(*E,E*)-**5a** (R^3 = NEt_2), 109929-06-8; (*E,E*)-**5a** (R^3 = $SiMe_2Ph$), 109929-08-0; (*E,Z*)-**5a** (R^3 = *n*-Bu), 109959-45-7; (*E,E*)-**5b** (R^3 = *n*-Bu), 109929-03-5; (*E,E*)-**5b** (R^3 = *t*-Bu), 109929-04-6; (*E,E*)-**5b** (R^3 = $SiMe_2Ph$), 109929-09-1; (*E*)-**5c** (R^3 = *n*-Bu), 78500-35-3; (*E*)-**5c** (R^3 = NEt_2), 101456-04-6; (*E*)-**5c** (R^3 = $SiMe_2Ph$), 109929-10-4; (*E*)-**5d** (R^3 = *n*-Bu), 109929-05-7; (*E*)-**5d** (R^3 = NEt_2), 109929-07-9; (*E*)-**5d** (R^3 = $SiMe_2Ph$), 109929-11-5; (*E,E*)-**6a**, 109929-12-6; (*Z,E*)-**6a**, 109929-13-7; (*E,E*)-**6b**, 109929-14-8; (*Z,E*)-**6b**, 109929-15-9; (*E*)-**6c**, 109929-16-0; (*Z*)-**6c**, 109929-17-1; (*E*)-**6d**, 109929-18-2; (Z)-**6d**, 109929-19-3; $Br(CH_2)_2Br$, 106-93-4; MeCH(CHO)Me, 78-84-2; *n*-BuLi, 109-72-8; *sec*-BuLi, 598-30-1; *t*-BuLi, 594-19-4; Et_2NLi, 816-43-3; $PhMe_2SiLi$, 3839-31-4; Me_3SnLi, 17946-71-3; octanal, 124-13-0; acetone, 67-64-1; cyclohexanal, 2043-61-0; pyridinium *p*-toluenesulfonate, 24057-28-1; (E)-6-pentadecene, 74392-31-7; 3-(tetrahydropyranoxy)-1-undecene, 109929-20-6.

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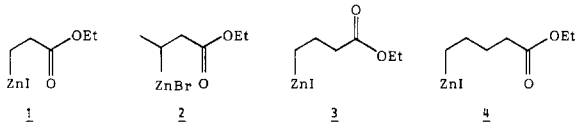
Received May 13, 1987

Unsaturated Ester Synthesis via Cu(I)-Catalyzed Allylation of Zinc Esters

Summary: CuCN-catalyzed allylation of ethyl β-(iodozincio)propionate (**1**), ethyl β-(bromozincio)butyrate (**2**), ethyl γ-(iodozincio)butyrate (**3**), and ethyl δ-(iodozincio)-pentanoate (**4**) with allylic halide or tosylate provides ethyl 5-hexenoates, ethyl 6-heptenoates, and ethyl 7-octenoates in high yields. Regioselectivity of the allylation and the reaction of **3** with propargyl tosylate are also discussed.

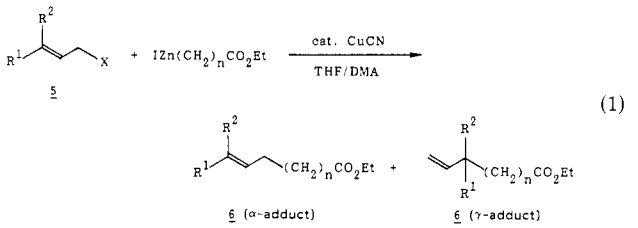
Sir: Recently we have shown that β-zinc ester **1** and γ-zinc ester **3** can be generated by a direct metalation of the corresponding iodides with Zn–Cu.[1] This method was found general for the generation of the higher homologues (δ- (**4**), ε-, and ζ-zinc esters) and secondary C–Zn derivatives (e.g., **2**). Here we report allylation of **1–4**, which, in



1 **2** **3** **4**

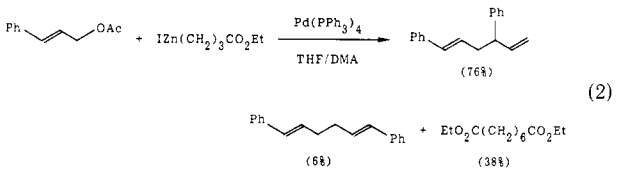
principle, coupled with a vinylation,[2] might constitute a general entry to the synthesis of unsaturated acid derivatives with olefin at any desired position more remote than the γ-position of carbonyl (eq 1).[3]

Owing to low nucleophilic reactivity, allylation has been successful for some organozincs, which possess a polarized



5 **6** (α-adduct) **6** (γ-adduct) (1)

