54-8; diethylzinc, 557-20-0; 3-phenyl-1-pentene, 19947-22-9; 1-phenyl-1-pentene, 826-18-6; ethylzinc iodide, 999-75-7; propargyl tosylate, 6165-76-0.

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Synthesis and Structure Reassignment of Mercaptohistidines of Marine Origin. Syntheses of L-Ovothiols A and C

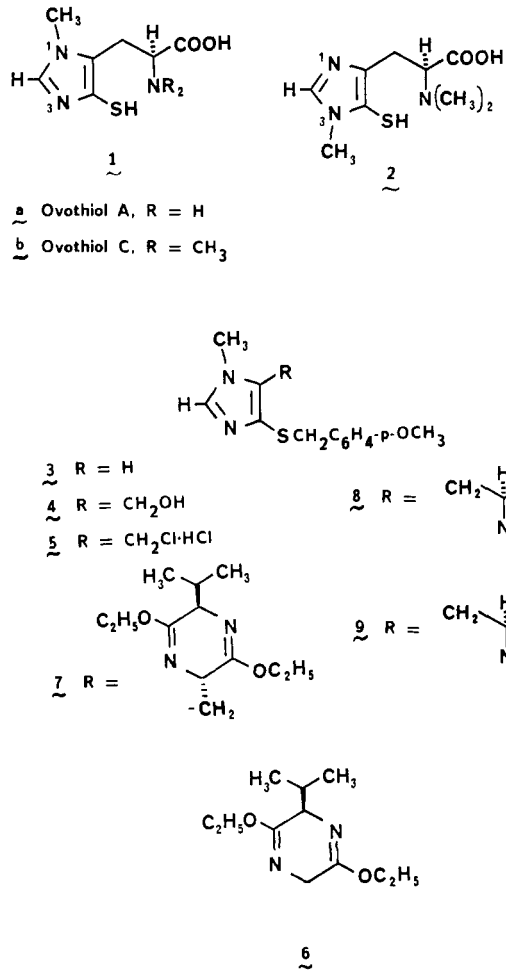
Summary: Synthetic and spectroscopic studies demonstrate that, in contrast to an earlier assignment, all ring-methylated mercaptohistidines of marine origin reported to date belong to the 1-methyl (e.g., 1) family.

Sir: The eggs of a variety of marine invertebrates contain N-methylated 4-mercaptohistidines[1,2] in concentrations (5 mM) comparable to relatively abundant constituents such as ATP and glutathione.[2a] Although the function of these thiols remains unknown, the facility with which they are oxidized in vitro has prompted speculation that they function in vivo as scavengers of active oxygen species.[2a] The functionality in these substances additionally suggests a potential role as metal chelating agents.[3] The N-methylated 4-mercaptohistidines have also been identified as structural subunits in marine natural products such as adenochromines[4] and, most recently, imbricatine,[5] an alkaloid isolated from starfish.

A structural dichotomy involving the methylation pattern of marine 4-mercaptohistidines has arisen, those isolated from the Pacific[2,5] having been characterized as 1-methyl-4-mercaptohistidines (e.g., 1) and those from organisms collected in the Bay of Naples as belonging to the 3-methyl-4-mercaptohistidine family (e.g., 2).[1,4] We report here that independent chemical synthesis of **1a** and **1b** confirms their identity to 4-mercaptohistidines isolated from Pacific organisms and present evidence that the structures of 4-mercaptohistidines and their derivatives from organisms in the Bay of Naples should be reformulated as their 1-methyl isomers (e.g., 1).

Authentic **1a** was prepared from the parent heterocycle **3**.[6] Hydroxymethylation of **3** (aqueous CH_2O, pH 4.6, NaOAc, HOAc, reflux, 3.5 h)[7] afforded imidazole **4**, mp 113-114 °C, in 76% yield.[8] Treatment of **4** with excess thionyl chloride (0.5 h 25 °C) afforded the chloride **5** (93%) which was coupled with the organolithium reagent derived from **6** in THF (−78 °C to 25 °C) to yield **7** (84% from **4**, a 5:1 mixture of epimers at the newly formed chiral center).[9] Chromatographic separation of the major diastereoisomer (silica gel) followed by hydrolysis (aqueous HCl, 25 °C to reflux) gave the thiol-protected amino acid **8** (58%) which was separated (silica gel) from the coproduct D-valine. Finally, deprotection of **8** [$Hg(OCOCF_3)_2$/HO-$COCF_3$/anisole][10] afforded 1-methyl-L-4-mercaptohistidine (ovothiol A, **1a**), the UV absorbance spectrum of which was identical with naturally derived ovothiol A.[2b] Air oxidation of synthetic ovothiol A[11] followed by chromatography on Sephadex LH-20 (80% aqueous ethanol) afforded the disulfide of **1a** in 94% yield from **8**, $[\alpha]^{20}_D$ +77° [*c* 6.5 mg/mL in 0.1 M HCl(aq)],[12] which was identical with the

