Synthesis of the Modified Dolastatin 3 Sequence *cyclo*-[L-Val-L-Leu-L-Pro-(*R*,*S*)-(gln)Thz-(gly)Thz][1]

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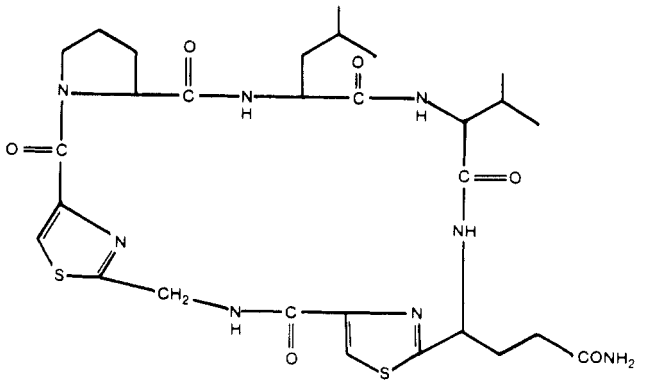
By employing a series of peptide bond forming reactions followed by a 2,4,5-trichlorophenol active ester promoted cyclization the synthesis of *cyclo*-[L-Val-L-Leu-L-Pro-(*R* and *S*)-(gln)Thz-(gly)Thz] (**2**) was accomplished. Neither of the diastereomers was identical with the Indian Ocean sea hare cell growth inhibitory constituent dolastatin 3. However, the mass spectra of the synthetic cyclic pentapeptides (**2**) closely approximated that of the natural product, suggesting a close structural relationship. The EI mass spectral fragmentation of cyclic peptides **2** and of two other structurally related cyclic pentapeptides was discussed.

In prior studies concerned with a structural assignment for the murine P388 lymphocytic leukemia cell growth inhibitory cyclic peptide dolastatin 3, from the marine mollusc *Dolabella auricularia*, structure **1** was tentatively



1, Cyclo[Pro-Leu-Val-(gln)Thz-(gly)Thz]
2, X = R and S Cyclo[L-Val-L-Leu-L-Pro-X-(gln)Thz-(gly)Thz]

assigned.[2] Both the reverse order of bonding[3] and the chiral isomers *cyclo*-[L-Pro-L-Leu-L-Val-(*R*,*S*)-(gln)Thz-(gly)Thz][1] were eliminated as representing dolastatin 3 by total synthesis and subsequent comparison with the natural product. The two most significant differences in the high resolution (400 MHz) ^{1}H NMR and ^{13}C NMR spectra of dolastatin 3 and the latter isomers[1] were noted in the Leu and (gln)Thz units and suggested the natural peptide might contain D-Leu and (*R*)-(gln)Thz instead of the L series. Alternatively, the possibility existed that another arrangement of the Pro-Leu-Val segment might actually correspond to dolastatin 3.[1] With the aid of a new computer technique for analyzing[4] peptide mass spectral data,

Scheme I

L-Pro-OMe → Boc-L-Leu-L-Pro-OMe → L-Leu-L-Pro-OMe (**3**)

→ Boc-L-Val-L-Leu-L-Pro-OMe → L-Val-L-Leu-L-Pro-OMe (**4**)

→ N-Boc-(gly)Thz-L-Val-L-Leu-L-Pro-OMe (**5**) → (gly)Thz-L-Val-L-Leu-L-Pro-OMe (**6**)

→ N-Z-R- and S-(gln)Thz-(gly)Thz-L-Val-L-Leu-L-Pro-OMe (**7**)

→ N-Z-R- and S-(gln)Thz-(gly)Thz-L-Val-L-Leu-L-Pro-OTcp → (**8**)

N-DL-(gln)Thz-(gly)Thz-L-Val-L-Leu-L-Pro-OTcp → **2c** (**9**)

one of the next most likely structural sequences for dolastatin 3 was deduced to be cyclic peptide **2**. Synthesis of isomer **2** in the all-L configuration was undertaken as summarized in Scheme I.

Synthesis of cyclic peptide **2** was simplified by our[3] earlier preparation of L-Val-L-Leu-L-Pro-OMe (**4**) hydrochloride by employing mixed carbonic anhydride peptide bond forming procedures and the route (**3** → **4**) outlined in Scheme I. The corresponding amine was coupled with *N*-Boc-(gly)Thz[3] by employing the OSu procedure (isobutyl chloroformate–*N*-hydroxysuccinimide). The resultant tetrapeptide derivative (**5**) was deprotected by treatment with trifluoroacetic acid and coupled with *N*-Z-(*R*,*S*)-(gln)Thz[5] using the OSu method to yield pentapeptide **7**. The ^{13}C NMR spectrum of pentapeptide **7** was readily interpreted and did not reflect the diastereomeric composition. In the ^{1}H NMR spectrum, the presence of two diastereomers was suggested only by the broadening of certain resonances, particularly hydrogens on the thiazole rings. Attempts at analytical high pressure liquid chromatography (Partisil) to separate the stereoisomers were unsuccessful.

