

Highly Diastereoselective Formation and Reactions of a Non-Mesomerically Stabilized, Lithiated α -Thiocarbanion

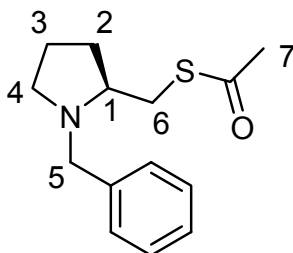
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Supporting Information

General remarks:

All solvents were dried and purified prior to use. Unless otherwise specified, materials were obtained from commercial sources and used without purification. Diethyl ether and toluene were distilled over sodium benzophenone ketyl, THF over potassium benzophenone ketyl and CH_2Cl_2 was distilled over CaH_2 . N,N,N',N' -Tetramethylethylenediamine (TMEDA), TMSCl and NEt_3 were distilled from powdered calcium hydride and stored under argon. All reactions were performed under argon atmosphere in flame-dried glassware. Flash column chromatography (FCC) was performed on Merck 60 silica gel, 0.040–0.063 mm, and monitored by thin layer chromatography (TLC) on Merck 60 F_{254} silica gel. Melting points: Gallenkamp MFB 595 (uncorrected values. MS: Finnigan MAT 8230 (EI); Micromass Quattro LCZ (ESI), Micromass MAT 8200 (GC-TOF/HRMS). Optical rotations: Perkin-Elmer 341 polarimeter. NMR: Bruker ARX 300, AM 360, AMX 400 or Varian Associated Unity Plus 600; spectra from solutions in CDCl_3 ($\delta_{\text{C}}=77.0$ ppm) are calibrated relative to residual content of CHCl_3 ($\delta_{\text{H}}=7.24$ ppm) or SiMe_4 ($\delta_{\text{H}}=0.0$ ppm). Elemental analyses: Heraeus CHN-O-Rapid or Elementar Analysensysteme Vario EL III. GC: Agilent 6890, 30 m \times 0.32 mm HP 5, 1.5 mL \times min $^{-1}$ H_2 start at 50 $^\circ\text{C}$ /10 $^\circ\text{C}\times$ min $^{-1}$ 20 min at 270 $^\circ\text{C}$.

(S)-(S-1-Benzylpyrrolidin-2-yl)methyl ethanethioate¹

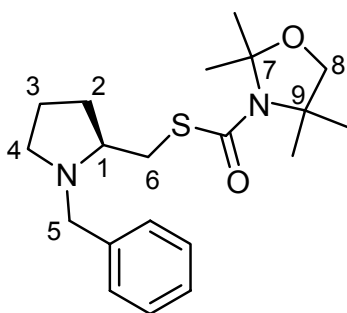


To a solution of *N*-benzyl prolinol^{2,3} (5.0 g, 26.1 mmol, 1.0 eq.) in 40 mL of dichloromethane was added abs. triethylamine (3.90 g, 39.1 mmol, 1.5 eq.). This solution was stirred at room temperature for 10 min then cooled to -78 $^\circ\text{C}$ and a solution of methanesulfonyl chloride (3.5 g, 30.7 mmol, 1.2 eq.) in 10 mL abs. dichloromethane was added. This mixture was stirred for 1 h. Afterwards, the solvent was removed under vacuum to get a pale yellow semisolid. A solution of potassium thioacetate (5 g,

43.8 mmol, 1.6 eq.) in 50 mL of water was added and the resulting solution was stirred at room temperature for 2 h. Afterwards, the reaction mixture was poured into 100 mL of dichloromethane, the layers were separated and the aqueous layer was washed with dichloromethane (3×25mL). The combined organic layer was dried with anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (EA:CH 1:6) to afford the desired thioester as a yellow oil.

