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Singlet oxygen conversion of indoles into α,β-unsaturated oxindoles in model compounds related to the welwitindolinone alkaloids

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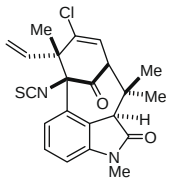
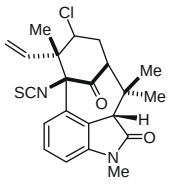
ABSTRACT

A series of conformationally restricted bridged indoles, having structures related to the natural alkaloid *N*-methylwelwitindolinone C isothiocyanate (welwistatin), are oxidised to the corresponding α,β-unsaturated oxindoles by treatment with singlet oxygen.

The welwitindolinones are a small group of oxindole alkaloids, first isolated from blue-green algae by Moore and co-workers in 1994.[1] Of the seven structures originally reported, one compound, *N*-methylwelwitindolinone C isothiocyanate (**1**), later named welwistatin, has provoked special synthetic interest, due both to its fascinating molecular architecture and its apparent ability to reverse multi-drug resistance (MDR).[2,3] Despite widespread interest in the development of routes towards **1**, no total synthesis has emerged to date.[4,5]



welwistatin **1**



2

Of the other members of this family, compound **2** is noteworthy in that it possesses a very closely related structure to **1** but is epimeric at the position α to the oxindole carbonyl function (C-3).

The absence of co-isolated analogous indole structures corresponding to these oxindoles led Moore and co-workers to speculate that indole oxidation might occur early in the biogenesis of the welwitindolinones.[1a] It was proposed that oxidation of 12-*epi*-hapalindole E **3** might generate an α,β-unsaturated oxindole **4**, which would undergo cyclisation to generate welwitindolinone A (**5**), from which the other members of this group would ultimately be formed, Scheme 1.

This idea was somewhat compromised by the finding that exposure of hapalindole **3** to singlet oxygen in the laboratory resulted only in indole C2–C3 cleavage, with no oxindole products, such as **4** being formed. Baran and Richter also pointed out the absence of known structures related to **4**, the unlikely nature of the proposed conversion of **4** into **5**, and established an alternative biosynthetic possibility.[6]

In contrast, in previous work, Moore's research group had demonstrated that oxidation of a related natural product, hapalindole A (**6**), with singlet oxygen, generated various products, depending upon the conditions, including anhydrohapaloxindole A (**7**) and the indole cleavage product fontonamide (**8**), Scheme 2.[7]

The transformation of **6** into **7** appears to be a unique example of singlet oxygen conversion of an indole into the corresponding α,β-unsaturated oxindole, whereas the formation of fontonamide (**8**) results from the aforementioned indole C2–C3 cleavage, which is known to be the usual pathway for such oxidations.[8,9]

Here, we describe our own studies in this area, which show that the type of singlet oxygen oxidation exemplified by conversion of **6** into **7** can be effected in synthetically useful yields for the first time, using model compounds having the welwistatin skeleton.[10] Our results appear to explain why the formation of unsaturated oxindoles has not been more widely observed previously, and specifically, why Moore's putative biosynthetic intermediate **4** is not formed from **3**.

We have also converted one unsaturated oxindole into a pair of saturated epimeric oxindoles that resemble the natural alkaloid C-3 pseudoepimers **1** and **2**, and demonstrated their equilibration.

Our interest in this area was stimulated by a chance finding that oxidation of a simple model compound **9**, having the characteristic [4.3.1]-skeleton of welwistatin,[10] occurred to give oxindole **10**, simply on heating as a solution in THF, open to the air, in the presence of an acid such as pTSA, Scheme 3.

This relatively clean transformation was surprising to us, since we were aware only of the precedent shown in Scheme 1. Although

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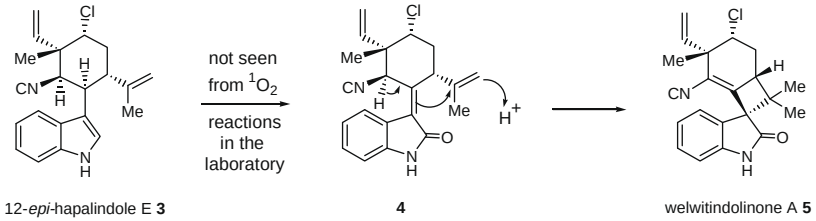
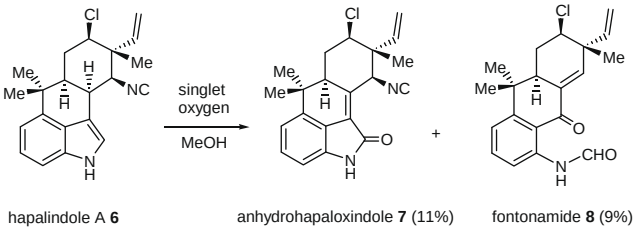
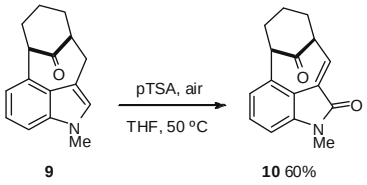


Scheme 1. Initially proposed biogenesis of welwitindolinones.



Scheme 2. Oxidation of hapalindole A.



