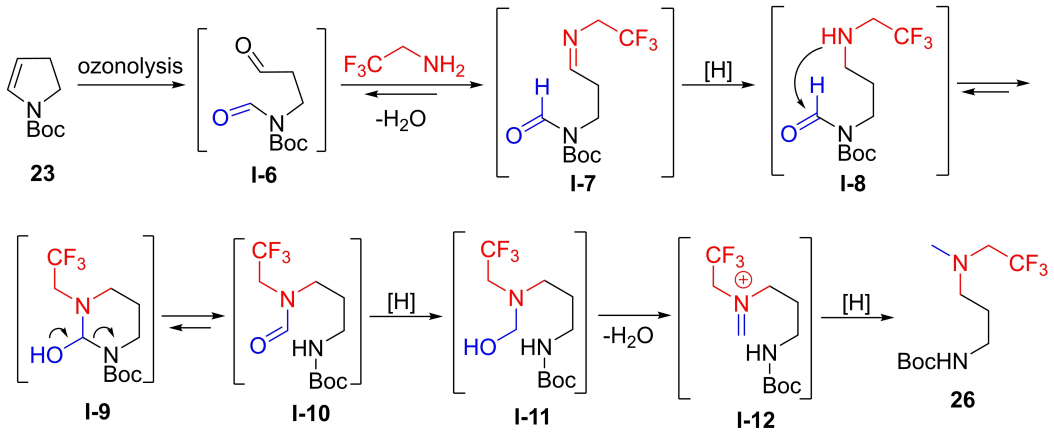
General Procedure for Lactam Ring Opening with Ethanolysis

To a solution of lactam (1 mmol) in EtOH (15 mL), NaOEt (1.2 equiv) was added at 0 °C, and the reaction mixture was stirred at the temperature and time indicated on Schemes. Then, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with water (3×10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by means of column chromatography.

General Procedure for Lactam Ring Opening with Sodium Benzyl Alcoholate

To a solution of lactam (1 mmol) 1.0 M sodium benzyloxide solution (1.2 equiv) was added at 0 °C, and the reaction mixture was stirred at the temperature and time indicated on Schemes. Then, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and washed with water (3×10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crud material was purified by means of column chromatography.

Characterization of the newly synthesized substances and the spectra of the prepared compounds are found in the supplementary material.



Scheme 6. Suggested synthetic route for the formation of compound **26**.

Acknowledgements

The authors gratefully acknowledge financial support from the National Research, Development and Innovation Office of Hungary (NKFIH/OTKA FK 145394 and K 142266). Project no. RRF-2.3.1-21-2022-00015 has been implemented with the support provided by the European Union. This work was supported by the János Bolyai Research Scholarship to M. N. of the Hungarian Academy of Sciences.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Amino acids · Azaheterocycles · Cyclization · Ring strain · Atereocontrol

[1] a) C. C. Marshall, J. G. Federice, C. N. Bell, P. B. Cox, J. T. Njardarson, *J. Med. Chem.* **2024**, *67*, 11622–11655; b) E. Marcantoni, M. Petrini, *Adv. Synth. Catal.* **2016**, *358*, 3657–3682, DOI: 10.1002/adsc.201600644; c) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274, DOI: 10.1021/jm501100b; d) M. G. Vinogradov, O. V. Turova, S. G. Zlotin, *Org. Biomol. Chem.* **2019**, *17*, 3670–3708, DOI: 10.1039/C8OB03034K; e) H. Mei, K. Aradi, L. Kiss, J. Han, *Chin. Chem. Lett.* **2023**, *34*, 108657, DOI: 10.1016/j.cclet.2023.108657; f) Y. Du, A. Semghouli, H. Mei, L. Kiss, J. Han, *Adv. Synth. Catal.* **2024**, *366*, 3050–3084, DOI: 10.1002/adsc.202400306.

