A Practical and Facile Synthesis of Azetidine Derivatives for Oral Carbapenem, L-084

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An orally active carbapenem L-084, which exhibits high bioavailability in humans, has a 1-(1,3-thiazolin-2-yl)azetidin-3-ylthio moiety at the C-2 position of the 1β-methylcarbapenem skeleton. We established a practical and cost-effective synthesis of 3-mercapto-1-(1,3-thiazolin-2-yl)azetidine (1) for further scale-up production of L-084. This synthesis method entails an industry-oriented reaction of azetidine ring-closure to yield *N*-benzyl-3-hydroxyazetidine (16), which is eventually converted to 1 *via* key intermediates, Bunte salts 19 and 20.

Key words L-084; carbapenem; azetidine; Bunte salt

Carbapenem antibiotics have long been in the spotlight because of their potent antimicrobial activity. The attention of both academic and industrial scientists has been attracted to the development of a new carbapenem for clinical use. Since imipenem[1)] was launched in 1987 by Merck Co., five additional compounds, panipenem,[2)] meropenem,[3)] biapenem,[4)] ertapenem[5)] and doripenem,[6)] are now on the market. However, all these were developed for parenteral use, and the development of carbapenems for oral use has been expected for a long time. The title compound L-084 is one of the hopeful candidates among recently reported oral carbapenems such as CS-834,[7—12)] GV-118819[13—17)] and DZ-2640.[18—27)] L-084, an ester-type prodrug of the active metabolite LJC11,036 (**2**), shows high bioavailability in humans,[28)] and exhibits high antimicrobial activity against Gram-positive and Gram-negative bacteria.[29)] The structural feature of L-084 is an achiral azetidine moiety at the C-2 position of the 1β-methylcarbapenem skeleton, whereas CS-834 and DZ-2640 have a chiral pyrrolidine moiety as shown in Chart 1. Synthesis of L-084 was carried out according to our reported procedure (Chart 2).[28)] The condensation of enolphosphate **11** and thiol **1** afforded the *p*-nitrobenzyl (PNB) ester **12**, which was then subjected to hydrogenolysis followed by esterification with pivaloyloxymethylchloride (POMCl) to give L-084.

In this paper, we describe a practical and facile synthesis of thiol **1** *via* Bunte salts **19** and **20** as key intermediates. This synthesis method for **1** is amenable to large-scale production.

Optimization of the Reaction for Azetidine Ring-Closure[30)] We have previously established the synthesis of **1** through 3-hydroxyazetidine hydrochloride (**5**) as a key intermediate.[28)] Compound **5** was obtained in two steps including cyclization of *N*-benzhydryl-3-chloro-2-hydroxypropylamine (**3**) and deprotection of the *N*-substituent according to the literature (Chart 2).[31,32)] Although compound **5** has been well recognized as a useful building block for various bioactive molecules such as antimicrobial agent WQ-2743,[33)] antiepileptic Dezinamide[34)] and antihypertensive Azelnidipine,[35)] it has been suggested that the above two-step procedure for **5** was too expensive to adopt for large-scale production. Therefore, we decided to develop an alternative synthetic method for **5**.

In the reaction of an azetidine ring-closure, one or more bulky substituents on the precursor were considered to be necessary to obtain the corresponding azetidine derivative effectively. A practical method for the scale-up production of derivatives of azetidinols bearing a less bulky substituent has not been developed yet.[31,36—40)] Regarding the preparation of

