Georg Höfner[a], Benedikt Streicher[b], Bernhard Wünsch[c]

[a] Institut für Pharmazie - Zentrum für Pharmaforschung der Universität München, Butenandt Str. 5-13, D-81377 München, Germany

[b] Klinge Pharma GmbH, Berg-am-Laim-Straße 129, D-81673 München, Germany

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

Synthesis and opioid-receptor binding of novel amino-substituted morphan analogues

Starting with methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**4**), an optimized procedure is reported for preparation of the bromide **7**, which is transformed into the *N*-acylated heptopyranosamine **9**. After introduction of an axially positioned azido moiety in position 3 intramolecular *N/O*-acetal formation succeeds to provide the morphan analogue **17**. In receptor binding studies with radioligands the amines **18b**-**18d** reveal higher affinity for μ-receptors than for κ-receptors. The most μ-active compound **18b** (K_i = 14 nM) contains two aryl substituents, which presumably may occupy both aryl binding sites of μ-receptors.

Key Words: Opioid receptor ligands; Morphan analogues; Intramolecular *N/O*-acetal formation; Receptor binding studies

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Introduction

Conditions of severe pain may be treated with opioid analgesics. Among the opioids κ-receptor agonists possess a unique activity profile, since they cause strong analgesic effects accompanied by minimal physical dependence, respiratory depression, and constipation liability. However, sedation, dysphoria, and strong diuresis are usually associated with κ-agonists, which limits their broad application[1].

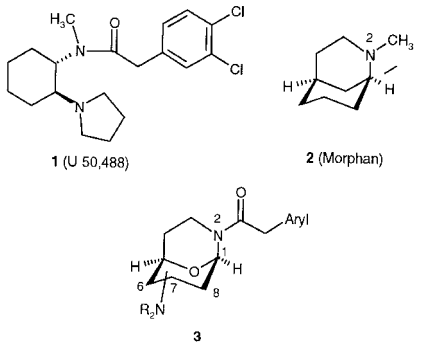

Figure 1

In Figure 1 the prototypical κ-agonist U 50,488 (**1**) is shown. Several highly potent κ-agonists have been derived from U 50,488, all containing the κ-pharmacophoric elements arylacetamide and pyrrolidine, usually at a distance of two carbon atoms[1,2].

In order to find novel ligands for opioid receptors, in particular for κ-receptors, we intended to combine the structural features of typical κ-ligands (arylacetamide, amine) with the morphan skeleton **2**. The morphan ring system **2** represents a substructure of the opioid analgesic morphine and strong analgesia as well as opioid receptor binding are observed with suitable substituted morphan derivatives[3].

Therefore, we planned to synthesize the morphan-analogous bicycles **3** with an arylacetyl residue at the ring nitrogen atom and amino substituents in different ring positions, particularly in position 6, 7, or 8. Here, the position and the stereochemistry of the amino moiety controls the three dimensional arrangement of the pharmacophoric elements arylacetamide and amino group.

Recently, we described the preparation of *N*-acylated epoxyazocanes without further substituents in the ring system[4]. Herein, we report on the synthesis of the first representatives of morphan analogous bicycles **3** with an additional amino functionality in position 6. The κ- and μ-receptor affinities of the amino substituted bicycles are also studied.

Chemistry

The glucose derivative methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**4**) was employed as enantiomerically pure starting material. At first the free hydroxy groups of **4** should be reductively eliminated to produce the alkene **5**. A few methods[5] are described for this transformation. We chose the one-pot procedure of Bessodes and coworkers using triphenylphosphane, iodoform, and imidazole[6]. After optimization of the reaction conditions we obtained the alkene **5** in 75% yield. The yield of the alkene **5** is strongly dependent on the reaction time. Shortening of the reaction time from 2.25 h to 1.75 h reduced the yield of the alkene **5** to 40% and the intermediate hydroxy-iodide **12**, giving an insight into the reaction course, was isolated in 23% yield (see Figure 2).

During hydrogenation of the alkene **5** with the catalyst Pd/C[7,8] hydrogenolytic cleavage of the benzaldehyde acetal occurred to afford the methyl didesoxy-glucoside **13** as main product. This hydrogenolysis could not be control-

Correspondence: Prof. B. Wünsch, Pharmazeutisches Institut der Universität Freiburg, Hermann-Herder-Straße 9, D-79104 Freiburg, Germany.
E-mail: wuensch@ruf.uni-freiburg.de
Fax: +49 761 203-6351

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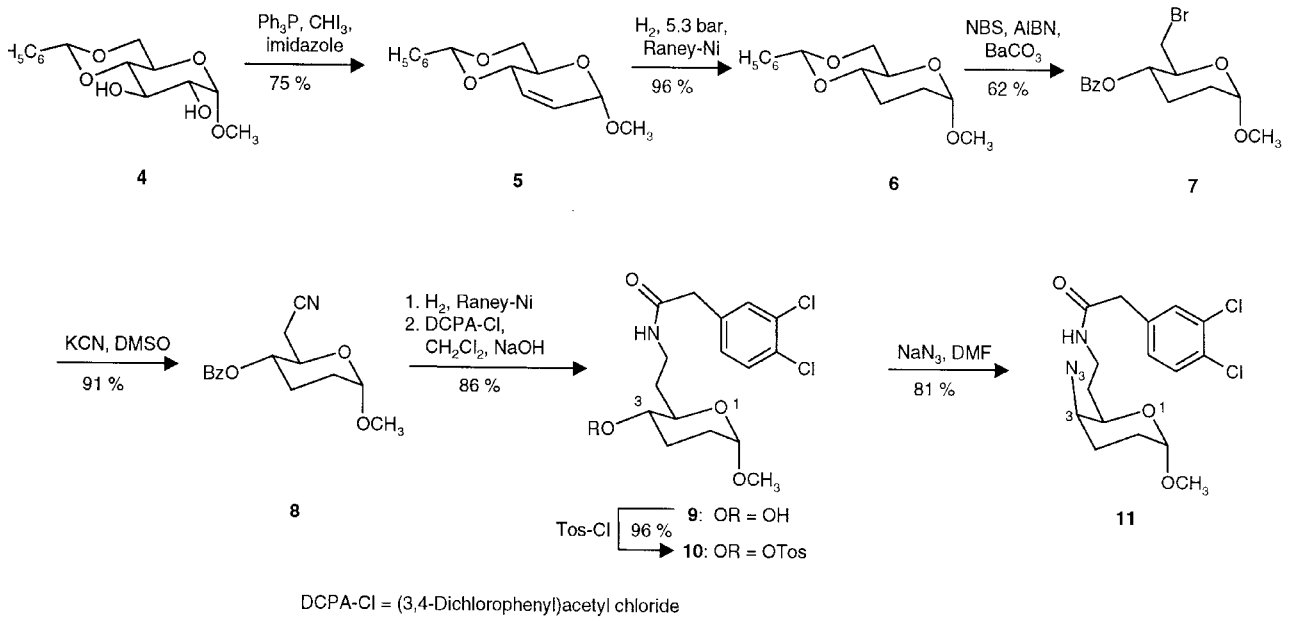


Scheme 1

led by the reaction conditions. However, catalyzing the hydrogenation with Raney nickel we obtained the pyran **6** in reproducible high yields (96%) without hydrogenolytic cleavage of the benzylidene protective group.

