The Cyclic Nitronate Route to Pharmaceutical Molecules: Synthesis of GSK’s Potent PDE4 Inhibitor as a Case Study

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Abstract: An efficient asymmetric synthesis of GlaxoSmithKline’s potent PDE4 inhibitor was accomplished in eight steps from a catechol-derived nitroalkene. The key intermediate (3-acyloxymethyl-substituted 1,2-oxazine) was prepared in a straightforward manner by tandem acylation/(3,3)-sigmatropic rearrangement of the corresponding 1,2-oxazine-N-oxide. The latter was assembled by a (4+2)-cycloaddition between the suitably substituted nitroalkene and vinyl ether. Facile acetal epimerization at the C-6 position in 1,2-oxazine ring was observed in the course of reduction with NaBH₃CN in AcOH. Density functional theory (DFT) calculations suggest that the epimerization may proceed through an unusual tricyclic oxazolo(1,2)oxazinium cation formed via double anchimeric assistance from a distant acyloxy group and the nitrogen atom of the 1,2-oxazine ring.

Keywords: C–H functionalization; total synthesis; pyrrolidines; anchimeric assistance; epimerization; PDE4 inhibitors

1. Introduction

Cyclic nitronates (1,2-oxazine-N-oxides 1 and isoxazoline-N-oxides 2) are useful intermediates in the synthesis of complex nitrogen containing scaffolds due to their versatile reactivity as 1,3-dipoles and accessibility from nitroalkenes (Scheme 1a) [1–10]. Denmark’s group extensively exploited the inter- and intramolecular (3 + 2)-cycloaddition reactions with six-membered cyclic nitronates 1 to construct various bi- and polycyclic nitroso acetal frameworks 3, which were then converted into fused pyrrolidine derivatives by an intramolecular reductive amination (Scheme 1b) [1,11]. Using this strategy, total syntheses of numerous pyrrolizidine and indolizidine alkaloids [12–14], as well as (5.5.5.5)- and (5.5.5.4)-azafenestanes [15,16], were accomplished.

Our group has a long-term interest in developing another approach towards the modification of cyclic nitronates, which utilizes C–H functionalization of the position next to the nitronate group (α-C-atom, Scheme 1c) [17]. Some time ago, we demonstrated that upon silylation, cyclic nitronates 1 and 2 are transformed into N-siloxyenamines 4, in which the double bond is shifted to the exocyclic α-position [18]. Enamines 4 exhibit umpolung reactivity and react with nucleophiles in the presence of Lewis acids (LA) to give α-substituted cyclic oxime ethers 5 (1,2-oxazines or isoxazolines) via S₅’ substitution of TMSO-group (Scheme 1c). Using this approach, nucleophilic halogenation [19], oxygenation [20–22], azidination [23] of cyclic nitronates were performed (route 1). Although we succeeded in using this methodology in the total synthesis of some pharmaceutical molecules, in
the case of nitronates having acid-sensitive groups (e.g., acetals), it proved to be not very efficient (vide infra) [20,24,25].

**a. Synthesis of cyclic nitronates from nitroalkenes**

\[
\begin{align*}
\text{R} &\quad (4+2) \quad \text{LA} \\
\text{N}=\text{N} &\quad \text{R} \\
\end{align*}
\]

**b. 1,3-Dipolar addition with cyclic nitronates and its application in total synthesis**

\[
\begin{align*}
\text{N} &\quad \text{R} \\
\end{align*}
\]

**c. C-H functionalization of cyclic nitronates via N-siloxyenamines (route 1)**

\[
\begin{align*}
\text{TMSBr} &\quad \text{Et}_3\text{N} \\
\text{N} &\quad \text{R} \\
\end{align*}
\]

**d. C-H functionalization of cyclic nitronates via [3,3]-rearrangement of N-acyloxyenamines (route 2)**

\[
\begin{align*}
\text{BuC(O)Cl} &\quad \text{Et}_3\text{N} \\
\text{N} &\quad \text{R} \\
\end{align*}
\]

Scheme 1. Approaches towards modification of cyclic nitronates. (a) Synthesis of cyclic nitronates from nitroalkenes; (b) 1,3-Dipolar addition with cyclic nitronates and its application in total synthesis; (c) C-H functionalization of cyclic nitronates via N-siloxyenamines (route 1); (d) C-H functionalization of cyclic nitronates via [3,3]-rearrangement of N-acyloxyenamines (route 2).

