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(3*R*,11a*R*)-3-Phenyl-2,3,11,11a-tetrahydro-[1,3]oxazolo[3,2-*b*]-[2]benzazepin-5(10*H*)-one as a chiral building block for the asymmetric synthesis of 3-substituted 2-benzazepines

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ABSTRACT

A five-step synthesis of the chiral building block *cis*-**2** is described. Key steps in the synthesis were a Heck reaction of 1-bromo-2-iodobenzene with allyl alcohol, the introduction of a carboxy group after Br/Li-exchange, and the diastereoselective formation of the tricyclic oxazolidine system *cis*-**2**. Activation of *cis*-**2** with $TiCl_4$ led to formation of a carbenium ion, which was attacked by allyltrimethylsilane exclusively from the *Re*-face leading to the (3*S*)-configured 2-benzazepinone **8** in 65% yield. The configuration of the new stereogenic center was determined by X-ray crystal structure analysis, which is the basis for the proposed mechanism of this transformation. Enantiomerically pure 3-substituted 2-benzazepines represent interesting drug candidates.

1. Introduction

Enantiomerically pure bi- and tricyclic oxazolidines have been widely used for the asymmetric synthesis of enantiomerically pure N-heterocycles including pyrrolidines, piperidines, and azepines.[1–6] Very recently we have reported on the synthesis of oxazolidine annulated 3-benzazepines of type **1**. The diastereoselective alkylation of **1** and subsequent reductive degradation led to enantiomerically pure 1-substituted 3-benzazepines with promising NMDA and σ receptor affinities (Fig. 1). Moreover, compounds **1** with a residue in position 11a (e.g., R = CH_3) could be reduced or reacted with Grignard reagents to form enantiomerically pure 2-mono- or 2,2-disubstituted 3-benzazepines, respectively.[7–12]

In addition to 3-benzazepines, our interest has been focused on the synthesis of enantiomerically pure 2-benzazepines, which are regioisomers of 3-benzazepines (shift of the *N*-atom by one position) or homologues of isoquinolines. Herein, we report on the extension of the oxazolidine strategy with regards to the synthesis of 3-substituted 2-benzazepines, which are expected to reveal interesting pharmacological properties. In particular, the synthesis of the enantiomerically pure central building block **2** is detailed, which is structurally derived from the analogous 3-benzazepine building block **1**.

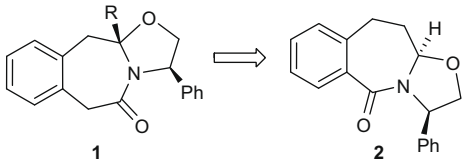

Figure 1. Relationship between the new chiral building block **2** with a 2-benzazepine substructure and the established building block **1** with a 3-benzazepine substructure.

2. Results and discussion

In the first approach (2-bromophenyl)propionaldehyde acetal **5** was prepared by homologation of 2-bromobenzaldehyde using a Wittig reaction and subsequent hydrogenation of the double bond. As reported in the literature, substantial debromination (5–10%) occurred during hydrogenation,[13] and the debrominated by-product disturbed the subsequent reactions leading to decreased yields after halogen/metal exchange.

Therefore, an alternate strategy for the synthesis of **5** was followed which avoided hydrogenation (Scheme 1). At first a Heck reaction of 1-bromo-2-iodobenzene **3** with allyl alcohol and catalytic amounts of $Pd(OAc)_2$ was performed to provide phenylpropionaldehyde **4**.[14] Acetalization of aldehyde **4** with ethylene glycol led to ethylene acetal **5**, without any side products, in 76% yield over two steps. An exchange of the bromine atom of **5** with *n*-BuLi at −80 °C and subsequent trapping of the resulting aryllithium intermediate with CO_2 led to the benzoic acid derivative **6** in 96%

