# Novel Hexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrroles]: Highly Selective Small-Molecule Nociceptin/Orphanin FQ Receptor Agonists

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Novel hexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrroles that act as potent and selective orphanin FQ/nociceptin (N/OFQ) receptor (NOP) agonists were identified. The best compound, (+)-**5a**, potently inhibited $^3$H−N/OFQ binding to the NOP receptor ($K_i$ = 0.49 nM) but was >1000-fold less potent in binding to MOP, KOP, and DOP opiate receptors. Further, (+)-**5a** potently stimulated GTP$\gamma$S binding to NOP membranes ($EC_{50}$ = 65 nM) and inhibited forskolin-mediated cAMP accumulation in NOP-expressing cells ($EC_{50}$ = 9.1 nM) with a potency comparable to that of the natural peptide agonist N/OFQ. These results indicate that (+)-**5a** is a highly selective and potent small-molecule full agonist of the NOP receptor.

## Introduction

The 17 amino acid peptide orphanin FQ/nociceptin (N/OFQ)[1,2] is the endogenous ligand of the opiate-like receptor NOP (previously named ORL1).[3] NOP, like DOP ($\delta$), KOP ($\kappa$), and MOP ($\mu$), is mainly coupled to the inhibitory G protein ($G_i$), which results in the inhibition of cAMP production upon receptor activation. Furthermore, it has been shown that NOP may modulate neuronal $Ca^{2+}$ and $K^+$ channels in vivo.[4]

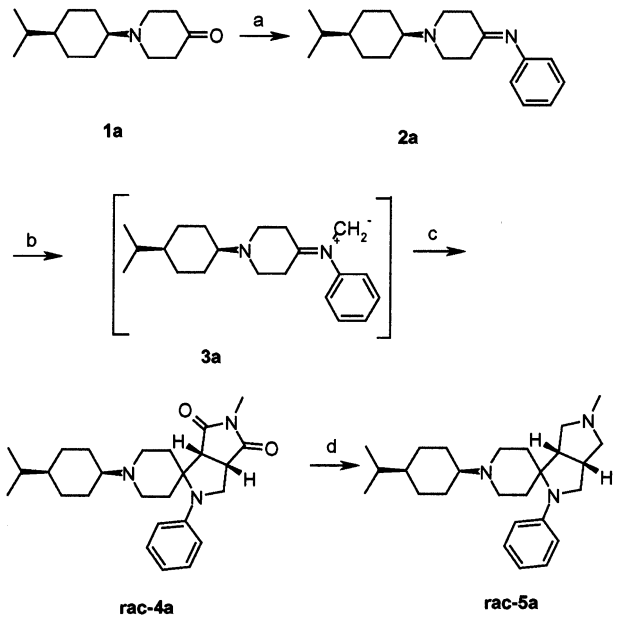
NOP plays important physiological roles in pain transmission,[5] cognition,[6] anxiety,[7] and anorexia nervosa.[8] We have recently published several studies on potent small-molecule NOP receptor agonists;[9−11] the most potent compound, Ro 64-6198, was >100-fold selective for the NOP receptor[12] and displayed anxiolytic-like activity without causing tolerance in vivo.[11−13] Although this compound may mediate its in vivo effects through the NOP receptor, it also shows moderate affinity toward KOP and MOP receptors as well as toward other receptor sites.[12,13]

In this paper we report the synthesis and characterization of a series of novel hexahydrospiropiperidine-4,1′-pyrrolo[3,4-*c*]pyrroles with improved selectivities versus opioid receptors.

## Chemistry

Spirocyclic hexahydropyrrolo[3,4-*c*]pyrroles, for example, *rac*-**5a**, were synthesized as outlined in Scheme 1. The key step is a [2 + 3] cycloaddition of *N*-methylmaleimide and azomethine ylide **3a** to give *rac*-**4a** and subsequent reduction with lithium aluminum hydride. The azomethine ylide **3a** was generated in situ from the imine precursor **2a** by sequential alkylation with (trimethylsilyl)methyl trifluoromethanesulfonate and ylide generation with cesium fluoride.[15] Imine **2a** was obtained from the corresponding piperidone **1a** and aniline by stirring in pentane at room temperature in the presence of molecular sieves.[16]

**Scheme 1**[a]




[a] (a) Aniline, molecular sieves 4 Å, pentane; (b) $(CH_3)_3SiCH_2OTf$, CsF, dimethoxyethane; (c) *N*-methylmaleimide; (d) $LiAlH_4$, $CH_2Cl_2$, ether.

Racemic N-methylated hexahydropyrrolo[3,4-*c*]pyrrole *rac*-**5a** was resolved by fractional crystallization with *O*,*O*-dibenzoyltartaric acid, and both enantiomers (+)-**5a** and (−)-**5a** were obtained with >98% ee. The absolute configuration was determined by X-ray crystallography of the tartrate salt of (+)-**5a**.

In cases where the N-substituted maleimides were not commercially available or gave insufficient yields in the [2 + 3] cycloaddition, the intermediate imides (*rac*-**4a**, *rac*-**4b**, *rac*-**4d**−**f**, *rac*-**4m**) were synthesized via Mitsunobu reaction of *rac*-**4g** and *rac*-**4l**, which gave exclusively N-alkylation as outlined in Scheme 2.[17]

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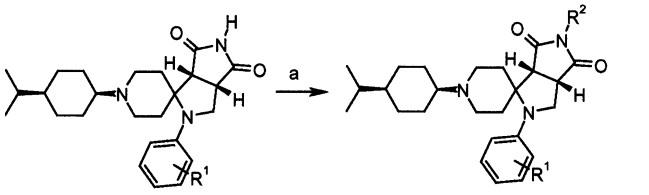
**Scheme 2**[a]

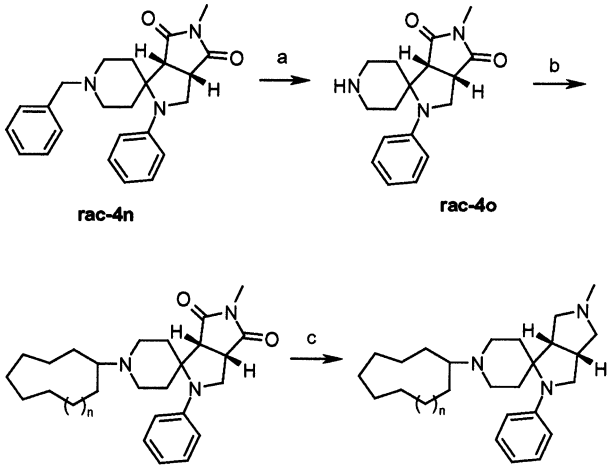


**rac-4g**: $R^1$ = H
**rac-4l**: $R^1$ = 4-F

**rac-4a**: $R^1$ = H, $R^2$ = $CH_3$
**rac-4b**: $R^1$ = H, $R^2$ = $CH_2Ph$
**rac-4d**: $R^1$ = H, $R^2$ = n-Bu
**rac-4e**: $R^1$ = H, $R^2$ = $(CH_2)_2$morpholine
**rac-4f**: $R^1$ = 4-F, $R^2$ = $CH_2$-cy-Pr
**rac-4m**: $R^1$ = H, $R^2$ = $(CH_2)_2OCH_2Ph$

[a] (a) $PPh_3$, $EtO_2C-N=N-CO_2Et$, $R^2OH$, THF.

**Scheme 3**[a]



**rac-4n** **rac-4o**

**rac-4l**: n = 1
**rac-4j**: n = 2

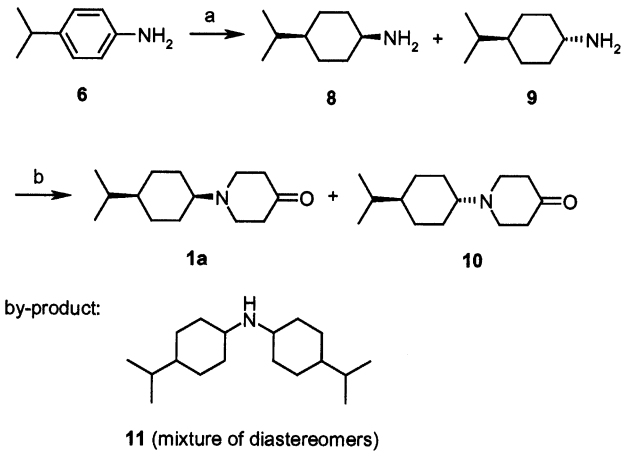
**rac-5l**: n = 1
**rac-5j**: n = 2

[a] (a) $H_2$, Pd/C, HOAc, MeOH; (b) (1) ketone, Ti(i-PrO)$_4$, THF, (2) $NaBH_3CN$, EtOH; (c) $LiAlH_4$, $CH_2Cl_2$, ether.

Cyclononyl (*rac*-**4i**) and cyclodecyl (*rac*-**4j**) substituted compounds were synthesized by reductive amination of the intermediate amine *rac*-**4o** and the corresponding ketones in the presence of titanium(IV) isopropoxide[18] as shown in Scheme 3. This methodology could be used with a variety of cyclic ketones and resulted in hexahydropyrrolo[3,4-*c*]pyrroles, which were less active as OFQ agonists (data not shown). Unfortunately, this reductive amination was not useful for 4-isopropylcyclohexanone and 2-oxodecahydronaphthalen because it produced diastereomeric mixtures of products.

The synthesis of *cis*-1-(4-isopropylcyclohexyl)piperidin-4-one (**1a**) starting from 4-isopropylaniline **6** is outlined in Scheme 4. A number of optimization experiments were carried out at 80−120 °C and 100 bar of $H_2$ to find suitable conditions for the hydrogenation of 4-isopropylaniline **6**. Ru/$Al_2O_3$ (Degussa H 213 B/D) in i-PrOH or hexane gave unfavorable cis/trans ratios of 1.1 to 1.4:1. Ru/C (JMC 19A) resulted in a 2:1 ratio of **8** and **9** and the formation of ca. 50% biscyclohexylamine **11**. Hydrogenation with both Ru/C (Degussa H 101 B/W) and Rh/C (Engelhard 8000) in HOAc gave substantial amounts (30−50%) of the N-acetylated amines. A good cis/trans ratio of 3:1 was obtained with Rh/$Al_2O_3$ (Degussa G 207 R/D) in hexane. However, the reaction was incomplete and accompanied by the formation of 11%

**Scheme 4**[a]



**6** **8** **9**

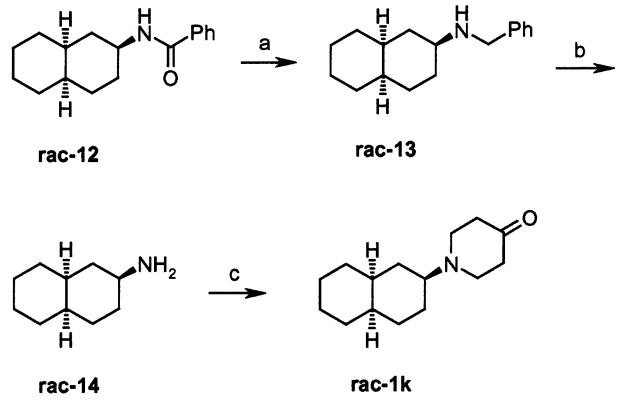
**1a** **10**

by-product:

**11** (mixture of diastereomers)

[a] (a) 5% Rh/$Al_2O_3$, 100 bar of $H_2$, i-PrOH; (b) 1-ethyl-1-methyl-4-oxopiperidinium iodide (**7**), $K_2CO_3$, i-PrOH, $H_2O$.

