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USEFUL SYNTHESIS OF VARIOUS THIAZOLE AND POLY-THIAZOLYL DERIVATIVES FROM THIOCARBOXAMIDE AND β-BROMOACYL COMPOUND

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Abstract-Useful synthesis and thiazole ring formations of the methyl β-bromo-α-oxoalkanoate and β-bromoacyl group containing-5-methylthiazole-4-carboxylate, which are very promising compounds for the synthesis of various polythiazole derivatives, were accomplished.

Previously,[1] we have reported that the bromination of alkyl α-(*N*-acyl)amino-α-alkenoate with *N*-bromo-succinimide (NBS) gave the corresponding β-bromo-α-alkenoate derivative. Recently, a similar synthesis of methyl α-(*N*-Boc)amino-β-bromo-α-alkenoate (**2**) (Boc=*t*-butoxycarbonyl) from methyl α-(*N*-Boc)amino-α-alkenoate (**1**) and the conversion to methyl β-bromo-α-oxoalkanoate (**3**) by the *N*-deprotection and then hydrolysis of **2** have been also briefly reported.[2] The obtained **3** was found to be a very promising substrate for the synthesis of various 2,5-disubstituted thiazoles. To synthesize the thiazolylthiazole segment of an important building block of the macrocyclic antibiotic, GE 2270 A,[3] thiazolation of **3** (R=Me and CH_2OMe) with L-α-amino acid thioamides (**5**; R^1=$CH_2CONHMe$ and $CHMe_2$) gave two kinds of 2-[1-(*N*-Boc)aminoalkyl]-5-substituted thiazole-4-carboxylates (**6**), which were coupled and further modified to give the expected segment (Figure 1). Furthermore, similar antibiotics, such as micrococcins P, P_1,[4-6] cyclothiazomycin,[7] and so on, are constituted of various thiazole and polythiazole moieties as the important structure.

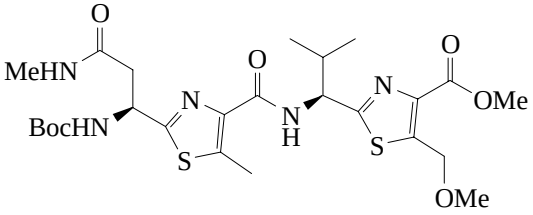
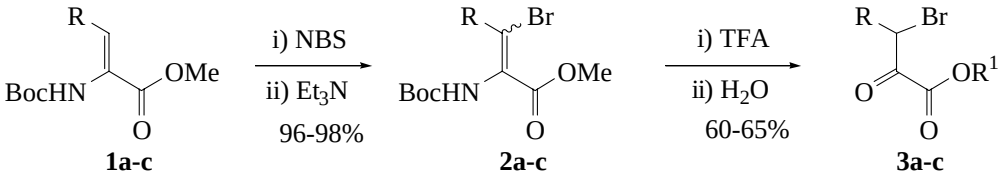


Figure 1

So far, the synthesis of **3** by brominations of ethyl α-oxoalkanoate with Br_2[8,9] and ethyl α-hydroxy-alkanoate with NBS[10,11] has been reported. By these methods, however, the synthesis of **3** possessing a complex functional group is likely to be restricted. To generalize our method, we carried out the bromination of α-dehydroamino acids (**1: a**; R=Me, **b**; R=*i*-Pr, **c**; R=C_6H_5), derived by reaction of the corresponding *N*-carboxy-α-dehydroamino acid anhydrides (ΔNCA) with $(Boc)_2O$ in MeOH,[12] with NBS, which proceeded smoothly to give methyl β-bromo-α-alkenoate (**2**) almost quantitatively. Subsequently, simultaneous *N*-deprotection and hydrolysis of the α-(*N*-Boc)amino group of **2** by using 70% trifluoroacetic acid (TFA) were tried successfully to give various **3** in 64% yield, as shown in Scheme 1. As a result, wide applications to not only **1** but also 2-(α–enamino)alkylthiazole compounds synthesized later were advanced to give various β-bromoacyl compounds, which were further thiazolated with appropriate thiocarboxamides.

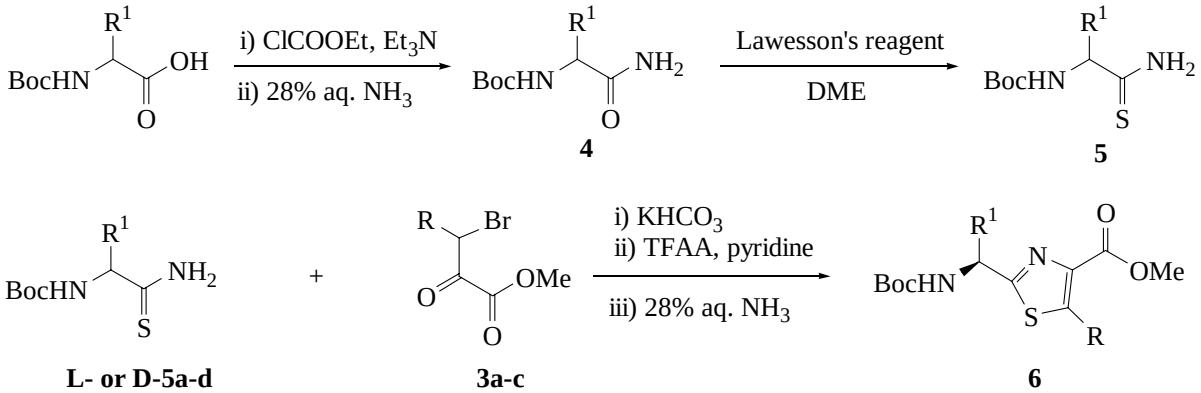


1a-c **2a-c** **3a-c**

a ; R=Me, **b** ; R=*i*-Pr, **c** ; R=Ph

Scheme 1.

On the other hand, L- and D-α-amino acid thioamides (**5**: **a**; R^1=Me, **b**; R^1=*i*-Pr, **c**; R^1=*i*-Bu, **d**; R^1=CH_2Ph)



4 **5**

L- or D-5a-d **3a-c** **6**

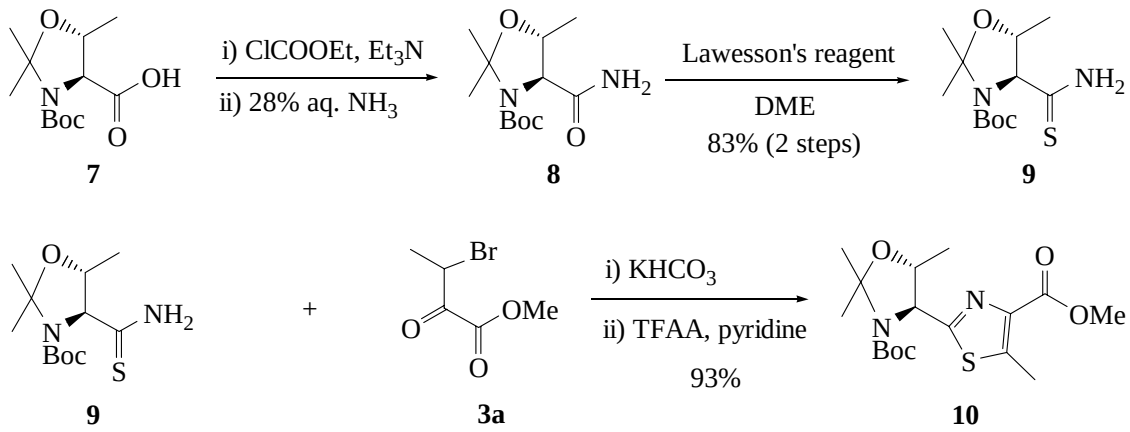
3 : **a** ; R=Me, **b** ; R=*i*-Pr, **c** ; R=Ph

5 : **a** ; R^1=Me, **b** ; R^1=*i*-Pr, **c** ; R^1=*i*-Bu, **d** ; R^1=CH_2Ph

Scheme 2.