Treatment of the benzaldehyde acetal **6** with *N*-bromosuccinimide (NBS) afforded the bromo-ester **7**[8]. In contrast to ref.[8], addition of the radical initiator AIBN was necessary for high yields of **7** (62%). Nevertheless, we were able to isolate small amounts of the anomeric β-glucoside **14** and the dibenzoate **16**, which were formed as side products during the radical substitution of the benzylidene derivative **6**.

The bromo-ester **7** as well as its β-anomer **14** reacted with KCN to provide the anomeric cyano-esters **8**[4] and **15**, respectively. After careful optimization of these four reaction steps, the cyano-ester **8** was accessible in 41% yield starting from the glucose derivative **4**.

Treatment of the cyano-ester **8** with H_2 and Raney nickel in the presence of NaOH led to reduction of the cyano group

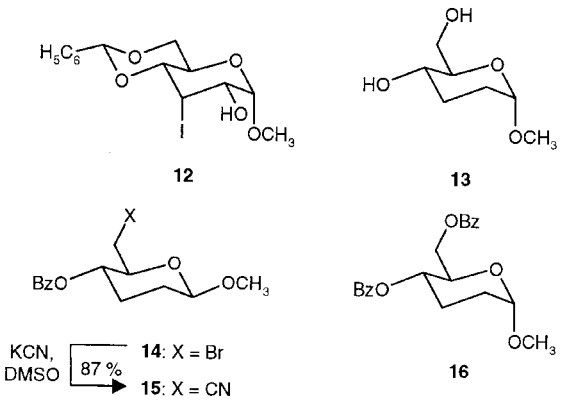


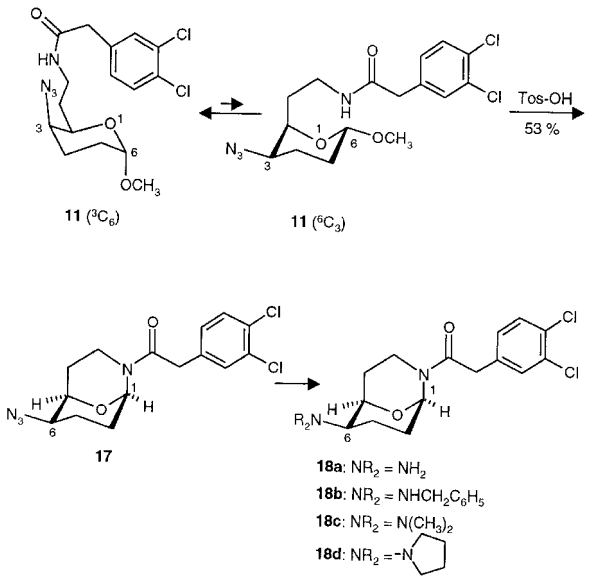
Figure 2

and saponification of the ester moiety to afford an amino-alcohol, which was acylated with (3,4-dichlorophenyl)acetyl chloride (DCPA-Cl) in a biphasic system (CH_2Cl_2/NaOH) to give the (dichlorophenyl)acetamide **9** in 86% yield.

Attempts to obtain a bicyclic *N/O*-acetal of general structure **3** by cyclization of the amide **9** with catalytic amounts of acid failed. Therefore the residual hydroxy group of **9** was first used to introduce an equivalent of the envisaged amino group. Reaction of the alcohol **9** with tosyl chloride furnished the tosylate **10**, which was substituted with NaN_3 to yield the azide **11**. The nucleophilic substitution of the equatorially oriented tosyloxy substituent of **10** with azide occurred with complete inversion of configuration providing a product with an axially positioned azido moiety. This inversion of configuration is clearly indicated by the structure of the 3-H signals in the ^{1}H NMR spectra. Whereas a ddd (J = 15.2/10.1/5.1 Hz) is caused by the axially positioned 3-H of the tosylate **10** only a broad singlet is observed for the equatorially positioned 3-H of the azide **11**.

Heating of the azido substituted amidoacetal **11** with a catalytic amount of *p*-toluenesulfonic acid provided the bicyclic *N/O*-acetal **17** in 53% yield. Obviously the axial orientation of the C-3 substituent promotes the intramolecular *N/O*-acetal formation. We presume, that the conformational equilibrium of the pyran chairs of **11** is shifted to a small extent towards the $^6C_3$-conformation, which is able to cyclize.

The bicyclic azide **17** was reduced with H_2 and Pd/C to yield the primary amine **18a**, which was reductively methylated with formaldehyde and $NaBH_3CN$[9] to afford the dimethylamine **18c**. The benzylamine **18b** was obtained by condensation of the primary amine **18a** with benzaldehyde and subsequent reduction with $NaBH_4$[10]. The pharmacologically most interesting pyrrolidin-1-yl substituent (**18d**) was introduced by reductive alkylation[9] of the primary amine



Scheme 2

18a with $NaBH_3CN$ and 2,5-dimethoxytetrahydrofuran as an equivalent of succinaldehyde.

Receptor binding studies

The affinity of the amines **18a–18d** for κ- and μ-receptors was determined in receptor binding studies with radioligands. Bovine striatal membrane preparations were used as receptor material. κ-receptors were labeled with the radioligand [^{3}H]-U-69.593 and the tritiated pentapeptide [^{3}H]-DAMGO was employed in μ-receptor affinity tests[11].

