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Synthesis of new polysubstituted piperazines and dihydro-2*H*-pyrazines by selective reduction of 2-oxo-piperazines

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ABSTRACT

New enantiomerically enriched 1,4,5-piperazines and 1,4,5-dihydro-2*H*-pyrazines have been prepared by reduction of the corresponding 2-oxo-piperazines. Selective reduction can be achieved by careful control of the reaction conditions using $LiAlH_4$. Notably the two nitrogen atoms of the final compounds are orthogonally protected.

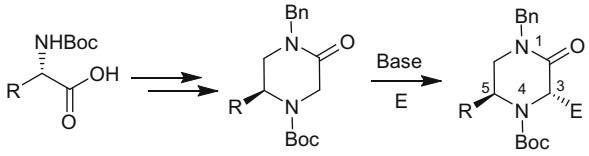
1. Introduction

Many pharmaceutical agents contain piperazines as part of their core structure.[1] Examples can be found in quinolone antibiotics,[2] HIV-protease inhibitors,[3] 5HT-anxiolytics,[4] anti-hypertensives[5] and δ- and κ-opioid receptor agonists.[6–8] In order to find novel receptor ligands, various substituents have been introduced onto the piperazine ring; for instance, derivatives bearing substituents at the 3-position have been shown to strongly interact with various receptors within the central nervous system.[9] In addition to being used as base templates and substituents to impart the desired pharmacological and pharmacokinetic properties to a compound, piperazines can also behave as bifunctional linking agents to couple two components of an analogue through a six-membered heterocycle.[10] In recent years, they have also been used as efficient chiral ligands in enantioselective catalysis.[11,12]

For these reasons, the synthesis of piperazines bearing substitution at different ring positions is of particular significance, and many methods have been developed to achieve this goal. The synthesis of piperazines and 2-substituted piperazines is usually performed by ring construction and reduction of diketopiperazines or 2-ketopiperazines,[13,14] by various cyclization reactions,[15–17] via alkylation and reduction of 2-methylpyrazines,[18,19] or by α-lithiation and alkylation of *N*-Boc piperazines.[20]

Stemming from our interest in the asymmetric synthesis of biologically interesting compounds, we have recently reported a general and highly stereoselective approach to 1,4,5-tri-substituted- and 1,3,4,5-tetra-substituted 2-oxo-piperazines.[21]

The method we designed, which takes advantage of naturally occurring amino acids as starting materials, allows us to prepare some new piperazinones in which the substitution and the stereochemistry at C-5 could be pivoted by the choice of the starting amino acid and the *anti* substitution at C-3 could be accomplished diastereoselectively via enolate formation and reaction with electrophiles (Scheme 1). In addition, the two nitrogens of the ring were orthogonally protected as this would be a crucial strategy to facilitate the stepwise positioning of substituents when it is required to use the oxopiperazine core as a molecular scaffold.



Scheme 1.

These oxopiperazines can be considered as starting materials to obtain the corresponding piperazines after reduction. Herein we report our results on the reduction of oxopiperazines **1a–d** and show that they can be selectively converted into the corresponding piperazines **2a–d** or dihydro-2*H*-pyrazines **3a–d** just depending on the reaction conditions (Scheme 2). These latter compounds have not been previously reported and might be useful building blocks for obtaining more decorated piperazine cores.

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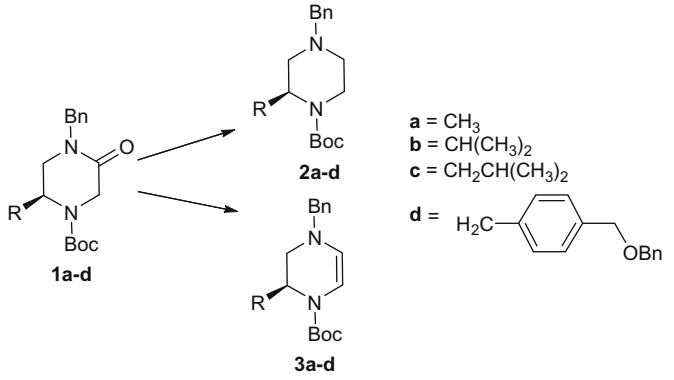
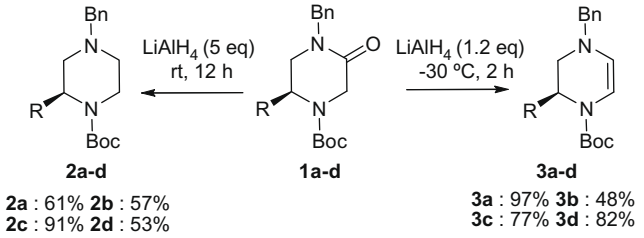
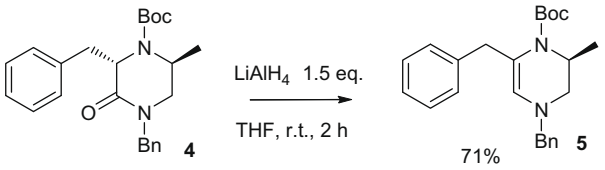