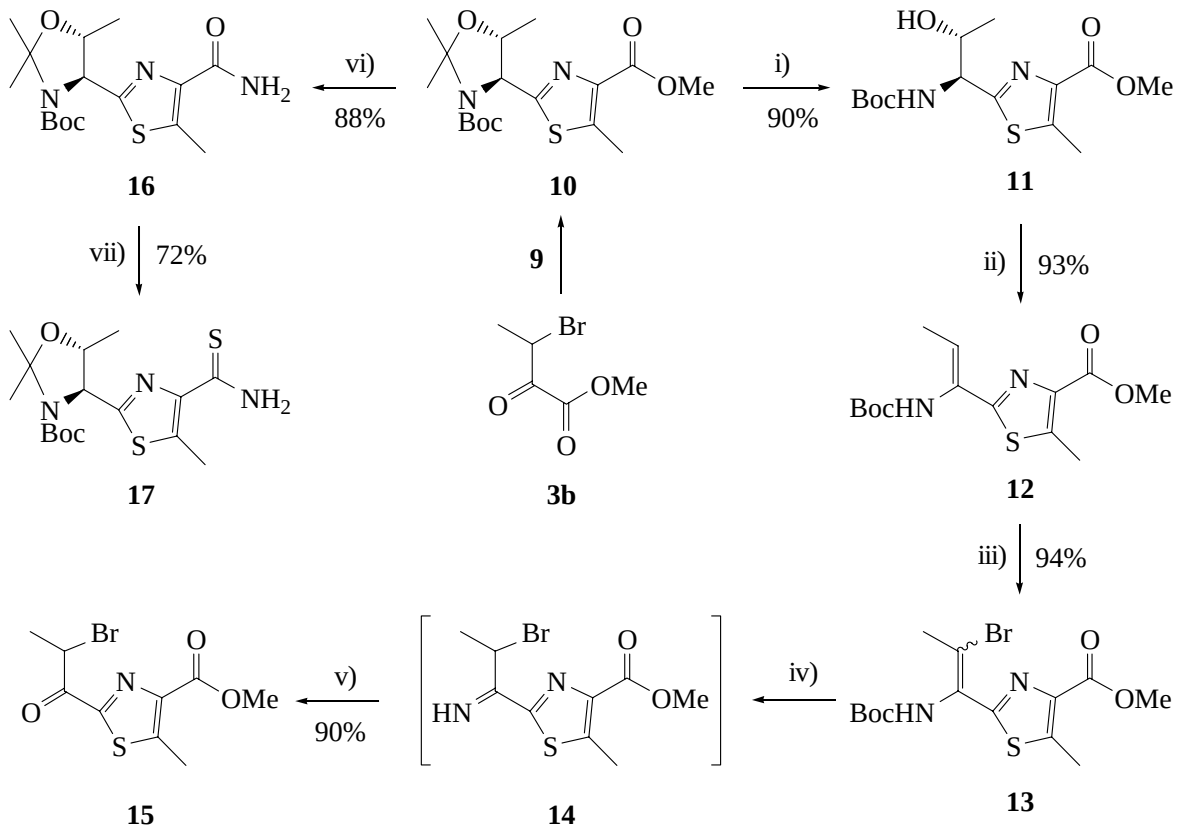
as another substrate were prepared by the method reported previously.[13,14] Subsequent thiazolation of **3a-c** with **5a-d** by using $KHCO_3$ and TFA in pyridine and then 28% aq. NH_3 was carried out to give the expected thiazole derivatives (**6a-l: a;** R=R^1=Me**, b;** R=Me, R^1=*i*-Pr, **c;** R=Me, R^1=*i*-Bu, **d;** R=Me, R^1=CH_2Ph, **e;**

R=*i*-Pr, R^1=Me, **f;** R=R^1=*i*-Pr, **g;** R=*i*-Pr, R^1=*i*-Bu, **h;** R=*i*-Pr, R^1=CH_2Ph, **i;** R=Ph, R^1=Me, **j;** R=Ph, R^1=*i*-Bu, **k;** R=Ph, R^1=*i*-Bu, **l;** R=Ph, R^1=CH_2Ph) by the Hantzsch method,[15] as shown in Scheme 2. Furthermore, similarly to the case of **5**, the *N*-Boc-*N*,*O*-isopropylidene (Isop)-L-Thr-(S)NH_2 (**9**) was also obtained from the protected L-Thr-OH (**7**) *via* the corresponding carboxamide (**8**). Subsequent thiazolation of L-**9** with **3a** by using $KHCO_3$ in 1,2-dimethoxyethane (DME) and then trifluoroacetic anhydride (TFAA) gave methyl (*R*)-2-[3-(*N*-Boc)-2,2,5-trimethyl(oxazolidin-4-yl)]-5-methylthiazole-4-carboxylate (**10**) in 93% yield, as shown in Scheme 3.



Scheme 3.

In the Hantzsch method, both the thioamide and β-bromoacyl functional groups were found to be essential. If two compounds have the two groups respectively, the synthesis of any polythiazole derivative is thought to be possible. To substantiate this idea, the promising starting compound (**10**), which is able to transform to two functional groups, the thioamide and β-bromo-α-oxo groups, was submitted to the polythiazole formation as follows. First, *N*,*O*-deprotection of the Isop group of **10**, derived from **3a** and **9**, by using a mixture of $CHCl_3$ and TFA (96 : 4 v/v), followed by dehydration of the formed secondary alcohol derivative (**11**) with methanesulfonyl chloride (Ms-Cl) in the presence of Et_3N and then 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the corresponding 2-(*N*-Boc)aminoalkenyl derivative (**12**) in a 1 : 1 mixture of *E*- and *Z*-isomers. Furthermore, usual bromination of **12** with NBS gave the corresponding geometric mixture of β-bromoalkenyl derivative (**13**). Treatment of **13** with TFA in $CHCl_3$ was performed to give the expected 2-bromopropanoyl derivative (**15**) *via* the corresponding β-bromoiminoalkyl derivative (**14**) as an unstable intermediate. On the other hand, similarly to the case of **4**, amidation of **10** with ClCOOEt in the presence of Et_3N and then 28% aq. NH_3 by the usual mixed acid anhydride (MA) method gave the corresponding carboxamide derivative (**16**), the amide of which was thioamidated with Lawesson's reagent to give the corresponding 4-thiocarboxamide derivative (**17**), as shown in Scheme 4.

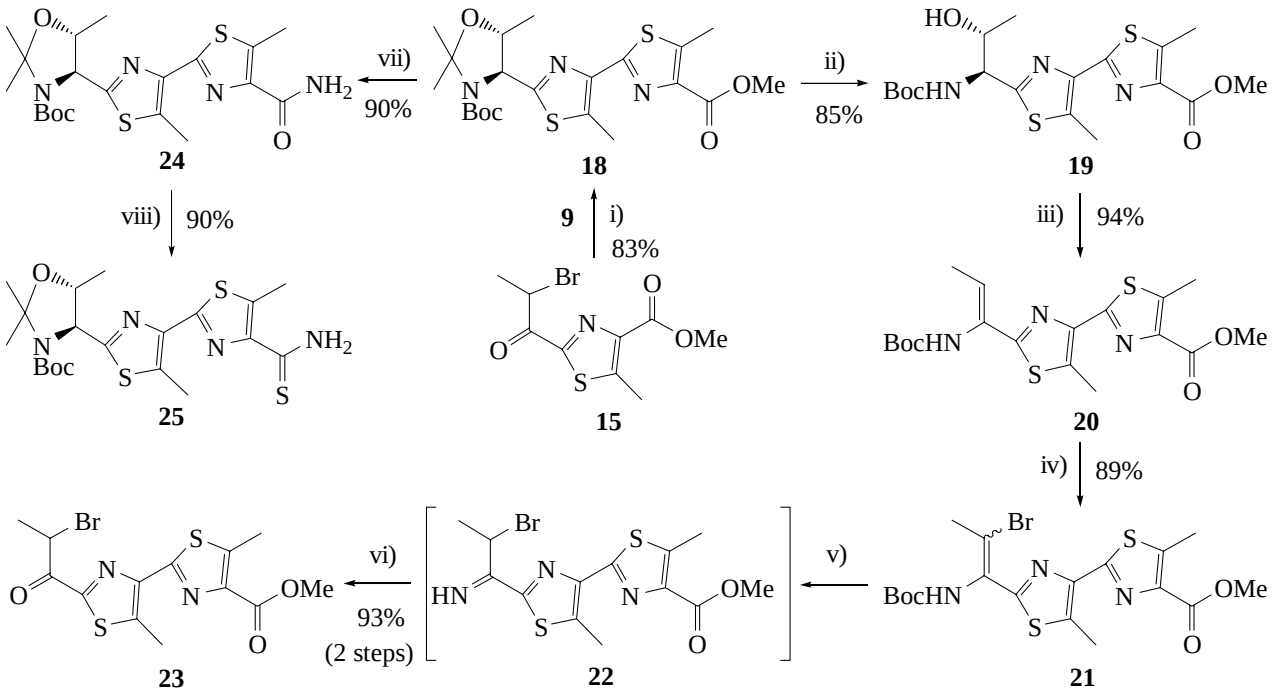


Scheme 4. Reactions and conditions: i) TFA-$CHCl_3$ (4:96 v/v), rt, 2 h, ii) a) MsCl, Et_3N, $CHCl_3$, 0 ^oC, 1 h, b) DBU, $CHCl_3$, rt, 6 h, iii) a) NBS, $CHCl_3$, rt, 30 min, b) Et_3N, $CHCl_3$, rt, 2 h, iv), v) TFA, $CHCl_3$, H_2O, rt, 2 h, vi) a) 1 M LiOH, H_2O-dioxane (1:1 v/v), 0 ^oC, 30 min, rt, 6 h, b) ClCOOEt, Et_3N, THF, 0 ^oC, 30 min, c), 28% aq. NH_3, THF, 0 ^oC, 10 min, vii) Lawesson's reagent, DME, rt, overnight.