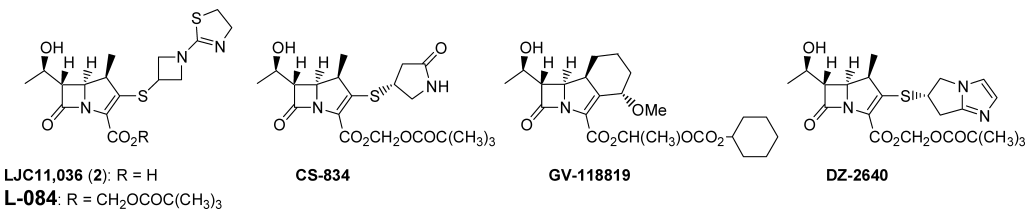

Chart 1

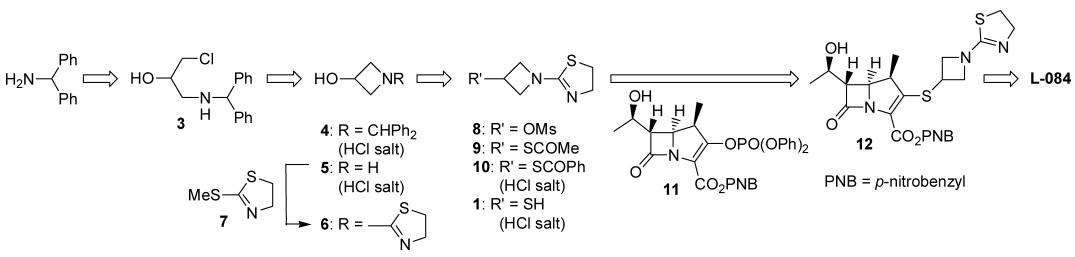

Chart 2

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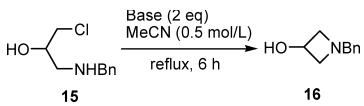
a less bulky *N*-benzyl derivative,[41,42] only the *O*-protected compound **14** has been obtained by cyclization of **13** in low yield (Entry 1 in Table 1). In order to provide an industry-oriented reaction of azetidine ring-closure, we focused on *N*-benzyl-3-chloro-2-hydroxypropylamine (**15**) as a precursor of the azetidine derivative **16**, because **15** was prepared from benzylamine which was less expensive than benzhydrylamine. We initially checked out whether the benzylamino group attacked the C-1 position of **15** under the same conditions of Entry 1, but the azetidine derivative **16** was not obtained at all (Entry 2 in Table 1). Because we had to avoid using a protecting reagent as much as we could from the cost point of view, we carefully carried out the optimization of reaction conditions to obtain **16** from **15** in the 10 mmol scale experiments summarized in Table 1. The yield was found to be critically dependent on the solvent. The reaction proceeded in 2-propanol (*i*-PrOH) or *tert*-butyl alcohol (*t*-BuOH) in the presence of triethylamine (Et_3N) (Entries 3 and 4 in Table 1). Moreover, the yield of **16** dramatically increased in acetonitrile (MeCN) when potassium hydrogencarbonate ($KHCO_3$) was added as a base (Entry 8 *vs.* 2 in Table 1). Finally, we could set the best reaction condition in which **16** was obtained in 90% yield (Entry 10 in Table 1). We then examined the reaction on a 250 mmol scale under the optimal conditions, but the yield of **16** decreased to 73%. In searching for the reason of less reproducibility, we found that the particle size of $KHCO_3$ affected the yield of this reaction (Table 2). Commercially available $KHCO_3$ was considered not to be an appropriate reagent because of its wide distribution range of particle size, whereas sodium hydrogencarbonate ($NaHCO_3$) showed a narrow distribution range. We demonstrated that the large particles contained in the commercial reagent caused the decreasing of the yield. So we investigated the use of $NaHCO_3$ instead of $KHCO_3$ and confirmed that $NaHCO_3$ was also a good reagent for this cyclization reaction (Entry 6 in Table 2). Further scale-up production was accomplished with excellent reproducibility (Entry 11 in Table 1). Through these experiments, we established the optimization of the reaction for azetidine ring-closure that was useful and applicable to the manufacturing of **16**.

