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Spiroleucettadine: synthetic studies and investigations towards structural revision

Nicholas Aberle,[a,b] Simon P. B. Ovenden,[c] Guillaume Lessene,[a] Keith G. Watson[a,*] and Brian J. Smith[a]

[a]*The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville 3050, Victoria, Australia*
[b]*Department of Medical Biology, The University of Melbourne, Parkville 3010, Victoria, Australia*
[c]*Defence Science and Technology Organisation, 506 Lorimer Street, Fishermans Bend 3207, Victoria, Australia*

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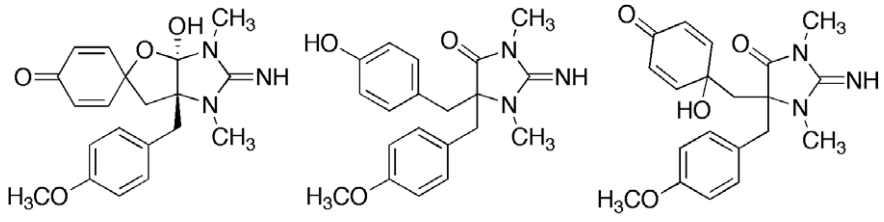
Abstract—Synthetic efforts towards spiroleucettadine are described, including the enantioselective synthesis of the presumed biosynthetic precursor. High level density functional theory calculations were used to predict the ^{13}C NMR shifts of possible alternative structures and, along with a re-evaluation of the available NMR data, allow the proposal of revised structures for this spirocyclic alkaloid.

Structurally interesting and biologically useful marine natural products have provided stimulation for advances in both synthetic chemistry and disease treatment. Recent work by Crews and co-workers on the bright yellow *Leucetta* sponge furnished the cyclic guanidine alkaloid spiroleucettadine (**1**, Fig. 1), possessing both anti-bacterial activity (a minimum inhibitory concentration of <6.25 μg/mL against *Enterococcus durans*) and a highly strained trans-fused imidazolidine–oxolane core ring system featuring an unusual orthoamide functionality.[1] Continuing our interest in 2-aminoimidazole alkaloids,[2] we sought to develop a synthetic route to the proposed structure and, following two recent papers also dealing with synthetic studies towards **1**, were inspired to report our own findings which include offering alternative structures for the alkaloid.

Teams led by Danishefsky[3] and Ciufolini[4] both pursued the final structure via the presumed biosynthetic precursor, glycocyamidine **2** (Fig. 1), in anticipation that oxidative intramolecular cyclisation in the fashion performed by Wong[5] would afford the ring system of **1**. Use of a hypervalent iodine species such as bis(trifluoroacetoxy)iodobenzene ('PIFA') to effect such a transformation also formed the final step in our synthetic plans, but we note that neither group of researchers could entice the desired cyclisation to occur. The presence of the free hydroxyl in the orthoamide moiety of



1 **2** **3**

Figure 1. Original structure of spiroleucettadine **1**, presumed biosynthetic precursor **2** and ring-opened isomer **3**.

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* Corresponding author. E-mail: kwatson@wehi.edu.au

