Development of a Novel Benzyl Mercaptan as a Recyclable Odorless Substitute of Hydrogen Sulfide

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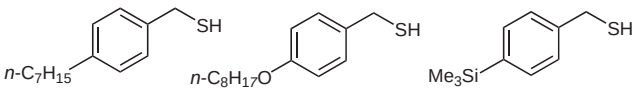
Abstract: 2,4,6-Trimethoxybenzyl mercaptan (**4**) was developed as an odorless substitute of hydrogen sulfide to afford β-mercapto carbonyl compounds in a Michael addition and to convert alkyl bromides into alkanethiols. Detrimethoxybenzylation of the Michael adducts prepared from **4** and α,β-unsaturated esters or ketones was facilely carried out by treatment with a solvent mixture of trifluoroacetic acid and toluene to give β-mercapto carbonyl compounds. Successive alkaline hydrolysis of 2,4,6-trimethoxybenzyl isothiouronium salt, which was obtained as a side product, regenerated **4** accompanying disulfide **8** in good yield. The disulfide **8** was also converted into **4** by reduction with $LiAlH_4$. A similar protocol was applicable to the synthesis of alkanethiols using the S_N2 reaction of alkyl bromides. Our method could be complementary to the classical method of using malodorous benzyl mercaptan as a nucleophile and Birch reduction for debenzylation.

Key words: odorless thiol, Michael addition, β-mercapto carbonyl compound, alkanethiol, organosulfur reagent

We have developed three types of odorless benzyl mercaptans, namely *p*-heptylphenylmethanethiol (**1a**), *p*-octyloxyphenylmethanethiol (**1b**), and *p*-trimethylsilylphenylmethanethiol (**1c**), useful as a source of the mercapto group, as a reagent for the synthesis of thiosugars, and as a synthetic equivalent of the benzylthio group, respectively (Figure 1).[1–3]



1a for the introduction of a mercapto group

1b for the synthesis of a thiosugar

1c for the introduction of a benzylthio group

Figure 1 Reported odorless benzyl mercaptans **1a–c**

The reagents **1a–c** showed high nucleophilicity in the Michael addition as well as in the S_N2 reaction, and were found to be useful for carrying out sulfur-involving reactions under completely odorless conditions. However, a high molecular weight, essential in making a reagent odorless by suppressing volatility, reduced their value in terms of atom economy. Actually, by employing the thiols **1a–c** as a substitute of hydrogen sulfide, *p*-substituted benzyl groups should be cleaved by Birch reduction requiring the tedious task of handling liquid ammonia. Therefore, we next embarked on the development of a novel benzyl mercaptan that could be regenerated by facile treatment of Michael adducts or S_N2 substitutes to afford β-mercapto carbonyl compounds and alkanethiols.

Benzyl mercaptans are often employed as nucleophiles in a Michael addition to afford β-mercapto carbonyl compounds, formal Michael adducts of hydrogen sulfide, by successive debenzylation reactions. Birch reduction has been the first choice for the debenzylation; however, the benzyl moieties cleaved by this method were not easily recycled to the original benzyl mercaptans. In order to regenerate an odorless benzyl mercaptan (**A**) from the Michael adducts (**B**), we designed a recycle pathway treating the Michael adducts with an odorless sulfur source, e.g., thiourea, under acidic condition followed by alkaline hydrolysis of isothiouronium salts (**C**),[4] which would be obtained as a product accompanying the desired β-mercapto carbonyl compounds (**D**) in the previous reaction (Scheme 1). The stability of the benzyl cation (**E**) generated as an intermediate in the S_N1 reaction should be significant enough to run the recycle pathway smoothly. We found the introduction of a few methoxy groups into the phenyl ring to be effective in making benzyl mercaptans odorless and stabilizing the benzyl cation. Thus, Michael addition of ethyl *p*-bromocinnamate with three methoxybenzyl mercaptans **2–4**[5] was attempted (Table 1). Interestingly, while the Michael addition[3] resulted in excellent yields (94–99%), debenzylation of the Michael adducts **5a** and **5b** with thiourea and trifluoroacetic acid in acetonitrile did not give the β-mercapto ester **6a** at all (Table 1, entries 1 and 2).[6] Only the debenzylation of **5c**[7] under the same conditions yielded the desired product **6a**[8] in a good yield (Table 1, entry 3). This result could be attributed to the presence of more *ortho*- and *para*-methoxy groups that can stabilize the benzyl cation intermediate derived from **5c**, as compared with the case of **5a** and **5b**.

