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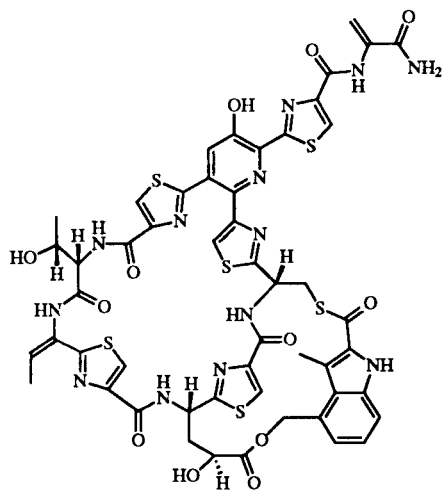
Received July 18, 1994

Revised May 17, 1995

The preparation of three new thiazole derivatives from natural products is described, as well as improvements in the synthesis of ethyl 2-aminomethyl-4-thiazolecarboxylate.

J. Heterocyclic Chem., **32**, 1309 (1995).

Nosiheptide, [1] is a secondary metabolite produced by *Streptomyces actuosus*. This compound is part of the micrococin family of about 20 highly modified cyclic antibiotics containing peptide residues and an elevated number of thiazole rings. Other known examples include thiostrepton and micrococcinic acid [2,3]. While the biosynthetic origin of Nosiheptide has been the object of recent studies [4], to the best of our knowledge, no synthetic activity has been directed toward this interesting antibiotic, currently employed as a growth promoter in chickens and pigs [5].



Nosiheptide

Nosiheptide.

Our synthetic efforts were focused on the construction of the pyridine ring system substituted in positions 2, 5, and 6 by thiazoles, this fragment being a key part in the total synthesis of Nosiheptide. In addition to the functionalized thiazoles around the pyridine ring, the hydroxy group in position 3 presented a challenging molecule, difficult to synthesize by more classical routes of pyridine elaboration. Successful reports of the synthesis of aza-heterocycles by electrocyclization reactions [6], or by [4 + 2] cycloaddition [7,8] led us to consider this approach for this *tetra*-substituted pyridine system.

The retrosynthetic route presented in Scheme 1 illustrates the general idea of pyridine assembly starting from three separate thiazole containing molecules. We would like to report here the synthesis of these thiazoles, precursors in the construction of the 3-hydroxypyridine ring of Nosiheptide.

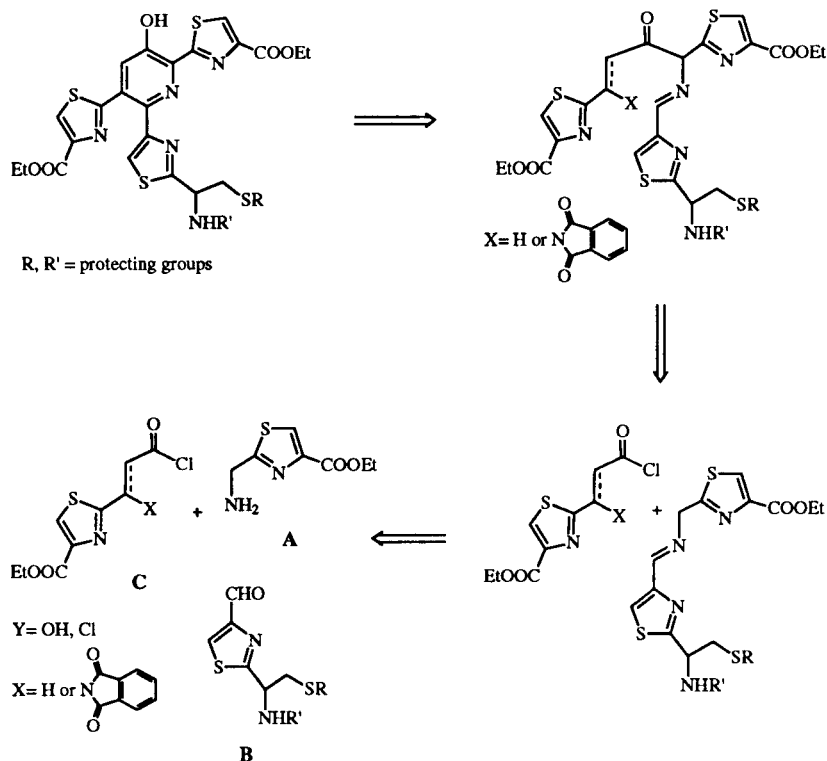
The 2,4-substitution pattern present in all of the thiazoles in Nosiheptide led us to employ a variation of the Hantzsch reaction between a thioamide and ethyl bromopyruvate. Although the synthesis of ethyl 2-aminomethyl 4-thiazolecarboxylate is known [9,10], several modifications and improvements over previously published procedures have been found during this work, and are illustrated here.

Protection of the commercially available glycinamide hydrochloride with a benzyloxycarbonyl proceeded in good yield. Treatment of the amide with Lawesson's reagent [11] provided the thioamide **2** in excellent yield, and avoided the utilization of hydrogen sulfide gas, frequently used to synthesize thioamides from cyanides. The thiazole was then formed by addition of ethyl bromopyruvate to compound **2** in the presence of potassium hydrogen carbonate in tetrahydrofuran. Deprotection of the amine was possible with hydrogen bromide in acetic acid, with isolation of the salt **A'** in 90% yield. This four step reaction sequence allowed an easy access to ethyl 2-aminomethyl-4-thiazolecarboxylate with an overall yield of nearly 70% on a 15-25 g scale [12].

