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Multigram Synthesis of 2-Azabicyclo[2.1.1]hexane-1-Carboxylates (2,4-Methanoprolines) – Promising Bicyclic Proline Analogs

Abstract

An optimized approach towards 4-substituted 2,4-methanoproline derivatives is reported. Careful selection of the starting materials and optimized isolation procedure provided easy access to a key bicyclic building block in a preparative yield of 32 % over five laboratory steps of up to 0.7 kg. Further modifications allowed us to obtain a number of useful derivatives, including those containing NH_2, COOH, CH_2NH_2, and CH_2F fragments with orthogonally protected functionalities.

Keywords: bicyclic compounds; building blocks; proline analog; bridged pyrrolidine; amino acid

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Масштабований синтез похідних 2-азабіцикло[2.1.1]гексан-1-карбоксилату (2,4-метанопроліну) – перспективних біциклічних аналогів проліну

Анотація

Запропоновано оптимізований підхід до 4-заміщених похідних 2,4-метанопроліну. Ретельний відбір вихідних речовин та удосконалена процедура виділення забезпечили простий доступ до ключового біциклічного будівельного блоку з препаративним виходом 32 % за п'ять стадій у масштабі до 0,7 кг. Подальші перетворення дозволили одержати низку корисних похідних, зокрема тих, що містять фрагменти NH_2, COOH, CH_2NH_2 та CH_2F з ортогонально захищеними функціональними групами.

Ключові слова: біциклічні сполуки; будівельні блоки; аналог проліну; містковий піролідин; амінокислоти

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Introduction

Introduced in the 2000s, the "escape from flatland" concept affected the medicinal chemistry paradigm considerably, setting novel trends in drug design [1, 2]. This catchphrase refers to shifting from the predominant use of planar (hetero)aromatic fragments to sp^3-enriched moieties with three-dimensional shapes in drug design [3–5]. The introduction of non-planar saturated structures may improve the compound's physicochemical parameters [6–8], lower binding entropic penalty [1, 9], provide precise spatial disposition of the side chain fragments [10], and increase metabolic stability [11]. As a part of this concept, the intensive development of structurally rigid analogs of naturally occurring compounds (especially amino acids) was observed. In particular, C_1-modified pyrrolidine analogs received considerable attention after the introduction of the antidiabetic agent "Boceprevir" [12] and the antihepatitic drug "Saxagliptin" [12, 13] (**Figure 1**, *B*). Since then, fused pyrrolidine analogs and approaches to their synthesis have been thoroughly studied, resulting in more than 6500 compounds reported in *Reaxys*® [14]. On the contrary, pyrrolidines with bridged C_1 units are less documented, either in biomedical application studies or in the development of synthetic approaches (**Figure 1**, *A*).

One of the bridged pyrrolidine scaffolds, 2-azabicyclo[2.1.1]hexane (2,4-methanopyrrolidine), has been of particular interest since the 1980s when the corresponding α-amino acid – 2,4-methanoproline (**1**, **Figure 2**, *A*, FG = H) – was isolated from *Ateleia Herbert smithii Pittier* [15, 16]. The conformational features introduced by the bicyclic skeleton of **1** were considered to stabilize the *trans*-amide bond configuration, which was of potential use in peptide-based drug design [17–20]. Thus, *Stammer* and colleagues studied a conformationally constrained analog of thyrotropin-releasing hormone (TRH) and demonstrated a determinative impact of the bicyclic core on the conformation of the whole molecule [21]. Furthermore, derivatives of 2,4-methanopyrrolidine demonstrated very promising results in the recent antimalarial discovery campaign [22] and the discovery of the potential nicotinic acetylcholine receptor (nAChR) ligands [23].

To date, several different approaches to the synthesis of 2,4-methanoproline (**1**) and its derivatives have been reported (**Figure 2**, *A*). The earliest method included intramolecular photochemical [2+2] cycloaddition of *N*-allylic dehydroalanine derivatives **2** [3, 24, 25]. In this way, carboxyalkyl-, alkyl-, F-, or non-substituted 2,4-methanoprolines could be obtained in moderate yields. Modification of the pre-formed 2-azabicyclo-[2.1.1]hexane core *via* the C–H lithiation – electrophile addition sequence gave the target unsubstituted product in the yield of 98% [26]. Alternative approaches were based on intramolecular nucleophilic substitution reactions. In particular, one-pot tandem Strecker reaction – S_N2-type nucleophilic cyclization (STRINC) of

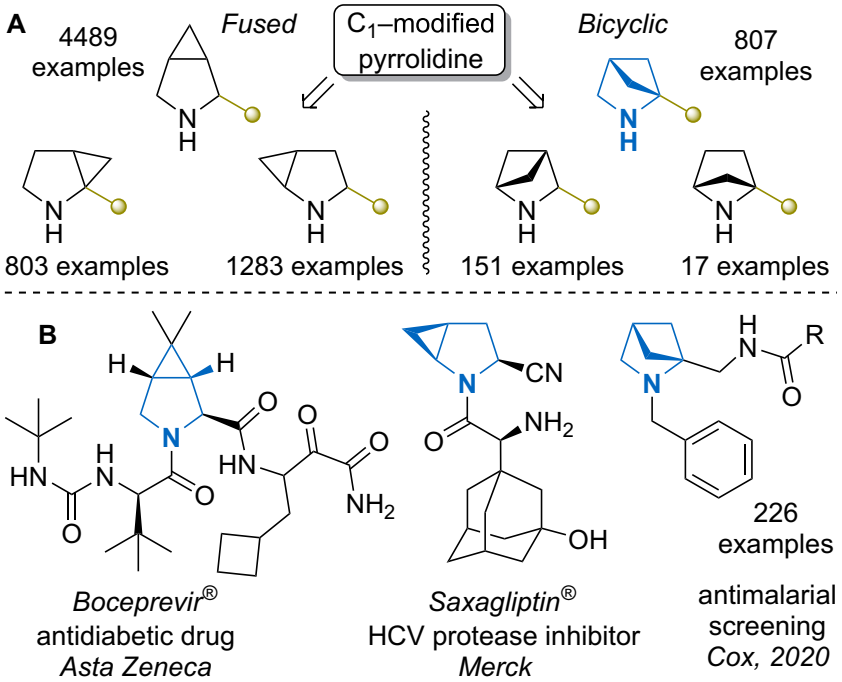

Figure 1. (*A*) Reported fused (left) and bridged (right) C_1-modified pyrrolidines ; (*B*) Drug substances with C_1-modified pyrrolidines

