# Synthesis of Enantiomerically Pure Morphan Analogues from α-D-Glucose

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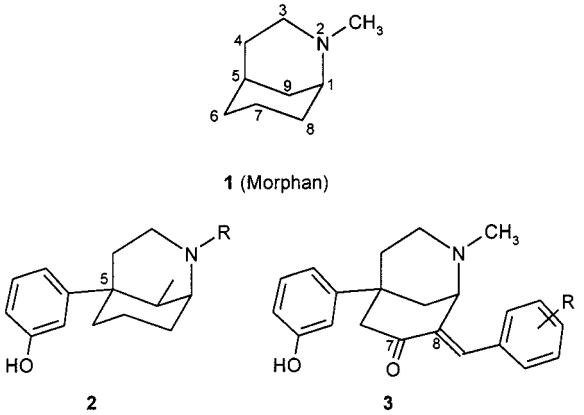
*Dedicated to Professor Dr. Fritz Eiden on the occasion of his 75th birthday*

**Keywords:** Medicinal chemistry / Carbohydrates / Cyclizations / EPC synthesis / Heterocycles / Morphan analogues

The synthesis of the enantiomerically pure morphan analogue **19** starting with the methyl glucopyranoside **6** is described. Homologation, reduction, and acylation provide the heptopyranosamine derivatives **9a**–**c**. After removal of the hydroxy group of **9c** the intramolecular N/O-acetal formation of the Cbz-protected heptopyranosamine **18** succeeds to yield the morphan analog epoxyazocane **19**.

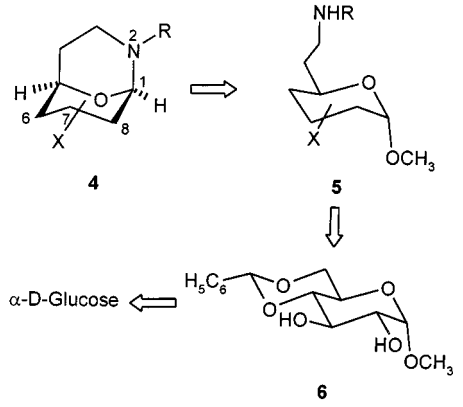
## Introduction

The bicyclic morphan ring system **1** represents a substructure of the opioid analgesic morphine. The introduction of a (3-hydroxyphenyl) residue in position 5 leads to morphan derivatives such as **2** or **3**, which, depending on the stereochemistry, bind with high affinity at opioid[1] and/or σ-receptors (Scheme 1).[2]




Scheme 1. Morphan derivatives with opioid and/or σ-receptor affinity

In the substance class of benzomorphan analgesics, exchange of the methano bridge by an epoxy bridge provides epoxybenzazocines with considerable effects on the central nervous system (CNS).[3] Therefore, we became interested in analogous morphan derivatives (e.g. **4**, Scheme 2) with an epoxy bridge instead of the methano bridge. After introduction of pharmacophoric elements (X = $NR_2$, OH, aryl, benzylidene, etc.) in positions 6, 7, and/or 8 of the bicyclic ring system (compare **3**) the affinities for CNS receptors, in particular opioid, NMDA and σ-receptors, should be investigated.




Scheme 2

In the literature only one example for the epoxyazocane ring system of **4** is given. The reported compound was used as intermediate in the synthesis of antibiotics.[4]

We intended to synthesize enantiomerically pure morphan analogues **4** by an intramolecular N/O-acetal formation of amino (R = H, alkyl) or amido [R = C(=O)R′] acetals **5**. The acetals **5** can be regarded as heptopyranosamine derivatives, which should be accessible by homologation and amination of suitable hexopyranoses (e.g. **6**). The hydroxy groups of the hexopyranose derivatives could be used for regio- and stereoselective introduction of pharmacophoric functional groups in positions 6, 7, and 8 of the bicyclic ring system.

## Results

In this communication we describe our initial studies in synthesizing morphan analogues with general structure **4** from the α-D-glucose derivative methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**6**). At first, the methyl glucopyranoside **6** was transformed into the bromoester **7** according to literature procedures.[5] Homologation of the bromo-substi-

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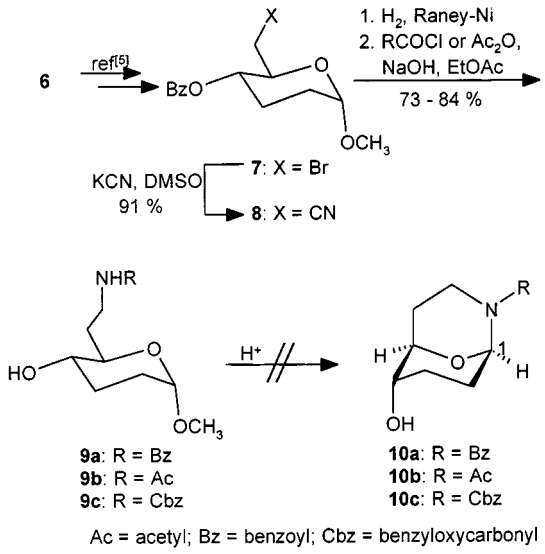
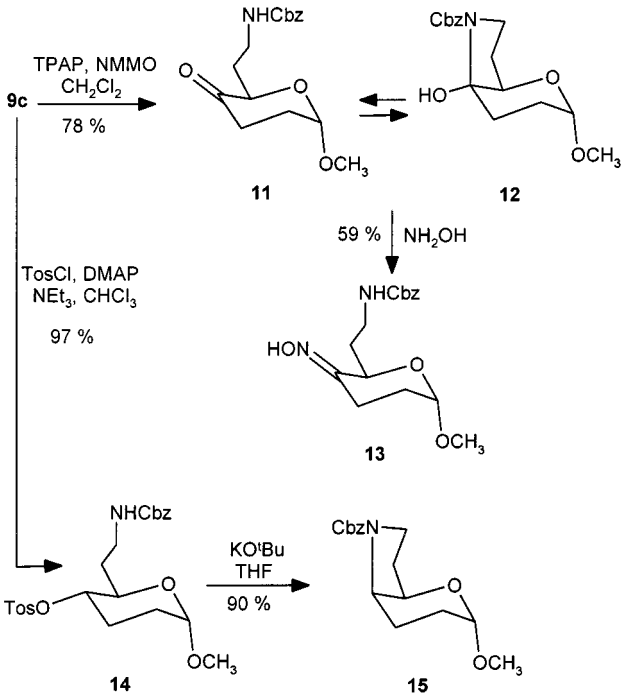