The same synthetic strategy was then directed to fragment **B**, which is unique in that it is linked to the pyridine ring through position 4 instead of position 2. The biosynthetic precursor of this fragment, L-cysteine [4], was used as the starting material for the following sequence of reactions.

Protection of both the thiol group and the amine followed by conversion of the acid to the primary amide gave **5** in 90% overall yield. Treatment of **5** with Lawesson's reagent in tetrahydrofuran afforded **6** in 96% yield, which was then transformed into the thiazole in the presence of ethyl bromopyruvate and potassium hydrogen carbonate. Reduction of the ethyl ester, and Swern oxidation of the corresponding primary alcohol gave fragment **B** in excellent yield.

Scheme 1

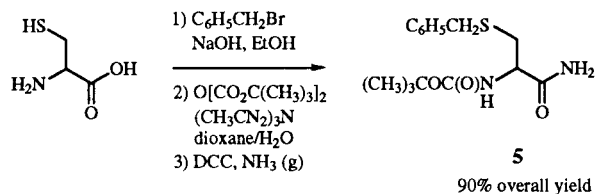


The first starting point for the synthesis of thiazole derivative **C** was aspartic acid. Monoprotection of the gamma ester function gave **9** [13], which was followed by the protection of the primary amine as a *t*-butyl carbamate. Formation of the amide under standard conditions laid the groundwork for thiazole synthesis as illustrated with ethyl 2-aminomethyl 4-thiazolecarboxylate **A** and ethyl *N*-*tert*-butoxycarbonyl-*S*-benzylcysteine-4-thiazolecarboxylate **7**. Unfortunately, treatment of **11** with Lawesson's reagent or phosphorus pentasulfide totally decomposed the starting material (Scheme 4). The failure of this transformation of amide to thioamide in the case of aspartic acid remains unclear, especially since the same

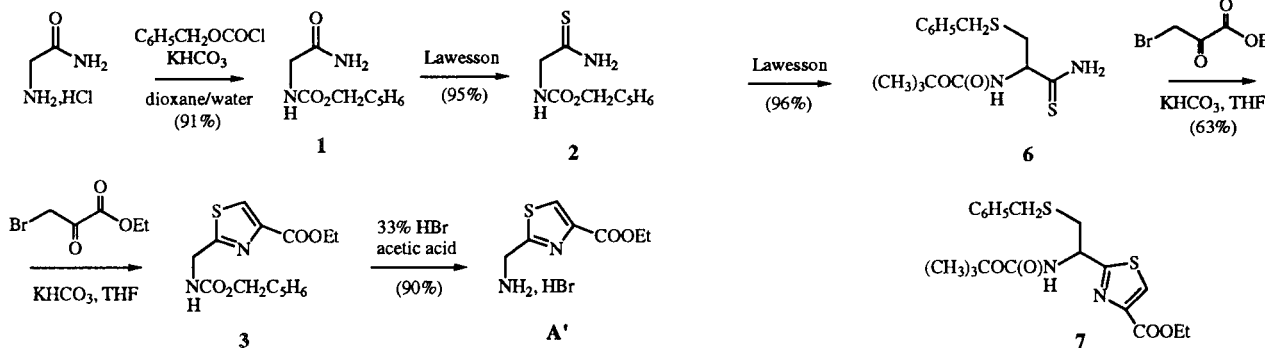
reaction has been successfully applied to glutamic acid in a similar thiazole synthesis [14].

An alternative solution to this problem was found by considering the desired compound as the product of an alkylation reaction between an anion equivalent of ethyl

