Biocatalytic Deracemization of 1,4-Benzodiazepines in the Synthesis of Enantiomerically Pure Serine

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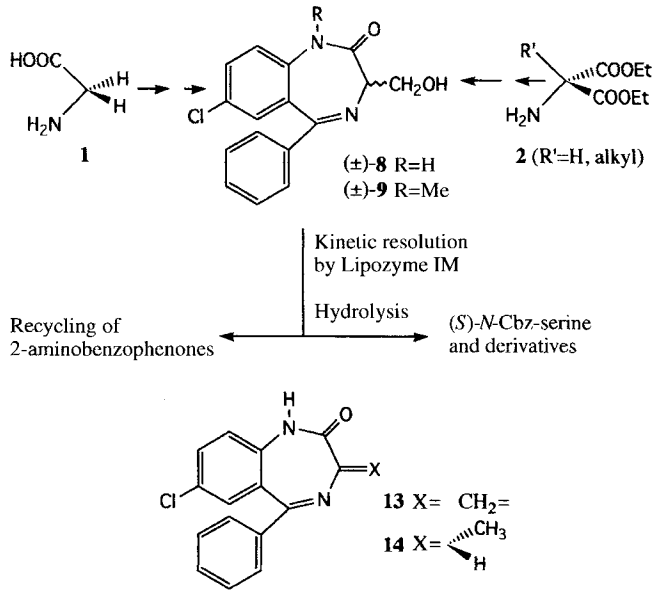
An efficient stereocontrolled synthesis of (*S*)-*N*-Cbz-serine (Cbz = benzyloxycarbonyl; **12**) and of its (*R*)-enantiomer is reported. Kinetic resolution of the easily available racemic 3-(hydroxymethyl)-1,4-benzodiazepin-2-ones is performed in the key step *via* acetylation by the immobilized *Mucor miehei* lipase (*Lipozyme IM*) at 60°. This method is characterized by high enantiomer purity (ee's ≥ 99%) of the intermediary alcohols (+)-**8** and (+)-**9** and acetates (−)-**10** and (−)-**11**, as well as of the final products (*S*)- and (*R*)-*N*-Cbz-serine, simple recycling of the biocatalyst, complete recovery of 2-aminobenzophenones (**3** and **4**) and their recycling into production of 1,4-benzodiazepines, and possibility to selectively racemize 'wrong' enantiomers of the alcohols **8** and **9** in the presence of *Amberlite CG 400*.

1. Introduction. – 1,4-Benzodiazepines enjoy a privileged structure status, with derivatives shown to have activity against a wide range of therapeutical targets. They are of general interest as central nervous system (CNS) active drugs [1], some derivatives are shown to possess anticancer [2] and antiviral activity [3]. Effective combinatorial synthesis of the libraries of these biologically active compounds has, therefore, been developed [4]. Peculiarity of the structure of 1,4-benzodiazepines resides in the glycine subunit incorporated *via* an amide and azomethine bond into conformationally rigid, nonplanar seven-membered ring. Because of their commercial availability in the ton-quantities and their specific structural and conformational features, we envisioned them as suitable precursors for the synthesis of enantiomerically pure α-amino acids and their congeners, based on their stereocontrolled functionalization at C(3)-atom. We have already reported one specific example of this concept for non-catalytic chirality transfer within 1,4-benzodiazepines [5]. Here, we report an efficient stereocontrolled approach to enantiomerically pure (*S*)- and (*R*)-serine, which is amenable to large-scale production of both enantiomers. (*S*)-Serine is cited in the recent US pharmacopeia [6], and, nowadays, used in parenteral nutriation as dietary supplement. It is starting material in the partial synthesis of unusual amino acids [7], of (*S*)- and (*R*)-prolinol derivatives [8], and in particular of new HIV protease inhibitors [9], whereas (*R*)-serine was used in the synthesis of 3-amino-β-lactam derivatives, the intermediates in preparation of the mimetics of HIV V3 loop [10], of some dipeptide mimetics [11], and recently in the combinatorial synthesis of the library of inhibitors of protein-DNA interactions. One congener of 3-(hydroxymethyl) derivatives described here exhibited therapeutically highly promising biological activity [4d].

