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Synthesis and NMDA Receptor Affinity of Ring and Side Chain Homologues of Dexoxadrol

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Dedicated to Prof. Dr. H. D. Stachel on the occasion of his 80th birthday

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Novel dexoxadrol derivatives with an expanded oxygen heterocycle (1,3-dioxane instead of 1,3-dioxolane), an enlarged distance between the two heterocycles, and an additional oxo group in the 4-position of the piperidine ring were synthesized and pharmacologically evaluated. The synthesis comprises a hetero-Diels–Alder reaction of imines with Danishefsky's diene (**3**), followed by a Lewis acid catalyzed conjugate reduction of the resulting dihydropyridones and hydrogenolytic debenzylation. The required aldehydes were synthesized by transacetalization of benzophenone dimethyl acetal (**8**) with pentane-1,3,5-triol (**7**), butane-1,2,4-triol (**15**), and 4-benzyloxybutane-1,3-diol (**31**), respectively, and subsequent Swern oxidation. Homodexoxadrols **39** were synthesized by the Cagliotti method with the use of *p*-toluenesulfonylhydrazide and $NaBH_4$ for the removal of the oxo group. The diastereomers were separated and the relative configuration was assigned by X-ray crystal structure analysis and comparison of spectroscopic and chromatographic data. Receptor binding studies with the radioligand [^{3}H]-(+)-MK-801 demonstrated that an expanded O-heterocycle, an enlarged distance between the heterocycles, and an additional oxo group led to a considerable loss of affinity towards the phencyclidine binding site of the NMDA receptor.

Introduction

The excitatory amino acid neurotransmitters (*S*)-aspartate and (*S*)-glutamate mediate their effects by activation of glutamate receptors. The class of glutamate receptors is subdivided into metabotropic (mGlu1-mGlu8) and ionotropic (iGlu) receptors. Within the class of ionotropic glutamate receptors (AMPA, kainate, NMDA), the NMDA receptor is the best-investigated subtype. It plays a crucial role in several neurological processes including learning and memory.[1,2] However, overstimulation of the NMDA receptor with the endogenous ligand (*S*)-glutamate leads to an increased opening of the associated cation channel and, subsequently, to a massive influx of Ca^{2+} ions into the neuron. The pathophysiological increase in the intracellular Ca^{2+} concentration causes acute damage of neurons (excitotoxicity), which is observed after stroke or brain injury. However, the NMDA receptor is also involved in the development of chronic neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, epilepsy, and amyotrophic lateral sclerosis. Therefore, the NMDA receptor represents an interesting target for the development of novel drugs for the therapy of CNS disorders.[3,4]

There are several binding sites for the modulation of the NMDA receptor activity. Our interest has been focused on ligands interacting with the phencyclidine (PCP) binding site, which is located within the ion channel pore. Because interaction of ligands with the PCP binding site of the NMDA receptor is only possible after opening of the cation channel by NMDA agonists [e.g., (*S*)-glutamate] in the presence of a coagonist (e.g., glycine), these ligands are termed open-channel blockers (uncompetitive NMDA receptor antagonists).

In the mid 1960s piperidine derivatives with an acetalic substituent in the 2-position were synthesized by Hardie and coworkers.[5] These efforts led to the enantiomerically pure compounds dexoxadrol and etoxadrol (Figure 1), which were clinically evaluated as analgesic and anesthetic drugs.[6,7] Unfortunately, in the clinical studies psychotomimetic side effects, unpleasant dreams and aberrations were observed, which brought the clinical evaluation to an end.[8,9] After detection of the NMDA receptor, it was

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shown that dexoxadrol and etoxadrol represent NMDA receptor antagonists, which block the cation channel by interacting with the PCP binding site.[3,10,11] The corresponding K_i values are 39 nM for dexoxadrol[12] and 20 nM for etoxadrol.[13]

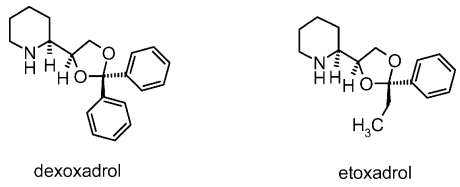


Figure 1. Lead compounds dexoxadrol and etoxadrol.

Some structure–affinity relationship studies related to these structurally and stereochemically interesting heterocycles are given in the literature.[14,15] However, there are only few studies concerning the size of the oxygen heterocycle and the distance between the oxygen heterocycle and the basic piperidine nitrogen atom.[13–16] Analogues with substituents in the piperidine ring were not included into structure–affinity relationship studies so far.

Our interest has been focused on dexoxadrol analogues and homologues **1** differing from dexoxadrol in three features: either the distance between the oxygen heterocycle and the basic nitrogen atom is enlarged (**1**, n = 1) or the oxygen heterocycle is expanded (**1**, m = 2) or both variations are performed (**1**, n = 1 and m = 2); furthermore, the piperidine ring includes an additional functional group in the 4-position (e.g., an oxo group; **1**, X = O), which allows further modifications of the piperidine heterocycle (Figure 2).

The concept for the synthesis of dexoxadrol analogues and homologues **1** is outlined in Figure 2. According to our plan, benzophenone acetals **4** with an aldehyde side chain will react after imine formation with Danishefsky's diene (**3**) in a hetero-Diels–Alder reaction to yield dihydropyridones **2**. Saturation of the double bond of vinylogous amide **2** and subsequent cleavage of the N-protecting group will end up with desired dexoxadrol homologues **1** bearing an additional oxo group in the 4-position (X = O). A critical issue of this reaction sequence is the compatibility of the benzophenone acetal substructure with the required reaction conditions, in particular for the Lewis acid catalyzed hetero-Diels–Alder reaction, the hydrogenation of the double bond and the cleavage of the N-protective group.

Following this strategy we recently synthesized racemic oxodexoxadrols **6** (general structure **1** with n = 0 and m = 1).[12] In receptor binding studies with radioligands *syn*-configured oxodexoxadrol *syn*-**6** with the same relative configuration as that of dexoxadrol showed moderate NMDA receptor affinity (K_i = 470 nM). The *anti*-configured derivative, *anti*-**6**, as well as intermediate benzyl derivatives *syn*-**5** and *anti*-**5** do not interact significantly with the NMDA receptor[12] (Figure 3).

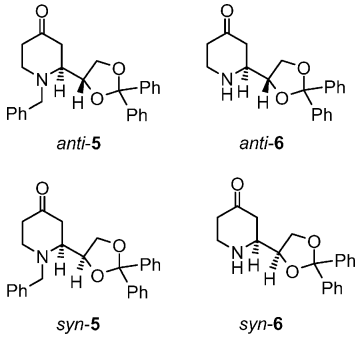


Figure 3. Dexoxadrol derivatives with an additional oxo group in the 4-position of the piperidine moiety (oxodexoxadrol; compounds are racemic, only one enantiomer is shown).

Herein, we wish to report on the synthesis, NMDA receptor affinity, and structure–affinity relationships of novel dexoxadrol homologues **1** with an enlarged piperidine–oxygen-heterocycle distance (n = 1), an expanded oxygen heterocycle (m = 2), an additional carbonyl moiety (X = O), and combinations thereof. The key step of the synthesis will be a hetero-Diels–Alder reaction[17] of imine intermediates with Danishefsky's diene (**3**).

Chemistry

At first, double homologues **14** of dexoxadrol with an expanded oxygen heterocycle (1,3-dioxane instead of 1,3-dioxolane) and an enlarged distance between the oxygen and nitrogen heterocycles were synthesized. For this purpose, dioxanylacetaldehyde **10** was required as the starting material. Aldehyde **10** was prepared by transacetalization of benzophenone dimethyl ketal (**8**) with pentane-1,3,5-triol (**7**)[18] and subsequent Swern oxidation[19] of resulting ethanol derivative **9** (Scheme 1).

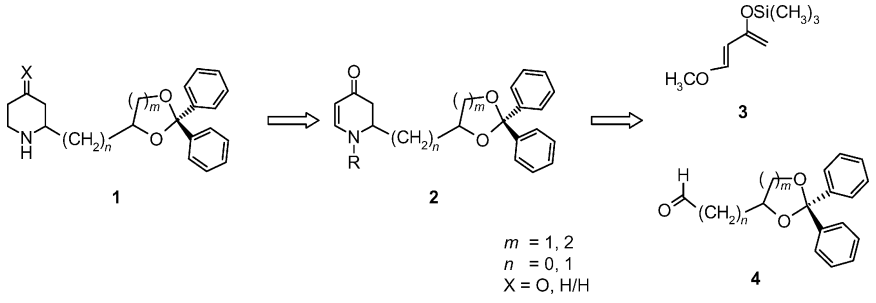
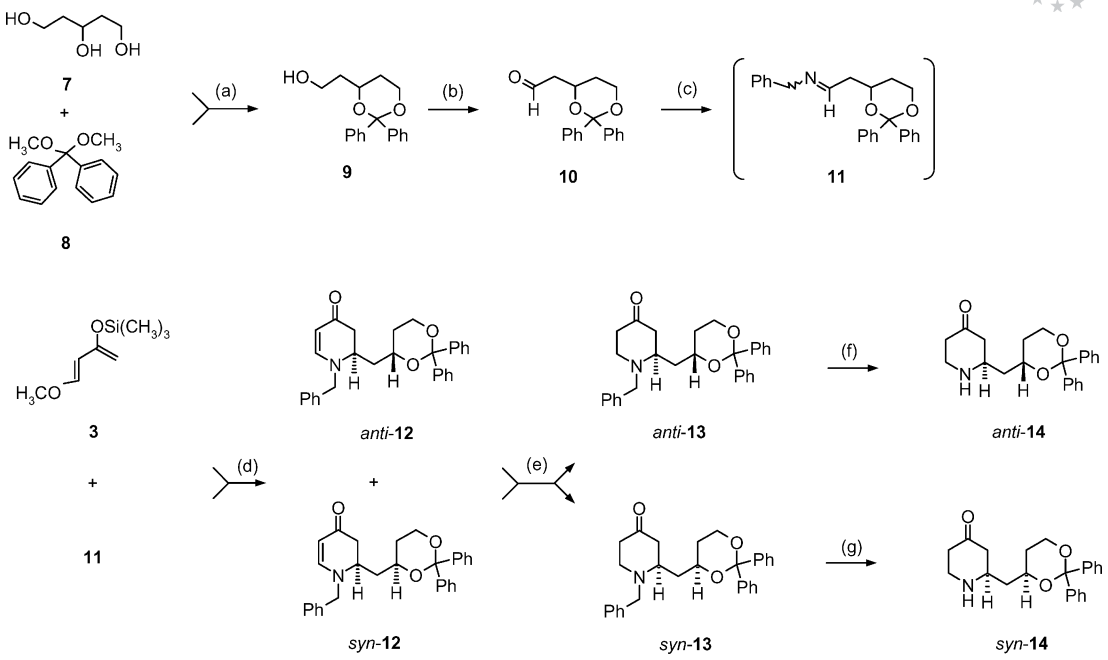


Figure 2. Strategy for the synthesis of novel ring and side chain homologues of dexoxadrol.

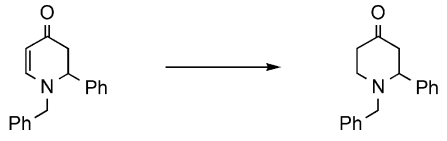


Scheme 1. (a) THF, TosOH, reflux, 7 h, 91%; (b) CH_2Cl_2, $(COCl)_2$, DMSO, NEt_3, –78 °C, 87%; (c) $HC(OCH_3)_3$, $BnNH_2$, room temp., 5 h; (d) THF, $Yb(OTf)_3$, 0 °C, 4 h, then room temp., 16 h, 74%; (e) THF, $LiBEt_3H$, $BF_3{\cdot}OEt_2$, –78 °C, 60 min, *anti*-**13**: 60%; *syn*-**13**: 23%; (f) MeOH, THF, Pd/C, H_2 (balloon), room temp., 3.5 h, 89%; (g) MeOH, Pd/C, H_2 (balloon), room temp., 5 h, 88%. All compounds are racemic, only one enantiomer is shown.

In the key step, aldehyde **10** was condensed with benzylamine in trimethyl orthoformate[20] to afford imine **11**. The progress of this transformation was controlled by IR spectroscopy. Appearance of the band at 1668 cm^{-1} indicated the formation of imine **11**, whereas the C=O band at 1724 cm^{-1} disappeared. Without purification, imine **11** was treated with Danishefsky's diene (**3**)[21] in the presence of the weak Lewis acid $Yb(OTf)_3$.[22] After flash chromatography, cycloaddition product **12** was isolated in 74% yield. Integration of characteristic signals (signal of 5-H) in the ^1H NMR spectrum revealed a 77:23 ratio of *anti*-**12**/*syn*-**12**. The *anti* and *syn* stereodescriptors refer to the orientation of the protons at the two centers of chirality in the heterocyclic rings. The basis of the assignment is the presentation of the structures in the way shown in Schemes 1–6.

According to the literature, the reduction of dihydropyridones can be performed with a small excess of L-Selectride in THF at low temperature.[23,24] However, the reduction of 1-benzyl-2-phenyl-2,3-dihydropyridin-4(1*H*)-one,[25] which served as a model compound, with L-Selectride alone afforded only low yields of the corresponding piperidin-4-one. Therefore, a small series of this model reaction was performed to investigate the reduction of the dihydropyridone double bond with various reducing agents in the absence and presence of the Lewis acids MAD [MAD = methyl aluminumbis(2,6-di-*tert*-butyl-4-methylphenoxide)[26]] and $BF_3{\cdot}OEt_2$ (Table 1). It was shown that the reduction with L-Selectride [$LiBH(secBu)_3$] and Superhydride ($LiBHEt_3$) without a Lewis acid catalyst gave only yields of 36–42% (Table 1, entries 1 and 2). Whereas in the presence of MAD the yield did not exceed 41% with L-Selectride (Table 1, entry 3) and Superhydride (Table 1, entry 4), a considerable improvement in the yield was obtained by using $BF_3{\cdot}OEt_2$ (Table 1, entries 5 and 6). Increasing the reaction temperature to –30 °C led to reduced yields (Table 1, entries 7 and 8). Thus, the best yield of the reduced piperidone (85%) was achieved with 1.1 equiv. of $LiBHEt_3$ in the presence of 1.1 equiv. of $BF_3{\cdot}OEt_2$ at –78 °C (Table 1, entry 6).

Table 1. Optimization of the reduction of the model compound 1-benzyl-2-phenyl-2,3-dihydropyridin-4(1*H*)-one.



