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The Synthesis of 2,5-Dioxaspiro[3.4]octane Building Blocks: Three-Dimensional Spirocyclic Analogs of 1,4-Dioxanes

Abstract

A ring-closing metathesis (RCM) strategy was employed for the synthesis of spirooxetane compounds with a tetrahydrofuran (THF) core. The approach proposed relied on the preparation of an unsaturated spirooxetane from vinyl oxetanol. The reaction sequence involved the NaH-mediated *O*-alkylation with methyl 2-(bromomethyl)acrylate in the presence of TBAI. The subsequent RCM reaction using the Grubbs' II catalyst gave the dihydrofuran carboxylate with a yield of 70 %. The hydrogenation under high-pressure conditions using a Pearlman's catalyst made it possible to obtain the saturated THF-derived carboxylate, which was then subjected to alkaline hydrolysis to give a stable lithium carboxylate. The corresponding alcohol obtained *via* $LiAlH_4$-mediated reduction of the ester was oxidized to the corresponding aldehyde using DMP. The alcohol was further converted into a mesylate serving as a precursor for the corresponding amine and bromide. The set of dioxane analogs proposed can serve as promising building blocks readily available on a multigram scale for the scientific community.

Keywords: oxetanes; dioxanes; spirocycles; building blocks

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Синтез 2,5-діоксаспіро[3.4]октанових будівельних блоків як тривимірних спіроциклічних аналогів 1,4-діоксанів

Анотація

Для синтезу спірооксетанових сполук із тетрагідрофурановим (ТГФ) фрагментом було застосовано реакцію метатезу із замиканням циклу. Запропонований підхід ґрунтувався на одержанні ненасиченого спірооксетану з вінілоксетанолу. Послідовність реакції передбачала NaH-опосередковане *O*-алкілування метил-2-(бромметил)акрилатом у присутності TBAI. Подальша побудова спіроциклічного каркаса у випадку використання каталізатора Граббса II дала дигідрофуранкарбоксилат із виходом 70 %. Гідрування під високим тиском за допомогою каталізатора Перлмана дозволило одержати насичений ТГФ-карбоксилат, який піддавали лужному гідролізу для утворення стабільного карбоксилату літію. Відповідний спирт, отриманий відновленням естеру під дією $LiAlH_4$, окиснювали за допомогою DMP до відповідного альдегіду. Спирт також перетворювали на мезилат, який слугував вихідною сполукою для синтезу відповідного аміну та броміду. Одержані аналоги діоксану постають перспективними будівельними блоками, відтепер доступними в багатограмових кількостях для наукової спільноти.

Ключові слова: оксетани; діоксани; спіроцикли; будівельні блоки

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Introduction

Oxetane is an emerging motif in medicinal chemistry due to its distinctive structural and physicochemical characteristics [1–4]. With an intrinsic ring strain comparable to that of epoxides, oxetanes have a nearly planar structure that minimizes strain and gauche interactions, which, in turn, is attributed to the presence of the oxygen atom [5, 6]. Nowadays, the incorporation of the oxetane moiety into molecules can significantly enhance physicochemical properties, i.e., aqueous solubility, lipophilicity, metabolic stability, acidity/basicity, and ADMET parameters (absorption, distribution, metabolism, excretion, and toxicity) [1, 2, 7, 8]. *Ziresovir* serves as a prominent example of hit optimization through the inclusion of an oxetane fragment (**Figure 1**, *A*) [9, 10].

Other noticeable examples of pharmaceutically relevant oxetanes have a bicyclic structure (**Figure 1**, *B*) [11]. Intriguingly, some oxetanes from the group, particularly bicyclic analogs of 1,4-dioxane, i.e. 2,5-dioxaspiro[3.4]octanes, have been largely overlooked in the scientific literature despite their potential as promising fragments for drug discovery. Therefore, in this study, we aim to synthesize spirocyclic oxetanes, specifically three-dimensional analogs of 1,4-dioxanes (**Figure 1**, *C*). These analogs are expected to provide a range of novel building blocks on a multigram scale, i.e., carboxylates, alcohols, amines, halides, etc.