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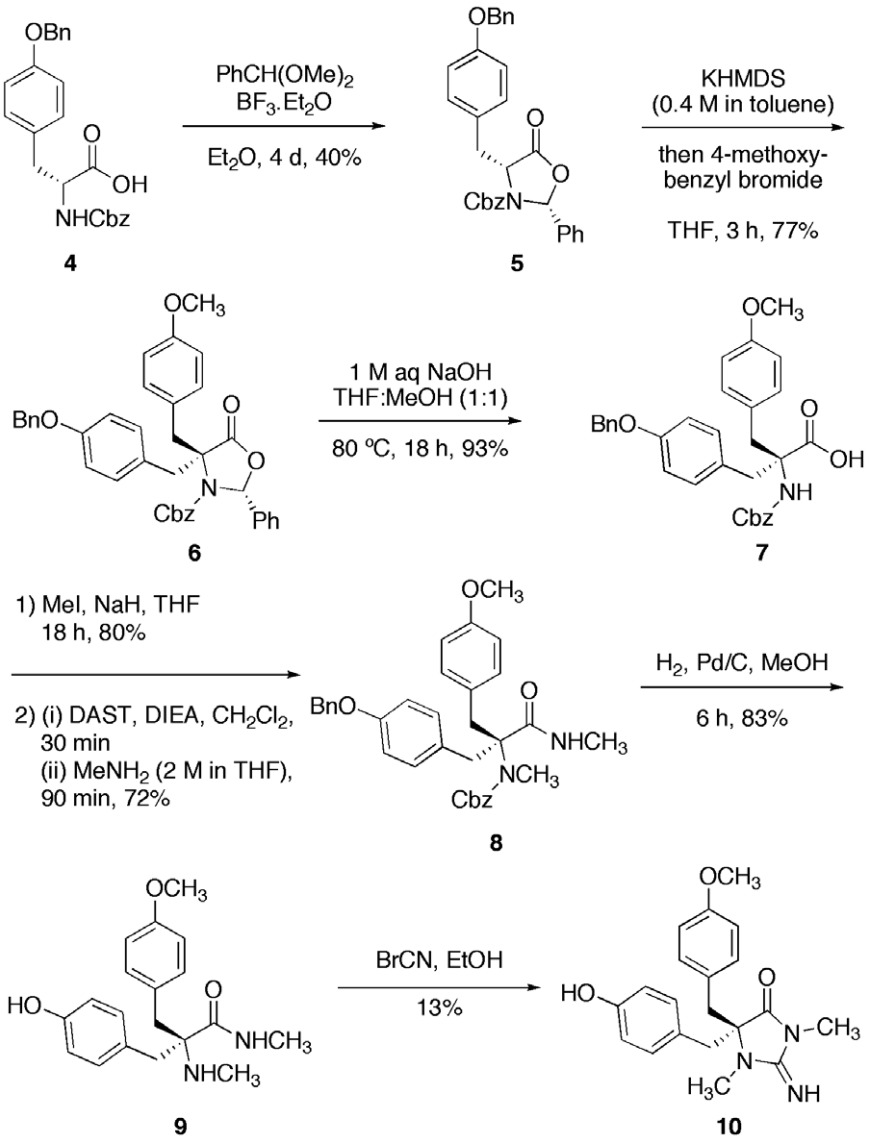
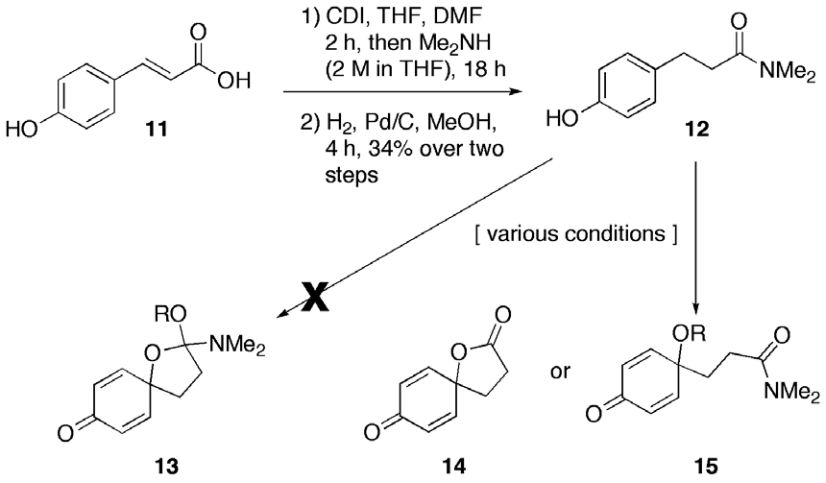


Scheme 1. Synthesis of chiral precursor.

1 presents the concern that the preferred form of the proposed structure might be the amide-containing *p*-quinol **3**, a fact confirmed in both of the aforementioned papers where N-protected derivatives of this species were isolated in variable yields. In the circumstance where the imine is unprotected, it appears that polymerisation through Michael additions to the dienone prevents isolation of **3** itself.[4]

Our stereospecific preparation of the precursor (Scheme 1) began with a commercially available and suitably protected tyrosine residue **4**, present as the unnatural enantiomer so as to provide, ultimately, the correct orientation of the benzyl groups about the sp^3 quaternary carbon of the imidazolidinone ring. To enable introduction of the *p*-methoxybenzyl moiety in a stereoselective manner, the protected tyrosine was first converted to the dominant cis-epimer of 5-oxazolidinone **5** by exposure to benzaldehyde dimethyl acetal in the presence of $BF_3{\cdot}Et_2O$.[6,7] Alkylation with 4-methoxybenzyl bromide proceeded smoothly to afford **6**. Ring opening of the 5-oxazolidinone to the α,α-disubstituted amino acid **7** under basic hydrolysis conditions was followed by selective N-methylation. The formation of amino-amide **8** was achieved through in situ preparation of the acid fluoride using DAST before addition of excess methylamine. Simultaneous removal of both the Cbz and Bn protecting groups provided compound **9** which, upon treatment with cyanogen bromide, cyclised to the desired precursor **10**.

