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Total Synthesis of (−)-Spiroleucettadine

Richard A. Lamb, Nicholas S. Aberle, Nigel, T. Lucas, Guillaume Lessene* and Bill C. Hawkins*

Abstract: Amongst an intriguing number of new alkaloids isolated from the *Leucetta* sp. sponge in 2004 was spiroleucettadine, which displayed unique structural features on a restricted scaffold: a *trans*-fused 5,5-bicyclic ring system, together with an amino-hemiketal moiety. Attempts at synthesizing the initially proposed structure failed, raising questions as to its veracity and as a result structure revision ensued in 2008; no successful synthetic approach has been reported to date. Herein, we describe the first enantiospecific total synthesis of (−)-spiroleucettadine using a highly efficient biomimetic approach starting from L-tyrosine. The key steps in the synthesis include two hypervalent iodine mediated oxidations: one forges the spirocyclic centre, while the other, in the penultimate step, allows for the installation of the methylamine side chain. Our work provides synthetic entry into a new class of spiro-annulated natural products and will enable future structure-biological activity relationship studies of these anti-bacterial compounds.

Among the rich chemical and biological diversity of marine natural products[1] is spiroleucettadine, originally isolated from the bright yellow *Leucetta* calcareous sponge in 2003.[2] The discovery of spiroleucettadine was met with international interest, not only due to its anti-bacterial activity (minimum inhibitory activity MIC < 6.25 μg/mL against *Enterococcus durans*) but also because of its seemingly unprecedented *trans*-fused 2-imino imidazole-oxolane core. The legitimacy of this structure (Figure 1, **1**) became uncertain following several failed attempts from independent research groups[3] to complete the requisite hypervalent iodine mediated oxidative spirocyclization. This called into question the viability of the 5,5-*trans*-fused system and its ability to form the seemingly unstable ortho-amide type functionality. Prompted by these failures, the analytical data for spiroleucettadine was revisited and the structure was revised to **2** which was further supported by DFT (Density Functional Theory) calculations and X-ray crystallography.[4] The revised structure of spiroleucettadine represents one of the more oxidized congeners of the *Leucetta* alkaloids, similar to spirocalcaridine A, B **5** (Figure 1)[5] and the more recently discovered spironaamidine **6**.[6] Attempts to access the *Leucetta* family of structures have typically relied on the elaboration of an existing imidazole framework rather than the *de novo* construction of the heterocycle. [7]

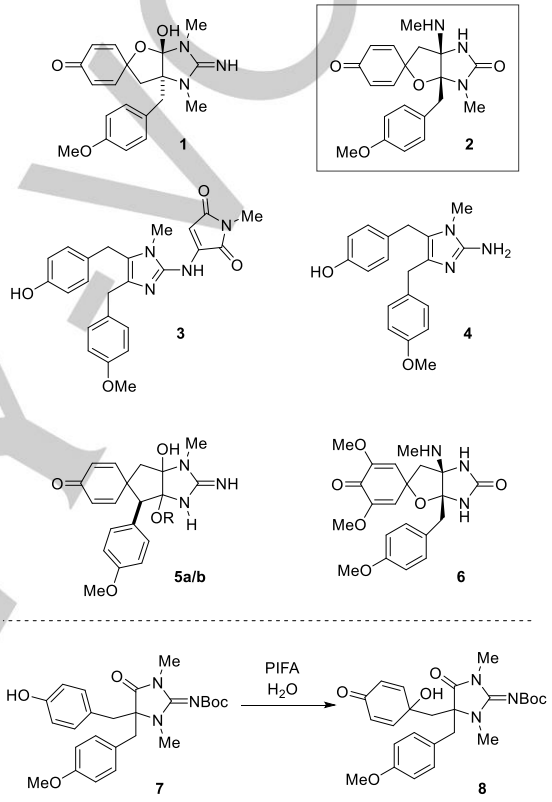

Figure 1. Originally assigned structure (**1**) and revised structure (**2**) of spiroleucettadine, representative *Leucetta* alkaloids naamidine A (**3**), naamine A (**4**), spirocalcalcaridine A (**5a**, R = OMe), spirocalcaridine B (**5b**, R = OH), spironaamidine (**6**) and failed oxidative spirocyclization towards **1**.

