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The Synthesis of Melohenine B and a Related Natural Product

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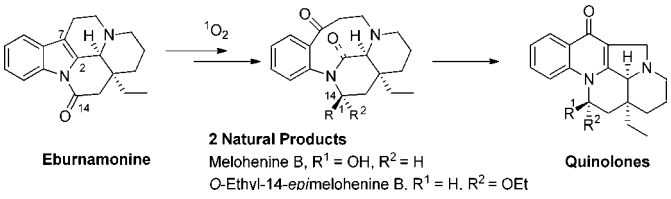
ABSTRACT



A concise synthesis of melohenine B and *O*-ethyl-14-*epi*melohenine B, from eburnamonine, was achieved *via* a biomimetic diastereoselective singlet oxygen-mediated oxidative cleavage of the indole C2–C7 bond. These studies enabled the assignment of the absolute configuration of the natural products. In line with a proposed biosynthetic pathway, the resulting nine-membered ring containing products could be converted to the corresponding quinolones.

The novel alkaloid melohenine B (**1**) (Figure 1) was recently isolated from the Chinese liana *Melodinus henryi*.[1] **1** possesses a striking 6/9/6/6 core skeleton, and since its isolation a number of related alkaloids (**2**–**4**) have been identified in other plants of the *Apocynaceae* family.[2]

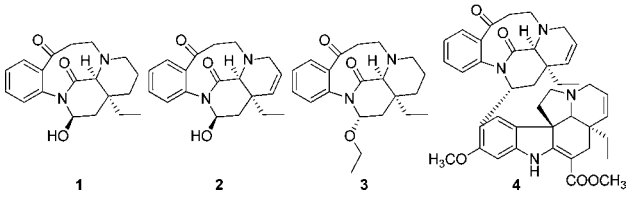


Figure 1. Recently isolated alkaloids drawn as reported.[1,2]

Our interest in **1** arose following our work on the oxidative cleavage of polycylic quinolones which allowed access to medium-sized *N*-acyl cyclic ureas (e.g., **5**, Figure 2)[3] that displayed atropisomerism arising from the inability of the carbonyl group to pass through the medium-sized ring.[4,5]

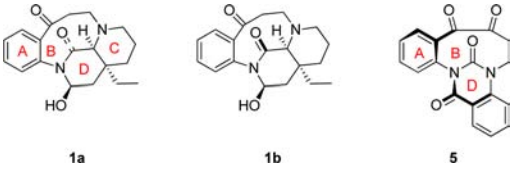


Figure 2. Structure of melohenine B (**1a**) as identified in the crystal structure,[1b] its proposed atropisomer **1b** and our previously prepared atropisomeric compound **5**.[3]

The similarity of **1**–**4** (Figure 1) to the structures previously reported by us led us to propose that **1**–**4** would also display atropisomerism. This raised stereochemical

(1) (a) Feng, T.; Cai, X.; Li, Y.; Liu, Y.; Xie, M.; Luo, X. *Org. Lett.* **2009**, *11*, 4834–4837. (b) In this report an X-ray crystal structure of the natural product shows that the amide carbonyl group is on the same face as the C3–H and C16–Et substituents.

(2) (a) Cai, X. H.; Li, Y.; Su, J.; Liu, Y. P.; Li, X. N.; Luo, X. D. *Nat. Prod. Bioprospect.* **2011**, *1*, 25–28. (b) Zhou, H.; He, H. P.; Wang, Y. H.; Hao, X. J. *Helv. Chim. Acta* **2010**, *93*, 2030–2032. (c) Fu, Y.; He, H.; Di, Y.; Li, S.; Zhang, Y.; Hao, X. *Tetrahedron Lett.* **2012**, *53*, 3642–3646.

(3) Jones, A. M.; Liu, G.; Lorion, M. M.; Patterson, S.; Lébl, T.; Slawin, A. M. Z.; Westwood, N. J. *Chem.—Eur. J.* **2011**, *17*, 5714–5718.