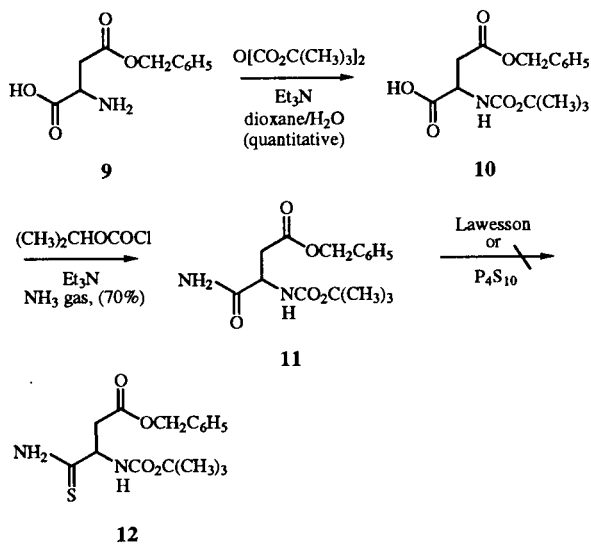
Scheme 3



Scheme 2

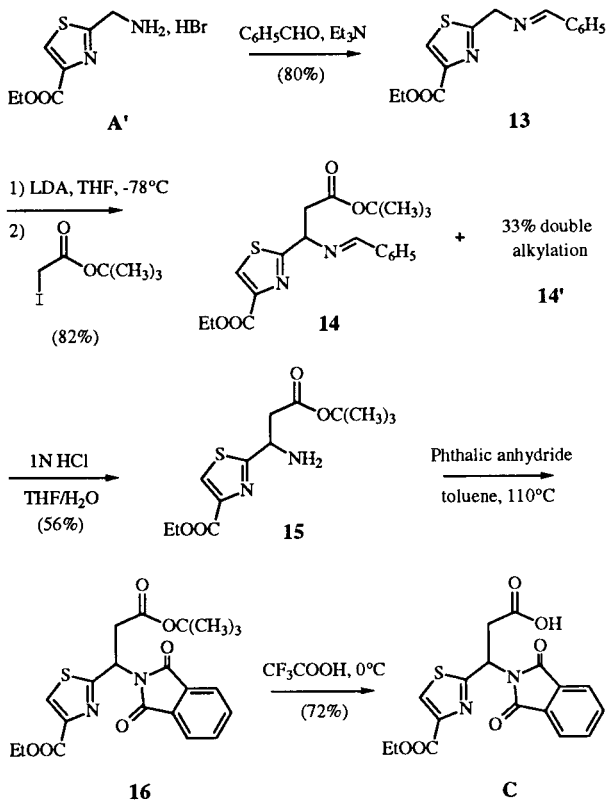


Scheme 4



2-aminomethyl-4-thiazolecarboxylate and a two carbon halide, containing an ester function. Imine chemistry and the use of Schiff bases have allowed deprotonation and alkylation *alpha* to a nitrogen atom [15,16]. Imine formation between the primary amine of ethyl 2-aminomethyl-4-thiazolecarboxylate and benzaldehyde was successful,

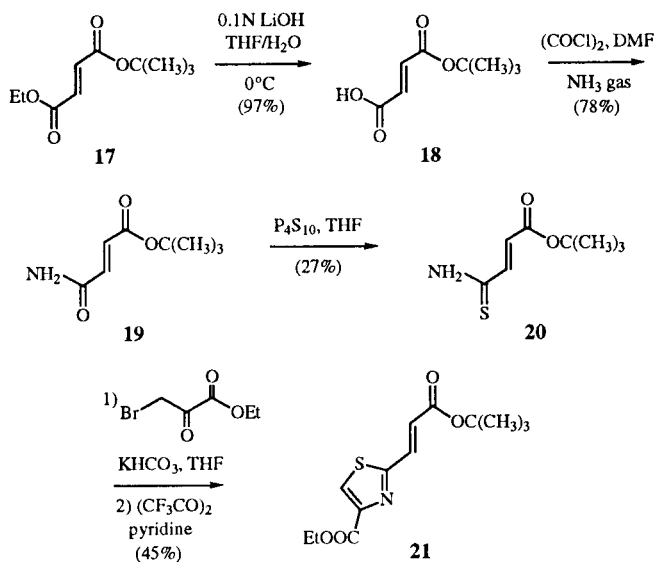
Scheme 5



giving the crystalline product **13** in 80% yield. Alkylation *alpha* to the amine by *t*-butyl bromoacetate in the presence of potassium *tert*-butoxide at -78° gave rise to an inseparable mixture of mono and di-alkylated products. Optimum reaction conditions proved to be the deprotonation of **13** with lithium diisopropylamide in tetrahydrofuran at -78° , followed by slow addition of the iodide, formed from the corresponding bromide *via* a Finkelstein reaction. In spite of careful manipulation, variable mixtures of **14** and **14'** were always isolated. Separation of the two compounds became possible during the deprotection of the amine, the monoalkylated derivative reacting more rapidly than the dialkylated counterpart. The protection of the amine with phthalic anhydride afforded compound **16**, where the acid was then deprotected in the presence of trifluoroacetic acid to give fragment **C** in 72% yield (Scheme 5).

The last thiazole fragment differs from ethyl 2-(1-amino-2-*t*-butoxycarbonylpropyl)-4-thiazolecarboxylate **15** by the lack of an amine function *alpha* to the thiazole and the incorporation of a *trans* double bond in the molecule. These two changes were implemented as an alternative, in case the envisioned electrocyclization reaction forming the pyridine ring encountered difficulties using ethyl 2-[1-(*N*-phthalimido)-2-carboxypropyl]-4-thiazolecarboxylate **C**. Application of the reaction sequence in Scheme 6 to the mono ethyl ester of fumaric acid resulted in the isolation of a new thiazole derivative **21**.

Scheme 6



Esterification of the acid was possible in the presence of DCC and *t*-butyl alcohol, giving the diester **17** in 80% yield [17]. Treatment of **17** with lithium hydroxide at 0° allowed mono saponification of the ethyl ester which was

then transformed into the primary amide in good yield. The passage of the amide to the corresponding thioamide proved once again to be delicate. The utilization of Lawesson's reagent was unsuccessful, but treatment with 0.12 molar equivalent of phosphorus pentasulfide gave 27% of the thioamide **20**. Thiazole formation was completed by addition of ethyl bromopyruvate followed by a mixture of trifluoroacetic anhydride/pyridine, giving thiazole **21**, a direct precursor to fragment C, in 45% yield.

In conclusion, the successful preparation of three new thiazole containing compounds has been performed. Two of the compounds are derived from the natural products cysteine and fumaric acid, and the other is a synthesized equivalent of aspartic acid. Equally described is an improved synthesis of ethyl 2-aminomethyl-4-thiazolecarboxylate as part of a program of total synthesis of Nosiheptide.

EXPERIMENTAL

Melting points were determined using a hot stage microscope, and are uncorrected. The ^1H (300 MHz) and ^{13}C (75 MHz) nmr spectra were recorded on a Bruker AC 300 spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Column chromatography was performed on Merck Geduran SI 60 (0.063-0.200 mm, 70-230 mesh ASTM), and Merck 60 (0.040-0.063 mm, 230-400 mesh ASTM) silica gels. Elemental analyses were performed at the Université de Reims Champagne-Ardenne's microanalysis laboratory.

N-Benzyloxycarbonylglycinamide (**1**).