Table 1

Compound	K_i (nM) ± SEM	
	κ (U-69.593)	μ (DAMGO)
18a	–	–
18b	832 ± 54	14 ± 1.3
18c	1,500 ± 80	1,150 ± 120
18d	18,900	9,530
Morphine	111 ± 12	1.64 ± 0.26
Tramadol	51,000 ± 3,700	1,690 ± 210
U 50,488	1.44 ± 0.025	–

The results of the receptor binding studies are summarized in Table 1. The K_i-values of the primary amine **18a** were not determined, because of low competition at the test concentration of 100 μM. In this series of compounds the κ-receptor affinity is decreasing in the order benzylamine **18b** > dimethylamine **18c** > pyrrolidine 1**8d**. The benzylamine **18b** represents the most κ-active ligand binding in the submicromolar range (K_i = 832 nM) at κ-receptors. In contrast to observations with known κ-agonists, κ-receptor binding of the pyrrolidine derivative **18d** is lower than κ-receptor binding of the analogous dimethylamine **18c** and benzylamine **18b**.

The same order of activity is found for μ-receptor binding of the amines **18** (**18b > 18c > 18d**). All investigated compounds reveal higher affinities for μ-receptors than for κ-receptors, the benzylamine **18b** showing the best μ/κ-selectivity (60:1). The very low K_i-value (14 nM) of the benzylamine **18b** is surprising. We presume, that the aryl substituents of the benzylamine **18b** occupy two different binding sites at μ-receptors as is postulated for the aryl residues (4-hydroxyphenyl of Tyr^1 and phenyl of Phe^4) of opioid peptides[12].

Acknowledgements

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Experimental

Chemistry

General: Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen.– Thin layer chromatography: Silica gel 60 F_{254} plates (Merck).– Flash chromatography (FC)[13]: Silica gel 60, 0.040–0.063 mm (Merck); parentheses include: Diameter of the column [cm], eluent, fraction size [mL], R_f.– Melting points: Melting point apparatus Dr. Tottoli (Büchi), uncorrected.– Optical rotation: Polarimeter 241 (Perkin Elmer); 1.0 dm tube; concentration *c* [g/100 ml]; temperature 20 °C.– Elemental analyses: CHN elemental analyzer Rapid (Heraeus) and Elemental Analyzer 240 (Perkin Elmer).– MS: Mass spectrometer 5989A (Hewlett Packard); EI = electron impact, CI = chemical ionization.– IR: IR spectrophotometer 1600 FT-IR and 2000 FT–IR.(Perkin-Elmer).– ^{1}H NMR (400 MHz): GSX FT NMR spectrometer (Jeol); tetramethylsilane as internal standard, δ in ppm; coupling constants are given with 0.5 Hz resolution.

*(2R,4aR,6S,8aS)-(+)-6-Methoxy-2-phenyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**5**)*[6]

Under a nitrogen atmosphere methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**4**, 3.0 g, 10.6 mmol) was dissolved in toluene (600 mL) and stirred for 30 min at room temperature. Then, PPh_3 (11.1 g, 42.4 mmol), CHI_3 (8.35 g, 21.2 mmol) and imidazole (1.44 g, 21.2 mmol) were successively added and the reaction mixture was heated to reflux for 2.25 h with vigorous stirring. After cooling to room temperature methanol (120 mL) and a saturated solution of $NaHCO_3$ (12 mL) were added. The organic layer was separated, the aqueous layer was extracted with petroleum ether (3 × 200 mL), the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (8 cm, petroleum ether/ethyl acetate 9:1, 50 mL). Fractions 15–23 were concentrated in vacuo. Colorless solid (petroleum ether), mp 117–119 °C (ref.[6] 118–120 °C), yield 1.94 g (75%).

*(2R,4aR,6S,8aS)-(+)-6-Methoxy-2-phenyl-4,4a,6,8a-tetrahydropyrano[3,2-d][1,3]dioxine (**5**) and*

*(2R,4aR,6S,7S,8S,8aR)-(+)-8-Iodo-6-methoxy-2-phenyl-4,4a,6,7,8,8a-hexahydropyrano[3,2-d][1,3]dioxin-7-ol (**12**)*

As described above a mixture of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**4**, 0.70 g, 2.48 mmol), triphenylphosphane (2.60 g, 9.90 mmol), iodoform (1.95 g, 4.97 mmol), imidazole

(339 mg, 4.97 mmol), and toluene (140 mL) was heated to reflux for 1.75 h. After work-up the products were purified by FC (4 cm, petroleum ether/ethyl acetate 9:1, then 7:3, 30 mL).

5 (fractions 8–12): Colorless solid, yield 248 mg (40%).

12 (fractions 18–24, R_f 0.08 with the eluent petroleum ether/ethyl acetate 9:1): Pale yellow solid (iPr_2O), mp 76 °C, yield 222 mg (23%).– $[\alpha]_{589}$ = +42.1 (0.97, $CHCl_3$).– $C_{14}H_{17}IO_5$ (392.2) calcd. C 42.9 H 4.37 found C 42.7 H 4.51.– MS (EI): *m/z* = 392 (M^+).– IR (KBr): ν = 3470 (OH), 1117 (C-O), 1085 (C-O), 1073 (C-O), 1057 cm^{-1} (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.75 (s, broad, 1 H, OH), 3.00 (dd, *J* = 9.0/3.8 Hz, 1 H, 8a-H), 3.43–3.50 (m, 4 H, OCH_3, 7-H), 3.82 (t, *J* = 10.3 Hz, 1 H, 4-H axial), 4.07 (td, *J* = 9.8/5.1 Hz, 1 H, 4a-H), 4.34 (dd, *J* = 10.3/5.1 Hz, 1 H, 4-H equatorial), 4.78 (d, *J* = 3.8 Hz, 1 H, 6-H), 4.83 (t, *J* = 4.0 Hz, 1 H, 8-H), 5.69 (s, 1 H, 2-H), 7.35–7.41 (m, 3 H, arom.), 7.53 (dd, *J* = 7.3/2.1 Hz, 2 H, arom.). The signals were assigned by a H/H-correlated spectrum.

*(2R,4aR,6S,8aS)-(+)-6-Methoxy-2-phenyl-4,4a,6,7,8,8a-hexahydropyrano[3,2-d][1,3]dioxine (**6**)*[8]

Raney nickel (1.58 g, Aldrich, 50% in water, pH > 9) and solid NaOH (236 mg) were added to a solution of **5** (1.58 g, 6.36 mmol) in methanol (20 mL). The reaction mixture was hydrogenated (5.3 bar, 40 °C) for 24 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. Colorless solid (petroleum ether), mp 81 °C (ref.[8] 82–84 °C), yield 1.53 g (96%).– $[\alpha]_{589}$ = +115 (0.98, $CHCl_3$) [ref.[8] $[\alpha]_{589}$ = +118±1 (1.0, $CHCl_3$).

