Novel Selective Phosphodiesterase (PDE4) Inhibitors. 4. Resolution, Absolute Configuration, and PDE4 Inhibitory Activity of *cis*-Tetra- and *cis*-Hexahydrophthalazinones

Margaretha Van der Mey,*[,†,‡] Hildegard Boss,[§] Dennis Couwenberg,[‡] Armin Hatzelmann,[§] Geert J. Sterk,[‡] Kees Goubitz,[∥] Henk Schenk,[∥] and Hendrik Timmerman[†]

Leiden/Amsterdam Center for Drug Research, Division of Medicinal Chemistry, Department of Pharmacochemistry, Vrije Universiteit, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands, Byk Nederland, Zwanenburg, The Netherlands, Laboratory for Crystallography, Institute for Molecular Chemistry (IMC), University of Amsterdam, Amsterdam, The Netherlands, and Byk Gulden, Konstanz, Germany

Received September 3, 2001

Recently, we reported that 4-catechol-substituted *cis*-(±)-4a,5,6,7,8,8a-hexa- and *cis*-(±)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-ones show potent inhibition of phosphodiesterase (PDE4) activity, while the corresponding trans racemic mixtures exhibit only weak to moderate activity. To determine the absolute configuration and PDE4 inhibitory activity of the individual *cis*-enantiomers, several optically active phthalazinones have been synthesized. The enantiomers of the various γ-keto acids, used as starting materials, were resolved in a classical way by the formation of diastereomeric salts, and each was converted to optically active phthalazinone in an enantioselective manner. The absolute configuration of the (+)-enantiomer of *cis*-hexahydrophthalazinone (+)-**12** was determined by X-ray crystallography. The carbon atoms at the 4a and 8a positions were found to have the *S*- and *R*-configuration, respectively. In the present series of hexa- and tetrahydrophthalazinones, stereoselectivity for PDE4 inhibition is observed; the *cis*-(+)-enantiomers of the phthalazinones display high inhibitory activity, whereas their (−)-counterparts exhibit only weak to moderate activity. It is likely that all *cis*-(+)-phthalazinones have a (4a*S*,8a*R*)-configuration and vice versa for the *cis*-(−)-analogues. In the current series, the *N*-adamantan-2-yl analogue (+)-**14** shows the most potent inhibition of PDE4 (pIC_{50} = 9.3); the corresponding (−)-enantiomer is 250-fold less active. In addition, the N-substituted tetrahydrophthalazinones under study were investigated for their in vivo antiinflammatory activities by examining the suppression of arachidonic acid (AA) induced mouse ear edema formation. In this assay analogues (+)-**14** and (+)-**15** were found to be potent antiinflammatory agents showing about 50% inhibition at 30 μmol/kg po.

Introduction

Recently, we presented a novel class of chiral 4a,5,6,7,8,8a-hexa- and 4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-ones as cAMP-specific phosphodiesterase (PDE4) inhibitors, for which the synthesis and preliminary structure−activity relationships (SARs) have been reported.[1−6] Studying the influence of several fused hydrocarbon rings on PDE4 inhibition, we found that the (4a,8a)-*cis*-racemates of these hexa- and tetrahydrophthalazinones show potent inhibition of PDE4 activity.[4] In contrast, the corresponding trans racemic mixtures exhibit only weak to moderate inhibitory activities. Besides potent PDE4 inhibition, several racemic *cis*-hexa- and tetrahydrophthalazinones were found to possess moderate to high in vitro and in vivo antiinflammatory potencies.[6] Therefore, these analogues are considered as promising agents for the treatment of rheumatoid arthritis, asthma, and other inflammatory diseases.

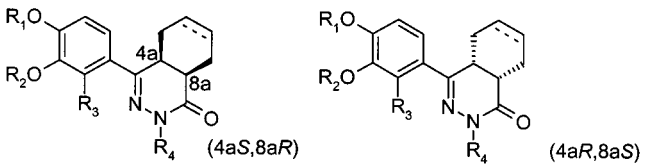


Figure 1. Target *cis*-hexa- and *cis*-tetrahydrophthalazinone enantiomers (general structures).

This paper describes the resolution of various *cis*-hexa- and tetrahydrophthalazinones (Figure 1) in order to examine the pharmacological profile of the individual *cis*-hexa- and tetrahydrophthalazinone enantiomers and to determine their absolute configurations.

Most target phthalazinones were selected from previous papers.[4−6] Because of their easy accessibility, initially a number of optically active phthalazinones in which R_4 is H (Figure 1) were synthesized to establish the influence of the configuration on PDE4 inhibitory activity. Subsequently, some optically active N-substituted tetrahydrophthalazinones have been prepared and tested for their PDE4 inhibitory and in vivo antiinflammatory activity.

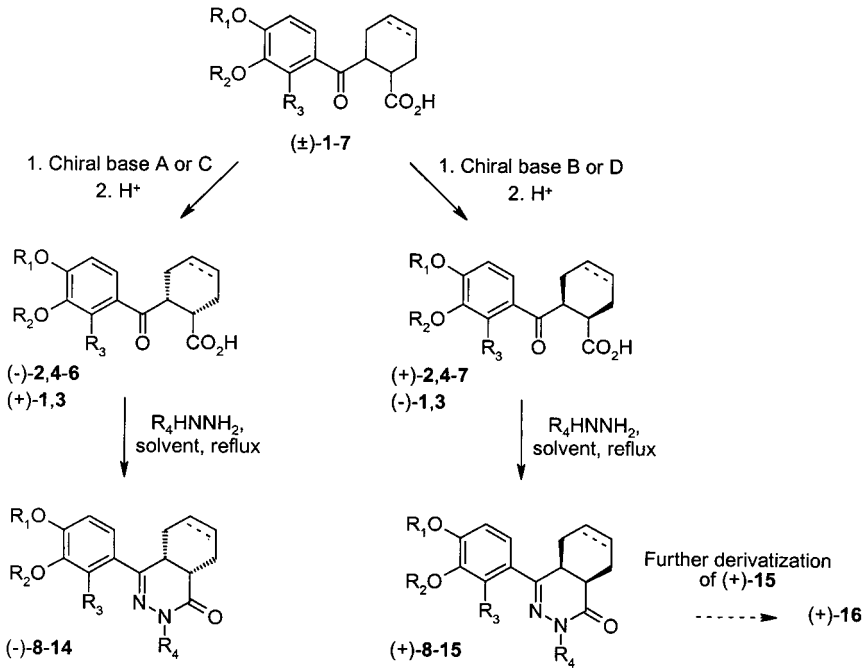
Chemistry

The target optically active *cis*-hexa- and tetrahydrophthalazinones with variations in the substituents at

* To whom correspondence should be addressed. Phone: +31 20 4449720. Fax: +31 20 4449121. E-mail: mmeij@rnc.vu.nl. Current address: Vrije Universiteit, Radionuclidencentrum, De Boelelaan 1085c, 1081 HV Amsterdam, The Netherlands.
† Vrije Universiteit.
‡ Byk Nederland.
§ Byk Gulden.
∥ University of Amsterdam.

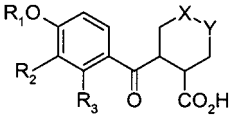
10.1021/jm0110338 CCC: $22.00
Published on Web 02/26/2002

Scheme 1[a]



[a] Reagents: (chiral base A) (*R*)-(+)-α-methylbenzylamine; (B) (*S*)-(−)-α-methylbenzylamine; (C) quinine; (D) (1*R*,2*S*)-(−)-ephedrine.

