

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

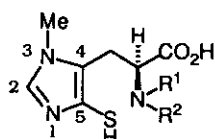
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Abstract—Syntheses of 3-methyl-5-phenylthio-L-histidine (**8a**) and 3-methyl-5-(1-naphthyl)thio-L-histidine (**8b**), selected as models for the asteroid alkaloid imbricatine (**7**), have now become feasible through a 10-step route starting from 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-

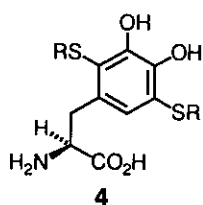
†Dedicated to Dr. Masatomo Hamana, Professor Emeritus of Kyushu University, on the occasion of his 75th birthday.



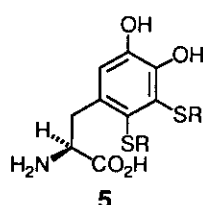
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2: R¹ = H; R² = Me

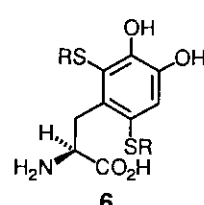
3: R¹ = R² = Me



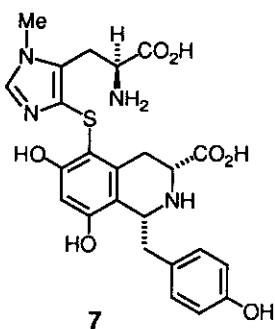
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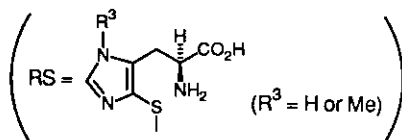
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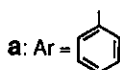


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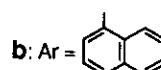


(R³ = H or Me)

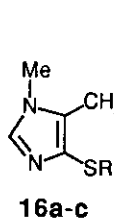
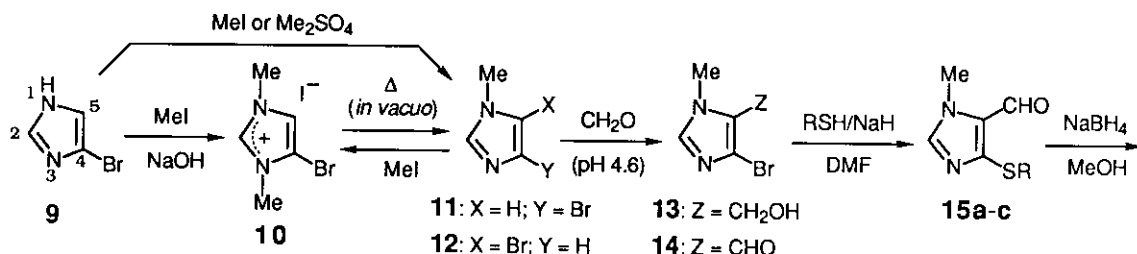
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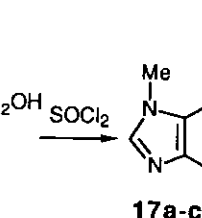
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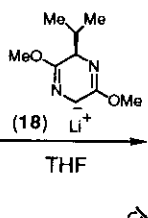
b: Ar =



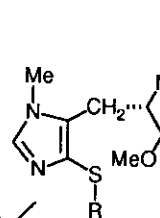
16a-c



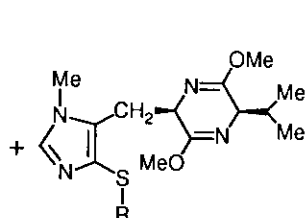
17a-c



(18)



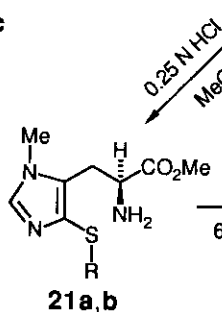
19a,b



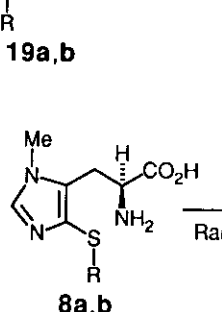
20a,b

(17c: refs. 16, 17)

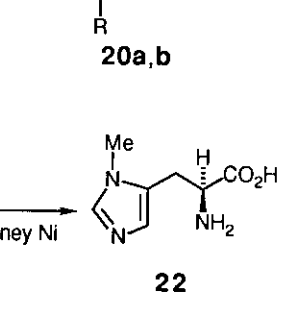
1 or 3



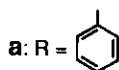
21a,b



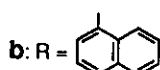
8a,b



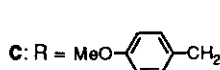
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a: R =



