Studies on 2-Aziridinecarboxylic Acid. IX.[1] Convenient Synthesis of Optically Active *S*-Alkylcysteine, *threo*-*S*-Alkyl-β-methylcysteine, and Lanthionine Derivatives *via* the Ring-opening Reaction of Aziridine by Several Thiols

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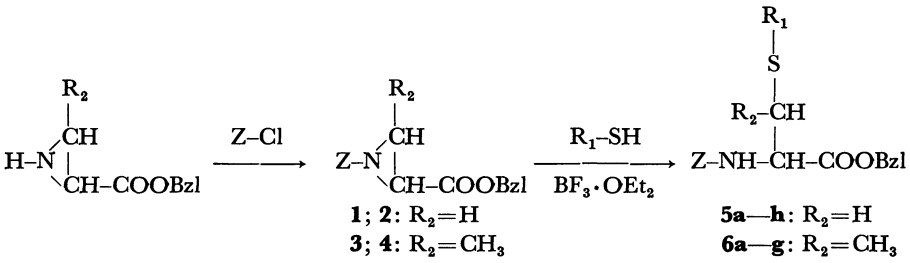
A convenient synthesis of optically active *S*-alkylcysteine, *threo*-*S*-alkyl-β-methylcysteine, and lanthionine derivatives has been investigated. Benzyl 1-benzyloxycarbonyl-(2*S*)-2-aziridinecarboxylate and benzyl (2*S*,3*S*)-1-benzyloxycarbonyl-3-methyl-2-aziridinecarboxylate, and their enantiomers were treated with several thiols, and the corresponding *S*-alkylcysteine, *threo*-*S*-alkyl-β-methylcysteine, and lanthionine derivatives were prepared *via* the ring-opening reaction of aziridine in the presence of a catalytic amount of boron trifluoride etherate in good yields.

Our previous paper[2] reported on the reaction of 1-aminoacyl-2-aziridinecarboxylic acid peptide, namely Z–Gly–L-Azy–Gly–OBzl, with thiophenol, and preparation of the corresponding *S*-phenylcysteine-containing peptide *via* the ring-opening reaction of the aziridine. Bernstein and Ben-Ishai[3] also reported that the 1-substituted 2-aziridinecarboxylate was transformed into the corresponding DL-*S*-methylcysteine derivative *via* a similar ring-opening reaction of the aziridine.

This study reports the synthesis of several optically active *S*-alkylcysteines, *threo*-*S*-alkyl-β-methylcysteines, and lanthionines *via* the ring-opening reaction of (2*S*)-Z–Azy–OBzl (**1**), (2*S*,3*S*)-Z–3-MeAzy–OBzl (**2**), and their enantiomers (**3**, **4**); these were prepared from the corresponding optically active serine and threonine as described in our previous papers.[4] The reactions were carried out with the appropriate thiols. The reaction procedure is shown in Scheme 1.



1; **2**: R_2=H
3; **4**: R_2=CH_3

5a—**h**: R_2=H
6a—**g**: R_2=CH_3

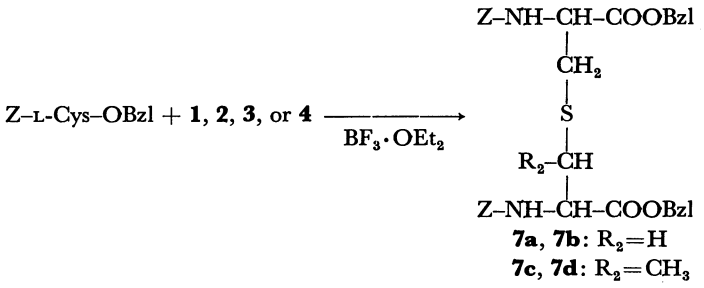
Scheme 1.