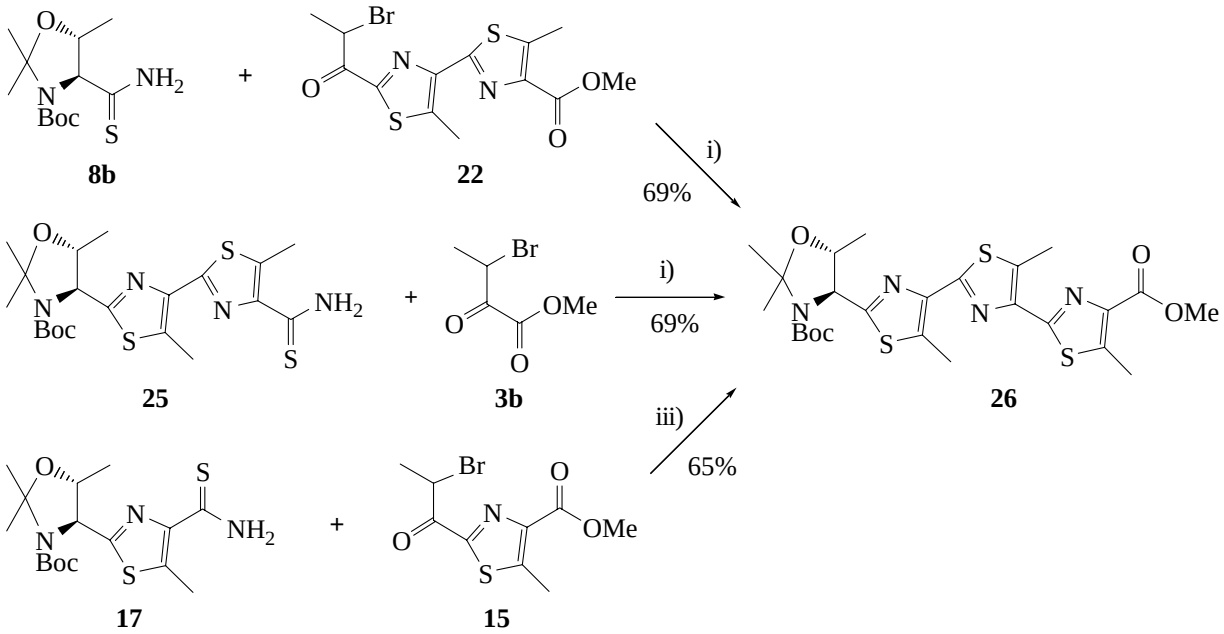
Secondly, to synthesize various 2-substituent bis(5-methyl)thiazole-4-carboxylate derivatives (**18**-**25**), quite similar reactions to the above-mentioned were worked up consecutively in each step. That is, thiazolation of **15** with **9** gave the corresponding *N,O*-diprotected bis(5-methyl)thiazole derivative (**18**), which was further subjected to two directional reactions. Successive transformations of **18** to 2-(1-amino-2-hydroxy)-propyl- (**19**), 2-(1-amino)-1-propenyl- (**20**), 2-(1-amino-2-bromo)-1-propenyl- (**21**), and final 2-(2-bromo-propanoyl)bis(5-methyl)thiazole-4-carboxylate (**23**) *via* the corresponding 2-bromo-1-iminopropyl derivative (**22**) were tried successfully. On the other hand, another bis(5-methyl)thiazolylthiocarboxamide (**25**) was also readily synthesized from **18** *via* the corresponding carboxamide derivative (**24**) by successive ester hydrolysis and by the MA method and then by treatment with Lawesson's reagent, as shown in Scheme 5.

Thirdly, in the case of the synthesis of a tristhiazole derivative (**26**), the desired derivative could be synthesized by the appropriate combination among the compounds obtained above. That is, thiazolations of **9** with **23**, similarly **25** with **3b**, and **17** with **15**, respectively, gave a kind of the corresponding tris(5-methyl)thiazole derivative (**26**), as shown in Scheme 6.

As a result, this synthetic method is applicable to the synthesis of a longer array of thiazole rings, for



Scheme 5. Reactions and conditions: i) a) **9**, $KHCO_3$, DME, 0 ^oC, 30 min, rt, overnight, b) TFAA, pyridine, 0 ^oC, 1 h, ii) TFA-$CHCl_3$ (4:96 v/v), rt, 2 h, iii) a) MsCl, Et_3N, $CHCl_3$, 0 ^oC, 2 h, b) DBU, $CHCl_3$, rt, 6 h, iv) a) NBS, $CHCl_3$, rt, 30 min, b) Et_3N, $CHCl_3$, rt, 3 h, v), vi) TFA, $CHCl_3$, H_2O, rt, 1 h, vii) a) 1 M LiOH, H_2O-dioxane (1:1 v/v), 0 ^oC, 30 min, rt, overnight, b) ClCOOEt, Et_3N, THF, 0 ^oC, 30 min, c), 28% aq. NH_3, THF, 0 ^oC, 10 min, viii) Lawesson's reagent, DME, rt, overnight.



Scheme 6. Reactions and conditions: i) a) $KHCO_3$, DME, 0 ^oC, 30 min, 50 ^oC, overnight, b) TFAA, pyridine, 0 ^oC, 1 h, ii) $KHCO_3$, DME, reflux, overnight.

example, tetrakis-, pentakis-, and so on. In fact, further thiazolation between **23** and **25** was also carried

out to give the expected pentakisthiazole derivative as entirely insoluble crystals in good yield.

The structures of all of the new compounds, thus obtained, were determined spectroscopically (IR and NMR spectrum) and gave satisfactory results in specific rotations and elemental analyses. In particular, in the IR spectra of **3**, the disappearance of the carbon-carbon double bond in the 1650-1660 cm^{-1} of **2** and the appearance of the characteristic strong absorption band in the 1740-1745 cm^{-1} region as a shoulder due to the oxo cabonyl group showed clearly the formation of **3**. Furthermore, in the ^{1}H NMR spectra, the signals of the β-protons of **3** appeared in the δ=4.85-5.16 ppm as a quartet, doublet, and singlet of one proton respectively. On the other hand, in the ^{13}C NMR spectra, the typical ^{13}C signals of **3** appeared in the δ=60.44-161.12, 183.60-185.71 ppm, and 42.24-56.49 ppm as the C_1, C_2, and C_3 carbons, respectively. On the other hand, in the case of mono-, bis-, and tristhiazole derivatives, in the IR spectra, a strong absorption bands in the 1699-1717 cm^{-1} and 698-1722 cm^{-1} regions of the carbonyl group of the methyl ester, amide, and thioamide, appeared. Furthermore, in the ^{1}H NMR spectra, the signals of the ring methyl and two methyl protons appeared in the δ=2.73-2.96 ppm as one singlet and δ=2.78-3.01 ppm as two singlets. In the case of **26**, the signals of the three ring methyl protons appeared in the δ=2.81, 2.87, and 2.93 ppm as three singlets. Furthermore, since it is often said that the 2-(1-amino)alkyl moiety attached to the thiazole ring may racemize, it was also studied to determine whether the racemization takes place or not during the synthesis and reaction of various kinds of (*S*)- and (*R*)-**6**. The compound (**6**) thus obtained was purified on reversed-phase high-pressure liquid chromatography (HPLC) chiral column using a mixture of hexane and isopropyl alcohol (9 : 1 v/v) as the eluent. As a result, it was found the racemization did not occur at all. In particular, it was found that the (*S*)- and (*R*)-enantiomeric excess (ee %) of **6** attained almost 100%.

In conclusion, it is worth noting that the α-*N*-acyl-α-enamino compounds involving α-dehydroamino acids were readily converted by treatment with NBS and by simultaneous *N*-deprotection and hydrolysis to the corresponding β-bromo-α-oxo compounds, which are useful to synthesize various thiazole derivatives.

EXPERIMENTAL

The melting points were measured using a Yamato (Model Mp-21) micromelting point apparatus, and are uncorrected. The IR spectra were recorded using a Hitachi EPI-G2 spectrophotometer in KBr. The ^{1}H NMR and ^{13}C NMR spectra were measured with JEOL EX 90, FX 200, and JNE 500 spectrometer in $CDCl_3$, DMSO-d_6, or CD_3OD solution with tetramethylsilane used as the internal standard. Specific rotations were measured in 0.5 dm tube using a JASCO DIP-4 polarimeter in MeOH or H_2O. HPLC analysis was done on the following column using a mixture of hexane and isopropyl alcohol (9 : 1 v/v) with a flow rate of 2.5 ml min^{-1} by detecting UV (254 nm) absorption: System: JASCO HSS-90. Column: CHIRALCEL OD (4.6ϕ x 25 cm).