Scheme 3




Scheme 4

tuted hexopyranose derivative **7** was achieved by nucleophilic substitution with KCN to afford the cyano ester **8** (Scheme 3).

The cyano and ester moieties of the cyano ester **8** were reduced with $LiAlH_4$ to yield an amino alcohol, which was *N*-acylated with benzoyl chloride or acetic anhydride to provide the amides **9a** (59%) and **9b** (51%), respectively. The yields of **9a** and **9b** were improved to 73−76% by using $H_2$ and Raney nickel instead of $LiAlH_4$ for the reduction of the cyano ester **8**. Hence, for the preparation of the Cbz derivative **9c** only the reduction method with $H_2$ and Raney nickel was applied, which gave, after acylation, the carbamate **9c** in 84% yield.

All attempts to obtain the epoxyazocane **10a** by acid-catalyzed intramolecular N/O-acetal formation of the benzamido acetal **9a**, however, failed. Therefore, the cyclization behaviors of the acetamide **9b** and the carbamate **9c** with different nitrogen nucleophilicity of the amide and carbamate moiety were investigated. Again, treatment of **9b** and **9c** with acid did not provide the morphan-analogous epoxyazocanes **10b** and **10c**.

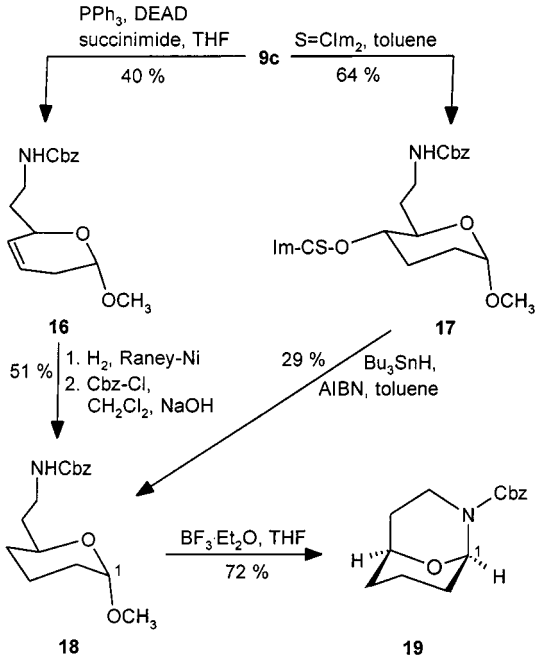
Since we presumed, that the hydroxy group of **9**, which has to adopt an axial orientation in the bicyclic N/O-acetals **10**, is disadvantageous for cyclization, the alcohol **9c** was oxidized using a catalytic amount of the oxidant tetrapropylammonium perruthenate (TPAP), and an excess of the reoxidant *N*-methylmorpholine *N*-oxide (NMMO).[6] Surprisingly, the $^1H$ NMR spectrum of the oxidation product showed a mixture of the desired ketone **11** and the N/O-hemiacetal **12** in a ratio of 30:70 (Scheme 4). The ketone **11** could not be separated from the **11/12** equilibrium, but a small amount (3%) of the N/O-hemiacetal **12** was isolated by flash chromatography. Reaction of the **11/12** mixture with hydroxylamine shifted the equilibrium towards the ketone **11**, affording the oxime **13** in 54% yield.

During our attempts to obtain epoxyazocane derivatives by acid-catalyzed cyclizations of the **11/12** mixture or the oxime **13**, either no transformation or decomposition was observed. We suspect that the reaction of the carbamate nitrogen with the adjacent carbonyl or hydroxyimino moiety is faster than the reaction with the methyl acetal.

A similar observation was made with the tosylate **14**, which was accessible by reaction of the hydroxycarbamate **9c** with tosyl chloride. Stirring of the tosylate **14** with potassium *tert*-butoxide did not lead to the elimination product **16**, but gave almost quantitatively the intramolecular substitution product **15**. As in the case of ketone **11**, the carbamate moiety reacts predominantly with the adjacent functional group. Comparison of the spectroscopic data of **15** and **12** provided additional evidence for the structure of the intramolecular N/O-hemiacetal **12**.

