Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 3205–3208

TETRAHEDRON: *ASYMMETRY*

Planar chiral indoles: synthesis and biological effects of the enantiomers

Birgit Ortner, Harald Hübner and Peter Gmeiner*

Department of Medicinal Chemistry, Emil Fischer Center, Friedrich-Alexander University, Schuhstrasse 19, D-91052 Erlangen, Germany

Received 26 November 2001; accepted 11 December 2001

Abstract—The paracyclophanyl triflates (*R*)-**4** and (*S*)-**4**, which were obtained from racemic precursors through enzymatic-kinetic resolution, could be employed as key intermediates for the synthesis of planar chiral [2.2](4,7)indoloparacyclophanes. Subjecting the double-layered test compounds (*R*)-**8** and (*S*)-**8** to in vitro ligand-binding experiments displayed stereoselective receptor recognition.

1. Introduction

Stereocontrolled recognition processes in chemistry, biochemistry and pharmacology have received much attention in modern drug discovery.[1] Due to the asymmetry of bioactive macromolecules including enzymes, G-protein coupled receptors, ion-channels and nucleic acids, the binding of chiral ligands and substrates proceeds stereoselectively. Thus, there is continuing interest in the development of drugs as single enantiomers. Astonishingly, structure–activity relationship studies are limited to drug candidates with central chirality. To the best of our knowledge, the ability of neuroreceptors to differentiate between planar chiral enantiomers such as paracyclophane, ferrocene or arene chromium(0) derivatives, which are receiving growing attention as valuable ligands for asymmetric catalysis,[2] has not been reported.

A few studies focusing on bioactive paracyclophanes are described in the literature.[3] Recent studies in this laboratory have resulted in an efficient approach to hitherto unknown [2.2](4,7)indoloparacyclophanes, taking advantage of Buchwald's variant of the Fischer indole synthesis.[4,5] According to receptor binding studies, one of the double-layered indolocyclophanes (±)-**8** clearly displayed substantial dopamine receptor affinity, demonstrating that sterically demanding cyclophane derivatives are capable of approaching and recognizing highly specific transmembrane receptor binding sites.

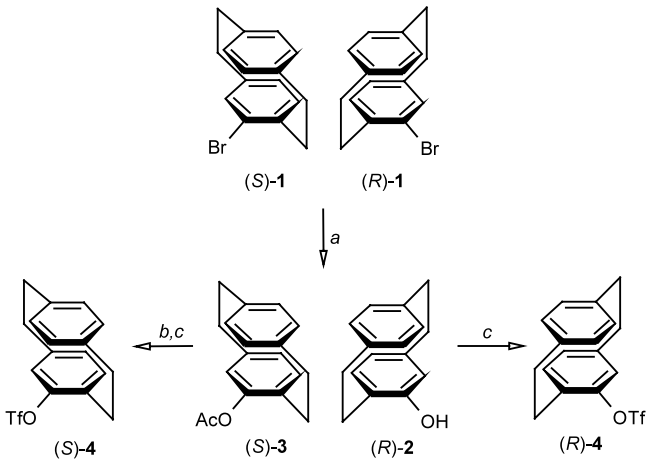
* Corresponding author. Fax: +4991318522585; e-mail: gmeiner@pharmazie.uni-erlangen.de

2. Results and discussion

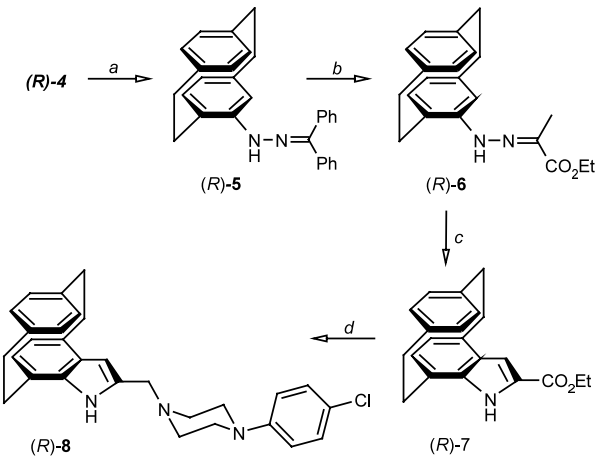
Herein, we present the stereoselective construction of the [2.2](4,7)indoloparacyclophane framework and the dopamine receptor binding profiles of the enantiomerically pure piperazinyl derivatives (*R*)-**8** and (*S*)-**8**.

