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Lipase-Catalyzed Kinetic Resolution of 2-Phenylethanol Derivatives and Chiral Oxa-Pictet–Spengler Reaction as the Key Steps in the Synthesis of Enantiomerically Pure Tricyclic Amines

Christian Ketterer[a] and Bernhard Wünsch*[a]

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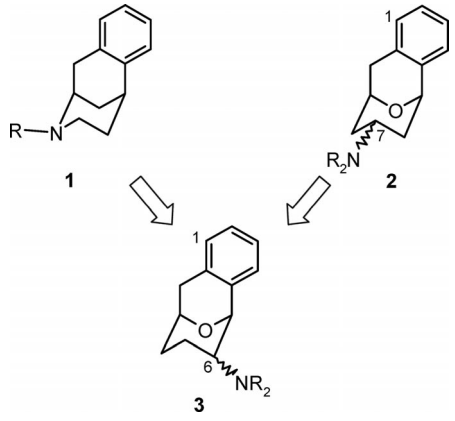
A series of 5,6,7,8,9,10-hexahydro-5,9-epoxybenzocyclooctен-6-amines have been synthesized and pharmacologically evaluated in receptor binding studies (σ_1, σ_2, NMDA, κ, and μ receptors). The first key step of the synthesis was a chiral oxa-Pictet–Spengler reaction with enantiomerically pure 2-phenylethanol derivatives (*S*)- and (*R*)-**14**. After transformation of the dimethylamide **18** into the ester **19**, the tricyclic system **20** was established by Dieckmann cyclization reaction. Finally, amino moieties were introduced diastereoselectively into the 6-position by reductive amination and S_N2 reaction. The enantiomerically pure building blocks (*S*)-**14** (>99.0 % *ee*) and (*R*)-**14** (98.4 % *ee*) were synthesized by enantioselective acetylation of racemic alcohol **14** catalyzed by *Pseudomonas fluorescens* lipase and enantioselective hydrolysis of racemic acetate **16** catalyzed by *Candida rugosa* lipase. The absolute configurations were determined by theoretical calculations of the specific optical rotation and CD spectra, as well as by X-ray crystal structure analysis of (*S*,*S*,*S*)-**25** by the three-beam interference method. Although enantiomerically pure dimethylamines (*S*,*R*,*S*)- and (*R*,*S*,*R*)-**29** with an axial amino moiety showed low-to-moderate affinity towards σ_1 and σ_2 receptors, a promising σ_2 affinity (K_i = 2.9 μM) was found for (*S*,*S*,*S*)-**24** with an equatorially oriented dimethylamino group.

Introduction

The tricyclic benzomorphan system **1** represents a substructure of the pentacyclic natural product morphine (Scheme 1). Originally benzomorphans were synthesized to increase the analgesic activity of morphine and to reduce its adverse side-effects, such as respiratory depression, constipation, dysphoria, and the development of tolerance and dependency. In addition to their analgesic activity, benzomorphans and their analogues produce manifold effects on the central nervous system (CNS).[1] These effects originate from their interaction with different CNS receptors, in particular opioid, NMDA, and σ receptors, depending on the substitution pattern and the stereochemistry of the benzomorphan system. (*R*,*R*,*R*)-Configured ketocyclazocine with an *N*-cyclopropylmethyl residue is a potent κ-opioid receptor agonist, which gave name to this opioid receptor subtype.[2] Benzomorphan derivatives with the (*S*,*S*,*S*) configuration and bearing a proton or a small methyl group at the N atom interact with high affinity with the phencyclidine binding site of the NMDA receptor. A larger N residue (dimethylallyl, benzyl) at the (*S*,*S*,*S*)-configured benzomorphan system shifts the receptor affinity from the NMDA receptor to the σ_1 receptor.[3] Within the benzomorphan system the 2-phenylethylamine substructure represents an important pharmacophoric element. Moreover, the tricyclic benzomorphan system also contains the 3-phenylpropylamine substructure.



Scheme 1. Structural development of 5,9-epoxybenzocycloocten-6-amines **3** from a combination of benzomorphans (**1**) and tricyclic amines **2**.

In an effort to find pharmacologically interesting compounds with new scaffolds analogous to benzomorphan,[4] we have focused our interest on 5,9-epoxybenzocycloocten-amines **2** and **3**. The three-dimensional structure of epoxy-

[a] Institut für Pharmazeutische und Medizinische Chemie der Westfälischen Wilhelms-Universität Münster,
Hittorfstrasse 58–62, 48149 Münster, Germany
Fax: +49-251-8332144
E-mail: wuensch@uni-muenster.de

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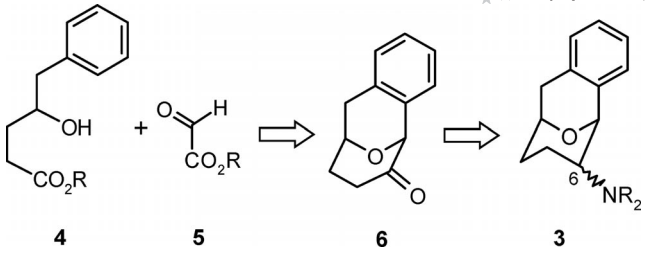
benzocyclooctenamines is very similar to that of benzomorphans. However, **2** and **3** differ from benzomorphans (**1**) by the replacement of the methano bridge with an epoxy bridge. Some years ago we reported on the synthesis of epoxybenzocycloocten-7-amines **2** with axially and equatorially oriented amino moieties. It was found that compounds **2a** [NR_2 = $N(CH_3)_2$, axial, K_i = 0.58 μM] and **2b** [NR_2 = $N(CH_3)_2$, equatorial, K_i = 2.49 μM] with a 3-phenylpropylamine substructure showed moderate affinity towards σ_1 receptors.[5] Based on these results the regioisomeric 5,9-epoxybenzocycloocten-6-amines **3** containing the 2-phenylethylamine substructure were envisaged. We report herein the synthesis of tricyclic amines of type **3** in enantiomerically pure form and their affinities towards σ_1 and σ_2 receptors, the phencyclidine binding site of the NMDA receptor, and κ- and μ-opioid receptors. Preliminary results have already been outlined in a short communication.[6]

Chemistry

Synthetic Plan

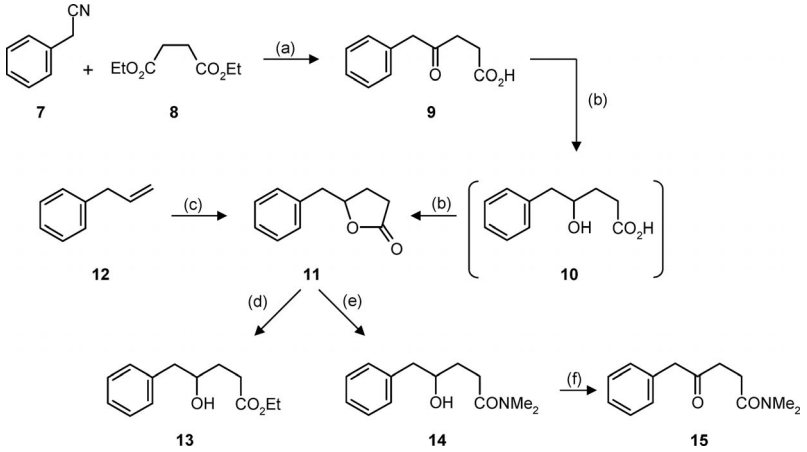
The plan for the synthesis of 5,9-epoxybenzocycloocten-6-amines **3** is depicted in Scheme 2. In the first key step, the oxa-Pictet–Spengler reactions of 4-hydroxy-5-phenylpentanoic acid derivatives **4** with glyoxylic acid derivative **5** provide 2-benzopyrans with two ester moieties. Dieckmann cyclization and subsequent decarboxylation gives the tricyclic ketone **6**, which is converted diastereoselectively into the tricyclic amines **3** with equatorially and axially oriented amino moieties. To obtain enantiomerically pure products **3**, enantiomerically pure 4-hydroxy-5-phenylpentanoic acid derivatives **4** will be used for the oxa-Pictet–Spengler reactions. Kinetic resolution of γ-hydroxypentanoates **4** with lipases represents a key step in the synthetic strategy.



Scheme 2. Plan for the synthesis of 5,9-epoxybenzocycloocten-6-amines **3** .

Synthesis of γ-Hydroxy Amide 14

A one-step synthesis of γ-lactone **11** by reaction of allylbenzene (**12**) with acetic acid in the presence of $Mn(OAc)_3$ has been reported in the literature (Scheme 3).[7] The Mn^{3+} salt was prepared in situ by conproportionation of MnO_4^- and Mn^{2+}. By using this method the γ-lactone **11** was obtained in 44% yield. Due to the moderate yields, the use of the toxic heavy metal Mn in a stoichiometric amount, and the inconvenient separation of Mn salts during the work-up procedure, an alternative route was investigated. According to a procedure described in a patent,[8] phenylacetonitrile (**7**) was treated with diethyl succinate (**8**) in the presence of NaOEt. After stirring the reaction mixture for 16 h at room temperature, concentrated HCl and acetic acid were added to give the γ-keto acid **9**. Treatment of the γ-keto acid **9** with $NaBH_4$ afforded the γ-hydroxy acid **10**, which cyclized quantitatively upon treatment with dilute HCl to form the γ-lactone **11**. After optimization of each step, this four-step procedure led to the γ-lactone **11** in 60% overall yield. Because a heavy metal was not required and the overall yield was higher than the yield resulting from the Mn^{3+}-induced synthesis of lactone **11**, this procedure was used for the large-scale preparation of **11**.



Scheme 3. Reagents and conditions: (a) NaOEt, EtOH, room temp., overnight; (b) $NaBH_4$, CH_3OH, room temp., overnight, then HCl, room temp., 30 min, 60% (related to phenylacetonitrile **7**); (c) $Mn(OAc)_3$, HOAc, ref.[7c] 44%; (d) EtOH, NEt_3, reflux, 20 h, 6%; (e) $(H_3C)_2$-NH, EtOH, room temp., 24 h, 94%; (f) $NaBrO_3$, $(NH_4)_2Ce(NO_3)_6$, acetonitrile, H_2O, reflux, 45 min, 91%.

For the synthesis of the γ-hydroxy ester **13**, which was required for the oxa-Pictet–Spengler reaction, the γ-lactone **11** was treated with ethanol in the presence of NEt_3 (Scheme 3). However, these reaction conditions led to an equilibrium of the γ-lactone **11** and the γ-hydroxy ester **13** in a ratio of about 3:1 and the γ-hydroxy ester **13** could be isolated in only 6% yield. This equilibrium could not be shifted towards the ester **13** by variation of the reaction conditions (e.g., time, temperature), the nucleophile (e.g., NaOEt), or the alcohol component (e.g., NaO*i*Pr, NaO*t*Bu). Because it was expected that the γ-hydroxy ester **13** would also produce the γ-lactone **11** very quickly during the acid-catalyzed oxa-Pictet–Spengler reaction, the γ-lactone **11** was alternatively treated with dimethylamine to afford the dimethylamide **14** in 94% yield. Owing to the high yield and low tendency to form the γ-lactone **11**, racemic γ-hydroxy amide **14** was employed in the lipase-catalyzed kinetic resolution.

Development of Chiral HPLC Methods

To find a strategy for the production of enantiomerically pure γ-hydroxypentanoate derivatives, chiral HPLC methods for the quantification of the enantiomeric γ-hydroxy amides (*S*)-**14**/(*R*)-**14**, γ-acetoxy amides (*S*)-**16**/(*R*)-**16**, and γ-lactones (*S*)-**11**/(*R*)-**11** were developed.

The chiral stationary phase Kromasil® CHI-TBB[9] turned out to give the best separations of the enantiomers. Kromasil® CHI-TBB is a three-dimensional network produced by the polymerization of (2*R*,3*R*)-*O*,*O*′-bis(4-*tert*-butylbenzoyl)-*N*,*N*′-diallyltartaramide monomers. After optimization of the mobile phase, the flow rate, injection volume, and separation temperature, the γ-hydroxy amide enantiomers (*S*)- and (*R*)-**14** were separated with a resolution of 1.47 by using the mobile phase *n*-hexane/THF (92.5:7.5; Figure 1, A). The addition of acidic or basic additives did not improve the resolution or the tailing.

The γ-acetoxy amide enantiomers (*S*)- and (*R*)-**16** as well as the γ-lactone enantiomers (*S*)- and (*R*)-**11** were separated by using the same stationary phase at a lower temperature. At 5 °C, resolutions of 1.32 (**16**) and 1.69 (**11**) were achieved, sufficient to determine the ratios of the enantiomers.

Lipase-Catalyzed Kinetic Resolution of 14

To synthesize the enantiomerically pure tricyclic amines **3**, the key intermediate **14** had to be synthesized in enantiomerically pure form. At first the γ-hydroxy amide **14** was oxidized with $NaBrO_3$ and catalytic amounts of $(NH_4)_2$-$Ce(NO_3)_6$ in aqueous acetonitrile[10] to afford the γ-keto amide **15** in 91% yield (Scheme 3). Reduction of γ-keto amide **15** with DIP chloride[11] [yield 11%, *ee* (*S*) 96%], CBS-oxazaborolidine[12] (yield 22%, *ee* 0%), and baker's yeast[13] (yield 7%, *ee* 60%) did not produce the γ-hydroxy amide **14** in satisfactory yield and enantiopurity.

Therefore kinetic resolution[14] of the racemic γ-hydroxy amide **14** was carried out by lipase-catalyzed enantioselective acetylation. At first the suitability of different lipases was screened. In this screening process, the γ-hydroxy amide **14** (100 mg) was shaken with the corresponding lipase (400 mg) at room temperature in the solvent *tert*-butyl methyl ether (TBME). Vinyl acetate and isopropenyl acetate were used as irreversible acylating agents. The results of the

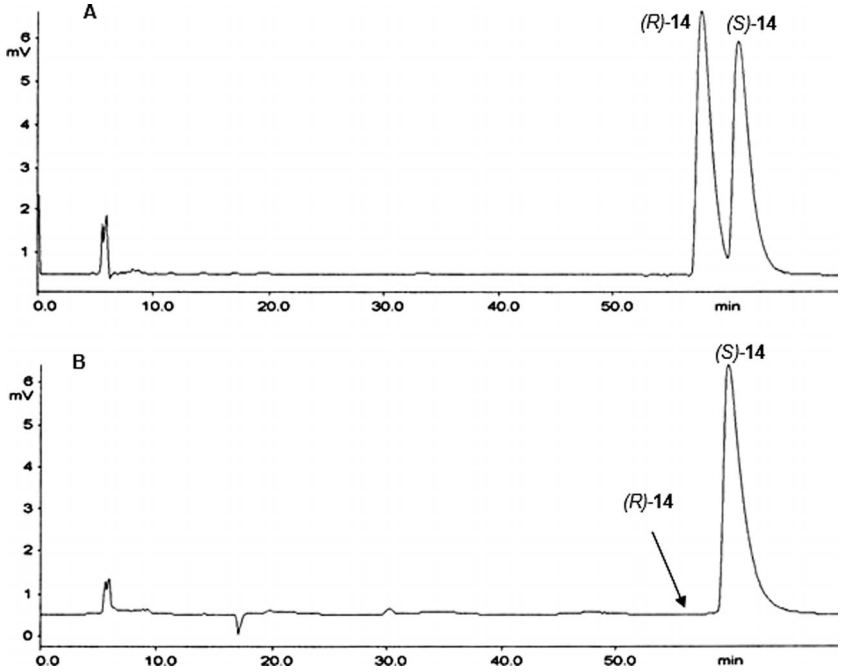


Figure 1. HPLC separation of racemic γ-hydroxyamide **14**. Kromasil® CHI-TBB, *n*-hexane/THF (92.5:7.5), flow rate 0.5 mL/min, injection volume 7.5 μL, T = 20 °C, detection at λ = 254 nm. A: racemic mixture of **14**; B: enantiomerically pure alcohol (*S*)-**14** produced by *Pseudomonas fluorescens* lipase catalyzed kinetic resolution.

Table 1. Screening of various lipases for the enantioselective acetylation of racemic alcohol **14**.

