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Synthesis of PDE IV inhibitors.† First asymmetric synthesis of two of GlaxoSmithKline's highly potent Rolipram analogues‡

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Asymmetric syntheses of two of GlaxoSmithKline's highly potent phosphodiesterase IV inhibitors CMPI **1** and CMPO **2** have been accomplished from nitroethane and simple precursors in 8 and 7 steps, respectively. The suggested synthetic strategy involves as a key stage the silylation of enantiopure six-membered cyclic nitronates. *In vitro* studies of PDE IVB1 inhibition revealed a significant difference in the activity of CMPI **1** and CMPO **2** enantiomers.

Introduction

Inhibitors of type IV phosphodiesterase (PDE), an enzyme that hydrolyzes cyclic adenosine monophosphate in cells, are considered a novel class of highly potent drugs for the complex therapy of asthma and chronic obstructive lung disease (COPD).[2] A prototype of these drugs is the natural alkaloid theophylline, which has been used to treat respiratory diseases since the middle of the XXth century.[2g,3] However, theophylline has a low therapeutic effect because of the weak and non-selective inhibition of the PDE IV enzyme (IC_{50} > 10 000 nM).[2b,3c] In the last two decades selective second generation PDE IV inhibitors active at micro- and nanomolar concentrations have been developed.[2] A gold standard in PDE IV inhibition research is the well-known pyrrolidinone Rolipram[2b,4] (Fig. 1), which, however, did not pass clinical trials due to adverse effects. In 2010–2011 the first oral PDE IV inhibitor Roflumilast (Daxas®)[2,5a,b] was approved by the FDA and European Medicines Agency for clinical use in the USA and European Union countries. At present, several other catechol-based PDE IV inhibitors (Apremilast,[5c] Tetomilast[5d] and others) are at different stages of clinical and pre-clinical development.[5e]

Bicyclic pyrrolidine derivatives CMPI **1** (7-[3-(cyclopentyloxy)-4-methoxyphenyl]hexahydro-3*H*-pyrrolo[1,2-c]imidazol-3-one, Fig. 1) and CMPO **2** (7-(3-(cyclopentyloxy)-4-methoxyphenyl)tetrahydropyrrolo[1,2-c]oxazol-3(1*H*)-one, Fig. 1) were introduced by GlaxoSmithKline as prospective PDE type IVB inhibitors.[6] CMPI **1** and CMPO **2** are considerably more potent than Rolipram (IC_{50} = 175 nM) and Cilomilast[5f] (IC_{50} = 92 nM).[7] At the same time biological studies of CMPI **1** and CMPO **2** were conducted for racemates due to the absence of an approach to the asymmetric synthesis of their enantiomers.[6a] It is likely that as in the case of Rolipram[8] the binding activity of enantiomers is different and one of them could be a more potent PDE IV inhibitor than another. In the present work, the problem of the asymmetric synthesis of CMPI **1** and

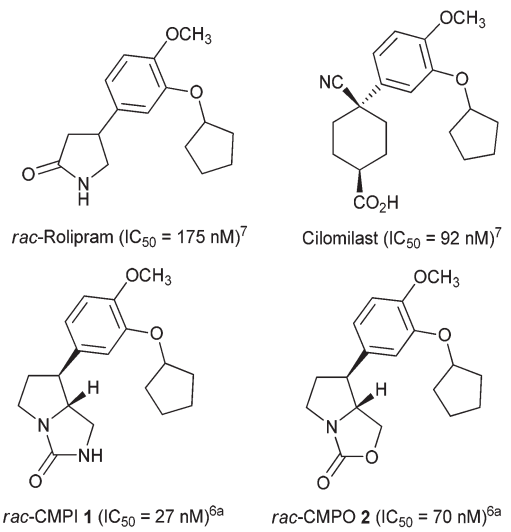

Fig. 1 PDE IV inhibitors.

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‡Electronic supplementary information (ESI) available: Copies of FTIR, NMR ^{1}H, ^{13}C, COSY, HSQC, NOESY spectra of new compounds, details of *in vitro* assay and molecular docking. See DOI: 10.1039/c3ob41646a

CMPO **2** was solved and the PDE IV inhibitory activity of their enantiomers was studied.

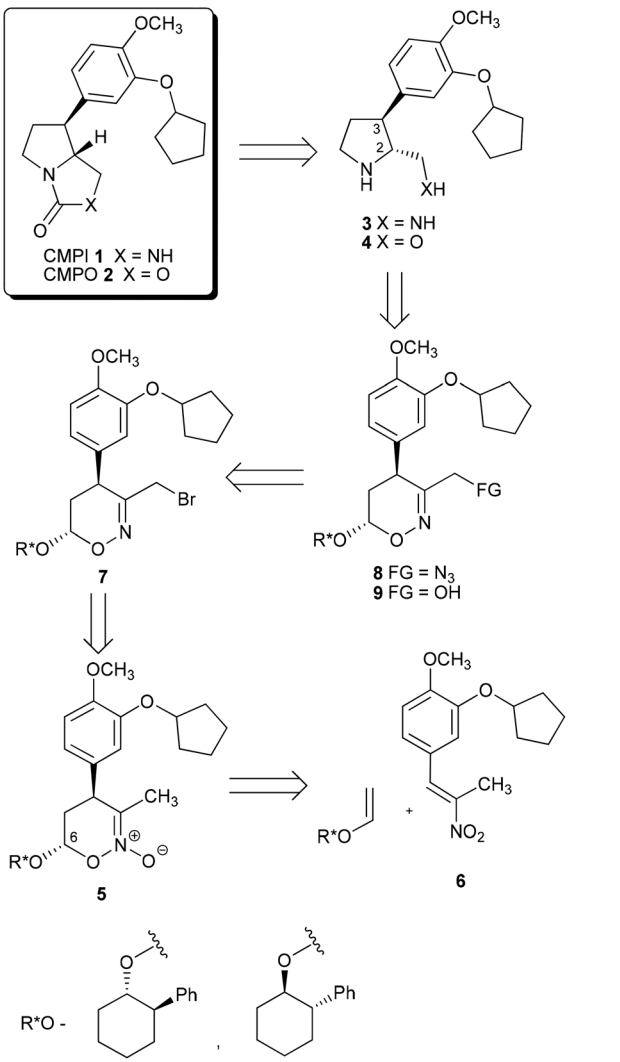
Results and discussion

Synthesis

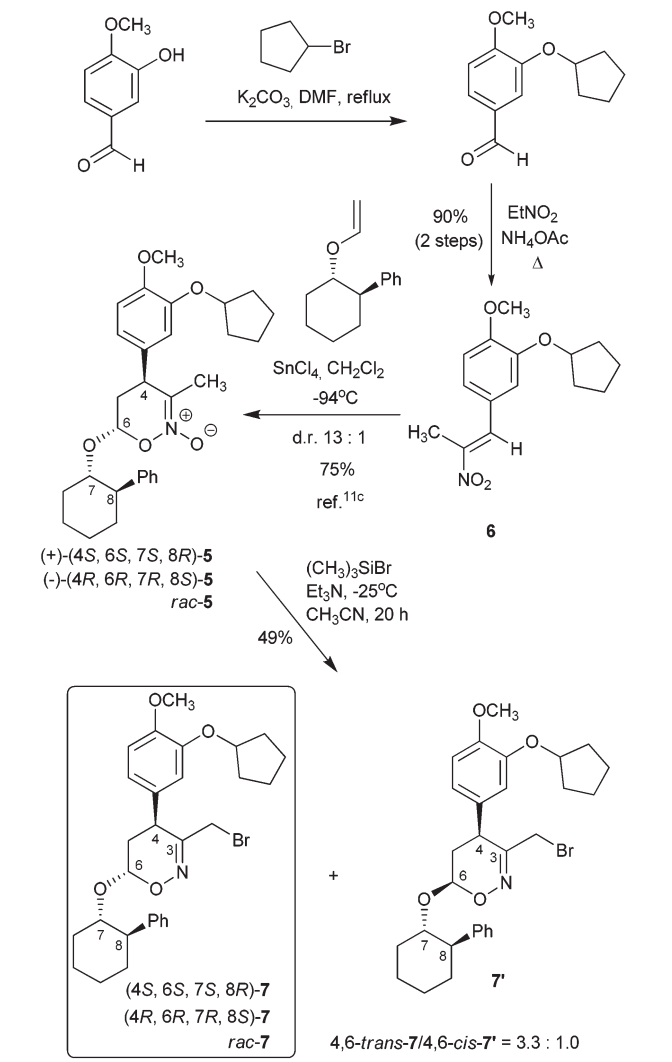
Evidently, the target enantiomerically pure products CMPI **1** and CMPO **2** could be formed in a single step from pyrrolidines **3** and **4**, respectively (Scheme 1). Generally, stereoselective synthesis of 2,3-disubstituted pyrrolidines represents a non-trivial task.[9] Recently, we developed an access to *trans*-2,3-disubstituted pyrrolidines bearing a $-CH_2FG$ fragment at position C-2 from available six-membered cyclic nitronates.[10] The key strategic operation in this synthesis is the silylation of cyclic nitronates leading to the activation of the methyl group at C-3.[10] This strategy was successfully employed in stereoselective synthesis of racemic PDE IV inhibitors CMPI **1** and CMPO **2**,[11a] as well as racemic[11b] and asymmetric[11c] synthesis of another analogue of Rolipram.

