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Total Synthesis of Haploscleridamine, Villagorgin A and an Approach Towards Lissoclin C

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An investigation of an asymmetric total synthesis of three indole-imidazole alkaloids from histidine is described. A common advanced piperidinone was contructed via a ring-closing metathesis which was then subjected to a modified Fischer indole synthesis. Deprotection of an N-tosyl group via a dissolving metal reduction affords haploscleridamine which upon reaction with aqueous formaldehyde in trifluoroethanol provided villagorgin A. On closer examination, it was found that villagorgin A was produced as a byproduct during the reductive detosylation in the presence of magnesium and methanol. Attempts to obtain the brominated haploscleridamine congener, lissoclin C through use of bromophenyl hydrazone were thwarted by reductive debromination during deprotection efforts. Investigation of the enantiopurity of the synthetic natural products revealed production of almost racemic materials in some batches as the result of partial racemization of an early stage intermediate. A revised approach routinely provided scalemic haploscleridamine and villagorgin in 30% ee. Analysis of the enantiomer composition of all intermediates by HPLC using columns with chiral stationary phases; this analysis revealed several steps where erosion of enantiomer composition occurred.

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Introduction

Marine organisms have proven to be repositories of structurally unique molecules which possess potentially useful pharmacological activities.[1] Imidazole-containing alkaloids,[2-3] most notably the oroidin family,[4] are a large collection of sponge-derived secondary metabolites, similarly indole-containing alkaloids abound, but alkaloids containing both frameworks are less common. Examples of the latter include chartellines,[5-6] chartellamides,[7] securamines,[8-9] nortopsentin,[10] didemnimides[11] and granulatimide (**1**-**6**, Figure 1).[12] Although β-carbolines are common structural elements, imidazole-containing β-carbolines are not and those containing the lower oxidation state tetrahydro-β-carboline framework are rarer still. The first of these, villagorgin A (**7**) and the more oxidized congener villagorgin B (**8**) were isolated by Riguero and colleagues from *Villagorgia rubra*, a marine gorgonian found off New Caledonia, and reported in 1993.[13] These alkaloids were described as exhibiting "strong inhibition" of acetyl choline-induced contraction of guinea pig illeum. Reported in 1994, lissoclin C (**10**) was isolated from specimens of *Lissoclinum sp.* found on the Great Barrier Reef and is essentially a nor-D ring analog of **7**.[14] **10** was described as a nearly racemic mixture and was devoid of any anti-fungal activity against *Candida albicans.* The non-brominated congener of **10**, haploscleridamine (**9**) was reported in 2002 and was shown to be an inhibitor of capthesin (IC_{50} = 26 μM).[15] Other derivatives, containing carboxyl groups, **11** and **12**,[16] have subsequently been isolated and thiomethylated nor-D ring analogs **13**-**16** of villagorgin B have been reported.[17]

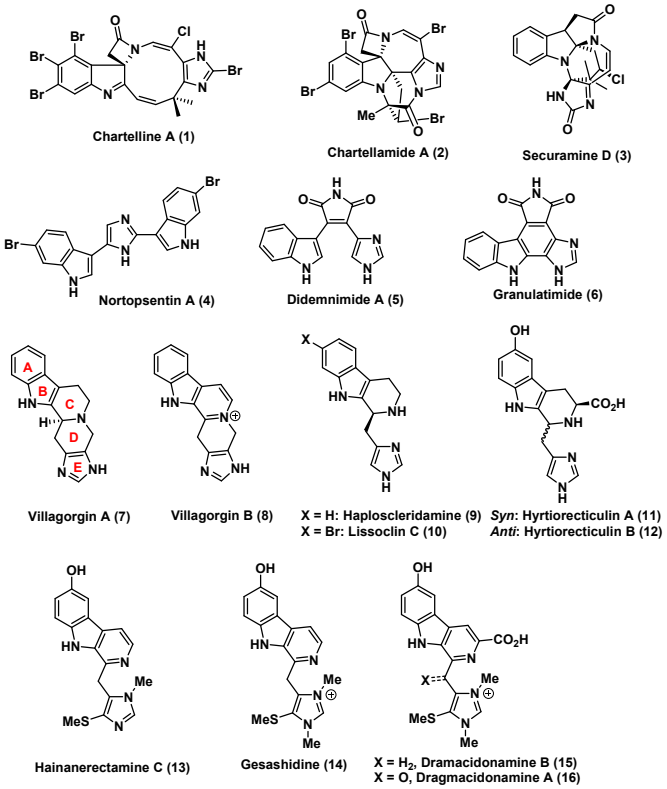


Figure 1: Selected indole-imidazole alkaloids

There are few reported synthetic studies on this family of natural products, the most notable in this area is from the Kuehne lab which reported a total synthesis of (±)-villagorgin A and B.[18] Their synthesis relied on reductive amination of imidazo[*d*]pyridine and indole alkylation via the iminium ion resulting in the construction of the C-ring. Oxidation of synthetic villagorgin A (**7**) resulted in the formation of the pyridinium species and villagorgin B (**8**). Recently, our own group has described a total synthesis of (-)-haploscleridamine (**9**).[19] In the present paper, we describe the development of this synthesis along with an extension of this chemistry to a total synthesis of villagorgin A (**7**) and our attempts to synthesize the initial member of this group of alkaloids, lissoclin C (**10**).

Results and Discussion

Our initial target in this family of natural products was actually villagorgin A (**7**) which we thought could be accessed via a late-stage indole formation on ketone **17** (Figure 2).[20-21] Ketone **17** would be derived from a Dieckmann-like process of diester **18**, which in turn would be derived from the spinacine derivative **19**. Spinacine is readily available from methylal and histidine.

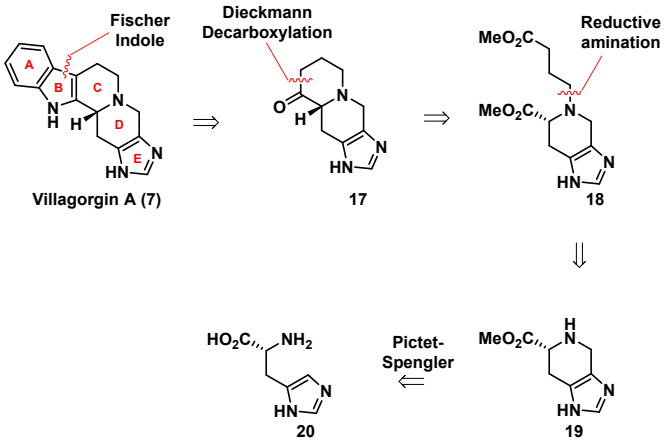
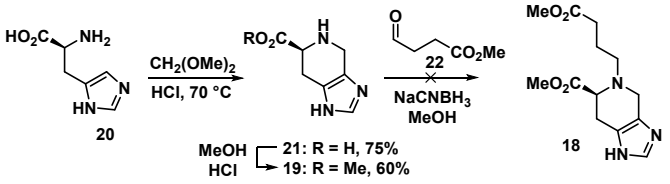


Figure 2: Initial retrosynthetic analysis of villagorgin A (**7**)

In a forward sense, (*S*)-histidine (**20**) was converted to spinacine **21** in 75% yield upon treatment with methylal and HCl (Scheme 1).[22] Subsequent treatment with methanolic HCl afforded the corresponding methyl ester **19**. The intention was to incorporate a four-carbon fragment to facilitate the Dieckmann reaction through a reductive amination with the butyrolactone derived aldehyde. While the aldehyde **22** could be prepared,[23] it failed to undergo reductive amination upon treatment with either $NaCNBH_3$ or pyridine•BH_3. The root cause of this failure was not fully investigated because at around this time we became aware of other members of this β-carboline family that may themselves serve as a precursor to villagorgin A (**7**) through a late-stage Pictet-Spengler reaction rather than performing this earlier in the sequence thus offering a more flexible approach.



Scheme 1: Attempted reductive amination

Specifically, a simple disconnection (a Pictet-Spengler reaction in the forward direction) reveals the β-carboline haploscleridamine (**9**) as the initial target (Figure 3). It was our hope to develop a synthesis which permitted access to several family members from a common intermediate. Given this, a late-stage Fischer indole synthesis seemed attractive and thus piperidinone **23** was identified as the initial target as its synthesis would permit access to two natural products. In turn, **23** would be derived from a Dieckmann reaction.

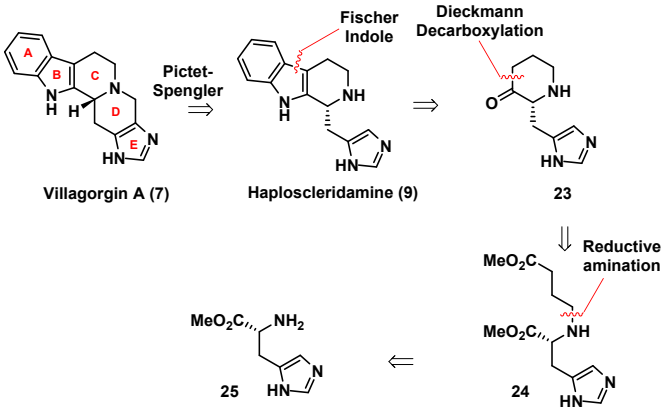
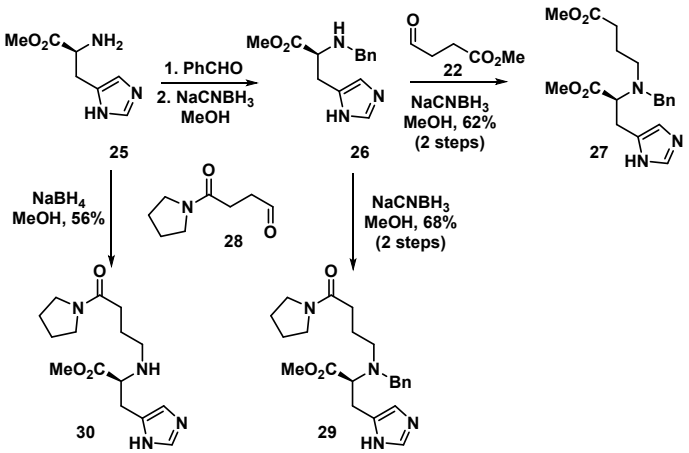


Figure 3: Modified retrosynthesis of villagorgin A (**7**) via haploscleridamine (**9**) via late-stage D-ring formation.