Results and Discussion. – The approach outlined in *Scheme 1* is based on efficient synthesis and enzymatic kinetic resolution of racemic 3-(hydroxymethyl)-1,4-benzodi-

azepin-2-ones **8** and **9**. It is prompted by our previous studies of conformational and chiroptical (CD) properties of enantiomerically pure 3-substituted 1,4-benzodiazepines [12].

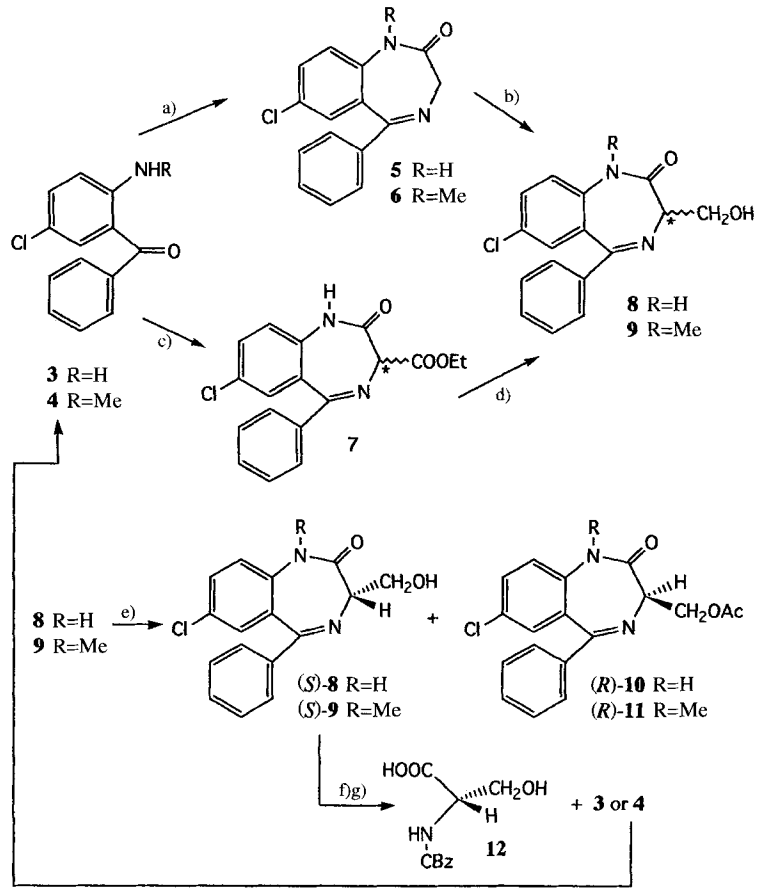
Scheme 1



In principle, enantioselective substitution of enantiotopic methylene protons in glycine (**1**), or elimination of the enantiotopic EtOCO groups in diethyl 2-alkyl-2-aminomalonate (**2**, R′ = alkyl), afford enantiomerically pure α-substituted amino acids. Only the first concept was developed to practical synthetic approach [13], whereas compounds **2** (R′ = alkyl) were decarboxylated to racemic α-amino acids [14]. It occurred to us that either precursor, **1** or **2**, could be used in preparation of racemic compounds **8** and **9** as the substrates for the enzyme-catalyzed kinetic resolution. Regioselective reduction of **7** by $NaBH_4$ afforded **8**, whereas formylation **6** by gaseous HCHO in the presence of LDA afforded **9**, both in high yields. In the resulting 3-(hydroxymethyl)-1,4-benzodiazepines, racemic serine is thus formally incorporated (*Scheme 2*).

