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Synthesis of PDE IVb Inhibitors. 3. Synthesis of (+)-, (−)-, and (±)-7-[3-(Cyclopentyloxy)-4-methoxyphenyl]hexahydro-3*H*-pyrrolizin-3-one via Reductive Domino Transformations of 3-β-Carbomethoxyethyl-Substituted Six-Membered Cyclic Nitronates

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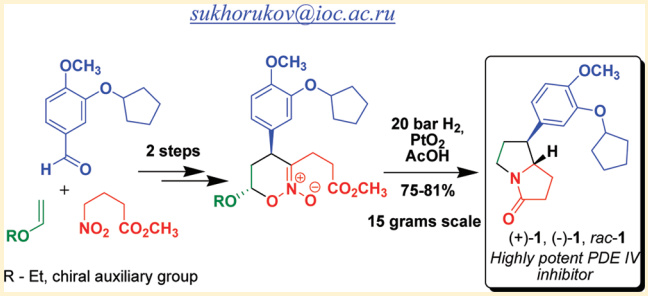
Supporting Information

ABSTRACT: Simple three-step asymmetric and racemic syntheses of GlaxoSmithKline's highly potent PDE IVb inhibitor **1** were developed. The suggested approach is based on reductive domino transformations of 3-β-carbomethoxyethyl-substituted six-membered cyclic nitronates, which are easily accessed by a stereoselective [4 + 2] cycloaddition of an appropriate nitroalkene to vinyl ethers. In vitro studies of PDE IVb inhibition by enantiomeric pyrrolizidinones (+)-**1** and (−)-**1** were performed.



7-[3-(Cyclopentyloxy)-4-methoxyphenyl]hexahydro-3*H*-pyrrolizin-3-one (**1**; Scheme 1) is a highly potent second-generation phosphodiesterase (PDE) IVb inhibitor considered as a drug candidate for the treatment of respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD).[1] Pyrrolizidinone **1** is several times more potent than the standard PDE IVb inhibitor Rolipram and the recently introduced anti-inflammatory drug Cilomilast.[1a] However, the biological activity of the pyrrolizidinone's **1** enantiomers still remains unknown. To perform full-scale biological studies, an efficient asymmetric synthesis of pyrrolizidinone **1** on a preparative scale is needed.

Previously, several approaches to the total synthesis of racemic[1a,2b] and enantiomerically pure[2a,c] pyrrolizidinone **1** were suggested. The major disadvantages of all these methods are low overall yield and large number of synthetic steps (minimum six steps for racemic **1** and seven steps for enantiomers) as well as low stereoselectivity on key stages. In the present work, a simple, scalable, three-step synthesis of the racemate and both enantiomers of pyrrolizidinone **1** from available precursors was developed.

We speculated that the target molecule **1** may result from a reductive domino transformation of the C-3-functionalized six-membered cyclic nitronate **2** shown in Scheme 1. This multistage process should involve the reduction of the nitronate fragment to an amino group, fragmentation of the resulting semiacetal **A** into aldehyde **B**, cyclization of intermediate **B** to pyrroline **C**, reduction of **C** to pyrrolidine **D**, and finally lactamization of **D** to give pyrrolizidinone **1**. Furthermore, in order to get the desired diastereomer of product **1**, the reduction of the C=N bond should occur trans stereoselective with respect to the substituent at C-4 of nitronate **2**.[3]

Cyclic nitronates **2** can be assembled by a Lewis acid catalyzed [4 + 2] cycloaddition of nitroalkene **3** to the corresponding vinyl ether according to Denmark's procedure.[4] Nitroalkene **3** in turn can be obtained by Henry condensation of commercially available 3-(cyclopentyloxy)-4-methoxybenzaldehyde and methyl 4-nitrobutyrate (Scheme 2). To obtain the target product **1** asymmetrically, it is necessary to incorporate a chiral auxiliary in nitronate **2** by employing an optically pure vinyl ether on the cycloaddition step. It is known that the vinyl ether of *trans*-2-phenylcyclohexanol produces the corresponding nitronates in [4 + 2] cycloaddition reactions with high stereocontrol.[2c,4a,c,5] Indeed, the reaction of nitroalkene **3** with racemic *trans*-1-phenyl-2-(vinyloxy)cyclohexane in the presence of $SnCl_4$ gave the corresponding cyclic nitronate *rac*-**2a** in 63% yield (Scheme 2). Only two of the four possible stereoisomers were formed with predominance of isomer **2a** (ratio **2a**/**2a**′ = 8.3:1). The isomers can be easily separated by flash chromatography or crystallization. The structure and stereochemistry (4*S**,6*S**,7*S**,8*R**) of major isomer **2a** was established by X-ray crystallographic analysis (Figure 1,