Accordingly, histidine methyl ester (**25**) was employed as a starting material and carried through a sequence of two reductive amination reactions (Scheme 2). First with benzaldehyde and $NaCNBH_3$ followed by addition of two different γ-butyrolactone derived aldehydes **22** and **28**[24] to afford two N-benzyl derivatives in 62% and 68% yields (**27** and **29** respectively) over two steps. Similarly, the NH-derivative **30** was accessed in one case by reaction with the aldehyde **28** and histidine **25** with reduction by $NaBH_4$ in modest, but unoptimized 56% yield. Unfortunately, attempts to effect a Dieckmann condensation with any of these substrates were singularly unsuccessful.



Scheme 2: Reductive amination of histidine derivatives

One of the flaws with the Dieckmann approach is that it would more than likely result in racemization and our long-term goal was to develop asymmetric syntheses. Accordingly, other approaches to the piperidine were considered. With this in mind, a revised strategy was devised in which the piperidinone **31** (*cf.* **23** Figure 3)

would be constructed through a ring-closing metathesis reaction[25]

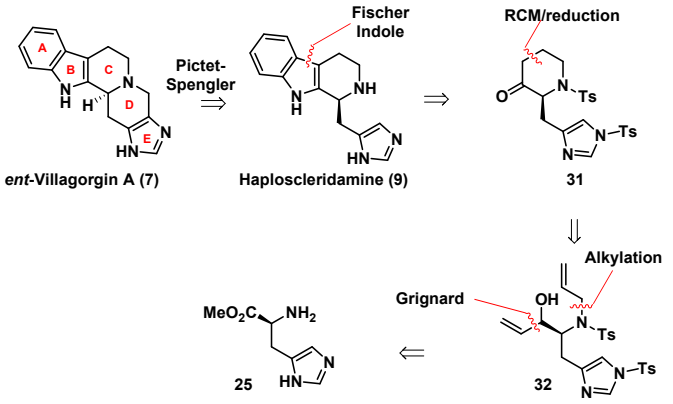
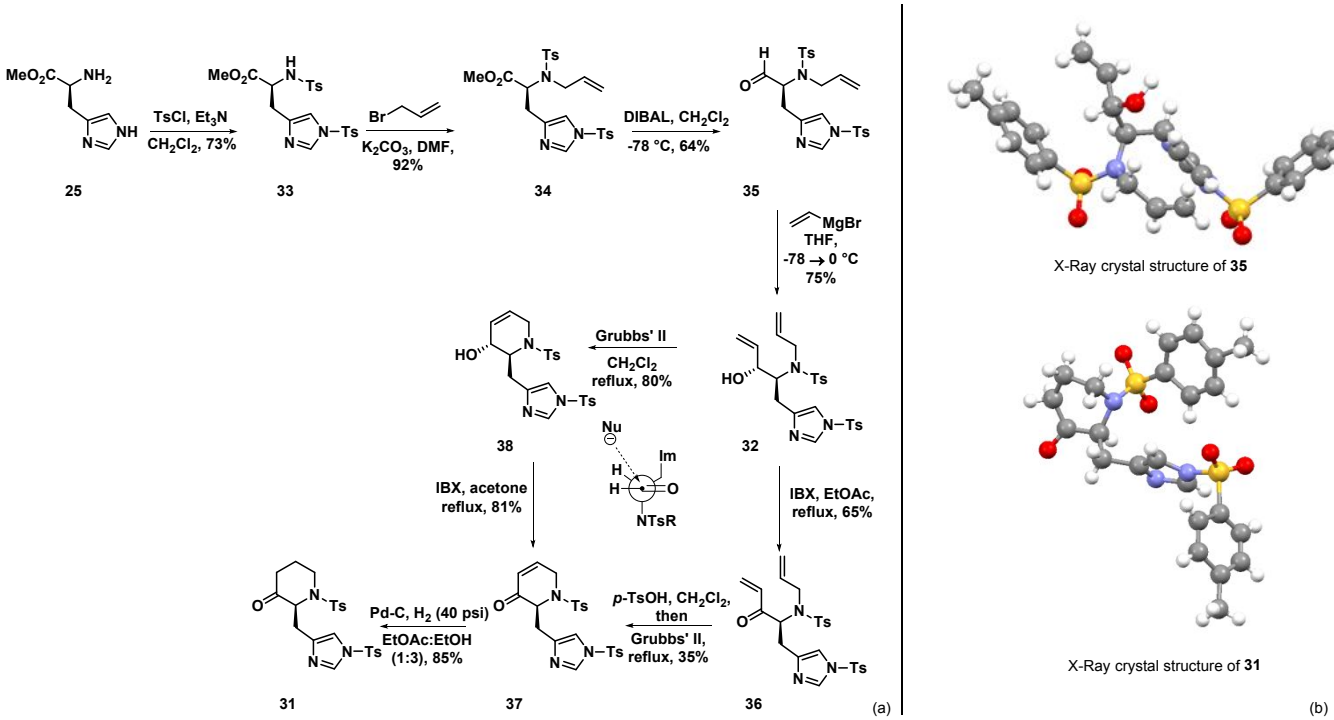


Figure 4: Ring closing metathesis approach to core piperidinone

and then reduction (Figure 4). Prior experience from our group[26-27] and others[28-33] has demonstrated that imidazoles can be tolerated by ruthenium metathesis catalysts and thus this sequence was investigated. The RCM precursor **32** would be obtained from a histidine derivative via Grignard and N-alkylation reactions.

Histidine methyl ester (**25**) was protected with a tosyl group both on the imidazole nitrogen and the amino nitrogen delivering **33** (Scheme 3).[34] In the latter case this was to facilitate N-allylation which was accomplished upon treatment with allyl bromide and K_2CO_3 in good yield. Reduction of ester **34** to the aldehyde **35** with DIBAL-H was accomplished in good efficiency which was then treated with vinylmagnesium bromide to afford the expected allylic alcohol **32** as a single diastereomer. The relative stereochemistry of this adduct was determined by X-ray crystallography and is consistent with a Felkin-Ahn model with the polar group anti to the incoming nucleophile.[35]



Scheme 3: (a) Successful access to key piperidinone **31**. (b) X-ray structures of intermediates **35** and **31**.

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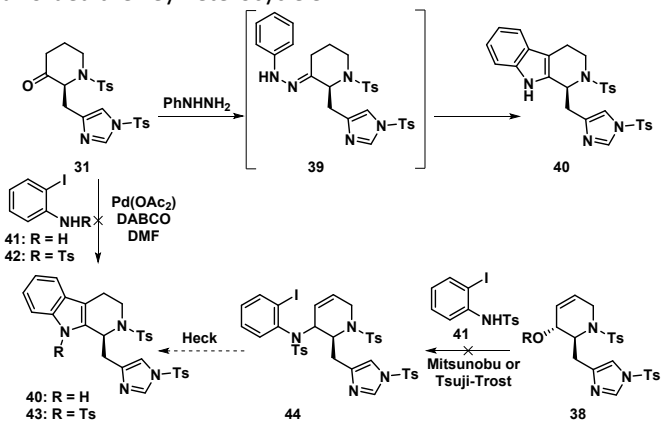
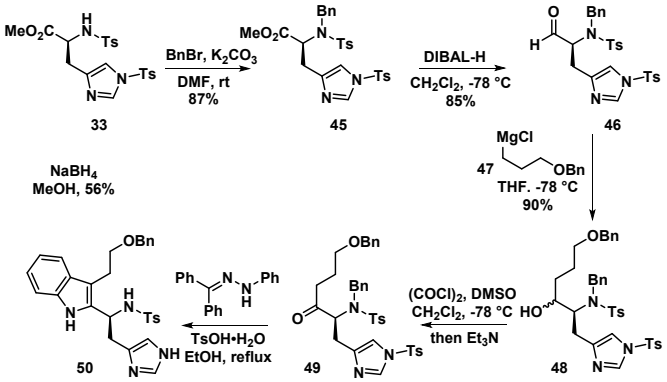
The alcohol **32** was oxidized to the ketone **36** which was then subjected to RCM with Grubbs' II generation catalyst in the presence of *p*-TsOH. While this substrate engaged in metathesis to afford the desired piperidenone **37**, the yield was quite low. Fortunately, the corresponding allylic alcohol **32** was a better substrate affording the corresponding cyclized product **38** in 80% yield on a gram scale. It was subsequently discovered that it was unnecessary to utilize *p*-TsOH to "protect" the imidazole, indeed, we were able to effectively carry out this reaction on a multigram scale in 80% yield. Oxidation of cyclohexenol **38** with IBX to enone **37** and catalytic hydrogenation of the enone double bond afforded the key heterocycle **31**.



