



Total synthesis of (–)-haploscleridamine

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ABSTRACT

Asymmetric total synthesis of the imidazole containing β-carboline natural product, haploscleridamine, from histidine is described. Key to the successful assembly of this alkaloid is a ring-closing metathesis reaction of an imidazole derived allylic alcohol to construct a 3-piperidinone. Application of the Buchwald-modification of the classical Fischer indolization and deprotection of the *N*-tosyl moiety delivered haploscleridamine.

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Examples of β-carboline-containing natural products abound in the literature [1]. These alkaloids are widely distributed and have been isolated both from terrestrial and marine sources [2]. Likewise, there are many examples of imidazole-containing alkaloids however [3], imidazole-containing β-carbolines are quite rare.

Haploscleridamine (**1**) is a novel tryptamine-derived alkaloid [4] isolated from a marine sponge of the order *Haplisclerida* collected in Palau as described in 2002 by Faulkner and coworkers (Fig. 1) [5]. This novel β-tetrahydrocarboline was shown to inhibit cathepsin K (IC₅₀ = 26 μM), a cysteine protease, involved in osteoporosis and thus this natural product may serve as a lead compound in the development of treatments for this disease. The brominated analog, lissoclin C (**2**) was one of five alkaloids isolated from a tropical Ascidian, *Lissoclinum* sp., and while the crude extract was active against *Candida albicans*, the purified alkaloid was inactive against in a disk diffusion assay [6].

Further related compounds include two diastereomeric carboxyl-containing derivatives, hyrtiorectulin A (**3**) and B (**4**) have been isolated from the marine sponge *Hyrtios reticulatus* [7]. Both of these natural products inhibited the E1-catalyzed ubiquitin-activation reaction with IC₅₀ values of 2.4 and 35 μM respectively [7]. Related, but more highly functionalized, examples have been described, in particular villagorgin A (**5**) which has an additional carbon atom compared to haploscleridamine (**1**) [8], formally requiring a Pictet-Spengler reaction from **1** for its synthesis [1d].

Villagorgin A (**5**) and the related and more highly oxidized congener villagorgin B were described as exhibiting acetylcholine antagonist activity and inhibiting human platelet aggregation, however their potency in these assays was not reported [8]. Other, more highly oxidized β-carbolines containing imidazole moieties have been isolated from marine sources, for example hainanerec-tamine C (**6**) [9], gesashidine (**7**) [10] and dragmacidonamines A (**9**) and B (**8**) [11].

It should be noted that the isolated sample of haploscleridamine (**1**) exhibited low optical activity, which the authors suggested, but did not demonstrate, was due to partial racemization of the sample during purification [5]. Similarly, Molinski and coworkers have shown that the related lissoclin C (**2**) was almost racemic by preparation and subsequent HPLC analysis of diastereomeric ureas [6]. These observations may be a function of the isolation protocol (acidic conditions) rather than the natural product being produced as a racemate or undergoing racemization after its biosynthesis. Villagorgin A (**5**) exhibited a low optical rotation, however, hyrtiorectulins A (**3**) and B (**4**) were reported to exhibit larger optical rotations, although their enantiomeric homogeneity was not established experimentally. Further, the absolute configuration of haploscleridamine was not determined and therefore an asymmetric synthesis would address these issues.

Our lab has been interested in developing synthetic approaches to natural products containing imidazole moieties [12], particularly those with additional heterocyclic rings and accordingly these alkaloids attracted our attention. Furthermore, the limited investigation of the pharmacological properties of these marine natural

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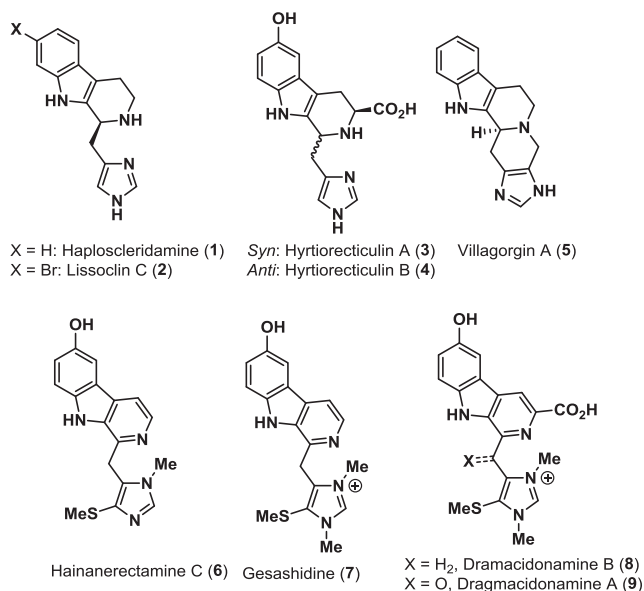


Fig. 1. Representative structures of imidazole-containing β -carboline natural products.

products encouraged us to develop a synthetic approach to these naturally-occurring compounds.