Entry	Reducing agent (equiv.)	Lewis acid (equiv.)	Temp. [°C]	Yield [%]
1	L-Selectride (1.2)	–	–78	36
2	Superhydride (1.1)	–	–78	42
3	L-Selectride (2)	MAD (2)	–78	41
4	Superhydride (2)	MAD (2)	–78	41
5	L-Selectride (1.1)	$BF_3{\cdot}OEt_2$ (1.1)	–78	69
6	Superhydride (1.1)	$BF_3{\cdot}OEt_2$ (1.1)	–78	85
7	L-Selectride (1.1)	$BF_3{\cdot}OEt_2$ (1.1)	–30	53
8	Superhydride (1.1)	$BF_3{\cdot}OEt_2$ (1.1)	–30	66

The reaction conditions optimized for the model system ($LiBHEt_3$, $BF_3{\cdot}OEt_2$, –78 °C) were applied to acetal-substituted dihydropyridone **12** and desired piperidone **13** was isolated in 83% yield. The potentially acid-labile acetal substructure was not affected by these reaction conditions. At the reduced piperidone stage the diastereomers were separated by flash chromatography to provide *anti*-**13** and *syn*-

13 in 60 and 23% yield, respectively. In the final step, the *N*-benzyl protecting group of *anti*-**13** and *syn*-**13** was removed. Hydrogenolytic cleavage by using H_2 (1 bar) in the presence of Pd/C catalyst in methanol led to secondary amines *anti*-**14** and *syn*-**14** in 89 and 88% yield, respectively.

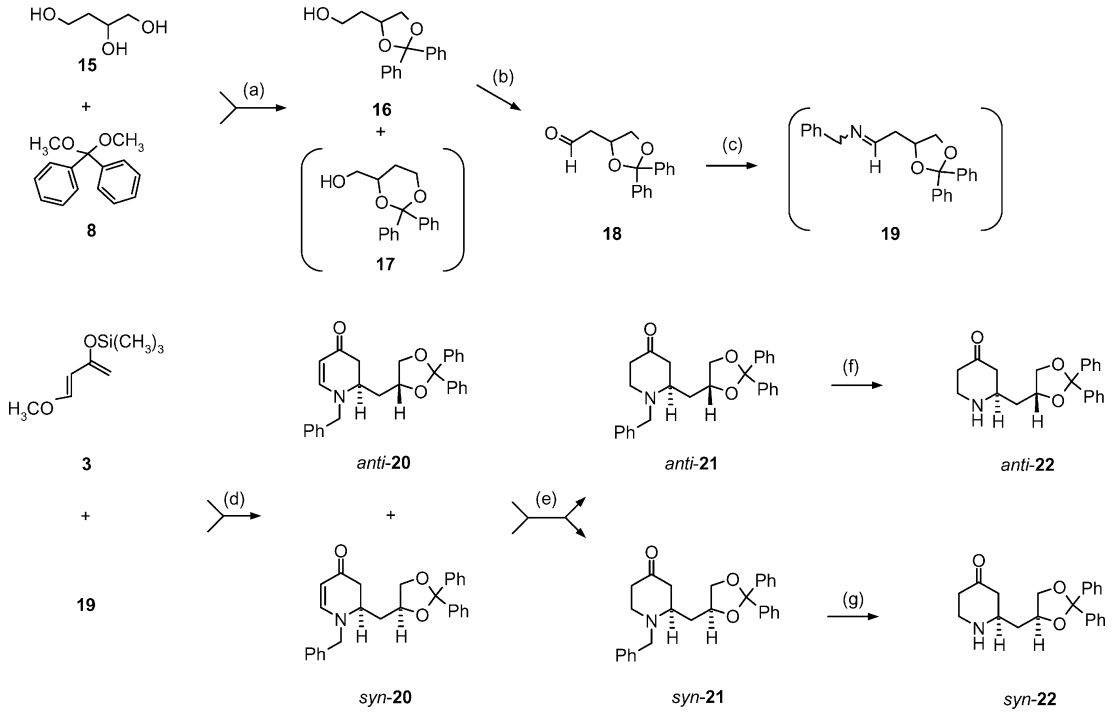
The second series of compounds comprises dexoxadrol homologues **22** with an additional methylene moiety between the piperidine and dioxolane heterocycles. It has been shown that transacetalization of the benzophenone dimethyl ketal (**8**) with the unsymmetrical butane-1,2,4-triol (**15**) under thermodynamic control predominantly led to five-membered ketal **16**.[16] Thus, heating of benzophenone ketal **8** with racemic triol **15** provided an 89:11 mixture of regioisomeric ketals **16** and **17**. The main regioisomer, **16**, was separated by flash chromatography (yield 64%) and subsequently oxidized with oxalyl chloride and DMSO (Swern oxidation) to yield aldehyde **18**.

Next, imine **19**, which was formed in situ by condensation of aldehyde **18** with benzylamine, was treated with Danishefsky's diene (**3**) and $Yb(OTf)_3$ to give dihydropyridone **20**. The 76:24 ratio of *anti*-**20**/*syn*-**20** is very similar to the *anti*/*syn* ratio of dioxane analogue **12** (*anti*-**12**/*syn*-**12**, 77:23). After reduction of dihydropyridones **20** with $LiBHEt_3$ and $BF_3{\cdot}OEt_2$, the diastereomeric piperidines were separated to give *anti*-**21** and *syn*-**21** in 49 and 16% yield, respectively. Finally, hydrogenolytic cleavage of the *N*-benzyl group led to homologous oxodexoxadrol derivatives *anti*-**22** and *syn*-**22**.

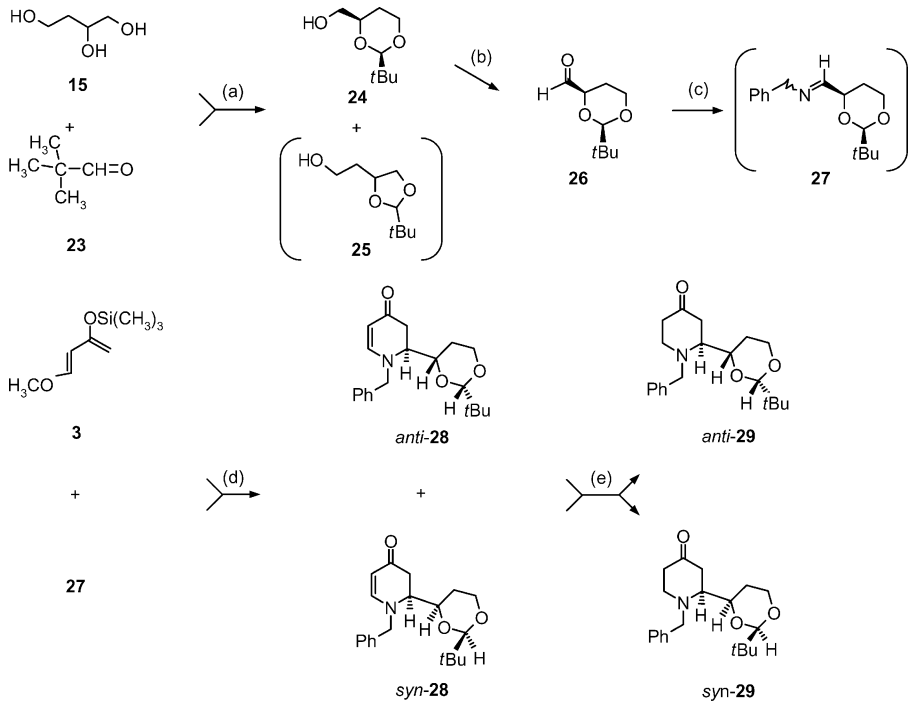
The NMDA receptor affinity and the pharmacological profile of dexoxadrol and its analogues are strongly dependent on the stereochemistry. The most potent stereoisomer is the enantiomer with (*S*)-configuration at both centers of chirality (i.e., dexoxadrol).[27,28] Therefore, the synthesis of oxodexoxadrol homologues **22** was also performed by starting with commercially available (*S*)-configured butane-1,2,4-triol [(*S*)-**15**]. Enantiomerically pure (*S*)-butanetriol (*S*)-**15** provided enantiomerically pure piperidines (*2S*,*4S*)-**21** (*anti*), (*2R*,*4S*)-**21** (*syn*), (*2S*,*4S*)-**22** (*anti*), and (*2R*,*4S*)-**22** (*syn*). Hereby, the stereochemistry of (*2R*,*4S*)-**22** (*syn*) corresponds to the stereochemistry of dexoxadrol.

1,3-Dioxolanylmethylpiperidones *anti*-**22** and *syn*-**22** represent dexoxadrol homologues with an enlarged distance between the piperidine and 1,3-dioxolane ring. In the next part, dexoxadrol homologues **37** with an enlarged O-heterocycle (1,3-dioxane instead of 1,3-dioxolane) were envisaged. At first it was tried to synthesize 1,3-dioxan-4-ylmethanol **17** by transacetalization of **8** with butanetriol **15** under kinetic control (Scheme 2). However, the yields of **17** were rather low and not reproducible, in particular, when the transformation was carried out on a large scale.

Therefore, alternatively pivalaldehyde (**23**) was treated with butanetriol **15** in refluxing THF to afford regioisomeric acetals **24** and **25** (Scheme 3).[29] Desired *cis*-configured dioxane **24** was isolated in 41% yield after flash chromatography. Swern oxidation of alcohol **24** led to aldehyde **26**, which reacted with benzylamine and trimethyl orthoformate to form imine **27**. Without isolation of **27**, the hetero-Diels–Alder reaction with Danishefsky's diene (**3**) was performed to obtain dihydropyridones **28**. Surprisingly, in this case the ratio *anti*-**28**/*syn*-**28** was 7:93.



Scheme 2. (a) THF, TosOH, reflux, 4 h, 64%; (b) CH_2Cl_2, $(COCl)_2$, DMSO, NEt_3, –78 °C, 37%; (c) $HC(OCH_3)_3$, $BnNH_2$, room temp., 2.5 h; (d) THF, $Yb(OTf)_3$, –10 °C - 0 °C, 4 h, then room temp. 16 h, 41%; (e) THF, $LiBEt_3H$, $BF_3{\cdot}OEt_2$, –78 °C, 90 min, *anti*-**21**: 49%; *syn*-**21**: 16%; (f) MeOH, Pd/C, H_2 (balloon), room temp., 3 h, 97%; (g) MeOH, Pd/C, H_2 (balloon), room temp., 3.5 h, 89%. All compounds are racemic, only one enantiomer is shown.

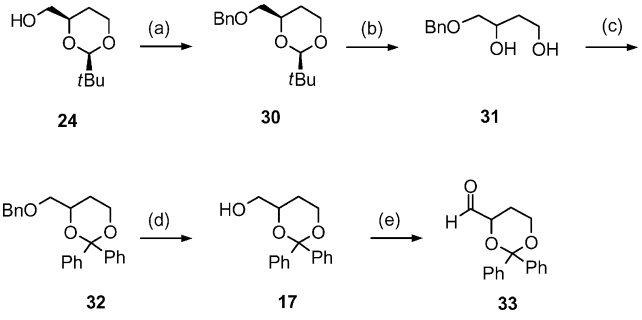


Scheme 3. (a) THF, TosOH, reflux, 23 h, **24**: 41%; **25**: 38%; (b) CH_2Cl_2, $(COCl)_2$, DMSO, NEt_3, –78 °C, 84%; (c) $HC(OCH_3)_3$, $BnNH_2$, room temp., 16 h; (d) THF, $Yb(OTf)_3$, 0 °C, 4 h, then room temp., 16 h, 90%; (e) THF, $LiBEt_3H$, $BF_3{\cdot}OEt_2$, –78 °C, 60 min, 72%. All compounds are racemic, only one enantiomer is shown.

According to our plan, pivalaldehyde acetal **28** should be hydrolyzed and the resulting 1,3-diol should be condensed with various ketones or ketals (e.g., **8**) to give dexoxadrol analogues and homologues. However, all attempts to cleave the pivalaldehyde acetal of **28** failed to produce the corresponding 1,3-diol. In particular, trifluoroacetic acid in methanol (51 h, room temp.) and *p*-toluenesulfonic acid in THF (3 h, 66 °C) were not able to hydrolyze the acetal, and HCl in aqueous dioxane at 50 °C led to complete decomposition of **28** within 2 h.

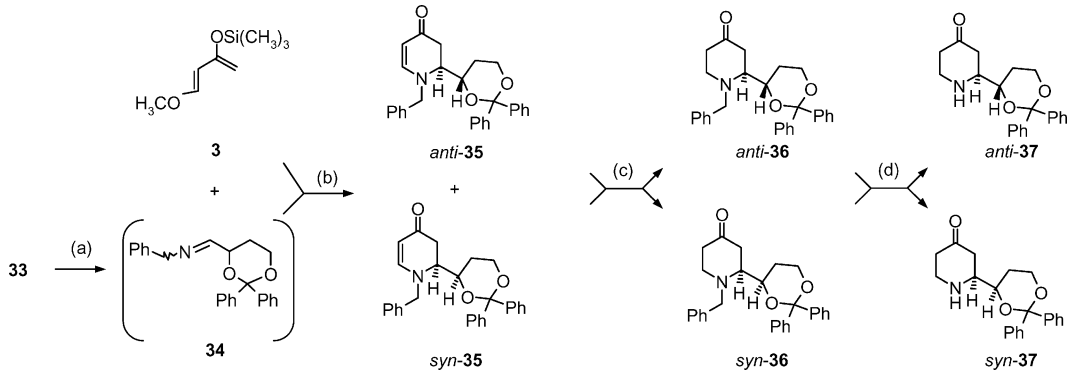
Diastereomeric mixture **28** was reduced with $LiBHEt_3$ and $BF_3{\cdot}OEt_2$ to give piperidones **29** (*anti*-**29**/*syn*-**29**, 7:93). Again, 10 equiv. of trifluoroacetic acid in aqueous dioxane at 50 °C did not lead to acetal cleavage and a reaction temperature of 70 °C led to decomposition of **29**.

Because the introduction of the benzophenone acetal at the piperidone stage failed, in an alternative strategy the benzophenone-derived 1,3-dioxane should be prepared at the beginning of the synthesis. Thus, methanol derivative **24** was transformed into benzyl ether **30** upon treatment with benzyl bromide and NaH (Scheme 4). The methanolysis of pivalaldehyde acetal **30** was catalyzed by a strong acidic ion exchange resin to obtain butane-1,3-diol **31**, which represents an interesting building block, as one of the three OH moieties of butane-1,2,4-triol is selectively protected. After filtration and evaporation of pivalaldehyde dimethyl acetal, diol **31** was used to form a new ketal with benzophenone dimethyl acetal (**8**). However, hydrogenolytic cleavage of the benzyl ether of **32** with H_2 and Pd/C in methanol predominantly led to thermodynamically more stable 1,3-dioxolane **16**. This isomerization was avoided by exchange of the protic solvent methanol for the aprotic solvent ethyl acetate, which led to 1,3-dioxane **17** in 88% yield. Subsequent oxidation of **17** with oxalyl chloride and DMSO afforded aldehyde **33** in 76% yield.