Next, we planned to eliminate the disadvantageous hydroxy group of the hydroxycarbamate **9c**. For the removal of this hydroxy group we made use of our observation, that under Mitsunobu conditions[7] [$PPh_3$, diethyl azodicarboxylate (DEAD), succinimide] the alcohol **9c** yielded the elimination product **16** (Scheme 5) instead of the expected substitution product. Hydrogenation followed by reacylation with Cbz−Cl provided the carbamate **18** without further substituents at the pyran ring. Alternatively, the reductive elimination of the hydroxy group was performed according to the procedure of Barton and McCombie.[8] Heating of the alcohol **9c** with 1,1′-thiocarbonyldiimidazole furnished the thionocarbamate **17**, which was reduced with tributyltin hydride in refluxing toluene to afford **18**.

Finally, the epoxyazocane **19** was obtained by cyclization of the amido acetal **18** with the Lewis acid $BF_3{\cdot}Et_2O$. The structure of the cyclization product **19** was unequivocally proven by analytical and spectroscopic data. In particular,




Scheme 5

the signal for the acetalic proton (1-H) in the $^1$H NMR spectrum appears at δ = 5.53, ca. 0.8 ppm downfield shifted in comparison with the signal of the acetalic proton (1-H) of the starting material **18** (δ = 4.70).

In summary, we have presented first model studies for the preparation of the enantiomerically pure morphan analogue **19** from the glucose derivative **6**. This concept will be further developed for the construction of novel morphan analogues of general structure **4** with pharmacophoric functional groups in positions 6, 7, and/or 8.

## Experimental Section

**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):[9] Silica gel 60, 0.040−0.063 mm (Merck); parentheses include: diameter of the column [cm]; eluent; fraction size [mL]; and $R_f$. − Melting points: Melting point apparatus Dr. Tottoli (Büchi), uncorrected values. − 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.

**(+)-(2*R*,3*S*,6*S*)-2-Cyanomethyl-6-methoxyoxan-3-yl Benzoate (8):** A solution of **7** (772 mg, 2.34 mmol) and KCN (457 mg, 7.02 mmol) in DMSO (10 mL) was stirred for 1 h at 70 °C. After addition of water (10 mL), the mixture was extracted with petroleum ether/ethyl acetate, 95:5 (4 × 20 mL), the organic layer was washed with a saturated solution of NaCl (20 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by FC (50 g of silica gel; 4 cm; petroleum ether/ethyl acetate, 9:1; 25 mL; $R_f$ = 0.25). Colorless solid (petroleum ether/$Et_2O$), m.p. 61−63 °C, yield 583 mg (91%). − $[\alpha]_{589}$ = +156.0 (*c* = 1.00, $CHCl_3$). − $C_{15}H_{17}NO_4$ (275.3): calcd. C 65.4, H 6.22, N 5.09; found C 65.3, H 6.35, N 5.05. − MS (EI); *m*/*z*: 244 [M − $OCH_3$]. − IR (KBr): $\tilde{\nu}$ = 2259 (C≡N), 1722 (C=O), 1269 (O=*C*−*O*), 1130 (C−O), 1047 $cm^{-1}$ (C−O). − $^1$H NMR ($CDCl_3$): δ = 1.82−1.95 (m, 3 H, 4-H, 2 × 5-H), 2.04−2.09 (m, 1 H, 4-H), 2.49 (dd, *J* = 16.7/8.1 Hz, 1 H, C$H_2$CN), 2.63 (dd, *J* = 16.7/3.4 Hz, 1 H, C$H_2$CN), 3.39 (s, 3 H, $OCH_3$), 4.07 (ddd, *J* = 9.6/8.3/3.4 Hz, 1 H, 2-H), 4.71 (d, *J* = 2.1 Hz, 1 H, 6-H), 4.77 (td, *J* = 9.8/4.9 Hz, 1 H, 3-H), 7.39 (td, *J* = 7.7/1.5 Hz, 2 H, arom.), 7.53 (td, *J* = 7.2/1.3 Hz, 1 H, arom.), 7.95 (dd, *J* = 8.1/1.3 Hz, 2 H, arom.).

**(+)-*N*-{2-[(2*R*,3*S*,6*S*)-3-Hydroxy-6-methoxyoxan-2-yl]ethyl}-benzamide (9a)**

**Method A (Reduction with $LiAlH_4$ and Subsequent Acylation):** At 0 °C a solution of **8** (100 mg, 0.36 mmol) in $Et_2O$ (2 mL) was added to a solution of $LiAlH_4$ (1 M in $Et_2O$, 3 mL) and the reaction mixture was stirred at room temperature for 3 h. Then, NaOH (2 N) was added with cooling until evolution of $H_2$ had finished. The mixture was dried with $MgSO_4$ (200 mg), filtered and the filtrate was concentrated in vacuo. The residue [colorless oil, 97.1 mg, $R_f$ = 0.14 (ethyl acetate/methanol/$NH_3$ conc., 85:10:5)] was dissolved in $CH_2Cl_2$ (2 mL) and $NEt_3$ (80 mg, 0.79 mmol). Then, benzoyl chloride (66.3 mg, 0.47 mmol) was added and the reaction mixture was stirred for 30 min at room temperature. The solvent was removed in vacuo and the residue was purified by FC (20 g of silica gel; 3 cm; ethyl acetate; 30 mL; $R_f$ = 0.38). Colorless solid (*i*$Pr_2O$), m.p. 103 °C, yield 60.0 mg (59%). − $[\alpha]_{589}$ = +68.6 (*c* = 0.99, $CHCl_3$). − $C_{15}H_{21}NO_4$ (279.3): calcd. C 64.5 H 7.58 N: 5.01 found C 64.4 H 7.60 N 5.00. − MS (CI); *m*/*z*: 280 [$MH^+$], 248 [$MH^+$ − $CH_3OH$]. − IR (KBr): $\tilde{\nu}$ = 3344 (NH, OH), 1636 (C=O), 1540 (amide-II), 1126 (C−O), 1056 $cm^{-1}$ (C−O). − $^1$H NMR ($CDCl_3$): δ = 1.72−1.92 (m, 5 H, 2 × 4-H, 2 × 5-H, C$H_2$$CH_2$NH), 2.19−2.26 (m, 1 H, C$H_2$$CH_2$NH), 3.32 (s, 3 H, $OCH_3$), 3.43 (td, *J* = 9.8/4.9 Hz, 1 H, 3-H), 3.51 (ddd, *J* = 13.2/8.8/4.3 Hz, 1 H, $CH_2$C$H_2$NH), 3.64 (td, *J* = 8.8/3.0 Hz, 1 H, 2-H), 3.76 (dt, *J* = 12.8/6.4 Hz, 1 H, $CH_2$C$H_2$NH), 4.68 (s, 1 H, 6-H), 7.26 (s, br., 1 H, NH), 7.42 (t, *J* = 7.3 Hz, 2 H, arom.), 7.49 (t, *J* = 7.3 Hz, 1 H, arom.), 7.76 (d, *J* = 8.5 Hz, 2 H, arom.); a signal for the proton of the OH group was not found.