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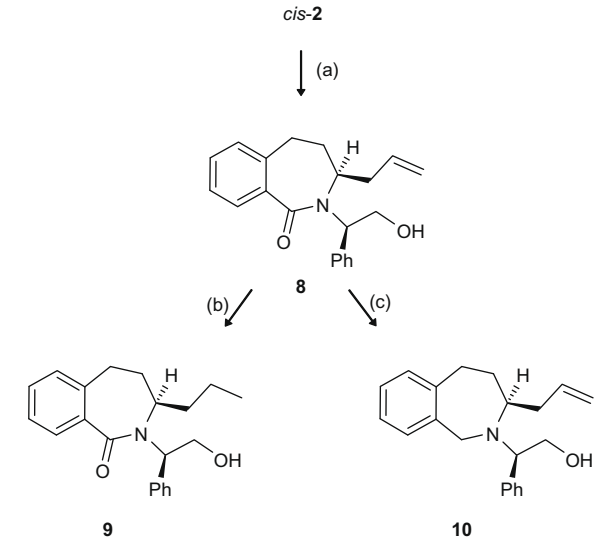
yield. After activation of the carboxy group of **6** with oxalyl chloride, condensation with (*R*)-phenylglycinol proceeded to give amide **7**. The stereoselective formation of *cis*-configured tricyclic oxazolidine *cis*-**2** was achieved via the treatment of enantiomerically pure amide **7** with HCl saturated $CHCl_3$ at room temperature. In addition to the main product *cis*-**2** (79% yield) small amounts of the diastereomer *trans*-**2** (7%) were isolated by flash chromatography. The stereodescriptor *cis* refers to the relative orientation of the protons in positions 3 and 11a in the oxazolidine moiety. The *cis*-configuration of *cis*-**2** was proven by NOE difference spectroscopy.

Having successfully established the stereoselective synthesis of the chiral building block *cis*-**2**, its potential for the stereoselective introduction of substituents at position 3 upon opening of the oxazolidine ring was investigated. Treatment of *cis*-**2** with allyltrimethylsilane and $TiCl_4$[15] at 70 °C under microwave irradiation led to the allyl-substituted 2-benzazepin-1-one **8** in 65% yield (Scheme 2). According to ^1H and ^{13}C NMR spectroscopy as well as LC–MS investigations of the crude reaction product, only one product **8** was formed indicating the excellent diastereoselectivity of this transformation. Variation of the reaction conditions (e.g., lower temperature, lack of microwave irradiation, prolonged reaction time) led to considerably reduced yields of **8**. Moreover, changing of the Lewis acid $TiCl_4$ with other Lewis acids (e.g., BF_3, $AlCl_3$) or using more reactive allyltrimethylstannane instead of allyltrimethylsilane did not lead to any conversion. Obviously, the tricyclic system *cis*-**2** is very sensitive to the reaction conditions.

The NMR spectra of **8** recorded at room temperature only led to very broad signals, which can be attributed to the slow conformational changes of the seven-membered 2-benzazepine ring. Recording of the NMR spectra at 110 °C in nitrobenzene-d_5 resulted in a considerable improvement of the fine structure of the signals. However, careful interpretation of these NMR spectra did not allow an unequivocal assignment of the absolute configuration of the new stereogenic center of **8**. Therefore, an X-ray crystal structure analysis was performed. For this purpose 2-benzazepin-1-one **8** was recrystallized from MeOH, which produced suitable crystals. The X-ray crystal structure of **8** (Fig. 2) clearly demonstrates the (*S*)-configuration at the 3-position of benzazepin-1-one **8**.

The (*S*)-configuration at the 3-position of **8** confirms the retention of configuration during the ring opening of *cis*-**2** with allyltrimethylsilane and $TiCl_4$. Therefore, the following mechanism[16] for the allylation of **8** is proposed: $TiCl_4$ first opens the oxazolidine ring. Coordination of $TiCl_4$ with the original *O*-atom of the oxazolidine ring and the *O*-atom of the carbonyl moiety brings the phenyl moiety 'under' the 2-benzazepine plane, thus shielding the



Scheme 2. Reagents and conditions: (a) allyltrimethylsilane 17 equiv, $TiCl_4$ 6 equiv, CH_2Cl_2, 70 °C, 5 min (CEM-microwave), 65%; (b) H_2, Pd/C, CH_3OH, 5 bar, 30 min, 95%; (c) $AlCl_3$ 1.0 equiv, $LiAlH_4$ 3.0 equiv, THF, 0 °C, 0.5 h, 54%.