*(+)-[(2S,3S,6S)-2-Bromomethyl-6-methoxyoxan-3-yl] benzoate (**7**)*[8] *and (+)-[(2S,3S,6R)-2-bromomethyl-6-methoxyoxan-3-yl] benzoate (**14**) and (+)-[(2R,3S,6S)-2-(benzoyloxymethyl)-6-methoxyoxan-3-yl] benzoate (**16**)*

A mixture of **6** (950 mg, 3.79 mmol), *N*-bromosuccinimide (NBS, 900 mg, 5.05 mmol), $BaCO_3$ (1.23 g), 2,2′-azodi(2-methylpropanenitrile) (AIBN, 47.5 mg), and CCl_4 (35 mL) was heated to reflux for 30 min. The mixture was washed with saturated solutions of $NaHSO_3$ (1 ×) and NaCl (1 ×), dried ($MgSO_4$), concentrated in vacuo and purified by FC (4 cm, petroleum ether/ethyl acetate 9:1, 25 mL).

7 (fractions 23–29, R_f 0.37): Colorless oil, yield 772 mg (62%).– $[\alpha]_{589}$ = +131 (0.95, $CHCl_3$) [ref.[8] $[\alpha]_{589}$ = +133 (1.1, $CHCl_3$).

14 (fractions 31–35, R_f 0.29): Colorless solid (petroleum ether/diethyl ether), mp 98 °C, yield 117 mg (9%).– $[\alpha]_{589}$ = +11.5 (1.02, $CHCl_3$).– $C_{14}H_{17}BrO_4$ (329.2) calcd. C 51.1 H 5.21 found C 51.2 H 5.05.– MS (CI): *m/z* = 331, 329 (MH^+), 299, 297 (MH^+– CH_3OH).– IR (KBr): ν = 1720 (C=O), 1267 (O=*C-O*), 1115 (C-O), 1063 cm^{-1} (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.67–1.77 (m, 2 H, 4-H, 5-H), 1.97–2.02 (m, 1 H, 5-H), 2.31–2.36 (m, 1 H, 4-H), 3.50 (dd, *J* = 11.1/7.7 Hz, 1 H, C*H*$_2$Br), 3.56 (s, 3 H, OCH_3), 3.62 (dd, *J* = 11.1/3.4 Hz, 1 H, C*H*$_2$Br), 3.85 (td, *J* = 8.2/3.4 Hz, 1 H, 2-H), 4.54 (dd, *J* = 8.3/2.3 Hz, 1 H, 6-H), 4.92 (td, *J* = 9.3/4.7 Hz, 1 H, 3-H), 7.46 (t, *J* = 7.7 Hz, 2 H, arom.), 7.60 (td, *J* = 7.4/1.5 Hz, 1 H, arom.), 8.02 (dd, *J* = 8.3/1.1 Hz, 2 H, arom.). The signals were assigned by a H/H-correlated spectrum.

16 (fractions 37–39, R_f 0.26): Colorless oil, yield 31 mg (2.9%).– $[\alpha]_{589}$ = +138.2 (0.91, $CHCl_3$).– $C_{21}H_{22}O_6$ (370.4) calcd. C 68.1 H 5.99 found C 68.3 H 6.23.– MS (EI): *m/z* = 339 (M^+–OCH_3).– IR (film): ν = 1722 (C=O), 1267 (O=*C-O*) , 1112 (C-O), 1053 cm^{-1} (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.91–2.06 [m, 3 H, 4-H, 5-H (2)], 2.15–2.20 (m, 1 H, 4-H), 3.43 (s, 3 H, OCH_3), 4.24 (ddd, *J* = 9.8/6.0/3.0 Hz, 1 H, 2-H), 4.41 (dd, *J* = 12.0/6.0 Hz, 1 H, C*H*$_2$OBz), 4.58 (dd, *J* = 12.0/2.6 Hz, 1 H, C*H*$_2$OBz), 4.79 (d, *J* = 2.6 Hz, 1 H, 6-H), 5.11 (ddd, *J* = 15.4/10.2/5.1 Hz, 1 H, 3-H), 7.41 (t, *J* = 7.5 Hz, 2 H, arom.), 7.43 (t, *J* = 7.7 Hz, 2 H, arom.), 7.54 (t, *J* = 7.5 Hz, 1 H, arom.), 7.56 (t, *J* = 7.5 Hz, 1 H, arom.), 8.03 (d, *J* = 8.1 Hz, 4 H, arom.).

*(+)-[(2R,3S,6S)-2-Cyanomethyl-6-methoxyoxan-3-yl] benzoate (**8**)*[4]

The bromide **7** (772 mg, 2.34 mmol) was dissolved in DMSO (10 mL). Then, KCN (457 mg, 7.02 mmol) was added and the solution was stirred for 1 h at 70 °C. After addition of water (10 mL) and petroleum ether (20 mL) the aqueous layer was separated and extracted with a mixture of petroleum ether and ethyl acetate (95:5, 3 × 20 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo and the residue was purified by FC (4 cm, petroleum ether/ethyl acetate 9:1, 25 mL, R_f 0.25). The solvent of the fractions 29–37 was evaporated in vacuo leaving the nitrile **8** as colorless solid, mp 61–63 °C (petroleum ether/diethyl ether), yield 583 mg (91%).

*(+)-[(2R,3S,6R)-2-Cyanomethyl-6-methoxyoxan-3-yl] benzoate (**15**)*

As described for the anomeric glycoside **8** the bromide **14** (214 mg, 0.65 mmol) was reacted with KCN (127 mg, 1.95 mmol) in DMSO (5 mL). Work-up and purification were performed as described for **8**. FC (2 cm, petroleum ether/ethyl acetate 9:1, 10 mL, R_f = 0.18). Colorless solid (petroleum ether/diethyl ether), mp 87 °C, yield 117 mg (87%).– $[\alpha]_{589}$ = +13.6 (0.99, $CHCl_3$).– $C_{15}H_{17}NO_4$ (275.3) calcd. C 65.4 H 6.22 N 5.09 found C 65.4 H 6.28 N 5.13.– MS (EI): *m/z* = 244 (M^+–OCH_3).– IR (KBr): ν = 2249 (CN), 1711 (C=O), 1268 (O=*C-O*) , 1061 cm^{-1} (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.69–1.85 (m, 2 H, 4-H, 5-H), 2.04–2.07 (m, 1 H, 5-H), 2.38–2.43 (m, 1 H, 4-H), 2.71 (dd, *J* = 16.9/8.3 Hz, 1 H, C*H*$_2$CN), 2.80 (dd, *J* = 16.9/4.1 Hz, 1 H, C*H*$_2$CN), 3.61 (s, 3 H, OCH_3), 3.96 (td, *J* = 8.6/4.3 Hz, 1 H, 2-H), 4.59 (dd, *J* = 8.5/2.1 Hz, 1 H, 6-H), 4.85 (td, *J* = 9.4/4.7 Hz, 1 H, 3-H), 7.52 (t, *J* = 7.7 Hz, 2 H, arom.), 7.65 (td, *J* = 8.1/1.3 Hz, 1 H, arom.), 8.07 (d, *J* = 7.7 Hz, 2 H, arom.).