TABLE 1. PROPERTIES AND YIELDS OF L-*S*-ALKYLCYSTEINE (**5**) AND L-*threo*-*S*-ALKYL-β-METHYLCYSTEINE (**6**) DERIVATIVES

Product[a]	R_1	Product yield/%	Mp θ_m/°C	$[\alpha]_D^{23}$/°(MeOH)	Reaction time/d
5a	$-CH_3$	86.0	Syrup	−20.7(*c* 1.2)	2
5b	$-CH(CH_3)_2$	81.9	Syrup	−7.0(*c* 0.9)	3
5c	$-CH(CH_3)CH_2CH_3$	74.2	Syrup	−16.2(*c* 1.0)	3
5d	$-C(CH_3)_3$	90.0	Syrup	−14.2(*c* 1.1)	4
5e	$-C_6H_{11}$	80.9	42—44	−16.2(*c* 1.2)	2
5f	$-C_6H_5$	77.8	53—55	−13.6(*c* 1.0)	2
5g	$-CH_2C_6H_5$	72.0	68—70	−45.3(*c* 1.1)	3
5h[b]	$-CH_2C_6H_5$	67.5	65—68	+45.9(*c* 0.9)	3
6a	$-CH_3$	92.3	Syrup	−15.9(*c* 1.1)	2
6b	$-CH(CH_3)_2$	73.4	Syrup	+1.0(*c* 1.0)	3
6c	$-CH(CH_3)CH_2CH_3$	69.5	Syrup	+4.2(*c* 1.0)	3
6d	$-C(CH_3)_3$	53.5	76.5—79.0	−5.8(*c* 1.1)	4
6e	$-C_6H_{11}$	52.5	99—100.5	−1.2(*c* 1.1)	4
6f	$-C_6H_5$	81.7	52—53	+41.3(*c* 1.0)	2
6g	$-CH_2C_6H_5$	68.3	115—118.5	−16.6(*c* 1.0)	5

a) The result of (2*S*)-Z–Azy–OBzl(**1**) and (2*S*, 3*S*)-Z–3-MeAzy–OBzl(**3**) with R_1SH. b) The result of (2*R*)-Z–Azy–OBzl(**2**) with $C_6H_5CH_2SH$.

We carried out the reaction of **1**, **2**, or **3** (1 mmol) with a large excess of thiol in a solution of dichloromethane (3 ml) containing a catalytic amount of boron trifluoride etherate at room temperature. The Azy derivatives were very stable in the thiol solution and the ring-opening reaction did not occur at all, but when boron trifluoride etherate was added, the expected ring-opening reaction easily occurred.



Scheme 2.

Table 2. Properties and yields of lanthionine derivatives (**7a—d**)

Product[a]		Yield/%	Mp θ_m/°C	$[\alpha]_D^{23}$/°(MeOH)
Z-L-Ala-OBzl, S, Z-L-Ala-OBzl	(**7a**)	37	94.5—95.0	−31.5(*c* 1.1)
Z-L-Ala-OBzl, S, Z-D-Ala-OBzl	(**7b**)	21	86—87	—
Z-L-Ala-OBzl, S, Z-L-Aba-OBzl	(**7c**)[b]	22	Syrup	−11.6(*c* 1.0)
Z-L-Ala-OBzl, S, Z-D-Aba-OBzl	(**7d**)[b]	12	104.5—107	−32.0(*c* 1.1)

a) The reaction was carried out in a CH_2Cl_2 solution at 20 °C for 5 d, and Z-L-Cys-OBzl used was 1 equimolar against the Azy derivatives (**1**, **2**, **3**, and **4**). b) Aba: *threo*-2-aminobutylic acid residue.

The reaction results summarized in Table 1 show that this ring-opening reaction of aziridine is very convenient for synthesizing the optically active *S*-substituted cysteine (**5**) and β-methylcysteine (**6**) derivatives. In paticular, the optically active *threo*-β-methylcysteine derivatives (**6**) retained the original configuration of the starting threonine *via* two stereospecific procedures. That is, the aziridine ring-formation and the ring-opening procedures. Thus, the *allo*-threonine derivative is not needed as the starting material to prepare *S*-alkyl-*threo*-β-methylcysteine derivatives (**6**).