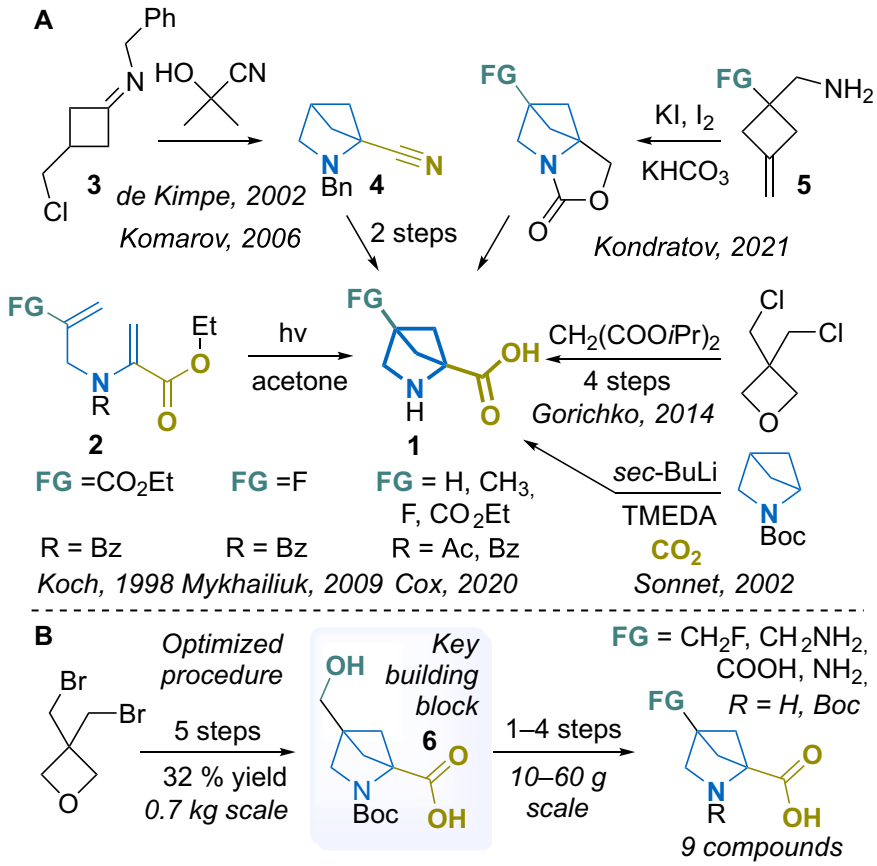

Figure 2. (*A*) Known synthesis of 2,4-methanoproline and its derivatives. (*B*) Results reported in this work

imine **3** produced nitrile **4** that could be easily converted to amino acid **1** in a few steps [27]. I_2-promoted cyclization of methylenecyclobutane **5** gave the corresponding tricyclic carbamate; the latter compound was converted to amino acid **1** upon the hydrolytic cleavage of the carbamate moiety with the subsequent oxidation of the hydroxymethyl fragment [28]. Finally, a sophisticated approach based on the double recyclization of oxetane ring allowed *Vasiuta* and *Gorichko* [29] the preparation of 4-hydroxymethyl-2-azabicyclo[2.1.1]hexane-1-carboxylic acid derivative (**1**, FG = CH_2OH) in only four steps.

In this work, we re-established the previously reported synthetic protocol towards *N*-Boc-4-hydroxymethyl-2,4-methanoproline (**6**) and adjusted it for the kilogram-scale production (**Figure 2**, *B*). The optimization of the starting points of the synthesis, as well as avoiding the product isolation with ion-exchange chromatography, allowed for the preparation of the key building block of up to 0.7 kg scale in a single run. Simple chemical transformations (including oxidation, deoxyfluorination, the Curtius reaction, or mesylation – nucleophilic substitution – azide reduction sequence) offered several valuable polyfunctionalized building blocks on a 10–60 g scale in preparative isolated yields.

■ Results and discussion

We started our investigation with the synthesis of the first important intermediate – bicyclic lactone **7** (**Scheme 1**). Repeating the original procedure [29], the application of dichloride **8** and diisopropyl malonate **9** as precursors led to spiro-derivative **10** in the yield of 64%, which upon acidic rearrangement produced compound **7** in the yield of 62% (40% over two-steps). Meanwhile, the use of the corresponding dibromide **11** and diethylmalonate **12** was more effective in our hands, giving products **13** and **7** in the yield of 77% (64% over two steps). Using these optimized procedures, the sequence was scaled up to 1.10 kg of product **7** with no noticeable loss in efficiency. The Curtius rearrangement of the carboxylic acid moiety with the subsequent recyclization of compound **14** under basic conditions afforded highly hydrophilic amino acid **15** (as a salt) in the yield of 80% (according to ^{1}H NMR spectra). The method reported for the isolation of this compound by ion-exchange column chromatography was considered impractical for the large-scale synthesis. To bypass the limitations caused by the amphiphilic nature of the amino acid obtained, compound **15** was converted to the corresponding *N*-Boc derivative by the treatment

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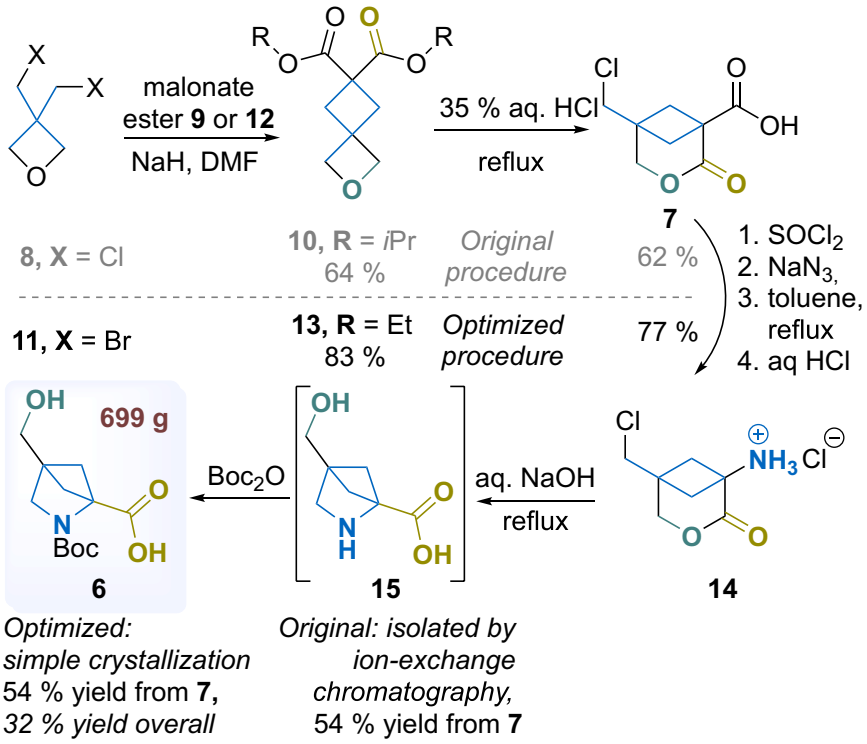
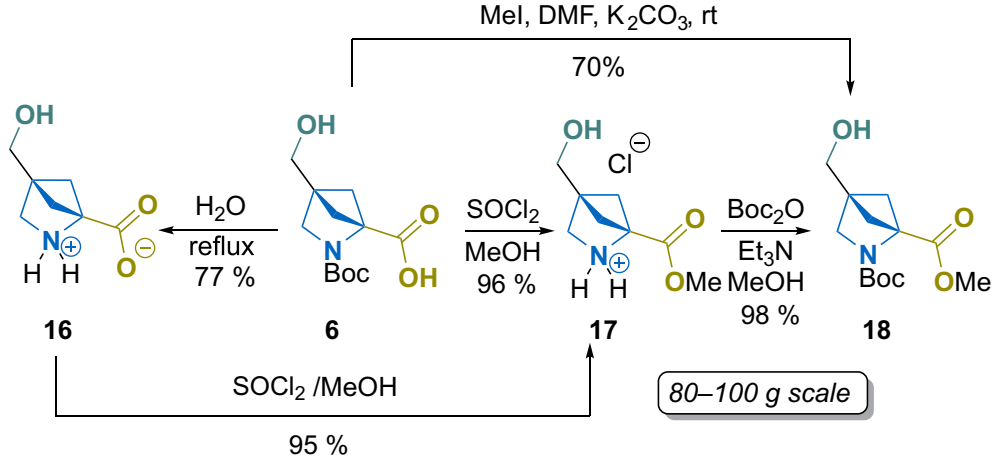