Yield:	5.0 g (20 mmol, 77%).
R _f :	0.60 (EA:CH = 1:1).
Optical rotation:	[α] _D ²⁰ = -111.0 (c = 1.25, CHCl ₃).
¹ H NMR (400 MHz):	δ/ppm = 1.42-1.80 (m, 3H, H3, H2a); 1.85 (m, 1H, H2b); 2.12 (ddd, 1H, H4a); 2.28 (s, 3H, H7); 2.67 (m, 1H, H1); 2.92 (m, 2H, H4b, H5a); 3.29(dd, 2H, H6a, H6b); 4.05 (d, 1H, H5b); 7.24 (m, 5H, Ph).
	² J _{5a,5b} = 13.3 Hz; ³ J _{1,6} = 3.0 Hz; ³ J _{6a,6b} = 13.3 Hz.
¹³ C NMR (100 MHz):	δ/ppm = 22.3 (C3); 29.9 (C2); 30.5 (C7); 33.1 (C6); 54.23 (C4); 58.4 (C5); 62.5 (C1); 126.8, 128.5, 128.7, 139.7 (Ph); 195.8 (C=O).
Elemental Analysis:	Calc. C 67.43 H 7.68 N 5.92
C ₁₄ H ₁₉ NOS (249.1)	Found C 67.52 H 7.72 N 6.04.
MS (ESI):	m/z = = 250.1279 [M + H] ⁺ .

(S)-(S-1-Benzylpyrrolidin-2-yl)methyl 2,2,4,4-tetramethyloxazolidine-3-carbothioate (1)



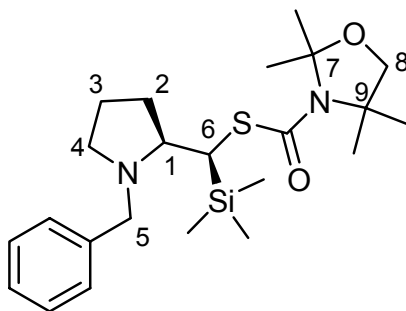
To a well stirred suspension of LiAlH₄ (1.1 g, 30 mmol, 1.5 eq.) in 50 mL of diethyl ether, a solution of thioester, obtained as above, (5.0 g, 20 mmol, 1.0 eq.) in 40 mL of diethyl ether was added in a dropwise manner at 0 °C (GEP 4). The resulting solution was stirred at 0 °C for 30 min and at room temperature for an additional hour. Afterwards, the reaction flask was cooled to 0 °C and the reaction was quenched by careful addition of 10

mL of water. After the standard workup, the crude thiol was obtained as a colourless liquid. The thiol was used in the subsequent step without further purification.

A solution of crude thiol in 20 mL of abs. THF was added to a stirred suspension of NaH (60% in mineral oil, 1.2 g, 30 mmol, 1.5 eq.) in 40 mL of abs. THF. The resulting solution was stirred at room temperature for 15 minutes and then a solution of *CbyCl* (5.74 g, 30 mmol, 1.5 eq.) in 25 mL of abs. THF was added to it. This mixture was stirred at room temperature for 24 h. Afterwards, the reaction flask was cooled to 0 °C and 10 mL of water was slowly injected into the flask. The layers were separated and the aqueous layer was extracted with diethyl ether (3×25 mL). The collective organic phase along with washing was dried over anhydrous MgSO₄, filtered through glass wool, and concentrated under reduced pressure to get the crude thiocarbamate which was subjected to column chromatography (E:P = 1:4) to furnish the desired thiocarbamate as a colourless, viscous oil.

Yield:	5.5 g (15.2 mmol, 76% over 2 steps).
R _f :	0.58 (E:P = 1:1).
Optical rotation:	$[\alpha]_{\text{D}}^{20} = -78.9$ ($c = 1.1$, CHCl ₃).
¹ H NMR (400 MHz):	δ /ppm = 1.60-1.80 (m, 15H, 7-CH ₃ , 9-CH ₃ , H2a, H3); 2.10 (m, 1H, H2b); 2.32 (m, 1H, H4a); 2.95 (m, 1H, H1); 3.12 (m, 2H, H4b, H6a); 3.50 (d, 1H, H5a); 3.70 (dd, 1H, H6b); 3.90 (s, 2H, H8); 4.30 (d, 1H, H5b) 7.30-7.55 (m, 5H, Ph). $^2J_{5a,5b} = 13.2$ Hz; $^3J_{1,6} = 3.5$ Hz; $^2J_{6a,6b} = 13.4$ Hz.
¹³ C NMR (100 MHz):	δ /ppm = 22.4 (C-3); 24.7 ((CH ₃) ₂ C-9); 25.7 ((CH ₃) ₂ C-7); 30.0 (C-2); 34.2 (C-6); 54.0 (C-9); 54.1 (C-4); 58.8 (C-5); 62.9 (C-1); 77.2 (C-8); 96.0 (C-7); 126.6, 128.1, 128.7, 139.4 (Ph); 163.8 (C=O).
Elemental Analysis:	Calc. C 66.26 H 8.34 N 7.73
C ₂₀ H ₃₀ N ₂ O ₂ S (362.2)	Found C 66.11 H 8.37 N 7.62.
MS (ESI):	m/z = 363.2064 [M + H] ⁺ ; 385.1870 [M + Na] ⁺ .