We also synthesized lanthionine derivatives from the reaction of **1**, **2**, **3**, and **4** (1 mmol) with benzyl *N*-benzyloxycarbonyl-L-cysteinate (1 mmol) as a thiol component under the same reaction conditions, except for the thiol amount, as shown in Scheme 2. Although the reaction results summarized in Table 2 show that the synthetic yield of each lanthionine derivative was not very good, this procedure is useful for synthesizing optically active lanthionines.

Experimental

Melting points are uncorrected. Optical rotations were determined at the D line on a Perkin-Elmer 141 polarimeter. NMR spectra were obtained with a Hitachi R-20 B high-resolution NMR spectrometer using TMS as the internal reference. The homogeneity of the products was checked by thin-layer chromatography on silica-gel plates.

*Benzyl (2S)-1-Benzyloxycarbonyl-2-aziridinecarboxylate (**1**).* To a solution of (2*S*)-H-Azy-OBzl[4] (2.4 g, 13.4 mmol) and Et_3N (1.52 ml, 10.8 mmol) in $CHCl_3$ was added Z-Cl[1] (1.72 ml, 10.8 mmol) at 0 °C with stirring. After being stirred overnight, the solution was washed with 10% citric acid, 1 M $NaHCO_3$, and water, then dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$) and the pure product was isolated as a syrup, 3.2 g (95% from Z-Cl), $[\alpha]_D^{23}$ −19.0° (*c* 1.0, MeOH). NMR ($CDCl_3$) δ: 2.37 (1H q, *J*=1.5, 5.0 Hz), 2.54 (1H q, *J*=1.5, 3.0 Hz), 3.08 (1H q, *J*=3.0, 5.0 Hz), 5.05, 5.07 (4H 2s), 7.26 (10H s).

Found: C, 69.15; H, 5.53; N, 4.42%. Calcd for $C_{18}H_{17}O_4N$: C, 69.44; H, 5.50; N, 4.50%.

*Benzyl (2R)-1-Benzyloxycarbonyl-2-aziridinecarboxylate (**2**).* This compound was prepared by the same procedure from (2*R*)-H-Azy-OBzl[4] and Z-Cl. Compound **2** was obtained as a syrup, $[\alpha]_D^{23}$ +20.0° (*c* 0.9, MeOH). NMR ($CDCl_3$) spectra of **2** was identified with that of **1**.

Found: C, 69.52; H, 5.60; N, 4.39%. Calcd for $C_{18}H_{17}O_4N$: C, 69.44; H, 5.50; N, 4.50%.

*Benzyl (2S, 3S)-1-Benzyloxycarbonyl-3-methyl-2-aziridinecarboxylate (**3**).* To a solution of (2*S*, 3*S*)-H-3-MeAzy-OBzl[4] (4.57 g, 24 mmol) and Et_3N (3.36 ml, 24 mmol) in THF (30 ml) was added Z-Cl (3.84 ml, 24 mmol) at 0 °C with stirring. After being stirred for 4 h, the solution was concentrated *in vacuo*. The residue was dissolved in ethyl acetate and washed with 10% citric acid, 1 M $NaHCO_3$, and water, then dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$). Compound **3** was obtained as a syrup, 7.62 g (98%), $[\alpha]_D^{23}$ −66.2° (*c* 1.0, MeOH). NMR ($CDCl_3$) δ: 1.26 (3H d, *J*=6.0 Hz), 2.75 (1H m), 3.18 (1H d, *J*=6.5 Hz), 5.06, 5.12 (4H 2s), 7.27 (10H s).

Found: C, 69.95; H, 5.92; N, 4.28%. Calcd for $C_{19}H_{19}O_4N$: C, 70.14; H, 5.89; N, 4.31%.

*Benzyl (2R, 3R)-1-Benzyloxycarbonyl-3-methyl-2-aziridinecarboxylate (**4**).* This compound was prepared by the same procedure from (2*R*, 3*R*)-H-3-MeAzy-OBzl[4] and Z-Cl. Compound **4** was obtained as a syrup, $[\alpha]_D^{23}$ +66.4° (*c* 1.2, MeOH). NMR ($CDCl_3$) spectra of **4** was identified with that of **3**.