**Scheme 5**[a]



**rac-12** **rac-13**

**rac-14** **rac-1k**

[a] (a) $LiAlH_4$, THF; (b) $H_2$, Pd/C, EtOH; (c) 1-ethyl-1-methyl-4-oxopiperinium iodide (**7**), $K_2CO_3$, EtOH, $H_2O$.

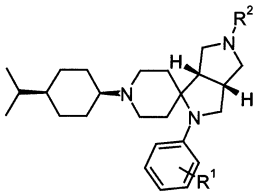
**11**. With Rh/C (Degussa G 101 S/G) in hexane, **8** and **9** were formed in a 4:1 ratio along with ca. 50% **11**. Addition of $NH_3$ to the hydrogenation decreased the dimer formation to 11%. Unfortunately, 11% starting material also remained. The best results were obtained with Rh/$Al_2O_3$ (Degussa G 207 R/D) in i-PrOH: complete conversion was achieved; **8** and **9** were obtained in a 2:1 ratio; and only about 5% **11** formed. In a Hofmann elimination and Michael addition sequence, a mixture of **8** and **9** was reacted with 1-ethyl-1-methyl-4-oxopiperinium iodide (**7**)[19] to give the piperidones **1a** and **10**. The desired *cis*-piperidone **1a** was separated from the trans compound **10** by careful chromatography on silica gel.

Racemic (2*RS*,4a*SR*,8a*RS*)1-(decahydronaphthalen-2yl)piperidin-4-one (*rac*-**1k**) was synthesized starting from the corresponding benzamide *rac*-**12**[20] by reduction and subsequent hydrogenation to give free amine *rac*-**14**, which in turn was converted to the piperidone *rac*-**1k** as shown in Scheme 5.

## Results and Discussion

The binding characteristics of spirocyclic hexahydropyrrolo[3,4-*c*]pyrroles **5a**−**k** to membranes isolated from cells expressing hDOP, hKOP, hMOP, or hNOP receptors were assessed (see Tables 1 and 2). In control experiments, high-affinity binding of the ligands N/OFQ

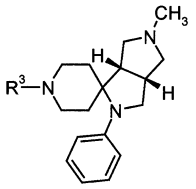
**Table 1.** Binding Affinities (p$K_i$ ± SEM) for Human NOP and Opioid (MOP, KOP, DOP) Receptors

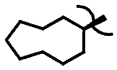
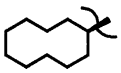
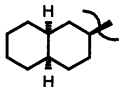


| | | | p$K_i$ ± SEM[a] | | | |
|---|---|---|---|---|---|---|
| compd | $R^1$ | $R^2$ | NOP | MOP | KOP | DOP |
| (+)-**5a** | H | $CH_3$ (3a*S*,6a*R*) | 9.26 ± 0.11 (5) | 6.27 ± 0.02 (5) | 6.51 ± 0.02 (4) | 5.67 ± 0.08 (3) |
| (−)-**5a** | H | $CH_3$ (3a*R*,6a*S*) | 8.92 ± 0.06 (3) | 6.47 ± 0.13 (3) | 6.55 ± 0.04 (3) | 5.63 ± 0.22 (3) |
| *rac*-**5b** | H | $CH_2$Ph | 8.67 ± 0.29 (3) | 6.81 ± 0.11 (3) | 6.81 ± 0.04 (2) | 6.04 ± 0.08 (2) |
| *rac*-**5c** | H | Ph | 8.78 ± 0.16 (3) | 6.87 ± 0.23 (3) | 6.29 ± 0.22 (2) | 6.66 ± 0.15 (2) |
| *rac*-**5d** | H | n-Bu | 9.18 ± 0.15 (4) | 6.56 ± 0.26 (3) | 6.60 ± 0.01 (2) | 6.41 ± 0.05 (2) |
| *rac*-**5e** | H | $(CH_2)_2$morphol | 8.68 ± 0.07 (4) | 6.75 ± 0.10 (3) | 6.83 ± 0.04 (2) | 5.53 ± 0.14 (2) |
| *rac*-**5f** | 4-F | $CH_2$-cyPr | 8.78 ± 0.09 (3) | 6.18 ± 0.04 (3) | 6.77 ± 0.19 (2) | 5.97 ± 0.01 (2) |
| *rac*-**5g** | H | H | 8.66 ± 0.25 (3) | 6.30 ± 0.13 (3) | 6.59 ± 0.07 (2) | 5.75 ± 0.06 (2) |
| *rac*-**5h** | H | $(CH_2)_2$OH | 9.11 ± 0.23 (3) | 6.76 ± 0.13 (3) | 6.88 ± 0.20 (2) | 6.03 ± 0.09 (2) |

[a] In parentheses is the number of experiments in triplicate.

**Table 2.** Binding Affinities (p$K_i$ ± SEM) for Human NOP and Opioid (MOP, KOP, DOP) Receptors



| | | p$K_i$ ± SEM[a] | | | |
|---|---|---|---|---|---|
| compd | $R^3$ | NOP | MOP | KOP | DOP |
| rac-**5i** |  | 9.19 ± 0.13 (4) | 6.14 ± 0.09 (4) | 7.25 ± 0.06 (2) | 6.05 ± 0.04 (2) |
| rac-**5j** |  | 9.35 ± 0.09 (3) | 7.06 ± 0.11 (2) | 7.57 ± 0.18 (2) | 6.43 ± 0.06 (2) |
| rac-**5k** |  | 9.28 ± 0.06 (3) | 6.38 ± 0.02 (2) | 6.88 ± 0.07 (2) | 5.99 ± 0.05 (2) |

[a] In parentheses is the number of experiments in triplicate.

(NOP), DAMGO (MOP), naloxone (KOP), and deltorphin II (DOP) was observed.[12]

All compounds show a high affinity at the NOP receptor and a good to excellent selectivity versus the opioid receptors. As already shown before for the 8-cycloalkyl-substituted 1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one series,[21] cyclodecyl (*rac*-**5j**), cyclononyl (*rac*-**5i**), and decahydronaphtha-2-yl (*rac*-**5k**, mixture of diastereomers) substituted spirocyclic hexahydro-pyrrolo[3,4-*c*]pyrroles are less selective compared to the *cis*-4-isopropylcyclohexyl substituted compounds (+)-**5a** and (−)-**5a**, especially regarding activity at the KOP receptor. We therefore focused our main efforts on the *cis*-4-isopropylcyclohexyl substituted compounds.

*rac*-**5a** was exemplarily resolved into its enantiomers. The 3a*S*,6a*R* enantiomer (+)-**5a** turned out to be superior concerning affinity at the NOP receptor and selectivity toward the other opiod receptors.

The binding properties of (3a*S*,6a*R*)-1-(*cis*-4-isopropylcyclohexyl)-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole], (+)-**5a**, are shown in Figure 1. We conducted GTP$\gamma$S stimulation studies on isolated membranes from cells expressing the NOP or

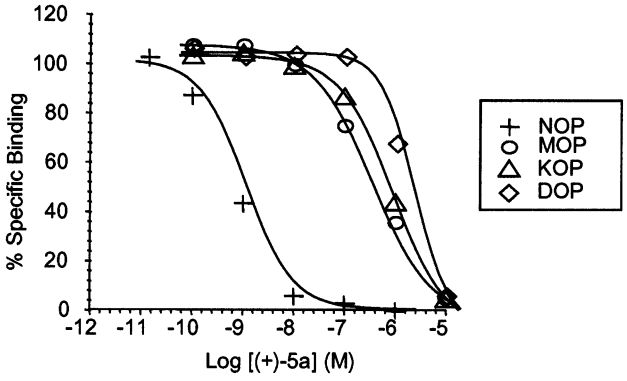



**Figure 1.** Binding properties of (+)-**5a**. Competitive binding was performed as described in Experimental Section. Data represent triplicates of one experiment repeated at least three times.

opiate receptors to assess (+)-**5a**'s agonist properties. Like N/OFQ, (+)-**5a** was a full agonist at the NOP receptors and produced a ∼3.2-fold stimulation over basal levels of GTP$\gamma$S binding to membranes of NOP-expressing cells (Figure 2A). The $EC_{50}$ values for N/OFQ ($EC_{50}$ = 38.1 ± 3.6 nM, $n$ = 6) or (+)-**5a** mediated

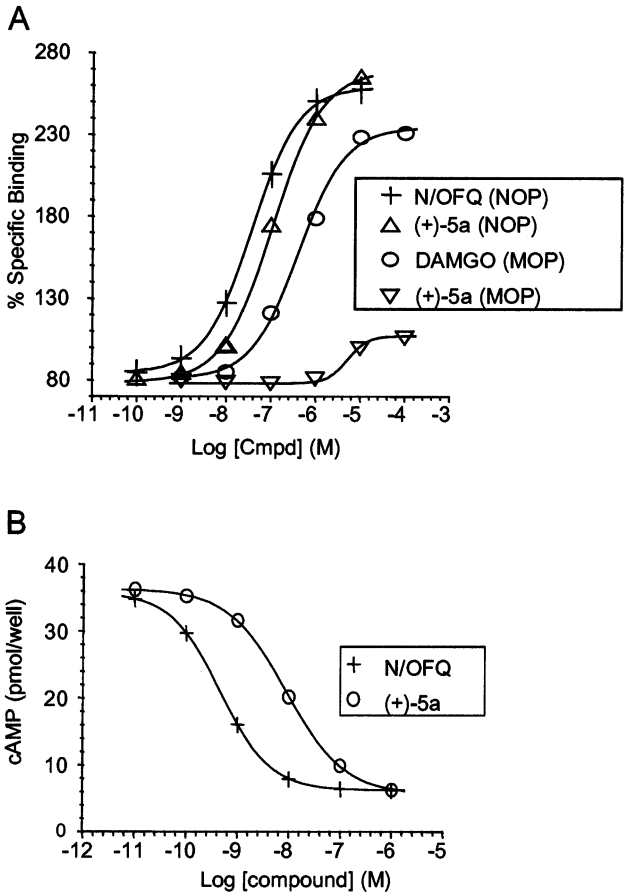



**Figure 2.** Stimulation of GTP$\gamma$S binding (A) and inhibiton of forskolin-mediated cAMP production (B) by (+)-**5a**: (A) GTP$\gamma$S-binding was assessed as described in Experimental Section; (B) HEK293 cells expressing the NOP receptor were stimulated with 1 $\mu$M forskolin and increasing concentrations ($10^{-6}$–$10^{-11}$ M) of agonists. Data are triplicates from one experiment repeated three times.