According to the suggested approach (Scheme 1) a general precursor of CMPI **1** and CMPO **2** is an optically pure nitronate **5** bearing a chiral alkoxyl group R* at atom C-6. Stereoselective asymmetric synthesis of nitronates **5** by [4 + 2] cycloaddition of nitrolkene **6** to optically pure vinyl ethers of (+)- or (−)-*trans*-2-phenylcyclohexanols (Denmark's approach[12]) was recently reported by us.[11c] Silylation of nitronate **5** to give bromide **7**[11c] followed by nucleophilic substitution of bromine for the azido or hydroxyl group could furnish the respective functionalized 5,6-dihydro-4*H*-1,2-oxazines **8** and **9**. The reduction of products **8** and **9** involving reductive cleavage of the N–O bond and recyclization should lead to the necessary optically pure pyrrolidines **3** and **4**, respectively. The latter can be transformed into target products CMPI **1** and CMPO **2** by trivial procedures.

To realize this strategy diastereomerically and enantiomerically pure cyclic nitronates (+)-(4*S*,6*S*,7*S*,8*R*)-**5** and (−)-(4*R*,6*R*,7*R*,8*S*)-**5** (d.e. >99%, Scheme 2) were synthesized according to a previously reported procedure from



Scheme 1 Retrosynthetic analysis of CMPI **1** and CMPO **2** molecules.



Scheme 2 Synthesis of 3-bromomethyl-substituted 1,2-oxazines **7**.

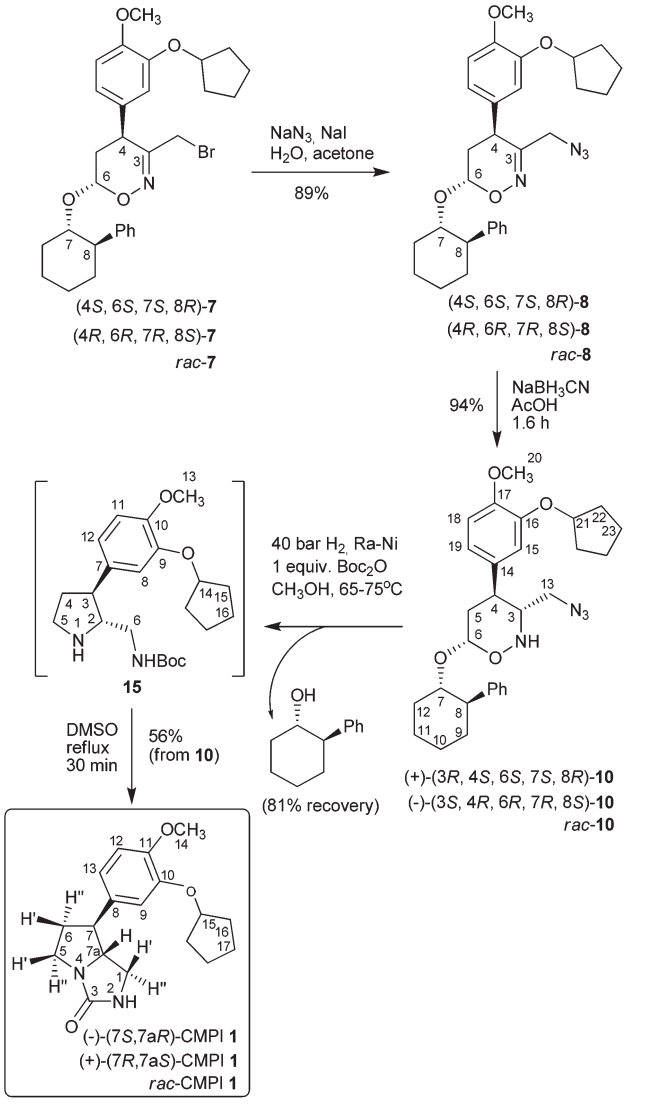
commercially available nitroethane, isovanillin, cyclopentyl bromide and (+)- or (−)-*trans*-2-phenylcyclohexanols (>98% ee).[11c] Silylation of nitronates **5** upon treatment with excess of trimethylsilyl bromide and triethylamine in dichloromethane furnished the corresponding 3-bromomethyl-substituted dihydrooxazines **7** accompanied by epimeric 4,6-*cis*-bromides **7′** as by-products. Diastereomerically pure bromides (4*S*,6*S*,7*S*,8*R*)-**7** and (4*R*,6*R*,7*R*,8*S*)-**7** were isolated from the reaction mixture by column chromatography. In an analogous fashion racemic bromide *rac*-**7** was synthesized from racemic *trans*-2-phenylcyclohexanol (Scheme 2).

Nucleophilic substitution of bromine in enantiomeric (4*S*,6*S*,7*S*,8*R*)-**7** and (4*R*,6*R*,7*R*,8*S*)-**7** for the azido group was accomplished by the reaction with sodium azide in the presence of a catalytic amount (20 mol%) of sodium iodide in aqueous acetone (Scheme 3).[13] Corresponding 3-azidomethyl substituted 5,6-dihydro-4*H*-1,2-oxazines (4*S*,6*S*,7*S*,8*R*)-**8** and (4*R*,6*R*,7*R*,8*S*)-**8** were isolated in high yields. Installation of the last stereocenter was achieved by stereoselective reduction of the oxime group upon action of sodium cyanoborohydride in acetic acid.[14] The resulting tetrahydrooxazines (+)-(3*R*,4*S*,6*S*,7*S*,8*R*)-**10** and (−)-(3*S*,4*R*,6*R*,7*R*,8*S*)-**10** were obtained as individual stereoisomers possessing the required 3,4-*trans*-configuration of stereocenters in the 1,2-oxazine ring (coupling constant $^3J_{H3-H4}$ = 11.0 Hz).