The interesting spiro framework of spiroleucettadine and its polar core densely packed with heteroatoms, as well as its biological activity, amounts to an enticing synthetic target. Given that X-ray crystallography is not always infallible[8] and NMR and MS studies were unable to solve the structure,[2, 4] the synthesis of spiroleucettadine would provide final corroboration. Furthermore, as the natural source is suspected of producing scalemic spiroleucettadine, an enantiopure source of the material could result in enhanced biological activity. Herein we present the total synthesis of spiroleucettadine, the first of the spiro-annulated *Leucetta* alkaloids to be synthesized.

Following a number of failed approaches and retrosynthetic analyses, we developed a biomimetically inspired strategy similar to those reported for naamine A and naamidine A (Scheme 1).[9] Following from this earlier work, it was surmised that an efficient

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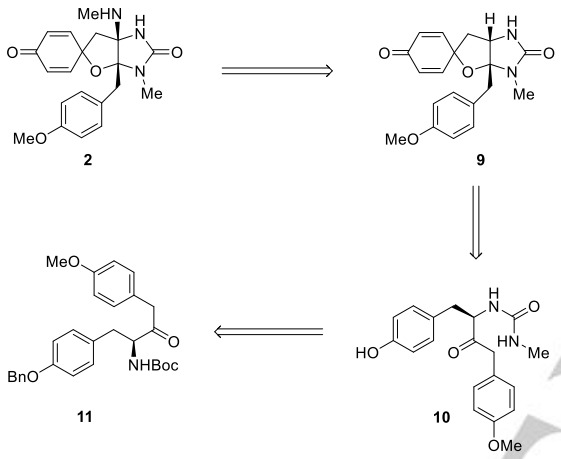
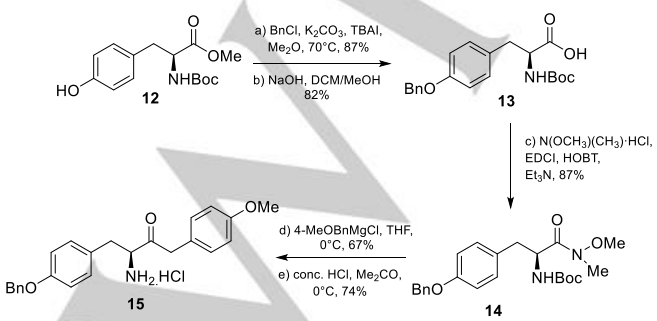
approach to the target would be the construction of the core framework followed by further elaboration, which would allow incorporation of the methylamine side chain *via* a challenging oxidation of the C-5 carbon of imidazolidinone **9**. Spiroquinone intermediate **9** itself would be accessible *via* a hypervalent iodine mediated oxidation/dicyclization sequence from urea **10**, which in turn could be accessed relatively straightforwardly from the tyrosine derived ketone **11**. We anticipated that the stereoselectivity of the reactions leading to spiroleucettadine, starting from **11**, would be controlled by the initial chiral L-tyrosine: the geometry of this amino acid would likely influence the formation of the *cis*-fused 5,5 bicyclic rings and as a consequence this step would position the hydroxyl group in the precursor to compound **9** in the correct orientation. We also expected that the method to execute the final step, leading to **2**, would retain the *cis*-fused ring arrangement.