The protected pentapeptide **7** was saponified and converted to the 2,4,5-trichlorophenol ester (**8**) using dicyclohexylcarbodiimide. The *N*-carbobenzoxy protecting group was removed by hydrogen bromide in acetic acid and a very dilute solution of the product (**9**) in tetrahydrofuran

(1) Contribution 111 of Antineoplastic Agents and 26 of Structural Biochemistry. And for parts 110 and 25, refer to: Pettit, G. R.; Holzapfel, C. W. *J. Org. Chem.*, previous paper in this issue.

(2) Pettit, G. R.; Kamano, Y.; Brown, P.; Gust, D.; Inoue, M.; Herald, C. L. *J. Am. Chem. Soc.* **1982**, *104*, 905-907.

(3) Pettit, G. R.; Nelson, P. S.; Holzapfel, C. W. *J. Org. Chem.* **1985**, *50*, 2654.

(4) We are pleased to thank Dr. A. Tuinman for important assistance with the computerized method he devised for analyzing peptide mass spectral sequence data. While the present manuscript was in press two peptide synthetic groups reported (in preliminary communications with no experimental), syntheses corresponding to all the D and L isomers of cyclic peptide **1**. But an exact match of physical properties with those of natural dolastatin 3 was not found. On the assumption that nothing has gone amiss in each of these two sets of 16 different syntheses, the tentative conclusion reached in our present study, namely, that a slight modification in the structure **1** peptide sequence may be necessary to define dolastatin 3, could be correct. For the two helpful cyclic peptide synthetic endeavors, consult: Schmidt, U.; Utz, R. *Angew. Chem.* **1984**, *96*, 725-726. Hamada, Y.; Kohda, K.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 5303-5306.

(5) Holzapfel, C. W.; Pettit, G. R. *J. Org. Chem.* **1985**, *50*, 2323. Conversion of iso-L-Gln to (gln)Thz employing a Hantzsch thiazole synthesis as the key step was found to cause complete racemization. Rather than resolve the (*R*)- and (*S*)-(gln)Thz for the present study it seemed more efficient to proceed with the racemic product and use one of the anticipated peptide derivatives as a means of obtaining both the (*R*)- and (*S*)-(gln)Thz cyclic peptides (**2a** and **2b**).

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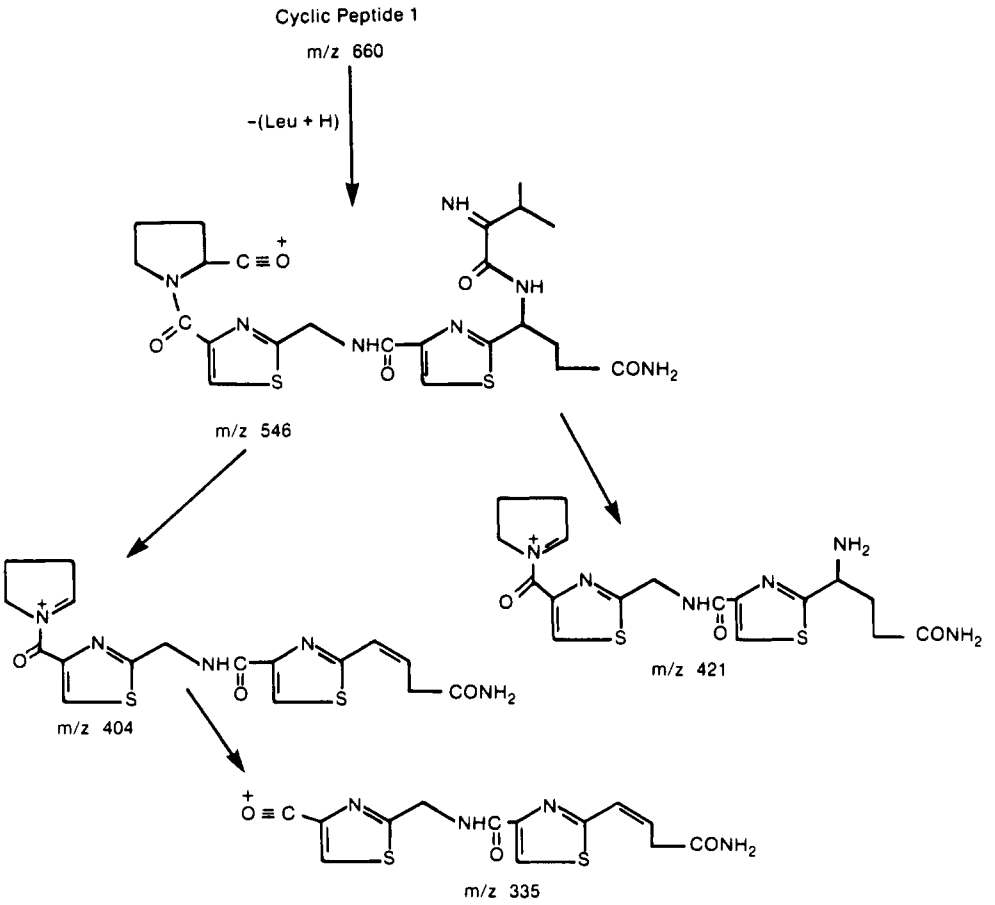
Scheme II. EI Mass Spectral Fragmentation of *cyclo*-[L-Pro-L-Leu-L-Val-(gln)Thz-(*R* and *S*)-(gly)Thz][1]