Scheme 4. (a) THF, BnBr, $Bu_4N^+I^-$, NaH, room temp., 16 h, 86%; (b) MeOH, Amberlyst® 15, reflux, 2 h (3x), 93%; (c) THF, **8**, TosOH, reflux, 19 h, 89%; (d) EtOAc, Pd/C, H_2 (balloon), room temp., 1.75 h, 88%; (e) CH_2Cl_2, $(COCl)_2$, DMSO, NEt_3, –78 °C, 76%. All compounds are racemic, only one enantiomer is shown.

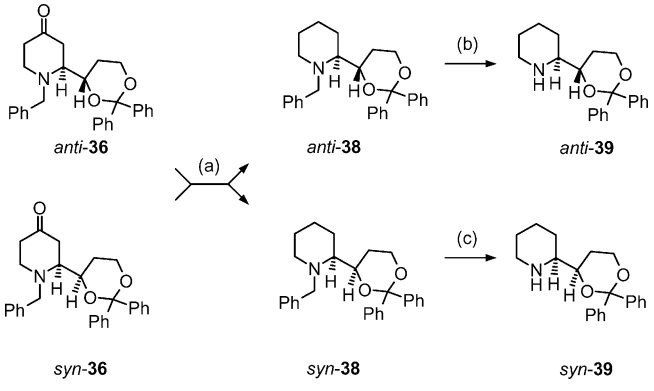
After condensation of aldehyde **33** with benzylamine, resulting imine **34** was treated without further purification with Danishefsky's diene (**3**) to yield diastereomeric dihydropyridones *anti*-**35** and *syn*-**35** in a 67:33 ratio (Scheme 5). $LiBHEt_3$ reduction of the double bond of **35** provided piperidines *anti*-**36** and *syn*-**36**. Because flash chromatographic separation of diastereomers *anti*-**36** and *syn*-**36** failed, only a small sample of the diastereomeric mixture of **36** was separated by preparative HPLC to get the pure compounds for pharmacological evaluation. After hydrogenolytic cleavage of the *N*-benzyl protective group,



Scheme 5. (a) $HC(OCH_3)_3$, $BnNH_2$, room temp., 3 h; (b) THF, $Yb(OTf)_3$, –15 °C, 1 h, then room temp., 16 h, 92%; (c) THF, $LiBEt_3H$, $BF_3{\cdot}OEt_2$, –78 °C, 60 min, 82%; the diastereomers *anti*-**36** and *syn*-**36** were separated by preparative HPLC; (d) MeOH, Pd/C, H_2 (balloon), room temp., 4.25 h, *anti*-**37**: 55%; *syn*-**37**: 34%. All compounds are racemic, only one enantiomer is shown.

diastereomers *anti*-**37** and *syn*-**37** were separated by flash chromatography.

Finally, the carbonyl moiety of **36** was removed to obtain dexoxadrol homologues **39** with a 1,3-dioxane moiety instead of the 1,3-dioxolane ring (homodexoxadrol **39**) (Scheme 6). For this purpose, the Cagliotti method using *p*-toluenesulfonylhydrazide and $NaBH_4$[30] was applied on the diastereomeric mixture of **36**. The resulting piperidines *anti*-**38** and *syn*-**38** were separated by flash chromatography and subsequently the benzyl protective group was removed by hydrogenolysis to end up with secondary amines *anti*-**39** and *syn*-**39**. Considering the stereochemistry, *syn*-**39** could be assigned as racemic homodexoxadrol.



Scheme 6. (a) MeOH, *p*-toluenesulfonylhydrazide, reflux, 2 h, then $NaBH_4$, reflux, 6 h, *anti*-**38**: 13%; *syn*-**38**: 12%; (b) MeOH, Pd/C, H_2 (balloon), room temp., 1 h, 97%; (c) MeOH, THF, Pd/C, H_2 (balloon), room temp., 1.5 h, 95%. All compounds are racemic, only one enantiomer is shown.

The relative stereochemistry of the respective *syn* and *anti* stereoisomers was determined by X-ray crystal structure analyses. Slow crystallization of *anti*-**14** from a mixture of CH_2Cl_2 and iPr_2O provided monoclinic crystals, which were suitable for X-ray crystal structure analysis (Figure 4). This analysis proves the *anti* configuration of the two centers.

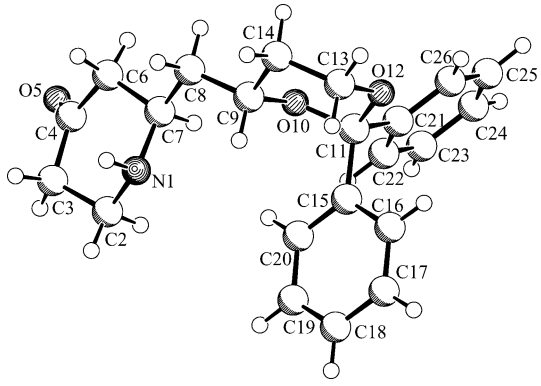


Figure 4. X-ray crystal structure analysis of *anti*-**14**.

Table 2. Comparison of characteristic properties of diastereomeric *anti*/*syn* pairs: Comparison of the ratio of diastereomers formed during the hetero-Diels–Alder reaction, the R_f values, and some characteristic signals in the ^1H and ^{13}C NMR spectra.

Compd.	Ratio of diastereomers		R_f value	Characteristic signals in the NMR spectra	
				^1H NMR	^{13}C NMR
5, **6**[12]	*anti*-**5**/*syn*-**5**	41:59	*anti*-**5**: 0.22	*anti*-**6**: 2.93 ("q", 2-H), 3.40 (ddd, 6-H)[a]	60.0 (C-2)
			syn-**5**: 0.16	*syn*-**6**: 3.10 (ddd, 2-H), 3.38 (ddd, 6-H)	59.1 (C-2)
12–**14**	*anti*-**12**/*syn*-**12**	77:23	*anti*-**13**: 0.30	*anti*-**14**: 3.34 (ddt, 2-H), 3.45 (ddd, 6-H)[a]	54.0 (C-2)
			syn-**13**: 0.19	*syn*-**14**: 3.19 (m, 2-H), 3.40 (ddd, 6-H)	55.8 (C-2)
20–**22**	*anti*-**20**/*syn*-**20**	76:24	*anti*-**21** 0.16	*anti*-**22**: 3.11 (m, 2-H), 3.29 (ddd, 6-H)	53.2 (C-2)
			syn-**21**: 0.11	*syn*-**22**: 3.08 (m, 2-H), 3.37 (ddd, 6-H)	56.4 (C-2)
28, **29**	*anti*-**28**/*syn*-**28**	7:93	*anti*.**29**: 0.35	*anti*-**29**: 3.13 (m, 2-H), 3.44 (ddd, 6-H)	62.3 (C-2)
			syn-**29**: 0.28	*syn*-**29**: 3.02 (m, 2-H), 3.13 (m, 6-H)	62.9 (C-2)
35–**37**	*anti*-**35**/*syn*-**35**	67:33	*anti*-**36**: 0.26	*anti*-**37**: 2.92 (ddd, 2-H), 3.42 (ddd, 6-H)	61.2 (C-2)
			syn-**36**: 0.26	*syn*-**37**: 3.00 (dt, 2-H), 3.40 (ddd, 6-H)	61.1 (C-2)

[a] The relative configuration of *anti*-**6** and *anti*-**14** was proven unambiguously by X-ray crystal structure analysis.

ters of chirality. Thus, the relative configuration of *syn*-**12**–**14** and *anti*-**12**–**14** is given as well. The *anti* configuration of oxodexoxadrol derivative *anti*-**6** was also proven by X-ray crystal structure analysis.[13] The relative configuration of the residual dexoxadrol analogues and homologues **20**–**22**, **28**, **29**, and **35**–**39** was unequivocally deduced from these two X-ray crystal structure analyses by comparison of ^{1}H and ^{13}C NMR spectra, chromatographic behavior, and the ratio of diastereomers that were formed during the hetero-Diels–Alder reaction. Details of this comparison are given in Table 2.

Receptor Affinity

The affinity of the novel dexoxadrol analogues and homologues for the PCP binding site of the NMDA receptor was determined in competition experiments by using the radioligand [^{3}H]-(+)-MK-801. Fresh pig brain cortex membrane preparations were employed as receptor material.[31] In addition to the NMDA receptor binding, the affinity towards σ receptors was also included in this study, because some potent NMDA antagonists also interact with σ receptors and vice versa.[32,33] In the σ assays the radioligands [^{3}H]-(+)-pentazocine (σ_1) and [^{3}H]-ditolylguanidine (σ_2) and membrane preparations from guinea pig brains (σ_1) and rat livers (σ_2) were used.[34,35]

At first, the displacement of the radioligands in the presence of relatively high concentrations (10 μM) of the test compounds is measured. Only when in this screening experiment a considerable reduction of radioligand binding was observed the complete competition curve was recorded. Otherwise in Table 3 only the inhibition (in%) of the radioligand binding at 10 μM of the test compound is given.

In Table 3 the receptor affinities of the synthesized compounds are summarized. In comparison to the NMDA receptor affinity of oxodexoxadrol *syn*-**6** (K_i = 470 nM),[13] oxygen ring-expanded analogues *anti*-**37** and *syn*-**37**, the compounds with an additional methylene moiety between the two heterocycles, *anti*-**22** and *syn*-**22**, and the compounds with additional methylene moieties in the oxygen heterocycle and in the spacer, *anti*-**14** and *syn*-**14**, reveal very-low NMDA receptor affinity. Moreover, homodexoxadrols *anti*-**39** and *syn*-**39** without the carbonyl moiety in the piperidine ring only interact in the low micromolar range (K_i = 9.2 and 6.4 μM) with the phencyclidine binding site of the NMDA receptor.

According to structure–affinity relationships, the nitrogen atom of dexoxadrol or etoxadrol should not be substituted.[15] Therefore, the negligible NMDA receptor affinity of the synthetic intermediates bearing a benzyl moiety at the N-atom (**13**, **21**, **36**, **38**) is not surprising.

In the σ_1 and σ_2 assays, very-low affinity of the test compounds was observed. Only the enantiomerically pure spacer homologous *N*-benzyl derivatives (2*S*,4*S*)-**21** (*anti*) and (2*R*,4*S*)-**21** (*syn*) interacted in the submicromolar range with the σ_1 receptor. However, the K_i values of 810 nM and 770 nM are still rather high. Nevertheless, the σ_1 receptor seems to prefer the stereoisomers with (*S*)-configuration at the 4-position of the 1,3-dioxolane ring, as corresponding racemates *anti*-**21** and *syn*-**21** are less potent.

Table 3. Affinity of the piperidine derivatives towards the phencyclidine binding site of the NMDA, σ_1, and σ_2 receptors.

Compd.	R	NMDA affinity	σ_1 affinity	σ_2 affinity
		Inhibition at c = 10 μM [%]	Inhibition at c = 10 μM [%]	Inhibition at c = 10 μM [%]
anti-**5**[13]	Bn	5	6	0
syn-**5**[13]	Bn	4	0	0
anti-**6**[13]	H	16	1.4 ± 0.09 μM[a]	46
syn-**6**[13]	H	470 ± 173 nM[a]	0	>80
anti-**13**	Bn	14	51%	27
syn-**13**	Bn	6	14 μM[a]	10
anti-**14**	H	0	29	32
syn-**14**	H	7–40	30	0
anti-**21** (*rac*)	Bn	12	1.1 ± 0.32 μM[a]	>95
syn-**21** (*rac*)	Bn	32	1.6 ± 0.35 μM[a]	>95
(2*S*,4*S*)-**21**	Bn	26	0.81 μM[a]	0
(2*R*,4*S*)-**21**	Bn	25	0.77 μM[a]	36
anti-**22** (*rac*)	H	0	5.53 μM[a]	5
syn-**22** (*rac*)	H	0	1.7 μM[a]	0
(2*S*,4*S*)-**22**	H	26	0	1
(2*R*,4*S*)-**22**	H	8	14	0
anti-**36**	Bn	0	4.5 μM[a]	3.6 μM[a]
syn-**36**	Bn	2	3.6 μM[a]	43
anti-**37**	H	0	4.0 μM[a]	0
syn-**37**	H	0	0	9
anti-**38**	Bn	15	3.4 μM[a]	6.9 μM[a]
syn-**38**	Bn	0	3.5 μM[a]	34
anti-**39**	H	9200 nM[a]	1.9 μM[a]	2.4 μM[a]
syn-**39**	H	6400 nM[a]	7.2 μM[a]	4.7 μM[a]
Dexoxadrol		39 ± 10 nM[a]	–	–

[a] K_i value: For potent compounds the K_i value was measured (n = 3). For compounds showing high K_i values (low potency) the K_i value was recorded only once.

Diastereomeric homodexoxadrols *anti*-**39** and *syn*-**39**, which only differ from dexoxadrol by expansion of the 1,3-dioxolane ring to a 1,3-dioxane ring, show σ_1 and σ_2 affinity in the low micromolar range. Thus, the σ_1 and σ_2 affinity of these compounds is comparable or even higher than that of their NMDA receptor affinity.

Conclusion

The potent NMDA receptor antagonist dexoxadrol has been modified in three directions: expansion of the 1,3-dioxolane ring to a 1,3-dioxane ring, enlargement of the distance between the two heterocycles, and introduction of an additional oxo group in the 4-position of the piperidine ring. The dexoxadrol modifications became accessible by following a novel synthetic strategy by using a hetero-Diels–Alder reaction. Receptor binding studies showed that all three variations of the parent molecule led to a considerable decrease in the affinity towards the phencyclidine binding site of the NMDA receptor.

Experimental

General: Unless otherwise noted, moisture-sensitive reactions were conducted under an atmosphere of dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use.

Methanol was dried with magnesium and iodine, distilled, and stored over 4 Å molecular sieves. DMF was dried with CaH_2, filtered, distilled, and stored over 3 Å molecular sieves. $Yb(OTf)_3$ (Aldrich) was stored in a desiccator over P_4O_{10} in vacuo at room temperature. Danishefsky's diene (**3**) was prepared according to ref.[21] and stored under an atmosphere of nitrogen at –25 °C.[12] Thin-layer chromatography (tlc): Silica gel 60 F_{254} plates (Merck). Flash chromatography (fc): Silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, eluent, fraction size, R_f. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. MS: MAT GCQ (Thermo-Finnigan). EI = electron impact, ESI = electrospray ionization. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco). Optical rotation: Polarimeter 341 (Perkin–Elmer); 1.0-dm tube, concentration *c* [g/100 mL], temperature 20 °C. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): Mercury-400BB spectrometer (Varian); δ in ppm relative to tetramethylsilane; coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and ^{1}H NMR signals were supported by 2D NMR techniques. Elemental analysis: CHN-Rapid Analysator (Fons-Heraeus). Preparative HPLC: Pump L-7150, autosampler L-7200, UV-detector L-7400, interface D-7000, data transfer D-line cable and PCI-GPIB card, HSM software (Merck-Hitachi).