Entry	Lipase	Time	Conversion [%][a]	(*S*)-**14**		(*R*)-**16**		*E*[c]
				Yield [%][b]	*ee* [%]	Yield [%][b]	*ee* [%]	
1	*Candida antarctica* lipase B, immobilized (Chirazyme L-2)[d]	24 h	33.6	49	42	29	83	16.2
2	*Candida antarctica* lipase B, immobilized (Chirazyme L-2)[e]	24 h	33.6	49	42	29	83	16.2
3	*Candida antarctica* lipase A, immobilized (Chirazyme L-3)[e]	144 h	38.8	48	44	28	71	9.0
4	*Candida rugosa* lipase (Chirazyme L-5)[d]	78 h	68.8	26	>99	53	45	12.1
5	*Porcine pancreas* lipase (Chirazyme-7)[d]	27 d	7.6	8	6	4	73	6.8
6	*Pseudomonas cepacia* lipase (Amano PS)[d,f]	12 d	14.9	65	17	14	97.0	77.6
7	*Pseudomonas cepacia* lipase, immobilized (Amano PS-CII)[e]	93 h	53.2	30	99.1	47	87	74.8
8	*Pseudomonas fluorescens* lipase (Amano AK)[e]	82 h	50.2	41	>99	38	98.4	>>100
9	*Pseudomonas fluorescens* lipase (Amano AK)[e,f]	356 h	50.5	24	>99	44	97.1	>>100
10	*Pseudomonas fluorescens* lipase (Amano AK)[e,g]	141 h	50.2	40	>99	46	98.4	>>100

[a] Yields after flash chromatographic purification. [b] Vinyl acetate. [c] Isopropenyl acetate. [d] 200 mg enzyme. [e] 5.0 g of racemic alcohol **14** were employed, for details see the Exp. Sect. [f] Enantioselectivity *E*: $E = \ln[1 - c(1 + ee_P)]/\ln[1 - c(1 - ee_P)]$.[15] [g] Conversion *c*: $c = ee_S/ee_S + ee_P$[15]

screening process are summarized in Table 1. In general, all lipases converted the (*R*)-configured alcohol (*R*)-**14** faster than the (*S*)-configured enantiomer. Although *Candida rugosa* lipase catalyzed a fast transformation of alcohol (*R*)-**14** to give enantiomerically pure alcohol (*S*)-**14** in 26% yield ($E^{[15]}$ = 12.1, entry 4), *Pseudomonas cepacia* lipase produced the acetate (*R*)-**16** with high enantiomeric purity but in low yield (*E* = 77.6, entry 6). Immobilization of *Pseudomonas cepacia* lipase (Amano PS-CII) on ceramic particles increased the catalytic activity leading to high yields and *ee* values for both the alcohol (*S*)-**14** and the acetate (*R*)-**16** (*E* = 74.8, entry 7). However, *Pseudomonas fluorescens* lipase (Amano AK) turned out to be the best catalyst for this transformation giving the highest enantioselectivity (*E* > 100) and enantiomeric excess. Treatment of the racemic alcohol **14** with *Pseudomonas fluorescens* lipase for 82 h in TBME at room temperature provided (*S*)-**14** and (*R*)-**16** in 41 and 38% yields with >99.0 and 98.4% *ee*, respectively (entry 8). The use of a reduced amount of lipase (200 mg) required a longer reaction time (356 h) to complete the transformation (entry 9). However, prolonged reaction times generally led to an increased formation of γ-lactone **11**, which could be isolated in chiral nonracemic form.

For the large-scale preparation of (*S*)-**14** and (*R*)-**16**, the *Pseudomonas fluorescens* lipase catalyzed acetylation was optimized. Finally, racemic γ-hydroxy amide **14** (5.0 g) was treated with isopropenyl acetate (7 equiv.) and *Pseudomonas fluorescens* lipase (3.75 g) in TBME at room temperature. The transformation was monitored by TLC and HPLC. The development of the enantiomeric excess of the alcohol

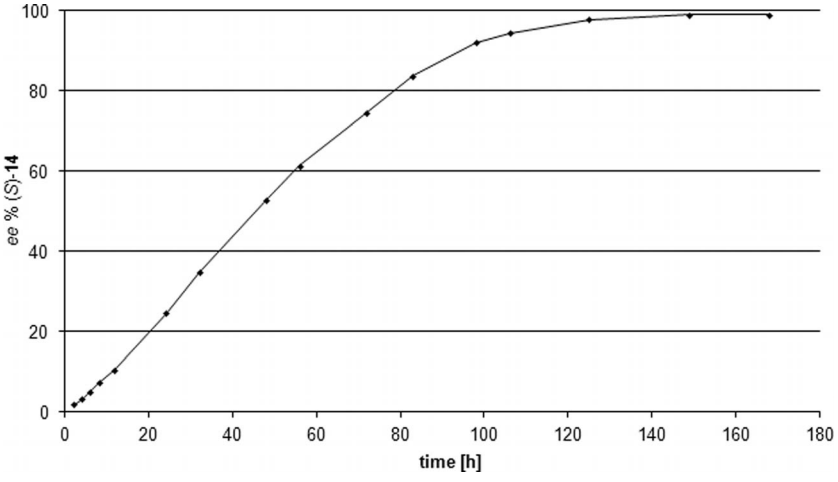
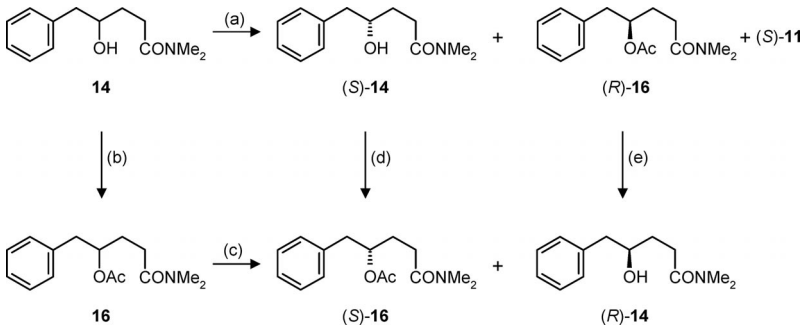


Figure 2. Development of the enantiomeric excess of (*S*)-**14** during the acetylation of racemic alcohol **14** with isopropenyl acetate in the presence of *Pseudomonas fluorescens* lipase.



Scheme 4. Reagents and conditions: (a) *Pseudomonas fluorescens* lipase (Amano AK lipase), isopropenyl acetate, TBME, room temp., 141 h, 40% [(*S*)-**14**], 46% [(*R*)-**16**], 10% [(*S*)-**11**]; (b) Ac_2O, NEt_3, DMAP, CH_2Cl_2, room temp., 4 h, 98%; (c) *Candida rugosa* lipase, (Chirazyme L-5), acetone, phosphate buffer pH 7, 37 °C, 96 h, 47% [(*S*)-**16**], 50% [(*R*)-**14**]; (d) Ac_2O, NEt_3, DMAP, CH_2Cl_2, room temp., 6 h, 90%; (e) CH_3OH, H_2O, K_2CO_3, room temp., 24 h, 92%.

Table 2. Screening of various lipases for the enantioselective hydrolysis of acetate **16**.

Entry	Lipase	Time [h]	Conversion [%][a]	(*R*)-**14**		(*S*)-**16**		*E*[c]
				Yield [%][b]	*ee* [%]	Yield [%][b]	*ee* [%]	
1	*Candida antarctica* lipase B, immobilized (Chirazyme L-2)	262	2.7	2	71	49	2	6.0
2	*Candida antarctica* lipase A, immobilized (Chirazyme L-3)	263	1.8	1	54	55	1	3.4
3	*Candida rugosa* lipase (Chirazyme L-5)	96	51.0	50	95.3	47	>99	>>100
4	*Porcine pancreas* lipase (Chirazyme L-7)	141	14.9	12	57	70	10	4.0
5	*Pseudomonas cepacia* lipase (Amano PS)	260	6.5	6	29	78	2	1.9
6	*Pseudomonas cepacia* lipase, immobilized (Amano PS-CII)	216	3.5	4	82	87	3	10.4
7	*Pseudomonas fluorescens* lipase (Amano AK)	190	18.0	16	82	77	18	12.1

[a] Conversion *c*: $c = ee_S/ee_S + ee_P$[15] [b] Yield after FC purification. [c] $E = \ln[1 - c(1 + ee_P)]/\ln[1 - c(1 - ee_P)]$.[15]

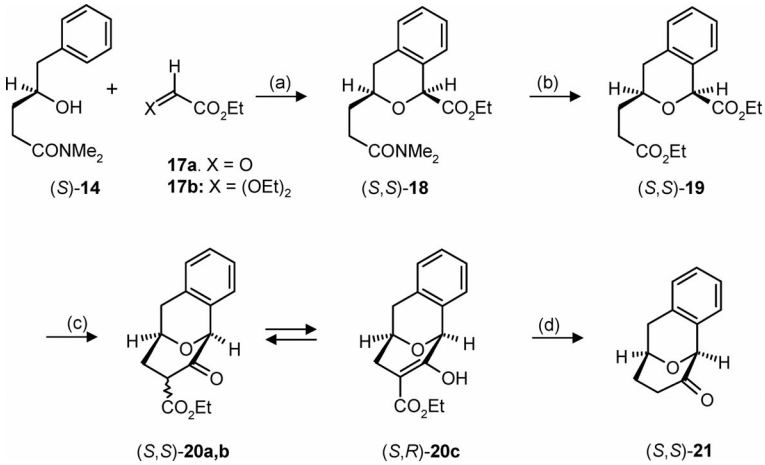
(*S*)-**14** during the transformation is shown in Figure 2. The transformation was terminated when the (*R*)-configured alcohol (*R*)-**14** had been completely consumed (ca. 140–160 h). Exemplarily, after shaking the reaction mixture for 141 h the alcohol (*S*)-**14** and the ester (*R*)-**16** were isolated in 40 and 46% yields with >99 and 98.4% *ee*, respectively (Table 1, entry 10, Figure 1, B). Furthermore, the γ-lactone (*S*)-**11** was isolated in 10% yield and 72% *ee*.

In addition, the enantioselectivities of the hydrolysis of racemic acetate **16**, which should produce the (*R*)-configured alcohol (*R*)-**14** and the (*S*)-configured ester (*S*)-**16**, with various lipases were determined (Scheme 4). After acetylation of racemic alcohol **14** with Ac_2O, the racemic acetate **16** was treated with the same lipases as used for the acetylation step (Table 2). The transformations were performed in phosphate buffer at pH 7.0 and 37 °C. All lipases showed a preference for the hydrolysis of the (*R*)-configured ester (*R*)-**16** to give the alcohol (*R*)-**14**. Although *Pseudomonas fluorescens* lipase gave only low enantioselectivity (E = 12.1; Table 2, entry 7), the lipase of *Candida rugosa* showed excellent enantioselectivity ($E > 100$, entry 3) in the hydrolysis step. After flash chromatographic purification, the alcohol (*R*)-**14** and acetate (*S*)-**16** were isolated in 50 and 47% yields with 95.3 and >99.0% *ee*, respectively.

In conclusion, the enantioselective acetylation of racemic alcohol **14** catalyzed by *Pseudomonas fluorescens* lipase and the enantioselective hydrolysis of racemic acetate **16** catalyzed by *Candida rugosa* lipase represent complementary procedures for the synthesis of enantiomeric alcohols (*S*)- and (*R*)-**14** as well as enantiomeric acetates (*R*)- and (*S*)-**16**. Because the direct acetylation of alcohol **14** was experimentally more convenient than the hydrolysis of acetate **16**, the *Pseudomonas fluorescens* lipase catalyzed acetylation was optimized for the large-scale production of alcohol (*S*)-**14** and acetate (*R*)-**16**. Subsequently, the corresponding enantiomeric alcohol (*R*)-**14** and enantiomeric acetate (*S*)-**16** were synthesized by hydrolysis of (*R*)-**16** and acetylation of (*S*)-**14**, respectively (Scheme 4).

Synthesis of the Tricyclic Amines

To synthesize the tricyclic scaffold, oxa-Pictet–Spengler reaction of the γ-hydroxy amide (*S*)-**14** was envisaged. Some examples of chiral oxa-Pictet–Spengler reactions have been reported in the literature. Most of these procedures used either donor-substituted benzene derivatives or electron-rich heterocycles.[16] However, only very few cyclizations of



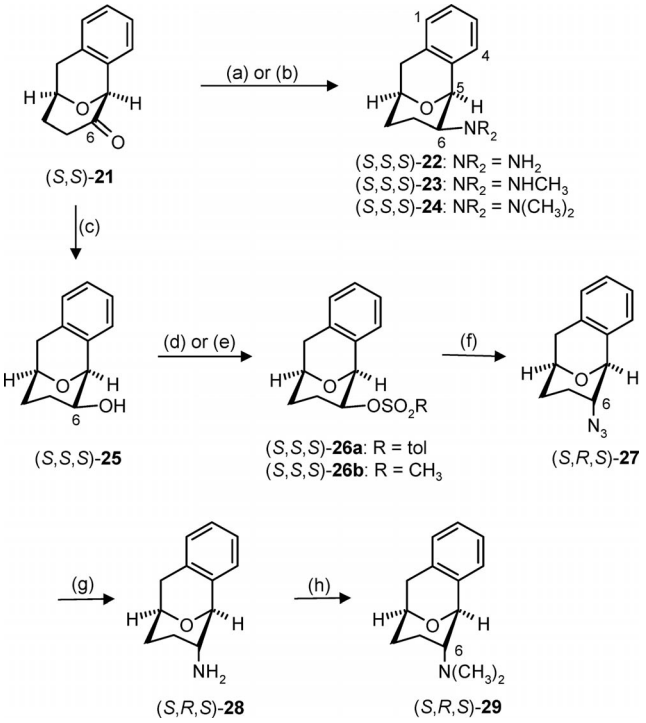
Scheme 5. Reagents and conditions: (a) CH_2Cl_2, $BF_3{\cdot}OEt_2$, room temp., 6 h, then 40 °C, 4 d, 93%; (b) Tf_2O, CH_2Cl_2, pyridine, –40 °C, 2 h, 0 °C, 12 h, then EtOH, room temp., 12 h, 83%; (c) NaH, EtOH, toluene, reflux, 2.5 h, 62%; (d) NaOH, EtOH, reflux, 3 h, 91%.

nonactivated benzene derivatives have been reported.[17] In this work, enantiomerically pure phenylethanol derivative (*S*)-**14**, without activation of the benzene moiety, was treated with ethyl glyoxylate (**17a**) in the presence of $BF_3{\cdot}Et_2O$ to form 2-benzopyran (*S*,*S*)-**18** in 93% yield (Scheme 5). The same yield (88%) was obtained with the corresponding diethyl acetal **17b** as carbonyl component. Both reactions provided exclusively the thermodynamically favored *cis*-configured 2-benzopyran (*S*,*S*)-**18**. The *cis* orientation of the protons in the 1- and 3-positions (1-H, 3-H) was unequivocally shown by a positive nuclear Overhauser effect after irradiation at δ = 5.37 ppm (1-H, increase of 3-H signal) and 3.76 ppm (3-H, increase of 1-H signal).

In the next step a Dieckmann cyclization of the amido ester (*S*,*S*)-**18** should produce the tricyclic system. However, all attempts to cyclize the amido ester (*S*,*S*)-**18** directly did not result in the formation of the desired tricyclic compound. Therefore the amide (*S*,*S*)-**18** was converted into the ethyl ester (*S*,*S*)-**19** by treatment with Tf_2O and subsequently with ethanol.[18] This procedure led to the diester (*S*,*S*)-**19** in 83% yield.

Several reaction conditions had to be investigated for the Dieckmann cyclization of diester (*S*,*S*)-**19** because decomposition (NaOEt) and isomerization (KO*t*Bu, KHMDS) to the *trans* isomer (1*R*,3*S*)-**19** occurred. Treatment of the diester (*S*,*S*)-**19** with 3.2 equiv. of NaH and 0.6 equiv. of ethanol in toluene at reflux for 2.5 h gave the tricyclic β-keto ester **20** in 69% yield. However, the interpretation of the NMR spectra of the resulting product **20** turned out to be very difficult due to the existence of three isomeric compounds: Two diastereomeric β-keto esters (*S*,*S*,*S*)-**20a** and (*S*,*R*,*S*)-**20b** and the enol ester (*S*,*R*)-**20c**. The NMR spectra recorded in $CDCl_3$ show a 20:15:65 ratio of the three compounds [(*S*,*S*,*S*)-**20a**/(*S*,*R*,*S*)-**20b**/(*S*,*R*)-**20c**], with the enol ester (*S*,*R*)-**20c** being the main component. The constant ratio of the three compounds in different samples, the different ratio of signals after recording the NMR spectra in DMSO (39:36:25), a molecular peak at *m*/*z* = 260 in the mass spectrum, and, moreover, the common product (*S*,*S*)-**21** proved unequivocally the existence of **20** in three isomeric forms.

The tricyclic ketone (*S*,*S*)-**21**, which represents the central intermediate in the synthesis of tricyclic amines, was



Scheme 6. Reagents and conditions: (a) NH_4OAc, $NaBH_3CN$, CH_3OH, room temp., 69 h, 38% (*S*,*S*,*S*)-**22**; (b) H_3CNH_2 or $(H_3C)_2$-NH, $Ti(OiPr)_4$, 4 Å mol. sieves, room temp., 63 h, then $NaBH_4$, room temp., 23–24 h, 65% [(*S*,*S*,*S*)-**23**], 72% [(*S*,*S*,*S*)-**24**]; (c) $NaBH_4$, CH_3OH, room temp., 90 min, 86%; (d) *p*-$TolSO_2Cl$, CH_2Cl_2, NEt_3, DMAP, room temp., 60 min, 72%: (e) H_3CSO_2Cl, CH_2Cl_2, NEt_3, 0 °C, 60 min, 97%; (f) (*S*,*S*,*S*)-**26b**, NaN_3, DMF, reflux, 38 h, 36%; (g) NH_4HCO_2, CH_3OH, Pd/C, reflux, 4 h, 80%; (h) $H_2C{=}O/H_2O$ (37%), $NaBH_3CN$, acetonitrile, room temp., 24 h, 68%.

formed by heating the β-keto ester **20** with NaOH in ethanol for 3 h. The yield of 91% could only be achieved when all three compounds (*S*,*S*)-**20a**,**b** and (*S*,*R*)-**20c** had been converted into the ketone (*S*,*S*)-**21**.