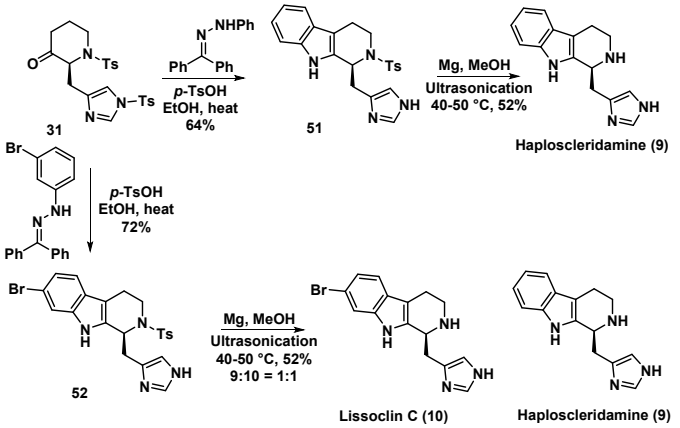
Scheme 4: Attempted indole construction

A number of classical Fischer indole reactions were performed with ketone **31** (Scheme 4). Treatment with phenyl hydrazine and catalytic acetic acid at reflux afforded the presumed hydrazine **39** which was isolated but not purified and then used directly in the cyclization. A variety of conditions examined, including PPA/160 °C, HCl/EtOH, $ZnCl_2$/AcOH, and AcOH/HCl, failed to deliver the indole **40**. Attempts were made to employ Heck type reactions to install the indole, for example reacting **31** with o-iodoaniline **41** or **42** but this failed affording product mixtures which were consistent intramolecular vinylation. Substitution reactions of allylic alcohol **38** or the corresponding carbonate were also investigated as a means to set up Heck-type processes with substrates like **44**, but these too were unsuccessful.



Scheme 5: Piperidine construction (C-ring) post indole formation

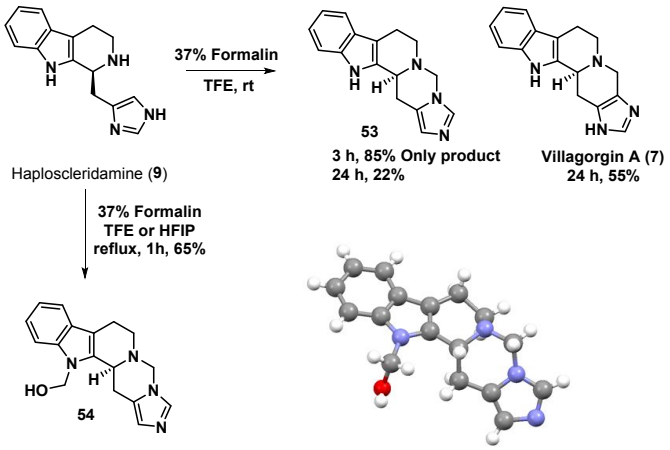
We briefly examined an alternative approach wherein the formation of the C-ring was postponed until the indole had been installed (Scheme 5). Commencing from the tosyl-protected histidine **33**, it was N-benzylated and reduced with DIBAL-H to afford the aldehyde **46**. Addition of Grignard **47** afforded the corresponding alcohol **48** which upon Swern oxidation afforded the ketone **49**. By this time, we had become aware of an alternative indole synthesis developed by the Buchwald lab which involved a hydrazone transfer reaction in the presence of *p*-TsOH.[36-37] Accordingly, ketone **49** was reacted with the benzophenone-derived hydrazone with TsOH in EtOH at reflux for 4 days. A material consistent with structure **50** was formed in which the indole had formed along with detosylation of the imidazole and debenzylation of the amino group. The full characterization of this material was thwarted by difficulties encountered in the purification and so the crude material was carried on to the next step which was reductive O-debenzylation prior to C-ring formation. Preliminary efforts to effect this sequence revealed two issues, one that the indole 2,3-bond was reactive and could be reduced and that O-debenzylation had not occurred. Although this result was disappointing, the successful indole formation under Buchwald Fischer indole conditions prompted us to re-examine the cyclic ketone **31** as a substrate. Gratifyingly, when **31** was subjected to similar conditions, the indole **51** was formed in moderate yield (Scheme 6). It is of note that the imidazole tosyl group underwent ethanolysis under these reaction conditions. Haploscleridamine (**9**) was obtained upon removal of the N-tosyl group by reduction with magnesium in methanol.[38-40] The spectroscopic data of the synthetic material matched that of the natural material. The specific rotation of the synthetic sample [α] = -19.8 (c 1.08, MeOH).[41]



Scheme 6: Completion of the synthesis of haploscleridamine and lissoclin C

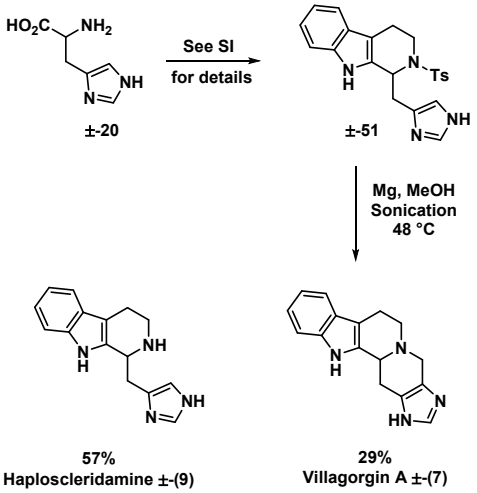
With a synthesis of haploscleridamine (**9**) completed, attention was turned to the brominated congener, lissoclin C which should be obtainable through use of the appropriate hydrazone derivative. Accordingly, when *m*-bromophenyl hydrazone was used in the Fischer indole reaction the corresponding bromoindole **52** was obtained in 72% yield. Completion of the synthesis required the removal of the N-Ts group. It was attempted with magnesium in methanol as had been used with haploscleridamine. Although the tosyl group was removed, partial reductive debromination also occurred producing inseparable mixtures of lissoclin C and haploscleridamine. Variation in equivalents of magnesium and reaction time did not improve the situation. Attempts to remove the Ts group under other conditions, including using Red-Al or Na naphthalide were either unsuccessful or resulted in reductive debromination (see SI for more details).

As noted above, the initial intent was to access villagorgin A (**7**) via a Pictet-Spengler reaction from haploscleridamine (**9**). Some scouting experiments with formalin and acid catalysts were unsuccessful, but conditions reported by the van Maarseveen group using formalin and trifluorethanol (TFE) were more encouraging.[42] Reaction of haploscleridamine with 3.2 equivalents of formalin for 3 h delivered a single new product in 85% yield. However, it was clear that this material was not villagorgin A (**7**) but a constitutional isomer **53** (Scheme 7). Gratifyingly, on allowing the reaction to proceed for an additional 12 h resulted in the formation of a second more polar material in addition to the initially-formed isomer. No change in composition occurred on stirring a further 12 h. Isolation and purification of the more polar material revealed that the total synthesis of villagorgin A (**7**) had been accomplished. The synthetic material had identical spectroscopic properties to the natural material. The specific rotation was found to be ([α] = -4.3 (c 0.17, MeOH)) which is opposite to the sponge derived material ([α] = +7.8 (MeOH)) confirming the original assignment of the absolute stereochemistry.[13] It was found the resubjection of the less polar material to the reaction conditions resulted in the formation of the mixture of **53** and **7** suggesting that **53** is the kinetic product and villagorgin A (**7**) is the thermodynamic product. The reaction was also performed at elevated temperature in either TFE or hexafluoroisopropanol (HFIP) resulting in the formation of a different product **54** containing the framework of the kinetic product but an additional carbinolamine moiety derived from formaldehyde and the indole nitrogen. This material was nicely crystalline which allowed confirmation of the structure through X-ray crystallography.



Scheme 7: Total synthesis of villagorgin A (**7**)

The stereochemical center in these natural products is prone to racemization, a feature that was noted in the isolation papers.[14-15] Both haploscleridamine and lissoclin C had low optical rotations and in the case of lissoclin C (**10**) treatment of α-methylbenzylisocyanate resulted in the preparation of an essentially 1:1 mixture of diastereomers.[14] Although in the present paper we have reported syntheses starting from *S*-histidine and we have obtained synthetic materials with higher rotation values than the natural materials, we do not know the enantiomer composition. In particular, we were concerned that the acidic conditions employed for the Buchwald Fischer indole sequence might lead to racemization. In order to address this, we performed the same synthetic sequence with racemic histidine (see SI) and noted one interesting observation. A second product was formed in the reductive detosylation, namely villagorgin A (**7**). Presumably, some formaldehyde (or surrogate) is produced from methanol which in turn then reacts with formed haploscleridamine.