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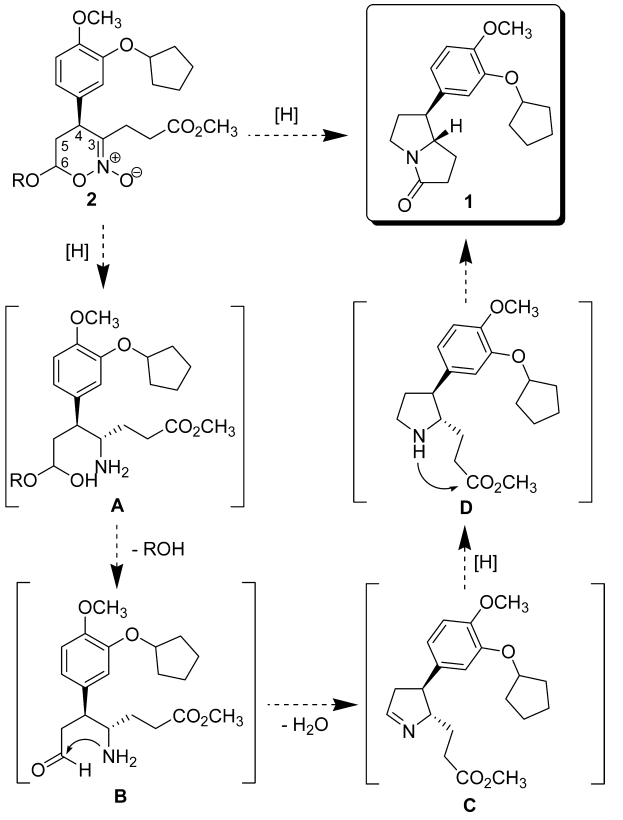
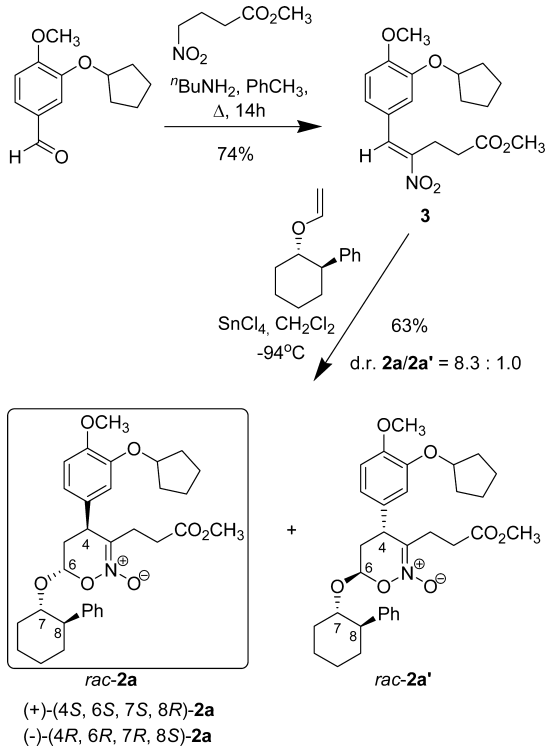
Scheme 1. Proposed Reductive Domino Transformation of Nitronates 2



Scheme 2. Synthesis of Nitronates 2a



Supporting Information).[6] The minor nitronate **2a′** according to NMR also has a 4,6-trans configuration of stereocenters in the 1,2-oxazine ring, thus being a facial isomer of **2a**.

To explore the possibility of the transformation **2** → **1** and to optimize this process, the reduction of nitronate **2a** under various conditions was studied (Scheme 3, Table 1).

As can be seen from Table 1, nitronate **2a** did not react with conventional N−O bond reducing agents such as zinc and sodium dithionite (entries 1 and 2). However, under catalytic hydrogenation conditions nitronate **2a** usually produced pyrrolizidinone **1** in good to high yields. The stereoselectivity of the reduction process depended on the nature of the catalyst. Thus, the hydrogenation of nitronate **2a** with Raney nickel led to a mixture of diastereomeric products **1** and **1′** with a slight predominance of the second isomer (entry 3, Table 1). Supported palladium and rhodium catalysts also afforded mixtures of **1** and **1′** in a similar ratio (entries 4−6 and 8, Table 1). The most efficient catalyst in terms of stereoselectivity and yield of target product proved to be the Adams catalyst (entry 7, Table 1). Hydrogenation of nitronate **2a** with Wilkinson's catalyst produced a multicomponent mixture of products rather than the desired pyrrolizidinone **1** (entry 9, Table 1).