Reductive amination of the tricyclic ketone (*S*,*S*)-**21** with NH_4OAc and $NaBH_3CN$[19] led to the primary amine (*S*,*S*,*S*)-**22** in 38% yield (Scheme 6). The same reaction conditions with methyl- or dimethylamine provided very low yields of the amines (*S*,*S*,*S*)-**23** and (*S*,*S*,*S*)-**24**. A considerable improvement in the yields was achieved by activation of the ketone (*S*,*S*)-**21** and methyl- or dimethylamine with the Lewis acid $Ti(OiPr)_4$ and subsequent reduction with $NaBH_4$.[20] By this method the secondary and tertiary amines (*S*,*S*,*S*)-**23** and (*S*,*S*,*S*)-**24** were prepared in 65 and

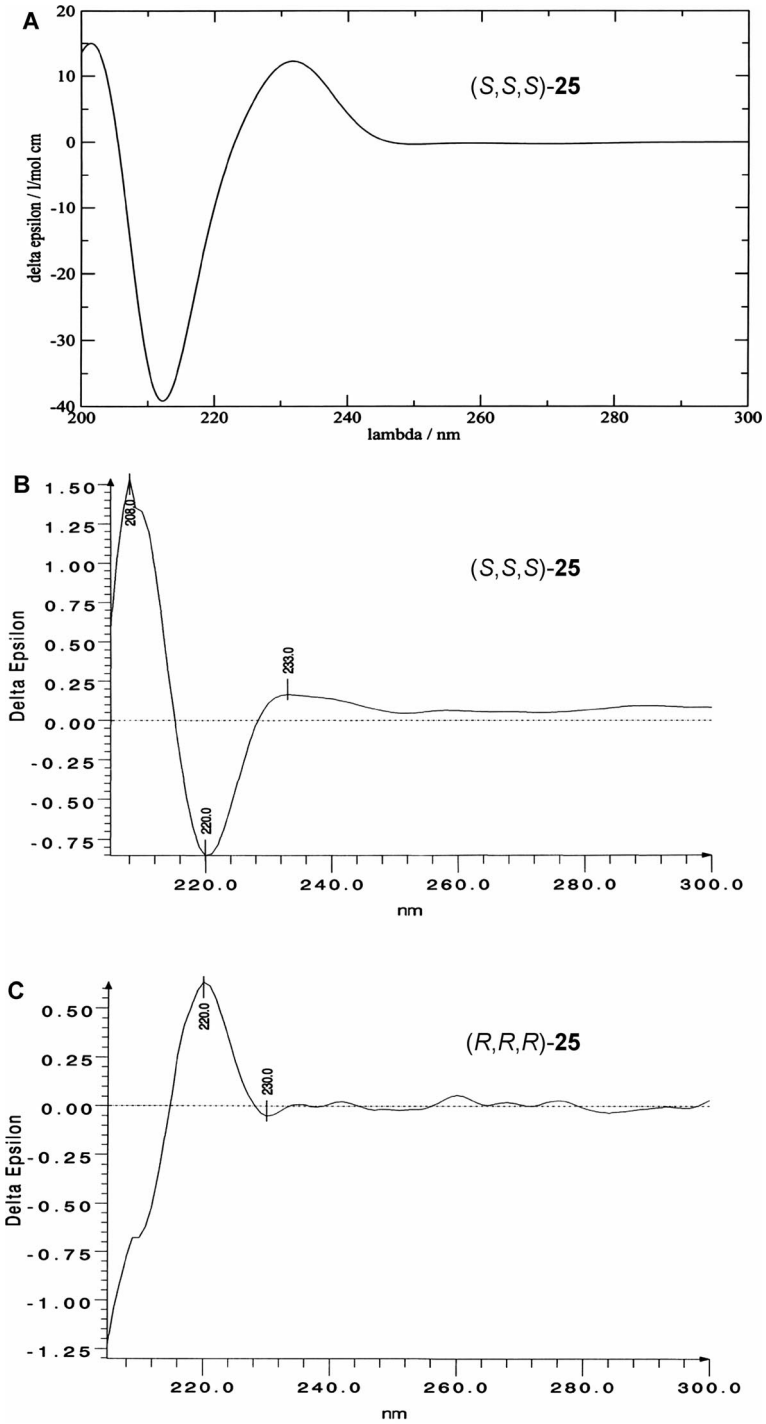


Figure 3. Comparison of (A) the calculated CD spectrum of (*S*,*S*,*S*)-**25** with the recorded CD spectra of (B) (*S*,*S*,*S*)-**25** (c = 3.46 mmol, CH_3OH) and (C) (*R*,*R*,*R*)-**25** (c = 3.46 mmol, CH_3OH).

72% yields, respectively. However, decreased yields of the primary amine (*S*,*S*,*S*)-**22** were obtained by using the Lewis acid $Ti(OiPr)_4$ for the reductive amination of (*S*,*S*)-**21** with NH_4OAc and $NaBH_4$.

The amines (*S*,*S*,*S*)-**22**–**24** were produced with excellent diastereoselectivity. With respect to the tetrahydropyran ring, the phenyl moiety of (*S*,*S*)-**21** is axially oriented and thus is shielding the *Si* face of the carbonyl moiety. Therefore nucleophiles (e.g., hydride equivalents) can only attack the intermediate imines or iminium ions from the *Re* face leading exclusively to the equatorial orientation of the amino moiety. The equatorial orientation of the dimethylamino moiety of (*S*,*S*,*S*)-**24** is deduced from characteristic signals in the ^1H NMR spectrum. In particular, the signals for 5-H (δ =4.97 ppm, d, J = 4.0 Hz), 6-H_{ax} (δ =2.54 ppm, dt, J = 12.5, 3.8 Hz), and 7-H_{ax} (δ =1.19 ppm, qd, J = 12.9, 4.7 Hz) clearly demonstrate the axial orientation of the proton in the 6-position (i.e., equatorial orientation of the amino moiety).

To synthesize the corresponding diastereomers (*S*,*R*,*S*)-**28** and (*S*,*R*,*S*)-**29** with axially oriented amino moieties, the ketone (*S*,*S*)-**21** was reduced with $NaBH_4$ to form the alcohol (*S*,*S*,*S*)-**25** with excellent diastereoselectivity (Scheme 6). After activation of the alcohol (*S*,*S*,*S*)-**25** as the tosylate (*S*,*S*,*S*)-**26a** or mesylate (*S*,*S*,*S*)-**26b**, S_N2 substitution with inversion of the configuration at C-6 should provide the axially substituted tricyclic compounds. However, the direct substitution of both sulfonates (*S*,*S*,*S*)-**26** with methylamine or dimethylamine did not lead to the corresponding substitution products. Therefore NaN_3 was employed for the S_N2 reaction. In fact, both sulfonates (*S*,*S*,*S*)-**26a** and (*S*,*S*,*S*)-**26b** reacted with the azide nucleophile with inversion of the configuration to form (*S*,*R*,*S*)-**27** with the axially oriented azido group. Reduction of the azide (*S*,*R*,*S*)-**27** under transfer hydrogenation conditions with ammonium formate and Pd/C[21] led to the primary amine (*S*,*R*,*S*)-**28**, which was methylated with formaldehyde and $NaBH_3CN$[22] to afford the dimethylamine (*S*,*R*,*S*)-**29**. The axial orientation of the dimethylamino moiety of (*S*,*R*,*S*)-**29** is clearly shown by the ^1H NMR signals for 5-H (δ = 4.97 ppm, br. s), 6-H_{eq} (δ = 2.07 ppm, td, J = 4.1, 1.7 Hz), and 7-H_{ax} (δ = 1.53 ppm, ddt, J = 14.5, 12.3, 4.3 Hz). In particular, a large 1,2-diaxial coupling constant for two adjacent axially oriented protons is missing in the signal for 6-H_{eq}.

The enantiomeric tricyclic amines (*R*,*R*,*R*)-**22**–**24**, (*R*,*S*,*R*)-**28**, and (*R*,*S*,*R*)-**29** were synthesized in the same manner starting with the enantiomeric γ-hydroxy amide (*R*)-**14**.

Absolute Configuration

The empirical rule for predicting which enantiomer of a secondary alcohol reacts faster in lipase-catalyzed reactions is based on the size of the substituents. It suggests that lipases distinguish between enantiomers of secondary alcohols primarily by comparing the sizes of the two substituents.[23] Application of this empirical rule to the secondary alcohol **14** is problematic, because both substituents at the CHOH group of **14** start with a CH_2 moiety. Therefore the specific optical rotation for the (*S*,*S*,*S*)-configured alcohol (*S*,*S*,*S*)-**25** was calculated theoretically ($[\alpha]_D$ = –13.2° mL dm^{-1} g^{-1}, TDDFT/B3LYP level)[6] and compared with the recorded value ($[\alpha]_D$ = –71.8° mL dm^{-1} g^{-1}).

In addition, the CD spectra of (*S*,*S*,*S*)- and (*R*,*R*,*R*)-**25** were recorded and compared with the theoretically calculated CD spectrum of (*S*,*S*,*S*)-**25** [double-hybrid time-dependent (TD)DFT level using the B2PLYP functional;[24] Figure 3]. Both the calculated and recorded spectra of the (*S*,*S*,*S*)-configured alcohol (*S*,*S*,*S*)-**25** show a positive Cotton effect at around 230 nm.

Finally, an X-ray crystal structure analysis of (*S*,*S*,*S*)-**25** using the three-beam interference method showed the absolute configuration (*S*,*S*,*S*) for the crystallized compound.[6] Altogether, these data prove unequivocally the (*S*) configuration of the enantiomerically pure alcohol (*S*)-**14** as well as the absolute configuration of all the intermediates and final products.

Receptor Affinity

The affinities of the enantiomerically pure tricyclic amines **22**–**24**, **28**, and **29** towards selected receptor systems (σ_1,[25] σ_2,[25] NMDA,[26] κ-opioid,[27] and μ-opioid receptors,[27] see Introduction) were investigated in competitive receptor binding studies. In these assays a tritium-labeled radioligand with high affinity and selectivity for a particular receptor was incubated together with the test compound and receptor preparation. At first, inhibition of radioligand binding at a rather high concentration of the test compound (10 μM) was recorded. Competition curves for six concentrations were recorded only for the test compounds, which showed an inhibition of radioligand binding greater than 50% at 10 μM in the first screening experiment.

The inhibition of radioligand binding to the σ_1, σ_2, NMDA, κ, and μ receptors in the presence of the test compounds is summarized in Table 3. In general, at a concentration of 10 μM, the test compounds did not compete strongly with the radioligands for the receptor sites, which indicates very low σ_1, σ_2, NMDA, κ, and μ receptor affinity.

As an exception, the amines (*S*,*R*,*S*)- and (*R*,*S*,*R*)-**29** with axially oriented dimethylamino moieties and (*S*,*S*,*S*)-**24** with an equatorial orientation of the amino group showed considerably reduced (+)-[^{3}H]pentazocine binding in the σ_1 assay and [^{3}H]ditolylguanidine binding in the σ_2 assay. Therefore the corresponding K_i values were determined by recording the competition curves for six concentrations. In the σ_1 assay, K_i values of 41 and 14 μM were found for (*S*,*R*,*S*)- and (*R*,*S*,*R*)-**29**, respectively, which indicates low σ_1 affinity. Despite promising results in the first screening, (*S*,*R*,*S*)- and (*R*,*S*,*R*)-**29** showed only low affinity in the σ_2 assay (K_i > 50 μM, K_i = 28 μM). Interestingly, the equatorially substituted dimethylamine (*S*,*S*,*S*)-**24** represents the most potent σ_2 ligand of this series of test compounds with

Table 3. σ_1, σ_2, NMDA, κ-opioid and μ-opioid receptor affinities of 5,9-epoxybenzocycloocten-6-amines.

	Inhibition of radioligand binding [%][a]				
	σ_1	σ_2	NMDA	κ	μ
(*S*,*S*,*S*)-**22**	11	28	19	9	7
(*R*,*R*,*R*)-**22**	9	2	12	0	0
(*S*,*S*,*S*)-**23**	6	3	9	7	4
(*R*,*R*,*R*)-**23**	9	3	19	2	0
(*S*,*S*,*S*)-**24**	6	61[b]	13	7	9
(*R*,*R*,*R*)-**24**	6	14	21	0	4
(*S*,*R*,*S*)-**28**	37	24	18	24	22
(*R*,*S*,*R*)-**28**	6	21	20	24	22
(*S*,*R*,*S*)-**29**	46[c]	45[d]	11	2	3
(*R*,*S*,*R*)-**29**	54[e]	56[f]	10	2	3
Haloperidol	2.2 ± 0.31[g]	34 ± 2.3[g]	–	–	–
(+)-Pentazocine	3.6 ± 0.20[g]	–	–	–	–
(+)-MK-801	–	–	5.2 nM[h]	–	–
Naloxone	–	–	–	0.68 ± 0.04 nM[g]	3.2 nM[h]

[a] All compounds were tested at a concentration of 10 μM of HCl salt. [b] For the reference compounds, K_i values are given, n = 3. [c] The given K_i values result from a single experiment. [d] $K_i(\sigma_1)$ = 41 ± 14 μM (n = 3). [e] $K_i(\sigma_1)$ = 14 ± 3.9 μM (n = 3). [f] $K_i(\sigma_2)$ = 2.9 ± 0.01 μM (n = 3). [g] $K_i(\sigma_2) > 50$ μM (n = 3). [h] $K_i(\sigma_2)$ = 28 ± 0.1 μM (n = 3).

an K_i value of 2.9 μM. Clearly, moderate-to-good σ_2 affinity of tricyclic amines is attained with an optimal stereochemistry [equatorially oriented amino moiety, (*S*,*S*,*S*) configuration] and the correct substitution pattern of the amino moiety. The tricyclic dimethylamine (*S*,*S*,*S*)-**24** represents a promising lead compound for the development of novel potent and selective σ_2 ligands in a second optimization cycle.

Conclusion

Seven-to-ten reaction steps were required to synthesize the tricyclic amines **22**–**24**, **28**, and **29**, which are derivatives of the tricyclic benzomorphan scaffold. Although the sizes of the substituents at the secondary alcohol **14** and the acetate **16** are very similar (benzyl, 2-carbamoylethyl), the lipases of *Pseudomonas fluorescens* and *Candida rugosa* are able to differentiate the corresponding enantiomers. Chiral oxa-Pictet–Spengler reaction, Dieckmann condensation, and stereoselective introduction of amino moieties represent the key steps of the synthesis. Investigation of the affinity towards σ_1, σ_2, NMDA, κ, and μ receptors revealed that the orientation and substitution pattern of the amino moiety and the absolute configuration of the ring system are responsible for high σ_2 receptor affinity: The dimethylamine (*S*,*S*,*S*)-**24** with equatorially oriented amino moiety showed remarkable σ_2 affinity in the low micromolar range (K_i = 2.9 μM).

Experimental Section

General Chemistry: Unless otherwise noted, moisture-sensitive reactions were conducted under dry nitrogen. Petroleum ether refers to the fraction boiling at 40–60 °C. Lipases were commercially available from Sigma–Aldrich and Alfa Aesar. TLC: Silica gel 60 F_{254} plates (Merck). Flash chromatography (FC): Silica gel 60, 0.040–0.063 mm (Merck); data in parentheses represent diameter of the column [cm], eluent, fraction size [mL], R_f. Melting points: SMP 2 apparatus (Stuart Scientific). Elemental analyses: CHN-Elementaranalysator Rapid (Heraeus), Elemental Analyzer 240 (Perkin–Elmer), and Vario EL (Elementaranalysesysteme GmbH). MS: MAT 448, MAT 312, MAT 8200, and TSQ 7000 spectrometers (Finnigan). EI = electron impact, CI = chemical ionization. HRMS: MAT 8200 spectrometer (Finnigan). IR: 1605 FT-IR and 2000 FT-ATR spectrophotometers (Perkin–Elmer); s = strong, m = medium, w = weak. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz): Unity 300 FT NMR spectrometer (Varian): δ in ppm relative to tetramethylsilane, coupling constants are given with 0.5 Hz resolution; the ^{13}C and ^{1}H NMR assignments are supported by 2D NMR techniques. Polarimetry: PE 241 polarimeter (Perkin–Elmer): d = 1 dm, λ = 589 nm, the unit of the specific optical rotation (° mL dm^{-1} g^{-1}) has been omitted for clarity. CD spectroscopy: CD6 circular dichrograph (Jobin Yvon Instruments S.A.). Microwave apparatus: CEM Discover LabMate Synthesizer, single mode cavity; Discover PC software (CEM Corporation, NC); reactions were performed in glass vessels (capacity 10 mL) sealed with the corresponding pressure adaptor. The pressure was controlled by using a piezoelectric pressure sensor. The temperature of the vessel contents was monitored by using an external infrared temperature control. HPLC: Waters equipment: UV detector: Waters 2487 Dual Absorbance detector; autosampler: Waters 710; pump: Waters 515, double piston pump, degasser: Waters inline degasser, 4-channel; Jetstream 2 plus, Peltier column thermostat; Software ChromStar light version 4.05. Enantiomerically pure compounds were synthesized by using procedures that had been optimized with racemic compounds.