GTP$\gamma$S binding ($EC_{50}$ = 65.4 ± 6.3 nM, $n$ = 4) did not differ more than 2-fold. In contrast to its high potency at the NOP receptor, (+)-**5a** was a weak agonist at the MOP receptor. While DAMGO ($EC_{50}$ = 220 ± 44 nM, $n$ = 8), a full MOP agonist,[12] stimulated a ~2.8-fold increase over basal levels in GTP$\gamma$S-binding, (+)-**5a** ($EC_{50}$ = 7.3 ± 1.1 $\mu$M, $n$ = 3) elicited only a small (~1.3-fold) increase of GTP$\gamma$S binding (Figure 2A). Similarly, (+)-**5a** weakly activated the KOP receptor ($EC_{50}$ ≈ 10 $\mu$M, $n$ = 2) and displayed no agonistic activity at the DOP receptor (not shown).

We further assessed (+)-**5a**'s agonist potency in cAMP inhibition studies using intact NOP-expressing HEK293 cells. (+)-**5a** and N/OFQ were equally efficacious and inhibited >80% of the forskolin-stimulated cAMP production (Figure 2B). However, in contrast to its only 2-fold lower agonist potency in the GTP$\gamma$S binding assays, (+)-**5a** ($EC_{50}$ = 9.1 ± 4.8 nM, $n$ = 3) was approximately 25-fold less potent than N/OFQ ($EC_{50}$ = 0.36 ± 0.08 nM, $n$ = 6).

We have pharmacologically characterized (+)-**5a** as a highly selective full agonist of the NOP receptor. In binding experiments, (+)-**5a** showed subnanomolar affinity for NOP comparable to the affinity of the natural peptide N/OFQ.[1,2] In contrast, higher (+)-**5a** concentrations (>1000-fold at KOP and MOP; >4000-fold at DOP) were needed to compete for opiate receptor binding. Thus, (+)-**5a** displays a significantly higher degree of selectivity than Ro 64-6198,[7,11,12] which is less selective toward the KOP and MOP receptors.[11] We believe that a >1000-fold selectivity especially toward the MOP receptor is an interesting property for a small-molecule N/OFQ mimetic to minimize undesired side effects due to opioid activity. Indeed, since activation of the MOP receptor may produce symptoms of drug addiction,[14] a non-peptide N/OFQ agonist with considerable affinity for this receptor is highly undesirable. (+)-**5a** was further assessed in a standard binding analysis against more than 30 additional receptors and channels. The compound interacted with histamine H3, muscarinic and $\sigma$ receptors, and sodium channels only at a concentration of 10 $\mu$M and above.

In two functional assays, (+)-**5a** behaved as a full agonist of the NOP receptor. In the GTP$\gamma$S binding assay, (+)-**5a** was almost as potent as the natural ligand N/OFQ. The observed 2-fold lower potency of (+)-**5a** compared to N/OFQ most likely reflects its 2-fold lower binding affinity. In contrast to its high potency and full efficacy at the NOP receptor, (+)-**5a** only weakly stimulated GTP$\gamma$S binding at membranes of cells expressing KOP or MOP receptors and was inactive at the DOP receptor. It appears unlikely that the compound activates opiate receptors in vivo.

(+)-**5a** was also a full agonist when tested for its ability to inhibit forskolin-mediated cAMP accumulation in HEK293 cells stably expressing the NOP receptor. However, in contrast to the small differences between N/OFQ and (+)-**5a** in the GTP$\gamma$S binding assays, we observed a ~25-fold lower potency of (+)-**5a** in the cAMP assays. This difference most likely reflects the hydrophobic nature of (+)-**5a**. We routinely observed a low aqueous solubility of the compound and nonspecific binding to plastic, which could not be improved by addition of carrier molecules such as bovine serum albumin. Also, the increase of organic solvents such as DMSO interfered with the cellular response and did not improve the potency of (+)-**5a**. Because the GTP$\gamma$S assay, like the binding but unlike the cAMP assay, tolerates higher amounts of organic solvents, we believe that the potency differences of (+)-**5a** between both functional readouts are mostly reflected by the compound's low aqueous solubility. In agreement with these findings, oral and intraperitoneal application of (+)-**5a** resulted in low bioavailability, a high volume of distribution, and unspecific tissue binding. In addition, no anxiolytic-like properties could be observed in vivo, in contrast to (1*S*,3a*S*)-8-(2,3,3a,4,5,6-hexahydro-1*H*-phenalen-1-yl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one[11] described previously. Thus, we believe that (+)-**5a** represents a valuable and highly selective NOP receptor agonist for in vitro but not in vivo use. Future attempts in this project will address improved in vivo activity of N/OFQ agonists.

In conclusion, we have characterized (+)-**5a** as a high-affinity and specific ligand for the NOP receptor. In two functional in vitro assays, (+)-**5a** behaves as a full agonist of the NOP receptor and only weakly activates the closely related KOP and MOP receptors. (+)-**5a** serves as an ideal tool for further improvement of non-peptide N/OFQ agonists.

## Experimental Section

**1. Chemistry. General Procedures.** Melting points were taken with a Büchi 510 melting point apparatus and are uncorrected. The $^1$H spectra were recorded on a Bruker AC250 instrument in DMSO (unless noted otherwise). Low-resolution EI-MS spectra (EI: 70 eV) were recorded on a MS9 updated with a VG ZAB console, Finnigan data system SS300, with direct sample introduction. Microanalysis (C, H, N) were performed on a Heraeus Vario EL. Halogens were determined by standard titrimetric procedures. NMR data are reported in parts per million ($\delta$) relative to internal tetramethylsilane and are referenced to the deuterium lock signal from the sample solvent. Coupling constants ($J$) are in hertz. All reactions were performed under argon. Drying of organic solutions was with $Na_2SO_4$, and evaporation was done in a rotary evaporator at 45 °C in vacuo as appropriate. For chromatography, Merck silica gel 60 (size 70−230 mesh) was used. Analytical TLC plates employed were Merck silica gel 60 F-254 plates. Starting materials were high-grade commercial products unless stated otherwise.

***cis*-1-(4-Isopropylcyclohexyl)piperidin-4-one (1a).** To the crude reaction solution obtained in the hydrogenation step containing 4-isopropylcyclohexylamine (**8** + **9**) (5.26 L containing 2.690 mol of **8** + **9**) was added 2.1 L of deionized water and $K_2CO_3$ (744 g, 5.38 mol, 2 equiv). The clear, brown solution was heated to boiling temperature (81°C). Within 2 h, a solution of ammonium salt **7** (869 g, 3.229 mol, 1.2 equiv) in 2.75 L of water was added, and stirring at boiling temperature was continued for 2 h. GC analysis of the reaction mixture indicated that only 1.2% of the starting material **8** + **9** were left. The reaction mixture was allowed to cool to 50 °C, and i-PrOH was removed by distillation at reduced pressure. The residue, 5 L of a biphasic mixture of water and precipitated product, was extracted with 5 L of EtOAc. The organic layer was washed with 5 L of 20% aqueous NaCl. To remove an apolar byproduct, the organic layer was extracted with 8 L of 5% aqueous HOAc. The organic layer was discarded. The aqueous layer was adjusted to pH 14 with 1 L of 28% NaOH and extracted with 5 L of EtOAc. The organic layer was dried over 300 g of $Na_2SO_4$, filtered, and concentrated at reduced pressure. A total of 544 g of a brown oil was obtained, a mixture of 56% cis product **1a** and 34% trans product **10** according to GC. The crude product was combined with another batch (509 g obtained from 2.562 mol **8** + **9**) and chromatographed on silica gel (12 kg, hexane/acetone/$Et_3N$ 95:5:0.4) to afford 419 g (1.876 mol, 35.7%) of cis compound **1a** and 193 g (0.864 mol, 16.4%) of trans compound **9** as yellow oils. For GC analyses, an RTx-200 (trifluoromethylpolysiloxane) fused silica column (30 m × 0.32 mm; 0.25 $\mu$m) was used with helium as carrier gas (150 kPa). A 1% solution in EtOAc was injected. The program was 50°C at 8°C/min to 300°C. Data for **1a**: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.88 (d, $J$ = 6.6, 6H), 1.15 (m, 1H), 1.34−1.76 (mm, 9H), 2.43 (t, $J$ = 6.1, 4H), 2.45 (m, 1H), 2.83 (t, $J$ = 6.1, 4H); IR (neat) 2953 (s), 2935 (s), 2868 (s), 2801 (s), 2761 (m), 1719 (s), 1445 (m), 1225 (s) cm$^{-1}$; MS (EI), $m/z$ 223 ($M^+$, 13), 180 (5), 152 (9), 138 (100), 96 (32); GC $t_R$ = 17.0 min; TLC $R_f$ = 0.32 (hexane/acetone/$Et_3N$ 90:10:0.4). Data for **10**: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.87 (d, $J$ = 6.8, 6H), 0.94−1.13 (mm, 3H), 1.18−1.35 (mm, 2H), 1.43 (m, 1H), 1.75−1.95 (mm, 4H), 2.43 (m, 1H), 2.44 (t, $J$ = 6.2, 5H), 2.86 (t, $J$ = 6.2, 4H); IR (neat) 2955 (s), 2930 (s), 2857 (s), 2804 (s), 2757 (m), 1720 (s), 1205 (s) cm$^{-1}$; MS (EI), $m/z$ 223 ($M^+$, 16), 205 (4), 180 (4), 152 (6), 138 (100), 96 (15); GC $t_R$ = 18.0 min; TLC $R_f$ = 0.20 (hexane/acetone/$Et_3N$ 90:10:0.4).