In light of the results disclosed in Refs. 3 and 4 and after several unsuccessful attempts at performing the oxidative spirocyclisation, we turned to a model system (Scheme 2). While not affected by the concerns of the peculiar ring-strain evident in spiroleucettadine, the model was aimed at determining whether amino-ketal **13** (R = alkyl) might support the unusual orthoamide ring system better than the required hemiketal (**13**, R = H). For this investigation, model compound **12** was prepared in two steps from *p*-hydroxycinnamic acid **11**. Unfortunately, under all attempted conditions only **14**



Scheme 2. Model system for oxidative spirocyclisation.

or **15** ($R = CH_3$), or mixtures thereof, were isolated, casting further doubt on the ability to isolate such an orthoamide functionality via hyper-valent iodine-mediated oxidative cyclisation.

Our experience with both the model system and the actual precursor **10**, along with the comments in both the Danishefsky and Ciufolini papers, led us to examine the available spectroscopic data of spiroleucettadine in greater detail. This highlighted several areas of concern with the initial structure assignment, based around the observed ^{13}C chemical shift values of C-4 (102.5 ppm) and C-5 (82.5 ppm) (and hence the regiochemistry of the oxygen in the oxolane ring), and the interpretation of the gHMBC and ROESY data. In particular, Ralifo and Crews state that there is a gHMBC correlation observed between H_2-8 and C-6. Our analysis of the available gHMBC data suggested that this correlation is in fact a coincidental correlation from H_2-8 into the $^1J_{C-H}$ of the ^{13}C resonance of MeOH, the solvent in which the two-dimensional NMR data were collected. Thus, in the absence of any evidence linking C-6 and C-8, we considered the possibility that the actual structure of spiroleucettadine has C-6 and the oxygen in the oxolane ring reversed (**16**, Fig. 2). This change in structure is consistent with the absence of gHMBC correlations between C-8 and C-6, and was also expected to better explain the observed ^{13}C resonances for both C-4 and C-5.

Density functional calculations of ^{13}C NMR chemical shifts generally show good agreement with the experiment[8] and, after their recent use to propose structural revision of the natural product hexacyclinol,[9] were used here to support an alternative structure of spiroleucettadine. The hybrid functional MPW1PW91 has been shown to perform particularly well in this regard, especially when employed with the 6-311+G(2d,p) basis set.[10–13]

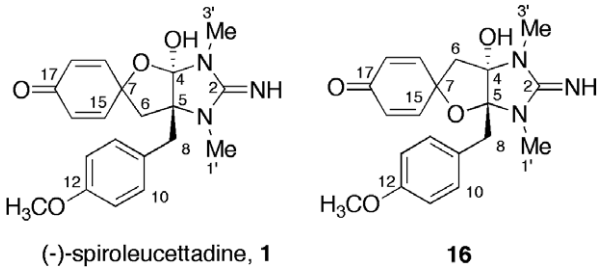


Figure 2. Spiroleucettadine **1** and oxolane-inverted version **16**.

The minimum energy conformation of each structure was located on the B3LYP/6-31G(d) potential energy surface, and the nuclear shielding determined at the MPW1PW91/6-311+G(2d,p) level upon these geometries. The ^{13}C chemical shifts were obtained by subtracting the predicted nuclear shielding for each atom from the predicted shielding for tetramethylsilane (TMS). The nuclear shielding of the carbon nucleus in TMS at this level, 186.49, compares very favourably with the experimental value, 186.4.[14] The calculated shifts were corrected from a least-squares correlation of the predicted and experimental shifts.[9,15]

The differences in experimental and calculated (corrected) ^{13}C chemical shifts for **1** and **16** are presented in Figure 3. The mean absolute error (MAE) for **1** is 4.3, whereas for **16** the MAE is 3.4 ppm. The error in ^{13}C shift for atoms C-4, -5, -6 and -7 of **1** are quite large, between 7.8 and 14.0 ppm. The error in ^{13}C shift for three of these four atoms in **16** remains high, but C-5 is within 0.6 ppm of the experimental value. Despite this, **16** appears to be a biosynthetically feasible alternative.