4-Oxo-5-phenylpentanoic Acid (9):[8] Phenylacetonitrile (**7**; 6.0 mL, 52 mmol) and diethyl succinate (**8**; 13.4 mL, 80 mmol) were added to a solution of sodium metal (1.53 g, 66.6 mmol) in absolute ethanol (25 mL). The mixture was stirred overnight at room temp. and diluted with cold water (50 mL). The aqueous layer was extracted with toluene (3 × 15 mL) and acidified with 2 M H_2SO_4. The resulting oil was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The Et_2O layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was dissolved in a mixture of H_2O (15 mL), conc. HCl (17 mL), and glacial acetic acid (52 mL). Then the mixture was heated at reflux for 48 h. The mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (4 × 40 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product (8.02 g) was recrystallized from petroleum ether. [After recrystallization, the yield of **9** was rather low (<10%), so the crude

product was used in the following transformation without purification.] Colorless needles, m.p. 55 °C (petroleum ether; ref.[28] 55–56 °C). IR: $\tilde{\nu}$ = 3414 (ν_{O-H}), 3029 ($\nu_{C-H\ arom.}$), 2958 ($\nu_{C-Haliph.}$), 1714 ($\nu_{C=O}$), 744, 699 ($\gamma_{monosubst.\ arom.}$) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.61 (t, J = 6.4 Hz, 2 H, 2-H), 2.76 (t, J = 6.4 Hz, 2 H, 3-H), 3.75 (s, 2 H, 5-H), 7.21–7.38 (m, 5 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.8 (1 C, C-2), 36.1 (1 C, C-3), 49.9 (1 C, C-5), 127.1 (1 C, C-4′), 128.7 (2 C, C-3′, C-5′), 129.4 (2 C, C-2′, C-6′), 133.9 (1 C, C-1′), 178.7 (1 C, C-1), 206.3 (1 C, C-4) ppm. MS (EI): *m*/*z* (%) = 192 (37) $[M]^+$, 174 (22) $[M - H_2O]^+$, 101 (100) $[M - CH_2Ph]^+$, 91 (75) $[CH_2Ph]^+$. $C_{11}H_{12}O_3$ (192.21): calcd. C 68.74, H 6.29; found C 68.25, H 6.56.

(*RS*)-(±)-5-Benzyltetrahydrofuran-2-one (11):[8] $NaBH_4$ (7.91 g, 209 mmol) was added to a solution of unpurified γ-keto acid **9** (8.02 g, 41.7 mmol) in methanol (250 mL) and the mixture was stirred for 15 h at room temp. After removal of the solvent in vacuo, the residue was dissolved in water (50 mL) and acidified with diluted HCl (pH < 2). After 30 min the suspension was extracted with Et_2O (4 × 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and the residue (8.13 g) was purified by FC (5.5 cm, petroleum ether/ethyl acetate = 3:1, 45 mL, R_f = 0.50). Colorless oil that solidified upon storage in the refrigerator as a colorless solid, m.p. 33 °C (ref.[7] 33 °C), yield 5.56 g (60%, based on phenylacetonitrile). IR (film): $\tilde{\nu}$ = 3029 ($\nu_{C-H\ arom.}$), 2942 ($\nu_{C-Haliph.}$), 1770 ($\nu_{C=O}$), 750, 702 ($\gamma_{monosubst.\ arom.}$) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.94 (dtd, J = 12.8, 9.4, 7.5 Hz, 1 H, 4-H), 2.23 (dddd, J = 12.8, 9.4, 6.7, 4.7 Hz, 1 H, 4-H), 2.35 (ddd, J = 17.7, 9.2, 4.7 Hz, 1 H, 3-H), 2.45 (dt, J = 17.7, 9.4 Hz, 1 H, 3-H), 2.91 (dd, J = 14.0, 6.1 Hz, 1 H, Ar-CH_2), 3.06 (dd, J = 14.0, 6.1 Hz, 1 H, Ar-CH_2), 4.72 (dq, J = 7.5, 6.4 Hz, 1 H, 5-H), 7.19–7.34 (m, 5 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.9 (1 C, C-4), 28.4 (1 C, C-3), 41.1 (1 C, Ar-*C*H_2), 80.6 (1 C, C-5), 126.7 (1 C, C-4′), 128.4 (2 C, C-3′, C-5′), 129.2 (2 C, C-2′, C-6′), 135.8 (1 C, C-1′), 176.9 (1 C, C-2) ppm. MS (EI): *m*/*z* (%) = 176 (23) $[M]^+$, 91 (20) $[CH_2Ph]^+$, 85 (100) $[M - CH_2Ph]^+$, 57 (11) $[OCHCH_2CH_2]^+$. $C_{11}H_{12}O_2$ (176.21): calcd. C 74.98, H 6.86; found C 74.68, H 6.81. HPLC: Kromasil® CHI-TBB, 5 µm, 250 × 4.6 mm (Akzo Nobel), mobile phase: *n*-hexane/TBME = 90:10, flow rate 0.5 mL/min, T = 5 °C, c = 1.0 mg/mL, injection volume 7.5 µL, detection at λ = 254 nm, retention times: (*R*)-**11** t = 40.7 min, (*S*)-**11** t = 43.2 min.

Ethyl (*RS*)-(±)-4-Hydroxy-5-phenylpentanoate (13): A mixture of **11** (374 mg, 2.12 mmol), ethanol (20 mL), and NEt_3 (1.0 mL, 7.21 mmol) was heated at reflux for 20 h. After removal of the solvent in vacuo, the residue was purified by FC (2 cm, petroleum ether/ethyl acetate = 5:1, 5 mL, R_f = 0.44). Colorless oil, yield 29 mg (6%). IR: $\tilde{\nu}$ = 3445 (ν_{O-H}), 3028 ($\nu_{C-H\ arom.}$), 2980, 2929 ($\nu_{C-Haliph.}$), 1730 ($\nu_{C=O}$), 1081 (ν_{C-O}), 744, 699 ($\gamma_{monosubst.\ arom.}$) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.26 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 1.77 (ddt, J = 14.2, 8.7, 7.1 Hz, 1 H, 3-H), 1.92 (dddd, J = 14.4, 10.8, 7.2, 3.5 Hz, 1 H, 3-H), 2.43–2.54 (m, 2 H, 2-H), 2.71 (dd, J = 13.6, 8.1 Hz, 1 H, 5-H), 2.83 (dd, J = 13.6, 4.7 Hz, 1 H, 5-H), 3.86 (tdd, J = 8.4, 4.5, 3.9 Hz, 1 H, 4-H), 4.14 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 7.19–7.35 (m, 5 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (1 C, OCH_2CH_3), 30.8 (1 C, C-2), 31.6 (1 C, C-3), 44.1 (1 C, C-5), 60.4 (1 C, OCH_2CH_3), 72.0 (1 C, C-4), 126.5 (1 C, C-4′), 128.6 (2 C, C-3′, C-5′), 129.4 (2 C, C-2′, C-6′), 138.1 (1 C, C-1′), 174.0 (1 C, C-1). MS (EI): *m*/*z* (%) = 204 (4) $[M - H_2O]^+$, 176 (9) $[M - EtOH]^+$, 131 (100) $[M - CH_2Ph]^+$, 91 (35) $[CH_2Ph]^+$. MS (CI, NH_3): *m*/*z* (%) = 223 (85) $[M + H]^+$, 205 (93) $[M + H - H_2O]^+$, 177 (100) $[M + H - EtOH]^+$. $C_{13}H_{18}O_3$ (222.28): calcd. C 70.25, H 8.16; found C 70.27, H 7.91.

(*RS*)-(±)-4-Hydroxy-*N*,*N*-dimethyl-5-phenylpentanamide (14): A mixture of **11** (4.62 g, 26.2 mmol) and a solution of dimethylamine in ethanol (5.6 M, 18.8 mL, 105 mmol) was stirred for 24 h at room temp. The mixture was acidified with diluted HCl (pH 1–2) and extracted with CH_2Cl_2 (5 × 40 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and the residue (5.7 g) was purified by FC (5.5 cm, ethyl acetate/acetone = 3:1, 30 mL, R_f = 0.30). Colorless oil, yield 5.48 g (94%). IR (film): $\tilde{\nu}$ = 3393 (ν_{O-H}), 3028 ($\nu_{C-H\ arom.}$), 2928 ($\nu_{C-Haliph.}$), 1622 ($\nu_{C=O}$), 1084 (ν_{C-O}), 747, 702 ($\gamma_{monosubst.\ arom.}$) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.76 (dddd, J = 14.4, 8.9, 7.3, 6.1 Hz, 1 H, 3-H), 1.90 (dddd, J = 14.4, 7.3, 5.8, 3.1 Hz, 1 H, 3-H), 2.44 (ddd, J = 16.2, 7.3, 5.8 Hz, 1 H, 2-H), 2.54 (ddd, J = 16.2, 7.3, 6.1 Hz, 1 H, 2-H), 2.76 (dd, J = 13.5, 6.1 Hz, 1 H, 5-H), 2.82 (dd, J = 13.5, 7.0 Hz, 1 H, 5-H), 2.95 (s, 3 H, NCH_3), 3.00 (s, 3 H, NCH_3), 3.86 (dtd, J = 8.9, 6.1, 3.1 Hz, 1 H, 4-H), 7.18–7.32 (m, 5 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.9 (1 C, C-2), 31.0 (1 C, C-3), 35.3 (1 C, N*C*H_3), 37.1 (1 C, N*C*H_3), 44.1 (1 C, C-5), 72.1 (1 C, C-4), 126.0 (1 C, C-4′), 128.1 (2 C, C-3′, C-5′), 129.2 (2 C, C-2′, C-6′), 138.5 (1 C, C-1′), 173.4 (1 C, C-1) ppm. MS (EI): *m*/*z* (%) = 203 (22) $[M - H_2O]^+$, 130 (100) $[M - CH_2Ph]^+$, 91 (29) $[CH_2Ph]^+$. MS (CI, NH_3): *m*/*z* = 222 $[M + H]^+$. $C_{13}H_{19}NO_2$ (221.30): calcd. C 70.56, H 8.65, N 6.33; found C 70.25, H 8.90, N 5.93. HPLC: Kromasil® CHI-TBB, 5 µm, 250 × 4.6 mm (Akzo Nobel), mobile phase: *n*-hexane/THF = 92.5:7.5, flow rate 0.5 mL/min, T = 20 °C, c = 1.08 mg/mL, injection volume 7.5 µL, detection at λ = 254 nm, retention times: (*R*)-**14** t = 55.4 min, (*S*)-**14** t = 58.7 min.

***N*,*N*-Dimethyl-4-oxo-5-phenylpentaneamide (15):** $NaBrO_3$ (0.68 g, 4.57 mmol) and $(NH_4)_2Ce(NO_3)_6$ (0.25 g, 0.45 mmol) were added to a solution of alcohol **14** (0.91 g, 4.12 mmol) in a mixture of acetonitrile/water (30 mL, 7:3). The mixture was heated at reflux for 45 min, diluted with H_2O (20 mL), and extracted with CH_2Cl_2 (50 mL). The organic layer was washed with a solution of saturated $NaHCO_3$ (30 mL) and brine (30 mL). The combined water layers were extracted with CH_2Cl_2 (3 × 50 mL) and the organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue (0.97 g) purified by FC (4 cm, ethyl acetate/petroleum ether = 5:1, 20 mL, R_f = 0.36). Pale-yellow oil, yield 0.82 g (91%). IR (KBr): $\tilde{\nu}$ = 3029 ($\nu_{C-H\ arom.}$), 2922 ($\nu_{C-H\ aliph.}$), 1713 ($\nu_{C=O}$), 1639 ($\nu_{C=O}$), 745, 699 ($\gamma_{monosubst.\ arom.}$) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.57 (t, J = 6.4 Hz, 2 H, 2-H), 2.77 (t, J = 6.4 Hz, 2 H, 3-H), 2.92 (s, 3 H, NCH_3), 3.00 (s, 3 H, NCH_3), 3.79 (s, 2 H, 5-H), 7.20–7.34 (m, 5 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.2 (1 C, C-2), 35.4 (1 C, N*C*H_3), 36.6 (1 C, C-3), 36.9 (1 C, N*C*H_3), 50.1 (1 C, C-5), 126.8 (1 C, C-4′), 128.5 (2 C, C-3′, C-5′), 129.4 (2 C, C-2′, C-6′), 134.2 (1 C, C-1′), 171.4 (1 C, C-1), 207.6 (1 C, C-4) ppm. MS (EI): *m*/*z* (%) = 174 (7) $[M - HNMe_2]^+$, 128 (100) $[M - CH_2Ph]^+$, 100 (36) $[CH_2CH_2CONMe_2]^+$, 91 (20) $[CH_2Ph]^+$. MS (CI, NH_3): *m*/*z* = 220 $[M + H]^+$. $C_{13}H_{17}NO_2$ (219.28): calcd. C 71.20, H 7.81, N 6.39; found C 71.07, H 8.03, N 6.28.

(*RS*)-(±)-[4-(Dimethylcarbamoyl)-1-phenyl-2-butyl] Acetate (16): Ac_2O (2.2 mL, 22.6 mmol) and 4-(dimethylamino)pyridine (205 mg, 1.68 mmol) were added to a solution of alcohol **14** (2.00 g, 9.04 mmol) in CH_2Cl_2 (40 mL) and triethylamine (5 mL, 36.2 mmol). After stirring for 4 h at room temp., the mixture was diluted with Et_2O (40 mL), washed with diluted HCl (50 mL) and H_2O (50 mL), and the organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue (2.69 g) purified by FC (4 cm, ethyl acetate/petroleum ether = 5:1, 20 mL, R_f = 0.34). Colorless oil that solidified in the refrigerator as a colorless solid, m.p. 61 °C, yield 2.33 g (98%). IR (film): $\tilde{\nu}$ = 3026 ($\nu_{C-H\ arom.}$), 2970, 2930 ($\nu_{C-H\ aliph.}$), 1728 ($\nu_{C=O}$), 1645 ($\nu_{C=O}$), 752, 710 ($\gamma_{monosubst.\ arom.}$). ^1H NMR ($CDCl_3$): δ = 1.76–2.08 (m, 2 H, 3-H), 1.97 (s, 3 H, O=CCH_3), 2.27 (dt, J = 15.7, 6.4 Hz, 1 H, 2-H), 2.36 (dt, J = 16.0, 6.4 Hz, 1 H, 2-H), 2.81 (dd, J = 13.7, 6.1 Hz, 1 H, 5-H), 2.89 (s, 3

H, NCH_3), 2.90 (dd, J = 13.7, 6.7 Hz, 1 H, 5-H), 2.92 (s, 3 H, NCH_3), 5.10 (dtd, J = 8.9, 6.5, 3.9 Hz, 1 H, 4-H), 7.15–7.29 (m, 5 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.0 (1 C, O=C*C*H_3), 29.0, 29.2 (2 C, C-2, C-3), 35.3 (1 C, N*C*H_3), 37.0 (1 C, N*C*H_3), 40.7 (1 C, C-5), 74.3 (1 C, C-4), 126.4 (1 C, C-4′), 128.2 (2 C, C-3′, C-5′), 129.3 (2 C, C-2′, C-6′), 137.2 (1 C, C-1′), 170.5 (1 C, O=*C*CH_3), 171.9 (1 C, C-1) ppm. MS (EI): m/z (%) = 203 (100) [M – CH_3COOH]$^+$, 159 (20) [M – CH_3COOH – $N(CH_3)_2$]$^+$, 130 (43) [M – CH_3COOH – $N(CH_3)_2$ – CO – H]$^+$, 91 (21) [CH_2Ph]$^+$. MS (CI, NH_3): m/z = 264 [M + H]$^+$. $C_{15}H_{21}NO_3$ (263.34): calcd. C 68.42, H 8.04, N 5.32; found C 68.36, H 8.28, N 5.20. HPLC: Kromasil® CHI-TBB, 5 µm, 250 × 4.6 mm (Akzo Nobel), mobile phase: *n*-hexane/THF = 92.5:7.5, flow rate 0.5 mL/min, T = 5 °C, c = 1.16 mg/mL, injection volume 7.5 µL, detection at λ = 254 nm, retention times: (*S*)-**16** t = 42.1 min, (*R*)-**16** t = 44.3 min.