Scheme 2.



Scheme 3.



Scheme 4.

2. Results and discussion

Lithium aluminum hydride ($LiAlH_4$) is the most commonly used reagent for the reduction of lactams, however milder and more chemoselective methods have also been developed using diisobutylaluminum hydride (DIBAL-H), borane or sodium borohydride.[22]

In order to find suitable and mild reaction conditions to reduce oxopiperazines **1**, compound **1c** was reacted in the presence of excess of $LiAlH_4$ at 0 °C. After one hour, the reaction mixture was worked up and ^1H NMR analysis of the crude revealed that two compounds in a roughly 1/1 ratio were present: the expected piperazine **2c** and the partially reduced dihydro-2*H*-pyrazines **3c.** Intrigued by this interesting result, we decided to screen different reaction conditions in order to verify the possibility of selectively obtaining the two different compounds. The results are reported in Table 1.

The use of a milder reducing agent such as DIBAL-H always gave reaction mixtures containing the partially reduced dihydro-2*H*-pyrazines as the major product, together with piperazine and unreacted starting material. On the other hand, BH_3 reacted sluggishly at room temperature, leading to a low conversion of the starting material. When a large amount of reagent was used at reflux temperature, piperazine **2c** was obtained in good yield with no trace amounts of the partially reduced compound **3c**. Finally $LiAlH_4$ proved to be the reagent of choice providing the total conversion into piperazine **2c** when used in large excess (5 equiv) at room temperature and a high yield of dihydro-2*H*-pyrazines **3c** when used in a stoichiometric amount at low temperature.

To prove the generality of the method, these reaction conditions were extended to three other substrates, compounds **1a,b,d**, and the corresponding reduced products were obtained in all cases, isolated in reasonable yields after flash chromatography and were fully characterized (Scheme 3).

Finally, we also tried to extend these procedures to the 3,5-disubstituted oxopiperazine **4** which was prepared as previously reported.[21] Thus we could understand that our optimized conditions were not suitable for such substrate which proved to be less reactive (Scheme 4). However, reduction to the corresponding dihydropiperazine **5** was achieved using 1.5 equiv of $LiAlH_4$ and by carrying out the reaction at room temperature. Although compound **5** was obtained in good yield after purification, it decomposed rapidly in solution, thus hampering a full characterization.

Attempts to obtain the corresponding fully reduced 3,5-disubstituted piperazine were not successful as the required reaction conditions were too harsh (50–60 °C for 12 h) for our substrate and only decomposition products were observed.

3. Conclusions

In conclusion, the reduction of orthogonally protected oxopiperazines has been studied and the conditions for the selective conversion into the corresponding enantiomerically enriched piperazines or dihydro-2*H*-pyrazines have been optimized using $LiAlH_4$ as a reagent. These latter compounds were previously unreported and their application for obtaining more decorated piperazine cores is currently under investigation.

4. Experimental part

4.1. General methods

The reactions were monitored by TLC on SiO_2, detection was made using a basic $KMnO_4$ solution. Flash column chromatography was performed using glass columns (10–50 mm wide) and SiO_2 (230–400 mesh). ^1H NMR were recorded at 200 or 400 MHz. ^{13}C

Table 1
Products of the reduction of oxopiperazine **1c**

Reducing agent	Number of equivalents (equiv)	*T* (°C)	Solvent and time	**2c**[a]	**3c**[a]
$LiAlH_4$	3	0	THF/1 h	60%	40%
DIBAL-H[b]	2	0	THF/1.30 h	15%	55%
DIBAL-H[b]	2	−25	THF/12 h	10%	70%
DIBAL-H	2	−25	Et_2O/12 h	15%	70%
BH_3[b]	4	Reflux	THF/2 h	82%	—
$LiAlH_4$	5	rt	THF/12 h	100% (91%)[c]	—
$LiAlH_4$	1.2	−30	THF/2 h	5%	95% (77%)[c]

[a] Determined by ^1H NMR analysis of the crude mixture.
[b] 1 M in THF solution.
[c] Yield of isolated compound.