Results and discussion

The ring-closing metathesis (RCM) reaction was considered as an effective approach for the synthesis of spirooxetane compounds with a tetrahydrofuran (THF) core. For this purpose, we used a bulk reagent, oxetanone **1**, which could be functionalized in optimized conditions, as recently disclosed [12]. The optimized Grignard reaction of **1** provided vinyl oxetanol **2** with a yield of 83% after the distillation *in vacuo* on over a 300 g scale in a single run (**Scheme 1**). The subsequent step included the NaH-mediated alkylation with methyl 2-(bromomethyl)acrylate in the presence of TBAI giving *bis*-allyl ether **3** with a yield of 49%, which was subjected to the RCM reaction. The second-generation Grubbs' catalyst was suitable for the latter reaction and gave the target dihydrofuran carboxylate **4** with a yield of

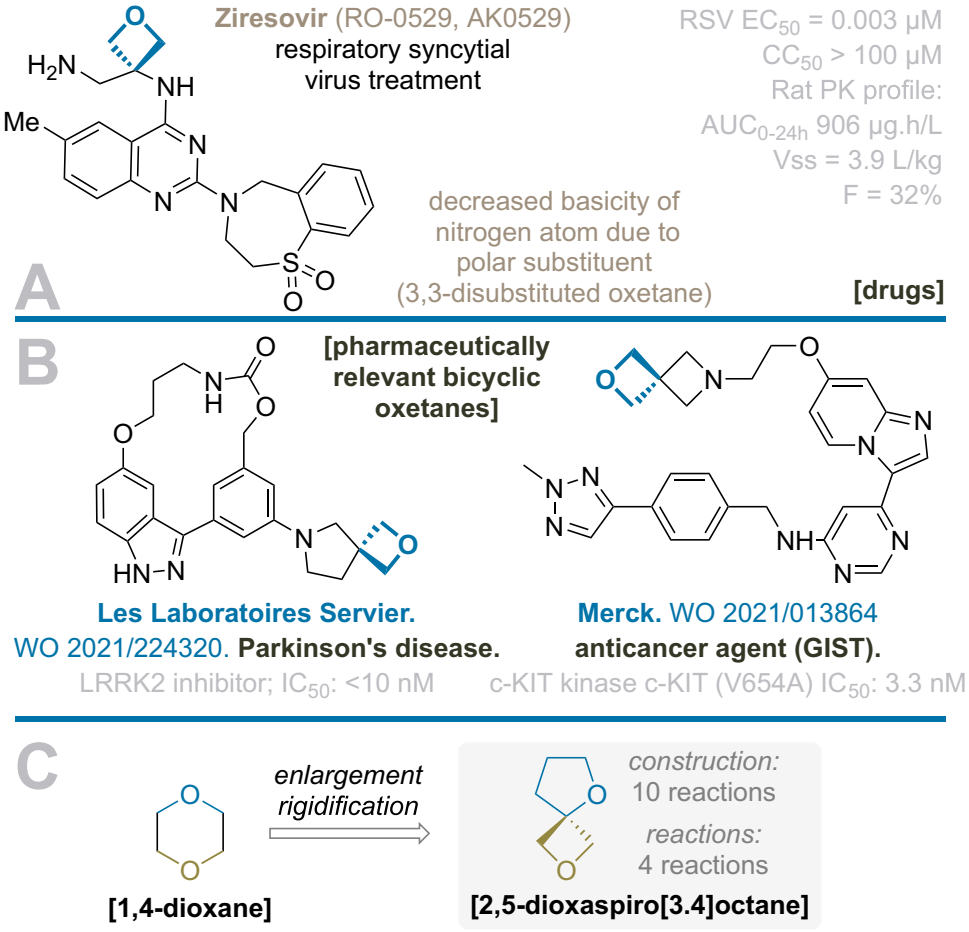
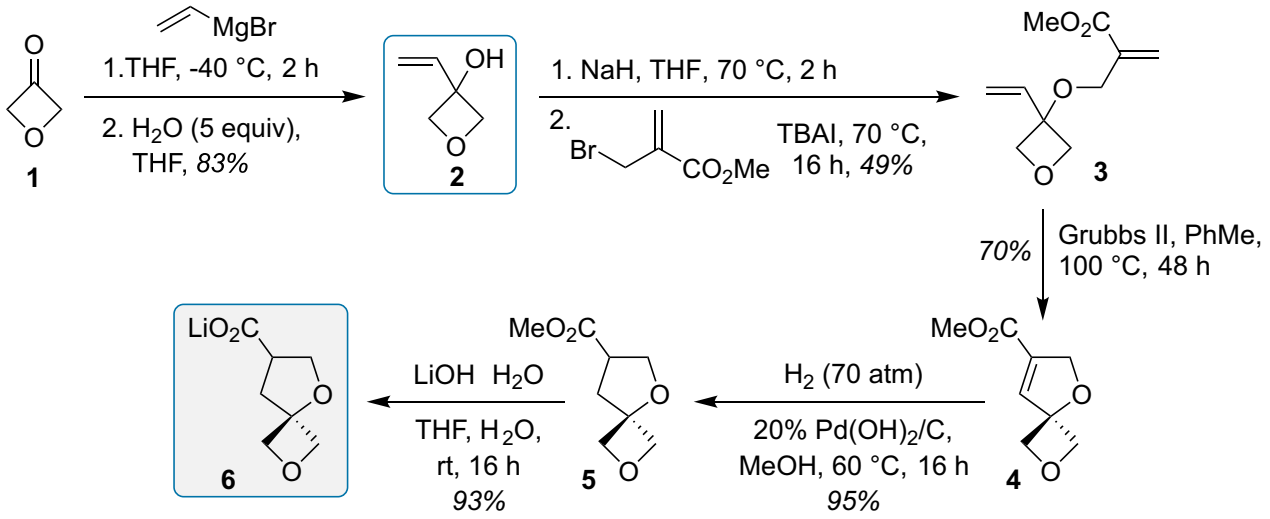