Starting Materials. Methyl 3-Bromo-2-alkenoate (2a-2c). The compound (**2**) was prepared by the method reported earlier.[1]

Methyl 3-Bromo-2-oxoalkanoate (3a-3c). General Procedure: A solution of **2a-c** (3.4 mmol) and TFA (20 mL, 260 mmol) in $CHCl_3$ (20 mL) was stirred at rt for 30 min. The reaction mixture was added to water (20 mL) and the resulting solution was neutralized with 9% aqueous $NaHCO_3$ solution (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure below 30 ^oC. The residual syrup was distilled *in vacuo* to give **3a-c** as a colorless or yellowish oil.

Methyl 3-Bromo-2-oxobutanoate (3a). Yield 62%. bp 38-39 ^oC/4 mmHg. IR :2956, 1751, 1731 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.82 (d, 3H, CHC*H*$_3$, *J*=6.8 Hz), 3.94 (s, 3H, OCH_3), 5.16 (q, 1H, C*H*CH_3, *J*=6.8 Hz). ^{13}C NMR: δ 18.42, 42.24, 53.34, 160.97, 185.71. *Anal*. Calcd for $C_5H_7O_3Br$: C, 30.79; H, 3.62. Found: C, 30.66; H, 3.92.

Methyl 3-Bromo-4-methyl-2-oxopentanoate (3b). Yield 64%. bp 50-51 ^oC/5 mmHg. IR: 2968, 1758, 1737 cm^{-1}. ^1H NMR: δ 1.05 and 1.14 (each d, 3H x 2, CH(C*H*$_3$)$_2$, *J*=6.5 Hz), 2.28-2.44 (m, 1H, C*H*$(CH_3)_2$), 3.92 (s, 3H, OCH_3), 4.85 (d, 1H, C*H*$CH(CH_3)_2$, *J*=8.0 Hz). ^{13}C NMR: δ 20.10, 20.21, 29.83, 53.31, 56.49, 161.12, 185.48. *Anal*. Calcd for $C_7H_{11}O_3Br$: C, 37.69, H, 4.97. Found: C, 37.48, H, 5.14.

Methyl 3-Bromo-2-oxo-3-phenylpropanoate (3c). Yield 65%. bp 109-110 ^oC/4 mmHg. IR: 2923, 1735 cm^{-1}. ^1H NMR: δ 3.88 (s, 3H, OCH_3), 6.21 (s, 1H, CH), 7.36-7.47 (m, 5H, Ph). ^{13}C NMR: δ 49.54, 53.51, 129.02, 129.61, 129.69, 132.98, 160.44, 183.60. *Anal.* Calcd for $C_{10}H_9O_3Br$: C, 46.72; H, 3.53. Found: C, 47.07; H, 3.78.

***N*-Boc-α–Amino Acid Thioamides (5a-5d).** The thioamides (**5**) were prepared by the method reported by Okumura *et al.*,[13] and Brain *et al*.[12]

Methyl 2-[(*S*)- and (*R*)-1-(*N*-Boc)aminoalkyl]-5-methylthiazole-4-carboxylates (6a-l). General Procedure: To a solution of thioamide (**5**: 0.86 mmol) and $KHCO_3$ (690 mg, 6.88 mmol) in DME (20 mL) under cooling was added, with stirring, **3a-c** (2.58 mmol). After stirring 30 min and then overnight at rt, the reaction solution was concentrated *in vacuo*. Th residual brown syrup was dissolved in $CHCl_3$ (20 mL), washed with water (10 mL x 2) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a brown syrup, which was dissolved again in DME (20 mL) and then stirred with TFAA (361 mg, 1.72 mmol) and pyridine (300 mg, 3.78 mmol) under cooling for 30 min. Concentration *in vacuo* gave a brown syrup, which was dissolved in EtOAc(20 mL). The solution was washed with brine (10 mL) and, after cooling, was stirred 28% aq. NH_3 (5 mL) for 10 min. The reaction mixture was washed with brine (10 mL x 2) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a brown residual syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give colorless crystals or a colorless syrup.

Methyl 2-[(*S*)- and (*R*)-1-(*N*-Boc)aminoethyl]-5-methylthiazole-4-carboxylate (6a). mp 80.5-81.5 ^oC.

(*S*)-6a: Yield 98%. $[\alpha]_D^{21}$ –29.2° (*c* 0.98, MeOH). 100% ee. **(*R*)-6a:** Yield 97%. $[\alpha]_D^{23}$ +29.4° (*c* 1.00, MeOH). 100% ee. IR: 3357, 2978, 2941, 1710, 1680, 1522 cm^{-1}. ^1H NMR: δ 1.45 (s, 9H, Boc's *t*-Bu), 1.60 (d, 3H, CHC*H*$_3$, *J*=6.9 Hz), 2.75 (s, 3H, Thiazole's CH_3), 3.93 (s, 3H, OCH_3), 4.50-5.06 (m, 1H, NHC*H*), 5.22-5.39 (m, 1H, NH). *Anal.* Calcd for $C_{13}H_{20}N_2O_4S$: C, 51.98; H, 6.71; N, 9.33. Found: C, 52.10; H, 6.36; N, 9.26.

Methyl 2-[(*S*)- and (*R*)-1-(*N*-Boc)amino-(2-methyl)propyl]-5-methylthiazole-4-carboxylate (6b). mp 91-92 °C. **(*S*)-6b:** Yield 95%. $[\alpha]_D^{26}$ –33.8° (*c* 0.72, MeOH). 100% ee. **(*R*)-6b**: Yield 94%. $[\alpha]_D^{25}$ +33.1° (*c* 0.72, MeOH). 100% ee. IR 3343, 2976, 2960, 2937, 2869, 1713, 1684, 1516 cm^{-1}. ^1H NMR: δ 0.90 (d, 6H, CH(C*H*$_3$)$_2$, *J*=6.9 Hz), 1.45 (s, 9H, Boc's *t*-Bu), 2.36-2.43 (m, 1H, C*H*$(CH_3)_2$), 2.73 (s, 3H, Thiazole's CH_3), 3.29 (s, 3H, OCH_3), 4.77-4.82 (m, 1H, C*H*NH), 5.19-5.21 (m, 1H, NH). *Anal*. Calcd for $C_{15}H_{24}N_2O_4S$: C, 54.86; H, 7.37; N, 8.58. Found: C, 54.48; H, 7.10; N, 8.62.

Methyl 2-[(*S*)- and (*R*)-1-(*N*-Boc)amino-(3-methyl)butyl]-5-methylthiazole-4-carboxylate (6c). mp 98.5-99 °C. **(*S*)-6c:** Yield 95%. $[\alpha]_D^{24}$ –36.2° (*c* 0.99, MeOH). 100% ee. **(*R*)-6c**: Yield 95%. $[\alpha]_D^{24}$ +35.2° (*c* 1.00, MeOH). 100% ee. IR 3351, 1953, 2870, 1716, 1689, 1524 cm^{-1}. ^1H NMR: δ 0.96 (d, 6H, CH(C*H*$_3$)$_2$, *J*=6.6 Hz), 1.44 (s, 9H, Boc's *t*-Bu), 1.50-1.94 (m, 3H, CH_2 and C*H*$(CH_3)_2$), 2.73 (s, 3H, Thiazole's CH_3), 3.92 (s, 3H, OCH_3), 4.91-5.05 (m, 2H, N*H*CH and NH). *Anal.* Calcd for $C_{16}H_{26}N_2O_4S$: C, 56.12; H, 7.65; N, 8.l8. Found: C, 56.17; H, 7.99; N, 8.56.

Methyl 2-[(*S*)- and (*R*)-1-(*N*-Boc)amino-2-phenylethyl]-5-methylthiazole-4-carboxylate (6d). mp 140-141 °C. **(*S*)-6d**: Yield 92%. $[\alpha]_D^{24}$ –25.2° (*c* 1.00, $CHCl_3$). 100% ee. **(*R*)-6d**: Yield 94%. $[\alpha]_D^{24}$ +24.6° (c 1.00, $CHCl_3$). 100% ee. IR: 3355, 3062; 3028, 2977, 2931, 1714, 1688, 1521 cm^{-1}. ^1H NMR: δ 1.38 (s, 9H, Boc's *t*-Bu), 2.71 (s, 3H, Thiazole's CH_3), 3.95 (s, 3H, OCH_3), 5.09-5.30 (m, 2H, C*H*NH and NH), 7.10-7.31 (m, 5H, Ph). *Anal.* Calcd for $C_{19}H_{24}N_2O_4S$: C, 60.62; H, 6.43; N, 7.44. Found: C, 60.48; H, 6.13; N, 7.52.