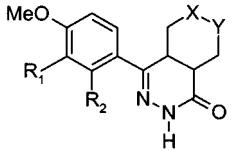
Table 1. Data for the Resolution of the *cis*-Cyclohex(a)ene γ-Keto Acids



compd	R_1	R_2	R_3	X-Y	chiral base[a]	cryst solvent	yield (%)[b]	free acid $[\alpha]^{25}D$ (°)[c]
(+)-**1**	Me	OMe	H	H_2C-CH_2	A	EtOH	67	+9.87
(-)-**1**	Me	OMe	H	H_2C-CH_2	B	EtOH	69	-9.51
(+)-**2**	Me	OMe	H	HC=CH	B	EtOAc	58	+29.1
(-)-**2**	Me	OMe	H	HC=CH	A	EtOAc	76	-27.4
(+)-**3**	Me	OcC_5H_9	H	H_2C-CH_2	C	EtOAc	70	+15.0
(-)-**3**	Me	OcC_5H_9	H	H_2C-CH_2	D	EtOH	35	-13.9
(+)-**4**	Me	OcC_5H_9	H	HC=CH	D	EtOAc	28	+20.8
(-)-**4**	Me	OcC_5H_9	H	HC=CH	C	EtOAc	73	-20.4
(+)-**5**	Me			H_2C-CH_2	D	EtOH	83	+10.7
(-)-**5**	Me	as (+)-**5**		H_2C-CH_2	C	EtOAc	81	-8.98
(+)-**6**	Me	as (+)-**5**		HC=CH	D	EtOH	28	+37.5
(-)-**6**	Me	as (+)-**5**		HC=CH	C	EtOAc	77	-40.1
(+)-**7**	Et	OEt	H	HC=CH	B	EtOAc	69	+27.4*

[a] (A) (*R*)-(+)-α-methylbenzylamine; (B) (*S*)-(−)-α-methylbenzylamine; (C) quinine; (D) (1*R*,2*S*)-(−)-ephedrine. [b] (Yield/maximum yield for each enantiomer) × 100. [c] The concentrations for the solutions applied are $c = 1$ except where noted * $c = 5.2$.

Table 2. PDE4 Inhibition Data of the Racemic and Corresponding Resolved 4-Aryl-Substituted Hexa- and Tetrahydrophthalazinones

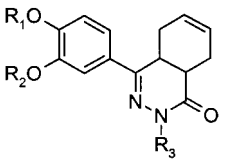


compd	R_1	R_2	X-Y	PDE4 pIC_{50}[a]
(±)-**8**	OMe	H	H_2C-CH_2	6.4
(+)-**8**	OMe	H	H_2C-CH_2	6.9
(-)-**8**	OMe	H	H_2C-CH_2	5.1
(±)-**9**	OMe	H	HC=CH	7.0
(+)-**9**	OMe	H	HC=CH	7.3
(-)-**9**	OMe	H	HC=CH	6.1
(±)-**10**	OcC_5H_9	H	H_2C-CH_2	6.8
(+)-**10**	OcC_5H_9	H	H_2C-CH_2	7.1
(-)-**10**	OcC_5H_9	H	H_2C-CH_2	5.8
(±)-**11**	OcC_5H_9	H	HC=CH	7.1
(+)-**11**	OcC_5H_9	H	HC=CH	7.4
(-)-**11**	OcC_5H_9	H	HC=CH	6.7
(±)-**12**			H_2C-CH_2	7.3
(+)-**12**	as (±)-**12**		H_2C-CH_2	7.8
(-)-**12**	as (±)-**12**		H_2C-CH_2	5.6
(±)-**13**	as (±)-**12**		HC=CH	8.0
(+)-**13**	as (±)-**12**		HC=CH	8.5
(-)-**13**	as (±)-**12**		HC=CH	6.6

[a] $pIC_{50} = -\log IC_{50}$. Inhibition of PDE4 was investigated in the cytosol of human neutrophils. The data are the means of two independent determinations in triplicate.

both N2 and the 4-catechol moiety were prepared from the corresponding racemic γ-keto acids as outlined in Scheme 1. The structures of the target phthalazinones are summarized in Tables 2 and 3. In the first step, the enantiomers of the γ-keto acids *cis*-(±)-**1**-**7**[5] (Table 1) were obtained by resolution. Subsequent treatment of the resolved γ-keto acids with the selected hydrazine in ethanol or pyridine provided the optically active target compounds (+)- and (−)-**8**−**15** in variable yields. Phthalazinone (+)-**16** was achieved after an additional reaction step.

Table 3. Summary of the PDE4 Inhibitory and in Vivo Antiinflammatory Activities of the Racemic and Analogous Resolved N-Substituted Tetrahydrophthalazinones



compd	R_1	R_2	R_3	PDE4 pIC_{50}[a]	% inhibition of AA-induced mouse ear edema[b]
(±)-**14**	Me	Me	adamantan-2-yl	9.2	51
(+)-**14**	Me	Me	adamantan-2-yl	9.3	49
(−)-**14**	Me	Me	adamantan-2-yl	6.9	*c*
(±)-**15**	Et	Et	4-$HO_2CC_6H_4$	7.7	48
(+)-**15**	Et	Et	4-$HO_2CC_6H_4$	8.3	47
(±)-**16**	Et	Et	4-$EtO_2CC_6H_4$	8.0	*c*
(+)-**16**	Et	Et	4-$EtO_2CC_6H_4$	8.2	27
(−)-Rolipram				7.3	55
CDP840				7.7	48
Ariflo				7.0	33

[a] See corresponding footnote from Table 2. [b] Percent inhibition of the formation of AA-induced mouse ear edema after pretreatment with the target compound (1 h before AA) at a drug concentration of 30 μmol/kg po. Results are given as mean from two independent experiments. [c] Not determined.

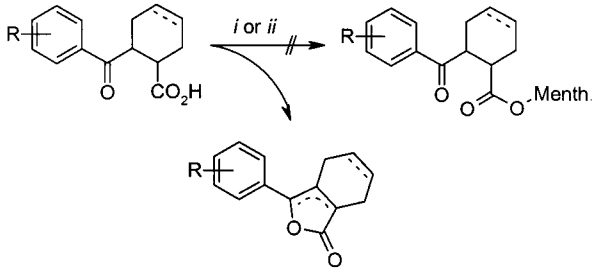
The racemates of targets **8**−**15** were synthesized, if not already available,[4−6] for pharmacological comparison.

The preparation of γ-keto acids *cis*-(±)-**1**−**6** has been described in preceding papers.[4,5] Friedel−Crafts acylation of 1,2-diethoxybenzene with *cis*-1,2,3,6-tetrahydrophthalic anhydride gave the corresponding cyclohex-3-enecarboxylic acid *cis*-(±)-**7**.

The conditions used for the resolution of γ-keto acids (−)-**1**−**6** and (+)-**1**−**7** ((−)-**7** was not isolated) are summarized in Table 1. From a number of chiral bases tested as potential resolving agents, (1*R*,2*S*)-(−)-ephedrine, quinine, and (*R*)- and (*S*)-(+)-α-methylbenzylamine were found to be the most suitable. The most diastereomerically pure salts were obtained using ethyl acetate or ethanol as solvents for crystallization. The diastereomeric salts were purified by recrystallization until a diastereomeric excess (de) of more than 96% was reached.[7] The diastereomeric excess was determined by means of ^{1}H NMR spectroscopy; the diastereomers could easily be distinguished because equimolar amounts of quinine and racemic γ-keto acid show duplication of the resonance of the H5 aromatic proton.

Treatment of the enantiomerically pure γ-keto acids **1**−**6** with the suitable hydrazines provided the corresponding optically active phthalazinones **8**−**15**. Esterification of benzoic acid (+)-**15** with acetyl chloride in ethanol yielded derivative (+)-**16**. The enantiomeric purity of the resolved phthalazinones was determined by means of ^{1}H NMR spectroscopy using a chiral shift reagent. The ^{1}H NMR spectra of the racemic phthalazinones **8**−**14** and **16** in the presence of 0.7−2 equiv of europium shift reagents Eu(hfc)$_3$, Eu(tfc)$_3$, or Eu(dcm)$_3$ (full names in Experimental Section) showed duplication of the resonances of the methoxy group(s) and/or the H5 aromatic proton, whereas samples of the two separate enantiomers each exhibited single resonances, thus indicating a high enantiomeric purity (>96% ee).[7] No contamination of one enantiomer by the other could be detected in the resolved samples. Unfortunately, we were not able to distinguish the two enantiomers of carboxylic acid **15** by ^{1}H NMR spectroscopy. However, the antipodes of ethyl ester **16** could easily be identified with ^{1}H NMR, using the europium shift reagent Eu(hfc)$_3$; since the benzoic acid (+)-**15** was used as a starting material for ester (+)-**16** (>96% ee), comparable enantiomeric purity is likely.

Scheme 2[a]



[a] Reagents: (i) 1, $SOCl_2$; 2, L-(−)-menthol; (ii) p-TosOH, L-(−)-menthol.

The preparation of phthalazinones (±)-**8**−**14** (Tables 2 and 3) has been described previously.[4−6] Condensation of γ-keto acid (±)-**7** with 4-hydrazinobenzoic acid in pyridine at reflux temperature afforded phthalazinone (±)-**15**. Ethyl ester (±)-**16** was prepared from (±)-**15** as explained above for (±)-**15**.