Figure 1. Prominent examples of oxetanes in drug discovery programs (*A*, *B*), and the target fragment of this study (*C*)



Scheme 1. The synthesis of lithium 2,5-dioxaspiro[3.4]octane-7-carboxylate (**6**)

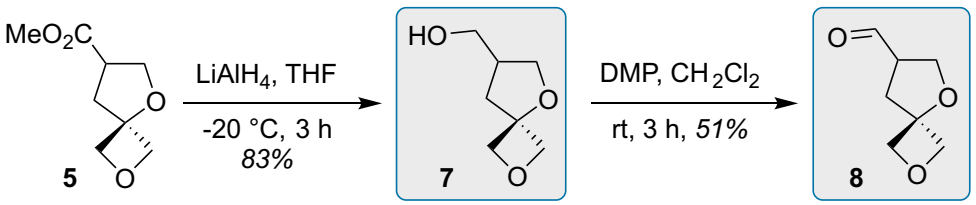
70% on over a 200 g scale. The subsequent catalytic hydrogenation of acrylate **4** in an autoclave (70 atm pressure of H_2) in the presence of Pearlman's catalyst gave a bicyclic THF scaffold **5**, which was subjected to the alkaline hydrolysis to give lithium carboxylate **6** with a yield of 93% (20 g scale). It should be noted that the acidification of **6** or attempted synthesis of the corresponding carboxylic acid were unfruitful due to instability of the oxetane core.

Alcohol **7** was obtained with a yield of 83% from ester **5** by the robust reduction with $LiAlH_4$ (**Scheme 2**). Notably, this approach allowed for the preparation of **7** on a 90 g scale in a single run. Then, the alcohol obtained was oxidized to aldehyde **8** using DMP (Dess-Martin periodinane) in CH_2Cl_2 (30 g scale, 51% yield).

