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A biogenetically inspired heterodimerization approach to the synthesis of the core structure of the alkaloid fissoldhimine

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Abstract—A biogenetically inspired heterodimerization reaction of N-substituted 2-pyrroline equivalents leads to the tricyclic core of the alkaloid fissoldhimine. Thus, pyrrolidin-2-ol derivatives, in which the nitrogen atom is substituted either with urea or thiourea functionality, serve as equivalents of the corresponding N-substituted 2-pyrrolines. Reaction of these compounds under Lewis acidic (e.g., lanthanide triflate) or Brønsted acid conditions leads to a diastereomeric form of the tricyclic core of fissoldhimine. The reaction can be envisaged to occur either via an asynchronous intermolecular inverse electron demand hetero-Diels–Alder reaction, or through a tandem Mannich/ring-closure reaction.

Fissoldhimine **1** was first isolated in 1994 by Wu et al. from the perennial shrub *Fissistigma oldhamii* (Hemsl.) Merr. (Annonaceae) (Fig. 1).[1] This shrub is distributed mainly in Southern China and Taiwan, and has been used as a folk medicine to treat conditions such as sciatica and arthritis. It is also known for its anti-inflammatory and anti-tumor properties.[2] The unique four-ring fused structure of **1** was confirmed by X-ray analysis. To date there have not been any reported approaches to the synthesis of this intriguing alkaloid. We now report our preliminary observations on the synthesis of the core structure, inspired by a plausible hypothesis of the biogenesis of fissoldhimine.

Fissoldhimine can be considered to be formally derived from a 2:1 or $AA'B$ coupling[3] of 2-pyrroline derivative **2** with butanal. It is also quite likely that fissoldhimine is an artifact of the isolation process, and that instead it is derived from tricyclic urea **3**. Thus, **1** may be derived from an aminoacetalization of **3** with butanal, present in trace amounts with the butanol used in the extraction process.[1] In turn tricyclic compound **3** would be formed by a heterodimerization of **2** or a synthetic equivalent. The heterodimerization involves C–C bond formation between C1 of **2** and C2 of a second equivalent of **2**, to form the bond C1–C2′ in **1** (Fig. 1). Wu has proposed a more detailed biogenetic hypothesis for fissoldhimine that involves the coupling of the tautomeric isomers 1-pyrroline **4** and 2-pyrroline **5** (Fig. 2). Heterodimerization of **4** with **5** via a Mannich reaction then gives **6**. Sequential *N*-carbamoyl transfer from carbamoyl phosphate can then lead to **3**, a putative precursor to

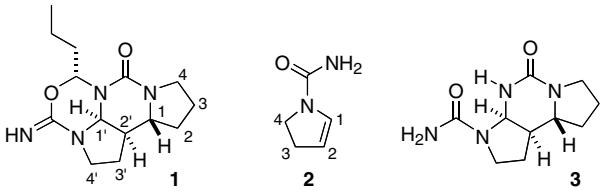

Figure 1. The alkaloid fissoldhimine **1** is formally derived from the heterodimerization of 2-pyrroline derivative **2**. Note: the numbering on **1** relates to its putative biogenesis from **2**.

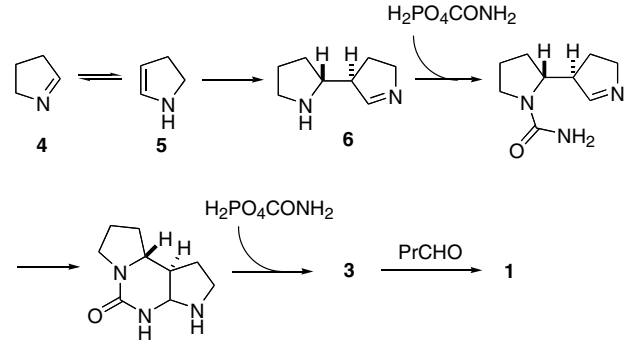

Figure 2. Biosynthetic hypothesis for fissoldhimine formation.

