

Synthesis and Structure of Highly Enantio- and Diastereoenriched 1-Aza-4-oxa-7-thiabicyclo[3.3.0]octan-8-ones Derived from Acyl-Substituted *S*-Benzyl Thiocarbamates

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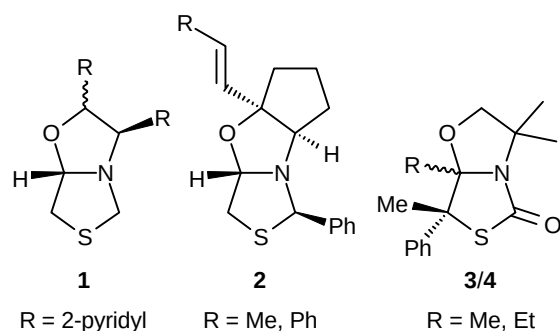
Dedicated to Prof. Dr. H. Kunz on the Occasion of his 60th Birthday

Keywords: Asymmetric synthesis, Cyclizations, Nitrogen heterocycles, Sulfur heterocycles, Diastereoselective cyclizations

Abstract. A convenient method for the synthesis of the title compounds **4a,b**, **3a,b** via an intramolecular condensation of thiourethanes, derived from the acylation of enantioenriched α -thio benzyl lithium compounds, is reported. The structure

of one of the major diastereomers was elucidated by a single-crystal X-ray analysis and compared to semiempirical calculations.

Only few synthesis have been reported for the 1-aza-4-oxa-7-thiabicyclo[3.3.0]octane system, such as for **1** [1] and **2** [2]. These heterocycles constitute an interesting type of amino acetal:



During our studies on acylation reactions of the highly enantioenriched, configurationally stable *S*-lithiobenzyl thiocarbamate **6**, [3] we unintentionally noticed a surprisingly facile method for the formation of the corresponding 8-oxo derivatives **3** and **4** (Scheme 1).

The ketones (*R*)-**7** are stereospecifically formed from the (*S*)-lithio derivative (*S*)-**6** with complete stereoinversion on reaction with acid chlorides. When these were treated with small amounts of acidic catalysts under the usual conditions of deblocking, [3] the bicyclic compounds **3/4** were obtained instead of the expected *N*-(β -hydroxyalkyl)thiourethanes **8**. Besides the major diastereomers **3a** and **3b**, small amounts of a second diastereomer (**4a** and **4b**, respectively) were detected. The major diastereomer of the methyl-substituted derivative **3a** formed suitable single crystals for an X-ray crystal structure analysis, which confirms its (5*R*,6*R*)-configuration [4] (Figure 1).

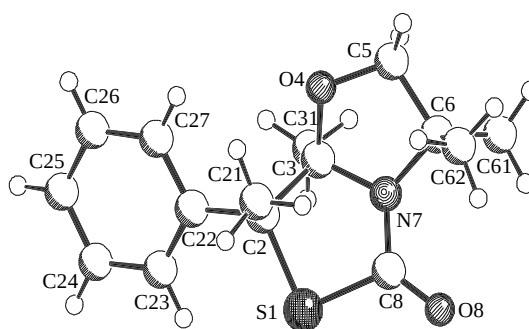


Fig. 1 X-ray crystal structure of **3a** [4]