[2] a) L. Kiss, F. Fülöp, *Chem. Rev.* **2014**, *114*, 1116–1169, DOI: 10.1021/cr300454h; b) R. A. Ábrahámi, S. Fustero, F. Fülöp, L. Kiss, *Synlett* **2018**, *29*, 2066–2070, DOI: 10.1055/s-0037-1609494; c) J. Liu, J. Han, K. Izawa, T. Sato, S. White, N. A. Meanwell, V. A. Soloshonok, *Eur. J. Med. Chem.* **2020**, *208*, 112736, DOI: 10.1016/j.ejmech.2020.112736; d) S. Wang, Z. Ying, Y. Huang, Y. Li, M. Hu, K. Kang, H. Wang, J. Shao, G. Wu, Y. Yu, Y. Du, W. Chen, *Eur. J. Med. Chem.* **2023**, *250*, 115185, https://doi.org/10.1016/j.ejmech.2023.115185; e) M. K. Singh, M. K. Lakshman, *Org. Biomol. Chem.* **2022**, *20*, 963, DOI: 10.1039/d1ob01329g; f) S. Ponra, B. Boudet, P. Phansavath, V. R. Vidal, *Synthesis* **2021**, *53*, 193–241, DOI: 10.1055/s-0040-1705939; g) R. J. Watson, P. Bamborough, H. Barnett, C. Chung, R. Davis, L. Gordon, P. Grandi, M. Petretich, A. Phillipou, R. K. Prinjha, I. Rioja, P. Soden, T. Werner, E. H. Demont, *J. Med. Chem.* **2020**, *63*, 9045–9069, https://doi.org/10.1021/acs.jmedchem.0c00614; h) K. H. Granberg, S. Sakamaki, R. Fuchigami, Y. Niwa, M. Fujio, H. Kato, F. Bergstrom, N. Larsson, M. Persson, I. C. Villar, T. Fujita, E. Sugikawa, M. Althage, N. Yano, Y. Yokoyama, J. Kimura, M. Lal, H. Mochida, *J. Med. Chem.* **2024**, *67*, 4442–4462, DOI: 10.1021/acs.jmedchem.3c02183; i) S. Richard-Bildstein, H. Aissaoui, J. Pothier, G. Schafer, C. Gnerre, E. Lindenberg, F. Lehembre, L. Pouzol, P. Guerry, *J. Med. Chem.* **2020**, *63*, 15864–15882, https://doi.org/10.1021/acs.jmedchem.0c01588; j) M. Cooper, A. Llinas, P. Hansen, M. Caffrey, A. Ray, S. Sjodin, I. Shamovsk, H. Wada, T. J. Jensen, U. Sivars, L. Hultin, U. Andersson, S. Lundqvist, K. Gedda, L. Jinton, N. Krutrok, R. Lewis, P. Jansson, C. Gardelli, *J. Med. Chem.* **2020**, *63*, 9705–9730, https://doi.org/10.1021/acs.jmedchem.0c00828.

[3] a) T. Irrgang, R. Kempe, *Chem. Rev.* **2020**, *120*, 9583–9674, https://doi.org/10.1021/acs.chemrev.0c00248; b) X. Guo, Y. Okamoto, M. R. Schreier, T. R. Ward, O. S. Wenger, *Eur. J. Org. Chem.* **2020**, 1288–1293, DOI: 10.1002/ejoc.201900777; c) P. G. Guerra, P. Clerici, L. Micouin, *J. Org. Chem.* **2017**, *82*, 7689; d) G. Malik, X. Guinchard, D. Crich, *Org. Lett.* **2012**, *14*, 596–599, DOI: 10.1021/ol203213f; e) S. J. Cully, T. E. Storr, M. J. Rawling, I. R. Abeysena, D. Hamza, G. Jones, C. A. Pearce, A. Quddus, W. Lewis, R. A. Stockman, *Bioorg. Med. Chem.* **2016**, *24*, 5249; f) I. Kumar, P. Ramaraju, N. A. Mir, A. Singh, *Org. Biomol. Chem.* **2015**, *13*, 1280–1293; g) N. Debreczeni, J. Hotzi, M. Bege, M. Lovas, E. Mező, I. Bereczki, P. Herczegh, L. Kiss, A. Borbás, *Chem. Eur. J.* **2023**, *29*, e202203248, https://doi.org/10.1002/chem.202203248; h) L. Kiss, L. Ouchakour, M. Nonn, A. M. Remete, *Synlett* **2022**, *33*, 307–328, DOI: 10.1055/s-0040-1719850.