was cyclized[6] in the presence of pyridine. Cyclic peptide **2** was isolated by careful chromatography employing steric exclusion (Sephadex LH-20) and silica gel column techniques. The high resolution (400 MHz) ^{1}H NMR spectrum of cyclic peptide **2** clearly showed a ca. 1:1 mixture of two diastereomers. While it was not possible to assign every ^{1}H NMR resonance to specific positions of the two isomers, it was clear from a comparison of the high resolution (400 MHz) spectra that neither diastereomer was identical with dolastatin 3. Also, thin layer chromatographic comparison showed the diastereomeric mixture to be slightly more polar than dolastatin 3. Contrary to our previous experience with dolastatin 3 isomers,[1,3] all attempts to separate the diastereomeric components by high pressure liquid chromatography were unsuccessful. When it was ascertained that neither isomer of **2** was identical with dolastatin 3, further attempts at separation were abandoned and attention was directed at a mass spectral evaluation of the synthetic cyclic peptides.

An electron impact fragmentation study of the synthetic cyclic pentapeptides corresponding to peptide **1** (all-L isomer, Scheme II), its reverse peptide bonded counterpart (Scheme III), and peptide **2** (Scheme IV) were considered significant for assisting in the structure elucidation of new cyclic peptides containing thiazole amino acids. Mass spectral data for cyclic peptide **1**[1] and the reverse peptide bonded isomers were recorded earlier without detailed interpretation. The present preliminary study was limited to establishing the composition (accurate mass analysis) of abundant fragments in the higher mass range. All three cyclic peptides showed a much greater tendency to lose leucine than any other single amino acid. Further fragmentation of the cyclic peptides (Schemes II–IV) was dominated by allylic cleavage of the C–N bond of the (gly)Thz and (gln)Thz side-chain amines or by McLafferty rearrangement of the (gln)Thz unit. These modes of fragmentation have been observed with simple substituted thiazoles.[7] Interestingly, the mass spectral fragmentation of the dolastatin 3 isomers **2** most nearly approximated that of the natural product and suggested a close structural relationship. But further definitive refinements in the structure (**1**) tentatively assigned[2] dolastatin 3 will require additional syntheses[4] and/or reavailability of the natural product.

Experimental Section

The Boc-L-Leu, L-Pro-OMe·HCl, and Boc-L-Val were employed as received from Sigma Chemical Co. Solvent (all redistilled) extracts of aqueous solution were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. Dimethylformamide and tetrahydrofuran were distilled from calcium hydride and lithium aluminum hydride, respectively. Ether refers to diethyl ether.

Thin layer chromatography (TLC) was accomplished with Analtech silica gel GF (0.25 mm) plates. Thin layer chromatograms were developed with sulfuric acid or 1% palladium chloride

(6) For leading references to such experimental methods, consult: Pettit, G. R. In *Synthetic Peptides*; Elsevier Sci. Pub. Co.: Amsterdam, 1976, 1980, 1982; Vols. 4–6, respectively. Ji, A.; Bodansky, M. *Int. J. Peptide Protein Res.* **1983**, *22*, 590–596. Rich, D. H.; Gardner, J. H. *Tetrahedron Lett.* **1983**, *24*, 5305–5308. Mukaiyama, T.; Kamekawa, K.; Watanabe, Y. *Chem. Lett.* **1981**, 1367–1370.