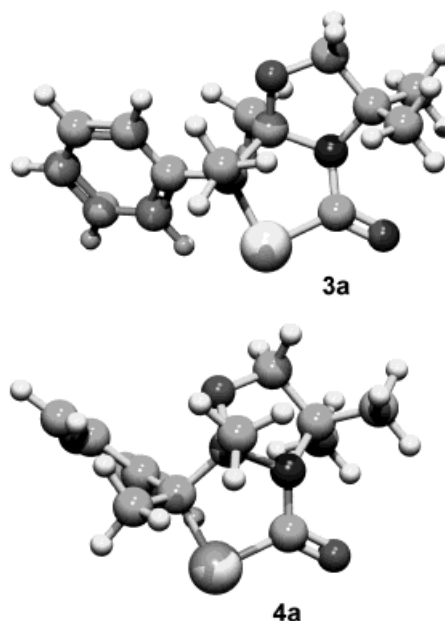


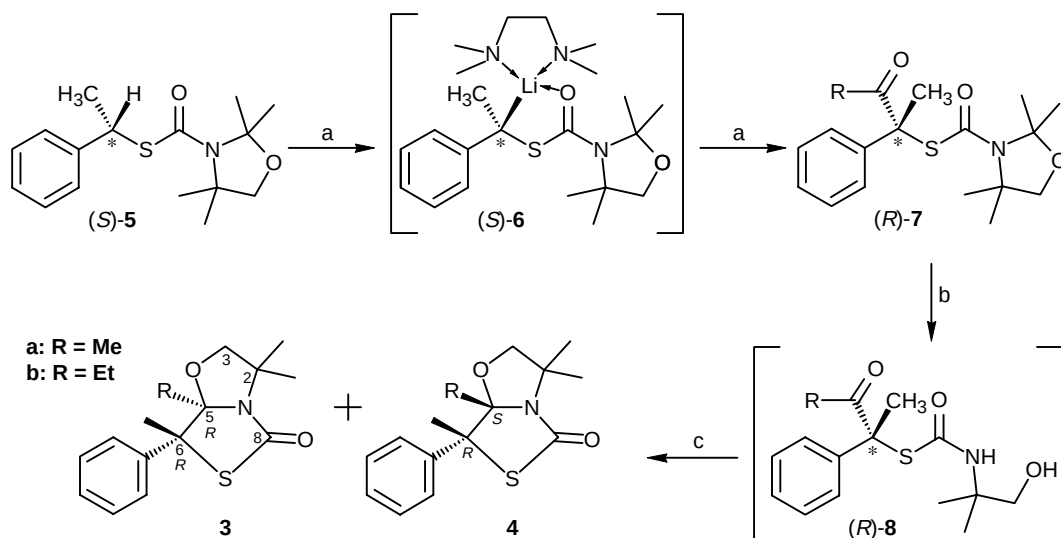
Fig. 2 PM3-calculated structures for **3a** ($\Delta_f H = -47.33 \text{ kcal}\cdot\text{mol}^{-1}$) and **4a** ($\Delta_f H = -45.88 \text{ kcal}\cdot\text{mol}^{-1}$)

¹⁾ X-ray crystal structure analysis

The observed diastereomeric ratios of 88:12 to 94:6, according to $\Delta\Delta G = 1.2$ to $1.6 \text{ kcal}\cdot\text{mol}^{-1}$, are in good agreement with the difference of $1.4 \text{ kcal}\cdot\text{mol}^{-1}$, estimated by semi-empirical calculations [5]. The structures of **3a** and **4a**, which are the calculated energy minima, are given in Figure 2.

The tendency for the formation of these heterocycles **3/4** and their stability is high. Even in the presence of an excess of 1,2-ethanedithiol or 1,3-propanedithiol and boron trifluoride etherate, the bicyclic compounds **3a** and **3b** are formed with high yields.

Scheme 1 shows the complete reaction path including the β -hydroxy thiourethane **8**, which is supposed to be an intermediate of the cyclization process. We applied the acidic cyclization conditions to the independently synthesized [3] ethyl substituted derivative **8b**. This open-chain compound directly fuses to the bicycle **3b/4b** and therefore gives an additional indication for the proposed reaction path (Scheme 1).



Scheme 1 Preparation of the Title Compounds **3** and **4** a) see ref. [3]; b) 1,3-propanedithiol, Amberlyst 15, CH_2Cl_2 , 8 d at *r.t.*, 99%; c) $\text{Et}_2\text{O}\cdot\text{BF}_3$, Et_2O , 5 d at *r.t.*, 87%.