Several attempts to obtain enantiomerically pure [2.2]paracyclophane derivatives have been made.[6–8] Our plan of synthesis involved palladium-catalyzed functionalization of the cyclophanyl triflates (*R*)-**4** and (*S*)-**4**, which should be available from the hydroxy substituted precursors (*R*)-**2** and (*S*)-**2**, respectively (Scheme 1). Thus, we took advantage of the kinetic-enzymatic resolution methodology described by Cipiciani.[8a] The racemic 4-hydroxy derivative (±)-**2** was obtained from the bromo substituted [2.2]paracyclophane **1**[9] by metallation and subsequent hydroboration.[10] After treatment with acetic anhydride, the racemic ester **3** was subjected to *Candida cylindracea* lipase (CCL)-catalyzed kinetic resolution[11] when predominant hydrolysis of (*R*)-**3** to give (*R*)-**2** was observed. Separation and saponification of (*S*)-**3** under alkaline conditions furnished enantiomerically pure (*S*)-**2**. In order to obtain (*R*)-**2** in enantiopure form, the acetylation–resolution process was repeated twice. The e.e. values were determined by HPLC-analysis using a CHIRALCEL OD chiral column.[12] Treatment of (*R*)-**2** and (*S*)-**2** to trifluoromethanesulfonic anhydride in the presence of pyridine gave ready access to the cyclophanyl triflates (*R*)-**4** and (*S*)-**4**, respectively.

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00558-4



Scheme 1. (a) Ref. 8a, 10; (b) NaOH, 85°C, 3 h; (c) Tf_2O, pyridine, 0°C to rt, 2 h (85%).



Scheme 2. (a) NaO*t*Bu, benzophenone hydrazone, dppf, $Pd_2(dba)_3$, toluene, 100°C, 48 h (58%); (b) 1. $TosOH{\cdot}H_2O$, $HO(CH_2)_2OH$, HCl/EtOH, reflux, 24 h; 2. ethyl pyruvate, EtOH, 70°C, 3 h (62%); (c) TosOH, benzene, 100°C, 45 min (42%); (d) $LiAlH_4$, (4-chlorophenyl)piperazine, THF, rt to reflux, 75 min (53%).

In order to approach the cyclophanylhydrazone (*R*)-**5** as a key intermediate, palladium-catalyzed cross-coupling of the triflate (*R*)-**4** with benzophenone hydrazone was elaborated.[13] Our initial investigations, involving the reagents $Pd_2(dba)_3$ and P*t*Bu_3, which we recently described for the functionalization of 2-bromo[2,2]paracyclophane, failed to promote cross-coupling. However, substantial activity was observed with a catalyst composed of $Pd_2(dba)_3$ and the ferrocene-derived ligand dppf, facilitating the clean synthesis of cyclophanylhydrazone (*R*)-**5** in 58% yield (Scheme 2). Employing a one-pot protocol, removal of the benzophenone hydrazone protecting group and subsequent condensation of the resulting hydrazine with ethyl pyruvate afforded the enolizable derivative (*R*)-**6** as precursor for the following Fischer cyclisation reaction. Treatment of (*R*)-**6** with anhydrous toluenesulfonic acid in refluxing benzene resulted in formation of the indolocyclophane (*R*)-**7**. The putative D4 receptor active phenyl piperazine (*R*)-**8** was obtained by reductive amination involving pre-treatment of (4-chlorophenyl)piperazine with $LiAlH_4$ and subsequent addition of the carboxylic ester (*R*)-**7**.[14] Starting from (*S*)-**4**, the enantiomer (*S*)-**8** was synthesized using the identical reaction sequence.

