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Asymmetric synthesis of 1-substituted tetrahydro-3-benzoazepines

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Dedicated to Prof. Dr. C. Herdeis on the occasion of his 60th birthday

Abstract—In order to develop a new asymmetric synthesis of enantiomerically pure 1-substituted tetrahydro-3-benzoazepines **3**, the synthesis of diastereomerically pure oxazolo[3]benzoazepinone **4** has been performed. The stereochemical information of the key intermediate **4** originates from the chiral auxiliary (*R*)-phenylglycinol. The tricyclic ring system of **4** allows the stereoselective introduction of a benzyl residue at the 6-position to obtain benzyl derivative **15** with a diastereoselectivity of 95.1:4.9. The relative configuration of the main product **15** was determined by X-ray crystal structure analysis. Reductive degradation of diastereomerically pure **15** led to enantiomerically pure (*R*)-1-benzyl-3-benzoazepine **17**.

1. Introduction

The NMDA receptor belongs to a group of excitatory ionotropic glutamate receptors and is activated by *N*-methyl-D-aspartate. The NMDA receptor is involved in a variety of complex physiological processes such as learning and memory. However, overstimulation causes acute and chronic neurodegenerative disorders including excitotoxicity, epilepsy, Alzheimer's or Parkinson's disease.[1] The tetracyclic MK-801 **1** represents a non-competitive NMDA receptor antagonist ($K_i = 1.2$ nM) interacting with the PCP binding site within the cation channel.[2] Formal cleavage of the C_{9a}/C_{10} bond of MK-801 results in tetrahydroisoquinoline **2**, also binding at the NMDA receptor. The enantiomers of **2** display considerable differences of their NMDA receptor interaction: (S)-**2**: $K_i = 35.4$ nM, (R)-**2**: $K_i = 3756$ nM.[3] 1-Substituted 3-benzoazepines **3** are also potent NMDA receptor antagonists. However, only racemic mixtures have been investigated[4] (see Fig. 1).

Since our interest has been focused on the NMDA receptor affinity of 3-benzoazepine enantiomers, we intended to develop an asymmetric synthesis of enantiomerically pure 1-substituted 3-benzoazepines.

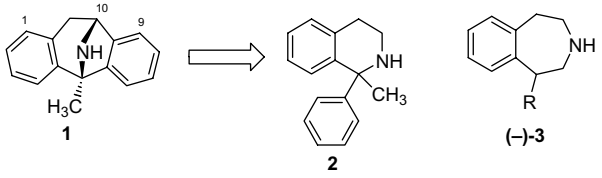

Figure 1.

Only a few methods for the synthesis of enantiomerically pure tetrahydro-3-benzoazepines have been reported.[5–8] Davies et al. elaborated a diastereoselective intramolecular Friedel–Crafts alkylation of a chiral $Cr(CO)_3$-complex leading to enantiomerically pure 1-phenyltetrahydro-3-benzoazepines.[5,6] The intramolecular Friedel–Crafts acylation of *N*-(phenethyl)amino acids provided 2-substituted tetrahydro-3-benzoazepines.[7] Tietze et al. described an intramolecular Heck reaction, which led to enantiomerically pure 3-benzoazepines.[8]

These methods belong to the class of chiral pool synthesis. An asymmetric synthesis using a chiral auxiliary has not been detailed. Furthermore, the already described methods do not allow the systematic variation of the 3-benzoazepine substitution pattern. In order to investigate the relationship between substituted 3-benzoazepines and their NMDA receptor affinity, we were interested in a method, which would allow a flexible

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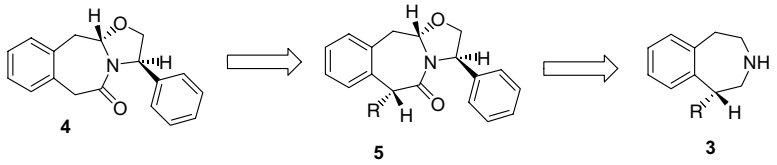


Figure 2.

