Stereoselective Synthesis and Receptor Binding of Conformationally Restricted and Flexible 2,4-Disubstituted 1,3-Dioxanes Derived from Benzomorphans

Bernhard Wünsch*[a], Gerd Bauschke[b], Heike Diekmann[c], and Georg Höfner[b]

[a] Pharmazeutisches Institut der Universität Freiburg, Hermann-Herder-Straße 9, D-79104 Freiburg, Germany

[b] Institut für Pharmazie – Zentrum für Pharmaforschung der Universität München, Butenandtstr. 7, D-81377 München, Germany

[c] Fujisawa GmbH, Levelingstr. 12, D-81673 München, Germany

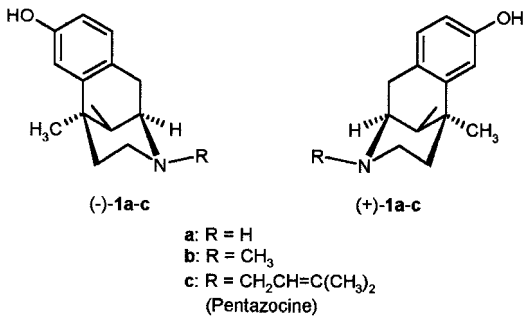
***Key Words**: Benzomorphan analogues; 1,3-dioxanes, 2,4-disubstituted; nitroalkenes, stereoselective addition of aryllithium to; transacetalization; receptor binding studies; affinity to NMDA receptors; μ-receptors, κ-receptors, σ-receptors*

Summary

The key steps in the stereoselective synthesis of the tricyclic aminomethyl derivatives **19** and **20** and the aminoethyl substituted 1,3-dioxanes **24** and **25** are nucleophilic addition of aryllithium intermediates to the nitroalkene **13**, intramolecular transacetalization of the addition products **15** and **16** (only for the tricyclic derivatives **19** and **20**) and subsequent reduction of the nitro group. The affinities of the secondary and tertiary amines **19c**,**d**, **20c**,**d**, **24c**,**d**, and **25c**,**d** for the ion channel binding site of the NMDA receptor, for μ-, κ-, and σ-receptors have been investigated. In the group of tricyclic compounds only **19d** shows remarkable σ-receptor affinity (K_i = 21.6/1.10 μM). In the 1,3-dioxane series the moderate μ- (K_i = 27.8 μM) and κ-receptor affinity (K_i = 36 μM) as well as the high σ-receptor affinity (K_i = 3.3 μM) of the (*S*,*S*,*S*)-configurated methylamine **24c** should be emphasized. The pentan-1-ol **26**, the side product isolated during the synthesis of **24c**, is of particular interest because of its considerable affinity to μ- (K_i = 16.0 μM), κ- (K_i = 2.8 μM), and σ-receptors (K_i = 14.5/1.26 μM). The biphasic competition curves obtained during σ-receptor binding studies of **19d** and **26** (two K_i values) may be explained by different interaction with σ-receptor subtypes.

Introduction

Depending on the substitution pattern and the stereochemistry, benzomorphans (**1**) can display high affinity for various receptors in the central nervous system (CNS) [1]. The best known benzomorphan derivative is the opioid analgesic pentazocine [(±)-**1c**, Fortral®] with a 3-methylbut-2-en-1-yl residue at the nitrogen atom (see Scheme 1) [2]. The mixed partial agonistic/partial antagonistic activity of pentazocine results from binding of the levorotatory enantiomer (–)-**1c** to κ-opioid receptors (agonistic) and μ-opioid-receptors (antagonistic). After application of pentazocine racemate (±)-**1c** psychotomimetic side effects are often observed, which are mainly caused by interaction of the dextrorotatory enantiomer (+)-**1c** with σ-receptors[3].



Scheme 1

The μ- and κ-receptor affinity is retained in levorotatory benzomorphans bearing a proton [(–)-**1a**] or a small methyl group [(–)-**1b**] instead of the 3-methylbut-2-en-1-yl residue at the nitrogen atom (see Scheme 1). However, the dextrorotatory enantiomers (+)-**1a** and (+)-**1b** show little σ-receptor affinity but high affinity and selectivity for the ion channel binding site of the NMDA receptor complex. Therefore, the dextrorotatory benzomorphan derivatives, in particular (+)-**1a** and (+)-**1b**, are of interest as neuroprotective and anticonvulsant agents [2,4].

A crucial structural feature for high receptor binding is the distance between the aromatic ring system and the basic nitrogen atom. Counting the carbon atoms the benzomorphans can be regarded as 2-phenylethylamine and 3-phenylpropylamine derivatives. In the course of our studies on novel CNS active compounds we have prepared several tricyclic benzomorphan analogues with heteroatoms in different ring positions. Especially strong CNS effects[5] and considerable receptor affinities have been found in those tricycles with a 2-phenylethylamine or a 3-phenylpropylamine substructure [6]. In particular, the high σ-receptor binding of 5,6,7,8,9,10-hexahydro-5,9-epoxybenzocycloocten-7-amines should be emphasized[7].

This concept of retaining the tricyclic benzomorphan structure but changing the electronic features of the tricyclic ring system by incorporation of heteroatoms in different ring positions led us to the design of 6-aminomethyl-1,5-epoxy-

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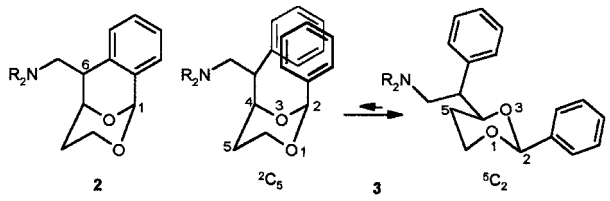
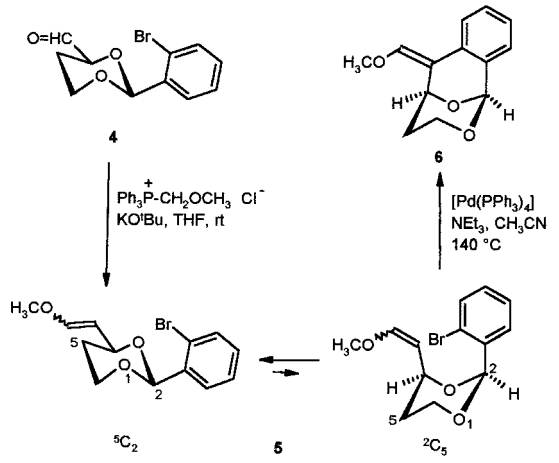


Scheme 2

2-benzoxocines **2**, which also include the 2-phenylethylamine substructure (see Scheme 2). In this communication we report on the stereoselective synthesis of the aminomethyl substituted tricycles **2** as well as their affinities to μ-, κ-, σ-, and NMDA-receptors. The 1,3-dioxanes **3**, which are derived from **2** by opening the tricyclic ring system (and doubling the phenyl moiety), are also included in this study. It should be mentioned that the compounds **3** differ distinctly from the tricycles **2**, since they prefer to adopt the $^5C_2$-conformation of the 1,3-dioxane ring with both substituents in the equatorial position.

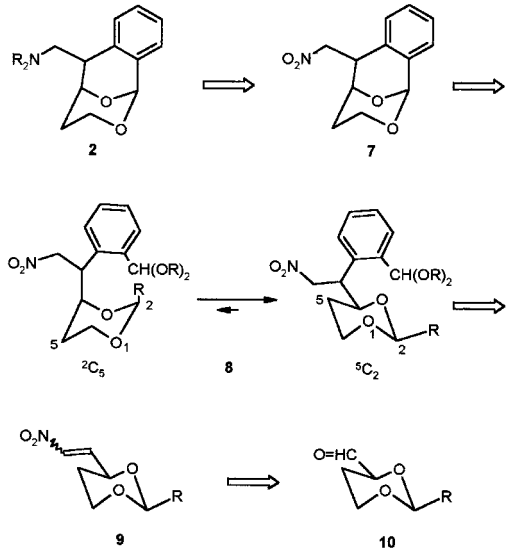
Chemistry

In our first approach an intramolecular Heck reaction[8] was planned as key step for the construction of the tricyclic framework (see Scheme 3). The educt for this synthesis was the 1,3-dioxane-4-carbaldehyde **4**, which was prepared by regio- and diastereoselective transacetalization of 2-bromobenzaldehyde dimethyl acetal with the (*S*)-butane-1,2,4-triol and subsequent Swern oxidation[5d,9]. Wittig reaction of the aldehyde **4** with (methoxymethyl)triphenylphosphonium chloride and potassium *tert*-butanolate furnished the enol ether **5** as mixture of (*Z*) and (*E*) isomers [(*Z*)-**5**:(*E*)-**5** = 56:44]. The intramolecular Heck reaction of the (methoxyvinyl) and (2-bromophenyl) substituted 1,3-dioxane **5** succeeded with the catalyst [$Pd(PPh_3)_4$] and triethylamine in a sealed tube at 140 °C to afford the tricyclic enol ether **6**. The chemical shift of the signal of the vinylic proton (δ = 6.82 ppm) points to (*Z*)-configuration of the double bond. In spite of several modifications of the Heck reaction conditions (catalyst, base, solvent, temperature, time) the yield of the cyclization product **6** was not reproducible and varied between 0 and 39%. Additionally, all attempts to hydrolyze the enol ether **6** to give the corresponding aldehyde failed. Therefore, we looked for another strategy to obtain the tricyclic amines **2**.



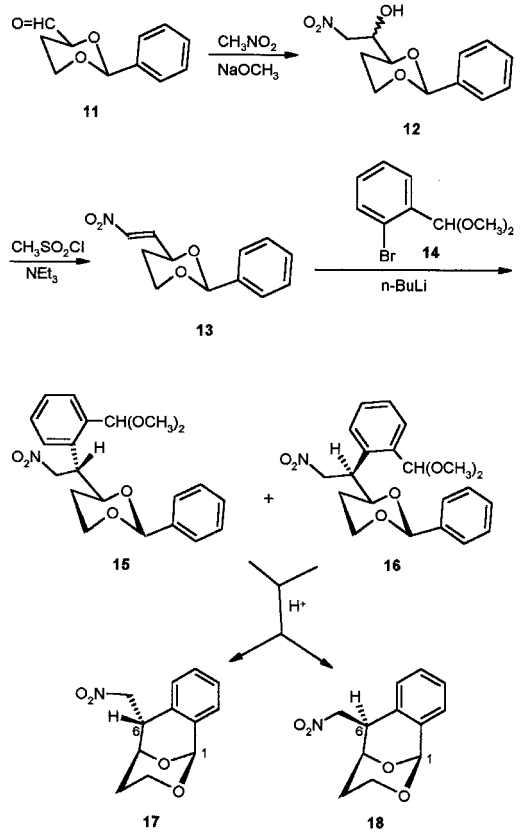
Scheme 3

In the second approach we intended to use the nitro group as precursor of the amino functionality of **2** (see Scheme 4). The nitromethyl substituted tricycle **7** should be built up by an intramolecular transacetalization of **8**, which already contains the aldehyde and 1,3-diol moieties both protected as acetals. The β-phenyl nitroalkane **8** should be prepared by a Michael addition of an aryl metal intermediate to the nitroalkene **9**, which in turn should be available by nitro aldol condensation of the aldehyde **10**.