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fissoldhimine. Related heterodimerizations of the *N*-methylpyrollinium ion have been reported to give the alkaloid 1,1′-dimethyl-[2,3′]bipyrrolidinyl.[4] Similar dimeric products have also been reported to be formed as by-products under other conditions, such as, for example, during the reduction of *N*-methyl-2-pyrrolidinone,[5] or from the mercuric acetate catalyzed oxidation of various substituted *N*-methylpyrrolidines.[6] Analogous dimeric alkaloids, such as ammonodendrine and orensine are also known to be formed through heterodimerization of Δ^1-piperideine.[7]

An alternative pathway to the biogenesis of **1**/**3** could involve an earlier stage *N*-carbamoyl transfer from **5** to give **2**. Urea **2** can also be formed through oxidation and cyclization of *N*-carbamoylputrescine. Protonation of **2** can then give iminium ion **7** (Fig. 3). Heterodimerization of **2** with **7** can be envisaged to occur either in a Mannich type process, via intermediate **8** to give **3**. Alternatively, an inverse electron demand hetero Diels–Alder reaction of **2** with **7** can give **9**, which on rearrangement leads to adduct **3**.

Our initial aim was to determine whether such a heterodimerization mechanism of **2** or some analog could be achieved chemically. Initial attempts used the thiourea precursor **10** which we had previously used in our studies on the synthesis of martinelline analogs.[8] We have demonstrated that under mildly Lewis acidic conditions, pyrrolidinols (such as **10**) serve as N-substituted pyrroline equivalents (i.e., a thiourea analog of **2**). An exposure of thiourea **10** to a lanthanide triflate catalyst afforded the dimerized product **11** as a single diastereoisomer in a 68% yield (Scheme 1). The stereochemistry of **11** was established by an X-ray crystallographic study (Fig. 4).[9] Compound **11** can be formed via either stepwise or concerted cycloaddition mechanisms analogous to those outlined for the conversion of **2** into **3** (Fig. 3). Thus, Lewis acid promoted ionization of **10** would give a thiourea analog of **7**, which could then lose a proton to give the corresponding thiourea protected

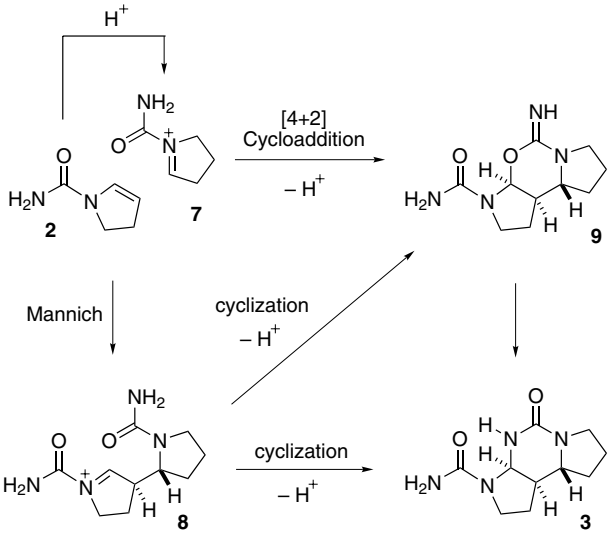
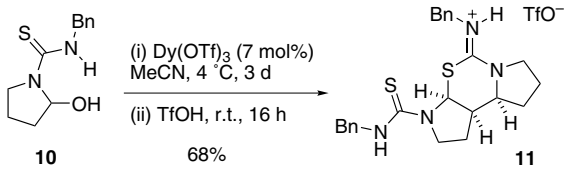


Figure 3. Alternative biosynthetic hypothesis for fissoldhimine formation.



Scheme 1.