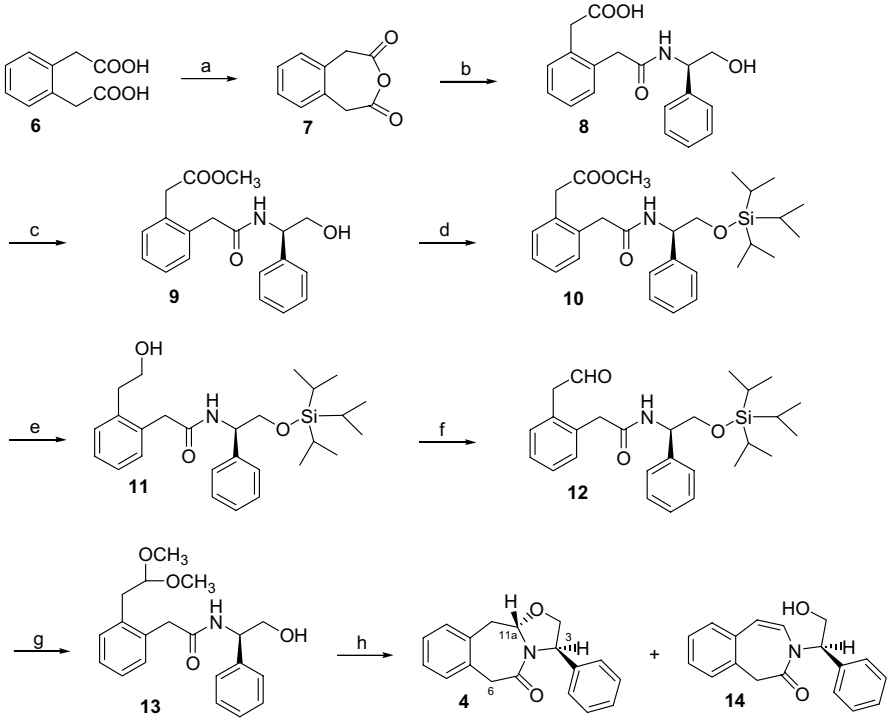
substitution of the 3-benzoazepine scaffold. Therefore, we planned a novel asymmetric synthesis of 1-substituted tetrahydro-3-benzoazepines **3**. Tricyclic oxazolo[3]-benzoazepinone **4** represents the key intermediate of the projected synthesis. After deprotonation, diastereoselective alkylation should provide diastereomerically pure products **5**, which should yield after reductive cleavage the enantiomerically pure 1-substituted 3-benzoazepines **3**. The chiral information of **4** originates from (*R*)-phenylglycinol (see Fig. 2).

An analogous oxazolo[3]benzoazepine has been synthesised by condensation of 2-[4,5-dimethoxy-2-(2-oxopropyl)phenyl]acetic acid with (*S*)-phenylglycinol. Alkylation of this intermediate is not described.[9]

2. Results and discussion

The synthesis of the oxazolo[3]benzoazepinone **4** was performed as shown in Scheme 1 by starting from commercially available *o*-phenylenediacetic acid **6**. In the first step, dicarboxylic acid **6** was transformed into anhydride **7**. Then, the chiral information was introduced by the reaction of anhydride **7** with enantiomerically pure (*R*)-phenylglycinol to give amido acid **8**.[10] For the synthesis of the oxazolo[3]benzoazepinone **4**, the carboxylic acid had to be reduced to the oxidation level of an aldehyde. Since the direct reduction of the ester **9** failed to give an aldehyde, a reduction/oxidation procedure was performed. For this purpose, the primary alcohol of **9** was protected with triisopropylsilyl chloride[11] to afford silyl ether **10**. Reduction of **10** with $LiBH_4$ yielded alcohol **11**, which was oxidised by Dess-Martin-Periodinane[12] to provide the desired aldehyde **12**. Next, the alcohol protecting group was cleaved with MeOH/HCl resulting in the simultaneous protection of the aldehyde moiety to give dimethyl acetal **13**. Finally amido acetal **13** was cyclised with a catalytic amount of HCl to obtain oxazolo[3]benzoazepinone **4** in 61% yield. A small amount (7%) of side product **14**, which was the main product after heating of **13** in toluene, could be isolated by flash chromatography. A further product could not be isolated. Even careful HPLC analysis and NMR experiments did not reveal the diastereomer of **4**.