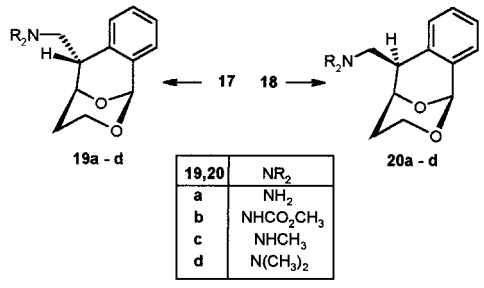
Scheme 4

(*S*)-2,4-Dihydroxybutanal with its 1,3-diol moiety protected as benzylidene acetal **11**[10] was selected as four carbon building block (see Scheme 5). Henry reaction[11] of the aldehyde **11** with nitromethane in the presence of sodium methanolate furnished the nitroaldol adduct **12** (75:25 mixture of diastereomers), which was dehydrated by methanesulfonyl chloride and triethylamine to give the (*E*)-configurated nitroalkene **13** in 95% yield. The aryl lithium intermediate, generated by bromine/lithium exchange at the bromobenzaldehyde acetal **14** with *n*-butyllithium, was added[12] to the nitro activated alkene **13** to provide the diastereomeric addition products **15** and **16** (ratio 67:33). Heating of the **15**/**16** mixture with dilute HCl led to hydrolysis of the acetals liberating an aldehyde and a 1,3-diol, which combined spontaneously to give the tricyclic acetals **17** and **18**. After flash chromatographic separation the diastereomeric nitromethyl substituted tricycles **17** and **18** were isolated in 49% and 25% yield, respectively. The configuration of the newly formed stereogenic center in position 6 of the tricycles **17** and **18** was deduced from the chemical shifts of the 6-H signals (**17**: δ = 3.55 ppm; **18**: δ = 4.35 ppm) and the 5-H/6-H coupling constants (**17**: $J_{5\text{-H/6-H}} \approx 0$ Hz, **18**: $J_{5\text{-H/6-H}} = 5.9$ Hz).



Scheme 5

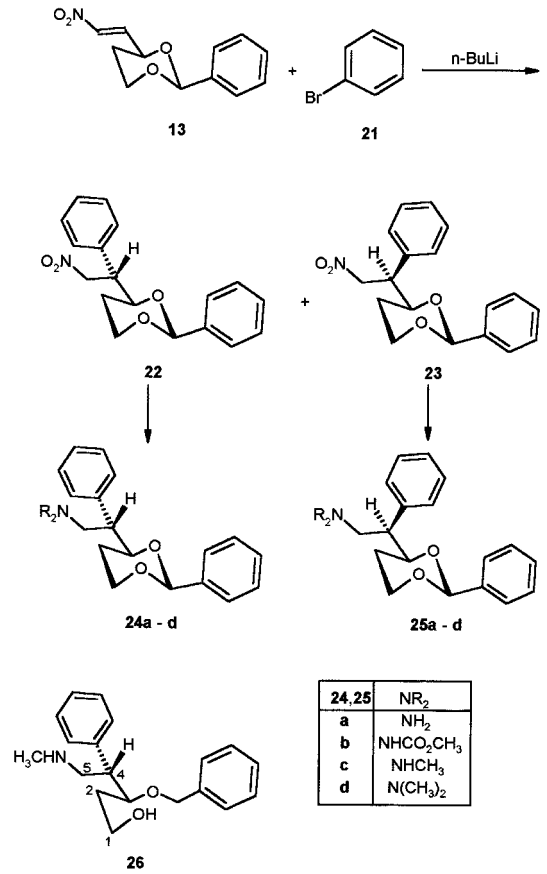
Reduction of the nitromethyl derivatives **17** and **18** with H_2 and Pd/C provided the primary amines **19a** and **20a**, respectively (see Scheme 6). The methylamines **19c** and **20c** were obtained by acylation of the primary amines **19a** and **20a** with methyl chloroformate (⇒ **19b**, ⇒ **20b**) and subsequent $LiAlH_4$ reduction. Reductive methylation with formaldehyde and $NaBH_3CN$[13] transformed the primary amines **19a** and **20a** into the dimethylamines **19d** and **20d**, respectively.



19,20	NR_2
a	NH_2
b	$NHCO_2CH_3$
c	$NHCH_3$
d	$N(CH_3)_2$

Scheme 6

In order to obtain the ring B opened analogues **3** phenyllithium without further substituents was added[12] to the nitroalkene **13** (see Scheme 7). The diastereomeric addition products **22** and **23** were formed in the same ratio (67:33) as the lithiobenzaldehyde acetal addition products **15** and **16**. The main diastereomer **22** could be separated by flash chromatography and purified by recrystallization. The configuration of the new stereogenic center in the side chain of **22** and **23** was deduced by comparison of the chromatographic behaviour and the ^1H NMR spectroscopic data of the phenyl addition products **22** and **23** with the 2-(dimethoxymethyl)-phenyl addition products **15** and **16**.



24,25	NR_2
a	NH_2
b	$NHCO_2CH_3$
c	$NHCH_3$
d	$N(CH_3)_2$

Scheme 7

In analogy to the tricyclic nitro derivatives **17** and **18** the reduction of the 2-nitroethyl substituted 1,3-dioxanes **22** and **23** succeeded by catalytic hydrogenation (see Scheme 7). However, reduction with $LiAlH_4$ followed by acylation of the resulting primary amines **24a** and **25a** with methyl chloroformate gave better yields of the carbamates **24b** and **25b**. Therefore, the $LiAlH_4$ reduction was chosen as standard procedure for the reduction of **22** and **23**. Since the quantitative separation of the nitro derivatives **22** and **23** turned out to be very troublesome, the diastereomeric separation was usually performed at the stage of the carbamates **24b** and **25b**. The separated carbamates **24b** and **25b** were reduced with $LiAlH_4$ to provide the methylamines **24c** and **25c**, which were reductively methylated with formaldehyde and $NaBH_3CN$[13] to yield the dimethylamines **24d** and **25d**, respectively.

In an initial attempt a very large excess of $LiAlH_4$ was employed for the reduction of the (*S*,*S*,*S*)-configurated carbamate **24b**. Surprisingly, the large excess of $LiAlH_4$ combined with the prolonged reaction time did not only lead to reduction of the carbamate moiety but also to reductive opening of the 1,3-dioxane ring to furnish the 3-benzyloxypentan-1-ol **26** as main product (50% yield). Because of

the structural similarity to the 1,3-dioxanes **24** and **25** the alcohol **26** was included into the receptor binding studies.

Receptor Binding Studies

The NMDA-[4a,14], μ-[15], κ-[15], and σ-receptor[16] affinities of the tricyclic and ring B opened methyl- and dimethylamines **19c**,**d**, **20c**,**d**, **24c**,**d**, and **25c**,**d** as well as the 1,3-dioxane ring opened derivative **26** were investigated in competition experiments with radioligands.

The following radioligands were employed: [^{3}H]-(+)-MK 801 for binding at the ion channel binding site of the NMDA-receptor, [^{3}H]-DAMGO for μ-receptor binding, [^{3}H]-U 69,593 for κ-receptor binding, and [^{3}H]-di-(*o*-tolyl)guanidine for σ-receptor binding. At first, the receptor affinity of each test compound was screened with two concentrations, 1 μM and 100 μM. The complete competition curves were only recorded for those compounds, which revealed considerable radioligand competition at these concentrations.

At the concentrations 1 μM and 100 μM only the 1,3-dioxane derivatives **24d** (tertiary amine) and **25c** (secondary amine) showed promising NMDA receptor affinity. However, recording of the whole competition curves with six concentrations of **24d** and **25c** led to K_i values of 58 μM for **24d** and 151 μM for **25c** (see Table 1). Thus, in this series of compounds the affinity for the ion channel binding site of the NMDA receptor complex was not further investigated.

Table 1. Affinities for the phencyclidine binding site of the NMDA receptor as well as for μ-, κ-, and σ-receptors

Cmpd	NMDA (K_i in μM)	μ (K_i in μM)	κ (K_i in μM)	σ (K_i in μM)
19c	–	–	–	180
19d	–	–	–	21.6/1.10
20c	–	–	–	–
20d	–	–	–	–
24c	–	27.8	36	3.3 (± 0.11)
24d	58	–	–	–
25c	151	46	–	35
25d	–	97	–	17.1
26	–	16.0	2.8	14.5 (± 0.4) / 1.26 (± 0.24)
Phencyclidine	0.109			
Tramadol		1.7	43	
Haloperidol				0.0085

–: At concentrations of 1 μM and 100 μM the test compounds did not compete significantly with the radioligands.

In the screening for μ-receptor affinity the 1,3-dioxanes **24c**, **25c**, and **25d** as well as the pentan-1-ol **26** competed well with the radioligand [^{3}H]-DAMGO. The exact determination of the μ-receptor affinity provided high K_i values: 27.8 μM for **24c**, 46 μM for **25c**, and 97 μM for **25d** (see Table 1). Surprisingly, the best μ-receptor affinity was found for the pentan-1-ol **26**, whose K_i value of 16.0 μM is only one order higher than the K_i value of tramadol (K_i = 1.7 μM).

The results of the κ-receptor screening made it reasonable only to determine the K_i values for the (*S*,*S*,*S*)-configurated 1,3-dioxane **24c** and the pentan-1-ol **26** (see Table 1). In comparison with tramadol (κ: K_i = 43 μM) the 1,3-dioxane **24c** displayed a similar κ-receptor affinity (K_i = 36 μM), whereas the pentan-1-ol **26** bound in the low micromolar range (K_i = 2.8 μM) to the κ-receptor.

In the group of the tricyclic compounds **19c**,**d**, **20c**,**d**, which are devoid of NMDA-, μ-, and κ-receptor affinity, the (*S*,*S*,*S*)-configurated dimethylamine **19d** showed considerable affinity for the σ-receptor (K_i = 4.8 μM). The mathematical description of the competition curve as a biphasic curve fits, however, much better to the experimental data, leading to two K_i values of 21.6 μM and 1.10 μM (see Table 1). Presumably, the biphasic competition curve results from different interactions of **19d** with σ_1- and σ_2-receptor subtypes, which are both labelled by the radioligand di-(*o*-tolyl)guanidine[16].