**(2*RS*,4a*SR*,8a*RS*)-1-(Decahydronaphthalen-2-yl)piperidin-4-one (*rac*-1k).** To a boiling suspension of (2*RS*,4a*SR*,8a*RS*)-decahydronaphthalen-2-ylamine (*rac*-**14**) (31 mmol) and potassium carbonate (18 mmol) in ethanol (70 mL) was added 1-ethyl-1-methyl-4-oxopiperidinium iodide (**7**) (46 mmol) dissolved in water (25 mL). The reaction mixture was boiled for another hour, cooled, and diluted with water (60 mL). Ethanol was removed in vacuo, and the residue was partitioned between sodium hydroxide solution (1 N, 100 mL) and ethyl acetate (3 × 150 mL). Organic phases were pooled, dried with $Na_2SO_4$, and concentrated. The residue was filtered with ethyl acetate through silica gel to yield the product (5.7 g, 79%) as a yellow oil. An analytical sample was crystallized as the HCl salt from ethyl acetate. (2*RS*,4a*SR*,8a*RS*)-1-(Decahydronaphthalen-2-yl)piperidin-4-one hydrochloride (1:1): mp 174−175 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.1−1.8 (m, 13 H), 1.8−2.0 (m, 3H), 2.1 (m, 1H), 2.5 (d, 2H), 3.2 (m, 2H), 3.7 (m, 4H), 13.2 (bs, 1H); MS $m/z$ 235 ($M^+$). Anal. ($C_{15}H_{26}ClN$) C, H, N.

***cis*-[1-(4-Isopropylcyclohexyl)piperidin-4-ylidene]-phenylamine (2a). Standard Procedure A.** *cis*-1-(4-Isopropylcyclohexyl)piperidine-4-on (**1a**) (5.0 g, 23.4 mmol), aniline (3.3 g, 35.3 mmol), and molecular sieves (20 g, 4 Å) were stirred in 100 mL of pentane at room temperature for 6 days. The molecular sieves was filtered off, and the solvent was evaporated. The crude product, which crystallized on storage at 4°C, was used without any further purification for the following step. $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.88 (d, $J$ = 6.6 Hz, 6H), 1.05−1.19 (m, 1H), 1.31−1.78 (m, 9H), 2.29−2.34 (m, 3H), 2.59 (dd, $J$ = 8.9, 5.9 Hz, 4H), 2.82 (dd, $J$ = 6.0 Hz, 2H), 6.73 (d, $J$ = 7.3 Hz, 2H), 7.05 (d, 7.4 Hz, 1H), 7.29 (dd, 7.4, 7.3, 2H).

**(4-Fluorophenyl)-[1-(*cis*-4-isopropylcyclohexyl)piperidin-4-ylidene]amine (2f).** The title compound was obtained according to the standard procedure A as a yellow oil from *cis*-1-(4-isopropylcyclohexyl)piperidine-4-on (**1a**) and 4-fluoroaniline and was used without any further purification for the following step. $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.88 (d, $J$ = 6.6 Hz, 6H), 1.07−1.21 (m, 1H), 1.31−1.75 (m, 9H), 2.27−2.42 (m, 3H), 2.58 (dt, $J$ = 5.8, 10.0 Hz, 4H), 2.81 (dd, $J$ = 5.8 Hz, 2H), 6.67 (dd, $J$ = 4.9, 8.7 Hz, 2H), 6.97 (t, $J$ = 8.7 Hz, 2H).

**(3′a*RS*,6′a*SR*)-1-(*cis*-4-Isopropylcyclohexyl)-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]-pyrrole]-4′,6′-dione (*rac*-4a).** *cis*-[1-(4-Isopropylcyclohexyl)-piperidin-4-ylidene]phenylamine (**2a**) (2.0 g, 6.7 mmol) in 70 mL of 1,2-dimethoxyethane was treated at 0 °C with (trimethylsilyl)methyltrifluoromethane sulfonate (1.58 g, 6.7 mmol) and stirred at room temperature for 1 h. *N*-Methylmaleimide (2.0 g, 18.0 mmol) and then cesium fluoride (1.02 g, 6.7 mmol) were added, and the reaction mixture was stirred at room temperature for 40 h. The title compound precipitated from the reaction mixture and was obtained after filtration and washing with 1,2-dimethoxyethane as a white solid (1.08 g, 38%): mp 184 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 0.82 (d, $J$ = 6.5, 6H), 1.01−1.93 (m, 15H), 2.88 (s, 3H), 3.10−3.42 (m, 6H), 3.38 (m, 1H), 3.89 (m, 1H), 7.04 (d, $J$ = 7.5, 2H), 7.13 (t, $J$ = 7.8, 1H), 7.30 (dd, $J$ = 7.8, 7.5, 2H); MS $m/z$ 424.5 $(MH)^+$.

**(3a*RS*,6a*SR*)-1-(*cis*-4-Isopropylcyclohexyl)-5′-benzyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-4b). Standard Procedure B.** *cis*-[1-(4-Isopropylcyclohexyl)piperidin-4-ylidene]phenylamine (**2a**) (1.0 g, 3.35 mmol) in 35 mL of 1,2-dimethoxyethane was treated at 0 °C with (trimethylsilyl)methyltrifluoromethane sulfonate (950 mg, 4.02 mmol) and stirred at room temperature for 1 h. *N*-Benzylmaleimide (3.14 g, 16.8 mmol) and then cesium fluoride (610 mg, 4.02 mmol) were added and the reaction mixture was stirred at room temperature for 20 h. The solvent was evaporated, and the residue was taken up in 150 mL of diethyl ether and extracted with sodium carbonate solution (2 N, 150 mL). The phases were separated, and the aqueous phase was extracted twice with diethyl ether (100 mL each). The combined organic phases were dried (magnesium sulfate) and concentrated. The residue was purified by column chromatography (ethyl acetate/hexane/triethylamine 30:10:1) to yield the title compound (400 mg, 24%) as an off-white foam.

**Standard Procedure C.** A total of 7.15 g (17.5 mmol) of (3a*RS*,6a*SR*)-1-(*cis*-4-isopropylcyclohexyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-**4g**) were dissolved in 150 mL of dry tetrahydrofuran. Triphenylphosphine (5.51 g, 21.0 mmol), benzyl alcohol (2.27 g, 21.0 mmol), and diethyl azodicarboxylate (3.66 g, 21.0 mmol) were added subsequently, and the mixture was stirred at room temperature for 24 h. The tetrahydrofuran was evaporated and the residue was purified by column chromatography (hexane/ethyl acetate/triethylamine 40:10:1) to yield 6.33 g (73%) of

the title compound. $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.82 (d, $J$ = 6.6, 6H), 1.03−1.12 (m, 1H), 1.21−1.88 (m, 13H), 2.10−2.28 (m, 2H), 2.55−2.70 (m, 1H), 2.93−3.08 (m, 2H), 3.28 (t, $J$ = 7.7, 1H), 3.43 (d, $J$ = 7.7, 1H), 3.49 (d, $J$ = 9.7, 1H), 3.88 (t, $J$ = 9.7, 1H), 4.72 (s, 2H), 6.97 (d, $J$ = 7.4, 2H), 7.09 (t, $J$ = 7.2, 1H), 7.23−7.35 (m, 7H); MS $m/z$ 500.3 $(MH)^+$.

**(3′a*RS*,6′a*SR*)-1-(*cis*-4-Isopropylcyclohexyl)-2′,5′-diphenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-4c).** The title compound was obtained according to standard procedure B from *cis*-[1-(4-isopropylcyclohexyl)piperidin-4-ylidene]phenylamine (**2a**) and *N*-phenylmaleimide as a yellow foam (58%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.83 (d, $J$ = 6.6, 6H), 1.01−1.15 (m, 1H), 1.23−2.03 (m, 14H), 2.13−2.31 (m, 2H), 2.62−2.74 (m, 1H), 2.96−3.11 (m, 2H), 3.40 (t, $J$ = 7.4 Hz, 1H), 3.59 (d, $J$ = 8.2 Hz, 2H), 3.96 (dd, $J$ = 7.4, 8.2, 1H), 7.02−7.07 (m, 3H), 7.24−7.33 (m, 4H), 7.40−7.48 (m, 3H); MS $m/z$ 486.4 $(MH)^+$.

**(3′a*RS*,6′a*SR*)-1-(*cis*-4-Isopropylcyclohexyl)-5′-butyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-4d).** The title compound was obtained from (3a*RS*,6a*SR*)-1-(*cis*-4-isopropylcyclohexyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-**4g**) and *n*-butanol according to standard procedure C as a yellow waxy solid (83%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.83 (d, $J$ = 6.6 Hz, 6H), 0.92 (t, $J$ = 7.2 Hz, 3H), 1.02−1.13 (m, 1H), 1.20−1.94 (m, 17H), 2.13−2.30 (m, 2H), 2.61−2.75 (m, 1H), 2.97−3.08 (m, 2H), 3.20 (t, $J$ = 7.2 Hz, 1H), 3.42 (t, $J$ = 9.9 Hz, 2H), 3.54 (t, $J$ = 7.1 Hz, 2H), 3.86 (dd, $J$ = 7.2, 9.6 Hz, 1H), 6.98 (d, $J$ = 7.4 Hz, 2H), 7.08 (t, $J$ = 7.9 Hz, 1H), 7.25 (dd, 7.3, 7.9 Hz, 2H); MS $m/z$ 466.4 $(MH)^+$.

**(3′a*RS*,6′a*SR*)-1-(*cis*-4-Isopropylcyclohexyl)-5′-(2-morpholin-4-yl-ethyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrole]-4′,6′-dione (*rac*-4e).** The title compound was obtained from (3a*RS*,6a*SR*)-1-(*cis*-4-isopropylcyclohexyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-**4g**) and *N*-(2-hydroxyethyl)morpholine according to standard procedure C as a crystalline solid (95%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.83 (d, $J$ = 6.6 Hz, 6H), 1.02−1.13 (m, 1H), 1.24−2.05 (m, 15H), 2.12−2.30 (m, 2H), 2.40−2.71 (m, 6H), 2.96−3.10 (m, 2H), 3.23 (t, $J$ = 6.6 Hz, 1H), 3.41 (d, $J$ = 6.6 Hz, 1H), 3.46 (d, $J$ = 11.9 Hz, 1H), 3.55−3.71 (m, 5H), 3.86 (dd, $J$ = 6.5, 10.1 Hz, 1H), 6.97 (d, $J$ = 7.0 Hz, 2H), 7.07 (t, 7.5 Hz, 1H), 7.25 (dd, $J$ = 7.5, 7.0 Hz, 2H); MS $m/z$ 523.3 $(MH)^+$.