*(+)-2-(3,4-Dichlorophenyl)-N-{2-[(2R,3S,6S)-3-hydroxy-6-methoxyoxan-2-yl]ethyl}acetamide (**9**)*

A solution of **8** (225 mg, 0.82 mmol) in methanol (12 mL) and 5 N NaOH (1 mL) was shaken for 10 min at room temperature. Then, freshly prepared Raney nickel (112 mg) and 5 N NaOH (3 mL) were added. The mixture was shaken under a H_2 atmosphere (5.3 bar) for 14 h at room temperature. Raney nickel was filtered off and after addition of water (7 mL) the filtrate was concentrated to about 13 mL. CH_2Cl_2 (15 mL) and 2-(3,4-dichloropenyl)acetyl chloride (365 mg, 1.63 mmol) were added and the mixture was stirred for 30 min at room temperature. The aqueous layer was separated, extracted with CH_2Cl_2 (4 × 15 mL), the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Colorless solid (iPr_2O/CH_2Cl_2), mp 124 °C, yield 158 mg (53%). FC purification (3 cm, ethyl acetate, 30 mL, R_f 0.36) of the mother liquor gave further 96 mg (32.4%) of **9**. Total yield 254 mg (86%).– $[\alpha]_{589}$ = +54.9 (0.93, $CHCl_3$).– $C_{16}H_{21}Cl_2NO_4$ (362.2) calcd. C 53.0 H 5.84 N 3.87 found C 53.2 H 5.71 N 3.86.– MS (EI): *m/z* = 334, 332, 330 (M^+–OCH_3).– IR (KBr): ν = 3312 (OH), 1652 (C=O), 1560 (amide II), 1128 (C-O), 1055 cm^{-1} (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.54–1.86 (m, 5 H, 2 × 4-H, 2 × 5-H, C*H*$_2$CH$_2$NH), 2.01–2.08 (m, 1 H, C*H*$_2$CH$_2$NH), 3.18 (s, 3 H, OCH_3), 3.19–3.26 (m, 1 H, CH$_2$C*H*$_2$NH), 3.28–3.33 (m, 1 H, CH$_2$C*H*$_2$NH), 3.45–3.49 (m, 1 H, 2-H), 3.50 (s, 2 H, aryl-CH_2), 3.61–3.64 (m, 1 H, 3-H), 4.37 (s broad, 1 H, 6-H), 6.17 (s broad, 1 H, NH), 7.12 (dd, *J* = 8.1/2.1 Hz, 1 H, 6-H arom.), 7.37 (d, *J* = 2.1 Hz, 1 H, 2-H arom.), 7.40 (d, *J* = 8.5 Hz, 1 H, 5-H arom.). A signal for the OH-proton was not found.

*(+)-(2R,3S,6S)-2-{2-[2-(3,4-Dichlorophenyl)acetylamino]-ethyl}-6-methoxyoxan-3-yl-4-methylbenzenesulfonate (***10***)*

At about 5 °C 4-(dimethylamino)pyridine (2.47 g, 12.5 mmol) was added to a solution of **9** (727 mg, 2.08 mmol), triethylamine (2.47 g, 24.4 mmol) and *p*-toluenesulfonyl chloride (3.62 g, 12.5 mmol) in $CHCl_3$ (60 mL). The mixture was heated to reflux for 1 h. The mixture was washed with 1 N HCl (2 × 60 mL), with saturated solutions of $NaHCO_3$ (30 mL) and NaCl (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by FC (4 cm, petroleum ether/ethyl acetate 3:7, 25 mL, R_f 0.38). The solvent of the fractions 8–14 was evaporated in vacuo. Colorless oil, yield 1.03 g (96%).– $[\alpha]_{589}$ = +35.0 (1.09, $CHCl_3$).– $C_{23}H_{27}Cl_2NO_6S$ (516.4) calcd. C 53.5 H 5.27 N 2.71 found C 53.4 H 5.36 N 2.66.– MS (EI): *m/z* = 488, 486, 484 (M^+–OCH_3).– IR (film): ν = 3299 (N-H), 1647 (C=O), 1560 (amide II), 1128 (C-O), 1055 cm^{-1} (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.56–1.65 (m, 2 H, 5-H), 1.79–1.94 (m, 4 H, 4-H, C*H*$_2$CH$_2$NH), 2.46 (s, 3 H, CH_3), 3.06–3.11 (m, 1 H, CH_2C*H*$_2$NH), 3.13 (s, 3 H, OCH_3), 3.46–3.56 (m, 1 H, CH_2C*H*$_2$NH), 3.48 (s, 2 H, aryl-C*H*$_2$), 3.64 (td, *J* = 10.2/2.3 Hz, 1 H, 2-H), 4.18 (ddd, *J* = 15.2/10.1/5.1 Hz, 1 H, 3-H), 4.33 (d, *J* = 2.6 Hz, 1 H, 6-H), 5.98 (s broad, 1 H, NH), 7.11 (dd, *J* = 8.1/1.7 Hz, 1 H, 6-H dichlorophenyl), 7.33–7.36 (m, 3 H, arom.), 7.41 (d, *J* = 8.1 Hz, 1 H, 5-H dichlorophenyl), 7.76 (d, *J* = 8.1 Hz, 2 H, tosyl).