With the exception of **24d** σ-receptor affinity was observed in the screening of the 1,3-dioxanes **24** and **25** (see Table 1). Whereas high K_i values were found for the (*S*,*S*,*R*)-configurated 1,3-dioxanes **25c** (K_i = 35 μM) and **25d** (K_i = 17.1 μM), the (*S*,*S*,*S*)-configurated 1,3-dioxane **24c** revealed noticeable σ-receptor affinity (K_i = 3.3 μM ± 0.11 μM).

A comparable σ-receptor affinity (K_i = 3.7 μM) was determined for the pentan-1-ol **26**, which differs from **24c** only in the reductive cleavage of the 1,3-dioxane ring (see Table 1). In contrast to the 1,3-dioxane **24c** the competition curve of the pentan-1-ol **26** was biphasic giving rise to two K_i values, 14.5 μM (± 0.4 μM) and 1.26 μM (± 0.24 μM). This phenomenon may be explained by different interactions of **26** with σ-receptor subtypes (compare **19d**).

Acknowledgements

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Experimental

Chemistry

General: Unless otherwise stated, moisture sensitive reactions were conducted under dry nitrogen.– THF was distilled from sodium benzophenone ketyl prior to use.– Flash chromatography (fc)[17]: Silica gel 60, 0.040–0.063 mm (Merck).– Melting points: Melting point apparatus Dr. Tottoli (Büchi), uncorrected.– Optical rotation: Polarimeter 241 (Perkin Elmer); 1.0 dm tube; concentration *c* [g/100 mL]; temperature 20 °C.– Elemental analyses: CHN elemental analyser Rapid (Heraeus).– MS: Mass spectrometer 5989A (Hewlett Packard); CI = chemical ionisation.– IR: IR spectrophotometer 1600 FT-IR and 2000 FT-IR (Perkin-Elmer).– ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): GSX FT NMR spectrometer (Jeol), tetramethylsilane as internal standard, δ in ppm.

*(2S,4S)-2-(2-Bromophenyl)-4-[(E) and (Z)-2-methoxyvinyl]-1,3-dioxane (***5***)*

Potassium *tert*-butanolate (0.70 g, 6.0 mmol) was slowly added to a cooled (–20 °C) suspension of methoxymethyl-triphenylphosphonium chloride (1.50 g, 4.4 mmol) in THF (8 mL). The orange mixture was stirred for 15 min at –10 °C, then a solution of **4**[9] (1.0 g, 3.7 mmol) in THF (10 mL) was added and the mixture was stirred for 20 min at –10 °C and for additional

16 h at room temperature. After addition of water (15 mL) and CH_2Cl_2 (15 mL) the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3×), the organic layers were dried ($MgSO_4$) and concentrated in vacuo. According to the ^1H NMR spectrum of the unpurified product the ratio of (*Z*)-**5**:(*E*)-**5** is 56:44. The residue was purified by fc (diameter of the column 3 cm, petroleum ether/acetone 9:1, R_f = 0.31). Colourless oil, yield 0.59 g (53%).– $C_{13}H_{15}BrO_3$ (299.2) calcd. C 52.2 H 5.05 found C 52.0 H 5.35.– MS (EI): *m/z* = 300, 298 (M^+).– IR (film): = 2927, 2854 cm^{-1} (C-H), 1654 (C=C), 1095 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.57–1.60 (m, 0.44 H, 5-H equatorial), 1.59 (dd, *J* = 13.2/1.5 Hz, 0.56 H, 5-H equatorial), 1.93 (qd, *J* = 13.2/4.4 Hz, 0.56 H, 5-H axial), 2.02 (qd, *J* = 13.2/4.4 Hz, 0.44 H, 5-H axial), 3.56 (s, 3 × 0.44 H, OCH_3), 3.63 (s, 3 × 0.56 H, OCH_3), 4.05 (td, *J* = 12.5/2.2 Hz, 1 H, 6-H axial), 4.25 (dd, *J* = 12.5/4.4 Hz, 1 H, 6-H equatorial), 4.28–4.36 (m, 0.44 H, 4-H), 4.56 (dd, *J* = 8.1/6.6 Hz, 0.56 H, C*H*=CHOCH$_3$), 4.85–4.93 (m, 0.56 H, 4-H), 4.88 (dd, *J* = 12.5/8.1 Hz, 0.44 H, C*H*=CHOCH$_3$), 5.82 (s, 0.44 H, 2-H), 5.86 (s, 0.56 H, 2-H), 5.98 (d, *J* = 6.6 Hz, 0.56 H, CH=C*H*OCH$_3$), 6.67 (d, *J* = 12.5 Hz, 0.44 H, CH=C*H*OCH$_3$), 7.15–7.19 (m, 1 H, arom.), 7.29–7.34 (m, 1 H, arom.), 7.50 (d, *J* = 8.1 Hz, 1 H, arom.), 7.70 (dd, *J* = 8.1/1.5 Hz, 1 H, arom.).– ^{13}C NMR ($CDCl_3$): (ppm) = 31.6 (t, C-5 (*Z*)), 32.5 (t, C-5 (*E*)), 55.8 (q, OCH_3, (*E*)), 60.0 (q, OCH_3 (*Z*)), 67.1 (t, C-6), 67.2 (t, C-6), 71.8 (d, C-4 (*E*)), 76.0 (d, C-4 (*Z*)), 100.3 (d, C-2), 100.6 (d, C-2), 103.0 (d, *C*H=CHOCH$_3$, (*E*)), 106.6 (d, *C*H=CHOCH$_3$ (*Z*)), 122.4 (s, arom.), 127.5 (d, arom.), 127.9 (d, arom.), 128.2 (d, arom.), 128.3 (d, arom), 130.1 (d; arom.), 130.2 (d, arom.), 132.49 (d, arom.), 132.54 (d, arom.), 137.4 (s, arom.), 137.5 (s, arom.), 148.0 (d, CH=*C*HOCH$_3$), 150.8 (d, CH=*C*HOCH$_3$).

*(1S,5S)-(Z)-(–)-6-(Methoxymethylene)-3,4,5,6-tetrahydro-1,5-epoxy-1H-2-benzoxocine (**6**)*

A mixture of **5** (0.46 g, 2.1 mmol, mixture of (*E*)- and (*Z*)-isomers), tetrakistriphenylphosphane palladium (0) [$Pd(PPh_3)_4$] (0.71 g, 0.64 mmol), triethylamine (0.4 mL, 2.1 mmol) and acetonitrile (20 mL) was heated in a sealed tube at 140 °C for 48 h. Then, the suspension was filtered, the filtrate was concentrated in vacuo and the residue was purified by fc (diameter of the column 3 cm, petroleum ether/acetone 9:1, R_f = 0.30). Colourless oil, yield 0.18 g (39%), $[\alpha]_{589}$ = –28.2 (*c* = 0.90 in $CHCl_3$).– $C_{13}H_{14}O_3$ (218.3) calcd. C 71.5 H 6.47 found C 71.4 H 6.64.– MS: *m/z* = 218 (M^+).– IR (film): ν = 1692 cm^{-1} (*C*=*C*HOCH$_3$), 1104 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.47 (dq, *J* = 13.2/1.5 Hz, 1 H, 4-H equatorial), 2.54 (tt, *J* = 13.2/5.5 Hz, 1 H, 4-H axial), 3.68–3.76 (m, 2 H, 3-H), 3.77 (s, 3 H, OCH_3), 5.20 (d, *J* = 5.5 Hz, 1 H, 5-H), 5.84 (s, 1 H, 1-H), 6.82 (s, 1 H, C*H*OCH$_3$), 7.14–7.18 (m, 2 H, arom.), 7.22–7.28 (m, 1 H, arom.), 7.47 (d, *J* = 8.1 Hz, 1 H, arom.).

*(1R)- and (1S)-2-Nitro-1-[(2S,4S)-2-phenyl-1,3-dioxan-4-yl]ethan-1-ol (**12**)*

A solution of $NaOCH_3$, prepared by addition of sodium metal (2.2 g, 96 mmol) to methanol (30 mL), was added to a solution of **11**[10] (4.97 g, 25.9 mmol) and nitromethane (4.42 g, 72.4 mmol) in methanol (70 mL). The reaction mixture was stirred for 24 h at room temperature, then a half saturated solution of NH_4Cl (60 mL) was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue was recrystallized from iPr_2O. Colourless solid (iPr_2O), m.p. 108–115 °C, yield 6.36 g (97%).– $C_{12}H_{15}NO_5$ (253.3) calcd. C 56.9 H 5.97 N 5.53 found C 56.7 H 6.04 N 5.52.– MS: *m/z* = 253 (M^+).– IR (KBr): ν = 3430 cm^{-1} (OH), 1559 (NO_2), 1387 (NO_2), 1094 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.81–1.85 (m, 2 H, 5-H), 2.66 (d, *J* = 7.3 Hz, 0.25 H, OH), 2.80 (d, *J* = 5.9 Hz, 0.75 H, OH), 3.91–4.06 (m, 2 H, 6-H axial and 4-H axial), 4.33–4.38 (m, 2 H, 6-H equatorial and C*H*OH), 4.54 (dd, *J* = 13.9/8.8 Hz, 0.75 H, C*H*$_2$NO$_2$), 4.56–4.64 (m, 2 × 0.25 H, C*H*$_2$NO$_2$), 4,73 (dd, *J* = 13.9/2.2 Hz, 0.75 H, C*H*$_2$NO$_2$), 5.52 (s, 0,75 H, 2-H), 5.56 (s, 0.25 H, 2-H), 7.37–7.46 (m, 5 H, arom.). Ratio of diastereomers 75:25.

*(2S,4S)-(–)-4-[(E)-2-Nitrovinyl]-2-phenyl-1,3-dioxane (**13**)*

To a cooled (0 °C) solution of **12** (1.36 g, 5.37 mmol) in CH_2Cl_2 (20 mL) solutions of NEt_3 (1.74 g, 17.2 mmol) in CH_2Cl_2 (2.5 mL) and CH_3SO_2Cl (0.81 g, 7.04 mmol) in CH_2Cl_2 (2.5 mL) were added successively. After stirring for 2.5 h at room temperature the reaction mixture was poured into 1 N HCl (50 mL), the organic layer was separated, dried (Na_2SO_4), and evaporated in vacuo. Pale yellow oil, yield 1.20 g (95%), $[\alpha]_{546}$ = –60.3, $[\alpha]_{578}$ = –50.9, $[\alpha]_{589}$ = –47.9 (*c* = 1.15 in $CHCl_3$).– $C_{12}H_{13}NO_4$ (235.2) calcd. C 61.3 H 5.57 N 5.95 found C 61.6 H 5.96 N 5.79.– MS (CI): *m/z* = 236 (M + H^+).– IR (film): ν = 1526 cm^{-1} (NO_2), 1353 (NO_2), 1140 (C-O), 1025 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.77 (dt, *J* = 12.5/2.2 Hz, 1 H, 5-H equatorial), 1.97 (qd, *J* = 12.5/5.1 Hz, 1 H, 5-H axial), 4.04 (td, *J* = 12.5/2.2 Hz, 1 H, 6-H axial), 4.36 (dd, *J* = 12.5/5.1 Hz, 1 H, 6-H equatorial), 4.71 (dt, *J* = 12.5/2.2 Hz, 1 H, 4-H axial), 5.61 (s, 1 H, 2-H), 7.21–7.26 (m, 2 H, arom.), 7.36–7.42 (m, 3 H, arom. and CH=C*H*NO$_2$), 7.47–7.51 (m, 2 H, arom. and C*H*=CHNO$_2$).