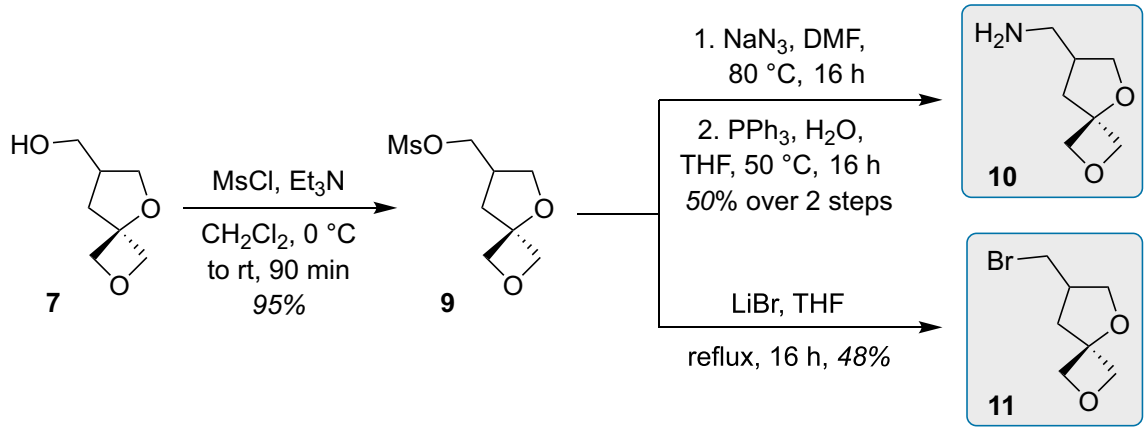
Alcohol **5** was transformed into mesylate **9** (**Scheme 3**), which was used as a precursor for the synthesis of amine **10** with a yield of 50% on up to a 25 g scale *via* the nucleophilic substitution with NaN_3 followed by the Staudinger reaction. Finally, the promising alkylating agent, e.g., bromide **11**, was obtained using the nucleophilic substitution with LiBr in THF (48% yield).

Conclusions

This study demonstrates the successful synthesis of spirocyclic oxetanes as three-dimensional



Scheme 2. The synthesis of 2,5-dioxaspiro[3.4]octane-derived alcohol **7** and aldehyde **8**



Scheme 3. The synthesis of 2,5-dioxaspiro[3.4]octane-derived amine **9** and bromide **10**

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bicyclic analogs of 1,4-dioxanes, expanding the range of available building blocks for medicinal chemistry. The key ring-closing metathesis (RCM) reaction proved to be an effective approach for constructing spiro-oxetane compounds with a THF core. The synthetic sequence developed enabled the preparation of key intermediates on a scale of more than 200 g through the NaH-mediated alkylation, metathesis of *bis*-allyl ether thus obtained, the catalytic hydrogenation of the acrylate fragment, and the functional group subsequent transformations. The ability to convert these intermediates into diverse derivatives, including aldehydes, amines, and bromides, highlights the synthetic versatility of the methodology proposed. Taking into account the significance of oxetane-containing motifs in drug discovery, the structures obtained may serve as valuable scaffolds for further development in medicinal chemistry and related applications.

■ Experimental part

The solvents were purified according to the standard procedures [13]. All starting compounds were available from Enamine Ltd or purchased from other commercial sources. Melting points were measured on the MPA100 OptiMelt automated melting point system. ^{1}H and $^{13}C\{^{1}H\}$ spectra were recorded on an Agilent ProPulse 600 spectrometer (at 151 MHz for ^{13}C NMR), a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, and 126 MHz for $^{13}C\{^{1}H\}$ NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and $^{13}C\{^{1}H\}$ in $CDCl_3$, 7.13 and 127.60 ppm for ^{1}H and $^{13}C\{^{1}H\}$ in C_6D_6, 2.48 and 39.50 ppm for ^{1}H and $^{13}C\{^{1}H\}$ in DMSO-d_6. Coupling constants (J) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), integration, multiplicity, and coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. LCMS and GCMS analyses were performed using an Agilent LC/MSD SL 1100 instrument [atmospheric pressure electrospray ionization (ES-API)] or an Agilent 5890 Series II 5972 GCMS instrument [electron impact (EI) ionization (70 eV)], respectively. High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

3-Vinyloxetan-3-ol (2)

