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# Synthesis of PDE IVb Inhibitors. 1. Asymmetric Synthesis and Stereochemical Assignment of (+)- and (−)-7-[3-(Cyclopentyloxy)-4-methoxyphenyl]hexahydro-3*H*-pyrrolizin-3-one

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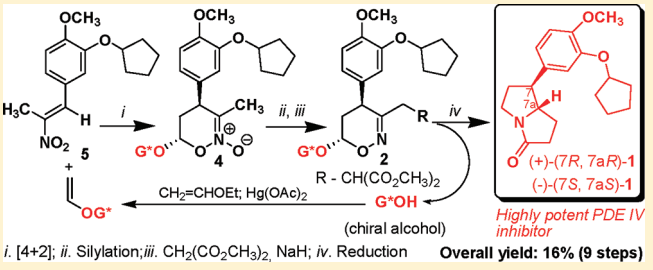
Supporting Information

**ABSTRACT:** Asymmetric synthesis of GlaxoSmithKline's highly potent phosphodiesterase inhibitor **1** has been accomplished in nine steps and 16% overall yield. The original strategy suggested involves as a key step the silylation of enantiopure six-membered cyclic nitronates **4** obtained by a highly stereoselective [4 + 2]-cycloaddition of an appropriate nitroalkene **5** to *trans*-1-phenyl-2-(vinyloxy)cyclohexane. Functionalization of the resulting 5,6-dihydro-4*H*-1,2-oxazine and subsequent stereoselective reduction of 1,2-oxazine ring in intermediate **2** furnished the pyrrolizidinone framework with the recovery of chiral auxiliary alcohol.




## INTRODUCTION

Inhibitors of type IV phosphodiesterase (PDE) are considered as perspective anti-inflammatory and antidepressant drugs,[1] among which are well-known rolipram[2] ($IC_{50}$ = 175 nM), Ro 20-1724[2c,3] ($IC_{50}$ = 1590 nM) and cilomilast[1a,2c,4] ($IC_{50}$ = 92 nM). 7-[3-(Cyclopentyloxy)-4-methoxyphenyl]hexahydro-3*H*-pyrrolizin-3-one **1** (Scheme 1) introduced by GlaxoSmithKline is a highly selective PDE IV inhibitor ($IC_{50}$ = 63 nM) several times more potent than rolipram.[5] However, the synthesis of pyrrolizidinone **1** proposed by GlaxoSmithKline is not stereoselective and cannot be accomplished in asymmetric variant.[5] It cannot be ruled out that only one of pyrrolizidinone's **1** enantiomers is able to efficiently bind to the protein, thus being an active PDE inhibitor. Therefore, to determine the active enantiomer one needs to develop an efficient synthesis of both pyrrolizidinones (+)-**1** and (−)-**1** and conduct in vitro inhibition experiments for each of them.[6]

In the present work, the asymmetric synthesis of pyrrolizidinones (+)-**1** and (−)-**1** was developed, and the absolute configuration of stereocenters in these enantiomers was unambiguously determined. To accomplish this synthesis, an original strategy based on the process of silylation of cyclic nitronates[7] was exploited. This strategy has never been used in asymmetric synthesis before.

## RESULTS AND DISCUSSION

Scheme 1 shows a possible retrosynthetic analysis of pyrrolizidinone **1**. The bicyclic core of molecule **1** can be constructed by the reduction of C-3-functionalized 5,6-dihydro-4*H*-1,2-oxazine **2**. The latter can be obtained by substitution of bromine by dimethyl malonate residue in product **3**, which in turn can be synthesized by silylation of six-membered cyclic nitronate **4** with trimethylsilyl bromide via the intermediacy of *N*,*N*-bis(oxy)enamine **A**.[7c] Similarly to other cyclic nitronates, intermediate **4** is assembled by the [4 + 2]-cycloaddition between nitroalkene **5** and a vinyl ether.[9]

Recently, we reported a successful realization of this scheme in racemic variant (with R = Et in Scheme 1) starting from ethyl vinyl ether, isovanillin, and nitroethane.[8] The most reasonable approach to accomplish the asymmetric synthesis of pyrrolizidinone **1** seems to be the application of a chiral vinyl ether in the [4 + 2]-cycloaddition with nitroalkene **5** (Denmark's procedure[9]). In this case, the problem of enantioselectivity comes to the facial stereoselectivity of the [4 + 2]-cycloaddition reaction. Furthermore, in this approach, the chiral auxiliary alcohol ROH can be recovered at the stage of 1,2-oxazine ring reduction in product **2**.

Denmark studied in detail the [4 + 2]-cycloaddition of chiral vinyl ethers to nitroalkenes.[9] In these studies, vinyl ethers of (+)- and (−)-*trans*-2-phenylcyclohexanols proved to be the most efficient chiral auxiliaries providing the corresponding cyclic nitronates with high stereoselectivity. Thus, vinyl ethers of (+)- and (−)-*trans*-2-phenylcyclohexanols were chosen as 2$\pi$-components for the synthesis of enantiopure nitronates **4** (Scheme 2).

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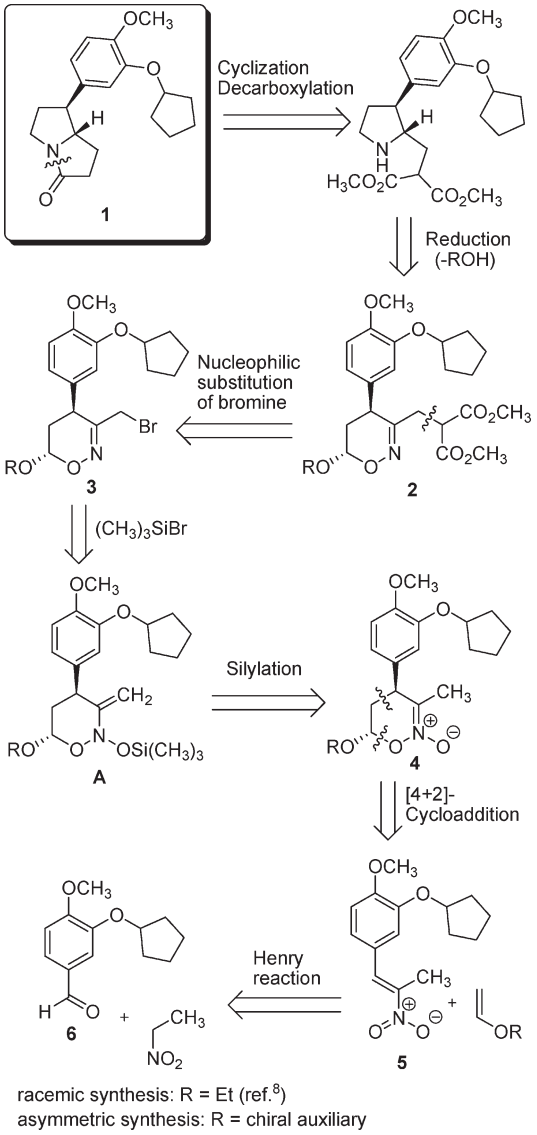
**Scheme 1. Retrosynthetic Analysis of Pyrrolizidinone 1**




The starting nitroalkene **5** was synthesized by the condensation with nitroethane of aldehyde **6**, readily available from isovanillin and cyclopentyl bromide[10] (Scheme 2). The synthesis of enantiopure vinyl ethers **7** was achieved by transvinylation of commercially available (+)- and (−)-*trans*-2-phenylcyclohexanols (>98% ee) with ethyl vinyl ether catalyzed by $Hg(OAc)_2$ at ambient temperature.

The [4 + 2]-cycloaddition of nitroalkene **5** with vinyl ethers (+)-**7** and (−)-**7** promoted by $SnCl_4$ furnished the cyclic nitronates (+)-**4** and (−)-**4**, respectively, in high yield (Scheme 2). Interestingly, only two of four possible stereoisomers were formed with high predominance of isomer **4** (ratio **4**/**4**′ = 13:1). These isomers were readily separated by column chromatography (nitronates (+)-**4** and (−)-**4** were isolated with de >98% according to NMR $^1$H 600 MHz analysis). According to 1D and 2D NMR data, both isomers **4** and **4**′ have a relative 4,6-*trans* configuration. Thus, the cycloaddition of *trans*-2-phenylcyclohexanol vinyl ether **7** to nitroalkene **5** proceeds with excellent *exo*-selectivity and high facial selectivity. It is noteworthy that enantiopure *trans*-2-phenylcyclohexanols can be partially recovered from minor isomers **4**′ by the catalytic hydrogenation followed by separation of nitrogen-containing products on DOWEX-50WX2 (H-form) exchange resin (Scheme 3, eq 1).