Screening of 14 enzymes for acetylation of **8** and **9** by vinyl acetate revealed, as the only active one, the immobilized *Mucor miehei* lipase (Lipozyme IM, commercialized by *Novo Nordisk*), and to much less extent *Pseudomonas species* lipase. Lipozyme IM afforded acetates (−)-**10** and (−)-**11** in 76.0 and 76.5% ee, and alcohols (+)-**8** and (+)-**9** in 92.6 and 92.4% ee, respectively. After single crystallization from the appropriate solvent, (+)-**8** and (+)-**9**, and (−)-**10** and (−)-**11** were obtained with over 99% ee. All ee values were determined on chiral HPLC columns, selected on the basis of complete separation of the racemic compounds **8**–**11**. AcOEt was the solvent of choice, since it assured high activity of the enzyme and solubility of the substrates and products. *Fig. 1* shows conversion in the three most effective solvents. Conformational stability of the

Scheme 2



a) $ClCH_2COCl$/Py; hexylamine, EtOH/Δ. b) LDA/THF/$-70°$; formaldehyde/$-25°$. c) $HN_2CH(COOEt)_2$/Δ/solv. d) $NaBH_4$/THF, r.t. e) Lipozyme IM/AcOEt/60°. f) HCl/MeOH/H_2O/75°. g) Cbz/pH 9.8 – 10/5°.

substrates and chemical stability of *Lipozyme IM* at elevated temperature led to effective resolution after 5 h at 60°; at 30°, nearly the same conversion and ee values were achieved as after 30 h (*Fig. 2*).

It is interesting to note that non-immobilized *Mucor miehei* lipase did not show any acylating activity for racemic substrates **8** and **9**. Obviously, *Mucor miehei* immobilized on *Duolit 568*-phenol-formaldehyde-type resin, commercialized as *Lipozyme IM*, is activated for acceptance of the conformationally rigid, reactive enantiomers of **8** and **9**. This activation presumably resides in the conformational change of the enzyme, and could be compared to interfacial activation by micelles or drop-like lipids [15]. As demonstrated in recent crystallographic studies, in this latter case the interfacial activation is the consequence of the opening of closed, inactive form of an enzyme in organic solvents [16][17].

Comparison of the CD spectrum of (+)-**8**, which shows strong positive *Cotton* effect (exciton coupling) for the bands at *ca.* 260 and 240 nm ($\Delta\Delta\varepsilon$ + 35), and of (–)-**10**, which

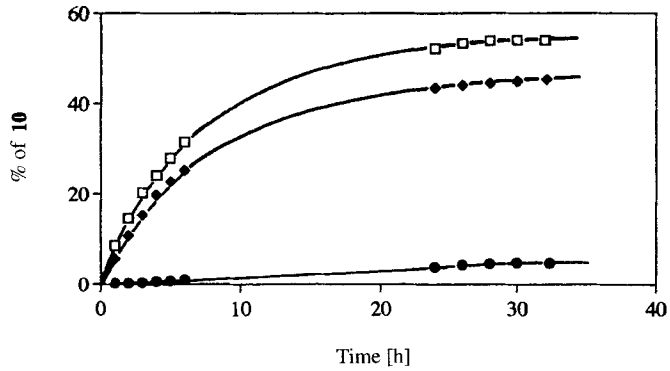


Fig. 1. *Solvent effect on the progress curves for acetylation of (±)-**8** by* Lypozyme IM. AcOEt: –□–□–□–, CH_2Cl_2: –◆–◆–◆–, THF: –●–●–●–.

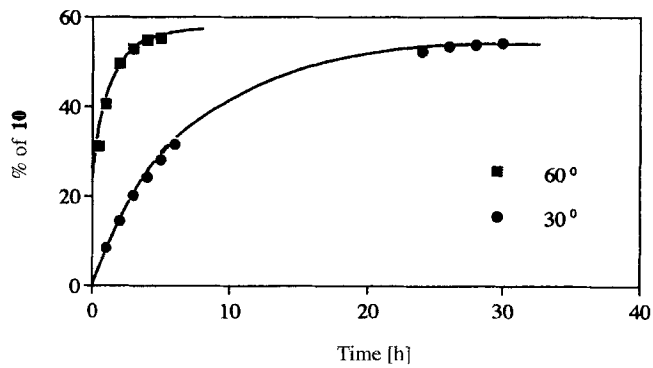


Fig. 2. *Temperature effect on the progress curves for acetylation of (±)-**8** by* Lipozyme IM