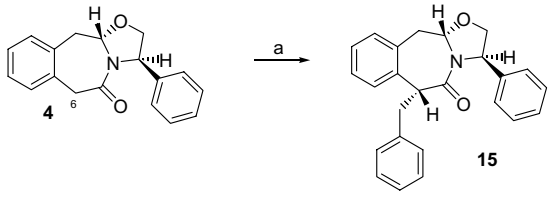
The relative configuration of **4** was determined by the nuclear Overhauser effect. Saturation of the proton at



Scheme 1. Reagents and conditions: (a) $SOCl_2$ 1.0 equiv, toluene, 110 °C, 18 h, 86%; (b) (*R*)-phenylglycinol 1.0 equiv, Et_3N 1.0 equiv, CH_2Cl_2, rt, 4 h, 85%; (c) TMS-Cl 3.0 equiv, MeOH abs., 0 °C, 18 h, 83%; (d) triisopropylsilyl chloride 1.2 equiv, imidazole 2.5 equiv, DMF, rt, 18 h, 91%; (e) $LiBH_4$ 4.0 equiv, THF abs., rt, 18 h, 94%; (f) Dess-Martin-Periodinane 1.15 equiv, CH_2Cl_2, rt, 30 min, 71%; (g) 1% methanolic HCl, rt, 3 h, 75%; (h) $CHCl_3/H^+$, rt, 5 h, 61% **4**, 7% **14**.

the 11a-position (5.06 ppm) resulted in intensifying of the signals of the phenyl protons. An increase of the signal at 5.40 ppm (3-H) was not observed, indicating a *trans*-arrangement of these protons. Thus, the configuration of the novel stereogenic centre at the 11a-position is (*S*).[13]

In order to introduce alkyl substituents at the 6-position, oxazolo[3]benzoazepinone **4** was deprotonated with LDA (1.1 equiv) and subsequently alkylated with benzyl bromide (1.0 equiv). The alkylation product **15** was isolated in 76% yield (Scheme 2).[14] Careful HPLC and LC/MS analysis of the crude alkylation product revealed a diastereomeric ratio of 95.1:4.9. For further transformations, **15** was purified by flash chromatography to yield a product with 99.85% de.



Scheme 2. Reagents and conditions: (a) benzyl bromide 1.0 equiv, LDA 1.1 equiv, THF abs., N_2, 0 °C, 4 h, 76%.

The relative configuration of alkylation product **15** was determined by X-ray crystal structure analysis (see Fig. 3). As shown in Figure 3, the benzyl moiety and the phenyl residue are trans configured. In several publications, highly diastereoselective alkylations of pyrrolidine, piperidine and piperazine derivatives using the chiral auxiliary phenylglycinol have already been described.[15–17]

The desired enantiomerically pure 1-benzyl tetrahydro-3-benzoazepine **17** was obtained by reductive degradation of **15** with $LiAlH_4/AlCl_3$ and debenzylation with ammonium formate Pd/C (Scheme 3).[18] HPLC and LC/MS analysis of **15** and **16** show that the $LiAlH_4$ reduction proceeded without any epimerisation. Performing the reductive degradation with diastereomerically pure **15** led to diastereomerically pure **16** and the desired enantiomerically pure (*R*)-1-benzyl-3-benzoazepine **17.**

3. X-ray crystal structure analysis for 15

Formula $C_{25}H_{23}NO_2$, $M = 369.44$, colourless crystal $0.45 \times 0.20 \times 0.15$ mm, $a = 8.925(1)$, $b = 13.894(1)$, $c = 16.015(1)$ Å, $V = 1985.9(3)$ Å^3, $\rho_{calc} = 1.236$ g cm^{-3}, $\mu = 6.13$ cm^{-1}, empirical absorption correction ($0.770 \leqslant T \leqslant 0.914$), $Z = 4$, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda = 1.54178$ Å, $T = 223$ K, ω and φ scans,