Recently, we designed another strategy for the site-selective functionalization of cyclic nitronates 1 and 2 via acylation with acyl halides/Et$_3$N (Scheme 1d) [26]. The initially formed N-acyloxyenamines 6 undergo a spontaneous (3,3)-rearrangement to give α-acyloxy-substituted cyclic oxime ethers 7 (route 2). This tandem C–H oxygenation process could be performed under very mild conditions. At present, we are testing the scope and limitation of this method in the total synthesis of some model target molecules to compare its efficacy with our previous C–H functionalization methods. In this study, a potent GlaxoSmithKline’s phosphodiesterase 4 (PDE4) inhibitor CMPO [27–29], which was previously synthesized using route 1 [24,30], was chosen as a target molecule.

Scheme 2 depicts our previous synthetic route to CMPO. The fused pyrrolidine core was prepared by carbamylation of a trans-3-aryl-substituted prolino 15. The latter was accessed in our strategy by the reductive contraction of the 1,2-oxazine ring in the intermediate 14, which was prepared by the stereoselective hydride reduction of the 5,6-dihydro-4H-1,2-oxazine 13 [24]. This intermediate was synthesized by the reduction of the ONO$_2$-group in the corresponding nitroxy-substituted 1,2-oxazine 12. Introduction of the nitroxy-group was accomplished by the LA-assisted functionalization of the methyl group in the N-oxide 10 using route 1 described above (see Scheme 1c). The required N-oxide...
10 was assembled in a stereoselective manner by the (4 + 2)-cycloaddition of nitroalkene 8 with the vinyl ether 9 bearing Whitesell's chiral auxiliary group ((+-)-trans-2-phenyl-1-cyclohexanol ether).

Oxygenation of the methyl group in the N-oxide 10 proved to be challenging, and several methods were tested (Scheme 3). N-Siloxyl-N-oxyenamine 16 was generated from the N-oxide 10 under mild conditions and then subjected to the LA-assisted nucleophilic addition of the bromide anion [24,25]. However, the desired 3-bromomethyl-1,2-oxazine 11, which served as a precursor to nitrate 12, was formed in moderate yields (best results are shown in Scheme 3a). Another issue was the epimerization of the sensitive C-6 acetal stereocenter leading to a mixture of 4,6-diastereomers 11 and 11', which had to be separated by column chromatography (Scheme 3a,b). Unfortunately, the epimer 11' could not be used in the synthesis of CMPO as it produced the undesired cis-stereoisomer upon the reduction of the C=N bond in 5,6-dihydro-4H-1,2-oxazine ring on the later stages of the synthesis (Scheme 3c) [25].

The reason for the epimerization may lie in the mechanism of the LA-promoted reaction of N-oxyenamines with nucleophiles, which involves heterolytic cleavage of the N–O bond (Scheme 3b). Experimental [20,22] and computational data [22] suggest that the SN' substitution of the TMSO-group may proceed through an epimerizable C=O bond, which involves heterolytic cleavage of the N–O bond (Scheme 3b).

Scheme 2. Previous asymmetric synthesis of (-)-CMPO.

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2. Results

We speculated that the pericyclic (3,3)-rearrangement of N-acyloxyenamine intermediate I1 generated by the acylation of nitronate 10 may proceed without any epimerization of the C-6 stereogenic center. To test this idea, cyclic nitronate 10 was treated with pivaloyl chloride/Et3N (1.5/2.0 equiv.) under conditions previously optimized for model 1,2-oxazine-N-oxides (MeCN, −30 °C, 2 h) [26]. The desired pivalate 17 was formed in a 61% yield together with some amount of unreacted N-oxide 10. After a short optimization of conditions, we found that the use of a bigger access of the PivCl/Et3N system (2.0/2.5 equiv.) and prolonged reaction time (18 h) at lower temperature resulted in an increase in the yield up to 76% (Scheme 4). Gratifyingly, no noticeable epimerization at the C-6 position was observed under these conditions.

We further investigated whether pivalate 17 could be used in the synthesis of CMPO. Hydrogenolysis of the pivalate group in 17 (to give alcohol 13) prior the reduction is challenging since 5,6-dihydro-4H-1,2-oxazines are known to undergo fragmentation via a retro-[4+2]-cycloaddition process under the action of bases [31]. Therefore, pivalate 17 was subjected to the hydride reduction with NaBH3CN in acetic acid (Scheme 5). Surprisingly, the reaction produced two separable isomeric products 18 and 18’ in 3: 1 ratio (62% combined yield, 91% based on converted 17). From the coupling constants in 1H-NMR spectra, it was deduced that both isomers had trans-arrangement of the