Scheme 1. Synthesis of key building block **6**

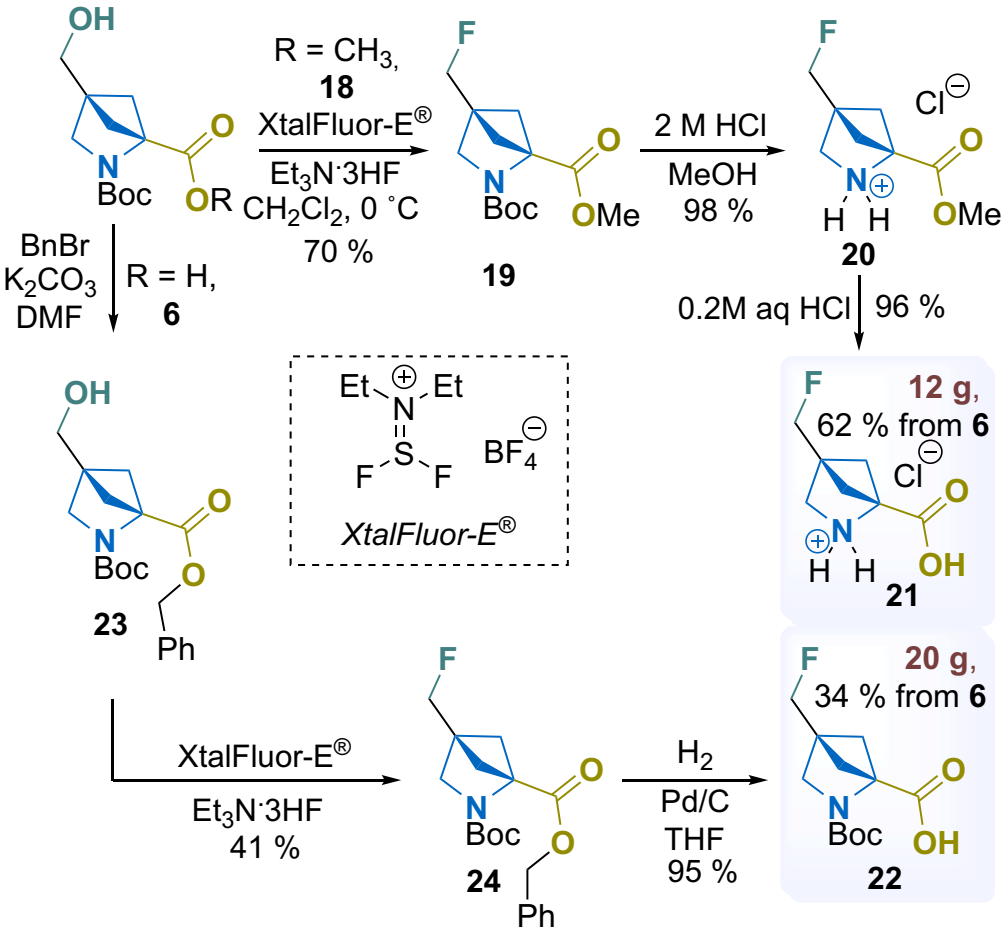
with Boc_2O without isolation. Upon completion of the reaction, pure *N*-Boc amino acid **6** was extracted from the aqueous solution after the acidification with $NaHSO_4$. This simple methodology allowed for the preparation of the key building block **6** on a 0.7 kg scale in a single run in the yield of 32% over four laboratory steps.

With a substantial amount of compound **6** in hand, we aimed to demonstrate its utility as the source of 2-azabicyclo[2.1.1]hexane derivatives (**Scheme 2**). Firstly, interconversions of the *N*,*O*-protective groups were performed. Refluxing the aqueous suspension of compound **6** led to amino acid **16** in the zwitterionic form in an isolated yield of 77%. $SOCl_2$-mediated esterification led to the simultaneous cleavage of the carbamate fragment, giving amine **17** as a HCl salt. The *N*-Boc-protection of the latter compound under basic conditions gave alcohol **18** (in the yield of 98%) that could also be obtained directly from *N*-Boc amino acid **6** using MeI – K_2CO_3 in DMF in an isolated yield of 70%.

Since introducing fluorinated substituents into organic molecules is a widely recognized strategy for fine-tuning the compound's physicochemical properties [30–35], we considered installing a fluorine atom into the 2,4-methanoproline core. We found that the treatment of the *N*,*O*-protected building block **18** with commercially available deoxyfluorination agents (DAST (*N*,*N*-diethylaminosulfur trifluoride) or Morph-DAST) led to the formation of the fluoromethyl derivative **19**



Scheme 2. Variation of the protective functional groups in the building block **6**



Scheme 3. Preparation of fluoromethyl derivatives **21** and **22**

in the unsatisfactory yield of 26–30%. At the same time, the application of an alternative fluorine source – XtalFluor-E® (DAST difluorosulfinium salt) [36, 37] produced target compound **19** in the preparative yield of 70% (**Scheme 3**). The subsequent cleavage of the *N*- and *O*-protection groups gave the building block **20** and then – amino acid hydrochloride **21** in the yields of 98% and 96%, respectively. Considering the potential incompatibility of the masked neopentyl fluoride fragment with nucleophilic reagents [38], *N*-Boc protected amino acid **22** was prepared by an alternative sequence. The base-promoted benzylation of amino acid **6** gave hydroxyester **23** that was transformed into fluoride **24** in the yield of 41%. The hydrogenolysis of the benzyl protection group cleanly produced the target *N*-Boc-amino acid **22** in the yield of 95%.

The amination of the primary alcohol moiety in the molecule of **6** was achieved by a standard three-step sequence (**Scheme 4**) [39, 40]. The mesylation with MsCl under mild conditions cleanly afforded mesylate **25** (in the yield of 99%), which upon the treatment with NaN_3 was converted into azide **26** in a high yield of 94%. The catalytic hydrogenolysis over Pd/C was found to be sluggish, giving the complex mixture of unidentified compounds. However, using saturated ammonia methanol as a solvent suppressed the undesired reactivity, producing target aminomethyl derivative **27** in the yield of 91% on a 20 g scale.

Finally, oxidation of the alcohol moiety in **6** with $RuCl_3/NaIO_4$ mixture [41, 42] afforded carboxylic acid **28** in the yield of 89% (**Scheme 5**). Upon acidic cleavage of derivative **28**, a protected bicyclic glutamate analog **29** was obtained in the yield of 93% (overall 83% from **6**). The latter compounds can be of special interest to bioorganic and medicinal chemists since promising peptidomimetic properties of its derivatives were disclosed previously by *Esslinger* and co-workers [43]. The Curtius rearrangement of carboxylic acid **28** gave orthogonally protected diamine **30** in the yield of 62%. Its subsequent hydrogenolysis produced diamino acid derivative **31** in the yield of 98% (overall 54% from **6**) on *ca.* 20 g scale.