Silylation of enantiomeric nitronates (+)-**4** and (−)-**4** with a mixture of trimethylsilyl bromide and triethylamine[7c,d] furnished relatively labile bromomethyloxazines **3** (**3**′) in 39% yield and unreacted nitronates **4** (35%) (Scheme 2). The latter could be again subjected to the silylation process. After two cycles, 52% yield of target bromides **3** (**3**′) was achieved. However, in the silylation of nitronates **4** a partial epimerization at C-6 atom took place, apparently, under the action of trimethylsilyl bromide (cf. with ref 7d). Consequently, bromides **3** are formed as a mixtures of necessary 4,6-*trans*-**3** and minor 4,6-*cis*-**3**′ stereoisomers (ratio 2.9:1.0). In addition, the formation of some amount of *trans*-2-phenylcyclohexanol (22%) was observed, which is possibly formed by the trimethylsilyl bromide induced oxazine ring-opening in intermediate **A** and subsequent hemiacetalic oxime fragmentation (cf. with ref 7d). Isomers **3** and **3**′ were readily separated by column chromatography on silica gel. The unnecessary minor bromide **3**′ like nitronate **4**′ could be hydrogenated to recover enantiopure *trans*-2-phenylcyclohexanol (Scheme 3, eq 2).[12]

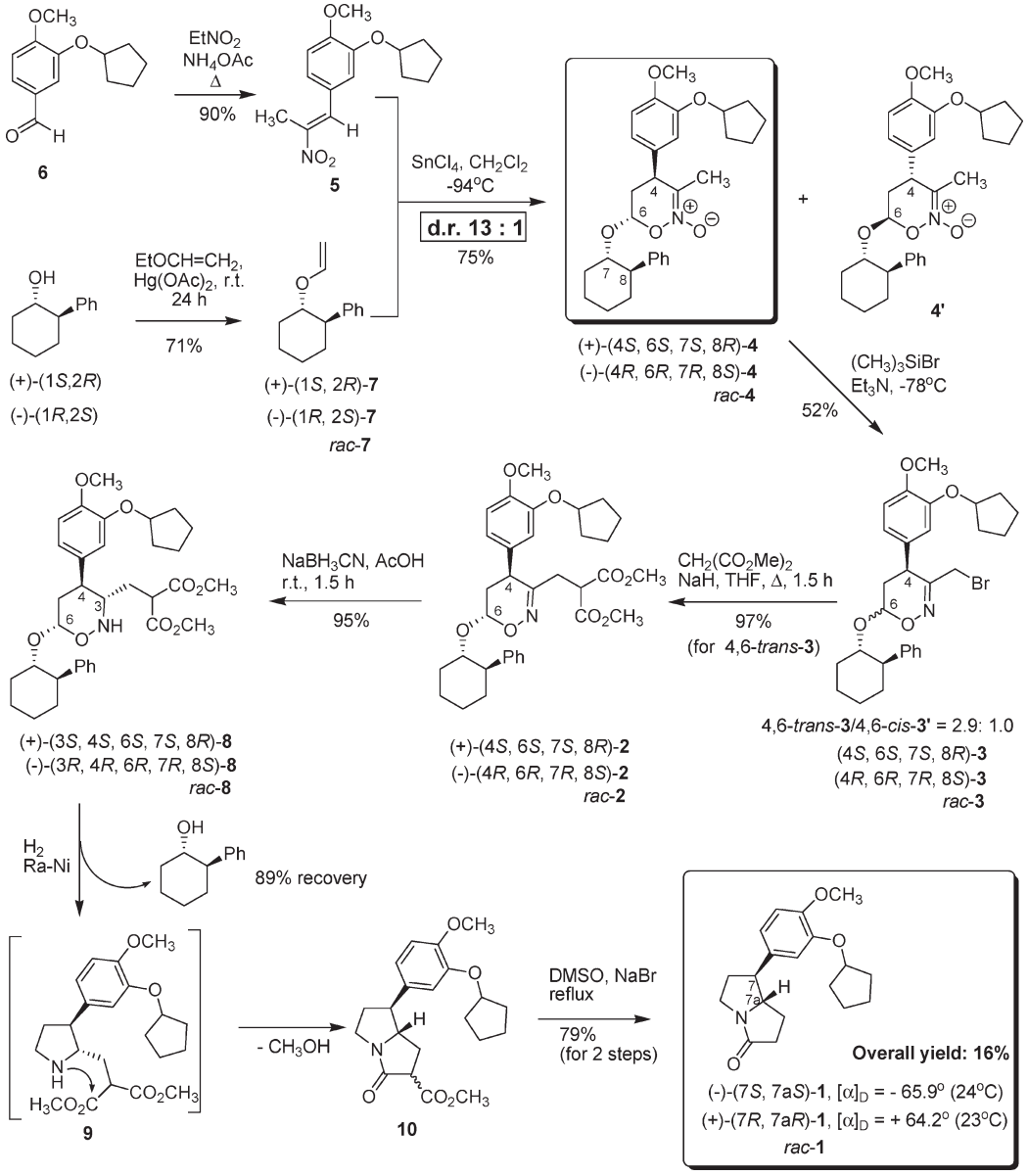
Nucleophilic substitution of bromine by dimethyl malonate moiety in each product (4*S*,6*S*,7*S*,8*R*)-**3** and (4*R*,6*R*,7*R*,8*S*)-**3** furnished dihydrooxazines (+)-(4*S*,6*S*,7*S*,8*R*)-**2** and (−)-(4*R*,6*R*,7*R*,8*S*)-**2**, respectively, in high yield (Scheme 2). Reduction of these products with sodium cyanoborohydride in acetic acid produces corresponding tetrahydrooxazines (+)-**8** and (−)-**8** also in high yield. The latter are formed exclusively as 3,4-*trans* isomers. This predictable stereochemical result is in accordance with a mechanistic model of dihydrooxazine's reduction process suggested recently.[7a,13]

The catalytic hydrogenation of each tetrahydrooxazine's **8** enantiomers ((+)-**8** and (−)-**8**) with Raney nickel led to a mixture of diastereomeric pyrrolizidinones **10** with a good recovery of enantiopure *trans*-2-phenylcyclohexanol (Scheme 2). The plausible mechanism of this transformation includes the hydrogenolysis of the N−O bond, elimination of the chiral auxiliary alcohol from the resulting semiacetal, subsequent cyclization, and reduction of the resulting aldimine to give pyrrolidine **9** and its lactamization into products **10**.[7a,8] The latter without purification were decarboxylated by refluxing in wet DMSO with sodium bromide to furnish target pyrrolizidinones (+)-**1** and (−)-**1** in 79% yield over two steps from tetrahydrooxazines **8**. Pyrrolizidinone (−)-**1** was obtained from tetrahydrooxazine (+)-**8**, and pyrrolizidinone (+)-**1** was prepared from tetrahydrooxazine (−)-**8**. Optical rotation angles of the enantiomers **1** obtained in (+) and (−) series are close by the absolute value and have opposite signs. Enantiopure (+)- and (−)-*trans*-2-phenylcyclohexanols were recovered in 89% yield.

The structures of previously unknown enantiopure products **2**, **3**, **4**, and **8** were confirmed by 1D $^1$H and $^{13}$C NMR, 2D NMR (COSY, HSQC), HRMS data, and elemental analysis.

The determination of the absolute configuration of stereocenters in pyrrolizidinones (+)-**1** and (−)-**1** represented a challenging task. Data in the literature are contradictory on this point. In the original report[5] on the synthesis of racemic pyrrolizidinone *rac*-**1** by GlaxoSmithKline, the relative configuration of stereocenters is reported as (7*R**,7a*R**)-**1**. On the other hand, in the recently published asymmetric synthesis of pyrrolizidinone (+)-**1** by Chen's group,[6] the absolute configuration (7*S*,7a*R*) is assigned for this product, though its $^1$H NMR spectra match data given in ref 5 for *rac*-**1**. In this situation, an

**Scheme 2. Total Synthesis of Pyrrolizidinones (+)-1 and (−)-1**[11]




unambiguous determination of the absolute stereochemistry in pyrrolizidinones (+)-**1** and (−)-**1** is essential.