Both enantiomers (*R*)-**8** and (*S*)-**8** were evaluated in vitro for their ability to displace [^{3}H]spiperone from the cloned human dopamine receptors $D2_{long}$, $D2_{short}$,[15] D3[16] and D4[17] being stably expressed in CHO cells. D_1 affinity was determined by employing bovine striatal membrane preparations and the D_1 selective antagonist [^{3}H]SCH 23390.[18]

The dopamine receptor binding profiles of the double-layered test compounds (*R*)-**8** and (*S*)-**8** clearly indicate substantial D4 affinity, which is comparable to that of the anti-psychotic agent clozapine, and remarkable subtype selectivity, especially over D1, $D2_{long}$, and $D2_{short}$ (Table 1). Due to the planar chirality of the indoloparacyclophane moiety, stereodifferentiation was observed when the (*R*)-enantiomer shows significantly higher affinity for all the receptor subtypes investigated. The ratio of Ki values was between 1.9 (for D4) and 6.8 (for $D2_{long}$). Thus, the double-layered molecular scaffold can serve as a pharmacophoric element that can be exploited for tuning the subtype selectivity of neuroreceptor ligands.

3. Experimental

3.1. General procedures

Melting points were determined on a Büchi 530 apparatus and are uncorrected. All ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution with Bruker AC spectrometers at 360 MHz as well as 90 and 63 MHz. Elemental analyses were performed by the Department of Organic Chemistry, University of Erlan-

Table 1. Dopamine receptor binding (Ki values [nM]) of the indoloparacyclophanes (*R*)-**8** and (*S*)-**8** compared to the anti-psychotic drug clozapine[a]

Cpd	D1	$D2_{long}$	$D2_{short}$	D3	D4
(*R*)-**8**	1300±87	370±6.5	340±34	99±14	12±2.6
(*S*)-**8**	5500±180	2500±200	1400±160	270±40	23±2.7
Clozapine	420±50	41±1.5	28±0.50	960±45	16±0.5

[a] Data are based on the means of four experiments performed in triplicate at eight concentrations ±SEM.

gen-Nürnberg. Optical rotations were measured with a Perkin–Elmer 241 spectropolarimeter. THF and toluene were freshly distilled from sodium–benzophenone and sodium, respectively. All reagents were of commercial quality and used as purchased. Flash chromatography was carried out with silica gel 60 (4.0–6.3 μm) eluting with the appropriate solution in the stated v/v proportions. Analytical thin-layer chromatography (TLC) was performed with silica gel plates on aluminium (silica gel 60 F_{254} from Merck). The HPLC equipment involved: a pump 305 from Gilson with a pulsation suppressor 805 from Gilson, a UV detector from Knauer and the chiral CHIRALCEL OD column from Diacel (length 20 cm and diameter 0.64 cm).