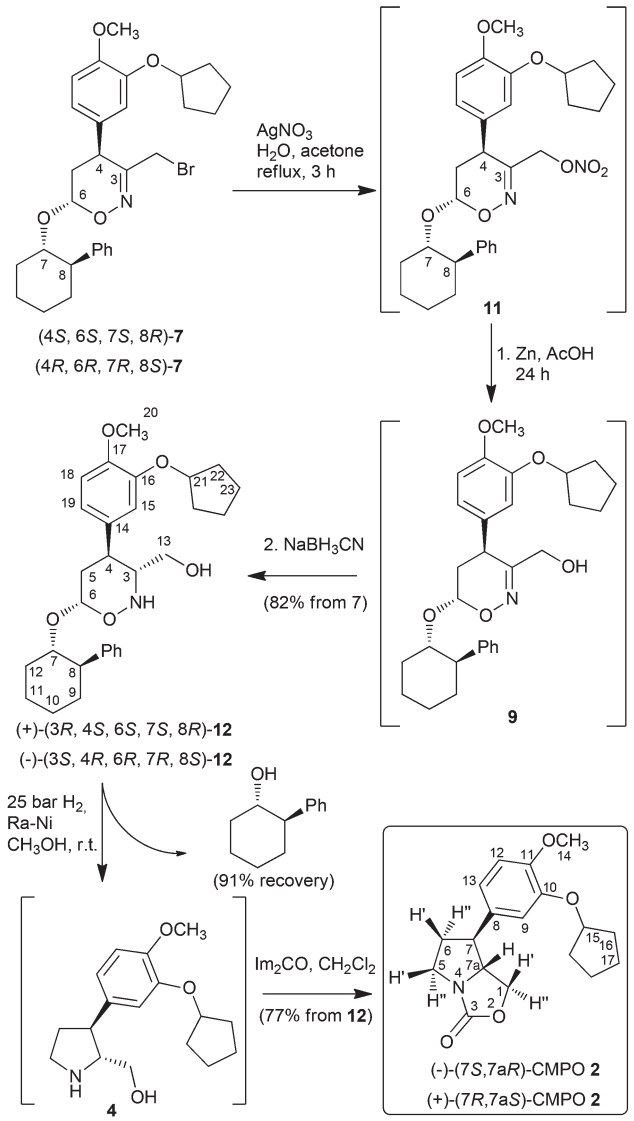
The synthesis of 3-hydroxymethyl-substituted 1,2-oxazines **9** (precursors of CMPO **2** enantiomers) proved to be a more challenging task. Thus, direct substitution of bromine for the hydroxyl group in bromooxazines **7** by hydrolysis with NaOH or Ag_2O in aqueous THF at ambient temperature or reflux conditions failed to provide the desired product. No conversion of the starting material was observed in these experiments. However, refluxing of oxazines **7** in aqueous acetone with an excess of $AgNO_3$ [15] resulted in the substitution of bromine for a nitrate anion.[16] The resulting nitrates **11** were identified in the reaction mixture (^{1}H NMR, HRMS data) and due to their instability were used in the next stage without special purification (Scheme 4). Reduction of nitrates **11** with zinc in acetic acid allowed a smooth transformation of the $-ONO_2$ fragment to the hydroxyl group.[17] Subsequent addition of sodium cyanoborohydride to the reaction mixture leads to selective C=N bond reduction. As a result of these operations tetrahydrooxazines (+)-(3*R*,4*S*,6*S*,7*S*,8*R*)-**12** and (−)-(3*S*,4*R*,6*R*,7*R*,8*S*)-**12** were obtained in 82% from bromooxazines (4*S*,6*S*,7*S*,8*R*)-**7** and (4*R*,6*R*,7*R*,8*S*)-**7**, respectively. Like products **10** tetrahydrooxazines **12** are formed exclusively as 3,4-*trans*-isomers ($^3J_{H3-H4}$ = 10.9 Hz).

The final step in both syntheses of target PDE IV inhibitors CMPI **1** and CMPO **2** was the reduction of the 1,2-oxazine cycle in intermediates **10** and **12** to form a pyrrolidine ring (see Scheme 3 for CMPI **1** synthesis and Scheme 4 for CMPO **2** synthesis). This multi-step domino process is realized under catalytic hydrogenation conditions, and its result depends on the nature of the substituent at the C-3 atom of the 1,2-oxazine ring.[10,14a–d] Thus, the reduction of tetrahydrooxazine **10** bearing an azidomethyl group at atom C-3 may proceed ambiguously (Scheme 5). In this process the generation of diaminoaldehyde **A** by a consequent reduction of the azido group and N–O bond can be expected (Scheme 5).[18] Intramolecular reductive amination of intermediate **A** may follow two pathways, leading to either the necessary pyrrolidine **3** or isomeric piperidine **13** (Scheme 5).

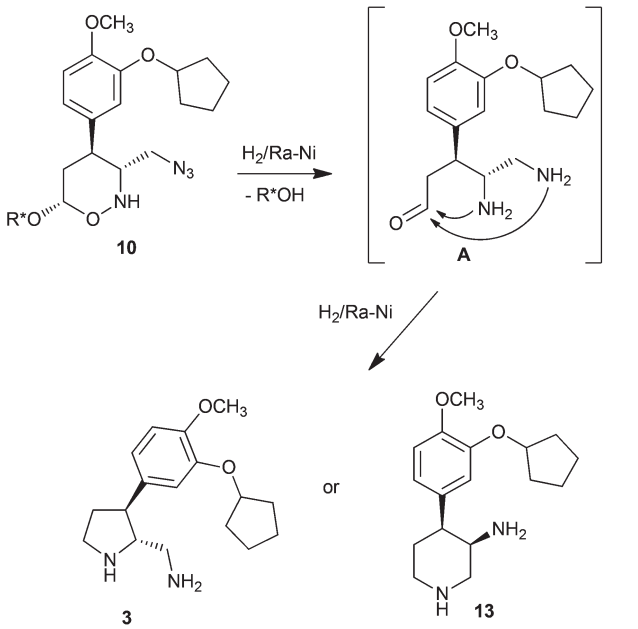
To prevent the formation of piperidine cycle protection of the amino group resulting from the azido group reduction is required. Thus, conducting hydrogenation of tetrahydrooxazine **10** in the presence of one equivalent of di(*tert*-butyl) dicarbonate (Boc_2O) at ambient temperature and a hydrogen pressure of 40 bar resulted in selective reduction of the azido group, leaving the N–O bond intact (Scheme 6).[19] The resulting 1,2-oxazine **14** possessing a Boc-protected primary amino group was characterized in the reaction mixture.[20] Increasing the temperature of hydrogenation led to the cleavage of the 1,2-oxazine cycle affording pyrrolidine **15** and *trans*-2-phenylcyclohexanol (^{1}H NMR and HRMS data). The plausible



Scheme 3 Synthesis of CMPI **1** enantiomers.



Scheme 4 Synthesis of CMPO **2** enantiomers.



Scheme 5 Two possible pathways of tetrahydrooxazine **10** reduction.

mechanism of pyrrolidine **15** formation involves the hydrogenolysis of the N–O bond in **14** generating hemiacetal **B**, elimination of *trans*-2-phenylcyclohexanol to give aldehyde **C**, its cyclization to pyrrolidine **D**, elimination of water forming pyrroline **E** and reduction of the latter (Scheme 6).[21] Pyrrolidine **15** is the final product of the hydrogenation and it is not transformed into pyrroloimidazolone CMPI **1** under reaction conditions. The cyclization of crude pyrrolidine **15** into the target product CMPI **1** could be accomplished only upon reflux in DMSO (see the bottom part of Scheme 3).[11a]

Employing this procedure, product (−)-(7*S*,7a*R*)-CMPI **1** was obtained from (+)-(3*R*,4*S*,6*S*,7*S*,8*R*)-**10**, and its enantiomer (+)-(7*R*,7a*S*)-CMPI **1** was prepared from (−)-(3*S*,4*R*,6*R*,7*R*,8*S*)-**10** in 56% average yield (Scheme 3). It should be noted that enantiopure (+)- and (−)-*trans*-2-phenylcyclohexanols were recovered after hydrogenation in 81% average yield.