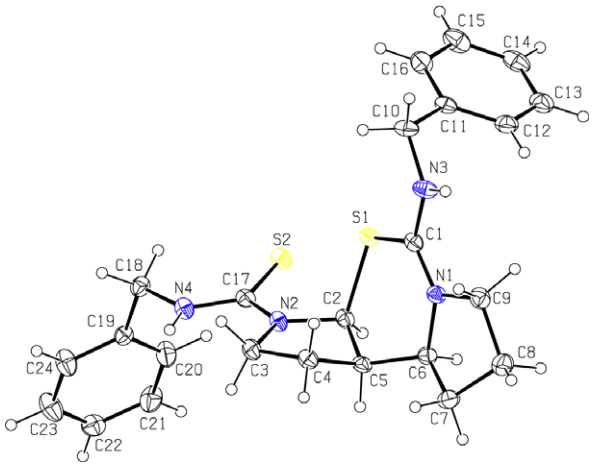
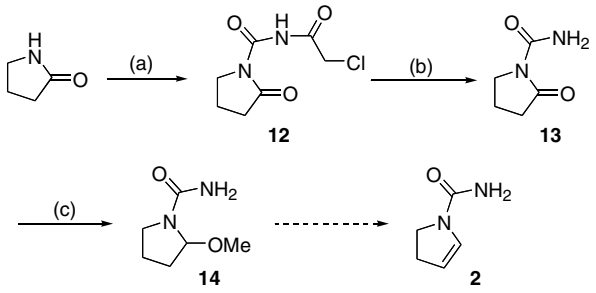


Figure 4. Solid-state structure of **11** as determined by X-ray crystallographic analysis. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

2-pyrroline (i.e., the thiourea analog of **2**). The stereochemistry of **11** (all-cis) would arise from an *endo* attack of the dienophile on the diene, assuming a hetero Diels–Alder mechanism. Compound **11** differs in two notable respects to compound **3**. Firstly, the relative stereochemistry is not that found in the natural product **1** or compound **3**. Secondly, the central ring of **11** is formed via attack of the sulfur atom, rather than the nitrogen atom of the thiourea, onto the electrophilic C-1′ atom. Conversely, the central ring of **1** and **3** are formed via attack of the nitrogen atom, rather than the oxygen atom of the urea. This difference provides some support for a hetero Diels–Alder reaction occurring for the formation of **11**, analogous to that shown in the direct [4+2] cycloaddition of **2** and **7** to give **9**. It may however, reflect the relative thermodynamic stability of **11** over the isomeric compound that would be formed through C–N ring closure of the central ring.

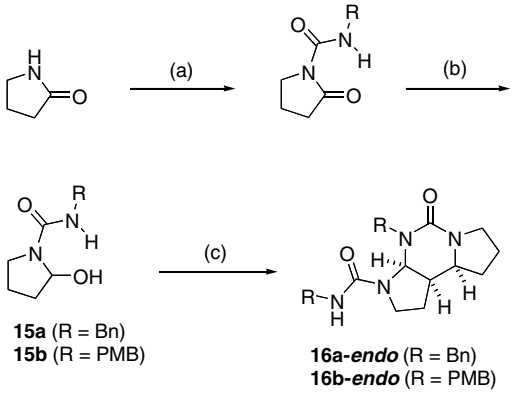
While the stereochemistry of **11** was not that required for fissoldhimine, we were encouraged that heterodimerization had occurred. We next set out to establish whether a similar approach could be used in a dimerization of urea **2** or an equivalent. Our initial approach to **2** utilized pyrrolidinone as the starting material (Scheme 2). The reaction of pyrrolidinone with chloroacetyl isocyanate formed imide **12**. Deprotection of the chloroacetyl group[10] was achieved by treatment with triethylamine in methanol to give **13**. Finally, the reduction of **13** using DIBAL–H followed by the addition of trimethylorthoformate in methanol gave the urea **14** in a 62% yield over the three steps. Unfortunately, all attempts



Scheme 2. Reagents and conditions: (a) chloroacetylisocyanate (1 equiv), benzene; (b) Et_3N (2 equiv), MeOH; and (c) DIBAL (1.5 equiv), CH_2Cl_2, −78 °C, then MeOH, methyl orthoformate, PPTS (cat.), rt.

to convert, either **14** or the initial reduction product from **13**, unambiguously, into **2** or heterodimerized adducts such as **3** or **9** were unsuccessful. An adduct formed from the reaction of **14** with $Dy(OTf)_3$ did show a molecular ion, $M^+ = 224$, consistent with dimerized adducts, but the severely broadened signals in the ^1H and ^{13}C precluded a definitive structural assignment.