3.1.1. (*R*)-Trifluoromethanesulfonic acid [2.2]paracyclophan-4-yl ester (*R*)-4. To a solution of (*R*)-**2**[8a] (250 mg, 1.12 mmol) in pyridine (3 mL) was added trifluoromethanesulfonic anhydride (276 μL, 1.67 mmol) at 0°C via a syringe. The solution was stirred at rt for 2 h. Then, H_2O was added and the aqueous layer was extracted with Et_2O. The organic layer was washed with 2 N HCl and H_2O, dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (petroleum ether–Et_2O 75:5) to afford (*R*)-**4** as a colorless solid (340 mg, 85%): mp 92°C; IR (KBr) *ν* 2935, 2857, 1419, 1211, 1141, 1064, 887, 836 cm^{-1}; ^1H NMR (360 MHz) *δ* 2.82 (ddd, 1H, *J*=13.5, 9.1, 6.7 Hz), 2.96–3.20 (m, 6H), 3.41 (ddd, 1H, *J*=13.5, 9.1, 4.3 Hz), 6.16 (d, 1H, *J*=1.5 Hz), 6.46 (dd, 1H, *J*=7.8, 1.9 Hz), 6.48 (dd, 1H, *J*=7.8, 1.9 Hz), 6.55 (dd, 1H, *J*=7.8, 1.9 Hz), 6.57 (d, 1H, *J*=7.8 Hz), 6.60 (dd, 1H, *J*=7.8, 1.5 Hz), 6.89 (dd, 1H, 7.8, 1.9 Hz), ^{13}C NMR (90 MHz) *δ* 31.5, 34.1, 34.7, 35.1, 118.7 (q, J_{C-F}=320 Hz), 127.8, 129.5, 132.0, 132.3, 132.5, 133.0, 133.5, 136.1, 139.1, 139.3, 143.0, 148.1; MS *m*/*z*=356 [M^+], $[\alpha]_D^{20}=-16.2$ (*c* 1, $CHCl_3$). Anal. calcd for $C_{17}H_{15}F_3O_3S$: C, 57.30; H, 4.24. Found: C, 57.62; H, 4.36%. Starting from (*S*)-**2**,[8a] (*S*)-**4** was prepared under identical conditions $[\alpha]_D^{20}=+15.8$ (*c* 1, $CHCl_3$).

3.1.2. (*R*)-*N*-Benzhydrylidene-*N*′-[2.2]paracyclophan-4-yl-hydrazine *(R)*-5. A solution of (*R*)-**4** (340 mg, 0.955 mmol), NaO*t*Bu (128 mg, 1.34 mmol), benzophenone hydrazone (193 mg, 0.955 mmol), $Pd_2(dba)_3$ (21.8 mg, 0.0238 mmol) and dppf (52.9 mg, 0.0955 mmol) in toluene (4 mL) was stirred in a sealed tube at 100°C for 48 h. After addition of Et_2O, the mixture was extracted with saturated Na_2CO_3. The combined organic layers were dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (petroleum ether–EtOAc 90:10) to afford (*R*)-**5** as a yellow solid (222 mg, 58%): mp 158°C; IR (KBr) *ν* 3350, 2925, 2850, 1570 cm^{-1}; ^1H NMR (360 MHz): *δ* 2.51–2.69 (m, 3H), 2.96–3.12 (m, 5H), 6.20 (dd, *J*=7.8, 1.8 Hz, 1H), 6.25 (d, *J*=7.8 Hz, 1H), 6.31 (dd, *J*=7.7, 1.9 Hz, 1H), 6.45 (d, *J*=1.8 Hz, 1H), 6.52 (dd, *J*=8.5, 1.9 Hz, 1H), 6.54 (dd, *J*=8.5, 1.9 Hz, 1H), 6.76 (dd, *J*=7.7, 1.9 Hz, 1H), 7.28–7.49 (m, 6H), 7.55–7.70 (m, 4H); ^{13}C NMR (63 MHz): *δ* 32.3, 33.3, 35.2, 35.4, 119.1, 122.6, 124.0, 125.8, 126.4, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 129.2, 129.3, 129.7, 130.0, 131.8, 132.4, 132.6, 133.0, 135.0, 138.6, 139.6, 141.6, 143.5; MS *m*/*z*=402 [M^+]; $[\alpha]_D^{20}=-267.2$ (*c* 1, $CHCl_3$). Anal. calcd for $C_{29}H_{26}N_2$: C, 86.53; H, 6.51; N, 6.96. Found: C, 86.93; H, 6.34; N, 6.63%. Starting from (*S*)-**4**, (*S*)-**5** was prepared under identical conditions $[\alpha]_D^{20}=+268.8$ (*c* 1, $CHCl_3$).