*2-{(1S)- and (1R)-2-Nitro-1-[(2S,4S)-2-phenyl-1,3-dioxan-4-yl]ethyl}benzaldehyde Dimethyl Acetal (**15** and **16**)*

n-Butyllithium (1.6 molar in *n*-hexane, 9.0 mL, 14.4 mmol) was added at –78 °C to a solution of 2-bromobenzaldehyde dimethyl acetal **14**[14] (3.3 g, 14.3 mmol) in THF (30 mL) and the reaction mixture was stirred for 15 min at –78 °C. Additionally, a solution of **13** (2.88 g, 12.3 mmol) in THF (30 mL) was added. After stirring the reaction mixture for 3.5 h at –78 °C a half concentrated solution of NH_4Cl (30 mL) and CH_2Cl_2 (30 mL) were added, the organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The residue was filtered over silica gel (petroleum ether/ethyl acetate 80:20, R_f = 0.40). Colourless oil, yield 4.27 g (90.0%).– $C_{21}H_{25}NO_6$ (387.4) calcd. C 65.1 H 6.50 N 3.62 found C 65.3 H 6.59 N 3.37 .– MS: *m/z* = 324 [M–63 (OCH_3, CH_3OH)], 163 (2-phenyl-1,3-dioxan-4-yl).– IR (film): ν = 2960 cm^{-1} (CH), 1553 (NO_2), 1382 (NO_2), 1101 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.25 (dd, *J* = 12.5/1.5 Hz, 0.67 H, 5-H equatorial), 1.41 (dd, *J* = 12.5/1.5 Hz, 0.33 H, 5-H equatorial), 1.62 (qd, *J* = 12.5/5.1 Hz, 0.33 H, 5-H axial), 1.86 (qd, *J* = 12.5/5.1 Hz, 0.67 H, 5-H axial), 3.33 (s, 3 × 0.33 H, OCH_3), 3.35 (s, 3 × 0.33 H, OCH_3), 3.36 (s, 3 × 0.67 H, OCH_3), 3.38 (s, 3 × 0.67 H, OCH_3), 3.87 (td, *J* = 12.5/2.2 Hz, 0.67 H, 6-H axial), 3.92 (td, *J* = 12.5/1.5 Hz, 0.33 H, 6-H axial), 4.15–4.31 [m, 3 × 0.67 H and 2 × 0.33 H, 4-H axial (1 H), 6-H equatorial (1 H), C*H*CH$_2$NO$_2$ (0.67 H)], 4.44 (td, *J* = 7.3/3.7 Hz, 0.33 H, C*H*CH$_2$NO$_2$), 4.65 (dd, *J* = 12.5/7.3 Hz, 0.33 H, CHC*H*$_2$NO$_2$), 4.78 (dd, *J* = 12.5/8.1 Hz, 0.67 H, CHC*H*$_2$NO$_2$), 4.98 (dd, *J* = 12.5/5.1 Hz, 1 H, CHC*H*$_2$NO$_2$), 5.41 [s, 0.33 H, aryl-C*H*(OR)$_2$], 5.50 [s, 0.33 H, aryl-C*H*(OR)$_2$], 5.52 [s, 0.67 H, aryl-C*H*(OR)$_2$], 5.54 [s, 0.67 H, aryl-C*H*(OR)$_2$], 7.29–7.44 (m, 6 H, arom.), 7.48–7.51 (m, 2 H, arom.), 7.57 (d, *J* = 8.1 Hz, 0.67 H, arom.), 7.65 (dd, *J* = 7.3/1.5 Hz, 0.33 H, arom.). Ratio **15**:**16** = 67:33.

*(1S,5S,6S)-(+)-6-(Nitromethyl)-3,4,5,6-tetrahydro-1,5-epoxy-1H-2-benzoxocine (**17**) and (1S,5S,6R)-(+)-6-(Nitromethyl)-3,4,5,6-tetrahydro-1,5-epoxy-1H-2-benzoxocine (**18**)*

A solution of **15**/**16** (ratio 67:33, 120 mg, 0.31 mmol) in 0.1 N HCl (2 mL) and dioxane (10 mL) was heated to reflux for 1 h and stirred at room temperature for 16 h. Then, water (10 mL) and CH_2Cl_2 were added, the organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by fc (diameter of the column 1 cm, petroleum ether/ethyl acetate 90:10, fractions 5 mL).

17 [fractions 9–22, R_f = 0.39 (petroleum ether/ethyl acetate 80:20)]: Pale yellow oil, yield 36 mg (49.4%), $[\alpha]_{546}$ = +57.2, $[\alpha]_{578}$ = +51.3, $[\alpha]_{589}$ = +49.4 (*c* = 0.635 in $CHCl_3$).– $C_{12}H_{13}NO_4$ (235.2) calcd. C 61.3 H 5.57 N 5.95 found C 61.8 H 5.68 N 5.69.– MS (CI): *m/z* = 236 (M + H^+).– IR (film): ν = 2925 cm^{-1} (C-H), 1548 (NO_2), 1375 (NO_2), 1113 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.23 (dd, *J* = 13.2/2.9 Hz, 1 H, 4-H equatorial), 2.67 (tt, *J* = 13.2/6.6 Hz, 1 H, 4-H axial), 3.50 (td, *J* = 13.2/2.9 Hz, 1 H, 3-H axial), 3.55 (dd, *J* = 9.9/3.7 Hz, 1 H, 6-H), 3.65 (dd, *J* = 13.2/6.6 Hz, 1 H, 3-H equatorial), 4.33 (d, *J* = 6.6 Hz, 1 H, 5-H), 4.47 (dd, *J* = 13.9/3.7 Hz, 1 H, CH_2NO_2), 4.74 (dd, *J* = 13.9/9.9 Hz, 1 H, CH_2NO_2), 5.87 (s, 1 H, 1-H), 7.22–7.25 (m, 2 H, arom.), 7.36–7.39 (m, 2 H, arom.).

18 [fractions 23–32, R_f = 0.33 (petroleum ether/ethyl acetate 80:20)]: Pale yellow oil, yield 18 mg (24.7%), $[\alpha]_{546}$ = +6.3, $[\alpha]_{578}$ = +4.7, $[\alpha]_{589}$ = +4.1 (*c* = 0.68 in $CHCl_3$).– $C_{12}H_{13}NO_4$ (235.2) calcd. C 61.3 H 5.57 N 5.95 found C 61.6 H 5.70 N 5.50.– MS (CI): *m/z* = 236 (M + H^+).– IR (film): ν = 2961 cm^{-1} (C-H), 1559 (NO_2), 1376 (NO_2), 1099 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.65 (dd, *J* = 13.2/2.2 Hz, 1 H, 4-H equatorial), 2.55 (tt, *J* = 13.2/6.6 Hz, 1 H, 4-H axial), 3.51 (td, *J* = 13.2/2.2 Hz, 1 H, 3-H axial), 3.69 (dd, *J* = 13.2/6.6 Hz, 1 H, 3-H equatorial), 4.35 (dt, *J* = 10.3/5.9 Hz, 1 H, 6-H), 4.44 ("t", *J* = 6.6 Hz, 1 H, 5-H), 4.52 (dd, *J* = 13.2/10.3 Hz, 1 H, CH_2NO_2), 5.07 (dd, *J* = 13.2/5.1 Hz, 1 H, CH_2NO_2), 5.90 (s, 1 H, 1-H), 7.18

(d, *J* = 6.6 Hz, 1 H, arom.), 7.23–7.25 (m, 1 H, arom.), 7.34–7.37 (m, 2 H, arom.).

*1-[(1S,5S,6S)-3,4,5,6-Tetrahydro-1,5-epoxy-1H-2-benzoxocin-6-yl]methanamine (***19a***)*

To a solution of **17** (70 mg, 0.30 mmol) in CH_3OH (3 mL) the catalyst Pd/C (10%, 20 mg) was added and the reaction mixture was stirred under a hydrogen atmosphere (1.3 bar) for 2 h. The reaction mixture was filtered and concentrated in vacuo. Colourless oil, yield 54 mg (88.4%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.38 (dd, *J* = 13.5/3.0 Hz, 1 H, 4-H equatorial), 1.91 (s broad, 2 H, CH_2NH_2), 2.53–2.63 (m, 2 H, 4-H axial, 6-H), 2.95 (d, *J* = 6.0 Hz, 2 H, CH_2NH_2), 3.48 (td, *J* = 12.0/3.0 Hz, 1 H, 3-H axial), 3.55 (dd, *J* = 12.0/6.6 Hz, 1 H, 3-H equatorial), 4.43 (d, *J* = 6.0 Hz, 1 H, 5-H), 5.77 (s, 1 H, 1-H), 7.08–7.23 (m, 3 H, arom.), 7.27 (td, *J* = 7.3/1.3 Hz, 1 H arom.). The primary amine **19a** was used for the preparation of **19b**–**19d** without further purification.