The use of a protecting group strategy could conceivably overcome these problems, as we had shown in the reaction of the analogous *N*-benzyl protected thiourea **11**. An *N*-benzyl protected urea **15a** (R = Bn) was chosen, due to the availability of the starting isocyanate, and the similarity with **10**. Hydroxyurea **15a** was obtained in two steps, in a 74% overall yield, from pyrrolidinone via reaction with benzylisocyanate followed by reduction using DIBAL–H (Scheme 3).[10] The reaction of **15a** with 10 mol % of $Dy(OTf)_3$ in acetonitrile at room temperature led to the formation of **16a-*endo*** (R = Bn) in a 73% yield. The X-ray crystallographic analysis of **16a-*endo*** revealed that the desired tricyclic core had been formed; however, as observed with adduct **11**, the product was obtained as the *endo* diastereoisomer (Fig. 5). Dimerization to **16a-*endo*** occurs through C–C and C–N bond formation, to give the same structural core observed with fissoldhimine. This contrasts with the formation of **11**, in which the dimerization occurred through C–C and C–S bond formation.



Scheme 3. Reagents and conditions: (a) RN=C=O (1.1 equiv), toluene, reflux; (b) DIBAL–H (2 equiv), CH_2Cl_2, −78 °C; and (c) $Dy(OTf)_3$ (10 mol %), MeCN.

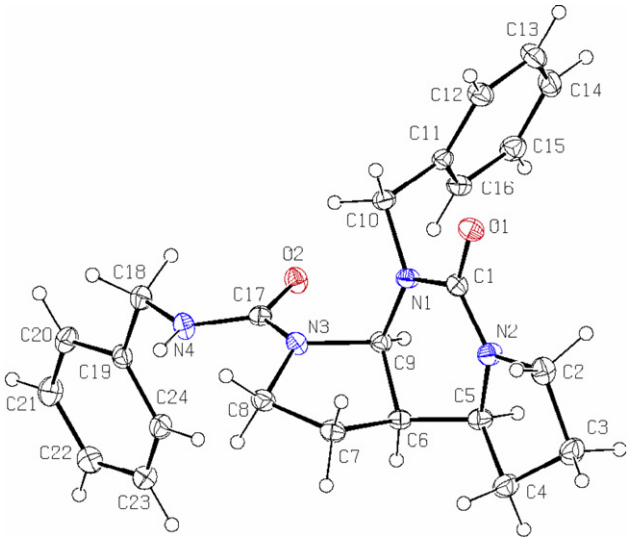


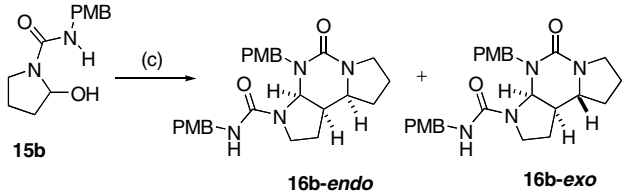
Figure 5. Solid-state structure of **16a-*endo*** (R = Bn) as determined by X-ray crystallographic analysis. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as spheres of arbitrary radii.

Attempts to deprotect the benzyl group of **16a-*endo***, under a variety of conditions, including hydrogenation with Pearlman's catalyst using a Parr hydrogenation apparatus, were unsuccessful. Consequently, we switched to the PMB (*para*-methoxybenzyl) protecting group, since it is generally more easily removed. The same two step strategy was used to form **15b** (R = PMB) in an 83% yield. Dimerization of **15b** (R = PMB) in the presence of 10 mol % of $Dy(OTf)_3$, gave **16b-*endo*** (R = PMB) in an 84% yield (Scheme 3). Once again the undesired *endo* diastereomer was obtained, as revealed by a comparison of the ^1H NMR spectrum with that of the *N*-benzyl analog.