Methyl 2-[(*S*)- and (*R*)-1-(*N*-Boc)amino-2-ethyl]-5-isopropylthiazole-4-carboxylate (6e). mp 107-108 °C. **(*S*)-6e:** Yield 95%. $[\alpha]_D^{24}$ –27.4° (*c* 1.00, MeOH). 98% ee. **(*R*)-6e**: Yield 91%. $[\alpha]_D^{24}$ +26.4° (*c* 1.00, MeOH). 100% ee. IR 3347, 2974, 1717, 1512 cm^{-1}. ^1H NMR: δ 1.32 (d, 6H, CH(C*H*$_3$)$_2$, *J*=6.6 Hz), 1.45 (s, 9H, Boc's *t*-Bu), 1.59 (d, 3H, CHC*H*$_3$, *J*=6.9 Hz), 3.92 (s, 3H, OCH_3), 4.12 (dq, 1H, C*H*$(CH_3)_2$, *J*=6.6, 6.6 Hz), 5.01-5.12 (m, 2H, NHC*H* and NH). *Anal*. Calcd for $C_{15}H_{24}N_2O_4S$: C, 54.86; H, 7.37; N, 8.53. Found: C, 54.85; H, 7.01; N, 8.87.

Methyl 2-[(*S*)- and (*R*)-1-(*N*-Boc)amino-2-(2-methyl)propyl]-5-isopropylthiazole-4-carboxylate (6f). mp 69-70 °C. **(*S*)-6f**: Yield 85%. $[\alpha]_D^{26}$ –35.5° (*c* 1.01, MeOH). 100 % ee. **(*R*)-6f**: Yield 88%. $[\alpha]_D^{25}$ +37.l° (*c* 1.03, MeOH). 100 % ee. IR 3263, 3002, 2966, 2872, 1699, 1537 cm^{-1}. ^1H NMR: δ 0.91 and 0.98 (each d, 6H, CH(C*H*$_3$)$_2$, *J*=6.6 Hz), 1.32 (d, 6H, CH(C*H*$_3$)$_2$, *J*=6.9 Hz), 1.45 (s, 9H, Boc's *t*-Bu), 2.27-2.46 (m, 1H, C*H*$(CH_3)_2$), 3.92 (s, 3H, OCH_3), 4.11 (dq, 1H, C*H*$(CH_3)_2$, *J*=6.9, 6.9 Hz), 4.73-4.95

(m, 1H, C*H*NH), 5.15-5.29 (m, 1H, NH). *Anal.* Calcd for $C_{17}H_{28}N_2O_4S$: C, 57.28; H, 7.92; N, 7.86. Found: C, 57.02; H, 7.75; N, 7.58.

Methyl (*R*)-1-(*N*-Boc)amino-2-(3-methyl)butyl]-5-isopropylthiazole-4-carboxylate (6g). Syrup. **(*S*)-6g**: Yield 95%. $[\alpha]_D^{24}$ –27.6° (*c* 1.00, MeOH). 100% ee. **(*R*)-6g**: Yield 93%. $[\alpha]_D^{24}$ +26.0° (*c* 1.00, MeOH). 98% ee. IR 3345, 2960, 2870, 1717, 1512 cm^{-1}. ^1H NMR: δ 0.97 (d, 6H, $CH_2CH(CH_3)_2$, *J*=5.6 Hz), 1.32 (d, 6H, $CH(CH_3)_2$, *J*=6.9 Hz), 1.44 (s, 9H, Boc's *t*-Bu), 1.60-1.89 (m, 3H, CH_2 and $CH_2CH(CH_3)_2$, 3.92 (s, 3H, OCH_3), 4.11 (dq, 1H, $CH(CH_3)_2$, *J*=6.9, 6.9 Hz), 4.90-5.14 (m, 2H, NHCH and NH). *Anal.* Calcd for $C_{18}H_{30}N_2O_4S$: C, 58.35; H, 8.16; N, 7.56. Found: 57.98; H, 8.08; N, 7.48

Methyl 2-[(*S*)- and (*R*)-1-(*N*-Boc)amino-2-phenylethyl]-5-isopropylthiazole-4-carboxylate (6h). mp127-128 °C. **(*S*)-6h**: Yield 88%. $[\alpha]_D^{23}$ –22.2° (*c* 1.00, $CHCl_3$). 100% ee. **(*R*)-6h**: Yield 92%. $[\alpha]_D^{25}$ +24.2° (*c* 1.00, $CHCl_3$). 100% ee. IR 3326, 3024, 2970, 1719, 1690, 1605, 1514 cm^{-1}. ^1H NMR: δ 1.28 and 1.29 (each d, 6H, $CH(CH_3)_2$, *J*=6.9 Hz), 1.38 (s, 9H, Boc's *t*-Bu), 3.23-3.37 (m, 2H, CH_2), 3.95 (s, 3H, OCH_3), 4.10 (dq, 1H, $CH(CH_3)_2$, *J*=6.9, 6.9 Hz), 5.10-5.29 (m, 2H, C*H*NH and NH), 7.10-7.30 (m, 5H, Ph). *Anal.* Calcd for $C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.66; N, 7.19. Found: C, 62.12; H, 7.07; N, 6.45**.**

Methyl 2-[(*S*)- and (*R*)-1-(*N*-Boc)amino-2-ethyl]-5-phenylthiazole-4-carboxylate (6i). mp 99-100 °C. **(*S*)-6i:** Yield 100%. $[\alpha]_D^{24}$ –45.6° (*c* 1.00, MeOH). 100% ee. **(*R*)-6i:** Yield 100%. $[\alpha]_D^{24}$ +43.4° (*c* 1.00, MeOH). 100% ee. IR 3379, 3340, 3019, 2980, 2938, 1957, 1887, 1723, 1685, 1507 cm^{-1}. ^1H NMR: δ 1.46 (s, 9H, Boc's *t*-Bu), 1.59 (d, 3H, $CHCH_3$, *J*=6.9 Hz), 3.82 (s, 3H, OCH_3), 5.09-5.12 (m, 1H, NHC*H*), 5.13-5.25 (m, 1H, NH), 7.39-7.49 (m, 5H, Ph). *Anal.* Calcd for $C_{18}H_{22}N_2O_4S$: C, 59.65; H, 6.12; N, 7.73. Found: C, 59.50; H, 5.68; N, 8.02.

Methyl 2-[(*S*)- and (*R*)-1-(*N*-Boc)amino-2-(2-methyl)propyl]-5-phenylthiazole-4-carboxylate (6j). mp 112-113 °C. **(*S*)-6j:** Yield 97%. $[\alpha]_D^{24}$ –51.6° (*c* 1.00, MeOH). 100% ee. **(*R*)-6j:** Yield 100%. $[\alpha]_D^{24}$ +50.8° (*c* 1.00, MeOH). 100% ee. IR 3353, 3068, 3007, 2982, 2961, 2871, 2360, 1725, 1685, 1510 cm^{-1}. ^1H NMR: δ 0.95 and 1.03 (each d, 6H, $CH(CH_3)_2$, *J*=6.6 Hz), 1.46 (s, 9H, Boc's *t*-Bu), 2.44-2.50 (m, 1H, $CH(CH_3)_2$), 3.81 (s, 3H, OCH_3), 4.87-4.92 (m, 1H, C*H*NH), 5.24-5.27 (m, 1H, NH), 7.40-7.49 (m, 5H, Ph). *Anal*. Calcd for $C_{20}H_{26}N_2O_4S$: C, 61.51; H, 6.71; N, 7.17. Found: C, 61.29; H, 6.81; N, 7.38.

Methyl 2-[(*S*)- and (*R*)-1-(N-Boc)amino-2-(3-methyl)butyl]-5-phenylthiazole-4-carboxylate (6k). mp 124-125 °C. **(*S*)-6k:** Yield 95%. $[\alpha]_D^{27}$ –56.6° (*c* 1.01, MeOH). 100 ee. **(*R*)-6k:** Yield 100%. $[\alpha]_D^{27}$ +54.6° (*c* 1.00, MeOH). 100% ee. IR 3362, 3062, 3010, 2979, 2951, 2868, 2362, 1725, 1692, 1523 cm^{-1}. ^1H NMR: δ 1.00 (d, 6H, $CH(CH_3)_2$, *J*=6.3 Hz), 1.45 (s, 9H, Boc's *t*-Bu), 1.74-2.00 (m, 3H, CH_2 and $CH(CH_3)_2$), 3.81 (s, 3H, OCH_3), 5.04-5.13 (m, 2H, NHCH and NH), 7.39-7.49 (m, 5H, Ph). *Anal.* Calcd for $C_{21}H_{28}N_2O_4S$: C, 62.35; H, 6.98; N, 6.93. Found: C, 62.04; H, 6.66; N, 7.01.