**Method B (Reduction with $H_2$/Raney-Ni and Subsequent Acylation):** A suspension of Raney-Ni (40 mg) in 5 N NaOH (1 mL) was added to a solution of **8** (80 mg, 0.29 mmol) in methanol (4.5 mL) and 5 N NaOH (0.5 mL). The reaction mixture was vigorously shaken under $H_2$ (5.3 bar) for 16 h at room temperature. After filtration of the suspension, water (5 mL) was added and the mixture was concentrated in vacuo (residue ca. 8 mL). Then, ethyl acetate (10 mL) and benzoyl chloride (65 mg, 0.46 mmol) were added and the mixture was stirred for 30 min at room temperature. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (4 × 10 mL) The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was purified by FC (see Method A). Colorless solid (*i*$Pr_2O$), yield 59.6 mg (73%).

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

**Method A (Reduction with $LiAlH_4$ and Subsequent Acylation):** As described for **9a** (Method A) the nitrile **8** (25 mg, 0.09 mmol) was reduced with $LiAlH_4$ (1 M in $Et_2O$, 2 mL) and, subsequently, acylated with $Ac_2O$ (26.8 mg, 0.20 mmol) and $NEt_3$ (50 mg, 0.49 mmol) in $CH_2Cl_2$ (2 mL). FC (4 g of silica gel; 1 cm; ethyl acetate/meth-

anol, 9:1; 5 mL; $R_f$ = 0.30). Colorless oil, yield 10.0 mg (51%). − $[\alpha]_{589}$ = +72.6 (*c* = 0.47, $CHCl_3$). − $C_{10}H_{19}NO_4$ (217.3): calcd. C 55.3, H 8.81, N 6.45; found C 55.5, H 9.02, N 6.21. − MS (CI); *m*/*z*: 218 [$MH^+$], 186 [$MH^+ - CH_3OH$]. − IR (film): $\tilde{\nu}$ = 3320 (NH, OH), 1652 (C=O), 1564 (amide-II), 1127 (C−O), 1056 $cm^{-1}$ (C−O). − $^1H$ NMR ($CDCl_3$): δ = 1.54−1.84 (m, 5 H, 2 × 4-H, 2 × 5-H, C$H_2$CH$_2$NH), 1.90 (s, 3 H, C$H_3$C=O), 1.99−2.06 (m, 1 H, C$H_2$CH$_2$NH), 2.42 (s, br, 1 H, OH), 3.27 (s, 3 H, $OCH_3$), 3.21−3.34 (m, 2 H, CH$_2$C$H_2$NH), 3.39−3.50 (m, 2 H, 2-H, 3-H), 4.57 (d, *J* = 1.7 Hz, 1 H, 6-H), 6.10 (s, br, 1 H, NH).

**Method B (Reduction with $H_2$/Raney-Ni and Subsequent Acylation):** As described for **9a** (Method B) the nitrile **8** (25 mg, 0.09 mmol) was hydrogenated ($H_2$, 5.3 bar) in the presence of Raney-Ni (12 mg) in methanol/NaOH and, subsequently, acylated with $Ac_2O$ (19.5 mg, 0.14 mmol) for 3 h at room temperature. FC (see Method A). Colorless oil, yield 15.0 mg (76%).