C–Zn bond: direct allylation of (trifluoromethyl)zinc bromide[4] and Pd(0)-catalyzed allylation of α-zinc ester[5] and phenylzinc chloride.[6] Making contrast to the latter two examples, the Pd(0)-catalyzed allylation of **3** resulted in a self-coupling, and no expected product **6** was detected (eq 2).[7] However, cuprous cyanide[8] was found to nicely



(76%) (6%) (38%) (2)

catalyze the allylation of zinc esters **1–4** (eq 1).[9] Results are summarized in Table I.[10] The allylation was undertaken either at 60 °C for 1 h (conditions A) or at room temperature overnight (conditions B). Under the conditions B, the zinc esters **1–4** were filtered under nitrogen to remove an excess of Zn–Cu before treating with **5**. Without the filtration, a homocoupling of allylic halide becomes a serious side reaction. Tosylates were directly used after preparation by treatment of the corresponding alcohols with 1 equiv of *n*-BuLi (*n*-hexane solution) in THF at −78 °C and then with 1 equiv of tosyl chloride at 0 °C. These tosylates readily undergo an exchange reaction with chloride ion at an ambient temperature, and an allylation agent in these experiments is a composite of a tosylate and a chloride (vide infra). The yields of **6** are generally high, irrespective of the wide structural variety of **5**. In the absence of CuCN, the yield of **6** was low (e.g., ethyl 3-(2′-cyclohexenyl)propionate in 33% yield at 60 °C for 2 h, cf. entry 3).

The regioselectivity for the unsymmetrical **5** was rather poor except for the cases in entries 14 and 15 and insensitive to the change in reaction conditions (entries 5 vs. 6), the kind of leaving groups (entries 6–8), and the structures of **5** and zinc esters. Generally the nucleophile was preferentially introduced to the γ-position. This general trend is apparent especially by a comparison of a pair of results (crotyl vs. α-methallyl tosylates, entries 10

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(2) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955.
(3) The chemistry of ε- and ζ-zinc esters is very similar to that of **1–4**, and hence only **1–4** were treated in this manuscript.
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(6) Chatterjee, S.; Negishi, E. *J. Org. Chem.* **1985**, *50*, 3406.
(7) Similar homocoupling was reported for Grignard reagents, allylic halides, and $FeCl_3$, $CoCl_2$, $NiCl_2$, or $CuCl_2$: Ohbe, Y.; Matsuda, T. *Tetrahedron* **1973**, *29*, 2989.
(8) For CuCN-mediated (stoichiometric) allylation of 4-pentenylzinc, see: Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 4427, 4431.
(9) One example of allylation of methyl α-methyl-β-(halozincio)-propionate was reported without experimental details: Nakamura, E.; Sekiya, K.; Kuwajima, I. *Tetrahedron Lett.* **1987**, *28*, 337.
(10) The reaction was performed as follows (entry 3, Table I): To a solution of 2-cyclohexenyl tosylate (1.2 mmol, see the text) were successively added 18 mg (0.2 mmol) of CuCN in 2 mL of dry THF and a solution of **1**, which had been prepared by heating a mixture of 1.5 mmol of ethyl 3-iodopropionate and 2.3 mmol of Zn–Cu in THF (4 mL)–DMA (*N,N*-dimethylacetamide, 2.2 mmol) at 60 °C for 3 h under nitrogen. The mixture was stirred at 60 °C for 1 h. After dilution with ether, washing with aqueous $NaHCO_3$, and drying over $MgSO_4$, followed by evaporation of the solvents, the residue was purified by column chromatography over silica gel (hexane–ether gradient) to provide ethyl 3-(2′-cyclohexenyl)-propionate in 82% yield based on 2-cyclohexenol.

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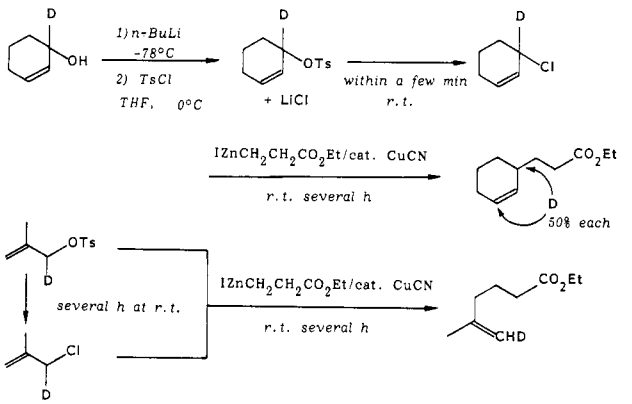
Table I. Copper(I)-Catalyzed Allylation of Zinc Esters 1–4[a]