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**Scheme 3.** Problems associated with C-6 epimerization in the LA-assisted functionalization of cyclic nitronate 10. (a) Functionalization of cyclic nitronate 10; (b) Mechanism of epimerization at C-6; (c) Hydride reduction of 4,6-cis-1,2-oxazines.
substituents at the C-3 and C-4 atoms, while the configuration of the C-6 stereocenter was different. Thus, the C-6 acetal moiety underwent epimerization in the course of the reduction (see Discussion section). The amount of 4,6-cis-isomer 18' increased with time, demonstrating that the isomerization took place in the reduced product 18 and not in the starting compound 17. This is also confirmed by the fact that stereoisomers 18 and 18' had same configuration of the newly formed C-3 stereocenter. If the epimerization preceded the reduction, the C-6 epimerized 5,6-dihydro-4H-1,2-oxazine of the newly formed C-3 stereocenter. Hence, the separation of epimers 18 and 18' was not required and a mixture could be converted into the product 19 in a 61% yield. The chiral auxiliary alcohol (trans-2-phenylcyclohexanol) was recovered at this stage in 77% yield.

**Scheme 4.** Tandem acylation/(3,3)-rearrangement of nitronate 10.

| conditions            | 10/PivCl/EtN (equiv.) | yield of 17 |
|-----------------------|-----------------------|-------------|
| -30°C, 1.5 h          | 1.0 : 1.5 : 2.0       | 61%         |
| -40 to -25°C, 18 h    | 1.0 : 2.0 : 2.5       | 76%         |

**Scheme 5.** Cyanoborohydride reduction of 3-hydroxymethyl 1,2-oxazine 13 and its pivalate 17.

Isomers 18 and 18' could be almost equally used in the reductive contraction of the 1,2-oxazine ring [32], since both produced the same amino aldehyde intermediate 13 upon cleavage of the N-O bond followed by fragmentation of the hemiacetal 12 (Scheme 6). Subsequent intramolecular reductive amination in the intermediate 13 and protection with the Boc-group afforded the desired prolinol ester 19. Hence, the separation of epimers 18 and 18' was not required and a mixture could be converted into the product 19 in a 61% yield. The chiral auxiliary alcohol (trans-2-phenylcyclohexanol) was recovered at this stage in 77% yield.

**Scheme 5.** Cyanoborohydride reduction of 3-hydroxymethyl 1,2-oxazine 13 and its pivalate 17.
Scheme 6. Conversion of 1,2-oxazines 18 and 18′ into target PDE4 inhibitor (−)-CMPO.

On the next step, careful saponification of the pivalate moiety in pyrrolidine 19 with KOH in aqueous methanol gave Boc-prolinol 20 in 84% yield (Scheme 6). It is noteworthy that hydrolysis of the Boc-group was also observed to some extent under these conditions. For this reason, the reaction mixture was treated with Boc₂O after neutralization to convert the unprotected prolinol into the N-Boc-derivative 20, which was isolated by column chromatography.

Finally, deprotection of the N-Boc moiety with TFA and treatment of the resulting prolinol trifluoroacetate with Im₂CO/Et₃N afforded the desired PDE4 inhibitor CMPO (Scheme 6). Thus, the asymmetric synthesis of PDE4 inhibitor CMPO was completed in seven steps from a known nitroalkene 8 in 8% overall yield. Chiral HPLC analysis revealed the enantiomeric purity of the product >97% ee. The racemic sample of CMPO for HPLC analysis was prepared according to the same synthetic sequence starting from the racemic trans-2-phenylcyclohexanol.

3. Discussion

Epimerization of the acetal moiety in the course of the hydride reduction of 5,6-dihydro-4-H-1,2-oxazine 17 is of special note. In the previously reported hydride reduction of 1,2-oxazine 13 possessing a free hydroxymethyl group, no epimerization at the C-6 atom was observed (cf. data in Scheme 2; Scheme 5) [24]. We hypothesized that such a difference in the behavior of 3-hydroxymethyl- and 3-acyloxymethyl-substituted 1,2-oxazines 13 and 17 may be attributed to an anchimeric assistance from the carbonyl group, which stabilizes the intermediate cation C2 [33] by forming a bridged system with an eight-membered ring (cation C3). In carbohydrates, a similar anchimeric assistance of the acyloxy group from the distant 1,4-position has been proposed, yet it was not confirmed unambiguously by experimental data [34–37]. In our case, density functional theory (DFT) calculations at the MN15/Def2TZVP level of theory (see Supplementary material for details) revealed that the bridged cation C3 is much less stable compared to the initial monocyclic cation C2. Interestingly, the formation of a third ring between the nitrogen atom and the acyloxy group may lead to a tricyclic cation C4, which is predicted to be much more stable than the mono- or bicyclic structures C2 and C3 (Scheme 7). The formation of such a stable tricyclic cation as an intermediate or a resting state may account for the observed facile epimerization of pivalate 18. The higher thermodynamic
stability of the 4,6-cis-isomer 18′ over the 4,6-trans-isomer 18, as shown by DFT calculations, is likely to be the driving force for the epimerization at the C-6 atom.