### (+)-Benzyl *N*-{2-[(2*R*,3*S*,6*S*)-3-Hydroxy-6-methoxyoxan-2-yl]-ethyl}carbamate (9c)

**Method B (Reduction with $H_2$/Raney-Ni and Subsequent Acylation):** As described for **9a** (Method B) the nitrile **8** (350 mg, 1.27 mmol) was hydrogenated ($H_2$, 5.3 bar) in the presence of Raney-Ni (175 mg) in methanol/NaOH and, subsequently, acylated with benzyl chloroformate (433 mg, 2.54 mmol) for 30 min at room temperature. The crude product was purified by FC (25 g of silica gel; 3 cm; petroleum ether/ethyl acetate, 1:1; 30 mL; $R_f$ = 0.27). Colorless oil, yield 331 mg (84%). − $[\alpha]_{589}$ = +77.3 (*c* = 0.93, $CHCl_3$). − $C_{16}H_{23}NO_5$ (309.4): calcd. C 62.1, H 7.49, N 4.53; found C 62.3, H 7.61, N 4.77. − MS (CI); *m*/*z*: 278 [$MH^+ - CH_3OH$]. − IR (film): $\tilde{\nu}$ = 3353 (NH, OH), 1701 (C=O), 1534 (amide-II), 1261 (O=*C*−*O*), 1127 (C−O), 1056 $cm^{-1}$ (C−O). − $^1H$ NMR ($CDCl_3$): δ = 1.59−1.87 (m, 5 H, 2 × 4-H, 2 × 5-H, C$H_2$CH$_2$NH), 2.05−2.13 (m, 1 H, C$H_2$CH$_2$NH), 2.26 (s, br, 1 H, OH), 3.24−3.48 (m, 6 H, 3-H, CH$_2$C$H_2$NH, $OCH_3$), 3.51 (td, *J* = 9.1/2.9 Hz, 1 H, 2-H), 4.62 (d, *J* = 1.7 Hz, 1 H, 6-H), 5.08 (s, 2 H, arylC$H_2$O) 5.31 (s, br, 1 H, NH), 7.27−7.35 (m, 5 H, arom.).

**Benzyl *N*-{2-[(2*R*,6*S*)-6-Methoxy-3-oxooxan-2-yl]ethyl}carbamate (11) and Benzyl (1*R*,3*S*,6*S*)-6-Hydroxy-3-methoxy-2-oxa-7-azabicyclo[4.3.0]nonane-7-carboxylate (12):** A mixture of **9c** (43.4 mg, 0.14 mmol), *N*-methylmorpholine *N*-oxide (NMMO, 31.5 mg, 0.23 mmol), tetrapropylammonium perruthenate (4.5 mg) and $CH_2Cl_2$ (5 mL) was stirred for 3 h at room temperature. The mixture was concentrated in vacuo and the residue (ca. 2 mL) was purified by FC (15 g of silica gel; 2 cm; petroleum ether/ethyl acetate, 7:3; 25 mL). − Concentration of fraction 9 provided pure **12**, $R_f$ = 0.27, colorless oil, yield 1.3 mg (3.0%). − $C_{16}H_{21}NO_5$ (307.3). − MS (EI); *m*/*z* = 289 [$M^+ - H_2O$]. − IR (film): $\tilde{\nu}$ = 3427 (OH), 1719 (C=O), 1057 (C−O), 1016 $cm^{-1}$ (C−O). − $^1H$ NMR ($CDCl_3$): δ = 1.71−1.80 (m, 4 H, 2 × 4-H, 2 × 9-H), 2.17−2.28 (m, 2 H, 2 × 5-H), 2.58 (s, br, 1 H, OH), 3.39 (s, 3 H, $OCH_3$), 3.57−3.63 (m, 1 H, 8-H), 3.75 (t, *J* = 9.4 Hz, 1 H, 8-H), 4.05 (d, *J* = 4.3 Hz, 1 H, 1-H), 4.67 (t, *J* = 3.6 Hz, 1 H, 3-H), 5.16 (s, 2 H, C$H_2$Ph), 7.31−7.39 (m, 5 H, arom.). − The fractions 10−14 contained a mixture of **11** and **12**, ratio 30:70, $R_f$(**11**) = 0.24, colorless oil, yield 33.6 mg (78%). − $C_{16}H_{21}NO_5$ (307.3): calcd. C 62.5, H 6.89, N 4.56; found C 62.3, H 6.71, N 4.33. − MS (CI); *m*/*z*: 308 [$MH^+$]. − IR (film): $\tilde{\nu}$ = 3423 (OH), 1713 (C=O), 1055 (C−O), 1016 $cm^{-1}$ (C−O). − $^1H$ NMR ($CDCl_3$): δ = 1.60−1.87 [m, 4 × 0.7 H and 1 × 0.3 H, 2 × 4-H, 2 × 9-H (**12**), 1 × C$H_2$CH$_2$N (**11**)], 1.93−2.01 [m, 0.3 H, C$H_2$CH$_2$N (**11**)], 2.07−2.31 [m, 2 H, 2 × 5-H (**12**), 2 × 5-H (**11**)], 2.38−2.55 [m, 2 × 0.3 H, 2 × 4-H (**11**)], 2.58 [s, br, 0.7 H, OH (**12**)], 3.30−3.39 [m, 0.3 H, CH$_2$C$H_2$N (**11**)], 3.39 [s, 3 × 0.7 H, $OCH_3$ (**12**)], 3.41 [s, 3 × 0.3 H, $OCH_3$ (**11**)], 3.56−3.62 [m, 1 H, 8-H (**12**), CH$_2$C$H_2$N (**11**)], 3.74 [t, *J* = 9.4 Hz, 0.7 H, 8-H (**12**)], 4.04 [d, *J* = 3.8 Hz, 0.7 H, 1-H (**12**)], 4.18 [dd, *J* = 8.3/4.1 Hz, 0.3 H, 2-H (**11**)], 4.66 [t, *J* = 3.6 Hz, 0.7 H, 3-H (**12**)], 4.89 [t, *J* = 4.7 Hz, 0.3 H, 6-H (**11**)] 5.09−5.19 [m, 2 H and 0.3 H, C$H_2$Ph, NH (**12**)], 7.30−7.39 (m, 5 H, arom.).

