Synthesis of phosphodiesterase IVb inhibitors
2.* Stereoselective synthesis of hexahydro-3*H*-pyrrolo[1,2-*c*]imidazol-3-one and tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one derivatives**

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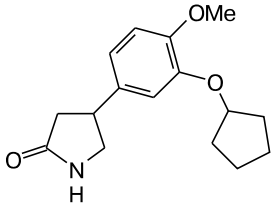
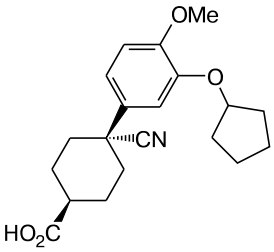
The total stereoselective synthesis of two highly potent phosphodiesterase IVb inhibitors from nitroethane, isovanillin, and ethyl vinyl ether was developed. The compounds obtained are the derivatives of hexahydro-3*H*-pyrrolo[1,2-*c*]imidazol-3-one and tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one. The strategy proposed involves silylation of six-membered cyclic nitronates as a key step leading to 5,6-dihydro-4*H*-1,2-oxazines with the group CH_2FG (FG = N_3 or OH) at the C(3) atom.

Key words: stereoselective synthesis, nitro compounds, cyclic nitronates, silylation, pyrrolidines, rolipram, phosphodiesterase, pyrrolo[1,2-*c*]imidazol-3-ones, pyrrolo[1,2-*c*][1,3]oxazol-3-ones.

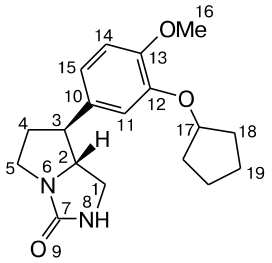
Phosphodiesterase (PDE) IVb inhibitors are considered to be promising drugs for the treatment of disorders of the central nervous system and respiratory diseases.[1] The well-known representatives are, *e.g.*, rolipram (antidepressant)[2] and cilomilast (antiasthmatic drug).[3] Bicyclic derivatives **1**—**3** proposed by GlaxoSmithKline Co.[4] are vastly superior to rolipram and cilomilast in the PDE IVb inhibition constants IC_{50}.[5] However, the syntheses of products **1**—**3** developed by GlaxoSmithKline Co. are nonstereoselective, yielding mixtures of diastereomers in nearly equimolar ratios.[4]



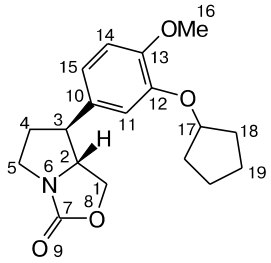
Rolipram
(IC_{50} = 175 nmol L^{-1})



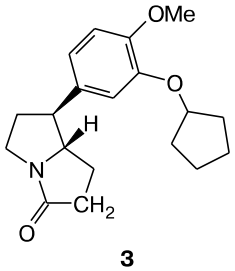
Cilomilast
(IC_{50} = 92 nmol L^{-1})



1
(IC_{50} = 27 nmol L^{-1})



2
(IC_{50} = 70 nmol L^{-1})



3
(IC_{50} = 63 nmol L^{-1})

* For Part 1, see Ref. 1a.
** Dedicated to Academician of the Russian Academy of Sciences O. M. Nefedov on the occasion of his 80th birthday.

Recently,[6] we have proposed a strategy for the stereoselective synthesis of 2,3-*trans*-disubstituted pyrrolidines from nitroethane, aldehydes, and vinyl ethers through in-

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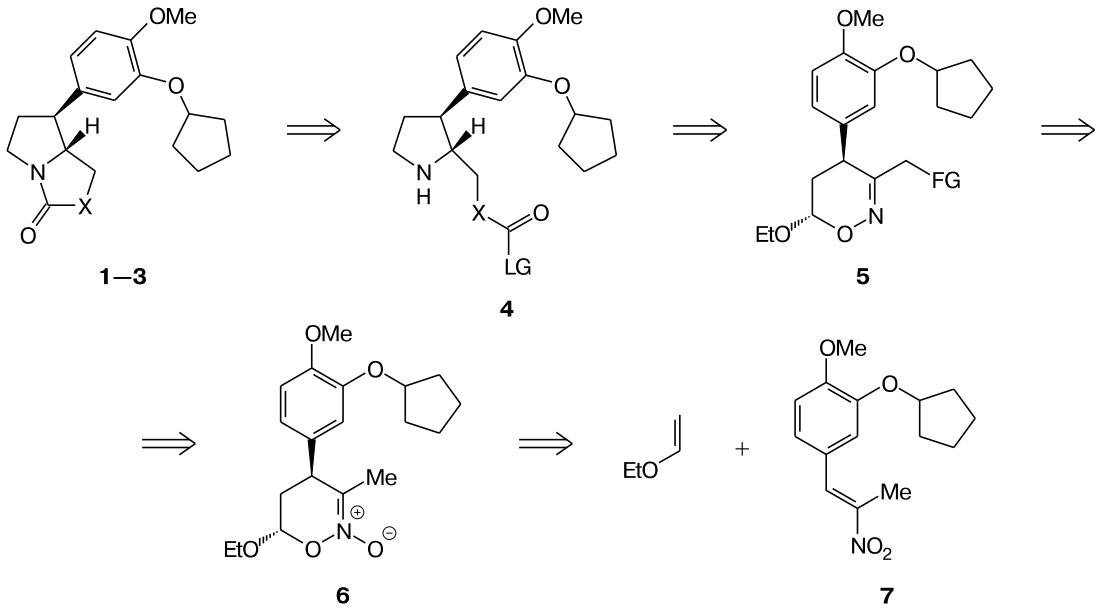
Scheme 1