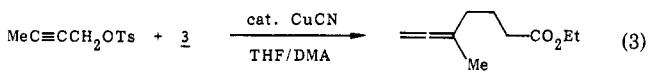
entry	zinc ester	allylating agent[b]	conditions[c]	% yield[d] of 6	6 (α:γ)[e]
1	1	allyl tosylate	A	89	
2	4	allyl tosylate	A	85	
3	1	2-cyclohexenyl tosylate	A	82	
4	1	2-methyl-5-isopropyl-2-cyclohexenyl tosylate	B	89	
5	1	cinnamyl tosylate	A	69	15:85
6	1	cinnamyl tosylate	B	80	13:87
7	1	cinnamyl bromide	B	93	12:88
8	1	cinnamyl chloride	B	99	13:87
9	2	cinnamyl bromide	B	85	14:86
10	3	crotyl tosylate	A	68	22:78
11	1	α-methallyl tosylate	B	50	28:72
12	3	3-methyl-2-butenyl tosylate	A	95	27:73
13	3	3-methyl-2-butenyl bromide	B	91	17:83
14	1	3-carbomethoxy-2-propenyl bromide	B	80	0:100
15	2	3-carbomethoxy-2-propenyl bromide	B	79	0:100

[a] Usual scale is as follows: 1–4 (generated from 1.5 mmol of the corresponding iodo (or bromo) ester and 2.3 mmol of Zn–Cu), allylating agent (1.2 mmol), CuCN (0.2 mmol) in THF (7 mL)–DMA (2.2 mmol). [b] In the case of tosylate, the allylating agent is a mixture of tosylate and chloride (see text). [c] Conditions for allylation. Conditions A: at 60 °C for 1 h. Conditions B: at room temperature overnight (involving a removal of Zn–Cu). [d] Isolated yield based on allylating agent. [e] See eq 1.

Scheme I



and 11) and makes a contrast to the sterically controlled Pd(0)-catalyzed allylation of α-zinc ester at the less substituted allylic terminus.[5]



(3)

In order to shed more light on the regioselectivity, the following label experiments were examined (Scheme I). Allylation of **1** with 1-deuterio-2-cyclohexenyl tosylate under the conditions B furnished ethyl 3-(2′-cyclohexenyl)propionate with an equal deuterium distribution at the C-1′ and C-3′ positions (90% yield). On the other hand, the similar treatment of 1-deuterio-2-methyl-2-propenyl tosylate with **1** regiospecifically gave ethyl 6-deuterio-5-methyl-5-hexenoate in 94% yield (a 1:1 mixture of cis and trans D). Independent experiments revealed that 1-deuterio-2-cyclohexenyl tosylate quickly underwent tosyloxy–chloride exchange to furnish 1-deuterio-2-cyclohexenyl chloride within a few minutes at room temperature.[11] The exchange of 1-deuterio-2-methyl-2-prepenyl tosylate was slow and completed after several hours at room temperature. The exchange was regiospecific within a limit of ^{1}H NMR detection and chloride was introduced at the carbon previously having been occupied by tosyloxy group.

The regioselectivity in Scheme I may constitute two extremes and suggests that a less reactive **5** undergoes substitution with organocopper (a presumable intermediate)[12] to give γ-product selectivity through an early transition state, while a reactive **5** reacts through a late transition state and provides a mixture of regioisomers. The results in entries 14 and 15 belong to the former and those of entries 5–13 may be the intermediate of the two extremes.[13]

Study on a stereoselection and an improvement of regioselectivity is under progress.

Acknowledgment. We are grateful for partial financial support from the Ministry of Education, Science and Culture, the Japanese Government (Grant-in-Aid for Special Project No. 60119002 and 61125002 and Scientific Research B No. 61470094).