2-(2,2-Diphenyl-1,3-dioxan-4-yl)ethanol (9): Pentane-1,3,5-triol[18] (**7**, 899 mg, 7.48 mmol) and benzophenone dimethyl acetal (**8**, 1.878 g, 8.23 mmol) were dissolved in THF (18 mL) and a spoon of Na_2SO_4 was added. Then, a dried (Na_2SO_4) solution of *p*-toluenesulfonic acid monohydrate in THF (0.033 M, 11.3 mL, 0.37 mmol) was added. The reaction mixture was heated to reflux for 7 h. After cooling, Et_2O and saturated $NaHCO_3$ were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2×). The combined organic layer was dried (K_2CO_3), filtered, and concentrated in vacuo, and the residue was purified by fc (5 cm; *n*-hexane/EtOAc, 60:40; 40 mL, R_f = 0.21). Colorless oil, which crystallized at 4 °C, colorless solid, m.p. 59.0 °C. Yield: 1.936 g (91%). IR (neat): $\tilde{\nu}$ = 3427 (br. m, O–H), 3026 (w, C=*C*–*H*), 2925 (m, C–H), 1196 (s)/1096 (s, C–O–C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.38–1.43 (m, 1 H, 5-H_{eq}), 1.82 (dddd, *J* = 14.5, 7.0, 4.9, 3.7 Hz, 1 H, CH_2CH$_2$OH), 1.91–2.03 (m, 2 H, 5-H_{ax} and CH_2CH$_2$OH), 2.20 (br. s, 1 H, -OH), 3.90–3.99 (m, 2 H, CH$_2$CH_2OH), 4.01–4.11 (m, 2 H, 6-H), 4.15–4.22 (m, 1 H, 4-H), 7.17–7.31 (m, 4 H, -Ph), 7.41 (t, *J* = 7.6 Hz, 2 H, -Ph), 7.47 (dd, *J* = 8.4, 1.4 Hz, 2 H, -Ph), 7.54 (dd, *J* = 8.4, 1.3 Hz, 2 H, -Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.2 (C-5), 36.6 (*C*H$_2$CH$_2$OH), 58.3 (CH$_2$*C*H$_2$OH), 59.7 (C-6), 68.0 (C-4), 99.6 (C-2), 123.3 (2 Ph-C), 125.6 (2 Ph-C), 125.9 (Ph-C), 126.0 (Ph-C), 126.2 (2 Ph-C), 127.1 (2 Ph-C), 138.1/143.0 (2 quart. Ph-C) ppm. $C_{18}H_{20}O_3$ (284.4). MS (70 eV): *m*/*z* (%) = 284 (4) [M]$^+$, 207 (54) [M – Ph], 105 (65) [PhCO], 77 (100) [Ph].

2-(2,2-Diphenyl-1,3-dioxan-4-yl)acetaldehyde (10): Under an atmosphere of N_2, CH_2Cl_2 (55 mL) and oxalyl chloride (1.02 mL, 11.95 mmol) were cooled down to –78 °C. Then, a solution of dry DMSO (1.70 mL, 23.90 mmol) in CH_2Cl_2 (14 mL) was added dropwise, and the mixture was stirred for 10 min at –78 °C. Afterwards, a solution of alcohol **9** (2.831 g, 9.96 mmol) in CH_2Cl_2 (14 mL) was added slowly, and the mixture was stirred for 30 min at –78 °C before NEt_3 (6.90 mL, 49.79 mmol) was added. After warming to room temperature, *n*-hexane was added (100 mL), the mixture was filtered, and the precipitate was washed with Et_2O. The organic layer was concentrated (600 mbar, 40 °C) and the filtration procedure was repeated. Then, the solvent was completely removed, and the residue was purified by fc (6 cm; petroleum ether/EtOAc, 80:20; 40 mL, R_f = 0.26). Colorless oil, which crystallized at 4 °C, colorless solid, m.p. 79.4 °C. Yield: 2.453 g (87%). IR (neat): $\tilde{\nu}$ = 3026 (w, Aryl-H), 2956 (m, –C–H), 2729 [w, *CH*(=O)], 1724 (s, C=O), 1196 (s)/1096 (s, C–O–C) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.41 (dq, *J* = 12.8, 2.2 Hz, 1 H, 5-H_{eq}), 1.87 (dddd, *J* = 12.9, 11.6, 10.1, 7.6 Hz, 1 H, 5-H_{ax}), 2.51 (ddd, *J* = 16.8, 4.3, 1.4 Hz, 1 H, CH_2CHO), 2.79 (ddd, *J* = 16.7, 7.9, 2.3 Hz, 1 H, CH_2CHO), 3.99–4.02 (m, 2 H, 6-H), 4.43 (dddd, *J* = 11.8, 7.9, 4.1, 2.7 Hz, 1 H, 4-H), 7.09–7.24 (m, 4 H, -Ph), 7.33 (t, *J* = 7.8 Hz, 2 H, -Ph), 7.40 (dd, *J* = 8.4, 1.4 Hz, 2 H, -Ph), 7.49 (dd, *J* = 8.6, 1.2 Hz, 2 H, -Ph), 9.88 (dd, *J* = 2.2, 1.5 Hz, 1 H, -C*H*O) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.1 (C-5), 50.1 (*C*H$_2$CHO), 61.5 (C-6), 66.4 (C-4), 101.8 (C-2), 125.3 (2 Ph-C), 127.6 (2 Ph-C), 128.0 (Ph-C), 128.15 (Ph-C), 128.25 (2 Ph-C), 129.2 (2 Ph-C), 140.0/144.9 (2 quart. Ph-C), 200.6 (-*C*HO) ppm. $C_{18}H_{18}O_3$ (282.3). MS (70 eV): *m*/*z* (%) = 282 (2) [M]$^+$, 205 (59) [M – Ph], 105 (77) [PhCO], 77 (100) [Ph].

(*RS*)-1-Benzyl-2-{[(*RS*) and (*SR*)-2,2-Diphenyl-1,3-dioxan-4-yl]-methyl}-2,3-dihydropyridin-4(1*H*)-one (*anti*-12 and *syn*-12): A solution of aldehyde **10** (2.43 g, 8.60 mmol) and benzylamine (940 μL, 8.60 mmol) in trimethyl orthoformate (30 mL) was stirred at room temperature for 5 h. The solvent was removed in vacuo, and the residual pale yellow oil (imine **11**, ν = 1668 cm^{-1}) was dissolved in THF (55 mL). A solution of $Yb(OTf)_3$ (1.066 g, 1.72 mmol) in THF (10 mL) was added, and the mixture was cooled down to 0 °C and stirred for 15 min. Then, Danishefsky's diene (**3**, 3.27 mL, 17.19 mmol) was added, and the mixture was stirred for 4 h at 0 °C and for 16 h at room temperature. Water (15 mL) and after 15 min Et_2O were added, and the mixture was washed with a mixture of saturated solutions of $NaHCO_3$/NaCl/water (1:1:1). The aqueous layer was extracted with Et_2O (2×), and the combined organic layer was dried (K_2CO_3), filtered, and concentrated in vacuo, and the residue was purified by fc (8 cm; petroleum ether/EtOAc, 25:75; 40 mL, R_f = 0.19). Pale yellow oil. Yield: 2.81 g (74%). IR (neat): $\tilde{\nu}$ = 3060 (w)/3028 (w, –C=*C*–*H*), 1636 (m, C=O), 1579 (s, C=C), 1197 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.32 (dq, *J* = 12.8, 2.3 Hz, 0.77 H, CH_2CH$_2$O°), 1.37 (dq, *J* = 13.0, 2.1 Hz, 0.23 H, CH_2CH$_2$O^x), 1.74–1.90 (m, 1.23 H, CHCH_2CH^x and CH_2CH$_2$O^x and CH_2CH$_2$°), 1.93 ("dt", *J* = 14.5, 4.8 Hz, 0.77 H, CHCH_2CH°), 2.14 (ddd, *J* = 13.6, 11.5, 2.1 Hz, 0.23 H, CHCH_2CH^x), 2.24 (ddd, *J* = 14.4, 7.8, 6.6 Hz, 0.77 H, CHCH_2CH°), 2.36 (dt, *J* = 16.5, 1.5 Hz, 0.23 H, 3-H^x), 2.37 (ddd, *J* = 16.3, 3.3, 0.9 Hz, 0.77 H, 3-H°), 2.75 (dd, *J* = 16.4, 6.7 Hz, 0.77 H, 3-H°), 2.82 (ddd, *J* = 16.5, 6.9, 1.1 Hz, 0.23 H, 3-H^x), 3.68 (tt, *J* = 7.1, 3.6 Hz, 0.77 H, 2-H°), 3.87 (tt, *J* = 11.0, 2.0 Hz, 0.23 H, OC*H*^{x}), 3.94–4.08 (m, 3 H, OC*H*° and 2×OCH_2° and 2-H^x and 2×OCH_2^{x}), 4.35 (d, *J* = 15.3 Hz, 0.77 H, PhCH_2°), 4.39 (d, *J* = 14.3 Hz, 0.23 H, PhCH_2^{x}), 4.41 (d, *J* = 15.3 Hz, 0.77 H, PhCH_2°), 4.43 (d, *J* = 14.8 Hz, 0.23 H, PhCH_2^{x}), 4.95 (dd, *J* = 7.4, 1.0 Hz, 0.23 H, 5-H^x), 5.00 (dd, *J* = 7.4, 0.9 Hz, 0.77 H, 5-H°), 7.06 (dd, *J* = 7.4, 0.9 Hz, 0.77 H, 6-H°), 7.11 (dd, *J* = 7.4, 1.1 Hz, 0.23 H, 6-H^x), 7.16–7.41 (m, 12 H, -Ph), 7.48 (m, 3 H, -Ph); ° = index for *anti*-**12** (77%, integration of 5-H° signal), ^{x} = index for *syn*-**12** (23%, integration of 5-H^x signal) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.0 (*C*H$_2$CH$_2$O°), 31.8 (*C*H$_2$CH$_2$O^x), 34.1 (CH*C*H$_2$CH^x), 36.5 (CH*C*H$_2$CH°), 38.7 (C-3^x), 41.3 (C-3°), 51.6 (C-2^x), 53.1 (C-2°), 57.8 (Ph*C*H$_2$^{x}), 58.2 (Ph*C*H$_2$°), 61.4 (O*C*H$_2$°), 61.6 (O*C*H$_2$^{x}), 66.6 (O*C*H^x), 68.5 (O*C*H°), 97.1 (C-5^x), 97.9 (C-5°), 101.3 (O*C*O^x), 101.6 (O*C*O°), 125.2/125.5/127.1/127.5/127.6/127.9/128.0/128.16/128.21/128.24/128.3/128.5/128.7/129.2/129.27/129.31 (15 Ph-C^x + 15 Ph-C°), 136.7/140.3/144.9 (quart. Ph-C°), 136.5/140.2/145.2 (quart. Ph-C^x), 152.9 (C-6°), 153.0 (C-6^x), 190.2 (C-4^x), 190.7 (C-4°) ppm. $C_{29}H_{29}NO_3$ (439.6). MS (70 eV): *m*/*z* (%) = 439 (5) [M]$^+$, 257 (72) [M – Ph_2CO], 186 (98) [M – diphenyldioxanylmethyl], 91 (100) [PhCH$_2$].

(2*RS*)-1-Benzyl-2-{[(4*RS*)-2,2-diphenyl-1,3-dioxan-4-yl]methyl}-piperidin-4-one (*anti*-13) and (2*RS*)-1-Benzyl-2-{[(4*SR*)-2,2-di-

phenyl-1,3-dioxan-4-yl]methyl}piperidin-4-one (*syn*-13): Under an atmosphere of N_2, dihydropyridone **12** (mixture of *anti*-**12** and *syn*-**12**, 413.3 mg, 0.94 mmol) was dissolved in THF (9.4 mL), and the solution was cooled down to –78 °C. Then, $BF_3{\cdot}OEt_2$ (131 μL, 1.03 mmol) was added and after stirring for 30 min at –78 °C a solution of Superhydride® ($LiBEt_3H$ 1 M in THF, 1.03 mL, 1.03 mmol) was added slowly. Stirring of the reaction mixture was continued for 60 min at –78 °C. Then, a saturated solution of $NaHCO_3$ (200 μL) and EtOAc (20 mL) were added. The mixture was warmed to room temperature, and it was then washed with saturated solutions of $NaHCO_3$ (1×) and NaCl (1×). The organic layer was dried (K_2CO_3), filtered, and concentrated in vacuo, and the residue was purified by fc (4 cm; petroleum ether/EtOAc, 70:30; 20 mL). At first *anti*-**13** then *syn*-**13** was eluted.

***anti*-13:** (R_f = 0.30): Colorless solid, m.p. 119.9 °C. Yield: 249 mg (60%). IR (neat): $\tilde{\nu}$ = 3026 (w, C=*C–H*), 2952 (m, C–H), 1707 (s, C=O), 1197 (s)/1098 (s, C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.32 (dq, *J* = 12.9, 2.1 Hz, 1 H, CH_2CH$_2$O), 1.77 (ddd, *J* = 14.5, 8.7, 5.6 Hz, 1 H, CHCH_2CH), 1.82–1.92 (m, 2 H, CHCH_2CH and CH_2CH$_2$O), 2.31–2.38 (m, 1 H, 5-H), 2.39–2.49 (m, 2 H, 3-H and 5-H), 2.69 (ddd, *J* = 14.1, 4.7, 1.2 Hz, 1 H, 3-H), 2.96 (dt, *J* = 13.1, 6.4 Hz, 1 H, 6-H), 3.09 (ddd, *J* = 13.3, 7.7, 5.3 Hz, 1 H, 6-H), 3.66–3.72 (m, 1 H, 2-H), 3.89 (s, 2 H, PhCH_2), 3.97–4.10 (m, 2 H, OCH_2), 4.13–4.22 (m, 1 H, OC*H*), 7.19–7.37 (m, 11 H, Ph), 7.49–7.56 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.7 (*C*H$_2$CH$_2$O), 38.2 (C-5), 39.0 (CH*C*H$_2$CH), 44.9 (C-3), 47.3 (C-6), 54.4 (Ph*C*H$_2$), 58.0 (C-2), 61.7 (O*C*H$_2$), 67.9 (O*C*H), 101.5 (O*C*O), 125.4/127.5/127.76/127.85/127.89/128.3/128.7/128.9/129.2 (15 Ph-C), 139.0/140.6/145.3 (3 quart. Ph-C), 209.6 (C-4) ppm. $C_{29}H_{31}NO_3$ (441.6): calcd. C 78.88, H 7.08, N 3.1; found C 78.47, H 7.12, N 3.01. MS (70 eV): *m*/*z* (%) = 442 (1) [M + H]$^+$, 364 (1) [M – Ph], 259 (10) [M – Ph$_2$CO], 188 (55) [1 – benzylpiperidin-4-one], 105 (17) [PhCO], 91 (100) [PhCH$_2$].