Methyl 2-[(*S*)- and (*R*)-1-(*N*-Boc)amino-2-phenylethyl]-5-phenylthiazole-4-carboxylate (6l). mp

122-123 °C. **(*S*)-6l:** Yield 100%. $[\alpha]_D^{27}$ –23.0° (*c* 1.01, MeOH). 100% ee. **(*R*)-6l:** Yield 100%. $[\alpha]_D^{27}$ +21.2° (*c* 1.01 MeOH). 100% ee. IR 3327, 3065, 3027, 2976, 2948, 2400, 1723, 1629, 1603, 1522 cm^{-1}. ^1H NMR: δ 1.39 (s, 9H, Boc's *t*-Bu), 3.21-3.41 (m, 2H, CH_2), 3.84 (s, 3H, OCH_3), 5.18-5.27 (m, 2H, C*H*NH and NH), 7.15-7.45 (m, 10H, 2 x Ph). *Anal.* Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.73; H, 5.98; N, 6.39. Found: C, 65.44; H, 5.54; N, 6.46.

***N*-Boc-*N,O*-isopropylidene-threoninethioamide (9).** A solution of **8** (1.0 g, 3.87 mmol) and Lawesson's reagent (0.86 g, 2.12 mmol) in DME (30 mL) was stirred at 40 °C overnight. After the insoluble substance was filtered off, the filtrate was concentrated *in vacuo* to give a yellowish syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give crude crystals. Recrystallization from a hexane-EtOAc gave colorless prisms. Yield 83%. mp 108.5-109.5 °C. $[\alpha]_D^{27}$ +9.17° (*c* 0.96, $CHCl_3$). ^1H NMR: δ 1.45 (s, 9H, Boc's *t*-Bu), 1.47 and 1.49 (each s, 3H x 2, Isop's CH_3 x 2), 1.63 (d, 3H, CHC*H*$_3$, *J*=5.4 Hz), 4.12-4.23 (m, 1H, C*H*CH_3), 4.28 (d, 1H, NC*H*CH, *J*=8.1 Hz), 7.39 (br s, 1H, NH), 7.54 (br s, 1H, NH). *Anal*. Calcd for $C_{12}H_{22}N_2O_3S$: C, 52.53; H, 8.08; N, 10.21. Found: C, 52.55; H, 8.12; N, 10.25.

Methyl (1*S*,2*R*)-2-[*N*-Butoxycarbonyl-2,2,5-trimethyl(oxazolidin-4-yl)]-5-methylthiazole-4-carboxylate (10). A solution of **9** (5.20 g, 18.9 mmol) in DME (100 mL) was stirred with $KHCO_3$ (5.69 g, 56.8 mmol) under cooling for 5 min and with **3a** (9.21 g, 4.72 mmol) for 30 min and then at rt overnight. Concentration *in vacuo* gave a reddish syrup, which was dissolved in $CHCl_3$ (100 mL) and washed with water (100 mL x 2) and then dried over anhydrous Na_2SO_4. The resulting solution was again concentrated *in vacuo* to give a residual syrup, which was dissolved in dimethoxyethane (100 mL). The solution was stirred with TFAA (5.30 mL, 37.8 mmol) and pyridine (6.80 mL, 83.2 mmol) under cooling for 30 min and at rt for 1 h. Concentration *in vacuo* gave a residual syrup, which was dissolved in EtOAc (100 mL) and washed with brine (100 mL x 2) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (3 : 1 v/v) to give **10** as a colorless syrup. Yield 93%. $[\alpha]_D^{23}$ –46.3° (*c* 0.99, MeOH). IR 2979, 2935, 1707 cm^{-1}. ^1H NMR: δ 1.22 (s, 9H, Boc's *t*-Bu), 1.42 (d, 3H, CHC*H*$_3$, *J*=6.1 Hz), 1.67 and 1.68 (each s, 6H, $C(CH_3)_2$), 2.77 (s, 3H, Thiazole's CH_3), 3.93 (s, 3H, $COOCH_3$), 4.11-4.18 (m, 1H, C*H*CH_3), 4.71 (br d, 1H, NCH, *J*=7.3 Hz). *Anal.* Calcd for $C_{17}H_{26}N_2O_5S$: C, 55.12; H, 7.07; N, 7.56. Found: C, 54.91; H, 6.87; N, 7.25.

Methyl 2-[(1*S*,2*R*)-1-(*N*-Buoxycarbonyl-2-hydroxy)]-5-methylthiazole-4-carboxylate (11). A solution of **10** (2.20 g, 6.14 mmol) in a mixture of TFA and $CHCl_3$ (250 mL; 4 : 96 v/v) was stirred at rt for 2 h. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and then mixed with diethyl ether (200 mL). The resulting solution was washed with brine (50 mL x 2) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a pale yellow syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give **11** as a colorless syrup. Yield 90%. $[\alpha]_D^{23}$ –34.3° (*c*

0.99, MeOH). IR 3436, 2978, 2933, 1717, 1516, 1498 cm^{-1}. ^1H NMR: δ 1.30 (d, 3H, CHC*H*$_3$, *J*=6.3 Hz), 1.46 (s, 9H, Boc's *t*-Bu), 2.73 (s, 3H, Thiazole's CH_3), 2.96 (br s, 1H, OH), 3.90 (s, 3H, $COOCH_3$), 4.53-4.59 (m, 1H, C*H*CH_3), 4.82 (d, 1H, NHC*H*, *J*=8.3 Hz), 5.68 (br d, 1H, NH, *J*=8.3 Hz). *Anal.* Calcd for $C_{14}H_{22}N_2O_5S$: C, 50.89; H, 6.71; N, 8.48. Found: C, 50.50; H, 6.55; N, 7.99.

Methyl 2-[(*Z*)-1-(*N*-Boc)amino-1-propenyl]-5-methylthiazole-4-carboxylate (12): To a solution of **11** (1.33 g, 4.04 mmol) in $CHCl_3$ (50 mL) were added, with stirring, Et_3N (2.56 mL, 18.4 mmol) and Ms-Cl (0.70 mL, 8.89 mmol) under cooling for 30 min and then at rt for 1 h. The resulting solution was stirred with DBU (0.92 g, 6.05 mmol) under cooling for 30 min and then at rt for 6 h. The reaction mixture was mixed with ether (50 mL), and washed with 10% citric acid (50 mL x 2), brine (50 mL x 3), and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a brown syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (3 : 2 v/v) to give crude crystals. Recrystallization from hexane-EtOAc gave colorless crystals. Yield 93%. mp 95.5-97.0 ^oC. IR 3317, 2976, 2948, 1712, 1696, 1654, 1514, 1495, 1436 cm^{-1}. ^1H NMR: δ 1.47 (s, 9H, Boc's *t*-Bu), 1.83 (d, 3H, CHC*H*$_3$, *J*=7.2 Hz), 2.74 (s, 3H, Thiazole's CH_3), 3.92 (s, 3H, $COOCH_3$), 6.16 (br s, 1H, NH), 6.37 (q, 1H, C=C*H*CH_3, *J*=7.2 Hz). *Anal*. Calcd for $C_{14}H_{20}N_2O_4S$: C, 53.83; H, 6.45; N, 8.97. Found: C, 53.68; H, 6.23; N, 9.10.

Methyl 2-[(*E*,*Z*)-1-(*N*-Boc)Amino-2-bromo-1-propenyl]-5-methylthiazole-4-carboxylate (13): A solution of **12** (1.29 g, 4.13 mmol) and NBS (0.82 g, 4.33 mmol) in $CHCl_3$ (50 mL) was stirred at rt for 30 min. To the resulting solution was added Et_3N (2.4 mL, 16.52 mmol) and then the mixture was stirred at rt for 2 h. The reaction solution was mixed with ether (50 mL) and washed with brine (50 mL x 3) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a brown syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3 : 1 v/v) to give crude crystals. Recrystallization from hexane-EtOAc gave **13** as colorless crystals. Yield 94%. mp 107-109.5 ^oC. IR 3207, 2985, 2976, 1714, 1627, 1504, 1487, 1430 cm^{-1}. ^1H NMR: δ 1.39 and 1.46 (s x 2, 9H x 2, Boc's *t*-Bu x 2), 2.54 and 2.67 (s x 2, 6H, CBr-C*H*$_3$ x 2), 2.76 and 2.78 (s x 2, 6H, Thiazole's CH_3 x 2), 3.91 and 3.92 (s x 2, 6H, $COOCH_3$ x 2), 6.26 and 6.57 (br s x 2, 2H, NH x 2). *Anal*. Calcd for $(C_{14}H_{19}N_2O_4BrS)x2$: C, 42.97; H, 4.89; N, 7.16. Found: C, 42.48; H, 4.57; N, 7.27.