Registry No. **1**, 104089-16-9; **2**, 109976-68-3; **3**, 104089-17-0; **4**, 109976-46-7; α-**6** (R^1 = R^2 = H, n = 2), 54653-25-7; α-**6** (R^1 = R^2 = H, n = 4), 35194-38-8; α-**6** (R^1 = H, R^2 = Ph, n = 2), 109976-51-4; γ-**6** (R^3 = H, R^2 = Ph, n = 2), 109976-52-5; α-**6** (R^1 = H, R^2 = CH_3, n = 3), 109976-55-8; γ-**6** (R^1 = H, R^2 = CH_3, n = 3), 109976-56-9; α-**6** (R^1 = R^2 = CH_3, n = 3), 109976-58-1; γ-**6** (R^1 = R^2 = CH_3, n = 3), 109976-59-2; γ-**6** (R^1 = H, R^2 = $COOCH_3$, n = 2), 109976-60-5; *cis*-**51**, 109976-65-0; *trans*-**51**, 109976-66-1; PhCH=CHCH$_2$CH(CH$_3$)CH$_2$COOEt, 109976-53-6; CH$_2$=CHCH(Ph)CH(CH$_3$)CH$_2$COOEt, 109976-54-7; CH$_2$=CHCH(CH$_3$)CH$_2$CH$_2$COOEt, 109976-57-0; CH$_3$CH=CHCH$_2$CH$_2$CH$_2$COOEt, 90646-46-1; MeOCOCH(CH=CH$_2$)CH(CH$_3$)CH$_2$COOEt, 109976-61-6; PhCH=CHCH$_2$CH(Ph)CH=CH$_2$, 69693-35-2; PhCH=CH(CH$_2$)$_2$CH=CHPh, 4439-45-6; EtOCO(CH$_2$)$_6$COOEt, 2050-23-9; *p*-CH$_3$C$_6$H$_4$SO$_2$OCH(D)C(CH$_3$)=CH$_2$, 109976-64-9; CH$_2$=C=C(CH$_3$)(CH$_2$)$_3$COOEt, 109976-67-2; CuCN, 544-92-3; Pd(PPh$_3$)$_4$, 14221-01-3; 3-cyclohexenyl tosylate, 109976-47-8; 2-methyl-5-isopropyl-3-cyclohexenyl tosylate, 109976-48-9; crotyl tosylate, 20443-68-9; α-methallyl tosylate, 20443-62-3; 3-methyl-2-butenyl tosylate, 66328-61-8; 3-methyl-2-butenyl bromide, 870-63-3; 3-carbomethoxy-2-propenyl bromide, 1117-71-1; ethyl 3-(3'-cyclohexenyl)propionate, 109976-49-0; ethyl 2-methyl-4-isopropyl-3-(cyclohexen-3-yl)-propanoate, 109976-50-3; 3-deuteriocyclohexen-3-ol, 55282-88-7; ethyl 3-(3-deuteriocyclohexen-3-yl)propanoate, 109976-62-7; ethyl 3-(1-deuteriocyclohexen-3-yl)propanoate, 109976-63-8; allyl tosylate, 4873-09-0; cinnamyl tosylate, 19627-30-6; cinnamyl bromide, 4392-24-9; cinnamyl chloride, 2687-12-9; cinnamyl acetate, 103-

(11) During standing at room temperature, 1-deuterio-2-cyclohexenyl chloride isomerized to 3-deuterio-2-cyclohexenyl chloride (1-D/3-D = 85:15 after 24 h).

(12) The same result as entry 3 (ref 10) was obtained by the use of 1.5 mmol of CuCN (1 equiv to zinc ester 1).

(13) The regioselectivity is also slightly dependent on the kind of organozincs: Diethylzinc, purified by distillation, reacted with cinnamyl chloride in the presence of 5 mol % of CuCN to provide a mixture of 3-phenyl-1-pentene and 1-phenyl-1-pentene (90:10) in 60% yield, while ethylzinc iodide, prepared in situ, provided a mixture of the same products in a ratio of 73:27 in 70% yield.

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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Received April 14, 1987

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

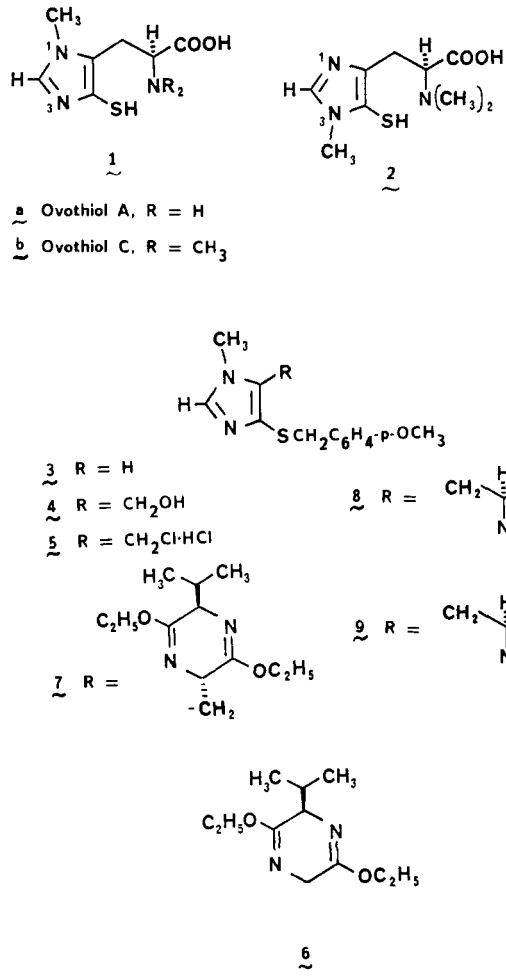
Summary: Synthetic and spectroscopic studies demonstrate that, in contrast to an earlier assignment, all ring-methylated mercaptohistidines of marine origin reported to date belong to the 1-methyl (e.g., 1) family.

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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(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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