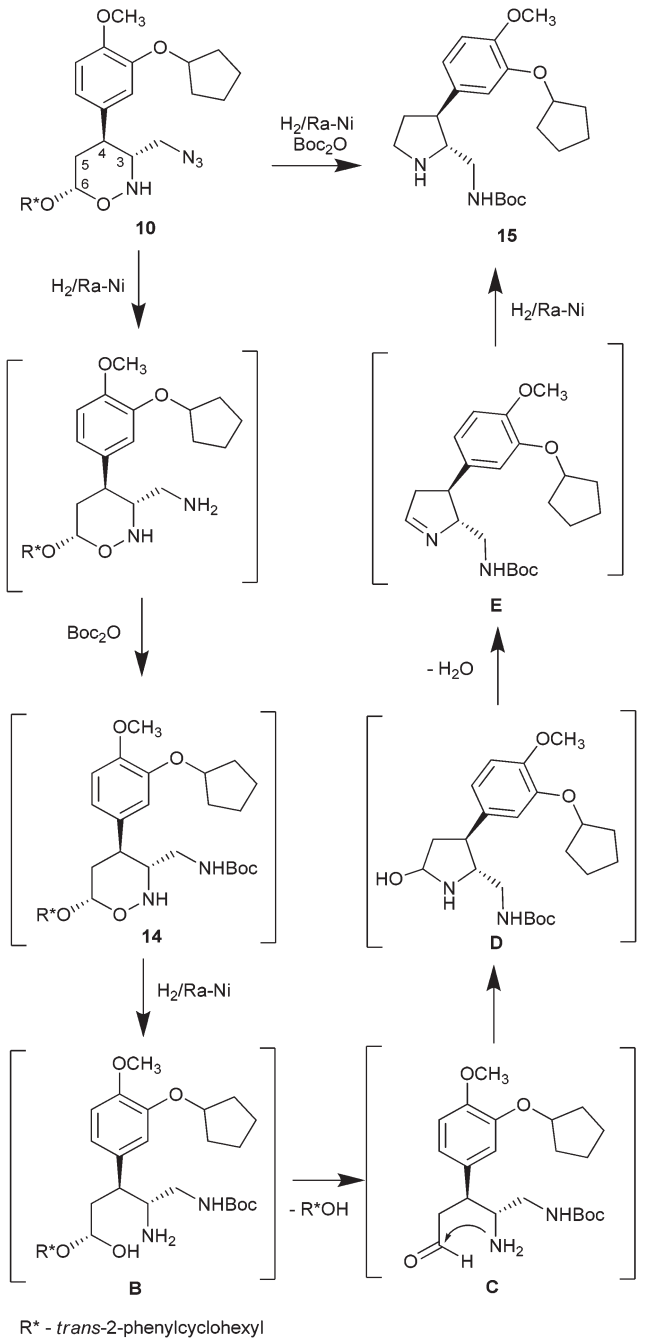
Catalytic hydrogenation of tetrahydrooxazines (+)-(3*R*,4*S*,6*S*,7*S*,8*R*)-**12** and (−)-(3*S*,4*R*,6*R*,7*R*,8*S*)-**12** proceeds smoothly in the presence of RANEY® nickel leading to enantiomerically pure prolinols **4** (see the bottom part of Scheme 4). The initial *trans*-2-phenylcyclohexanols were recovered at this stage in 91% yield. Crude prolinols **4** without purification were transformed into target CMPO **2** enantiomers upon treatment with Im_2CO in dichloromethane.[22] As a result, (−)-(7*S*,7a*R*)-CMPO **2** was obtained from tetrahydrooxazine (+)-(3*R*,4*S*,6*S*,7*S*,8*R*)-**12**, and (+)-(7*R*,7a*S*)-CMPO **2** was obtained from (−)-(3*S*,4*R*,6*R*,7*R*,8*S*)-**12** in 77% yield.

NMR data of enantiomerically pure products CMPI **1** and CMPO **2** are in agreement with literature data for corresponding racemates. Optical rotation angles in pairs (−)-CMPI-**1**/(+)-CMPI-**1** and (+)-CMPO-**2**/(−)-CMPO-**2** are close to the absolute value and have opposite signs. The structure of previously unknown products (+)-**8**, (−)-**8**, *rac*-**8**, (+)-**10**, (−)-**10**, *rac*-**10**, (+)-**12** and (−)-**12** was confirmed by NMR (^1H, ^{13}C, COSY, HSQC and NOESY), high-resolution mass spectrometry, FTIR-spectroscopy and elemental analysis.

In vitro and molecular docking studies

The obtained enantiomers (−)-CMPI-**1**/(+)-CMPI-**1** and (+)-CMPO-**2**/(−)-CMPO-**2** were tested for their ability to inhibit FAM-cAMP hydrolysis catalyzed by recombinant human PDE IVB1 using standard *in vitro* enzymatic assay. The results are summarized in Table 1 (column 2).

As can be seen from the data in Table 1 (−)-(7*S*,7a*R*)-CMPI **1** is ten times more potent than its enantiomer (+)-(7*R*,7a*S*)-CMPI **1**. For CMPO **2** the (−)-enantiomer is also more potent than the (+)-enantiomer, although the difference is smaller compared to CMPI **1**. Interestingly, IC_{50} values for (+)-(7*R*,7a*S*)-CMPI **1** and (+)-(7*R*,7a*S*)-CMPO **2** are essentially the same



Scheme 6 Plausible mechanism of hydrogenation of tetrahydrooxazine **10** to pyrrolidine **15**.

(within the accuracy of the experiment), indicating that the nature of heteroatom in position 2 does not influence the inhibition activity.

To reveal the nature of the difference in PDE IVB inhibitory activity of these enantiomers molecular docking studies were performed using the AutoDock Vina[23] software. 3KKT[24] structures were selected taking into account the quality of the structure and the similarity of the co-crystallized compounds with studied ones.[25] The predicted affinities of CMPI **1** and CMPO **2** enantiomers to PDE IVB are very similar despite the differences in the experimentally detected IC_{50} (Table 1, column 3). An accurate prediction of the ligand's affinity to the studied protein is a very complicated task, and most of the docking software is not well suited for it.[26]

Table 1 PDEIVB1 inhibition data and predicted affinities for enantiomers and racemates of CMPI-**1** and CMPO-**2**

Compound	IC_{50} (nM)	Affinity (kcal mol^{-1}) (AutoDock Vina)
(−)-(7*S*,7a*R*)-CMPI **1**	15	−10.2
(+)-(7*R*,7a*S*)-CMPI **1**	150	−10.5
rac-CMPI **1**	27[a]	—
(−)-(7*S*,7a*R*)-CMPO **2**	35	−10.5
(+)-(7*R*,7a*S*)-CMPO **2**	150	−10.4
rac-CMPO **2**[11a]	70, 75[a]	—

[a] Data from ref. 6*a*.

On the other hand, qualitative analysis of interactions of the ligands with the protein reveals some differences in their binding which may influence the inhibition activity (Fig. 2). All of the compounds share identical lipophilic interactions with pockets formed by Phe414, Phe446, Phe506, Met411, Met503, Ile410 and partly by Tyr233 and Thr407. The main difference is the interactions with Zn^{2+} ions and with amino acids that bind Mg^{2+} and Zn^{2+} ions: His234, His238, His278, Asp275 and Asp392. Thus, (−)-(7*S*,7a*R*)-CMPI **1** and (−)-(7*S*,7a*R*)-CMPO **2** form strong interactions with Zn^{2+}, that does not occur for (+)-enantiomers (Fig. 2). The NH-group of the (−)-(7*S*,7a*R*)-CMPI **1** also forms hydrogen bonds with Asp392 and, probably, His234 (Fig. 2). This may explain the higher activity of (−)-(7*S*,7a*R*)-CMPI **1** compared to (−)-(7*S*,7a*R*)-CMPO **2**, which cannot serve as a hydrogen bond donor. In general, (−)-(7*S*,7a*R*)-CMPI **1** and (−)-(7*S*,7a*R*)-CMPO **2** enantiomers fit better into the protein pocket as compared to (+)-(7*R*,7a*S*)-CMPI **1** and (+)-(7*R*,7a*S*)-CMPO **2**. Though this model is plausible, we suppose that these interactions account for the higher inhibition activity (around 5–10 times) of (−)-CMPI **1** and (−)-CMPO **2** over their (+)-enantiomers. These results can be used in further design and development of new highly potent PDE IV inhibitors.

Experimental

All reactions were performed in oven-dried (150 °C) glassware. Catalytic hydrogenations were carried out in a steel autoclave with external stirring and heating. Column chromatography was performed using Kieselgel 40–60 μm 60A silica gel. 1D and 2D NMR spectra were recorded at room temperature in $CDCl_3$. The chemical shifts (^1H, ^{13}C) are given ppm (δ) in relation to the solvent signal. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Numeration of atoms is given in Schemes 3 and 4. Peaks in IR-spectra data are reported in cm^{-1} with the following relative intensities: s (strong), m (medium), w (weak), br (broad), sh (shoulder). Elemental analysis was performed by the Analytical