Methyl 2-(2-Bromopropanoyl)-5-methylthiazole-4-carboxylate (15): A solution of **13** (1.63 g, 4.17 mmol) and TFA (25 mL) in $CHCl_3$ (50 mL) was stirred at rt for 2 h. The reaction reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution (25 mL) . The resulting solution was mixed with ether (50 mL) and washed with brine (50 mL x 3). Concentration *in vacuo* gave a brown syrup, which was purified on a silica gel column using a mixture of hexane and EtOAc (3 : 1 v/v) to give crude crystals. Recrystallization from hexane-EtOAc gave **15** as colorless crystals. Yield 90%. mp 67-68.5 ^oC. IR 2958, 1710, 1687, 1492, 1460, 1445, 1423 cm^{-1}. ^1H NMR: δ 1.90 (d, 3H, CHC*H*$_3$, *J*=6.8 Hz), 2.87 (s, 3H, Thiazole's CH_3), 3.97 (s, 3H, $COOCH_3$), 5.75 (q, 1H, C*H*CH_3, *J*=6.8 Hz). ^{13}C NMR: δ 14.1, 19.7, 40.9,

52.4, 143.1, 152.8, 159.2, 162.3, 187.1. *Anal*. Calcd for $C_9H_{10}NO_3BrS$: C, 37.0; H, 3.45; N, 4.79. Found: C, 37.04; H, 3.27; N, 5.20.

2-(*N*-Butoxycarbonyl-2,2,5-trimethyloxazolidinyl)-5-methylthiazole-4-carboxamide (16) A solution of **10** (2.54 g, 6.86 mmol) in a mixture of H_2O and dioxane (100 mL, 1 : 1 v/v) was stirred with 1 M LiOH (10.3 mL, 10.3 mmol) under cooling for 30 min. After stirring at rt for 6 h, the resulting solution was washed with diethyl ether (100 mL x 2) , acidified with citric acid hydrate and then extracted with EtOAc (100 mL x 2). The combined extracts were washed with brine (100 mL x 3) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a crude syrup, which was dissolved in THF (200 mL). The resulting solution was stirred with Et_3N (1.05 mL, 7.55 mmol) and ClCOOEt (0.75 mL, 7.87 mmol) below 0 ^oC for 40 min. The reaction mixture was stirred with 28% aqueous NH_3 (30 mL) for 35 min under cooling and then mixed with saturated aqueous NH_4Cl solution (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a crude syrup, which was purified on silica gel column using a mixture of hexane and EtOAc (1 : 1 v/v) to give crude crystals. Recrystallization from hexane-EtOAc gave **16** as colorless crystals. Yield 88%. mp 116.5-117.5 ^oC. $[\alpha]_D^{23}$ –62.8^o (*c* 1.00, MeOH). IR 3472, 3412, 2979, 2933, 2874, 1708, 1678, 1587 cm^{-1}. ^1H NMR: δ 1.15 (s, 9H, Boc's *t*-Bu), 1.32 (d, 3H, CHC*H*$_3$, *J*=6.1 Hz), 1.61 (s, 6H, C(CH_3)$_2$), 2.74 (s, 3H, Thiazole's CH_3), 4.03-4.13 (m, 1H, C*H*CH_3), 4.41-4.55 (m, 1H, NCH), 4.47 (br s, 1H, NH), 7.16 (br s, 1H, NH). *Anal*. Calcd for $C_{16}H_{25}N_3O_4S$: C, 54.06; H, 7.09; N, 11.82. Found: C, 53.60; H, 6.97; N, 11.67.

2-(*N*-Butoxycarbonyl-2,2,5-trimethyloxazolidinyl)-5-methylthiazole-4-thiocarboxamide (17). A solution of **16** (2.24 g, 6.02 mmol) and the Lawesson's reagent (1.47 g, 3.63 mmol) in diethoxyethane (50 mL) was stirred at rt for 12 h. After filtering the residual Lawesson's reagent, the filtrate was concentrated *in vacuo* to give a crude residue, which was purified on a silica gel column using a mixture of hexane and EtOAc (3 : 1 v/v) to give yellow crystals. Recrystallization from hexane-EtOAc gave **17** as pale yellow crystals. Yield 72%. mp 126.0-127.5 ^oC. $[\alpha]_D^{24}$ –70.5^o (*c* 1.03, MeOH). IR 3345, 3260, 3168, 2977, 2929, 1699, 1617, 1514 cm^{-1}. ^1H NMR: δ 1.22 (s, 9H, Boc's *t*-Bu), 1.35 (d, 3H, CHC*H*$_3$, *J*=6.1 Hz), 1.66 and 1.68 (each s, 6H, C(CH_3)$_2$), 2.96 (s, 3H, Thiazole's CH_3), 4.01-4.22 (m, 1H, C*H*CH_3), 4.50-4.68 (m, 1H, NCH), 7.50 (br s, 1H, NH), 8.77 (br s, 1H, NH). *Anal*. Calcd for $C_{16}H_{25}N_3O_3S_2$: C, 51.73; H, 6.78; N, 11.31. Found: C, 51.72; H, 6.72; N, 11.64.

Methyl 2-{2-[(4S,5R)-3-Butoxycarbonyl-2,2,5-trimethyl(oxazolidin-4-yl)]-5-methyl(thiazol-4-yl)}-5-methylthiazole-4-carboxylate (18). Similarly to the case of **10**, thiazolation of **9** (1.80 g, 6.56 mmol) with **15** (2.35 g, 16.4 mmol) in DME (50 mL) and then treatment with TFAA (1.85 mL, 13.1 mmol) and pyridine (2.32 mL, 28.9 mmol) was worked up to give **18** as a colorless syrup. Yield 83%. $[\alpha]_D^{24}$ –38.4^o (*c* 1.01, MeOH). IR 2979, 2932, 1707 cm^{-1}. ^1H NMR: δ 1.20 (s, 9H, Boc's *t*-Bu), 1.42 (d, 3H, CHC*H*$_3$, *J*=6.1 Hz), 1.69 (s, 6H, C(CH_3)$_2$), 2.78 (s, 3H, Thiazole's CH_3), 2.89 (s, 3H, Thiazole's CH_3), 3.94 (s, 3H,

$COOCH_3$), 4.17-4.21 (m, 1H, C*H*CH_3), 4.50-4.65 (m, 1H, NC*H*CH). *Anal*. Calcd for $C_{21}H_{29}N_3O_5S_2$: C, 53.94; H, 6.25; N, 8.99. Found: C, 53.50; H, 6.27; N, 8.87.

Methyl 2-{2-[(4*S*,5*R*)-1-(Butoxycarbonyl)amino-2-hydroxy]propyl-5-methyl(thiazol-4-yl)}-5-methyl-thiazole-4-carboxylate (19). Similarly to the case of **11**, deprotection of **18** (0.54 g, 1.15 mmol) with a mixture of TFA and $CHCl_3$ (100 mL, 4 : 96 v/v) was worked up to give **19** as colorless crystals. Yield 85%. mp 143.5-144.5 ^oC. $[\alpha]_D^{23}$ –35.2^o (*c* 1.01, MeOH). IR 3346, 2973, 2932, 1722, 1685, 1519, 1444, 1435 cm^{-1}. ^1H NMR: δ 1.31 (d, 3H, CHC*H*$_3$, *J*=6.3 Hz), 1.48 (s, 9H, Boc's *t*-Bu), 2.79 (s, 3H, Thiazole's CH_3), 2.86 (s, 3H, Thiazole's CH_3), 3.40 (br s, 1H, OH), 3.94 (s, 3H, $COOCH_3$), 4.52-4.63 (m, 1H, C*H*CH_3), 4.81 (d, 1H, NHC*H*, *J*=9.3 Hz), 5.54 (d, 1H, NH, *J*=9.3 Hz). *Anal.* Calcd for $C_{18}H_{25}N_3O_5S_2$: C, 5057; H, 5.83; N, 9.83. Found: C, 50.50; H, 5.69; N, 9.87.