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Experimental

General methods

^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 300 instrument at 300 MHz and 75.5 MHz, respectively. Chemical shifts are reported in ppm in relation to Me_4Si as internal standard. IR spectra were registered on a Perkin-Elmer 298 spectrometer; only the strongest bands are given. Optical rotations were obtained with a Perkin-Elmer 241 polarimeter and are specified in the unit $\text{degree}\cdot\text{mL}\cdot\text{dm}^{-1}\cdot\text{g}^{-1}$. Melting points were measured on a Mettler FP 61 apparatus and are uncorrected. The Mikroanalytische Abteilung des

Organisch-Chemischen Institutes der Universität Münster performed the elementary analyses on a Heraeus CHN-O-Rapid Elementaranalysator. All yields are given referring to neat products, purified by flash column chromatography [6] on silica gel (Merck, 60–200 mesh). Solvents and reagents were distilled and, if necessary, dried prior to use. Et_2O and CH_2Cl_2 were freshly distilled from Na/benzophenone and CaH_2 , respectively. Isomer ratios of diastereomeric mixtures were derived from suitable ^1H NMR or GC integrals (Hewlett Packard HP 5890 II chromatograph with a 25 m HP 1 column or Hewlett Packard HP 6890 II chromatograph with a 25 m HP 1701 column). Values belonging to the minor diastereomer are given in curled brackets {}. All numbers in the spectroscopic data follow Scheme 1.

The ketone (**7a**) and the β -hydroxy thiourethane (**8b**) were synthesized as described in ref. [3].

(5*R*,6*R*)- and (5*S*,6*R*)-2,2,5,6-Tetramethyl-6-phenyl-1-aza-4-oxa-7-thiabicyclo[3.3.0]octan-8-one (**3a** and **4a**) [7]

The ketone (*R*)-**7a** (125 mg, 0.37 mmol, *er* > 99:1) and 1,3-propanedithiol (0.10 mL, 0.11 g, 1.0 mmol) were diluted in the suspension of the cationic ion exchanger Amberlyst 15 (34 mg) in anhydrous CH_2Cl_2 (2.0 mL). The reaction mixture was stirred for 8 d at 19°C and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (Et_2O /hexanes, 1:4) and afforded **3a/4a** (102 mg, 0.37 mmol) as a colourless solid with 99% yield. The diastereomeric ratio of 88:12 was determined *via* GC (HP 1 and HP 1701).

3a/{4a}

$[\alpha]_D^{20} = -53.1$ ($c = 1.06$ in CH_2Cl_2 , $dr = 88:12$, $er \geq 99:1$ at C-6 in the starting material); $R_F = 0.58$ (E/P, 1:1); $R_F = 0.39$ (E/P, 1:2); $R_F = 0.28$ (E/P, 1:4); $t_R = 18.4 \text{ min}$ {17.7 min}; $\Delta t_R =$

0.72 min (HP 1); $t_R = 23.7$ min [22.6 min]; $\Delta t_R = 1.12$ min (HP 1701); $m.p.$ 94–96 °C. – ^1H NMR (300 MHz, CDCl_3): $\delta/\text{ppm} = 1.34$ {1.31} (s, 3H, 5- CH_3); 1.50, 1.65 {1.59, 1.83} (s, 6H, 2- CH_3); 1.94 {1.89} (s, 3H, 6- CH_3); 4.21 (d, 1H, 3- H_a); 4.24 (d, 1H, 3- H_b); 7.26–7.35 (m, 5H, Ph-H); $^2J_{3\text{Ha}, 3\text{Hb}} = 14.7$ Hz. – ^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 21.7, 23.9, 26.6, 29.7$ {22.3, 22.9, 23.1, 30.1} (q, 6- CH_3 , 5- CH_3 , 2- CH_3); 59.0 {60.4} (s, C-6); 66.6 (s, C-2); 84.1 {82.0} (t, C-3); 104.2 {104.2} (s, C-5); 127.4, 128.9 {127.4, 129.3} (d, Ph: o-C, m-C); 128.0 {127.9} (d, Ph: p-C); 140.1 (s, Ph: i-C); 163.7 (s, C-8). – GC-MS (CI, NH_3): m/z (%) = 295 (82 {82}, $[\text{M}+\text{NH}_4]^+$); 278 (100 {100}, $[\text{M}+\text{H}]^+$); 277 (10 {10}, M^+); 136 (6 {6}, $[\text{C}_8\text{H}_8\text{S}]^+$). – GC-MS (EI, 70 eV): m/z (%) = 277 (100 {56}, M^+); 202 (0 {5}, $[\text{M}-\text{CH}_3-\text{COS}]^+$); 141 (22 {22}, $[\text{Cby}-\text{CH}_3]^+$); 136 (94 {100}, $[\text{C}_8\text{H}_8\text{S}]^+$); 121 (36 {62}, $[\text{C}_8\text{H}_8\text{S}-\text{CH}_3]^+$); 114 (34 {42}, $[\text{Cby}-\text{CH}_3-\text{C}_2\text{H}_3]^+$); 113 (18 {32}, $[\text{Cby}-\text{CH}_3-\text{CO}]^+$); 98 (34 {62}, $[\text{C}_5\text{H}_8\text{NO}]^+ = [\text{Cby}-\text{C}_3\text{H}_6\text{O}]^+$). – IR (KBr): $\tilde{\nu}/\text{cm}^{-1} = 1690$ (C=O), 1680 (C=O).