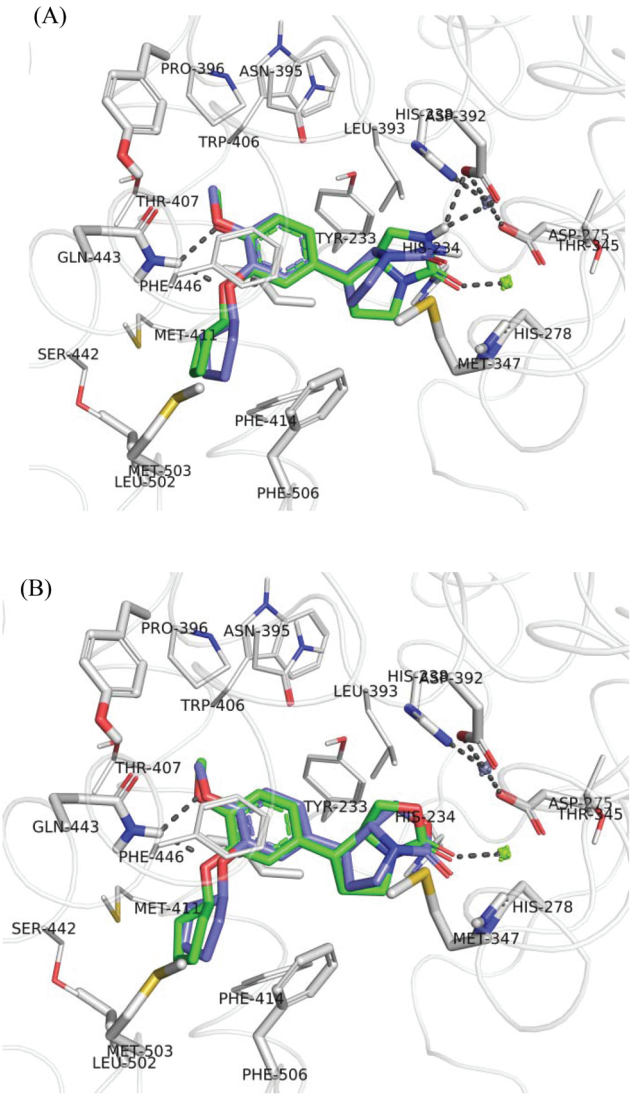


Fig. 2 Prediction of interactions of CMPI **1** (A) and CMPO **2** (B) enantiomers with PDE IVB (PDB ID: 3KKT) by AutoDock Vina. Green – (–)-(7*S*,7a*R*)-CMPI **1** and (–)-(7*S*,7a*R*)-CMPO **2**, blue – (+)-(7*R*,7a*S*)-CMPI **1** and (+)-(7*R*,7a*S*)-CMPO **2**. Important amino acids are shown in bulk, main chain of amino acids is hidden, protein structure is visualized as a thin tube, Zn^{2+} ion is shown in green, Mg^{2+} ion is shown in grey.

Laboratory of the Institute of Organic Chemistry. Concentrations *c* in optical rotation angles are given in g per 100 mL. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Analytical thin-layer chromatography was performed on silica gel plates with QF-254. Visualization was accomplished with UV light, solution of $FeCl_3$ in HCl/H_2O–Et_2O or the solution of anisaldehyde/H_2SO_4 in ethanol. Glacial acetic acid was recrystallized two times. CH_2Cl_2 (technical grade), MeCN (technical grade), Et_3N, and Me_3SiBr were redistilled from CaH_2, acetone was redistilled from Na_2SO_4. Hexane, EtOAc and methanol were technical grade and distilled without drying agents. (+)-(1*S*,2*R*)-2-Phenylcyclohexanol (>98% ee), (–)-(1*R*,2*S*)-2-phenylcyclohexanol (99% ee), ethyl vinyl ether, $SnCl_4$, NaN_3, NaI, $NaBH_3CN$, NH_4OAc, nitroethane, isovanillin, cyclopentyl bromide, DMSO, RANEY® nickel (50% slurry in water), Im_2CO were purchased from commercial sources and used as received. Diastereomerically pure (d.e. >98%) cyclic nitronates (+)-**5**, (–)-**5** and *rac*-**5** were synthesized according to a previously described procedure.[11c]

PDE inhibition studies were conducted at BPS Bioscience (San Diego, USA). PDE IVB1 assay kit was used (BPS catalogue number 60342) for this purpose.

For docking studies with AutoDock Vina[23] human PDE IVB (PDB ID: 3KKT[24]) was selected. The protein structure was prepared according to a classical AutoDock scenario: ligand and water molecules were removed, atoms of Zn^{2+} and Mg^{2+} were retained in the protein structure, nonpolar hydrogens, Gasteiger–Huckel charges and studied ligands CMPI **1** and CMPO **2** were added to proteins. Spatial structures of the ligands were calculated with OpenBabel.[27] Top scoring poses of docked molecules according to predicted free energy of binding were selected for further discussion of protein–ligand interactions (Table 1). Visualization of interactions of molecules CMPI **1** and CMPO **2** with PDE IVB was done using Pymol v. 0.99.[28]

trans-3-(Azidomethyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-6-{[*trans*-2-phenylcyclohexyl]oxy}-5,6-dihydro-4*H*-1,2-oxazine (8)

Me_3SiBr (1.37 mL, 10.4 mmol) was added to a solution of racemic or enantiopure nitronate **5** (1.0 g, 2.09 mmol) and Et_3N (0.43 mL, 3.1 mmol) in 6.0 mL of MeCN at −25 °C under argon. The mixture was kept at −25 °C for 18 h with occasional stirring, and then it was diluted with EtOAc (20 mL) and poured into a mixture of EtOAc (200 mL) and a saturated solution of K_2CO_3 (200 mL). The aqueous layer was back-extracted with EtOAc (2 × 75 mL). The combined organic layers were washed with a saturated solution of K_2CO_3 (100 mL), water (100 mL), and brine (100 mL), dried (Na_2SO_4), and evaporated under vacuum. The residue was preadsorbed on silica gel and subjected to a column chromatography (eluent: heptane–EtOAc = 20 : 1 → 10 : 1 → 5 : 1 → 1 : 1) to give 0.081 g (7%) of bromide 4,6-*cis*-**7′**,[11c] 0.29 g (26%) of labile bromide 4,6-*trans*-**7**[11c] (containing *ca*. 5% of *trans*-2-phenylcyclohexanol) and 0.42 g (42%) of initial nitronate **5**. The recovered nitronate **5** can be silylated again by the same procedure to give additional 0.135 g of bromide 4,6-*trans*-**7** and 0.046 g of 4,6-*cis*-**7′**. The overall yield of racemic or enantiopure bromide 4,6-*trans*-**7** *ca*. 38%.

To a stirred solution of enantiopure or racemic bromide **7** (0.367 g, 0.677 mmol) in acetone (12 mL) was added a solution of NaN_3 (0.205 g, 3.15 mmol) and NaI (0.022 g, 0.15 mmol) in water (2.5 mL). The mixture was stirred at r.t. for 24 h, then evaporated under vacuum. The residue was preadsorbed on silica gel and subjected to a column chromatography (eluent: hexane–EtOAc = 20 : 1 → 10 : 1 → 5 : 1 → 3 : 1) to give 0.303 g (89%) of enantiopure (oil) or racemic (crystalline) azide **8**. For analytical purposes racemic azide **8** was recrystallized from MeOH (mp 100–101 °C). R_f 0.72 (hexane–EtOAc = 1 : 1). Found: C, 69.01; H, 7.54; N, 11.12. Calc. for $C_{29}H_{36}N_4O_4$: C, 69.02; H, 7.19; N, 11.10. FTIR (KBr, characteristic bands): ν_{max}/cm^{-1}