**(+)-Benzyl *N*-{2-[(2*R*,6*S*)-*cis*- and -*trans*-3-Hydroxyimino-6-methoxyoxan-2-yl]ethyl}carbamate (13):** $NH_2OH{\cdot}HCl$ (33.7 mg, 0.48 mmol) and NaOAc (26.6 mg, 0.32 mmol) were added to a solution of **11**/**12** (49.7 mg, 0.16 mmol) in methanol (5 mL) and the mixture was heated to reflux for 7 h. Methanol was evaporated in vacuo, the residue was dissolved in water (5 mL) and extracted with ethyl acetate (3 × 5 mL). The ethyl acetate layer was washed with 2 N HCl (10 mL), saturated solutions of $NaHCO_3$ (10 mL) and NaCl (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (10 g of silica gel; 2 cm; petroleum ether/ethyl acetate, 6:4; 15 mL; $R_f$ = 0.36). Colorless oil, yield 31.0 mg (59%). − $[\alpha]_{589}$ = +35.2 (*c* = 0.83, $CHCl_3$). − $C_{16}H_{22}N_2O_5$ (322.4:) calcd. C 59.6, H 6.88, N 8.69; found C 59.5, H 7.04, N 8.86. − MS (CI); *m*/*z*: 323 [$MH^+$]. − IR (film): $\tilde{\nu}$ = 3357 (OH, NH), 1705 (C=O), 1530 (amide-II), 1255 (O=*C*−*O*), 1125 (C−O), 1057 $cm^{-1}$ (C−O). − $^1H$ NMR ($CDCl_3$): δ = 1.76−1.97 (m, 3 H, 2 × 5-H, C$H_2$CH$_2$NH), 2.12−2.17 (m, 1 H, C$H_2$CH$_2$NH), 2.48 (ddd, *J* = 15.9/9.5/6.1 Hz, 1 H, 4-H), 2.79 (dt, *J* = 16.2/6.2 Hz, 1 H, 4-H), 3.32−3.39 (m, 1 H, CH$_2$C$H_2$NH), 3.39 (s, 3 H, $OCH_3$), 3.41−3.48 (m, 1 H, CH$_2$C$H_2$NH), 4.36 (t, *J* = 4.1 Hz, 1 H, 2-H), 4.78 (t, *J* = 3.8 Hz, 1 H, 6-H), 5.09 (s, 2 H, C$H_2$Ph), 5.19 (s, br, 1 H, NH), 7.28−7.38 (m, 5 H, arom.), 8.00 (s, br, 0.8 H, OH), 8.78 (s, br, 0.2 H, OH). *cis*-**13**/*trans*-**13** = 80:20.

**(+)-Benzyl *N*-{2-[(2*R*,3*S*,6*S*)-6-Methoxy-3-(tosyloxy)oxan-2-yl]-ethyl}carbamate (14):** At 0 °C *p*-toluenesulfonyl chloride (906 mg, 3.12 mmol) and 4-(dimethylamino)pyridine (381 mg, 3.12 mmol) were successively added to a solution of **9c** (161 mg, 0.52 mmol) and $NEt_3$ (500 mg, 4.94 mmol) in $CHCl_3$ (12 mL). The reaction mixture was stirred for 10 min at 0 °C and for 3 h at 65 °C. Then, the $CHCl_3$ layer was washed with 1 N HCl (2 × 10 mL) and saturated solutions of $NaHCO_3$ (10 mL) and NaCl (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by FC (40 g of silica gel; 4 cm; petroleum ether/ethyl acetate, 7:3; 30 mL; $R_f$ = 0.27). Colorless oil, yield 233 mg (97%). − $[\alpha]_{589}$ = +27.8 (*c* = 1.04, $CHCl_3$). − $C_{23}H_{29}NO_7S$ (463.6): calcd. C 59.6, H 6.31, N 3.02, S 6.92; found C 59.7, H 6.31, N 2.94, S 6.85. − MS (CI); *m*/*z*: 465 [$MH^+$]. − IR (film): $\tilde{\nu}$ = 3359 (N−H), 1715 (C=O), 1520 (amide-II), 1055 (C−O), 1019 $cm^{-1}$ (C−O). − $^1H$ NMR ($CDCl_3$): δ = 1.28−1.37 (m, 1 H, C$H_2$CH$_2$NH), 1.55−1.91 (m, 5 H, 2 × 4-H, 2 × 5-H, 1 × C$H_2$CH$_2$NH), 2.37 (s, 3 H, arylC$H_3$), 3.05−3.16 (m, 1 H, CH$_2$C$H_2$NH), 3.19 (s, 3 H, $OCH_3$), 3.23−3.29 (m, 1 H, CH$_2$C$H_2$NH), 3.62 (td, *J* = 9.5/2.4 Hz, 1 H, 2-H), 4.14 (td, *J* = 10.3/5.1 Hz, 1 H, 3-H), 4.51 (d, *J* = 3.0 Hz, 1 H, 6-H), 4.95 (s, br, 1 H, NH), 5.01 (s, 2 H, C$H_2$Ph), 7.23−7.29 (m, 7 H, arom.), 7.71 (d, *J* = 8.1 Hz, 2 H, arom.).