Another remarkable observation was that 1,2-oxazine 18 (as well as its precursor 17) did not undergo epimerization in acetic acid (rt, 2 h). Isomerization to the cis-isomer 18′ was observed only in the presence of NaBH₃CN. Hence, the fragmentation of the acetal moiety is most likely promoted by some Lewis acidic boron species generated from NaBH₃CN in acidic medium. Indeed, slow epimerization of 1,2-oxazine 18 was observed upon treatment of 18 with B(OBu)₃ or BF₃·Et₂O in acetic acid.

It is noteworthy that an anchimeric-assisted epimerization in 1,2-oxazine series has not been reported previously. Moreover, to our knowledge, this is the first reported example of a remote neighboring group participation from the 1,4-position in a six-membered ring confirmed by DFT calculations [38–40]. The formation of an eight-membered ring in this case may be driven by an unusual secondary anchimeric interaction involving the nitrogen atom of the 1,2-oxazine ring leading to an unusual tricyclic oxazolo(1,2)oxazinium cation C₄.

4. Materials and Methods

All reactions were carried out in oven-dried (150 °C) glassware. NMR spectra (Bruker AM 300 spectrometer, Karlsruhe, Germany) were recorded at room temperature (if not stated otherwise) with residual solvents peaks as an internal standard. Peak multiplicities are indicated by s (singlet), d (doublet), t (triplet), dd (doublet of doublets), q (quartet), quint (quintet), ddd (doublet of doublets of doublets), tt (triplet of triplets), tdd (triplets of doublets of doublets), m (multiplet), br (broad). The numeration of atoms used in the assignment of NMR spectra is given in Figure 1.

HRMS were measured on the electrospray ionization (ESI) (Bruker MicroTOF, Karlsruhe, Germany) instrument with a time-of-flight (TOF) detector. Concentrations c in optical rotation [α]D values are given in 10⁻¹ deg cm² g⁻¹. Column chromatography was performed using Kieselgel (Merck, Germany) 40–60 μm 60A. Analytical thin-layer chromatography was performed on silica gel plates with QF 254. Visualization was accomplished with UV light and solution of anisaldehyde/H₂SO₄ in ethanol. Chiral HPLC analysis was performed on a chromatograph with a UV-VIS photodiode array detector (Shimadzu LC-20, Shimadzu, Japan). All reagents were commercial grade and used as received. Et₃N, dichloromethane (DCM), and MeCN were distilled over CaH₂ prior to the experiments; MeOH, hexane and ethyl acetate were distilled without drying agents.
(80 mg, 0.14 mmol) was dissolved in acetic acid (0.8 mL) and sodium cyanoborohydride (120 mg, 1.12 mmol) was added. The solution was cooled to $-40^\circ$C and pivaloyl chloride (174 µL, 1.41 mmol) was added. The reaction mixture was stirred at $-40^\circ$C for 2 h and then kept in a freezer (ca. $-25^\circ$C) overnight. The mixture was diluted with EtOAc (5 mL) and transferred into a separating funnel containing EtOAc (20 mL) and 0.25 M aq. NaHSO4 solution (20 mL). The aqueous layer was extracted with EtOAc (20 mL), the combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na2SO4 and concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 10/1) to give 311 mg (76%) of enantiopure or racemic pivalate 17.