A two necked round bottom flask was equipped with two dropping funnels. To the first one was added 1.0 g (9 mmoles) of glycine in 10 ml of water, to the second, 1.94 ml (2.31 g, 13.6 mmoles) of benzyl chloroformate in 5 ml of dioxane. These two solutions were slowly added simultaneously to a stirring solution of 2.0 g of potassium hydrogencarbonate in 12 ml of a 2:1 mixture of water and dioxane. After two hours, the dioxane was evaporated under reduced pressure. The reaction mixture was filtered, giving a first batch of powder. The filtrate was extracted with ethyl acetate (3 x 150 ml). The combined organic layers were dried over sodium sulfate, and evaporated under reduced pressure. The combined precipitate was washed with ether to remove any traces of benzyl chloroformate that remained to give a white powder (1.7 g, 91%) mp 132°; ir (potassium bromide): 3376, 3326, 3183, 1688, 1649 cm^{-1} ; ^1H nmr (deuteriochloroform): δ 3.79 (s, 2H), 5.1 (s, 2H), 7.35 (m, 5H); ^{13}C nmr (deuteriochloroform): δ 43, 66.4, 127.3, 127.5, 127.9, 135.8, 156.9, 172.8.

N-Benzyloxycarbonylglycine thioamide (**2**).

To a solution of 15 g (72.1 mmoles) of **1** in 250 ml of tetrahydrofuran under argon was added 17.5 g (43.2 mmoles, 0.6 equivalent) of Lawesson's reagent. After stirring for 4 hours at 25°, the solvent was evaporated under reduced pressure. The residue was suspended in ethyl acetate and washed with 200 ml of a 1%

sodium hydroxide solution. The aqueous layer was extracted with ethyl acetate (3 x 150 ml). The combined organic layers were dried over sodium sulfate, and the solvent removed under reduced pressure to give a light yellow powder (15.7 g, 95%) which was used without further purification; ^1H nmr (deuteriochloroform): δ 4.15 (s, 2H), 5.15 (s, 2H), 7.35 (s, 5H); ^{13}C nmr (deuteriochloroform): δ 50.3, 67.1, 127.8, 128.1, 128.4, 135.8, 157, 204.1.

Ethyl 2-(*N*-Benzyloxycarbonylaminoethyl)-4-thiazolecarboxylate (**3**).

To a solution of 5.05 g (22.5 mmoles) of **2** in 75 ml of tetrahydrofuran under argon were added, 4.24 ml (6.59 g, 33.8 mmoles) of ethyl bromopyruvate, followed by 4.96 g (45.1 mmoles) of potassium hydrogencarbonate. After 4 hours, the reaction was quenched with water and extracted with ethyl acetate (3 x 75 ml). The combined organic layers were dried over sodium sulfate, and concentrated to give an orange powder (8.0 g) which was used without further purification. This product was identical to that reported in the literature [11].

Ethyl 2-Aminomethyl-4-thiazolecarboxylate Hydrobromide (**A'**).

To a solution of 10 ml (41 mmoles) of hydrogen bromide (33% in acetic acid) was added 7.21 g (22.5 mmoles) of **3**. After 45 minutes, the reaction mixture was rapidly filtered on a pre-weighed sintered glass filter. The pale orange powder was dried under reduced pressure to give 5.4 g (90%) of **4**. A small sample was transformed to the free amine for spectral identification; ^1H nmr (deuteriochloroform): δ 1.4 (t, 3H, $J = 7$ Hz), 2.69 (s, 2H), 4.25 (s, 2H), 4.41 (q, 2H, $J = 7$ Hz), 8.1 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 14.3, 43.6, 61.2, 127.2, 146.8, 161, 175.

N-*tert*-Butoxycarbonyl-*S*-benzylcysteine (**4**).

To a rapidly stirring solution of L-cysteine (5 g, 41 mmoles) in 25 ml of a 2*N* sodium hydroxide solution and 48 ml of ethanol was added 4.91 ml (7.06 g, 41 mmoles) of benzyl bromide. After 30 minutes the reaction mixture was neutralized to pH 6-7 by careful addition of concentrated hydrochloric acid, and cooled. The precipitate was filtered and washed successively with water, ethanol, and ether to give *S*-benzylcysteine as a white powder (8.1 g, 93%); ^1H nmr (perdeuteriomethanol, deuteriotrifluoroacetic acid): δ 2.91 (dd, 1H, $J = 14.4$ and 7.2 Hz), 3.05 (dd, 1H, $J = 14.4$ and 3.6 Hz), 3.75 (s, 2H), 4.05 (dd, 1H, $J = 7.2$ and 3.6 Hz), 6.8 (s, 3H), 7.3 (m, 5H).

To a solution of 2 g (9.5 mmoles) of *S*-benzylcysteine in 19 ml of a 1:1 mixture of water/dioxane (1 ml per mmole of starting material) were added 2.07 g (9.5 mmoles) of *tert*-butyl dicarbonate, and 1.98 ml (1.44 g, 14 mmoles) of triethylamine. After 4 hours the dioxane was evaporated under reduced pressure, the aqueous layer acidified to pH 1, and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were dried (sodium sulfate) and concentrated to give a colorless oil in a quantitative yield; ^1H nmr (deuteriochloroform): δ 1.48 (s, 9H), 2.9 (m, 2H), 3.75 (s, 2H), 4.55 (s, 1H), 5.35 (d, 1H), 7.3 (m, 5H), 10.34 (s, 1H).

N-*tert*-Butoxycarbonyl-*S*-benzylcysteinamide (**5**).