**(3′a*RS*,6′a*SR*)-5′-Cyclopropylmethyl-2′-(4-fluorophenyl)-1-(*cis*-4-isopropylcyclohexyl)hexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-4f).** Reaction of (3′a*RS*,6′a*SR*)-1-(*cis*-4-Isopropylcyclohexyl)-2′-(4-fluorophenyl)-tetrahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-**4l**) (1.10 g, 2.57 mmol) and hydroxymethylcyclopropane (0.25 mL, 3.16 mmol) according to standard procedure C yielded *rac*-**4f** (0.84 g, 68%) as a light-yellow solid: mp 139°C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 0.27−0.36 (m, 2 H), 0.41−0.55 (m, 2 H), 0.83 (d, $J$ = 6.5 Hz, 6 H), 0.92−1.74 (m, 14 H), 1.84 ($m_c$, 1 H), 2.04−2.31 (m, 2 H), 2.64 ($m_c$, 1 H), 2.92−3.09 (m, 2 H), 3.22 (t, $J$ = 7.0 Hz, 1 H), 3.31−3.49 (m, 4 H), 3.79 (dd, $J$ = 8.5 Hz, 1 H), 6.94 (d, $J$ = 6.5 Hz, 4 H). MS (FAB) $m/z$ 482.5 $(M + H^+)$.

**(3′a*RS*,6′a*SR*)-1-(*cis*-4-Isopropylcyclohexyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-4g).** The title compound was obtained according to standard procedure B from *cis*-[1-(4-isopropylcyclohexyl)piperidin-4-ylidene]phenylamine (**2a**) and maleimide as a yellow solid (57%). $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.82 (d, $J$ = 6.6 Hz, 6H), 1.01−1.13 (m, 1H), 1.24−1.69 (m, 13H), 1.79 (dt, $J$ = 4.0, 12.3 Hz, 1H), 1.90−2.00 (m, 1H), 2.12−2.27 (m, 2H), 2.61 (dt, $J$ = 2.1 Hz, 12.3, 1H), 2.97−3.09 (m, 2H), 3.24 (t, $J$ = 8.2 Hz, 1H), 3.42 (d, $J$ = 6.2 Hz, 1H), 3.45 (d, $J$ = 7.6 Hz, 1H), 3.84 (dd, $J$ = 8.2, 9.2 Hz, 1H), 7.01 (d, $J$ = 7.3 Hz, 2H), 7.08 (t, $J$ = 8.2 Hz, 1H), 7.25 (dd, $J$ = 7.3, 8.2 Hz, 2H); MS $m/z$ 410.5 $(MH)^+$.

**(3′a*RS*,6′a*SR*)- and (3′a*SR*,6′a*RS*)-1-[(2*RS*,4a*SR*,8a*RS*)-Decahydronaphthalen-2-yl]-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3.4-*c*]pyrrole]-4′,6′-dione (*rac*-4k).** Aniline (6.3 mmol) and molecular sieves (4 Å, 4 g) were added to a solution of (2*RS*,4a*SR*,8a*RS*)-1-(decahydro-naphthalen-2-yl)piperidin-4-one (*rac*-**1k**) (4.2 mmol) in pentane (60 mL). The mixture was stirred at room temperature for a week, molecular sieves were filtered off, and the solvent was removed to yield inter alia the corresponding imine as a yellow oil (raw 1.5 g). The material was, without further purification, dissolved in dimethoxyethane (30 mL). (Trimethylsilyl)methyltrifluoromethanesulfonate (2.4 mmol) was added at 0 °C within 15 min. The mixture was stirred at room temperature for 15 min. *N*-Methylmaleimide (8.4 mmol) and cesium fluoride (2.4 mmol) were consecutively added, and the mixture was stirred at room temperature for 24 h. The solvent was removed in vacuo, and sodium bicarbonate solution (10%, 80 mL) was added to the residue. The mixture was extracted with $CH_2Cl_2$ (3 × 40 mL), the organic phases were pooled, dried with $Na_2SO_4$, and evaporated. The residue (2.6 g), a yellow oil, was purified by chromatography on silica gel with $CH_2Cl_2$/MeOH (2%) to yield the product (0.21 g, 10%) as a yellow oil. An analytical sample was crystallized as the HCl salt from ethyl acetate. (3′a*RS*,6′a*SR*) and (3′a*SR*,6′a*RS*)-1-[(2*RS*,4a*SR*,8a*RS*)-Decahydronaphthalen-2-yl]-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3.4-*c*]pyrrole]-4′,6′-dione hydrochloride (1:1): mp 168−171 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.1−2.1 (m, 21 H), 1.8−2.0 (m, 3H), 2.90 (s, 3H), 3.1−3.7 (m, 8H), 3.9 (t, 1H), 7.07 (d, 2H), 7.15 (t, 1H), 7.31 (t, 2H), 9.1 (bs, 1H); MS $m/z$ 436.5 $(M + H)^+$. Anal. ($C_{27}H_{38}ClN_3O_2$) C, H, N.

**(3′a*RS*,6′a*SR*)-1-(*cis*-4-Isopropylcyclohexyl)-2′-(4-fluorophenyl)tetrahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]-pyrrole]-4′,6′-dione (*rac*-4l).** The title compound was obtained according to standard procedure B from (4-fluorophenyl)-[1-(*cis*-4-isopropylcyclohexyl)piperidin-4-ylidene]amine (**2f**) and maleimide as a white solid (20%): mp 217°C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.83 (d, $J$ = 6.6 Hz, 6H), 1.02−1.16 (m, 1H), 1.24−1.76 (m, 12H), 1.84−1.96 (m, 1H), 2.12−2.30 (m, 2H), 2.44−2.70 (m, 1H), 2.94−3.12 (m, 2H), 3.22 (t, $J$ = 7.8 Hz, 1H), 3.36−3.45 (m, 2H), 3.77 (t, $J$ = 9.0 Hz, 1H), 6.93−7.00 (m, 4H); MS $m/z$ 428.6 $(MH)^+$.

**(3′a*RS*,6′a*SR*)-5′(2-Benzyloxyethyl)-1-(*cis*-4-isopropylcyclohexyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrole]-4′,6′-dione (*rac*-4m).** The title compound was obtained from (3a*RS*,6a*SR*)-1-(*cis*-4-isopropylcyclohexyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]-pyrrole]-4′,6′-dione (*rac*-**4g**) and 2-benzyloxyethanol according to standard procedure C as a yellow waxy solid that was further purified by salt formation. A total of 200 mg (0.37 mmol) of the basic compound was dissolved in 10 mL of diethyl ether and treated with 41 mg (0.35 mmol) of fumaric acid in 1 mL of methanol. After being stirred for 16 h, the white precipitate was filtered off and washed with diethyl ether. The product (150 mg, 61%) was further characterized as its 1:1 fumarate salt: mp 155°C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 0.82 (d, $J$ = 6.4, 6H), 1.00−1.86 (m, 14H), 2.42−2.62 (m, 3H), 2.69−2.91 (m, 1H), 3.03−3.18 (m, 3H), 3.38 (t, $J$ = 7.8 Hz, 1H), 3.51−3.72 (m, 5H), 3.86 (t, $J$ = 9.0 Hz, 1H), 4.46 (s, 2H), 6.49 (s, 2H), 6.95 (d, $J$ = 7.8 Hz, 2H), 7.07 (t, $J$ = 6.6 Hz, 1H), 7.19−7.29 (m, 7H); MS $m/z$ 544.3 $(MH)^+$.

**(3′a*RS*,6′a*SR*)-1-Benzyl-5′-methyl-1′-phenylhexahydrospiro[piperidine-4,1′(2′*H*)-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-4n).** A solution of 1-benzyl-4-piperidone (9.44 mL, 52.8 mmol), aniline (4.82 mL, 52.8 mmol), and *p*-toluenesulfonc acid (120 mg) in toluene (300 mL) was heated on a Dean−Stark trap over a period of 17 h. The solvent was evaporated to give the crude imine, which was subsequently dissolved in DME (300 mL) and treated with *N*-methylmaleimide (21.0 g, 189 mmol), trimethylsilylmethyl trifluoromethansulfonate (10.5 mL, 52.8 mmol), and cesium fluoride (8.02 g, 52.8 mmol) according to standard method B to give *rac*-**4n** (10.4 g, 51%) as a white solid: mp 196 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.43 (dt, $J$ = 12, 4.5 Hz, 1 H), 1.63 ($m_c$, 2 H), 1.81−1.91 (m, 1 H), 2.14 (dt, $J$ = 12, 3 Hz, 1 H), 2.65 (dt, $J$ = 10.5, 4.5 Hz, 1 H), 2.85−2.98 (m, 2 H), 3.02 (s, 3 H), 3.22 (t, $J$ = 7.5 Hz, 1 H), 3.43 (d, $J$ = 8.5 Hz, 2 H), 3.48 (s, 2 H), 3.83 (t, $J$ = 8.5 Hz, 1

H), 6.98 (d, $J$ = 7.5 Hz, 2 H), 7.09 (t, $J$ = 7.5 Hz, 1 H), 7.18−7.33 (m, 7 H); MS (FAB) $m/z$ 390.3 ($M + H^+$).

**(3′a*RS*,6′a*SR*)-5′-Methyl-1′-phenylhexahydrospiro[piperidine-4,1′(2′*H*)-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-4o).** (3′a*RS*,6′a*SR*)-1-Benzyl-5′-methyl-1′-phenylhexahydrospiro[piperidine-4,1′(2′*H*)-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-**4n**) (10.4 g, 26.6 mmol) was dissolved in methanol (500 mL) and acetic acid (50 mL) and hydrogenated on Pd/C (1.5 g, 10%) at room temperature over a period of 16 h. The catalyst was filtered off, the filtrate was evaporated, and the residue was dissolved in ammonium hydroxide (25%)/ice (100 mL) and extracted with dichloromethane (2 × 200 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and evaporated. Crystallization of the crude product from diethyl ether yielded *rac*-**4o** (7.32 g, 92%) as a light-yellow solid: mp 181 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.29 (dt, $J$ = 12, 4.5 Hz, 1 H), 1.59−1.73 (m, 2 H), 1.83−1.97 (m, 2 H), 2.79 (dt, $J$ = 12, 3 Hz, 1 H), 3.03 (s, 3 H), 3.06−3.19 (m, 2 H), 3.20−3.36 (m, 2 H), 3.43 (m, 2 H), 3.88 (t, $J$ = 8.5 Hz, 1 H), 7.01 (d, $J$ = 7.5 Hz, 2 H), 7.10 (t, $J$ = 7.5 Hz, 1 H), 7.26 (t, $J$ = 7.5 Hz, 2 H); MS (FAB) $m/z$ 300.3 ($M + H^+$).