[(1R), 1(2S)]-(1-Benzylpyrrolidin-2-yl)-1-(trimethylsilyl)methyl 2,2,4,4-tetramethyl - oxazolidine-3-carbothioate (3a).



R_f: 0.55 (EA:CH = 1:4).

¹H NMR (400 MHz): δ/ppm = 0.18 (s, 9H, Si(CH₃)₃); 1.60-1.80 (m, 15H, 4×CH₃(C_{by}), H2a, H3); 1.95 (m, 1H, H2b); 2.07 (m, 1H, H4a); 2.83 (m, 1H, H1); 2.89 (m, 1H, H4b); 3.23 (d, 1H, H5a); 3.35 (d, 1H, H6); 3.75 (s, 2H, H8); 4.30 (d, 1H H5b) 7.30-7.55 (m, 5H, Ph).

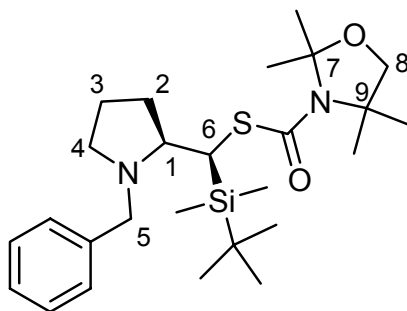
²J_{5a,5b} = 13.2 Hz; ³J_{1,6} = 4.2 Hz.

¹³C NMR (100 MHz): δ/ppm = 0.01 (Si(CH₃)₃); 22.7 (C-3); 24.7 ((CH₃)₂C-9); 25.7 ((CH₃)₂C-7); 30.2 (C-2); 33.2 (C-6); 54.0 (C-9); 54.1 (C-4); 58.8 (C-5); 68.1 (C-1); 77.2 (C-8); 96.0 (C-7); 126.6, 128.1, 128.7, 139.4 (Ph); 164.3 (C=O).

Elemental Analysis:	Calc.	C 63.54	H 8.81	N 6.44
C ₂₃ H ₃₈ N ₂ O ₂ SSi (434.7)	Found	C 63.43	H 8.88	N 6.22.

MS (ESI): m/z = 434.2477 [M + H]⁺, 457.2335 [M + Na]⁺

[(1*R*), 1(2*S*)]-(1-Benzylpyrrolidin-2-yl)-1-(*t*-butyldimethylsilyl)-methyl 2,2,4,4-tetramethyloxazolidine-3-carbothioate (3b)



R_f: 0.62 (E:P = 1:2).

¹H NMR (300 MHz): δ/ppm = 0.00 (s, 3H, Si-CH₃a); 0.12 (s, 3H, Si-CH₃b); 0.08 (s, 9H, Si-C(CH₃)₃); 1.40-1.60 (m, 15H, 4×CH₃(C_{by}), H2a, H3); 1.95 (m, 2H, H2b, H4a); 2.53 (m, 1H, H1); 2.75 (m, 1H, H4b); 3.0 (d, 1H,

H5a); 3.45 (d, 1H, H6); 3.58 (s, 2H, H8); 4.20 (d, 1H H5b) 7.00-7.35 (m, 5H, Ph).

$^2J_{5a,5b} = 13.2$ Hz; $^3J_{1,6} = 4.2$ Hz.