Next, the conditions for the detrimethoxybenzylation of **5c** were optimized by changing the solvent and the amount of trifluoroacetic acid (Table 2). Toluene gave the best result among the employed solvents (Table 2, entries 1–3) and the suitable amount of trifluoroacetic acid was one-fifth of the solvent in volume (Table 2, entries 4 and 6). Moreover, the amount of thiourea could be reduced to two equivalents in the debenzylation reaction of **5c** (Table 2, entry 6).

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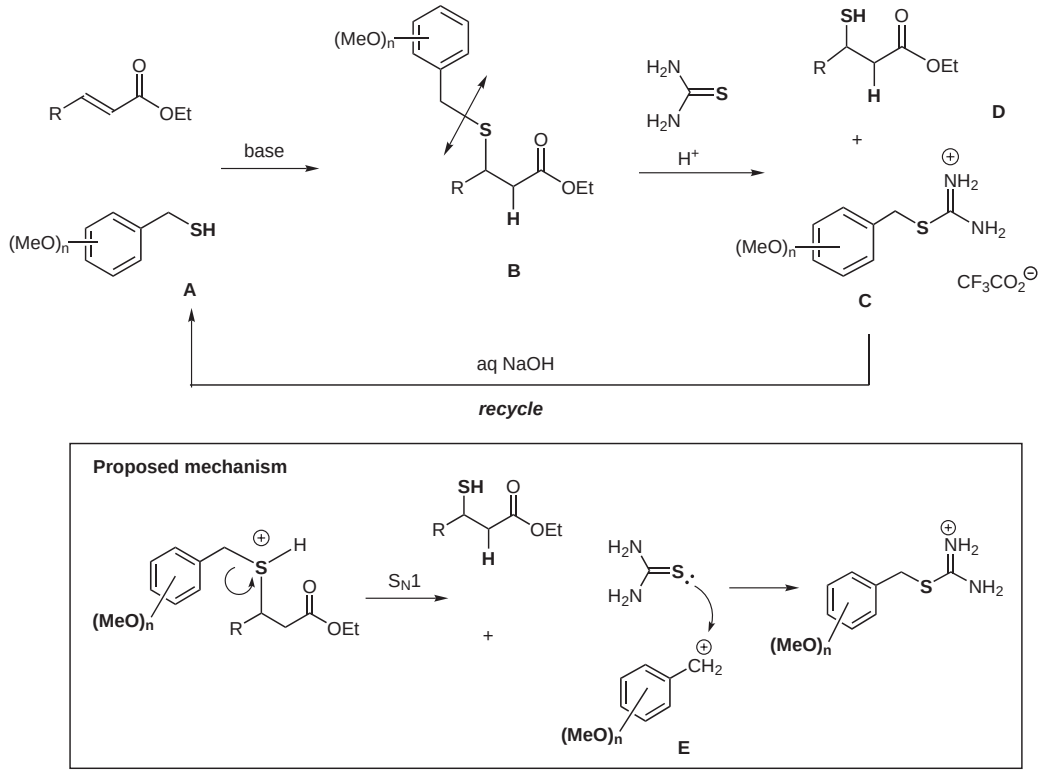
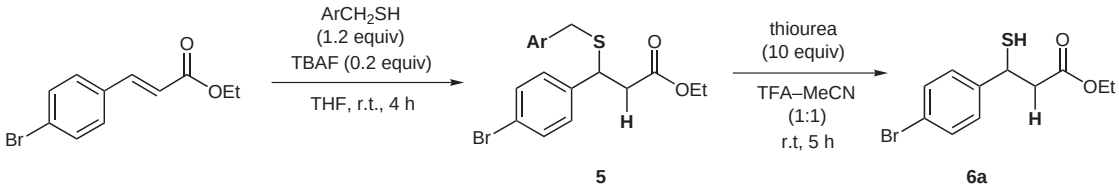
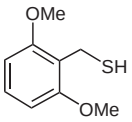
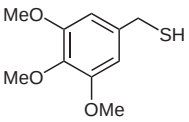
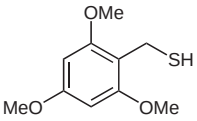


