SYNTHESIS OF 5-ARYLTHIO-3-METHYL-L-HISTIDINE, A MODEL FOR THE STARFISH ALKALOID IMBRICATINE†

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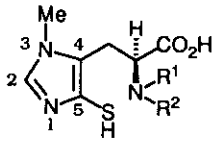
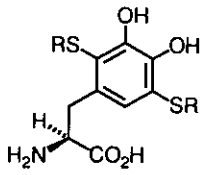
Abstract——Syntheses of 3-methyl-5-phenylthio-L-histidine (**8a**) and 3-methyl-5-(1-naphthyl)thio-L-histidine (**8b**), selected as models for the asteroid alkaloid imbricatine (**7**), have now become feasible through a 10-step route starting from 4(5)-bromoimidazole (**9**). The key steps involve replacement of the 4-bromo group by an arylthio group in the aldehyde (**14**) and construction of the L-alanine moiety in the chlorides (**17a,b**) by the "bis-lactim ether" method.

The 5-mercapto-3-methyl-L-histidine moiety has been found incorporated into constituents of several marine invertebrate animals. These constituents include ovothiol A (**1**) (and the corresponding disulfide) from unfertilized eggs of the sea urchin Paracentrotus lividus,[1] from the ripe gonads of the starfish Evasterias troschelii,[2a] and from the eggs of the sea urchin Arbacia lixula,[1b,c] of the holothurian Holothuria tubulosa,[1b,c] and of the asteroids Marthasterias glacialis[1b,c] and Astropecten aurantiacus;[1b,c] ovothiol B (**2**) from the ovarian tissue of the scallop Chlamys hastata;[2a] ovothiol C (**3**) (and the corresponding disulfide) from the eggs of sea urchins P. lividus,[1b,c] Sphaerechinus granularis,[1b,c] and Strongylocentrotus purpuratus;[2] adenochromines A, B, and C (**4**, **5**, and **6**), structural units in adenochrome (an iron(III)-binding peptide pigment) from the branchial heart of Octopus vulgaris;[1c,3] and im-

†Dedicated to Dr. Masatomo Hamana, Professor Emeritus of Kyushu University, on the occasion of his 75th birthday.



1: $R^1 = R^2 = H$
2: $R^1 = H$; $R^2 = Me$
3: $R^1 = R^2 = Me$



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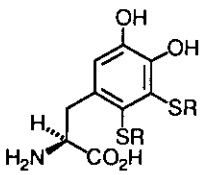

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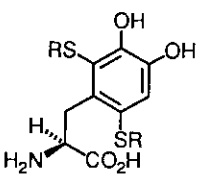

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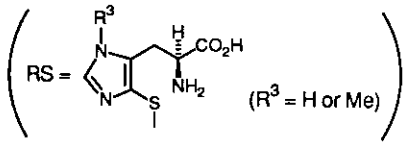

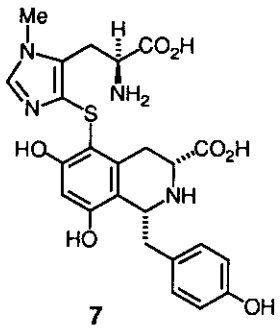

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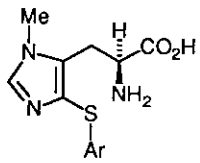
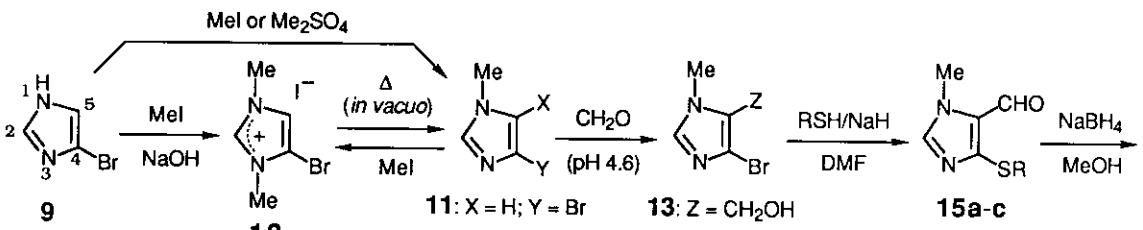