2955s, 2930s, br, 2855m, 2855m, 2839w, 2106s (N_3), 1603w (C═N), 1591m, 1514s, 1443m, sh, 1334m, sh, 1276m, 1245s, 1212m, 1139m, sh, 1108s, 1037s, 1007m, 913m, 872m, sh, 759m, sh, 705m. ^{1}H NMR (300 MHz, COSY, HSQC): 1.20–1.32 (m, 1 H, HC(12)), 1.34–1.49 (m, 1 H, HC(11)), 1.51–1.57 (m, 1 H, HC(9)), 1.58–1.69 (m, 2 H, HC(23)), 1.74–1.96 (m, 10 H, HC(9), H_2C(10), HC(11), H_2C(22) and HC(23)), 1.97–2.05 (m, 2 H, H_2C(5)), 2.34–2.45 (m, 1 H, HC(12)), 2.59 (ddd, J = 11.9, 11.0, 3.2 Hz, 1 H, H_{ax}C(8)), 2.80 (dd, J = 11.9, 7.7 Hz, 1 H, H_{ax}C(4)), 3.20 (s, 2 H, H_2C(13)), 3.81 (s, 3 H, H_3C(20)), 3.94 (ddd, J = 11.0, 10.2, 4.0 Hz, 1 H, H_{ax}C(7)), 4.70 (m, 1 H, HC(21)), 5.39 (dd, J = 2.3, 1.8 Hz, 1 H, H_{eq}C(6)), 6.48 (d, J = 1.7 Hz, 1 H, HC(15)), 6.52 (dd, J = 8.1, 1.7 Hz, 1 H, HC(19)), 6.77 (d, J = 8.1 Hz, 1 H, HC(18)), 7.18–7.35 (m, 5 H, Ph). ^{13}C NMR (75.47 MHz, HSQC, DEPT): 24.0 (9-C), 24.6 (23-C), 26.1 (10-C), 30.4 (12-C), 32.1 (13-C), 32.7 (22-C), 33.8 (11-C), 34.2 (4-C), 50.8 (8-C), 51.4 (13-C), 56.1 (20-C), 76.1 (7-C), 80.5 (21-C), 90.7 (6-C), 112.3 (18-C), 114.8 (15-C), 120.7 (19-C), 125.8 (*p*-Ph), 127.9 and 128.0 (*o*- and *m*-Ph), 130.7 (14-C), 144.6 (i-Ph), 148.0 and 149.6 (16-C and 17-C), 155.8 (3-C). HRMS: *m*/*z* 505.2809 (positive ions); calcd for $[C_{29}H_{37}N_4O_4^+]$: 505.2809.

3,4-*trans*-3,6-*trans*-3-(Azidomethyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-6-{[*trans*-2-phenylcyclohexyl]oxy}-1,2-oxazinane (10)

To a stirred solution of enantiopure or racemic 1,2-oxazine **8** (0.300 g, 0.6 mmol) in AcOH (3 mL) was added $NaBH_3CN$ (0.134 g, 2.13 mmol) under argon atmosphere. After 40 min a second portion of $NaBH_3CN$ (0.045 g, 0.71 mmol) was added and the mixture was stirred for an additional 1 h. The resulting solution was poured into a mixture of EtOAc (100 mL)/saturated solution of K_2CO_3 (100 mL). The aqueous layer was back-extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with a saturated solution of K_2CO_3 (50 mL), water (50 mL), brine (50 mL), dried with Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: EtOAc–hexane = 1 : 10 → 1 : 5 → 1 : 3) to yield 0.286 g (94%) of tetrahydro-1,2-oxazine **10**. For analytical purposes racemic product *rac*-**10** was recrystallized from MeOH. R_f 0.56 (hexane–EtOAc = 1 : 1). Found: C, 68.80; H, 7.63; N, 11.20. Calc. for $C_{29}H_{38}N_4O_4$: C, 68.75; H, 7.56; N, 11.06. FTIR (KBr, characteristic bands) ν_{max}/cm^{-1} 3217m, sh (N–H), 2933s, br, 2859m, 2095s (N_3), 1593m, 151s, sh, 1445m, 1336m, sh, 1273s, 1261s, 1164m, 1141m, 1096m, 1081w, 901m, 806m, 759m, 702m, 535m. ^{1}H NMR (300 MHz, COSY, HSQC): 1.25–1.49 (m, 2 H, HC(10) and HC(12)), 1.56–1.73 (m, 3 H, HC(9) and HC(23)), 1.77–2.02 (m, 12 H, H_2C(5), HC(9), HC(10), H_2C(11), H_2C(22) and HC(23)), 2.18–2.26 (m, 1 H, HC(12)), 2.36 (ddd, J = 11.7, 11.0, 4.3 Hz, 1 H, H_{ax}C(4)), 2.45 (dd, J = 12.5, 7.3 Hz, 1 H, HC(13)), 2.68 (ddd, J = 11.8, 11.8, 3.6 Hz, 1 H, H_{ax}C(8)), 2.79 (dd, J = 12.5, 2.0 Hz, 1 H, HC(13)), 3.00 (dddd, J = 12.5, 11.0, 7.3, 2.0 Hz, 1 H, H_{ax}C(3)), 3.75–3.82 (s and m, 4 H, HC(7) and H_3C(20)), 4.12 (d, J = 12.5 Hz, 1 H, HN(2)), 4.74 (m, 1 H, HC(21)), 4.98 (d, J = 1.8 Hz, 1 H, H_{eq}C(6)), 6.57 (s, 1 H, HC(15)), 6.59 (d, J = 8.1 Hz, 1 H, HC(19)), 6.77 (d, J = 8.1 Hz, 1 H, HC(18)), 7.29–7.47 (m, 5 H, Ph). ^{13}C NMR (75.47 MHz, HSQC, DEPT): 24.0 (9-C), 24.7 (23-C), 26.0 (10-C), 31.2 (12-C), 32.7 and 32.8 (22-C), 33.4 (5-C), 36.6 (11-C), 37.3 (4-C), 50.2 (13-C), 50.9 (8-C), 56.1 (20-C), 61.4 (3-C), 77.5 (7-C), 80.5 (21-C), 93.4 (6-C), 112.3 (18-C), 114.3 (15-C), 119.4 (19-C), 126.7 (*p*-Ph), 128.0 and 128.8 (*o*- and *m*-Ph), 133.8 (14-C), 144.5 (i-Ph), 147.8 and 149.0 (16-C and 17-C). HRMS: *m*/*z* 507.2962 (positive ions); calcd for $[C_{29}H_{39}N_4O_4^+]$: 507.2966.

(+)-(3*R*,4*S*,6*S*,7*S*,8*R*)-**10** (obtained from (4*S*,6*S*,7*S*,8*R*)-**8**): colorless oil, $[\alpha]_D^{24}$ +174.8 (*c* 0.87 in MeOH).

(−)-(3*S*,4*R*,6*R*,7*R*,8*S*)-**10** (obtained from (4*R*,6*R*,7*R*,8*S*)-**8**): colorless oil, $[\alpha]_D^{27}$ −172.8 (*c* 0.87 in MeOH).

Rac-**10** (obtained from *rac*-**8**): white solid, mp 109–112 °C (crystallized from MeOH).

3,4-*trans*-3,6-*trans*-3-(Hydroxymethyl)-4-[3-(cyclopentyloxy)-4-methoxyphenyl]-6-{[*trans*-2-phenylcyclohexyl]oxy}-1,2-oxazinane (12)

To a stirred solution of enantiopure bromide (4*S*,6*S*,7*S*,8*R*)-**7** or (4*R*,6*R*,7*R*,8*S*)-**7** (0.125 g, 0.23 mmol) in a mixture of water (3 mL) and acetone (5 mL) was added $AgNO_3$ (0.196 g, 1.15 mmol). The mixture was refluxed for 3 h, then cooled to r.t. and acetone was removed under vacuum. The residue was diluted with AcOEt (100 mL) and water (50 mL) and transferred into a separating funnel. The aqueous layer was back-extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried with Na_2SO_4 and evaporated under vacuum to give crude nitrates **11** [^{1}H NMR (300 MHz): 1.23–1.45, 1.55–1.96 and 1.96–2.04 (3 m, 17 H, H_2C(5), H_2C(9), H_2C(10), H_2C(11), HC(12), H_2C(22) and H_2C(23)), 2.36 (m, 1 H, HC(12)), 2.58 (ddd, J = 12.2, 10.5, 3.4 Hz, 1 H, H_{ax}C(8)), 2.90 (dd, J = 12.2, 7.3 Hz, 1 H, H_{ax}C(4)), 3.81 (s, 3 H, H_3C(20)), 3.96 (ddd, J = 10.5, 10.1, 3.7 Hz, 1 H, H_{ax}C(7)), 4.22 (d, J = 13.2 Hz, 1 H, HC(13)), 4.36 (d, J = 13.2 Hz, 1 H, HC(13)), 4.70 (m, 1 H, HC(21)), 5.37 (dd, J = 2.0, 1.5 Hz, 1 H, H_{eq}C(6)), 6.52 (d, J = 1.6 Hz, 1 H, HC(15)), 6.55 (dd, J = 8.2, 1.6 Hz, 1 H, HC(19)), 6.77 (d, J = 8.2 Hz, 1 H, HC(18)), 7.14–7.36 (m, 5 H, Ph). HRMS: *m*/*z* 525.2588 (positive ions); calcd for $[C_{29}H_{37}N_2O_7^+]$: 525.2601]. The crude product was dissolved in AcOH (6 mL) and Zn powder (0.15 g) was added. After stirring the mixture for 3 h an additional portion of Zn (0.05 g) was added and the mixture was left overnight. Then $NaBH_3CN$ (0.087 g, 1.38 mmol) was added and the mixture was left stirring for 0.5 h. Then the second portion of $NaBH_3CN$ (43 mg, 0.68 mmol) was added and after stirring for 0.5 h the resulting mixture was poured into EtOAc (100 mL)/saturated solution of K_2CO_3 (100 mL). The aqueous layer was back-extracted with EtOAc (50 mL). Combined organic layers were washed with a saturated solution of K_2CO_3 (50 mL), water (50 mL), brine (50 mL), dried with Na_2SO_4 and evaporated under vacuum. The residue was subjected to a column chromatography on silica gel (eluent: EtOAc–hexane = 1 : 10 → 1 : 5 → 1 : 3 → 1 : 1) to yield 0.091 g (82% from bromide **7**) of tetrahydro-1,2-oxazine (+)-**12** or (−)-**12** as oil. R_f 0.19 (hexane–EtOAc = 1 : 1). Found: C, 72.08; H, 8.04; N, 2.85. Calc. for $C_{29}H_{39}NO_5$: C, 72.32; H, 8.16; N, 2.91. ^{1}H NMR (300 MHz, COSY, HSQC): 1.20–1.45 (m, 2 H, HC(10) and HC(12)), 1.56–1.74 (m, 3 H,