Our initial target was haploscleridamine (**1**) as it was thought a successful approach to this family member would permit access to the other congeners through minor modifications, including conversion to villagorgin A (**5**). As we considered approaches to the β -carboline, the obvious route involving a Pictet–Spengler reaction [13] was not pursued as the construction of the requisite imidazolyl aldehyde was rather step intensive [14] and we were concerned about the propensity of these systems to racemize under the usual reaction conditions (see above) [15]. As a result, we decided to explore an approach in which the indole was constructed through a Fischer indole [16] synthesis [17] on the corresponding 3-piperidinone as this would potentially offer flexibility for divergency at a late stage of the synthesis (**1** \rightarrow **10**, Fig. 2). Several approaches were considered for the formation of the piperidinone, however ring-closing metathesis of a diene [18] then reduction emerged as the most viable strategy (**10** \rightarrow **11** \rightarrow **12**, Fig. 2) [19]. Such an approach would then permit an asymmetric synthesis of the natural product through the use of histidine as the starting material (**12** \rightarrow **13**, Fig. 2) [20].

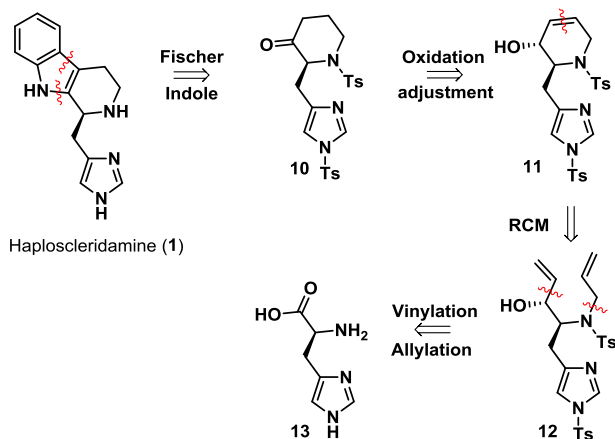


Fig. 2. Retrosynthetic analysis of haploscleridamine (**1**).