However, we were not able to perform X-ray crystallographic analysis for the final pyrrolizidinones (+)-**1** and (−)-**1** as well as for any of enantiopure intermediates **2**, **3**, **4**, and **8**, since they were not crystalline. Only when the synthesis was repeated starting from the racemic *trans*-2-phenylcyclohexanol (Scheme 2, racemic series) was a crystalline racemic tetrahydrooxazine *rac*-**8** obtained. X-ray analysis of *rac*-**8**[14] (see the Supporting Information) revealed the relative configuration of all five stereocenters in the molecule of tetrahydrooxazine **8** that allowed us to establish the relationship between the absolute configuration of starting *trans*-2-phenylcyclohexanol and the absolute configuration of the final enantiomer of pyrrolizidinone **1**. Thus, enantiomer (+)-(7*R*, 7a*R*)-**1** was obtained from (−)-(1*R*, 2*S*)-2-phenylcyclohexanol, and (−)-(7*S*,7a*S*)-**1** was obtained from (+)-(1*S*,2*R*)-2-phenylcyclohexanol. Accordingly, for the pyrrolizidinone (+)-**1** the true configuration is (7*R*,7a*R*), not (7*S*,7a*R*), as was reported in ref 6 previously.[15]

## CONCLUSIONS

In conclusion, the asymmetric synthesis of both enantiomers of highly potent PDE IV inhibitor **1** was accomplished, and the absolute configuration of stereocenters was unambiguously determined. The suggested strategy provides target pyrrolizidinones (+)-**1** and (−)-**1** in a 16% yield over nine steps (eight steps in the longest lineal sequence) starting from nitroethane and isovanillin. Inhibition of PDE IV enzyme with (+)-**1** and (−)-**1** will be studied in the near future. The suggested strategy for the asymmetric assembly of pyrrolizidinone unit is novel, and it can be applied in the total synthesis of some pyrrolizidine alkaloids. Furthermore, the silylation of chiral six-membered cyclic nitronates realized here for the first time can be employed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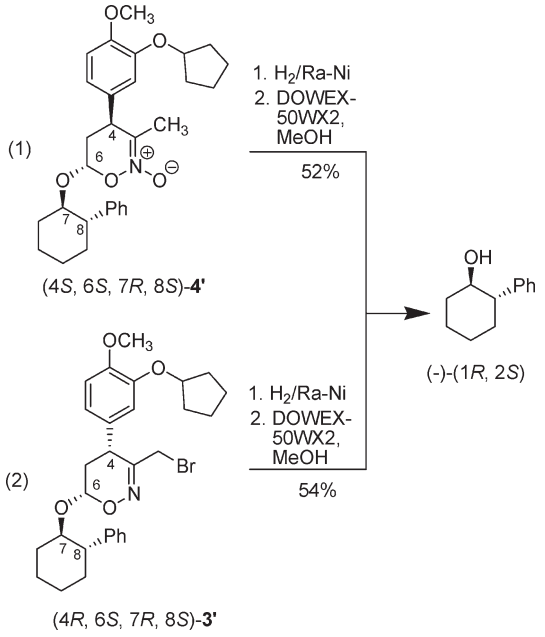
**Scheme 3. Recovery of *trans*-2-Phenylcyclohexanol from Minor Isomers 3′ and 4′**




in the synthesis of other enantiomerically pure PDE IV inhibitors (cf. with ref 5).

## EXPERIMENTAL SECTION

Catalytic hydrogenations were carried out in a steel autoclave with external stirring and heating. Column chromatography was performed using Kieselgel 40−60 $\mu$m 60A silica gel or basic Brockmann I aluminum oxide, 50−200 $\mu$m. Glacial acetic acid was recrystallized two times. $CH_2Cl_2$ (technical grade), MeCN (technical grade), $Et_3N$, ethyl vinyl ether, and $Me_3SiBr$ were redistilled from $CaH_2$. THF was redistilled from sodium diphenyl ketyl. Hexane and EtOAc for chromatography and extractions and methanol for hydrogenation were distilled without drying agents. Nitroalkene **5**[8] and racemic *trans*-2-phenylcyclohexanol[17] were synthesized according to known procedures.

1D and 2D NMR spectra were recorded at room temperature in $CDCl_3$. The chemical shifts ($^1H$, $^{13}C$) are given in ppm ($\delta$) and relative to the solvent signal.[16] Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), br (broad). Atom numbering is depicted in Figure 1. $|\delta|$ values in the HR mass spectra data correspond to the accuracy of the measurement in ppm. 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 standard solution of ninhydrin in ethanol, or a solution of anisaldehyde/$H_2SO_4$ in ethanol.

***trans*-1-Phenyl-2-(vinyloxy)cyclohexane (7).** Ethyl vinyl ether (18 mL) was added to a mixture of (+)-, (−)-, or *rac-trans*-2-phenylcyclohexanol (1.00 g, 5.68 mmol) and $Hg(OAc)_2$ (0.56 g, 1.73 mmol), and the mixture was kept at 25 °C for 24 h. The resulting solution was filtered through an $Al_2O_3$ column (diameter = 3.5 cm, height = 4 cm, eluent, hexane) to remove mercury acetate. After the product was washed off the column (eluent, hexane; TLC control), the filtrate was evaporated under reduced pressure and the residue was subjected to a flesh chromatography on $Al_2O_3$ (eluent, hexane; the same column can be used) to give *trans*-2-phenylcyclohexanol vinyl ether **7** (0.81 g, 71% yield, >95% purity by NMR with external standard). Further elution (hexane/EtOAc = 3:1) provided the unreacted *trans*-2-phenylcyclohexanol (0.20 g, 20%). $^1H$ NMR spectra of products **7** is in accordance with literature data.[9b]