HC(9) and HC(23)), 1.75–2.00 (m, 12 H, $H_2C(5)$, HC(9), HC(10), $H_2C(11)$, $H_2C(22)$ and HC(23)), 2.18–2.27 (m, 1 H, HC(12)), 2.30 (ddd, J = 12.2, 10.9, 3.8 Hz, 1 H, $H_{ax}C(4)$), 2.57 (dd, J = 11.2, 9.0 Hz, 1 H, HC(13)), 2.68 (ddd, J = 12.5, 10.3, 3.3 Hz, 1 H, $H_{ax}C(8)$), 3.01 (ddd, J = 10.9, 9.0, 1.0 Hz, 1 H, $H_{ax}C(3)$), 3.10 (dd, J = 11.2, 1.0 Hz, 1 H, HC(13)), 3.74 (ddd, J = 10.5, 10.2, 3.6 Hz, 1 H, $H_{ax}C(7)$), 3.81 (s, 3 H, $H_3C(20)$), 3.92 (br., 2 H, NH(2) and OH), 4.74 (m, 1 H, HC(21)), 4.99 (s, 1 H, $H_{eq}C(6)$), 6.58 (s, 1 H, HC(15)), 6.61 (d, 1 H, J = 8.2 Hz, HC(19)), 6.76 (d, J = 8.2 Hz, 1 H, HC(18)), 7.29 (m, 1 H, *p*-Ph), 7.40–7.46 (m, 4 H, *o*- and *m*-Ph). ^{13}C NMR (75.47 MHz, HSQC, DEPT): 24.0 (9-C), 24.7 (23-C), 25.9 (10-C), 31.2 (12-C), 32.7 and 32.8 (22-C), 32.9 (5-C), 36.5 (11-C), 36.8 (4-C), 50.8 (8-C), 56.0 (20-C), 61.6 (13-C), 63.1 (3-C), 77.6 (7-C), 80.5 (21-C), 93.7 (6-C), 112.3 (18-C), 114.4 (15-C), 119.4 (19-C), 126.6 (*p*-Ph), 128.2 and 128.7 (*o*- and *m*-Ph), 134.0 (14-C), 144.7 (i-Ph), 147.7 and 148.8 (16-C and 17-C). HRMS: *m*/*z* 482.2901 (positive ions); calcd for $[C_{29}H_{40}NO_5^+]$: 482.2901.

(+)-(3*R*,4*S*,6*S*,7*S*,8*R*)-**12** (obtained from (4*S*,6*S*,7*S*,8*R*)-7): colorless oil, $[\alpha]_D^{25}$ +193.9 (*c* 1.0 in MeOH).

(−)-(3*S*,4*R*,6*R*,7*R*,8*S*)-**12** (obtained from (4*R*,6*R*,7*R*,8*S*)-7): colorless oil, $[\alpha]_D^{25}$ −191.2 (*c* 1.0 in MeOH).

trans-7-[3-(Cyclopentyloxy)-4-methoxyphenyl]hexahydro-3*H*-pyrrolo[1,2-c]imidazol-3-one (CMPI 1)

RANEY® nickel (*ca*. 50 mg, washed with MeOH) was placed in a test tube equipped with a magnetic stirrer and charged with a solution of enantiopure or racemic tetrahydro-1,2-oxazine **10** (0.119 g, 0.24 mmol) and Boc_2O (0.05 mL, 0.24 mmol) in MeOH (5 mL). The test tube was placed in a steel autoclave which was then flushed and filled with H_2 to a pressure of 40 bar. The autoclave was slowly (1 h) heated to 70–75 °C and the mixture was stirred at this temperature for 4.5 h. Then the autoclave was cooled to r.t., slowly depressurized and the catalyst was filtered off. The solvent was evaporated, and the residual mixture of *trans*-2-phenylcyclohexanol and pyrrolidine **15** was dried under vacuum [data for **15**: ^{1}H NMR (300 MHz): 1.42 (s, 9 H, Boc), 1.55–1.68, 1.76–1.99 and 2.18–2.30 (3 m, 11 H, $H_2C(4)$, $H_2C(15)$, $H_2C(16)$, NH), 2.75 (ddd, J = 8.3, 8.1, 8.1 Hz, 1 H, HC(3)), 3.02–3.21 (m, 4 H, HC(2), $H_2C(5)$, HC(6)), 3.26 (dd, J = 5.7, 9.3 Hz, 1 H, HC(6)), 3.83 (s, 3 H, $H_3C(13)$), 4.78 (m, 1 H, HC(14)), 4.92 (br, 1 H, NHBoc), 6.75 (d, J = 8.0 Hz, 1 H, HC(12)), 6.77 (s, 1 H, HC(8)), 6.81 (d, J = 8.0 Hz, 1 H, HC(11)). HRMS: *m*/*z* 391.2586 (positive ions); calcd for $[C_{22}H_{35}N_2O_4^+]$: 391.2591].

The residue was dissolved in DMSO (5.4 mL) and the solution was gently refluxed for 30 min under argon. Then the solvent was evaporated under vacuum (*ca*. 100 °C/10 Torr) and the residue was subjected to column chromatography on silica gel (eluent: EtOAc–hexane = 1 : 10 → 1 : 5 → 1 : 1 → MeOH–EtOAc = 0 : 1 → 1 : 10). Two fractions were collected: the EtOAc–hexane fraction contained *trans*-2-phenylcyclohexanol (34 mg, 81%) and the EtOAc–MeOH fraction contained target enantiopure or racemic pyrroloimidazolone CMPI **1** (42 mg, 56% from **10**). R_f 0.71 (MeOH–EtOAc = 1 : 3). ^{1}H NMR (300 MHz, COSY, HSQC): 1.56–1.71 (m, 2 H, HC(17)), 1.79–1.94 (m, 6 H, $H_2C(16)$ and HC(17)), 2.05 (dddd, J = 12.8, 11.9, 10.1, 9.2 Hz, 1 H, H′C(6)), 2.38 (dddd, J = 12.8, 10.1, 8.2, 4.6 Hz, 1 H, H″C(6)), 2.74 (ddd, J = 11.0, 10.1, 9.2 Hz, 1 H, HC(7)), 3.26–3.31 (m, 1 H, H′C(5)), 3.33 (dd, J = 9.9, 9.9 Hz, 1 H, H″C(1)), 3.51 (dd, J = 9.9, 7.7 Hz, 1 H, H′C(1)), 3.64–3.75 (m, 2 H, HC(7a) and H′C(5)), 3.82 (s, 3 H, $H_3C(14)$), 4.76 (m, 1 H, HC(15)), 5.55 (br, 1 H, HN(2)), 6.72 (s, 1 H, HC(9)), 6.73 (d, J = 7.3 Hz, 1 H, HC(13)), 6.83 (d, J = 7.3 Hz, 1 H, HC(12)). ^{13}C NMR (75.47 MHz, HSQC, DEPT): 24.0 (17-C), 32.7 (16-C), 34.4 (6-C), 41.3 (1-C), 45.2 (5-C), 48.5 (7-C), 56.2 (14-C), 66.1 (7a-C), 80.6 (15-C), 112.4 (12-C), 114.7 (9-C), 119.6 (13-C), 131.7 (8-C), 147.9 and 149.3 (10-C and 11-C), 165.8 (3-C). Characteristic 2D-NOESY correlations: HC(7a)/HC(9) and HC(13), $H_3C(14)$/HC(12), HC(7)/H″C(6), H″C(6)/H″C(5), H′C(6)/H′C(5), HC(7a)/H′C(1). NMR spectra are in accordance with literature data for racemic CMPI **1**.[6a,11a]

(−)-(7*S*,7a*R*)-CMPI **1** (obtained from (+)-**10**): colorless oil; $[\alpha]_D^{26}$ −33.6 (*c* 1.0 in MeOH).