**(3a*RS*,6a*SR*)-1-(*cis*-4-Isopropylcyclohexyl)-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]-pyrrole] (*rac*-5a). Standard Procedure D.** (3a*RS*, 6a*SR*)1-(*cis*-4-Isopropylcyclohexyl)-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrol]-4′,6′-dione (*rac*-**4a**) (212 mg, 0.5 mmol) was dissolved in methylene chloride (4 mL) and diethyl ether (5 mL), and lithium aluminum hydride (55 mg, 1.45 mmol) was added at 0°C. The reaction mixture was stirred at room temperature for 1.5 h and then subsequently treated with 0.05 mL of water, 0.05 mL of 15% sodium hydroxide solution, and 0.15 mL of water. The solid material was filtered off, and the filtrate was evaporated. Column chromatography (hexane/ethyl acetate/triethylamine 10:10:1) of the residue gave the desired product (140 mg, 70%), which was precipitated as its 1:1.5 fumarate salt from a mixture of methanol and diethyl ether as described for *rac*-**4m**: mp (salt) > 165 °C (dec); $^1$H NMR (250 MHz, $CDCl_3$, free base) $\delta$ 0.84 (d, $J$ = 6.6 Hz, 6H), 1.02−1.15 (m, 1H), 1.24−1.75 (m, 13H), 1.88−2.05 (m, 3H), 2.06−2.27 (m, 3H), 2.38 (s, 3H), 2.72−3.09 (m, 5H), 3.32 (t, $J$ = 7.2 Hz, 1H), 3.65 (dd, $J$ = 7.2, 9.00 Hz, 1H), 6.96 (t, $J$ = 7.2 Hz, 1H), 7.02 (d, $J$ = 7.2 Hz, 2H), 7.22 (t, $J$ = 7.2 Hz, 2H); MS $m/z$ 396.4 $(MH)^+$.

**(3a*S*,6a*R*)-1-(*cis*-4-Isopropylcyclohexyl)-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole] ((+)-5a). Standard Procedure E.** An amount of 3.04 g (7.68 mmol) of the racemic mixture (3a*SR*,6a*RS*)-1-(*cis*-4-isopropylcyclohexyl)-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole] (*rac*-**5a**) was dissolved in 70 mL of methanol and water (95:5), and an amount of 1.65 g (4.61 mmol) of (−)-*O*,*O*-dibenzoyl-L-tartaric acid was added. The mixture was refluxed until a complete solution was attained, and the solvent was partly distilled off until the first precipitate occurred. Slow cooling resulted in the precipitation of 1.3 g (22%) of crystals. The enantiomeric excess was determined by chiral HPLC to be 98.6%. The tartrate salt was reconverted to the free base by extraction with dichloromethane/sodium bicarbonate solution and precipitated as its 1:2.1 fumarate salt from a mixture of methanol and diethyl ether as described for *rac*-**4m**: $[\alpha]_{589}^{20}$ +101.08°, $[\alpha]_{546}^{20}$ +124.22° (fumarate salt, $c$ 0.9982, methanol). Anal. ($C_{26}H_{41}N_3 \cdot 2.1C_4H_4O_4$) C, H, N.

**(3a*R*,6a*S*)-1-(*cis*-4-Isopropylcyclohexyl)-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole] ((−)-5a).** The title compound was prepared in accordance with standard procedure E from the racemic mixture (3a*SR*, 6a*RS*)-1-(*cis*-4-isopropylcyclohexyl)-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole] (*rac*-**5a**) and (+)-*O*,*O*-dibenzoyl-D-tartaric acid. The enantiomeric excess was determined by chiral HPLC to be 98.4%. The tartrate salt was reconverted to the free base by extraction with dichloromethane/sodium bicarbonate solution and precipitated as its 1:1.8 fumarate salt from a mixture of methanol and diethyl ether as described for *rac*-**4m**: $[\alpha]_{589}^{20}$ −112.49°, $[\alpha]_{546}^{20}$ −137.91° (fumarate salt, $c$ 0.7947, methanol). Anal. ($C_{26}H_{41}N_3 \cdot 1.8C_4H_4O_4$) C, H, N.

**(3′a*RS*,6′a*SR*)-4-(*cis*-4-Isopropylcyclohexyl)-5′-benzyl-2′-phenylhexahydrospiro[piperidine-4,1′(2′H)-pyrrolo-[3,4-*c*]pyrrole (*rac*-5b).** The title compound was obtained from (3a*RS*,6a*SR*)-1-(*cis*-4-isopropylcyclohexyl)-5′-benzyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-**4b**) according to standard procedure D as a colorless oil (95%), which was transformed into its HCl salt by the following procedure. An amount of 800 mg (1.70 mmol) of the basic compound was dissolved in 20 mL of diethyl ether, and 1.5 mL of HCl in dioxane (approximately 2.26 N) were added dropwise. The precipitate was filtered off, washed with diethyl ether, and recrystallized from a mixture of ethyl acetate and ethanol to give 514 mg (54%) of a 1:2.3 HCl salt: mp (salt) >190 °C (dec); $^1$H NMR (250 MHz, $CDCl_3$, free base) $\delta$ 0.83 (d, $J$ = 6.6 Hz, 6H), 1.00−1.13 (m, 1H), 1.17−2.29 (m, 18H), 2.68−2.99 (m, 5H), 3.05 (t, $J$ = 7.2 Hz, 1H), 3.31 (t, $J$ = 9.0 Hz, 1H), 3.56−3.74 (m, 3H), 6.95 (t, $J$ = 7.8 Hz, 1H), 7.03 (d, $J$ = 8.4 Hz, 2H), 7.20−7.35 (m, 7H); MS $m/z$ 472.4 $(MH)^+$. Anal. ($C_{32}H_{45}N_3 \cdot 2.3HCl$) C, H, N.

**(3′a*RS*,6′a*SR*)-4-(*cis*-4-Isopropylcyclohexyl)-2′,5′-diphenylhexahydrospiro[piperidine-4,1′(2′H)-pyrrolo-[3,4-*c*]pyrrole (*rac*-5c).** The title compound was obtained from (3′a*RS*,6′a*SR*)-1-(*cis*-4-isopropylcyclohexyl)-2′,5′-diphenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-**4c**) according to standard procedure D as a colorless oil (88%) and was precipitated as its 1:1 fumarate salt from a mixture of methanol and diethyl ether as described for *rac*-**4m**: mp (salt) > 255 °C (dec); $^1$H NMR (250 MHz, DMSO-$d_6$, salt) $\delta$ 0.87 (d, $J$ = 6.5 Hz, 6H), 1.07−1.18 (m, 1H), 1.27−1.42 (m, 2H), 1.48−1−78 (m, 9H), 2.29−2.82 (m, 5H), 3.03−3.31 (m, 7H), 3.50−3.64 (m, 3H), 6.56 (s, 2H), 7.08−7.20 (m, 4H); MS $m/z$ 458.5 $(MH)^+$. Anal. ($C_{31}H_{43}N_3 \cdot 1C_4H_4O_4$) C, H, N

**(3′a*RS*,6′a*SR*)-4-(*cis*-4-Isopropylcyclohexyl)-5′-butyl-2′-phenylhexahydrospiro[piperidine-4,1′(2′*H*)-pyrrolo[3,4-*c*]pyrrole (*rac*-5d).** The title compound was obtained from (3′a*RS*,6′a*SR*)-1-(*cis*-4-isopropylcyclohexyl)-5′-butyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-**4d**) according to standard procedure D as a colorless oil (89%) and was precipitated as its 1:2.2 fumarate salt from a mixture of methanol and diethyl ether as described for *rac*-**4m**: mp (salt) >220°C (dec); $^1$H NMR (250 MHz, $CDCl_3$, free base) $\delta$ 0.84 (d, $J$ = 6.6 Hz, 6H), 0.93 (t, $J$ = 7.2 Hz, 3H), 1.00−1.13 (m, 1H), 1.23−1.74 (m, 16H), 1.93−2.26 (m, 6H), 2.37−2.51 (m, 2H), 2.69−3.00 (m, 5H), 3.10 (t, $J$ = 7.9 Hz, 1H), 3.39 (t, $J$ = 8.5 Hz, 1H), 3.65 (dd, $J$ = 7.9, 9.3 Hz, 1H), 6.97 (t, $J$ = 7.2 Hz, 1H), 7.01 (d, $J$ = 7.6 Hz, 2H), 7.22 (dd, $J$ = 7.2, 7.4 Hz, 2H); MS $m/z$ 438.5 $(MH)^+$. Anal. ($C_{29}H_{47}N_3 \cdot 2.2C_4H_4O_4$) C, H, N.

**(3′a*RS*,6′a*RS*)-1-(*cis*-4-Isopropylcyclohexyl)-5′-(2-morpholin-4-yl-ethyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole] (*rac*-5e).** The title compound was obtained from (3′a*RS*,6′a*SR*)-1-(*cis*-4-isopropylcyclohexyl)-5′-(2-morpholin-4-yl-ethyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-**4e**) according to standard procedure D as a colorless oil (62%) and was precipitated as its 1:3.2 fumarate salt from a mixture of methanol and diethyl ether as described for *rac*-**4m**: mp (salt) 145 °C; $^1$H NMR (250 MHz, $CDCl_3$, free base) $\delta$ 0.84 (d, $J$ = 6.6 Hz, 6H), 1.02−1.15 8m, 1H), 1.24−1.38 (m, 3H), 1.42−1.72 (m, 10H), 1.89−2.26 (m, 7H), 2.46−3.00 (m, 12H), 3.12 (t, $J$ = 7.8 Hz, 1H), 3.42 (t, $J$ = 8.7 Hz, 1H), 3.62−3.74 (m, 4H), 6.95 (t, $J$ = 6.6 Hz, 1H), 7.01 (d, $J$ = 7.6 Hz, 2H), 7.22 (dd, $J$ = 6.6, 7.6 Hz, 2H); MS $m/z$ 495.5 $(MH)^+$. Anal. ($C_{31}H_{50}N_4O \cdot 3.2C_4H_4O_4$) C, H, N.