Chart I



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(6) Spaltenstein, A.; Holler, T. P.; Hopkins, P. B. *J. Org. Chem.* **1987**, *52*, 2977. Prepared in three steps (54% overall yield) by (i) treatment of *N*-(cyanomethyl)-*N*-methylformamide and Et_3N in EtOH with H_2S [-CN → -C(=S)NH_2]; (ii) cyclization with 6 equiv of Et_3N and 4.5 equiv of $(CH_3)_3SiCl$ in CH_2Cl_2; and (iii) alkylation with *p*-methoxybenzyl chloride.

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(8) Structures were supported (unless otherwise specified) by ^1H NMR, IR, and, where applicable, low resolution MS and UV spectra. Satisfactory high resolution MS were obtained for selected intermediates.

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(10) Nishimura, O.; Chieko, K.; Fujino, M. *Chem. Pharm. Bull.* **1978**, *26*, 1576.

(11) A trace of Cu^{2+} is necessary for clean conversion.

(12) A value of $[\alpha]^{20}_D$ +76° (*c* 1.2, 0.1 N HCl) is reported in ref 1a for the substance that we now reformulate as the disulfide of L-ovothiol A (**1a**).

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naturally obtained disulfide[2b] (500-MHz ^{1}H NMR,[13] UV). The S-protected 4-mercaptohistidine **8** was diverted to L-ovothiol C (**1b**) by reductive methylation (aqueous CH_2O, $NaBH_3CN$) followed by deprotection as described above, to afford L-ovothiol C (**1b**, 78% from **8**). Again, air oxidation[11] afforded a disulfide, $[\alpha]^{20}_D$ +77° (*c* 10 mg/mL, H_2O),[14] which was identical with natural ovothiol C disulfide[2a] (500-MHz ^{1}H NMR,[13] UV). These results clearly support the assignment of Pacific 4-mercaptohistidines to the 1-methyl family.

A sample of the substance previously identified as the disulfide of **2** became available to us.[15] A 1:1 mixture of the putative disulfide of **2** and the disulfide of naturally derived[2a] ovothiol C (**1b**) showed only a single set of proton resonances at 500 MHz. The unlikely possibility that **1b** and **2** might simply be indistinguishable by 500-MHz ^{1}H NMR was ruled out by the observation of nuclear Overhauser enhancements in the putative **2** of both the H-α and one of the H-β resonances on irradiation of the aromatic N-methyl resonance. These results are only consistent with the reformulation of **2** as **1b**.[16,17]

The methylated 4-mercaptohistidines (and in all probability this unit of their derivatives) isolated independently in the Bay of Naples and the Pacific are thus identical with regard to the methylation pattern of the imidazole ring, and all belong to the 1-methyl (ovothiol) family. The incorrect assignments appear to have resulted from nomenclatural confusion[18] regarding the commercial authentic samples of histidine derivatives to which Raney nickel reduction products were compared.[1,4] It is likely that this structural unit will be found in other marine natural products; the involvement of the ovothiols in active oxygen detoxification or metal ligation remains to be studied. Further studies on the chemistry and biochemistry of the ovothiols are in progress.

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Supplementary Material Available: Experimental procedures and physical data for synthetic intermediates and ovothiols A and C and their disulfides; 500-MHz ^{1}H NMR mixing and NOE experiments (17 pages). Ordering information is given on any current masthead page.