Found: C, 70.26; H, 5.95; N, 4.21%. Calcd for $C_{19}H_{19}O_4N$: C, 70.14; H, 5.89; N, 4.31%.

*N-Benzyloxycarbonyl-S-methyl-L-cysteine Benzyl Ester (**5a**).* *General Procedure for The Reaction of Azy with Thiol*: To a solution of **1** (200 mg, 0.64 mmol) in $CHCl_3$ (3 ml) was added a solution of MeSH (1 g, excess) in $CHCl_3$ (15 ml) and $BF_3 \cdot OEt_2$ (3 drops). After being left for 2 d at room temperature, the solution was concentrated *in vacuo*. The residue was dis-

solved in ethyl acetate, washed with 1 M $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica-gel column chromatography ($CHCl_3$–hexane, 2 : 1 v/v). Compound **5a** was obtained as a syrup, 199 mg (86%), $[\alpha]_D^{23}$ −20.7° (*c* 1.2, MeOH). NMR ($CDCl_3$) δ: 1.96 (3H s), 2.86 (2H d, J=5.9 Hz), 4.59 (1H m), 5.08, 5.12 (4H 2s), 5.80 (1H bd), 7.28 (10H s).

Found: C, 63.41; H, 5.96; N, 3.99; S, 8.86%. Calcd for. $C_{19}H_{21}O_4NS$: C, 63.49; H, 5.89; N, 3.90; S, 8.92%.

N-Benzyloxycarbonyl-S-benzyl-L-cysteine Benzyl Ester (5g). To a solution of **1** (200 mg, 0.64 mmol) in $CHCl_3$ (3 ml) was added α-toluenethiol (3 ml, excess) and $BF_3 \cdot OEt_2$ (3 drops) at room temperature. After being left for 3 d, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate, washed with 1 M $NaHCO_3$, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography ($CHCl_3$). Compound **5g** was obtained as crystals from $CHCl_3$–hexane, 196 mg (72%), mp 68—70 °C, $[\alpha]_D^{23}$ −45.3° (*c* 1.1, MeOH). [Standard sample prepared from L-Cys(Bzl): mp 68—70 °C, $[\alpha]_D^{23}$ −45.1° (*c* 1.0, MeOH)].

Found: C, 68.76; H, 5.82; N, 3.16; S, 7.42%. Calcd for $C_{25}H_{25}O_4NS$: C, 68.94; H, 5.79; N, 3.22; S, 7.36%.

N,N′-Dibenzyloxycarbonyl-L-lanthionine Dibenzyl Ester (7a). To a solution of **1** (427 mg, 1.37 mmol) in CH_2Cl_2 (5 ml) was added Z-L-Cys-OBzl (473 mg, 1.37 mmol) and $BF_3 \cdot OEt_2$ (3 drops) at room temperature. After 5 d, the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and was worked up as described above. The crude product was purified by silica-gel column chromatography (hexane–ethyl acetate, 3 : 1 v/v). Compound **7a** was obtained as crystals from ethyl acetate–hexane, 335.5 mg (37.3%), mp 94.5—96.0 °C, $[\alpha]_D^{23}$ −31.5° (*c* 1.1, MeOH).

Found: C, 65.46; H, 5.48; N, 4.24; S, 4.99%. Calcd for $C_{36}H_{36}O_8N_2S$: C, 65.84; H, 5.53; N, 4.27; S, 4.88%.

N,N′-Dibenzyloxycarbonyl-meso-lanthionine Dibenzyl Ester (7b). To a solution of **2** (311 mg, 1 mmol) in CH_2Cl_2 (5 ml) was added Z-L-Cys-OBzl (345 mg, 1 mmol) and $BF_3 \cdot OEt_2$ (3 drops) at room temperature. After 5 d, the reaction mixture was worked up as described above. Compound **7b** was obtained as crystals from ethyl acetate–ether–hexane, 149 mg (21%), mp 86—87 °C.