The optical rotation values for the resolved γ-keto acids **1**−**7** and phthalazinones **8**−**6** are summarized in Table 1 and the Experimental Section, respectively.

Attempts were made to synthesize diastereomeric esters by acid-catalyzed condensation of γ-keto acids with a chiral alcohol (e.g., L-(−)-menthol) or by conversion of the γ-keto acids into the corresponding acid chlorides, which were then coupled with a chiral alcohol (Scheme 2). However, these efforts failed because the γ-keto acids and the corresponding acid chlorides undergo intramolecular lactonization as shown in Scheme 2. A similar lactonization was published for analogous oxybutyric acids.[8]

X-ray Structure and Absolute Configuration of (+)-12

The ideal method for determination of the absolute configuration of the antipodes is X-ray crystallography. From a solution of benzofuran (+)-**12** in diethyl ether, crystals suitable for an X-ray analysis could be grown. It was found that the asymmetric unit cells contain two identical independent molecules and one solvent molecule (Figures 2 and 3). Matching both molecules led to a root-mean square (rms) value of 0.33 Å. The crystal structure depicted in Figure 2 revealed that two hydrogen bonds are formed between the two target molecules in a unit cell, one from N2A (N2, molecule A) to O9B (O9, molecule B) and the other from N2B to O9A with lengths of 2.943(5) and 2.890(5) Å, respectively. In the crystal, the cis-fused cyclohexane ring of (+)-**12** possesses an undistorted chair conformation. The carbonyl moieties in both molecules are oriented axially, whereas the N=C-carbon atom (C4) attached to C4a occupies the equatorial position, thus confirming the cis configuration. The benzofuran moiety, the 4-methoxy group, and the heterocyclic ring are nearly coplanar. According to

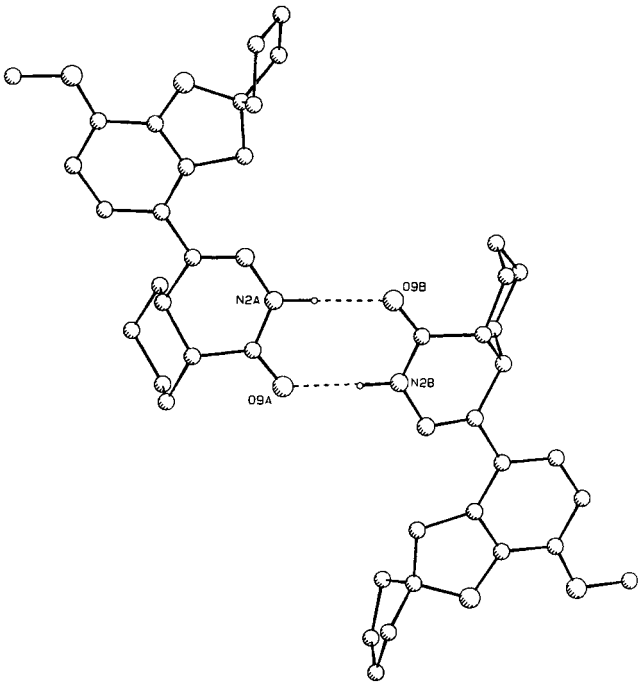


Figure 2. Crystal structure of benzofuran (+)-**12**. The unit cells contain one solvent molecule (not shown) and two target molecules (A and B) that form two hydrogen bonds with one another.

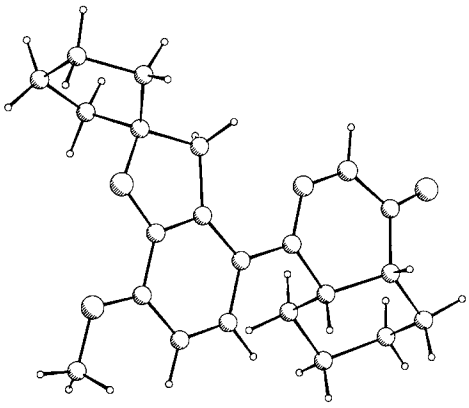


Figure 3. Structure of molecule B as found in the unit cells of a crystal of (+)-**12**. The positions of the hydrogen atoms are calculated.

the Cahn−Ingold−Prelog convention, the annealed carbon atoms at the 4a and 8a positions have the (*S*)- and (*R*)-configuration, respectively.

The crystal structure of benzofuran (+)-**12** is, not surprisingly, very similar to the calculated (modeled) 3-D structures of the analogous phthalazinones we described earlier.[4]

Pharmacology

The PDE4 inhibitory activities of the hexa- and tetrahydrophthalazinones under investigation were determined as described previously[4] and are listed in Tables 2 and 3. Structure−activity relationships for the present series of optically active *cis*-phthalazinones are discussed below.

Structure−Activity Relationships. Recently, we discussed the modeling and superimposition of a number of phthalazinones with various fused hydrocarbon rings and proposed that steric interactions of these fused rings with the binding site play an important role in PDE4 inhibition.[4] Now, this hypothesis is further strengthened by the observation that the *cis*-(+)-enantiomers of phthalazinones **8**−**14** display potent PDE4 inhibition, whereas their (−)-counterparts exhibit only weak to moderate PDE4 inhibitory activities (Tables 2 and 3); up to a 250-fold difference in activity (compound **14**) is observed. The *cis*-(+)-phthalazinones most likely have the same absolute configuration.

In Vivo Antiinflammatory Activity. The in vivo antiinflammatory properties of selected N-substituted phthalazinones (Table 3) have been determined in a standard model of inflammation. In this assay, the suppression of the formation of arachidonic acid (AA) induced mouse ear edema was measured after pretreatment with the target compound (1 h before AA) at a drug concentration of 30 μmol/kg po.[6]

Analogues (±/+)-**14** and (±/+)-**15** are potent inhibitors of arachidonic acid (AA) induced mouse ear edema formation. Esterification of benzoic acid (+)-**15** leads to a considerable decrease of in vivo activity, while the PDE4 inhibitory activity remains equal (compare (+)-**15** with (+)-**16**). This reduction in inhibition of mouse ear edema may be caused by an increase in lipophilicity; however, the *N*-adamantyl derivatives (±/+)-**14** are more lipophilic than (+)-**16** but have higher in vivo antiinflammatory activities.

Conclusion

In this study, various γ-keto acids were successfully resolved by resolution. Subsequently, the resolved γ-keto acids were converted into optically active phthalazinones in an enantioselective manner, as confirmed by ^{1}H NMR spectroscopy using a suitable europium shift reagent. The absolute configuration of *cis*-(+)-(4a*S*,8a*R*)-hexahydrophthalazinone (+)-**12** was determined by X-ray crystallography.

In the present series of hexa- and tetrahydrophthalazinones, stereoselectivity for PDE4 inhibition is observed like for the well-known chiral PDE4 inhibitors including rolipram,[9] CDP840,[10] and ariflo.[11] The *cis*-(+)-enantiomers of the phthalazinones display high PDE4 inhibitory activity, whereas their (−)-counterparts exhibit only weak to moderate activity. Therefore, we assume that all *cis*-(+)-phthalazinones have a (4a*S*,8a*R*)-configuration, the arrangement found for (+)-**12**. The N-substituted tetrahydrophthalazinones under study also possess in vivo antiinflammatory activity. In particular, analogues (±/+)-**14** and (±/+)-**15** were found to be potent antiinflammatory agents showing about 50% inhibition of formation of mouse ear edema at a dose of 30 μmol/kg po. We plan to investigate an extended series of N-substituted *cis*-(+)-phthalazinones for their in vitro and in vivo antiinflammatory properties, applying various assays.