Performing the same calculations on various known structures (Fig. 4)[16–18] confirmed the accuracy of the predictions (with the exception of brominated carbons, due to the omission in the calculations of relativistic and spin–orbit coupling effects[19]) to within about 5 ppm. These results also provided evidence that the previously unassigned rings of spirocalcaridines A and B (**17** and **18**)[16] are likely to be cis-fused (MAEs 2.4 and 2.7 ppm, respectively) rather than trans-fused (MAEs 3.9 and 4.3 ppm, respectively).

A range of structural and conformational variants of **1** and **16** were then modelled following the method outlined

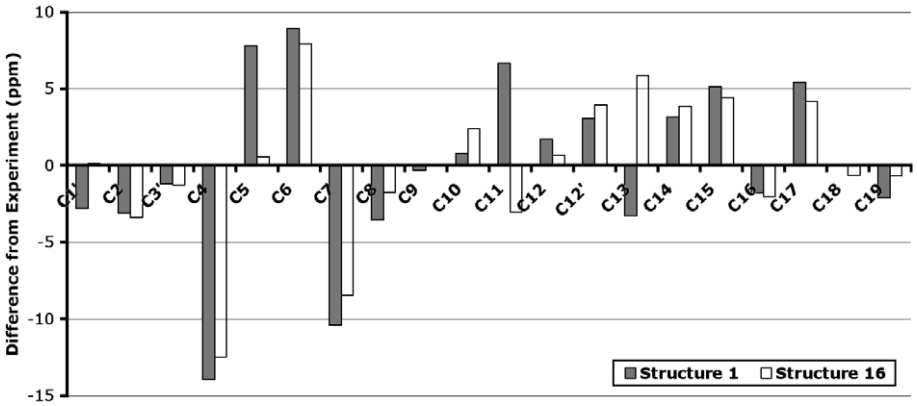


Figure 3. Difference in ppm between calculated and experimental ^{13}C NMR chemical shifts for **1** and **16**.

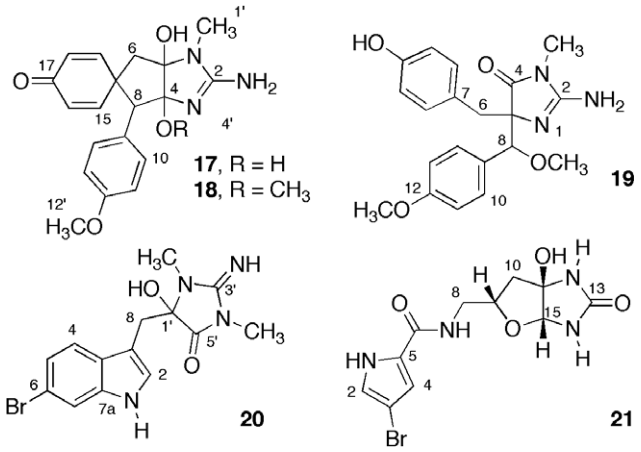
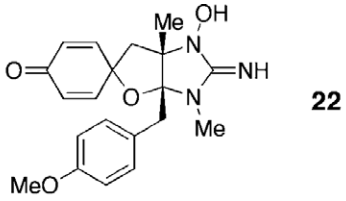


Figure 4. Related structures with acceptably low deviations from the experiment. Spirocalcaridines A **17** and B **18**, calcaridine **19**, 6-bromo-1′-hydroxy-1′,8-dihydroaplysinopsin **20** and slagenin A **21**.

above, without significant improvements in either mean average error or maximum individual atom error, focussing primarily on the ring junction atoms C-4 and C-5. Analysis of these results revealed that, in order to obtain chemical shift predictions similar to the experimental values of 82.5 and 102.5 ppm for those two atoms, one of these two carbons must be connected to three other carbon atoms and one nitrogen, and the other connected to two other carbons, one nitrogen and one oxygen. It was also observed that the accurate prediction of the shift for C-7 required the fused [5,5] ring system to be cis-fused. Further structures matching these rules were investigated, with the lowest mean average error being obtained for *cis*-**22** (MAE 2.2 ppm, Fig. 5), which also had the lowest maximum individual error (5.1 ppm).