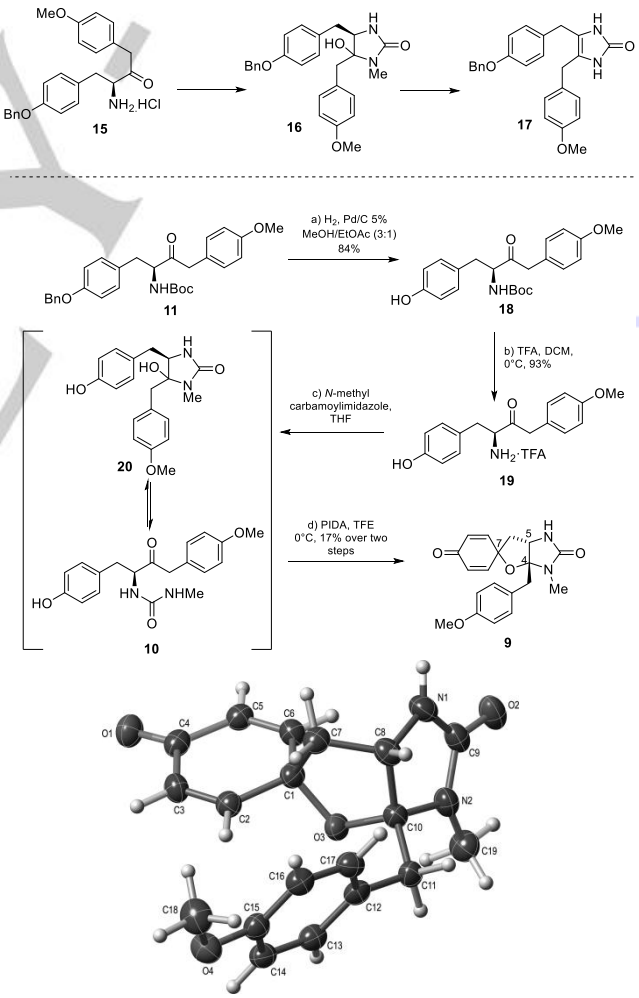
Scheme 1. Retrosynthetic analysis of spiroleucettadine **2**.

In a forward synthetic sense our synthesis began with the commercially available starting material *N*-Boc-L-tyrosine methyl ester (Scheme 2). The phenol was protected as the benzyl ether[10] and the methyl ester hydrolyzed to the carboxylic acid **13**[11] which was smoothly converted to the corresponding Weinreb amide **14** using EDCI and HOBT amide coupling reagents[12] without need for purification following workup. Treatment with freshly prepared 4-methoxybenzylmagnesium chloride[13] followed by removal of the Boc group with concentrated HCl in acetone furnished the *α*-amino ketone as the HCl salt **15**.



Scheme 2. Synthesis of HCl α-ammonium ketone **15**.

Having established a robust approach to prepare the carbon backbone of spiroleucettadine, our focus was directed to addition of the *N*-methyl urea component. Following neutralization of the HCl salt **15**, reaction with *N*-methyl carbamoyl imidazole[14] yielded **16** (Scheme 3). This reaction had to be carefully monitored until complete consumption of the starting material was observed (TLC). Dilute reaction concentrations were required to circumvent dimerization and formation of the tetrasubstituted pyrazine (not shown). Furthermore, mildly acidic conditions, such as those required for the standard hydrogenolysis of benzyl ethers (EtOAc, Pd/C), led to dehydration and formation of imidazolone **17** which complicated the benzyl ether deprotection step. However, it was found this unwanted dehydration/imidazolone formation pathway could be circumvented by simply changing the order of deprotections. With this strategy we were able to install the *N*-methyl urea in the presence of the unprotected phenol. Thus, hydrogenolysis of **11** using 5% Pd/C followed by removal of the Boc group with TFA and treatment with *N*-methyl carbamoyl imidazole in the presence of trimethylamine, yielded compounds **10** and **20**, which were not isolated and the crude residue was taken forwards without further purification. The formation of compound **20** provided some evidence that our strategy towards elaboration of the fused bicyclic core was indeed feasible.

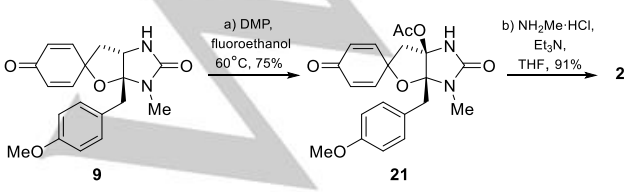


Scheme 3. Synthesis of compound **9** and an X-ray crystal structure diagram showing the absolute stereochemistry of **9** (50% ellipsoids, ethyl acetate solvate omitted for clarity).