Experimental Section

I. Crystallographic Studies. A crystal of (+)-**12** with approximate dimensions 0.30 mm × 0.45 mm × 0.50 mm was used for data collection on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Cu Kα radiation and $\omega-2\theta$ scan. A total of 4656 unique reflections was measured within the range $-13 \le h \le 13$, $0 \le k \le 11$, $0 \le l \le 26$. Of these, 4323 were above the significance level of 2.5 $\sigma(I)$. The range of $(\sin\theta)/\lambda$ was 0.046−0.626 Å^{-1} ($4.1° < \theta < 74.7°$). Two

reference reflections (0 1 5; $\bar{3}$ 1 4) were measured hourly and showed no decrease during the 72 h collecting time. In addition, around 969 "Friedel" reflections were measured, which were used in the determination of the absolute configuration. Unit-cell parameters were refined by a least-squares fitting procedure using 23 reflections with $80° \leq 2\theta \leq 84°$. Corrections for Lorentz and polarization effects were applied. The structure was solved by the program package CRUNCH.[12] The hydrogen atoms were calculated. Full-matrix least-squares refinement on F (anisotropic for the non-hydrogen atoms and isotropic for the hydrogen atoms (the ADP's of the solvent hydrogen atoms were kept fixed at $U = 0.1$ Å^2) with restraint of the latter in such a way that the distance to their carrier remained constant at approximately 1.0 Å) converged to $R = 0.040$, $R_w = 0.040$, $(\Delta/\sigma)_{max} = 0.15$, $s = 1.101$. A weighting scheme $w = [0.5 + 0.5(\sigma(F_{obs})^2 + 0.005/(\sigma(F_{obs}))]^{-1}$ was used. The secondary isotropic extinction coefficient[13,14] was refined to EXT = 0.67(2). The absolute structure parameter[15] was refined to $X_{abs} = 0.03$, thus confirming the correct enantiomer. A final difference Fourier map revealed a residual electron density between −0.15 and 0.17 e Å^{-3}. Scattering factors were taken from Cromer and Mann[16] and International Tables for X-ray Crystallography.[17] All calculations were performed with XTAL[18] unless stated otherwise. The asymmetric unit contains two identical independent molecules and one solvent molecule. Matching both molecules led to rms = 0.33 Å. There are two hydrogen bonds between the two molecules. One from N2a to O9b and one from N2b to O9a with lengths of 2.943(5) and 2.890(5) Å, respectively. Crystal data are the following: $C_{21}H_{26}N_2O_3 \cdot 0.5(CH_3CH_2)_2O$, $M_r = 354.5$, monoclinic, $P2_1$, $a = 11.0427(7)$ Å, $b = 9.355(2)$ Å, $c = 21.186(2)$ Å, $\beta = 102.326(5)°$, $V = 2138.2(5)$ Å^3, $Z = 4$, $D_x = 1.22$ g cm^{-3}, λ(Cu Kα) = 1.5418 Å, μ(Cu Kα) = 6.19 cm^{-1}, $F(000) = 844$, room temperature. Final R is 0.040 for 4323 observed reflections.

II. Chemistry. General Methods and Materials. Pyridine was stored over 4 Å molecular sieves. All the other solvents were used as received. Starting materials were commercially available. Tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]europium(III) [Eu(tfc)$_3$], tris(d,d-dicampholylmethanato)europium(III) [Eu(dcm)$_3$], and tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]europium(III) [Eu(hfc)$_3$] were purchased from Fluka. Reactions were performed under anhydrous conditions unless noted otherwise. Friedel−Crafts acylations were performed under an N_2 atmosphere. Reactions were followed by TLC analysis on Merck TLC aluminum sheets Silicagel 60 F254. Flash column chromatography was performed on silicagel, 30−60 μm (J. T. Baker). Melting points were measured on an Electrothermal IA9200 apparatus or a Mettler FP-5 + FP-052 apparatus equipped with a microscope and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 200 (^{1}H NMR: δ 200.1 MHz). The ^{1}H NMR chemical shifts (δ) are expressed in ppm values relative to $CDCl_3$ ($\delta = 7.26$ ppm). Abbreviations used in description of NMR spectra are the following: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, m = multiplet, and bs = broad singulet. The limit of detection is <4% of one enantiomer in the other using ^{1}H NMR spectroscopy. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. All phthalazinones had an elemental analysis (C, H, and N) within ±0.4% of the theoretical value. The synthesis of γ-keto acids (±)-**1**−**6**[4,5] and phthalazinones (±)-**8**−**14**[4−6] has been described in previous papers.

Resolution of *cis*-(±)-2-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1′-cyclopentane-4-carbonyl)cyclohexanecarboxylic Acid ((−)-5 and (+)-5). A stirred solution of γ-keto acid (±)-**5** (12.5 g, 34.8 mmol) in ethyl acetate (250 mL) was treated with quinine (11.3 g, 34.8 mmol). Crystallization occurred within 30 min. After 4 h the crystalline precipitate was filtered off and washed twice with ethyl acetate. The product was dried in vacuo to give 10.4 g of quinine salt of crude (−)-**5**, as determined by ^{1}H NMR (see below). The solid was recrystallized from ethyl acetate to afford 9.65 g (81%) of pure (−)-**5** as quinine salt: >96% de; mp 165−167 °C; $[\alpha]^{25}_D$ −101.8° (*c* 1.0, $CHCl_3$). A small sample of the diastereomeric salt was dissolved in dichloromethane (15 mL) and washed twice with 1 N HCl (15 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford pure γ-keto acid (−)-**5**: >96% ee; $[\alpha]^{25}_D$ −8.98° (*c* 1.1, $CHCl_3$).

Crude γ-keto acid (+)-**5** was obtained from the combined and concentrated mother liquors containing oily diastereomeric salt using the same procedure as mentioned above (CH_2Cl_2, 1 N HCl). The oily residue (6.85 g, 19.1 mmol) was dissolved in absolute ethanol (150 mL), and (1*R*,2*S*)-(−)-ephedrine (3.16 g, 19.1 mmol) was added. The solution was cooled to 0 °C and kept at this temperature for 72 h. The precipitate was filtered off, washed twice with ethanol, and dried in vacuo to give 6.51 g (72%) of (1*R*,2*S*)-(−)-ephedrine salt of pure (+)-**5**: >96% de; mp 143−146 °C; $[\alpha]^{25}_D$ −2.82° (*c* 1.0, $CHCl_3$). The mother liquor was concentrated to 75 mL, and after it was stirred overnight, a second crop of pure diastereomeric salt (1.00 g, 11%) was collected. The γ-keto acid (+)-**5** was obtained as described above: >96% ee; $[\alpha]^{25}_D$ 10.7° (*c* 1.0, $CHCl_3$).

The enantiomeric purity of (−)-**5** and (+)-**5** was determined by ^{1}H NMR ($CDCl_3$). Quinine (1 equiv) was added to racemic (±)-**5**, resulting in a separation of the resonance of aromatic H5 (doublet) into two resonances that appeared at 6.54 and 6.69 ppm for (+)-**5** and (−)-**5**. Independent treatment of samples of (−)-**5** and (+)-**5** with quinine (1 equiv) resulted in retention of single resonances for the aromatic H5 resonance, and no detectable contamination by the other enantiomer was found (>96% de).

***cis*-(−)-4-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1′-cyclopentan-4-yl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one ((−)-12).** The quinine salt of (−)-**5** (1.91 g, 2.80 mmol) was dissolved in dichloromethane (25 mL) and washed twice with 1 N HCl (20 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The remainder was dissolved in ethanol (25 mL), hydrazine monohydrate (0.21 g, 4.2 mmol) was added, and the solution was acidified with acetic acid and refluxed for 24 h. Next, the reaction mixture was diluted with ethyl acetate and washed with 1 N HCl and water. The organic layer was dried over $MgSO_4$, and the solvents were removed under reduced pressure. The remaining oil was purified by flash column chromatography using 1:2 ethyl acetate/petroleum ether (40−60 °C) to give enantiopure (−)-**12**, which was crystallized from diethyl ether. Yield 0.40 g (40%). A second crop of 0.28 g (28%) of enantiopure product crystallized after concentration of the filtrate. Total yield 68%; mp 87−88 °C; >96% ee; $[\alpha]^{25}_D$ −339.5° (*c* 0.96, $CHCl_3$). Anal. ($C_{21}H_{26}N_2O_3 \cdot 0.6C_4H_{10}O$) C, H, N.

***cis*-(+)-4-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1′-cyclopentan-4-yl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one ((+)-12).** (+)-**12** was prepared from the (1*R*,2*S*)-(−)-ephedrine salt of pure (+)-**5** (1.10 g, 2.10 mmol) as described for the preparation of (−)-**12**. The title compound was crystallized from diethyl ether. Yield 0.10 g (13%). Another 0.40 g (53%) of enantiopure product crystallized upon concentration of the filtrate. Total yield 66%; mp 87−88 °C; >96% ee; $[\alpha]^{25}_D$ 336.8° (*c* 1.0, $CHCl_3$). Anal. ($C_{21}H_{26}N_2O_3 \cdot 0.5C_4H_{10}O$) C, H, N.