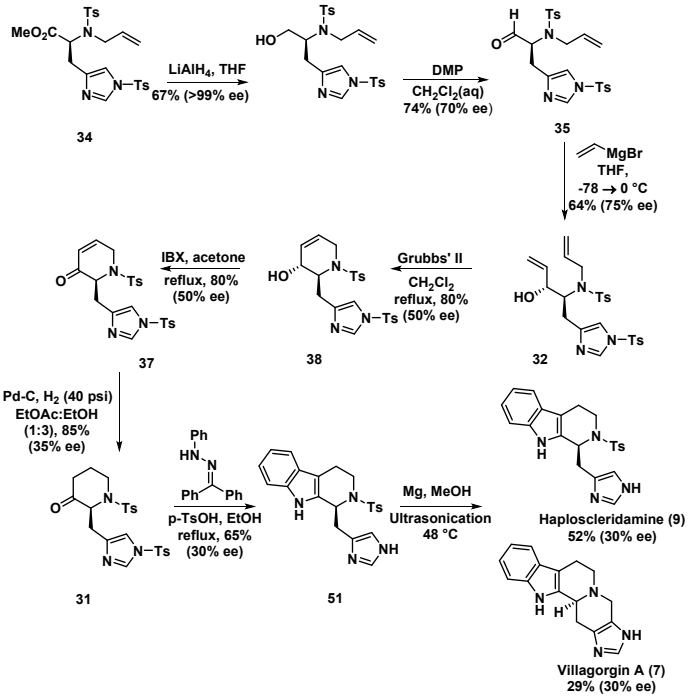


Scheme 8: An unexpected result

When both racemic and non-racemic haploscleridamine and villagorgin A were assessed using HPLC analysis, they essentially gave identical results; each showed low levels of enantioselectivity < 5% ee.[43] These results suggested that either our asymmetric syntheses had delivered racemic products or that the synthetic natural products had racemized during analysis. While this was certainly a possibility, the fact that the optical rotations were > 0 for the synthetic natural products suggested that while they may have been scalemic, they were not racemates. Since we had access to both racemic and non-racemic, HPLC analysis was used to assess when racemization occurred (for details see SI).[44-46] It was quickly apparent that it was at a very early stage in the synthesis, at the reduction of the methyl ester to the corresponding aldehyde using DIBAL-H.

Racemization of α-substituted aldehydes is a common issue in synthesis and there are a variety of methods to circumvent the problem,[47] including via the oxidation of the corresponding alcohol. The allyl ester (both racemic and non-racemic series) was reduced to the alcohol in 67% yield (>99% ee) with $LiAlH_4$. Oxidation with Dess-Martin periodinane using conditions reported by Myers and co-workers afforded the aldehyde in 75% yield (70% ee).[48] At this stage the sequence through to the piperidinone **31** was followed as previously described, with largely similar yields. The final steps involved the Fischer indole cyclization which provided mono tosylated haploscleridamine in 65% yield (30% ee). Reductive detosylation then delivered haploscleridamine (**9**) in 53% yield (30% ee) and villagorgin A (**7**) in 23% yield (30% ee). In both cases, the optical rotations were about twice the magnitude than previously obtained ([α] = -13.7, c 0.28, MeOH; [α] = -13.5, c 0.31, MeOH respectively).

As expected, the first three intermediates maintain high levels of enantiopurity, but on oxidation to the aldehyde some partial racemization is observed giving material of 70% ee. Interestingly, after ring-closing metathesis there is a drop in the enantiopurity which was unanticipated as this requires inversion at both centers. Examination of the HPLC analyses for the pre-RCM allylic alcohol and the cyclohexanol are interesting as the precursor **32** is a single scalemic diastereomer but the product **38** contained a second set of signals which were attributed to the other diastereomer. Finally, some loss of enantiopurity is noted at the piperidinone stage which presumably is related to the racemization of the α-center. The last two steps, including the Fischer indole synthesis and the reductive detosylation provide both natural products with similar levels of enantiopurity but no further erosion of the enantiomeric composition.



Scheme 9: Revised synthesis of haploscleridamine and villagorgin A

In summary, we have completed the asymmetric syntheses of two indolyl imidazole alkaloids, haploscleridamine and villagorgin A, from (*S*)-histidine. Key steps include a ring-closing metathesis and the Buchwald modification of the Fischer indole synthesis. Syntheses of both non-racemic and racemic versions were achieved which permitted an assessment of the enantiopurity of the synthetic material by HPLC. These analyses showed that the initial samples were almost racemic and this was due to racemization of an intermediate α-amino aldehyde. Modification of the sequence to access the aldehyde via the oxidation of the corresponding alcohol permitted its routine access in much higher enantiopurity. Use of this intermediate allowed access to the natural products with modest enantioselectivities. Attempts to prepare the brominated congener of haploscleridamine, lissoclin

C was compromised by reductive debromination during the attempted removal of the N-tosyl group.

Experimental

4-{Benzyl-[2-(1H-imidazol-4-yl)-1-methoxycarbonylethyl]amino}butyric acid methyl ester (27): Histidine methyl ester free base **25** (0.25 g, 1.5 mmol) was dissolved in methanol (100 mL). To this solution benzaldehyde (0.19 g, 1.6 mmol) was added in one portion. The reaction was stirred at room temperature for 1 h. Then, 1.05 equivalents of $NaBH_3CN$ (0.2 g, 3.0 mmol) was added and the reaction was allowed to stir at room temperature for 18 h, after which 1.0 equivalent of aldehyde **22** (0.17 g, 1.5 mmol) was added. An additional 1.05 equivalents of $NaBH_3CN$ was added and the reaction was allowed to stir at room temperature for 18 h. After this period the reaction mixture was concentrated in vacuo, taken up in CH_2Cl_2 (10 mL) and washed twice with de-ionized water (5 mL). The organic solution was dried with anhydrous $MgSO_4$ and concentrated in vacuo, to give the final product as a sticky oily compound. The crude product was purified by chromatography (silica gel, EtOAc/hexanes: 60/40) to give the title compound **27** as a viscous oil (0.33 g, 62%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 6.2 Hz, 2H), 7.49 (s, 1H), 7.39 (d, *J* = 4.9 Hz, 2H), 7.23 (d, *J* = 4.9 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 6.74 (s, 1H), 3.90 (d, *J* = 13.8 Hz, 1H), 3.72 (s, 3H), 3.64 (s, 3H), 3.55 (d, *J* = 13.8 Hz, 1H), 3.10 (dd, *J* = 4.8, 12.0 Hz, 2H), 2.84 – 3.00 (m, 2H), 2.52 -2.72 (m, 4H), 1.76 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 174.7, 174.4, 139.4, 134.7, 129.1, 128.8, 128.7, 127.7, 127.4, 127.2, 62.6, 60.7, 55.5, 52.2, 51.7, 49.8, 31.3, 29.5; FT-IR (neat, cm^{-1}): 3654, 2840, 1894, 1754, 1433, 1181. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{19}H_{26}N_3O_4$ 360. 360.1923, found 360.1883.

2-[Benzyl-(4-oxo-4-pyrrolidin-1-yl-butyl)amino]-3-(1*H*-imidazol-4-yl)propionic acid methyl ester (29): The free base **25** (0.50 g, 2.9 mmol) was dissolved in methanol (100 mL). To this solution benzaldehyde (0.20 g, 3.0 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h. Then, 1.05 equivalents of $NaBH_3CN$ (0.2 g, 3.0 mmol) was added and the reaction was allowed to stir at room temperature for 18 h, after which 1.0 equivalent of aldehyde **28** (0.47 g, 3.0 mmol) was added. An additional 1.05 equivalent $NaBH_3CN$ was added and the reaction was allowed to stir at room temperature for 18 h. After this period the reaction mixture was concentrated in vacuo, taken up in CH_2Cl_2 (10 mL) and washed twice with water (2×5 ml). The organic extract was dried with anhydrous $MgSO_4$ and concentrated in vacuo, to give the final product as a sticky oil. The crude product was purified by chromatography (EtOAc/hexanes: 60/40) to give the title compound **29** as a viscous oil (0.66 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 6.9, 1H), 7.34 (d, *J* = 5.5, 2H), 7.28 (d, *J* = 5.5, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 2H), 6.65 (d, *J* = 6.9 Hz, 2H), 3.90 (dd, *J* = 3.8, 13.8 Hz, 2H), 3.70 (s, 3H), 3.43 (t, *J* = 6.9 Hz, 2H), 3.40 (t, *J* = 6.9 Hz, 2H), 3.30 (d, *J* = 6.9 Hz, 1H), 2.80 – 3.10 (m, 2H), 2.50 – 2.71 (m, 2H), 2.06 - 2.25 (m, 2H), 1.94 (q, *J* = 7.6 Hz, 2H), 1.86 (q, *J* = 7.6 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 172.9, 171.8, 139.6, 134.7, 128.7, 128.6, 128.3, 127.0, 77.3, 70.8, 62.5, 55.5, 51.3, 49.5, 46.7, 46.0, 31.6, 26.1, 24.5, 23.0. FT-IR (neat, cm^{-1}): 3769, 3131, 2891, 1734, 1620, 1456, 1357, 1193, 1027, 477. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{22}H_{31}N_4O_3$ 399.2396, found 399.2391.

