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 glacialis1b,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-

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Mel or Me$_2$SO$_4$

9

10

11: X = H; Y = Br
12: X = Br; Y = H

13: Z = CH$_2$OH
14: Z = CHO

15a-c

16a-c

17a-c

18

19a,b

20a,b

1 or 3

21a,b

8a,b

22

a: R = \( \text{Ph} \)

b: R = \( \text{C}_{10}H_{13} \)

c: R = MeO-\( \text{Ph}-\text{CH}_2 \)
bricatine (7), a benzyltetrahydroisoquinoline alkaloid from the starfish Dermasterias imbricata. 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 and that it displays significant activity in antineoplastic assays. 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) furnished the dimethyl derivative (10) [mp 197-199.5°C (decomp)] in 86% yield. This one-step procedure for dimethylation represents an abbreviation of the two-step procedure of Balaban and Pyman, 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. Pyrolysis of 10 was then effected at 235-245°C in vacuo (28 mm-Hg) according to the literature, and the distillate [bp 135-145°C (28 mmHg)] was purified by flash chromatography (AcOEt) to give 11 and 12 in 61% and 13% yields, respectively. Application of the hydroxymethylation conditions of Godefroi et al. to 11 [35% aqueous CH_2O, AcOH-AcONa buffer (pH 4.6), reflux, 24 h] afforded the 5-hydroxymethyl derivative (13) (mp 120-125°C) in 76% yield. 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. 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; mp 103-104°C)) 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, was carried out at −50°C for 18 h, giving the trans isomer (19a) [mp 117.5–118.5°C; [α]D20 −5.80° (c 0.50, CHCl3)] and the cis isomer (20a) ([α]D20 −68.9° (c 0.50, CHCl3)) in 70% and 5% yields, respectively. A similar coupling reaction of 17b·HCl produced 19b ([α]D21 −28.6° (c 0.50, CHCl3)) and 20b ([α]D21 −48.6° (c 0.50, CHCl3)) 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; [α]D21 +24.5° (c 0.50, MeOH)] and (21b) [84%; [α]D21 +25.5° (c 0.51, MeOH)], both of which were shown 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); [α]D19 +29.8° (c 0.50, 0.1 N aqueous HCl)] and (8b) [mp 212.5–213.5°C (decomp); [α]D23 +29.4° (c 0.50, 0.1 N aqueous HCl)] 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); [α]D26 +13.2° (c 0.30, 0.1 N aqueous HCl)] 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 has already been led to 1 and 3 through 17c·HCl via a similar "bis-lactim ether" route.

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11. The undesired isomer (12) was converted into 11 through 107 to raise the total yield of 11.


13. Satisfactory analytical and/or spectroscopic data were obtained for all new compounds described.

14. The 2,5-bis(hydroxymethyl) derivative (mp 151–152°C) was also isolated in 7% yield.


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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