(4) For examples of atropisomerism in other medium sized ring containing natural products, see: (a) Nicolaou, K. C.; Harrison, S. T. *J. Am. Chem. Soc.* **2007**, *129*, 429–440. (b) Burns, N. Z.; Krylova, I. N.; Hannoush, R. N.; Baran, P. S. *J. Am. Chem. Soc.* **2009**, *131*, 9172–9173.

(5) Lébl, T.; Lorion, M. M.; Jones, A. M.; Philp, D.; Westwood, N. J. *Tetrahedron* **2010**, *66*, 9694–9702.

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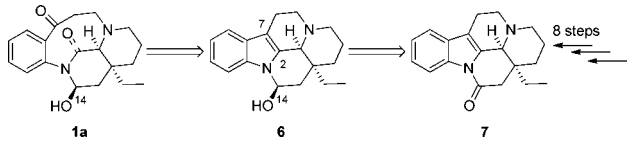
issues which were not discussed in the original reports (compare **1a** and atropisomer **1b**, Figure 2).[1a,2] A synthesis of both **1a** and **3**, which was reported to possess moderate cytotoxic activity,[2b] was therefore planned, and the results of these studies are reported here.

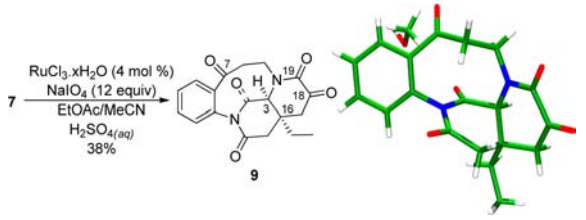
Scheme 1. Retrosynthetic Analysis of **1a**



As the biosynthesis of **1a** may involve the oxidative cleavage of the indole double bond in *epi*eburnamine (**6**), an alkaloid that is also present in *M. henryi*,[2] it was decided that eburnamonine (**7**)[6] would serve as the key starting point (Scheme 1) for the synthesis of **1a** and **3**.

Our initial attempts to cleave the C2−C7 indole bond focused on **7** to avoid possible complications arising from the presence of the labile C14 hydroxyl in **6**. Attempts to cleave the C2−C7 bond with $NaIO_4$ in aq MeOH or *m*CPBA in DCM were both unsuccessful, leading to either recovery of starting material or isolation of eburnamonine-*N*-oxide (**8**),[7] respectively. Moving to the more reactive RuO_4 generated from $RuCl_3$ using $NaIO_4$ as a co-oxidant proved successful in cleaving the desired C2−C7 bond (Scheme 2).

Scheme 2. Preparation of **9** from Eburnamonine (**7**)[6a] and a Representation of the X-ray Crystal Structure of **9** with a Methanol of Crystallization



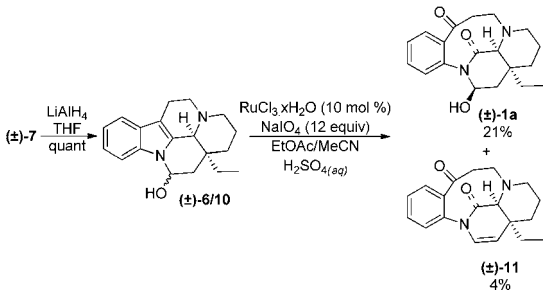
Interestingly, with a low number of equivalents of co-oxidant the reaction gave a complex mixture of products. However, by increasing the number of equivalents, **9** could be isolated as the major product, displaying double oxidation at C18 and C19 (Scheme 2). Importantly, X-ray crystallographic analysis of **9** confirmed that the C2 carbonyl oxygen was on the same face as the C3−H and C16−Et groups in **9**.