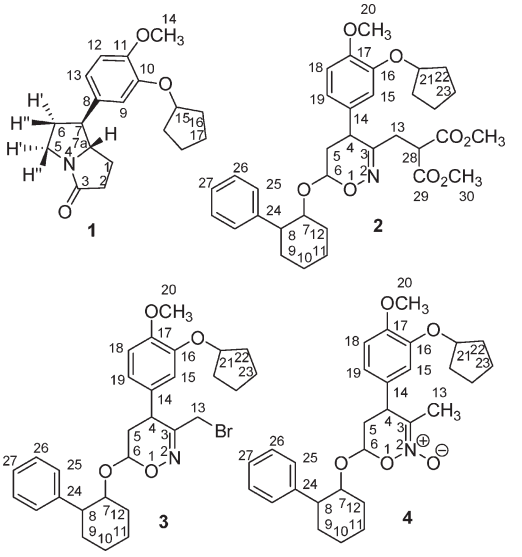



**Figure 1.** Atom numbering in products **1**−**4**.

***trans*-4-[3-(Cyclopentyloxy)-4-(methyloxy)phenyl]-3-methyl-6-[*trans*-(2-phenylcyclohexyl)oxy]-5,6-dihydro-4*H*-1,2-oxazine 2-Oxide (4).** A solution of nitroalkene **5** (0.39 g, 1.4 mmol) and enantiopure or racemic *trans*-2-phenylcyclohexanol vinyl ether **7** (0.37 g, 1.83 mmol) in $CH_2Cl_2$ (18.5 mL) was cooled to −90 °C (acetone/liquid nitrogen) in a Schlenk flask, and $SnCl_4$ (0.165 mL, 0.368 g, 1.4 mmol) was added under argon with intensive stirring. The resulting dark-colored solution was stirred at the same temperature for 10 min and poured into a mixture of EtOAc (200 mL) and 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 in vacuum. The *rac*-**4** was isolated by recrystallization of the final residue from a mixture $Et_2O$/hexane = 5:1 (0.40 g of pure *rac*-**4**). The filtrate was evaporated, and the residue was preadsorbed on silica gel and subjected to a column chromatography on silica gel to give 51 mg of *rac*-**4** and 36 mg of *rac*-**4′** (eluent EtOAc/heptane = 10:1 → 5:1 → 3:1 → 1:1). Enantiopure nitronates (+)-**4** and (−)-**4**, which are not crystalline, were isolated and separated from the respective minor isomers **4′** by column chromatography on silica gel. Overall yield of nitronates **4** + **4′**: 75% (based on nitroalkene), 57% (based on vinyl ether). Ratio **4**/**4′** = 13:1. $R_f$ = 0.33 (hexane/EtOAc = 1:1). HRMS (for *rac*-**4**): *m*/*z* = 480.2734 (positive ions); calcd for $[C_{29}H_{38}NO_5^+]$: 480.2744, /$\delta$/ = 2.1 ppm. $^1H$ NMR (300 MHz, COSY, HSQC): 1.24 (ddd, *J* = 11.8, 11.0, 8.3 Hz, 1 H, 12-$CH_{ax}$), 1.30 (s, 3 H, 13-$CH_3$), 1.32−1.58 (m, 1 H, 11-CH), 1.59−1.64 (m, 2 H, 23-CH), 1.78−1.89 (m, 11 H, 9-$CH_2$, 10-$CH_2$, 11-CH, 22-$CH_2$ and 23-CH), 1.92 (ddd, *J* = 12.9, 11.1, 2.3 Hz, 1 H, 5-$CH_{ax}$), 2.01 (ddd, *J* = 12.9, 8.7, 1.7 Hz, 1 H, 5-$CH_{eq}$), 2.36 (ddd, *J* = 11.8, 4.0, 3.1 Hz, 1 H, 12-$CH_{eq}$), 2.61 (ddd, *J* = 12.2, 10.7, 3.3 Hz, 1 H, 8-$CH_{ax}$), 3.11 (dd, *J* = 11.1, 8.7 Hz, 1 H, 4-$CH_{ax}$), 3.80 (s, 3 H, 20-$CH_3$), 4.19 (ddd, *J* = 11.0, 10.7, 4.0 Hz, 1 H, 7-$CH_{ax}$), 4.70 (m, 1 H, 21-CH), 5.53 (dd, *J* = 2.3, 1.7 Hz, 1 H, 6-$CH_{eq}$), 6.47 (d, *J* = 1.8 Hz, 1 H, 15-CH), 6.54 (dd, *J* = 8.2, 1.8 Hz, 1 H, 19-CH), 6.75 (d, *J* = 8.2 Hz, 1 H, 18-CH), 7.16 (t, *J* = 7.1 Hz, 1 H, 27-CH), 7.28 (d, *J* = 7.2 Hz, 2 H, 25-CH), 7.33 (dd, *J* = 7.2, 7.1 Hz, 2 H, 26-CH). $^{13}C$ NMR (75.47 MHz, HSQC): 17.2 (13-C), 24.0 (9-C), 24.6 (23-C), 26.2 (10-C), 30.2 (12-C), 32.7 and 32.8 (22-C), 33.9 and 34.2 (5-C and 11-C), 39.5 (4-C), 51.1 (8-C), 56.2 (20-C), 76.1 (7-C), 80.6 (21-C), 95.1 (6-C), 112.4 (18-C), 114.7 (15-C),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120.5 (19-C), 123.1 (C-3), 126.1 (27-C), 127.7 (25-C), 128.3 (26-C), 132.4 (14-C), 144.3 (24-C), 148.2 and 149.7 (16-C and 17-C). Anal. Calcd for $C_{29}H_{37}NO_5$: C, 72.62; H, 7.78; N, 2.92. Found (for *rac*-**4**): C, 72.45; H, 7.96; N, 2.89.

*rac*-**4** (obtained from *rac*-**7**): mp 110−114 °C (crystallized from $Et_2O$/hexane).

(+)-(4*S*,6*S*,7*S*,8*R*)-**4** (obtained from (+)-**7**): white foam; $[\alpha]_D$ = +243.0 ($CH_2Cl_2$, *c* = 1, 28 °C).

(−)-(4*R*,6*R*,7*R*,8*S*)-**4** (obtained from (−)-**7**): white foam; $[\alpha]_D$ = −235.6 ($CH_2Cl_2$, *c* = 1, 21 °C).

***trans*-4-[3-(Cyclopentyloxy)-4-(methyloxy)phenyl]-3-methyl-6-[*trans*-(2-phenylcyclohexyl)oxy]-5,6-dihydro-4*H*-1,2-oxazine 2-Oxide (4′).** *rac*-**4′** (obtained from *rac*-**7**). Unstable oil. $R_f$ = 0.43 (hexane/EtOAc = 1:1). HRMS: *m*/*z* = 480.2747 (positive ions), calcd for $[C_{29}H_{38}NO_5^+]$ 480.2744, $|\delta|$ = 0.6 ppm. $^1$H NMR (300 MHz, COSY, HSQC): 1.34 (m, 1 H, 11-CH), 1.54−1.64 and 1.84−1.95 (2 m, 10 H, 10-$CH_2$, 22-$CH_2$ and 23-$CH_2$), 1.48 (m, 1 H, 12-CH), 1.60 (m, 1 H, 9-CH), 1.65 (ddd, *J* = 11.7, 10.5, 2.8 Hz, 1 H, 5-$CH_{ax}$), 1.72 (ddd, *J* = 11.7, 8.5, 2.0 Hz, 1 H, 5-$CH_{eq}$), 1.79 (m, 1 H, 11-CH), 1.82 (s, 3 H, 13-$CH_3$), 1.92 (m, 1 H, 9-CH), 2.23 (m, 1 H, 12-CH), 2.57 (ddd, *J* = 12.5, 10.9, 3.6 Hz, 1 H, 8-$CH_{ax}$), 3.65 (dd, *J* = 10.5, 8.5 Hz, 1 H, 4-$CH_{ax}$), 3.83 (s, 3 H, 20-$CH_3$), 3.86 (m, 1 H, 7-CH), 4.48 (dd, *J* = 2.8, 2.0 Hz, 1 H, 6-$H_{eq}$), 4.72 (m, 1 H, 21-CH), 6.56 (d, *J* = 2.0 Hz, 1 H, 15-CH), 6.64 (dd, *J* = 8.1, 2.0 Hz, 1 H, 19-CH), 6.78 (d, *J* = 8.1 Hz, 1 H, 18-CH), 7.16−7.30 (2 m, 5 H, 25-CH, 26-CH and 27-CH). $^{13}$C NMR (75.47 MHz, HSQC): 17.4 (13-C), 24.0 (9-C), 25.2 (23-C), 25.8 (11-C), 32.7 (10-C), 32.8 (22-C), 34.0 (5-C), 34.3 (12-C), 40.2 (4-C), 51.6 (8-C), 56.2 (20-C), 80.6 (21-C), 82.8 (7-C), 101.6 (6-C), 112.4 (18-C), 114.6 (15-C), 120.4 (19-C), 123.6 (C-3), 126.7 (27-C), 127.9 (25-C), 128.4 (26-C), 132.5 (14-C), 143.9 (24-C), 148.3 and 149.7 (16-C and 17-C).