Methyl 2-{2-[(*Z*)-1-(Butoxycarbonyl)amino-1-propenyl]-5-methyl(thiazol-4-yl)}-5-methylthiazole-4-carboxylate (20). Similarly to the case of **12**, elimination of **19** (1.31 g, 3.06 mmol) with Et_3N (1.90 mL, 13.5 mmol) and MsCl (0.53 mL, 6.73 mmol) for 2 h at rt was worked up to give **20** as colorless crystals. Yield 94%. mp 158-159 ^oC. IR 3313, 2978, 2952, 2925, 2853, 1711, 1693, 1494 cm^{-1}. ^1H NMR: δ 1.48 (s, 9H, Boc's *t*-Bu), 1.86 (d, 3H, CHC*H*$_3$, *J*=7.2 Hz), 2.79 (s, 3H, Thiazole's CH_3), 2.87 (s, 3H, Thiazole's CH_3), 3.94 (s, 3H, $COOCH_3$), 6.13 (br s, 1H, NH), 6.34 (q, 1H, =C*H*CH_3, *J*=7.2 Hz). *Anal.* Calcd for $C_{18}H_{23}N_3O_4S_2$: C, 52.79; H, 5.66; N, 10.26. Found: C, 53.06; H, 5.68; N, 9.80.

Methyl 2-{2-[(*E*,*Z*)-1-(Butoxycarbonyl)amino-2-bromo-1-propenyl]-5-methyl(thiazol-4-yl)}-5-methyl-thiazole-4-carboxylate (21). Similarly to the case of **13**, bromonation of **20** (0.39 g, 0.96 mmol) with NBS (0.19 g, 0.99 mmol) in $CHCl_3$ (30 mL) in the presence of Et_3N (0.5 mL, 3.8 mmol) was worked up to give **21** as colorless crystals. Yield 89%. mp 123-126 ^oC. IR 3296, 2975, 2950, 1704, 1622, 1490, 1434 cm^{-1}. ^1H NMR: δ 1.42 and 1.48 (each s, 9H x 2, Boc's *t*-Bu x 2), 2.79 (each s, 3H x 2, Thiazole's CH_3 x 2), 2.80 and 2.82 (each s, 3H x 2, $CBrCH_3$ x 2), 2.90 (each s, 3H x 2, Thiazole's CH_3 x 2), 3.94 (s, 3H x 2, $COOCH_3$ x 2), 6.20 (each br s, 1H x 2, NH x 2). *Anal*. Calcd for $(C_{18}H_{22}N_3O_4S_2Br)$x2: C, 44.26; H, 4.54; N, 8.60. Found: 43.84; H, 4.06; N, 8.44.

Methyl 2-[2-(2-Bromopropionyl)-5-methyl(thiazol-4-yl)]-5-methylthiazole-4-carboxylate (23). Similarly to the case of **15**, deprotection and hydrolysis of **21** (0.26 g, 0.53 mmol) with TFA (10 mL) in $CHCl_3$ (25 mL) was worked up to give **23** as colorless crystals. Yield 93%. mp 166.5-167.5 ^oC. IR 2998, 2984, 2950, 2932, 1716, 1684, 1435, 1422 cm^{-1}. ^1H NMR: δ 1.93 (d, 3H, CHC*H*$_3$, *J*=6.8 Hz), 2.82 (s, 3H, Thiazole's CH_3), 3.01 (s, 3H, Thiazole's CH_3), 3.96 (s, 3H, $COOCH_3$), 5.70 (q, 1H, C*H*CH_3, *J*=6.8 Hz). *Anal.* Calcd for $C_{13}H_{13}N_2O_3S_2Br$: C, 40.11; H, 3.37; N, 7.20. Found: C, 40.10, 2.91; N, 7.34.

2-{2-[2-(*N*-Butoxycarbonyl-2,2,5-trimethyl(oxazolidin-4-yl))-5-methyl(thiazol-4yl)]}-5-methylthiazole-4-carboxamide (24). Similarly to the case of **16**, amidation of **18** (0.83 g, 1.78 mmol) consecutively with 1 M LiOH (2.66 mL, 2.67 mmol), Et_3N (0.27 mL, 1.91 mmol), ClCOOEt (0.18 mL, 1.91 mmol), and 28%

aqueous NH_3 (7 mL) was worked up to give **24** as colorless crystals. Yield 90%. mp 168-169 ^oC. $[\alpha]_D^{25}$ –39.8^o (*c* 1.02, MeOH). IR 3469, 3272, 3221, 2979, 2932, 2901, 2872, 1698, 1684, 1661, 1589 cm^{-1}. ^1H NMR: δ 1.22 (s, 9H, Boc's *t*-Bu), 1.42 (d, 3H, CHC*H*$_3$, *J*=6.1 Hz), 1.70 (s, 6H, C(CH_3)$_2$), 2.82 (s, 3H, Thiazole's CH_3), 2.84 (s, 3H, Thiazole's CH_3), 4.20-4.28 (m, 1H, C*H*CH_3), 5.53-5.62 (m, 1H, NHC*H*), 5.58 (br s, 1H, NH), 7.19 (br s, 1H, NH). *Anal.* Calcd for $C_{20}H_{28}N_4O_4S_2$: C, 53.08; H, 6.24; N, 12.38. Found: C, 52.07; H, 6.08; N, 12.32.

2-{2-[2-(4*S*,5*R*)-(*N*-Butoxycarbonyl-2,2,5-trimethyl(oxazolidin-4-yl))-5-methyl(thiazol-4-yl)]}-5-methyl-thiazole-4-thiocarboxamide (25). Similarly to the case of **17**, thioamidation of **24** (0.58 g, 1.28 mmol) with the Lawesson's reagent (0.16 g, 0.77 mmol) in DME (20 mL) for 16 h was worked up to give **25** as colorless crystals. Yield 90%. mp 110.5-111.5 ^oC . $[\alpha]_D^{26}$ –67.4^o (*c* 0.95, $CHCl_3$). ^1H NMR: δ 1.21 (s, 9H, Boc's *t*-Bu), 1.42 (d, 3H, CHC*H*$_3$, *J*=6.1 Hz), 1.69 (s, 6H, C(CH_3)$_2$), 2.80 (s, 3H, Thiazole's CH_3), 3.00 (s, 3H, Thiazole's CH_3), 4.17-4.25 (m, 1H, C*H*CH_3), 4.57-4.64 (m, 1H, NHC*H*), 7.39 (br s, 1H, NH), 8.71 (br s, 1H, NH). *Anal*. Calcd for $C_{20}H_{28}N_4O_3S_3$: C, 51.26; H, 6.02; N, 11.95. Found: C, 51.30; H, 6.12; N, 12.00.

Methyl 2-(2-{2-[2-(4*S*,5*R*)-(*N*-Butoxycarbonyl-2,2,5-trimethyl(oxazolidin-4-yl)-5-methyl(thiazol-4-yl))-5-methyl(thiazol-4-yl)]-5-methylthiazole}-4-carboxylate (26). A solution of **9** (0.44 g, 1.61 mmol) in DME (20 mL) in the presence of $KHCO_3$ (0.27 g, 2.65 mmol) was stirred for 5 min under cooling. To the resulting solution was added **23** (0.50 g, 1.33 mmol) and the solution was stirred for 30 min at 50 ^oC and then overnight at rt. The resultant solution was concentrated *in vacuo* to give a reddish syrup, which was dissolved in $CHCl_3$ (20 mL) and washed with water (200 mL x 2) and then dried over anhydrous Na_2SO_4. Concentration *in vacuo* gave a reddish syrup, which was again dissolved in DME (50 mL). To the resulting solution were added, with stirring, TFAA (0.38 mL, 2.69 mmol) and pyridine (0.47 mL, 3.84 mmol) under cooling for 30 min. After stirring for 1 h at rt, the reaction mixture was concentrated *in vacuo* to give a reddish syrup, which was diluted with EtOAc (20 mL). The solution was washed with brine (2 x 20 mL) and dried over anhydrous Na_2SO_4 and then concentrated *in vacuo*. The obtained reddished syrup was purified on a silica gel column using a mixture of hexane and EtOAc (3 : 1 v/v) to give **26** as colorless crystals. Yield 69%. mp 115.0-117.5 ^oC. $[\alpha]_D^{27}$ –35.3^o (*c* 0.98, $CHCl_3$). IR 2979, 2930, 1707 cm^{-1}. ^1H NMR: δ 1.23 (s, 9H, Boc's *t*-Bu), 1.42 (d, 3H, CHC*H*$_3$, *J*=6.1 Hz), 1.70 (s, 6H, Isop's CH_3 x 2), 2.81 (s, 3H, thiazole's CH_3), 2.87 (s, 3H, thiazole's CH_3), 2.93 (s, 3H, thiazole's CH_3), 3.95 (s, 3H, $COOCH_3$), 4.16-4.30 (m, 1H, C*H*CH_3), 4.57-4.70 (m, 1H, NC*H*CH). *Anal*. Calcd for $C_{25}H_{32}N_4O_5S_3$: C, 53.17; H, 5.71; N, 9.92. Found: C, 53.13; H, 5.68; N, 9.89.

Similarly, compound (**26**) were further derived from two routes, by reaction of **3a** and **25** in 69% yield and of **15** with **17** in 65% yield.

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