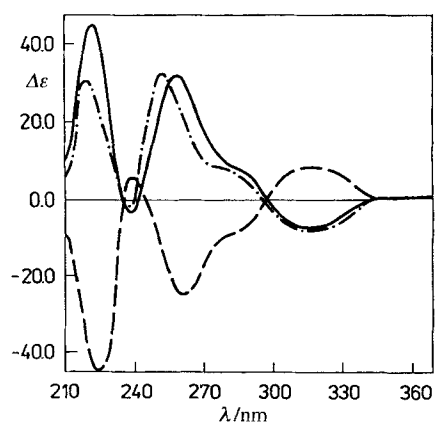
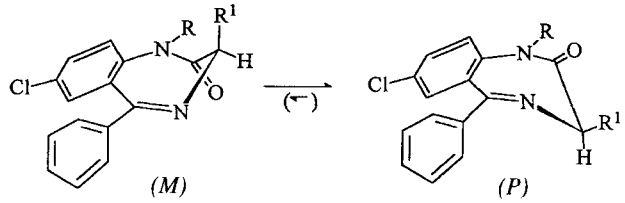


Fig. 3. *CD Spectra of (+)-**8** (———), (–)-**10** (– – – –), and (+)-(S)-**14** (– · – · – ·)*

shows a nearly mirror-image CD curve to that of (+)-**8** and to that of (3*S*)-**14**, derived from (*S*)-alanine [12], revealed that (+)-**8** possesses the (3*S*)-configuration and acetate (−)-**10** the (3*R*)-configuration (*Fig. 3*). It is known that (*S*)-enantiomers of 3-substituted 1,4-benzodiazepines possess (*M*)-absolute conformation [12] (*Scheme 3*). CD Spectra thus revealed that stable (*P*)-conformer of (*R*)-**8** and (*R*)-**9** is preferred for acylation by the immobilized *Mucor miehei*.

Scheme 3



R = H, Me; R^1 = Me, Me_2CH, $PhCH_2$ *etc.*

After chromatographic separation of acetates (−)-**10** and (−)-**11** from alcohols (+)-**8** and (+)-**9**, and their subsequent hydrolysis, the isolation of (*S*)-serine in its *N*-protected form turned out to be particularly convenient in view of high solubility of the non-protected serine in H_2O (36 g/l at 20°) [14b]. Optically active compounds (+)-compounds (+)-(*S*)- and (+)-(*S*)-**9** are hydrolyzed under acidic conditions without any loss of optical purity, since ≥99% ee was found for the final product (+)-**12**. 2-Aminobenzophenones **3** and **4** are recovered in *ca.* 95% yield, and can be recycled into 1,4-benzodiazepines. *N*-Protecting benzyloxycarbonyl (Cbz) group is introduced according to the standard procedure [18], without isolation of crude(*S*)-serine, and optically pure (+)-**12** was isolated in *ca.* 70% overall yield from (±)-**8**.

Though both (*S*)- and (*R*)-serine are valuable products [4c][6–10], in the case that (*S*)-**8** and (*S*)-**9**, or (*R*)-**8** and (*R*)-**9** are regarded as the precursors of the 'wrong' enantiomer, they can be racemized by heating in AcOEt in the presence of *Amberlite CG 400*, and recycled into enzymatic kinetic resolution. Interestingly, less basic *Amberlite IRA-68* or Et_3N proved ineffective for racemization. This finding confirms high configurational stability of 3-substituted 1,4-benzodiazepines, though they could be regarded as vinylogous congeners of configurationally unstable imidazol-4-ones and oxazol-4-ones [14c][19]. One of the origins of higher configurational stability of 3-substituted 1,4-benzodiazepines presumably resides in their reluctance to adopt highly strained planar conformation in the enamide form. The above-mentioned, specific racemization conditions can be applied only to alcohols **8** and **9**, however, since, under the same conditions, acetyl derivative **10**, possessing a better leaving group, undergoes base-catalyzed elimination to the methylidene derivative **13**.