$\text{C}_{15}\text{H}_{19}\text{NO}_2\text{S}$ Calcd.: C 64.95 H 6.90 N 5.05 (277.39) Found: C 64.94 H 6.88 N 5.10.

Stirring of *rac*-**7a** for 17 d at 20 °C yielded **3a/4a** with 85% yield and a diastereomeric ratio of 91:9 ($m.p.$: 87–89 °C).

(5*R*,6*R*)- and (5*S*,6*R*)-5-Ethyl-2,2,6-trimethyl-6-phenyl-1-aza-4-oxa-7-thiabicyclo[3.3.0]octan-8-one (**3b** and **4b**)

Boron trifluoride etherate (0.10 mL, 0.11 g, 0.78 mmol) was injected to a solution of the β -hydroxy thiourethane (*R*)-**8b** (66 mg, 0.21 mmol, $er > 98:2$) in anhydrous Et_2O (2.0 mL). At 21 °C the reaction mixture was stirred for 5 d and poured into a mixture of Et_2O (5 mL) and NaOH (2 M, 5 mL). The organic layer was separated and the aqueous solution extracted with Et_2O (3*10 mL). The combined organic layers were dried over solid Mg_2SO_4 . Evaporation of the solvent and flash chromatography of the crude product on silica gel (Et_2O /hexanes, 1:1) yielded the colourless solid **3b/4b** (54 mg, 0.19 mmol, 87%). The diastereomeric ratio **3b**:**4b** = 90:10 was determined by GC (HP 1). The enantiomeric ratio of (*R*):(*S*) > 98:2 concerning C-6 results from the starting material (*R*)-**7a**.

3b/4b

$[\alpha]_D^{21} = -67.7$ ($c = 0.24$ in CH_2Cl_2 , $dr = 90:10$, $er > 98:2$ at C-6 in the starting material); $R_F = 0.66$ (E/P, 1:1); $t_R = 19.1$ min {18.6 min}; $\Delta t_R = 0.51$ min (HP 1). – ^1H NMR (300 MHz, CDCl_3): $\delta/\text{ppm} = 0.66$ (dd, 3H, 5- CH_2-CH_3); 1.50, 1.67 (s, 6H, 2- CH_3); 1.74–1.94 (m, 2H, 5- CH_2-CH_3); 1.96 (s, 3H, 6- CH_3); 4.17 (d, 1H, 3- H_a); 4.25 (d, 1H, 3- H_b); 7.14–7.41 (m, 5H, Ph-H); $^3J_{5-\text{CH}_2-\text{CH}_3, 5-\text{CH}_2-\text{CH}_3} = 7.4$ Hz; $^3J_{5-\text{CH}_2-\text{CH}_3, 5-\text{CH}_2-\text{CH}_3} = 7.7$ Hz; $^2J_{3-\text{Ha}, 3-\text{Hb}} = 8.7$ Hz. – ^{13}C NMR (75 MHz, CDCl_3): $\delta/\text{ppm} = 9.4$ {8.8} (q, 5- CH_2-CH_3); 26.2, 26.3 {22.5, 22.8} (q, 2- CH_3); 28.7 {34.0} (t, 5- CH_2-CH_3); 30.4 {32.2} (q, 6- CH_3); 58.6 {59.4} (s, C-6); 65.9 {66.1} (s, C-2); 84.0 {81.9} (t, C-3); 105.6 (s, C-5); 127.3, 128.3 {127.0, 128.7} (d, Ph: o-C, m-C); 127.5 {127.7} (d, Ph: p-C); 139.6 (s, Ph: i-C); 164.7 (s, C-8). – IR (film): $\tilde{\nu}/\text{cm}^{-1} = 1695$ (C=O), 1665 (C=O). – GC-MS (EI, 70 eV): m/z (%) = 291 (52 {24}, M^+); 262 (4 {2}, $[\text{M}-\text{C}_2\text{H}_5]^+$); 202 (20 {8}, $[\text{M}-\text{C}_2\text{H}_5-\text{COS}]^+$); 155 (24 {20}, $[\text{M}-\text{C}_8\text{H}_8\text{S}]^+$); 136 (100 {100}, $[\text{C}_8\text{H}_8\text{S}]^+$); 127 (44