The enantiomeric purity of (+)-**12** and (−)-**12** was determined by ^{1}H NMR ($CDCl_3$). Chiral shift reagent Eu(hfc)$_3$ (12 mg, 0.7 equiv) was added to racemic (±)-**12** (5 mg), resulting in a separation of the resonance of the methoxy group and aromatic H5 into two resonances each. The resonances appeared at 4.15 ppm (OCH_3) and 7.34 ppm (H5-arom) for (−)-**12** and at 4.16 and 7.37 ppm for (+)-**12**. Independent treatment of samples of (−)-**12** and (+)-**12** with Eu(hfc)$_3$ (0.7 equiv) resulted in retention of single resonances, and no detectable contamination by the other enantiomer was found (>96% ee).

Resolution of *cis*-(±)-2-(3,4-Dimethoxybenzoyl)cyclohexanecarboxylic Acid ((−)-1 and (+)-1). The resolution was performed in a similar way as described for γ-keto acid (±)-**5** using (*R*)-(+)-α-methylbenzylamine (2.01 g, 16.6 mmol), γ-keto acid (±)-**1** (4.85 g, 16.6 mmol), and ethanol (200 mL). Within 15 min a white precipitate was formed. The crystals (2.51 g) were collected after 16 h. A second crop (0.64 g) was obtained after concentration of the mother liquor to 100 mL

and stirring the mixture for 4 h. The combined diastereomeric salts were recrystallized from ethanol. Yield 2.31 g (67%); >96% de; mp 160−162 °C; $[\alpha]^{25}_D$ 24.8° (*c* 0.97, $CHCl_3$).

(+)-**1**: $[\alpha]^{25}_D$ 9.87° (*c* 1.0, $CHCl_3$).

The other antipode was obtained using crude γ-keto acid (−)-**1**, ethanol (100 mL), and (*S*)-(−)-α-methylbenzylamine (1.00 g, 8.25 mmol). The pure diastereomeric salt was collected after 16 h. Yield 2.35 g (69%); >96% de; mp 153−156 °C; $[\alpha]^{25}_D$ −25.3° (*c* 1.0, $CHCl_3$).

(−)-**1**: $[\alpha]^{25}_D$ −9.51° (*c* 0.86, $CHCl_3$).

^{1}H NMR ($CDCl_3$) of (±)-**1** plus quinine (1 equiv) showed resonances for aromatic H5 at 6.73 ppm for (+)-**1** and 6.49 ppm for (−)-**1**. No detectable contamination by the other enantiomer was found (>96% ee) upon independent treatment of samples of (−)-**1** and (+)-**1** with quinine (1 equiv).

Resolution of *cis*-(±)-6-(3,4-Dimethoxybenzoyl)cyclohex-3-enecarboxylic Acid ((−)-2 and (+)-2). The resolution was performed in a similar way as described for γ-keto acid (±)-**5**, using (*S*)-(−)-α-methylbenzylamine (2.29 g, 18.9 mmol), γ-keto acid (±)-**2** (5.49 g, 18.9 mmol), and ethyl acetate (100 mL). Within 30 min a white precipitate was formed. The crystals (2.00 g) were collected after 16 h. A second crop (0.41 g) was obtained after concentration of the mother liquor and stirring the mixture for 72 h. The combined diastereomeric salts were recrystallized from ethyl acetate. Yield 2.26 g (58%); >96% de; mp 136−139 °C; $[\alpha]^{25}_D$ 5.09° (*c* 0.98, $CHCl_3$).

(+)-**2**: $[\alpha]^{25}_D$ 29.1° (*c* 0.97, $CHCl_3$).

The other antipode was obtained using crude γ-keto acid (−)-**2**, ethyl acetate (100 mL), and (*R*)-(+)-α-methylbenzylamine (1.15 g, 9.49 mmol). The crude diastereomeric salt was filtered off after the mixture was stirred overnight and was recrystallized from ethyl acetate. Yield 2.95 g (76%); >96% de; mp 138−141 °C; $[\alpha]^{25}_D$ −6.57° (*c* 1.1, $CHCl_3$).

(−)-**2**: $[\alpha]^{25}_D$ −27.4° (*c* 0.98, $CHCl_3$).

^{1}H NMR ($CDCl_3$) of (±)-**2** plus quinine (1 equiv) showed resonances for aromatic H5 at 6.59 ppm for (+)-**2** and 6.70 ppm for (−)-**2**. No detectable contamination by the other enantiomer was found (>96% ee) upon independent treatment of samples of (−)-**2** and (+)-**2** with quinine (1 equiv).

Resolution of *cis*-(±)-2-(3-Cyclopentyloxy-4-methoxybenzoyl)cyclohexanecarboxylic Acid ((−)-3 and (+)-3). The resolution was performed in a similar way as described for γ-keto acid (±)-**5**, using quinine (7.32 g, 22.6 mmol), γ-keto acid (±)-**3** (7.81 g, 22.6 mmol), and ethyl acetate (200 mL). Within 30 min a white precipitate was formed. The crystals (5.59 g) were collected after 16 h. A second crop (2.13 g) was obtained after concentration of the mother liquor and stirring the mixture for 16 h. The combined diastereomeric salts were recrystallized from ethyl acetate. Yield 5.30 g (70%); >96% de; mp 165−168 °C; $[\alpha]^{25}_D$ −91.0° (*c* 0.97, $CHCl_3$).

(+)-**3**: $[\alpha]^{25}_D$ 15.0° (*c* 0.96, $CHCl_3$).

The other antipode was obtained using crude γ-keto acid (−)-**3**, ethanol (100 mL), and (1*R*,2*S*)-(−)-ephedrine (1.86 g, 11.3 mmol). The crude diastereomeric salt was filtered off after the mixture was stirred for 72 h and was recrystallized from ethanol. Yield 2.01 g (35%); >96% de; mp 143−145 °C; $[\alpha]^{25}_D$ −32.4° (*c* 1.1, $CHCl_3$).

(−)-**3**: $[\alpha]^{25}_D$ −13.9° (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$) of (±)-**3** plus quinine (1 equiv) showed resonances for aromatic H5 at 6.76 ppm for (+)-**3** and 6.47 ppm for (−)-**3**. No detectable contamination by the other enantiomer was found (>96% ee) upon independent treatment of samples of (−)-**3** and (+)-**3** with quinine (1 equiv).

Resolution of *cis*-(±)-6-(3-Cyclopentyloxy-4-methoxybenzoyl)cyclohex-3-enecarboxylic Acid ((−)-4 and (+)-4). The resolution was performed in a similar way as described for γ-keto acid (±)-**5**, using (1*R*,2*S*)-(−)-ephedrine (7.78 g, 47.1 mmol), γ-keto acid (±)-**4** (16.2 g, 47.1 mmol), and ethyl acetate (350 mL). Within 1 h a white precipitate was formed. The crude product (15.4 g) was collected after 72 h and was recrystallized from ethyl acetate. Yield 3.40 g (28%); >96% de; mp 133−135 °C; $[\alpha]^{25}_D$ −1.46° (*c* 1.0, $CHCl_3$).

(+)-**4**: $[\alpha]^{25}_D$ 20.8° (*c* 1.0, $CHCl_3$).

The other antipode was obtained using crude γ-keto acid (−)-**4**, ethyl acetate (250 mL), and quinine (7.64 g, 23.6 mmol). The crude diastereomeric salt was filtered off after the mixture was stirred overnight and was recrystallized from ethyl acetate. Yield 11.5 g (73%); >96% de; mp 167−170 °C; $[\alpha]^{25}_D$ −103.6° (*c* 1.1, $CHCl_3$).

(−)-**4**: $[\alpha]^{25}_D$ −20.4° (*c* 0.92, $CHCl_3$).

^{1}H NMR ($CDCl_3$) of (±)-**4** plus quinine (1 equiv) showed resonances for aromatic H5 at 6.45 ppm for (+)-**4** and 6.66 ppm for (−)-**4**. No detectable contamination by the other enantiomer was found (>96% ee) upon independent treatment of samples of (−)-**4** and (+)-**4** with quinine (1 equiv).

Resolution of *cis*-(±)-2-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1′-cyclopentane-4-carbonyl)-1,2,3,6-tetrahydrobenzoic Acid ((−)-6 and (+)-6). The resolution was performed in a similar way as described for γ-keto acid (±)-**5**, using quinine (9.02 g, 27.8 mmol), γ-keto acid (±)-**6** (9.90 g, 27.8 mmol), and ethyl acetate (350 mL). Within 1 h a white precipitate was formed. The crude crystals (8.74 g) were collected after the mixture was stirred overnight and were recrystallized from ethyl acetate. Yield 7.25 g (77%); >96% de; mp 163−165 °C; $[\alpha]^{25}_D$ −107.2° (*c* 0.99, $CHCl_3$).

