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Chiral synthesis of tri-*O*-methylimbricatine, an etherified derivative of the starfish alkaloid imbricatine

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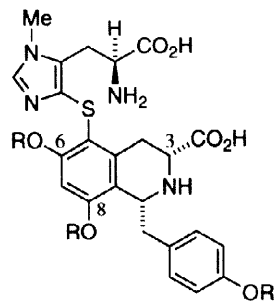
Abstract

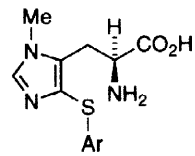
A chiral synthesis of tri-*O*-methylimbricatine (**2**), the tri-*O*-methyl derivative of the unique benzyltetrahydroisoquinoline alkaloid imbricatine (**1**) isolated from the starfish *Dermasterias imbricata*, has been accomplished. As a result of the synthesis, the correctness of the structure and absolute stereochemistry proposed for imbricatine has been unequivocally confirmed.

Keywords: amino acids and derivatives; imidazoles/imidazolines; isoquinolines; thioethers

Imbricatine (**1**), isolated from the starfish *Dermasterias imbricata*, is a benzyltetrahydroisoquinoline alkaloid responsible for eliciting the unusual "swimming" behavior in the sea anemone *Stomphia coccinea* at very low concentrations [1–3]. The structure and absolute stereochemistry of **1** have been deduced on the basis of spectroscopic analysis, chemical degradation, and partial synthesis of the benzyltetrahydroisoquinoline substructure [1,2]. Imbricatine (**1**) is unique in that it is a benzyltetrahydroisoquinoline alkaloid obtained for the first time from a marine organism; it possesses some structural features (*e.g.*, the carboxyl group at the 3-position, the 6,8-dihydroxylation pattern, and the aromatic thioether linkage to the 3-methyl-L-histidine moiety) not previously encountered in this class of alkaloids; and it exhibits significant antineoplastic activity [1,2]. This uniqueness has led us to investigate the chiral synthesis of 5-arylthio-3-methyl-L-histidines (**3a,b**) as a preliminary to a total synthesis of imbricatine (**1**) [4,5]. In the present communication, we describe the chiral synthesis of tri-*O*-methylimbricatine (**2**), which has confirmed the correctness of the above deduction about the structure and absolute stereochemistry of imbricatine.

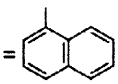


1: R = H
2: R = Me



3a,b

a: Ar = 

b: Ar = 

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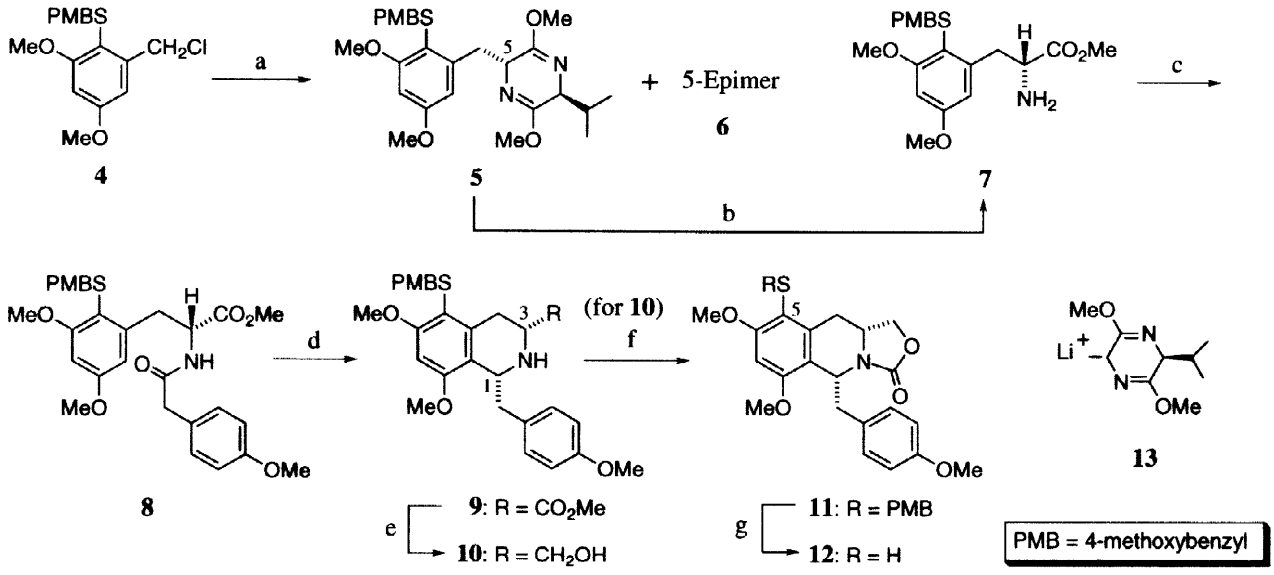
The synthesis of the benzyltetrahydroisoquinoline moiety **12** containing a sulfur substituent at the 5-position started from the benzyl chloride **4**, which was prepared according to the procedure reported by us [6]. Coupling reaction of **4** with the organolithium reagent **13** generated *in situ* from (2*S*)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine and LDA in THF at –78 °C, an application of the "bis-lactim ether" method of Schöllkopf [7,8], provided **5** in 75% yield along with its 5-epimer **6** (9% yield) (Scheme 1). The *trans* and *cis* structures of **5** and **6** were assigned, respectively, on the basis of our precedent [6]. The major isomer **5** was then subjected to hydrolysis with 0.25 N aqueous HCl in MeOH to afford the amino ester **7** [mp 51–52 °C; $[\alpha]_D^{21}$ –8.9° (*c* 0.92, MeOH)] in 97% yield. The enantiomeric purity of **7** thus obtained was determined to be 96% ee by ^{1}H NMR spectroscopy exploiting the chiral shift reagent Eu(hfc)$_3$.