***Pseudomonas fluorescens* Lipase Catalyzed Kinetic Resolution of Racemic γ-Hydroxy Amide 14 (Enantioselective Acetylation of 14):** Isopropenyl acetate (17.5 mL, 159 mmol) and Amano AK lipase (3.75 g) were added to a solution of racemic alcohol **14** (5.00 g, 22.6 mmol) in TBME (200 mL). The suspension was shaken (150 rpm) for 141 h at room temp. Then the lipase was filtered off, the filtrate was concentrated in vacuo, and the residue (6.81 g) was purified by FC (5.5 cm, ethyl acetate/acetone = 3:1, 45 mL).

(*S*)-14: R_f = 0.30. Colorless oil that solidified in the refrigerator as a colorless solid, m.p. 47 °C, yield 2.02 g (40%), >99% *ee*. $[\alpha]_{589}$ = –9.7 (c = 10.2 mg/mL, CH_3OH).

(*R*)-16: R_f = 0.34 (ethyl acetate/petroleum ether = 5:1), colorless oil, yield 2.75 g (46%), 98.4% *ee*. $[\alpha]_{589}$ = +3.4 (c = 9.9 mg/mL, CH_3OH).

(*S*)-11: R_f = 0.79 (ethyl acetate/petroleum ether = 5:1), colorless oil, yield 0.41 g (10%), 72% *ee*.

***Candida rugosa* Lipase Catalyzed Kinetic Resolution of Racemic γ-Acetoxy Amide 16 (Enantioselective Hydrolysis of 16):** A mixture of *Candida rugosa* lipase (Chirazyme L-5, 400 mg) and racemic ester **16** (99 mg, 0.37 mmol) in acetone (1 mL) and phosphate buffer pH 7.0 (10 mL) was shaken for 96 h at 37 °C. The enzyme was filtered off, the filtrate was extracted with Et_2O (5 × 15 mL), and the combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and the residue (92 mg) purified by FC (2 cm, ethyl acetate/petroleum ether = 5:1, 2.5 mL).

(*S*)-16: R_f = 0.34, colorless oil, yield 46 mg (47%), >99% *ee*. $[\alpha]_{589}$ = –3.5 (c = 10.5 mg/mL, CH_3OH).

(*R*)-14: R_f = 0.30 (ethyl acetate/acetone = 3:1), colorless oil, 95.3% *ee*, yield 42 mg (50%).

(*R*)-(+)-4-Hydroxy-*N*,*N*-dimethyl-5-phenylpentaneamide [(*R*)-14]: H_2O (3 mL) and K_2CO_3 (494 mg, 3.58 mmol) were added to a solution of ester (*R*)-**16** (182 mg, 0.69 mmol) in methanol (5 mL). The mixture was stirred for 24 h at room temp. After the addition of NaOH (0.01 M, 5 mL), the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue (153 mg) was purified by FC (2 cm, ethyl acetate/acetone = 3:1, 2.5 mL, R_f = 0.30). Colorless oil, yield 141 mg (92%), 98.4% *ee*. $[\alpha]_{589}$ = +9.7 (c = 9.75 mg/mL, CH_3OH).

(*S*)-(–)-[4-(Dimethylcarbamoyl)-1-phenyl-2-butyl] Acetate [(*S*)-16]: Triethylamine (0.5 mL, 3.6 mmol), acetic anhydride (0.25 mL, 2.64 mmol), and 4-(dimethylamino)pyridine (28 mg, 0.23 mmol) were added to a solution of alcohol (*S*)-**14** (216 mg, 0.97 mmol) in CH_2Cl_2 (6 mL), After stirring for 6 h at room temp., the mixture was diluted with Et_2O (10 mL), the organic layer was washed with diluted HCl (10 mL) and H_2O (10 mL), dried (Na_2SO_4), and concentrated in vacuo and the residue (246 mg) was purified by FC (2 cm, ethyl acetate/petroleum ether = 5:1, 2.5 mL, R_f = 0.34). Colorless oil, yield 231 mg (90%), >99% *ee*. $[\alpha]_{589}$ = –3.5 (c = 10.5 mg/mL CH_3OH).

Ethyl (1*RS*,3*RS*)-(±)-3-[2-(Dimethylcarbamoyl)ethyl]-3,4-dihydro-1*H*-2-benzopyran-1-carboxylate (18): Under N_2 a solution of ethyl glyoxylate (**17a**; 50% in toluene, 9.0 mL, 45.2 mmol) was added to a solution of **14** (2.04 g, 9.2 mmol) in CH_2Cl_2 (40 mL). After stirring for 30 min at 0 °C, $BF_3{\cdot}OEt_2$ (9.2 mL, 72.3 mmol) was added dropwise. The mixture was stirred for 6 h at room temp. and then for 4 d at 40 °C. After diluting with 2 M HCl (70 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and the residue purified by FC (5.5 cm, ethyl acetate/petroleum ether = 4:1, 25 mL, R_f = 0.30). The same yield was obtained by the same procedure by using diethyl acetal **17b** instead of the aldehyde **17a**. Colorless oil that solidified upon standing in the refrigerator, m.p. 64–65 °C, yield 2.64 g (88%). IR: $\tilde{\nu}$ = 2927 ($\nu_{C-Haliph.}$), 1751 ($\nu_{C=O}$), 1650 ($\nu_{C=O}$), 1175 ($\nu_{C-O\ ester}$), 733 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.92–2.16 (m, 2 H, $CH_2CH_2CONMe_2$), 2.47–2.64 (m, 2 H, $CH_2CH_2CONMe_2$), 2.67–2.90 (m, 2 H, 4-H), 2.94 (s, 3 H, NCH_3), 3.00 (s, 3 H, NCH_3), 3.76 (ddt, J = 11.2, 8.3, 3.1 Hz, 1 H, 3-H), 4.25 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.37 (s, 1 H, 1-H), 7.10 (dd, J = 6.7, 1.5 Hz, 1 H, 5-H), 7.15–7.22 (m, 2 H, 6-H, 7-H), 7.25 (dd, J = 6.9, 1.7 Hz, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (1 C, OCH_2CH_3), 28.8 (1 C, $CH_2CH_2CONMe_2$), 30.9 (1 C, $CH_2CH_2CONMe_2$), 34.1 (1 C, C-4), 35.3 (1 C, N*C*H_3), 37.1 (1 C, N*C*H_3), 61.3 (1 C, OCH_2CH_3), 73.6 (1 C, C-3), 77.4 (1 C, C-1), 124.3 (1 C, C-8), 126.3, 127.4, (2 C, C-6, C-7), 129.0 (1 C, C-5), 131.6, 134.3 (2 C, C-4a, C-8a), 170.6 (1 C, *C*OOEt), 172.6 (1 C, *C*$ONMe_2$) ppm. MS (EI): m/z (%) = 305 (25) [M]$^+$, 232 (100) [M – COOEt]$^+$, 214 (72) [M – CH_2Ph]$^+$, 91 (29) [CH_2Ph]$^+$, 46 (98) [NH_2Me_2]$^+$. $C_{17}H_{23}NO_4$ (305.37): calcd. C 66.86, H 7.59, N 4.59; found C 66.76, H 7.36, N 4.22.

Ethyl (1*S*,3*S*)-(+)-3-[2-(Dimethylcarbamoyl)ethyl]-3,4-dihydro-1*H*-2-benzopyran-1-carboxylate [(*S*,*S*)-18]: Compound (*S*,*S*)-**18** was prepared as described for (±)-**18**: (*S*)-**14** (2.04 g, 9.21 mmol) was treated with a solution of **17a** (9.0 mL, 45.2 mmol) and $BF_3{\cdot}OEt_2$ (9.2 mL, 72.5 mmol). Colorless oil that solidified upon storage in the refrigerator as a colorless resin, yield 2.64 g (93%). $[\alpha]_{589}$ = +8.2 (c = 10.2 mg/mL, CH_3OH).

Ethyl (1*R*,3*R*)-(–)-3-[2-(Dimethylcarbamoyl)ethyl]-3,4-dihydro-1*H*-2-benzopyran-1-carboxylate [(*R*,*R*)-18]: Compound (*R*,*R*)-**18** was prepared as described for (±)-**18**: (*R*)-**14** (3.60 g, 16.2 mmol) was treated with a solution of **17a** (16.1 mL, 81.2 mmol) and $BF_3{\cdot}OEt_2$ (16.5 mL, 130 mmol). Colorless oil that solidified in the refrigerator as a colorless resin, yield 4.28 g (86%). $[\alpha]_{589}$ = –7.9 (c = 10.0 mg/mL, CH_3OH).

Ethyl (1*RS*,3*RS*)-(±)-3-[2-(Ethoxycarbonyl)ethyl]-3,4-dihydro-1*H*-2-benzopyran-1-carboxylate (19): Under N_2 the amido ester **18** (3.74 g, 12.2 mmol) was dissolved in CH_2Cl_2 (50 mL) and pyridine (3.0 mL, 36.7 mmol) was added. At –40 °C, trifluoromethanesulfonic anhydride (3.1 mL, 18.3 mmol) was added slowly. The mixture was warmed to 0 °C over 2 h and stirred for an additional 12 h at 0 °C. Then ethanol (21.3 mL) was added and the mixture was stirred for 12 h at room temp. After addition of Et_2O (50 mL), the mixture was washed with a solution of 1 M HCl (50 mL) and a saturated solution of $NaHCO_3$ (2 × 50 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by FC (5.5 cm, petroleum ether/ethyl acetate = 6:1, 25 mL, R_f = 0.41). Colorless oil that crystallized in the refrigerator as a color-

less solid (iPr$_2$O), m.p. 42 °C, yield 3.22 g (86%). IR: $\tilde{\nu}$ = 2982, 2925 ($\nu_{C-H\ aliph.}$), 1755 ($\nu_{C=O}$), 1724 ($\nu_{C=O}$), 1168 (ν_{C-O}), 743 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.25 (t, J = 7.2 Hz, 3 H, OCH_2CH_3, ester at C-3), 1.30 (t, J = 7.2 Hz, 3 H, OCH_2CH_3, ester at C-1), 2.00–2.09 (m, 2 H, CH_2CH_2COOEt), 2.47–2.65 (m, 2 H, CH_2CH_2COOEt), 2.69 (dd, J = 15.9, 2.4 Hz, 1 H, 4-H), 2.90 (dd, J = 15.9, 11.0 Hz, 1 H, 4-H), 3.73 (dddd, J = 10.8, 7.7, 4.8, 2.9 Hz, 1 H, 3-H), 4.14 (q, J = 7.2 Hz, 2 H, OCH_2CH_3, ester at C-3), 4.27 (q, J = 7.2 Hz, 2 H, OCH_2CH_3, ester at C-1), 5.38 (s, 1 H, 1-H), 7.11 (dd, J = 6.1, 2.1 Hz, 1 H, 5-H), 7.18–7.23 (m, 2 H, 6-H, 7-H), 7.28 (dd, J = 6.7, 1.8 Hz, 1 H, 8-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1 (2 C, OCH_2CH_3), 30.2 (1 C, CH_2CH_2COOEt), 30.6 (1 C, CH_2CH_2COOEt), 34.0 (1 C, C-4), 60.2 (1 C, OCH_2CH_3, ester at C-3), 61.3 (1 C, OCH_2CH_3, ester at C-1), 73.3 (1 C, C-3), 77.4 (1 C, C-1), 124.4 (1 C, C-8), 126.3, 127.4, (2 C, C-6, C-7), 128.9 (1 C, C-5), 131.6, 134.0 (2 C, C-4a, C-8a), 170.4 (1 C, COOEt, ester at C-1), 173.3 (1 C, COOEt, ester at C-3) ppm. MS (EI): m/z (%) = 306 (4) [M]$^+$, 233 (100) [M – COOEt]$^+$, 215 (74) [M – CH_2Ph]$^+$, 187 (29) [M – PhCH=CO]$^+$. $C_{17}H_{22}O_5$ (306.36): calcd. C 66.65, H 7.24; found C 66.44, H 7.13.

Ethyl (1*S*,3*S*)-(+)-3-[2-(Ethoxycarbonyl)ethyl]-3,4-dihydro-1*H*-2-benzopyran-1-carboxylate [(*S*,*S*)-19]: Compound (*S*,*S*)-**19** was prepared as described for (±)-**19**: (*S*)-**18** (1.97 g, 6.45 mmol) was treated with pyridine (1.6 mL, 19.4 mmol), trifluoromethanesulfonic acid anhydride (1.6 mL, 9.5 mmol), and ethanol (15 mL). Colorless oil that froze in the refrigerator and melted at room temp., yield 1.63 g (83%). $[\alpha]_{589}$ = +9.1 (c = 9.6 mg/mL, CH_3OH).

Ethyl (1*R*,3*R*)-(–)-3-[2-(Ethoxycarbonyl)ethyl]-3,4-dihydro-1*H*-2-benzopyran-1-carboxylate [(*R*,*R*)-19]: Compound (*R*,*R*)-**19** was prepared as described for (±)-**19**: (*R*)-**18** (4.28 g, 14.0 mmol) was treated with pyridine (3.4 mL, 42.1 mmol), trifluoromethanesulfonic acid anhydride (3.6 mL, 21.0 mmol), and ethanol (30 mL). Colorless oil that froze in the refrigerator and melted at room temp., yield 3.39 g (79%). $[\alpha]_{589}$ = –9.4 (c = 10.2 mg/mL, CH_3OH).

Ethyl (5*RS*,7*RS*,9*RS*)-(±)-6-Oxo-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocyclooctene-7-carboxylate (20a), Ethyl (5*RS*,7*SR*,9*RS*)-(±)-6-Oxo-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocyclooctene-7-carboxylate (20b), and Ethyl (5*RS*,9*SR*)-(±)-6-Hydroxy-5,8,9,10-tetrahydro-5,9-epoxybenzocyclooctene-7-carboxylate (20c): Under N_2 NaH (1.24 g, 31.1 mmol, 60% dispersion in mineral oil, which was removed by washing several times with petroleum ether before use) was suspended in toluene (100 mL). After 5 min a solution of **19** (3.04 g, 9.9 mmol) in toluene (30 mL) was added dropwise followed by the addition of absolute ethanol (360 µL). When the evolution of gas had finished, the mixture was heated at reflux for 2.5 h. Diluted HCl (75 mL) was added and the organic layer was separated, dried (Na_2SO_4), concentrated in vacuo, and the residue (2.68 g) was purified by FC (5.5 cm, petroleum ether/ethyl acetate = 10:1, 25 mL, R_f = 0.38). Colorless oil, yield 2.03 g (78%). The ratio of **20a/20b/20c** was 20:15:65. IR: $\tilde{\nu}$ = 3023 ($\nu_{C-H\ arom.}$), 2935 ($\nu_{C-Haliph.}$), 1747 ($\nu_{C=O}$), 1728 ($\nu_{C=O}$), 1662 ($\nu_{C=O}$), 1623 ($\nu_{C=C}$), 1213 ($\nu_{C-O\ ester}$), 1087 (ν_{C-O-C}), 735 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.23 (t, J = 7.0 Hz, 0.4 H, OCH_2CH_3, keto ester 2), 1.28 (t, J = 7.0 Hz, 1.95 H, OCH_2CH_3, enol), 1.29 (t, J = 7.0 Hz, 0.6 H, OCH_2CH_3, keto ester 1), 1.77 (ddd, J = 14.0, 6.1, 4.9 Hz, 0.2 H, 8-H, keto ester), 2.15 (d, J = 16.2 Hz, 0.65 H, 8-H, enol), 2.52–2.63 (m, 0.2 H, 8-H, keto ester), 2.60 (d, J = 17.7 Hz, 1.2 H, 10-H, enol + keto ester 1 + 2), 2.89–3.00 (m, 0.3 H, 8-H, keto ester), 2.93 (dd, J = 16.2, 6.7 Hz, 0.65 H, 8-H, enol), 3.27 (t, J = 4.9 Hz, 0.2 H, 7-H, keto ester 1), 3.34 (m, 0.3 H, 10-H, enol + keto ester 1 + 2), 3.37 (dd, J = 16.8, 6.1 Hz, 0.5 H, 10-H, enol + keto ester 1 + 2), 3.88 (dd, J = 13.1, 6.1 Hz, 0.15 H, 7-H, keto ester 2), 4.13 (q, J = 7.0 Hz, 0.3 H, OCH_2CH_3, keto ester 2), 4.19 (q, J = 7.0 Hz, 1.3 H, OCH_2CH_3, enol), 4.26 (q, J = 7.0 Hz, 0.4 H, OCH_2CH_3, keto ester 1), 4.70–4.77 (m, 1 H, 9-H, enol + keto ester 1 + 2), 4.97 (s, 0.65 H, 5-H, enol), 5.00 (s, 0.15 H, 5-H, keto ester 2), 5.02 (s, 0.2 H, 5-H, keto ester 1), 7.11–7.32 (m, 4 H, arom.), 11.73 (s, 0.65 H, OH, enol) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.05 (0.2 C, OCH_2CH_3, keto ester 2), 14.11 (0.15 C, OCH_2CH_3, keto ester 1), 14.22 (0.65 C, OCH_2CH_3, enol), 26.63 (0.15 C, C-8, keto ester 1), 28.62 (0.2 C, C-8, keto ester 2), 29.66 (0.65 C, C-8, enol), 32.32 (0.65 C, C-10, enol), 33.00 (0.2 C, C-10, keto ester 2), 33.05 (0.15 C, C-10, keto ester 1), 48.99 (0.15 C, C-7, keto ester 1), 49.43 (0.2 C, C-7, keto ester 2), 60.51 (0.65 C, OCH_2CH_3, enol), 61.32 (0.15 C, OCH_2CH_3, keto ester 1), 61.73 (0.2 C, OCH_2CH_3, keto ester 2), 65.24 (0.2 C, C-9, keto ester 2), 65.89 (0.15 C, C-9, keto ester 1), 66.14 (0.65 C, C-9, enol), 70.19 (0.65 C, C-5, enol), 77.88 (0.2 C, C-5, keto ester 2), 77.99 (0.15 C, C-5, keto ester 1), 92.61 (0.65 C, C-7, enol), 125.71, 125.73, 126.22, 126.29, 126.68, 126.74, 127.72, 128.11, 128.18, 128.68, 129.78, 129.97, (4 C, C-1, C-2, C-3, C-4), 130.65, 131.01, 131.14, 131.53, 132.25, 135.67 (2 C, C-4a, C-10a), 167.94 (0.2 C, COOC$_2$H$_5$, keto ester 2), 169.00 (0.15 C, COOC$_2$H$_5$, keto ester 1), 170.02 (0.65 C, COOC$_2$H$_5$, enol), 171.68 (0.65 C, C-6, enol), 203.98 (0.2 C, C-6, keto ester 2), 204.78 (0.15 C, C-6, keto ester 1) ppm. MS (EI): m/z (%) = 260 (60) [M]$^+$, 232 (75) [M – C_2H_4]$^+$, 186 (51) [M – $COOC_2H_5$ – H]$^+$, 169 (17) [M – CH_2Ph]$^+$, 141 (50) [M – CH_2Ph – C_2H_4]$^+$, 132 (100) [2-benzopyran – 2H]$^+$, 91 (46) [CH_2Ph]$^+$. $C_{15}H_{16}O_4$ (260.28): calcd. C 69.22, H 6.20; found C 69.09, H 6.22.