To perform asymmetric synthesis of pyrrolizidinone **1**, optically pure cyclic nitronates (+)-**2a** and (−)-**2a** were prepared from nitroalkene **3** and available (+)- and (−)-*trans*-1-phenyl-2-(vinyloxy)cyclohexanes, respectively (Scheme 2). The nitronates (+)-**2a** and (−)-**2a** were isolated by crystallization with high diastereomeric purity (de > 99%). The catalytic hydrogenation of each enantiomer (+)-**2a** or (−)-**2a** in acetic acid with the Adams catalyst (entry 7, Table 1) afforded pyrrolizidinones **1** + **1′** in high yield (75%) and stereoselectivity (ca. 7:1).[7] Diastereomerically pure products (+)-**1** and (−)-**1** were isolated by flash chromatography of reaction mixtures. As a result, pyrrolizidinone (−)-(7*S*,7a*S*)-**1** was obtained from nitronate (+)-**2a**, and pyrrolizidinone (+)-(7*R*,7a*R*)-**1** was prepared from nitronate (−)-**2a**. All physicochemical characteristics of products (+)-**1** and (−)-**1** were consistent with literature data.[1a,2] It should be noted that enantiopure (+)- and (−)-*trans*-2-phenylcyclohexanols were recovered after hydrogenation in 90% yield (Scheme 3).

The developed process was employed for the synthesis of racemic pyrrolizidinone **1** on a preparative scale (Scheme 4). In this synthesis racemic cyclic nitronate **2b** was prepared by $SnCl_4$-promoted [4 + 2] cycloaddition of nitroalkene **3** to ethyl vinyl ether. Subsequent hydrogenation of nitronate **2b** with Adams catalyst provided a mixture of racemic pyrolizidinones **1** and **1′** in a 4.5:1 ratio and 81% yield (Scheme 4). The pure diastereomer *rac*-**1** could be isolated by flash chromatography and crystallization. Hydrogenation of nitronate **2b** with Adams catalyst in MeOH led to pyrrolizidinone **1** with the same stereoselectivity, but considerably less yield (57%).

The sequence shown in Scheme 4 was successfully tested on 12.5 g of nitroalkene **3** (ca. 15 grams of nitronate **2b** was hydrogenated at once). As a result, ca. 5.5 g of pure *rac*-**1** (47% yield from nitroalkene **3**) was obtained. For the catalytic hydrogenation only 2% mass of PtO_2 was used, and 98% of the platinum was recovered.

Thus, the target PDE IVb inhibitor **1** was synthesized in only three steps in overall yields of 28% (for enantiomers (+)-**1** and (−)-**1**) and 38% (for racemate *rac*-**1**) starting from commercially available precursors (methyl 4-nitrobutyrate and 3-(cyclopentyloxy)-4-methoxybenzaldehyde). The best previous syntheses afforded enantiopure **1** in 16% yield (seven steps[2c]) and *rac*-**1** in 23% yield (six steps[2b]).

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Scheme 3. Reduction of Racemic and Chiral Nitronates 2a

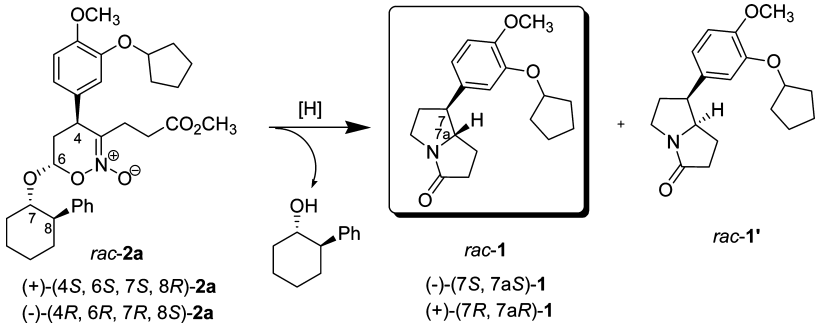
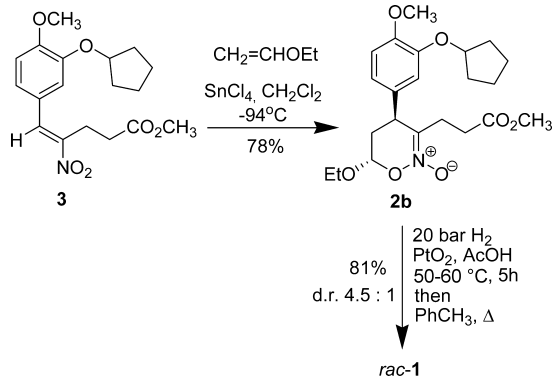