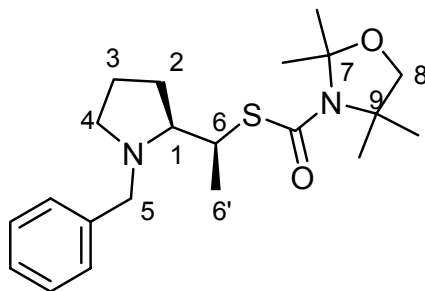
^{13}C NMR (75 MHz): $\delta/\text{ppm} = -3.4$ (Si-CH₃a); -3.1 (Si-CH₃b); 18.1 (Si-C(CH₃)₃); 22.6 (C-3); 25.3 ((CH₃)₂C-9); 26.2 ((CH₃)₂C-7); 27.4 (Si-C(CH₃)₃); 30.6 (C-2); 30.6 (C-6); 54.0 (C-9); 54.4 (C-4); 59.6 (C-5); 70.2 (C-1); 77.2 (C-8); 98.0 (C-7); 126.7, 128.3, 129.0, 140.7 (Ph); 164.5 (C=O).

Elemental Analysis: Calc. C 65.50 H 9.30 N 5.88
C₂₆H₄₄N₂O₂SSi (476.2) Found C 65.19 H 9.56 N 5.51.

MS (ESI): $m/z = 477.2933$ [M + H]⁺, 499.2747 [M + Na]⁺.

In situ deprotonation: **1** (100 mg, 0.27 mmol, 1.0 eq.) was dissolved in 5 mL of toluene, TMEDA (37 mg, 0.32 mmol, 1.2 eq.) and *t*-butyldimethylsilyl triflate (0.21 gm, 0.81 mmol, 3.0 eq.) was added and the reaction flask was cooled to -78 °C. To this mixture, *n*-BuLi (1.36 M, 0.23 mL, 0.32 mmol, 1.2 eq.) was injected in a dropwise manner. The reaction mixture was stirred at -78 °C for 3 h. The reaction mixture was then quenched with 2 mL of water, phases were separated and the aqueous phase was extracted with diethyl ether (3×10 mL). The collective organic phase was dried over anhydrous MgSO₄, filtered through glass wool, and concentrated under reduced pressure. The crude product was subjected to column chromatography (E:P = 1:6) to obtain the desired product in 65% yield.

[(1*S*),1(2*S*)]-(1-Benzylpyrrolidin-2-yl)ethyl 2,2,4,4-tetramethyl-oxazolidine-3-carbothioate (3c)



R_f: 0.45 (E:P = 1:2).

^1H NMR (300 MHz): $\delta/\text{ppm} = 1.25$ (d, 3H, H6'); 1.29-1.80 (m, 16H, 4×CH₃(C_{by}), H2, H3); 2.10 (m, 1H, H4a); 2.83 (m, 2H, H1, 4Hb); 3.23 (d, 1H, H5a); 3.67 (s, 2H, H8); 3.90 (m, 1H, H6) 4.11 (d, 1H H5b) 7.10-7.45 (m, 5H, Ph).

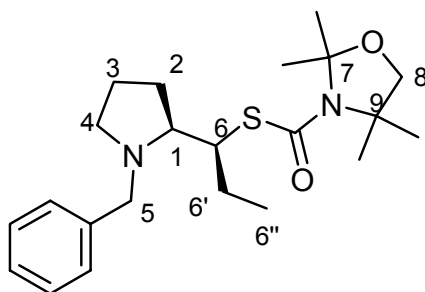
$^2J_{5a,5b} = 13.5$ Hz; $^3J_{6,6'} = 6.8$ Hz.

^{13}C NMR (75 MHz): $\delta/\text{ppm} = 15.1$ (C6'); 23.7 (C-3); 25.2 ((CH₃)₂C-9); 26.1 ((CH₃)₂C-7); 28.2 (C-2); 41.8 (C-6); 53.0 (C-9); 54.7 (C-4); 58.9 (C-5); 67.0 (C-1); 77.2 (C-8); 94.0 (C-7); 124.4, 126.9, 128.7, 140.0 (Ph); 164.1 (C=O).

