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.

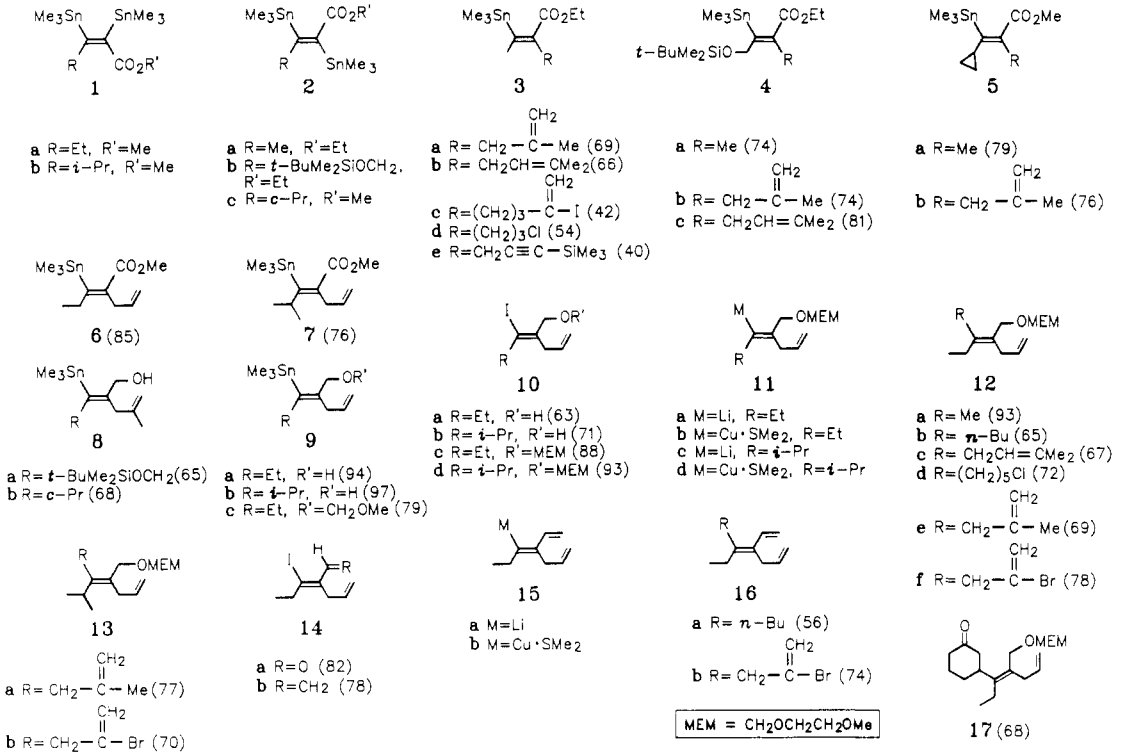
Transmetalation–alkylation of (*Z*)-2,3-bis(trimethylstannyl)-2-alkenoates **1** provides products with the *same* stereochemistry as those derived from the *E* isomers **2**. For example, treatment of **1a** and **1b** with methyllithium in THF (−98 °C), followed by alkylation of the resultant intermediates 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

(1) Reucroft, J.; Sammes, P. G. *Q. Rev. Chem. Soc.* **1971**, *25*, 135. Faulkner, D. J. *Synthesis* **1971**, 175. Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87. Bennett, G. B. *Synthesis* **1977**, 589. Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. Chan, T. H. *Acc. Chem. Res.* **1977**, *10*, 442. Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.
(2) For recent reports, see: (a) Chu, K. H.; Wang, K. K. *J. Org. Chem.* **1986**, *51*, 767. (b) Negishi, E.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem.* **1986**, *51*, 4080.
(3) (a) Piers, E.; Skerlj, R. T. *J. Chem. Soc., Chem. Commun.* **1986**, 626. (b) Piers, E.; Chong, J. M. *J. Org. Chem.* **1982**, *47*, 1602.
(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.

0022-3263/87/1952-4421$01.50/0

Chart I



^{1}H NMR spectroscopy. For example, in difference nuclear Overhauser enhancement experiments involving compound **6**, irradiation at δ 3.72 (CO_2Me) caused enhancement of the singlet at δ 0.15 ($SnMe_3$), while irradiation at δ 2.44 (CH_2CH_3) intensified the signals at δ 3.18 ($CH_2CH{=}CH_2$) and 0.15 ($SnMe_3$).