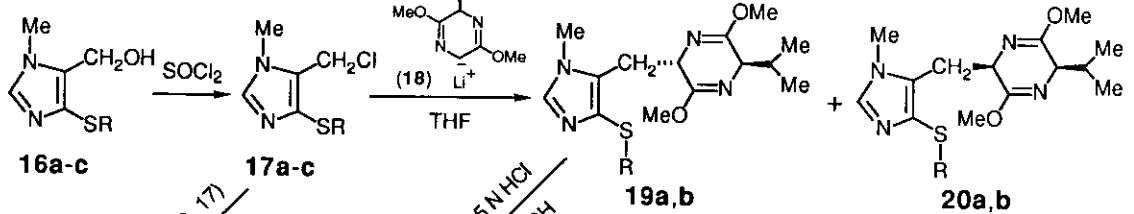
8

a: Ar = 

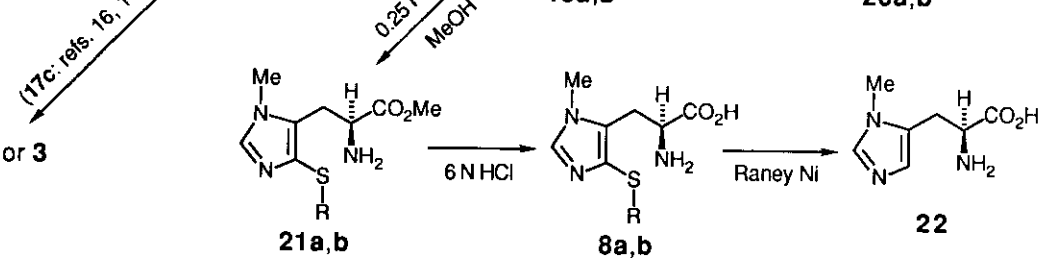
b: Ar = 



9, **10**, **11**: X = H; Y = Br, **12**: X = Br; Y = H, **13**: Z = CH_2OH, **14**: Z = CHO, **15a-c**



16a-c, **17a-c**, (18), **19a,b**, **20a,b**



21a,b, **8a,b**, **22**

a: R = 

b: R = 

c: R = MeO-  -CH_2

bricatine (**7**), a benzyltetrahydroisoquinoline alkaloid from the starfish Dermasterias imbricata.[4] Among these histidine derivatives, imbricatine (**7**) is unique in that it is capable of inducing sea anemone (Stomphia coccinea) "swimming" behavior at very low concentrations[4] and that it displays significant activity in antineoplastic assays.[4] A generalized form of structure **7** would be 5-arylthio-3-methyl-L-histidine (**8**), and thus the synthesis of the 5-phenylthio and 5-(1-naphthyl)thio analogues (**8a** and **8b**) was undertaken in the present study as a preliminary to a total synthesis of **7**.

On methylation with an excess of MeI in EtOH at 65°C for 10 h in the presence of 1 molar equiv. of NaOH, 4(5)-bromoimidazole (**9**)[5] furnished the dimethyl derivative (**10**) [mp 197–199.5°C (decomp)][6] in 86% yield. This one-step procedure for dimethylation represents an abbreviation of the two-step procedure of Balaban and Pyman,[7] who prepared **10** by methylation (with MeI) of 5-bromo-1-methylimidazole (**12**) or 4-bromo-1-methylimidazole (**11**), obtainable from **9** by methylation (with MeI or Me_2SO_4) in which the former isomer (**12**) was always the major product.[7-9] Pyrolysis of **10** was then effected at 235–245°C in vacuo (28 mmHg) according to the literature,[7] and the distillate [bp 135–145°C (28 mmHg)] was purified by flash chromatography[10] (AcOEt) to give **11** and **12** in 61% and 13% yields, respectively.[11] Application of the hydroxymethylation conditions of Godefroi et al.[12] to **11** [35% aqueous CH_2O, AcOH–AcONa buffer (pH 4.6), reflux, 24 h] afforded the 5-hydroxymethyl derivative (**13**) (mp 124–125°C)[13] in 76% yield.[14] The correctness of the structure of **13** was supported by hydrogenolysis (10% Pd–C/H_2, MeOH, 1 atm, room temp., 30 min), which led to the formation of known 5-hydroxymethyl-1-methylimidazole [mp 114–115.5°C (lit.[15] mp 113–114°C)] in 69% yield. Oxidation of **13** with active MnO_2 in boiling $CHCl_3$ for 1 h produced the corresponding aldehyde (**14**) (mp 89.5–90.5°C) in 96% yield.