Repeating this reaction on a mixture of **6** and its C14-epimer eburnamine (**10**), prepared from racemic **7**,[6b]

(6) (a) Small quantities of (−)-**7** were purchased from Maybridge. (b) (±)-**7** was prepared using a modified version of the Sclessinger approach: Herrmann, J. L.; Cregge, R. J.; Richman, J. E.; Kieczykowski, G. R.; Normandin, S. N.; Quesada, M. L.; Semmelhack, C. L.; Poss, A. J.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 1540–1544 (for details of our modifications see Supporting Information).

(7) See Supporting Information for more details.

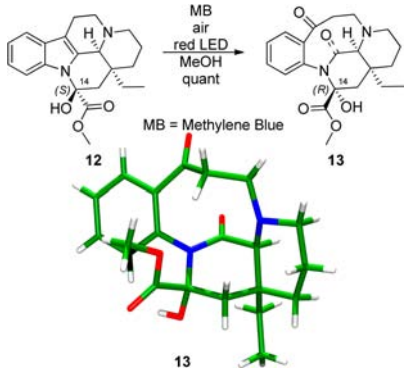
Scheme 3. RuO_4-Mediated Cleavage of Epimers **6** and **10**[6b]



afforded an inseparable mixture of racemic **1a** and the dehydrated derivative **11** (Scheme 3).[8] The analytical data of the impure sample of **1a** prepared by this method was consistent with the literature.[1a] Despite significant efforts to improve the reproducibility and yield of this reaction, no progress was achieved and therefore alternative oxidation conditions were explored.

The use of singlet oxygen as a reagent was next investigated in line with previous reports on the oxidative cleavage of the indole ring of vincamine (**12**).[9]

Scheme 4. Photo-oxidative Cleavage of **12** and a Representation of the X-ray Crystal Structure of **13**



Attempts to repeat this reaction using **12** confirmed that cleavage of the indole double bond occurred to generate **13** which X-ray crystallography revealed to have the C2 carbonyl positioned on the same face as the C3−H and C16−Et substituents, as in **1a**. This analysis also showed that an unexpected and previously unreported inversion of stereochemistry at C14 occurred on conversion of **12** to **13** (Scheme 4).[9]

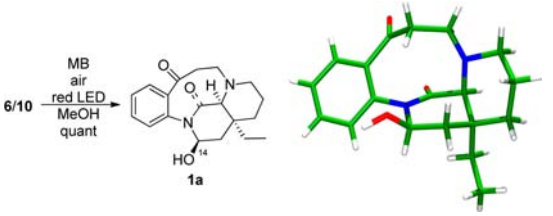
Applying the same singlet oxygen methodology to the synthesis of **1a** was also successful (Scheme 5). Treatment of a mixture of (±)-**6** and (±)-**10** with singlet oxygen gave **1a** as a single diastereomer in quantitative yield, irrespective

(8) The stereochemistry of **11** is tentatively assigned as shown. The yield of **1a** and **11** was calculated following ^1H NMR analysis of an isolated mixture of the two compounds.

(9) Beugelmans, R.; Herlem, D.; Husson, H. P.; Khuong-Huu, F.; Le Geoff, M. T. *Tetrahedron Lett.* **1976**, *17*, 435–438.

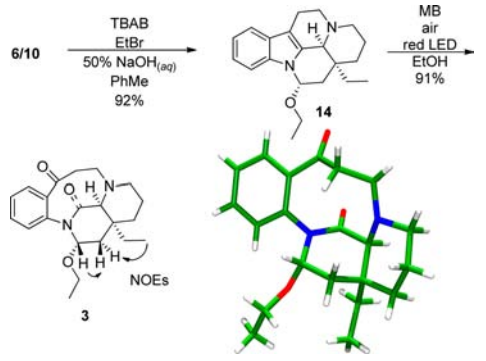
of the starting ratio of **6** and **10**.[10] In order to determine the absolute configuration of natural **1a**, a highly enantioenriched sample was prepared from (−)-**7**.[6a] As the absolute stereochemistry of (−)-**7** is known to be 3*S*, 16*S*,[11] our sample of optically enriched **1a** has the absolute configuration *a*R,3*S*,14*R*,16*S*. Comparison of the optical rotation of our synthetic **1a** with the literature value[1a,12a] showed that synthetic **1a** was in the opposite enantiomeric series, and therefore the absolute configuration of naturally occurring **1a** can now be assigned as *a*S,3*R*,14*S*,16*R*.[12b]