Found: C, 65.33, H, 5.34; N, 4.29; S, 4.90%. Calcd for $C_{36}H_{36}O_8N_2S$: C, 65.84; H, 5.53; H, 4.27; S, 4.88%.

N,N′-Dibenzyloxycarbonyl-threo-β-methyl-L-lanthionine Dibenzyl Ester (7c). To a solution of **3** (325 mg, 1 mmol) in CH_2Cl_2 (5 ml) was added Z-L-Cys-OBzl (345 mg, 1 mmol) and $BF_3 \cdot OEt_2$ (3 drops) at room temperature. After 5 d, the reaction mixture was worked up as described above. Compound **7c** was obtained as a syrup, 145 mg (22%), $[\alpha]_D^{23}$ −11.6° (*c* 1.0, MeOH).

Found: C, 66.32; H, 5.86; N, 4.06; S, 4.74%. Calcd for $C_{37}H_{38}O_8N_2S$: C, 66.25; H, 5.71; N, 4.18; S, 4.78%.

N,N′-Dibenzyloxycarbonyl-threo-β-methyl-meso-lanthionine Dibenzyl Ester (7d). To a solution of **4** (325 mg, 1 mmol) in CH_2Cl_2 (5 ml) was added Z-L-Cys-OBzl (345 mg, 1 mmol) and $BF_3 \cdot OEt_2$ (3 drops) at room temperature. After 5 d, the reaction mixture was worked up as described above. Compound **7c** was obtained as crystals from ethyl acetate–ether–hexane, 81.4 mg (12%), mp 104.5—107.0 °C, $[\alpha]_D^{23}$ −32.0° (*c* 1.1, MeOH).

Found: C, 66.24; H, 5.81; N, 4.04; S, 4.71%. Calcd for $C_{37}H_{38}O_8N_2S$: C, 66.25; H, 5.71; N, 4.18; S, 4.78%.

References

1) Part VIII: K. Nakajima, T. Tanaka, M. Neya, and K. Okawa, *Bull. Chem. Soc. Jpn.*, **55**, 3237 (1982). The abbreviations of the IUPAC-IUB commision (*J. Biol. Chem.*, **247**, 977 (1972)) are used. Z: benzyloxycarbonyl; Bzl: benzyl; Z-Cl: benzyloxycarbonyl chloride; "Azyline" is used as the name of 2-aziridinecarboxylic acid, "Azy" being its abbreviation. 3-MeAzy: 3-methyl-2-aziridinecarboxylic acid.

2) K. Okawa, K. Nakajima, T. Tanaka, and T. Maeda, "Peptide Chemistry 1976," ed by T. Nakajima, Protein Research Foundation, Osaka (1977), p. 13.

3) Z. Bernstein and D. Ben-Ishai, *Tetrahedron*, **33**, 881 (1976).

4) N^{α}-free Azy-OBzl, N^{α}-free 3-MeAzy-OBzl, and their enantiomers were prepared from 1-Trt-Azy-OBzl and 1-Trt-3-MeAzy-OBzl by the treatment of TFA or HCOOH in MeOH as described in our papers: K. Okawa, K. Nakajima, T. Tanaka, and Y. Kawana, *Chem. Lett.*, **1975**, 591; K. Okawa and K. Nakajima, *Biopolymers*, **20**, 1811 (1981). (2*S*)-Azy-OBzl: syrup, $[\alpha]_D^{23}$ −27.7 (*c* 0.97, MeOH), +11.8 (*c* 0.99, THF). (2*R*)-Azy-OBzl: syrup, $[\alpha]_D^{23}$ +26.5 (*c* 1.0, MeOH), −10.9 (c 1.0, THF). (2*S*, 3*S*)-3-MeAzy-OBzl: mp 52.5—3.5 °C, $[\alpha]_D^{23}$ −38.6 (*c* 0.9, MeOH), +5.6 (*c* 1.0, THF). (2*R*, 3*R*)-3-MeAzy-OBzl: $[\alpha]_D^{23}$ +40.0 (*c* 1.1, MeOH), −5.6 (*c* 0.96, THF), mp 51—52 °C.