X = NH (**1**), O (**2**), CH_2 (**3**)

LG stands for a leaving group; FG = N_3, OH, $CH(CO_2Me)_2$

termediate formation of six-membered cyclic oxime ethers with a functionalized methyl group at the C(3) atom. The key step in this synthesis was silylation of six-membered cyclic nitronates.[7] Obviously, this strategy can be employed for stereocontrolled synthesis of PDE IVb inhibitors **1**—**3** (Scheme 1). For instance, immediate precursors of products **1**—**3** are pyrrolidines **4**, which can be obtained by reduction of cyclic oxime ethers **5**. In turn, such oxime ethers can be derived from cyclic nitronate **6** according to our recent silylation-based procedures. Cyclic nitronate **6** is assembled *via* a [4+2] cycloaddition[8] of nitroalkene **7** (accessible from isovanillin) to ethyl vinyl ether.

Following Scheme 1, we have earlier[9] succeeded in the stereoselective synthesis of pyrrolizidinone **3**. In the present work, we pioneered in the total stereoselective synthesis of pyrroloimidazolone **1** and pyrrolooxazolone **2**.

The key intermediates in the synthesis of target products **1** and **2** are six-membered cyclic oxime ethers **5a** and **5b**, respectively (Scheme 2). They were obtained in two steps from nitronate **6** described earlier.[9]

For the synthesis of azide **5a**, nitronate **6** was transformed into bromomethyldihydrooxazine **8** according to a known method[7a] using an excess of trimethylsilyl bromide and triethylamine. To replace the Br atom by azido group, compound **8** was treated with NaN_3 in aqueous acetone in the presence of catalytic amounts of NaI.[10]

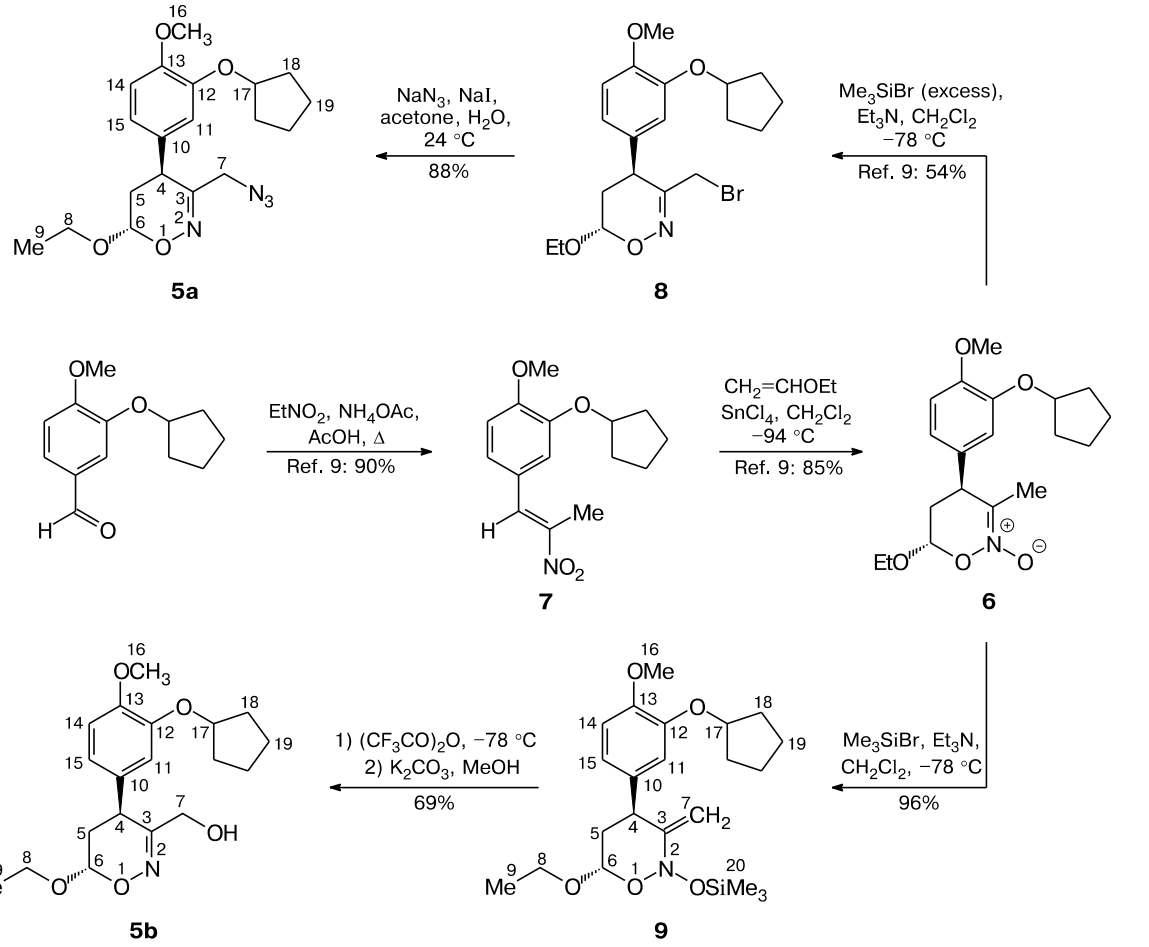
For the synthesis of hydroxymethyldihydrooxazine **5b**, we used our recent procedure for rearrangement of Me_3Si-protected 1,2-oxazines.[11] To do this, nitronate **6** was initially transformed into cyclic compound **9** by monosilylation with trimethylsilyl bromide in the presence of triethylamine.[7b] Treatment of compound **9** with trifluoroacetic anhydride followed by methanolysis of the reaction mixture gave product **5b** in good yield.