(−)-**6**: $[\alpha]^{25}_D$ −40.1° (*c* 1.0, $CHCl_3$).

The other antipode was obtained using crude γ-keto acid (+)-**6**, ethanol (200 mL), and (1*R*,2*S*)-(−)-ephedrine (2.30 g, 13.9 mmol). The pure diastereomeric salt was collected after the mixture was stirred for 72 h. Yield 2.03 g (28%); >96% de; mp 126−128 °C; $[\alpha]^{25}_D$ 13.8° (*c* 1.0, $CHCl_3$).

(+)-**6**: $[\alpha]^{25}_D$ 37.5° (*c* 1.0, $CHCl_3$).

^{1}H NMR ($CDCl_3$) of (±)-**6** plus quinine (1 equiv) showed resonances for aromatic H5 at 6.62 ppm for (+)-**6** and 6.65 ppm for (−)-**6**. No detectable contamination by the other enantiomer was found (>96% ee) upon independent treatment of samples of (−)-**6** and (+)-**6** with quinine (1 equiv).

***cis*-6-(3,4-Diethoxybenzoyl)cyclohex-3-enecarboxylic Acid ((±)-7).** Aluminum chloride (73.3 g, 0.55 mol) was suspended in dichloromethane (800 mL), the mixture was cooled to 5 °C, and 1,2-diethoxybenzene (83.1 g, 0.50 mol) was added. After 30 min, *cis*-1,2,3,6-tetrahydrophthalic anhydride (76.1 g, 0.50 mol) was added, and the reaction mixture was allowed to reach room temperature and was refluxed for 4 h. The mixture was poured into ice−water, the organic layer was dried over magnesium sulfate, and the solvent was removed in vacuo. The remainder was dissolved in CH_2Cl_2 and filtered over silicagel to remove the dicarboxylic acid formed during workup. The organic layer was extracted with 1 N NaOH, and the combined basic extracts were acidified and extracted with diethyl ether. The associated organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The title compound crystallized from diethyl ether as a white solid. Yield 93.7 g (59%). Mp 125−127 °C. ^{1}H NMR ($CDCl_3$): δ 1.38−1.59 (m, 6H, CH_3), 2.32−2.60 (m, 3H, CH_2, C*H*H′), 2.72−3.10 (m, 2H, CH*H*′, H1), 3.89−4.04 (m, 1H, H6), 4.05−4.27 (m, 4H, OCH_2), 5.58−5.88 (m, 2H, HC=CH), 6.87 (d, 1H, ^3J = 8.2 Hz, H5-arom), 7.43−7.59 (m, 2H, H2-arom, H6-arom).

Resolution of *cis*-(±)-6-(3,4-Diethoxybenzoyl)cyclohex-3-enecarboxylic Acid ((+)-7). The resolution was performed in a similar way as described for γ-keto acid (±)-**5**, using (*S*)-(−)-α-methylbenzylamine (2.29 g, 18.9 mmol), γ-keto acid (±)-**7** (6.01 g, 18.9 mmol), and ethyl acetate (100 mL). The solution was kept at 5 °C for 72 h. Subsequently, the mixture was allowed to reach room temperature, upon which within 30 min a white precipitate was formed. The pure diastereomeric salt (1.89 g) was collected after 16 h. A second crop (0.96 g) was collected after concentration of the mother liquor. Total yield 69%; >96% de; mp 116−118 °C; $[\alpha]^{25}_D$ 1.87° (*c* 0.99, $CHCl_3$).

(+)-**7**: $[\alpha]^{25}_D$ 27.4° (*c* 5.2, $CHCl_3$). The ^{1}H NMR ($CDCl_3$) spectrum of (±)-**7** plus quinine (1 equiv) showed resonances for aromatic H5 at 6.56 ppm for (+)-**7** and 6.71 ppm for (−)-**7**. No detectable contamination by the other enantiomer was found (>96% ee) upon treatment of a sample of (+)-**7** with quinine (1 equiv).

***cis*-4-(3,4-Dimethoxyphenyl)-4a,5,6,7,8,8a-hexahydro-2*H*-phthalazin-1-one ((−)-8 and (+)-8).** A mixture of γ-keto

acid (+)-**1** (0.84 g, 2.9 mmol), hydrazine monohydrate (0.15 g, 3.0 mmol), and ethanol (30 mL) was acidified with acetic acid and refluxed for 4 h. Workup was performed as described for (−)-**12**. The title compound ((−)-**8**) was crystallized from diethyl ether. Yield 0.24 g (29%); >96% ee; mp 153−155 °C; $[\alpha]^{25}_D$ −452.0° (*c* 0.96, $CHCl_3$). Anal. ($C_{16}H_{20}N_2O_3$) C, H, N.

Analogue (+)-**8** was synthesized analogously to the preparation of (−)-**8** using γ-keto acid (−)-**1** (0.81 g, 2.8 mmol). The product was purified by flash column chromatography using 3:1 petroleum ether (60−80 °C)/ethyl acetate. The title compound ((+)-**8**) was crystallized from diethyl ether. Yield 0.31 g (39%); >92% ee; mp 153−155 °C; $[\alpha]^{25}_D$ 441.1° (*c* 1.1, $CHCl_3$). Anal. ($C_{16}H_{20}N_2O_3$) C, H, N.

For ^{1}H NMR ($CDCl_3$), chiral shift reagent Eu(tfc)$_3$ (0.9 equiv) was used to determine the enantiomeric purity of the enantiomers. The resonances of the methoxy groups appeared at 4.05 and 4.16 ppm for (−)-**8** and 4.03 and 4.15 ppm for (+)-**8**. No detectable contamination by the other enantiomer was found (>96% ee) upon independent treatment of samples of (−)-**8** and (+)-**8** with Eu(tfc)$_3$ (0.9 equiv).

***cis*-4-(3,4-Dimethoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one ((−)-9 and (+)-9).** (−)-**9** was synthesized analogously to the preparation of (−)-**8** using γ-keto acid (−)-**2** (1.20 g, 4.14 mmol). The title compound ((−)-**9**) was crystallized from diethyl ether. Yield 0.84 g (71%); >80% ee; mp 151−154 °C; $[\alpha]^{25}_D$ −678.4° (*c* 0.98, $CHCl_3$). Anal. ($C_{16}H_{18}N_2O_3$) C, H, N.

Analogue (+)-**9** was synthesized analogously to the preparation of (−)-**8** using γ-keto acid (+)-**2** (1.64 g, 5.66 mmol) and hydrazine monohydrate (0.42 g, 8.4 mmol). The title compound ((+)-**9**) was crystallized from diethyl ether. Yield 1.41 g (87%); >96% ee; mp 152−156 °C; $[\alpha]^{25}_D$ 726.1° (*c* 0.97, $CHCl_3$). Anal. ($C_{16}H_{18}N_2O_3$) C, H, N.

For ^{1}H NMR ($CDCl_3$), chiral shift reagent Eu(dcm)$_3$ (0.9 equiv) was used to determine the enantiomeric purity of the enantiomers. The resonances of the methoxy groups appeared at 4.02 and 4.11 ppm for (−)-**9** and at 4.07 and 4.13 ppm for (+)-**9**. No detectable contamination by the other enantiomer was found (>96% ee) upon independent treatment of samples of (−)-**9** and (+)-**9** with Eu(dcm)$_3$ (0.9 equiv).

***cis*-4-(3-Cyclopentyloxy-4-methoxyphenyl)-4a,5,6,7,8,-8a-hexahydro-2*H*-phthalazin-1-one ((−)-10 and (+)-10).** (−)-**10** was synthesized analogously to the preparation of (−)-**8** using γ-keto acid (+)-**3** (1.46 g, 4.22 mmol) and hydrazine monohydrate (0.32 g, 6.4 mmol). The title compound ((−)-**10**) was crystallized from diethyl ether. Yield 1.19 g (82%); >96% ee; mp 119−120 °C; $[\alpha]^{25}_D$ −383.6° (*c* 1.0, $CHCl_3$). Anal. ($C_{20}H_{26}N_2O_3$) C, H, N.

Analogue (+)-**10** was synthesized analogously to the preparation of (−)-**8** using γ-keto acid (−)-**3** (1.50 g, 4.34 mmol) and hydrazine monohydrate (0.43 g, 8.6 mmol). The title compound ((+)-**10**) was crystallized from diethyl ether. Yield 1.19 g (80%); >96% ee; mp 119−120 °C; $[\alpha]^{25}_D$ 384.7° (*c* 1.0, $CHCl_3$). Anal. ($C_{20}H_{26}N_2O_3$) C, H, N.