b: R =



c: R =

bricatine (**7**), a benzyltetrahydroisoquinoline alkaloid from the starfish Dermasterias imbricata.⁴ Among these histidine derivatives, imbricatinine (**7**) is unique in that it is capable of inducing sea anemone (Stomphia coccinea) "swimming" behavior at very low concentrations⁴ 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 Me₂SO₄) 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 mm-Hg) according to the literature,⁷ and the distillate [bp 135–145°C (28 mmHg)] was purified by flash chromatography¹⁰ (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 CH₂O, 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/H₂, 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 MnO₂ in boiling CHCl₃ 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 thioetheraldehydes (**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°C¹⁷)] by NaBH₄ reduction (MeOH, room temp., 20–30 min). Chlorinations of **16a–c** with SOCl₂ (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 $117.5\text{--}118.5^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{20} -5.80^{\circ}$ (c 0.50, CHCl_3)] and the cis isomer (**20a**) [$[\alpha]_{\text{D}}^{20} -68.9^{\circ}$ (c 0.50, CHCl_3)] in 70% and 5% yields, respectively. A similar coupling reaction of **17b**·HCl produced **19b** [$[\alpha]_{\text{D}}^{21} -28.6^{\circ}$ (c 0.50, CHCl_3)] and **20b** [$[\alpha]_{\text{D}}^{21} -48.6^{\circ}$ (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; $[\alpha]_{\text{D}}^{21} +24.8^{\circ}$ (c 0.50, MeOH)] and (**21b**) [84%; $[\alpha]_{\text{D}}^{21} +25.5^{\circ}$ (c 0.51, MeOH)], both of which were shown¹⁹ 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 $193.5\text{--}194.5^{\circ}\text{C}$ (decomp); $[\alpha]_{\text{D}}^{19} +29.8^{\circ}$ (c 0.50, 0.1 N aqueous HCl)]^{20a} and (**8b**) [mp $212.5\text{--}213.5^{\circ}\text{C}$ (decomp); $[\alpha]_{\text{D}}^{23} +29.4^{\circ}$ (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 $231\text{--}233^{\circ}\text{C}$ (decomp); $[\alpha]_{\text{D}}^{26} +13.2^{\circ}$ (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}

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REFERENCES

1. (a) A. Palumbo, M. d'Ischia, G. Misuraca, and G. Prota, Tetrahedron Lett., 1982, **23**, 3207; (b) A. Palumbo, G. Misuraca, M. d'Ischia, F. Donaudy, and G. Prota, Comp. Biochem. Physiol., 1984, **78B**, 81; (c) For the correction of an error in the assignment of the position of the ring methyl group due to a confusion arising from conflicting systems of nomenclature for the imidazole ring of substituted histidines, see refs. 2a (Appendix at p. 4035 therein), 4b, 16, and 17.
2. (a) E. Turner, R. Klevit, L. J. Hager, and B. M. Shapiro, Biochemistry, 1987, **26**, 4028; (b) E. Turner, R. Klevit, P. B. Hopkins, and B. M. Shapiro, J. Biol. Chem., 1986, **261**, 13056.
3. (a) S. Ito, G. Nardi, and G. Prota, J. Chem. Soc., Chem. Commun., 1976, 1042; (b) S. Ito, G. Nardi, A. Palumbo, and G. Prota, J. Chem. Soc., Perkin Trans. 1, 1979, 2617.
4. (a) C. Pathirana and R. J. Andersen, J. Am. Chem. Soc., 1986, **108**, 8288; (b) D. L. Burgoyne, S. Miao, C. Pathirana, R. J. Andersen, W. A. Ayer, P. P. Singer, W. C. M. C. Kokke, and D. M. Ross, Can. J. Chem., 1991, **69**, 20.
5. I. E. Balaban and F. L. Pyman, J. Chem. Soc., 1922, **121**, 947.
6. Lit.⁷ mp 202–204°C (decomp).
7. I. E. Balaban and F. L. Pyman, J. Chem. Soc., 1924, **125**, 1564.
8. B. E. Boulton and B. A. W. Collier, Aust. J. Chem., 1974, **27**, 2331.
9. B. Iddon and B. L. Lim, J. Chem. Soc., Perkin Trans. 1, 1983, 735.
10. W. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 1978, **43**, 2923.
11. The undesired isomer (**12**) was converted into **11** through **10**⁷ to raise the total yield of **11**.
12. (a) E. F. Godefroi, H. J. J. Loozen, and J. Th. J. Luderer-Platje, Recl. Trav. Chim. Pays-Bas, 1972, **91**, 1383; (b) M. Masui, K. Suda, M. Inoue, K. Izukura, and M. Yamauchi, Chem. Pharm. Bull., 1974, **22**, 2359.
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.
15. R. G. Jones and K. C. McLaughlin, J. Am. Chem. Soc., 1949, **71**, 2444.
16. T. P. Holler, A. Spaltenstein, E. Turner, R. E. Klevit, B. M. Shapiro, and P. B. Hopkins, J. Org. Chem., 1987, **52**, 4420.

17. T. P. Holler, F. Ruan, A. Spaltenstein, and P. B. Hopkins, J. Org. Chem., 1989, **54**, 4570.
18. (a) U. Schöllkopf, Top. Curr. Chem., 1983, **109**, 66; (b) Idem, Pure Appl. Chem., 1983, **55**, 1799.
19. By means of ^1H nmr spectroscopy using the chiral shift reagent tris[3-(heptafluoropropyl-hydroxymethylene)-(+)-camphorato]europium(III) $[\text{Eu}(\text{hfc})_3]$ in CDCl_3 .
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.
22. A. Spaltenstein, T. P. Holler, and P. B. Hopkins, J. Org. Chem., 1987, **52**, 2977.

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