To a solution of 6.1 g (20 mmoles) of **4** in 150 ml of dichloromethane at 0° was added 4.09 g (20 mmoles) of 1,3-dicyclohexylcarbodiimide (DCC). Ammonia gas was bubbled through the reaction mixture for 10 minutes at 0°, then 5 min-

utes at 25°. After 3-4 hours the solvent was evaporated under reduced pressure. The reaction was taken up in a minimal amount of ethyl acetate and filtered. The filtrate was diluted with 100 ml of solvent and washed successively with 2*N* hydrochloric acid and brine. The organic layer was dried (sodium sulfate) and concentrated. The residue was purified by column chromatography (50% ethyl acetate/50% cyclohexane) to give a white solid (6.17 g, 97%) mp 130°; ir (potassium bromide): 3391, 3345, 3196, 2986, 1680, 1665 cm⁻¹; uv (methanol) 203 nm; ¹H nmr (deuteriochloroform): δ 1.45 (s, 9H), 2.81 (m, 2H), 3.79 (s, 2H), 4.32 (s, 1H), 5.6 (d, 1H), 6.4 (s, 1H), 6.61 (s, 1H), 7.3 (m, 5H); ¹³C nmr (deuteriochloroform): δ 28.2, 33.5, 36.3, 53.2, 80.2, 127.1, 128.4, 128.9, 137.8, 155.4, 173.5; [α]_D = +1.7 (chloroform).

Anal. Calcd. for C₁₆H₂₂N₂O₃S: C, 58.04; H, 7.14; N, 9.02. Found: C, 58.08; H, 7.09; N, 8.94.

N-*tert*-Butoxycarbonyl-*S*-benzylcysteinethioamide (6).

To a solution of 6.2 g (20 mmoles) of **5** in 150 ml of tetrahydrofuran under argon at 25° was added 6.44 g (16 mmoles) of Lawesson's reagent. After 4 hours, the solvent was evaporated under reduced pressure and the reaction was taken up in ethyl acetate. The organic layer was washed with a 1% sodium hydroxide solution and dried (sodium sulfate). The crude thioamide was filtered over alumina (70% ethyl acetate/30% cyclohexane) and concentrated to give a yellow powder (6.49 g, 96%) mp 130°; ir (potassium bromide): 3318, 3260, 3164, 2980, 1740, 1690, 1657 cm⁻¹; uv (methanol): 209, 271 nm; ¹H nmr (perdeuteriomethanol, 323K): δ 1.49 (d, 9H), 2.75 (dd, 1H, J = 14.4 and 7.2 Hz), 2.99 (dd, 1H, J = 14.4 and 5.4 Hz), 3.79 (s, 2H), 4.5 (m, 1H), 7.3 (m, 5H); ¹³C nmr (perdeuteriomethanol): δ 27.2, 27.6, 37.3, 37.7, 81, 86.4, 128, 129.4, 130, 140, 157, 209; [α]_D = -1.8 (chloroform).

Anal. Calcd. for C₁₅H₂₂N₂O₂S₂: C, 55.18; H, 6.79; N, 8.58. Found: C, 55.49; H, 6.87; N, 8.40.

Ethyl *N*-*tert*-butoxycarbonyl-*S*-benzylcysteine-4-thiazolecarboxylate (7).

To a solution of 2 g (6 mmoles) of **6** in 75 ml of tetrahydrofuran under argon at 25° was added 0.78 ml (1.21 g, 6 mmoles) of ethyl bromopyruvate. After 4 hours the solvent was evaporated under reduced pressure and the residue taken up in ethyl acetate and water. The aqueous layer was extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine and dried (sodium sulfate). The crude product was purified by column chromatography (50% ethyl acetate/50% cyclohexane) to give a pale orange powder (1.6 g, 63%) mp 80°; ir (potassium bromide): 3362, 3110, 2984, 1715, 1684 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.45 (m, 12H), 3.05 (dd, 1H, J = 14.4 and 7.1 Hz), 3.15 (dd, 1H, J = 14.4 and 5.4 Hz), 3.6 (s, 2H), 4.42 (q, 4H, J = 7 Hz), 5.2 (m, 1H), 5.59 (s, 1H), 7.3 (m, 5H), 8.1 (s, 1H); ¹³C nmr (deuteriochloroform): δ 14.2, 28.2, 36.3, 36.6, 52.2, 61.3, 80.3, 127.1, 127.5, 128.5, 128.8, 137, 147, 155, 161, 172.

Anal. Calcd. for C₂₀H₂₆N₂O₄S₂: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.47; H, 6.46; N, 6.51.

2-(*N*-*tert*-Butoxycarbonyl-*S*-benzylcysteine)-4-(1-hydroxymethyl)thiazole (8).

To a solution of 0.692 g (1.6 mmoles) of **7** in 10 ml of tetrahydrofuran under argon at 25° was added 0.062 g (1.6 mmoles) of lithium aluminium hydride. After 4 hours the reaction was quenched by careful addition of water, and extracted with ethyl

acetate (3 x 20 ml). The combined organic layers were washed with brine and dried (sodium sulfate). The crude residue was purified by column chromatography (50% ethyl acetate/50% cyclohexane) to give a white powder (0.623 g, 96%) mp 103°; ir (potassium bromide): 3366, 3306, 3110, 2978, 1698 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.49 (s, 9H), 3.0 (m, 2H), 3.6 (s, 2H), 4.75 (s, 2H), 5.15 (s, 1H), 5.55 (s, 1H), 7.12 (s, 1H), 7.3 (m, 5H); ¹³C nmr (deuteriochloroform): δ 28.3, 36.5, 36.6, 52, 60.6, 80.2, 114.9, 127.1, 128.5, 128.9, 137.7, 155, 156.5, 171.8.

Anal. Calcd. for C₁₈H₂₄N₂O₃S₂: C, 56.82; H, 6.36; N, 7.36. Found: C, 56.90; H, 6.15; N, 7.26.