Table 1. Optimization of Nitronate's 2a Reduction

entry	cat.	reduction conditions	yield of **1** + **1′**, %[a]	**1**/**1′** ratio[a]
1		Zn, EtOH, reflux	n.r.[b]	
2		$Na_2S_2O_4$, EtOH, H_2O, reflux	n.r.[b]	
3	Ra–Ni	20 bar H_2, 50–60 °C, CH_3OH, 2 h	65	1.0:1.5
4	5% Pd/C	25 bar H_2, 50–60 °C, CH_3OH, 6 h	58	1.4:1.0
5	0.5% Pd/Al_2O_3	20 bar H_2, 60–70 °C, EtOH, 2 h	92	1.0:2.3
6	5% $Pd/CaCO_3$ (3.5% Pb)	20 bar H_2, 50–60 °C, CH_3OH, 2 h	55	1.7:1.0
7	PtO_2	20 bar H_2, 50–60 °C, AcOH, 2 h	77	7.0:1.0
8	5% Rh/Al_2O_3	20 bar H_2, 50–60 °C, CH_3OH, 2 h	52	1.8:1.0
9	$Rh(PPh_3)_3Cl$	20 bar H_2, 50–60 °C, CH_3OH, 2 h	0[c]	

[a]Determined by ^1H NMR analysis with external standard. [b]n.r. = no reaction. [c]Complex mixture of unidentified products.

Scheme 4. Synthesis of Racemic Pyrrolizidinone *rac*-1



The enantiomers (−)-(7*S*,7a*S*)-**1** and (+)-(7*R*,7a*R*)-**1** were both tested for their ability to inhibit cAMP hydrolysis catalyzed by PDE IVb. The (−)-**1** enantiomer inhibited PDE IVb with an IC_{50} of 84 nM, and the (+)-**1** enantiomer had an IC_{50} of 161 nM, thus being 2 times less active.

In conclusion, a simple three-step synthesis of racemic and enantiopure PDE IVb inhibitor **1** was developed. The suggested approach is based on a novel reductive domino transformation of C-3-functionalized six-membered cyclic nitronates, which are available by [4 + 2] cycloaddition of nitroalkenes to vinyl ethers. This strategy involves only two C–C bond formation steps and one ring formation step and can be considered as the most rapid method for the construction of a pyrrolizine scaffold which is present in many natural and bioactive molecules. Pyrrolizidinone (−)-(7*S*,7a*S*)-**1** was shown to be a more potent PDE IVb inhibitor than its enantiomer (+)-(7*R*,7a*R*)-**1**.

EXPERIMENTAL SECTION

1D and 2D NMR spectra were recorded at room temperature in $CDCl_3$. The chemical shifts (^1H, ^{13}C) are given in ppm (δ) relative to the solvent signal.[8] Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), and br (broad). The numbering of atoms in products **2a**,**a′**,**b** and **3** is given in the Supporting Information. HRMS were measured on a electrospray ionization (ESI) instrument with a time-of-flight (TOF) detector. Concentrations *c* in the optical rotation angles are given in g/100 mL. Analytical thin-layer chromatography was performed on silica gel plates with QF-254. Visualization was accomplished with UV light, a solution of $FeCl_3$ in aqueous hydrochloric acid, or a solution of anisaldehyde/H_2SO_4 in ethanol. Catalytic hydrogenations were carried out in a steel autoclave with external stirring and heating. Flash chromatography was performed using Kieselgel 40–60 μm 60A silica gel. Glacial acetic acid was recrystallized two times. CH_2Cl_2 (technical grade) and ethyl vinyl ether were redistilled from CaH_2. Hexane, ethyl acetate, diethyl ether, toluene, ethanol, and methanol were distilled without drying agents. Racemic, (+)-*trans*-, and (−)-*trans*-1-phenyl-2-(vinyloxy)cyclohexanes were synthesized from commercially available racemic, (+)-*trans*-, and (−)-*trans*-2-phenylcyclohexanols (>98% ee) according to known procedures.[2c] Adams catalyst (PtO_2), Raney nickel (50% slurry in water), palladium on activated carbon (5% Pd), palladium on γ-Al_2O_3 (0.5% Pd), palladium on calcium carbonate (5% Pd, 3.5% Pb), rhodium on activated alumina (5% Rh), and $Rh(PPh_3)_3Cl$ were purchased from commercial sources. PDE IVb activity was monitored by using a PDE assay kit (Enzo) adapted to human recombinant phosphodiesterase isoform PDE IVb expressed in *E. coli* (for details see the Supporting Information).