{32}, $[\text{M}-\text{C}_8\text{H}_8\text{SCO}]^+$); 121 (54 {48}, $[\text{C}_8\text{H}_8\text{S}-\text{CH}_3]^+$); 112 (70 {76}, $[\text{M}-\text{C}_8\text{H}_8\text{SCO}-\text{CH}_3]^+$); 103 (20 {22}, $[\text{C}_8\text{H}_7]^+$); 77 (10 {16}, $[\text{C}_6\text{H}_5]^+$); 56 (12 {21}, $[\text{C}_4\text{H}_8]^+$). – MS (EI, 70 eV): m/z (%) = 291 (52, M^+); 262 (4, $[\text{M}-\text{C}_2\text{H}_5]^+$); 202 (15, $[\text{M}-\text{C}_2\text{H}_5-\text{COS}]^+$); 155 (23, $[\text{M}-\text{C}_8\text{H}_8\text{S}]^+$); 136 (100, $[\text{C}_8\text{H}_8\text{S}]^+$); 127 (54, $[\text{M}-\text{C}_8\text{H}_8\text{SCO}]^+$); 121 (78, $[\text{C}_8\text{H}_8\text{S}-\text{CH}_3]^+$); 112 (92, $[\text{M}-\text{C}_8\text{H}_8\text{SCO}-\text{CH}_3]^+$); 103 (36, $[\text{C}_8\text{H}_7]^+$); 77 (24, $[\text{C}_6\text{H}_5]^+$); 56 (36, $[\text{C}_4\text{H}_8]^+$). HR-MS (EI, 70 eV) calcd. for $\text{C}_{16}\text{H}_{21}\text{NO}_2\text{S}$ [M^+] 291.1293, found 291.1294.

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- [7] Different conditions for preparing **3a/4a**: A) Stirring of the ketone (*R*)-**7a** (105 mg, 0.31 mmol, $er > 98:2$) in anhydrous CH_2Cl_2 (3.0 mL), 1,2-ethanedithiol (0.42 mL, 0.47 g, 5.0 mmol) and boron trifluoride etherate (0.10 mL, 0.11 g, 0.78 mmol) for 10 d resulted in **3a/4a** (52 mg, 0.19 mmol, 61 %) with $m.p.$ 94–96 °C and $[\alpha]_D^{20} = -57.2$ ($c = 0.75$ in CH_2Cl_2 , $dr = 94:6$, $er \geq 98:2$ at C-6 in the starting material). B) Without enclosure of moisture the ketone *rac*-**7a** (133 mg,

0.40 mmol), Amberlyst 15 (40 mg) and CH₃OH (0.5 mL) were heated for 34 h to 100 °C in a pressure-proof vessel. After the solvent had been evaporated *in vacuo*, the residue was purified by flash chromatography **3a/4a** (89 mg, 0.32 mmol) were isolated with 81% yield and a diastereomeric ratio of 89:11 (GC: HP 1; *m.p.* 89–90 °C).

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