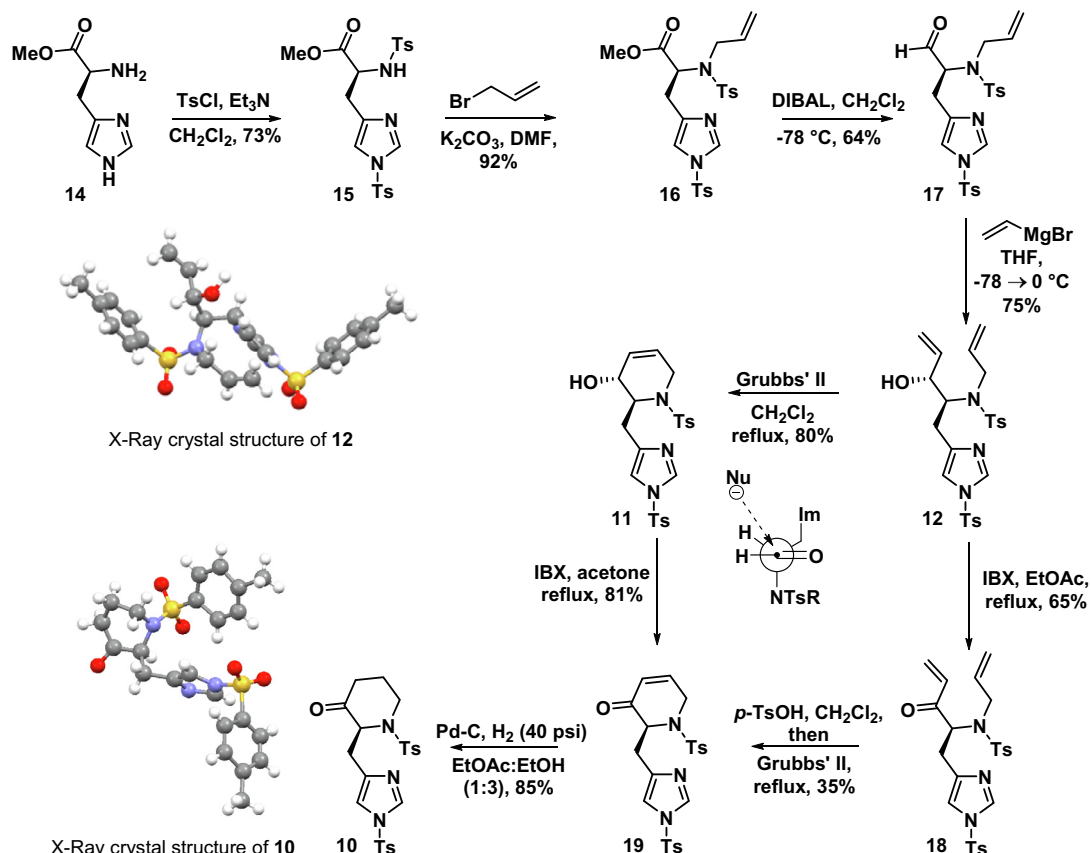
In a forward sense, the synthesis commenced with the tosylation of histidine methyl ester **14** to provide the known bis sulfonamide **15** in good yield as a single isomer (Scheme 1) [21]. The choice of the Ts-protecting group was predicated on several considerations, first it would facilitate N_α -alkylation and second, and most importantly, it would reduce the likelihood of acid-induced racemization by exposure to acidic conditions. N -Alkylation was accomplished readily through exposure of **15** to allyl bromide and potassium carbonate affording ester **16** [22]. The corresponding aldehyde **17** was obtained through semi-reduction of ester **16** with DIBAL-H. Subsequent reaction of the aldehyde with vinylmagnesium bromide delivered a single allylic alcohol diastereomer **12** [23]. While the configuration of the alcohol was unimportant in the context of the synthesis as the carbinol stereocenter would ultimately be destroyed, the configuration of the newly installed stereocenter was determined by X-ray crystallography [24]. The observed sense of stereoinduction is consistent with the Felkin–Ahn model with a polar substituent oriented perpendicular to the carbonyl moiety [25].

In initial experiments, alcohol **12** was converted to the enone **18** in moderate yield by exposure to IBX and investigated in the RCM reaction. The basis for this decision was predicated on issues associated with rearrangement of allylic alcohols to ethyl ketones that are periodically observed [26]. It was found that the enone would engage in a RCM reaction in the presence of p -TsOH delivering the cyclohexenone derivative **19**, however the yield was quite modest.

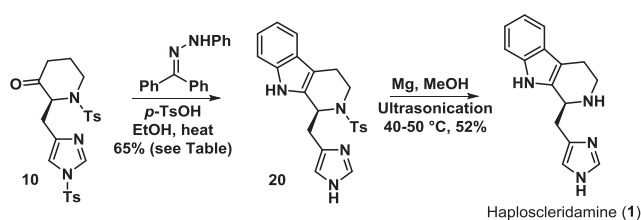
In the end our concern over the use of the allylic alcohol **12** as a substrate in RCM was unfounded as using second generation Grubbs' catalyst delivered the corresponding piperidine derivative **11** in excellent yield [27]. The use of p -TsOH was not necessary in this case. Subsequent oxidation with IBX then produced enone **19** in good yield. Hydrogenation of enone using Pd-C and medium hydrogen pressure afforded the piperidinone **10** in good yield. The structure of this key intermediate was confirmed through X-ray crystallography (Scheme 1) [28].

Initial attempts to effect indole formation through classical methods [16] were routinely unsuccessful but use of the hydrazone transfer method reported by Buchwald provided a satisfactory solution to indole construction [29]. Specifically, exposure of an ethanolic solution of ketone **10** (1.5 equiv) to benzophenone N -phenyl hydrazone (1.0 equiv) in the presence of tosic acid followed by heating at reflux resulted in the rapid formation of the hydrazone which upon heating for a further 72 h produced a single indole product **20** in 65% yield (Scheme 2 and entry 2, Table 1). Under these acidic conditions, concomitant detosylation of the imidazole nitrogen occurred but this was of no consequence. Shorter reaction times (entry 1) or microwave irradiation afforded the indole but in lower yields (entry 3). The reported conditions employed excess ketone and since ketone **10** was rather valuable, we attempted to reduce the excess used in this transformation; generally this was not successful (entries 4–7, Table 1) although use of microwave heating led to some improvement (entry 7, Table 1). Subjection of tosylamide **20** to reductive detosylation using magnesium in methanol [30] delivered haploscleridamine (**1**) in good yield and purity [31].