**(+)-Benzyl (1*R*,3*S*,6*R*)-3-Methoxy-2-oxa-7-azabicyclo[4.3.0]nonane-7-carboxylate (15):** Potassium *tert*-butoxide (58.8 mg, 0.52 mmol) was added to a solution of **14** (40.4 mg, 0.09 mmol) in THF (5 mL). After stirring for 2 h at room temperature, water (5 mL) and $Et_2O$ (5 mL) were added, the organic layer was separated and the aqueous layer was extracted with $Et_2O$ (2 × 5 mL). The combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was purified by FC (10 g of silica gel; 2 cm; petroleum ether/ethyl acetate, 75:25; 25 mL; $R_f$ = 0.37). Colorless oil, yield 22.7 mg (90%). − $[\alpha]_{589}$ = +14.0 (*c* = 0.56, $CHCl_3$). − $C_{16}H_{21}NO_4$ (291.3): calcd. C 66.0, H 7.26, N 4.81; found C 66.1,

H 7.36, N 4.59. − MS (EI); *m/z*: 291 [$M^+$]. − IR (film): $\tilde{\nu}$ = 1700 (C=O), 1108 (C−O), 1052 $cm^{-1}$ (C−O). − $^1H$ NMR ($CDCl_3$): δ = 1.61−2.05 (m, 6 H, 2 × 4-H, 2 × 5-H, 2 × 9-H), 3.32 (s, 3 H, $OCH_3$), 3.44 (ddd, *J* = 17.4/10.7/6.7 Hz, 1 H, 8-H), 3.63−3.70 (m, 2 H, 6-H, 8-H), 4.22 (s, br, 1 H, 1-H), 4.62 (t, *J* = 4.1 Hz, 1 H, 3-H), 5.02 (d, *J* = 12.4 Hz, 1 H, C$H_2$Ph), 5.10 (d, *J* = 12.4 Hz, 1 H, C$H_2$Ph), 7.19−7.30 (m, 5 H, arom.).

**(+)-Benzyl *N*-{2-[(2*R*,6*S*)-6-Methoxy-5,6-dihydro-2*H*-pyran-2-yl]-ethyl}carbamate (16):** Compound **9c** (100.8 mg, 0.33 mmol), triphenylphosphane (170.9 mg, 0.65 mmol), and succinimide (64.6 mg, 0.65 mmol) were dissolved in THF (10 mL). Subsequently, a solution of diethyl azodicarboxylate (113.5 mg, 0.65 mmol) in THF (5 mL) was added and the reaction mixture was stirred for 24 h at room temperature. The solvent was removed in vacuo and the residue was purified by FC (20 g of silica gel; 3 cm; petroleum ether/ethyl acetate, 75:25; 30 mL; $R_f$ = 0.39). Colorless oil, yield 37.9 mg (40%). − $[\alpha]_{589}$ = +58.9 (*c* = 0.94, $CHCl_3$). − $C_{16}H_{21}NO_4$ (291.3): calcd. C 66.0, H 7.27, N 4.81; found C 66.2, H 7.41, N 5.04. − MS (EI); *m/z*: 291 [$M^+$]. − IR (film): $\tilde{\nu}$ = 3356 (NH), 1716 (C=O), 1540 (amide-II), 1249 (O=*C*−*O*), 1118 (C−O), 1049 $cm^{-1}$ (C−O). − $^1H$ NMR ($CDCl_3$): δ = 1.68−1.77 (m, 1 H, C$H_2$CH$_2$NH), 1.80−1.88 (m, 1 H, C$H_2$CH$_2$NH), 2.00−2.07 (m, 1 H, 5-H), 2.37−2.45 (m, 1 H, 5-H), 3.30−3.42 (m, 2 H, CH$_2$C$H_2$NH), 3.42 (s, 3 H, $OCH_3$), 4.28 (t, *J* = 3.5 Hz, 1 H, 2-H), 4.86 (d, *J* = 4.3 Hz, 1 H, 6-H), 5.09 (s, 2 H, C$H_2$Ph), 5.19 (s, br, 1 H, NH), 5.62 (d, *J* = 10.7 Hz, 1 H, 4-H), 5.70−5.75 (m, 1 H, 3-H), 7.29−7.36 (m, 5 H, arom.).

**(+)-Benzyl *N*-{2-[(2*R*,3*S*,6*S*)-3-(Imidazol-1-ylthiocarbonyloxy)-6-methoxyoxan-2-yl]ethyl}carbamate (17):** A solution of **9c** (71.7 mg, 0.23 mmol) and 1,1′-thiocarbonyldiimidazole (413 mg, 2.32 mmol) in toluene (15 mL) was heated to reflux for 5 h. After addition of 2 N HCl (10 mL), the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated solutions of $NaHCO_3$ (10 mL) and NaCl (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by FC (25 g of silica gel; 3 cm; ethyl acetate; 25 mL; $R_f$ = 0.39). Pale yellow oil, yield 62.0 mg (64%). − $[\alpha]_{589}$ = +105.5 (*c* = 0.93, $CHCl_3$). − $C_{20}H_{25}N_3O_5S$ (419.5): calcd. C 57.3, H 6.01, N 10.01; found C 57.2, H 6.26, N 9.83. − MS (CI); *m/z*: 420 [$MH^+$], 388 [$M^+$ − $OCH_3$]. − IR (film): $\tilde{\nu}$ = 3356 (NH), 1721 (C=O), 1530 (amide-II), 1231 (C=S), 1125 (C−O), 1053 $cm^{-1}$ (C−O). − $^1H$ NMR ($CDCl_3$): δ = 1.56−1.66 (m, 1 H, C$H_2$CH$_2$NH), 1.77−1.89 (m, 4 H, 2 × 5-H, 4-H, C$H_2$CH$_2$NH), 2.10−2.16 (m, 1 H, 4-H), 3.21−3.27 (m, 1 H, CH$_2$C$H_2$NH), 3.30 (s, 3 H, $OCH_3$), 3.32−3.40 (m, 1 H, CH$_2$C$H_2$NH), 3.95 (td, *J* = 9.4/2.6 Hz, 1 H, 2-H), 4.65 (d, *J* = 2.1 Hz, 1 H, 6-H), 5.02 (s, br, 3 H, NH, C$H_2$Ph), 5.26 (td, *J* = 9.8/4.7 Hz, 1 H, 3-H), 6.97 (d, *J* = 0.8 Hz, 1 H, imidazole), 7.22−7.29 (m, 5 H, arom.), 7.52 (s, 1 H, imidazole), 8.24 (s, 1 H, imidazole).