3-(1H-Imidazol-4-yl)-2-oxo-4-pyrrolidin-1-yl-butylamino-propionic acid methyl ester (30): Histidine methyl ester free base **25** (1.7 g, 10 mmol) was dissolved in methanol (10 mL) containing molecular sieves 4 Å (1 g). To this solution was added 4-oxopyrrolidine **28** (1.6 g, 10.0 mmol) added and stirred at room temperature for 5 h. Then, 5 equivalents of $NaBH_4$ (1.9 g, 50 mmol) added, cooling at 0 °C, stirred for 5 h at this temperature. The reaction mixture was worked up by ethyl acetate and water (1:1) extraction and then concentrated to obtain the crude compound. The crude product was purified by chromatography (EtOAc/hexanes: 60/40) to give the title compound **30** as a viscous oil (1.74 g, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 4.8 Hz, 1H), 6.84 (d, *J* = 4.8 Hz, 1H), 4.43 (dd, *J* = 1.4, 5.5 Hz, 1H), 3.72 (d, *J* = 1.4 Hz, 2H) 3.50 (t, *J* = 6.5 Hz, 2H), 3.4 (t, *J* = 6.9 Hz, 2H), 3.3 (d, *J* = 1.7 Hz, 3H), 3.03 – 3.12 (m, 1H), 2.84 – 2.92 (m, 1H) , 2.62 - 2.69 (m, 1H), 2.34 (t, *J* = 6.9 Hz, 2H), 2.30 (t, *J* = 7.2 Hz, 2H), 1.92 (q, *J* = 7.2 Hz, 2H), 1.76 (q, *J* = 7.2 Hz, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 174.8, 171.6, 135.1, 131.6, 120.0, 61.4, 52.0, 47.4, 46.7, 45.8, 32.3, 29.8, 26.1, 25.1, 24.2. EI-MS (*m/z*): calcd. for $[M+H]^+$ $C_{15}H_{25}N_4O_3$ 309.1, found 309.3.

(*S*)-Methyl 2-(*N*-benzyl-4-methylphenylsulfonamido)-3-(1-tosyl-1*H*-imidazol-4-yl)propanoate (45): Tosyl protected *L*-histidine methyl ester **33** (12.0 g, 25.0 mmol) was dissolved in DMF (30 mL) and K_2CO_3 (6.0 g, 44.0 mmol) was added and stirred for 15 min. Then benzyl bromide (5.4 mL, 45.0 mmol) was added all at once and the reaction was stirred at room temperature overnight. After filtration to remove residual solids, the solution was diluted with 500 mL ethyl acetate and an equal amount of water. The organic extract was washed with brine (3 ××x 30 ml) and water (3 × 30 ml). The organic extract was dried over anhydrous Na_2SO_4, filtered and concentrated to provide the crude product. The crude product was purified by flash chromatography (silica gel, EtOAc/hexanes = 1:2) to afford the pure benzyl protected ditosyl L-histidine methyl ester **45** (12.3 g, 87% yield) as a white solid: m.p. = 130-132 °C. [α] = - 2.76 (c = 1.50, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79 (d, *J* = 8.2 Hz, 2H), 7.75 (s, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 7.20 - 7.19 (m, 5H), 6.77 (s, 1H), 4.78 (dd, *J* = 7.5, 9.0 Hz, 1H), 4.52 (d, *J* = 16.0 Hz, 1H), 4.26 (d, *J* = 16.0 Hz, 1H), 3.39 (s, 1H), 3.01 (dd, *J* = 6.3, 15.5 Hz, 1H), 2.79 (dd, *J* = 6.3, 15.5 Hz, 1H), 2.42 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 170.5, 146.3, 143.7, 140.2, 137.1, 136.7, 136.0, 135.1, 134.3, 130.5, 129.6, 128.6, 128.4, 127.8, 127.6, 127.4, 115.2, 59.1, 52.1, 50.1, 29.4, 21.8, 21.6. FT-IR: 1746, 1371, 1153,

674, 604, 572, 539. HR-ESIMS (*m/z*): calcd. for $[M+H]^+$ $C_{28}H_{30}N_3O_6S_2$ 568.1571, found 568.1582.

(*S*)-*N*-Benzyl-4-methyl-*N*-(1-oxo-3-(1-tosyl-1*H*-imidazol-4-yl)propan-2-yl)benzenesulfonamide (46): Benzyl protected derivative **45** (11.3 g, 20.0 mmol) was dissolved in dry CH_2Cl_2 (150 mL) and cooled to -78 °C. A precooled (-78 °C) solution of DIBAL-H (30 mL, 30.0 mmol) was slowly added to the reaction solution. After stirring for 2 h at this temperature the reaction was quenched with methanol (100 mL), warmed to room temperature and the resulting mixture was stirred for 1 h with saturated K-Na-tartrate solution, then the mixture was extracted with CH_2Cl_2. The combined organic solutions were washed with brine (3 × 50 ml) and water (50 ml), dried over anhydrous Na_2SO_4. The concentrated residue was purified by flash chromatography (silica gel, EtOAc/Hexanes = 1:2) to furnish the aldehyde **46** as a colorless solid (9.4 g, 85% yield): m. p. = 120-121 °C. [α] = - 1.46 (c = 1.25, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.35 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H),7.72 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.29 (m, 5H), 4.50 (d, *J* = 15.0 Hz, 1H), 4.34 (dd, *J* = 5.0, 10.0 Hz, 1H), 4.11 (d, *J* = 15.0 Hz, 1H), 3.12 (dd, *J* = 5.0, 10.0 Hz, 1H), 2.70 (dd, *J* = 9.0, 15.0 Hz, 1H), 2.49 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 197.9, 146.5, 144.2, 140.4, 137.6, 136.1, 135.7, 135.0, 130.5, 130.0, 129.1, 128.9, 128.6, 127.3, 114.9, 65.4, 51.0, 25.5, 29.4, 21.8, 21.7. FT-IR: 1723, 1378, 1330, 1155, 1072, 672. HR-ESIMS (*m/z*): calcd. for $[M+H]^+$ $C_{27}H_{28}N_3O_5S_2$ 538.1465, found 538.1473.

(*S*)-*N*-Benzyl-*N*-(6-(benzyloxy)-3-hydroxy-1-(1-tosyl-1*H*-imidazol-4-yl)hexan-2-yl)-4-methylbenzenesulfonamide (48): A solution of (3-(benzyloxy)propyl) magnesium chloride **47** (ca. 1.0 M in THF, (40 mL), prepared from 1-((3-chloropropoxy) methyl) benzene (18.4 g, 100 mmol) and magnesium turnings (3.0 g, 125 mmol) was added to a solution of aldehyde **46** (10.7 g, 20.0 mmol) in THF (100 mL) at -78 °C, and the mixture was stirred for 2 h at the same temperature. After stirring for an additional 1 h at 25 °C, a saturated solution of NH_4Cl (50 mL) was added to the mixture which was then extracted with EtOAc. The organic phase was washed with brine, dried (Na_2SO_4), and then evaporated to give oil. The crude product was purified by flash chromatography (silica gel, EtOAc/hexane = 50/50), to give the desired alcohol **48** (12.4 g, 90%) as a clear viscous oil: [α] = - 0.11 (c = 1.62, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 2H), 7.68 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.35 - 7.20 (m, 14H), 6.58 (m, 1H), 4.48 - 4.38 (m, 4H), 3.90-3.92 (m, 1H), 3.62 - 3.68 (m, 1H), 3.48 - 3.42 (m, 1H), 3.34 – 3.25 (m, 2H), 2.70 - 2.74 (m, 2H), 2.43 (s, 3H), 2.41 (s, 3H), 1.51 – 1.47 (m, 2H), 1.47 – 1.38 (m, 1H), 1.20 - 1.25 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 146.4, 143.5, 141.9, 138.4, 138.1, 135.8, 135.1, 130.6, 130.0, 129.8, 129.3, 129.1, 128.9, 128.5, 127.7, 127.3, 127.2, 126.0, 114.8, 73.5, 72.9, 63.3, 49.2, 32.5, 26.9, 26.2, 21.8, 21.6. FT-IR: 3400, 1596, 1494, 1454, 1172, 1088, 813, 727, 699, 671, 656. HR-ESIMS (*m/z*): calcd. for $[M+H]^+$ $C_{37}H_{42}N_3O_6S_2$ 688.2510, found 688.2534.

(*S*)-*N*-Benzyl-*N*-(6-(benzyloxy)-3-oxo-1-(1-tosyl-1*H*-imidazol-4-yl)hexan-2-yl)-4-methylbenzenesulfonamide (49): To a dry round bottom flask was added oxalyl chloride (4 mL), dry dichloromethane (100 mL). After cooling the solution to -78 °C, anhydrous DMSO (6 mL) was added dropwise over 10 min and then stirred for 10 min. Alcohol **48** (14.0 g, 20.4 mmol) in anhydrous DCM (10 mL) was added slowly over 15 min. On completion of the addition, the solution was stirred over 30 min at same temperature. Triethylamine (37 mL) was added over 20 min and then the temperature of reaction was slowly raised to rt. The mixture was filtered by passing through a pad of silica gel (10 g), then, washed by anhydrous diethyl ether (100 mL). The solution was concentrated to get comparably pure 3-benzyloxypropyl ketone **49** as pale-yellow viscous oil (14.0 g, >99%). The crude ketone can be used directly for next step. [α] = - 0.83 (c = 1.25, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (s, 1 H), 7.72 (t, *J* = 14.0 Hz, 4H), 7.38 - 7.21 (m, 14.0 Hz, 1H), 6.54 (s, 1H), 6.58 (m, 1H), 4.56 (t, *J* = 11.0 Hz, 4H), 4.42 – 4.32 (m, 3H), 4.14 (d, *J* = 15.0 Hz, 1H), 3.27 - 3.24 (m, 2H), 3.12 (dd, *J* = 11.0 Hz, 1H), 2.62 – 2.49 (m, 2H), 2.43 (s, 3H), 2.45 (s, 3H), 2.41 (s, 3H), 2.24 – 2.12 (m, 1H), 1.68 – 1.53 (m, 2H), 1.49 – 1.38 (m, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 206.3, 146.4, 144.0, 140.8, 138.6, 137.6, 136.1, 135.9, 135.8, 135.0, 130.5, 130.0, 129.6, 129.1, 128.6, 128.5, 127.7, 127.5, 127.4, 115.0, 73.0, 69.3, 63.9, 50.4, 36.3, 26.0, 23.7, 21.8, 21 .7**.** FT-IR: 1718, 1356, 1336, 1190, 1074, 813, 720, 699, 671. HR-ESIMS (*m/z*): calcd. for $[M+H]^+$ $C_{37}H_{40}N_3O_6S_2$ 686.2353, found 686.2355.