(+)-(7*R*,7a*S*)-CMPI **1** (obtained from (−)-**10**): colorless oil; $[\alpha]_D^{27}$ +32.3 (*c* 1.0 in MeOH).

Rac-**1** (obtained from *rac*-**10**): mp 134–139 °C (lit. mp 139–141 °C,[11a] 118–120 °C[6a]).

(−)-*trans*-2-Phenylcyclohexanol (obtained from (−)-**10**): mp 61–64 °C (lit. 63–66 °C, Aldrich), $[\alpha]_D^{27}$ = −53.0 (*c* 1.83 in MeOH) [lit.[29] $[\alpha]_D$ −56.8 (*c* 1.42 in MeOH)]. ^{1}H NMR spectra are in accordance with literature data.[29]

(+)-*trans*-2-Phenylcyclohexanol (obtained from (+)-**10**): mp 64–65 °C (lit. 64–66 °C, Aldrich), $[\alpha]_D^{24}$ +55.2 (*c* 1.83 in MeOH) [lit.[30] $[\alpha]_D^{20}$ +57.3 (*c* 5.0 in MeOH)]. ^{1}H NMR spectra are in accordance with literature data.[29]

trans-7-[3-(Cyclopentyloxy)-4-methoxyphenyl]hexahydro-1*H*-pyrrolo[1,2-c][1,3]oxazol-3-one (CMPO 2)

RANEY® nickel (*ca*. 0.03 g, washed with MeOH) was placed in a test tube equipped with a magnetic stirrer and charged with a solution of enantiopure tetrahydro-1,2-oxazine (+)-(3*R*,4*S*,6*S*,7*S*,8*R*)-**12** or (−)-(3*S*,4*R*,6*R*,7*R*,8*S*)-**12** (0.081 g, 0.168 mmol) in MeOH (2 mL). The test tube was placed in a steel autoclave which was then flushed and filled with H_2 to a pressure of 25 bar. After the mixture was stirred at r.t. for 3.5 h, the autoclave was slowly depressurized and the catalyst was filtered off. The solvent was evaporated, and the residue was dried under vacuum. The product was dissolved in CH_2Cl_2 (1 mL) and 1,1′-carbonyldiimidazole (0.054 g, 0.336 mmol) was added. After stirring at r.t. for 2 h the mixture was concentrated under vacuum and the residue was subjected to column chromatography on silica gel (eluent: EtOAc–hexane = 1 : 10 → 1 : 5 → 1 : 1). The first fraction contained (+)- or (−)-*trans*-2-phenylcyclohexanol (0.027 g, 91%) and the second fraction contained target (−)- or (+)-pyrrolooxazolidinone CMPO **2** (0.041 g, 77%). R_f 0.33 (EtOAc–hexane = 1 : 1). ^{1}H NMR (300 MHz, COSY, HSQC): 1.54–1.72 (m, 2 H) and 1.80–1.98 (m, 6 H) ($H_2C(16)$ and $H_2C(17)$), 2.15 (dddd, J = 12.7, 11.7, 9.5, 8.8 Hz, 1 H, H′C(6)), 2.49 (dddd, J = 12.7, 10.3, 8.1, 2.2 Hz, 1 H, H″C(6)), 2.79 (ddd, J = 10.3, 9.2, 7.3 Hz, 1 H, HC(7)), 3.48 (ddd, J = 11.0, 9.5, 2.2 Hz, 1 H, H′C(5)), 3.74 (ddd, J = 11.0, 8.8, 8.1 Hz, 1 H,

H″C(5)), 3.82–3.88 (m, 1 H, HC(7a)), 3.84 (s, 3 H, H_3C(14)), 4.22 (dd, J = 9.2, 2.1 Hz, 1 H, H″C(1)), 4.43 (dd, J = 9.2, 8.4 Hz, 1 H, H′C(1)), 4.73–4.81 (m, 1 H, HC(15)), 6.73 (s, 1 H, HC(9)), 6.75 (d, J = 7.9 Hz, 1 H, HC(13)), 6.86 (d, J = 7.9 Hz, 1 H, HC(12)). ^{13}C NMR (75.47 MHz, HSQC, DEPT): 24.0 (17-C), 32.8 (16-C), 34.5 (6-C), 45.8 (5-C), 49.2 (7-C), 56.2 (14-C), 65.8 (7a-C), 66.2 (1-C), 80.7 (15-C), 112.5 (12-C), 114.5 (9-C), 119.4 (13-C), 130.4 (8-C), 148.1 and 149.6 (10-C and 11-C), 161.8 (3-C). Characteristic 2D-NOESY correlations: HC(7a)/HC(9) and HC(13), HC(7)/H″C(6), HC(7)/H″C(1), HC(9)/H′C(6), H″C(6)/H″C(5), H′C(6)/H′C(5). NMR spectra are in accordance with literature data for racemic CMPO **2**.[6a,11a]

(−)-(7*S*,7a*R*)-CMPO **2** (obtained from (+)-**12**): mp 137–139 °C; $[\alpha]_D^{26}$ −69.1 (*c* 0.83 in MeOH).

(+)-(7*R*,7a*S*)-CMPO **2** (obtained from (−)-**12**): mp 138–139 °C; $[\alpha]_D^{26}$ +71.4 (*c* 0.83 in MeOH).

(−)-*trans*-2-Phenylcyclohexanol (obtained from (−)-**12**): mp 61–63 °C (lit. 63–66 °C, Aldrich), $[\alpha]_D^{24}$ = −54.9 (*c* 0.5 in MeOH) [lit.[29] $[\alpha]_D$ −56.8 (*c* 1.42 in MeOH)]. ^{1}H NMR spectra are in accordance with literature data.[29]

(+)-*trans*-2-Phenylcyclohexanol (obtained from (+)-**12**): mp 59–60 °C (lit. 64–66 °C, Aldrich), $[\alpha]_D^{26}$ +54.8 (*c* 1.0 in MeOH) [lit.[30] $[\alpha]_D^{20}$ +57.3 (*c* 5.0 in MeOH)]. ^{1}H NMR spectra are in accordance with literature data.[29]

Conclusions

In conclusion, the first asymmetric syntheses of two highly potent PDE IV inhibitors CMPI **1** and CMPO **2** were developed. These syntheses provide both enantiomers of each product CMPI **1** and CMPO **2** in 8 and 7 steps (11% and 15% overall yields, respectively) starting from available isovanillin, nitroethane and (+)- or (−)-*trans*-2-phenylcyclohexanols. The suggested strategy is based on the original process of silylation of easily available six-membered cyclic nitronates. This strategy is flexible, providing a wide variation of substituents in the pyrrolidine unit, and, thus, enabling the synthesis of large libraries of CMPI **1** and CMPO **2** analogs. (−)-(7*S*,7a*R*) enantiomers of CMPI **1** and CMPO **2** were shown to be considerably more potent inhibitors of the PDE IVB1 enzyme compared to their (+)-(7*R*,7a*S*) enantiomers. A rational model based on molecular docking studies was suggested to explain the difference in the PDE inhibitory activity of CMPI **1** and CMPO **2** enantiomers.

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