Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2018, **16**, 6882

Received 31st August 2018,
Accepted 13th September 2018

DOI: 10.1039/c8ob02142b

rsc.li/obc

# Biomimetic synthesis of the bisindole framework present in sciodole, an alkaloid from *Tricholoma sciodes*†

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**A synthesis of the unique bisindole framework present in the mushroom-derived alkaloid sciodole has been achieved, validating a biosynthesis proposal that the C–N bisindole bond present in the natural product is forged by amination of an azafulvenium.**

The *Tricholoma* genus of mushrooms are known to produce several indole natural products harbouring a methyl group at the C2 position.[1] Perhaps the most structurally intriguing member of this family is (+)-sciodole (**1**),[2] a reduced N1′–C7 dimer of 5-methoxy-2,4-dimethylindole (**2**)[3] which itself is also found in *Tricholoma*[1c,f] (Fig. 1).

Unlike most indole alkaloids, sciodole (**1**) is not biosynthetically derived from tryptophan. It can be proposed that sciodole (**1**) is derived from lascivol (**3**), a predation deterrant present in *Tricholoma lascivum*[4] but also likely to exist in the sciodole source, *Tricholoma sciodes* (Scheme 1). Cleavage of the glutamic acid residue[4] from lascivol would afford the cyclohexenone **4** that upon cyclisation and double dehydration would give tetrahydroindole **5**. Elimination of methanol generates azafulvenium **6** that upon attack by **4** would forge the key C–N bond to give **7** possessing the requisite *anti*-stereochemistry. Cyclisation–aromatisation of the 'lower half' would then afford sciodole (**1**). The key dimerisation event raises interesting questions from a biosynthesis perspective; dimerisation *via* an $S_N2$ pathway (*i.e.*, from **4** or **5**) would not lead to the *anti*-stereochemistry present in sciodole (**1**). Moreover, it is likely that an amine (*i.e.*, **4**) serves as the nucleophile in the dimerisation, as the indole **2** (formed from **4** and/or **5**) would attack the azafulvenium **6** *via* C3 and not N1.

Our ongoing interest in biomimetic synthesis[5] led us to instigate a synthetic programme to test the hypothesis outlined in Scheme 1, focusing in particular on the amination event.[6] Generating an azafulvenium in the presence of the *exo*-methylene group (*i.e.*, **5** → **6**) was predicted to be troublesome under acidic conditions commonly used to access this electrophile.[7] In view of this, the 7-acetoxy-4-indolone **8**[8] was chosen as the precursor from which the azafulvenium **9** would be generated (Scheme 2). With regard to the *N*-nucleophile, indoline **10** was chosen as the surrogate for the amine **4**. Thus, successful amination of the azafulvenium **9** at C7 with indoline **10** would lead to the bisindole derivative **11** bearing the unique bisindole core structure of sciodole (**1**). This transformation poses strategic and methodological challenges; the indoline **10** could feasibly react at any of the C2, C3 and C4 sites in the

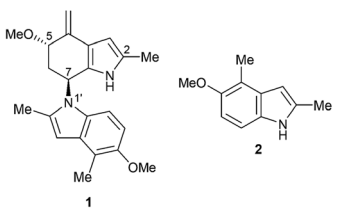
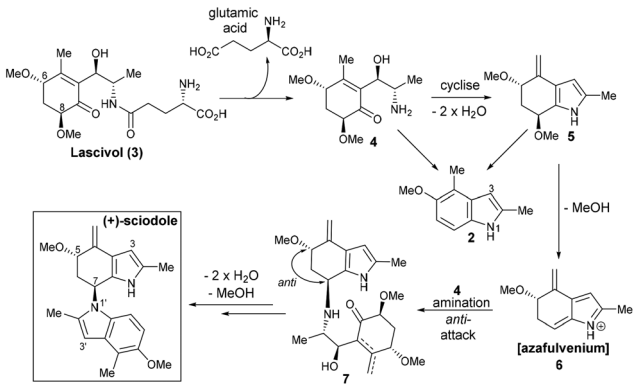


Fig. 1 (+)-Sciodole (**1**) and 5-methoxy-2,4-dimethylindole (**2**).




Scheme 1 Proposed biosynthesis of sciodole (**1**) from lascivol (**3**).

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ob02142b



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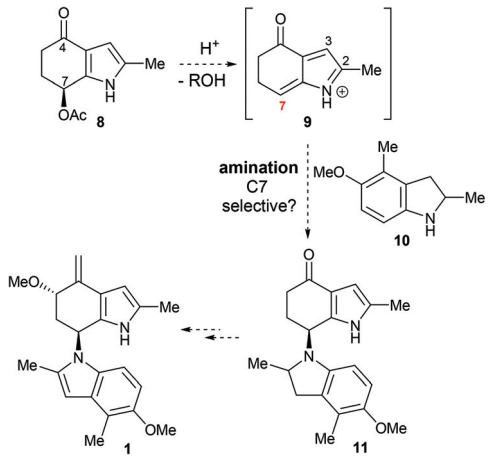
1-azafulvenium **9** and the C–N bond in the desired product **11** is somewhat hindered.