(S)-1-((1H-Imidazol-5-yl)methyl)-7-bromo-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (52): A suspension of piperidinone **31** (104 mg, 0.21 mmol), benzophenone hydrazone (50 mg, 0.142 mmol) and PTSA (67 mg, 0.355 mmol) was in EtOH (6 mL) heated to reflux for 72 h. The reaction mixture was cooled to room temperature, diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate solution (3 × 25 ml) followed by water (20 mL) and brine (20 mL). The organic part was dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by column chromatography (MeOH:EtOAc = 1:49) to afford desired compound **52** (50 mg, 72%). m.p. = 144-148 °C, [α] = -9.9 (c = 0.15, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 10.52 (d, *J* = 8.8 Hz, 1H), 7.68 (s, 1H), 7.58 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.42 (d, *J* = 1.7 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 8.4, 1.7 Hz, 3H), 6.87 (s, 1H), 5.36 (t, *J* = 6.3 Hz, 1H), 4.16 (dd, *J* = 14.4, 5.4 Hz, 1H), 3.41 – 3.34 (m, 1H), 3.23 (d, *J* = 6.3 Hz, 2H), 2.50 (dd, *J* = 15.5, 3.6 Hz, 1H), 2.40 – 2.30 (m, 1H), 2.28 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 143.5, 138.0, 136.8, 134.8, 134.2, 129.7, 126.7, 125.4, 122.2, 119.2, 115.0, 114.3, 107.3, 53.3, 40.5, 34.8, 29.8, 21.5, 20.2. FT-IR (neat, cm^{-1}): 3361, 2922, 2852, 1618, 1596, 1560, 1465, 1459, 1450, 1438, 1377, 1326, 1302, 1151, 1090, 910, 799, 717, 654, 584. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{22}H_{22}BrN_4O_2S$ 487.0626, found 487.0606.

(S)-1-((1H-imidazol-5-yl)methyl)-7-bromo-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole - Lissoclin C (10): Mg (turnings) was added (4.5 mg, 0.195 mmol) to a solution of indole (19 mg, 0.039 mmol) in dry MeOH (2 mL), and the mixture was sonicated at 48 °C until all magnesium turnings were consumed. The TLC of the reaction mixture was checked and that exactly matched with haploscleridamine. MeOH was evaporated, saturated ammonium chloride (15 mL) was added and extracted with dichloromethane (2 × 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The crude product was purified by column chromatography (Ammoniacal MeOH: DCM = 1: 9) to provide a 1:1 mixture of haploscleridamine and lissoclin C (11.5 mg, 52%) as colorless solid. Protons and carbons which correspond to lissoclin C are highlighted. ^{1}H NMR (500 MHz, Methanol-d_4) δ ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.83 (s, 1H), 7.82 (s, 1H), 7.50 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.38 (q, *J* = 0.9 Hz, 1H), 7.37 (s, 1H), 7.20 (d, *J* = 0.8 Hz, 1H), 7.19 (dd, *J* = 3.2, 1.4 Hz, 1H), 7.18 – 7.17 (m, 1H), 7.16 (d, *J* = 1.0 Hz, 1H), 7.09 – 7.05 (m, 1H), 7.05 – 7.01 (m, 1H), 4.98 (dd, *J* = 9.3, 4.0 Hz, 1H), 4.98 (dd, *J* = 9.3, 4.0 Hz, 1H), 3.78 – 3.70 (m, 3H), 3.56 (ddd, *J* = 15.1, 10.0, 4.4 Hz, 4H), 3.51 – 3.40 (m, 5H), 3.25 (ddd, *J* = 15.6, 9.1, 4.4 Hz, 4H), 3.15 – 3.04 (m, 4H). ^{13}C NMR (125.8 MHz, Methanol-d_4) δ 139.3, 138.3, 136.8, 132.7, 130.8, 129.2, 127.3, 126.1, 124.5, 123.9, 123.7, 120.8, 120.7, 119.2, 117.7, 117.0, 115.4, 114.6, 112.5, 112.0, 108.5, 107.9, 54.6, 54.5, 42.9, 42.7, 30.0, 29.9, 21.7, 19.5.

Villagorgin A (7): A solution of haploscleridamine (**9**) (12.7 mg, 0.05 mmol) and 37% aqueous formaldehyde (1.7 µL, 0.16 mmol) in 2,2,2-trifluoroethanol (0.5 mL) was stirred during 3 h at room temperature. TLC showed total consumption of starting material and one non-polar spot found compared to starting material. The reaction was continued for another 12 h, a new more polar spot was observed. After an additional 12 h, no apparent change by TLC had occurred and thus the reaction mixture was concentrated under reduced pressure. The crude material was purified by column chromatography (ammoniacal MeOH:CH_2Cl_2 = 1:19) to afford the less polar product **53** (3.0 mg, 22%) and using (ammoniacal MeOH:CH_2Cl_2 = 1:9) to afford the desired compound **9** (7.2 mg, 55%) as colorless solid.

Isovillagorgin A (53): m.p. = 148-152 °C, [α] = - 5.3 (c = 0.28, MeOH), ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.64 (s, 1H), 7.42 (dd, *J* = 8.9, 1.8 Hz, 1H), 7.30 (dd, *J* = 8.1, 3.7 Hz, 1H), 7.09 – 7.04 (m, 1H), 7.02 – 6.96 (m, 1H), 6.80 (s, 1H), 5.24 (dd, *J* = 9.7, 7.3 Hz, 1H), 4.72 (d, *J* = 9.8 Hz, 1H), 4.04 – 3.98 (m, 1H), 3.48 (dt, *J* = 16.0, 4.7 Hz, 1H), 3.27 (d, *J* = 6.3 Hz, 1H), 2.97 – 2.79 (m, 4H).^{13}C NMR (125.8 MHz, Methanol-d_4): δ 138.3, 134.7, 128.0, 124.5, 122.4, 120.0, 118.8, 112.0, 108.0, 67.1, 55.9, 50.1, 49.1, 49.0, 26.9, 22.3. FT-IR (neat, cm-1): 2918, 2849, 1561, 1498, 1452, 1322, 1292, 1271, 1162, 1098, 1050, 1009, 941, 801, 739, 657, HR-MS (*m/z*): Calcd. for $[M+H]^+$ $C_{16}H_{17}N_4$ 265.1448, found 265.1448.

Villagorgin A (7): m.p. = 145-150 °C, [α] = - 4.3 (c = 0.17, MeOH), ^{1}H NMR (500 MHz, Methanol-d_4): δ 7.60 (d, *J* = 2.7 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.31 (dd, *J* = 7.0, 3.9 Hz, 1H), 7.09 – 7.04 (m, 1H), 7.01 – 6.96 (m, 1H), 4.00 (dd, *J* = 14.1, 3.3 Hz, 1H), 3.84 (m, 1H), 3.62 (m, 1H), 3.37 (m, 1H), 3.34 (m, 1H), 3.05 (m, 1H), 2.89 (ddd, *J* = 3.8, 8.4, 15 Hz, 1H), 2.79 (m, 1H), 2.73 (m, 1H). ^{13}C NMR (125.8 MHz, Methanol-d_4): δ 138.4, 135.6, 134.8, 129.8, 128.0, 122.3, 119.9, 118.8, 112.0, 108.4, 73.8, 58.5, 54.0, 53.3, 29.2, 22.3. FT-IR (neat, cm-1): 3096, 2957, 1717, 1616, 1526, 1440, 1349, 1288, 1268, 1193, 1134, 1072, 978, 924, 822, 777, 718. HR-MS (*m/z*): Calcd. for $[M+H]^+$ $C_{16}H_{17}N_4$ 265.1448, found 265.1444.