Methyl (4*E*)-5-[3-(Cyclopentyloxy)-4-methoxyphenyl]-4-nitropent-4-enoate (3). To a solution of 3-(cyclopentyloxy)-4-methoxybenzaldehyde[9] (15.0 g, 68.0 mmol) in toluene (40 mL) was added methyl 4-nitrobutyrate (10.0 g, 68.0 mmol) and *n*-butylamine (1.0 mL, 0.74 g, 10.0 mmol). The mixture was refluxed with a Dean–Stark water trap. After the theoretical amount of water was collected (ca. 14 h), the reaction mixture was concentrated under vacuum. The residue was crystallized from EtOH to give 17.5 g (74%) of nitroalkene **3** as yellow crystals. Mp: 75–77 °C. HRMS: *m*/*z* 372.1419 (positive ions), calcd for $[C_{18}H_{23}NO_6Na^+]$ 372.1418. Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.84; H, 6.94; N, 4.16. ^1H NMR (300 MHz, HSQC): 1.56–1.60 and 1.75–2.03 (2 m, 2 and 6 H, 15-CH_2 and 16-CH_2), 2.69 and 3.24 (dd, J = 8.7, 8.0 Hz and dd, J = 8.7, 8.0 Hz, 2 and 2 H, 3-CH_2 and 4-CH_2), 3.69 (s, 3 H, 6-CH_3), 3.89 (s, 3 H, 13-CH_3), 4.79 (m, 1 H, 14-CH), 6.93 (d, J = 8.4 Hz, 1 H, 12-CH), 7.01 (s, 1 H, 8-CH), 7.07 (d, J = 8.4 Hz, 1 H, 11-CH), 8.07 (s, 1 H, 1-CH). ^{13}C NMR (75.47 MHz, HSQC, DEPT): 23.2 and 31.8 (3-C and 4-C), 24.0 and 32.8 (15-C and 16-C), 51.8 (6-C), 56.0 (13-C), 80.7 (14-C), 112.0 (11-C), 116.0 (8-C), 124.1 (7-C),

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124.2 (12-C), 135.4 (1-C), 147.6 and 148.0 (9-C and 10-C), 152.4 (2-C), 172.3 (5-C).

Methyl 3-{4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-2-oxo-6-[(2-phenylcyclohexyl)oxy]-5,6-dihydro-4*H*-1,2-oxazin-3-yl}-propanoate (2a). A solution of nitroalkene **3** (0.790 g, 2.26 mmol) and enantiopure or racemic *trans*-1-phenyl-2-(vinyloxy)cyclohexane (0.750 g, 3.71 mmol) in CH_2Cl_2 (37.5 mL) was cooled to −94 °C (acetone/liquid nitrogen), and $SnCl_4$ (0.334 mL, 0.745 g, 2.85 mmol) was added under argon with intensive stirring. The resulting dark solution was stirred at the same temperature for 15 min and poured into a mixture of EtOAc (150 mL) and a saturated solution of K_2CO_3 (150 mL). The aqueous layer was back-extracted with EtOAc (2 × 50 mL). The combined organic layers were then washed with a saturated solution of K_2CO_3 (100 mL), water (100 mL), and brine (100 mL), dried with Na_2SO_4, and evaporated under vacuum. The residue was preadsorbed on silica gel and subjected to flash chromatography on silica gel (eluent EtOAc/hexane 10/1 → 5/1 → 3/1 → 1/1). Three fractions were collected. The first fraction contained 0.233 g of unreacted nitroalkene **3** (30% recovered), the second fraction contained 0.084 g of nitronate **2a′** (7%), and the third fraction contained 0.702 g of nitronate **2a** (56%). The major nitronate **2a** was crystallized from MeOH to give analytically pure material with de > 99% (determined by ^{1}H 500 MHz NMR spectroscopy analysis).

*Data for Major Isomer **2a**.* R_f = 0.30 (hexane/EtOAc 1/1). HRMS (for *rac*-**2a**): *m*/*z* 552.2953 (positive ions), calcd for $[C_{32}H_{42}NO_7^+]$ 552.2956. Anal. Calcd for $C_{32}H_{41}NO_7$: C, 69.67; H, 7.49; N, 2.54. Found: C, 69.50; H, 7.70; N, 2.58. ^{1}H NMR (500 MHz, COSY, HSQC): 1.29 (ddd, *J* = 12.6, 11.0, 10.4, 3.0 Hz, 1 H, 12-CH_{ax}), 1.37 (m, 1 H, 11-CH), 1.40−1.57 (2 m, 2 H, 9-CH and 10-CH), 1.58−1.64 (m, 2 H, 26-CH), 1.67 (ddd, *J* = 16.6, 11.5, 4.3 Hz, 1 H, 28-CH), 1.75−1.95 (2 m, 10 H, 9-CH, 10-CH, 11-CH, 25-CH_2, 26-CH and 27-CH), 2.03 (m, 3 H, 5-CH_2 and 27-CH), 2.22 (ddd, *J* = 16.6, 11.4, 4.9 Hz, 1 H, 28-CH), 2.35 (ddd, *J* = 12.6, 3.7, 2.9 Hz, 1 H, 12-CH_{eq}), 2.61 (ddd, *J* = 12.8, 10.4, 3.1 Hz, 1 H, 8-CH_{ax}), 3.24 (dd, *J* = 9.8, 9.2 Hz, 1 H, 4-CH_{ax}), 3.58 (s, 3 H, 30-CH_3), 3.81 (s, 3 H, 23-CH_3), 4.18 (ddd, *J* = 10.4, 10.4, 3.7 Hz, 1 H, 7-CH_{ax}), 4.70 (m, 1 H, 24-CH), 5.57 (dd, *J* = 2.3, 1.7 Hz, 1 H, 6-CH_{eq}), 6.52 (d, *J* = 1.5 Hz, 1 H, 18-CH), 6.59 (dd, *J* = 8.6, 1.5 Hz, 1 H, 22-CH), 6.75 (d, *J* = 8.6 Hz, 1 H, 21-CH), 7.20 (t, *J* = 7.0 Hz, 1 H, 16-CH), 7.27 (d, *J* = 7.6 Hz, 2 H, 14-CH), 7.34 (dd, *J* = 7.6, 7.0 Hz, 2 H, 15-CH). ^{13}C NMR (75.47 MHz, HSQC, DEPT): 24.1 (9-C), 24.5 (26-C), 26.0 and 26.3 (10-C and 27-C), 28.0 (28-C), 30.2 (12-C), 32.7 and 32.8 (25-C), 33.5 and 34.5 (5-C and 11-C), 38.9 (4-C), 50.7 (8-C), 51.6 (30-C), 56.0 (23-C), 76.5 (7-C), 80.3 (24-C), 95.5 (6-C), 111.8 (21-C), 114.2 (18-C), 120.6 (22-C), 124.4 (3-C), 126.3 (16-C), 127.4 (14-C), 129.0 (15-C), 131.0 (17-C), 144.1 (13-C), 147.8 and 149.4 (19-C and 20-C), 172.8 (29-C).