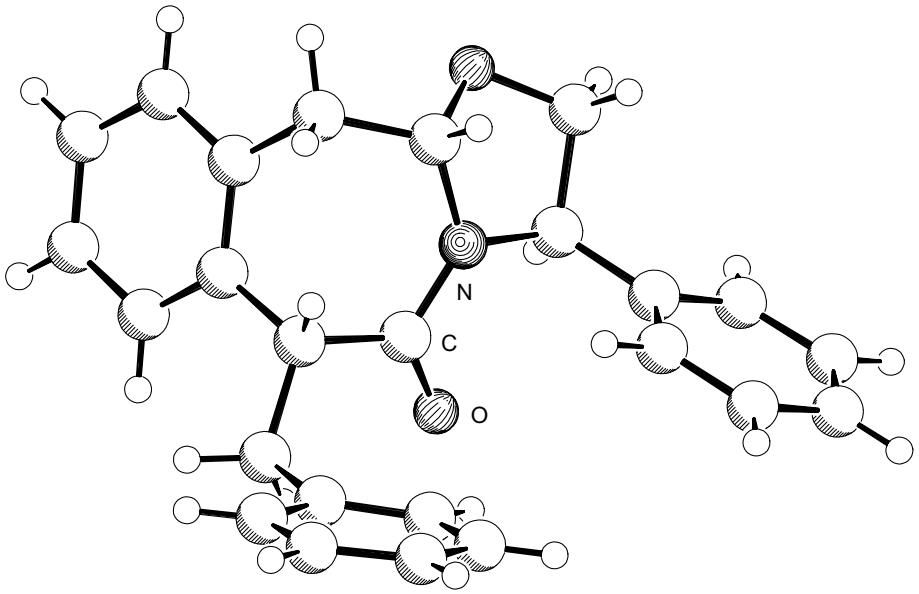
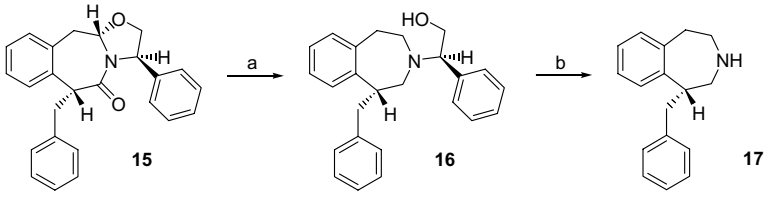


Figure 3. ORTEP-plot of X-ray crystal structure analysis of **15**.



Scheme 3. Reagents and conditions: (a) $AlCl_3$ 0.92 equiv, $LiAlH_4$ 2.78 equiv, THF abs., N_2, 0 °C, 1.5 h, 80%; (b) $HCOONH_4$ 10 equiv, Pd/C (10%), MeOH, 80 °C, 2.5 h, 74%.

8999 reflections collected ($\pm h$, $\pm k$, $\pm l$), [$(\sin\theta)/\lambda$] = 0.59 Å^{-1}, 3242 independent (R_{int} = 0.042) and 2864 observed reflections [$I \geqslant 2\sigma(I)$], 254 refined parameters, R = 0.040, wR^2 = 0.106, max. residual electron density 0.20 (−0.14) eÅ^{-3}, Flack parameter 0.3(3), hydrogens calculated and refined as riding atoms.

Data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B. V., 1998), data reduction Denzo-SMN,[19] absorption correction SORTAV,[20,21] structure solution SHELXS-97,[22] structure refinement SHELXL-97 (Sheldrick, G. M. Universität Göttingen, 1997), graphics SCHAKAL (Keller, E. Universität Freiburg, 1997).

Crystallographic data (excluding structure factors) for the structure reported herein, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-249401. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44 (0) 1223 336033, e-mail: deposit@ccdc.cam.ac.uk].

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13. NMR data of compound **4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33–3.41 (m, 2H, CH_2 CHON); 3.74 (dd, J = 8.8/7.2 Hz, 1H, OCH_2CH); 3.85 (d, J = 16.4 Hz, 1H, CH_2C═O); 3.96 (d, J = 16.4 Hz, 1H, CH_2C═O); 4.46 (t, J = 8.4 Hz, 1H, OCH_2CH); 5.06 (dd, J = 7.0/5.1 Hz, 1H, CH$_2$CHNO); 5.40 (t, J = 7.6 Hz, 1H, OCH$_2$CH); 7.17–7.31 (m, 9H, Ar).
14. The NMR data of compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (dd, J = 14.1/7.0 Hz, 1H, CH_2CHC═O); 3.21 (dd, J = 15.3/5.1 Hz, 1H, CH_2CHNO); 3.43 (dd, J = 15.6/3.9 Hz, 1H, CH_2CHNO); 3.60 (dd, J = 16.3/8.1 Hz, 1H, OCH_2CH); 3.59 (dd, J = 13.4/7.0 Hz, 1H, CH_2CHC═O); 4.04 (t, J = 7.0 Hz, 1H, CH$_2$CHC═O); 4.29 (t, J = 8.2 Hz, 1H, OCH_2CH); 5.14 (t, J = 4.3 Hz, 1H, CH$_2$CHNO); 5.22 (t, J = 8.3 Hz, 1H, OCH$_2$CH); 6.95–7.23 (m, 14H, Ar).
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