***syn*-13:** (R_f = 0.19): Colorless oil. Yield: 94 mg (23%). IR (neat): $\tilde{\nu}$ = 3026 (w, C=*C–H*), 2957 (s, C–H), 1711 (s, C=O), 1197 (s)/1099 (s, C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.34 (br. d, *J* = 13.3 Hz, 1 H, CH_2CH$_2$O), 1.51 (ddd, *J* = 13.5, 9.9, 3.3 Hz, 1 H, CHCH_2CH), 1.80–1.94 (m, 1 H, CH_2CH$_2$O), 2.09 (ddd, *J* = 13.6, 9.2, 4.2 Hz, 1 H, CHCH_2CH), 2.28–2.44 (m, 2 H, 3-H und 5-H), 2.56 (m, 1 H, 5-H), 2.77 (dd, *J* = 14.1, 5.1 Hz, 1 H, 3-H), 2.92 (dt, *J* = 12.0, 5.8 Hz, 1 H, 6-H), 3.05 (ddd, *J* = 12.6, 9.3, 3.7 Hz, 1 H, 6-H), 3.59–3.67 (m, 1 H, 2-H), 3.84 (d, *J* = 13.5 Hz, 1 H, PhCH_2), 3.89 (d, *J* = 13.7 Hz, 1 H, PhCH_2), 3.92–4.00 (m, 1 H, OC*H*), 4.02–4.09 (m, 2 H, OCH_2), 7.17–7.43 (m, 15 H, -Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.8 (*C*H$_2$CH$_2$O), 36.5 (CH*C*H$_2$CH), 40.2 (C-5), 44.7 (C-3), 47.8 (C-6), 55.7 (C-2), 56.9 (Ph*C*H$_2$), 61.8 (O*C*H$_2$), 67.7 (O*C*H), 101.4 (O*C*O), 125.3 (2 Ph-C), 127.4 (2 Ph-C), 127.5 (Ph-C), 127.8 (Ph-C), 128.0 (Ph-C), 128.2 (2 Ph-C), 128.7 (2 Ph-C), 128.9 (2 Ph-C), 129.1 (2 Ph-C), 139.0/140.6 (2 quart. Ph-C), 145.2 (quart. Bn-C), 210.0 (C-4) ppm. $C_{29}H_{31}NO_3$ (441.6): calcd. C 78.88, H 7.08, N 3.17; found C 78.68, H 7.14, N 2.92. MS (70 eV): *m*/*z* (%) = 441 (1) [M]$^+$, 258 (19) [M – Ph$_2$CO], 187 (47) [1-benzylpiperidin-4-one], 104 (16) [PhCO], 90 (100) [PhCH$_2$].

(2*RS*)-2-{[(4*RS*)-2,2-Diphenyl-1,3-dioxan-4-yl]methyl}piperidin-4-one (*anti*-14): To a solution of benzylpiperidinone *anti*-**13** (221.8 mg, 0.50 mmol) dissolved in MeOH (8.4 mL) and THF (2.0 mL) was added Pd/C 10% (88.7 mg), and the suspension was vigorously stirred under an H_2 atmosphere (balloon) for 3.5 h at room temperature. The reaction mixture was filtered through Celite, which was rinsed with MeOH several times, the filtrate was concentrated to dryness, and the residue was purified by fc (3 cm; EtOAc/MeOH/NH_{3conc} = 94:5:1; 10 mL; R_f = 0.37). Colorless oil, which crystallized upon standing at room temperature. Yield: 156.2 mg (89%). Recrystallization from CH_2Cl_2/*i*Pr_2O gave colorless crystals, which were suitable for X-ray crystal structure analysis, m.p. 151.9 °C (decomp.). IR (neat): $\tilde{\nu}$ = = 3279 (w, N–H), 3060 (w, C=*C–H*), 2956 (s)/2882 (m, C–H), 1699 (s, C=O), 1191 (s)/1104 (s)/1023 (s, C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.37 (dq, *J* = 12.9, 2.3 Hz, 1 H, CH_2CH$_2$O), 1.70 (ddd, *J* = 14.4, 9.2, 3.4 Hz, 1 H, CHCH_2CH), 1.80 (ddd, *J* = 14.3, 8.2, 3.4 Hz, 1 H, CHCH_2CH), 1.87 (br. s, 1 H, NH), 1.94 (dtd, *J* = 13.0, 11.7, 6.0 Hz, 1 H, CH_2CH$_2$O), 2.20 (dd, *J* = 13.7, 11.3 Hz, 1 H, 3-H), 2.37–2.48 (m, 3 H, 3-H and 2×5-H), 2.98 (ddd, *J* = 12.4, 10.2, 5.3 Hz, 1 H, 6-H), 3.34 (ddt, *J* = 11.7, 8.9, 3.1 Hz, 1 H, 2-H), 3.45 (ddd, *J* = 12.4, 5.8, 3.2 Hz, 1 H, 6-H), 4.01–4.15 (m, 3 H, OC*H* und 2×OCH_2), 7.19–7.21 (m, 1 H, Ph), 7.25–7.29 (m, 3 H, Ph), 7.38 (dd, *J* = 8.4, 6.9 Hz, 2 H, Ph), 7.49–7.53 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.2 (*C*H$_2$CH$_2$O), 43.0 (CH*C*H$_2$CH), 43.1 (C-5), 45.8 (C-6), 50.3 (C-3), 54.0 (C-2), 61.9 (O*C*H$_2$), 67.9 (O*C*H), 101.5 (O*C*O), 125.2 (2 Ph-C), 127.5 (2 Ph-C), 128.0 (1 Ph-C), 128.1 (1 Ph-C), 128.3 (2 Ph-C), 129.1 (2 Ph-C), 140.6/145.1 (2 quart. Ph-C), 209.4 (C-4) ppm. $C_{22}H_{25}NO_3$ (351.4): calcd. C 75.19, H 7.17, N 3.99; found C 74.81, H 7.09, N 4.26. MS (70 eV): *m*/*z* (%) = 351 (4) [M]$^+$, 274 (5) [M – Ph], 169 (56) [M – Ph$_2$CO], 111 (80) [2-methylenpiperidin-4-one], 105 (62) [PhCO], 98 (44) [piperidin-4-one], 77 (100) [Ph].

(2*RS*)-2-{[(4*SR*)-2,2-Diphenyl-1,3-dioxan-4-yl]methyl}piperidin-4-one (*syn*-14): To a solution of benzylpiperidinone *syn*-**13** (52.2 mg, 0.12 mmol) dissolved in MeOH (4 mL) was added Pd/C 10% (21.4 mg), and the suspension was vigorously stirred under an H_2 atmosphere (balloon) for 5 h at room temperature. The mixture was filtered through Celite, which was rinsed with MeOH several times, the filtrate was concentrated to dryness, and the residue was purified by fc (2 cm; EtOAc/MeOH/NH_{3conc}, 94:5:1; 10 mL; R_f = 0.24). Colorless oil, which crystallized upon standing at room temperature, colorless solid, m.p. 140.1 °C. Yield: 36.3 mg (88%). IR (neat): $\tilde{\nu}$ = 3355 (w)/3318 (w, N–H), 3060 (w, C=*C–H*), 2954 (m)/2874 (m, C–H), 1710 (s, C=O), 1197 (m)/1100 (s, C–O–C) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.40 (dq, *J* = 13.0, 2.2 Hz, 1 H, CH_2CH$_2$O), 1.58 (ddd, *J* = 14.2, 4.9, 3.6 Hz, 1 H, CHCH_2CH), 1.84–2.04 (m, 2 H, CHCH_2CH and CH_2CH$_2$O), 2.20 (ddd, *J* = 13.9, 11.3, 0.9 Hz, 1 H, 3-H), 2.38 (ddt, *J* = 14.3, 3.6, 2.1 Hz, 1 H, 5-H), 2.42–2.51 (m, 2 H, 3-H and 5-H), 2.83 (br. s, 1 H, NH), 2.97 (td, *J* = 11.9, 3.7 Hz, 1 H, 6-H), 3.16–3.22 (m, 1 H, 2-H), 3.40 (ddd, *J* = 12.0, 6.7, 2.4 Hz, 1 H, 6-H), 4.00–4.08 (m, 3 H, OC*H* and 2×OCH_2), 7.19–7.32 (m, 4 H, Ph), 7.40–7.49 (m, 6 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 31.6 (*C*H$_2$CH$_2$O), 42.8 (C-5), 43.4 (CH*C*H$_2$CH), 45.8 (C-6), 49.7 (C-3), 55.8 (C-2), 61.8 (O*C*H$_2$), 69.7 (O*C*H), 101.6 (O*C*O), 125.5 (2 Ph-C), 127.6 (2 Ph-C), 128.1 (1 Ph-C), 128.2 (1 Ph-C), 128.3 (2 Ph-C), 129.2 (2 Ph-C), 140.1/144.9 (2 quart. Ph-C), 209.1 (C-4) ppm. $C_{22}H_{25}NO_3$ (351.4). MS (70 eV): *m*/*z* (%) = 351 (1.3) [M]$^+$, 182 (40) [Ph$_2$CO], 169 (12) [M – Ph$_2$CO], 111 (75) [2-methylenepiperidin-4-one], 105 (73) [PhCO], 98 (33) [piperidin-4-one], 77 (100) [Ph]. Purity by HPLC, Method 1: stat. phase: RP18 Supersphere (Merck), mob. phase: methanol/phosphate buffer (pH 7.5) = 7/3, flow 0.8 mL/min, volume of injection 5 μL (*c* = 2 mg/mL), *T* = 20 °C, λ = 220 nm: t_R = 9.5 min, purity 95.2%. Method 2: stat. phase: RP8e LiChrosphere (Merck), mob. phase: methanol/phosphate buffer (pH 7.5) = 6/4, flow 1.0 mL/min, volume of injection 10 μL (*c* = 10 mg/mL), *T* = 20 °C, λ = 249 nm: t_R = 12.5 min, purity = 97.0%.

(2*RS*)-1-Benzyl-2-{[(4*RS*)-2,2-diphenyl-1,3-dioxolan-4-yl]methyl}piperidin-4-one (*anti*-21) and (2*RS*)-1-Benzyl-2-{[(4*SR*)-2,2-diphenyl-1,3-dioxolan-4-yl]methyl}piperidin-4-one (*syn*-21): Under an atmosphere of N_2 the mixture of diastereomers *anti*-**20** and

syn-**20** (780 mg, 1.83 mmol) was dissolved in THF (18 mL), whereupon the solution was cooled down to –78 °C. $BF_3{\cdot}OEt_2$ (256 μL, 2.0 mmol) was added, and the mixture was stirred for 15 min at –78 °C. Then, a Superhydride® solution (1 M in THF, 2.0 mL, 2.0 mmol) was added dropwise, and the mixture was stirred for 90 min at –78 °C. Then, a saturated solution of $NaHCO_3$ (360 μL) and EtOAc (36 mL) were added, whereupon the mixture was warmed to room temperature. The organic layer was separated, washed with brine (1×), dried (K_2CO_3), and filtered. After evaporation of the solvent the diastereomers were separated by fc (5.5 cm; petroleum ether/EtOAc, 80:20; 30 mL).

***anti*-21:** (R_f = 0.16): Colorless solid, m.p. 106.7 °C. Yield: 381 mg (49%). IR (neat): $\tilde{\nu}$ = 3060 (w, C=*C*–*H*), 2942 (m, C–H), 1710 (s, C=O), 1205 (m)/1069 (m, C–O–C–) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.76 (ddd, *J* = 14.3, 8.1, 6.1 Hz, 1 H, CHCH_2CH), 1.86 (ddd, *J* = 14.3, 8.3, 4.6 Hz, 1 H, CHCH_2CH), 2.23 (dtd, *J* = 14.3, 4.4, 1.8 Hz, 1 H, 5-H), 2.31 (ddd, *J* = 14.0, 4.3, 1.9 Hz, 1 H, 3-H), 2.52 (dddd, *J* = 14.8, 9.1, 5.6, 1.2 Hz, 1 H, 5-H), 2.76 (ddd, *J* = 14.0, 5.6, 1.2 Hz, 1 H, 3-H), 2.89 (ddd, *J* = 13.6, 5.9, 4.8, 1.0 Hz, 1 H, 6-H), 3.01 (ddd, *J* = 13.6, 9.5, 4.2 Hz, 1 H, 6-H), 3.42–3.49 (m, 1 H, 2-H), 3.64 (t, *J* = 7.6 Hz, 1 H, OCH_2), 3.84 (d, *J* = 13.3 Hz, 1 H, PhCH_2), 3.91 (d, *J* = 13.7 Hz, 1 H, PhCH_2), 4.12 (dd, *J* = 7.6, 6.5 Hz, 1 H, OCH_2), 4.31 (qd, *J* = 7.3, 4.6 Hz, 1 H, OC*H*), 7.23–7.36 (m, 11 H, Ph), 7.44–7.47 (m, 2 H, Ph), 7.49–7.52 (m, 2 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 35.9 (CH*C*H_2CH), 38.6 (C-5), 44.6 (C-3), 46.9 (C-6), 56.7 (Ph*C*H_2), 58.9 (C-2), 70.3 (O*C*H_2), 74.5 (O*C*H), 109.7 (O*C*O), 126.3 (2 Ph-C), 126.4 (2 Ph-C), 127.6 (1 Ph-C), 128.17 (1 Ph-C), 128.26 (1 Ph-C), 128.28 (2 Ph-C), 128.4 (2 Ph-C), 128.7 (2 Ph-C), 128.8 (2 Ph-C), 139.1 (quart. benzyl-C), 142.85/142.86 (2 quart. benzophenone-C), 209.5 (C-4) ppm. $C_{28}H_{29}NO_3$ (427.6): calcd. C 78.66, H 6.84, N 3.28; found C 78.58, H 6.88, N 3.25. MS (70 eV): *m*/*z* (%) = 350 (1.8) [M – Ph]$^+$, 245 (4) [M – Ph_2CO], 188 (61) [M – diphenyldioxolanylmethyl = 1-benzylpiperidin-4-one], 105 (16) [PhCO], 91 (100) [$PhCH_2$].