For ^{1}H NMR ($CDCl_3$), chiral shift reagent Eu(tfc)$_3$ (0.7 equiv) was used to determine the enantiomeric purity of the enantiomers. The resonance of the methoxy group and aromatic H5 appeared at 4.04 and 7.20 ppm for (−)-**10** and at 4.03 and 7.18 ppm for (+)-**10**. No detectable contamination by the other enantiomer was found (>96% ee) upon independent treatment of samples of (−)-**10** and (+)-**10** with Eu(tfc)$_3$ (0.7 equiv).

***cis*-4-(3-Cyclopentyloxy-4-methoxyphenyl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one ((−)-11 and (+)-11).** (−)-**11** was synthesized analogously to the preparation of (−)-**8** using γ-keto acid (−)-**4** (0.98 g, 2.9 mmol). The title compound ((−)-**11**) was crystallized from ethyl acetate/petroleum ether (60−80 °C). Yield 0.65 g (67%); >92% ee; mp 98−102 °C; $[\alpha]^{25}_D$ −605.1° (*c* 1.0, $CHCl_3$). Anal. ($C_{20}H_{24}N_2O_3$) C, H, N.

Analogue (+)-**11** was synthesized analogously to the preparation of (−)-**8** using γ-keto acid (+)-**4** (1.50 g, 4.36 mmol) and hydrazine monohydrate (0.44 g, 8.8 mmol). The title compound ((+)-**11**) was crystallized from diethyl ether. Yield 1.11 g (75%); >96% ee; mp 125−126 °C; $[\alpha]^{25}_D$ 626.4° (*c* 0.98, $CHCl_3$). Anal. ($C_{20}H_{24}N_2O_3$) C, H, N.

For ^{1}H NMR ($CDCl_3$), chiral shift reagent Eu(dcm)$_3$ (0.7 equiv) was used to determine the enantiomeric purity of the enantiomers. The resonances of the methoxy group appeared at 3.99 ppm for (−)-**11** and 3.97 ppm for (+)-**11**. No detectable contamination by the other enantiomer was found (>96% ee) upon independent treatment of samples of (−)-**11** and (+)-**11** with Eu(dcm)$_3$ (0.7 equiv).

***cis*-4-(2,3-Dihydro-7-methoxybenzofuran-2-spiro-1′-cyclopentan-4-yl)-4a,5,8,8a-tetrahydro-2*H*-phthalazin-1-one ((−)-13 and (+)-13).** (−)-**13** was synthesized analogously to the preparation of (−)-**8** using γ-keto acid (−)-**6** (1.57 g, 4.41 mmol) and hydrazine monohydrate (0.33 g, 6.6 mmol). The title compound ((−)-**13**) was crystallized from diethyl ether. Yield 0.90 g (58%); >96% ee; mp 185−186 °C; $[\alpha]^{25}_D$ −616.2° (*c* 0.99, $CHCl_3$). Anal. ($C_{21}H_{24}N_2O_3 \cdot 0.2H_2O$) C, H, N.

Analogue (+)-**13** was synthesized analogously to the preparation of (−)-**8** using γ-keto acid (+)-**6** (1.36 g, 3.82 mmol) and hydrazine monohydrate (0.29 g, 5.8 mmol). The title compound ((+)-**13**) was crystallized from diethyl ether. Yield 0.89 g (66%); >96% ee; mp 182−183 °C; $[\alpha]^{25}_D$ 598.7° (*c* 1.1, $CHCl_3$). Anal. ($C_{21}H_{24}N_2O_3 \cdot 0.2H_2O$) C, H, N.

For ^{1}H NMR ($CDCl_3$), chiral shift reagent Eu(hfc)$_3$ (0.9 equiv) was used to determine the enantiomeric purity of the enantiomers. The resonance of the methoxy group and aromatic H5 appeared at 4.25 and 7.55 ppm, respectively, for (−)-**13** and at 4.26 and 7.57 ppm, respectively, for (+)-**13**. No detectable contamination by the other enantiomer was found (>96% ee) upon independent treatment of samples of (−)-**13** and (+)-**13** with Eu(hfc)$_3$ (0.9 equiv).

***cis*-2-Adamantan-2-yl-4-(3,4-dimethoxyphenyl)-4a,5,8,-8a-tetrahydro-2*H*-phthalazin-1-one ((+)-14 and (−)-14).** A solution of γ-keto acid (+)-**1** (0.64 g, 2.2 mmol) and adamantylhydrazine hydrochloride (0.54 g, 2.7 mmol) in pyridine (50 mL) was refluxed for 5 h. The reaction mixture was concentrated in vacuo, and the remainder was dissolved in ethyl acetate and washed with 1 N HCl and a solution of $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure, and the title compound ((+)-**14**) was crystallized from diethyl ether. Yield 60%; >96% ee; mp 157−159 °C; $[\alpha]^{25}_D$ 574.0° (*c* 0.99, $CHCl_3$). Anal. ($C_{26}H_{32}N_2O_3$) C, H, N.

Analogue (−)-**14** was synthesized analogously to the preparation of (+)-**14** using γ-keto acid (−)-**1** (2.0 g, 3.3 mmol) and adamantylhydrazine hydrochloride (1.0 g, 5.0 mmol). The title compound ((−)-**14**) was crystallized from petroleum ether (60−80 °C)/diethyl ether. Yield 58%; >96% ee; mp 157−159 °C; $[\alpha]^{25}_D$ −582.9° (*c* 1.0, $CHCl_3$). Anal. ($C_{26}H_{32}N_2O_3$) C, H, N.

For ^{1}H NMR ($CDCl_3$), chiral shift reagent Eu(tfc)$_3$ (0.9 equiv) was used to determine the enantiomeric purity of the enantiomers. The resonances of the aromatic H5 appeared at 7.08 ppm for (−)-**14** and 7.11 ppm for (+)-**14**. No detectable contamination by the other enantiomer was found (>96% ee) upon treatment of a sample of (+)-**14** with Eu(tfc)$_3$ (0.9 equiv).

***cis*-4-[4-(3,4-Diethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1*H*-phthalazin-2-yl]benzoic Acid ((±)-15).** (±)-**15** was prepared in a similar way as described for (+)-**14** using γ-keto acid (±)-**7** (10.0 g, 31.4 mmol), 4-hydrazinobenzoic acid (9.0 g, 59 mmol), and pyridine hydrochloride (8.0 g, 69 mmol). The title compound was crystallized from ethyl acetate. Yield 71%. Mp 204−207 °C. ^{1}H NMR ($CDCl_3$): δ 1.49 (t, 6H, ^3J = 6.9 Hz, CH_3), 2.17−2.44 (m, 3H, H5, H8), 2.98−3.19 (m, 2H, H8a, H8′), 3.39−3.57 (m, 1H, H4a), 4.15 (q, 4H, ^3J = 6.9 Hz, OCH_2), 5.65−5.91 (m, 2H, HC=CH), 6.91 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.34 (dd, 1H, ^4J = 2.0 Hz, ^3J = 8.5 Hz, H6-arom), 7.53 (d, 1H, ^4J = 2.0 Hz, H2-arom), 7.83 (d, 2H, ^3J = 8.8 Hz, H−Ph), 8.15 (d, 2H, ^3J = 8.8 Hz, H−Ph). Anal. ($C_{25}H_{26}N_2O_5$) C, H, N.

***cis*-4-[4-(3,4-Diethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1*H*-phthalazin-2-yl]benzoic Acid ((+)-15).** (+)-**15** was prepared in a similar way as described for (+)-**14** using γ-keto acid (+)-**7** (1.84 g, 5.79 mmol), 4-hydrazinobenzoic acid (1.50 g, 9.86 mmol), and pyridine hydrochloride (1.0 g, 8.7 mmol). The title compound was crystallized from ethanol/water. Yield 59%; >96% ee; mp 204−207 °C; $[\alpha]^{25}_D$ 516.4° (*c* 0.96, $CHCl_3$). Anal. ($C_{25}H_{26}N_2O_5$) C, H, N.

For ^{1}H NMR ($CDCl_3$), no suitable shift reagent was found to ascertain the enantiomeric purity of (+)-**15**. However, it was possible to determine the enantiomeric purity of (+)-**16** by ^{1}H NMR ($CDCl_3$) (>96% ee, see below), and because acid (+)-**15** was used as a starting material for (+)-**16**, it is assumed that it has the same or higher enantiomeric purity.