■ Conclusions

In this work, the multigram synthesis of 2-azabicyclo[2.1.1]hexane-1-carboxylate (2,4-methanoproline) derivatives has been developed. An optimized

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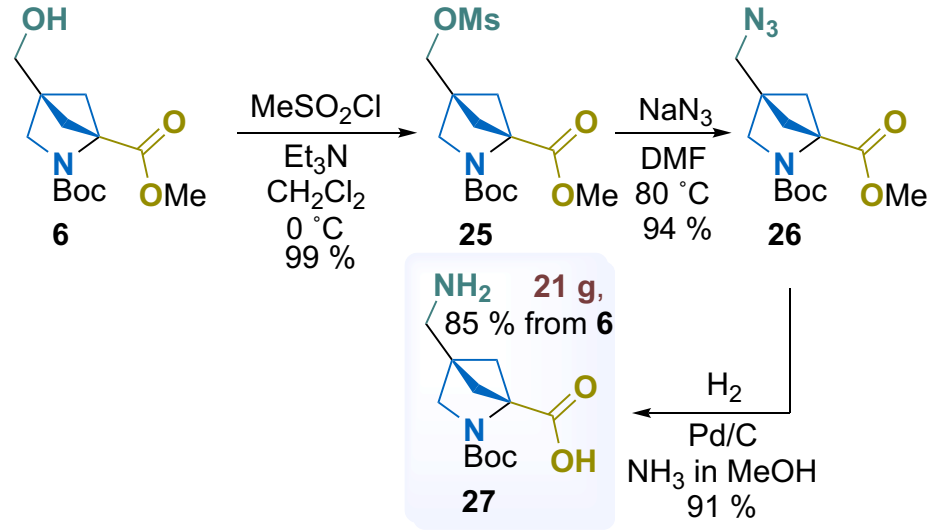
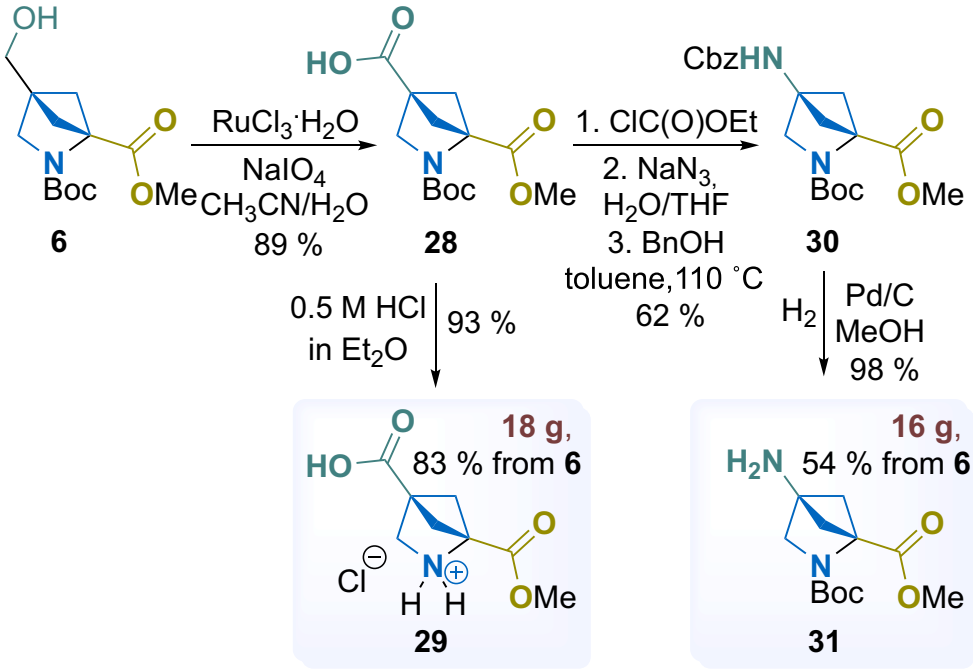


Scheme 4. Preparation of diamino acid derivative **27**



Scheme 5. Ru-mediated oxidation of alcohol **6** and further transformations

protocol for synthesizing the key building block – *N*-Boc-4-(hydroxymethyl)-2,4-methanoproline – has allowed for the preparation of the latter compound on a 700-g scale with the improved overall yield and avoiding the resource-demanding ion-exchange chromatography step. Further functional group transformations have offered several building blocks valuable for medicinal chemists, including those bearing CH_2F, CH_2NH_2, COOH, and NH_2 groups in position C-4. Operationally simple transformations, high overall yields, as well as large amounts of the products obtained, offer easy access to privileged saturated scaffolds. We believe that the results of this work will promote the use of the title chemotype in future drug development campaigns.

■ Experimental part

The solvents were purified according to the standard procedures [44]. Compound **11**, Xtal-Fluor-E® ((Diethylamino)difluorosulfonium tetrafluoroborate), and all other starting materials were obtained from Enamine Ltd. stock. Melting points were measured on the MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C{^{1}H} NMR), on an Agilent ProPulse 600

spectrometer (at 151 MHz for ^{13}C) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for $^{13}C\{^{1}H\}$ NMR and 376 MHz for $^{19}F\{^{1}H\}$ NMR). NMR chemical shifts were reported in ppm (δ scale) downfield from TMS as an internal standard and referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. For $^{19}F\{^{1}H\}$, NMR CCl_3F was used as an internal standard. Coupling constants (*J*) were given in Hz. Spectra were reported as follows: chemical shift (δ, ppm), integration, multiplicity, coupling constants (Hz), and signals assignment if applicable. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

Diethyl 2-oxaspiro[3.3]heptane-6,6-dicarboxylate (13)

To the suspension of NaH pre-cooled to 0 °C (60% dispersion in mineral oil, 0.750 kg, 18.8 mol) in DMF (3.5 L), neat diethyl malonate (3.00 kg, 18.7 mol) was slowly added, keeping the temperature below 10 °C (CAUTION! Application of the mechanical stirring apparatus and intensive ventilation of the fume hood is necessary due to massive solidification of the reaction mixture and large amounts of the evolved gas!). The resulting mixture was stirred for 1 h at rt, then slowly heated to 60 °C, and the solution of 3,3-*bis*-(bromomethyl)oxetane (**11**) (2.20 kg, 9.02 mol) in DMF (0.5 L) was added gradually at this temperature. The resulting mixture was heated to reflux and stirred for 16 h at the same temperature. Upon completion of the reaction (concluded by ^{1}H NMR spectroscopy of the small aliquot of the reaction mixture), the mixture was cooled to rt, diluted with water (6 L), and extracted with *t*BuOMe (5 L). The organic layer was washed with water (2×2 L), dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The oily residue was distilled in a high vacuum to give the title compound **13**. The compound was mentioned previously in the literature without proper characterization [45].

A colorless liquid. Yield – 1.82 kg (83%). B. p. 95–98 °C (1 mmHg). Anal. Calcd. for $C_{12}H_{18}O_5$, %: C 59.49, H 7.49. Found, %: C 59.35, H 7.55. ^{1}H NMR (400 MHz, $CDCl_3$), *δ*, ppm: 1.23 (3H, t, *J* = 7.1 Hz, $\underline{CH_3}CH_2O$), 2.72 (2H, s, CH_2), 4.17 (2H, q, *J* = 7.1 Hz, $CH_3\underline{CH_2}O$), 4.65 (2H, s, CH_2). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$), *δ*, ppm: 171.5, 83.3, 77.2, 61.7, 48.1, 39.0, 38.3, 14.1.