rac-**2a** (obtained from racemic *trans*-1-phenyl-2-(vinyloxy)-cyclohexane): mp 63−69 °C.

(+)-(4*S*,6*S*,7*S*,8*R*)-**2a** (obtained from (+)-*trans*-1-phenyl-2-(vinyloxy)cyclohexane): mp 115 −118 °C; $[\alpha]_D$ = +224.5° (MeOH, *c* = 1, 26 °C).

(−)-(4*R*,6*R*,7*R*,8*S*)-**2a** (obtained from (−)-*trans*-1-phenyl-2-(vinyloxy)cyclohexane): mp 114 −117 °C; $[\alpha]_D$ = −213.8° (MeOH, *c* = 1, 28 °C).

*Data for Minor Isomer rac-**2a′**.* Colorless oil. R_f = 0.43 (hexane/EtOAc 1/1). HRMS: *m*/*z* 552.2956 (positive ions), calcd for $[C_{32}H_{42}NO_7^+]$ 552.2956. ^{1}H NMR (300 MHz, COSY, HSQC): 1.33 (dddd, *J* = 13.5, 11.6, 8.3, 3.6 Hz, 1 H, 12-CH_{ax}), 1.40−1.52 (m, 2 H, 10-CH and 11-CH), 1.52−1.63 (m, 3 H, 9-CH, 26-CH), 1.64−1.80 (m, 3 H, 5-CH_2, 11-CH), 1.80−1.96 (m, 8 H, 9-CH, 10-CH, 25-CH_2, 26-CH), 2.14 (ddd, *J* = 13.5, 8.1, 3.0 Hz, 1 H, 12-CH_{eq}), 2.21−2.47 (m, 3 H, 27-CH_2, 28-CH), 2.53 (ddd, *J* = 12.2, 9.0, 4.5 Hz, 1 H, 8-CH_{ax}), 2.81 (ddd, *J* = 14.9, 8.2, 6.7 Hz, 1 H, 28-CH), 3.66 (s, 3 H, 30-CH_3), 3.77−3.87 (s and m, 5 H, 4-CH, 7-CH and 23-CH_3), 4.41 (dd, *J* = 2.6, 2.3 Hz, 1 H, 6-CH_{eq}), 4.71 (m, 1 H, 24-CH), 6.59 (d, 1.7 Hz, 1 H, 18-CH), 6.68 (dd, *J* = 8.2, 1.7 Hz, 1 H, 22-CH), 6.77 (d, *J* = 8.2 Hz, 1 H, 21-CH), 7.11−7.34 (m, 5 H, 14-CH, 15-CH and 16-CH). ^{13}C NMR (75.47 MHz): 24.0 (26-C), 25.1 (9-C), 25.7 (10-C), 26.2 (27-C), 27.6 (28-C), 32.4 (11-C), 32.7 (25-C), 33.9 and 34.0 (5-C and 12-C), 39.6 (4-C), 51.5 (8-C), 51.6 (30-C), 56.1 (23-C), 80.5 (24-C), 82.5 (7-C), 101.6 (6-C), 112.3 (21-C), 114.5 (18-C), 120.5 (22-C), 125.7 (3-C), 126.6 (16-C), 127.9 (14-C), 128.3 (15-C), 132.0 (17-C), 143.7 (13-C), 145.7 and 148.1 (19-C and 20-C), 173.6 (29-C).