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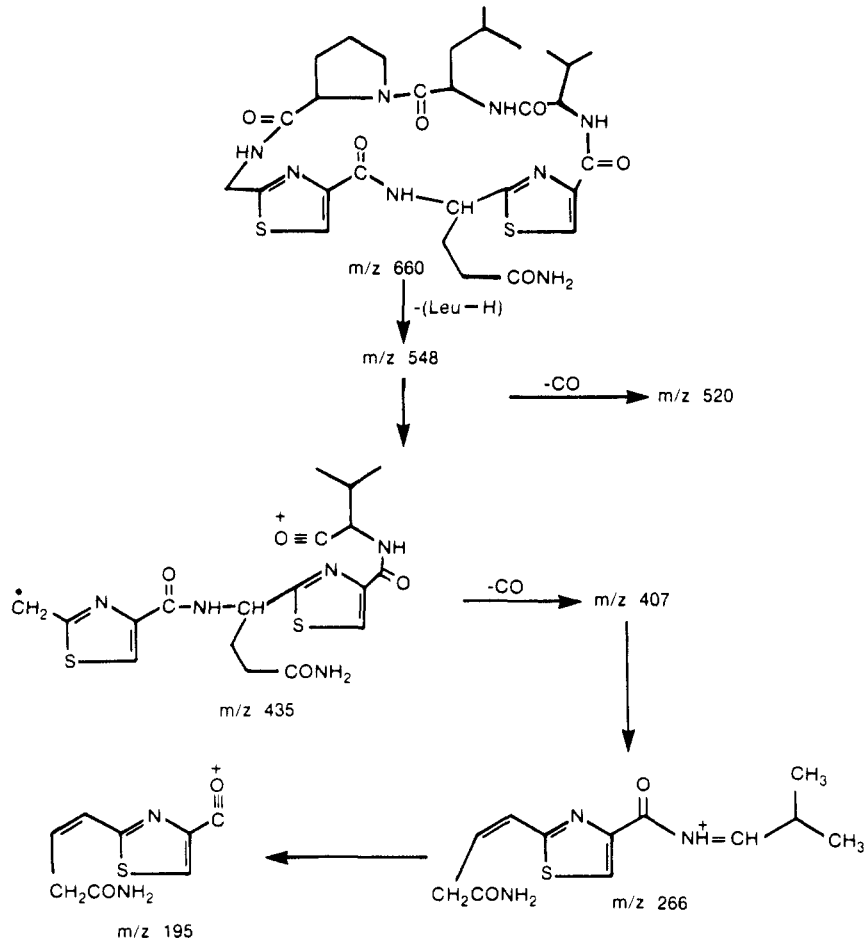
(9) Barber, M.; Bordoli, R. S.; Sedgwick, R. D.; Tyler, A. N. *J. Chem. Soc., Chem. Commun.* **1981**, 325–327.

Scheme III. EI Mass Spectral Fragmentation of *cyclo*-[(gly)Thz-(*R* and *S*)-(gln)Thz-L-Val-L-Leu-L-Pro][3]



sprays or by ultraviolet light. Column chromatography procedures were accomplished with silica gel (70–230 mesh) supplied by E. Merck (Darmstadt) or Sephadex LH-20 supplied by Pharmacia Fine Chemicals, AB, Uppsala, Sweden.

All melting points are uncorrected. Ultraviolet spectra were recorded in methanol solution. Nuclear magnetic resonance data were recorded by using tetramethylsilane as an internal standard.