[4] a) S. Kihakh, K. P. Melnykov, V. Bilenko, S. Trofymchuk, O. S. Liashuk, O. O. Grygorenko, *J. Org. Chem.* **2024**, *89*, 10440–10450, https://doi.org/10.1021/acs.joc.4c00326; b) J. Turkowska, J. Durka, D. Gryko, *Chem. Commun.* **2020**, *56*, 5718–5734, DOI: 10.1039/d0cc01771j; c) M. Yasir, P. Liu, J. C. Markwart, O. Suraeva, F. R. Wurm, J. Smart, M. Lattuada, A. F. M. Kilbinger, *Angew. Chem. Int. Ed.* **2020**, *59*, 13597–13601, https://doi.org/10.1002/anie.202005366; d) A. Semghouli, Z. Benke, A. M. Remete, T. T. Novák, S. Fustero, L. Kiss, *Chem. Asian J.* **2021**, *16*, 3873–3881, doi.org/10.1002/asia.202100956 and cited references herein.

[5] L. Kiss, E. Forró, R. Sillanpää, F. Fülöp, *Synthesis* **2010**, 153–160, DOI: 10.1055/s-0029-1217088.

[6] M. Nonn, S. Fustero, L. Kiss, *Chem. Rec.* **2024**, *24*, e202400070, DOI: 10.1002/tcr.202400070.

[7] a) L. Ouchakour, R. A. Ábrahámi, E. Forró, M. Haukka, F. Fülöp, L. Kiss, *Eur. J. Org. Chem.* **2019**, 2202–2211, https://doi.org/10.1002/ejoc.201801540; b) L. Ouchakour, M. Nonn, A. M. Remete, L. Kiss, *Eur. J. Org. Chem.* **2021**, 3874–3885, https://doi.org/10.1002/ejoc.202100540.

[8] L. Kiss, E. Forró, R. Sillanpää, F. Fülöp, *J. Org. Chem.* **2007**, *72*, 8786–8790.

[9] M. Nonn, D. Kara, L. Ouchakour, E. Forró, M. Haukka, L. Kiss, *Synthesis* **2021**, *53*, 1163–1173, DOI: 10.1055/s-0040-1706637.

[10] a) D. W. Zhang, X. Zhao, J. L. Hou, Z. T. Li, *Chem. Rev.* **2012**, *112*, 5271–5316, https://doi.org/10.1021/cr300116k; b) J. Morimoto, J. Kim, D. Kuroda, S. Nagatoishi, K. Tsumoto, S. Sando, *J. Am. Chem. Soc.* **2020**, *142*, 2277–2284, https://doi.org/10.1021/jacs.9b10496; c) I. M. Mándity, A. Monsignori, L. Fülöp, E. Forró, F. Fülöp, *Chem. Eur. J.* **2014**, *20*, 4591, https://doi.org/10.1002/chem.201304448; d) G. Tan, M. Das, H. Keum, P. Bellotti, C. Daniliuc, F. Glorius, *Nat. Chem.* **2022**, *14*, 1174–1184, https://doi.org/10.1038/s41557-022-01008-w; e) M. Zhou, Z. Feng, X. Zhang, *Chem. Commun.* **2023**, *59*, 1434–1448, DOI: 10.1039/D2CC06787K; f) M. Zhou, Z. Feng, X. Zhang, *Chem. Commun.* **2023**, *59*, 1434–1448, DOI: 10.1039/D2CC06787K; g) J. Leppkes, T. Hohmann, B. Koksch, *J. Fluorine Chem.* **2020**, *232*, 109453, https://doi.org/10.1016/j.jfluchem.2020.109453.

Manuscript received: December 31, 2024
Revised manuscript received: January 29, 2025
Accepted manuscript online: January 30, 2025
Version of record online: February 10, 2025

[Correction added on 25 March 2025, after first online publication: A new affiliation was added for author Melinda Nonn.]