***trans*-3-(Bromomethyl)-4-[3-(cyclopentyloxy)-4-(methyloxy)phenyl]-6-[*trans*-(2-phenylcyclohexyl)oxy]-5,6-dihydro-4*H*-1,2-oxazine (3).** $Me_3SiBr$ (1.0 mL, 7.6 mmol) was added to a solution of racemic or enantiopure nitronate **4** (750 mg, 1.56 mmol) and $Et_3N$ (0.33 mL, 2.4 mmol) in 4.3 mL of MeCN at −30 °C under argon. The mixture was kept at −30 °C for 24 h with occasional stirring, and then it was diluted with EtOAc (10 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 × 50 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 in 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). Four fractions were collected: the first one contained minor isomer **3′** (85 mg, 10%), the second contained *trans*-2-phenylcyclohexanol (60 mg, 22%), the third one contained major isomer **3** (241 mg, 29%), and the last one contained initial nitronate **4** (260 mg, 35%). The recycled nitronate **4** was silylated again by the same procedure to yield 87 mg of bromide **3** and 30 mg of bromide **3′**. Overall yield of bromides **3** + **3′** (after 2 cycles): 52%, ratio **3**/**3′** = 2.9:1.0. $R_f$ = 0.39 (hexane/EtOAc = 3:1). HRMS: *m*/*z* = 542.1905 (positive ions), calcd for $[C_{29}H_{37}BrNO_4^+]$ 542.1900, $|\delta|$ = 0.9 ppm. $^1$H NMR (300 MHz, COSY, HSQC): 1.38 (m, 1 H, 12-CH), 1.52 (m, 1 H, 9-CH), 1.56−1.65 and 1.77−1.91 (2 m, 13 H, 9-CH, 10-$CH_2$, 11-$CH_2$, 22-$CH_2$, 23-$CH_2$), 1.93 (ddd, *J* = 13.2, 12.5, 2.3, 1 H, 5-$CH_{ax}$), 2.04 (ddd, *J* = 13.2, 8.1, 2.0 Hz, 1 H, 5-$CH_{eq}$), 2.36 (m, 1 H, 12-$CH_{eq}$), 2.61 (ddd, *J* = 11.7, 10.3, 3.7 Hz, 1 H, 8-$CH_{ax}$), 3.24 (dd, *J* = 12.5, 8.1 Hz, 1 H, 4-$CH_{ax}$), 3.41 (d, *J* = 10.3 Hz, 1 H, 13-CH), 3.48 (d, *J* = 10.3 Hz, 1 H, 13-CH), 3.82 (s, 3 H, 20-$CH_3$), 4.02 (ddd, *J* = 10.3, 10.3, 3.7 Hz, 1 H, 7-$CH_{ax}$), 4.72 (m, 1 H, 21-CH), 5.37 (dd, *J* = 2.3, 2.0 Hz, 1 H, 6-$CH_{eq}$), 6.59 (s, 1 H, 15-CH), 6.61 (dd, *J* = 8.1, 2.2 Hz, 1 H, 19-CH), 6.78 (d, *J* = 8.1 Hz, 1 H, 18-CH), 7.18 (t, *J* = 7.3 Hz, 1 H, 27-CH), 7.24 (d, *J* = 6.6 Hz, 2 H, 25-CH), 7.32 (dd, *J* = 8.1, 6.6 Hz, 2 H, 26-CH). $^{13}$C NMR (75.47 MHz, HSQC): 24.1 (9-C), 24.8 and 26.3 (11-C and 23-C), 30.2 (13-C), 31.0 (12-C), 32.1 (5-C), 32.8 and 32.9 (22-C), 33.5 (4-C), 34.5 (10-C), 50.6 (8-C), 56.2 (20-C), 77.0 (7-C), 80.6 (21-C), 91.8 (6-C), 112.4 (18-C), 115.7 (15-C), 120.9 (19-C), 126.1 (27-C), 127.8 (25-C), 128.3 (26-C), 130.9 (14-C), 144.2 (24-C), 148.0 and 149.6 (16-C and 17-C), 156.4 (3-C).

*rac*-**3** (obtained from *rac*-**4**): unstable oil.

(4*S*,6*S*,7*S*,8*R*)-**3** (obtained from (+)-**4**): unstable oil.

(4*R*,6*R*,7*R*,8*S*)-**3** (obtained from (−)-**4**): unstable oil.

***cis*-3-(Bromomethyl)-4-[3-(cyclopentyloxy)-4-(methyloxy)phenyl]-6-[*trans*-(2-phenylcyclohexyl)oxy]-5,6-dihydro-4*H*-1,2-oxazine (3′).** $R_f$ = 0.45 (hexane/EtOAc = 3:1). HRMS: *m*/*z* = 542.1898 (positive ions), calcd for $[C_{29}H_{37}BrNO_4^+]$ 542.1900, $|\delta|$ = 0.4 ppm. $^1$H NMR (300 MHz, COSY, HSQC): 1.33−1.37 (m, 1 H, 11-C), 1.47 (m, 1 H, 12-CH), 1.52−1.56 and 1.83−1.95 (3 m, 14 H, 5-CH, 9-$CH_2$, 10-$CH_2$, 11-CH, 22-$CH_2$, 23-$CH_2$), 1.79 (dd, *J* = 13.2, 8.1, 6.6 Hz, 1 H, 5-$CH_{ax}$), 2.34 (m, 1 H, 12-CH), 2.51 (ddd, *J* = 12.5, 10.3, 3.7 Hz, 1 H, 8-$CH_{ax}$), 3.56 (dd, *J* = 7.3, 8.1 Hz, 1 H, 4-$CH_{eq}$), 3.60 (d, *J* = 9.5 Hz, 1 H, 13-CH), 3.70 (ddd, *J* = 10.3, 10.3, 4.4 Hz, 1 H, 7-CH), 3.84 (s, 3 H, 20-$CH_3$), 3.91 (d, *J* = 9.5 Hz, 1 H, 13-CH), 4.29 (dd, *J* = 6.6, 2.9 Hz, 1 H, 6-$CH_{eq}$), 4.76 (m, 1 H, 21-C), 6.73−6.76 (m, 2 H, 15-CH and 19-CH), 6.81 (d, *J* = 8.8 Hz, 1 H, 18-CH), 7.18−7.30 (m, 5 H, 25-C, 26-C and 27-CH). $^{13}$C NMR (75.47 MHz, HSQC): 24.1 (9-C), 25.3 (23-C) and 25.8 (11-C), 30.9 (13-C), 32.4 (10-C), 32.8 and 32.9 (C-22), 33.2 (5-C), 34.7 (12-C), 37.7 (4-C), 51.6 (8-C), 56.2 (20-C), 80.6 (21-C), 84.5 (7-C), 99.7 (6-C), 112.3 (18-C), 115.3 (15-C), 121.1 (19-C), 126.5 (27-C), 128.1 and 128.3 (25-C and 26-C), 131.5 (14-C), 144.0 (24-C), 148.1 and 149.6 (16-C and 17-C), 158.2 (3-C). Anal. Calcd for $C_{29}H_{36}BrNO_4$: C, 64.20; H, 6.69; N, 2.58. Found: C, 64.27; H, 6.69; N, 2.48.

*rac*-**3′** (obtained from *rac*-**4**): mp 118−126 °C (crystallized from $Et_2O$/hexane).

(+)-(4*S*,6*R*,7*S*,8*R*)-**3′** (obtained from (+)-**4**): mp 117−120 °C (crystallized from $Et_2O$/hexane); $[\alpha]_D$ = +61.0 (MeOH, *c* = 0.75, 22 °C).

(−)-(4*R*,6*S*,7*R*,8*S*)-**3′** (obtained from (−)-**4**): mp 118−120 °C (crystallized from $Et_2O$/hexane).

**Dimethyl 2-[*trans*-[4-[3-(Cyclopentyloxy)-4-(methyloxy)phenyl]-6-[(*trans*-2-phenylcyclohexyl)oxy]-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methyl]propanedioate (2).** NaH (41 mg, 1.03 mmol, 60% in mineral oil) was added to stirred solution of dimethyl malonate (0.088 mL, 0.775 mmol) in 2.1 mL of THF at 0 °C under argon. After 5 min, a solution of enantiopure or racemic bromide **3** (258 mg, 0.48 mmol) in 3.1 mL of THF was added, and the resulting mixture was heated at 50−60 °C for 2 h. Then the mixture was cooled to rt and quenched with MeOH (ca. 5 mL). The resulting solution was poured into a mixture of EtOAc (100 mL) and water (100 mL). The aqueous layer was back-extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried with $Na_2SO_4$, and evaporated in vacuum. The residue was subjected to column chromatography on silica gel (eluent EtOAc/hexane = 1:10 → 1:5) to yield dihydrooxazine **2** (274 mg, 97%). $R_f$ = 0.63 (hexane/EtOAc = 1:1). HRMS: *m*/*z* = 594.3057 (positive ions), calcd for $[C_{34}H_{44}NO_8^+]$ 594.3061, $|\delta|$ = 0.7 ppm. $^1$H NMR (300 MHz, COSY, HSQC): 1.22 (m, 1 H, 12-CH), 1.33−1.46, 1.57−1.65 and 1.78−2.00 (3 m, 2 H, 3 and 10 H, 5-$CH_2$, 9-CH, 10-$CH_2$, 11-$CH_2$, 22-$CH_2$, 23-$CH_2$), 1.54 (m, 1 H, 9-CH), 1.73 (dd, *J* = 17.6, 2.9 Hz, 1 H, 13-CH), 2.37 (m, 1 H, 12-CH), 2.42 (dd, *J* = 17.6, 11.5 Hz, 1 H, 13-CH), 2.57 (ddd, *J* = 12.5, 10.3, 3.7 Hz, 1 H, 8-$CH_{ax}$), 2.72 (dd, *J* = 12.5, 7.3 Hz, 1 H, 4-$CH_{ax}$), 3.65 (dd, *J* = 11.5, 2.9 Hz, 1 H, 28-CH), 3.71 and 3.72 (2 s, 6 H, 30-$CH_3$), 3.82 (s, 3 H, 20-$CH_3$), 3.91 (ddd, *J* = 11.0, 10.3, 3.7 Hz, 1 H, 7-$CH_{ax}$), 4.79 (m, 1 H, 21-CH), 5.31 (dd, *J* = 2.2, 2.0 Hz, 1 H, 6-$CH_{eq}$), 6.53 (d, *J* = 2.2 Hz, 1 H, 15-CH), 6.55 (dd, *J* = 8.1, 2.2 Hz, 1 H, 19-CH), 6.79 (d, *J* = 8.1 Hz, 1 H, 18-CH), 7.16 (t, *J* = 7.3 Hz, 1 H, 27-CH), 7.27 (d, *J* = 8.1 Hz, 2 H, 25-CH), 7.31 (dd, *J* = 8.1, 7.3 Hz, 2 H,