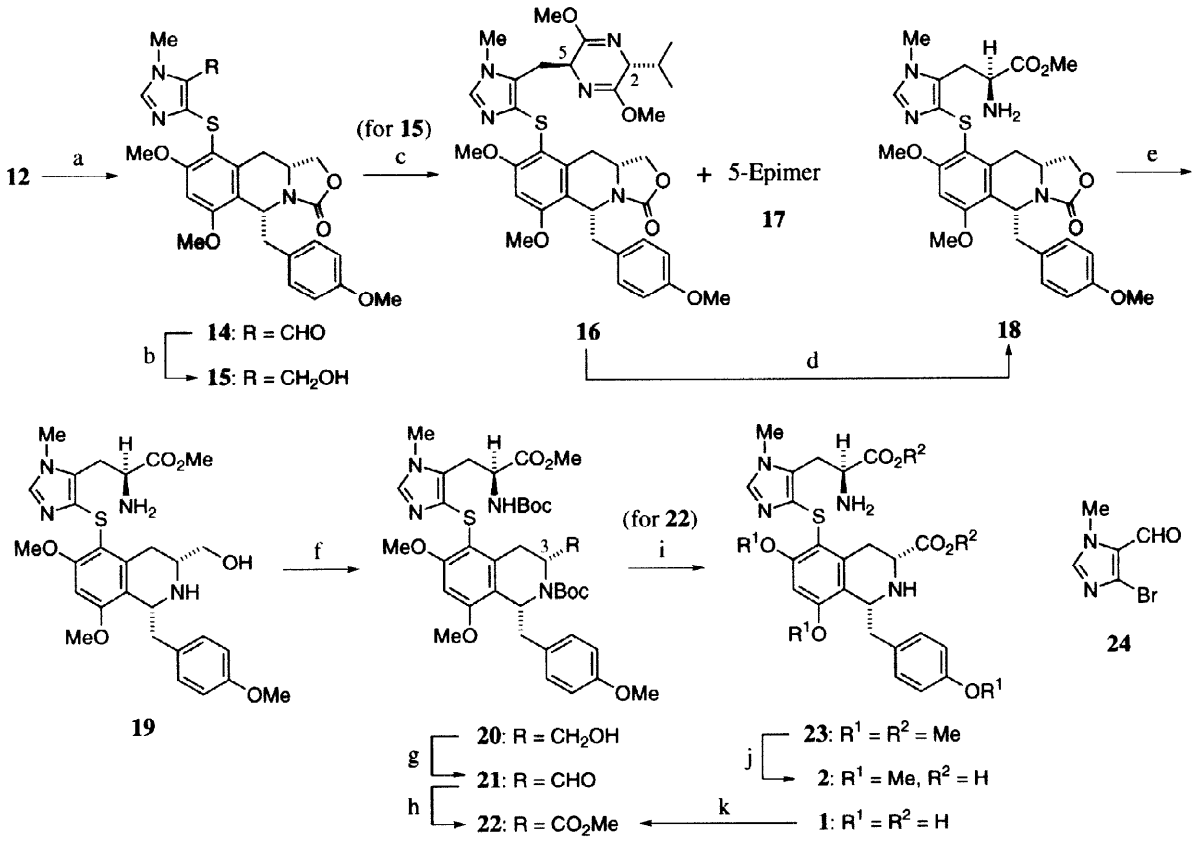


Scheme 1. *Reagents, conditions, and yields:* (a) **13**, THF, –78 °C, 2 h, –50 °C, 18 h, **5**: 75%, **6**: 9%; (b) 0.25 N aq. HCl, MeOH, rt, 4 h, 97%; (c) 4-methoxyphenylacetyl chloride, Na_2CO_3, H_2O–benzene, 8–10 °C, 30 min, 96%; (d) 1) PPSE, $CHCl_3$, reflux, 10 h; 2) $NaBH_4$, MeOH, –78 °C, 1 h, 81%; (e) $LiAlH_4$, THF, rt, 1.5 h, 91%; (f) $(EtO)_2CO$, NaOEt, EtOH, reflux, 20 h, 98%; (g) 1) $(CF_3CO_2)_2Hg$, anisole, EtOH, rt, 16 h; 2) $NaBH_4$, 0 °C, 15 min, 95%.

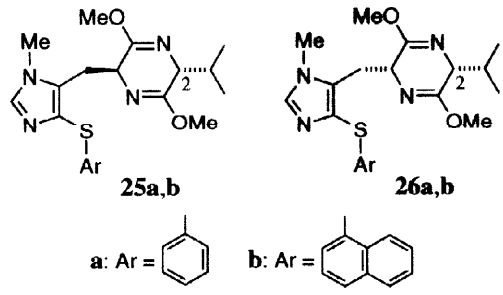
Condensation of **7** with 4-methoxyphenylacetyl chloride was carried out under Schotten–Baumann conditions, giving the amide **8** (mp 120–121 °C) in 96% yield. Bischler–Napieralski cyclization of **8** using trimethylsilyl polyphosphate (PPSE) [9,10], followed by $NaBH_4$ reduction in MeOH at –78 °C [11], furnished the 1,3-*cis* isomer **9** as a sole product in 81% yield. Although partial racemization (91% ee) was detected in the crude product **9**, recrystallization from MeOH readily provided optically pure **9** [mp 134–135.5 °C; $[\alpha]_D^{28}$ +230° (*c* 0.29, $CHCl_3$)]. The 1,3-*cis* structure of **9** was secured from a 5.8% NOE enhancement observed for the C(1)-proton signal on irradiation of the C(3)-proton signal. In order to avoid possible epimerization assumed to occur at a later stage, the ester group of **9** was then reduced with $LiAlH_4$ to give **10** (mp 169.5–173.5 °C) in 91% yield, and the resulting OH group was protected, together with the NH group, as the oxazolidinone **11**. Removal of the sulfur-protecting group of **11** was effected by the literature procedure [12,13] with a slight

modification. Thus, treatment of **11** with $(CF_3CO_2)_2Hg$ in EtOH containing anisole and subsequent $NaBH_4$ reduction of the resulting mercaptide gave the thiol **12** in excellent yield.