We have already shown that H–C(3) acidity of *N*(1)-α-phenylethyl analogue of **7** is high enough to assure fast H/D exchange at C(3), and we have also demonstrated complete retention of deuterium on reduction of ethoxycarbonyl group [5]. Thus, the stereocontrolled method reported here also represents an elegant entry to α-deuterated enantiomerically pure (*S*)- and (*R*)-serine.

In conclusion, we completed a simple and efficient stereocontrolled synthesis of both enantiomers of serine, starting from the easily available 1,4-benzodiazepines, comprising a high-yield *C*(3)-formylation, followed by the *Lipozyme-IM*-catalyzed kinetic resolution, recycling of the enzyme, recovery of 2-aminobenzophenone derivatives for production of 1,4-benzodiazepines, and isolation of optically pure *N*-CBz-serines. We are presently extending this method to preparation of therapeutically interesting congeners of 1,4-benzodiazepines and various non-natural α-amino acids.

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Experimental Part

General. HPLC: *HP 1050* chromatograph with *C18 RP* (*Supelco*, 250 × 4.6 mm) reverse phase column; separation was monitored by *HP 1050* UV detector set up at 254 nm and connected to *HP 3396A* integrator. The following chiral columns were used in this work: *Chiralcel OD-R* for separation of (±)-**8** and (±)-**10**, *Chiralpak AS* for separation of (±)-**9** and (±)-**11**, and *Chiralcel OD-H* for separation of (±)-**12**. Using these columns, ee values were determined for enantiomerically enriched compounds. M.p.: *Electrothermal* Apparatus, not corrected. Optical rotations: *Optical Activity AA-10* automatic polarimeter in a 1-dm cell; *c* in g/100 ml. IR: *Perkin-Elmer 297* spectrometer for KBr pellets. ^{1}H- and ^{13}C-NMR: *Varian Gemini XL 300* spectrometer for $CDCl_3$ solns., δ in ppm relative to TMS as internal reference, *J* in Hz.

Enzymes from the following microorganisms were screened for enzymatic acetylation: *Penicillium camemberti*, *Candida lipolytica*, *Humicola lanuginosa*, *Penicillium roqueforti*, *Pseudomonas* species, *Mucor javanicus*, *Geotrichum candidum*, *Rhizopus niveus*, *Rhizopus delemar*, *Aspergillus niger*, *Candida cylindracea*, *Rhizopus oryzae* (all from Amano), *Candida cylindracea* Type VII (from *Sigma*), *Candida cylindracea*, *Mucor miehei*, and *Pseudomonas fluorescens* (all from *Fluka*), *Mucor miehei*, Lipolase, Lipozyme IM (all from *Novo Nordisk*), and Palatase (from *Novo Ferment*).

1,4-Benzodiazepines **5**, **6**, and **7** were samples from *CRC*, *Compagnia di Ricerca Chimica*. All commercial reagents were used as received.

During usual workup, all org. extracts were dried over Na_2SO_4 or $MgSO_4$, and evaporated *in vacuo* on a *Büchi* rotavapor.

*(±)-7-Chloro-3-(hydroxymethyl)-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one* (**8**). Ethyl 7-chloro-2-oxo-5-phenyl-2,3-dihydro-1*H*-dihydro-1,4-benzodiazepine-3-carboxylate (1.0 g, 2.92 mmol) is dissolved in dry THF (10 ml), and, to the resulting soln., $NaBH_4$ (0.3 g, 7.9 mmol) was added. After 2.5 h, ice-water (30 ml) was added to the mixture, and resulting slurry was extracted by AcOEt (3 × 20 ml). Org. extracts were washed with H_2O (3 × 20 ml), and submitted to usual workup. Crude product was recrystallized from the solvent mixture MeOH/Et_2O/light petroleum affording crystalline **8** (0.66 g, 75.3%). M.p. 197–199°. IR: 1700, 1620, 1480, 1330, 700. ^{1}H-NMR: 3.07 (*s*, 1 H); 3.79 (*t*, *J* = 7.0, 1 H): 4.26 (*dd*, *J* = 1.5, 5.3, 1 H); 4.43 (*dd*, *J* = 11.5, 7.3, 1 H); 7.10–7.64 (*m*, 8 H); 9.78 (*s*, 1 H). ^{13}C-NMR: 62.44; 63.75; 122.74; 128.40; 128.81; 129.08; 129.69; 130.57; 130.81; 131.98; 136.55; 138.30, 169.27, 172.38. Anal. calc. for $C_{16}H_{13}ClN_2O_2$ (300.74): C 63.90, H 4.36, N 9.31; found: C 64.08, H 4.54, N 9.20.