Reduction of **4b**, **5b**, **6**, and **7** with $LiAlH_4$ or *i*-Bu_2AlH in diethyl ether provided the functionalized allylic alcohols **8a**, **8b**, **9a**, and **9b**, respectively. It may be noted that **8a** is a *trans*-2-butene-1,4-diol derivative in which one of the hydroxyl groups is protected.

Although substance **9a** is readily transformed ($MeOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2) into the ether **9c**, all attempts to effect clean transmetalation of the latter material with different alkyllithium reagents under a variety of conditions met with failure. Presumably, the sterically hindered nature of the Me_3Sn function is primarily responsible for the fact that the transmetalation process is very sluggish.[2a,8]

Treatment of **9a** and **9b** with I_2 in CH_2Cl_2[9] produced smoothly the iodides **10a** and **10b**, which were transformed ($MeOCH_2CH_2OCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2) into the ethers **10c** and **10d**, respectively. Facile lithium–iodine exchange was effected by treatment of the latter substances with either 1.1 or 2.2 equiv of *n*-BuLi in THF at −78 °C for 10 min.[10] Direct alkylation of the vinyllithium species **11a** with MeI, *n*-BuI, and reagents B[4] and G[4] afforded the stereochemically homogeneous tetrasubstituted alkenes **12a–d**, respectively. However, treatment of **11a** with reagent A,[4] an allylic iodide, returned the iodide **10c** (93%) via a "reverse" lithium–iodine exchange. This problem could be avoided by conversion (1 equiv of $CuBr{\cdot}Me_2S$, −48 °C) of **11a** into the corresponding vinylcopper(I) species **11b**, which cleanly coupled with the allylic halides A[4] and H[4] to provide substances **12e** and **12f**, respectively. Similarly, **13a** and **13b** could be obtained readily by reaction of A[4] and H[4] with the vinylcopper(I) reagent **11d** (derived from **11c**).

That the presence of the metal-coordinating $OCH_2OCH_2CH_2OMe$ function is not necessary for effecting conversions of the type **10c** → **12** and **10d** → **13** was shown as follows. Oxidation (pyridinium chlorochromate, NaOAc, CH_2Cl_2) of **10a** afforded the aldehyde **14a**, which was cleanly transformed ($Ph_3P{=}CH_2$) into the triene **14b**. Subjection of the latter substance to lithium–iodine exchange (1.2 equiv of *n*-BuLi), followed by reaction of the resultant vinyllithium reagent **15a** with *n*-BuI, gave **16a**. Similarly, **16b** could be obtained readily by coupling the vinylcopper(I) species **15b** (derived from **15a**) with reagent H.[4]

Interestingly, hindered vinylmetallics derived from (some of) the vinyl iodides described above can be added conjugately to enones. For example, successive addition of $MgBr_2{\cdot}Et_2O$ (1.1 equiv), $CuBr{\cdot}Me_2S$ (0.25 equiv), 2-cyclohexen-1-one (1.05 equiv), and $BF_3{\cdot}Et_2O$ (1.1 equiv) to a THF–Et_2O solution (−78 °C) of the vinyllithium reagent **11a**, followed by stirring of the reaction mixture at −78 °C for 3 h, afforded the substituted cyclohexanone **17**.

In conclusion, it is worthwhile to note that in the tetrasubstituted alkenes prepared via the methods summarized above, two (trans) substituents on the double bond are derived from readily synthesized α,β-acetylenic esters, while the other two (trans) groups are introduced by alkylation reactions. The demonstrated and potential feasibility of synthetically manipulating the ester function, along with the possibility of employing a wide variety of functionalized alkylating reagents in addition to A–H,[4] indicates that a versatile and effective synthesis of functionalized, stereochemically defined tetrasubstituted al-

(8) Collins, P. W.; Jung, C. J.; Gasiecki, A.; Pappo, R. *Tetrahedron Lett.* **1978**, 3187.

(9) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851 and references given therein.