An oven-dried round-bottomed flask filled with 2 M vinylmagnesium bromide solution in THF (2.07 L, 4.14 mol) was cooled to –40 °C. To the above-precooled solution 3-oxetanone (336 g, 3.72 mol) in THF (3 L) was added dropwise under Ar atmosphere, maintaining the temperature below –40 °C and stirred at –40 °C for 1 h. Upon completion, the reaction was quenched with careful addition of THF–H_2O mixture (240 mL, 1:1, *v*/*v*, 2 equiv. of H_2O). Then, H_2O (300 mL) was added in portions. The resulting suspension was filtered, and the filter cake was washed with THF (2 × 1 L). The combined filtrates were dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by distillation in *vacuo* (0.3 mmHg, 44–47 °C) to obtain alcohol **2**.

A colorless liquid. Yield – 83% (311 g). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.16 (1H, br. s), 4.64 (2H, d, J = 6.8 Hz), 4.66 (2H, d, J = 6.8 Hz), 5.24 (1H, d, J = 10.8 Hz), 5.39 (1H, d, J = 17.4 Hz), 6.25 (1H, dd, J = 17.4, 10.8 Hz). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 74.5, 83.8, 114.3, 139.0. HRMS (ESI–TOF), m/z: $[M–H_2O+H]^+$ calcd for C_6H_7O 83.0497, found 83.0551; $[M+H]^+$ calcd for $C_5H_9O_2$ 101.0603, found 101.0604; $[M+NH_4]^+$ calcd for $C_5H_{12}NO_2$ 118.0868, found 118.0863.

Methyl 2,5-dioxaspiro[3.4]oct-7-ene-7-carboxylate (4)

NaH (2.5 equiv, 5.84 mol) was added in portions to a solution of compound **2** (292 g, 2.92 mol) in THF (5 L) under Ar atmosphere, and the resulting mixture was stirred at 70 °C for 2 h. Then, the reaction mixture was cooled to 0 °C, and methyl 2-(bromomethyl)prop-2-enoate (902 g, 4.67 mol) followed by TBAI (1 mol%) were added, and the resulting mixture was stirred at 70 °C for 16 h. After that, the resulting mixture was poured into saturated aq. NH_4Cl (388 g, 7.26 mol), and then extracted with EtOAc (3×1 L). Combined organic layers were washed with brine (1 L), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product obtained was purified by the flash column chromatography using hexanes–EtOAc (4:1, *v*/*v*) as an eluent. The resulting diene **3** (1.44 mol) in toluene (8 L) was degassed 3 times and refilled with Ar. Then, Grubbs II catalyst (14.5 g, 17.1 mmol, 1.5 mol%) was added, and the resulting mixture was stirred at 100 °C for 48 h. Then, the reaction mixture was concentrated *in vacuo*. The product obtained was purified by the flash column chromatography using hexanes–EtOAc (4:1, *v*/*v*) as an eluent.

Fusible brownish crystals. Yield – 70% (172 g). Anal. Calcd for $C_8H_{10}O_4$, %: C 56.47, H 5.92.

Found, %: C 56.33, H 5.84. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.78 (3H, s), 4.70 (2H, d, J = 7.0 Hz), 4.79 (2H, d, J = 2.4 Hz), 4.88 (2H, d, J = 7.0 Hz), 7.01 (1H, t, J = 2.4 Hz). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$), δ, ppm: 52.1, 74.3, 83.0, 90.4, 134.2, 138.1, 162.7. GCMS (EI), m/z: 140 $[M-CH_2O]^+$.

Methyl 2,5-dioxaspiro[3.4]octane-7-carboxylate (5)

20% $Pd(OH)_2$/C (25.0 g) was added to the compound **4** (207 g) solution in MeOH (2 L), and the resulting solution was stirred at H_2 (70 atm; in autoclave), 50 °C for 48 h. After that, the catalyst was filtered thought a pad of silica gel, and the filtrate obtained was concentrated in *vacuo*, and immediately used in the next step. Yield – 95% (194 g).