(1S*,2R*,4S*,6S*)-(4-(3-(cyclopentyloxy)-4-methoxyphenyl)-6-((2-phenylcyclohexyl)oxy)-5,6-dihydro-4H-1,2-oxazin-3-yl)methyl pivalate. Rf = 0.44 (hexane/EtOAc = 3/1). 1H-NMR (300 MHz, COSY, HSQC, CDCl3) δ 7.41–7.13 (m, 5H, H14, H15, H16), 6.75 (d, J = 13.5 Hz, 1H, H17′), 4.08 (d, J = 13.0 Hz, 1H, H17′), 4.02 (dd, J = 10.3, 10.2, 4.0 Hz, 1H, Hα7), 3.98 (d, J = 13.5 Hz, 1H, H17′), 3.80 (s, 3H, H27), 2.92 (dd, J = 11.9, 7.7 Hz, 1H, Heq5), 2.61 (dd, J = 11.1, 10.3, 3.6 Hz, 1H, Hα8), 2.37 (m, 1H, H12), 2.01 (dd, J = 13.0, 7.7, 2.7 Hz, 1H, Heq5), 1.98–1.73 (m, 10H, Hα3, 3H, H9′, H10, H29, H30′). 13C-NMR (75 MHz, HSQC, CDCl3) δ 177.4 (C18), 155.3 (C3), 149.3 and 147.9 (C24 and C25), 144.4 (C13), 131.1 (C21), 128.0 and 127.8 (2 C14 and 2 C15), 125.9 (C16), 120.7 (C22), 114.9 (C26), 112.2 (C23), 91.0 (C6), 80.4 (C28), 76.1 (C7), 63.6 (C17), 56.1 (C27), 50.7 (C8), 38.6 (C19), 34.3 (C9), 33.8 (C4), 32.8 and 32.7 (C29 and C29′), 32.5 (C5), 30.6 (C12), 27.1 (3 C20), 26.1 (C11), 24.7 (C10), 24.0 (C30 and C30′). HRMS (ESI): m/z calcd. for [C34H46NO6]$: +$564.3320, found 564.3316 [M + H]$^+$. 

(+)-(1S,2R,4S,6S)-17. Colorless oil. [α]D = +188.6 (c = 0.09, EtOAc, 20 °C). rac-17. Colorless oil.

Hydride reduction of 5,6-dihydro-4H-1,2-oxazine 17. Procedure 1: Enantiopure or racemic pivalate 17 (80 mg, 0.14 mmol) was dissolved in acetic acid (0.8 mL) and sodium cyanoborohydride (120 mg, 1.9 mmol) was added to the solution upon intensive stirring. The reaction mixture was stirred under argon for 30 min at rt, then diluted with EtOAc (3 mL) and transferred into a separating funnel containing EtOAc (20 mL) and a sat. aq. NaHCO3 solution (20 mL). The aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with sat. aq. NaHCO3 solution (20 mL) and brine (40 mL), then dried over Na2SO4 and concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 10/1→5/1→3/1) to yield...
49 mg (62%) of a mixture of 1,2-oxazines 18 and 18′ (d.r. 3: 1). Also, 26 mg (33%) of unreacted pivalate 17 was isolated from the column chromatography.

Procedure 2: Enantiopure or racemic pivalate 17 (190 mg, 0.34 mmol) was dissolved in acetic acid (1.8 mL) and sodium cyanoborohydride (250 mg, 3.97 mmol) was added to the solution upon intensive stirring. The reaction mixture was stirred under argon for 1.5 h, then diluted with EtOAc (3 mL) and transferred into a separating funnel containing EtOAc (20 mL) and a sat. aq. NaHCO₃ solution (20 mL). The aqueous layer was extracted with EtOAc (20 mL). The combined organic layers were washed with sat. aq. NaHCO₃ solution (20 mL) and brine (40 mL), then dried over Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to a column chromatography on silica gel (Hexane/EtOAc = 10/1→5/1→3/1) to yield 48 mg (25%) of the fast moving isomer 18 and 69 mg (36%) of the slow moving isomer 18′.