***cis*-(±)-4-[4-(3,4-Diethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1*H*-phthalazin-2-yl]benzoic Acid Ethyl Ester ((±)-16).** Benzoic acid (±)-**15** (1.00 g, 2.30 mmol) was dissolved in ethanol (50 mL), and acetyl chloride (2.0 mL, 2.2 g, 28.1 mmol) was added. After the mixture was stirred overnight, the solvent was removed in vacuo and the title compound was crystallized from ethanol. Yield 85%. Mp 128−129 °C. ^{1}H NMR ($CDCl_3$): δ 1.40 (t, 3H, ^3J = 7.1 Hz, CH_3), 1.48 (t, 3H, ^3J = 7.0 Hz, CH_3), 1.49 (t, 3H, ^3J = 7.0 Hz, CH_3), 2.17−2.42 (m, 3H, H5, H8), 2.95−3.18 (m, 2H, H8a, H8′), 3.38−3.56 (m, 1H, H4a), 4.14 (q, 2H, ^3J = 7.0 Hz, OCH_2), 4.15 (q, 2H, ^3J = 7.0 Hz, OCH_2), 3.88 (q, 2H, ^3J = 7.1 Hz, CH_2CO_2), 5.65−5.91 (m, 2H, HC=CH), 6.90 (d, 1H, ^3J = 8.5 Hz, H5-arom), 7.33 (dd, 1H, ^4J = 2.1 Hz, ^3J = 8.5 Hz, H6-arom), 7.52 (d, 1H, ^4J = 2.0 Hz, H2-arom), 7.77 (d, 2H, ^3J = 8.7 Hz, H−Ph), 8.08 (d, 2H, ^3J = 8.7 Hz, H−Ph). Anal. ($C_{27}H_{30}N_2O_5$) C, H, N.

***cis*-(+)-4-[4-(3,4-Diethoxyphenyl)-1-oxo-4a,5,8,8a-tetrahydro-1*H*-phthalazin-2-yl]benzoic Acid Ethyl Ester ((+)-16).** (+)-**16** was prepared as described for (±)-**16** from benzoic acid (+)-**15** (1.00 g, 2.30 mmol). The title compound was crystallized from ethanol at −20 °C. Yield 65%; >96% ee; mp 128−129 °C; $[\alpha]^{25}_D$ 543.4° (*c* 0.99, $CHCl_3$). Anal. ($C_{27}H_{30}N_2O_5$) C, H, N.

For ^{1}H NMR ($CDCl_3$), chiral shift reagent Eu(hfc)$_3$ (2 equiv) was used to determine the enantiomeric purity of (+)-**16**. The resonances of the aromatic H_{ortho}−Bz appeared at 8.68 ppm for (−)-**16** and 8.70 ppm for (+)-**16**. No detectable contamination by the other enantiomer was found (>96% ee) upon independent treatment of a sample of (+)-**16** with Eu(hfc)$_3$ (2 equiv).

References

(1) Van der Mey, M.; Van der Laan, I. J.; Timmerman, H.; Hatzelmann, A.; Boss, H.; Häfner, D.; Beume, R.; Kley, H. P.; Sterk, G. J. Preparation of arylphthalazinones as inhibitors of cyclic nucleotide phosphodiesterase. Patent WO 9831674, 1998.

(2) Hatzelmann, A.; Boss, H.; Häfner, D.; Beume, R.; Kley, H. P.; Van der Mey, M.; Van der Laan, I. J.; Timmerman, H.; Sterk, G. J. Preparation of phthalazinones as phosphodiesterase IV inhibitors. Patent WO 9931071, 1999.

(3) Thibaut, U.; Hatzelmann, A.; Boss, H.; Häfner, D.; Beume, R.; Kley, H. P.; Timmerman, H.; Van der Laan, I. J.; Ulrich, W. R.; Sterk, G. J.; Van der Mey, M. Preparation of phthalazinyldihydrobenzofurans as cyclic nucleotide phosphodiesterase inhibitors. Patent WO 9931090, 1999.

(4) Van der Mey, M.; Hatzelmann, A.; Van der Laan, I. J.; Sterk, G. J.; Thibaut, U.; Timmerman, H. Novel Selective PDE4 Inhibitors. 1. Synthesis, Structure−Activity Relationships, and Molecular Modeling of 4-(3,4-Dimethoxyphenyl)-2*H*-phthalazin-1-ones and Analogues. *J. Med. Chem.* **2001**, *44*, 2511−2522.

(5) Van der Mey, M.; Hatzelmann, A.; Van Klink, G. P. M.; Van der Laan, I. J.; Sterk, G. J.; Thibaut, U.; Ulrich, W. R.; Timmerman, H. Novel Selective PDE4 Inhibitors. 2. Synthesis and Structure−Activity Relationships of 4-Aryl-Substituted *cis*-Tetra- and *cis*-Hexahydrophthalazinones. *J. Med. Chem.* **2001**, *44*, 2523−2535.

(6) Van der Mey, M.; Boss, H.; Hatzelmann, A.; Van der Laan, I. J.; Sterk, G. J.; Timmerman, H. Unpublished results. Novel Selective PDE4 Inhibitors. 3. In Vivo Anti-inflammatory Activity of a New Series of N-Substituted *cis*-Tetra- and *cis*-Hexahydrophthalazinones. *J. Med. Chem.* **2002**, *45*, 2520−2525.

(7) About 4% contamination of one enantiomer by the other in the resolved samples could be detected by ^{1}H NMR.

(8) Jonas, R.; Klockow, M.; Lues, I.; Prücher, H.; Schliep, H. J.; Wurziger, H. Synthesis and biological activities of meribendan and related heterocyclic benzimidazolo-pyridazinones. *Eur. J. Med. Chem.* **1993**, *28*, 129−140.

(9) Marivet, M. C.; Bourguignon, J. J.; Lugnier, C.; Mann, A.; Stoclet, J. C.; Wermuth, C. G. Inhibition of cyclic adenosine-3′,5′-monophosphate phosphodiesterase from vascular smooth muscle by rolipram analogues. *J. Med. Chem.* **1989**, *32*, 1450−1457.

(10) Hughes, B.; Owens, R.; Perry, M.; Warrellow, G.; Allen, R. PDE IV inhibitors: the use of molecular cloning in the design and development of novel drugs. *Drug Discovery Today* **1997**, *2*, 89−101.

(11) Christensen, S. B.; Guider, A.; Forster, C. J.; Gleason, J. G.; Bender, P. E.; Karpinski, J. M.; De Wolf, W. E., Jr.; Barnette, M. S.; Underwood, D. C.; Griswold, D. E.; Cieslinski, L. B.; Burman, M.; Bochnowicz, S.; Osborn, R. R.; Manning, C. D.; Grous, M.; Hillegas, L. M.; Bartus, J. O.; Ryan, M. D.; Eggleston, D. S.; Haltiwanger, R. C.; Torphy, T. J. 1,4-Cyclohexanecarboxylates: potent and selective inhibitors of phosphodiesterase 4 for the treatment of asthma. *J. Med. Chem.* **1998**, *41*, 821−835.

(12) De Gelder, R.; De Graaff, R. A. G.; Schenk, H. Automatic Determination of Crystal Structures Using Karle-Hauptman Matrices. *Acta Crystallogr.* **1993**, *A49*, 287−293.

(13) Larson, A. C. The inclusion of secondary extinction in least-squares refinement of crystal structures. In *Crystallographic Computing*; Ahmed, F. R., Hall, S. R., Huber, C. P., Eds.; Munksgaard: Copenhagen, 1969; pp 291−294.

(14) Zachariasen, W. H. A general theory of X-ray diffraction in crystals. *Acta Crystallogr.* **1967**, *A23*, 558.

(15) Flack, H. D. On Enantiomorph-Polarity Estimation. *Acta Crystallogr.* **1983**, *A39*, 876.

(16) Cromer, D. T.; Mann, J. B. X-ray scattering factors computed from numerical Hartree−Fock wavefunctions. *Acta Crystallogr., Sect. A* **1968**, *24*, 321−324.

(17) *International Tables for X-ray Crystallograph*y l D. Reidel: Dordrecht, The Netherlands, 1974; Vol. IV, p 55.

(18) *XTAL3.4 User's Manual*; Hall, S. R., King, G. S. D., Stewart, J. M., Eds.; University of Western Australia: Lamb, Perth, Australia, 1995.

JM0110338