For high stereoselectivity to be achieved, reductive transformation[6a] of the dihydrooxazine ring into a pyrrolidine one was carried out in two steps (Scheme 3): successive hydride reduction of the C=N bond and catalytic hydrogenation of the N—O bond.[6a]

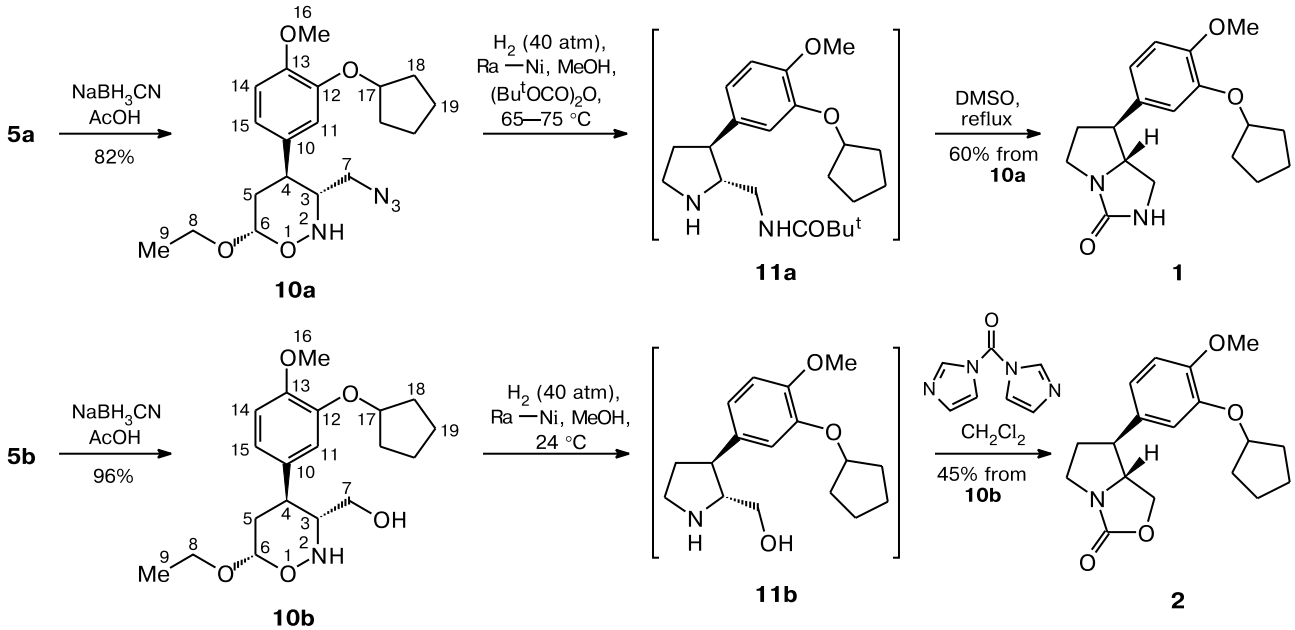
Reduction of dihydrooxazines **5a** and **5b** with sodium cyanoborohydride in acetic acid stereoselectively gave only tetrahydro-2*H*-1,2-oxazines **10a** and **10b**, respectively, with the required 3,4-*trans*-configuration of the substituents in the oxazine ring. Catalytic hydrogenation of compounds **10a** and **10b** on Raney nickel yielded, *via* the 1,2-oxazine→pyrrolidine transformation, products **11a** and **11b**, respectively (see Scheme 3). Oxazine **10a** was hydrogenated in the presence of di-*tert*-butyl dicarbonate (1 equiv.) for protection of the primary amino group in an intermediate resulting from the first-step reduction of the azido group. Pyrrolidine **11a** was transformed without further purification into the target product **1** in boiling DMSO (see Scheme 3). Cyclization of pyrrolidine **11b** into the target product **2** was carried out under the action of 1,1′-carbonyldiimidazole[12] in CH_2Cl_2.