3.1.3. (*R*)-2-([2.2]Paracyclophan-4-ylhydrazono)propionic acid ethyl ester (*R*)-6. A solution of (*R*)-**5** (215 mg, 0.535 mmol), TosOH·H_2O (509 mg, 2.68 mmol) and ethylene glycol (0.2 mL, 4.06 mmol) was heated under reflux in HCl/EtOH (4 mL) for 24 h. After cooling to rt, the solvent was removed. 17.5% aqueous HCl was added to the residue and washed three times with Et_2O. The aqueous layer was basified with Na_2CO_3 and extracted for three times with Et_2O and CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated and the residue was redissolved in EtOH (40 mL) and ethyl pyruvate (62.1 mg, 0.535 mmol). After stirring for 3 h at 70°C, the solvent was removed by evaporation. After purification by flash chromatography (petroleum ether–EtOAc 98:2), (*R*)-**6** was obtained as yellow solid (110 mg, 62%): mp 132°C; IR (KBr) *ν* 3263, 2919, 2853, 1665, 1567, 1545, 1163, 774 cm^{-1}; ^1H NMR (360 MHz): *δ* 1.41 (t, 3H, *J*=7.2 Hz), 2.21 (s, 3H), 2.71–2.83 (m, 1H), 2.96–3.20 (m, 6H), 3.33 (ddd, 1H, *J*=14.1, 9.2, 1.5 Hz), 4.34 (q, 2H, *J*=7.2 Hz), 6.27 (dd, 1H, *J*=7.7, 1.9 Hz), 6.36 (d, 1H, J=7.5 Hz), 6.38 (d, 1H, *J*=1.7 Hz), 6.39 (dd, 1H, *J*=7.5, 1.7 Hz), 6.44 (dd, 1H, *J*=7.7, 1.9 Hz), 6.55 (dd, 1H, *J*=7.7, 1.9 Hz), 6.66 (dd, 1H, *J*=7.7, 1.9 Hz), 12.01 (s, 1H); ^{13}C NMR (90 MHz): *δ* 14.3, 19.6, 32.3, 33.4, 35.2, 35.3, 60.6, 119.2, 124.0, 125.2, 125.5, 128.5, 131.7, 132.8, 133.1, 135.2, 138.9, 139.1, 141.6, 142.4, 164.2; MS *m*/*z*=336 [M^+]; $[\alpha]_D^{20}=-150.5$ (*c* 1, $CHCl_3$). Anal. calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.32. Found: C, 74.82; H, 7.32; N, 7.95%. Starting from (*S*)-**5**, (*S*)-**6** was prepared under identical conditions $[\alpha]_D^{20}=+151.1$ (*c* 1, $CHCl_3$).

3.1.4. (*R*)-[2.2](4,7)Indoloparacyclophane-2-carboxylic acid ethyl ester (*R*)-7. From a solution of TosOH·H_2O (1.01 g, 5.32 mmol) in benzene (10 mL) (previously heated under reflux in a Dean–Stark-apparatus) was taken a 1 mL portion, which was added to (*R*)-**6** (100 mg, 0.298 mmol). The solution was stirred in a sealed tube at 100°C for 45 min. After cooling to rt, the organic layer was washed with $NaHCO_3$ and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (petroleum ether–EtOAc 95:5) to afford (*R*)-**7** as a colorless solid (39 mg, 42%): mp 142°C; IR (KBr) *ν* 3335, 2930, 2855, 1680, 1595 cm^{-1}; ^1H NMR: *δ* 1.47 (t, *J*=7.1 Hz, 3H; OCH_2CH_3), 2.86–3.05 (m, 6H; CH_2), 3.26–3.37 (m, 1H; H-8_{syn}), 3.37–3.48 (m, 1H; H-17_{syn}), 4.45 (q, *J*=7.1 Hz, 2H; OCH_2CH_3), 5.93 (dd, *J*=7.7, 1.7 Hz, 1H; H-15), 5.97 (dd, *J*=7.7, 1.7 Hz, 1H; H-14), 6.39 (dd, *J*=7.7, 1.7 Hz, 1H; H-12), 6.46 (d, *J*=7.4 Hz, 1H; H-6), 6.48 (dd, *J*=7.7, 1.7 Hz, 1H; H-11), 6.54 (d, *J*=7.4 Hz, 1H; H-5), 6.99 (d, *J*=2.1 Hz, 1H; H-3), 8.74 (s, 1H; NH); ^{13}C NMR (63 MHz): *δ* 14.5 ($CO_2CH_2\underline{CH_3}$), 31.1 (C-17), 32.5 (C-8), 33.8 (C-16), 34.6 (C-9), 61.0 ($CO_2\underline{CH_2}CH_3$), 109.7 (C-3),