Conversion of OH Group on Hydroxyazetidine Derivatives to SH Group[43—47] The introduction of an acylthio group using a metal acylthiolate is one of the general method for the synthesis of various thiols and related compounds. In the early stage of the development of L-084, thiol **1** was prepared from the acetylthio compound **9** according to the above method we previously reported.[28] As for a large-scale production, the oily compound **9** was considered not to be an appropriate precursor, and the second generation precursor, crystalline compound **10**, was omitted due to the cost of a metal thiobenzoate (Chart 2). As a more convenient method for the preparation of **1**, the introduction of a dithiosulfonate group was investigated. A variety type of alkylthiosulfate compounds, so-called Bunte salt,[48] were known to be readily prepared using economical sodium thiosulfate ($Na_2S_2O_3$). However, probably due to its high polarity and poor solubility in organic solvents, there have been few applications utilizing this functionalized intermediate for a large-scale synthesis. Bunte salt **20**, the precursor of **1**, was successfully obtained from *N*-benzyl-3-hydroxyazetidine (**16**) in 4 steps. Mesylation of **16** followed by hydrogenolysis gave rise to 3-methanesufonyloxyazetidine hydrochloride (**18**), which was easily converted to Bunte salt **19** in 52% yield after stirring with $Na_2S_2O_3$ at 50 °C in methanol and water. The condensation of **19** and 2-methylthio-2-thiazoline (**7**) afforded **20** in 67% yield. Although the two sequential reactions from **18** to **20** both proceeded in moderate yield, we envisioned that the reactions could also proceed in a one-pot manner in a mixed

Table 2. Effect of the Particle Size of $KHCO_3$ and $NaHCO_3$

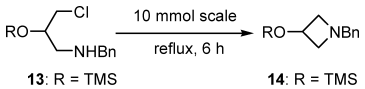


15 **16**

Entry	Base	Particle size (μm)	Distribution ratio (%)[a]	Reaction yield (%)[b]
1	$KHCO_3$	335—500	53.5	58
2	$KHCO_3$	250—355	14.8	54
3	$KHCO_3$	177—250	13.0	98
4	$KHCO_3$	150—177	3.3	97
5	$KHCO_3$	<150	15.4	97
6	$NaHCO_3$	<250	96.9	98

a) Distribution ratio in commercially available materials. *b*) HPLC yield.

Table 1. Optimization of the Reaction Conditions for Azetidine Ring-Closure

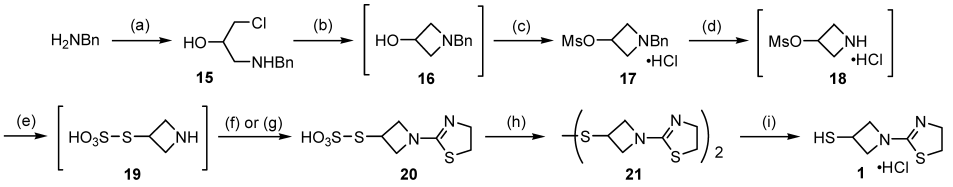


13: R = TMS
15: R = H

14: R = TMS
16: R = H

Entry	Substrate	Solvent	Conc. (mol/l)	Base (eq)	Product	Yield (%)[a]
1[b]	**13**[41]	MeCN	1.0	Et_3N (3)	**14**[41]	38
2	**15**	MeCN	1.0	Et_3N (2)	**16**	N.R.[c]
3	**15**	*t*-BuOH	1.0	Et_3N (2)	**16**	70
4	**15**	*i*-PrOH	1.0	Et_3N (2)	**16**	60
5	**15**	*i*-PrOH	1.0	—	**16**	N.R.[c]
6	**15**	*i*-PrOH	1.0	$KHCO_3$ (2)	**16**	40
7	**15**	*t*-BuOH	1.0	$KHCO_3$ (2)	**16**	57
8	**15**	MeCN	1.0	$KHCO_3$ (2)	**16**	58
9	**15**	*t*-BuOH	0.5	$KHCO_3$ (2)	**16**	85
10	**15**	MeCN	0.5	$KHCO_3$ (2)	**16**	90
11[d]	**15**	MeCN	0.5	$NaHCO_3$ (2)	**16**	93

a) Isolated yield. *b*) Refluxed for 3 d. *c*) No reaction. *d*) 3.2 mol scale.