((3R,4S,6S)- and (3R*,4S*,6S*)-4-(3-(Cyclopentyl)oxy)-4-methoxyphenyl)-6-((1S,2R)-2-phenylcyclohexyl) oxyl-1,2-oxazinan-3-yl)methyl pivalate (18). Colorless oil (both enantiopure and racemic). Rₐ = 0.37 (hexane/EtOAc = 3/1). ¹H-NMR (300 MHz, COSY, HSQC, CDECS) δ 7.55–7.32 (m, 4H, H14, H15), 7.29–7.21 (m, 1H, H16), 6.76 (d, J = 8.0 Hz, 1H, H23), 6.61 (dd, J = 8.0, 2.1 Hz, 1H, H22), 6.59 (br s, 1H, H26), 4.99 (d, J = 3.0 Hz, 1H, H6), 4.79–4.68 (m, 1H, H28), 4.03 (br d, J = 10.7 Hz, 1H, H30), 3.80 (s, 3H, H27), 3.78 (dd, J = 10.0, 10.0, 3.0 Hz, 1H, H31), 3.51 (dd, J = 11.8, 2.8 Hz, 1H, H32), 3.22 (br ddd, J = 10.7, 9.8, 8.5 Hz, 1H, H33), 3.08 (dd, J = 11.8, 8.5 Hz, 1H, H17), 2.68 (ddd, J = 12.3, 10.3, 3.7 Hz, 1H, H33α), 2.32 (ddd, J = 11.9, 11.9, 4.5 Hz, 1H, H4), 2.21 (br d, J = 10.6 Hz, 1H, H33β), 2.05–1.75 (m, 11H, H5, H9′, H10, H29, H30′), 1.70–1.54 (m, 3H, H9″, H30″), 1.48–1.25 (m, 3H, H11, H30′, 1.12 (s, 9H, H20). ¹³C-NMR (75 MHz, HSQC, HMBC, DEPT135, CDECS) δ 178.1 (C18), 149.1 and 147.8 (C24 and C25), 144.5 (C13), 133.9 (C21), 128.8 and 128.0 (2 × C14 and 2 × C15), 126.9 (C16), 119.5 (C22), 114.2 (C26), 112.3 (C23), 93.5 (C6), 80.5 (C28), 77.7 (C7), 63.3 (C17), 56.1 (C27), 50.7 (C8), 38.6 (C19), 37.2 (C4), 37.0 (C5), 33.3 (C9), 32.7 and 32.8 (C28 and C29′), 31.3 (C12), 27.1 (3 × C20), 26.0 (C11), 24.8 (C10), 24.0 (C30 and C30′). HRMS (ESI): m/z calc. for [C₉₅H₄₆NO₁₃]⁺ 566.3476, found 566.3474 [M + H]⁺.

((3R,4S,6R)- and (3R*,4S*,6R*)-4-(3-(Cyclopentyl)oxy)-4-methoxyphenyl)-6-((1S,2R)-2-phenylcyclohexyl) oxyl-1,2-oxazinan-3-yl)methyl pivalate (18′). Characterized in mixture with 18 (d.r. 18/18′ = 1: 4). Colorless oil (both enantiopure and racemic). Rₐ = 0.30 (hexane/EtOAc = 3/1). ¹H-NMR (300 MHz, COSY, HSQC, CDECS) δ 7.55–7.32 (m, 5H, H14, H15, H16), 6.79 (d, J = 8.2 Hz, 1H, H23), 6.60 (dd, J = 8.2, 2.2 Hz, 1H, H22), 6.55 (d, J = 2.2 Hz, 1H, H26), 5.43 (d, J = 10.4 Hz, 1H, H2), 5.28 (d, J = 2.9 Hz, 1H, H6), 4.73 (m, 1H, H28), 3.93 (dd, J = 10.3, 10.2, 4.0 Hz, 1H, H7), 3.81 (s, 3H, H27), 3.59 (d, J = 12.9 Hz, 1H, H17), 3.48 (ddd, J = 11.2, 10.4, 5.7 Hz, 1H, H33), 3.38 (dd, J = 12.9, 5.7 Hz, 1H, H17), 2.71 (ddd, J = 10.6, 10.3, 3.3 Hz, 1H, H8), 2.63 (ddd, J = 12.5, 11.2, 4.0 Hz, 1H, H30), 2.24 (br d, J = 11.9 Hz, 1H, H31), 2.06 (td, J = 13.3, 12.5, 2.9 Hz, 1H, H30), 1.99–1.76 (m, 10H, H33, H9′, H10, H29, H30′), 1.72–1.53 (m, 3H, H9″, H30″), 1.53–1.25 (m, 3H, H11, H30′), 1.10 (s, 9H, H20). ¹³C-NMR (75 MHz, HSQC, HMBC, DEPT135, CDECS) δ 177.4 (C18), 149.9 and 148.2 (C24 and C25), 143.7 (C13), 130.6 (C21), 129.6 (C16), 127.7 and 127.5 (2 × C14 and 2 × C15), 120.0 (C22), 113.7 (C26), 112.4 (C25), 95.2 (C6), 80.7 (C28), 78.5 (C7), 65.8 (C3), 61.3 (C17), 56.0 (C27), 50.5 (C8), 38.5 (C19), 36.7 (C4), 36.4 (C5), 33.1 (C9), 32.8 and 32.7 (C29 and C29′), 30.7 (C12), 27.0 (3 × C20), 25.8 (C11), 24.4 (C10), 24.0 (C30 and C30′). HRMS (ESI): m/z calc. for [C₉₅H₄₆NO₁₃]+ 566.3476, found 566.3476 [M + H]⁺.