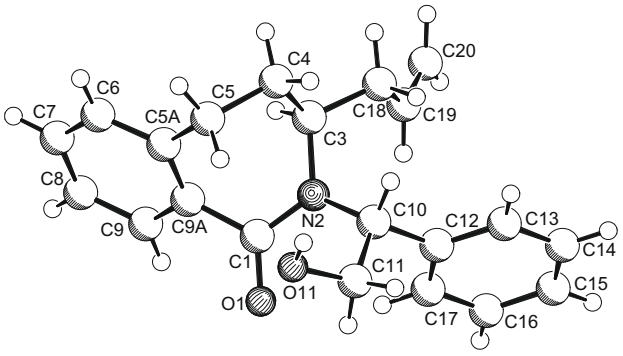
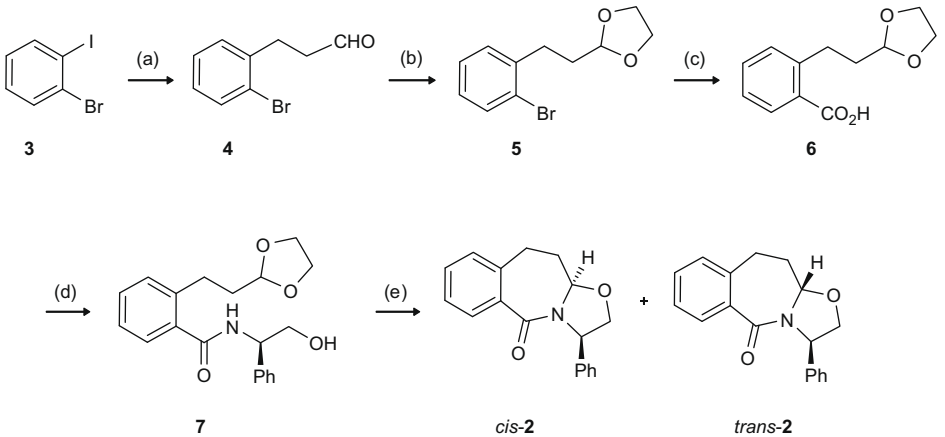


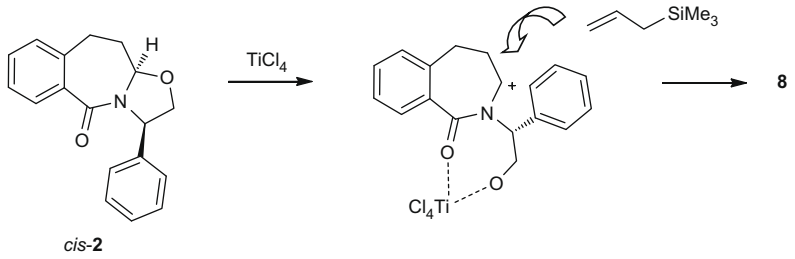
Figure 2. X-ray crystal structure analysis of **8**.

Si-face of the carbenium ion, which results in exclusive attack of allyltrimethylsilane from the *Re*-face. (Scheme 3)

The allyl moiety of **8** was reduced with H_2 in the presence of Pd/C to give the propyl derivative **9** in 95% yield. Even at a pressure of 5 bar, the (2-hydroxy-1-phenylethyl) residue on the *N*-atom of **8** was not cleaved. Reduction of the lactam moiety of **8** proceeded



Scheme 1. Reagents and conditions: (a) 1-bromo-2-iodobenzene 1.0 equiv, allyl alcohol 3.0 equiv, $NaHCO_3$ 2.5 equiv, $BnEt_3NCl$ 1 equiv, $Pd(OAc)_2$ 0.02 equiv, DMF, 45 °C, 6 h; (b) *p*-$TolSO_3H$, 0.2 equiv, ethylene glycol 1.8 equiv, $CHCl_3$ reflux (Dean–Stark trap), 76%; (c) *n*-BuLi 1.05 equiv, CO_2 gas, THF, −80 °C, 1.4 h, 96%; (d) (1) oxalyl chloride 1.2 equiv, DMF catalytic, Et_2O; (2) (*R*)-phenylglycinol 1 equiv, $NaOH_{aq}$ 9 equiv, CH_2Cl_2, 45%; (e) HCl_{concd} catalytic, $CHCl_3$, 79% (*cis*-**2**), 7% (*trans*-**2**).



Scheme 3. Proposed mechanism for the stereoselective transfer of the allyl group at C-3 of the 2-benzazepine ring.

with AlH_3, which was formed in situ by mixing $LiAlH_4$ and $AlCl_3$ in a 1:3 ratio.[17] The 3-allyl-substituted 2-benzazepine **10** was isolated in 54% yield.

3. Conclusion

The tricyclic oxazolidine *cis*-**2** represents an interesting new chiral building block for the synthesis of enantiomerically pure 3-substituted 2-benzazepines. The carefully optimized synthesis of *cis*-**2** comprises five reaction steps including the diastereoselective intramolecular formation of the tricyclic oxazolidine ring system from **7**. Ring opening of the oxazolidine ring of *cis*-**2** with allyltrimethylsilane and $TiCl_4$ exclusively took place from the *Re*-face leading to 2-benzazepines with (*S*)-configuration in position 3.