Reagents and conditions: (a) epichlorohydrin (0.95 eq), H_2O, 15 °C, 18 h, 89%; (b) $NaHCO_3$ (2.0 eq), MeCN, reflux, 6.5 h; (c) MsCl (1.1 eq), Et_3N (1.2 eq), MeCN, 5 °C, 7 h, 80% (2 steps); (d) 10% Pd-C, H_2O-MeOH, H_2 (500 kPa), 40 °C, 24 h; (e) $Na_2S_2O_3$ (1.0 eq), H_2O-MeOH, 50 °C, 22 h; (f) Et_3N (1.1 eq), chloroethylisothiocyanate (1.1 eq), H_2O-MeOH, 5 °C, 0.5 h, 82% (3 steps); (g) 2-methylthio-2-thiazoline (1.1 eq), H_2O-MeOH, reflux, 17 h, 42% (3 steps); (h) conc. HCl (5.0 eq), 55 °C, 2 h, then H_2O_2 (0.5 eq), 5 °C, 45 min, 93%; (i) Ph_3P (1.2 eq), H_2O (2.0 eq), HCl in MeOH (2.5 eq), MeCN, rt, 1.5h, 93%.

Chart 3

solvent of methanol and water. After removal of the catalysts in the hydrogenolysis of **17**, to the resulting solution of **18** was successively added $Na_2S_2O_3$ at 50 °C and **7** under reflux. Unexpectedly, the overall yield of **20** in a one-pot manner was disappointingly low (42% yield from **17**). The reason of the low yield of **20** might be due to the severe reaction condition for the reaction of **19** with **7** (reflux, 17 h). As shown in Chart 3, the use of chloroethylisothiocyanate instead of **7** enabled the reaction to proceed under mild conditions, and the overall yield from **17** to **20** was improved (82% yield without isolation of **18** and **19**).

Deprotection of **20** was carried out to obtain **1** by acid hydrolysis with conc. HCl.[47] However, disulfide **21** concomitantly formed in 10% yield and could not be separated from crude **1**. In order to obtain pure **1**, we quitted studying the direct conversion and tried to add an oxidation step. The resulting crude **1** was treated with hydrogen peroxide to afford **21** in quantitative yield as illustrated in Chart 3. Reduction of **21** with triphenylphosphine also proceeded quantitatively, and thiol **1** was obtained in crystalline form, which was suitable for use in the synthesis of L-084.

Conclusion

We accomplished the synthesis of 3-mercapto-1-(1,3-thiazolin-2-yl)azetidine (**1**) in 52% overall yield starting from benzylamine and epichlorohydrin. The new synthesis method not only increases the yield but also reduces the cost by half and is amenable to large-scale production. The reaction of azetidine ring-closure was achieved even in the case of a less bulky precursor **15** to afford **16** in quantitative yield. Compound **16** was eventually converted to **1** *via* zwitterionic Bunte salt **20** without isolation of **18** and **19**.

Experimental

Melting points were determined using Yanagimoto micromelting point apparatus. NMR spectra were obtained on JEOL JNM-EX270 (270 MHz) or Bruker Avance DPX400 (400 MHz) spectrometers using tetramethylsilane (TMS) or sodium 3-(trimethylsilyl)propionate-d_4 (TSP) as an internal standard. IR spectra were recorded on a JASCO FT-IR (VALOR-III) spectrometer. Mass spectra were recorded on JEOL JMS-DX300 or JMS-SX102A spectrometers. Elemental analysis was recorded on a Yanako CHN-Corder.