*(+)-N-{2-[(2R,3R,6S)-3-Azido-6-methoxyoxan-2-yl]ethyl}-2-(3,4-dichlorophenyl)acetamide (***11***)*

A solution of **10** (1.03 g, 2.00 mmol) and NaN_3 (1.30 g, 20.0 mmol) in DMSO (30 mL) was heated to reflux for 2.5 h. After cooling to room temperature water (100 mL) was added and the mixture was extracted with diethyl ether (5 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Colorless needles (ethyl acetate/iPr_2O), mp 158 °C, yield 495 mg (64%). The mother liquor was purified by FC (3 cm, petroleum ether/ethyl acetate 3:7, 25 mL, R_f 0.52). The solvent of the fractions 4–8 was evaporated in vacuo to provide 129 mg (17%) of the azide **11**. Total yield 624 mg (81%).– $[\alpha]_{589}$ = +10.2 (1.16, $CHCl_3$).– $C_{16}H_{20}Cl_2N_4O_3$ (387.3) calcd. C 49.6 H 5.20 N 14.47 found C 49.6 H 5.32 N 14.41.– MS (EI): *m/z* = 359, 357, 355 (M^+–OCH_3).– IR (KBr): ν = 3297 (N-H), 2108 (N_3), 1645 (C=O), 1558 (amide II), 1126 (C-O), 1043 cm^{-1} (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.51–1.56 (m, 1 H, 5-H), 1.57–1.61 (m, 1 H, C*H*$_2$CH$_2$NH), 1.70–1.78 (m, 1 H, C*H*$_2$CH$_2$NH), 1.79–1.89 (m, 2 H, 4-H, 5-H), 2.03–2.08 (m, 1 H, 4-H), 3.00–3.08 (m, 1 H, CH_2C*H*$_2$NH), 3.11 (s, 3 H, OCH_3), 3.38 (s broad, 1 H, 3-H equatorial), 3.42 (s, 2 H, aryl-C*H*$_2$), 3.57–3.61 (m, 1 H, CH_2C*H*$_2$NH), 3.75 (dd, *J* = 9.9/4.7 Hz, 1 H, 2-H), 3.46 (s, 1 H, 6-H), 5.86 (s broad, 1 H, NH), 7.05 (dd, *J* = 8.3/1.9 Hz, 1 H, 6-H arom.), 7.30 (d, *J* = 1.7 Hz, 1 H, 2-H arom.), 7.35 (d, *J* = 8.1 Hz, 1 H, 5-H arom.).– ^{1}H NOE (PD = 8, IRATN = 300): After irradiation at δ = 3.75 ppm (2-H) a NOE was found at δ = 1.57–1.61 ppm (C*H*$_2$CH$_2$NH), 1.70–1.78 ppm (C*H*$_2$CH$_2$NH), 2.03–2.08 ppm (4-H), 3.11 ppm (OCH_3), and 3.38 ppm (3-H).– A ^{1}H/^{1}H-COSY-spectrum was recorded to assign the signals.

*(+)-1-[(1R,5R,6R)-6-Azido-9-oxa-2-azabicyclo[3.3.1]-nonan-2-yl]-2-(3,4-dichlorophenyl)ethan-1-one (***17***)*

A solution of **11** (60.5 mg, 0.16 mmol) and *p*-toluenesulfonic acid (29.7 mg, 0.16 mmol) in 1,2-dichloroethane (7 mL) was heated to reflux for 55 min. A saturated solution of $NaHCO_3$ (7 mL) was added, the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was purified by FC (2 cm, petroleum ether/ethyl acetate 5:5 (200 mL) then petroleum ether/ethyl acetate 3:7, 30 mL, R_f 0.43 (petroleum ether/ethyl acetate 5:5). The solvent of the fractions 3–5 was removed in vacuo. Colorless oil, yield 29.6 mg (53%).– $[\alpha]_{589}$ = –7.86 (0.56, $CHCl_3$).– $C_{15}H_{16}Cl_2N_4O_2$ (355.2) calcd. C 50.7 H 4.54 N 15.77 found C 50.6 H 4.76 N 15.65.– MS (CI): *m/z* = 359, 357, 355 (MH^+).– IR (film): ν = 2100 (N_3), 1647 (C=O), 1046 cm^{-1} (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.63–2.13 (m, 6 H, 4-C*H*$_2$, 7-C*H*$_2$, 8-C*H*$_2$), 3.26–3.34 (m, 0.22 H, 3-H) 3.40 (ddd, *J* =12.4/9.0/6.0 Hz, 0.78 H, 3-H), 3.50–3.60 (m, 0.78 H, 3-H), 3.58 (s, 2 H, aryl-C*H*$_2$), 3.77 (dt, *J* = 10.4/5.1 Hz, 0.78 H, 6-H), 3.88 (dt, *J* = 11.1/5.7 Hz, 0.22 H, 6-H), 3.97 (t, *J* = 5.8 Hz, 0.22 H, 5-H), 4.07 (dt, *J* = 9.0/4.7 Hz, 0.78 H, 5-H), 4.24–4.28 (m, 0.22 H, 3-H), 5.33 (d, *J* = 3.4 Hz, 0.22 H, 1-H), 5.55 (d, *J* = 3.0 Hz, 0.78 H, 1-H), 7.00 (dd, *J* = 8.1/2.1 Hz, 1 H, 6-H arom.), 7.26 (d, *J* = 1.7 Hz, 1 H, 2-H arom.), 7.32 (d, *J* = 8.1 Hz, 0.22 H, 5-H arom.), 7.33 (d, *J* = 8.5 Hz, 0.78 H, 5-H arom.). Ratio of rotational isomers 78:22. A ^{1}H/^{1}H-COSY-spectrum was recorded to assign the signals. After irradiation at δ = 5.55 ppm (1-H) a NOE was found at δ = 1.79–1.91 ppm (8-H), 3.50–3.60 ppm (3-H), 3.58 ppm (aryl-C*H*$_2$), 7.00, 7.26, and 7.33 ppm (H arom.). The signal at δ = 5.33 ppm (1-H) was also saturated after irradiation at δ = 5.55 ppm, showing the existence of rotational isomers.– ^{1}H NMR (100 °C, Cl_2CD-$CDCl_2$): δ (ppm) = 1.67–2.10 (m, 6 H, 4-C*H*$_2$, 7-C*H*$_2$, 8-C*H*$_2$), 3.54–3.62 (m, 2 H, 3-H), 3.58 (s, 2 H, aryl-C*H*$_2$), 3.80–3.85 (m, 1 H, 6-H), 4.05–4.11 (m, 1 H, 5-H), 5.57 (s, 1 H, 1-H), 7.05 (dd, *J* = 8.1/2.1 Hz, 1 H, 6-H arom.), 7.31 (d, *J* = 2.1 Hz, 1 H, 2-H arom.), 7.37 (d, *J* = 8.1 Hz, 1 H, 5-H arom.).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.0 (C-7), 21.8 (C-7), 22.3 (C-4), 24.3 (C-4), 27.2 (C-8), 29.7 (C-8), 37.0 (C-3), 38.7 (C-3), 39.7 (aryl-*C*H$_2$), 40.3 (aryl-*C*H$_2$), 58.2 (C-6), 58.3 (C-6), 66.7 (C-5), 67.5 (C-5), 76.7 (C-1), 77.0 (C-1), 128.3 (C arom.), 128.3 (C arom.), 130.6 (C arom.), 130.8 (C arom.), 130.9 (C arom.), 131.2 (C arom.), 132.7 (C arom.), 134.5 (C arom.), 168.0 (C=O), 169.1 (C=O).– ^{1}H/^{13}C-COSY- and ^{13}C-DEPT-spectra were recorded to assign the signals.