The structures of novel intermediate products **5a**,**b**, **9**, and **10a**,**b** were confirmed by 1D (^1H and ^{13}C) and 2D NMR spectroscopy (COSY and HSQC), high-resolution

Scheme 2



Scheme 3



mass spectrometry, and elemental analysis. The spectroscopic characteristics of the target products **1** and **2** agree well with the literature data.[4]

To sum up, starting from nitroethane and isovanillin, we performed the stereoselective seven-step syntheses of the known PDE IVb inhibitors **1** and **2** in overall 18 and 22% yields, respectively. The previously described schemes for their syntheses are nonstereoselective[4] and inferior in yields: 2% over nine steps for product **1** and 5% over six steps for product **2**.

Experimental

Catalytic hydrogenation was carried out in a steel autoclave (Parr) with external heating and stirring. Column chromatography was carried out on silica gel (Merck Kieselgel 40—60 μm 60A). 1D and 2D NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 MHz). Chemical shifts are referenced to the residual signal of the solvent.[13] High-resolution mass spectra were recorded on a MicroTOFF instrument. Elemental analysis was performed at the analytical laboratory of the N. D. Zelinsky Institute of Organic Chemistry (Russian Academy of Sciences). Melting points were measured on a Kofler hot stage and are given uncorrected.

Acetic acid was recrystallized twice. Dichloromethane, MeCN, Et_3N, ethyl vinyl ether, and Me_3SiBr were distilled over CaH_2; DMSO (Sigma-Aldrich), $SnCl_4$ (Aldrich), $NaBH_3CN$ (Acros), NaN_3 (Aldrich), $(CF_3CO)_2O$ (Aldrich), $(Bu^tOCO)_2O$ (Aldrich), Raney nickel (Acros, 50% suspension in water), and 1,1′-carbonyldiimidazole (Acros) were used as purchased. Nitronate **6**, nitroalkene **7**, and bromooxazine **8** were prepared as described earlier.[9]

(4*S,6*S**)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-6-ethoxy-3-methylidene-2-trimethylsilyloxy-1,2-oxazinane (9).** Triethylamine (0.19 mL, 1.3 mmol) and TMSBr (0.16 mL, 1.2 mmol) were successively added under argon at −78 °C to a stirred solution of oxazine *N*-oxide **6** (0.389 g, 1.11 mmol) in CH_2Cl_2 (2.2 mL). The reaction mixture was kept at −78 °C for 48 h, diluted with hexane (5 mL), and poured into the two-phase system hexane (40 mL)—H_2O (20 mL). The organic layer was washed with a solution of $NaHSO_4$ (0.12 g) in water (20 mL) and with brine (2×20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The resulting labile nitroso acetal **9** (0.449 g, 96%) as a colorless oil was further used without purification. ^{1}H NMR ($CDCl_3$), δ: 0.26 (s, 9 H, $H_3C(20)$); 1.27 (t, 3 H, $H_3C(9)$, J = 7.3 Hz); 1.57—1.67 (m, 2 H) and 1.78—1.97 (m, 6 H) ($H_2C(18)$ and $H_2C(19)$); 2.10 (ddd, 1 H, $H_{eq}C(5)$, J = 13.2 Hz, J = 5.5 Hz, J = 5.5 Hz); 2.23 (ddd, 1 H, $H_{ax}(5)$, J = 13.2 Hz, J = 9.5 Hz, J = 4.4 Hz); 3.59 (dq, 1 H, HC(8), J = 9.5 Hz, J = 7.3 Hz); 3.85 (s, 3 H, $H_3C(16)$); 3.89—4.14 (m, 3 H, HC(4), HC(7), HC(8)); 4.74—4.79 (m, 1 H, HC(17)); 4.95 (br.s, 1 H, HC(7)); 5.10 (t, 1 H, HC(6), J = 4.4 Hz); 6.83 (br.s, 3 H, HC(11), HC(14), HC(15)). ^{13}C NMR ($CDCl_3$), δ: −0.8 (C(20)); 15.0 (C(9)); 24.0 (C(19)); 32.8, 36.6 (C(5), C(18)); 40.5 (br, C(4)); 56.1 (C(16)); 64.1 (C(8)); 80.4 (C(17)); 97.4 (br, C(7)); 99.3 (C(6)); 111.9, 115.9, 120.6 (C(11), C(14), C(15)); 133.0 (br, C(10)); 147.5, 149.0 (C(12), C(13)); 158.4 (br, C(3)).

