according to the procedure of Posner.[2] Commercial 3-(dimethylamino)-1-propyne was obtained from Story Chemical Corp. (Farchan Division) and used without further purification. Isophorone was purchased from the Aldrich Chemical Co.

Preparation of $CH_3[(CH_3)_2NCH_2C{\equiv}C-]CuLi$ (2a). To a solution of 0.5 g (6.02 mmol) of 3-(dimethylamino)-1-propyne in 30 mL of ether cooled to 0 °C was added dropwise and with stirring 4.23 mL of 1.42 M methyllithium (6.02 mmol). The resulting mixture (a white precipitate had formed) was stirred for 45 min and then added dropwise with stirring via a syringe with a wide bore needle to a slurry of 1.15 g (6.02 mmol) of CuI in 2 mL of ether cooled to 0 °C. After stirring at 0 °C for 30 min, 4.23 mL of 1.42 M methyllithium (6.02 mmol) was added. The resulting mixture was then stirred for an additional 30 min at 0 °C.

Preparation of $[CH_2{=}CH-][(CH_3)_2NCH_2C{\equiv}C-]CuLi$ (2b). The reagent was prepared in exactly the same manner as **2a** with the following exceptions: (1) triethylamine was employed as the solvent; (2) the final step in which the mixed copper lithium reagent was formed was carried out at −50 °C, and vinyllithium was used instead of methyllithium.

Reaction of 2a with Isophorone. To a solution of **2a** (prepared above) cooled to 0 °C was added dropwise with stirring a solution of isophorone (0.67 g, 4.8 mmol) and an internal standard dissolved in an equal volume of ether. The resulting mixture, which progressively became darker, was then stirred for 1 h at room temperature. At this time an aliquot was removed and quenched with a saturated solution of ammonium chloride. The organic layer was extracted with HCl and then analyzed via gas chromatography. The reaction was repeated with THF as solvent and also at various temperatures. For results, see Table I. The product obtained in the reaction had an infrared spectrum identical with that of an authentic sample.

Reaction of 2b with Isophorone. The reaction was carried out in exactly the same manner as described for **2a** with the following exceptions: (1) the solution of **2b** (prepared above) was cooled to −50 °C before the isophorone and internal standard were added; (2) after the isophorone was added, the reaction mixture was stirred for 90 min at 0 °C. For results, see Table I. The product obtained in the reaction had IR and NMR spectra identical in every respect with those of an authentic sample.[6]

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Registry No.—1, 7223-38-3; 3, 78-59-1; CH_3Li, 917-54-4; CuI, 7681-65-4; $CH_2{=}CHLi$, 917-57-7.

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(6) We are greatly indebted to Professor H. O. House for supplying us with spectra of the ketone **4b**. Both compounds **4a** and **4b** have been thoroughly characterized by Professor House. See ref 1 for published spectral data.

Telluroamino Acids: Synthesis of Telluromethionine[1]

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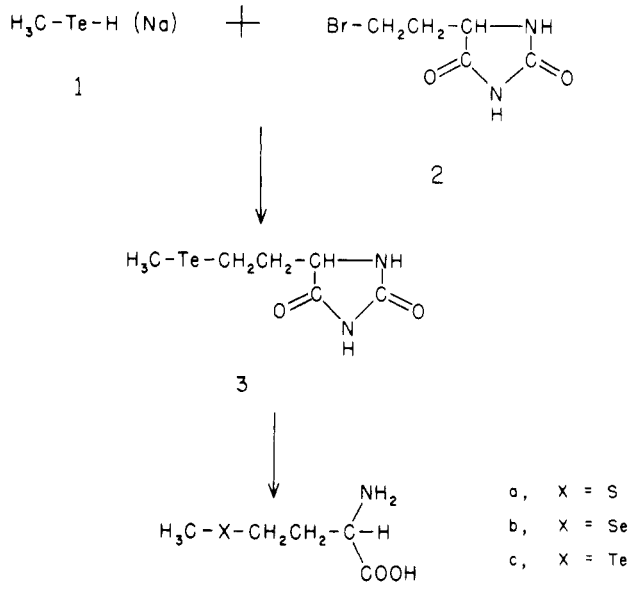
The general field of organoselenium chemistry is well documented because many of these compounds are of biological importance.[2] In addition, selenium reagents have been used in preparative organic chemistry for many years. In contrast, the chemistry of organotellurium compounds has not been well established as a result of both a lack of interest in this area and also the problems associated with the preparation and handling of many of these substances.[3] We have been interested in the preparation of telluroamino acids because of the potential clinical use of the ^{123m}Te-labeled compounds as pancreatic imaging agents. Reported attempts to prepare ^{123m}Te-labeled telluroamino acids by microbiological approaches have been unsuccessful.[4] Previous reports from this laboratory have described the preparation of aryltelluro-substituted α-amino acids.[5] We now report the synthesis of the first known alkyltelluro-substituted α-amino acid, DL-α-amino-γ-(methyltelluro)butyric acid (**4c**, "telluromethionine").