(10) Careful examination of the **10c**–*n*-BuLi reaction showed that the use of 1.1 equiv of *n*-BuLi produced cleanly the desired vinyllithium reagent **11a**, presumably accompanied by 1 equiv of *n*-BuI. On the other hand, when 2.2 equiv of *n*-BuLi was employed, 1 equiv of *n*-octane was produced in addition to the vinyllithium species. In order to avoid the presence of *n*-BuI most of our experiments were done with 2.2 equiv of *n*-BuLi.

kenes has been developed. Work in this area is continuing.

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Supplementary Material Available: Representative experimental procedures for the preparation of and spectral data for compounds **6**, **9a**, **10a**, **10c**, **12d**, **12e**, **14a**, **14b**, and **16b** (6 pages). Ordering information is given on any current masthead page.

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Intramolecular Cyclization via Onium Salts. A Novel Synthesis of 1,3-Thiazolidines from Chloromethyl (Trimethylsilyl)methyl Sulfide and Nitrogen-Containing Heteroaromatic Compounds

Summary: Polycyclic 1,3-thiazolidines were prepared by the fluoride ion promoted desilylation, followed by intramolecular 1,5-cyclization, of onium salts derived from the sulfide 1 and a variety of heteroaromatics.

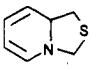
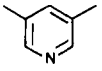
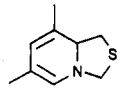
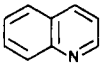
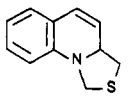
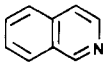
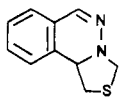
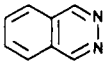
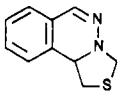
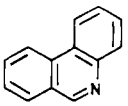
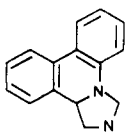
Sir: In the course of our studies on the use of organosilicon compounds to obtain nonstabilized 1,3-dipolar reagents, we have found a new type of desilylation which leads to fused ring 1,3-thiazolidines. In this process, reaction of chloromethyl (trimethylsilyl)methyl sulfide (**1**)[1b] with nitrogen heterocycles (e.g., **2**) including pyridine, quinoline, isoquinoline, phthalazine, and phenathridine gives the isolable onium salts, e.g., **3**. Treatment of these salts with cesium fluoride in acetonitrile at room temperature gave fused polycyclic 1,3-thiazolidines **4** in quite high yields (Scheme I). The results are listed in Table I.

The synthesis of **4** can be conveniently attained without isolation of the onium salts by a one-pot operation starting from a mixture of **1**, heterocycles **2**, and cesium fluoride in acetonitrile at room temperature. Formation of the intermediate onium salts **3** is not confirmed in this case; However, reactions of **1** with heteroaromatics as the heterodipolarophile are presumably stepwise, contrary to reactions of **1** with activated alkenes and alkynes, which give tetrahydro- and dihydrothiophenes.[1b,3]

The present method provides a new type of 1,5-dipolar cyclization reaction which is accompanied by the fluoride ion promoted desilylation[4,5] and is formally a [3 + 2] cycloaddition between the carbon–nitrogen double bond and thiocarbonyl ylide. In this sense, it is the first example of the introduction of the thiocarbonyl ylide synthon to heteroaromatic compounds.

In a typical procedure a mixture of the sulfide **1** (1.2 mmol) and the nitrogen-containing heteroaromatic compound **2** (1.0 mmol) was heated at 60 °C for 1 h and the resulting salt **3** was washed with dry acetone. Dried cesium fluoride (1.0 mmol) and acetonitrile (5 mL) were added and the mixture was stirred at room temperature for the time indicated in Table I. After the addition of water (5 mL) and diethyl ether (30 mL), usual workup and prepa-

Table I. Synthesis of 1,3-Thiazolidines 4[a]

entry	2	% yield[b] of 3	reactn time, h[c]	4	% yield[d] of 4
1	 **3a**	94	25	 **4a**	96
2	 **3b**	91	70	 **4b**	91
3	 **3c**	98	45	 **4c**	95
4	 **3d**	98	48	 **4d**	91
5	 **3e**	96	48	 **4e**	92
6	 **3f**	75	234	 **4f**	43

[a] The synthesis of the salts **3** was conducted at 60 °C for 1 h. All reactions of **3** with cesium fluoride were carried out in acetonitrile at room temperature. [b] Isolated yield. Not optimized. [c] Reaction time for cyclization. [d] Isolated yield by TLC. Not optimized. All products showed satisfactory spectral data.

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