NMR spectra were recorded at 50.3 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$, δ 7.26 ppm for ^1H NMR; $CHCl_3$, δ 77.00 ppm for ^{13}C NMR). For those compounds which are present as slowly interconverting rotamers, the signals of the most abundant rotamer are reported and those of the less abundant are in parenthesis. When possible, ^1H NMR experiments were performed at 50 °C and signals of the averaged spectrum are given. Polarimetric measurements were performed at λ = 589 nm, and the temperature is specified case by case. All commercial reagents were used without further purification. Oxopiperazines **1a**–**d** were prepared according to the literature.[21] THF was dried by distillation over sodium benzophenone ketyl. CH_2Cl_2 was dried over $CaCl_2$ and was stored over 4 Å molecular sieves. DMF was distilled over $CaCl_2$ and was stored over 4 Å molecular sieves. Petroleum ether, unless specified, is the 40–70 °C boiling fraction.

4.2. Synthesis of piperazines 2a–d: general procedure

Oxopiperazines **1a**–**d** (1 equiv) were dissolved in dry THF and the solution was cooled to 0 °C. Next, $LiAlH_4$ (5 equiv) was added and, after heating to room temperature, the mixture was stirred overnight. After the addition of water and extraction with ethyl acetate, the organic phase was washed with brine, dried over Na_2SO_4 and then concentrated to afford piperazines **2a**–**d**, which were purified by flash chromatography.

4.2.1. (*S*)-*tert*-Butyl-2-methyl-4-benzylpiperazine-1-carboxylate 2a

Oxopiperazine **1a** (60 mg, 0.2 mmol) was dissolved in THF (5 mL) and was reacted with $LiAlH_4$ (40 mg, 1.0 mmol). Workup and purification [petroleum ether/ethyl acetate = 25/1] gave **2a** as a colourless oil (35 mg, 61%). R_f: 0.2 **2a**: ^1H NMR (200 MHz) δ: 7.33–7.25 [m, 5H]; 4.23–4.10 [m, 1H]; 3.76 [d, 1H, J = 13.2 Hz]; 3.55 [d, 1H, J_{AB} = 13.2 Hz]; 3.41 [d, 1H, J_{AB} = 13.2 Hz]; 3.10 [m, 1H]; 2.75 [d, 1H, J = 10.0 Hz]; 2.59 [d, 1H, J = 11.3 Hz]; 2.16–1.95 [m, 2H]; 1.45 [s, 9H]; 1.24 [d, 3 H, J = 7.0 Hz]. ^{13}C NMR (50.3 MHz) δ: 154.3; 137.1; 128.4 (×2); 127.9 (×2); 126.6; 79.1; 62.5; 57.1; 53.0; 48.6; 38.8; 28.2; 15.7. $[\alpha]_D^{28} = +21.3$ (c 0.5, $CHCl_3$) {lit.[23] $[\alpha]_D^{25} = +56$ (c 0.44, EtOH)}. Anal. Calcd for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.27; H, 9.05; N, 9.57.

4.2.2. (*S*)-*tert*-Butyl-2-isopropyl-4-benzylpiperazine-1-carboxylate 2b

Oxopiperazine **1b** (92 mg, 0.3 mmol) was dissolved in THF (5 mL) and was reacted with $LiAlH_4$ (49 mg, 1.2 mmol). Workup and purification [petroleum ether/ethyl acetate = 3/1] gave **2b** as a low melting white solid (51 mg, 57%). R_f: 0.2 **2b**: ^1H NMR (200 MHz) δ: 7.32–7.27 (m, 5H); 3.93 (3.58) [br s, 1H]; 3.54 [d, 1H, J_{AB} = 12.8 Hz]; 3.34 [d, 1H, J_{AB} = 12.8 Hz]; 2.99 [m, 1H]; 2.84 [d, 1H, J = 12.0 Hz]; 2.75 [d, 1H, J = 12.0 Hz]; 2.48–2.29 [m, 1H]; 2.06 [dd, 1H, J = 3.6 Hz, J = 11.0 Hz]; 1.97 [dd, 1H, J = 3.6 Hz, J = 11.0 Hz]; 1.74 [m, 1H]; 1.45 [s, 9H]; 0.84 [d, 3H, J = 8.0 Hz]; 0.79 [d, 3H, J = 8.0 Hz]. ^{13}C NMR (50.3 MHz) δ: 154.8; 138.3; 128.7 (×2); 128.0 (×2); 126.9; 79.2; 63.0; 60.9; 53.7; 53.5; 39.1; 29.7; 28.5; 26.4; 20.2. $[\alpha]_D^{28} = +31.0$ (c 1.25, $CHCl_3$). Anal. Calcd for $C_{19}H_{30}N_2O_2$: C, 71.66; H, 9.50; N, 8.80. Found: C, 71.63; H, 9.54; N, 8.78.