Elemental Analysis: Calc. C 66.98 H 8.57 N 7.44
C₂₁H₃₂N₂O₂S (376.2) Found C 67.12 H 8.65 N 7.30.

MS (ESI): $m/z = 377.2257$ [M + H]⁺, 399.2046 [M + Na]⁺.

[(1*S*),1(2*S*)]-(1-Benzylpyrrolidin-2-yl)propyl 2,2,4,4-tetramethyl -oxazolidine-3-carbothioate (3d)



R_f: 0.36 (E:P = 1:2).

^1H NMR (300 MHz): $\delta/\text{ppm} = 1.27$ (t, 3H, H6''); 1.60-1.95 (m, 17H, 4×CH₃(C_{by}), H2a, H3, H6'); 2.10 (m, 1H, H2b); 2.41 (m, 2H, H4a); 3.14 (m, 2H, H1, H4b); 3.54 (d, 1H, H5a); 3.95 (m, 3H, H8, H6); 4.45 (d, 1H, H5b) 7.30-7.55 (m, 5H, Ph).

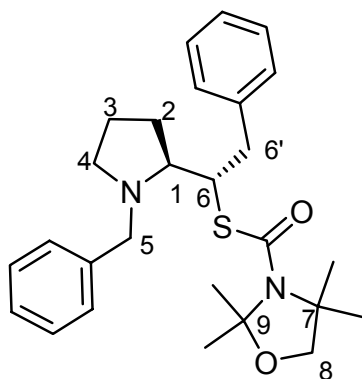
$^2J_{5a,5b} = 13.5$ Hz; $^3J_{6',6''} = 7.5$ Hz.

^{13}C NMR (75 MHz): $\delta/\text{ppm} = 12.7$ (C6''); 21.8 (C6'); 23.8 (C-3); 25.2 ((CH₃)₂C-9); 26.2 ((CH₃)₂C-7); 27.5 (C-2); 50.0 (C-6); 54.8 (C-4); 59.1 (C-5); 67.6 (C-1); 77.2 (C-8); 96.0 (C-7); 126.9, 128.4, 129.0, 140.6 (Ph); 164.4 (C=O).

Elemental Analysis: Calc. C 67.65 H 8.77 N 7.17
C₂₂H₃₄N₂O₂S (390.2) Found C 67.70 H 8.82 N 7.04.

MS (ESI): $m/z = 391$ [M + H]⁺.

[(1*S*),1(2*S*)]-(1-Benzylpyrrolidin-2-yl)-2-phenylethyl 2,2,4,4-tetramethyloxazolidine-3-carbothioate (3e)



R_f: 0.50 (E:P = 1:2).

¹H NMR (400 MHz): δ/ppm = 1.25-1.70 (m, 15H, 4×CH₃(C*bt*), H2a, H3); 1.90 (m, 1H, H2b); 2.15 (m, 1H, H4a); 2.61 (m, 1H, H4b); 2.91 (bs, 2H, H1, H6'); 3.25 (d, 1H, H5a); 3.45 (dd, 1H, H6'b); 3.60 (s, 2H, H8); 4.10 (dd, 1H, H6'a); 4.25 (d, 1H, H5b); 7.07-7.41 (m, 10H, Ph).

²J_{5a,5b} = 13.5 Hz; ³J_{6,6'} = 2.9 Hz; ²J_{6'a,6'b} = 14.5 Hz.

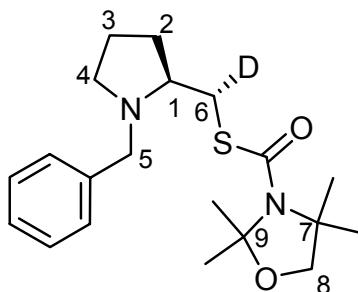
¹³C NMR (100 MHz): δ/ppm = 23.4 (C-3); 24.8 ((CH₃)₂C-9); 25.5 ((CH₃)₂C-7); 29.5 (C-2); 34.8 (C-6'); 49.0 (C-6); 53.0 (C-9); 54.4 (C-4); 58.7 (C-5); 66.9 (C-1); 77.2 (C-8); 94.0 (C-7); 125.7, 126.5, 127.9, 128.0, 128.5, 129.1, 129.4 139.9 (Ph); 163.0 (C=O).