Methyl 3-{4-[3-(Cyclopentyloxy)-4-methoxyphenyl]-6-ethoxy-2-oxo-5,6-dihydro-4*H*-1,2-oxazin-3-yl}propanoate (2b). $SnCl_4$ (0.143 mL, 0.299 g, 1.15 mmol) was added to a solution of nitroalkene **3** (0.400 g, 1.15 mmol) in CH_2Cl_2 (7.5 mL) at −94 °C under an argon atmosphere. Ethyl vinyl ether (0.27 mL, 0.203 g, 2.82 mmol) was added dropwise to the reaction mixture with intensive stirring. The resulting solution was warmed to −40 °C within 30 min and then 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 × 50 mL). The combined organic layers were then washed with a saturated solution of K_2CO_3 (100 mL), water (100 mL), and brine (100 mL), dried with Na_2SO_4, and evaporated under vacuum. The residue was subjected to flash chromatography on silica gel (eluent EtOAc/hexane 10/1 → 5/1 → 3/1 → 1/1) to give 0.378 g (78%) of nitronate **2b**. Colorless oil. R_f = 0.21 (hexane/EtOAc = 1:1). HRMS: *m*/*z* = 422.2187 (positive ions); calcd for $[C_{22}H_{32}NO_7^+]$: 422.2184. Anal. Calcd for $C_{22}H_{31}NO_7$: C, 62.69; H, 7.41; N, 3.32. Found: C, 62.67; H, 7.45; N, 3.36. ^{1}H NMR (300 MHz, COSY, HSQC): 1.27 (t, *J* = 7.0 Hz, 3 H, 8-CH_3), 1.53−1.67 (m, 2 H, 18-CH), 1.76−1.98 (m, 6 H, 17-CH_2 and 18-CH), 2.12 (ddd, *J* = 13.8, 11.1, 2.5 Hz, 1 H, 5-CH_{ax}), 2.26 (ddd, *J* = 13.8, 7.9, 1.6 Hz, 1 H, 5-CH_{eq}), 2.36 (ddd, *J* = 15.0, 7.1, 3.6 Hz, 1 H, 20-CH), 2.40 (ddd, *J* = 14.6, 7.1, 3.0 Hz, 1 H, 19-CH), 2.53 (ddd, *J* = 14.6, 11.5, 3.6 Hz, 1 H, 19-CH), 2.84 (ddd, *J* = 15.0, 11.5, 3.0 Hz, 1 H, 20-CH), 3.56 (s, 3 H, 22-CH_3), 3.72 (m, 1 H, 7-CH), 3.84 (s, 3 H, 15-CH_3), 3.94 (dd, *J* = 11.1, 7.9 Hz, 1 H, 4-CH_{ax}), 4.02 (m, 1 H, 7-CH), 4.76 (m, 1 H, 16-CH), 5.36 (dd, *J* = 2.5, 1.6 Hz, 1 H, 6-CH_{eq}), 6.70 (d, *J* = 1.4 Hz, 1 H, 10-CH), 6.77 (dd, *J* = 8.1, 1.4 Hz, 1 H, 14-CH), 6.83 (d, *J* = 8.1 Hz, 1 H, 13-CH). ^{13}C NMR (75.47 MHz, HSQC, DEPT): 15.0 (8-C), 24.0 (18-C), 26.3 (19-C), 27.7 (20-C), 32.7 (17-C), 34.4 (5-C), 39.8 (4-C), 51.6 (22-C), 56.1 (15-C), 64.8 (7-C), 80.5 (16-C), 101.2 (6-C), 112.5 (13-C), 114.7 (10-C), 120.5 (14-C), 125.7 (3-C), 131.9 (9-C), 148.2 and 149.7 (11-C and 12-C), 172.8 (21-C).

The reaction was performed on 12.5 g of nitroalkene **3**. Instead of flash chromatography a simple filtration through a short pad of silica gel (h = 3 cm, d = 6 cm) was used to remove ethyl vinyl ether polymer. C.a. Fifteen g of crude nitronate **2b** was obtained, which was subjected to hydrogenation without special purification.