Lithium 2,5-dioxaspiro[3.4]octane-7-carboxylate (6)

$LiOH\times H_2O$ (6.50 g, 0.155 mol) was added to a solution of compound **5** (26.7 g, 0.155 mol) obtained in THF/H_2O (100 mL/100 mL), and the resulting mixture was stirred at rt for 16 h. After that, the reaction mixture was concentrated *in vacuo* until it became solid. The title product was obtained after trituration with acetone (2×50 mL) and Et_2O (2×50 mL) resulting in the target product.

A colorless solid. Yield – 93% (23.7 g). M. p. 94–96 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 2.15 (1H, dd, J = 12.5, 8.2 Hz), 2.33 (1H, dd, J = 12.5, 6.9 Hz), 2.71 (1H, p, J = 7.4 Hz), 3.81 (2H, d, J = 7.4 Hz), 4.34 – 4.62 (4H, m). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 176.4, 83.1, 82.9, 82.4, 71.2, 46.4, 39.0. HRMS (ESI-TOF), m/z: $[M-Li]^-$ calcd for $C_7H_9O_4$ 157.0501, found 157.0509.

(2,5-Dioxaspiro[3.4]octan-7-yl)methanol (7)

$LiAlH_4$ (29.9 g, 0.788 mol) was added to THF (2 L), and the mixture was cooled to –20 °C. Then, ester **5** (135 g, 0.788 mol) in THF (200 mL) was added dropwise at –20 °C. The mixture was stirred at –20 °C for 3 h, then 30 % aq. KOH (65 mL) was added at –20 °C. The mixture was warmed up to rt, stirred for an additional 2 h, then filtered and evaporated *in vacuo*.

A colorless oil. Yield – 83% (94.2 g). ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.89 (1H, dd, J = 12.8, 6.3 Hz), 2.19 (1H, dd, J = 12.8, 7.8 Hz), 2.25–2.36 (1H, m), 3.21–3.32 (2H, m), 3.53 (1H, dd, J = 8.4, 5.8 Hz), 3.77 (1H, t, J = 7.8 Hz), 4.37–4.60 (4H, m), 4.66 (1H, t, J = 5.1 Hz). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 37.2, 41.2, 62.1, 69.9, 82.0, 82.7, 83.1. HRMS (ESI-TOF), m/z: $[M+H]^+$ calcd for $C_7H_{13}O_3$ 145.0865, found 145.0860.

2,5-Dioxaspiro[3.4]octane-7-carbaldehyde (8)

DMP (240 g, 0.566 mol) was added in portions to a solution of **7** (62.0 g, 0.431 mol) in CH_2Cl_2 (800 mL) at rt, and the resulting mixture was stirred at rt for 3 h. Then, the reaction mixture was poured into saturated aq. $NaHCO_3$ (145 g, 2.72 mol) and saturated aq. $Na_2S_2O_3\cdot 5H_2O$ (321 g, 1.29 mol), and the resulting mixture was stirred at rt for 1 h. Then, the organic layer was separated, washed with H_2O (700 mL), brine (700 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product obtained was purified by the flash column chromatography using hexanes–EtOAc (7:3, *v*/*v*) as an eluent.

A colorless oil. Yield – 51% (31.2 g). ^{1}H NMR (500 MHz, C_6D_6), δ, ppm: 1.49 (1H, dd, J = 13.2, 8.6 Hz), 1.93 (1H, dd, J = 13.2, 5.1 Hz), 2.02–2.10 (1H, m), 3.22–3.28 (1H, m), 3.61 (1H, dd, J = 9.1, 4.5 Hz), 4.16 (1H, d, J = 6.6 Hz), 4.34 (1H, d, J = 6.6 Hz), 4.59 (1H, d, J = 6.6 Hz), 4.65 (1H, d, J = 6.6 Hz), 8.94 (1H, s). ^{13}C{^{1}H} NMR (151 MHz, C_6D_6), δ, ppm: 34.8, 51.1, 66.7, 82.8, 82.9, 83.2, 198.8. HRMS (ESI-TOF), m/z: $[M+H]^+$ calcd for $C_7H_{11}O_3$ 143.0708, found 143.0702.