Ethyl (5*S*,7*S*,9*S*)-6-Oxo-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocyclooctene-7-carboxylate [(*S*,*S*,*S*)-20a], Ethyl (5*S*,7*R*,9*S*)-6-Oxo-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocyclooctene-7-carboxylate [(*S*,*R*,*S*)-20b], and Ethyl (5*S*,9*R*)-6-Hydroxy-5,8,9,10-tetrahydro-5,9-epoxybenzocyclooctene-7-carboxylate [(*S*,*R*)-20c]: The Dieckmann cyclization of (*S*,*S*)-**19** was performed as described for the synthesis of (±)-**20a/20b/20c**: (*S*,*S*)-**19** (3.61 g, 11.8 mmol) was treated with NaH (60% dispersion, 1.42 g, 35.5 mmol) and absolute ethanol (430 µL, 7.4 mmol). Colorless oil, yield 1.90 g (62%). $[\alpha]_{589}$ = –62.4 (c = 7.4 mg/mL, CH_3OH).

Ethyl (5*R*,7*R*,9*R*)-6-Oxo-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocyclooctene-7-carboxylate [(*R*,*R*,*R*)-20a], Ethyl (5*R*,7*S*,9*R*)-6-Oxo-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocyclooctene-7-carboxylate [(*R*,*S*,*R*)-20b], and Ethyl (5*R*,9*S*)-6-Hydroxy-5,8,9,10-tetrahydro-5,9-epoxybenzocyclooctene-7-carboxylate [(*R*,*S*)-20c]: The Dieckmann cyclization of (*R*,*R*)-**19** was performed as described for the synthesis of (±)-**20a/20b/20c**: (*R*,*R*)-**19** (3.38 g, 11.0 mmol) was treated with NaH (60% dispersion, 1.41 g, 35.3 mmol) and absolute ethanol (410 µL, 7.0 mmol). Colorless oil, yield 1.99 g (69%). $[\alpha]_{589}$ = +58.6 (c = 10.3 mg/mL, CH_3OH).

(5*RS*,9*RS*)-(±)-7,8,9,10-Tetrahydro-5,9-epoxybenzocyclooctene-6(5*H*)-one (21): A 0.1 M NaOH solution (20 mL) was added to a solution of **20a/20b/20c** (0.98 g, 5.21 mmol) in ethanol (12 mL) and the mixture was heated at reflux for 3 h. After cooling to room temp., the mixture was extracted with Et_2O (3 × 40 mL). The organic extracts were dried (Na_2SO_4), concentrated in vacuo, and the residue (0.68 g) was purified by FC (4 cm, petroleum ether, 20 mL, R_f = 0.41). Colorless oil that froze in the refrigerator as a colorless solid, m.p. 50–51 °C, yield 0.66 g (93%). IR: $\tilde{\nu}$ = 3023 ($\nu_{C-H\ arom.}$), 2933 ($\nu_{C-H\ aliph.}$), 1724 ($\nu_{C=O}$), 1081 (ν_{C-O-C}), 745 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.74 (ddt, J = 13.7, 10.4, 5.2 Hz, 1 H, 8-H$_{ax}$), 2.30 (dt, J = 15.6, 5.5 Hz, 1 H, 7-H$_{eq}$), 2.46 (ddt, J = 13.7, 7.9, 6.1 Hz, 1 H, 8-H$_{eq}$), 2.60 (d, J = 16.8 Hz, 1 H, 10-H$_{ps.\ eq}$), 2.63 (ddd, J = 16.2, 10.0, 6.1 Hz, 1 H, 7-H$_{ax}$), 3.39 (dd, J = 16.8, 6.4 Hz, 1 H, 10-H$_{ps.\ ax}$), 4.64 (dt, J = 7.7, 5.8 Hz, 1

H, 9-H), 4.92 (s, 1 H, 5-H), 7.11–7.26 (m, 4 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.7 (1 C, C-8), 32.5, 32.7 (2 C, C-10, C-7), 65.8 (1 C, C-9), 78.8 (1 C, C-5), 126.0, 126.4, 127.9, 129.6 (4 C, C-1, C-2, C-3, C-4), 131.7, 131.8 (2 C, C-4a, C-10a), 209.2 (1 C, C-6) ppm. MS (EI): *m*/*z* (%) = 188 (39) $[M]^+$, 160 (63) $[M - C{=}O]^+$, 131 (100) [benzopyrylium]$^+$, 91 (23) $[CH_2Ph]^+$. $C_{12}H_{12}O_2$ (188.23): calcd. C 76.57, H 6.43; found C 76.47, H 6.52.

(5*S*,9*S*)-(–)-7,8,9,10-Tetrahydro-5,9-epoxybenzocycloocten-6(5*H*)-one [(*S*,*S*)-21]: Compound (*S*,*S*)-**21** was prepared as described for (±)-**21**: (*S*,*S*,*S*)-**20a**/(*S*,*R*,*S*)-**20b**/(*S*,*R*)-**20c** (1.73 g, 6.65 mmol) was treated with ethanol (24 mL) and 0.1 M NaOH (40 mL). Colorless oil, yield 1.14 g (91%). $[\alpha]_{589}$ = –221.0 (*c* = 4.9 mg/mL, CH_3OH).

(5*R*,9*R*)-(+)-7,8,9,10-Tetrahydro-5,9-epoxybenzocycloocten-6(5*H*)-one [(*R*,*R*)-21]: Compound (*R*,*R*)-**21** was prepared as described for (±)-**21**: (*R*,*R*,*R*)-**20a**/(*R*,*S*,*R*)-**20b**/(*R*,*S*)-**20c** (1.92 g, 7.38 mmol) was treated with ethanol (24 mL) and 0.1 M NaOH (40 mL). Colorless oil, yield 1.24 g (89%). $[\alpha]_{589}$ = +222.2 (*c* = 10.0 mg/mL, CH_3OH).

(5*RS*,6*RS*,9*RS*)-(±)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocycloocten-6-amine (22): A mixture of ketone **21** (100 mg, 0.53 mmol), NH_4OAc (412 mg, 5.35 mmol) and $NaBH_3CN$ (75 mg, 1.19 mmol) in absolute methanol (5 mL) was stirred at room temp. for 69 h. The mixture was acidified with conc. HCl and the solvent was removed in vacuo. The residue was dissolved in H_2O (15 mL), the aqueous layer was washed with Et_2O (3 × 10 mL), and KOH (solid) was added to the aqueous layer, which was then extracted with Et_2O (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and the residue (73 mg) was purified by FC (2 cm, ethyl acetate/ethanol = 1:5, 2.5 mL, R_f = 0.26). Colorless solid, m.p. 109 °C, yield 39 mg (39%). The residue was dissolved in ethyl acetate and **22**·HCl was formed by addition of a solution of HCl in Et_2O. **22**·HCl: Colorless solid, decomposed at >280 °C. **22**·HCl: IR (KBr): $\tilde{\nu}$ = 2926 ($\nu_{C-H\ aliph.}$), 1636 (δ_{N-H}), 1072 ($\nu_{C-O-C\ as.}$), 735 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. **22**: ^{1}H NMR ($CDCl_3$): δ = 1.07 (qd, *J* = 12.8, 4.5 Hz, 1 H, 7-H_{ax}), 1.18 (s, 2 H, N*H*$_2$), 1.60–1.72 (m, 2 H, 7-H_{eq}, 8-H_{eq}), 2.10 (tt, *J* = 13.6, 4.8 Hz, 1 H, 8-H_{ax}), 2.59 (d, *J* = 17.4 Hz, 1 H, 10-$H_{ps.\ eq}$), 3.20 (dt, *J* = 11.9, 4.3 Hz, 1 H, 6-H_{ax}), 3.34 (dd, *J* = 17.7, 7.9 Hz, 1 H, 10-$H_{ps.\ ax}$), 4.38 (dd, *J* = 7.9, 4.9 Hz, 1 H, 9-H), 4.68 (d, *J* = 4.6 Hz, 1 H, 5-H), 7.05–7.26 (m, 4 H, arom.) ppm. **22**: ^{13}C NMR ($CDCl_3$): δ = 26.2 (1 C, C-7), 31.9 (1 C, C-10), 32.6 (1 C, C-8), 51.2 (1 C, C-6), 66.5 (1 C, C-9), 75.3 (1 C, C-5), 124.8, 126.8, 127.2, 128.2 (4 C, C-1, C-2, C-3, C-4), 133.0, 135.1 (2 C, C-4a, C-10a) ppm. **22**: MS: (EI): *m*/*z* (%) = 189 (100) $[M]^+$, 172 (80) $[M - NH_3]^+$, 91 (32) $[CH_2Ph]^+$. **22**: $C_{12}H_{15}NO$ (189.26). **22**·HCl: $C_{12}H_{16}ClNO$ (225.72). **22**·HCl (225.72): calcd. C 63.86, H 7.14, N 6.21; found C 63.46, H 7.38, N 5.85.

(5*S*,6*S*,9*S*)-(–)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocycloocten-6-amine [(*S*,*S*,*S*)-22]: Compound (*S*,*S*,*S*)-**22** was prepared as described for (±)-**22**: Ketone (*S*,*S*)-**21** (105 mg, 0.56 mmol) was treated with NH_4OAc (438 mg, 5.68 mmol) and $NaBH_3CN$ (79 mg, 1.25 mmol) in absolute methanol (5 mL). Colorless solid, m.p. 80 °C, yield 40 mg (38%). (*S*,*S*,*S*)-**22**·HCl: Colorless solid, decomposed at >270 °C. $[\alpha]_{589}$ = –46.7 (*c* = 2.55 mg/mL, CH_3OH, *T* = 24 °C). (*S*,*S*,*S*)-**22**·HCl (225.72): calcd. C 63.86, H 7.14, N 6.21; found C 63.82, H 7.67, N 5.85.

(5*R*,6*R*,9*R*)-(+)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocycloocten-6-amine [(+)-(*R*,*R*,*R*)-22]: Compound (*R*,*R*,*R*)-**22** was prepared as described for (±)-**22**: Ketone (*R*,*R*)-**21** (106 mg, 0.56 mmol) was treated with NH_4OAc (453 mg, 5.87 mmol) and $NaBH_3CN$ (98 mg, 1.55 mmol) in absolute methanol (5 mL). Colorless solid, m.p. 86 °C, yield 46 mg (43%). (*R*,*R*,*R*)-**22**·HCl: Colorless solid, decomposed at >280 °C. $[\alpha]_{589}$ = +44.7 (*c* = 2.75 mg/mL, CH_3OH, *T* = 25 °C). (*R*,*R*,*R*)-**22**·HCl (225.72): calcd. C 63.86, H 7.14, N 6.21; found C 63.51, H 7.30, N 6.00.

(5*RS*,6*RS*,9*RS*)-(±)-*N*-Methyl-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocycloocten-6-amine (23): Ti(O*i*Pr)$_4$ (0.32 mL, 1.07 mmol) was added to an ethanolic solution of methylamine (8 M, 0.25 mL, 2.00 mmol). Then ketone **21** (99 mg, 0.53 mmol) and 4 Å molecular sieves were added. After stirring at room temp. for 63 h, $NaBH_4$ (22 mg, 0.57 mmol) was added and stirring was continued for 24 h. H_2O was added and the precipitate was filtered off and washed with H_2O and Et_2O. The organic layer of the filtrate was separated and the aqueous layer was extracted with Et_2O (2 × 25 mL). The Et_2O layer was extracted with dilute HCl (2 × 30 mL). Then solid NaOH was added to the aqueous layer and it was extracted with Et_2O (3 × 30 mL). The combined Et_2O layers were dried (Na_2SO_4), concentrated in vacuo, and the residue (87 mg) was purified by FC (2 cm, ethyl acetate/ethanol = 1:1, 2.5 mL, R_f = 0.26). Colorless, viscous oil, yield 69 mg (65%). The residue was dissolved in ethyl acetate and **23**·HCl was formed by addition of a solution of HCl in Et_2O. **23**·HCl: Colorless solid, decomposed at >275 °C. **23**·HCl: IR: $\tilde{\nu}$ = 3029 ($\nu_{C-H\ arom.}$), 2937 ($\nu_{C-H\ aliph.}$), 2705 (ν_{H-N^+}), 1074 (ν_{C-O-C}), 733 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. **23**: ^{1}H NMR ($CDCl_3$): δ = 0.96 (qd, *J* = 12.9, 4.6 Hz, 1 H, 7-H_{ax}), 1.03 (s, 1 H, N*H*), 1.68–1.76 (m, 2 H, 7-H_{eq}, 8-H_{eq}), 2.08 (tt, *J* = 13.4, 5.3 Hz, 1 H, 8-H_{ax}), 2.54 (s, 3 H, NC*H*$_3$), 2.56 (d, *J* = 17.4 Hz, 1 H, 10-$H_{ps.\ eq}$), 2.92 (td, *J* = 4.3, 12.2 Hz, 1 H, 6-H_{ax}), 3.32 (dd, *J* = 7.9, 17.4 Hz, 1 H, 10-$H_{ps.\ ax}$), 4.37 (dd, *J* = 7.9, 5.5 Hz, 1 H, 9-H), 4.90 (d, *J* = 4.3 Hz, 1 H, 5-H), 6.99–7.02 (m, 1 H, 4-H), 7.10–7.22 (m, 3 H, 1-H, 2-H, 3-H) ppm. **23**: ^{13}C NMR ($CDCl_3$): δ = 23.0 (1 C, C-7), 31.9 (1 C, C-10), 32.4 (1 C, C-8), 33.5 (1 C, N*C*H$_3$), 59.1 (1 C, C-6), 66.8 (1 C, C-9), 72.0 (1 C, C-5), 124.9, 126.9, 128.0 (3 C, C-1, C-2, C-3), 126.1 (1 C, C-4), 133.6, 134.8 (2 C, C-4a, C-10a) ppm. **23**: MS: (EI): *m*/*z* (%) = 203 (47) $[M]^+$, 91 (6) $[CH_2Ph]^+$, 57 (100) $[H_3CNHCHCH_2]^+$. **23**: $C_{13}H_{17}NO$ (203.28). **23**·HCl: $C_{13}H_{18}ClNO$ (239.74). **23**·HCl (239.74): calcd. C 65.13, H 7.57, N 5.84; found C 64.89, H 7.44, N 5.71.