Hydroxymethylated β-carboline (54): A solution of haploscleridamine (10 mg, 0.03 mmol) and 37% aqueous formaldehyde (1.5 µL, 0.14 mmol) in 2,2,2-trifluoroethanol (0.5 mL) was heated at reflux 1 h. The reaction mixture was concentrated under reduced pressure. The resulting crude product was purified by column chromatography (ammoniacal MeOH:CH_2Cl_2 = 1:19) to afford (7.5 mg, 65%), the structure of which was confirmed by X-ray. m.p. = 150-155 °C [α] = - 37.7 (c = 0.33, MeOH), ^{1}H NMR (500 MHz, Methanol-d_4): δ 7.61 (d, *J* = 3.6 Hz, 1H), 7.46 (ddd, *J* = 19.3, 7.8, 3.6 Hz, 2H), 7.19 – 7.04 (m, 2H), 6.76 (d, *J* = 2.8 Hz, 1H), 5.64 – 5.54 (m, 2H), 5.48 (d, *J* = 4.5 Hz, 1H), 5.33 – 5.18 (m, 2H), 4.62 – 4.54 (m, 1H), 3.46 (dt, *J* = 16.6, 4.5 Hz, 1H), 3.22 (dd, *J* = 9.9, 5.0 Hz, 1H), 3.12 – 2.92 (m, 3H), 2.83 (dd, *J* = 15.3, 2.8 Hz, 1H). ^{13}C NMR (125.8 MHz, Methanol-d_4): δ 138.6, 137.0, 135.2, 130.6, 127.3, 121.6, 119.5, 117.7, 117.6, 109.2, 107.5, 66.0, 65.5, 50.2, 44.1, 29.4, 21.4. FT-IR (neat, cm-1): 3584, 3096, 2957, 1717, 1616, 1526, 1440, 1349, 1330, 1288, 1268, 1193, 1134, 1072, 978, 924, 822, 777, 718. HR-MS (*m/z*): Calcd. for $[M+H]^+$ $C_{17}H_{19}N_4O$ 295.1502, found 295.1490

(*S*)-N-Allyl-N-(1-hydroxy-3-(1-tosyl-1H-imidazol-4-yl) propan-2-yl)-4-methylbenzenesulfonamide (**55**):The ester **27** (300 mg, 0.58 mmol) in freshly distilled THF (15mL) was added dropwise to a cooled suspension of $LiAlH_4$ (0.021 g, 0.58 mmol) in dry THF (10 mL), and the mixture was stirred at 0 °C. After stirring for 3 h at this temperature the reaction was quenched while still at 0 °C with ethyl acetate (excess). After warming to room temperature, the resulting mixture was stirred for another 2 h. Then, the residue was filtered and rinsed with ethyl acetate and the filtrate was concentrated. The crude product was purified by flash chromatography (Silica gel, EtOAc/hexanes: 60/40) to provide the pure title compound **55** (200 mg, 67%) as a white solid. m.p. 96-98 °C. [α] = -51.8 (c = 0.80, MeOH). ^{1}H NMR (500 MHz, Chloroform-*d*): δ 7.78 (d, *J* = 8.1 Hz, 3H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.94 (s, 1H), 5.81 (ddt, *J* = 16.6, 10.1, 6.2 Hz, 1H), 5.31 – 5.15 (m, 1H), 5.07 (d, *J* = 10.2 Hz, 1H), 4.10 – 4.01 (m, 1H), 3.98 – 3.82 (m, 2H), 3.57 (qd, *J* = 12.1, 5.6 Hz, 2H), 2.79 (dd, *J* = 14.6, 8.0 Hz, 1H), 2.64 (dd, *J* = 14.6, 6.8 Hz, 1H), 2.41 (d, *J* = 6.7 Hz, 6H).; ^{13}C NMR (126 MHz, Chloroform- *d*): δ 146.5, 143.5, 141.1, 137.8, 136.2, 136.0, 134.9, 130.6, 129.8, 127.4, 127.1, 117.7, 114.7, 63.3, 59.9, 47.6, 28.8, 21.8, 21.6; FT-IR (neat,

cm^{-1}): 3163, 3124, 2928, 2875, 1646, 1593, 1493, 1379, 1170, 1152, 1076, 979,863, 588, 539. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{23}H_{27}N_3O_5$, 490.1487 found 490.1464.

(*S*)-N-allyl-4-methyl-N-(1-oxo-3-(1-tosyl-1H-imidazol-4-yl)propan-2-yl) benzenesulfonamide (**46**): The alcohol **55** (85 mg, 0.17 mmol) was dissolved in 12 mL of H_2O-saturated CH_2Cl_2. (Using a separatory funnel, the CH_2Cl_2 was shaken with several milliliters of H_2O and then separated from the water layer). DMP was added (94 mg, 0.22 mmol), the clear solution turned cloudy toward the end of wet CH_2Cl_2 addition, which required 30 min. The resultant cloudy reaction mixture was vigorously stirred for 16 h. The mixture was diluted with ether, then concentrated until a few mL of solvent by rotary evaporator. The residue was taken in 30 mL of ether and then washed with 15 mL of 1:1 10% $Na_2S_2O_3$: saturated aqueous $NaHCO_3$, followed by 10 mL of H_2O and 10 mL of brine. The aqueous washings were back extracted with 20 mL of Et_2O, and this organic layer was washed with H_2O and brine. The combined organic part was dried with Na_2SO_4 and concentrated. Flash column chromatography (SiO_2, EtOAc/hexane = 40:60) to furnish the aldehyde **46** as a colorless solid (62 mg, 74%) as a crystalline solid. m.p. 108-110 °C. [α] = -30.4 (c = 0.92, MeOH). ^{1}H NMR (500 MHz, Chloroform- *d*): δ= 9.65 (s, 1H), 7.76 – 7.72 (m, 3H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.32 (m, 2H), 7.28 – 7.26 (m, 2H), 5.72 – 5.62 (m, 1H), 5.16 (s, 1H), 5.13 (dd, *J* = 7.3, 1.2 Hz, 1H), 4.47 (dd, *J* = 9.2, 5.1 Hz, 1H), 3.86 (dd, *J* = 15.5, 6.7 Hz, 1H), 3.68 – 3.60 (m, 1H), 3.19 (dd, *J* = 16.5, 5.1 Hz, 1H), 2.70 (dd, *J* = 15.4, 9.2 Hz, 1H), 2.46 (s, 3H), 2.42 (s, 4H). ^{13}C NMR (126 MHz, Chloroform- *d*): δ 198.8, 146.4, 144.1, 140.3, 137.5, 136.2, 135.0, 133.3, 130.5, 129.9, 127.3, 127.2, 120.5, 114.9, 65.5, 49.9, 25.9, 21.8, 21.7. FT-IR (KBr, cm^{-1}): 3157, 3126, 2924, 2863, 1909, 1731, 1596, 1478, 1256, 1217, 1154, 940, 793, 625, 520. HR-MS (*m/z*): calcd. for $[M+H]^+$ $C_{23}H_{26}N_3O_5S_2$ 488.1314, found 488.1308

(3*S*,4*R*)-N-Allyl-N-{2-hydroxy-1-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl-methyl]-but-3-enyl}-4-methyl-benzenesulfonamide (**26**)**:** A solution of **46** (200 mg, 4.12 mmol) in THF (5.0 mL) was added to a solution of vinyl magnesium bromide (1.3 M in THF, 5.3 mL) at -78 °C, and the mixture was stirred for 2 h. After stirring for an additional 1 h at 25 °C, a saturated aqueous solution of NH_4Cl (25 mL) was added to the mixture which was then extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, and then evaporated to give an oil. The crude product was purified by flash chromatography (silica gel, EtOAc/hexane 50/50), to give the desired alcohol **26** (0.33 g, 75%): [α] = -27.6 (c = 0.45, MeOH). ^{1}H NMR (500 MHz, Chloroform- *d*) δ 7.81 – 7.69 (m, 3H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.20 (s, 1H), 6.83 (s, 1H), 5.87 – 5.69 (m, 2H), 5.18 (t, *J* = 15.9 Hz, 2H), 5.05 (t, *J* = 9.8 Hz, 2H), 4.30 (s, 1H), 4.10 – 3.98 (m, 1H), 3.94 – 3.83 (m, 2H), 2.86 – 2.69 (m, 2H), 2.43 (d, *J* = 2.1 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform- *d*) δ 146.4, 143.5, 141.4, 138.2, 137.8, 136.1, 135.9, 135.0, 130.5, 129.6, 127.3, 127.2, 117.7, 116.0, 114.8, 74.9, 62.5, 48.5, 26.6, 21.8, 21.6; FT-IR (neat, cm^{-1}): 3112, 1749, 1641, 1515, 1240, 1174, 1090, 994, 925, 824, 771, 674, 592, 478, 455, 417. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{25}H_{30}N_3O_5S_2$ 516.1627, found 516.1621

(3*S*,4*R*)-1-(Toluene-4-sulfonyl)-3-[1-(toluene-4-sulfonyl)-1H-imidazol-4-yl-methyl]-1,2,3,4- tetrahydropyridin-4-ol (**25**)**:** The allylic alcohol **26** (4.6 g, 8.93 mmol), was dissolved in dry CH_2Cl_2 (60 mL). The Grubbs' second-generation catalyst (0.38 g, 0.45 mmol, 5 mol%) was added, followed by heating the mixture at reflux for 3 h. The mixture was stirred at room temperature for 6 h, at which time TLC analysis indicated the completion of the reaction. The solvent was concentrated. The crude product was purified by chromatography (EtOAc/hexanes = 75:25) to give the title compound **25** as a colorless solid (3.4 g, 80%): m.p. 147-149 °C, [α] = - 27.9 (c = 0.27, MeOH). ^{1}H NMR (500 MHz, Chloroform- *d*) δ 7.84 – 7.75 (m, 3H), 7.66 – 7.59 (m, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 1.3 Hz, 1H), 5.92 – 5.83 (m, 2H), 4.36 (ddd, *J* = 8.4, 6.6, 1.7 Hz, 1H), 4.12 – 4.06 (m, 1H), 3.97 – 3.89 (m, 1H), 3.59 – 3.51 (m, 1H), 2.45 (dd, *J* = 17.6, 7.6 Hz, 2H), 2.38 (d, *J* = 9.0 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform- *d*) δ 146.4, 143.6, 140.9, 136.8. 136.2, 134.9, 130.5, 129.8, 127.4, 127.3, 126.9, 125.7, 114.4, 64.9, 58.5, 40.6, 27.7, 21.8, 21.6; FT-IR (neat, cm^{-1}): 3747, 3115, 1796, 1592, 1388, 1173, 1080, 930, 840, 770, 550. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{23}H_{26}N_3O_5S_2$ 488.1314, found 488.1308.