*(+)-{(1R,5R,6R)-2-[2-(3,4-Dichlorophenyl)acetyl]-9-oxa-2-azabicyclo[3.3.1]nonan-6-yl}-ammonium chloride (***18a***.HCl)*

A mixture of **17** (269 g, 0.76 mmol), Pd/C (10%, 50 mg), and ethyl acetate (25 mL) was hydrogenated (1 bar) for 3 h at room temperature. It was filtered and the solvent was evaporated in vacuo. Colorless oil of **18a** (base), yield 245 mg (98%).– ^{1}H NMR spectrum of the primary amine **18a** ($CDCl_3$): δ (ppm) = 1.46–2.04 (m, 6 H, 4-C*H*$_2$, 7-C*H*$_2$, 8-C*H*$_2$), 3.08–3.15 (m, 1 H, 6-H), 3.38–3.41 (m, 0.31 H, 3-H), 3.42–3.60 (m, 2 × 0.69 H, 2 × 3-H), 3.58 (s, 2 H, aryl-C*H*$_2$), 3.80–3.84 (m, 0.31 H, 5-H), 3.93 (dt, *J* = 8.8/4.3 Hz, 0.69 H, 5-H), 4.13–4.17 (m, 0.31 H, 3-H), 5.32 (d, *J* = 4.7 Hz, 0.31 H, 1-H), 5.55 (d, *J* = 3.0 Hz, 0.69 H, 1-H), 7.01 (dd, *J* = 8.1/2.1 Hz, 1 H, 6-H arom.), 7.27 (d, *J* = 2.1 Hz, 1 H, 2-H arom.), 7.32 (d, *J* = 8.1 Hz, 0.31 H, 5-H arom.), 7.33 (d, *J* = 8.1 Hz, 0.69 H, 5-H arom.). Signals for the NH_2-protons were not found. Ratio of rotational isomers 69:31.

For the preparation of **18a**.HCl the crude amine **18a** (245 mg, 0.74 mmol) was dissolved in Et_2O (10 mL), a saturated solution of gaseous HCl in Et_2O was added and the precipitate was collected. Colorless solid (methanol/ethyl acetate), mp 237 °C (decomposition), yield 147 mg (54%). Concentration of the mother liquor gave further 112 mg (41%) of **18a**.HCl. Total yield 259 mg (95%).– $[\alpha]_{589}$ = +14.2 (0.25, CH_3OH).– $C_{15}H_{19}Cl_3N_2O_2$ (365.7) calcd. C 49.3 H 5.24 N 7.66 found C 49.2 H 5.26 N 7.69.– MS (CI): *m/z* = 333, 331, 329 (MH^+–HCl).– IR (KBr): ν = 3426 (NH_3+), 1637 (C=O), 1025 cm^{-1} (C-O).

*(+)-N-Benzyl-N-{(1R,5R,6R)-2-[2-(3,4-dichlorophenyl)-acetyl]-9-oxa-2-azabicyclo[3.3.1]nonan-6-yl}ammonium sulfate ((**18b**)$_2$.H_2SO_4)*

A mixture of **18a**.HCl (50 mg, 0.14 mmol), benzaldehyde (21.7 mg, 0.20 mmol), abs. CH_2Cl_2 (5 mL), Na_2SO_4 (100 mg, 0.7 mmol) and Na_2CO_3 (50 mg, 0.5 mmol) was stirred for 72 h at room temperature. Then, it was filtered and the filtrate was concentrated in vacuo. The residue (56.9 mg, 0.14 mmol) was dissolved in methanol (5 mL) and after addition of $NaBH_4$ (15.5 mg, 0.4 mmol) the mixture was stirred for 11 h at room temperature. After concentration in vacuo 2 N NaOH (5 mL) and CH_2Cl_2 (5 mL) were added, the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was purified by FC (3 cm, CH_2Cl_2/methanol 95:5, 30 mL, R_f 0.52) to provide the benzylamine **18b**. Colorless oil, yield 40.7 mg (71%).– ^{1}H NMR spectrum of the benzylamine **18b** ($CDCl_3$): δ (ppm) = 1.43–2.11 (m, 6 H, 4-C*H*$_2$, 7-C*H*$_2$, 8-C*H*$_2$), 3.01 (dt, *J* = 11.5/4.7 Hz, 0.76 H, 6-H), 3.09–3.14 (m, 0.24 H, 6-H), 3.37–3.83 (m, 1.76 H, 3-H), 3.63 (s, 2 H, aryl-C*H*$_2$), 3.75 (s, 2 × 0.76 H, C_6H_5-C*H*$_2$), 3.76 (s, 2 × 0.24 H, C_6H_5-C*H*$_2$), 4.04 (t, *J* = 5.1 Hz, 0.24 H, 5-H), 4.12 (dt, *J* = 8.5/4.1 Hz, 0.76 H, 5-H), 4.23–4.30 (m, 0.24 H, 3-H), 5.39 (d, *J* = 4.3 Hz, 0.24 H, 1-H), 5.62 (d, *J* = 3.4 Hz, 0.76 H, 1-H), 7.07 (dd, *J* = 8.1/2.1 Hz, 1 H, 6-H dichlorophenyl), 7.23–7.40 (m, 7 H, arom.). The signal for the NH-proton was not found. Ratio of rotational isomers 76:24.

(**18b**)$_2$.H_2SO_4 was prepared by addition of a stoichiometric amount of conc. H_2SO_4 (4.4 mg, 0.044 mmol) to a solution of **18b** (36.2 mg, 0.09 mmol) in Et_2O (10 mL). Colorless solid (ethyl acetate/methanol) mp 178 °C (decomposition), yield 21.9 mg (54%).– $[\alpha]_{589}$ = +24.6 (0.49, CH_3OH).– ($C_{22}H_{24}Cl_2N_2O_2$)$_2$ · H_2SO_4 (936.7) calcd. C 56.4 H 5.38 N 5.98 S 3.42 found C 56.5 H 5.52 N 5.72 S 3.36.– MS (CI): *m/z* = 423, 421, 419 (MH^+–H_2SO_4).– IR (KBr): ν = 3318 (R_2NH_2+), 1640 (C=O), 1044 cm^{-1} (C-O).