4.2.3. (*S*)-*tert*-Butyl-2-isobutyl-4-benzylpiperazine-1-carboxylate 2c

Oxopiperazine **1c** (102 mg, 0.3 mmol) was dissolved in THF (5 mL) and was reacted with $LiAlH_4$ (50 mg, 1.2 mmol). Workup and purification [petroleum ether/ethyl acetate = 3/1] gave **2c** as a colourless oil (88 mg, 91%). R_f: 0.1. **2c**: ^1H NMR (200 MHz) δ: δ ($CDCl_3$, 200 MHz): 7.34–7.23 [m, 5H]; 4.03 [br s, 1H]; 3.79 [d, 1H, J = 13.5 Hz] ; 3.53 [d, 1H, J_{AB} = 12.5 Hz]; 3.36 [d, 1H, J_{AB} = 12.5 Hz]; 2.98 [m, 1H]; 2.65 [d, 1H, J = 9.5 Hz]; 2.55 [d, 1H, J = 11.0 Hz]; 1.98 [dd, 1H, J = 3.7 Hz, J = 10.0 Hz]; 1.92 [dd, 1H, J = 3.7 Hz, J = 10.0 Hz]; 1.63–1.56 [m, 1H]; 1.45 [s, 9H]; 1.39–1.33 [m, 2H]; 0.91 [d, 3H, J = 11.8 Hz]; 0.89 [d, 3H, J = 11.8 Hz]. ^{13}C NMR (50.3 MHz) δ: 154.6; 138.1; 128.4 (×2); 127.9 (×2); 126.7 79.0; 62.6; 55.3; 53.2; 49.5; 49.3; 38.7; 28.2; 24.5; 22.7; 22.5. $[\alpha]_D^{25} = +27.1$ (c 1.19, $CHCl_3$). Anal. Calcd for $C_{20}H_{32}N_2O_2$: C, 72.25; H, 9.70; N, 8.43. Found: C, 72.28; H, 9.65; N, 8.38.

4.2.4. (*S*)-*tert*-Butyl-2-[4-(benzyloxy)benzyl]-4-benzyl-piperazine-1-carboxylate 2d

Oxopiperazine **1d** (100 mg, 0.2 mmol) was dissolved in THF (5 mL) and was reacted with $LiAlH_4$ (43 mg, 1.0 mmol). Workup and purification [hexane/ethyl acetate = 3/1] gave **2d** as a low melting white solid (47 mg, 53%). R_f: 0.1. **2d**: ^1H NMR (200 MHz) δ: 7.33–7.28 [m, 5H]; 7.23–7.19 [m, 5H]; 6.88 [d, 2H, J = 8.6 Hz]; 6.71 [d, 2H, J = 8.6 Hz]; 4.93 [s, 2H]; 4.04–3.78 [m, 1H+1H]; 3.46 [d, 1H, J_{AB} = 12.8 Hz]; 3.27 [d, 1H, J_{AB} = 12.5 Hz]; 3.11 [m, 1H]; 3.00–2.87 [m, 1H]; 2.81–2.64 [m, 2H]; 2.56 [d, 1H, J = 11.4 Hz]; 1.99 [dd, 1H, J = 3.0 Hz, J = 11.4 Hz]; 1.93 [dd, 1H, J = 3.8 Hz, J = 11.4 Hz]; 1.32 [s, 9H]. ^{13}C NMR (50.3 MHz) δ: 156.9; 151.2; 138.2; 137.1;131.6; 130.2 (×2); 129.1 (×2); 128.4 (×2); 128.1 (×2); 127.7; 127.3 (×2); 127.1; 114.6 (×2); 79.4; 70.0; 63.0; 53.6; 53.4 (×2); 39.4; 35.2; 28.5. $[\alpha]_D^{27} = +1.0$ (c 0.5, $CHCl_3$). Anal. Calcd for $C_{30}H_{36}N_2O_3$: C, 76.24; H, 7.68; N, 5.93. Found: C, 76.35; H, 7.72; N, 5.91.