*(+)-Methyl N-{1-[(1S,5S,6S)-3,4,5,6-tetrahydro-1,5-epoxy-1H-2-benzoxocin-6-yl]methyl}carbamate (***19b***)*

To an ice-cold solution of **19a** (80 mg, 0.39 mmol) in THF (2 mL) solutions of triethylamine (55 mg, 0.54 mmol) in THF (0.5 mL) and methyl chloroformate (50 mg, 0.53 mmol) in THF (0.5 mL) were added successively. After stirring for 4 h at room temperature an aqueous solution of Na_2CO_3 (10%, 10 mL) and CH_2Cl_2 (15 mL) were added, the organic layer was separated, dried (Na_2SO_4), concentrated in vacuo, and the residue was recrystallized. Colourless solid (iPr_2O), m.p. 182–183 °C, yield 84 mg (81.8%), $[\alpha]_{546}$ = +8.6, $[\alpha]_{578}$ = +8.8, $[\alpha]_{589}$ = +8.2 (*c* = 0.575 in $CHCl_3$).– $C_{14}H_{17}NO_4$ (263.3) calcd. C 63.9 H 6.51 N 5.32 found C 64.2 H 6.67 N 5.09.– MS: *m/z* = 263 (M^+), 176 (M–$CHNHCO_2CH_3$).– IR (KBr): ν = 3353 cm^{-1} (NH), 1696 (C=O), 1529 (amide II), 1272 (C-O), 1094 (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.38 (dd, *J* = 13.3/3.4 Hz, 1 H, 4-H equatorial), 2.57 (tt, *J* = 13.3/6.4 Hz, 1 H, 4-H axial), 2.84 (dd, *J* = 6.8/5.6 Hz, 1 H, 6-H), 3.28–3.41 (m, 2 H, CH_2NH), 3.46 (ddd, *J* = 13.3/11.5/3.4 Hz, 1 H, 3-H axial), 3.55 (dd, *J* = 11.5/6.4 Hz, 1 H, 3-H equatorial), 3.60 (s, 3 H, OCH_3), 4.27 (d, *J* = 6.4 Hz, 1 H, 5-H), 5.01 (s broad, 1 H, NH), 5.78 (s, 1 H, 1-H), 7.11 (d, *J* = 7.3 Hz, 1 H, arom.), 7.20–7.30 (m, 3 H, arom.).

*(+)-N-Methyl-1-[(1S,5S,6S)-3,4,5,6-tetrahydro-1,5-epoxy-1H-2-benzoxocin-6-yl]methanamine (***19c***)*

At 0 °C a solution of **19b** (68 mg, 0.26 mmol) in Et_2O (3 mL) and THF (3 mL) was slowly added to a suspension of $LiAlH_4$ (120 mg, 3.2 mmol) in Et_2O (3 mL). The reaction mixture was stirred for 30 h at room temperature, then water (0.5 mL) was cautiously added, and the mixture was filtered. The filtrate was extracted with 1 N HCl (3 × 5 mL), after addition of 2 N NaOH (pH 10) the aqueous layer was extracted with CH_2Cl_2 (5 × 15 mL), the CH_2Cl_2 layer was dried ($MgSO_4$), and concentrated in vacuo. Colourless oil, yield 47.1 mg (83.2%), $[\alpha]_{546}$ = +85.0, $[\alpha]_{578}$ = +74.1, $[\alpha]_{589}$ = +71.3 (*c* = 0.32 in $CHCl_3$).– $C_{13}H_{17}NO_2$ (219.3) calcd. C 71.2 H 7.81 N 6.39 found C 71.5 H 7.93 N 5.91.– MS (CI): *m/z* = 220 (M + H^+).– IR (film): ν = 3322 cm^{-1} (NH), 2951 (C-H), 1107 (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.38 (dd, *J* = 12.7/2.7 Hz, 1 H, 4-H equatorial), 2.24 (s broad, 1 H, NH), 2.41 (s, 3 H, $NHCH_3$), 2.58 (tt, *J* = 12.7/6.6 Hz, 1 H, 4-H axial), 2.68 (dd, *J* = 9.2/4.3 Hz, 1 H, 6-H), 2.72 (dd, *J* = 12.0/4.3 Hz, 1 H, CH_2NHCH_3), 2.88 (dd, *J* = 12.0/9.2 Hz, 1 H, CH_2NHCH_3), 3.48 (td, *J* = 12.7/2.7 Hz, 1 H, 3-H axial), 3.55 (dd, *J* = 12.7/6.6 Hz, 1 H, 3-H equatorial), 4.44 (d, *J* = 6.6 Hz, 1 H, 5-H), 5.77 (s, 1 H, 1-H), 7.10 (d, *J* = 7.3 Hz, 1 H, arom.), 7.17–7.22 (m, 2 H, arom.), 7.27 (td, *J* = 7.3/1.3 Hz, 1 H, arom.).

*(+)-N,N-Dimethyl-1-[(1S,5S,6S)-3,4,5,6-tetrahydro-1,5-epoxy-1H-2-benzoxocin-6-yl]methanamine (***19d***)*

$NaBH_3CN$ (110 mg, 1.75 mmol) was added to a solution of **19a** (53.5 mg, 0.26 mmol) and formaldehyde (35% in water, 1.2 mL) in methanol (5 mL) and the reaction mixture was stirred for 2 h at room temperature. CH_2Cl_2 (10 mL) and a solution of Na_2CO_3 (10%, 5 mL) were added, the organic layer was separated, dried ($MgSO_4$), concentrated in vacuo, and the residue was filtered over silica gel (10 g of silica gel, CH_2Cl_2/CH_3OH 90:10, R_f = 0.57). Colourless oil, which solidified on standing, yield 54.5 mg (89.6%), $[\alpha]_{546}$ = +78.6, $[\alpha]_{578}$ = +68.8, $[\alpha]_{589}$ = +66.1 (*c* = 2.53 in $CHCl_3$).– $C_{14}H_{19}NO_2$ (233.3) calcd. C 72.1 H 8.21 N 6.00 found C 71.8 H 8.50 N 5.78.– MS: *m/z* = 233 (M^+).– IR (film): ν = 2947 cm^{-1} (C-H), 1109 (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.42 (dd, *J* = 13.7/3.0 Hz, 1 H, 4-H equatorial), 2.15 [dd, *J* = 12.0/3.0 Hz, 1 H, $CH_2N(CH_3)_2$], 2.31 [s, 6 H, $CH_2N(CH_3)_2$], 2.60–2.70 (m, 2 H, 4-H axial and 6-H), 2.76 ["t", *J* = 12.0 Hz, 1 H, $CH_2N(CH_3)_2$], 3.56 (td, *J* = 11.8/3.0 Hz, 1 H, 3-H axial), 3.63 (dd, *J* = 11.8/7.1 Hz, 1 H, 3-H equatorial), 4.60 (d, *J* = 6.0 Hz, 1 H, 5-H), 5.83 (s, 1 H, 1-H), 7.15–7.19 (m, 2 H, arom.), 7.26 (dd, *J* = 7.3/1.3 Hz, 1 H, arom.), 7.32 (td, *J* = 7.3/1.3 Hz, 1 H, arom.).

*1-[(1S,5S,6R)-3,4,5,6-Tetrahydro-1,5-epoxy-1H-2-benzoxocin-6-yl]methanamine (***20a***)*

Pd/C (10%, 35 mg) was added to a solution of **18** (75 mg, 0.32 mmol) in methanol (10 mL) and the reaction mixture was stirred under a hydrogen atmosphere (1.3 bar) for 23 h at room temperature. Then, it was filtered and the solvent was evaporated in vacuo. Colourless oil, yield 53 mg (81.0%). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.79 (d, *J* = 13.2 Hz, 1 H, 4-H equatorial), 2.07 (s broad, 2 H, CH_2NH_2), 2.44–2.54 (m, 2 H, 4-H axial, CH_2NH_2), 2.94 (dd, *J* = 11.7/9.1 Hz, 1 H, CH_2NH_2), 3.51–3.68 (m, 3 H, 3-H axial, 3-H equatorial, 6-H), 4.53 ("t", *J* = 5.8 Hz, 1 H, 5-H), 5.88 (s, 1 H, 1-H), 7.19 (d, *J* = 7.3 Hz, 1 H, 7-H or 10-H), 7.26 (t, *J* = 7.3 Hz, 1 H, 8-H or 9-H), 7.32 (t, *J* = 7.3 Hz, 1 H, 9-H or 8-H), 7.40 (d, *J* = 7.3 Hz, 1 H, 10-H or 7-H). The primary amine **20a** was used for the preparation of **20b**–**20d** without further purification.

*Methyl N-{1-[(1S,5S,6R)-3,4,5,6-tetrahydro-1,5-epoxy-1H-2-benzoxocin-6-yl]methyl}carbamate (***20b***)*

As described for **19b** the primary amine **20a** (245 mg, 1.20 mmol) was acylated with methyl chloroformate (370 mg, 3.92 mmol) and triethylamine (395 mg, 3.91 mmol) in THF (10 mL). The residual colourless oil (**20b**, 270 mg, 85.9%) was reduced without purification.

*(+)-N-Methyl-1-[(1S,5S,6R)-3,4,5,6-tetrahydro-1,5-epoxy-1H-2-benzoxocin-6-yl]methanamine (***20c***)*

At 0 °C a solution of unpurified **20b** (196 mg, 0.75 mmol) in THF (10 mL) was added to a suspension of $LiAlH_4$ (400 mg, 10.5 mmol) in THF (30 mL). The reaction mixture was stirred for 48 h at room temperature, then water (2 mL) was cautiously added, the mixture was filtered, the filtrate was dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by fc (diameter of the column 1 cm, CH_2Cl_2/CH_3OH 80:20, fractions of 5 mL). The fractions 2–10 (R_f = 0.33) were concentrated in vacuo. Colourless oil, yield 64.2 mg (39.3%), $[\alpha]_{546}$ = +19.6, $[\alpha]_{578}$ = +16.3, $[\alpha]_{589}$ = +15.5 (*c* = 1.3 in $CHCl_3$).– $C_{13}H_{17}NO_2$ (219.3) calcd. C 71.2 H 7.81 N 6.39 found C 71.5 H 7.96 N 6.55.– MS: *m/z* = 219 (M^+), 176 (M–$CHNHCH_3$).– IR (film): ν = 3322 cm^{-1} (NH), 2936 (C-H), 1095 (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.76 (dd, *J* = 12.6/1.5 Hz, 1 H, 4-H equatorial), 2.41–2.50 (m, 1 H, 4-H axial), 2.51 (s, 3 H, $NHCH_3$), 2.76 (dd, *J* = 12.0/9.8 Hz, 1 H, CH_2NHCH_3), 3.27 (dd, *J* = 12.0/5.6 Hz, 1 H, CH_2NHCH_3), 3.50–3.57 and 3.63–3.72 (m, together 4 H, 3-H axial, 3-H equatorial, 6-H, $NHCH_3$), 4.44 ("t", *J* = 6.4 Hz, 1 H, 5-H), 5.88 (s, 1 H, 1-H), 7.18 (dd, *J* = 7.7/1.5 Hz, 1 H, 7-H or 10-H), 7.25 (t, *J* = 7.7 Hz, 1 H, 8-H or 9-H), 7.32 (td, *J* = 7.7/1.5 Hz, 1 H, 9-H or 8-H), 7.46 (d, *J* = 7.7 Hz, 1 H, 10-H or 7-H).