Elemental Analysis: Calc. C 71.64 H 8.02 N 6.19

C₂₇H₃₆N₂O₂S (452.2) Found C 71.46 H 8.22 N 5.96.

MS (ESI): m/z = 453.25 [M + H]⁺; 475.23 [M + Na]⁺.

[(1*S*),1(2*S*)]-(1-Benzylpyrrolidin-2-yl)-deuteromethyl 2,2,4,4-tetramethyl-oxazolidine-3-carbothioate (5)



(100 mg, 0.27 mmol, 1.0 eq.) was dissolved in 5 mL of toluene, TMEDA (37 mg, 0.32 mmol, 1.2 eq.) was added and the reaction flask was cooled to -78 °C. To this mixture,

s-BuLi (1.36 M, 0.23 mL, 0.32 mmol, 1.2 eq.) was injected in a dropwise manner. The reaction mixture was stirred at -78°C for 3 h. Then, CH₃OD (90 mg, 2.70 mmol, 10.0 eq.) was injected and the reaction mixture stirred for 10 min. After that, CH₃COOD (0.1 mL) was added to quench the residual lithium species. The reaction mixture was added with anhydrous MgSO₄, filtered through glass wool, and concentrated under reduced pressure. The crude product was subjected to column chromatography (E:P = 1:6) to obtain **5** as a colourless, viscous liquid. Mass and NMR spectra indicate no trace of undeuterated species implying that the deuteration is quantitative.

Yield: 98 mg (0.26 mmol, 99%).

R_f: 0.42 (E:P = 1:2).

T_R: 20.39 min (HP-5).

Optical rotation: $[\alpha]_{\text{D}}^{20} = -69.5$ ($c = 0.63$, CHCl₃).

¹H NMR (400 MHz): δ /ppm = 1.40-1.80 (m, 15H, 4×CH₃(*Cb*), H2a, H3); 1.90 (m, 1H, H2b); 2.12 (m, 1H, H4a); 2.65 (m, 1H, H1); 2.85 (m, 2H, 4Hb, 6H); 3.25 (d, 1H, H5a); 3.65 (s, 2H, H8); 4.05 (d, 1H, H5b); 7.11-7.45 (m, 5H, Ph).

$^2J_{5a,5b} = 13.2$ Hz; $^3J_{1,6} = 3.5$ Hz; $^2J_{6a,6b} = 13.4$ Hz.

¹³C NMR (100 MHz): δ /ppm = 22.4 (C-3); 24.7 ((CH₃)₂C-9); 25.7 ((CH₃)₂C-7); 30.0 (C-2); 34.2 (C-6); 54.0 (C-9); 54.1 (C-4); 58.8 (C-5); 62.9 (C-1); 77.2 (C-8); 96.0 (C-7); 126.6, 128.1, 128.7, 139.4 (Ph); 163.8 (C=O).

IR (film): $\tilde{\nu}$ /cm⁻¹ = 3064, 3030 (m, C-H_{aro}); 2974, 2926, 2869 (s, C-H_{ali}); 1632 (s, C=O); 1690 (s); 1458 (s); 1364 (s); 1267 (s); 1241 (s); 1076 (s); 919 (s); 885 (s); 799 (s).

Elemental Analysis:	Calc.	C 66.08	H 8.59	N 7.71
C ₂₀ H ₃₀ DN ₂ O ₂ S (363.2)	Found	C 66.11	H 8.37	N 7.62.

MS (ESI): $m/z = 364.2170$ [M + H]⁺.

References:

1. According to M-J. Jin, S. Kim, J. Jung, H. Lee, *Bull. Korean Chem. Soc.* **2000**, *21*, 33
2. D. Enders, H. Eichenauer, *Chem. Ber.* **1979**, *112*, 2933.
3. T. R. Govindachari, *J. Chem. Soc. Perkin Trans. 1* **1974**, 1161.