(*S*)-1-Tosyl-2-((1-tosyl-1H-imidazol-4-yl) methyl)-1,6-dihydropyridin-3(2H) -one (**48**)**:** To a stirred solution of **25** (3.6 g, 7.38 mmol) in acetone (60 ml) was added IBX (2.27 g, 8.11 mmol) at 0 °C. The resulting reaction mixture was heated to reflux for 6 h. The reaction mixture was cooled to room temperature, and resulting slurry was filtered and washed with ethyl acetate. The filtrated was concentrated under reduced pressure. Crude product was purified by column chromatography (EtOAc/Hexanes = 4:1) to afford compound **48** (2.9 g, 81%) as off-white solid. m.p. = 103-105 °C. [α] = -30.8 (c = 0.37, MeOH). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.86 (d, *J* = 1.3 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 7.51 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 3H), 6.68 (ddd, *J* = 10.4, 4.9, 1.9 Hz, 1H), 5.76 (dt, *J* = 10.4, 2.3 Hz, 1H), 4.64 (t, *J* = 7.5 Hz, 1H), 4.40 (ddd, *J* = 21.0, 4.9, 1.6 Hz, 1H), 4.00 (dt, *J* = 21.1, 2.1 Hz, 1H), 2.90 (d, *J* = 7.5 Hz, 2H), 2.39 (d, *J* = 16.2 Hz, 6H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 193.4, 146.3, 144.3, 144.1, 139.3, 136.3, 136.1, 134.9, 130.5, 130.3, 130.0, 127.4, 127.2, 127.0, 126.7, 115.4, 61.1, 41.3, 29.2, 21.8, 21.6. FT-IR (neat, cm^{-1}): 3427, 3129, 2940, 1686, 1490, 1464, 1387, 1163, 1154, 1100, 757, 698, 550, 520. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{23}H_{24}N_3O_5S_2$ 486.1157, found 486.1152.

(*S*)-1-(Toluene-4-sulfonyl)-3-[1-(toluene-4-sulfonyl)-1H-imidazol-4-ylmethyl]-piperidin-4-one (**24**)**:** The enone **48** (800 mg, 1.63 mmol) and 10% Pd/C (160 mg) were placed in a 1:3 mixture of ethyl acetate and ethanol (10 mL) and under H_2 (40 psi). Then, the catalyst was filtered and rinsed with ethyl acetate and the filtrate

was concentrated. The crude product was purified by flash chromatography (EtOAc/hexanes: 80/20) to provide the pure title compound **24** (680 mg, 85%) as a yellow solid. [α] = -13.8 (c = 0.93, MeOH). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.76 (s, 1H), 7.74 (d, 2H, *J* = 8.3 Hz), 7.53 (d, 2H, *J* = 8.3 Hz), 7.30 (d, 2H,), 7.2 (d, 2H, *J* = 8.3 Hz), 7.03 (s, 1H), 4.49 (t, 1H, *J* = 7.3 Hz), 3.73 (ddd, 1H, *J* = 19.3, 9.6, 4.6, Hz), 3.20 (ddd, 1H, *J* = 19.3, 9.6, 5.0 Hz), 2.95 (d, 2H, *J* = 7.3 Hz), 2.42 (dd, 2H, *J* = 14.7, 6.9 Hz), 2.43 (s, 6H), 2.20 (ddd, 1H, *J* = 21.5, 11.0, 5.5, Hz), 1.64-1.74 (m, 2H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 206.2, 146.3, 143.9, 139.5, 137.2, 136.2, 135.0, 130.5, 130.0, 127.3, 127.0, 115.5, 63.7, 40.3, 36.5, 30.1, 23.2, 21.8, 21.6; FT-IR (neat, cm^{-1}): 3422, 3119, 2930, 1738, 1620, 1510, 1360, 1260, 1210, 1100, 1010, 720, 680, 550, 530, 510. HR-MS (m/z): calcd. for $[M+H]^+$ $C_{23}H_{26}N_3O_5S_2$ 488.1314, found 488.1308.

(*S*)-1-((1H-Imidazol-5-yl) methyl)-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (23): A suspension of enone (67 mg, 0.13 mmol), benzophenone phenylhydrazone (25 mg, 0.09 mmol) and p-TsOH·H_2O (43 mg, 0.23 mmol) was in EtOH (2.0 mL) heated to reflux for 72 h. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (15 mL) and washed with saturated aqueous sodium bicarbonate solution (3 ×x 25 mL) followed by water (15 mL) and brine (15 mL). The organic part was dried over sodium sulfate and concentrated under reduced pressure. The crude was purified by column chromatography (MeOH/EtOAc = 2:8) to afford desired compound **23** (24 mg, 65%) as an off-white solid. m.p. = 138-142 °C. [α] = -14.9 (c = 0.43, MeOH); ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.70 (s, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.95 – 6.83 (m, 3H), 6.68 (dd, *J* = 18.4, 8.3 Hz, 3H), 6.61 (t, *J* = 7.8 Hz, 1H), 6.46 (bs, 1H), 5.03– 4.97 (m, 1H), 3.76 (dd, *J* = 14.4, 5.2 Hz, 1H), 2.98 (ddd, *J* = 14.4, 12.3, 5.2 Hz, 1H), 2.84 (m, 2H), 2.13 (dd, *J* = 15.4, 3.5 Hz, 2H), 2.04-2.03 (m, 1H), 1.95 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-*d*) δ 143.5, 137.9, 136.1, 135.2, 129.7, 126.7, 126.6, 121.8, 119.2, 118.1, 111.5, 107.4, 53.6, 40.4, 21.5, 20.2; FT-IR (neat, cm^{-1}): 3376, 3055, 2921, 2850, 1739, 1492, 1325, 1150, 1090, 919, 812. HR-MS (m/z): calc for $[M+Na]^+$ $C_{22}H_{22}N_4NaO_2S$, 429.1356, found: 429.1351

(*S*)-1-((1H-Imidazol-5-yl)methyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-*b*]indole (Haploscleridamine) (1): Mg (turnings) was added (14.6 mg, 0.61 mmol) to a solution of indole (-)- **23** (25 mg, 0.061 mmol) in dry MeOH (2 mL), and the mixture was sonicated at 48 °C until all magnesium turnings were consumed. MeOH was evaporated, saturated ammonium chloride (15 mL) was added and extracted with dichloromethane (2 × 30 mL). The combined extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure. During the reaction, a non-polar spot formed villagorgin A (**7**) along with haploscleridamine (**9**). The crude product was purified by column chromatography (ammoniacal MeOH:DCM = 1: 19) to provide as colorless solid villagorgin A **(-)-(7)** (3.8 mg 23%) and by using (ammoniacal MeOH: DCM = 1: 9) provided haploscleridamine (-)-**(9)** (8 mg, 52%) as a colorless solid.; [α] = -13.7 (c = 0.28, MeOH). ^{1}H NMR (Methanol-d_4): δ = 7.65 (bs, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.00 (dt, *J* = 8.0, 1.0 Hz, 1H), 6.98 (dt, *J* = 7.8, 1.0 Hz, 1H), 6.87 (bs, 1H), 4.48 (dd, *J* = 9.1, 4.1 Hz, 1H), 3.37 (td, *J* = 9.1, 4.1 Hz, 1H), 3.32 (td, *J* = 9.1, 4.1 Hz, 1H), 3.05 (ddd, *J* = 13.9, 9.1, 5.2 Hz, 1H), 3.00 (dd, *J* = 13.9, 9.0 Hz, 1H), 2.87-2.74 (m, 2H). ^{13}C NMR (Methanol-d_4) δ137.9, 136.6, 135.5, 134.3, 128.2, 122.5, 120.0, 118.8, 117.8, 112.0, 108.7, 54.3, 43.0, 32.2, 21.9. FT-IR (neat, cm^{-1}): 3151, 2923, 2846, 1735, 1619, 1450, 1372, 1228, 1100, 739. HR-MS (m/z): calc for $[M-H]^+$ $C_{15}H_{16}N_4$, 251.1302, found: 251.1307

Villagorgin A (5) m.p. = 145-150 °C, [α] = -13.5 (c = 0.31, MeOH), ^{1}H NMR (500 MHz, Methanol-d_4): δ 7.60 (d, *J* = 2.7 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.31 (dd, *J* = 7.0, 3.9 Hz, 1H), 7.09 – 7.04 (m, 1H), 7.01 – 6.96 (m, 1H), 4.00 (dd, *J* = 14.1, 3.3 Hz, 1H), 3.84 (m, 1H), 3.62 (m, 1H), 3.37 (m, 1H), 3.34 (m, 1H), 3.05 (m, 1H), 2.89 (ddd, *J* = 3.8, 8.4, 15 Hz, 1H), 2.79 (m, 1H), 2.73 (m, 1H). ^{13}C NMR (126 MHz, Methanol-d_4): δ 138.4, 135.6, 134.8, 129.8, 128.0, 122.3, 119.9, 118.8, 112.0, 108.4, 73.8, 58.5, 54.0, 53.3, 29.2, 22.3. FT-IR (neat, cm^{-1}): 3096, 2957, 1717, 1616, 1526, 1440, 1349, 1288, 1268, 1193, 1134, 1072, 978, 924, 822, 777, 718. HR-MS (*m/z*): Calcd. for $[M+H]^+$ $C_{16}H_{17}N_4$ 265.1448, found 265.1444.

Conflicts of interest

There are no conflicts to declare.

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