Selenomethionine (**4b**) has been prepared by both microbiological methods[6] and a variety of chemical methods.[7] Many of the latter approaches involved the generation of benzylselenol, but our early attempts to prepare telluroamino acids by similar methods were unsuccessful because of the extreme instability of benzyltellurol.[8] In the present investigation we had hoped to use benzyltellurol to prepare a derivatized form of **4c**. Our inability to use benzyltellurol precluded the preparation of the requisite benzyltelluro-substituted intermediates that were envisioned as substrates for DuVigneaud reduction[9] and subsequent transformation to the desired methyltelluro-substituted product. An alternate method involving the direct introduction of the methyltelluro moiety was therefore considered, and we have now prepared **4c** by a method involving the initial reaction of methyltellurol (**1**) with 5-(β-bromoethyl)hydantoin (**2**).

Results and Discussion

Sodium ditelluride (Na_2Te_2) was generated by reaction of tellurium powder with metallic sodium in liquid ammonia.[10] Alkylation with CH_3I gave dimethyl ditelluride (CH_3–Te–Te–CH_3),[11] which was subsequently reduced with $NaBH_4$ in MeOH–C_6H_6 to yield methyltellurol (**1**). The tellurol **1** readily reacted with 5-(β-bromoethyl)hydantoin (**2**) at room temperature in MeOH–C_6H_6 to yield 5-[(methyltelluro)ethyl]-hydantoin (**3**). It was necessary to control carefully the reaction conditions in order to isolate **3** in reasonable yield, and the generation of the intermediate **3** was found to be a critical step in the overall synthesis of **4c**. Because of the strongly basic reductive conditions, the subsequent coupling of **1** with

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2 gave the substituted hydantoin product 3 as the water-soluble sodium enolate. An acidification step was therefore required prior to solvent extraction of 3, and the type of acid used was found to be extremely important. As an example, coupling of phenyltellurol with 2 gave 5-[β-(phenyltelluro)-ethyl]hydantoin in acceptable yield (58%) when the product was extracted from the crude reaction mixture after HCl acidification.[5] In the present study even cautious HCl acidification of the reaction mixture obtained following the coupling of 1 and 2 gave only low yields (5–20%) of 3 after solvent extraction. Alternatively, acidification of such a reaction mixture with H_2SO_4 has resulted in the isolation of the hydantoin 3 in reasonable yield (55%). The 5-[β-(methyltelluro)ethyl]hydantoin (3) was homogenous upon TLC and GC analyses and exhibited the expected UV, IR, MS, and NMR properties that were consistent with the proposed structure. In our hands this material could be stored indefinitely, with only negligible decomposition, as a crystalline solid (mp 132 °C) in the dark at 8 °C.