*(±)-7-Chloro-3-(hydroxymethyl)-1-methyl-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one* (**9**). To the soln. of $(i\text{-}Pr)_2NH$ (0.84 ml, 6 mmol) in dry THF (8 ml), 2.5M soln. of BuLi (2.54 ml, 6 mmol) was added at 0°. After 30 min under N_2, the mixture was cooled to −78° (dry ice i-PrOH), and a soln. of **6** (1.0 g, 3.51 mmol) in THF (5.0 ml) was added by syringe. After 30 min, the mixture was warmed up to −25°, and dry HCOH, obtained by thermal decomposition of paraformaldehyde (0.29 g, 9.7 mmol), was bubbled by the N_2 stream. After 30 min, the reaction was quenched by addition of 10% aq. HCl (3 ml). The mixture was extracted by CH_2Cl_2 (3 × 15 ml), and, after usual workup, crude product was purified by FC (CH_2Cl_2/AcOEt 7:3): 0.77 g (69.7%) of **9**. Pale-yellow crystals. M.p. 112–115°. IR: 1750, 1680, 1480, 1330, 700. ^{1}H-NMR: 2.88 (*s*, 1 H); 3.41 (*s*, 3 H); 3.76 (*dd*, *J* = 7.3, 5.3, 1 H); 4.18–4.22 (*m*, 1 H); 4.42–4.46 (*m*, 1 H); 7.27–7.62 (*m*, 8 H). ^{13}C-NMR: 34.73; 62.94; 63.97; 122.74; 128.34; 128.40; 129.54; 129.77; 130.48; 130.81; 131.58; 137.80; 141.84; 168.20; 170.75. Anal. calc. for $C_{17}H_{15}ClN_2O_2$ (314.77): C 64.87, H 4.80, N 8.90; found: C 64.63, H 4.95, N 8.99.

*(±)-(7-Chloro-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl)methyl Acetate* (**10**). Alcohol **8** (75 mg, 0.25 mmol) was dissolved in DMF (3 ml), and, to this soln., pyridine (0.2 ml) and, after 10 min, AcCl (0.05 ml,

0.76 mmol) were added. After 2 h, the reaction was stopped by addition of H_2O (5 ml), and resulting slurry was extracted by AcOEt (3 × 10 ml). Org. layer was washed with H_2O (2 × 10 ml) and worked up. Crystallization of the crude product from $(i\text{-}Pr)_2NH$ afforded 78 mg (91.2%) of **10**. M.p. 157–160°. IR: 1750, 1690, 1440, 1230, 700. ^{1}H-NMR: 2.16 (*s*, 3 H); 3.88 (*t*, *J* = 6.5, 1 H); 4.82 (*dd*, *J* = 11.2, 6.5, 1 H); 4.94 (*dd*, *J* = 11.2, 6.6, 1 H); 7.16–7.53 (*m*, 8 H); 9.83 (*s*, 1 H). ^{13}C-NMR: 20.77; 61.77; 63.94; 122.97; 128.41; 128.66; 129.08; 129.72; 130.55; 130.81; 132.06; 136.70; 138.24; 169.00; 170.37; 171.04. Anal. calc. for $C_{18}H_{15}ClN_2O_3$ (342.78): C 63.07, H 4.41, N 8.17; found: C 63.12, H 4.30, N 8.31.