***N*-Benzyl-3-chloro-2-hydroxypropylamine (15)** To a solution of benzylamine (138.8 g, 1.58 mol) in water (1.5 l) was added epichlorohydrin (138.8 g, 1.50 mol) at 5 °C, and the reaction mixture was stirred for 18 h at 15 °C. *n*-Hexane and *i*-PrOH (1 : 15, 300 ml) were added to the reaction mixture, and the mixture was stirred for 2 h at 15 °C. The resulting precipitate was filtered and dried *in vacuo* to obtain **15** as colorless crystals (265.2 g, 89%), mp 72—73 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.72 (1H, dd, J=7.8, 12.4 Hz), 2.84 (1H, dd, J=4.1, 12.4 Hz), 3.56 (2H, d, J=5.6 Hz), 3.81 (2H, d, J=2.0 Hz), 3.84—3.92 (1H, m), 7.23—7.37 (5H, m). IR (KBr) cm^{-1}: 3292, 2899, 1453, 1346, 1252, 1072, 882. FAB-MS *m/z*: 200.0833 (Calcd for $C_{10}H_{15}ClNO$: 200.0842). MS *m/z*: 200 (M^++H). *Anal.* Calcd for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.07; N, 7.01. Found: C, 60.12; H, 7.03; N, 6.98.

***N*-Benzyl-3-hydroxyazetidine (16)** (Entry 11 in Table 1) A mixture of **15** (643.7 g, 3.22 mol) and $NaHCO_3$ (542.0 g, 6.45 mol) in MeCN (6.4 l) was refluxed for 7 h and allowed to cool to room temperature. The reaction mixture was filtered, and the filtrate was evaporated to 600 g. To the residue were added AcOEt (300 ml) and heptane (3200 ml), and the mixture was stirred for 1 h at room temperature. The resulting precipitate was filtered and dried *in vacuo* to obtain **16** as colorless crystals (488.1 g, 93%), mp 64—65 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.93—2.97 (2H, m), 3.59—3.63 (4H, m), 4.39—4.45 (1H, m), 7.23—7.33 (5H, m). IR (KBr) cm^{-1}: 2837, 1496, 1476, 1453, 1342, 1174, 1083, 949. EI-MS *m/z*: 163.0997 (Calcd for $C_{10}H_{14}NO$: 163.1025). MS *m/z*: 163 (M^+−Cl).

3-Benzoylthio-1-(1,3-thiazolin-2-yl)azetidine hydrochloride (10) To the warmed AcO*n*-Bu (20 ml) were added 3-methanesulfonyloxy-1-(1,3-thiazolin-2-yl)azetidine (**8**)[28] (2.36 g, 10.0 mmol) and potassium thiobenzoate (2.64 g, 15.0 mmol) under stirring. After being refluxed for 5.5 h, the reaction mixture was cooled to room tempreture, and 5% aqueous $KHCO_3$ (7 ml) was added. The organic layer was separated, dried over $MgSO_4$ and filtered. To the filtrate was added 4 mol/l HCl in dioxane (2.5 ml, 10 mmol) at 15 °C, and the mixture was stirred for 1 h at 10 °C. The resulting precipitate was filtered and dried *in vacuo* to obtain **10** as colorless crystals (2.70 g, 86%), mp 166—167 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.58 (2H, t, J=7.6 Hz), 4.15 (2H, t, J=7.6 Hz), 4.20—4.25 (1H, m), 4.52—4.60 (1H, m), 4.81—4.87 (2H, m), 5.23—5.31 (1H, m), 7.46—7.52 (2H, m), 7.60—7.67 (1H, m), 7.88—7.91 (2H, m). IR (KBr) cm^{-1}: 3443, 2980, 1656, 1446, 1305, 1208, 912. FAB-MS *m/z*: 279.0642 (Calcd for $C_{13}H_{15}N_2OS_2$: 279.0626). MS *m/z*: 279 (M^+−Cl).