Basic hydrolysis of the hydantoin 3 in a bomb at 165–167 °C gave DL-α-amino-γ-(methyltelluro)butyric acid (**4c**, "telluromethionine"). Analysis of the hydrolysis mixture by TLC (BuOH–HOAC–H_2O, 4:1:1) indicated the presence of a single UV-absorbing, ninhydrin-positive component that exhibited the mobility expected for **4c** in this system (R_f 0.49). As expected, both L-methionine (**4a**, R_f 0.40) and DL-selenomethionine (**4b**, R_f 0.43) were slightly more polar and exhibited the expected relative mobility when analyzed under these same chromatographic conditions. Attempts to crystallize **4c** by acidification of crude reaction mixtures were unsuccessful, although lyophilization of such mixtures did yield solid material consisting of inorganic salts and **4c**. Mass spectral analysis of such material indicated the presence of the expected parent peak of **4c** at *m/z* 247. The fragmentation pattern induced by electron impact was consistent with structure **4c** and contained the major peaks that were expected from a comparison of the peaks detected upon mass spectral fragmentation of L-methionine (**4a**) and DL-selenomethione (**4b**).[12] The ^1H NMR spectrum of this material in D_2O (Figure 1c) exhibited the expected proton resonances and could be compared directly to the spectra of L-methionine (**4a**) (Figure 1a) and DL-selenomethionine (**4b**) (Figure 1b). The multiplets detected in the spectrum of **4c** at δ ~2.04, 2.57, and 3.25 represent the β-methylene, γ-methylene, and α-methine protons, respectively. The three-proton methyl singlet in the spectrum of **4c** is observed at the expected higher field position (δ 1.88) relative to the position of the methyl resonances observed in the spectra of **4a** (δ 2.10) and **4b** (δ 1.98). These MS and NMR data are fully consistent with structure **4c**.

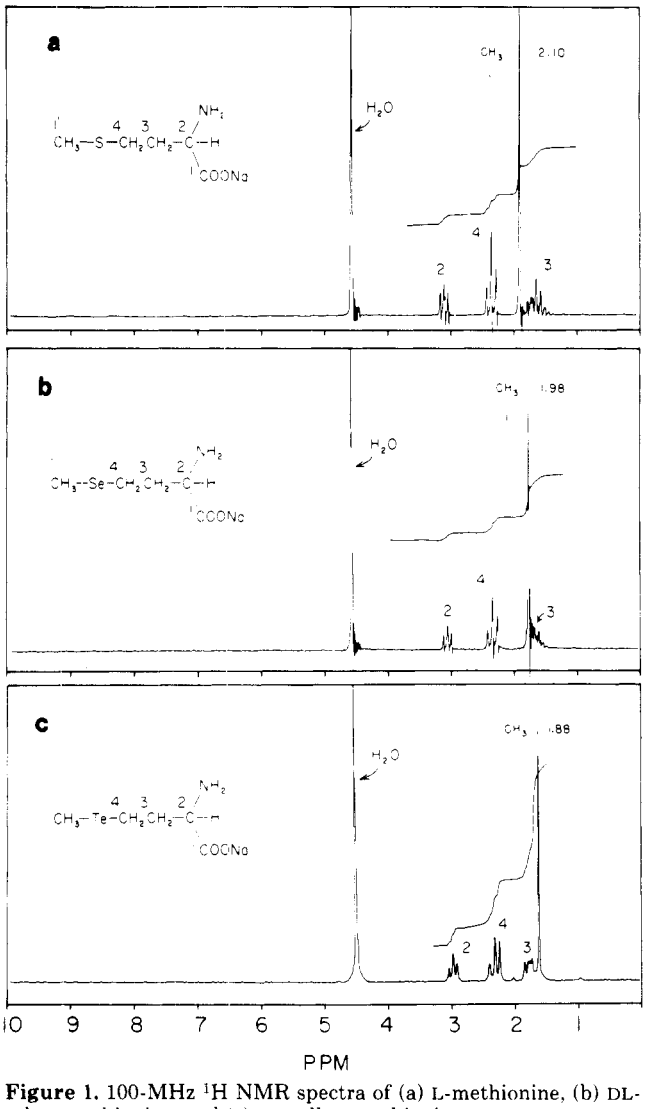

Figure 1. 100-MHz ^1H NMR spectra of (a) L-methionine, (b) DL-selenomethionine, and (c) DL-telluromethionine.

The identification of **4c** as the product obtained upon basic hydrolysis of 3 was further confirmed by NaOD hydrolysis of 3 under the conditions described earlier. The product exhibited a single UV-absorbing, ninhydrin-positive component that cochromatographed with the unlabeled **4c** using the TLC system described earlier. The NMR spectrum of the deuterated product contained resonances at δ 1.88, 1.99, and 2.57 that corresponded to the methyl, β-methylene, and γ-methylene protons of **4c**, respectively. The α-methine resonance that was observed at 3.25 ppm in the spectrum of unlabeled **4c** (Figure 1c) was absent in the spectrum of the product obtained upon NaOD hydrolysis of 3. These data demonstrate the expected incorporation of one deuterium atom to form 2-deuterio-DL-α-amino-γ-(methyltelluro)butyric acid. The presence of one deuterium at this position in the NaOD hydrolysis product was further confirmed by mass spectral analysis of the material obtained upon H_2SO_4 acidification of the NaOD hydrolysis mixture. A parent peak was observed at *m/z* 248 (i.e., M^+ of **4c** + 1 amu), and the presence of other fragmentation peaks confirmed the incorporation of one deuterium at the α-methine carbon.