Hydrogenation of 1,2-oxazines 18 and 18′. A glass vial was charged with a solution of enantiopure 1,2-oxazine 18 (48 mg, 0.086 mmol) and Boc₂O (58 mg, 0.264 mmol) in methanol (0.5 mL). A suspension of Raney nickel (ca. 100 mg, prepared from 50% slurry in water) in methanol (ca. 0.5 mL) was added, and the vial was placed in a steel autoclave, which was then flushed and filled with hydrogen to a pressure of ca. 40 bar and heated to 50 °C. The hydrogenation was conducted for 2 h with intensive stirring. Then, the autoclave was cooled to rt, slowly depressurized, and the catalyst was removed using a magnet and washed with methanol. The solution was concentrated to dryness under reduced pressure. The residue was subjected to a column chromatography on silica gel (hexane/EtOAc = 20/1→10/1) to yield 31 mg (74%) of N-Boc pyrrolidine 19. The column was then washed with hexane/EtOAc = 5/1 to recover (+)-trans-2-phenylcyclohexanol (12 mg, 77%).
Application of the same procedure for the reduction of enantiopure 1,2-oxazine 18 (69 mg, 0.13 mmol) afforded 36 mg (60%) of N-Boc pyrrolidine 19 and 15 mg (66%) of (+)-trans-2-phenylcyclohexanol.

Application of the same procedure for the reduction of a mixture of racemic 1,2-oxazines rac-18 and rac-18' (90 mg, 0.159 mmol, d.r. 1: 1.4) afforded 46 mg (61%) of racemic N-Boc pyrrolidine rac-19.

Tert-butyl (2R,3S)- and (2R*,3S*)-3-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-((pivaloyloxy)methyl) pyrrolidine-1-carboxylate (19). Rf = 0.30 (hexane/EtOAc = 3/1). 1H-NMR (300 MHz, CDCl3) δ 6.82 (d, J = 7.6 Hz, 1H, H13), 6.76 (d, J = 7.6 Hz, 1H, H12), 6.74 (s, 1H, H16), 5.13–4.88 (br, 1H, H10), 4.77 (m, 1H, H18), 3.97–3.85 (br m, 1H, H2), 3.83 (s, 3H, H17), 3.80–3.66 (br m, 2H, H9, H5*), 3.63 (dd, J = 11.5, 6.8 Hz, 1H, H5), 3.44–3.27 (br m, 1H, H5*), 2.89–2.79 (br m, 1H, H3), 2.22–2.07 (br m, 1H, H4*), 2.02–1.75 (m, 7H, H20, H19, H4'), 1.67–1.57 (m, 2H, H20'), 1.51 (s, 9H, H8). 13C-NMR (75 MHz, CDCl3) δ 178.2 (C10), 154.2 (C6), 148.9 and 147.9 (C16 and C22), 135.1 (C13), 119.2 (C14), 114.0 (C21), 112.3 (C15), 80.5 (C18), 80.0 (C7), 63.5 (br, 1H, H3), 2.35–2.18 (m, 1H, H4*), 2.01–1.76 (m, 7H, H4*, H19, H20'), 1.72–1.54 (m, 2H, H20'), 1.49 (s, 9H, H8), 1.21 (s, 9H, H12).

Saponification of pivalate 19. Enantiopure or racemic pivalate 19 (67 mg, 0.14 mmol) was dissolved in MeOH (2.8 mL) and a solution of KOH (237 mg, 4.2 mmol) in H2O (1.4 mL) was added. The mixture was stirred at room temperature for 24 h. Then, acetic acid (0.4 mL) was added and the reaction mixture was stirred for 5 min. The resulting solution was concentrated in vacuum. To the residue, MeOH (2 mL) and Boc2O (0.065 g, 0.28 mmol) were added and the resulting solution was stirred for 1 h. Then, volatiles were removed in vacuum and the residue was subjected to a column chromatography on silica gel (hexane/EtOAc = 5/1→3/1→1/1) to yield 46 mg (84%) of prolinol 20.