***N*-Benzyl-3-methanesulfonyloxyazetidine hydrochloride (17)** A mixture of **15** (225 g, 1.13 mol) and $NaHCO_3$ (189.3 g, 2.26 mol) in MeCN (2.25 l) was refluxed for 6.5 h, and the solvent including water was then removed under reduced pressure to yield the residual solution of **16** (917 g). After adding MeCN (1.24 l) and Et_3N (140.5 g, 1.40 mol) to the solution, methanesulfonyl chloride (140.0 g, 1.22 mol) was added dropwise over 7 h under 5 °C. The reaction was quenched with 13% HCl in MeCN (359 g, 1.3 mol) under 5 °C, and the resulting precipitate was filtered and dried *in vacuo* to obtain **17** as colorless crystals (245.6 g, 80%), mp 137—138 °C. ^{1}H-NMR (CD_3OD) δ: 3.21 (3H, s), 4.33—4.65 (4H, m), 4.82 (2H, s), 5.36—5.39 (1H, m), 7.48 (5H, m). IR (KBr) cm^{-1}: 2986, 2507, 2454, 1351, 1169. FAB-MS *m/z*: 242.0849 (Calcd for $C_{11}H_{16}NO_3S$: 242.0851). MS *m/z*: 242 (M^+−Cl). *Anal.* Calcd for $C_{11}H_{16}ClNO_3S$: C, 47.56; H, 5.81; N, 5.04. Found: C, 47.66; H, 5.82; N, 5.03.

3-Methanesulfonyloxyazetidine hydrochloride (18) To a solution of **17** (55.5 g, 200 mmol), MeOH (320 ml) and water (80 ml) was added 10% Pd–C (0.56 g, dry reduced), and the mixture was stirred vigorously for 20 h under 400 kPa pressure of hydrogen at room temperature. The catalyst was removed by filtration, and the filtrate was concentrated and triturated with MeOH–THF (15 ml : 45 ml). The resulting precipitate was filtered and dried *in vacuo* to obtain **18** as colorless crystals (35.8 g, 95%), mp 106—107 °C. ^{1}H-NMR (CD_3OD) δ: 3.11 (3H, s), 4.28—4.32 (2H, m), 4.49—4.54 (2H, m), 5.41—5.47 (1H, m). IR (KBr) cm^{-1}: 2985, 1575, 1354, 1174, 1064. FAB-MS *m/z*: 152.0378 (Calcd for $C_4H_{10}NO_3S$: 152.0381). MS *m/z*: 152 (M^+−Cl).

Azetidin-3-ylthiosulfonic acid (19) To a suspension of **18** (7.5 g, 40 mmol), MeOH (64 ml) and water (16 ml) was added $Na_2S_2O_3\cdot 5H_2O$ (10.0 g, 40 mmol), and the mixture was stirred for 20 h at 50 °C and then cooled to room temperature. The resulting precipitate was filtered and dried *in vacuo* to obtain **19** as colorless crystals (3.52 g, 52%), mp 225 °C (dec.).

^{1}H-NMR (D_2O) δ: 4.19—4.27 (2H, m), 4.44—4.54 (3H, m). IR (KBr) cm^{-1}: 3230, 1556, 1308, 1193, 1029. FAB-MS *m/z*: 169.9932 (Calcd for $C_3H_8NO_3S_2$: 169.9946). MS *m/z*: 170 (M^++H). *Anal.* Calcd for $C_3H_7NO_3S_2$: C, 21.29; H, 4.17; N, 8.28. Found: C, 21.25; H, 4.08; N, 8.12.