5-(Chloromethyl)-2-oxo-3-oxabicyclo-[3.1.1]heptane-1-carboxylic acid (7)

To a refluxing aq. HCl (6 M, 900 mL), a neat compound **13** (100.0 g, 0.413 mol) was added within 2–3 min in a few portions. The resulting mixture was refluxed for 30 min and then concentrated under reduced pressure at 70 °C. The crude residue was triturated with Et_2O (400 mL), the precipitate formed was filtered off, washed with Et_2O (200 mL), and dried under a high vacuum (1 mmHg) at 50–60 °C with a P_2O_5 drying trap to give a pure compound **7**.

A colorless solid. Yield – 65.2 g (77%). M. p. >250 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$), *δ*, ppm: 2.26 (2H, dd, *J* = 7.3, 2.8 Hz, CH_2), 2.72 (2H, dd, *J* = 7.3, 2.9 Hz, CH_2), 3.62 (2H, s, CH_2Cl), 4.55 (2H, s, CH_2OCO). All other spectral data are in accordance with those reported in the literature [29].

1-Amino-5-(chloromethyl)-3-oxabicyclo-[3.1.1]heptan-2-one hydrochloride (14)

A neat $SOCl_2$ (1.92 kg, 16.128 mol) was slowly added to the solution of compound **7** (1.10 kg, 5.376 mol) in CH_2Cl_2 (5.6 L) and DMF (120 mL, 2% *v*/*v*) over *ca.* 1 hour at rt. The reaction mixture was heated to reflux for 3 h, then cooled to rt, and the solvent evaporated under reduced pressure. The solution of the residual compound, which was used in the next step as obtained (1.15 kg, 5.16 mol), in THF (2 L) was added to the solution of NaN_3 pre-cooled to 0 °C (2.00 kg, 30.8 mol) in water (4 L). The resulting mixture was stirred for 1 hour at rt, then poured on water (2 L) and extracted with toluene (4 L). The organic phase was separated, dried over anhydrous Na_2SO_4, concentrated under reduced pressure to *ca.* 2.5 L, transferred to a dropping funnel, and the later was installed on a separate 10 L three-necked round bottom flask. A fresh portion of toluene (2.5 L) was added to this flask, heated to 85 °C, and the organic solution in a dropping funnel was slowly added to the heated solvent (*ca.* 1 h). The resulting mixture was heated to reflux and stirred for an additional 30 min at the same temperature, then left stirring without heating bath upon cooling to room temperature. The inhomogeneous mixture was carefully decanted from the precipitate, and the organic solvent was concentrated under reduced pressure to *ca.* 2–2.5 L. To the precipitate left, aq. HCl (8 M, 3L) was added in one portion, and the resulting mixture was slowly heated to reflux with intensive stirring

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(CAUTION! A possible violent gas evolution!). To the refluxing aqueous mixture, the toluene solution previously obtained was gradually added, controlling the addition rate by the rate of gas evolution. The resulting mixture was refluxed for an additional 2 hours, then cooled to room temperature, and the layers were separated. The aqueous phase was evaporated under reduced pressure, giving crude amine **14** as a HCl salt, which was used in the next step without purification. The analytical sample was obtained by trituration of the small amount of the crude material in Et_2O.

A colorless solid. M. p. 189–191 °C (*lit.* 194–196 °C [29]). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.20 (2H, dd, J = 6.7, 3.0 Hz, CH_2), 2.64 (2H, d, J = 7.0 Hz, CH_2), 3.80 (2H, s, CH_2Cl), 4.44 (2H, s, CH_2OCO), 9.23 (3H, br. s, NH_3^+). All other spectral and physical data are in accordance with those reported in the literature [29].

2-[(*tert*-Butoxy)carbonyl]-4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid (6)

Product **14** was dissolved in 4 L of water, and then a solid NaOH (800.0 g, 20.0 mol) was added in portions, keeping the internal temperature below 40–45 °C. After additional stirring for 15 min, the mixture was cooled to rt, and the solution of Boc_2O (1.80 kg, 8.25 mol) in THF (1.8 L) was added dropwise. The resulting mixture was stirred for 3 h at rt, extracted with *t*BuOMe (2.0 L), and the aqueous layer was separated, acidified with $NaHSO_4$ to pH = 2, and extracted with EtOAc (3×2 L). The organic phases were combined, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was triturated with EtOAc (1.5 L) until solidification, and the precipitate formed was filtered to give a pure *N*-Boc-amino acid **6** (475.0 g, 1.85 mol, 36%). The filtrate was evaporated under reduced pressure to give a crude Boc-amino acid **6** (224.0 g, 0.871 mol, 17%) with sufficient purity, which could be used in the next step without purification.

A colorless solid. Yield – 699 g (53% from **7**). M. p. 143–146 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.36 (9H, s, $C(CH_3)_3$), 1.52 (2H, d, J = 5.0 Hz, CH_2), 1.85 (2H, d, J = 3.3 Hz, CH_2), 3.21 (2H, s, CH_2O), 3.56 (2H, d, J = 5.0 Hz, CH_2N), 4.71 (1H, t, J = 5.3 Hz, OH), 12.42 (1H, br. s, CO<u>OH</u>). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6), δ, ppm: 27.8, 43.0, 48.0, 53.4, 60.1, 67.8, 79.4, 156.4, 169.5. HRMS (ESI/QTOF), *m/z*: calcd for $C_{12}H_{19}NO_5Na^+$ 280.1155 $[M + Na]^+$, found 280.1156.

4-(Hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid (16)

A crude *N*-Boc-amino acid **6** (224.0 g, 0.871 mol) was mixed with 2 L of distilled water and heated to reflux with intensive stirring. Upon completion of the reaction (concluded by ^{1}H NMR spectrum of the small aliquot of the reaction mixture), the solvent was evaporated under reduced pressure to dryness, the solid residue was washed with a dry EtOH (1.0 L), filtered, and re-dissolved in a dry MeOH (3.4 L). Insoluble parts were filtered off, the filtrate was carefully evaporated under reduced pressure to give a pure amino acid **16**.

A colorless solid. Yield – 105.1 g (77%). M. p. 224–225 °C. Anal. Calcd. for $C_7H_{11}NO_3$, %: C 53.49, H 7.05, N 8.91. Found, %: C 53.41, H 6.98, N 8.83. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.55 (2H, d, J = 5.2 Hz, CH_2), 1.90 (2H, d, J = 5.3 Hz, CH_2), 2.99 (2H, s, CH_2N), 3.54 (2H, s, CH_2O), 4.82 (1H, s, CO<u>OH</u>). ^{13}C{^{1}H} NMR (101 MHz, D_2O), δ, ppm: 40.9, 49.4, 50.2, 59.8, 71.3, 172.1.

Methyl 4-(hydroxymethyl)-2-azabicyclo-[2.1.1]hexane-1-carboxylate hydrochloride (17)

A neat $SOCl_2$ (84.0 mL, 1.16 mol) was slowly added to a suspension of compound **6** pre-cooled to 0 °C (100.0 g, 0.389 mol) in MeOH (800 mL), keeping the internal temperature below 10 °C. The reaction mixture was heated to reflux and stirred at the same temperature for 40 min. Upon completion of the reaction (concluded by ^{1}H NMR spectrum of the small aliquot of the reaction mixture), the reaction mixture was cooled to room temperature, concentrated under reduced pressure, and co-evaporated the residue with fresh MeOH portions (2×350 mL). The residue was dried under a high vacuum (1 mmHg) to give a pure compound **17**. Yield – 77.3 g (96%).