(4*S,6*S**)-3-Azidomethyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-6-ethoxy-5,6-dihydro-4*H*-1,2-oxazine (5a).** A solution of NaN_3 (0.249 g, 3.8 mmol) and NaI (0.035 g, 0.23 mmol) in water (2.5 mL) was added to a solution of bromooxazine **8** (0.410 g, 1.0 mmol) in acetone (12 mL).[9] The reaction mixture was stirred at room temperature for 24 h and concentrated. The residue was preadsorbed on silica gel (~2 g) and then chromatographed on silica gel with gradient elution in hexane—EtOAc (10 : 1 → 5 : 1). The resulting colorless oil crystallized on cooling, m.p. 38—41 °C. The yield of compound **5a** was 0.330 g (88%), R_f 0.68 (EtOAc—hexane, 1 : 1). Found (%): C, 60.76; H, 7.27; N, 14.86. $C_{19}H_{26}N_4O_4$. Calculated (%): C, 60.95; H, 7.00; N, 14.96. HRMS, *m/z*: 375.2030 $[MH]^+$, calculated for $[MH]^+$: 375.2027. ^{1}H NMR ($CDCl_3$, COSY, HSQC), δ: 1.27 (t, 3 H, $H_3C(9)$, J = 7.0 Hz); 1.57—1.66 (m, 2 H, HC(19)); 1.81—1.97 (m, 6 H, $H_2C(18)$, HC(19)); 2.14 (ddd, 1 H, $H_{ax}C(5)$, J = 13.9 Hz, J = 12.5 Hz, J = 2.2 Hz); 2.31 (ddd, 1 H, $H_{eq}C(5)$, J =13.9 Hz, J = 7.3 Hz, J = 1.8 Hz); 3.48 (d, 1 H, HC(7), J = 13.2 Hz); 3.65 (m, 1 H, HC(8)); 3.7 (dd, 1 H, HC(4), J = 12.5 Hz, J = 7.3 Hz); 3.82 (d, 1 H, HC(7), J = 13.2 Hz); 3.93 (s, 3 H, $H_3C(16)$); 3.91 (m, 1 H, HC(8)); 4.76 (m, 1 H, HC(17)); 5.20 (dd, 1 H, HC(6), J = 2.2 Hz, J = 1.8 Hz); 6.70 (d, 1 H, HC(11), J = 1.5 Hz); 6.75 (dd, 1 H, HC(15), J = 8.1 Hz, J = 1.5 Hz); 6.85 (d, 1 H, HC(14), J = 8.1 Hz). ^{13}C NMR ($CDCl_3$, HSQC), δ: 15.0 (C(9)); 24.0 (C(19)); 32.8 (C(5), C(18)); 34.4 (C(4)); 52.5 (C(7)); 56.1 (C(16)); 63.8 (C(8)); 80.5 (C(17)); 95.9 (C(6)); 112.6, 114.9, 120.5 (C(11), C(14), C(15)); 131.1 (C(10)); 148.2, 149.6 (C(12), C(13)); 157.2 (C(3)).

(4*S,6*S**)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-6-ethoxy-3-hydroxymethyl-5,6-dihydro-4*H*-1,2-oxazine (5b).** Trifluoroacetic anhydride (0.105 mL, 0.74 mmol) was added under argon at −78 °C to a stirred solution of nitroso acetal **9** (0.312 g, 0.74 mmol) in CH_2Cl_2 (3.7 mL). The reaction mixture was stirred at −78 °C for 1 h. Then K_2CO_3 (0.19 g) and MeOH (0.8 mL) were successively added. The reaction mixture was stirred without cooling for 2.5 h and poured into the two-phase system EtOAc (60 mL)—brine (20 mL). The organic layer was washed with brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The product was isolated by column chromatography with gradient elution in hexane—EtOAc (3 : 1 → 1 : 1). The resulting faintly yellow oil solidified upon storage, m.p. 97—99 °C. The yield of the target oxazine **5b** was 0.179 g (69%), R_f 0.39 (EtOAc—hexane, 1 : 1). HRMS, *m/z*: 350.1962 $[MH]^+$, calculated for $[MH]^+$: 350.1962. ^{1}H NMR ($CDCl_3$), δ: 1.26 (t, 3 H, $H_3C(9)$, J = 7.3 Hz); 1.53—1.68 (m, 2 H, HC(19)); 1.73—1.95 (m, 6 H, $H_2C(18)$, HC(19)); 2.11 (ddd, 1 H, $HC_{ax}(5)$, J = 13.9 Hz, J = 12.5 Hz, J = 2.9 Hz); 2.26 (ddd, 1 H, $H_{eq}(5)$, J = 13.9 Hz, J = 7.3 Hz, J = 2.2 Hz); 2.56 (br.s, 1 H, HO); 3.59 (dd, 1 H, HC(4), J = 12.5 Hz, J = 7.3 Hz); 3.66 (dq, 1 H, HC(8), J = 9.5 Hz, J = 7.3 Hz); 3.84 (s, 3 H, $H_3C(16)$); 3.91 (dq, 1 H, HC(8), J = 9.5 Hz, J = 7.3 Hz); 3.98 (s, 2 H, HC(7)); 4.76 (m, 1 H, HC(17)); 5.20 (br.s, 1 H, HC(6)); 6.68 (d, 1 H, HC(11), J = 1.9 Hz); 6.73 (dd, 1 H, HC(15), J = 8.1 Hz, J = 1.9 Hz); 6.83 (d, 1 H, HC(14), J = 8.1 Hz). ^{13}C NMR ($CDCl_3$), δ: 15.0 (C(9)); 24.0 (C(19)); 32.6, 32.7 (C(5), C(18)); 34.2 (C(4)); 56.1 (C(16)); 62.6, 63.9 (C(7), C(8)); 80.5 (C(17)); 96.1 (C(6)); 112.4, 114.8, 120.6 (C(11), C(14), C(15)); 131.0 (C(10)); 148.1, 149.6 (C(12), C(13)); 159.0 (C(3)).