The results described in this paper represent the first reported synthesis of an alkyltelluro-substituted α-amino acid. The intermediate 5-(alkyltelluro)-substituted hydantoins can be readily prepared by reaction of alkyltellurols with the required 5-(haloalkyl)hydantoins. Therefore, we believe this approach may be of general use for the preparation of a wide variety of telluroamino acids.

Experimental Section

Low-resolution mass spectral analyses were performed using the Oak Ridge National Laboratory's low-resolution instrument under the following conditions: ionizing energy, 70 eV; probe temperature, 300–380 °C; source temperature, 120 °C; trap current, 100 μA. High-resolution measurements were performed with an AEI MS 50 mass spectrometer equipped with a DS 50 data system: ionizing energy, 70 eV; source temperature, 280–320 °C; probe temperature, ~200 °C; trap current, 500 μA; resolution, 10^4; scan rate, 10 s/decade; accelerating potential, 8000 V. All tellurium-containing mass peaks are reported for ^{130}Te. Infrared spectra were obtained with a Beckman IR-18A. Ultraviolet spectra were obtained in MeOH with a Beckman DB instrument. A Varian XL-100 spectrometer was used for determining NMR spectra in either Me_2SO-d_6 (internal tetramethylsilane standard) or NaOD (internal sodium 2,2-dimethyl-2-silapentane-5-sulfonate standard) solution. The TLC analyses were performed using 250-μm layers of silica gel PF-254: system 1, MeOH–$CHCl_3$, 5:95; system 2, BuOH–HOAc–H_2O, 4:1:1. Melting points were determined in open capillary tubes and are uncorrected.

The 5-(β-bromoethyl)hydantoin was prepared from DL-homoserine in the usual manner[13] and exhibited the expected physical properties.

All other chemicals and solvents were analytical grade and were used without further purification.

5-[(β-Methyltelluro)ethyl]hydantoin (3). Sodium ditelluride (Na_2Te_2) was generated by reaction of tellurium powder (45 μm) with metallic sodium in liquid ammonia[10] and was alkylated with methyl iodide to give dimethyl ditelluride.[11] Sodium borohydride reduction[3] of the ditelluride (~11 mmol) in benzene–methanol (1:1) under an argon atmosphere generated methyltellurol. The 5-(β-bromoethyl)-hydantoin[13] (880 mg, 4.2 mmol) was added in a small volume of methanol, and the mixture was stirred at room temperature for 30 min, at which time TLC (system 1) indicated the reaction to be complete. The mixture was poured into water, and the aqueous solution was extracted with benzene, acidified to pH 2–3 with 10% H_2SO_4, and extracted with EtOAc. The desired product was extracted in the EtOAc layer, which was washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness in vacuo. The resulting tan-colored solid was crystallized from acetone–petroleum ether to give a white solid: 632 mg (55%); mp 132 °C; UV λ_{max} (MeOH) 232, 217 nm; IR ν_{max} (KBr) 1725, 1767 cm^{-1}; MS *m/z* 271.9815 (M^+; calculated for $C_6H_{10}O_2N_2Te$, 271.9820), 257 (M – CH_3), 186 (M – C_2O_2NH), 173 (M – hydantoin ring), 127 (M – CH_3Te), 99 (M – C_3H_7Te); ^1H NMR (Me_2SO-d_6, internal Me_4Si standard) δ 1.86 (s, 3 H, CH_3), ~1.94 (m, 2 H, β-CH_2), 2.56 (m, 2 H, γ-CH_2), 4.03 (m, 1 H, α-CH), 6.45 (s, 1 H, NH), 7.91 (s, 1 H, NH). The δ 6.45 and 7.91 resonances were absent in the spectrum of the sample shaken with D_2O.