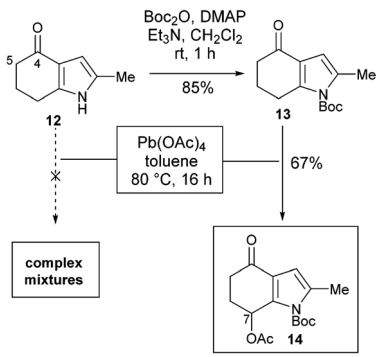
It was decided that the azafulvenium precursor **8** would be accessible by a C–H acetoxylation strategy. When attempting this transformation on the known 4-indolone **12**[9] using lead tetracetate,[10–12] a plethora of products were formed, likely resulting from competing α-acetoxylation[13] and oxidation of the pyrrole ring.[14] We reasoned that de-activating the pyrrole ring would help reduce side-reactions at this site and as a result, the 4-indolone **12** was converted into its *N*-Boc derivative **13**. Subjecting **13** to lead tetracetate pleasingly led to regioselective C–H acetoxylation at the desired C7 site to give **14**, as confirmed by NOE analysis (Scheme 3).[15]

With the azafulvenium precursor **14** in hand, attention turned to the biomimetic amination (Scheme 4). Subjecting **14** to a variety of Brønsted and Lewis acidic conditions, both prior to the addition of, and in the presence of indoline **10**,[15] was met with failure. Extensive degradation was observed, with $^1$H NMR analysis of the crude reaction mixtures indicating trace quantities of indoles were present (likely formed by aromatisation of both **10** and **14**); no sign of **11** was detected.

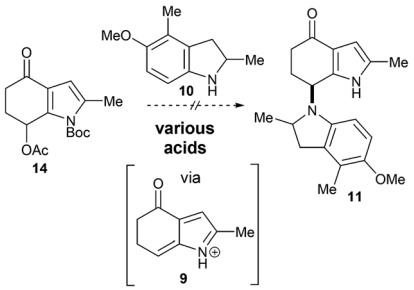
Considering the incompatibility of the biomimetic amination with acid, an alternative strategy was considered. The




**Scheme 2** Initial synthetic plan.



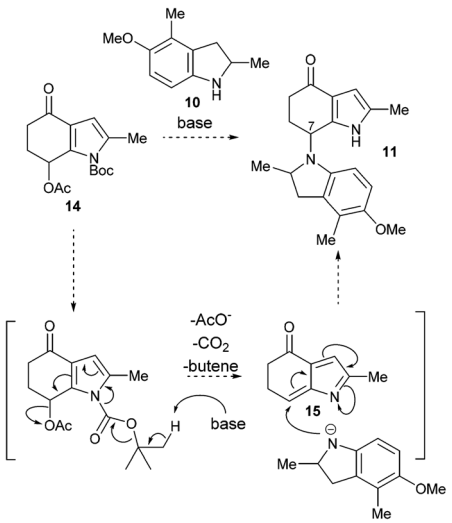

**Scheme 3** Synthesis of the azafulvenium precursor **14**.




**Scheme 4** Failed biomimetic dimerisation under acidic conditions.

generation 1-azafulveniums from hydroxy-, alkoxy- and acetoxymethylpyrroles under acidic conditions is a well-established method to generate this electrophile,[7,8] but we pictured a base-mediated process following a mechanistic scenario akin that outlined in Scheme 5. Base-mediated cleavage[16] of the Boc group in **14** would drive elimination of acetate, generating the 1-azafulvene **15**[17] that upon reaction with indoline **10** (likely the anion) would give the desired product **11**.

When considering how best to approach the proposal in Scheme 5, several factors were considered. Azafulvene formation and indoline deprotonation would each require one equivalent of base and in view of this, three equivalents of base were used, representing an excess (1.5 equiv.) for each of these two operations. Moreover, in order to avoid side-reactions with the carbonyl, acetoxy group and the azafulvene, it was prudent to employ non-nucleophilic bases in the first instance. The condensed details of a study examining the base-mediated dimerisation are outlined in Table 1. The non-nucleophilic bases sodium hexamethyldisilazide (NaHMDS), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 2,6-lutidine all led to no reaction, with degradation observed upon increasing the reaction temperature (entries 1–3). Trialling more nucleo-




**Scheme 5** Proposed biomimetic amination by base-mediated azafulvene generation.

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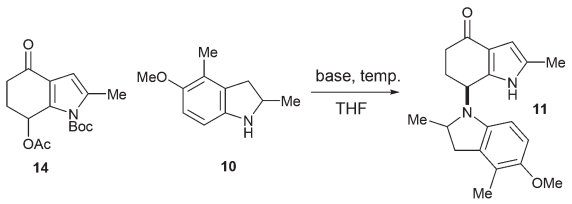
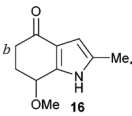
**Table 1** Biomimetic amination *via* base-mediated azafulvene generation