Scheme 1 Strategy for designing a new odorless benzyl mercaptan

Table 1 Comparison of Utility of New Odorless Benzyl Mercaptans **2**–**4** as Substitute of H_2S in Michael Addition

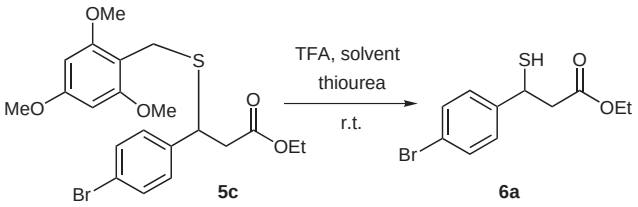


Entry	$ArCH_2SH$	Michael adduct	Yield of **5** (%)	Yield of **6** (%)
1	 **2**	**5a**	99	0
2	 **3**	**5b**	94	0
3	 **4**	**5c**	99	75

Other α,β-unsaturated esters as well as ketones were applied to the Michael addition where **4** was used as the nucleophile (Table 3). When a catalytic amount of *n*-tetrabutylammonium fluoride and sodium hydroxide was added to the reaction of α,β-unsaturated esters (Table 3, entries 2–5) and ketones (Table 3, entries 6 and 7), respectively, the reaction provided an excellent yield.

Herein, the practicability of regenerating an odorless benzyl mercaptan **4** from Michael adducts **5** was scrutinized (Table 4).

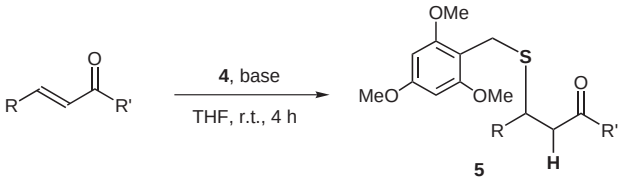
Table 2 Optimization of Condition in Debenzylation of **5c** with Thiourea



5c **6a**

Entry	Solvent	Ratio TFA–Solvent	$SC(NH_2)_2$ (equiv)	Time (h)	Yield of **6** (%)
1	MeCN	1:1	10	5	75
2	THF	1:1	10	5	75
3	Toluene	1:1	10	4	95
4	Toluene	1:5	10	4	95
5	Toluene	1:10	10	12	86
6	Toluene	1:5	2	4	95
7	Toluene	1:5	1	12	72

Table 3 Michael Addition of α,β-Unsaturated Carbonyl Compounds with **4**



5

Entry	R	R′	(equiv)	Base[a]	Yield (%)
1	4-BrC_6H_4	OEt	1.2	none	0
2	4-BrC_6H_4	OEt	1.2	TBAF	99
3	4-BrC_6H_4	OBn	1.2	TBAF	97
4	Ph	OBn	1.2	TBAF	91
5	4-$MeOC_6H_4$	OBn	1.2	TBAF	100
6	Ph	Ph	1.3	NaOH	90
7	Ph	Me	1.3	NaOH	99

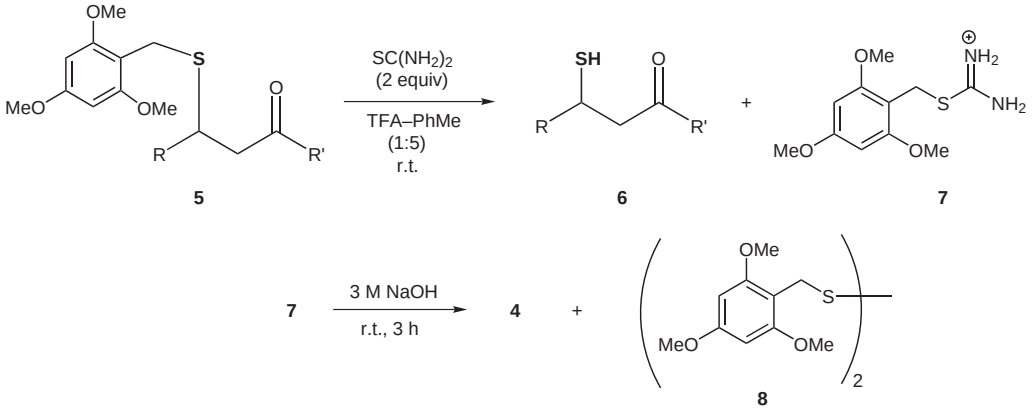
[a] TBAF (0.2 equiv) or NaOH (0.1 equiv) was added.