123.3 (C-4), 124.3 (C-14), 125.8 (C-2), 126.4 (C-6), 126.8 (C-15), 130.9 (C-7a), 131.1 (C-5), 131.6 (C-12), 132.0 (C-11), 135.1 (C-7), 137.4 (C-13), 137.7 (C-10), 138.0 (C-3a), 162.5 ($CO_2CH_2CH_3$); MS m/z 319 [M^+]; $[\alpha]_D^{20}=+130.6$ (c 0.33, $CHCl_3$). Anal. calcd for $C_{21}H_{21}NO_2$: C, 78.97; H, 6.63; N, 4.39. Found: C, 78.91; H, 6.39; N, 4.24%. Starting from (*S*)-**6**, (*S*)-**7** was prepared under identical conditions $[\alpha]_D^{20}=-129.6$ (c 0.5, $CHCl_3$).

3.1.5. (*R*)-1-{[2.2](4,7)Indoloparacyclophan-2-ylmethyl}-4-(4-chlorophenyl)piperazine (*R*)-8. To a vigorously stirred solution of (4-chlorophenyl)piperazine (18 mg, 0.094 mmol) and $LiAlH_4$ (0.5 mL of a 1 M solution in THF) in THF (0.5 mL) at rt was added a solution of (*R*)-**7** (30 mg, 0.094 mmol) in THF (1 mL). After heating the mixture under reflux for 75 min, the reaction was quenched with aqueous NaOH (2N, 0.5 mL) under cooling with ice. After stirring for 1 h, the reaction mixture was diluted with saturated $NaHCO_3$ and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated and the residue was purified by flash chromatography (petroleum ether–acetone 9:1) to afford (*R*)-**8** as a colorless solid (22.8 mg, 53%): mp 215°C; IR (KBr) ν 3450, 2925, 2820, 1595 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.61–2.70 (m, 2H), 2.71–2.79 (m, 2H), 2.81–3.04 (m, 6H), 3.11–3.41 (m, 6H), 3.64 (d, $J=13.5$ Hz, 1H), 3.82 (d, $J=13.5$ Hz, 1H), 5.92 (dd, $J=7.8$, 1.8 Hz, 1H), 6.01 (dd, $J=7.8$, 1.8 Hz, 1H), 6.16 (d, $J=2.1$ Hz, 1H), 6.38 (d, $J=7.5$ Hz, 1H), 6.40 (dd, $J=7.8$, 1.8 Hz, 1H), 6.47 (d, $J=7.5$ Hz, 1H), 6.47 (dd, $J=7.8$, 1.8 Hz, 1H), 6.81–6.88 (m, 2H), 7.17–7.24 (m, 2H), 8.18 (s, 1H); MS m/z 455 [M^+]; $[\alpha]_D^{20}=+46.6$ (c 0.15, $CHCl_3$); Anal. calcd for $C_{29}H_{30}ClN_3$: C, 76.55; H, 6.42; N, 9.23. Found: C, 76.32; H, 6.59; N, 9.04%. Starting from (*S*)-**6**, (*S*)-**7** was prepared under identical conditions $[\alpha]_D^{20}=-48.0$ (c 0.5, $CHCl_3$).