**(3′a*RS*,6′a*SR*)-5′-Cyclopropylmethyl-2′-(4-fluorophenyl)-1-(*cis*-4-isopropylcyclohexyl)hexahydrospiro[piperine-4,1′-pyrrolo[3,4-*c*]pyrrole] (*rac*-5f).** Reduction of (3′a*RS*, 6′a*SR*)-5′-cyclopropylmethyl-2′-(4-fluorophenyl)-1-(*cis*-4-isopropylcyclohexyl)hexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]-pyrrole]-4′,6′-dione (*rac*-**4f**) (0.84 g, 1.74 mmol) with lithium aluminum hydride (199 mg, 5.24 mmol) according to standard

procedure D and subsequent formation of the fumarate yielded *rac*-**5f** (0.86 g, 74%) as a white solid: mp 209°C; $^1$H NMR (DMSO-$d_6$) $\delta$ 0.21−0.32 (m, 2 H), 0.44−0.61 (m, 2 H), 0.82 (d, $J$ = 6.0 Hz, 6 H), 0.94−1.14 (m, 3 H), 1.21−1.43 (m, 3 H), 1.44−1.87 (m, 10 H), 2.33−2.65 (m, 6 H), 2.66−2.93 (m, 2 H), 2.94−3.07 (m, 1 H), 3.09−3.23 (m, 2 H), 3.42−3.55 (m, 1 H), 3.56−3.74 (m, 2 H), 6.51 (s, 4 H), 7.06 (d, $J$ = 6.5 Hz, 4 H); MS (FAB) $m/z$ 454.6 (M + H$^+$). Anal. ($C_{29}H_{44}N_3$ F·2 $C_4H_4O_4$) C, H, N.

**(3′a*RS*,6′a*SR*)-4-(*cis*-4-Isopropylcyclohexyl)-2′-phenylhexahydrospiro[piperidine-4,1′(2′*H*)-pyrrolo[3,4-*c*]pyrrole] (*rac*-5g).** (3′a*RS*,6′a*SR*)-4-(*cis*-4-Isopropylcyclohexyl)-5′-benzyl-2′-phenylhexahydrospiro[piperidine-4,1′(2′*H*)-pyrrolo[3,4-*c*]pyrrole] (*rac*-**5b**) (5.5 g, 11.6 mmol) and 10% Pd/C (0.67 g) in 67 mL of methanol and 6.7 mL of glacial acetic acid were hydrogenated with 1 atm of hydrogen for 20 h. Pd/C was filtered off, and the methanol and acetic acid coevaporated with toluene. Chromatography (dichloromethane/methanol/ammonium hydroxide 140:10:1) of the residue gave 3.77 g (85%) of the desired product as a white powder, mp 127°C, which was precipitated as its 1:1.5 fumarate salt from a mixture of methanol and diethyl ether as described for *rac*-**4m**. $^1$H NMR (250 MHz, DMSO-$d_6$, free base) $\delta$ 0.82 (d, $J$ = 6.6 Hz, 6H), 0.98−1.12 (m, 1H), 1.22−1.72 (m, 17H), 1.72−2.25 (m, 5H), 2.50−2.79 (m, 7H), 2.81−3.07 (m, 5H), 3.17−3.27 (m, 1H), 3.53−3.63 (m, 1H), 3.86 (t, $J$ = 7.3 Hz, 1H), 6.93 (d, $J$ = 7.9 Hz, 2H), 7.20 (dd, $J$ = 7.3, 7.9 Hz, 2H); MS $m/z$ 382.4 (MH)$^+$. Anal. ($C_{25}H_{39}N_3$·1.5$C_4H_4O_4$) C, H, N.

**(3a*RS*,6a*RS*)-1-(*cis*-4-Isopropylcyclohexyl)-5′-(2-hydroxyethyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo-[3,4-*c*]pyrrole] (*rac*-5h).** (3a*RS*,6a*RS*)-5′-(2-Benzyloxyethyl)-1-(*cis*-4-isopropylcyclohexyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole] (*rac*-**5m**) (430 mg, 0.833 mmol) and 10% Pd/C (50 mg) in 10 mL of methanol and 5 mL of 2.7 N HCl/MeOH were hydrogenated with 1 atm of hydrogen for 20 h. Pd/C was filtered off, and the methanol was evaporated. The residue was taken up in ethyl acetate and extracted with 2 N NaOH solution. The organic phase was dried with $MgSO_4$ and concentrated. Column chromatography (dichloro methane/methanol/ ammonium hydroxide 140:10:1) gave 170 mg (48%) of the desired product, which was precipitated as its fumarate salt from a mixture of methanol and diethyl ether as described for *rac*-**4m**: mp 194°C; $^1$H NMR (250 MHz, $CDCl_3$, free base) $\delta$ 0.85 (d, 6.6 Hz, 6H), 1.02−1.14 (m, 1H), 1.24−1.38 (m, 3H), 1.42−1.73 (m, 10H), 1.89−2.45 (m, 6H), 2.66−3.02 (m, 7H), 3.12 (t, $J$ = 8.4 Hz, 1H), 3.40 (t, $J$ = 7.2 Hz, 1H), 3.62−3.72 (m, 4H), 6.97 (t, $J$ = 7.2 Hz, 1H), 7.02 (d, $J$ = 7.5 Hz, 2H), 7.23 (dd, $J$ = 7.2, 7.5 Hz, 2H); MS $m$/z 426.6 (MH)$^+$. Anal. ($C_{27}H_{43}N_3O$·1.7$C_4H_4O_4$) C, H, N.

**(3′a*RS*,6′a*SR*)-1-Cyclononyl-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′(2′H)-pyrrolo[3,4-*c*]pyrrole] (*rac*-5i). Standard Procedure E.** A mixture of (3′a*RS*,6′a*SR*)-5′-methyl-1′-phenylhexahydrospiro[piperidine-4,1′(2′*H*)-pyrrolo-[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-**4o**) (0.76 g, 2.54 mmol), cyclononanone (0.36 g, 2.57 mmol), tetraisopropyl orthotitanate (0.92 mL, 3.12 mmol), and THF (3 mL) was stirred at room temperature for 19 h. The reaction mixture was evaporated and dissolved in ethanol (5 mL), and sodium cyanoborohydride (0.12 g, 1.72 mmol) was added at room temperature. The mixture was stirred for 22 h, water (12 mL) was added, the precipitate was filtered off, and the filtrate was evaporated. The crude product was dissolved in 1.5 N sodium hydroxide solution (90 mL) and extracted with dichloromethane (3 × 70 mL). The combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), and evaporated. Further purification by column chromatography (MeOH/dichloromethane, 1:9) yielded (3′a*RS*,6′a*SR*)-1-cyclononyl-5′-methyl-2′-phenylhexahydrospiro-[piperidine-4,1′(2′*H*)-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (0.24 g, 0.57 mmol) as a white foam, which was subsequently reduced with lithium aluminum hydride (41 mg, 1.71 mmol) according to standard procedure D. Formation of the fumarate with fumaric acid (122 mg, 1.05 mmol) in diethyl ether (10 mL) gave *rac*-**5i** (0.24 g, 14%) as an orange solid: mp 242 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.35−1.86 (m, 18 H), 2.06 ($m_c$, 1 H), 2.39 ($m_c$, 1 H), 2.50 (s, 3 H), 2.51−3.17 (m, 16 H), 3.29 ($m_c$, 1 H), 3.44 ($m_c$, 1 H), 3.61 ($m_c$, 1 H), 6.52 (s, 4.5 H), 6.96 (t, $J$ = 7.5 Hz, 1 H), 7.02 (d, $J$ = 7.5 Hz, 2 H), 7.22 (t, $J$ = 7.5 Hz, 2 H); MS (FAB) $m/z$ 396.4 (M + H$^+$). Anal. ($C_{26}H_{41}N_3$·2.25$C_4H_4O_4$) C, H, N.

**(3′a*RS*,6′a*SR*)-1-Cyclodecyl-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′(2′H)-pyrrolo[3,4-*c*]pyrrole] (*rac*-5j).** Reaction of (3′a*RS*,6′a*SR*)-5′-methyl-1′-phenylhexahydrospiro[piperidine-4,1′(2′*H*)-pyrrolo[3,4-*c*]pyrrole]-4′,6′-dione (*rac*-**4o**) (1.0 g, 3.34 mmol) with cyclodecanone (516 mg, 3.34 mmol) and subsequent reduction with lithium aluminum hydride according to standard procedure E gave *rac*-**5j** (0.34 g, 15%) as a pale-pink solid: mp 240°C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.31−1.79 (m, 20 H), 2.02 ($m_c$, 1 H), 2.40 ($m_c$, 1 H), 2.50 (s, 3 H), 2.51−3.13 (m, 16 H), 3.29 ($m_c$, 1 H), 3.44 ($m_c$, 1 H), 3.61 ($m_c$, 1 H), 6.52 (s, 4.4 H), 6.94 (t, $J$ = 7.5 Hz, 1 H), 7.02 (d, $J$ = 7.5 Hz, 2 H), 7.22 (t, $J$ = 7.5 Hz, 2 H); MS (FAB) $m/z$ 410.5 (M + H$^+$). Anal. ($C_{27}H_{43}N_3$ ·2.2$C_4H_4O_4$) C, H, N.

**(3′a*RS*,6′a*SR*)- and (3′a*SR*,6′a*RS*)-1-[(2*RS*,4a*SR*,8a*RS*)-Decahydronaphthalen-2-yl]-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3.4-*c*]pyrrole] (*rac*-5k).** To a solution of (3′a*RS*,6′a*SR*)- and (3′a*SR*,6′a*RS*)-1-[(2*RS*,4a*SR*,8a*RS*)-decahydronaphthalen-2-yl]-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3.4-*c*]pyrrole]-4′,6′-dione (*rac*-**4k**) (0.3 mmol) in THF (10 mL) was added lithium aluminum hydride (1.5 mmol). The mixture was stirred for 30 min at room temperature and for 2 h at reflux temperature and hydrolyzed by addition of water (50 $\mu$L), sodium hydroxide solution (15%, 100 $\mu$L), and again water (150 $\mu$L). Ethyl acetate (20 mL) and $Na_2SO_4$ were added, and the solvent was removed to yield the product (120 mg, 99%) as a yellow oil. Crystallization with fumaric acid in ethanol yielded (3′a*RS*,6′a*SR*)- and (3′a*SR*,6′a*RS*)-1-[(2*RS*,4a*SR*,8a*RS*)-decahydronaphthalen-2-yl]-5′-methyl-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo-[3.4-*c*]pyrrole] fumarate (1:2.4) as colorless solid: mp >152 °C (dec); $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.1−1.8 (m, 20 H), 1.95 (t, 1H), 2.2 (t, 1H), 2.43 (s, 3H), 2.4−3.2 (m, 9H), 3.34 (t, 1H), 3.62 (t, 1H), 6.90 (t, 1H), 6.52 (s, 4H), 7.01 (d, 2H), 7.22 (t, 2H), 12.9 (bs, 4H); MS $m/z$ 408.5 (M + H)$^+$. Anal. ($C_{27}H_{41}N_3$·2.4$C_4H_4O_4$) C,H,N.