(+) and (−)-7-[3-(Cyclopentyloxy)-4-methoxyphenyl]-hexahydro-3*H*-pyrrolizin-3-ones (1). PtO_2 (0.0145 g) was added to a solution of nitronate (+)-**2a** or (−)-**2a** (0.25 g, 0.45 mmol) in AcOH (5.0 mL). The mixture was hydrogenated at 20 bar H_2 and 60 °C for 4 h in a steel autoclave with external stirring. Then autoclave was slowly depressurized and the catalyst was filtered off. The solvent was evaporated in vacuum, the residue was dissolved in toluene (8 mL) and the solution was gently refluxed for 30 min. The solvent was evaporated in vacuum and the residue was preadsorbed on silica gel. Flash chromatography (eluent EtOAc/hexane 1/10 → 1/5 → 1/1 then MeOH/EtOAc 0/1 → 1/10) provided three fractions: the EtOAc/hexane fraction contained *trans*-2-phenylcyclohexanol (0.072 g, 90%), the EtOAc fraction contained 0.013 g (9%) of the minor isomer **1′**, and the EtOAc/MeOH fraction contained 0.094 g (66%) of target pyrrolizidinone (−)-**1** or (+)-**1** (de > 95%). ^{1}H NMR ($CDCl_3$, 300 MHz): 1.55−1.68 and 1.75−1.97 (2 m, 2 and 7 H), 2.17−2.32 (m, 2 H), 2.45−2.53 (m, 2 H), 2.63−2.80 (m, 2 H), 3.33 (dd, *J* = 10.8, 10.3 Hz, 1 H), 3.63 (ddd, *J* = 10.6, 9.6, 8.7 Hz, 1 H), 3.82 (s, 3 H), 3.91 (ddd, *J* = 9.4, 7.2, 7.1 Hz, 1 H), 4.77 (m, 1 H), 6.72 (s, 1 H), 6.73 (d, *J* = 8.1 Hz, 1 H), 6.83 (d, *J* = 8.1 Hz, 1 H). NMR data of obtained pyrrolizidinones **1** are consistent with those previously reported in the literature.[1a,2]

*(−)-(7S,7aS)-**1** (Obtained from (+)-**2a**):* colorless oil; $[\alpha]_D$ = −63.2° ($CHCl_3$, *c* = 0.3, 25 °C) (lit.[2c] $[\alpha]_D$ = −65.9° ($CHCl_3$, *c* = 0.35, 24 °C)).

*(+)-(7R,7aR)-**1** (Obtained from (−)-**2a**):* colorless oil; $[\alpha]_D$ = +64.9° ($CHCl_3$, *c* = 0.3, 29 °C) (lit.[2c] $[\alpha]_D$ = +64.2° ($CHCl_3$, *c* = 0.35, 23 °C), lit.[2a] $[\alpha]_D$ = +62.6 ($CHCl_3$, *c* = 0.35, 20 °C)).

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*(+)-trans-2-Phenylcyclohexanol (Obtained from (+)-**2a**):* mp 60–61 °C (lit. 63–66 °C, Aldrich); $[\alpha]_D$ = +54.6° (MeOH, *c* = 1.83, 26 °C) (lit. [10] $[\alpha]_D$ = +57.3° (MeOH, *c* = 5, 20 °C)). ^{1}H NMR spectra is in accordance with literature data.[11]

*(−)-trans-2-Phenylcyclohexanol (Obtained from (−)-**2a**):* mp 60–64 °C (lit. 63–66 °C, Aldrich); $[\alpha]_D$ = −55.1° (MeOH, *c* = 1.83, 25 °C) (lit. [11] $[\alpha]_D$ = −56.8° (MeOH, *c* = 1.42)). The ^{1}H NMR spectrum is in accordance with literature data.[11]

***rac*-7-[3-(Cyclopentyloxy)-4-(methyloxy)phenyl]hexahydro-3*H*-pyrrolizin-3-one (1).** PtO_2 (0.050 g) was added to a solution of nitronate **2b** (1.0 g, 2.37 mmol) in AcOH (20.0 mL). The mixture was hydrogenated at 20 bar of H_2 and 50–60 °C for 5 h in a steel autoclave with external stirring. Then the autoclave was slowly depressurized and the catalyst was filtered off. The solvent was evaporated under vacuum, and the residue was dissolved in toluene (40 mL). The solution was gently refluxed for 30 min, and then the solvent was evaporated under vacuum. Flash chromatography of the residue and subsequent crystallization from Et_2O provided 0.110 g (15%) of *rac*-**1′** as an oil and 0.496 g of *rac*-**1** (66%) as white crystals (mp 66–70 °C, lit.[1a] mp 64–66 °C, lit.[2c] mp 67–68 °C). ^{1}H NMR spectra of *rac*-**1** and *rac*-**1′** are in accordance with literature data.[1a,2]

Hydrogenation was performed on ca. 15 g of nitronate **2b** with 0.35 g of PtO_2 in 190 mL of AcOH (10 h). As a result, 5.35 g of *rac*-**1** (47% from nitroalkene **3**) was isolated by dry column vacuum chromatography[12] and subsequent crystallization from Et_2O. 0.296 g (98%) of platinum black was recovered.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving NMR spectra of new compounds, a CIF file giving crystallographic data for compound **2a**, and text and figures giving details of the PDE assay. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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