*(–)-N,N-Dimethyl-1-[(1S,5S,6R)-3,4,5,6-tetrahydro-1,5-epoxy-1H-2-benzoxocin-6-yl]methanamine (***20d***)*

As described for **19d** the primary amine **20a** (37 mg, 0.18 mmol) was reductively methylated with formaldehyde (35% in water, 1.2 mL) and $NaBH_3CN$ (110 mg, 1.75 mmol) in methanol (5 mL). FC purification (diameter of the column 1 cm, CH_2Cl_2/ethyl acetate 70:30, R_f = 0.18) gave a colourless oil, yield 31.1 mg (74.0%), $[\alpha]_{546}$ = –6.2, $[\alpha]_{578}$ = –6.1, $[\alpha]_{589}$ = –6.4 (*c* = 0.99 in $CHCl_3$).– $C_{14}H_{19}NO_2$ (233.3) calcd. C 72.1 H 8.21 N 6.00 found C 72.1 H 8.31 N 5.71.– MS (CI): *m/z* = 234 (M + H^+).– IR (film): ν = 2955 cm^{-1} (C-H), 1099 (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.70 (dd, *J* = 14.1/2.4 Hz, 1 H, 4-H equatorial), 2.29 [s, 6 H, $N(CH_3)_2$], 2.42–2.52 [m, 2 H, 4-H axial, $CH_2N(CH_3)_2$], 2.81 [dd, *J* = 12.4/6.0 Hz, 1 H, $CH_2N(CH_3)_2$], 3.52 (td, *J* = 12.5/2.4 Hz, 1 H, 3-H axial), 3.57–3.67 (m, 2 H, 3-H equatorial, 6-H), 4.39 ("t", *J* = 6.4 Hz, 1 H, 5-H), 5.88 (s, 1 H, 1-H), 7.18 (dd, *J* = 7.3/1.7 Hz, 1 H, 7-H or 10-H), 7.24 (t, *J* = 7.3 Hz, 1 H, 8-H or 9-H), 7.31 (td, *J* = 7.3/1.7 Hz, 1 H, 9-H or 8-H), 7.48 (d, *J* = 7.3 Hz, 1 H, 10-H or 7-H).

*(2S,4S)-4-[(S)-2-Nitro-1-phenylethyl]-2-phenyl-1,3-dioxane (**22**) and (2S,4S)-4-[(R)-2-Nitro-1-phenylethyl]-2-phenyl-1,3-dioxane (**23**)*

At –78 °C a solution of *n*-butyllithium (1.6 molar in *n*-hexane, 15.9 mL, 25.4 mmol) was added to a solution of bromobenzene (**21**, 3.99 g, 25.4 mmol) in THF (50 mL). The reaction mixture was stirred for 15 min at –78 °C, then a solution of **13** (5.3 g, 22.6 mmol) in THF (50 mL) was slowly added. After stirring for 5.5 h at –78 °C a half concentrated solution of NH_4Cl (300 mL) was added and the mixture was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated in vacuo, and the residue was purified by fc [diameter of the column 2 cm, petroleum ether/ethyl acetate 95:5, R_f = 0.49–0.51 (petroleum ether/ethyl acetate 80:20)]. Colourless oil, yield 6.3 g (89%).– $C_{18}H_{19}NO_4$ (313.4) calcd. C 69.0 H 6.11 N 4.47 found C 69.4 H 6.19 N 3.97.– MS: *m/z* = 313 (M^+).– IR (film): ν = 1552 cm^{-1} (NO_2), 1380 (NO_2), 1139 (C-O), 1100 (C-O), 1022 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.25 (dt, *J* = 12.2/2.1 Hz, 0.67 H, 5-H equatorial), 1.36 (dt, *J* = 12.2/2.1 Hz, 0.33 H, 5-H equatorial), 1.66 (qd, *J* = 12.0/4.5 Hz, 0.33 H, 5-H axial), 1.79 (qd, *J* = 12.0/4.5 Hz, 0.67 H, 5-H axial), 3.65–3.75 (m, 1 H, C*H*CH_2NO_2), 3.86 (td, *J* = 12.0/2.1 Hz, 0.67 H, 6-H axial), 3.93 (td, *J* = 12.0/2.1 Hz, 0.33 H, 6-H axial), 4.06 (ddd, *J* = 12.0/9.4/2.1 Hz, 0.67 H, 4-H axial), 4.16–4.22 [m, 1.33 H, 4-H axial (0.33 H) and 6-H equatorial (1 H)], 4.72 (dd, *J* = 13.0/9.4 Hz, 0.67 H, CHCH_2NO_2), 4.76 (dd, *J* = 13.3/7.9 Hz, 0.33 H, CHCH_2NO_2), 4.99 (dd, *J* = 13.3/7.3 Hz, 0.33 H, CHCH_2NO_2), 5.07 (dd, *J* = 13.0/4.9 Hz, 0.67 H, CHCH_2NO_2), 5.51 (s, 0.33 H, 2-H axial), 5.53 (s, 0.67 H, 2-H axial), 7.25–7.49 (m, 10 H, arom.). Ratio of diastereomers **22** and **23** = 67:33.

The main diastereomer **22** could be separated and purified by fc [conditions see above, R_f = 0.49 (petroleum ether/ethyl acetate 80:20)] and recrystallization. Colourless solid (iPr_2O), m.p. 86–87 °C, $[\alpha]_{546}$ = +85.4, $[\alpha]_{578}$ = +74.0, $[\alpha]_{589}$ = +71.3 (*c* = 0.24 in $CHCl_3$).– $C_{18}H_{19}NO_4$ (313.4) calcd. C 69.0 H 6.11 N 4.47 found C 68.8 H 6.20 N 4.53.– MS: *m/z* = 313 (M^+).– IR (KBr): ν = 1553 cm^{-1} (NO_2), 1385 (NO_2), 1138 (C-O), 1101 (C-O), 1026 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.25 (dt, *J* = 12.2/2.1 Hz, 1 H, 5-H equatorial), 1.79 (qd, *J* = 12.0/4.5 Hz, 1 H, 5-H axial), 3.68 (td, *J* = 9.4/4.9 Hz, 1 H, C*H*CH_2NO_2), 3.86 (td, *J* = 12.0/2.1 Hz, 1 H, 6-H axial), 4.06 (ddd, *J* = 12.0/9.4/2.1 Hz, 1 H, 4-H axial), 4.21 (dd, *J* = 12.0/4.5 Hz, 1 H, 6-H equatorial), 4.72 (dd, *J* = 13.0/9.4 Hz, 1 H, CHCH_2NO_2), 5.07 (dd, *J* = 13.0/4.9 Hz, 1 H, CHCH_2NO_2), 5.53 (s, 1 H, 2-H axial), 7.27–7.49 (m, 10 H, arom.).

*(+)-Methyl N-{(2S)-2-phenyl-2-[(2S,4S)-2-phenyl-1,3-dioxan-4-yl]ethyl}-carbamate (**24b**) and (–)-Methyl N-{(2R)-2-Phenyl-2-[(2S,4S)-2-phenyl-1,3-dioxan-4-yl]ethyl}carbamate (**25b**)*

At 0 °C a solution of **22** and **23** (ratio 67:33, 500 mg, 1.6 mmol) in Et_2O (40 mL) was added to a suspension of $LiAlH_4$ (600 mg, 15.8 mmol) in Et_2O (15 mL). The reaction mixture was stirred for 22 h at room temperature. Water (5 mL) was cautiously added at 0 °C, then the mixture was dried (Na_2SO_4), the Et_2O layer was separated and concentrated in vacuo. The residue (the primary amines **24a**, **25a**, colourless oil, 400 mg, 88%) was dissolved in CH_2Cl_2 (30 mL), cooled in an ice bath, and treated successively with solutions of NEt_3 (300 mg, 2.98 mmol) in CH_2Cl_2 (2.5 mL) and methyl chloroformate (275 mg, 2.91 mmol) in CH_2Cl_2 (2.5 mL). After stirring for 20 h at room temperature a saturated solution of Na_2CO_3 (15 mL) was added, the organic layer was separated, dried (Na_2SO_4), and concentrated in vacuo. The residue (450 mg) was separated by fc (diameter of the column 3 cm, petroleum ether/ethyl acetate 80:20, fractions 15 mL).

24b (fractions 11–19, R_f = 0.18): Colourless solid (iPr_2O), m.p. 106–107 °C, yield 175 mg (32%, calculated from **22**/**23**), $[\alpha]_{546}$ = +51.9, $[\alpha]_{578}$ = +45.2, $[\alpha]_{589}$ = +43.4 (*c* = 0.58 in $CHCl_3$).– $C_{20}H_{23}NO_4$ (341.4) calcd. C 70.4 H 6.79 N 4.10 found C 70.4 H 6.77 N 4.09.– MS (CI): *m/z* = 342 ($M + H^+$).– IR (KBr): ν = 3440 cm^{-1} (NH), 1724 (C=O), 1511 (amide II), 1248 (C-O), 1097 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.20 (dd, *J* = 12.4/2.6 Hz, 1 H, 5-H equatorial), 1.71–1.80 (m, 1 H, 5-H axial), 2.92–2.96 (m, 1 H, $C_6H_5CHCH_2$), 3.51–3.56 (m, 1 H, CH_2N), 3.59 (s, 3 H, CO_2CH_3), 3.86 (td, *J* = 12.0/2.6 Hz, 1 H, 6-H axial), 3.88–3.98 (m, 1 H, CH_2N), 4.05 ("t", *J* = 9.4 Hz, 1 H, 4-H axial), 4.19 (dd, *J* = 12.0/4.3 Hz, 1 H, 6-H equatorial), 4.86 (s broad, 1 H, NH), 5.55 (s, 1 H, 2-H axial), 7.21 (d, *J* = 7.3 Hz, 2 H, arom.), 7.28–7.40 (m, 6 H, arom.), 7.53 (d, *J* = 7.3 Hz, 2 H, arom.).

25b (fractions 20–32, R_f = 0.12): yield 88 mg (16%, calculated from **22**/**23**), $[\alpha]_{546}$ = –44.1, $[\alpha]_{578}$ = –38.5, $[\alpha]_{589}$ = –36.7 (*c* = 1.10 in $CHCl_3$).– $C_{20}H_{23}NO_4$ (341.4) calcd. C 70.4 H 6.79 N 4.10 found C 69.9 H 7.03 N 4.30.– MS (CI): *m/z* = 342 ($M + H^+$).– IR (KBr): ν = 3346 cm^{-1} (NH), 1722 (C=O), 1526 (amide II), 1258 (C-O), 1114 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.37 (d broad, *J* = 12.0 Hz, 1 H, 5-H equatorial), 1.74 (qd, *J* = 12.0/4.9 Hz, 1 H, 5-H axial), 3.05–3.08 (m, 1 H, $C_6H_5CHCH_2$), 3.58–3.78 (m, 2 H, CH_2N), 3.65 (s, 3 H, CO_2CH_3), 3.93 (td, *J* = 12.0/2.1 Hz, 1 H, 6-H axial), 4.15–4.20 (m, 2 H, 4-H axial, 6-H equatorial), 4.77 (s broad, 1 H, NH), 5.50 (s, 1 H, 2-H axial), 7.27–7.40 (m, 8 H, arom.), 7.45 (dd, *J* = 7.7/1.7 Hz, 2 H, arom.).