***syn*-21:** (R_f = 0.11): Colorless oil. Yield: 127.7 mg (16%). IR (neat): $\tilde{\nu}$ = 3062 (w, C=*C*–*H*), 2924 (s, C–H), 1714 (s, C=O), 1206 (m)/1069 (m, C–O–C–) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.52 (ddd, *J* = 13.3, 8.8, 4.8 Hz, 1 H, CHCH_2CH), 1.96 (ddd, *J* = 13.9, 8.5, 5.3 Hz, 1 H, CHCH_2CH), 2.22 (dtd, *J* = 14.4, 4.8, 1.7 Hz, 1 H, 5-H), 2.30 (ddd, *J* = 14.1, 4.8, 1.9 Hz, 1 H, 3-H), 2.42 (dddd, *J* = 14.5, 8.9, 5.8, 1.2 Hz, 1 H, 5-H), 2.66 (ddd, *J* = 14.0, 5.4, 0.9 Hz, 1 H, 3-H), 2.76 (dt, *J* = 12.3, 6.0 Hz, 1 H, 6-H), 2.94 (ddd, *J* = 13.1, 9.0, 4.3 Hz, 1 H, 6-H), 3.31 (m, 1 H, 2-H), 3.55 (dd, *J* = 7.8, 6.9 Hz, 1 H, OCH_2), 3.63 (d, *J* = 13.7 Hz, 1 H, PhCH_2), 3.71 (d, *J* = 13.3 Hz, 1 H, PhCH_2), 3.99 (dd, *J* = 7.8, 6.5 Hz, 1 H, OCH_2), 4.21 (dtd, *J* = 8.4, 6.6, 4.7 Hz, 1 H, OC*H*), 7.19–7.28 (m, 11 H, Ph), 7.37–7.42 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.5 (CH*C*H_2CH), 39.9 (C-5), 44.5 (C-3), 47.7 (C-6), 56.9 (Ph*C*H_2), 57.7 (C-2), 70.2 (O*C*H_2), 73.9 (O*C*H), 109.9 (O*C*O), 126.29 (2 Ph-C), 126.31 (2 Ph-C), 127.5 (1 Ph-C), 128.2 (1 Ph-C), 128.28 (3 Ph-C), 128.4 (2 Ph-C), 128.7 (2 Ph-C), 128.8 (2 Ph-C), 139.1 (quart. benzyl-C), 142.7/142.9 (2 quart. benzophenone-C), 209.8 (C-4) ppm. $C_{28}H_{29}NO_3$ (427.6): calcd. C 78.66, H 6.84, N 3.28; found C 78.11, H 6.82, N 3.57. MS (70 eV): *m*/*z* (%) = 350 (2) [M – Ph]$^+$, 245 (3) [M – Ph_2CO], 188 (70) [M – diphenyldioxolanylmethyl = 1-benzylpiperidin-4-one], 105 (14) [PhCO], 91 (100) [$PhCH_2$].

(2*RS*)-2-[(4*RS*)-2,2-Diphenyl-1,3-dioxolan-4-ylmethyl]piperidin-4-one (*anti*-22): 10% Pd/C (105 mg) was added to a solution of *N*-benzylpiperidinone *anti*-**21** (261 mg, 0.61 mmol) in dry MeOH/THF (2:1, 12 mL), and the suspension was vigorously stirred under an H_2 atmosphere (balloon) at room temperature for 3 h. The reaction mixture was filtered through Celite, which was rinsed with MeOH several times, the filtrate was concentrated, and the residue was purified by fc (3 cm; EtOAc/MeOH/NH_{3conc}, 94:5:1; 20 mL; R_f = 0.19). Pale yellow oil. Yield: 199 mg (97%). IR (neat): $\tilde{\nu}$ = 3330 (w, *N*–H), 3060 (w, C=*C*–*H*), 2950 (m, C–H), 1709 (s, C=O), 1206 (s)/1068 (s, C–O–C–) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.73–1.84 (m, 3 H, 2 × CHCH_2CH and NH), 2.16 (dd, *J* = 13.5, 11.5 Hz, 1 H, 3-H), 2.30–2.42 (m, 2 H, 2 × 5-H), 2.46 (ddd, *J* = 14.0, 3.0, 1.5 Hz, 1 H, 3-H), 2.82 (ddd, *J* = 12.5, 10.6, 5.1 Hz, 1 H, 6-H), 3.08–3.14 (m, 1 H, 2-H), 3.29 (ddd, *J* = 12.6, 5.9, 3.1 Hz, 1 H, 6-H), 3.71 (dd, *J* = 7.9, 7.1 Hz, 1 H, OCH_2), 4.15 (dd, *J* = 7.6, 6.7 Hz, 1 H, OCH_2), 4.34 (qd, *J* = 6.8, 5.1 Hz, 1 H, OC*H*), 7.24–7.35 (m, 6 H, Ph), 7.45–7.52 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 38.3 (CH*C*H_2CH), 40.9 (C-5), 43.6 (C-6), 47.9 (C-3), 53.2 (C-2), 68.0 (O*C*H_2), 72.2 (O*C*H), 107.9 (O*C*O), 124.1 (2 Ph-C), 124.2 (2 Ph-C), 126.19 (1 Ph-C), 126.23 (2 Ph-C), 126.25 (1 Ph-C), 126.32 (2 Ph-C), 140.4/140.6 (2 quart. benzophenone-C), 207.1 (C-4) ppm. ppm. $C_{21}H_{23}NO_3$ (337.4): calcd. C 74.75, H 6.87, N 4.15; found C 74.82, H 7.05, N 4.24. MS (70 eV): *m*/*z* (%) = 338 (5) [M + H]$^+$, 260 (11) [M – Ph], 165 (30) [$C_{13}H_9$ fluorenyl cation], 138 (36) [M – Ph_2CO_2 – H = 2-allyl-4-oxopiperidiniume], 111 (39) [2-methylenepiperidinone], 98 (100) [piperidinone].

(2*RS*)-2-[(4*SR*)-2,2-Diphenyl-1,3-dioxolan-4-ylmethyl]piperidin-4-one (*syn*-22): 10% Pd/C (42.1 mg) was added to a solution of *N*-benzylpiperidinone *syn*-**21** (103.5 mg, 0.24 mmol) in dry MeOH/THF (2:1, 6 mL), and the mixture was vigorously stirred under an H_2 atmosphere (balloon) at room temperature for 3.5 h. The reaction mixture was filtered through Celite, which was rinsed with MeOH several times, the filtrate was concentrated, and the residue was purified by fc (2 cm; EtOAc/MeOH/NH_{3conc}, 94:5:1; 10 mL; R_f = 0.19). Colorless oil. Yield: 72.4 mg (89%). IR (neat): $\tilde{\nu}$ = 3352 (w, *N*–H), 3060 (w, C=*C*–*H*), 2923 (m, C–H), 1711 (s, C=O), 1207 (s)/1067 (s, C–O–C–) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.68 (ddd, *J* = 14.1, 4.7, 3.7 Hz, 1 H, CHCH_2CH), 1.93 (ddd, *J* = 14.1, 9.1, 7.6 Hz, 1 H, CHCH_2CH), 2.22 (ddd, *J* = 14.0, 11.3, 0.9 Hz, 1 H, 3-H), 2.35 (ddt, *J* = 14.4, 3.6, 2.1 Hz, 1 H, 5-H), 2.40–2.51 (m, 2 H, 3-H and 5-H), 2.90 (td, *J* = 12.0, 3.6 Hz, 1 H, 6-H), 2.91 (br. s, 1 H, NH), 3.05–3.12 (m, 1 H, 2-H), 3.37 (ddd, *J* = 12.0, 6.7, 2.4 Hz, 1 H, 6-H), 3.68 (t, *J* = 7.5 Hz, 1 H, OCH_2), 4.14 (dd, *J* = 7.9, 6.6 Hz, 1 H, OCH_2), 4.28 (dtd, *J* = 9.2, 6.9, 3.6 Hz, 1 H, OC*H*), 7.25–7.36 (m, 6 H, Ph), 7.45–7.50 (m, 4 H, Ph) ppm. ^{13}C NMR ($CDCl_3$): δ = 40.3 (CH*C*H_2CH), 42.6 (C-5), 45.6 (C-6), 49.3 (C-3), 56.4 (C-2), 70.4 (O*C*H_2), 75.2 (O*C*H), 110.3 (O*C*O), 126.40 (2 Ph-C), 126.43 (2 Ph-C), 128.32 (2 Ph-C), 128.37 (1 Ph-C), 128.43 (1 Ph-C), 128.44 (2 Ph-C), 142.4/142.5 (2 quart. benzophenone-C), 208.9 (C-4) ppm. $C_{21}H_{23}NO_3$ (337.4): calcd. C 74.75, H 6.87, N 4.15; found C 74.76, H 6.91, N 4.30. MS (70 eV): *m*/*z* (%) = 338 (5) [M + H]$^+$, 260 (13) [M – Ph], 239 (5) [M – piperidinone = diphenyldioxolanylmethyl], 138 (36) [M – Ph_2CO_2 = 2-allyl-4-oxopiperidiniume], 98 (100) [piperidinone].

***cis*-4-(Benzyloxymethyl)-2-*tert*-butyl-1,3-dioxane (30):** Under an atmosphere of N_2 benzyl bromide (6.46 mL, 54.4 mmol) was added to a solution of $Bu_4N^+I^-$ (1.01 g, 2.72 mmol) and **24** (2.37 g, 13.6 mmol) in THF (200 mL). Then, a dispersion of NaH (60%, 0.598 g, 15 mmol) was slowly added, and the mixture was stirred for 16 h at room temperature. The mixture was filtered and after addition of a small amount of silica gel the filtrate was concentrated in vacuo. The residue was purified by fc (8 cm; *n*-hexane/EtOAc, 9:1; 40 mL; R_f = 0.34). Colorless oil. Yield: 3.08 g (86%). IR (neat): $\tilde{\nu}$ = 3064 (w, C=*C*–*H*), 2956 (s, C–H), 1044 (s, C–O–C), 734 (m, Aryl–C–H), 696 (m, out-of-plane) cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.93 [s, 9 H, C(CH_3)$_3$], 1.43 (dtd, *J* = 13.1, 2.6, 1.4 Hz, 1 H, 5-H_{eq}), 1.68 (dddd, *J* = 13.0, 12.5, 11.5, 5.1 Hz, 1 H, 5-H_{ax}), 3.47 (dd, *J* = 10.5, 4.6 Hz, 1 H, BnOCH_2), 3.58 (dd, *J* = 10.5,

5.9 Hz, 1 H, BnOCH_2), 3.72 (ddd, J = 12.4, 11.4, 2.6 Hz, 1 H, 6-H), 3.83–3.89 (m, 1 H, 4-H), 4.13 (s, 1 H, 2-H), 4.14 (ddd, J = 11.3, 5.2, 1.4 Hz, 1 H, 6-H), 4.59 (d, J = 12.1 Hz, 1 H, PhCH_2), 4.66 (d, J = 12.1 Hz, 1 H, PhCH_2), 7.27–7.37 (m, 5 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 25.0 [3 C, C(CH_3)$_3$], 28.5 (C-5), 35.1 [-C(CH_3)$_3$], 66.7 (C-6), 73.4 (BnOCH_2), 73.7 (PhCH_2), 76.9 (C-4), 107.6 (C-2), 127.77 (*para* Ph-C), 127.84 (2 C, *ortho* Ph-C), 128.6 (2 C, *meta* Ph-C), 138.7 (quart. Ph-C) ppm. $C_{16}H_{24}O_3$ (264.4). MS (70 eV): m/z (%) = 265 (9) [M + H]$^+$, 178 (15) [M – *tert*-butylCHO], 105 (33) [PhCO], 91 (100) [PhCH_2].

4-(Benzyloxy)butane-1,3-diol (31): 1,3-Dioxane **30** (1.00 g, 3.78 mmol) was dissolved in methanol (38 mL) and Amberlyst® 15 (378 mg) was added. The mixture was heated to reflux for 2 h, and it was then concentrated in vacuo. Methanol (38 mL) was added, and the mixture was heated to reflux for another 2 h. The procedure was repeated once more for 1 h. After complete transformation (tlc control), the mixture was filtered, the filtrate was concentrated in vacuo, and the residue was purified by fc (5 cm, EtOAc, 30 mL, R_f = 0.22). Colorless solid, m.p. 74.9–75.5 °C. Yield: 689 mg (93%). IR (neat): $\tilde{\nu}$ = 3368 (br. s, O–H), 3062 (w, C=C–H), 2921 (s, C–H), 1072 (s, C–O), 736 (m, aryl–C–H), 697 (m, out-of-plane) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.67–1.72 (m, 2 H, 2-H), 2.70 (s, 2 H, -OH), 3.40 (dd, J = 9.5, 7.4 Hz, 1 H, 4-H), 3.49 (dd, J = 9.5, 3.6 Hz, 1 H, 4-H), 3.79–3.84 (m, 2 H, 1-H), 4.02–4.09 (m, 1 H, 3-H), 4.56 (s, 2 H, PhCH_2), 7.27–7.39 (m, 5 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 35.1 (C-2), 61.2 (C-1), 70.4 (C-3), 73.6 (PhCH_2), 74.6 (C-4), 128.0 (2 C, *ortho* Ph-C), 128.1 (*para* Ph-C), 128.7 (2 C, *meta* Ph-C), 138.0 (quart. Ph-C) ppm. $C_{11}H_{16}O_3$ (196.3): calcd. C 67.32, H 8.2; found C 67.27, H 8.16. MS (70 eV): m/z (%) = 107 (51) [PhCH_2O], 91 (100) [PhCH_2].

(2*RS*)-1-Benzyl-2-[(4*RS*) and (4*SR*)-2,2-Diphenyl-1,3-dioxan-4-yl]-piperidin-4-one (*anti*-36 and *syn*-36): Under an atmosphere of N_2 dihydropyridone **35** (1.90 g, 4.47 mmol) was dissolved in THF (44.7 mL), and the solution was cooled down to –78 °C. BF_3·OEt_2 (622 μL, 4.91 mmol) was added, and the mixture was stirred for 55 min at –78 °C. Then, Superhydride® (1 M in THF, 4.91 mL, 4.91 mmol) was added dropwise, and the mixture was stirred for 60 min at –78 °C. A saturated $NaHCO_3$ solution (1.2 mL) and EtOAc (100 mL) were added at –78 °C, and the mixture was warmed to room temperature and subsequently washed with a saturated solution of $NaHCO_3$, water, and a saturated solution of NaCl. The organic layer was dried (K_2CO_3), filtered, and concentrated in vacuo, and the residue was purified by fc (8 cm; *n*-hexane/EtOAc, 7:3; 100 mL; R_f = 0.26). Colorless resin. Yield: 1.58 g (82%). According to the ^{1}H NMR spectrum the ratio of diastereomers *anti*-**36**/*syn*-**36** was 68:32. $C_{28}H_{29}NO_3$ (427.6): calcd. C 78.66, H 6.84, N 3.28; found C 78.25, H 6.88, N 3.25.