An alternative method from **16**: A neat $SOCl_2$ (97.0 mL, 1.34 mol) was added dropwise to the solution of compound **16** pre-cooled to 0 °C (70.0 g, 0.445 mol) in MeOH (700 mL), keeping the internal temperature below 10 °C. The reaction mixture was heated to reflux and stirred at the same temperature for 40 min. Upon completion of the reaction (concluded by ^{1}H NMR spectrum of the small aliquot of the reaction mixture), the reaction mixture was cooled to room temperature, concentrated under reduced pressure, and co-evaporated the residue with fresh MeOH portions (2×350 mL). The residue was dried under a high vacuum (1 mmHg) to give a pure compound **17**.

A yellow powder. Yield – 87.8 g (95% from **16**). M. p. 150–153 °C. ^{1}H NMR (500 MHz, DMSO-d_6),

δ, ppm: 1.86 (2H, d, J = 5.1 Hz, CH_2), 2.18 (2H, d, J = 4.5 Hz, CH_2), 3.20 (2H, s, CH_2O), 3.61 (2H, s, CH_2N), 3.78 (3H, s, CH_3), 4.96 (1H, br. s, OH), 10.09 (2H, br. s, NH_2^+). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6), δ, ppm: 41.1, 48.7, 50.8, 52.9, 58.8, 67.0, 166.0. HRMS (ESI/QTOF), m/z: calcd for $C_8H_{14}NO_3^+$ 172.0968 $[M + H]^+$, found 172.0968.

2-*tert*-Butyl 1-methyl 4-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (18)

Method A. MeI (11.0 mL, 0.177 mol) was added to a mixture of compound **6** (22.0 g, 85.51 mmol) and K_2CO_3 (17.7 g, 128.3 mmol) in DMF (100 mL). The resulting suspension was stirred at room temperature overnight, poured on water (300 mL), and extracted with EtOAc (2×250 mL). The organic phases were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dried in a high vacuum (1 mmHg) to give a pure compound **18**. Yield – 16.21 g (70%).

Method B. The solution of Boc_2O (94.8 g, 0.435 mol) in MeOH (100 mL) was added to the solution of compound **17** (82.0 g, 0.395 mol) and Et_3N (137.6 ml, 0.987 mol) in MeOH (700 mL). The reaction mixture was stirred at room temperature overnight and then concentrated under reduced pressure. The residual oil was triturated with THF (500 mL), and the resulting cloudy mixture was filtered. The filtrate was evaporated under reduced pressure, triturated with *t*BuOMe (700 mL), and filtered, and the solvent was concentrated under reduced pressure to give product **18**.

A yellow viscous oil. Yield – 105.3 g (98% from **17**). Anal. Calcd. for $C_{13}H_{21}NO_5$, %: C 57.55, H 7.80, N 5.16. Found, %: C 57.46, H 7.72, N 4.96. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.40 (9H, s, $C(CH_3)_3$), 1.80–1.67 (2H, m, CH_2), 2.00 (2H, d, J = 3.5 Hz, CH_2), 2.44 (1H, s, OH), 3.36 (2H, s, CH_2O), 3.75 (3H, s, CH_3), 3.78 (2H, s, CH_2N). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 28.3, 43.7, 48.3, 52.1, 53.6, 61.9, 68.0, 81.0, 157.2, 169.2.

2-*tert*-Butyl 1-methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (19)

Et_3N×3HF (142.7 g, 0.885 mol) and Xtal-Fluor-E® (81.1 g, 0.354 mol) were sequentially added to the solution of compound **18** pre-cooled to 0 °C (80.0 g, 0.295 mol) in CH_2Cl_2 (1 L). The cooling bath was removed, and the resulting mixture was left overnight with stirring. The clear solution was slowly poured on sat. aq. $NaHCO_3$ (700 mL), the organic phase was washed with sat. aq. $NaHCO_3$ (500 mL), water (500 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product obtained was purified by flash column chromatography (hexanes/EtOAc, gradient = 4:1 to 1:1 v/v) to give a pure compound **19**.

A yellow viscous oil. Yield – 56.5 g (70%). ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.34 (9H, s, $C(CH_3)_3$), 1.73 (2H, dd, J = 4.5, 1.5 Hz, CH_2), 2.00 (2H, d, J = 4.5 Hz, CH_2), 3.33 (2H, s, CH_2N), 3.70 (3H, s, CH_3), 4.50 (2H, d, J_{HF} = 47.2 Hz, CH_2F). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 28.1, 43.5 (d, J_{CF} = 4.6 Hz), 46.2 (d, J_{CF} = 21.9 Hz), 51.9, 52.7 (d, J_{CF} = 5.8 Hz), 67.9, 80.9, 81.9 (d, J_{CF} = 167.1 Hz), 156.9, 168.5. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$), δ, ppm: –226.3. HRMS (ESI/QTOF), m/z: calcd for $C_{13}H_{20}FNO_4Na^+$ 296.1269 $[M + Na]^+$, found 296.1267.

Methyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]-hexane-1-carboxylate hydrochloride (20)

Compound **19** (55.0 g, 0.201 mol) was mixed with the anhydrous HCl methanolic solution (2 M, 500 mL) and stirred for 30 min at room temperature. After the gas evolution ceased, the solvent was carefully evaporated under reduced pressure at 30 °C. The crude residue was triturated with CH_3CN (100 mL), and the precipitate formed was collected by filtration to give a pure compound **20**.

A colorless solid. Yield – 41.5 g (98%). M. p. 196–199 °C. ^1H NMR (500 MHz, DMSO-d_6), δ, ppm: 2.03 (2H, d, J = 5.0 Hz, CH_2), 2.22–2.32 (2H, m, CH_2), 3.30 (2H, s, CH_2N), 3.77 (3H, s, CH_2), 4.71 (2H, d, J_{HF} = 47.0 Hz, CH_2F), 10.58 (2H, br. s, NH_2^+). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6), δ, ppm: 40.9 (d, J_{CF} = 4.9 Hz), 47.8 (d, J_{CF} = 5.3 Hz), 48.0 (d, J_{CF} = 21.8 Hz), 53.0, 67.2, 80.9 (d, J_{CF} = 161.7 Hz), 165.6. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6), δ, ppm: –227.3. HRMS (ESI/QTOF), m/z: calcd for $C_8H_{13}FNO_2^+$ 174.0925 $[M + H]^+$, found: 174.0925.

4-(Fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid hydrochloride (21)

Compound **20** (13.0 g, 0.062 mol) was dissolved in aq. HCl (0.2 M, 100 mL), and the resulting solution was heated to reflux. After additional stirring for 2 h, the mixture was cooled to rt, and the solvent was evaporated under reduced pressure to dryness. The residue was additionally dried in a high vacuum (1 mmHg) to give a pure compound **21**.