Separate treatments of **14** in N,N-dimethylformamide (DMF) with thiophenol (120°C, 3 h), with 1-naphthalenethiol (100°C, 3 h), and with 4-methoxy-α-toluenethiol (110°C, 1 h) in the presence of NaH gave the corresponding thioethers (**15a**) (mp 70–71.5°C), (**15b**), and (**15c**) (mp 80–81.5°C) in 73%, 83%, and 73% yields, respectively. The thioethereal aldehydes (**15a–c**) were then converted into the alcohols (**16a**) (97% yield; mp 130.5–131.5°C), (**16b**) (97%; mp 169–170°C), and (**16c**) [100%; mp 113.5–115°C (lit. mp 113–114°C;[16] mp 103–104°C[17])] by $NaBH_4$ reduction (MeOH, room temp., 20–30 min). Chlorinations of **16a–c** with $SOCl_2$ (at 0°C for 30

min, then at room temp. for 30 min) provided the chlorides (**17a–c**), which were isolated in the form of crude solid hydrochlorides (**17a–c**·HCl) in 97–98% yields.

Coupling of **17a**·HCl with the organolithium reagent (**18**) generated in situ from (2R)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine in tetrahydrofuran (THF) at –78°C, an application of the "bis-lactim ether" method of Schöllkopf,[18] was carried out at –50°C for 18 h, giving the trans isomer (**19a**) [mp 117.5–118.5°C; $[\alpha]_D^{20}$ –5.80° (c 0.50, $CHCl_3$)] and the cis isomer (**20a**) [$[\alpha]_D^{20}$ –68.9° (c 0.50, $CHCl_3$)] in 70% and 5% yields, respectively. A similar coupling reaction of **17b**·HCl produced **19b** [$[\alpha]_D^{21}$ –28.6° (c 0.50, $CHCl_3$)] and **20b** [$[\alpha]_D^{21}$ –48.6° (c 0.50, $CHCl_3$)] in 88% and 5% yields, respectively. Hydrolyses of **19a** and **19b** (0.25 N aqueous HCl/MeOH, room temp., 1.5 h) afforded the amino esters (**21a**) [98% yield; $[\alpha]_D^{21}$ +24.8° (c 0.50, MeOH)] and (**21b**) [84%; $[\alpha]_D^{21}$ +25.5° (c 0.51, MeOH)], both of which were shown[19] to be of 98% enantiomeric purity. Finally, **21a** and **21b** were separately hydrolyzed in boiling 6 N aqueous HCl for 1 h, furnishing the desired compounds (**8a**) [mp 193.5–194.5°C (decomp); $[\alpha]_D^{19}$ +29.8° (c 0.50, 0.1 N aqueous HCl)][20a] and (**8b**) [mp 212.5–213.5°C (decomp); $[\alpha]_D^{23}$ +29.4° (c 0.50, 0.1 N aqueous HCl)][20b] in 83% and 86% yields, respectively. The structures, absolute configurations, and high optical purities of **8a** and **8b** were confirmed by desulfurization (Raney Ni/aqueous EtOH, reflux, 8 h), which led in each case to the isolation of known 3-methyl-L-histidine (**22**) [mp 231–233°C (decomp); $[\alpha]_D^{26}$ +13.2° (c 0.30, 0.1 N aqueous HCl)][20a,21] in 83–87% yield.

In conclusion, it is hoped that the above 10-step synthetic route to the 5-arylthio-3-methyl-L-histidines (**8a,b**) from 4(5)-bromoimidazole (**9**) would be applicable to the synthesis of the structurally analogous, starfish alkaloid imbricatine (**7**). Furthermore, the first half of this route in series **c** (**9**→→**17c**·HCl) represents new syntheses of ovothiols A and C (**1** and **3**) in a formal sense, since **16c** prepared by a different multistep synthesis[16,17,22] has already been led to **1** and **3** through **17c**·HCl via a similar "bis-lactim ether" route.[16,17]

ACKNOWLEDGMENT

We are grateful to Emeritus Professor Dr. Shun-ichi Yamada (University of Tokyo) for financial assistance in the form of a grant from the Japan Research Foundation for Optically Active Compounds.

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20. The elemental analysis suggested that this sample contained the following amount of water of crystallization: (a) 1 molar equiv.; (b) 0.5 molar equiv.

21. Identified by comparison with an authentic sample.

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Received, 22nd August, 1991