*(±)-(7-Chloro-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-1,4-benzodiazepin-3-yl)methyl Acetate* (**11**). Starting from **9** (75 mg, 0.24 mmol), and using the method described for **10**, crude **11** was obtained. Crystallization from $(i\text{-}Pr)_2NH$ afforded 76 mg (89.3%) of pure **11**. M.p. 205–207°. IR: 1750, 1685, 1250, 830, 700. ^{1}H-NMR: 2.08 (*s*, 3 H); 3.42 (*s*, 3 H); 3.87 (*t*, *J* = 6.5, 1 H); 4.82 (*dd*, *J* = 11.2, 6.5, 1 H); 4.94 (*dd*, *J* = 11.2, 7.0, 1 H); 7.31–7.62 (*m*, 8 H). ^{13}C-NMR: 20.74; 34.79; 61.91; 64.33; 122.88; 128.38; 128.66; 129.53; 129.80; 130.21; 130.81; 131.64; 137.70; 141.90; 167.87; 168.52; 170.93. Anal. calc. for $C_{19}H_{17}ClN_2O_3$ (356.81): C 63.96, H 4.80, N 7.58; found: C 63.74, H 4.92, N 7.52.

*Enantioselective Acetylation of (±)-***8**. Compound (±)-**8** (2.0 g, 6.64 mmol) and Lipozyme IM (4.0 g) were slurried in AcOEt (80 ml) and, at 30°, shaked at 225 rpm. The reaction was initiated by addition of vinyl acetate (10 ml). The samples (20 µl) were taken off over regular time intervals, filtered through *Teflon* filter, and analyzed by HPLC. The reaction was stopped after 16 h, when 60.1% conversion to 3-AcO derivative was reached, the catalyst was filtered off, and solvent evaporated to dryness. Crude product was purified by FC (CH_2Cl_2/AcOEt 7:3). On crystallization from THF/light petroleum, 670 mg (33.5%, ee 99%) of (+)-**8** in the form of colorless crystalls were obtained. M.p. 198–200°. $[\alpha]_D$ = + 310.7 (*c* = 0.90, THF). Compound (–)-(*R*)-**10** (990 mg, 43.4%, ee 97.8%) was isolated from crystallization from $(i\text{-}Pr)_2NH$ as colorless crystals. M.p. 156–158°. $[\alpha]_D$ = – 278.2 (*c* = 0.90, THF).

Effect of the Temperature on the Enantioselective Acetylation by Lipozyme IM. Using the same quantities of (±)-**8**, Lipozyme IM, acylating agent, and solvents as in the previous procedure, the reaction was performed over 5 h and stopped at 55.2% conversion. After usual workup and crystallization from THF/light petroleum, 634 mg (31.7%, ee 99%) of (+)-**8** were obtained. Compound (–)-**10** (935 mg, 41%, ee 97.6%) was isolated by crystallization from $(i\text{-}Pr)_2NH$.

*Enantioselective Acetylation of (±)-***9**. Using the same molar quantities and conditions as described for enzymatic acetylation of **8**, (±)-**9** was acylated for 20 h at 30° to reach, after 59.4% conversion, ≥99% ee of the remaining alcohol. Alcohol (+)-(*S*)-**9** (704 mg, 35.2%, ee 99%) was isolated as colorless crystalline substance. M.p. 113–115°. $[\alpha]_D$ = + 309.5 (*c* = 0.84, THF). Acetate (–)-(*R*)-**11** was isolated after two crystallizations from EtOH as colorless crystals (1.02 g, 45.0%, ee 99%). M.p. 204–206°. $[\alpha]_D$ = – 284.3 (*c* = 0.83, THF).