Interestingly, we prepared batches of haploscleridamine in three separate reactions [32] and noticed that while the spectroscopic data were similar to one another and to the data reported for the as isolated natural product, there were minor differences in the data for each sample; in particular the signal for H1 differed as much as 0.20–0.49 ppm, synthetic (**1**) $\delta_H = 4.48$ –4.97 vs natural (**1**) $\delta_H = 4.48$ [33]. We suspected that since formic acid was used as part of the eluant during HPLC purification of the natural product that it was in fact isolated as the salt. Accordingly, we converted a sample of the synthetic material to the TFA salt and several changes were noted, including the H1 signal moving **downfield**



Scheme 1. Construction of the key piperidinone 10.



Scheme 2. Completion of the synthesis of haploscleridamine (1) via Buchwald modification of Fischer indole reaction.

($\delta_{\text{H}} = 5.09$) and was now at a similar shift as the corresponding H1 signal as lissoclin C ($\delta_{\text{H}} = 5.09$) [6] and hyrtioreticulins A and B ($\delta_{\text{H}} = 5.17$ and 5.01 respectively) [7], all of which were purified by HPLC using eluants containing TFA. Interestingly, when the

TFA salt of haploscleridamine was treated with aqueous NaHCO_3 the NMR spectra matched almost perfectly with that reported by the isolation group and with the data obtained for the first synthetic sample with H1 now at $\delta_{\text{H}} = 4.37$. The specific rotation of the synthetic haploscleridamine was determined to be $[\alpha] -19.8$ (c 1.08, MeOH) which is in contrast to the low value observed for the natural product ($[\alpha] -3.4$ (c 0.78, MeOH)). It was noted that the sample which was converted to the TFA salt and then neutralized exhibited a reduced specific rotation value ($[\alpha] = -6.2$ (c 0.54, MeOH)) which is consistent with the observations in the isolation report of racemization during purification.

In summary, we have completed the first asymmetric total synthesis of the β -carboline alkaloid, haploscleridamine (1). Critical to the success of this synthesis campaign was a ring-closing metathesis reaction of an imidazole derivative to facilitate construction of the key piperidinone. Subsequent application of the Buchwald

Table 1
Optimization of the Buchwald-Fischer indole synthesis.

Entry	TsOH (equiv)	Hydrazone (equiv)	Ketone 10 (equiv)	Conditions	Time/h	Yield of 20 ^a /%
1	2.5	1	1.5	Reflux	24	21 ^b
2	2.5	1	1.5	Reflux	72	65 ^b
3	2.5	1	1.5	μW , 90 °C ^c	1	21 ^b
4	4	3	1	Reflux	24	<5 ^c
5	4	3	1	Reflux	48	<5 ^c
6	5	4	1	Reflux	96	20 ^d
7	5	4	1	μW , 90 °C ^e	1	46 ^d

^a Isolated yields after flash column chromatography.

^b TsOH (0.45 mmol), hydrazone (0.18 mmol), ketone **10** (0.28 mmol), EtOH (2 ml).

^c TsOH (0.40 mmol), hydrazone (0.30 mmol), ketone **10** (0.28 mmol), EtOH (2 ml).

^d TsOH (0.50 mmol), hydrazone (0.40 mmol), ketone **10** (0.10 mmol), EtOH (2 ml).

^e For more details see [Supplementary information](#).

modification of the classical Fischer indole synthesis provides the β -carboline framework. Reductive removal of an *N*-tosyl group was accomplished by dissolving metal reduction. The rotation of the synthetic material was higher but in the same direction as the natural material indicating that the chiral center possesses an *S*-configuration. Efforts to extend this work to other members of this class of alkaloids are underway and will be reported in due course.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tetlet.2019.03.004>.

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- [33] We were unable to obtain an authentic sample and no copies of the original spectra were available through Supplementary information or from the original authors.