As mentioned above, the Michael adducts **5** were treated with thiourea in a solvent mixture comprised of trifluoroacetic acid and toluene to afford β-mercapto carbonyl compounds **6** and isothiouronium salt **7**,[9] which was next hydrolyzed in an alkaline solution. In general, 2,4,6-trimethoxybenzyl mercaptan (**4**) could be regenerated accompanying the disulfide **8** in satisfactory yields (Table 4, entries 1–5) by this protocol. The disulfide **8** was facilely reduced to **4** with lithium aluminum hydride. Finally, the usefulness of **4** and of **1a** were compared in the formal reductive Michael addition of hydrogen sulfide where (+)-pregone (**9**) was chosen as an acceptor substrate (Scheme 2).[10,11] In the reaction using **1a** as an odorless thiol, the Michael adduct **10a** was obtained in excellent yield (95%). Successive reduction of **10a** with sodium borohydride followed by debenzylation with sodium metal in liquid ammonia afforded the β-mercapto alcohol **11** in 61% overall yield. Meanwhile, the nucleophilic attack of **4** on **9** gave the Michael adduct **10b** in good yield (84%), and the successive reduction with sodium borohydride and the debenzylation developed in the present paper yielded **11** in 84% overall yield. Although the total yield from **9** to **11** in the latter reaction route (70%) was as high as that in the former route (61%), the latter route evaded the dangerous and perplexing task of handling sodium metal and liquid ammonia, which was required for debenzylation in the former reaction. In addition, **4** was applicable as a source of the mercapto group in the synthesis of alkanethiols **12** by using the S_N2 reaction of alkyl bromides **13** and successive treatment of the substitutes **14** with thiourea under acidic conditions (Table 5).

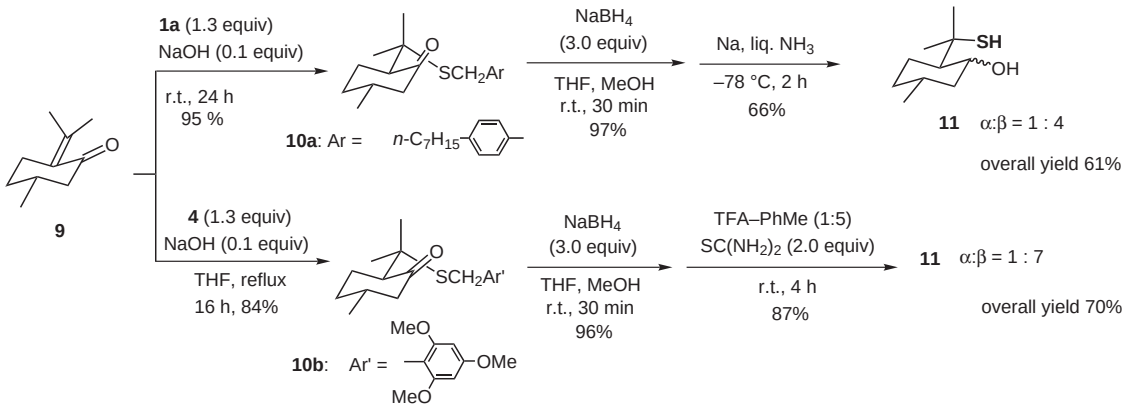
In conclusion, we have succeeded in the development of a novel odorless benzyl mercaptan **4**, which is an excellent nucleophile not only in the Michael addition but also in the S_N2 reaction, and behaves as a useful odorless substitute of hydrogen sulfide by treating the products **5** and **14** with thiourea under acidic condition.[12] Furthermore, after the treatment, **4** could be facilely regenerated by alkaline hydrolysis of the isothiouronium salt **7** generated along with the desired β-mercapto carbonyl compounds **6**, namely the formal Michael adducts of hydrogen sulfide, or alkanethiols **12**. The disulfide **8** generated as a by-product in the alkaline hydrolysis was also converted into **4** by reduction with $LiAlH_4$.