2-(*N*-*tert*-Butoxycarbonyl-*S*-benzylcysteine)-4-thiazolecarboxaldehyde (B).

To a solution of 0.950 ml (1.38 g, 11 mmoles) of oxalyl chloride in 28 ml of dry dichloromethane under argon at -78° was slowly added 1.55 ml (1.70 g, 22 mmoles) of dimethyl sulfoxide in 7 ml of dichloromethane. After 15 minutes, 2.07 g (5 mmoles) of **8** was added, and the reaction was kept at -78° for another 45 minutes. Triethylamine (4.93 ml, 3.58 g, 35 mmoles) was then added, and the reaction was slowly brought to room temperature. The reaction mixture was quenched by addition of water, and extracted with dichloromethane (3 x 30 ml). The crude product was purified by column chromatography (30% ethyl acetate/70% cyclohexane) to give a light yellow powder (1.94 g, 97%) mp 92-94°; ir (film): 3349, 2978, 2930, 1703 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.49 (s, 9H), 3.1 (m, 2H), 3.69 (s, 2H), 5.2 (s, 1H), 5.6 (s, 1H), 7.3 (m, 5H), 8.15 (s, 1H), 9.99 (s, 1H); ¹³C nmr (deuteriochloroform): δ 28.2, 36.2, 36.6, 52.1, 80.5, 127.2, 128.5, 128.7, 128.8, 137.5, 143.2, 154.7, 162.2, 184.4.

Anal. Calcd. for C₁₈H₂₂N₂O₃S₂: C, 57.12; H, 5.86; N, 7.40. Found: C, 56.81; H, 5.64; N, 7.25.

2-[(*N*-*tert*-Butoxycarbonyl)amino]-3-benzyloxycarbonylbutanoic Acid (10).

The procedure described for **4** was employed with 1.2 g (5.4 mmoles) of **9** in 10.8 ml of a water-dioxane mixture. After isolation, the viscous oil (2.0 g, quantitative yield) was used without purification in the next step; ¹H nmr (deuteriochloroform): δ 1.45 (s, 9H), 2.95 (m, 2H), 4.61 (s, 1H), 5.15 (d, 2H, J = 1.8 Hz), 5.6 (s, 1H), 7.35 (s, 5H), 9.9 (s, 1H).

2-[(*N*-*tert*-Butoxycarbonyl)amino]-3-benzyloxycarbonylbutanamide (11).

To a stirred solution of 0.743 g (2.3 mmoles) of **10** in 2 ml of dry tetrahydrofuran at -13° under argon was added 0.321 ml (0.232 g, 2.3 mmoles) of triethylamine followed by 0.258 ml (0.281 g, 2.3 mmoles) of isopropyl chloroformate. After 15 minutes, ammonia gas was bubbled through the solution at -13° for 5 minutes, then at room temperature for 10 minutes. Water was added, the mixture extracted with dichloromethane, and dried (sodium sulfate). Evaporation under reduced pressure gave a clear oil (0.531 g, 70%) which was used without further purification; ¹H nmr (deuteriochloroform): δ 1.45 (s, 9H), 2.95 (m, 2H), 4.38 (m, 1H), 5.1 (s, 2H), 5.65 (s, 1H), 7.35 (s, 5H).

Ethyl 2-[*N*-(Benzylidene)aminomethyl]-4-thiazolecarboxylate (13).

To a solution of 5.34 g (20 mmoles) of **A'** in 75 ml of dichloromethane were added 5.57 ml (4.04 g, 40 mmoles) of triethylamine followed by 1.93 ml (2 g, 20 mmoles) of benzaldehyde. A small amount of magnesium sulfate was added to the

reaction mixture. After 4 hours the reaction was filtered, and the filtrate evaporated under reduced pressure. The residue was taken up in water, and extracted with ether (3 x 50 ml). The combined organic layers were washed with brine, dried over sodium sulfate, and evaporated to give a pale yellow powder (4.4 g, 80%); mp 110–112°; uv (methanol): 210, 248 nm; ¹H nmr (deuteriochloroform): δ 1.42 (t, 3H, J = 7 Hz), 4.45 (q, 2H, J = 7 Hz), 5.14 (s, 2H), 7.45 (m, 3H), 7.8 (m, 2H), 8.15 (s, 1H), 8.49 (s, 1H); ¹³C nmr (deuteriochloroform): δ 14.3, 61.3, 61.6, 127.6, 128.4, 128.7, 131.4, 135.4, 147, 161.5, 164.2, 171.4.

Anal. Calcd. for C₁₄H₁₄N₂O₂S: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.23; H, 5.21; N, 10.21.

Ethyl 2-[1-(*N*-Benzylidene)-2-*t*-butoxycarbonylpropyl]-thiazolecarboxylate (**14**).