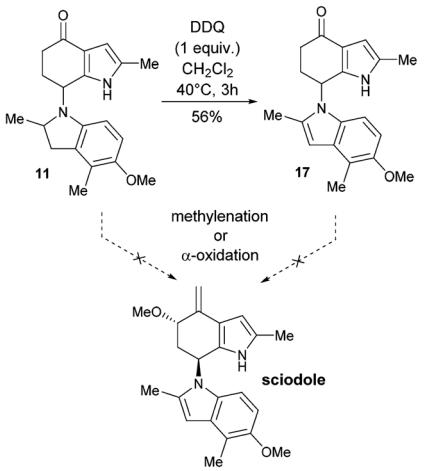

| Entry | Indoline (**10**) (equiv.) | Base (equiv.) | Temp (°C) | Time (h) | Yield (**11**)[a] (%) |
|---|---|---|---|---|---|
| 1 | 1 | NaHMDS (3) | −78–rt | 4 | — |
| 2 | 1 | DBU (3) | rt–80 | 6.5 | — |
| 3 | 1 | 2,6-Lutidine (3) | rt–80 | 6 | — |
| 4 | 1 | $K_2CO_3$ (3) | rt–80 | 4 | — |
| 5 | 1 | KF-Alumina (3) | rt–80 | 4 | — |
| 6 | 1 | $K_3PO_4$ (3) | rt–80 | 6 | Trace |
| 7 | 1 | NaOMe (3) | rt | 0.5 | **11** (5%) **16**[b] (35%) |
| 8[c] | 3 | NaOMe (5) | rt | 5 | 26 |
| 9[c] | 5 | NaOMe (3) | rt | 6 | 23 |
| **10**[c] | **3** | **NaOMe (3)** | **rt** | **6** | **40** |
| 11 | 3 | NaOAc (3) | rt–80 | 8 | — |

[a] **11** was isolated as a 2 : 1 mixture of diastereomers (entries 7–10). [b]  [c] Base added in 0.5 eq. portions and **16** was not detected.



philic bases was initially disappointing, with potassium carbonate, KF-alumina[18] and tripotassium phosphate all leading to a similar outcome (entries 4–6). The first positive result was obtained when sodium methoxide was used, affording the desired product **11** in 5% yield, alongside significant amounts of **16** resulting from reaction of the azafulvene with the base (entry 7). In an effort to reduce the amount of **16** being produced, the amount of indoline **10** was increased and the base was added portionwise, which pleasingly led to a significantly improved yield of **11** and only trace amounts of **16** being formed (entry 8). Employing an excess of the indoline **10** with respect to the base had a negligible effect on the yield of **11** (entry 9). Using equimolar quantities of indoline **10** and base led to the best yield of **11** (entry 10). The acetate eliminated during azafulvene formation is unlikely to be acting as a base in this process, as no reaction was observed when using sodium acetate (entry 11).

We are confident **10** and **14** are not reacting *via* an $S_N2$ pathway. It has been reported[7c] that 2-hydroxymethylpyrroles will only divert from an azafulvenium ($S_N1$) to an $S_N2$ pathway upon deactivation of the pyrrole by strong electron withdrawing groups (*i.e.*, triflate), while the corresponding *N*-Boc derivative still reacts *via* the $S_N1$ pathway. Moreover, the reaction between **10** and **14** turns from colourless to orange upon addition of sodium methoxide, indicative of azafulvene formation.[6d]




**Scheme 6** Selective dehydrogenation and attempted completion of the synthesis.

With the bisindole **11** in hand, dehydrogenation of the 'lower half' was considered (Scheme 6). Upon subjecting **11** to one equivalent of DDQ, selective dehydrogenation successfully occurred, affording **17** comprising the sciodole framework. This selective aromatisation is another result that supports the biosynthesis proposal outlined in Scheme 2. Although the conversion of **11** and/or **17** into sciodole (**1**) appears relatively straightforward, we were unable to complete the total synthesis. Unfortunately upon subjecting **11** and **17** to methylenation and α-oxidation procedures, no reaction or degradation was observed under a variety of different reaction conditions.

In conclusion, we have validated a proposal that the biosynthesis of sciodole (**1**) involves the amination of an azafulvene followed by selective aromatisation. Further studies will focus on employing alternative nucleophiles in the biomimetic dimerization and hence completing the total synthesis of sciodole. Moreover, the base-mediated azafulvene generation reported herein may form the basis for a conceptually distinct method for generating this electrophile.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We are indebted to the University of Auckland for a doctoral scholarship (J. A. H) and the Royal Society of New Zealand for a Rutherford Discovery Fellowship (J. S). We thank Professor Martin Banwell (Australian National University) for helpful discussions.

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