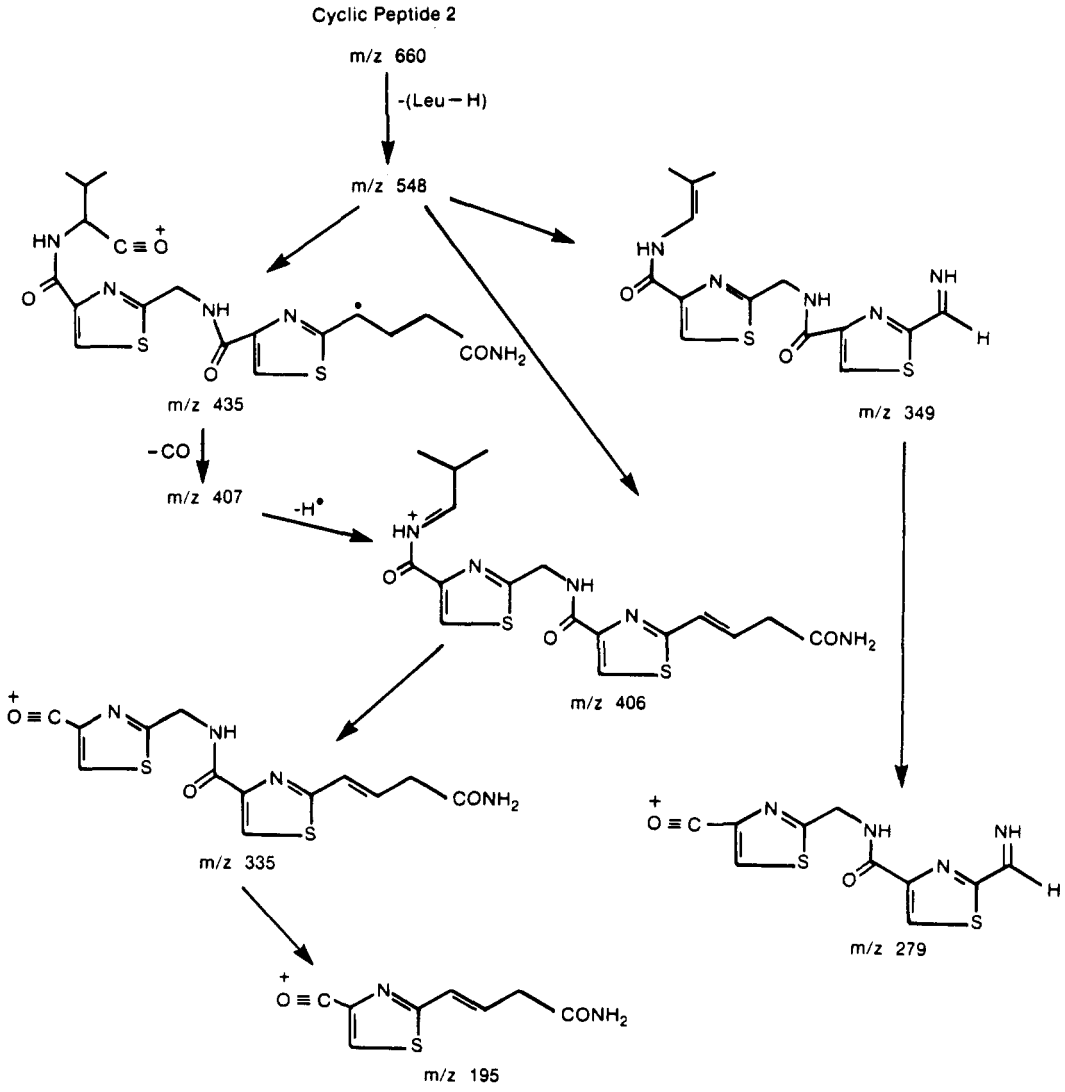
***N*-Boc-(gly)Thz-L-Val-L-Leu-L-Pro-OMe (5) and (gly)-Thz-L-Val-L-Leu-L-Pro-OMe (6) Hydrobromide.** To a solution of *N*-Boc-(gly)Thz (1.16 g, 0.45 mM)[1] in dry tetrahydrofuran (20 mL) was added *N*-methylmorpholine (0.47 mL, 0.47 mM), and the solution was cooled to −23 °C (carbon tetrachloride–dry ice). Next, isobutyl chloroformate (0.69 mL, 0.47 mM) was added and 3 min later *N*-hydroxysuccinimide (0.494 g, 0.47 mM). The mixture was allowed to come to room temperature. After 12 h at room temperature, the solution was filtered, the precipitated solid was washed with tetrahydrofuran, and the combined filtrate was concentrated to a light yellow gum. To a solution of the residue in dry tetrahydrofuran (20 mL)–dimethylformamide (4 mL, dry) were added *N*-methylmorpholine (0.47 mL, 0.47 mM) with stirring (at room temperature) followed by finely powdered L-Val-L-Leu-L-Pro-OMe·HCl (1.5 g, 4 mM)[3] in small portions over a period of 5 min. The reaction mixture was left at room temperature for 16 h, the solvent was removed, and the residue was dissolved in chloroform (200 mL). The chloroform solution was washed with 3% citric acid (3 × 10 mL), aqueous sodium bicarbonate (2 × 10 mL), and water (10 mL) and dried. The solvent was evaporated and the residue was chromatographed on a column of silica gel (100 g). Elution with 97.5:2.5 chloroform–methanol furnished ***N*-Boc-(gly)Thz-L-Val-L-Leu-L-Pro-OMe (5)** (1.98 g, 86%) as a colorless foam: mp 111–113 °C; $[\alpha]^{25}_D$ −62.2° (*c* 2, CH_3OH); MS (EI) exact mass, *m/z* 581.2856 (M^+, calcd 581.2883 for $C_{27}H_{43}N_5O_7S$).

A portion (0.64 g, 1.1 mM) of peptide **5** in chloroform (2 mL) was treated with 3 N hydrogen bromide in glacial acetic acid (3 mL) for 2 h at 0 °C. Dry ether (20 mL) was slowly added to the stirred solution and the precipitated solid (520 mg) was collected. The salt was crystallized from acetic acid–ether to afford **(gly)Thz-L-Val-L-Leu-L-Pro-OMe (6) hydrobromide** (0.34 g). After drying at 65 °C in vacuo a pure specimen displayed mp 217–219 °C dec and $[\alpha]^{25}_D$ −57.2° (*c* 2, CH_3OH).

Anal. Calcd for $C_{22}H_{36}N_5O_5SBr$: C, 46.98; H, 6.45; N, 12.45; Br, 14.20. Found: C, 46.63; N, 6.17; N, 12.17; Br, 14.57.