26-CH). $^{13}$C NMR (75.47 MHz, HSQC): 24.1 (9-C), 24.7 and 26.2 (11-C and 23-C), 30.4 (12-C), 32.1 (13-C), 32.8 and 32.9 (22-C), 33.0 and 33.7 (5-C and 10-C), 35.4 (4-C), 47.2 (28-C), 51.0 (8-C), 52.4 and 52.6 (30-C), 56.2 (20-C), 75.8 (C-7), 80.6 (21-C), 90.3 (6-C), 112.5 (18-C), 115.3 (15-C), 120.8 (19-C), 126.1 (27-C), 127.9 (25-C and 26-C), 132.2 (14-C), 144.8 (24-C), 148.1 and 149.4 (16-C and 17-C), 156.9 (3-C), 169.2 and 170.0 (29-C). Anal. Calcd for $C_{34}H_{43}NO_8$: C, 68.78; H, 7.30; N, 2.36. Found: C, 68.92; H, 7.21; N, 2.32.

*rac*-**2** (obtained from *rac*-**3**): mp 108−110 °C (crystallized from $Et_2O$/hexane).

(+)-(4*S*,6*S*,7*S*,8*R*)-**2** (obtained from (4*S*,6*S*,7*S*,8*R*)-**3**): white foam; $[\alpha]_D$ = +257.5 (MeOH, *c* = 1, 27 °C).

(−)-(4*R*,6*R*, 7*R*,8*S*)-**2** (obtained from (4*R*,6*R*,7*R*,8*S*)-**3**): white foam; $[\alpha]_D$ = −263.0 (MeOH, *c* = 1, 20 °C).

**Dimethyl 2-[*cis*-[4-[3-(Cyclopentyloxy)-4-(methyloxy)phenyl]-6-[*trans*-(2-phenylcyclohexyl)oxy]-5,6-dihydro-4*H*-1,2-oxazin-3-yl]methyl]propanedioate (2′).** *rac*-**2′** was obtained in 51% yield from *rac*-**3′** according to the procedure given above for the synthesis of dihydrooxazine **2**. Oil. $R_f$ = 0.58 (hexane/EtOAc = 1:1). HRMS: *m*/*z* = 594.3066 (positive ions), calcd for $[C_{34}H_{44}NO_8^+]$ 594.3061, $|\delta|$ = 0.8 ppm. $^1$H NMR (300 MHz, COSY, HSQC): 1.45 (m, 2 H, 11-CH and 12-CH), 1.56−1.65 and 1.84−1.98 (2 m, 13 H, 9-$CH_2$, 10-$CH_2$, 11-CH, 22-$CH_2$, 23-$CH_2$), 1.70 (ddd, *J* = 13.9, 8.1, 6.6 Hz, 1 H, 5-$CH_{ax}$), 1.82 (ddd, *J* = 13.9, 8.1, 2.7 Hz, 1 H, 5-$CH_{eq}$), 2.30 (m, 1 H, 12-CH), 2.45 (dd, *J* = 17.6, 7.3 Hz, 1 H, 13-CH), 2.49 (ddd, *J* = 12.5, 10.0, 3.9 Hz, 1 H, 8-$CH_{ax}$), 2.60 (dd, *J* = 17.6, 7.3 Hz, 1 H, 13-CH), 3.07 (dd, *J* = 8.1, 8.1 Hz, 1 H, 4-$CH_{eq}$), 3.68 and 3.70 (2 s and m, 7 H, 7-CH and 30-$CH_3$), 3.84 (s, 3 H, 20-$CH_3$), 3.88 (dd, *J* = 7.3, 7.3 Hz, 1 H, 28-CH), 4.18 (dd, *J* = 6.6, 2.7 Hz, 1 H, 6-$CH_{eq}$), 4.79 (m, 1 H, 21-CH), 6.67 (dd, *J* = 8.1, 1.5 Hz, 1 H, 19-CH), 6.71 (d, *J* = 1.5 Hz, 1 H, 15-CH), 6.79 (d, *J* = 8.1 Hz, 1 H, 18-CH), 7.15−7.27 (m, 5 H, 25-CH, 26-CH and 27-CH). $^{13}$C NMR (75.47 MHz, HSQC): 24.1 (9-C), 25.3 (11-C), 25.9 (23-C), 32.6 and 32.7 (10-C and 13-C), 32.8 and 32.9 (22-C), 34.2 (5-C), 34.7 (12-C), 41.0 (4-C), 48.0 (28-C), 51.6 (8-C), 52.5 and 52.6 (30-C), 56.2 (20-C), 80.6 (21-C), 83.8 (7-C), 98.8 (6-C), 112.2 (18-C), 115.4 (15-C), 121.2 (19-C), 126.4 (27-C), 128.1 and 128.2 (25-C and 26-C), 132.4 (14-C), 144.1 (24-C), 148.1 and 149.5 (16-C and 17-C), 158.7 (3-C), 169.3 and 169.5 (29-C).

**Dimethyl 2-[[3,4-*trans*-3,6-*cis*-4-[3-(Cyclopentyloxy)-4-(methyloxy)phenyl]-6-[*trans*-(2-phenylcyclohexyl)oxy]-1,2-oxazinan-3-yl]methyl]propanedioate (8).** $NaBH_3CN$ (76 mg, 2.3 mmol) was added to a solution of enantiopure or racemic dihydrooxazine **2** (240 mg, 0.4 mmol) in AcOH (1.75 mL), and the mixture was stirred under argon for 1 h. Then a second portion of $NaBH_3CN$ (76 mg, 2.3 mmol) was added, and the mixture was stirred for an additional 0.5 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), and brine (50 mL), dried with $Na_2SO_4$, and evaporated in vacuum. The residue was subjected to column chromatography on silica gel (eluent EtOAc/hexane = 1:10 → 1:5 →1:3) to yield 228 mg (95%) of tetrahydrooxazine **8**. $R_f$ = 0.51 (hexane/EtOAc = 1:1). HRMS: *m*/*z* = 596.3218 (positive ions); calcd for $[C_{34}H_{46}NO_8^+]$: 596.3218, $|\delta|$ = 0.0 ppm. $^1$H NMR (300 MHz, COSY, HSQC): 0.68 (ddd, *J* = 14.7, 11.0, 3.7 Hz, 1 H, 13-CH), 1.26 (m, 1 H, 12-CH), 1.31−1.45, 1.60−1.65 and 1.82−2.01 (3 m, 15 H, 5-CH, 9-$CH_2$, 10-$CH_2$, 11-$CH_2$, 22-$CH_2$, 23-$CH_2$), 1.72 (ddd, *J* = 14.7, 12.2, 2.2 Hz, 1 H, 13-CH), 1.78 (dd, *J* = 5.3, 1.5 Hz, 1 H, 5-$CH_{eq}$), 2.14 (ddd, *J* = 11.7, 10.3, 5.3 Hz, 1 H, 4-$CH_{ax}$), 2.20 (m, 1 H, 12-CH), 2.67 (ddd, *J* = 12.5, 10.3, 3.7 Hz, 1 H, 8-$CH_{ax}$), 2.91 (dddd, *J* = 12.2, 11.0, 10.3, 2.2 Hz, 1 H, 3-$CH_{ax}$), 3.39 (dd, *J* = 11.7, 3.7 Hz, 1 H, 28-CH), 3.63 and 3.72 (2 s, 7 H, 2-NH and 30-$CH_3$), 3.69 (ddd, *J* = 10.3, 9.5, 4.4 Hz, 1 H, 7-$CH_{ax}$), 3.81 (s, 3 H, 20-$CH_3$), 4.78 (m, 1 H, 21-CH), 4.93 (dd, *J* = 2.0, 1.5 Hz, 1 H, 6-$CH_{eq}$), 6.59 (d, *J* = 8.1 Hz, 1 H, 15-CH), 6.60 (dd, *J* = 2.2 Hz, 8.1 Hz, 1 H, 19-CH), 6.77 (d, *J* = 8.1 Hz, 1 H, 18-CH), 7.23 (m, 1 H, 27-CH), 7.41 (m, 4 H, 25-CH and 26-CH). $^{13}$C NMR (75.47 MHz, HSQC): 24.1 (9-C), 24.8 and 26.1 (11-C and 23-C), 29.4 (12-C), 31.2 and 32.7 (5-C and 10-C), 32.8 and 32.9 (22-C), 37.6 (13-C), 41.0 (4-C), 47.4 (28-C), 50.9 (8-C), 52.2 and 52.4 (30-C), 56.2 (20-C), 58.1 (3-C), 77.3 (7-C), 80.6 (21-C), 93.4 (6-C), 112.5 (18-C), 114.7 (15-C), 119.8 (19-C), 126.9 (27-C), 128.3 and 128.8 (25-C and 26-C), 134.7 (14-C), 144.7 (24-C), 147.9 and 149.0 (16-C and 17-C), 169.3 and 170.1 (29-C). Anal. Calcd for $C_{34}H_{45}NO_8$: C, 68.55; H, 7.61; N, 2.35. Found: C, 68.85; H, 7.68; N, 2.35.