With the benzyltetrahydroisoquinoline portion possessing the thiol group at the 5-position in hand, we next investigated the application to **12** of our route [4,5] for the synthesis of 5-arylthio-3-methyl-L-histidines (**3a,b**). Treatment of **12** with the aldehyde **24** [4,5] in DMF in the presence of NaH provided the corresponding thioether **14**, which was then converted into the alcohol **15** (mp 249–250 °C) by $NaBH_4$ reduction (Scheme 2). Chlorination of **15** with $SOCl_2$ followed by a coupling reaction with the enantiomeric organolithium reagent *ent*-**13** afforded **16** and **17** in 58% and 34% yields, respectively. The stereochemical assignments to **16** and **17** were based on comparison of the chemical shifts of their C(2)-protons. In $CDCl_3$, the C(2)-proton signal of **16** appeared at δ 3.78, whereas that of **17** at δ 3.93. The C(2)-protons of the *trans* isomers **25a,b** are known to resonate at higher field by 0.12–0.13 ppm than those of the *cis* isomers **26a,b**, respectively, because of the shielding effect induced by the imidazole ring [5]. Therefore, **16** and **17** were assigned the *trans* and *cis* structures, respectively. At present, however, we have no answer to the observed low diastereoselectivity (1.7 : 1) in the formation of **16** and **17**, compared with the cases of **25a,b** and **26a,b** (**25a** : **26a** = 14 : 1; **25b** : **26b** = 17 : 1) in a similar alkylation of *ent*-**13** [5].



Scheme 2. *Reagents, conditions, and yields:* (a) **24**, NaH, DMF, 100 °C, 3 h, 68%; (b) $NaBH_4$, MeOH, rt, 1 h, 80%; (c) 1) $SOCl_2$, rt, 1 h; 2) *ent*-**13**, THF, –78 °C, 2 h, –50 °C, 14 h, **16**: 58%, **17**: 34%; (d) 0.25 N aq. HCl, MeOH, rt, 2.5 h, 91%; (e) 1) 6 N aq. HCl, 100 °C, 1 h; 2) 2 N aq. NaOH, MeOH, 80–85 °C, 60 h; 3) 10% methanolic HCl, reflux, 7 h, 73%; (f) $(Boc)_2O$, $CHCl_3$, rt, 6 h, 91%; (g) 1) $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h; 2) Et_3N, 81%; (h) I_2, KOH, MeOH, 0 °C, 5 h, 71%; (i) CF_3CO_2H, CH_2Cl_2, rt, 1.5 h, 83%; (j) 1) 3 N aq. HCl, reflux, 1 h; 2) Dowex 50W–X8, 78%; (k) 1) 12% methanolic HCl, reflux, 3 h; 2) $(Boc)_2O$, Et_3N, $CHCl_3$, rt, 6 h; 3) CsF–alumina, MeI, CH_3CN, rt, 1 h, 30%.



The *trans* bis-lactim ether **16** was then hydrolyzed with 0.25 N aqueous HCl in MeOH to give the amino ester **18** in 91% yield. Conversion of **18** into the amino alcohol **19** was achieved in 3 steps *via* acid hydrolysis of the ester group, alkaline hydrolysis of the oxazolidinone moiety, and esterification of the carboxy group. After protection of the amino functions in **19** with $(Boc)_2O$, Swern oxidation [14] of the hydroxymethyl group at the 3-position of the resulting *N*-blocked product **20** and subsequent alkaline iodine oxidation [15] of the aldehyde **21** in MeOH yielded the dimethyl ester **22** [$[\alpha]_D^{22}$ −15.3° (*c* 0.50, $CHCl_3$)]. The IR ($CHCl_3$), ^1H NMR ($CDCl_3$), and mass spectra and TLC mobility (three solvent systems) of **22** thus obtained were found to be virtually identical with those of authentic **22** [$[\alpha]_D^{24}$ −13.5° (*c* 0.085, $CHCl_3$)] derived from natural imbricatine (**1**) in 30% overall yield through methyl esterification, protection with $(Boc)_2O$, and *O*-methylation with CsF–alumina and MeI [16] (Scheme 2). Finally, *N*-deprotection of **22** with CF_3CO_2H followed by acid hydrolysis of the resulting amino ester **23** afforded tri-*O*-methylimbricatine (**2**) [$[\alpha]_D^{25}$ +62.2° (*c* 0.67, MeOH)]. Unfortunately, however, we were unable to accomplish exhaustive *O*-demethylation of **2** to give **1**.

In conclusion, the structure and absolute stereochemistry of the starfish alkaloid imbricatine have now been unequivocally established to be those in formula **1**, as a result of the chiral synthesis of tri-*O*-methylimbricatine (**2**).

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