Diastereomeric mixture *anti*-**36** and *syn*-**36** (200 mg) was separated by preparative HPLC: column RP18 Gemini 5 μm (Phenomenex), 250 mm × 21.2 mm, room temperature., flow 20 mL/min, mobile phase acetonitrile/water = 6:4 + 0.1% *N*,*N*-dimethylethylamine, detection at λ = 220 nm, injection volume 400 μL (c = 50 mg/mL), 10 runs. The fractions containing *anti*-**36** and *syn*-**36** were combined, respectively, a saturated solution of $NaHCO_3$ and solid NaCl were added, and the mixture was extracted with EtOAc (3×). The combined organic layer was dried (K_2CO_3), filtered, and concentrated in vacuo, and the residues were purified by fc, respectively (2 cm; *n*-hexane/EtOAc, 7:3; 10 mL; R_f = 0.26).

***anti*-36:** Colorless oil, "yield" 117 mg (59%). IR (neat): $\tilde{\nu}$ = 3060 (w, C=C–H), 2929 (w, C–H), 1711 (s, C=O), 1090 (s, C–O–C), 747 (m)/732 (m, Aryl–C–H), 708 (s)/696 (s, out-of-plane) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.22–1.31 (m, 1 H, CH_2CH$_2$O-), 2.25–2.38 (m, 2 H, CH_2CH$_2$O and 5-H), 2.47–2.60 (m, 2 H, 3-H and 5-H), 2.79 (dd, J = 14.8, 6.9 Hz, 1 H, 3-H), 2.92–3.01 (m, 1 H, 6-H), 3.18–3.24 (m, 1 H, 2-H), 3.60 (ddd, J = 13.4, 9.7, 3.9 Hz, 1 H, 6-H), 3.95–4.08 (m, 4 H, OCH and OCH_2 and 2×PhCH_2), 4.09–4.16 (m, 1 H, OCH_2), 7.14–7.19 (m, 1 H, Ph-H), 7.21–7.41 (m, 10 H, Ph-H), 7.44–7.49 (m, 2 H, Ph-H), 7.51–7.56 (m, 2 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.6 (CH_2CH$_2$O), 38.2 (C-5), 40.4 (C-3), 48.6 (C-6), 58.8 (PhCH_2), 61.7 (OCH_2), 62.9 (C-2), 73.9 (OCH), 102.1 (OCO), 125.1 (2 Ph-C), 127.4 (2 Ph-C), 127.5 (Ph-C), 127.7 (Ph-C), 128.0 (Ph-C), 128.2 (2 Ph-C), 128.6 (2 Ph-C), 128.7 (2 Ph-C), 129.2 (2 Ph-C), 139.5/140.4 (quart. benzophenone-C), 145.2 (quart. PhCH_2-C), 209.50 (C-4) ppm. $C_{28}H_{29}NO_3$ (427.6): calcd. C 78.66, H 6.84, N 3.28; found C 78.04, H 6.93, N 3.25. MS (70 eV): m/z (%) = 427 (0.4) [M]$^+$, 350 (3) [M – Ph], 188 (42) [M – diphenyldioxanyl = 1-benzylpiperidin-4-on-2-yl], 91 (100) [PhCH_2].

***syn*-36:** Colorless oil, "yield" 67 mg (33%). IR (neat): $\tilde{\nu}$ = 3060 (w, C=C–H), 2931 (m, C–H), 1706 (s, C=O), 1093 (s, C–O–C), 744 (s, aryl–C–H), 707 (s)/696 (s, out-of-plane) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.67–1.84 (m, 2 H, 2 × CH_2CH$_2$O), 2.23 (br. d, J = 14.7 Hz, 1 H, 5-H), 2.60 (ddd, J = 15.1, 8.9, 6.5 Hz, 1 H, 5-H), 2.76 (dd, J = 14.5, 6.2 Hz, 1 H, 3-H), 2.92–3.07 (m, 3 H, 3-H and 2 × 6-H), 3.15–3.24 (m, 1 H, 2-H), 3.88 (d, J = 13.5 Hz, 1 H, PhCH_2), 3.91–4.05 (m, 3 H, OCH and OCH_2 and PhCH_2), 4.06–4.14 (m, 1 H, OCH_2), 7.13–7.20 (m, 1 H, Ph-H), 7.20–7.44 (m, 10 H, Ph-H), 7.44–7.50 (m, 2 H, Ph-H), 7.50–7.56 (m, 2 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 28.9 (CH_2CH$_2$O), 38.2 (C-5), 39.0 (C-3), 48.1 (C-6), 57.8 (PhCH_2), 61.7 (OCH_2), 64.8 (C-2), 70.9 (OCH), 101.8 (OCO), 125.3 (2 Ph-C), 127.7 (2 Ph-C), 127.9 (Ph-C), 128.0 (Ph-C), 128.2 (2 Ph-C), 128.7 (2 Ph-C), 128.8 (2 Ph-C), 129.2 (2 Ph-C), 139.0/140.0 (quart. benzophenone-C), 145.0 (quart. PhCH_2-C), 209.4 (C-4) ppm. $C_{28}H_{29}NO_3$ (427.6): calcd. C 78.66, H 6.84, N 3.28; found C 78.07, H 6.95, N 3.17. MS (70 eV): m/z (%) = 427 (0.2) [M]$^+$, 350 (2.3) [M – Ph], 188 (48) [M – diphenyldioxanyl = 1-benzylpiperidin-4-on-2-yl], 91 (100) [PhCH_2].

(2*RS*)-2-[(4*RS*)-2,2-Diphenyl-1,3-dioxan-4-yl]piperidin-4-one (*anti*-37) and (2*RS*)-2-[(4*SR*)-2,2-Diphenyl-1,3-dioxan-4-yl)]piperidin-4-one (*syn*-37): To a solution of benzylpiperidinone **36** (mixture of *anti*-**36** and *syn*-**36**, 712 mg, 1.67 mmol) dissolved in dry MeOH (35 mL) was added 10% Pd/C (285 mg), and the suspension was vigorously stirred under an H_2 atmosphere (balloon) at room temperature for 4.25 h. The reaction mixture was filtered through Celite, which was rinsed with MeOH several times, the filtrate was concentrated in vacuo, and the residue was purified by fc (5.5 cm; cyclohexane/EtOAc, 1:1 + 1% *N*,*N*-dimethylethylamine; 40 mL).

***anti*-37:** (R_f = 0.13): Colorless solid, m.p. 153.2 °C (decomp.). Yield: 343 mg (55%). IR (neat): $\tilde{\nu}$ = 3341 (w, N–H), 3059 (w, C=C–H), 2925 (w, C–H), 1711 (s, C=O), 1097 (s, C–O), 748 (m, aryl–C–H), 706 (m)/696 (m, out-of-plane) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.31 (dq, J = 12.9, 2.0 Hz, 1 H, OCH$_2$C$H_{2,eq}$), 1.95 (qd, J = 12.4, 5.3 Hz, 1 H, OCH$_2$C$H_{2,ax}$), 1.98 (s wide, 1 H, NH), 2.24 (dd, J = 13.8, 11.4 Hz, 1 H, 3-H), 2.28–2.37 (m, 2 H, 3-H and 5-H), 2.45 (ddd, J = 14.1, 12.4, 6.8 Hz, 1 H, 5-H), 2.85 (td, J = 12.1, 3.5 Hz, 1 H, 6-H), 2.92 (ddd, J = 10.8, 6.8, 3.9 Hz, 1 H, 2-H), 3.42 (ddd, J = 12.2, 6.7, 2.1 Hz, 1 H, 6-H), 3.86 (ddd, J = 11.6, 6.6, 2.5 Hz, 1 H, OCH), 3.94 (td, J = 12.0, 2.5 Hz, 1 H, OCH_2), 4.03 (ddd, J = 11.5, 5.2, 1.4 Hz, 1 H, OCH_2), 7.13–7.26 (m, 4 H, Ph-H), 7.33–7.40 (m, 4 H, Ph-H), 7.43–7.47 (m, 2 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 27.5 (OCH$_2$CH_2), 42.8 (C-5), 44.7 (C-3), 45.5 (C-6), 61.3 (OCH_2), 61.8 (C-2), 73.5 (OCH), 101.8 (OCO), 125.6 (2 Ph-C), 127.8 (2 Ph-C), 128.21 (Ph-C), 128.24 (Ph-C), 128.28 (2 Ph-C), 129.3 (2 Ph-C), 139.6/144.9 (2 quart. Ph-C), 209.0 (C-4) ppm. $C_{21}H_{23}NO_3$ (337.4): calcd. C 74.75, H 6.87, N 4.15; found C 74.37,

H 6.94, N 3.97. MS (70 eV): *m*/*z* (%) = 260 (6) [M – Ph]$^+$, 239 (2-diphenyl-1,3-dioxan-4-yl, 10) [2], 167 (28) [Ph_2CH], 98 (100) [M – diphenyldioxanyl = piperidin-4-on-2-yl].

***syn*-37:** (R_f = 0.08): Colorless solid, m.p. 144 °C (decomp.). Yield: 190 mg (34%). IR (neat): $\tilde{\nu}$ = 3339 (w, N–H), 3060 (w, C=*C*–*H*), 1711 (s, C=O), 1101 (s, C–O–C), 748 (m, aryl–C–H), 707 (m)/696 cm^{-1}. (m, out-of-plane). ^{1}H NMR ($CDCl_3$): δ = 1.33 (dq, *J* = 12.8, 1.7 Hz, 1 H, $OCH_2CH_{2,eq}$), 2.01 (qd, *J* = 12.3, 5.2 Hz, 1 H, $OCH_2CH_{2,ax}$), 2.10 (br. s, 1 H, NH), 2.29–2.42 (m, 3 H, 1×3-H and 2×5-H), 2.50 (ddd, *J* = 13.9, 3.0, 1.6 Hz, 1 H, 3-H), 2.86 (td, *J* = 12.0, 4.3 Hz, 1 H, 6-H), 3.00 (dt, *J* = 11.4, 3.6 Hz, 1 H, 2-H), 3.40 (ddd, *J* = 12.6, 6.2, 2.4 Hz, 1 H, 6-H), 3.91–3.99 (m, 2 H, OC*H* and OCH_2), 4.01–4.08 (m, 1 H, OCH_2), 7.12–7.25 (m, 4 H, Ph-H), 7.32–7.39 (m, 4 H, Ph-H), 7.43–7.46 (m, 2 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 26.6 (OCH_2CH_2), 43.4 (C-5), 44.5 (C-3), 45.9 (C-6), 61.1 (C-2), 61.6 (OCH_2), 73.0 (O*C*H), 101.8 (O*C*O), 125.6 (2 Ph-C), 127.8 (2 Ph-C), 128.18 (Ph-C), 128.23 (Ph-C), 128.27 (2 Ph-C), 129.2 (2 Ph-C), 139.7/144.9 (2 quart. Ph-C), 209.5 (C-4) ppm. $C_{21}H_{23}NO_3$ (337.4): calcd. C 74.75, H 6.87, N 4.15; found C 74.52, H 6.92, N 4.16. MS (70 eV): *m*/*z* (%) = 260 (6) [M – Ph]$^+$, 239 (2-diphenyl-1,3-dioxan-4-yl, 13) [2], 238 (2-diphenyl-4*H*-1,3-dioxin, 15) [2], 183 (25) [Ph_2CHO], 105 (59) [PhCO], 98 (100) [M – diphenyldioxanyl = piperidin-4-on-2-yl].

(2*RS*)-1-Benzyl-2-[(4*RS*)-2,2-diphenyl-1,3-dioxan-4-yl]piperidine (*anti*-38) and (2*RS*)-1-Benzyl-2-[(4*SR*)-2,2-diphenyl-1,3-dioxan-4-yl]-piperidine (*syn*-38): To a solution of benzylpiperidinone **36** (mixture of *anti*-**36** and *syn*-**36**, 1.09 g, 2.54 mmol) dissolved in dry MeOH (50 mL) was added *p*-toluenesulfonylhydrazide (947 mg, 5.08 mmol), and the mixture was heated to reflux for 2 h. After cooling down, $NaBH_4$ (961.6 mg, 25.4 mmol) was added, and the mixture was heated at reflux for 6 h. After cooling down, MeOH, Et_2O, and a saturated solution of $NaHCO_3$ were added. The formed precipitate was dissolved by addition of water and Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2×). The organic layer was dried (K_2CO_3), filtered, and concentrated in vacuo, and the residue was purified by fc (7.5 cm; *n*-hexane/EtOAc, 8:2; 40 mL).

***anti*-38:** (R_f = 0.36): Colorless oil. Yield: 141 mg (13%). IR (neat): $\tilde{\nu}$ = 3060 (w, C=*C*–*H*), 2929 (s, C–H), 1095 (s, C–O), 743 (m, Aryl–C–H), 705 (m)/694 (s, out-of-plane) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.22–1.35 (m, 1 H, 5-H), 1.44–1.63 (m, 3 H, 4-H and 5-H and OCH_2CH_2), 1.65–1.79 (m, 3 H, 2×3-H and 4-H), 1.87 (qd, *J* = 12.4, 5.1 Hz, 1 H, OCH_2CH_2), 2.19–2.27 (m, 1 H, 6-H), 2.53–2.60 (m, 1 H, 2-H), 2.64–2.72 (m, 1 H, 6-H), 3.43 (d, *J* = 13.9 Hz, 1 H, $PhCH_2$), 3.97 (td, *J* = 11.8, 2.3 Hz, 1 H, OCH_2), 4.02–4.16 (m, 3 H, $PhCH_2$ and OC*H* and OCH_2), 7.06–7.31 (m, 11 H, Ph), 7.40–7.49 (m, 4 H, *ortho*-benzophenone-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.8 (C-5), 20.8 (C-4), 21.0 (C-3), 26.2 (OCH_2CH_2), 47.9 (C-6), 55.3 ($PhCH_2$), 60.2 (OCH_2), 61.3 (C-2), 69.0 (O*C*H), 99.4 (O*C*O), 123.2 (2 Ph-C), 124.7 (1 Ph-C), 125.5 (2 Ph-C), 125.6 (1 Ph-C), 125.7 (1 Ph-C), 126.1 (2 Ph-C), 126.2 (2 Ph-C), 126.6 (2 Ph-C), 126.9 (2 Ph-C), 138.4/138.7 (2 quart. benzophenone-C), 143.3 (quart. $PhCH_2$-C) ppm. $C_{28}H_{31}NO_2$ (413.6): calcd. C 81.32, H 7.56, N 3.39; found C 80.87, H 7.56, N 3.38. MS (70 eV): *m*/*z* (%) = 336 (4) [M – Ph]$^+$, 174 (100) [M – diphenyldioxane = *N*-benzylpiperidin-2-yl], 91 (99.6) [$PhCH_2$].