[1-(1,3-Thiazolin-2-yl)azetidin-3-yl]thiosulfonic Acid (20) a) To a suspension of **19** (1.69 g, 10 mmol), MeOH (16 ml) and water (4 ml) was added 2-methylthio-2-thiazoline (1.60 g, 10 mmol), and the mixture was refluxed for 17 h and then cooled to room temperature. The resulting precipitate was filtered and dried *in vacuo* to obtain **20** as colorless crystals (1.70 g, 67%), mp 218 °C (dec.). ^{1}H-NMR (CD_3OD) δ: 3.65 (2H, t, J=7.5 Hz), 4.00 (2H, t, J=7.5 Hz), 4.43—4.56 (3H, m), 4.70 (2H, dd, J=8.4, 9.3 Hz). IR (KBr) cm^{-1}: 3129, 3041, 1656, 1453, 1242, 1205, 1024. FAB-MS *m/z*: 254.9953 (Calcd for $C_6H_{11}N_2O_3S_3$: 254.9932). MS *m/z*: 255 (M^++H).

b) To a solution of **17** (2.22 g, 8 mmol), MeOH (6 ml) and water (2 ml) was added 10% Pd–C (0.22 g, dry reduced), and the mixture was stirred vigorously for 24 h under 500 kPa pressure of hydrogen at 40 °C. The catalyst was removed by filtration, and to the filtrate was added $Na_2S_2O_3\cdot 5H_2O$ (1.98 g, 8 mmol). After stirring for 22 h at 50 °C and being cooled to 5 °C, Et_3N (1.23 ml, 8.8 mmol) and chloroethylisothiocyanate (1.07 g, 8.8 mmol) were added to the reaction mixture. The reaction mixture was stirred for 0.5 h and concentrated under reduced pressure to give crude **20**. To a solution of 28% NaOMe (1.53 g, 8 mmol) and MeOH (16 ml) was added crude **20** at room temperature with stirring, and the insoluble material was removed by filtration. To the filtrate were added 1.33 mol/l HCl in MeOH (7.4 ml, 9.6 mmol) and IPA (25 ml) at 5 °C, and the mixture was stirred for 15 min. The resulting precipitate was filtered and dried *in vacuo* to obtain **20** including 1 equivalent of NaCl as colorless crystals (gross 1.96 g, 85% purity, net 6.6 mmol, 82% yield).

Bis[1-(1,3-thiazolin-2-yl)azetidin-3-yl] Disulfide (21) The mixture of **20** (gross 63.8 g, 51.8% purity, net 130 mmol) and conc. HCl (54.8 ml, 650 mmol) was stirred for 2 h at 55 °C. To the reaction mixture were added MeOH (27.4 ml) and water (27.4 ml), and $KHCO_3$ (104.1 g, 1.04 mol) was then added to the mixture over 25 min at 5 °C. After stirring for 1 h, 30% aqueous H_2O_2 (7.39 g, 65 mmol) was added to the mixture over 45 min, and $Na_2SO_3\cdot 7H_2O$ (3.28 g, 13 mmol) and water (164 ml) were then added at 5 °C. The reaction mixture was stirred for 1 h at room temperature. The resulting precipitate was filtered, washed successively with water and heptane and dried *in vacuo* to obtain **21** as colorless crystals (20.9 g, 93%), mp 54—55 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.36 (4H, t, J=7.6 Hz), 3.88 (2H, m), 3.92 (2H, dd, J=5.3, 8.0 Hz), 3.94 (2H, dd, J=5.3, 8.0 Hz), 4.02 (4H, t, J=7.6 Hz), 4.30 (4H, d, J=8.0 Hz). IR (KBr) cm^{-1}: 1613, 1344, 1116, 1005. EI-MS *m/z*: 347.0359 (Calcd for $C_{12}H_{19}N_4S_4$: 347.0493). MS *m/z*: 347 (M^++H).

3-Mercapto-1-(1,3-thiazolin-2-yl)azetidine Hydrochloride (1) To a solution of **21** (17.3 g, 50 mmol) in MeCN (25 ml) were added Ph_3P (16.2 g, 60 mmol), water (1.92 g, 100 mmol) and 8 mol/l HCl in MeOH (15.6 ml, 125 mmol), and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was triturated with THF (375 ml), and the resulting precipitate was filtered and dried *in vacuo* to obtain **1** as colorless crystals (19.6 g, 93%). Physical and spectral properties are in accord with the disclosed data.[28)]

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