(2,5-Dioxaspiro[3.4]octan-7-yl)methyl methanesulfonate (9)

MsCl (81.1 g, 0.708 mol) was added dropwise to a solution of compound **7** (51.0 g, 0.354 mol) and Et_3N (71.7 g, 0.708 mol) in CH_2Cl_2 (500 mL) at 0 °C, and the resulting solution was stirred at rt for 90 min. Then, the reaction mixture was washed with 1 M $NaHCO_3$ (2×200 mL), brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. After that, the residue obtained was dissolved in *t*BuOMe (300 mL), concentrated *in vacuo* twice, and immediately used in the next steps. Yield – 95% (74.6 g).

(2,5-Dioxaspiro[3.4]octan-7-yl)methanamine (10)

NaN_3 (45.8 g, 0.705 mol) was added to a solution of compound **9** (78.0 g, 0.351 mol) in DMF (400 mL), and the resulting mixture was stirred at 80 °C for 16 . After that, the reaction mixture was poured into H_2O (1.2 L), and it was extracted with *t*BuOMe (4×350 mL). Combined organic layers were washed with H_2O (300 mL), brine (300 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Then, Ph_3P (123 g, 0.469 mol) followed by H_2O (17.0 mL, 0.944 mol) were added to a solution of the crude azide obtained (ca. 0.310 mol) in THF (500 mL), and the resulting mixture was stirred at 50 °C for 16 h. After that, the reaction mixture was cooled to rt and concentrated

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in vacuo. The product obtained was purified by the flash column chromatography using hexanes–EtOAc (4:1, *v*/*v*) as an eluent.

A yellowish solid. Yield – 50% over two steps (25.0 g). M. p. 100–101 °C. Anal. Calcd for $C_7H_{13}NO_2$, %: C 58.72, H 9.15, N 9.78. Found, %: C 58.81, H 9.20, N 9.63. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.56 (1H, d, J = 10.7 Hz), 1.67–1.76 (1H, m), 2.19–2.27 (1H, m), 2.41–2.47 (2H, m), 2.60 (1H, d, J = 12.8 Hz), 2.64–2.70 (1H, m), 3.27 (1H, d, J = 11.4 Hz), 3.33 (1H, d, J = 11.4 Hz), 3.39 (2H, s), 3.70 (1H, dd, J = 7.5, 4.5 Hz), 3.92 (1H, d, J = 7.5 Hz). LCMS (ESI), m/z: 144 $[M+H]^+$.

7-(Bromomethyl)-2,5-dioxaspiro[3.4]octane (11)

LiBr (31.4 g, 0.362 mol) was added to a solution of compound **9** (26.8 g, 0.121 mol) in THF (250 mL), and the resulting mixture was refluxed for 16 . After that, the reaction mixture was concentrated *in vacuo*, and the residue obtained was dissolved in H_2O (100 mL) and extracted with CH_2Cl_2 (3×100 mL). Combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product obtained was purified by the flash column chromatography using hexanes–EtOAc (4:1, *v*/*v*) as an eluent.

A dark oil. Yield – 48% (12.0 g). Anal. Calcd for $C_7H_{11}BrO_2$, %: C 40.60, H 5.35. Found, %: C 40.48, H 5.41. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 4.79 (1H, d, J = 6.7 Hz), 4.74 (1H, d, J = 6.7 Hz), 4.60 (1H, d, J = 6.7 Hz), 4.53 (1H, d, J = 6.7 Hz), 3.98 (1H, dd, J = 9.0, 7.0 Hz), 3.64 (1H, dd, J = 9.0, 6.4 Hz), 3.40–3.27 (2H, m), 2.76–2.63 (1H, m), 2.46 (1H, dd, J = 13.2, 7.7 Hz), 2.03 (1H, dd, J = 13.2, 7.0 Hz). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$), δ, ppm: 34.2, 40.7, 41.7, 72.1, 82.8, 83.5, 84.5. GCMS (EI), m/z: 176/178 (intensity ration 1:1) $[M–CH_2O]^+$.

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