A colorless solid. Yield – 11.6 g (96%). M. p. 205–207 °C. ^1H NMR (500 MHz, D_2O), δ, ppm: 2.11 (2H, dd, J = 5.9, 2.3 Hz, CH_2), 2.58 (2H, d, J = 5.8 Hz, CH_2), 3.60 (2H, s, CH_2N), 4.84 (2H, d, J_{HF} = 46.6 Hz, CH_2F). $^{13}C\{^1H\}$ NMR (151 MHz, D_2O), δ, ppm: 41.0 (d, J_{CF} = 4.5 Hz), 48.3 (d, J_{CF} = 21.1 Hz), 49.0 (d, J_{CF} = 6.0 Hz), 69.1, 81.2 (d,

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J_{CF} = 161.6 Hz), 168.5. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6), δ, ppm: –227.3. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_7H_{11}FNO_2^+$ 160.0768 $[M + H]^+$, found: 160.0773.

2-[(*tert*-Butoxy)carbonyl]-4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1-carboxylic acid (22)

Compound **24** (28.0 g, 0.080 mol) was dissolved in THF (300 mL), and Pd/C (10% *w*/*w*, 5.00 g) was added in one portion. The flask was vacuumed and backfilled with H_2 from the balloon of the appropriate size, and the resulting mixture was stirred overnight. After the reaction was complete (concluded by ^1H NMR spectra of the small aliquot of the reaction mixture), the suspension was filtered through a celite pad, and the filtrate was concentrated under reduced pressure to give a pure compound **22**.

A colorless solid. Yield – 19.7 g (95%). M. p. 136–137 °C. ^1H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.50 (9H, s, $C(CH_3)_3$), 1.93 (2H, s, CH_2), 2.37 (2H, s, CH_2), 3.49 (2H, s, CH_2N), 4.59 (2H, d, J_{HF} = 47.1 Hz, CH_2F). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 28.3, 44.9, 45.7 (d, J_{CF} = 22.9 Hz), 53.9, 70.0 (d, J_{CF} = 16.5 Hz), 82.1 (d, J_{CF} = 167.6 Hz), 82.9, 157.6, 169.7. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$), δ, ppm: –226.8. HRMS (ESI/QTOF), m/z: calcd for $C_{12}H_{18}FNO_4Na^+$ 282.1118 $[M + Na]^+$, found: 282.1112.

1-Benzyl 2-*tert*-butyl 4-(hydroxymethyl) bicyclo[2.1.1]hexane-1,2-dicarboxylate (23)

Benzyl bromide (30.5 mL, 0.257 mol) was added to a mixture of compound **6** (63.0 g, 0.245 mol) and K_2CO_3 (50.4 g, 0.365 mol) in DMF (400 mL) at room temperature. The resulting mixture was stirred at room temperature overnight, then diluted with water (1 L) and extracted with EtOAc (2×600 mL). The organic phases were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dried under a high vacuum (1 mmHg) to give a pure compound **23**.

A colorless solid. Yield – 73.6 g (87%). M. p. 68–69 °C. ^1H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.33 (9H, s, $C(CH_3)_3$), 1.68 (2H, s, CH_2), 1.93 (2H, s, CH_2), 2.87 (1H, s, OH), 3.29 (2H, s, CH_2O), 3.67 (2H, s, CH_2N), 5.11 (2H, s, $\underline{CH_2}Ph$), 7.26 (5H, s, PhH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 28.2, 43.6, 48.3, 53.6, 61.6, 66.5, 67.9, 80.9, 128.0, 128.1, 128.5, 135.7, 157.2, 168.5. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{20}H_{26}O_5Na^+$ 370.1630 $[M + Na]^+$, found: 370.1625.

1-Benzyl 2-*tert*-butyl 4-(fluoromethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (24)

$Et_3N{\cdot}3HF$ (164.0 mL, 1.01 mol) and XtalFluor-E® (69.2 g, 0.302 mol) were added sequentially to the solution of compound **23** pre-cooled to 0 °C (70.0 g, 0.202 mol) in DCM (1 L). The resulting mixture was slowly warmed to room temperature and stirred at the same temperature overnight. Then, the mixture was quenched with saturated aq. $NaHCO_3$ (2×700 mL), the organic layer was washed with water (700 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The crude product obtained was purified by flash column chromatography (hexanes/EtOAc, 5:1 to 1:1 gradient, *v*/*v*) to give a pure compound **24**.

A yellow viscous oil. Yield – 28.5 g (41%). ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.35 (9H, s, $C(CH_3)_3$), 1.75 (2H, d, J = 4.6 Hz, CH_2), 2.01 (2H, d, J = 4.3 Hz, CH_2), 3.33 (2H, s, CH_2N), 4.47 (2H, d, J_{HF} = 47.0 Hz, CH_2F), 5.13 (2H, s, $\underline{CH_2}Ph$), 6.96–7.59 (m, 5H, PhH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 28.3, 43.6 (d, J_{CF} = 4.6 Hz), 46.4 (d, J_{CF} = 21.9 Hz), 52.9 (d, J_{CF} = 5.7 Hz), 66.7, 68.1, 81.0, 82.1 (d, J_{CF} = 167.4 Hz), 128.1, 128.2, 128.6, 135.8, 157.0, 168.0. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$), δ, ppm: –226.1. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{19}H_{24}FNO_4Na^+$: 372.1582 $[M + Na]^+$, Found: 372.1583.

2-*tert*-Butyl 1-methyl 4-[(methanesulfonyloxy)methyl]-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (25)

To the solution of compound **6** pre-cooled to 0 °C (31.9 g, 0.118 mol) and Et_3N (25.0 mL, 0.179 mol) in CH_2Cl_2 (300 mL) under Ar atmosphere, a neat $MeSO_2Cl$ (16.2 g, 0.141 mol) was added dropwise keeping temperature below 5 °C. The resulting mixture was stirred for 1 h at the same temperature, washed with water (2×200 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was dried in a high vacuum (1 mmHg) for 1 h at 35–38 °C to give compound **25**.

A yellow solid. Yield – 40.5 g (99%). M. p. 91–93 °C. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.39 (9H, s, $C(CH_3)_3$), 1.83–1.79 (2H, m, CH_2), 2.04–2.09 (2H, m, CH_2), 3.00 (3H, s, CH_3), 3.39 (2H, s, CH_2N), 3.74 (3H, s, CH_3), 4.36 (s, 2H, CH_2O). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 28.2, 37.5, 44.0, 45.2, 52.1, 53.1, 67.9, 81.2, 156.8, 168.3. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{14}H_{23}NNaO_7S^+$ 372.1093 $[M + Na]^+$, found: 372.1088.

2-*tert*-Butyl 1-methyl 4-(azidomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (26)

To the solution of compound **25** (40.0 g, 0.114 mol) in DMF (300 mL), a solid NaN_3 (23.0 g, 0.354 mol) was added in one portion. The resulting mixture was stirred overnight at 80 °C, diluted with water (750 mL), and extracted with *t*BuOMe (750 mL). The organic layer was separated, washed with

brine (2×500 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give a pure compound **26**.

Yield – 31.9 g (94%). A yellow oil. Anal. Calcd. for $C_{13}H_{20}N_4O_4$, %: C 52.69; H 6.80; N 18.91. Found, %: C 52.38; H 6.87; N 19.25. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 1.41 (9H, s, $C(CH_3)_3$), 1.80 (2H, d, J = 3.6 Hz, CH_2), 2.03 (2H, d, J = 3.6 Hz, CH_2), 3.37 (2H, s, CH_2N), 3.53 (2H, s, CH_2N), 3.76 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$), δ, ppm: 28.3, 44.5, 46.5, 51.8, 52.1, 53.9, 68.0, 81.1, 157.0, 168.6.