(5*S*,6*S*,9*S*)-(–)-*N*-Methyl-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocycloocten-6-amine [(*S*,*S*,*S*)-23]: Compound (*S*,*S*,*S*)-**23** was prepared as described for (±)-**23**: Ketone (*S*,*S*)-**21** (100 mg, 0.53 mmol) was treated with Ti(O*i*Pr)$_4$ (0.32 mL, 1.01 mmol), an ethanolic solution of methylamine (8 M, 0.25 mL, 2.0 mmol), and $NaBH_4$ (24 mg, 0.64 mmol). Colorless oil that froze in the refrigerator as a colorless solid, m.p. 50 °C, yield 70 mg (65%). (*S*,*S*,*S*)-**23**·HCl: Colorless solid, decomposed at >270 °C. (*S*,*S*,*S*)-**23**·HCl: $[\alpha]_{589}$ = –40.8 (*c* = 2.5 mg/mL, CH_3OH, *T* = 24 °C). (*S*,*S*,*S*)-**23**·HCl (239.74): calcd C 65.13, H 7.57, N 5.84; found C 65.10, H 7.47, N 5.57.

(5*R*,6*R*,9*R*)-(+)-*N*-Methyl-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocycloocten-6-amine [(*R*,*R*,*R*)-23]: Compound (*R*,*R*,*R*)-**23** was prepared as described for (±)-**23**: Ketone (*R*,*R*)-**21** (100 mg, 0.53 mmol) was treated with Ti(O*i*Pr)$_4$ (0.32 mL, 1.01 mmol), an ethanolic solution of methylamine (8 M, 0.25 mL, 2.0 mmol), and $NaBH_4$ (27 mg, 0.71 mmol). Colorless oil that froze in the refrigerator as a colorless solid, m.p. 53 °C, yield 92 mg (68%). (*S*,*S*,*S*)-**23**·HCl: Colorless solid, decomposed at >275 °C. (*R*,*R*,*R*)-**23**·HCl: $[\alpha]_{589}$ = +41.2 (*c* = 2.6 mg/mL, CH_3OH, *T* = 24 °C). (*R*,*R*,*R*)-**23**·HCl (239.74): calcd C 65.13, H 7.57, N 5.84; found C 65.07, H 7.55, N 5.64.

(5*RS*,6*RS*,9*RS*)-(±)-*N*,*N*-Dimethyl-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocycloocten-6-amine (24): Ti(O*i*Pr)$_4$ (0.32 mL, 1.07 mmol) was added to an ethanolic solution of dimethylamine (5.6 M, 0.38 mL, 2.13 mmol). Then ketone **21** (102 mg, 0.54 mmol) and 4 Å molecular sieves were added. After stirring at room temp. for 63 h, $NaBH_4$ (21 mg, 0.55 mmol) was added and stirring was continued

for 23 h. H_2O was added and the precipitate was filtered off and washed with H_2O and Et_2O. The organic layer of the filtrate was separated and the aqueous layer was extracted with Et_2O (2 × 25 mL). The Et_2O layer was extracted with dilute HCl (2 × 30 mL). Then solid NaOH was added to the aqueous layer and it was extracted with Et_2O (3 × 30 mL). The combined Et_2O layers were dried (Na_2SO_4) and concentrated in vacuo. Colorless oil that froze in the refrigerator as a colorless solid, m.p. 50 °C, yield 81 mg (69%). The residue was dissolved in ethyl acetate and **24**·HCl was formed by addition of a solution of HCl in Et_2O. **24**·HCl: Colorless solid, decomposed at >215 °C. **24**·HCl: IR (KBr): $\tilde{\nu}$ = 2947 ($\nu_{C-H\ aliph.}$), 2462 (ν_{H-N^+}), 1636 (δ_{N-H}), 1070 (ν_{C-O-C}), 744 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. **24**: ^1H NMR ($CDCl_3$): δ = 1.19 (qd, J = 12.9, 4.7 Hz, 1 H, 7-H_{ax}), 1.67–1.77 (m, 2 H, 7-H_{eq}, 8-H_{eq}), 2.06 (tt, J = 13.2, 4.9 Hz, 1 H, 8-H_{ax}), 2.26 [s, 6 H, N(CH_3)$_2$], 2.54 (dt, J = 12.5, 3.8 Hz, 1 H, 6-H), 2.56 (d, J = 17.4 Hz, 1 H, 10-$H_{ps.\ eq}$), 3.33 (dd, J = 17.4, 7.9 Hz, 1 H, 10-$H_{ps.\ ax}$), 4.35 (br. dd, J = 7.9, 5.2 Hz, 1 H, 9-H), 4.97 (d, J = 4.0 Hz, 1 H, 5-H), 7.07–7.20 (m, 4 H, arom.) ppm. **24**: ^{13}C NMR ($CDCl_3$): δ = 20.1 (1 C, C-7), 32.3 (1 C, C-10), 32.4 (1 C, C-8), 43.3 [2 C, N(CH_3)$_2$], 66.1 (1 C, C-6), 66.6 (1 C, C-9), 71.4 (1 C, C-5), 124.7, 126.5, 127.5, 127.7 (4 C, C-1, C-2, C-3, C-4), 134.2, 134.8 (2 C, C-4a, C-10a) ppm. **24**: MS: (EI): m/z (%) = 217 (81) $[M]^+$, 84 (49) $[Me_2NCH(CH)CH_2]^+$, 71 (100) $[Me_2NCHCH_2]^+$. **24**: MS: (CI, NH_3): m/z = 218 $[M + H]^+$. **24**: $C_{14}H_{19}NO$ (217.31). **24**·HCl: $C_{14}H_{20}ClNO$ (253.77). **24**·HCl (253.77): calcd. C 66.26, H 7.94, N 5.52; found C 66.03, H 7.98, N 5.37.

(5*S*,6*S*,9*S*)-(–)-*N*,*N*-Dimethyl-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocycloocten-6-amine [(*S*,*S*,*S*)-24]: Compound (*S*,*S*,*S*)-**24** was prepared as described for (±)-**24**: Ketone (*S*,*S*)-**21** (95 mg, 0.50 mmol) was treated with Ti(O*i*Pr)$_4$ (0.32 mL, 1.01 mmol), an ethanolic solution of dimethylamine (5.6 M, 0.38 mL, 2.13 mmol), and $NaBH_4$ (22 mg, 0.59 mmol). Colorless oil that froze in the refrigerator as a colorless solid, m.p. 40 °C, yield 79 mg (72%). (*S*,*S*,*S*)-**24**·HCl: Colorless solid, decomposed at >235 °C. (*S*,*S*,*S*)-**24**·HCl: $[\alpha]_{589}$ = –40.4 (c = 2.6 mg/mL, CH_3OH, T = 25 °C). (*S*,*S*,*S*)-**24**·HCl (253.77): calcd. C 66.26, H 7.94, N 5.52; found C 66.36, H 7.99, N 5.29.

(5*R*,6*R*,9*R*)-(+)-*N*,*N*-Dimethyl-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocycloocten-6-amine [(*R*,*R*,*R*)-24]: Compound (*R*,*R*,*R*)-**24** was prepared as described for (±)-**24**: Ketone (*R*,*R*)-**21** (102 mg, 0.54 mmol) was treated with Ti(O*i*Pr)$_4$ (0.32 mL, 1.01 mmol), an ethanolic solution of dimethylamine (5.6 M, 0.38 mL, 2.13 mmol), and $NaBH_4$ (24 mg, 0.63 mmol). Colorless oil that froze in the refrigerator as a colorless solid, m.p. 40 °C, yield 92 mg (78%). (*R*,*R*,*R*)-**24**·HCl: Colorless solid, decomposed at >250 °C. (*R*,*R*,*R*)-**24**·HCl: $[\alpha]_{589}$ = +39.4 (c = 2.6 mg/mL, CH_3OH, T = 25 °C). (*S*,*S*,*S*)-**24**·HCl (253.77): calcd. C 66.26, H 7.94, N 5.52; found C 66.02, H 8.09, N 5.44.

(5*RS*,6*RS*,9*RS*)-(±)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocycloocten-6-ol (25): $NaBH_4$ (86 mg, 2.28 mmol) was added to a solution of ketone **21** (202 mg, 1.07 mmol) in methanol (10 mL) and the mixture was stirred at room temp. for 90 min. The mixture was concentrated in vacuo, the residue was dissolved in H_2O, and the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by FC (2 cm, petroleum ether/ethyl acetate = 1:1, 2.5 mL, R_f = 0.47). Colorless solid, m.p. 122 °C, yield 187 mg (92%). IR: $\tilde{\nu}$ = 3231 (ν_{O-H}), 2930 ($\nu_{C-Haliph.}$), 1046 (ν_{C-O}), 765 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.15 (br. qd, J = 12.8, 4.5 Hz, 1 H, 7-H_{ax}), 1.69–1.81 (m, 2 H, 7-H_{eq}, 8-H_{eq}), 2.10 (tt, J = 13.9, 5.3 Hz, 1 H, 8-H_{ax}), 2.58 (d, J = 17.7 Hz, 1 H, 10-$H_{ps.\ eq}$), 3.35 (dd, J = 17.4, 7.9 Hz, 1 H, 10-$H_{ps.\ ax}$), 4.02 (dt, J = 11.6, 4.7 Hz, 1 H, 6-H), 4.35 (br. dd, J = 7.9, 4.9 Hz, 1 H, 9-H), 4.77 (d, J = 5.2 Hz, 1 H, 5-H), 7.08–7.26 (m, 4 H, arom.) ppm; a signal for the OH group was not detected. ^{13}C NMR ($CDCl_3$): δ = 25.6 (1 C, C-7), 31.8 (1 C, C-10), 32.0 (1 C, C-8), 66.4 (1 C, C-9), 69.1 (1 C, C-6), 73.6 (1 C, C-5), 125.1, 127.0, 127.3, 128.1 (4 C, C-1, C-2, C-3, C-4), 132.7, 134.9 (2 C, C-4a, C-10a) ppm. MS (EI): m/z (%) = 190 (100) $[M]^+$, 172 (78) $[M - H_2O]^+$, 145 (66) $[M - HOCHCH_2 - H]^+$, 131 (94) [benzopyrylium]$^+$, 91 (22) $[CH_2Ph]^+$. $C_{12}H_{14}O_2$ (190.25): calcd. C 75.76, H 7.42; found C 75.71, H 7.64.

(5*S*,6*S*,9*S*)-(–)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocycloocten-6-ol [(*S*,*S*,*S*)-25]: Compound (*S*,*S*,*S*)-**25** was prepared as described for (±)-**25**: Ketone (*S*,*S*)-**21** (222 mg, 1.18 mmol) was treated with $NaBH_4$ (182 mg, 4.82 mmol) in methanol (4 mL). Colorless solid, m.p. 158 °C, yield 193 mg (86%). $[\alpha]_{589}$ = –71.8 (c = 4.7 mg/mL, CH_3OH). $C_{12}H_{14}O_2$ (190.25): calcd. C 75.76, H 7.42; found C 75.50, H 7.25.

(5*R*,6*R*,9*R*)-(+)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocycloocten-6-ol [(*R*,*R*,*R*)-25]: Compound (*R*,*R*,*R*)-**25** was prepared as described for (±)-**25**: Ketone (*R*,*R*)-**21** (43 mg, 0.23 mmol) was treated with $NaBH_4$ (34 mg, 0.90 mmol) in methanol (3 mL). Colorless solid, m.p. 155 °C, yield 41 mg (95%). $[\alpha]_{589}$ = +71.7 (c = 4.6 mg/mL, CH_3OH). $C_{12}H_{14}O_2$ (190.25): calcd. C 75.76, H 7.42; found C 75.21, H 7.51.

(±)-[(5*RS*,6*RS*,9*RS*)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocycloocten-6-yl] 4-Methylbenzenesulfonate (26a): *p*-Toluenesulfonyl chloride (301 mg, 1.58 mmol), NEt_3 (0.35 mL, 2.52 mmol), and 4-(dimethylamino)pyridine (209 mg, 1.71 mmol) were added to a solution of alcohol **25** (49 mg, 0.26 mmol) in CH_2Cl_2 (10 mL). After stirring at room temp. for 60 min, the mixture was diluted with Et_2O and washed with 0.5 M HCl (2 × 25 mL) and 0.5 M NaOH (25 mL). The organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by FC (2 cm, petroleum ether/ethyl acetate = 5:1, 2.5 mL, R_f = 0.32). Colorless solid, m.p. 116 °C, yield 64 mg (72%). IR: $\tilde{\nu}$ = 3032 ($\nu_{C-H\ arom.}$), 2953, 2918 ($\nu_{C-H\ aliph.}$), 1352, 1176 (δ_{SO_2}), 767 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.47 (br. qd, J = 12.4, 4.9 Hz, 1 H, 7-H_{ax}), 1.61–1.73 (m, 2 H, 7-H_{eq}, 8-H_{eq}), 2.05 (tt, J = 13.9, 5.3 Hz, 1 H, 8-H_{ax}), 2.44 (s, 3 H, Ar-CH_3), 2.54 (d, J = 17.7 Hz, 1 H, 10-$H_{ps.\ eq}$), 3.32 (dd, J = 17.7, 7.9 Hz, 1 H, 10-$H_{ps.\ ax}$), 4.30 (dd, J = 7.9, 5.5 Hz, 1 H, 9-H), 4.79 (dt, J = 11.4, 4.7 Hz, 1 H, 6-H_{ax}), 4.84 (d, J = 4.6 Hz, 1 H, 5-H), 7.13–7.27 (m, 4 H, 1-H, 2-H, 3-H, 4-H), 7.35 (d, J = 8.2 Hz, 2 H, 3′-H, 5′-H), 7.82 (d, J = 8.5 Hz, 2 H, 2′-H, 6′-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.6 (1 C, Ar-CH_3), 22.6 (1 C, C-7), 31.5 (1 C, C-10), 31.8 (1 C, C-8), 66.4 (1 C, C-9), 70.8 (1 C, C-5), 78.0 (1 C, C-6), 125.3, 127.5, 127.8, 128.0 (4 C, C-1, C-2, C-3, C-4), 127.7 (2 C, C-2′, C-6′), 129.9 (2 C, C-3′, C-5′), 131.5, 134.0 (2 C, C-4a, C-10a), 134.1 (1 C, C-4′), 144.8 (1 C, C-1′) ppm. MS (EI): m/z (%) = 212 (29) $[CH_2CH_2CHOTos]^+$, 155 (63) $[CH_3C_4H_4SO_2]^+$, 91 (100) $[CH_2Ph]^+$. MS (CI, NH_3): m/z = 362 $[M + H + NH_3]^+$. $C_{19}H_{20}O_4S$ (344.43): calcd. C 66.26, H 5.85, S 9.31; found C 65.86, H 5.92, S 9.19.

(±)-[(5*RS*,6*RS*,9*RS*)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocycloocten-6-yl] Methanesulfonate (26b): NEt_3 (0.6 mL, 4.33 mmol) and methanesulfonyl chloride (200 μL, 2.58 mmol) were added to a solution of alcohol **25** (201 mg, 1.05 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at 0 °C for 60 min. Then the solvent was removed in vacuo and the residue was purified by FC (2 cm, petroleum ether/ethyl acetate = 2:1, 2.5 mL, R_f = 0.30). Colorless oil that froze in the refrigerator, m.p. 105 °C, yield 282 mg (97%). IR: $\tilde{\nu}$ = 3010 ($\nu_{C-H\ arom.}$), 2965, 2930 ($\nu_{C-Haliph.}$), 1352, 1172 (δ_{SO_2}), 761 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.58 (dddd, J =

13.7, 12.5, 11.4, 4.6 Hz, 1 H, 7-H_{ax}), 1.69–1.81 (m, 2 H, 7-H_{eq}, 8-H_{eq}), 2.19 (tt, J = 13.9, 5.7 Hz, 1 H, 8-H_{ax}), 2.60 (d, J = 17.7 Hz, 1 H, 10-$H_{ps.\ eq}$), 3.03 (s, 3 H, SO_2CH_3), 3.37 (dd, J = 17.4, 7.9 Hz, 1 H, 10-$H_{ps.\ ax}$), 4.37 (dd, J = 7.9, 5.5 Hz, 1 H, 9-H), 5.00 (d, J = 4.6 Hz, 1 H, 5-H), 5.04 (dt, J = 11.3, 4.3 Hz, 1 H, 6-H_{ax}), 7.13–7.27 (m, 4 H, arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.9 (1 C, C-7), 31.6 (1 C, C-10), 31.8 (1 C, C-8), 38.6 (1 C, SO_2CH_3), 66.4 (1 C, C-9), 71.1 (1 C, C-5), 77.3 (1 C, C-6), 125.3, 127.6, 127.88, 127.91 (4 C, C-1, C-2, C-3, C-4), 131.6, 134.3 (2 C, C-4a, C-10a) ppm. MS (EI): m/z (%) = 268 (26) $[M]^+$, 189 (54) $[M - CH_3 - SO_2]^+$, 129 (100) $[C_6H_4CH{=}CHCH{=}CH_2]^+$, 91 (17) $[CH_2Ph]^+$. $C_{13}H_{16}O_4S$ (268.33): calcd. C 58.19, H 6.01, S 11.95; found C 58.36, H 6.11, S 11.71.