(3*R,4*S**,6*S**)-3-Azidomethyl-4-(3-cyclopentyloxy-4-methoxyphenyl)-6-ethoxy-1,2-oxazinane (10a).** Sodium cyanoborohydride (0.127 g, 2.05 mmol) was added to a stirred solution of azidomethyloxazine **5a** (0.250 g, 0.67 mmol) in acetic acid (3 mL). The reaction mixture was vigorously stirred at room

temperature for 1 h and poured into the system EtOAc (150 mL)—K_2CO_3 (150 mL). The aqueous layer was washed with EtOAc (50 mL). The combined organic layer was successively washed with a saturated aqueous solution of K_2CO_3 (70 mL), water (100 mL), and brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was preadsorbed on silica gel (~2 g) and then chromatographed on silica gel with gradient elution in hexane—EtOAc (10 : 1 → 5 : 1 → 3 : 1). The yield of compound **10a** was 0.207 g (82%), colorless oil, R_f 0.71 (EtOAc—hexane, 1 : 1). Found (%): C, 60.74; H, 7.56; N, 14.18. $C_{19}H_{28}N_4O_4$. Calculated (%): C, 60.62; H, 7.50; N, 14.88. HRMS, *m/z*: 377.2169 $[MH]^+$, calculated for $[MH]^+$: 377.2183. ^{1}H NMR ($CDCl_3$, COSY, HSQC), δ: 1.30 (t, 3 H, $H_3C(9)$, J = 7.0 Hz); 1.55—1.67 (s, 2 H, HC(19)); 1.78—1.97 (m, 6 H, $H_2C(18)$, HC(19)); 1.94 (ddd, 1 H, $H_{eq}C(5)$, J = 13.2 Hz, J = 5.9 Hz, J = 1.4 Hz); 2.04 (ddd, 1 H, $H_{ax}C(5)$, J = 13.2 Hz, J = 10.3 Hz, J = 2.9 Hz); 3.02 (ddd, 1 H, $H_{ax}C(4)$, J = 11.0 Hz, J = 10.3 Hz, J = 5.9 Hz); 3.16 (dd, 1 H, HC(7), J = 12.5 Hz, J = 5.1 Hz); 3.27 (ddd, 1 H, $H_{ax}C(3)$, J = 11.0 Hz, J = 5.1 Hz, J = 2.2 Hz); 3.33 (dd, 1 H, HC(7), J = 12.5 Hz, J = 2.2 Hz); 3.58 (dq, 1 H, HC(8), J = 9.5 Hz, J = 7.3 Hz); 3.83 (s, 3 H, $H_3C(16)$); 3.85 (dq, 1 H, HC(8), J = 9.5 Hz, J = 7.3 Hz); 4.75 (m, 1 H, HC(17)); 4.89 (dd, 1 H, HC(6), J = 2.9 Hz, J = 1.4 Hz); 5.39 (br.s, 1 H, HN(2)); 6.69—6.75 (m, 2 H, HC(11), HC(15)); 6.83 (d, 1 H, HC(14), J = 8.1 Hz). ^{13}C NMR ($CDCl_3$, HSQC), δ: 15.2 (C(9)); 24.0 (C(19)); 32.8 (C(18)); 36.3 (C(5)); 37.3 (C(4)); 51.0 (C(7)); 56.1 (C(16)); 61.5 (C(3)); 63.6 (C(8)); 80.4 (C(17)); 98.0 (C(6)); 112.5, 114.5, 119.3 (C(11), C(14), C(15)); 133.7 (C(10)); 147.9, 149.1 (C(12), C(13)).