***N*-Z-(*R*,*S*)-(gln)Thz-(gly)Thz-L-Val-L-Leu-L-Pro-OMe (7).** To a solution (cooled to 0 °C) of *N*-Boc-(gly)Thz-L-Val-L-Leu-L-Pro-OMe (17.4 g, 3 mmol) in dry methylene chloride (20 mL) was added trifluoroacetic acid (20 mL). After 15 min at 0 °C, the mixture was allowed to come to room temperature and 1 h later the solvent was removed. Carbon tetrachloride (20 mL) was added to the residue and allowed to evaporate, leaving the tetrapeptide (**6**) trifluoroacetate as a colorless gum. To a solution of *N*-Z-(*R*)- and -(*S*)-(gln)Thz (1.05 g, 3 mM) in dry dimethylformamide (5 mL)–tetrahydrofuran (35 mL, dry) was added *N*-methylmorpholine (0.36 mL, 3.3 mM). The mixture was cooled to −23 °C, and isobutyl chloroformate (0.45 mL, 3.3 mM) was added and 3 min later *N*-hydroxysuccinimide (0.345 g, 3.3 mM). The reaction mixture was left at room temperature for 16 h, and the solution was filtered to remove precipitated salts and added to the trifluoroacetate salt of tetrapeptide **6** (described above) in tetrahydrofuran (10 mL, cooled in ice). After 16 h at room temperature, solvent was removed and the oily residue in chloroform (250 mL) washed with 3% citric acid (3 × 25 mL), aqueous sodium bicarbonate (3 × 25 mL), and brine (24 mL). The chloroform solution was dried and solvent evaporated to a colorless gum which was chromatographed on a column of silica gel (200 g). Elution with 94:6 chloroform–methanol yielded ***N*-Z-(*R*,*S*)-(gln)Thz-(gly)Thz-L-Val-L-Leu-L-Pro-OMe (7**, 1.95 g, 79%) as a colorless foam which appeared as a single spot (R_f 0.28) upon TLC analysis using 9:1 methylene chloride–methanol as mobile phase. After precipitation from ethyl acetate with hexane and drying in vacuo at 65° C a sample of the isomers melted at 124–126 °C: $[\alpha]^{25}_D$ −41.0° (*c* 2, CH_3OH); MS (EI), exact mass *m/z* 826.3173

Scheme IV. EI Mass Spectral Fragmentation of *cyclo*-[L-Val-L-Leu-L-Pro-(*R* and *S*)-(gln)Thz-(gly)Thz]



(M^+, calcd 826.3142 for $C_{38}H_{50}N_8O_9S_2$).

***cyclo*-[L-Val-L-Leu-L-Pro-(*R*,*S*)-(gln)Thz-(gly)Thz] (2).** To a solution of *N*-Z-(*R*)- and -(*S*)-(gln)Thz-(gly)Thz-L-Val-L-Leu-L-Pro-OMe (0.578 g, 0.7 mM) in dioxane (6 mL)–water (5 mL) was added 1 mL of 1 N sodium hydroxide. The clear solution was left at room temperature for 2 h and extracted with ether (2 × 75 mL), and the aqueous phase was acidified to pH 2 with 3 N hydrochloric acid. The oil which separated was extracted with chloroform. The extract was dried and solvent evaporated to give a colorless foam (0.50 g); MS (SP-SIMS, in glycerol), *m/z* 813 [M = *N*-Z-(*R*,*S*)-(gln)Thz-(gly))Thz-Val-Leu-Pro + H]$^+$. To solution of the carboxylic acid in dry dimethylformamide (10 mL) was added 2,4,5-trichlorophenol (0.134 g, 0.7 mM). The mixture was cooled (ice bath) and dicyclohexylcarbodiimide (0.145 g, 0.7 mM) in dimethylformamide (1 mL) was added. After 16 h at room temperature the solvent was removed and the residue chromatographed on a column of silica gel (60 g). Elution with 97.5:2.5 chloroform–methanol led to the main component (**8**) as a colorless foam (0.44 g); MS (SP-SIMS, sodium iodide in sulfolane),[8] *m/z* 1013 [M = *N*-Z-(*R*,*S*)-(gln)Thz-(gly)Thz-Val-Leu-Pro-OTcp + Na]$^+$, homogenous by TLC (R_f 0.55 in 9:1 methylene chloride–methanol).