It was anticipated that, after acid catalyzed hemi-aminal formation, a phenol oxidation mediated by a hypervalent iodine reagent[15] would promote *ipso* attack of the resultant tertiary

alcohol and form the desired 5,5,6-tricyclic core. Indeed, treatment of compounds **10** and **20** with PIDA in 2,2,2-trifluoroethanol at 0°C (Scheme 3) yielded one major product,[16] as indicated by TLC analysis and inspection of the proton NMR spectrum of the crude residue. Following purification, analysis of the proton NMR spectrum indicated the presence of the cyclohexadienone with the appearance of characteristic resonances at 6.84, 6.35, 6.12 and 6.07 ppm. In addition, in the ^{13}C NMR spectrum the resonances at 102.7 and 79.7 ppm were assigned as the quaternary carbon C4 and the spiro carbon C7, respectively. Compound **9** crystallises in a non-centrosymmetric space group ($P2_1$) indicating the presence of an enantiopure compound for which the absolute configuration was determined (Scheme 3).[17]

For incorporation of the methylamine sidechain, it was decided to employ Nicolaou's hypervalent iodine-mediated oxidation of secondary amides to imides for oxidation of the C-5 carbon.[18] We suspected that oxidation of the tertiary substituted C-5 would yield either the corresponding hemiaminal or imine depending on work-up conditions. Gratifyingly, this oxidation step proceeded straightforwardly using Dess-Martin periodinane to furnish the corresponding acetate substituted derivative **21** in 75% yield (Scheme 4). Notably, this oxidation extends the known scope of this reaction to now include cyclic ureas, which will undoubtedly facilitate the synthesis of congeners within this structure class. Substitution of the acetate for the requisite *N*-methyl amine was achieved by treatment with methylamine hydrochloride and triethylamine in THF at room temperature to afford spiroleucettadine (**2**) in a 91% yield. The spectroscopic data of the synthetic material was identical to that reported for the natural product.[19] The addition of the methylamine occurs either through a discrete carbocation or the imine, regardless only the stable *cis* isomer was observed. The specific rotation of the synthetic material was found to be $[\alpha]^{25}_D = -2.5^\circ$ which is consistent with that reported in the re-isolation paper $[\alpha]_D = -5.1^\circ$. However, the original isolation paper reported the specific rotation to be $[\alpha]_D = -27.1^\circ$, leading the authors to speculate that scalemic mixtures of spiroleucettadine were being isolated. With a robust method developed to make spiroleucettadine, we repeated the synthesis starting with DL-tyrosine to provide *rac*-spirolecuettadine. Using a Chiralpak IC-3 column, high pressure liquid chromatographic analysis was conducted to compare the two materials.[19] Pleasingly, our study confirmed that our synthetic approach was indeed enantiospecific and that none of the reaction conditions led to racemization, especially aminoketone **18** and related compounds. Moreover, this study suggests that (−)-spiroleucettadine is produced by the sponge, rather than a scalemic mixture.



Scheme 4. DMP mediated cyclic urea oxidaton and completion of the total synthesis.

In summary, we have completed the first total synthesis of spiroleucettadine in 11 steps starting from L-tyrosine as starting material. This synthesis is simple, robust and concise with only two deprotection steps needed despite spiroleucettadine being such a heteroatom rich molecule. It relies on two hypervalent iodine mediated oxidations to install the spiro cyclohexadienone-oxolane core and the *N*-methyl decoration at the oxolane–imidazolidinone ring junction. The *Leucetta* alkaloids continue to be of keen interest to our group. Biological evaluation and structure-activity relationship studies will be reported in due course.

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Keywords: oxidation reactions • hypervalent iodine • marine alkaloid • natural products • total synthesis

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[17] Crystallographic details for **9**·$(EtOAc)_{0.5}$: Colourless plate crystals were grown by evaporation of an ethyl acetate solution at room temperature. $C_{21}H_{24}N_2O_5$, M_r = 384.42, 0.48 × 0.10 × 0.03 mm^3, monoclinic, $P2_1$, a = 11.5527(10) Å, b = 6.2534(5) Å, c = 14.2729(15) Å, α = 90°, β = 108.271(11)°, γ = 90°, V = 979.14(17) $Å^3$, Z = 2, ρ_{calcd} 1.304 g cm^{-3}, μ(Cu-Kα) = 0.77 mm^{-1}, T = 100 K, $2\theta_{max}$ = 149.8°, 6492 reflections measured, 3836 unique (R_{int} = 0.0454), R_1 = 0.0636, wR_2 = 0.1706 (all data), residual electron density 0.45 e $Å^3$, Flack parameter = 0.1(2). CCDC 1567132 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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[19] See Supporting Information for details.

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