4. Experimental

4.1. Synthesis of (3*S*)-3-allyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3,4,5-tetrahydro-2-benzazepin-1-one 8

Under N_2, tricyclic oxazolidine *cis*-**2** (300 mg, 1.07 mmol) was dissolved in CH_2Cl_2 (6 mL). Allyltrimethylsilane (2.9 mL, 18.2 mmol) and $TiCl_4$ (6.4 mL, 6.4 mmol) were added carefully to the solution. After microwave irradiation (CEM Discover LabMate Microwave, ramp 5 min, run 5 min, P = 80 W, T = 70 °C), the mixture was poured into water and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4, and filtered, after which silica gel was added and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 8/2). Colorless needles, mp 156 °C, yield 223 mg (65%). $C_{21}H_{23}NO_2$ (M_r = 321.4). MS (ESI): *m/z* (%) = 665 (2M+Na, 100), 322 (M+H, 10). HRMS (ESI): *m/z* = calcd for $C_{21}H_{23}NO_2H^+$ 322.1801, found 322.1802; *m/z* = calcd for $C_{21}H_{23}NO_2Na^+$ 344. 1621, found 344.1621; *m/z* = calcd for $(C_{21}H_{23}NO_2)_2Na^+$ 665.3349, found 665.3350. ^{1}H NMR (nitrobenzene-d_5, 110 °C): δ (ppm) = 1.18–1.22 (m, broad, 2H, CH_2CH=CH$_2$), 1.50–154 (m, broad, 1H, ArCH$_2$CH_2), 1.84–1.88 (m, broad, 1H, ArCH$_2$CH_2), 2.34–2.38 (m, broad, 1H, ArCH_2), 2.64–2.68 (m, broad, 1H, ArCH_2), 3.19–3.22 (m, broad, 1 H, ArCH$_2$CH$_2$CH), 3.88–3.93 (m, broad, 1H, CHCH_2OH), 3.96–4.07 (m, broad, 2H, CHCH_2OH, CH=CH_2), 4.20 (d, J = 10.2 Hz, 1H, CH=CH_2), 4.659–4.63 (m broad, 1H, CH=CH$_2$), 5.52–5.56 (s, broad, 1H, CHCH$_2$OH), 6.84–7.35 (m, 9H, Ar-H). The correct assignment of the signals was accomplished by high temperature COSY experiments. IR (neat): ν (cm^{-1}) = 3347 (OH), 1608 (CONR$_2$), 916 (C=CH$_2$). Specific rotation: $[\alpha]_D$ = +7.9 (*c* 1.04, $CHCl_2$). Purity by HPLC: 99.6% (t_R = 18 min).

A sample of **8** was recrystallized from MeOH, which gave colorless crystals suitable for X-ray crystal structure analysis.

4.2. X-ray crystal structure analysis of 8

Formula $C_{21}H_{23}NO_2$, M = 321.40, light colorless crystal 0.55 × 0.20 × 0.04 mm, a = 8.7429(3), b = 17.4383(6), c = 23. 1886(10) Å, V = 3535.4(2) Å^3, ρ_{calcd} = 1.208 g cm^{-3}, μ = 0.607 mm^{-1}, empirical absorption correction ($0.731 \leqslant T \leqslant 0.976$), Z = 8, orthorhombic, space group $P2_12_12_1$ (No. 19), λ = 1.54178 Å, T = 223(2) K, ω and φ scans, 44474 reflections collected (±*h*, ±*k*, ±*l*), [(sinθ)/λ] = 0.60 Å^{-1}, 6268 independent (R_{int} = 0.081) and 5307 observed reflections [$I \geqslant 2\sigma(I)$], 436 refined parameters, R = 0.044, wR^2 = 0.112, Flack parameter 0.0(2), max. (min.) residual electron density 0.19 (−0.14) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms, two almost identical molecules in the asymmetric unit.

Data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius, B.V. 1998), data reduction Denzo-SMN,[18] absorption correction Denzo,[19] structure solution SHELXS-97,[20] structure refinement SHELXL-97,[21] graphics SCHAKAL.[22]

CCDC 742207 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336 033, E-mail: deposit@ccdc.cam.ac.uk].

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