Acknowledgements

The authors wish to thank Dr. H. H. M. Van Tol (Clarke Institute of Psychiatry, Toronto), Dr. J.-C. Schwartz and Dr. P. Sokoloff (INSERM, Paris) as well as Dr. J. Shine (The Garvan Institute of Medical Research, Sydney) for providing dopamine D4, D3 and D2 receptor-expressing cell lines, respectively. Thanks are also due to Mrs. H. Szczepanek, Mrs. P. Schmitt and Mrs. P. Hübner for skillful technical assistance. This work was supported by the *BMBF* and the *Fonds der Chemischen Industrie*.

References

1. Casy, A. F. *The Steric Factor in Medicinal Chemistry*: *Dissymmetric Probes of Pharmacological Receptors*; Plenum Press: New York, London, 1993.
2. Wu, X.-W.; Hou, X.-L.; Dai, L.-X.; Tao, J.; Cao, B.-X.; Sun, J. *Tetrahedron: Asymmetry* **2001**, *12*, 529 and references citated herein.
3. (a) Aly, A. A.; Hassan, A. A.; Mourad, A.-F. E.; Hopf, H. *Arch. Phar. (Weinheim)* **1992**, *325*, 625; (b) Mamyrbekova, Z. A.; Soldatova, S. A.; Abelentsev, V. I.; Solovyeva, T. I.; Guryshev, A. T. *Khim.-Farm. Zh.* **1994**, *28*, 48; (c) Imming, P.; Graf, M.; Tries, S.; Hirschelmann, R.; Krause, E.; Pawlitzki, G. *Inflammation Res.* **2001**, *50*, 371.
4. Ortner, B.; Waibel, R.; Gmeiner, P. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1283.
5. (a) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621; (b) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251.
6. (a) Cipiciani, A.; Fringuelli, F.; Mancini, V.; Piermatti, O.; Pizzo, F. *J. Org. Chem.* **1997**, *62*, 3744; (b) Harada, N.; Soutome, T.; Murai, S.; Uda, H. *Tetrahedron: Asymmetry* **1993**, *4*, 1755.
7. Hopf, H.; Grahn, W.; Barrett, D. G.; Gerdes, A.; Hilmer, J.; Hucker, J.; Okamoto, Y.; Kaida, Y. *Chem. Ber.* **1990**, *123*, 841.
8. (a) Cipiciani, A.; Fringuelli, F.; Mancini, V.; Piermatti, O.; Scappini, A. M. *Tetrahedron* **1997**, *53*, 11853; (b) Pamperin, D.; Schulz, C.; Hopf, H.; Syldatk, C.; Pietzsch, M. *Eur. J. Org. Chem.* **1998**, 1441; (c) Pamperin, D.; Hopf, H.; Syldatk, C.; Pietzsch, M. *Tetrahedron: Asymmetry* **1997**, *8*, 319.
9. Cram, D. J.; Day, A. C. *J. Org. Chem.* **1966**, *31*, 1227.
10. Krohn, K.; Rieger, H.; Hopf, H.; Barrett, D.; Jones, P. G.; Döring, D. *Chem. Ber.* **1990**, *123*, 1729.
11. CCL from Fluka, 2.4 U/mg $M_r\sim67000$.
12. Petroleum ether–*iso*-propanol 9:1; flowrate 1 mL/min; 210 nm; R_t (***R***)-**3** = 15.1 min, R_t (*S*)-**3** = 12.6 min.
13. Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268.
14. Löber, S.; Hübner, H.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 97.
15. Hayes, G.; Biden, T. J.; Selbie, L. A.; Shine, J. *J. Mol. Endocrinol.* **1992**, *6*, 920.
16. Sokoloff, P.; Andrieux, M.; Besancon, R.; Pilon, C.; Martres, M.-P.; Giros, B.; Schwartz, J.-C. *Eur. J. Pharmacol.* **1992**, *225*, 331.
17. Agashari, V.; Sanyal, S.; Buchwaldt, S.; Paterson, A.; Jovanovic, V.; Van Tol, H. H. M. *J. Neurochem.* **1995**, *65*, 1157.
18. Hübner, H.; Haubmann, C.; Utz, W.; Gmeiner, P. *J. Med. Chem.* **2000**, *43*, 756.