Our previous studies on the synthesis of martinelline, which is also formed from a 2-pyrroline, had revealed that subtle changes in reaction conditions, particularly the choice of Lewis or protic acid and the solvent employed, can lead to substantial changes in diastereoselectivity.[11] Screening the reaction of **15b** under a variety of conditions led to the product as a mixture of the undesired *endo* and desired *exo* diastereomers, **16b-*endo*** and **16b-*exo*** (Table 1). In every case **16b-*endo*** was the predominant product. The best conditions found for the formation of the desired diastereomer **16b-*exo*** were the use of trifluoroacetic anhydride (1.1 equiv) in THF, which gave a 2:1 (*endo*:*exo*) ratio as judged by crude ^1H NMR analysis. However, we were unable to establish chromatographic conditions to separate the two diastereomers.

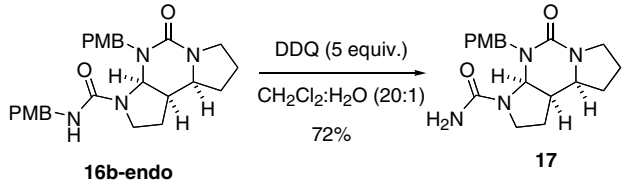
We therefore elected to investigate further the feasibility of converting **16b-*endo***, which can be stereoselectively formed, into *epi*-fissoldhimine. Optimal conditions for the formation of **16b-*endo***, employed the reaction of **15b** using 1.1 equiv of trifluoroacetic anhydride in toluene, to give the product in an 88% yield as the TFA salt, with an *endo*:*exo* selectivity of >95:5 (*endo*:*exo*). Several methods were attempted to remove the PMB protecting

Table 1.



Reagents	Diastereoselectivity of **16b** (***endo*:*exo***)[a]
CSA (5 mol %), THF	90:10
HCl (10% soln.), MeOH	90:10
$Sc(OTf)_3$ (10 mol %), THF	85:15
$BF_3{\cdot}OEt_2$, THF	>95:5
TFAA (1.1 equiv), MeCN	>95:5
TFAA (1.1 equiv), THF	65:35
TFAA (1.1 equiv), toluene	>95:5

[a] Ratio determined by the analysis of the crude ^1H NMR spectra.



Scheme 4.

groups of **16b-*endo***. The use of Pd/C under H_2 or $AlCl_3$ in anisole, TFA, lithium powder in naphthalene or *p*-toluenesulfonic acid resulted in either no reaction or decomposition. However, the use of DDQ resulted in removal of just one of the PMB groups to give **17** (Scheme 4). Unfortunately, further attempts to deprotect **17** under a variety of conditions resulted in the decomposition.

In conclusion, fissoldhimine is an example of a heterodimerized alkaloid. A plausible biogenetic route to fissoldhimine involves the heterodimerization of pyrroline derivatives, via either a stepwise Mannich type pathway, or an intermolecular aza-Diels–Alder reaction. The reaction of both urea and thiourea pyrrolidinol derivatives using Lewis acidic catalysis results in the formation of tricyclic adducts analogous to fissoldhimine. The *endo*:*exo* ratio of the diasteroemeric tricyclic adducts depended upon the reaction conditions. However, in all cases the reactions led preferentially to the formation of the adducts having an *endo* relative stereochemistry. This contrasts with the relative stereochemistry of the natural product fissoldhimine which has an *exo* stereochemistry for the corresponding tricyclic core. Nevertheless, these results provide a laboratory analog to the key step of the proposed biogenesis of fissoldhimine. Further studies on synthetic approaches to this structurally unique alkaloid will be reported in due course.

Acknowledgements

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