*(2S)-(+)-N-Methyl-2-phenyl-2-[(2S,4S)-2-phenyl-1,3-dioxan-4-yl]ethan-1-amine (**24c**)*

At 0 °C a solution of **24b** (66.8 mg, 0.20 mmol) in Et_2O (10 mL) was slowly added to a solution of $LiAlH_4$ (1.0 molar in THF, 0.4 mL, 0.4 mmol). The reaction mixture was stirred for 23 h at room temperature. Water (0.5 mL) was cautiously added, the mixture was dried (Na_2SO_4), filtered, the filtrate was concentrated in vacuo, and the residue was purified by fc (diameter of the column 1 cm, CH_2Cl_2/CH_3OH 9:1, R_f = 0.25). Colourless oil, yield 49.5 mg (85%), $[\alpha]_{546}$ = +39.0, $[\alpha]_{578}$ = +34.1, $[\alpha]_{589}$ = +32.5 (*c* = 0.88 in $CHCl_3$).– $C_{19}H_{23}NO_2$ (297.4) calcd. C 76.7 H 7.80 N 4.71 found C 76.6 H 8.15 N 4.50.– MS (CI): *m/z* = 298 ($M + H^+$).– IR (film): ν = 3450–3400 cm^{-1} (broad, NH), 2959 (C-H), 1107 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.11 (dt, *J* = 12.0/2.1 Hz, 1 H, 5-H equatorial), 1.68 (qd, *J* = 12.0/4.4 Hz, 1 H, 5-H axial), 1.98 (s, broad, 1 H, NH), 2.33 (s, 3 H, NHCH_3), 2.91 (dd, *J* = 11.8/8.3 Hz, 1 H, CHCH_2N), 3.03 (td, *J* = 8.3/5.6 Hz, 1 H, C*H*CH_2N), 3.27 (dd, *J* = 11.8/5.6 Hz, 1 H, CHCH_2N), 3.78 (td, *J* = 12.0/2.1 Hz, 1 H, 6-H axial), 4.00 (ddd, *J* = 11.6/8.3/2.1 Hz, 1 H, 4-H axial), 4.11 (dd, *J* = 11.5/4.4 Hz, 1 H, 6-H equatorial), 5.48 (s, 1 H, 2-H axial), 7.17–7.22 (m, 3 H, arom.), 7.26–7.34 (m, 5 H, arom.), 7.44 (dd, *J* = 7.3/1.3 Hz, 2 H, arom.).

*(2S)-(+)-N,N-Dimethyl-2-phenyl-2-[(2S,4S)-2-phenyl-1,3-dioxan-4-yl]-ethan-1-amine (**24d**)*

At 0 °C a solution of the pure diastereomer **22** (130 mg, 0.42 mmol) in THF (10 mL) was slowly added to a suspension of $LiAlH_4$ (160 mg, 4.2 mmol) in Et_2O (8 mL). After stirring for 23 h at room temperature water (3 mL) was cautiously added, then it was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue (the primary amine **24a**, yield 108 mg, 0.38 mmol, 91.9%) was dissolved in methanol (10 mL). Subsequently, formaldehyde (35% in water, 2.0 mL) and $NaBH_3CN$ (170 mg, 2.7 mmol) were added and the reaction mixture was stirred for 3.5 h at room temperature. Then, a solution of Na_2CO_3 (10%, 20 mL) and CH_2Cl_2 (20 mL) were added, the organic layer was separated, dried ($MgSO_4$), evaporated in vacuo, and the residue was purified by fc (diameter of the column 2 cm, CH_2Cl_2/CH_3OH 95:5, R_f = 0.36). Colourless oil, yield 71 mg (55.0% calculated from **22**), $[\alpha]_{546}$ = +16.8, $[\alpha]_{578}$ = +14.9, $[\alpha]_{589}$ = +14.3 (*c* = 0.325 in $CHCl_3$).– $C_{20}H_{25}NO_2$ (311.4) calcd. C 77.1 H 8.09 N 4.50 found C 77.0 H 8.21 N 4.50.– MS: *m/z* = 311 (M^+).– IR (film): ν = 2856 cm^{-1} (C-H), 1127 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.03 (dt, *J* = 13.2/1.9 Hz, 1 H, 5-H equatorial), 1.63 (qd, *J* = 13.2/4.5 Hz, 1 H, 5-H axial), 2.11 [s, 6 H, $N(CH_3)_2$], 2.73 (dd, *J* = 13.4/9.8 Hz, 1 H, CHCH_2NMe_2), 2.84–2.97 (m, 2 H, C*H*CH_2NMe_2), 3.76 (td, *J* = 11.5/1.9 Hz, 1 H, 6-H axial), 3.85 (ddd, *J* = 13.2/5.6/1.9 Hz, 1 H, 4-H axial); 4.03 (dd, *J* = 11.5/4.5 Hz, 1 H, 6-H equatorial), 5.44 (s, 1 H, 2-H axial), 7.14–7.20 (m, 3 H, arom.), 7.23–7.31 (m, 6 H, arom.), 7.43 (d, *J* = 6.6 Hz, 1 H, arom.).

*(2R)-(–)-N-Methyl-2-phenyl-2-[(2S,4S)-2-phenyl-1,3-dioxan-4-yl]ethan-1-amine (**25c**)*

As described for **24c** the carbamate **25b** (233.7 mg, 0.68 mmol) was reduced with $LiAlH_4$ (500 mg, 12.5 mmol) in Et_2O (40 mL) during 18 h at room temperature. The crude reaction product was purified by fc (diameter of the column 1 cm, CH_2Cl_2/CH_3OH 9:1, R_f = 0.23). Colourless oil, yield 188 mg (92.4%), $[\alpha]_{546}$ = –47.7, $[\alpha]_{578}$ = –41.0, $[\alpha]_{589}$ = –38.7 (*c* = 0.15 in $CHCl_3$).– $C_{19}H_{23}NO_2$ (297.4) calcd. C 76.7 H 7.80 N 4.71 found C 76.3 H 8.13 N 4.81.– MS (CI): *m/z* = 298 ($M + H^+$).– IR (film): ν = 3325 cm^{-1} (broad, NH), 2848 (C-H), 1111 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.33 (dd, *J* = 12.4/2.6 Hz, 1 H, 5-H equatorial), 1.66 (qd, *J* = 12.4/4.9 Hz, 1 H, 5-H axial), 2.11 (s broad, 1 H, N*H*CH_3), 2.31 (s, 3 H, NHCH_3), 2.95–3.02 (m, 3 H, C*H*CH_2N), 3.85 (td, *J* = 12.4/2.6 Hz, 1 H, 6-H axial), 4.07–4.13 (m, 2 H, 4-H

axial and 6-H equatorial), 5.42 (s, 1 H, 2-H axial), 7.17–730 (m, 8 H, arom.), 7.36 (dd, *J* = 7.3/1.3 Hz, 2 H, arom.).

*(2R)-(–)-N,N-Dimethyl-2-phenyl-2-[(2S,4S)-2-phenyl-1,3-dioxan-4-yl]-ethan-1-amine (***25d***)*

$NaBH_3CN$ (120 mg, 1.9 mmol) was added to a solution of **25c** (85 mg, 0.29 mmol) and formaldehyde (35% in water, 1.4 mL) in methanol (10 mL) and the reaction mixture was stirred for 20 h at room temperature. Then, a solution of Na_2CO_3 (10%, 20 mL) and CH_2Cl_2 (20 mL) were added, the organic layer was separated, dried ($MgSO_4$), and the residue was purified by fc (diameter of the column 1 cm, CH_2Cl_2/CH_3OH 90:10, R_f = 0.34). Colourless oil, yield 31 mg (34.8%), $[\alpha]_{546}$ = –61.1, $[\alpha]_{578}$ = –52.6, $[\alpha]_{589}$ = –51.1 (*c* = 0.23 in $CHCl_3$).– $C_{20}H_{25}NO_2$ (311.4) calcd. C 77.1 H 8.09 N 4.50 found C 76.8 H 8.30 N 4.65.– MS: *m/z* = 311 (M^+).– IR (film): ν = 2856 cm^{-1} (C-H), 1113 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.29 (dt, *J* = 12.4/2.1 Hz, 1 H, 5-H equatorial), 1.61 (qd, *J* = 12.4/5.1 Hz, 1 H, 5-H axial), 2.18 [s, 6 H, $N(CH_3)_2$], 2.56 (dd, *J* = 15.2/9.8 Hz, 1 H, $CHCH_2NMe_2$), 2.84–2.90 (m, 2 H, $CHCH_2NMe_2$), 3.86 (td, *J* = 12.4/2.1 Hz, 1 H, 6-H axial), 4.08 (dd, *J* = 12.4/5.1 Hz, 1 H, 6-H equatorial), 4.15 (dt, *J* = 12.4/2.1 Hz, 1 H, 4-H axial), 5.45 (s, 1 H, 2-H axial), 7.14–7.20 (m, 2 H, arom.), 7.21–7.24 (m, 3 H, arom.), 7.29–7.30 (m, 3 H, arom.), 7.38–7.40 (m, 2 H, arom.).

*(3S,4S)-(–)-3-Benzyloxy-5-(methylamino)-4-phenylpentan-1-ol (***26***)*

A solution of **24b** (54.5 mg, 0.16 mmol) in Et_2O (6 mL) was slowly added to an ice cold suspension of $LiAlH_4$ (150 mg, 3.75 mmol) in Et_2O (4 mL). The ice bath was removed and the reaction mixture was stirred for 17 h at room temperature. Then, $LiAlH_4$ (95 mg, 2.4 mmol) was added, the reaction mixture was stirred for 3 h, and an additional portion of $LiAlH_4$ (270 mg, 6.75 mmol) was added. After stirring for additional 24 h at room temperature water (2 mL) was cautiously added, the suspension was dried (Na_2SO_4), filtered, and the organic layer was concentrated in vacuo. The residue (48.1 mg) was dissolved in 1 N HCl (10 mL), the aqueous layer was washed with Et_2O, then 1 N NaOH (13 mL) was added, the aqueous layer was extracted with Et_2O (5 ×), the Et_2O layer was dried ($MgSO_4$) and concentrated in vacuo. Colourless oil, yield 23.7 mg (49.6%), $[\alpha]_{546}$ = –30.0, $[\alpha]_{578}$ = –26.8, $[\alpha]_{589}$ = –24.1 (*c* = 0.11 in $CHCl_3$).– $C_{19}H_{25}NO_2$ (299.4) calcd. C 76.2 H 8.41 N 4.68 found C 76.1 H 8.52 N 4.72.– MS (CI): *m/z* = 300 ($M + H^+$).– IR (film): ν = 3314 cm^{-1} (OH, NH), 2855 (C-H), 1101 (C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.53–1.58 (m, 2 H, 2-H), 2.45 (s, 3 H, $NHCH_3$), 2.75 (td, *J* = 9.8/3.8 Hz, 1 H, 4-H), 2.97 (dd, *J* = 12.0/3.8 Hz, 1 H, 5-H), 3.14 (dd, *J* = 12.0/9.8 Hz, 1 H, 5-H), 3.58 (td, *J* = 6.4/2.1 Hz, 2 H, 1-H), 4.13 (td, *J* = 9.8/4.0 Hz, 1 H, 3-H), 4.43 (d, *J* = 12.0 Hz, 1 H, $C_6H_5CH_2O$), 4.46 (d, *J* = 12.0 Hz, 1 H, $C_6H_5CH_2O$), 7.14 (d, *J* = 7.3 Hz, 2 H, arom.), 7.22 (d, *J* = 7.3 Hz, 1 H, arom.), 7.26–7.32 (m, 7 H, arom.). Signals for the OH and NH protons could not be detected.