To a solution of 3.8 ml (6.0 mmoles) of *n*-butyllithium (1.6 M hexanes) in 50 ml of dry tetrahydrofuran at -78° under argon was added 0.958 ml (0.692 g, 6.8 mmoles) of diisopropylamine. The reaction was kept at -78° for 15 minutes, at -50° for 15 minutes, then cooled down to -78° again. The imine **13** (1.5 g 5.5 mmoles) in 5 ml of tetrahydrofuran was then added during 5 minutes followed by 1.24 ml (0.953 g, 8.2 mmoles) of tetramethylethylenediamine (TMEDA). After 40 minutes 1.45 g (6.0 mmoles) of *tert*-butyl iodoacetate was added. After 1 hour at -78° the temperature was slowly brought up to 25°. The reaction was quenched by addition of a saturated ammonium chloride solution, and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine and dried (sodium sulfate). Evaporation of the solvent under reduced pressure gave an orange oil (1.74 g) which was used without purification in the next step. Characterization of the mono alkylated product was possible due to the isolation of a small quantity of pure product obtained in a small scale experiment; ¹H nmr (deuteriochloroform): δ 1.39 (t, 3H, J = 7 Hz), 1.42 (s, 9H), 2.89 (dd, 1H, J = 15.1 and 10.8 Hz), 3.22 (dd, 1H, J = 15.1 and 3.6 Hz), 4.44 (q, 4H, J = 7 Hz), 5.29 (dd, 1H, J = 10.8 and 3.6 Hz), 7.46 (m, 3H), 7.85 (m, 2H), 8.15 (s, 1H), 8.54 (s, 1H); ¹³C nmr (deuteriochloroform): δ 14.3, 28, 43.2, 61.3, 68.1, 81, 128.5, 128.6, 131.4, 135.4, 146.9, 164.4, 166.8, 169.2, 174.2.

Ethyl 2-[1-(*N*-Benzylidene)-2,2'-*t*-butoxycarbonylpropyl]-4-thiazolecarboxylate **14'**.

This compound was obtained in another small scale experiment as the sole product of the reaction; ¹H nmr (deuteriochloroform): δ 1.25 (s, 18 H), 1.4 (t, 3H, J = 7 Hz), 3.22 (d, 2H, J = 15.1 Hz), 3.38 (d, 2H, J = 15.1 Hz), 4.42 (q, 2H, J = 7 Hz), 7.48 (m, 3H), 7.86 (m, 2H), 8.16 (s, 1H), 8.5 (s, 1H); ¹³C nmr (deuteriochloroform): δ 13.9, 27.3, 27.5, 44.8, 45.9, 60.5, 65.8, 80.3, 80.7, 128.2, 128.5, 131, 135.2, 146.5, 160.3, 161.1, 167.8, 169.6.

Ethyl 2-[1-Amino-2-*t*-butoxycarbonylpropyl]-4-thiazolecarboxylate (**15**).

To a solution of 3.046 g (7.8 mmoles) of a mixture of mono and di-alkylation products **14** and **14'** in 10 ml of ethyl ether was added 7.9 ml (7.9 mmoles) of a 1*N* hydrochloric acid solution. After 2.5 hours, the two layers were separated, the aqueous layer was extracted with a small amount of ether, and evaporated under reduced pressure to give a yellow foam (1.5 g, 56%). Spectral determination was based on analysis of a small quantity of the free amine; ¹H nmr (deuteriochloroform): δ 1.3–1.5 (m, 12 H), 2.3 (s, 1H), 2.68 (dd, 1H, J = 16.2 and 7.9 Hz), 3.05 (dd, 1H, J = 16.2 and 3.6 Hz), 4.41 (q, 4H, J = 7 Hz), 4.69 (dd, 1H, J =

7.9 and 3.6 Hz), 8.15 (s, 1H); ¹³C nmr (deuteriochloroform): δ 14.2, 27.9, 43.2, 50.8, 61.2, 81.2, 132.2, 146.9, 161.3, 170.2, 176.6.

Ethyl 2-[1-(*N*-Phthalimido)-2-*t*-butoxycarbonylpropyl]-4-thiazolecarboxylate (**16**).

A mixture of 1.5 g (4.5 mmoles) of **15**, 1.24 ml (0.903 g, 8.9 mmoles) of triethylamine, and 0.727 g (4.9 mmoles) of phthalic anhydride in 50 ml of toluene was heated to reflux. After 1 hour at 110°, part of the solvent was eliminated by distillation. When the reaction was complete by tlc, the mixture was cooled, 1*N* hydrochloric acid was added, and the product was extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried (sodium sulfate), and concentrated to give 2.1 g of **16**. The product was used without further purification; ¹H nmr (deuteriochloroform): δ 1.36 (m, 12 H), 3.49 (dd, 1H, J = 15.1 and 5.4 Hz), 3.59 (dd, 1H, J = 15.1, and 10.8 Hz), 4.4 (q, 4H, J = 7 Hz), 6.18 (dd, 1H, J = 10.8 and 5.4 Hz), 7.76 (m, 2H), 7.9 (m, 2H), 8.11 (s, 1H); ¹³C nmr (deuteriochloroform): δ 14.3, 28.8, 37.3, 49.4, 61.4, 81.5, 123.7, 131.6, 134.4, 146.7, 161.2, 167.2, 168.6, 168.7.

Ethyl 2-[1-(*N*-Phthalimido)-2-carboxypropyl]-4-thiazolecarboxylate (**C**).

To a solution of 2.1 g (4.5 mmoles) of crude **16** in 2 ml of dichloromethane was added 3 ml of trifluoroacetic acid. After 1 hour at 35° the reaction was quenched by a saturated bicarbonate solution, and extracted with dichloromethane (2 x 10 ml). The aqueous layer was then acidified to pH 1 with concentrated hydrochloric acid and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried (sodium sulfate), and concentrated to give 1.2 g (72%) of fragment **C**; ¹H nmr (deuteriochloroform): δ 1.39 (t, 3H, J = 7 Hz), 3.68 (m, 2H), 4.39 (q, 2H, J = 7 Hz), 6.18 (dd, 1H, J = 10 and 5.4 Hz), 7.76 (m, 2H), 7.88 (m, 2H), 8 (s, 1H), 8.15 (s, 1H); ¹³C nmr (deuteriochloroform): δ 14.1, 35.5, 48.3, 61.7, 123.8, 131.3, 134.5, 136.2, 146.6, 161.1, 167.2, 168.6, 173.8.