The trichlorophenol ester **8** in 1 mL of chloroform was treated (2 h at 0 °C) with 2 mL of 4 N hydrogen bromide in glacial acetic acid. Ether (20 mL) was added and the precipitated hydrobromide (0.40 g) was collected by filtration and dried. To a solution of the colorless hydrobromide in dimethylformamide was added (1 mL) silver acetate (0.12 g), and the yellow silver bromide precipitated immediately. The mixture was diluted with tetrahydrofuran (500 mL), and dry pyridine (10 mL) was added slowly with stirring. After 2 days at room temperature, the solvent was removed and the solution of the residue in chloroform (200 mL) was washed with 1 N hydrochloric acid (2 × 50 mL), aqueous sodium bicarbonate (2 × 25 mL), and water (25 mL) and dried. The chloroform was evaporated and the residue (0.38 g) in methanol was chromatographed on a column of Sephadex LH-20 (200 g). The main fraction (97 mg) eluted from the gel permeation column was chromatographed on a column of silica gel (50 g). Elution with 94:6 chloroform–methanol afforded ***cyclo*-[L-Val-L-Leu-L-Pro-(*R*,*S*)-(gln)Thz-(gly)Thz] (2)** as a colorless amorphous powder (47 mg, 18% yield from the trichlorophenol ester) which appeared homogenous on TLC (R_f 0.26 in 9:1:0 chloroform–methanol–water). After precipitation from methylene chloride with methanol and drying in vacuo at 65 °C, the cyclic peptide isomers (**2**) melted at 171–174 °C: $[\alpha]^{25}_D$ −62.5° (*c* 1, CH_3OH); MS (EI) exact mass, *m/z* 660.2501 (M^+, calcd 660.2512 for $C_{29}H_{40}N_8O_6S_2$), 548.1766 (M^+, calcd 548.1750 for $C_{23}H_{30}N_7O_5S_2$), 435.1021 (M^+, calcd 435.1035 for $C_{18}H_{21}N_5O_4S_2$), 406.1025 (M^+, calcd 406.1008 for $C_{17}H_{20}N_5O_3S_2$), 349.0678 (M^+, calcd 349.0667 for $C_{14}H_{15}N_5O_2S_2$), 279.0024 (M^+, calcd 279.0010 for $C_{10}H_7N_4O_2S_2$); MS (EI), *m/z* (relative intensity) 660 (M^+, 14), 604 (12), 574 (17), 548 (35), 489 (7), 435 (49), 407 (35), 406 (20), 349 (37), 335 (5), 279 (10), 278 (12), 256 (5), 221 (3), 209 (9), 195 (19), 178 (24), 152 (26), 139 (22), 124 (46), 112 (20), 86 (34), 70 (100); MS (SP-SIMS, glycerol matrix),[9] *m/z* (relative intensity) 661 (MH^+, 66), 633 (16), 548 (19), 520 (54), 450 (11), 448 (10), 435 (11), 423 (19), 406 (51), 349 (43), 335 (31), 251 (50), 211 (100); UV λ_{max} 250 (ϵ 7750); ν_{max} 3390, 3175 br, 3035, 1658 br, 1550, 1500, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) at 400 MHz, 0.8–1.0 (m, 12 H, 4 × CH_3), 3.35–3.80 (m, 2 H, CH_2NCO), 5.15–5.55 (m, 2 H, 2 × $CHNHCO$), 4.2–5.85 (m, 6 H, 4 × $CHNHO$ + Thz CH_2NHCO), 5.90 (br s, 1 H), 6.30 (br s) ($CONH_2$), 7.46 (br m, 1 H), 7.62 (br

m, 1 H), 7.95 (br m, 1 H, 3 × NHCO), 8.07 (br s, 1 H), 8.13 (br s, 1 H, 2 × thiazole CH), 8.63 (br m, 1 H, NHCO).

Acknowledgment. The very necessary financial assistance for this research was contributed by Mary Dell Pritzlaff, the Olin Foundation (S.T. and A.W.), the Fannie E. Rippel Foundation, Eleanor W. Libby, the Waddell Foundation (Donald Ware), The Upjohn Co., the Flinn Foundation, and the Robert B. Dalton Endowment Fund. In addition, this investifation was supported by PHS Grant CA-16049-08A2, awarded by the National Cancer Institute, DHHS, the South African Council for Scientific and Industrial Research (financial support for C.W.H.), and the National Science Foundation Regional Facility at the University of South Carolina (CH78-18723).

Registry No. (*R*)-**2**, 104549-00-0; (*S*)-**2**, 104639-79-4; **4**·HCl, 96363-14-3; **5**, 104549-01-1; **6**·HBr, 104549-02-2; **6**·TFA, 104549-04-4; (*R*)-**7**, 104549-05-5; (*S*)-**7**, 104639-80-7; (*R*)-**8**, 104640-66-6; (*S*)-**8**, 104549-06-6; (*R*)-**9**·HBr, 104549-07-7; (*S*)-**9**·HBr, 104639-81-8; *N*-Boc-(gly)Thz, 71904-80-8; *N*-Boc-(gly)Thz-ONSu, 104549-09-9; (*R*)-Z-(gln)Thz-OH, 96363-15-4; (*S*)-Z-(gln)Thz-OH, 95716-10-2; (*R*)-*N*-Z-(gln)Thz-(gly)Thz-Val-Leu-Pro-OH, 104549-08-8; (*S*)-*N*-Z-(gln)Thz-(gly)Thz-Val-Leu-Pro-OH, 104639-82-9; dolastatin 3, 80387-90-2.