*rac*-**8** (obtained from *rac*-**2**): white crystals; mp 137−141 °C (crystallized from MeOH).

(+)-(3*S*,4*S*,6*S*,7*S*,8*R*)-**8** (obtained from (+)-**2**): white solid; mp 129−130 °C; $[\alpha]_D$ = +144.0 (MeOH, *c* = 1, 22 °C).

(−)-(3*R*,4*R*,6*R*,7*R*,8*S*)-**8** (obtained from (−)-**2**): white solid; mp 127−130 °C; $[\alpha]_D$ = −142.0 (MeOH, *c* = 1, 21 °C).

**Dimethyl 2-[[3,4-*trans*-3,6-*trans*-4-[3-(Cyclopentyloxy)-4-(methyloxy)phenyl]-6-[*trans*-(2-phenylcyclohexyl)oxy]-1,2-oxazinan-3-yl]methyl]propanedioate (*rac*-8′) and Dimethyl 2-[[3,4-*cis*-3,6-*cis*-4-[3-(Cyclopentyloxy)-4-(methyloxy)phenyl]-6-[*trans*-(2-phenylcyclohexyl)oxy]-1,2-oxazinan-3-yl]methyl]-propanedioate (*rac*-8″).** $NaBH_3CN$ (10 mg, 0.15 mmol) was added to a solution of racemic dihydrooxazine *rac*-**2′** (30 mg, 0.05 mmol) in AcOH (1.0 mL), and the mixture was stirred under argon for 1 h. Then a second portion of $NaBH_3CN$ (10 mg, 0.15 mmol) was added, and the mixture was stirred for additional 0.5 h. An additional portion of $NaBH_3CN$ (10 mg, 0.15 mmol) was added to the mixture to reach the full conversion of starting material (TLC control). The resulting solution was poured into a mixture EtOAc (50 mL)/saturated solution of $K_2CO_3$ (50 mL). The aqueous layer was back-extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with saturated solution of $K_2CO_3$ (20 mL), water (20 mL), and brine (20 mL), dried with $Na_2SO_4$, and evaporated in vacuum. The residue was subjected to a column chromatography on silica gel (eluent EtOAc/hexane =1:10 → 1:5 →1:3) to yield 23 mg (76%) of an unseparable mixture of racemic tetrahydrooxazines *rac*-**8′** and *rac*-**8″** (ratio 1.0: 1.7). Colorless oil. $R_f$ = 0.57 (hexane/EtOAc = 1:1). HRMS: *m*/*z* = 596.3211 (positive ions), calcd for $[C_{34}H_{46}NO_8^+]$ 596.3218, $|\delta|$ = 1.2 ppm. *rac*-**8′**. $^1$H NMR (300 MHz, COSY, HSQC, selected signals): 2.05 (ddd, *J* = 6.0, 4.2, 1.5 Hz, 1 H, 4-$CH_{eq}$), 2.23 (m, 1 H, 12-CH), 2.56 (ddd, *J* = 12.5, 9.5, 3.7, 1 H, 8-$CH_{ax}$), 3.01 (dddd, *J* = 11.0, 6.0, 4.2, 3.7 Hz, 1 H, 3-$CH_{eq}$), 3.52 (dd, *J* = 9.5, 5.1 Hz, 1 H, 28-CH), 3.64 and 3.66 (2 s and m, 8 H, 2-NH, 7-CH and 30-$CH_3$), 3.97 (dd, *J* = 3.9 Hz, 1.5 Hz, 1 H, 6-$H_{eq}$), 3.81 (s, 3 H, 20-$CH_3$), 4.72 (m, 1 H, 21-CH), 6.58 (s, 1 H, 15-CH), 6.59 (d, *J* = 8.1 Hz, 1 H, 19-CH), 6.79 (d, *J* = 8.1 Hz, 1 H, 18-CH). $^{13}$C NMR (75.47 MHz, HSQC): 24.0, 25.0, and 25.8 (C-9, C-11 and C-23), 35.1 (12-C), 43.1 (4-C), 49.0 (28-C), 51.6 (8-C), 56.2 (20-C), 57.2 (3-C), 80.5 (21-C), 84.1 (7-C), 105.3 (6-C), 112.3 (18-C), 114.3 (15-C), 119.5 (19-C), 126.5 (27-C), 128.1 and 128.3 (25-C and 26-C), 132.4 (14-C), 144.1 (24-C). *rac*-**8″**. $^1$H NMR (300 MHz, COSY, HSQC, selected signals): 2.03 (ddd, *J* = 7.3, 7.3, 2.0 Hz, 1 H, 4-$CH_{eq}$), 2.23 (m, 1 H, 12-CH), 2.51 (ddd, *J* = 13.2, 9.5, 3.7, 1 H, 8-$CH_{ax}$), 2.91 (dddd, *J* = 10.3, 9.5, 7.3, 2.2 Hz, 1 H, 3-$CH_{ax}$), 3.40 (dd, *J* = 7.3, 7.3 Hz, 1 H, 28-CH), 3.62 (s and m, 8 H, 2-NH, 7-CH and 30-$CH_3$), 3.81 (s, 3 H, 20-$CH_3$), 3.98 (dd, *J* = 3.7 Hz, 1.5 Hz, 1 H, 6-$H_{eq}$), 4.72 (m, 1 H, 21-CH), 6.58 (s, 1 H, 15-CH), 6.59 (d, *J* = 8.1 Hz, 1 H, 19-CH), 6.75 (d, *J* = 8.1 Hz, 1 H, 18-CH). $^{13}$C NMR (75.47 MHz, HSQC): 24.0, 25.3, and 25.8 (9-C, 11-C and 23-C), 35.1 (12-C), 46.6 (4-C), 48.9 (28-C), 51.5 (8-C), 56.2 (20-C), 60.4 (3-C), 80.6 (21-C), 84.0 (7-C), 104.6 (6-C), 112.3 (18-C), 114.7 (15-C), 120.1 (19-C), 126.4 (27-C), 128.1 and 128.3 (25-C and 26-C), 133.6 (14-C), 144.1 (24-C). Unassigned Signals of Both Isomers. $^1$H NMR (300 MHz, COSY, HSQC): 1.27−1.52, 1.55−1.68 and 1.75−1.93 (3 m, 17 H, 5-$CH_2$, 9-$CH_2$, 10-$CH_2$, 11-$CH_2$, 12-CH, 13-$CH_2$, 22-$CH_2$, 23-$CH_2$), 7.17−7.30 (m, 5 H, 25-CH, 26-CH and 27-CH). $^{13}$C NMR (75.47 MHz,

HSQC): 29.5, 29.8, 30.1, 30.4, 32.8, 32.9, and 37.4 (5-C, 10-C, 22-C and 13-C), 52.4, 52.5, and 52.6 (30-C), 147.8, 147.9, 149.1, and 149.2 (16-C and 17-C), 169.6, 169.8, and 170.0 (29-C).