(3*R,4*S**,6*S**)-4-(3-Cyclopentyloxy-4-methoxyphenyl)-6-ethoxy-3-hydroxymethyl-1,2-oxazinane (10b).** Sodium cyanoborohydride (0.109 g, 1.73 mmol) was added under argon to a stirred solution of oxazine **5b** (0.170 g, 0.49 mmol) in acetic acid (3.1 mL). The reaction mixture was stirred at room temperature for 80 min and poured into the two-phase system EtOAc (60 mL)—saturated aqueous Na_2CO_3 (30 mL). The aqueous layer was washed with EtOAc (2×20 mL). The combined organic layer was washed with saturated aqueous Na_2CO_3 (20 mL), water (20 mL), and brine (2×20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The product was isolated by column chromatography with gradient elution from $CHCl_3$ to $CHCl_3$—MeOH (20 : 1). The yield of the target tetrahydrooxazine **10b** was 0.165 g (96%), faintly yellow oil. For analytical purposes, the product was recrystallized from hexane—EtOAc (2 : 1), m.p. 87—89 °C, R_f 0.49 ($CHCl_3$—MeOH, 10 : 1). Found (%): C, 64.59; H, 8.37; N, 3.99. $C_{19}H_{29}NO_5$. Calculated (%): C, 64.93; H, 8.32; N, 3.99. ^{1}H NMR ($CDCl_3$), δ: 1.30 (t, 3 H, $H_3C(9)$, J = 7.0 Hz); 1.52—1.67 (m, 2 H, HC(19)); 1.72—2.12 (m, 8 H, $H_2C(18)$, $H_2C(19)$, $H_2C(5)$); 2.95 (ddd, 1 H, $H_{ax}C(4)$, J = 11.3 Hz, J = 11.3 Hz, J = 4.4 Hz); 3.21—3.35 (m, 2 H) and 3.45—3.55 (m, 1 H) (HC(3) and HC(7)); 3.58 (dq, 1 H, HC(8), J = 9.5 Hz, J = 7.0 Hz); 3.81 (s, 3 H, $H_3C(16)$); 3.85 (dq, 1 H, HC(8), J = 9.5 Hz, J = 7.0 Hz); 4.76 (m, 1 H, HC(17)); 4.90 (br.s, 1 H, HC(6)); 6.68—6.75 (m, 2 H) and 6.81 (d, 1 H, J = 8.8 Hz) (HC(11), HC(14), HC(15)). ^{13}C NMR ($CDCl_3$), δ: 15.2 (C(9)); 24.0 (C(19)); 32.8, 36.5, 37.0 (C(4), C(5), C(18)); 56.2 (C(16)); 61.5, 63.7, 77.3 (C(3), C(7), C(8)); 80.5 (C(17)); 98.3 (C(6)); 112.5, 114.6, 119.4 (C(11), C(14), C(15)); 134.2 (C(10)); 147.8, 149.1 (C(12), C(13)).

(7*S,7a*R**)-7-(3-Cyclopentyloxy-4-methoxyphenyl)hexahydro-3*H*-pyrrolo[1,2-*c*]imidazol-3-one (1).** Raney nickel as a 50% suspension in water (~0.2 mL) was washed with MeOH (4×2 mL) and added in MeOH (0.5 mL) to a solution of oxazine **10a** (0.058 g, 0.154 mmol) and di-*tert*-butyl dicarbonate (0.033 mL, 0.154 mmol) in MeOH (2.0 mL). The mixture was hydrogenated in an autoclave (65—75 °C, H_2, p = 40 atm) for 4.5 h, filtered through a short pad of Celite to remove the catalyst, and concentrated *in vacuo*. The residue was dissolved in DMSO (3.0 mL). The resulting solution was gently refluxed under argon for 30 min. Then the solvent was removed *in vacuo* (100 °C, 1 Torr) and the residue was chromatographed on silica gel with gradient elution from hexane—EtOAc (10 : 1 → 5 : 1 → 3 : 1 → 1 : 1) to EtOAc. The resulting oily product was recrystallized from Et_2O. The yield of the target compound **1** was 0.029 g (60%), m.p. 139—141 °C (*cf.* Ref. 4: m.p. 118—120 °C), R_f 0.54 (EtOAc—MeOH, 3 : 1). Found (%): C, 68.39; H, 7.73; N, 8.67. $C_{18}H_{24}N_2O_3$. Calculated (%): C, 68.33; H, 7.65; N, 8.85. HRMS, *m/z*: 317.1866 $[MH]^+$, calculated for $[MH]^+$: 317.1860. ^{1}H NMR ($CDCl_3$), δ: 1.56—1.71 (m, 2 H, HC(19)); 1.79—1.94 (m, 6 H, $H_2C(18)$, HC(19)); 2.05 (dddd, 1 H, HC(4), J = 12.8 Hz, J = 11.9 Hz, J = 10.1 Hz, J = 9.2 Hz); 2.38 (dddd, 1 H, HC(4), J = 12.8 Hz, J = 10.1 Hz, J = 8.2 Hz, J = 4.6 Hz); 2.74 (ddd, 1 H, HC(3), J = 11.0 Hz, J = 10.1 Hz, J = 9.2 Hz); 3.33 (dd, 1 H, HC(1); J = 9.9 Hz, J = 9.9 Hz); 3.51 (dd, 1 H, HC(1), J = 9.9 Hz, J = 7.7 Hz); 3.26—3.31 (m, 1 H) and 3.64—3.75 (m, 2 H) (HC(2), $H_2C(5)$); 3.82 (s, 3 H, $H_3C(16)$); 4.76 (m, 1 H, HC(17)); 5.55 (br.s, 1 H, HN(8)); 6.72 (s, 1 H, HC(11)), 6.73 (d, 1 H, J = 7.3 Hz) and 6.83 (d, 1 H, J = 7.3 Hz) (HC(14), HC(15)). ^{13}C NMR ($CDCl_3$, JMOD), δ: 24.0, 32.7, 34.4, 41.3, 45.2 (C(1), C(4), C(5), C(18), C(19)); 48.5, 56.2, 66.1 (C(2), C(3), C(16)); 80.6 (C(17)), 112.4, 114.7, 119.6 (C(11), C(14), C(15)); 131.7 (C(10)); 147.9, 149.3 (C(12), C(13)); 165.8 (C(7)). The spectroscopic characteristics are in full agreement with the literature data[4] for compound **1**.