Synthesis of (*R*)- and (*S*)-(glu)Thz and the Corresponding Bisthiazole Dipeptide of Dolastatin 3

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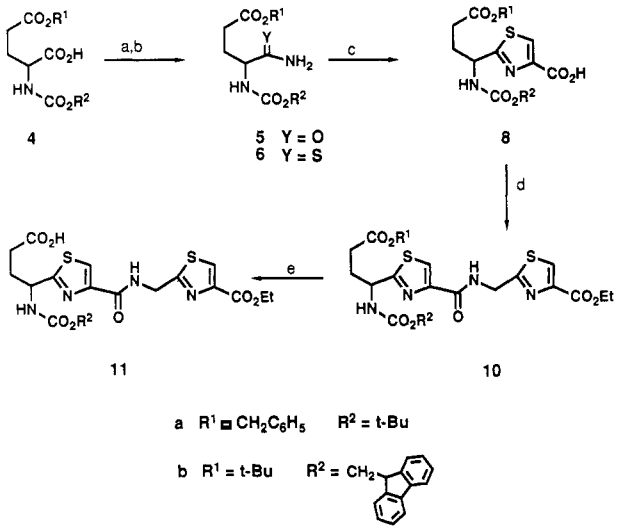
Dolastatin 3 (**1**) has been reported to be a cyclic pentapeptide containing two thiazole amino acids, (gly)Thz (**2**) and (gln)Thz (**3**). The syntheses of (*R*)- and (*S*)-(glu)Thz (**8a,b**) and (glu)Thz-(gly)Thz (**11a,b**) derivatives suitable for elaboration to dolastatin 3 are described. A key feature of the (glu)Thz syntheses is the selective thiation of a primary amide with Lawesson's reagent in the presence of ester and urethane functionalities.

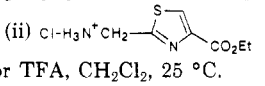
Pettit and co-workers have disclosed their work on a series of compounds from the Indian Ocean sea hare (Dolabella auricularia) which they have named dolastatin.[1] These compounds exhibit high cytotoxicity against the in vitro P388 leukemic cell line and have given good increases in life span in mice inoculated with the same cell line.[1a] Due to shortages of materials only fragmentary structures have been decipherable for most of these materials, but it is clear that they all are peptidic in nature. One of these compounds, dolastatin 3, was sufficiently characterized that a tentative bonding proposal as a cyclic pentapeptide (**1**), lacking stereochemistry, was possible.[1b]

The high activity, the unusual structure, and the structural uncertainty in this family prompted us to begin synthetic studies aimed at providing more definitive structural information.[2] Our first point of focus in developing synthetic plans for this series was the amino acid thiazoles (gly)Thz (**2**) and (gln)Thz (**3**). Several members of this class, including (gly)Thz, (ala)Thz, and (val)Thz have been described previously as constitutents of certain antibiotic and cytotoxic peptides.[3] A method has been developed for the synthesis of these simple bifunctional amino acids,[4] and we adopted this method in our preparation of (gly)Thz derivatives.

The (gln)Thz, on the other hand, is new[5] and as a result of additional functionality brings extra complexity to the

Scheme I[a]



[a] (a) (i) *i*-BuOCOCl, Et_3N or DCC; (ii) NH_3(g); (b) (p-$MeOC_6H_4PS_2)_2$, C_6H_6, 80 °C; (c) $BrCH_2COCO_2H$ (**7**); (d) (i) DCC, HOBt, DMF; (ii)  (**9**), Et_3N; (e) H_2,Pd/C or TFA, CH_2Cl_2, 25 °C.

(1) (a) Pettit, G. R.; Kamano, Y.; Fujii, Y.; Herald, C. H.; Inoue, M.; Brown, P.; Gust, D.; Kitahara, K.; Schmidt, J. M.; Doubek, D. L.; Michael, C. *J. Nat. Prod.* **1981**, *44*, 482. (b) Pettit, G. R.; Kamano, Y.; Brown, P.; Gust, D.; Inoue, M.; Herald, C. L. *J. Am. Chem. Soc.* **1982**, *104*, 905.

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(5) The workers in ref 2 generated syntheses of (glu)Thz differing substantially from ours. See ref 2a,b and Holzapfel, C. W.; Pettit, G. R. *J. Org. Chem.* **1985**, *50*, 2323.

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