(13) Identity was established by the presence of a single set of resonances on admixture of equimolar quantities of the independent samples.
(14) A value of $[\alpha]^{20}_D$ +79° (*c* 6.5, H_2O) is reported in ref 1b for the substance that we now reformulate as the disulfide of L-ovothiol C (**1b**).
(15) We thank Professor A. Palumbo for a gift of the disulfide of what we reformulate as **1b** from the Bay of Naples.
(16) Professor A. Palumbo has reexamined the samples of mercaptohistidines from the Bay of Naples and concurs with our structure reassignment. Her group will independently communicate their studies (private communication to B. M. Shapiro).
(17) The assignment in ref 1a and 1b of the methylated 4-mercaptohistidines to the L family of amino acids is unchanged.
(18) IUPAC Commission on Nomenclature of Amino Acids and IUPAC-IUB Commission on Biochemical Nomenclature *Biochemistry* **1975**, *14*, 449.

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Synthesis of Functionalized, Stereochemically Defined Tetrasubstituted Alkenes

Summary: The use of alkyl (*E*)- or (*Z*)-2,3-bis(trimethylstannyl)-2-alkenoates as excellent precursors for the synthesis of functionalized, tetrasubstituted alkenes is demonstrated.

Sir: A number of excellent methods for the stereochemically controlled formation of di- and trisubstituted alkenes are known.[1] However, methodology aimed at or leading to processes useful for the preparation of stereochemically homogeneous tetrasubstituted alkenes has been rather scarce.[2] Recently, we reported[3a] that alkyl (*Z*)-2,3-bis(trimethylstannyl)-2-alkenoates **1** are readily available via $(Ph_3P)_4Pd$-catalyzed addition of $(Me_3Sn)_2$ to the corresponding α,β-acetylenic esters ($RC{\equiv}CCO_2R'$). Furthermore, it was shown[3a] that substances of general structure **1** readily undergo thermally induced isomerization to the corresponding *E* isomers **2**. We report herein that compounds **1** and **2** are valuable precursors for the synthesis of diversely functionalized, stereochemically defined tetrasubstituted alkenes.

Treatment of **2a** with 1.1 equiv of methyllithium in dry tetrahydrofuran (THF) (−98 °C, 20 min)[3b] effected clean transmetalation of the α-Me_3Sn group. Alkylation of the resultant anion with reagent A[4] (−98 °C, 30 min; −78 °C, 1.5 h) gave **3a**[5] as the sole substitution product (69%, Chart I),[6] while alkylation with reagents B–E[4] produced the β-trimethylstannyl α,β-unsaturated esters **3b–e**,[7] respectively. In similar fashion, transmetalation of the substrates **2b** and **2c** and treatment of the resultant nucleophiles with various alkylating agents (**2b**, MeI, A,[4] B;[4] **2c**, MeI, A[4]) afforded, efficiently, substances **4** and **5**. In each case, the alkylation product was formed as a single isomer.

Transmetalation–alkylation of (*Z*)-2,3-bis(trimethylstannyl)-2-alkenoates **1** provides products with the *same* stereochemistry as those derived from the *E* isomers **2**. For example, treatment of **1a** and **1b** with methyllithium in THF (−98 °C), followed by alkylation of the resultant intermediates with reagent F,[4] gave exclusively products **6** and **7**, respectively. Presumably, transmetalation of **1** and **2** leads to the formation of allenoate anions, which alkylate from the side opposite to the bulky Me_3Sn group. Notably, the alkylations were quite efficient even with substrates (**1b**, **2c**) containing fairly bulky R groups (isopropyl, cyclopropyl, respectively).

The fact that substances **3–7** possess the depicted stereochemistry was confirmed in representative cases by

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(4) A, 3-iodo-2-methylpropene; B, 1-bromo-3-methyl-2-butene; C, 2,5-diiodo-1-pentene; D, 3-chloro-1-iodopropane; E, 3-bromo-1-(trimethylsilyl)propyne; F, 3-iodopropene; G, 5-chloro-1-iodopentane; H, 2,3-dibromopropene.
(5) All compounds reported herein exhibited spectra in full accord with structural assignments. For new compounds, molecular masses were determined by high resolution mass spectrometry. For compounds that did not exhibit molecular ions, accurate measurements were done on an identifiable fragment [trimethylstannyl compounds, $M^+ - Me$ (15); 2-(methoxyethoxy)methyl ethers, $M^+ - C_3H_7O_2$ (75) or $M^+ - C_4H_9O_2$ (89)].
(6) The numbers given in parentheses in Chart I represent yields of purified, distilled products. The yields of the various reactions involved have not been optimized.
(7) Substances **3c–e** were accompanied by varying (minor) amounts of the corresponding products in which R = H.

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