(–)-[(5*S*,6*S*,9*S*)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocyclooctenyl-6-yl] Methanesulfonate [(*S*,*S*,*S*)-26b]: Compound (*S*,*S*,*S*)-**26b** was prepared as described for (±)-**26b**: Alcohol (*S*,*S*,*S*)-**25** (520 mg, 2.73 mmol) was treated with NEt_3 (1.5 mL, 10.8 mmol) and methanesulfonyl chloride (0.6 mL, 7.89 mmol) in CH_2Cl_2 (20 mL). Colorless oil, yield 710 mg (97%). $[\alpha]_{589}$ = –107.7 (c = 3.25 mg/mL, CH_3OH, T = 24 °C).

(+)-[(5*R*,6*R*,9*R*)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocyclooctenyl-6-yl] Methanesulfonate [(*R*,*R*,*R*)-26b]: Compound (*R*,*R*,*R*)-**26b** was prepared as described for (±)-**26b**: Alcohol (*R*,*R*,*R*)-**25** (700 mg, 3.68 mmol) was treated with NEt_3 (2.0 mL, 14.7 mmol) and methanesulfonyl chloride (0.42 mL, 5.52 mmol) in CH_2Cl_2 (20 mL). Colorless oil, yield 977 mg (99%). $[\alpha]_{589}$ = +104.9 (c = 3.25 mg/mL, CH_3OH, T = 24 °C).

(5*RS*,6*SR*,9*RS*)-(±)-6-Azido-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocyclooctene (27): NaN_3 (5.79 g, 89.1 mmol) was added to a solution of mesylate **26b** (0.84 g, 3.15 mmol) in DMF (40 mL). After sonification for 5 min, the suspension was heated at reflux for 38 h. Then H_2O (40 mL) was added, the mixture was extracted with Et_2O (5 × 50 mL), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo, and the residue was purified by FC (3 cm, petroleum ether/ethyl acetate = 30:1, 7.5 mL, R_f = 0.19). In addition to the azide **27**, alcohol **25** (182 mg, 30%, petroleum ether/ethyl acetate = 1:1, R_f = 0.47) was isolated. Colorless oil, yield 332 mg (49%). IR: $\tilde{\nu}$ = 3024 ($\nu_{C-H\ arom.}$), 2934 ($\nu_{C-H\ aliph.}$), 2090 ($\nu_{N3\ sym.}$), 1098 (ν_{C-O-C}), 763 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.45–1.52 (m, 1 H, 8-H_{eq}), 1.60–1.78 (m, 2 H, 7-H_{eq}, 7-H_{ax}), 2.38 (tt, J = 13.0, 6.4 Hz, 1 H, 8-H_{ax}), 2.61 (d, J = 17.7 Hz, 1 H, 10-$H_{ps.\ eq}$), 3.42 (dd, J = 17.7, 7.9 Hz, 1 H, 10-$H_{ps.\ ax}$), 3.52 (m, 1 H, 6-H), 4.46 (br. t, J = 6.6 Hz, 1 H, 9-H), 4.83 (s, 1 H, 5-H), 6.97–7.00 (m, 1 H, 4-H), 7.13–7.24 (m, 3 H, 1-H, 2-H, 3-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.4 (1 C, C-7), 26.7 (1 C, C-8), 31.5 (1 C, C-10), 60.2 (1 C, C-6), 67.0 (1 C, C-9), 72.2 (1 C, C-5), 125.1 (1 C, C-4), 125.8, 127.3, 128.5 (3 C, C-1, C-2, C-3), 134.4, 135.0 (2 C, C-4a, C-10a) ppm. MS (EI): m/z (%) = 144 (32) $[M - N_3CHCH_2 - 2H]^+$, 131 (100) [benzopyrylium]$^+$, 104 (31) $[PhCH{=}CH_2]^+$, 91 (29) $[CH_2Ph]^+$. MS (CI, NH_3): m/z = 233 $[M + H + NH_3]^+$, 188 $[M - N_2, + H]^+$. $C_{12}H_{13}N_3O$ (215.25): calcd. C 66.96, H 6.09, N 19.52; found C 66.94, H 6.25, N 19.26.

(5*S*,6*R*,9*S*)-(–)-6-Azido-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocyclooctene [(*S*,*R*,*S*)-27]: Azide (*S*,*R*,*S*)-**27** was prepared as described for (±)-**27**: Mesylate (*S*,*S*,*S*)-**26b** (710 mg, 2.65 mmol) was treated with NaN_3 (6.14 g, 94.5 mmol) in DMF (40 mL). Colorless oil that solidified in the refrigerator as a colorless solid, m.p. 53 °C, yield 203 mg (36%). $[\alpha]_{589}$ = –42.1 (c = 3.0 mg/mL, CH_3OH, T = 25 °C). In addition, (*S*,*S*,*S*)-**25** (159 mg, 31%, petroleum ether/ethyl acetate = 1:1, R_f = 0.47) was isolated.

(5*R*,6*S*,9*R*)-(+)-6-Azido-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocyclooctene [(*R*,*S*,*R*)-27]: Azide (*R*,*S*,*R*)-**27** was prepared as described for (±)-**27**: Mesylate (*R*,*R*,*R*)-**26b** (977 mg, 3.64 mmol) was treated with NaN_3 (7.0 g, 107.7 mmol) in DMF (40 mL). Colorless oil that solidified in the refrigerator as a colorless solid, m.p. 54 °C, yield 321 mg (41%). $[\alpha]_{589}$ = +42.8 (c = 3.0 mg/mL, CH_3OH, T = 25 °C). In addition, (*R*,*R*,*R*)-**25** (155 mg, 23%, petroleum ether/ethyl acetate = 1:1, R_f = 0.47) was isolated.

(5*RS*,6*SR*,9*RS*)-(±)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocyclooctene-6-amine (28): Ammonium formate (1.31 g, 20.8 mmol) and Pd/C (10%, 261 mg) were added to a solution of the azide **27** (442 mg, 2.05 mmol) in methanol (40 mL) and the mixture was heated at reflux for 4 h. After filtration the solvent was evaporated in vacuo and the residue (374 mg) was purified by FC (3 cm, ethyl acetate/ethanol = 1:5, 7.5 mL, R_f = 0.17). Colorless oil, yield 304 mg (78%). The residue was dissolved in ethyl acetate and **28**·HCl was formed by addition of a solution of HCl in Et_2O. **28**·HCl: Colorless solid, decomposed at >215 °C. **28**·HCl: IR: $\tilde{\nu}$ = 3389 (ν_{N-H}), 2933 ($\nu_{C-H\ aliph.}$), 1040 (ν_{C-O-C}), 738 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. **28**: ^{1}H NMR ($CDCl_3$): δ = 1.30–1.45 (m, 2 H, 7-H_{eq}, 8-H_{eq}), 1.60–1.72 (tt, J = 14.0, 4.3 Hz, 1 H, 7-H_{ax}), 2.26–2.39 (m, 3 H, 8-H_{ax}, NH_2), 2.56 (d, J = 17.4 Hz, 1 H, 10-$H_{ps.\ eq}$), 2.87 (m, 1 H, 6-H), 3.36 (dd, J = 17.4, 7.9 Hz, 1 H, 10-$H_{ps.\ ax}$), 4.38 (br. t, J = 6.8 Hz, 1 H, 9-H), 4.61 (s, 1 H, 5-H), 6.96–6.98 (m, 1 H, 4-H), 7.08–7.19 (m, 3 H, 1-H, 2-H, 3-H) ppm. **28**: ^{13}C NMR ($CDCl_3$): δ = 22.5 (1 C, C-7), 25.9 (1 C, C-8), 31.7 (1 C, C-10), 50.7 (1 C, C-6), 67.2 (1 C, C-9), 76.0 (1 C, C-5), 125.0 (1 C, C-4), 125.5, 126.6, 128.1 (3 C, C-1, C-2, C-3), 133.9, 137.0 (2 C, C-4a, C-10a) ppm. **28**: MS: (EI): m/z (%) = 189 (100) $[M]^+$, 172 (82) $[M - NH_3]^+$, 91 (22) $[CH_2Ph]^+$. **28**: $C_{12}H_{15}NO$ (189.26). **28**·HCl: $C_{12}H_{16}ClNO$ (225.72). **28**·HCl (225.72): calcd. C 63.86, H 7.14, N 6.21; found C 63.67, H 7.21, N 6.28.

(5*S*,6*R*,9*S*)-(–)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocyclooctene-6-amine [(*S*,*R*,*S*)-28]: Compound (*S*,*R*,*S*)-**28** was prepared as described for (±)-**28**: Azide (*S*,*R*,*S*)-**27** (203 mg, 0.94 mmol) was treated with ammonium formate (0.62 g, 9.80 mmol) and Pd/C (10%, 127 mg) in methanol (30 mL). Colorless oil that solidified in the refrigerator as a colorless solid, m.p. 33 °C, yield 142 mg (80%). (*S*,*R*,*S*)-**28**·HCl: Colorless solid, decomposed at >230 °C. (*S*,*R*,*S*)-**28**·HCl: $[\alpha]_{589}$ = –7.2 (c = 2.65 mg/mL, CH_3OH, T = 23 °C). (*S*,*R*,*S*)-**28**·HCl (225.72): calcd. C 63.86, H 7.14, N 6.21; found C 63.64, H 7.25, N 6.06.

(5*R*,6*S*,9*R*)-(+)-5,6,7,8,9,10-Hexahydro-5,9-epoxybenzocyclooctene-6-amine [(*R*,*S*,*R*)-28]: Compound (*R*,*S*,*R*)-**28** was prepared as described for (±)-**28**: Azide (*R*,*S*,*R*)-**27** (322 mg, 1.49 mmol) was treated with ammonium formate (0.96 g, 15.2 mmol) and Pd/C (10%, 187 mg) in methanol (30 mL). Colorless oil that solidified in the refrigerator as a colorless solid, m.p. 35 °C, yield 244 mg (91%). (*R*,*S*,*R*)-**28**·HCl: Colorless solid, decomposed at >230 °C. (*R*,*S*,*R*)-**28**·HCl: $[\alpha]_{589}$ = +6.8 (c = 3.25 mg/mL, CH_3OH, T = 23 °C). (*R*,*S*,*R*)-**28**·HCl (225.72): calcd. C 63.86, H 7.14, N 6.21; found C 64.08, H 7.21, N 6.12.

(5*RS*,6*SR*,9*RS*)-(±)-*N*,*N*-Dimethyl-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocyclooctene-6-amine (29): A solution of formaldehyde in water (formalin 37%, 1.3 mL, 16.7 mmol) and $NaBH_3CN$ (145 mg, 2.31 mmol) were added to a solution of primary amine **28** (100 mg, 0.53 mmol) in acetonitrile (5 mL) and the mixture was stirred at room temp. for 24 h. Then 1 M NaOH (10 mL) was added, the mixture was extracted with Et_2O (3 × 20 mL), the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo, and the residue (130 mg) was purified by FC (2 cm, ethyl acetate/ethanol = 1:5, 2.5 mL, R_f = 0.19). Colorless oil, yield 92 mg (80%). The residue was dissolved in ethyl acetate and **29**·HCl was formed by addition of a solution of HCl in Et_2O. **29**·HCl: Colorless solid, decomposed at >220 °C. **29**·HCl: IR: $\tilde{\nu}$ = 2944 ($\nu_{C-Haliph.}$), 2667 (ν_{H-N^+}), 1157

(ν_{C-O-C}), 754 ($\gamma_{1,2\text{-disubst. arom.}}$) cm^{-1}. **29**: ^1H NMR ($CDCl_3$): δ = 1.30–1.38 (m, 1 H, 8-H_{eq}), 1.53 (ddt, J = 14.5, 12.3, 4.3 Hz, 1 H, 7-H_{ax}), 1.70 (br. dq, J = 14.4, 4.8 Hz, 1 H, 7 H_{eq}), 2.07 (td, J = 4.1, 1.7 Hz, 1 H, 6-H_{eq}), 2.29 (tt, J = 12.2, 6.1 Hz, 1 H, 8-H_{ax}), 2.46 [s, 6 H, N(CH_3)$_2$], 2.56 (d, J = 17.2 Hz, 1 H, 10-$H_{ps.\ eq}$), 3.37 (dd, J = 17.2, 7.3 Hz, 1 H, 10-$H_{ps.\ ax}$), 4.45 (td, J = 6.8, 2.4 Hz, 1 H, 9-H), 4.97 (br. s, 1 H, 5-H), 6.94–6.96 (m, 1 H, 4-H), 7.10–7.19 (m, 3 H, 1-H, 2-H, 3-H) ppm. **29**: ^{13}C NMR ($CDCl_3$): δ = 17.8 (1 C, C-7), 26.5 (1 C, C-8), 32.4 (1 C, C-10), 43.4 [2 C, N(CH_3)$_2$], 65.8 (1 C, C-6), 66.8 (1 C, C-9), 70.6 (1 C, C-5), 125.0 (1 C, C-4), 125.4, 126.4, 128.5 (3 C, C-1, C-2, C-3), 134.1, 138.0 (2 C, C-4a, C-10a) ppm. **29**: MS: (EI): m/z (%) = 217 (49) $[M]^+$, 84 (57) $[Me_2NCH(CH)CH_2]^+$, 71 (100) $[Me_2NCHCH_2]^+$. **29**: HRMS: calcd. 217.1467; found 217.1468. **29**: $C_{14}H_{19}NO$ (217.31). **29**·HCl: $C_{14}H_{20}ClNO$ (253.77). **29**·HCl (253.77): calcd. C 66.26, H 7.94, N 5.52; found C 66.01, H 8.10, N 5.58.

(5*S*,6*R*,9*S*)-(–)-*N*,*N*-Dimethyl-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocycloocten-6-amine [(*S*,*R*,*S*)-29]: Compound (*S*,*R*,*S*)-**29** was prepared as described for (±)-**29**: Amine (*S*,*R*,*S*)-**28** (106 mg, 0.56 mmol) was treated with formalin (37%, 1.3 mL, 16.7 mmol) and $NaBH_3CN$ (143 mg, 2.23 mmol) in acetonitrile (10 mL). Colorless oil, yield 82 mg (68%). (*S*,*R*,*S*)-**29**·HCl: Colorless solid, decomposed at >220 °C. (*S*,*R*,*S*)-**29**·HCl: $[a]_{589}$ = –30.4 (c = 2.7 mg/mL, CH_3OH, T = 23 °C). (*S*,*R*,*S*)-**29**·HCl (253.77): calcd. C 66.26, H 7.94, N 5.52; found C 66.35, H 8.03, N 5.44.

(5*R*,6*S*,9*R*)-(+)-*N*,*N*-Dimethyl-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocycloocten-6-amine [(*R*,*S*,*R*)-29]: Compound (*R*,*S*,*R*)-**29** was prepared as described for (±)-**29**: Amine (*R*,*S*,*R*)-**28** (168 mg, 0.89 mmol) was treated with formalin (37%, 2.1 mL, 26.9 mmol) and $NaBH_3CN$ (224 mg, 3.5 mmol) in acetonitrile (10 mL). Colorless oil, yield 126 mg (65%). (*R*,*S*,*R*)-**29**·HCl: Colorless solid, decomposed at >220 °C. (*R*,*S*,*R*)-**29**·HCl: $[a]_{589}$ = +30.3 (c = 2.65 mg/mL, CH_3OH, T = 23 °C). (*S*,*R*,*S*)-**29**·HCl (253.77): calcd. C 66.26, H 7.94, N 5.52; found C 66.34, H 7.90, N 5.52.

Receptor Binding Studies

σ_1 Assay:[25] In the σ_1 assay, membrane preparations from guinea pig brains were used as receptor material and (+)-[^{3}H]pentazocine was employed as radioligand.

σ_2 Assay:[25] In the σ_2 assay, membrane preparations from rat liver were used as receptor material and [^{3}H]bis(*o*-tolyl)guanidine was employed as radioligand. σ_1 receptors were saturated with an excess of (+)-pentazocine.

NMDA Assay:[26] To investigate the affinity towards the phencyclidine binding site of the NMDA receptor, membrane preparations obtained from pig brain cortex served as receptor material and (+)-[^{3}H]MK-801 as radioligand.

κ Assay:[27] Guinea pig brain membrane preparations were used as receptor material and [^{3}H]U-69593 was the radioligand in the κ assay.

μ Assay:[27] In the μ assay, the same membrane preparation as for the κ assay obtained from guinea pig brains was employed as receptor material. The μ assay was performed with the peptidic radioligand [^{3}H]DAMGO in the presence of the peptidase inhibitor phenylmethanesufonyl chloride.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra as well as some 2D spectra.

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