Our method is complementary to the classical Michael addition of benzyl mercaptans, either odorless or odorous, followed by debenzylation using Birch reduction that requires a tedious procedure involving treatment with liquid ammonia.

Table 4 Regeneration Efficiency of a New Odorless Benzyl Mercaptan **4**

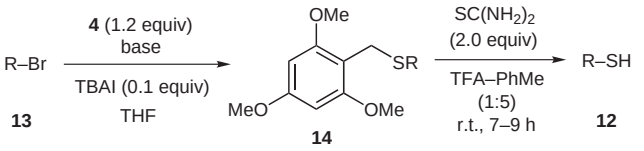


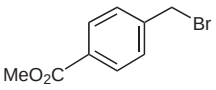
Entry	R	R′	Time (h)	Yield (%) of **6**	Yield (%) of **4** + **8**
1	4-BrC_6H_4	OEt	4	95	72 (1.0:1.0)
2	4-BrC_6H_4	OBn	5	92	70 (2.2:1.0)
3	Ph	OBn	5	94	78 (3.3:1.0)
4	4-MeOC_6H_4	OBn	8	94	77 (1.0:1.8)
5	Ph	Ph	4	96	72 (1.0:1.2)



Scheme 2 Comparison of formal reductive Michael addition of H_2S to **9** in classical and new methods

Table 5 Application of **4** in the Synthesis of Alkanethiols **12**



Entry	RBr	Base (equiv)	Temp. (°C)	Time (h)	Yield (%) (2 steps)
1	$C_{12}H_{25}Br$		60	12	93
2			r.t.	2	90
3	$AcO(CH_2)_{12}Br$		60	3	91

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(2) Hasegawa, J.; Hamada, M.; Miyamoto, T.; Nishide, K.; Kajimoto, T.; Uenishi, J.; Node, M. *Carbohydr. Res.* **2005**, 2360.
(3) Nishide, K.; Miyamoto, T.; Kumar, K.; Ohsugi, S.; Node, M. *Tetrahedron Lett.* **2002**, *43*, 8569.
(4) Cossar, B. C.; Fournier, J. O.; Fields, D. L.; Reynolds, D. D. *J. Org. Chem.* **1962**, *27*, 93.

(5) Each benzyl mercaptan was prepared starting with the reduction of the appropriate methoxybenzaldehyde with sodium borohydride to afford the corresponding benzyl alcohol, which was treated with thiourea under acidic conditions (for 2,6-dimethoxybenzyl alcohol: thiourea, HCl in aqueous acetone, for 3,4,5-trimethoxybenzyl alcohol: $SOCl_2$ in Et_2O and then thiourea in acetonitrile, for 2,4,6-trimethoxybenzyl alcohol: thiourea, *p*-TsOH in acetonitrile). Hydrolysis of the obtained isothiouronium salts with aq NaOH gave **2**–**4** in 51–76% yields.

(6) Lin, C.-E.; Richardson, S. K.; Garvey, D. S. *Tetrahedron Lett.* **2002**, *43*, 4531.