Biosynthetically, **16** can be explained by a speculative dihydroxylation of the common naamine-type skeleton **23**, followed by intramolecular spirocyclisation and subsequent methylations (Scheme 3). Such a dioxygenated intermediate can also explain the spirocalcaridines **17** and **18** and, via a pinacol-type rearrangement, the carbon structure of calcaridine **19**. Structure **22** could be derived from an epoxidation of **23**. Various states of N- and O-methylation are known to exist amongst *Leuc-*



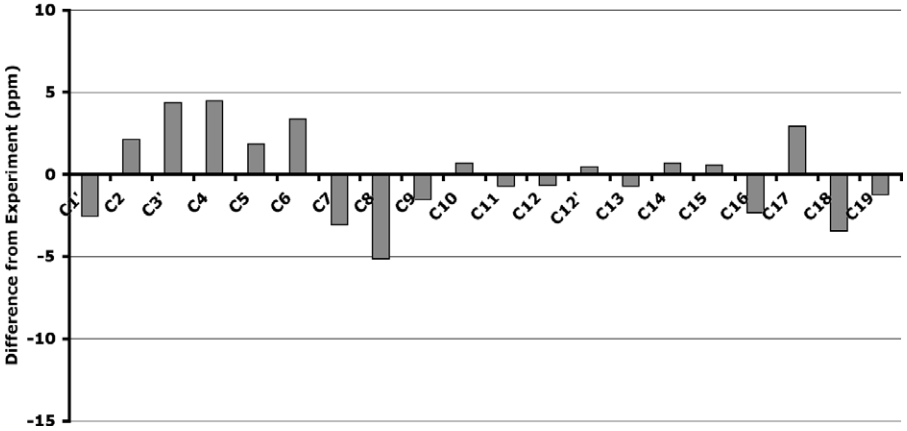
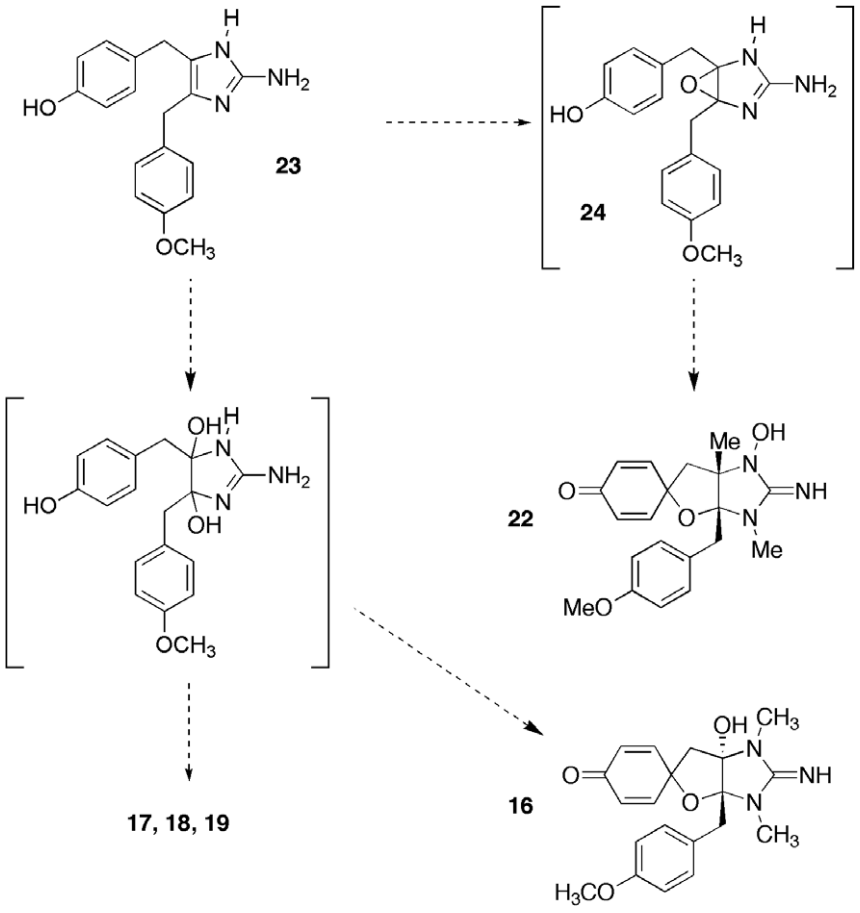


Figure 5. Difference in ppm between calculated and experimental ^{13}C NMR chemical shifts for *cis*-**22**. MAE = 2.2 ppm.



Scheme 3. Possible biosyntheses of **16** and **22**.

etta alkaloids, and it is conceivable that the corresponding introduction of the C-4 methyl would result in the opening of epoxide **24** before an intramolecular cyclisation to give **22**.

As an alternative structure, **16** appears to be more biosynthetically feasible, but the modelling results show **22** to be the best match of the ^{13}C NMR data. In view of the apparent error in the existing assignment of spiroleucettadine, our focus now shifts to providing synthetic evidence for our proposals.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.088.

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