*(+)-N-{(1R,5R,6R)-2-[2-(3,4-Dichlorophenyl)acetyl]-9-oxa-2-azabicyclo[3.3.1]nonan-6-yl}-N,N-dimethylammonium chloride (**18c**.HCl)*

A solution of **18a**.HCl (101 mg, 0.28 mmol), formaldehyde (40% in water, 0.2 mL, 2.6 mmol) and $NaBH_3CN$ (173.4 mg, 2.76 mmol) in methanol (10 mL) was stirred at room temperature for 6 h. 2 N NaOH (10 mL) was added and the mixture was extracted with CH_2Cl_2 (5 × 10 mL). The organic layer was dried ($MgSO_4$), concentrated in vacuo and the residue was purified by FC (2 cm, ethyl acetate/methanol/conc. NH_3 85:10:5, 10 mL, R_f 0.57). The solvent of the fractions 4–6 was evaporated in vacuo to provide the dimethylamine **18c**. Colorless oil, yield 76.3 mg (77%).– ^{1}H NMR spectrum of the dimethylamine **18c** ($CDCl_3$): δ (ppm) = 1.46–2.41 (m, 6 H, 4-C*H*$_2$, 7-C*H*$_2$, 8-C*H*$_2$), 2.22 (s, 3 H, N(CH_3)$_2$), 2.24 (s, 3 H, N(CH_3)$_2$), 3.38–3.51 (m, 1 H, 6-H), 3.55–3.61 (m, 0.78 H, 3-H), 3.64 (s, 2 H, aryl-C*H*$_2$), 3.63–3.67 (m, 1 H, 3-H), 4.14–4.17 (m, 0.22 H, 5-H), 4.24–4.30 (m, 1 H, 3-H, 5-H), 5.38 (d, *J* = 4.3 Hz, 0.22 H, 1-H), 5.62 (d, *J* = 3.5 Hz, 0.78 H, 1-H), 7.08 (dd, *J* = 8.5/2.1 Hz, 1 H, 6-H arom.), 7.34 (d, *J* = 2.1 Hz, 1 H, 2-H arom.), 7.38 (d, *J* = 8.1 Hz, 1 H, 5-H arom.). Ratio of rotational isomers 78:22.

For the preparation of **18c**.HCl the dimethylamine **18c** (34.8 mg, 0.097 mmol) was dissolved in Et_2O and a saturated solution of gaseous HCl in Et_2O was added. Colorless solid (methanol/ethyl acetate), mp 167 °C (decomposition), yield 20.6 mg (54%).– $[\alpha]_{589}$ = +36.3 (0.84, $CHCl_3$).– $C_{17}H_{23}Cl_3N_2O_2$ (393.7) calcd. C 51.8 H 5.89 N 7.11 found C 51.6 H 6.09 N 7.04.– MS (CI): *m/z* = 361, 359, 357 (MH^+–HCl).– IR (KBr): ν = 3332 (R_3NH^+), 1644 (C=O), 1033 cm^{-1} (C-O).

*(+)-2-(3,4-Dichlorophenyl)-1-[(1R,5R,6R)-6-(pyrrolidin-1-yl)-9-oxa-2-azabicyclo[3.3.1]nonan-2-yl]ethan-1-one (**18d**)*

18a.HCl (102.6 mg, 0.28 mmol) was dissolved in a mixture of THF (20 mL), water (20 mL) and acetic acid (20 mL). Subsequently, 2,5-dimethoxytetrahydrofuran (48.2 mg, 0.36 mmol) and $NaBH_3CN$ (176.3 mg, 2.81 mmol) were added and the reaction mixture was heated to reflux for 4 h. The mixture was concentrated to a volume of about 10 mL, then 2 N NaOH (40 mL) and CH_2Cl_2 (50 mL) were added, the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by FC (2 cm, CH_2Cl_2/methanol 95:5, 20 mL, R_f 0.38). Fractions 6–10 contained **18d**. Colorless oil, yield 24.2 mg (23%).– $[\alpha]_{589}$ = +13.8 (0.84, $CHCl_3$).– $C_{19}H_{24}Cl_2N_2O_2$ (383.3) calcd. C 59.5 H 6.31 N 7.31 found C 59.8 H 6.57 N 7.15.– MS (EI): *m/z* = 386, 384, 382 (M^+).– IR (film): ν = 1635 (C=O), 1047 cm^{-1} (C-O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.47–2.05 (m, 10 H, C*H*$_2$C*H*$_2$ (pyrrolidine), 4-C*H*$_2$, 7-C*H*$_2$, 8-C*H*$_2$), 2.26–2.49 (m, 4 H, C*H*$_2$NC*H*$_2$ (pyrrolidine)), 3.18–3.79 (m, 2.74 H, 3-H, 6-H), 3.52 (s, 2 H, aryl-C*H*$_2$), 3.98–4.01 (m, 0.26 H, 5-H), 4.10 (dt, *J* = 8.6/4.3 Hz, 0.74 H, 5-H), 4.20–4.25 (m, 0.26 H, 3-H), 5.32 (d, *J* = 4.7 Hz, 0.26 H, 1-H), 5.59 (d, *J* = 3.0 Hz, 0.74 H, 1-H), 7.01 (dd, *J* = 8.1/2.1 Hz, 1 H, 6-H arom.), 7.26 (d, *J* = 2.1 Hz, 1 H, 2-H arom.), 7.32 (d, *J* = 8.1 Hz, 1 H, 5-H arom.). Ratio of rotational isomers 74:26.

Receptor binding studies[11]

General: Filter: Whatman GF/C, presoaked in buffer for 1–1.5 h before use.– Filtration was performed with a Brandel 24-well cell harvester.– Scintillation cocktail: Rotiszint eco plus (Carl Roth GmbH).– Liquid scintillation analyzer: TriCarb 1600 (Canberra Packard), counting efficiency 55%.– All experiments were carried out in triplicates.– IC_{50} values were determined with the program Inplot 4.0 (GraphPad Software TM) by nonlinear regression analysis.– K_i values were calculated according to Cheng and Prusoff[14].– For compounds with high affinity (low K_i values) mean values ± SEM from three independent experiments are given.

Investigation of the μ-receptor affinity[11]

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

Performance: According to ref.[11a].

Investigation of the κ-receptor affinity[11]

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

Performance: According to ref.[11a].

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