Tert-butyl (2R,3S)- and (2R*,3S*)-3-(3-(cyclopentyloxy)-4-methoxyphenyl)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (20). Rf = 0.21 (hexane/EtOAc = 1/1). 1H-NMR (300 MHz, CDCl3) δ 6.81 (d, J = 7.6 Hz, 1H, H13), 6.76 (d, J = 7.6 Hz, 1H, H12), 6.74 (s, 1H, H16), 5.13–4.88 (br, 1H, H10), 4.77 (m, 1H, H18), 3.97–3.85 (br m, 1H, H2), 3.83 (s, 3H, H17), 3.80–3.66 (br m, 2H, H9, H5*), 3.63 (dd, J = 11.5, 6.8 Hz, 1H, H5), 3.44–3.27 (br m, 1H, H5*), 2.89–2.79 (br m, 1H, H3), 2.22–2.07 (br m, 1H, H4*), 2.02–1.75 (m, 7H, H20, H19, H4'), 1.67–1.57 (m, 2H, H20'), 1.51 (s, 9H, H8). 13C-NMR (75 MHz, CDCl3) δ 178.2 (C10), 154.2 (C6), 151.0 (C5), 149.9 and 147.9 (C16 and C22), 135.1 (C13), 119.2 (C14), 114.0 (C21), 112.3 (C15), 80.5 (C18), 80.0 (C7), 63.5 (br, C9), 63.1 (br, C2), 56.2 (C17), 47.2 (C3), 46.3 (C5), 38.8 (C11), 32.8 (C19 and C19'), 31.8 (C4), 28.5 (3 C8), 27.2 (3 C12), 24.0 (C20 and C20') (signals are broadened due to the presence of N-Boc rotamers). HRMS (ESI): m/z calcld. for [C27H42NO6]+ 476.3007, found 476.3006 [M + H]+.

Synthesis of (−) and rac-CMPO. To a stirred solution of enantiopure or racemic prolinol 20 (45 mg, 0.115 mmol) in DCM (0.9 mL) was added CF3COOH (0.18 mL, 2.4 mmol) at 0–5 °C. The cooling bath was removed, and the solution was stirred for 1 h. Then, volatiles were removed under reduced pressure and the residue was dried until constant weight. The resulting trifluoroacetate was dissolved in DCM (0.85 mL), and Et3N (0.08 mL, 0.58 mmol) and 1,1′-carbonyldimidazole (47 mg, 0.29 mmol) were added at rt. The solution was stirred for 18 h at rt, and then concentrated under reduced pressure. The product was isolated by column chromatography on silica gel (hexane/EtOAc = 3/1) followed by recrystallization from hexane/diethyl ether (ca. 1: 1). Yield: 18 mg (49%). 1H NMR spectra were in agreement with previously published data [24].

(−)-(7S,7aR)-CMPO. White solid. Mp = 134–137 °C (lit.[24] 137–139 °C). HPLC analysis: ee > 97% (RT 9.8 min; column CHIRALPAK IA-3 (15 cm); solvent Hexane/i-PrOH = 90:10; temperature 40 °C; flow rate 1 mL/min). [α]D = −63.0 (c = 0.5, EtOAc, 25 °C). lit.[24] [α]D = −69.1 (c = 0.83, MeOH, 26 °C).

rac-CMPO. White solid. Mp = 103–104 °C (lit.[30] 99–101 °C). HPLC analysis: (+)-(7R,7aS)-CMPO (RT 8.8 min) and (−)-(7S,7aR)-CMPO (RT 9.8 min); column CHIRALPAK IA-3 (15 cm); solvent Hexane/i-PrOH = 90:10; temperature 40 °C; flow rate 1 mL/min.
5. Conclusions

In conclusion, we were able to solve the problem of site-selective C–H oxygenation of the cyclic nitronate intermediate in the asymmetric synthesis of a potent PDE4 inhibitor CMPO by using tandem acylation/(3,3)-sigmatropic rearrangement. In comparison with the previous synthesis, this method afforded the required 3-oxyethyl-substituted 1,2-oxazine intermediate in a much higher yield (76% vs. 27%). This key intermediate could be readily converted into the target (−)-CMPO by the reductive contraction of the 1,2-oxazine ring followed by deprotection and carbamylation with Im$_2$CO. A rapid epimerization of the C-6 acetal moiety was observed upon the reduction of the 5,6-dihydro-4H-1,2-oxazine ring with NaBH$_3$CN in acetic acid. DFT calculations suggest that the epimerization is favored by an unprecedented double anchimeric assistance from a remote acyloxy group and the nitrogen atom of the 1,2-oxazine ring.

**Supplementary Materials:** The following are available online: NMR spectra for compounds 10, 17, 18, 18’, 19, 20 and CMPO, chiral phase HPLC chromatograms for rac-CMPO and (−)-CMPO, Cartesian coordinates, absolute energies for all optimized geometries.

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**Sample Availability:** Samples of racemic and enantiopure PDE4 inhibitor CMPO are available from the authors.

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