**(3′a*RS*,6′a*SR*)-5′(2-Benzyloxyethyl)-1-(*cis*-4-isopropylcyclohexyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrrole] (*rac*-5m).** The title compound was obtained from (3′a*RS*,6′a*SR*)-5′(2-benzyloxyethyl)-1-(*cis*-4-isopropylcyclohexyl)-2′-phenylhexahydrospiro[piperidine-4,1′-pyrrolo[3,4-*c*]pyrole]-4′,6′-dione (*rac*-**4m**) according to standard procedure D as a colorless oil (62%) and was precipitated as its 1:2 fumarate salt from a mixture of methanol and diethyl ether as described for *rac*-**4m**, mp (salt) 169 °C; $^1$H NMR (250 MHz, $CDCl_3$, free base) $\delta$ 0.84 (d, $J$ = 6.6 Hz, 6H), 1.01−1.15 (m, 1H), 1.24−1.38 (m, 1H), 1.41−1.76 (m, 10H), 1.82−2.25 (m, 7H), 2.68−3.00 (m, 17H), 3.15 (t, $J$ = 7.8 Hz, 1H), 3.42 (t, $J$ = 8.7 Hz, 1H), 3.57−3.80 (m, 3H), 4.56 (s, 2H), 6.93 (t, $J$ = 6.6 Hz, 1H), 7.01 (d, $J$ = 7.6 Hz, 2H), 7.19−7.36 (dd, m, 7H); MS $m/z$ 516.4 (MH)$^+$.

**1-Ethyl-1-methyl-4-oxopiperidinium Iodide (7).** To a stirred solution of 1-ethyl-4-piperidone (481 g, 3.782 mol) in 3 L of acetone was added $CH_3I$ (644 g, 1.2 equiv) over 30 min. Occasionally the reaction mixture was cooled with a water bath to maintain the temperature between 20 and 25 °C. The reaction mixture changed color from brown to greenish, and a yellow precipitate formed. Stirring at room temperature was continued for 23 h. The reaction mixture was cooled to 3 °C and stirred for 1 h at this temperature. The product was collected by filtration, washed with 3 L of acetone at 0−5 °C, and dried (50 °C, 1 mbar, 17 h). A total of 967 g (3.593 mol, 95%) of 1-ethyl-1-methyl-4-oxopiperidinium iodide was obtained as a yellow solid. $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.31 (t, $J$ = 7.2, 3H), 2.72 (m, 4H), 3.17 (s, 3H), 3.57 (q, $J$ = 7.2, 2H), 3.72 (t, $J$ = 7.2, 4H).

**4-Isopropylcyclohexylamine (8 + 9).** To a solution of 4-isopropylaniline **6** (693 g, 5.125 mol) in 6.93 L of i-PrOH was added 5% Rh/$Al_2O_3$ (70 g, Degussa G 207 R/D). The mixture was hydrogenated at 80 °C and 100 bar of $H_2$ in an oil-heated 12 L stainless steel autoclave equipped with a hollow shaft

gassing agitator and a reaction temperature control via PC. Hydrogen uptake was monitored by a temperature-controlled hydrogen reservoir connected to the reactor via a reducing valve to keep the autoclave pressure constant. After 10 h of reaction time, the reaction mixture was allowed to cool to room temperature and a sample was taken and analyzed by TLC. Because that not all of the starting material was consumed, an additional 20 g of catalyst was added and the hydrogenation (80 °C, 100 bar of $H_2$) was continued for 5 h. A third portion of 20 g of catalyst and another 3 h were needed to bring the reaction to completion. The reaction mixture was allowed to cool to room temperature, and the catalyst was removed by filtration over a suction filter equipped with a cellulose filter plate (Filtrox AF40) and a Speedex pad (20 g). The solid residue was rinsed with 1 L of i-PrOH. Both filtrates were combined and used in the next step.

For GC analyses a DB17+ (50% phenyl/50% methylpolysiloxane) fused silica column (15 m × 0.32 mm; 0.25 μm) was used with helium as the carrier gas (50 kPa). A sample (0.5% amine) was derivatized in a 5:1 mixture of pyridine and MBTFA at room temperature. The program was 50 °C, 8°C/min to 140°C, 16°C/min to 300°C, and 3.75 min at 300 °C. $t_R$ of cis compound **8** was 7.73 min (59%), $t_R$ of *trans* compound **9** was 8.39 min (32%), $t_R$ of 4-isopropylaniline **6** was 9.36 min (1.5%), $t_R$ of bis(4-isopropylcyclohexyl)amine **11** was 14.59 min (2.8%) and 14.99 min (2.7%).

**(2*RS*,4a*SR*,8a*RS*)-Benzyl(decahydronaphthalen-2-yl)-amine (*rac*-13).** A solution of (2*RS*,4a*SR*,8a*RS*)-*N*-(decahydronaphthalen-2-yl)benzamide (*rac*-**12**)[20] (64 mmol) in THF (150 mL) was added to a suspension of lithium aluminum hydride (128 mmol) in THF (300 mL). This mixture was heated to reflux for 20 h. After cooling, water (9 mL), sodium hydroxide solution (15%, 25 mL), and again water (40 mL) were added. THF was removed in vacuo, the residue was suspended in $CH_2Cl_2$ and washed with sodium hydroxide solution (2 N). The water phase was extracted with $CH_2Cl_2$, the organic phases were pooled, dried with $Na_2SO_4$, and concentrated to yield the product as a colorless oil (15.6 g, 99%). An analytical sample was crystallized as HCl salt from ethyl acetate. (2*RS*,4a*SR*,8a*RS*)-Benzyl(decahydronaphthalen-2-yl)amine hydrochloride (1:1): mp 196−200 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.1−1.8 (m, 14 H), 1.8−2.0 (m, 1 H), 2.1 (q, $J$ = 12 Hz, 1 H), 2.8 (bs, 1 H), 4.0 (s, 2 H), 7.37 (m, 3 H), 7.65 (d, $J$ = 6.3 Hz, 2 H), 9.8 (bs, 2 H); MS $m/z$ 243 ($M^+$). Anal. Calcd ($C_{17}H_{26}ClN$) C,H,N.

**(2*RS*,4a*SR*,8a*RS*)-Decahydronaphthalen-2-ylamine (*rac*-14).** Palladium on charcoal (10%, 1.6 g) was added to a solution of (2*RS*,4a*SR*,8a*RS*)-benzyl(decahydronaphthalen-2-yl)amine (*rac*-**13**) (64 mmol) in ethanol (700 mL). The mixture was hydrogenated at room temperature for 17 h. Catalyst and solvent were removed to yield the product (9.7 g, 99%) as a colorless oil. An analytical sample was crystallized as the HCl salt from ethyl acetate. (2*RS*,4a*SR*,8a*RS*)-Decahydronaphthalen-2-yl-amine hydrochloride (1:1): mp 238−248 °C; $^1$H NMR (250 MHz, DMSO-$d_6$) $\delta$ 1.1−1.8 (m, 16 H), 2.96 (m, 1H), 8.02 (bs, 3H); MS $m/z$ 153 ($M^+$). Anal. ($C_{10}H_{20}ClN$) C, H, N.

**2. Biochemistry. Peptides and Reagents.** All cell culture reagents were purchased from Life Technologies (Basel, Switzerland). Bovine serum albumin (BSA, fraction V) was obtained from Sigma (Munich, Germany). N/OFQ, DAMGO, and naloxone were from Calbiochem (purity >95%). The radioligands [leucyl-$^3$H]-N/OFQ (specific activity 150 Ci/mmol), [D-ala$^2$,*N*-methyl-phe$^4$,glyol$^5$][tyrosyl-3,5-$^3$H]-enkephalin ($^3$H-DAMGO; specific activity 78 Ci/mmol), [*N*-allyl-2,3-$^3$H]-naloxone (specific activity 54.5 Ci/mmol), and [Ile$^{5,6}$-$^3$H]-deltorphin (specific activity 72 Ci/mmol) were from Amersham (Little Chalfont, U.K.).

**Membrane Isolation and Radioligand Binding Assay.** Membranes from cells transiently expressing human DOP (hDOP) and hKOP or stably producing hMOP and hNOP were isolated as described previously.[12] Competitive binding displacements were performed with membranes prepared from the receptor preparations by scintillation proximity analysis (SPA) as described.[12] Nonspecific binding was defined in the presence of 1 μM unlabeled N/OFQ (hNOP), 1 μM DAMGO (hMOP), 10 μM naloxone (hKOP), or 10 μM deltorphin (hDOP).

**γ[$^{35}$S]Thio-GTP (GTPγ$^{35}$S) Binding Assay.** Agonist-stimulated binding of GTPγ$^{35}$S was investigated in the SPA format using membranes from hNOP, hDOP, hKOP, or hMOP receptors as described previously.[10,13] Binding was accomplished in the presence of 1 mg of wheat germ agglutinin SPA beads (Amersham) and N/OFQ (0.1 nM to 10 μM), DAMGO, or **5b** (1 nM to 100 μM). Reactions were performed on a shaker at 22 °C for 120 min and read in a TopCount scintillation counter (Packard).

**cAMP Inhibition Assay.** The inhibition of forskolin-mediated cAMP accumulation was determined in 96-well plates as described recently.[12] Reactions were performed in the presence of 0.1 mM rolipram and 1 μM forskolin (both from Sigma) with increasing concentrations of agonists (10 pM to 100 nM) for 15 min at 37 °C. The cAMP content was determined from the supernatant using the Biotrak non-radioactive cAMP kit (Amersham) according to the manufacturer's instructions.

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