Receptor Binding Studies

General: Filter: Whatman GF/C, presoaked in buffer for 1–1.5 h before use.– Filtration was performed with a Brandel 24-well cell harvester.– Scintillation cocktail: Rotiszint eco plus (Carl Roth GmbH).– Liquid scintillation analyzer: TriCarb 1600 (Canberra Packard), counting efficiency 55%.– All experiments were carried out in triplicate.– IC_{50} values were determined with the program Inplot 4.0 (GraphPad Software TM) by nonlinear regression analysis.– K_i values were calculated according to Cheng and Prussoff[18].– For compounds with high affinity (low K_i values) mean values ± SEM from three independent experiments are given.

Investigation of the Affinity for the Phencyclidine Binding Site of the NMDA Receptor[14]

The test was performed with the radioligand [^{3}H]-(+)-MK 801 (825 GBq/mmol; Du Pont de Nemours) and receptor preparations from rat brain (cerebral cortex, Du Pont de Nemours, suspension in HEPES buffer, storage at –20 °C) [14c]. Buffer: HEPES 20 mM (HEPES = 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid), pH = 7.4.

Performance: 200 μL of receptor preparation was incubated in 250 μL medium (total volume) containing 100 μM glutamic acid, 30 μM glycine, 20 μM HEPES (pH 7.4), about 2 nM [^{3}H]-(+)-MK 801 and various concentrations of test compounds for 80 min at 25 °C. The samples were rapidly filtered under reduced pressure through GF/C filters and the filters were washed with ice-cold buffer (10 mL). Bound radioactivity trapped on the filters was determined by liquid scintillation spectrometry. Nonspecific binding was determined with 1 μM (+)-MK 801.

Investigation of the μ*-Receptor Affinity*[15]

The test was performed with the radioligand [^{3}H]-DAMGO (2053.5 GBq/mmol; Du Pont de Nemours) and bovine striatal membrane preparations as receptor material. Buffer: Tris HCl 50 mM, pH = 7.5. Nonspecific binding was determined with 1 μM Naloxon.

Performance: According to ref.[15a].

Investigation of the κ*-Receptor Affinity*[15]

The test was performed with the radioligand [^{3}H]-U 69,593 (1753 GBq/mmol; Du Pont de Nemours) and bovine striatal membrane preparations as receptor material. Buffer: Tris HCl 50 mM, pH = 7.5. Nonspecific binding was determined with 1 μM U 50,488.

Performance: According to ref.[15a].

Investigation of the σ*-Receptor Affinity*[16]

The test was performed with the radioligand [^{3}H]-Ditolylguanidine (1302.4 GBq/mmol; Du Pont de Nemours) and homogenised guinea pig brain (Dunkin Hartley, Harlan) preparations as receptor material. Buffer: Tris HCl 50 mM, pH = 7.4.

Performance: 250 μg of protein were incubated with various concentrations of test compounds (usually solutions in buffer), 3 nM [^{3}H]-Ditolylguanidine, 50 mM Tris HCl pH 7.4 in 250 μL medium (total volume) for 90 min at 25 °C. The samples were rapidly filtered under reduced pressure through GF/C filters and the filters were washed with ice-cold buffer (5 × 1 mL). Bound radioactivity trapped on the filters was determined by liquid scintillation spectrometry after addition of the scintillation cocktail. Nonspecific binding was determined with 10 μM Haloperidol.

References and Notes

[1] [1a] G. R. Lenz, S. M. Evans, D. E. Walters, A. I. Hopfinger, *Opiates*, Academic Press, New York, London, **1986**, pp. 250ff.– [1b] A. F. Casy, R. T. Parfitt, *Opioid Analgesics*, Pergamon Press, new York, London, **1986**, pp. 153ff.

[2] [2a] E. Freye, *Schmerz – pain – doleur* **1986**, 44–54.– [2b] *Arzneistoff-profile* **1981**, 1–4.

[3] [3a] F. I. Carroll, P. Abraham, K. Parham, X. Bai, X. Zhang, G. A. Brine, S. W. Mascarella, B. R. Martin, E. L. May, C. Sauss, L. Di Paolo, P. Wallace, J. M. Walker, W. D. Bowen, *J. Med. Chem.* **1992**, *35*, 2812–2818.– [3b] F. I. Carroll, X. Bai, X. Zhang, G. A. Brine, S. W. Mascarella, L. Di Paolo, P. Wallace, J. M. Walker, W. D. Bowen, *Med. Chem. Res.* **1992**, *2*, 3–9.– [3c] E. L. May, M. D. Aceto, E. R. Bowman, C. Bentley, B. R. Martin, L. S. Harris, F. Medzihradsky, M. V. Mattson, A. E. Jacobson, *J. Med. Chem.* **1994**, *37*, 3408–3418. [3d] S. W. Mascarella, X. Bai, W. Williams, B. Sine, W. D. Bowen, F. I. Carroll, *J. Med. Chem.* **1995**, *38*, 565–569.– [3e] M. Grauert, W. D. Bechtel, H. A. Ensinger, H. Merz, A. J. Carter, *J. Med. Chem.* **1997**, *40*, 2922–2930.

[4] [4a] E. H. F. Wong, J. A. Kemp, *Annu. Rev. Pharmacol. Toxicol.* **1991**, *31*, 401–425.– [4b] P. L. Ornstein, V. J. Klimkowski, In *Excitatory Amino Acid Receptors–Design of Agonists and Antagonists*; P. Krogsgaard-Larsen, J. J. Hensen, Ed.; Ellis Horwood Ltd., Chichester, **1992**; pp 183 ff.

[5] [5a] B. Wünsch, M. Zott, G. Höfner, *Liebigs Ann. Chem.* **1992**, 1225–1230.– [5b] B. Wünsch, G. Höfner, G. Bauschke, *Arch. Pharm. (Weinheim, Ger.)* **1993**, *326*, 101–113.– [5c] Wünsch, M. Zott, G. Höfner, *Arch. Pharm. (Weinheim, Ger.)* **1993**, *326*, 823–830.– [5d] B. Wünsch, H. Diekmann, G. Höfner, *Tetrahedron: Asymmetry* **1995**, *6*, 1527–1530.

[6] The receptor affinities of the tricyclic amines described in ref.[5] will be published in due course.

[7] The K_i values (σ-receptor affinity) of the diastereomeric *N,N*-dimethyl-5,6,7,8,9,10-hexahydro-5,9-epoxybenzocycloocten-7-amines are 3.0 μM and 0.70 μM, respectively.[6]

[8] [8a] A. deMeijere, *Angew. Chem.* **1994**, *106*, 2473–2506.– [8b] L. Overman, *Pure Appl. Chem.* **1994**, *66*, 1423–1430.

[9] B. Wünsch, H. Diekmann, *Liebigs Ann. Chem.* **1996**, 69–76.

[10] [10a] U. Schmidt, A. Kleefeldt, R. Mangold, *J. Chem. Soc. Chem. Commun.* **1992**, 1687–1689.– [10b] M. Thiam, A. Slassi, F. Chastrette, R. Amouroux, *Synth. Commun.* **1992,** *22*, 83–95.– [10c] M. Labelle, Y. Guindon, *J. Am. Chem. Soc*. **1989,** *111*, 2204–2210.– [10d] J. Pawlak, K. Nakanishi, T. Iwashita, E. Borowski, *J. Org. Chem.* **1987**, *52*, 2896–2901.– [10e] B. Herradon, *Tetrahedron: Asymmetry* **1991**, *2*, 191–194.

[11] G. Rosini, R. Ballini, *Synthesis* **1988**, 833–847.

[12] [12a] R. S. C. Lopes, C. C. Lopes, C. H. Heathcock, *Tetrahedron Lett.* **1992**, *33*, 6775–6778.– [12b] C.-F. Yao, K.-H. Kao, J.-T. Liu, C.-M. Chu, Y. Wang, W.-C. Chen, Y.-M. Lin, W.-W. Lin, M.-C. Yan, J.-Y. Liu, M.-C. Chuang, J.-L. Shiue, *Tetrahedron* **1998**, *54*, 791–822.

[13] R. F. Borch, M. D. Bernstein, H. D. Durst, *J. Am. Chem. Soc*. **197***1*, *93*, 2897–2904.

[14] [14a] F. Eiden, F. Denk, G. Höfner, *Arch. Pharm. (Weinheim, Ger.)* **1994**, *327*, 405–412.– [14b] R. M. McKernan, S. Castro, J. A. Poat, E. H. F. Wong, *J. Neurochem*. **1989**, *52*, 777–785.– [14c] Information sheet *Drug Discovery System: Glutamate Receptor NMDA Subtype*, Du Pont NEN.

[15] [15a] K. Th. Wanner, I. Praschak, G. Höfner, H. Beer, *Arch. Pharm. Pharm. Med. Chem.* **1996**, *329*, 11–22.– [15b] S. Archer, A. Seyed-Mozaffari, Q. Jiang, J. M. Bidlack, *J. Med. Chem.* **1994**, *37*, 1578–1585.

[16] [16a] K. Th. Wanner, H. Beer, G. Höfner, M. Ludwig, *Eur. J. Org. Chem.* **1998**, 2019–2029.– [16b] E. Weber, M. Sondres, M. Quarum, S. McLean, S. Pou, J. F. W. Keana, *Proc. Natl. Acad. Sci.* **1986**, *83*, 8784–8788.

[17] W. S. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

[18] Y. Cheng, W. H. Prussoff, *Biochem. Pharmacol*. **1973**, *22*, 3099–3108.

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