2-*tert*-Butyl 1-methyl 4-(aminomethyl)-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (27)

The mixture of compound **26** (25.0 g, 84.4 mmol) and Pd/C (10% *w*/*w*, 5.00 g) in the saturated NH_3 methanolic solution (300 mL) was vacuumed and backfilled with H_2 from the balloon of the appropriate size. The resulting mixture was left overnight with intensive stirring. After the reaction was complete (concluded by ^{1}H NMR spectra of the small aliquot of the reaction mixture), the suspension was filtered through a thin celite pad, and the filtrate was evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexanes/EtOAc/Et_3N = 1:4:0.25 *v*/*v*) to give a pure compound **27**.

A colorless solid. Yield – 20.8 g (91%). M. p. 57–60 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.43 (9H, s, $C(CH_3)_3$), 1.76 (2H, dd, J = 4.8, 1.8 Hz, CH_2), 1.91 (2H, br s, NH_2), 1.98 (2H, d, J = 4.5 Hz, CH_2), 2.98 (2H, s, CH_2N), 3.37 (2H, s, CH_2N), 3.78 (3H, s, CH_3). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 28.4, 42.4, 43.8, 48.7, 52.1, 54.2, 67.9, 80.9, 157.2, 169.1. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{13}H_{23}N_2O_4^+$ 271.1652 $[M + H]^+$, found: 271.1646.

2-[(*tert*-Butoxy)carbonyl]-1-(methoxycarbonyl)-2-azabicyclo[2.1.1]hexane-4-carboxylic acid (28)

$RuCl_3 \times H_2O$ (1.07 g, 5.16 mmol) was added in one portion to the solution of alcohol **6** (56.0 g, 0.206 mol) and $NaIO_4$ (88.3 g, 0.413 mol) in the H_2O/MeCN mixture (900 mL, 2:1 *v*/*v*). The resulting solution was stirred for 2 h at rt, diluted with water (200 mL), and quenched with a solid $NaHCO_3$ to pH = 7 (CAUTION! Intensive stirring is required due to the heavy foaming effect). The suspension obtained was filtered, and the filtrate was extracted with $CHCl_3$ (400 mL). The organic layer was discarded, and the aqueous layer was acidified with 10% aq. $NaHSO_4$ to pH = 2 (CAUTION! Intensive stirring is required due to the heavy foaming effect) and extracted with EtOAc (2×700 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a pure acid **28**.

A colorless solid. Yield – 52.2 g (89%). M. p. 122–125 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.36 (9H, s, $C(CH_3)_3$), 1.88 (2H, d, J = 4.1 Hz, CH_2), 2.27 (2H, d, J = 4.4 Hz, CH_2), 3.48 (2H, s, CH_2N), 3.66 (3H, s, CH_3), 12.92 (1H, br. s, COOH). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6), δ, ppm: 27.8, 44.7, 47.0, 51.6, 52.4, 66.9, 80.0, 156.0, 167.5, 170.5. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{13}H_{19}NO_6Na^+$ 308.1105 $[M + Na]^+$, found: 308.1102.

1-(Methoxycarbonyl)-2-azabicyclo[2.1.1]-hexane-4-carboxylic acid hydrochloride (29)

Compound **28** (25.0 g, 87.6 mmol) was mixed with an anhydrous HCl ethereal solution (0.5 M, 300 mL). The reaction mixture was stirred for 24 h at room temperature, filtered, and the precipitate obtained was washed with Et_2O (150 mL) and dried on air to give a pure compound **29**.

A colorless powder. Yield – 18.1 g (93%). M. p. 196–198 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 2.19 (2H, dd, J = 5.3, 2.0 Hz, CH_2), 2.52 (2H, d, J = 1.9 Hz, CH_2 overlapped with the solvent residual peak), 3.46 (2H, s, CH_2N), 3.79 (3H, s, CH_3), 10.33 (2H, s, NH_2^+), 13.29 (1H, br. s, COOH). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6), δ, ppm: 42.8, 48.2, 49.0, 53.1, 66.7, 165.2, 168.8. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_8H_{12}NO_4^+$ 186.0761 $[M + H]^+$, found: 186.0760.

2-*tert*-Butyl 1-methyl 4-{[(benzyloxy)carbonyl]amino}-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (30)

To the solution of acid **28** pre-cooled to 0 °C (30.0 g, 0.105 mol) and Et_3N (22.0 mL, 0.158 mol) in THF (300 mL) under Ar atmosphere, a neat ethyl chloroformate (13.8 g, 0.127 mol) was added dropwise with mechanical stirring. The resulting mixture was stirred at 0 °C for 1 h, then cooled to –10 °C, and the solution of NaN_3 (50.0 g, 0.769 mol) in water (200 mL) was slowly added. The cooling bath was removed, and the reaction mixture was stirred for another 1 h, diluted with water (200 mL), and extracted with EtOAc (2×300 mL). The organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure to ca. 60 mL, and mixed with the benzylic alcohol (21.9 mL, 0.211 mol) solution in toluene (300 mL). The resulting mixture was gradually heated to reflux (over *ca.* 30 min) and stirred at the same temperature overnight. Upon completion, the mixture was concentrated under reduced pressure, and the crude residue was triturated with *t*BuOMe (75 mL). The resulting precipitate was filtered and dried on air to give a pure compound **30**.

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A colorless solid. Yield – 25.6 g (62%). M. p. 153–156 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.41 (9H, s, $C(CH_3)_3$), 2.06 (2H, s, CH_2), 2.39 (2H, br. s, CH_2), 3.51 (2H, s, CH_2N), 3.76 (3H, s, CH_3), 5.07 (2H, s, $\underline{CH_2}Ph$), 5.48 (1H, s, NH), 7.33 (5H, s, PhH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 27.1, 28.3, 46.8, 52.2, 52.3, 53.6, 54.8, 65.3, 67.0, 77.2, 81.3, 128.3, 128.5, 128.7, 136.1, 155.0, 156.9, 168.5. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{20}H_{26}N_2O_6Na^+$ 413.1683 $[M + Na]^+$, found: 413.1680.

2-*tert*-Butyl 1-methyl 4-amino-2-azabicyclo[2.1.1]hexane-1,2-dicarboxylate (31)

Compound **30** (25.0 g, 64.1 mmol) was dissolved in MeOH (300 mL), and Pd/C (10% *w*/*w*, 5.00 g) was added in one portion. The reaction vessel was evacuated and backfilled with H_2 from a balloon (repeated 2 times), and the suspension was stirred under the H_2 atmosphere overnight. After the reaction was completed (concluded by ^{1}H NMR spectra of the small aliquot of the reaction mixture), the catalyst was filtered off through a short pad of celite, and the solvent was evaporated under reduced pressure to give a pure compound **31**.

A colorless solid. Yield – 16.1 g (98%). M. p. 98–99 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.42 (s, 9H, $C(CH_3)_3$), 1.93–2.05 (br. m, 6H, $2\times CH_2+NH_2$), 3.33 (s, 2H, CH_2N), 3.77 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 28.4, 49.5, 52.1, 55.9, 57.3, 64.7, 81.0, 157.0, 168.9. HRMS (ESI/QTOF), *m*/*z*: calcd for $C_{12}H_{21}N_2O_4^+$ 257.1496 $[M + H]^+$, found: 257.1495.

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