***trans*-7-[3-(Cyclopentyloxy)-4-(methyloxy)phenyl]hexahydro-3*H*-pyrrolizin-3-one (1).** Raney nickel (c.a. 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 tetrahydrooxazine **8** (180 mg, 0.3 mmol) in MeOH (7.2 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. After the mixture was stirred at rt for 3 h, the autoclave was slowly depressurized and the catalyst was filtered off. The solvent was evaporated, and the residue was dried in vacuum. The product was dissolved in DMSO (7 mL). Then NaBr (31 mg, 0.3 mmol) and $H_2O$ (0.011 mL, 0.6 mmol) were added. The mixture was gently refluxed for 45 min, and then the solvent was evaporated in vacuo (c.a. 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 (47 mg, 89%) and the EtOAc/MeOH fraction contained target pyrrolizidinone **1** (75 mg, 79%). $R_f$ = 0.71 (EtOAc/MeOH, 1:3). $^1$H NMR ($CDCl_3$, 300 MHz, COSY, NOESY, HSQC): $\delta$ = 1.54−1.65 and 1.76−1.95 (2 m, 2 and 7 H, 1-CH, 16-$CH_2$ and 17-$CH_2$), 2.15−2.30 (m, 2 H, 6-CH″ and 1-CH), 2.43−2.53 (m, 2 H, 6-CH′ and 2-CH), 2.63−2.79 (m, 2 H, 7-CH and 2-CH), 3.31 (dd, $J$ = 11.0, 10.3 Hz, 1 H, 5-CH″), 3.61 (ddd, $J$ = 11.0, 9.2, 8.8 Hz, 1 H, 5-CH′), 3.81 (s, 3 H, 14-$CH_3$), 3.89 (ddd, $J$ = 9.5, 7.3, 7.0 Hz, 1 H, 7a-CH), 4.75 (m, 1 H, 15-CH), 6.72 (s, 1 H, 9-CH), 6.73 (d, $J$ = 8.1 Hz, 1 H, 13-CH), 6.82 (d, $J$ = 8.1 Hz, 1 H, 12-CH). $^{13}$C NMR ($CDCl_3$, 75 MHz, INEPT, HSQC): $\delta$ = 23.9 (17-C), 25.5 (1-C), 32.7 (16-C), 34.7 (2-C), 35.2 (6-C), 40.9 (5-C), 50.8 (7-C), 56.0 (14-C), 67.7 (7a-C), 80.5 (15-C), 112.1, 114.3, and 119.1 (9-C, 12-C and 13-C), 131.5 (8-C), 147.7 and 149.1 (10-C and 11-C), 174.7 (3-C). Characteristic 2D-NOESY correlations: 9-CH/7a-CH, 9-CH/6-CH″, 6-CH″/5-CH″, 6-CH′/5-CH′. NMR data were consistent with those previously reported for pyrrolizidinone *rac*-**1**.[5,6,8]

*rac*-**1** (obtained from *rac*-**8**): mp 67−68 °C (lit.[5] mp 64−66 °C).

(+)-(7*R*,7a*R*)-**1** (obtained from (−)-**8**): colorless oil; $[\alpha]_D$ = +64.2 ($CHCl_3$, $c$ = 0.35, 23 °C) [lit.[6] $[\alpha]_D$ = +62.6 (97% ee, $CHCl_3$, $c$ = 0.35, 20 °C)].

(−)-(7*S*,7a*S*)-**1** (obtained from (+)-**8**): colorless oil; $[\alpha]_D$ = −65.9 ($CHCl_3$, $c$ = 0.35, 24 °C).

*rac-trans*-2-Phenylcyclohexanol (obtained from *rac*-**8**): mp 54−56 °C (lit. 53−55 °C, Sigma-Aldrich). $^1$H NMR spectra are in accordance with literature data.[17,18]

(+)-*trans*-2-Phenylcyclohexanol (obtained from (+)-**8**): $[\alpha]_D$ = +55.9 (MeOH, $c$ = 1.83, 20 °C) [lit.[19] $[\alpha]_D$ = +57.3 (MeOH, $c$ = 5, 20 °C)]. $^1$H NMR spectra are in accordance with literature data.[17,18]

(−)-*trans*-2-Phenylcyclohexanol (obtained from (−)-**8**): $[\alpha]_D$ = −54.8 (MeOH, $c$ = 0.5, 24 °C) [lit.[18] $[\alpha]_D$ = −56.8 (MeOH, $c$ = 1.42)]. $^1$H NMR spectra is in accordance with literature data.[17,18]

**Regeneration of *trans*-2-Phenylcyclohexanol from Minor Isomers 3′ and 4′.** 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 nitronate (4*S*,6*S*,7*R*,8*S*)-**4′** (48 mg, 0.1 mmol) or bromide (4*R*,6*S*,7*R*,8*S*)-**3′** (54 mg, 0.1 mmol) in 2.7 mL of MeOH. The test tube was placed in a steel autoclave which was then flushed and filled with $H_2$ to a pressure of 40 bar. After the mixture was stirred at 50 °C for 1 h, the autoclave was slowly depressurized and the catalyst was filtered off. DOWEX-50WX2 (150 mg) was added to the resulting solution, and the mixture was kept with occasional shaking for 24 h. Then the ion-exchange resin was filtered off, and the solution was concentrated in vacuum. The residue contained crude (−)-*trans*-2-phenylcyclohexanol, which could be purified by flash chromatography on silica gel or recrystallization from hexane (yield 52−54%). (−)-*trans*-2-Phenylcyclohexanol: $[\alpha]_D$ = −56.3 (MeOH, $c$ = 1.83, 23 °C) [lit.[18] $[\alpha]_D$ = −56.8 (MeOH, $c$ = 1.42)]. $^1$H NMR spectra were in accordance with literature data.[17,18]

## ■ ASSOCIATED CONTENT

**Supporting Information.** NMR spectra of new compounds and crystallographic data of compound *rac*-**8** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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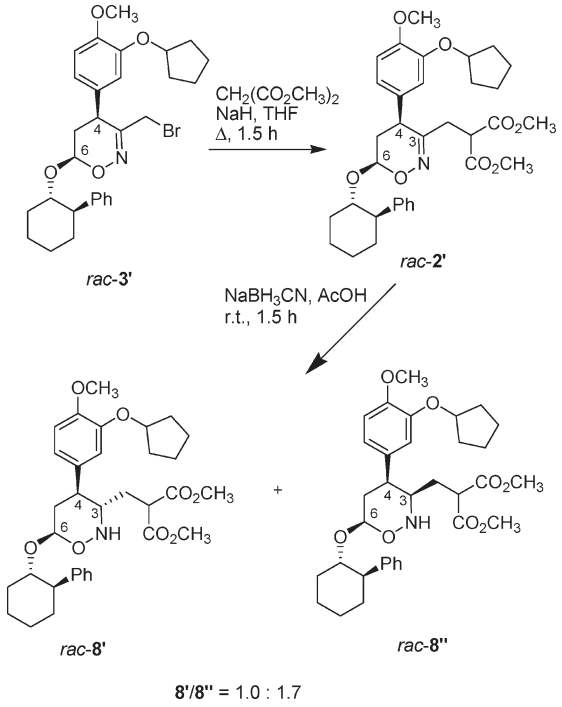
(11) The formulas in Scheme 2 correspond to the synthesis of pyrrolizidinone (−)-**1** from (+)-*trans*-2-phenylcyclohexanol.

(12) The minor bromide **3′** cannot be used in the synthesis of pyrrolizidinones **1**. Dihydrooxazine **2′** obtained from bromide **3′** analogously to product **2**, upon the reduction with $NaBH_3CN$ produces

an unseparable mixture of diastereomeric tetrahydrooxazines **8′** and **8″** (demonstrated on racemic substrates).

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(14) CCDC 827039 contains the supplementary crystallographic data for *rac*-**8**. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB21EZ, UK; or deposit@ccdc.cam.ac.uk).

(15) $^1$H NMR spectra and the optical rotation angle of the obtained pyrrolizidinone (+)-**1** matched those reported in ref 6 ($[\alpha]_D$ = +62.6 (97% ee, $CHCl_3$, *c* = 0.35, 20 °C)).

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