4.3. Synthesis of 3,4-dihydropyrazine-1(*2H*)-carboxy-lates 3a–d: general procedure

Oxopiperazines **1a**–**d** (1 equiv) were dissolved in dry THF and the solution was cooled to −30 °C. $LiAlH_4$ (1.2 equiv) was added and stirred at −30 °C for 2 h. After the addition of water, the reaction mixture was warmed up to room temperature and was extracted with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4 and then concentrated to afford pirazines **3a**–**d**, which were purified by flash chromatography.

4.3.1. (*S*)-*tert*-Butyl-2-methyl-4-benzyl-3,4-dihydro-pyrazine-1(*2H*)-carboxylate 3a

Oxopiperazine **1a** (75 mg, 0.2 mmol) was dissolved in THF (8 mL) and was reacted with $LiAlH_4$ (11 mg, 0.3 mmol). Workup and purification [petroleum ether/ethyl acetate = 25/1] gave **3a** as a colourless oil (72 mg, 97%). R_f: 0.3. **3a**: ^1H NMR (400 MHz) δ: 7.34–7.25 [m, 5H]; 5.79 (5.95) [d, 1H, J = 6.0 Hz]; 5.37 (5.48) [d, 1H, J = 6.0 Hz]; 4.36 [br m, 2H]; 4.23 [br m, 1H]; 4.07–3.99 [d, 1H, J_{AB} = 14.3.0 Hz]; 4.07–3.99 [d, 1H, J_{AB} = 14.3 Hz]; 3.97–3.90 [d, 1H, J_{AB} = 14.3 Hz]; 2.80 [br s, 2H]; 1.47 [s, 9H]; 1.20 [d, 3H, J = 6.6 Hz]. ^{13}C NMR (50.3 MHz) δ: 152.2; 137.9; 128.42 (×2); 128.23 (×2); 127.33; 118.92; 101.13; 79.73; 59.0; 50.7; 45.9; 28.4; 17.1. $[\alpha]_D^{28} = -78.0$ (c 0.85, $CHCl_3$). Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found: C, 70.76; H, 8.35; N, 9.76.

4.3.2. (*S*)-*tert*-Butyl-2-isopropyl-4-benzyl-3,4-dihydro-pyrazine-1(*2H*)-carboxylate 3b

Oxopiperazine **1b** (50 mg, 0.2 mmol) was dissolved in THF (5 mL) and was reacted with $LiAlH_4$ (8 mg, 0.3 mmol). Workup and purification [hexane/ethyl acetate = 9/1] gave **3b** as a colourless oil (25 mg, 48%). R_f: 0.3. **3b**: ^1H NMR (200 MHz) δ: 7.35–7.27 [m, 5H]; 5.79 (5.87) [d, 1H, J = 6.2 Hz]; 5.39 (5.45) [d, 1H, J = 6.2 Hz]; 4.06–3.88 [m, 2H]; 3.89 (3.76) [d, 1H, J = 6.2 Hz]; 3.16–2.98 [m, 1H]; 2.69 [dd, 1H, J = 11.7, J = 3.5 Hz]; 2.07–1.88 [m, 1H]; 1.46 [s, 9H]; 0.87 [d, 3H, J = 8.8 Hz]; 0.78 [d, 3H, J = 8.8 Hz].^{13}C NMR (50.3 MHz) δ: 151.1; 137.9; 128.3 (×2); 127.4

(×2); 127.0; 119.9; 101.1; 79.8; 59.0; 57.1; 55.4; 47.1; 28.4; 19.7; 19.3. $[\alpha]_D^{26} = -39.6$ (*c* 1.05, $CHCl_3$). Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 72.18; H, 8.88; N, 8.76.