Scheme 5. Synthesis of **1a** and a Representation of the X-ray Crystal Structure of **1a**



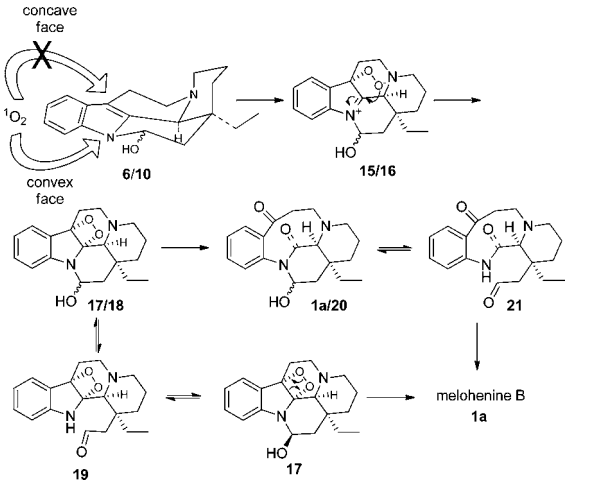
Our attention next turned to the synthesis of **3**, as the reported structure showed that **3** was epimeric to **1a** at C14. *O*-Ethyleburnamine (**14**) was prepared as a single diastereomer by alkylation of a mixture of **6** and **10** under phase transfer conditions.[13] Subsequent oxidative cleavage of **14** gave **3** as a single diastereoisomer (Scheme 6), the ^{13}C NMR of which was identical to that previously reported in the literature.[2b,14]

Scheme 6. Preparation of **3** and a Representation of the X-ray Crystal Structure of **3**



A detailed assessment of NOEs associated with **3** and X-ray crystallographic analysis confirmed the relative stereochemistry of **3** to be as shown in Scheme 6 and indicated that, unlike the reactions involving **10** and **12**, the oxidative cleavage of **14** had occurred with retention of the C14 stereochemistry (Scheme 6). A highly enantioenriched sample of **3**[15] was prepared from (−)-**7** in three steps and was found to be in the opposite enantiomeric series to the isolated natural product. Natural occurring (+)-**3** can therefore be assigned the absolute configuration a*S*,3*R*,14*R*,16*R*.

Scheme 7. Proposed Mechanism of Photooxidative Cleavage



A possible rationalization of the stereochemical outcome of the reaction involves addition of singlet oxygen to the indole C7 position from the convex face of **6** and **10** to give diastereomers **15**/**16**. Subsequent ring closure would form dioxetanes **17**/**18** which could undergo C14 equilibration, *via* the aldehyde **19**, to give only **17** with the required stereochemistry to yield **1a** after collapse of the dioxetane ring.[16] Alternatively collapse of the dioxetane in **17**/**18** could give **1a** and its C14 epimer which could undergo equilibration to only **1a** *via* **21** (Scheme 7).[17]

When **1a** was first isolated it was proposed that it could serve as a biosynthetic precursor of quinolone alkaloids.[1a] More recently a quinolone alkaloid was isolated alongside its proposed biosynthetic keto-lactam and eburnane type alkaloid precursors,[2a] adding weight to this proposal. With a reliable route to keto-lactams of type **1a** and **3** in hand, we decided to investigate this intramolecular aldol reaction. In our case, treatment of **1a** with sodium methoxide brought about the desired condensation, giving a 3:1 mixture of C14 diastereomers **22** and **23** (Scheme 8).[18] Similar reaction

(10) Performing the reaction starting with varying diastereomeric ratios of **6**/**10** always exclusively returned **1a**. A more detailed discussion of the mechanism of this reaction is provided later in the text.