(7) **5c**: colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 7.1 Hz, 3 H), 2.77 (dd, A part of AB, J_{AB} = 15.6 Hz, *J* = 10.0 Hz, 1 H), 2.96 (dd, B part of AB, J_{AB} = 15.6 Hz, *J* = 5.6 Hz, 1 H), 3.63 (s, 2 H), 3.77 (s, 6 H), 3.80 (s, 3 H), 4.00 (q, *J* = 7.1 Hz, 2 H), 4.30 (dd, *J* = 5.6, 10.0 Hz, 1 H), 6.08 (s, 2 H), 7.24 (d, *J* = 8.8 Hz, 2 H), 7.40 (d, *J* = 8.8 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 23.8, 41.7, 45.0, 55.3, 55.7 (2 × C), 60.5, 90.4 (2 × C), 107.4, 120.7, 129.6 (2 × C), 131.1 (2 × C), 140.9, 158.5 (2 × C), 160.2, 170.5. IR ($CHCl_3$): 2941, 2839, 1728, 1609, 1597, 1466, 1437, 1420, 1371 cm^{-1}. MS (20 eV): *m*/*z* = 470 [M^+ + 2], 468 [M^+], 348, 256, 254, 228, 226, 211, 209, 181, 168. HRMS: *m*/*z* [M^+] calcd for $C_{21}H_{25}{}^{79}BrO_5S$: 468.0605; found: 468.0612.

(8) **6a**: colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.2 Hz, 3 H), 2.23 (d, *J* = 6.0 Hz, 1 H), 2.94 (d, *J* = 7.6 Hz, 2 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 4.45 (dt, *J* = 6.0, 7.6 Hz, 1 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 7.46 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 39.0, 44.4, 60.9, 121.3, 128.5 (2 × C), 131.8 (2 × C), 141.8, 170.2. IR ($CHCl_3$): 2985, 1730, 1489, 1406, 1373 cm^{-1}. MS (70 eV): *m*/*z* = 290 [M^+ + 2], 288 [M^+], 257, 255, 215, 213, 203, 201, 187, 185, 132, 104. HRMS: *m*/*z* [M^+] calcd for $C_{11}H_{13}{}^{79}BrO_2S$: 287.9819; found: 287.9826.

(9) **7**: amorphous powder. ^{1}H NMR (200 MHz, DMSO-d_6): δ = 3.79 (s, 3 H), 3.81 (s, 6 H), 4.28 (s, 2 H), 6.29 (s, 2 H), 8.98 (br s, 4 H). ^{13}C NMR (50 MHz, DMSO-d_6): δ = 24.9, 55.7, 56.3 (2 × C), 91.2 (2 × C), 101.1, 158.9 (2 × C), 161.7, 171.1. MS (FAB+): *m*/*z* = 257 [$M^+ - CF_3COO^-$], 181, 154, 136. HRMS: *m*/*z* [$M^+ - CF_3COO^-$] calcd for $C_{11}H_{17}N_2O_3S$: 257.0960; found: 257.0968.

(10) Lynch, J. E.; Eliel, E. L. *J. Am. Chem. Soc.* **1984**, *106*, 29843.

(11) Eliel, E. L.; Lynch, J. E. *Tetrahedron Lett.* **1981**, *22*, 2855.

(12) **Typical Procedure**: 2,4,6-Trimethoxybenzyl mercaptan (**4**, 606 mg, 2.83 mmol) was added to a solution of ethyl *p*-bromocinnamate (601 mg, 2.36 mmol) in THF (5.0 mL) in the presence of TBAF (0.54 mmol), and the mixture was stirred for 4 h at r.t. After the reaction was complete, the reaction mixture was poured into 1 M HCl acid and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc = 4:1) to afford **5c** (1.10 g, 99%).
Next, trifluoroacetic acid (0.2 mL) was added to a suspension of **5c** (274 mg, 0.584 mmol) and thiourea (89 mg, 1.17 mmol) in toluene (1 mL), and the mixture was stirred for 4 h at r.t. After the reaction was finished, the solvents were removed in vacuo and the residue was washed with hexane at 60 °C. A soluble part with hexane was evaporated and purified by silica gel column chromatography (hexane–EtOAc, 4:1) to afford **6a** (160 mg, 95%). Meanwhile, an insoluble part of the residue was treated with 3 M aq NaOH at r.t. for 3 h. After the reaction was complete, the mixture was poured into 1 M HCl acid and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel column chromatography (hexane–EtOAc, 4:1 → 2:1) to afford **4** (36.3 mg, 36%) and the disulfide **8** (36.5 mg, 36%), which could be converted into **4** by reduction with $LiAlH_4$.