(*E*)-3-*t*-Butoxycarbonyl-2-butenic Acid (**18**).

To a solution of 1.68 g (8.4 mmoles) of *tert*-butyl ethyl fumarate **17** in 50 ml of tetrahydrofuran cooled to 0° was added 86 ml (8.6 mmoles) of a 1*M* lithium hydroxide solution in water. After 1 hour the solvent was evaporated under reduced pressure, the aqueous layer was neutralized with concentrated hydrochloric acid, and extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried (sodium sulfate), and concentrated to give a white solid (1.4 g, 97%). ¹H nmr (perdeuteriomethanol): δ 1.5 (s, 9H), 6.78 (9, 2H); ¹³C nmr (perdeuteriomethanol): δ 28.2, 83, 134.3, 136.3, 165.7, 168.

(*E*)-3-*t*-Butoxycarbonyl-2-butenamide (**19**).

To a solution of 1.45 ml (2.1 g, 16.6 mmoles) of oxalyl chloride in 50 ml of dichloromethane cooled to 0° was added 2.38 g (13.8 mmoles) of **18** in 25 ml of dichloromethane. A catalytic amount (10 drops) of dimethylformamide was then added to the reaction. The cooling bath was then removed and after 2 hours the reaction mixture was again cooled to 0° where ammonia gas was bubbled through for 5 minutes at 0° and then 5 minutes at 25°. After 2 hours the solvent was evaporated under reduced pressure and the residue was taken up in 120 ml of ethyl acetate. The mixture was filtered, the filtrate washed with water, and then extracted with ethyl acetate (3 x 50 ml). The combined

organic layers were washed with brine, dried (sodium sulfate), and concentrated to give a white powder (1.85 g, 78%); ^1H nmr (deuteriochloroform): δ 1.5 (s, 9H), 6.53 (s, 2H), 6.72 (d, 1H, $J = 14.4$ Hz), 6.92 (d, 1H, $J = 14.4$ Hz); ^{13}C nmr (deuteriochloroform): δ 27.9, 81.7, 133, 134.8, 164.5, 166.2.

(*E*)-3-*t*-Butoxycarbonyl-2-butenethioamide (**20**).

To a solution of 3.0 g (17.5 mmol) of **19** in 40 ml of dry tetrahydrofuran under argon was added 0.935 g (2.1 mmol, 0.12 molar equivalent) of phosphorus pentasulfide. After 1 hour the solvent was evaporated under reduced pressure, and the residue purified by column chromatography (50% ethyl acetate/50% cyclohexane) or filtration on alumina gel to give a light yellow powder (0.890 g, 27%); ^1H nmr (deuteriochloroform): δ 1.5 (s, 9H), 6.73 (d, 1H, $J = 15.1$ Hz), 7.2 (d, 1H, $J = 15.1$ Hz), 7.3 (s, 1H), 7.7 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 28, 82.1, 131.8, 139.3, 164.8, 196.6.

(*E*) Ethyl 2-(2-*t*-Butoxycarbonyl-1-propenyl)-4-thiazolecarboxylate (**21**).

To a solution of 1.74 g (9.3 mmol) of **20** in 50 ml of dry tetrahydrofuran under argon was added 4.6 g (46.3 mmol) of potassium hydrogencarbonate followed by 3.5 ml (5.42 g, 27.8 mmol) of ethyl bromopyruvate. After 2 minutes the reaction was cooled to 0°, and a mixture of 5.24 ml (7.8 g, 37.1 mmol) of trifluoroacetic anhydride and 6.3 ml (6.15 g, 77.9 mmol) of pyridine in 15 ml of tetrahydrofuran was added. After 2 hours at 25° the solvent was evaporated under reduced pressure, the residue was taken up in dichloromethane and water, and extracted with dichloromethane (3 x 40 ml). The combined organic layers were dried (sodium sulfate) and the crude product was purified by column chromatography (30% ethyl acetate/70% cyclohexane) to give an orange solid (1.19 g, 45%), mp 78°; ir (potassium bromide): 3412, 3110, 2980, 2932, 1721, 1713, 1645 cm^{-1} ; uv (methanol): 223, 299 nm; ^1H nmr (deuteriochloroform): δ 1.43 (t, 3H, $J = 7$ Hz), 1.52 (s, 9H), 4.45 (q, 2H, $J = 7$ Hz), 6.75 (d, 1H, $J = 16.2$ Hz), 7.75 (d, 1H, $J = 16.2$ Hz), 8.2 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 14.3, 28, 61.6, 81.4, 128.4, 127.1, 134.5, 148.6, 160.9, 164.4; ms: m/z 283 (M^+ , 15), 238 (19), 210 (50), 183 (83), 57 (100).

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- [12] The same series of reactions was first applied to the *N*-(*t*-butoxycarbonyl) derivative. Unfortunately, the poor yields observed in both the thioamide and thiazole formations, and the problems encountered during the deprotection of the amino group, lead us to search for a better nitrogen protecting group. The ethyl 2-(*N*-*t*-butoxycarbonylaminoethyl)-4-thiazolecarboxylate has been previously described by C. Bailly, R. Houssin, J.-L. Bernier, and J.-P. Henichart, *Tetrahedron*, **44**, 5833 (1988) as an unstable white powder, while in fact, this compound is quite stable for long periods of time at ambient temperature. The product that fits their description is the *alcohol* obtained after condensation of the thioamide and ethyl bromopyruvate before loss of water and aromatization to the thiazole.
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