DL-α-Amino-γ-(methyltelluro)butyric Acid (4c, "Telluromethionine"). The hydantoin **3** (40 mg, 0.15 mmol) was hydrolyzed with a 2 molar excess of 1 N NaOH in a teflon-lined bomb by heating at 165–167 °C for 1 h. The solution was carefully acidified to pH 5–6 with 10% H_2SO_4, filtered, and lyophilized to give a tan solid (**4c** and inorganic salts): UV λ_{max} (H_2O) 232, 217 nm; MS *m/z* 246.9879 (M^+; calculated for $C_5H_{11}NO_2Te$, 246.9881), 232 (M – CH_3), 202 (M – CO_2H), 186 (M – H_2O – CH_3 – CO), 173 (M – CO_2H – CH_3N), 74 (M – CH_3Te – H_2O), 56 (C_3H_6N); ^1H NMR (D_2O) (Figure 1).

A second sample of the hydantoin (0.15 mmol) was hydrolyzed in 1 N NaOD and worked up in the same manner: UV λ_{max} (H_2O) 232, 217 nm; MS *m/z* 248 (M^+), 233 (M – CH_3), 203 (M – CO_2H), 187 (M – H_2O – CH_3 – CO), 173 (M – CO_2H – CH_2DN), 75 (M – CH_3Te – H_2O), 57 (C_3M_5DN); ^1H NMR (D_2O, internal, 2,2-dimethyl-2-silapentane-5-sulfonate standard) δ 1.88 (s, 3 H, CH_3), 1.99 (m, 2 H, β-CH_2), and 2.57 (m, 2 H, γ-CH_2).

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Registry No.—**1**, 25284-83-7; **2**, 68876-71-1; **3**, 68876-72-1; **4a**, 63-68-3; **4b**, 2578-28-1; **4c**, 68876-73-3.

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Reinvestigation of the Structure of Ristomycinic Acid, a Bis(amino acid) Obtained from Ristomycin

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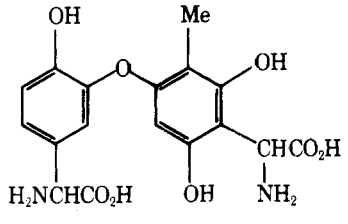
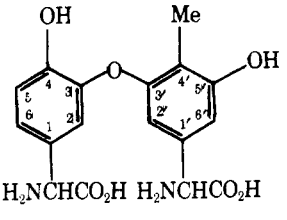
Ristomycinic acid is a component of the peptide in ristomycin A, which is an antibiotic elaborated by *Proactinomyces fructiferi* var. *ristomycini*. The compound was assigned as **1** on the basis of the empirical formula $C_{17}H_{18}N_2O_8$ which was established by elemental analyses, NMR spectra, and other data, the most important being the structures of hydrogenolysis products.[1] This compound has been claimed[2] to be present in a similar antibiotic, ristocetin A, which is a metabolite of *Nocardia lurida*, but studies by Fehlner et al.[3] indicated a different empirical formula ($C_{17}H_{18}N_2O_7$) for the corresponding substance from that source. Harris et al.[4] assigned structure **2** to the compound from ristocetin on the basis of oxidative degradation to esters **3** and **4**, followed by an independent synthesis of **4**. A recent investigation of the mass spectrum of the dimethyl ester of tri-*O*-acetyl-*N*,*N'*-diacetylristomycinic acid by Katrukha et al.[5] showed that unprotected ristomycinic acid has the empirical formula $C_{17}H_{18}N_2O_7$, identical with that assigned by Fehlner et al.[3] for the compound from ristocetin. On the basis of this spectrum, Katrukha concluded that the compounds from ristomycin A and ristocetin A appear to be identical, but the data do not exclude the possibility that ristomycinic acid and the compound from ristocetin are structural isomers with similar chemical and chromatographic behavior. We now wish to report our studies of ristomycinic acid which establish **2** as its structure.



1



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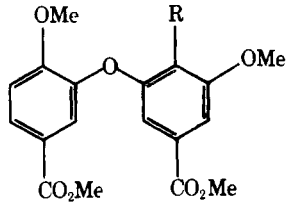

3, R = Me
4, R = CO_2Me

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