***syn*-38:** (R_f = 0.27): Colorless oil. Yield: 123.6 mg (12%). IR (neat): $\tilde{\nu}$ = 3060 (w, C=*C*–*H*), 2931 (s, C–H), 1196 (s)/1101 (s)/1025 (s, C–O), 745 (m)/731 (m, aryl–C–H), 705 (s)/695 (s, out-of-plane) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.26–1.74 (m, 6 H, 3-H and 2×4-H and 2×5-H and OCH_2CH_2), 1.99–2.11 (m, 2 H, 3-H and OCH_2CH_2), 2.15–2.25 (m, 1 H, 6-H), 2.64–2.71 (m, 1 H, 2-H), 2.85–2.92 (m, 1 H, 6-H), 3.44 (d, *J* = 14.0 Hz, 1 H, $PhCH_2$), 3.88 (d, *J* = 13.8 Hz, 1 H, $PhCH_2$), 3.92 (td, *J* = 11.8, 3.9 Hz, 1 H, OCH_2), 4.06 (ddd, *J* = 11.3, 4.9, 1.3 Hz, 1 H, OCH_2), 4.41 (ddd, *J* = 11.5, 5.1, 1.9 Hz, 1 H, OC*H*), 7.17–7.34 (m, 9 H, Ph), 7.42 (t, *J* = 7.6 Hz, 2 H, *para*-benzophenone-H), 7.48–7.53 (m, 2 H, *ortho*-benzophenone-H), 7.56–7.61 (m, 2 H, *ortho*-benzophenone-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 21.5 (C-4), 23.2 (C-3 + C-5), 23.8 (OCH_2CH_2), 50.5 (C-6), 56.8 ($PhCH_2$), 60.0 (OCH_2), 62.1 (C-2), 68.3 (O*C*H), 99.7 (O*C*O), 123.5 (2 Ph-C), 124.7 (1 Ph-C), 125.6 (2 Ph-C), 125.7 (1 Ph-C), 125.9 (1 Ph-C), 126.0 (2 Ph-C), 126.2 (2 Ph-C), 126.6 (2 Ph-C), 126.9 (2 Ph-C), 138.0/138.5 (2 quart. benzophenone-C), 143.2 (quart. $PhCH_2$-C) ppm. $C_{28}H_{31}NO_2$ (413.6): calcd. C 81.32, H 7.56, N 3.39; found C 80.77, H 7.57, N 3.71. MS (70 eV): *m*/*z* (%) = 336 (3) [M – Ph]$^+$, 174 (100) [M – diphenyldioxane = *N*-benzylpiperidin-2-yl], 91 (84) [$PhCH_2$].

(2*RS*)-2-[(4*RS*)-2,2-Diphenyl-1,3-dioxan-4-yl]piperidine (*anti*-39): To a solution of *anti*-**38** (118.1 mg, 0.29 mmol) dissolved in dry MeOH (6 mL) was added 10% Pd/C (43.3 mg), and the suspension was vigorously stirred under an H_2 atmosphere (balloon) at room temperature for 1 h. The reaction mixture was filtered through Celite, which was rinsed with MeOH several times, the filtrate was concentrated in vacuo, and the residue was purified by fc (2 cm; EtOAc/MeOH/NH_{3conc}, 94:5:1; 10 mL; R_f = 0.27). Colorless oil, which crystallized upon standing at 4 °C, m.p. 107.3 °C. Yield: 89.7 mg (97%). IR (neat): $\tilde{\nu}$ = 3337 (w, NH), 3059 (w, C=*C*–*H*), 2930 (s, C–H), 1195 (s)/1098 (s, C–O), 745 (m, aryl–C–H), 705 (s)/694 (s, out-of-plane) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.17–1.45 (m, 4 H, 3-H and 4-H and 5-H and $OCH_2CH_{2,eq}$), 1.50–1.60 (m, 1 H, 5-H), 1.75–1.84 (m, 2 H, 3-H and 4-H), 2.01 (qd, *J* = 12.4, 5.2 Hz, 1 H, $OCH_2CH_{2,ax}$), 2.09 (br. s, 1 H, NH), 2.60 (td, *J* = 11.8, 2.7 Hz, 1 H, 6-H), 2.68 (ddd, *J* = 10.7, 4.9, 2.1 Hz, 1 H, 2-H), 3.03–3.10 (m, 1 H, 6-H), 3.77 (ddd, *J* = 11.7, 5.0, 2.4 Hz, 1 H, OC*H*), 3.91 (td, *J* = 11.9, 2.5 Hz, 1 H, OCH_2), 4.02 (ddd, *J* = 11.4, 5.1, 1.5 Hz, 1 H, OCH_2), 7.10–7.24 (m, 4 H, Ph-H), 7.32 (t, *J* = 7.6 Hz, 2 H, *para*-Ph-H), 7.38–7.48 (m, 4 H, Ph-H) ppm. ^{13}C NMR ($CDCl_3$): δ = 24.7 (C-4), 26.7 (OCH_2CH_2 and C-5), 28.1 (C-3), 47.2 (C-6), 60.6 (C-2), 61.8 (OCH_2), 74.0 (O*C*H), 101.5 (O*C*O), 125.6 (2 Ph-C), 127.8 (2 Ph-C), 127.95 (Ph-C), 127.97 (Ph-C), 128.2 (2 Ph-C), 129.1 (2 Ph-C), 140.2/145.3 (2 quart. Ph-C) ppm. $C_{21}H_{25}NO_2$ (323.4): calcd. C 77.99, H 7.79, N 4.33; found C 77.50, H 7.73, N 4.71. MS (70 eV): *m*/*z* (%) = 323 (0.6) [M]$^+$, 124 (14) [2-allylpiperidinyl], 84 (100) [M – diphenyldioxanyl = piperidin-2-yl].

(2*RS*)-2-[(4*SR*)-2,2-Diphenyl-1,3-dioxan-4-yl]piperidine (*syn*-39): To a solution of *syn*-**39** (90.2 mg, 0.22 mmol) dissolved in dry MeOH/THF (5:1, 6 mL) was added 10% Pd/C (37 mg), and the suspension was vigorously stirred under an H_2 atmosphere (balloon) at room temperature for 1.5 h. The reaction mixture was filtered through Celite, which was rinsed with MeOH several times, the filtrate was concentrated in vacuo, and the residue was purified by fc (2 cm; EtOAc/MeOH/NH_{3conc}, 94:5:1; 10 mL; R_f = 0.37). Colorless oil, which crystallized upon standing at 4 °C, colorless solid, m.p. 143.7 °C. Yield: 67.4 mg (95%). IR (neat): $\tilde{\nu}$ = 3335 (m, N–H), 3054 (w, C=*C*–*H*), 2933 (s)/2909 (s, C–H), 1197 (s)/1092 (s)/1006 (s, C–O), 759 (s, aryl–C–H), 705 (m)/695 (s, out-of-plane) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.08 (qd, *J* = 12.1, 3.7 Hz, 1 H, 3-H), 1.27 (qt, *J* = 12.7, 4.0 Hz, 1 H, 4-H), 1.37 (dq, *J* = 12.9, 2.2 Hz, 1 H, $OCH_2CH_{2,eq}$), 1.40–1.60 (m, 3 H, 3-H und 2×5-H), 1.71–1.80 (m, 1 H, 4-H), 1.81 (qd, *J* = 12.3, 5.3 Hz, 1 H, $OCH_2CH_{2,ax}$), 2.53–2.62 (m, 3 H, 2-H and 6-H and NH), 3.06–3.13 (m, 1 H, 6-H), 3.76 (ddd, *J* = 11.4, 7.9, 2.7 Hz, 1 H, OC*H*), 3.91 (td, *J* = 12.0, 2.6 Hz, 1 H, OCH_2), 4.00 (ddd, *J* = 11.5, 5.3, 1.4 Hz, 1 H, OCH_2), 7.10–7.23 (m, 4 H, Ph-H), 7.33 (t, *J* = 7.7 Hz, 2 H, *para*-Ph-H), 7.39–7.43 (m, 2 H, Ph-H), 7.47–7.49 (m, 2 H, Ph-H) ppm. ^{13}C NMR

($CDCl_3$): δ = 24.6 (C-4), 26.2 (C-5), 27.4 (C-3), 27.8 (OCH_2CH_2), 47.0 (C-6), 61.4 (OCH_2), 62.0 (C-2), 74.2 (OCH), 101.4 (OCO), 125.6 (2 Ph-C), 127.9 (2 Ph-C), 127.94 (Ph-C), 127.97 (Ph-C), 128.2 (2 Ph-C), 129.2 (2 Ph-C), 140.0/145.3 (2 quart. Ph-C) ppm. $C_{21}H_{25}NO_2$ (323.4). MS (70 eV): *m*/*z* (%) = 246 (7) $[M - Ph]^+$, 105 (10) [PhCO], 84 (100) [M – diphenyldioxanyl = piperidin-2-yl]. Purity by HPLC. Method 1: stationary phase: RP18 Supersphere (Merck), mobile phase: methanol/water = 7:3, flow 0.8 mL/min, volume of injection 10 μL (*c* = 2 mg/mL), *T* = 20 °C, λ = 220 nm: t_R = 19.7 min, purity 94.6%. Method 2: stationary phase: RP18 Gemini 5 μm, (Phenomenex), mobile phase: acetonitrile/water = 6:4 + 0.1% of *N*,*N*-dimethylethylamine, flow 1.0 mL/min, volume of injection 15 μL (*c* = 10 mg/mL), *T* = 20 °C, λ = 248 nm: t_R = 13.0 min, purity = 94.6%.

X-ray Crystal Structure Determination: Data set was collected with a Nonius KappaCCD diffractometer, equipped with a rotating anode generator. Programs used: data collection COLLECT,[36] data reduction Denzo-SMN,[37] absorption correction SORTAV,[38,39] structure solution SHELXS-97,[39] structure refinement SHELXL-97,[40] graphics SCHAKAL.[41] Data for *anti*-**14**: Formula $C_{22}H_{25}NO_3$, *M* = 351.43, colorless crystal 0.40 × 0.30 × 0.25 mm, *a* = 15.784(1) Å, *b* = 8.310(1) Å, *c* = 14.109(1) Å, β = 93.33(1)°, *V* = 1847.5(3) Å^3, $\rho_{calcd.}$ = 1.263 g cm^{-3}, μ = 0.084 mm^{-1}, empirical absorption correction ($0.967 \leq T \leq 0.979$), *Z* = 4, monoclinic, space group $P2_1/c$ (No. 14), λ = 0.71073 Å, *T* = 198(2) K, ω and ϕ scans, 10905 reflections collected ($\pm h$, $\pm k$, $\pm l$), [($\sin\theta$)/λ] = 0.66 Å^{-1}, 4389 independent (R_{int} = 0.044) and 3050 observed reflections [$I \geq 2\sigma(I)$], 240 refined parameters, *R* = 0.046, wR^2 = 0.121, max. (min.) residual electron density 0.21 (–0.19) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms. CCDC-693633 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Receptor Binding Studies

Materials and General Procedures: Homogenizer: Elvehjem Potter (B. Braun Biotech International). Centrifuge: High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Finnigan). Filter: Printed Filtermat Typ B (Perkin–Elmer), presoaked in 0.5% aqueous polyethylenimine for 2 h at room temperature before use. The filtration was carried out with a MicroBeta FilterMate-96 Harvester (Perkin–Elmer). The scintillation analysis was performed by using Meltilex (Typ A) solid scintillator (Perkin–Elmer). The solid scintillator was melted on the filtermat at a temperature of 95 °C for 5 min. After solidification of the scintillator at room temperature, the scintillation was measured by using a MicroBeta Trilux scintillation analyzer (Perkin–Elmer). The counting efficiency was 40%. All experiments were carried out in triplicates by using standard 96-well-multiplates (Diagonal). The IC_{50} values were determined in competition experiments with six concentrations of the test compounds and were calculated with the program GraphPad Prism® 3.0 (GraphPad Software) by nonlinear regression analysis. The K_i values were calculated according to Cheng and Prusoff[42] and are given as mean value + SEM from three independent experiments.

Membrane Preparation for the NMDA Assay:[31] Fresh pig brain cortex was homogenized with the potter (500–800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200 × g for 10 min at 4 °C. The supernatant was separated and centrifuged at 23500 × g for 20 min at 4 °C. The pellet was resuspended in buffer (5 mM Tris-acetate with 1 mM EDTA, pH 7.5) and centrifuged again at 31000 × g (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in buffer, the protein concentration was determined according to the method of Bradford[43] by using bovine serum albumin as standard, and subsequently the preparation was frozen (–83 °C) in 1.5 mL portions containing about 0.8 mg of protein/mL.

Performing of the NMDA Assay:[31] The test was performed with the radioligand [^{3}H]-(+)-MK–801 (22.0 Ci/mmol; Perkin–Elmer). The thawed membrane preparation (about 100 μg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]–(+)–MK–801, and TRIS/EDTA-buffer (5 mM/1 mM, pH 7.5) in a total volume of 200 μL for 180 min at room temperature. The incubation was terminated by rapid filtration through the presoaked filtermats by using the cell harvester. After washing each well with water (5 × 1300 μL), the filtermats were dried at 95 °C. Subsequently, the solid scintillator was placed on the filtermat and melted at 95 °C. After 5 min, the solid scintillator was allowed to solidify at room temperature. The bound radioactivity trapped on the filters was counted in the scintillation analyzer. The nonspecific binding was determined with 10 μM (+)–MK–801. The K_d value of the radioligand [^{3}H]-(+)-MK-801 is 2.26 nM.

Determination of the σ_1 and σ_2 Receptor Affinity: The receptor preparations for the σ_1 (guinea pig brains) and σ_2 (rat liver) assays were obtained as described in the literature. The assays were performed according to ref.[31,34]

Supporting Information (see footnote on the first page of this article): Experimental details and analytical and spectroscopic data of compounds **16**–**18**, **20**, **24**–**26**, **28**, **29**, **32**, **33**, and **35** and those of enantiomerically pure compounds (*S*)-**16**, (*S*)-**18**, (*S*,*S*)-**20**, (*R*,*S*)-**20**, (*S*,*S*)-**21**, (*S*,*R*)-**21**, (*S*,*S*)-**22**, and (*R*,*S*)-**22**.

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