4.3.3. (*S*)-*tert*-Butyl-2-isobutyl-4-benzyl-3,4-dihydro-pyrazine-1(*2H*)-carboxylate 3c

Oxopiperazine **1c** (310 mg, 0.9 mmol) was dissolved in THF (20 mL) and was reacted with $LiAlH_4$ (38 mg, 1.0 mmol). Workup and purification [hexane/ethyl acetate = 30/1] gave **3c** as white crystals (230 mg, 77%). R_f: 0.4. **3c**: ^{1}H NMR (200 MHz) δ: 7.33–7.28 [m, 5H]; 5.78 (5.94) [d, 1H, *J* = 5.9 Hz]; 5.38 (5.50) [d, 1H, *J* = 5.9 Hz]; 4.38–4.21 (4.08–4.19) [m, 1H]; 4.04 [d, 1H, J_{AB} = 14.3 Hz]; 3.93 [d, 1H, J_{AB} = 14.3 Hz]; 2.95–2.72 [m, 2H]; 1.54–1.51 [m, 1H]; 1.48 [s, 9H]; 146–1.40 [m, 2H]; 0.95–0.91 [m, 6H].^{13}C NMR (50.3 MHz) δ: 151.1; 137.6; 128.1 (×2); 127.8 (×2); 127.1; 118.9; 100.7; 79.6; 58.7; 49.3; 48.2; 39.5 28.2; 24.5; 23.1; 22.0. $[\alpha]_D^{26} = -17.7$ (*c* 1.42, $CHCl_3$). Anal. Calcd for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.57; H, 9.19; N, 8.52.

4.3.4. (*S*)-*tert*-Butyl-2-[4-(benzyloxy)benzyl]-4-benzyl-3,4-dihydropyrazine-1(*2H*)-carboxylate 3d

Oxopiperazine 1**d** (100 mg, 0.2 mmol) was dissolved in THF (5 mL) and was reacted with $LiAlH_4$ (10 mg, 0.3 mmol). Workup and purification [hexane/ethyl acetate = 8/1] gave **3d** as a pale yellow oil (80 mg, 82%). R_f: 0.3. **3d**: ^{1}H NMR (400 MHz) δ: 7.43–7.39 [m, 5H]; 7.34–7.28 [m, 5H]; 7.02 (6.94) [d, 2H, *J* = 8.2 Hz]; 6.81 (6.79) [d, 2H, *J* = 8.2 Hz]; 5.86 (6.01) [d, 1H, *J* = 6.2 (6.6) Hz]; 5.43 (5.56) [d, 1H, *J* = 6.2 (6.6) Hz]; 5.05–4.9) [d_{app}, 2H]; 4.37–4.28 (4.23–4.14) [m, 1H]; 3.98 [dd, 1H, J_{AB} = 14.0 J_{AC} = 4.3 Hz]; 3.92 [dd, 1H, J_{AB} = 14.0 J_{AC} = 4.3 Hz]; 2.85–2.62 [m, 2H+2H]; 1.45 (1.37) [s, 9H]. ^{13}C NMR (50.3 MHz) δ: 157.3 (156.9); 154.5; 137.6; 134.6 (134.3); 131.0; 130.9; 130.4 (×2); 129.2; 128.5 (×2); 128.4 (×2); 127.3 (×2); 127.8 (×2); 127.3 (×2); 120.2 (119.1); 114.8 (114.5); 101.3 (101.1); 80.1 (79.6); 70.0; 59.2; 46.8 (47.2); 36.7 (36.1); 28.4. $[\alpha]_D^{26} = -86.0$ (*c* 0.6, $CHCl_3$). Anal. Calcd for $C_{30}H_{34}N_2O_3$: C, 76.57; H, 7.28; N, 5.95. Found: C, 76.51; H, 7.34; N, 5.89.

4.4. Synthesis of (*S*)-*tert*-butyl-4,6-dibenzyl-2-methyl-3,4-dihydropyrazine-1(*2H*)-carboxylate 5

Oxopiperazine **4** (40 mg, 0.1 mmol) was dissolved in THF (5 mL) and the solution was cooled to 0 °C. Next, $LiAlH_4$ (6 mg, 0.15 mmol) was added, and the reaction mixture was warmed at room temperature and stirred for 2 h. After the addition of water and extraction with ethyl acetate, the organic phase was washed with brine, dried over Na_2SO_4 and then concentrated. Purification [petroleum ether/ethyl acetate = 20/1] gave 27 mg (71%) of **5** as a yellow oil which rapidly decomposed in solution ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.40–7.24 [m, 10H]; 5.60 [s, 1H]; 4.37 [br s, 1H]; 4.08–4.01 [m, 2H]; 3.28 [d, 2 H, *J* = 15 Hz]; 2.88 [dd, 1H, *J* = 3.7 Hz, *J* = 11.5 Hz]; 2.71 [d, 1H, *J* = 11.5 Hz]; 1.47 [s, 9H]; 0.78 [s, 3H].

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