(11) Toh-Seok, K.; Poh-suan, T.; Chen, W. *Phytochemistry* **1993**, *33*, 921–924.

(12) (a) (−)-**1a** $[\alpha]_D$ = −154 (*c* = 0.29, $CHCl_3$) (lit. $[\alpha]_D$ +166 (*c* = 0.18, $CHCl_3$).[1a1a] (b) Our assignment of the absolute configuration of the isolated natural product raises interesting issues relating to the structural assignments of the potential precursors of **1a** in *M. henryi* previously reported in the literature (see Supporting Information).

(13) (a) Arambewela, L. S. R.; Khoung-Huu, F. *Phytochemistry* **1981**, *20*, 349–350. (b) Khoung-Huu *et al.* reported the synthesis of *O-iso*-methyleburnamine from *epi*eburnamine **6** using this methodolgy; however we were unable to replicate this when alkylating with either MeI or EtBr.

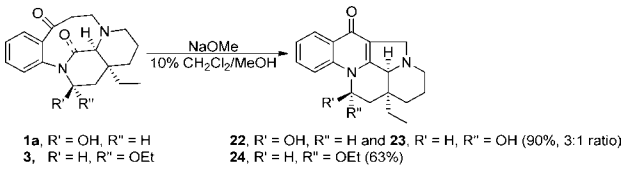
(14) For a detailed comparison of the ^{1}H NMR spectrum of our material with the reported spectrum for **3**, see Supporting Information.

(15) $[\alpha]_D$ = −92 (*c* = 0.27, $CHCl_3$) (lit.[2b2b] +126.66 (*c* = 0.65, $CHCl_3$)).

(16) An alternative C14 epimerization mechanism *via* a N1−C14 iminium ion is unlikely, as these reactions were run in methanol and no C14 OMe substituted products were observed.

(17) As the C14 O-alkyl substrate **14** did not undergo C14 epimerization during the oxidative cleavage reaction, the presence of a C14 hydroxy group seems to be a requirement for this mechanism to operate.

Scheme 8. Synthesis of Keto-Lactam Derived Quinolones



1a, R' = OH, R'' = H
3, R' = H, R'' = OEt

22, R' = OH, R'' = H and **23**, R' = H, R'' = OH (90%, 3:1 ratio)
24, R' = H, R'' = OEt (63%)

conditions also converted **3** to the *O*-ethyl substituted quinolone **24** as a single diastereomer (Scheme 8). These initial results suggest that keto-lactam alkaloids such as **1a** and **3** are indeed viable intermediates in the biosynthesis of quinolone alkaloids.

In summary, the first synthesis of both melohenine B (**1a**) and *O*-ethyl-14-*epi*melohenine B (**3**) from eburnamonine (**7**) has been achieved. It has also been shown that alkaloids of this type can be converted to quinolone alkaloids *via* an intramolecular aldol condensation. The absolute stereochemistry of each natural product was assigned by comparison of the reported optical rotations to those of the authentic samples synthesized by us from (−)-**7**. The use of singlet oxygen as a selective oxidant for the cleavage of indole moieties proceeded in excellent yields under straightforward and safe conditions. This work highlights an additional stereochemical element associated with this alkaloid class.

(18) A 2D EXSY NMR experiment (see Supporting Information) indicated that **22** and **23** were in equilibrium in solution. This suggested epimerization at the C14 position in **1a** under the reaction conditions was not required to explain the product stereochemistry obtained.

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Supporting Information Available. Experimental procedures, ^{1}H and ^{13}C NMR spectra for all new compounds, and CIF data for compounds **1a**, **3**, **9**, and **13** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.