**(+)-Benzyl *N*-{2-[(2*S*,6*S*)-6-Methoxyoxan-2-yl]ethyl}carbamate (18)**

**a)** Freshly prepared Raney-Ni (38 mg) was added to a solution of **16** (37.9 mg, 0.13 mmol) in methanol (12 mL) and the mixture was shaken under hydrogen (5.0 bar) for 24 h at room temperature. Then, the mixture was filtered and the solvent was evaporated in vacuo. After dissolving the residue (ca. 1 mL) in water (10 mL) and $CH_2Cl_2$ (10 mL), benzyl chloroformate (76 mg, 0.45 mmol) was added and the mixture was stirred for 4 h at room temperature. The organic layer was separated, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL), the combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was purified by FC (7 g of silica gel; 2 cm; petroleum ether/ethyl acetate, 8:2; 25 mL; $R_f$ = 0.22). Colorless oil, yield 19.3 mg (51%). − $[\alpha]_{589}$ = +58.9 (*c* = 0.72, $CHCl_3$). − $C_{16}H_{23}NO_4$ (293.4): calcd. C 65.5, H 7.90, N 4.77; found C 65.3, H 7.76, N 4.92. − MS (EI); *m/z*: 262 [$M^+$ − $OCH_3$]. − IR (film): $\tilde{\nu}$ = 3330 (NH), 1705 (C=O), 1540 (amide-II), 1248 (O=*C*−*O*), 1124 (C−O), 1031 $cm^{-1}$ (C−O). − $^1H$ NMR ($CDCl_3$): δ = 1.25−1.38 (m, 1 H, 4-H), 1.54−1.86 (m, 7 H, 2 × 3-H, 2 × 5-H, C$H_2$CH$_2$NH, 1 × 4-H), 3.25 (ddd, *J* = 13.2/6.9/4.3 Hz, 1 H, CH$_2$C$H_2$NH), 3.32 (s, 3 H, $OCH_3$), 3.45 (dt, *J* = 13.2/6.4 Hz, 1 H, CH$_2$C$H_2$NH), 3.75−3.81 (m, 1 H, 2-H), 4.70 (s, 1 H, 6-H), 5.09 (s, 2 H, C$H_2$Ph), 5.19 (s, br, 1 H, NH), 7.29−7.36 (m, 5 H, arom.).

**b)** AIBN (5 mg) was added to a solution of **17** (45.9 mg, 0.11 mmol) and tributyltin hydride (20 mg) in toluene (5 mL) and the mixture was heated to reflux for 4 h. During this period further portions of AIBN (2 × 5 mg) and tributyltin hydride (5 × 20 mg) were added. The solvent was evaporated in vacuo and the residue was purified by FC (10 g of silica gel; 2 cm; petroleum ether/ethyl acetate, 9:1; 25 mL). Colorless oil, yield 9.3 mg (29%).

**(+)-Benzyl (1*R*,5*S*)-9-Oxa-2-azabicyclo[3.3.1]nonane-2-carboxylate (19):** $BF_3$·$Et_2O$ (0.1 mL) was added to a solution of **18** (40 mg, 0.14 mmol) in THF (5 mL) and the mixture was heated to reflux for 9 h. Then, water (5 mL) and $Et_2O$ (5 mL) were added, the organic layer was separated, the aqueous layer was extracted with $Et_2O$ (2 × 5 mL), the combined organic layers were dried ($MgSO_4$), concentrated in vacuo and the residue was purified by FC (10 g of silica gel; 2 cm; petroleum ether/ethyl acetate, 8:2; 25 mL; $R_f$ = 0.39). Colorless oil, yield 25.8 mg (72%). − $[\alpha]_{589}$ = +28.9 (*c* = 0.49, $CHCl_3$). − $C_{15}H_{19}NO_3$ (261.3): calcd. C 68.9, H 7.33, N 5.36; found C 69.1, H 7.56, N 5.63. − MS (EI); *m/z*: 261 [$M^+$]. − IR (film): $\tilde{\nu}$ = 1700 (C=O), 1034 $cm^{-1}$ (C−O). − $^1H$ NMR ($CDCl_3$): δ = 1.60−1.70 (m, 2 H, 7-H), 1.85−1.99 (m, 5 H, 2 × 4-H, 2 × 6-H, 1 × 8-H), 2.08−2.15 (m, 1 H, 8-H), 3.70−3.78 (m, 2 H, 3-H), 4.10−4.15 (m, 1 H, 5-H), 5.09 (d, *J* = 12.4 Hz, 1 H, C$H_2$Ph), 5.14 (d, *J* = 12.4 Hz, 1 H, C$H_2$Ph), 5.53 (s, br, 1 H, 1-H), 7.32−7.38 (m, 5 H, arom.).

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