*(+)-(*S*)-*N*-(Benzyloxy)carbonyl)serine* (**12**) *Preparation from (+)-(*S*)-***8**. Alcohol (+)-(*S*)-**8** (0.5 g, 1.66 mmol) is dissolved in MeOH/conc. HCl/H_2O 3:3:0.5, and the mixture is warmed up to 70°. Hydrolysis is completed in 3 h, the solvent mixture was evaporated nearly to dryness, H_2O was added (5 ml), and pH adjusted to 9.8 by 2M NaOH. The product mixture was extracted by CH_2Cl_2 (3 × 10 ml), and, after usual workup, 2-amino-5-chlorobenzophenone (361 mg, 93.7%) was obtained. Aq. phase is placed into a reaction vessel equipped by a pH-meter, cooled to 5–8°, and benzyl chloroformate (0.3 ml, 2.16 mmol) was added in small portions over 6 h. The pH was maintained at 9.8–10 by addition of 1M NaOH. After 6 h, the mixture was warmed up to 12°, and, under stirring pH was adjusted to 10–10.5 in order to decompose *O*,*N*-bis(benzyloxycarbonyl)serine. Thereafter, the mixture was extracted by Et_2O (2 × 10 ml), aq. layer was separated, and AcOEt (10 ml) was added. Under vigorous stirring, the resulting emulsion was adjusted to pH 3 by addition of conc. HCl. Org. phase was separated, and aq. layer was extracted by AcOEt (2 × 10 ml). After usual workup of the extract, **12** (268 mg, 67.3%, ee 99%) was obtained. Colorless crystals. M.p. 117–119°. $[\alpha]_D$ = + 5.7 (*c* = 6.0, AcOH). IR: 3300, 1700, 1530, 1250, 1060, 700. ^{1}H-NMR ((D$_7$)DMF): 4.04 (*d*, *J* = 2.7, 2 H); 4.42–4.48 (*m*,1 H); 5.27 (*s*, 2 H); 7.33–7.57 (*m*, 5 H). ^{13}C-NMR ((D$_7$)DMF): 58.60; 63.71; 67.34; 129.42; 129.49; 130.09; 139.14; 158.16; 173.95. Anal. calc. for $C_{11}H_{13}NO_5$ (225.21): C 55.23, H 5.48, N 5.85; found: C 55.15, H 5.63, N 5.93.

*Preparation from (+)-(*S*)-***9**. Alcohol (+)-(*S*)-**9** (0.5 g, 1.59 mmol) was dissolved in MeOH/conc. HCl/H_2O 1:4:1, and the mixture was warmed up to 70–75°. Hydrolysis was completed in 9 h and followed by HPLC. From workup as described above, 5-chloro-2-(methylamino)benzophenone (356 mg, 94.2%) was obtained. Treatment of the aq. phase as described for (+)-(*S*)-**8** afforded (+)-(*S*)-**12** (245 mg, 64.5%, ee 99%). M.p. 117–119°. $[\alpha]_D$ = + 5.8 (*c* = 6.0, AcOH).

*7-Chloro-5-phenyl-3-methylidene-2,3-dihydro-1*H*-1,4-benzodiazepin-2-one* (**13**). Acetate (–)-**10** (0.32 g, 0.95 mmol, ee 78.9) and *Amberlite CG-400* (1.5 g, OH form) are slurried in AcOEt (30 ml) at 60–65° under magnetic stirring. After 24 h, reaction was stopped, *Amberlite CG-400* was filtered off, and solvent evaporated to

dryness. Crude product was purified by FC (CH_2Cl_2/AcOEt 8:2). From crystallization from $(i\text{-}Pr)_2NH$, 165 mg (61.3%) of **13** was obtained. Colorless crystals. M.p. 153–155°. IR: 1680, 1630, 1485, 1320, 700. ^{1}H-NMR ($CDCl_3$): 5.13 (*s*, 1 H); 5.40 (*s*, 1 H); 6.93–7.73 (*m*, 8 H); 9.62 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 108.49; 122.77; 128.05; 128.29; 128.41; 128.69; 129.83; 130.14; 130.69; 131.03; 132.00; 138.24; 147.42; 172.18. Anal. calc. for $C_{16}H_{11}ClN_2O$ (282.73): C 67.97, H 3.93, N 9.90; found: C 67.85, H 3.98, N 9.97.

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