(7*S,7a*R**)-7-(3-Cyclopentyloxy-4-methoxyphenyl)tetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (2).** Raney nickel as a 50% suspension in water (~1 mL) was washed with MeOH (4×2 mL) and added, under a layer of MeOH (1.5 mL), to a solution of tetrahydrooxazine **10b** (0.15 g, 0.43 mmol) in MeOH (2.5 mL). The mixture was hydrogenated in a steel autoclave (24 °C, H_2, p = 40 atm) for 6 h and filtered through a short pad of Celite. The Celite filter was washed with MeOH (50 mL). The filtrate was concentrated *in vacuo*. The residue (0.104 g) was dissolved in CH_2Cl_2 (3.0 mL) and 1,1′-carbonyldiimidazole (0.063 g, 0.39 mmol) was added with stirring under argon. The reaction mixture was kept for 72 h and poured into the two-phase system EtOAc (50 mL)—0.07 *M* aqueous HCl (20 mL). The organic layer was washed with brine (2×15 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The product was isolated by column chromatography with gradient elution in hexane—EtOAc (2 : 1 → 1 : 1). The yield of the target compound **2** was 0.061 g (45%), colorless oil. For analytical purposes, the product was recrystallized from hexane—EtOAc (2 : 1), m.p. 99—101 °C (*cf.* Ref. 4: m.p. 97—98 °C), R_f 0.37 (hexane—EtOAc, 1 : 1). HRMS, *m/z*: 340.1517 $[MNa]^+$, calculated for $[MNa]^+$: 340.1519. ^{1}H NMR ($CDCl_3$, COSY), δ: 1.55—1.72 (m, 2 H) and 1.79—1.98 (m, 6 H) ($H_2C(18)$, $H_2C(19)$); 2.15 (dddd, 1 H, HC(4), J = 12.7 Hz, J = 11.7 Hz, J = 9.5 Hz, J = 8.8 Hz); 2.49 (dddd, 1 H, HC(4), J = 12.7 Hz, J = 10.3 Hz, J = 8.1 Hz, J = 2.2 Hz); 2.79 (ddd, 1 H, HC(3), J = 10.3 Hz, J = 9.5 Hz, J = 7.3 Hz); 3.48 (ddd, 1 H, HC(5), J = 11.0 Hz, J = 9.5 Hz, J = 2.2 Hz); 3.74 (ddd, 1 H, HC(5), J = 11.0 Hz, J = 8.8 Hz, J = 8.1 Hz); 3.82—3.88 (m, 1 H,

HC(2)); 3.84 (s, 3 H, H_3C(16)); 4.22 (dd, 1 H, HC(1), J = 9.5 Hz, J = 2.9 Hz); 4.43 (dd, 1 H, HC(1), J = 9.5 Hz, J = 8.1 Hz); 4.73—4.81 (m, 1 H, HC(17)); 6.70—6.77 (m, 2 H) and 6.85 (d, 1 H, J = 8.1 Hz) (HC(11), HC(14), HC(15)). ^{13}C NMR ($CDCl_3$, HSQC), δ: 24.0 (C(19)); 32.8 (C(18)); 34.5 (C(4)); 45.8 (C(5)); 49.2 (C(3)); 56.2 (C(16)); 65.8 (C(2)); 66.2 (C(1)); 80.7 (C(17)); 112.5, 114.5, 119.4 (C(11), C(14), C(15)); 130.4 (C(10)); 148.1, 149.7 (C(12), C(13)); 161.7 (C(7)). The spectroscopic characteristics are in full agreement with the literature data[4] for compound **2**.

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