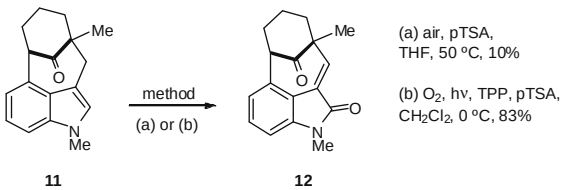
Scheme 3. Synthesis of an α,β-unsaturated oxindole.

aspects of 'indole autoxidation' are documented, there is little in the way of systematic study, especially for N-alkylated variants. In general, N–H indoles undergo oxidation to indolenine-3-hydroperoxides, which can then be transformed in various ways according to the substitution pattern.[11] We had a selection of bridgehead alkylated and silylated compounds, prepared from ketone **9**, with which to further probe this type of oxidation, for example, methylated derivative **11**. We decided to compare the efficiency of the autoxidation using air, and the use of singlet oxygenation, both under acidic conditions, Scheme 4.

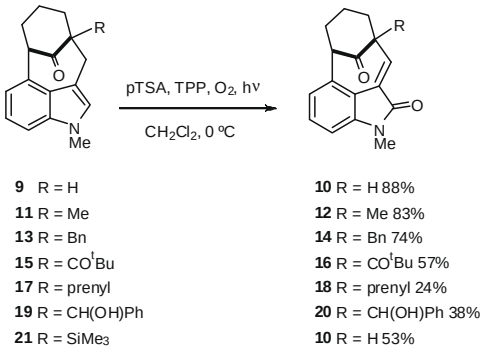
To our surprise, the indole system in the methylated ketone **11** reacted extremely sluggishly under autoxidation conditions compared to the parent compound **9**, and only a 10% yield of **12** was formed after heating for 24 h. Unlike with indole **9**, further heating and addition of more pTSA led only to decomposition, and bubbling of air or oxygen through the solution gave no improvement. In contrast, conversion of indole **11** into oxindole **12** was effected smoothly in 83% yield under photooxygenation conditions using tetraphenylporphyrin (TPP) as sensitiser.[12]

This oxidative conversion could be carried out on a number of related indoles, having various types of substituent installed at the bridgehead position, Scheme 5.

For simple alkylated systems **11** and **13** the conversion was clean and high-yielding, and a little less so for the single acylated



Scheme 4. Two modes of indole oxidation.



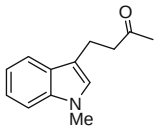
Scheme 5. Oxindole synthesis using singlet oxygen.

derivative **15**. Unsurprisingly, the presence of additional sites that can be oxidised, such as the prenyl group in **17**, or the benzylic alcohol in **19** compromises the yield. In the case of silylated keto-indole **21** the major product was **10**, in which in situ desilylation had occurred.

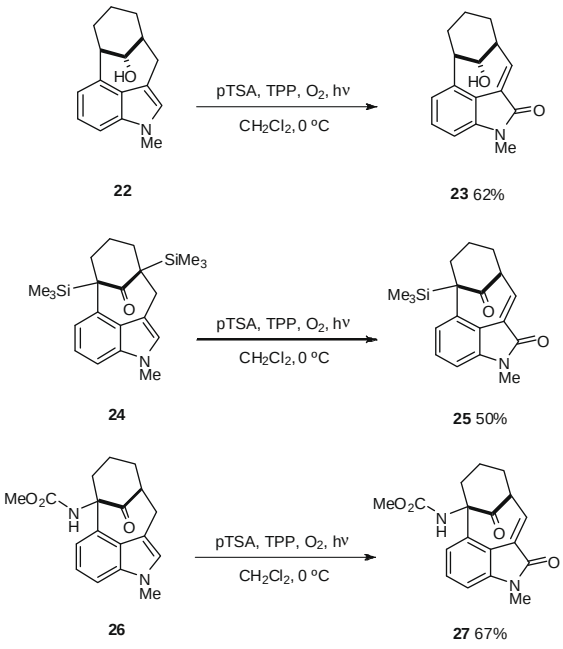
We were interested to see if the bridging ketone was playing some role in the effectiveness of this indole oxidation, and also to establish if the process tolerated substituents at the alternative bridgehead position. Three additional substituted indoles were available to us, which allowed us to probe these issues, and proved to be successful substrates (Scheme 6).

The successful reaction of secondary alcohol **22** (the sole product from reduction of **9** with $LiBH_4$ in THF) shows that a bridging ketone is not required. Monodesilylation was observed in the oxidation of **24** to give **25**, which mirrors that observed for silyl-ketone **21**. Clearly in **24**, the silyl substituent distal to the site of oxidation is the more robust of the two. Finally, carbamate **26** also participated satisfactorily in the oxidation reaction.

The successful singlet oxygen oxidations of our welwistatin model compounds substantially expand upon the single previous (low yielding) conversion of **6** and to **7**. However, when we attempted to apply our optimised conditions to keto-indoles lacking the conformational constraints seen in systems such as **9**, for example compound **28**, the reaction failed completely.



Thus, it seems that the viability of this indole to α,β-unsaturated oxindole oxidative process depends upon conformational restriction at the methylene group at the C-3 position of the indole. The mechanism of singlet oxygen reactions has been a contentious issue for many years, but there appears to be some consensus that

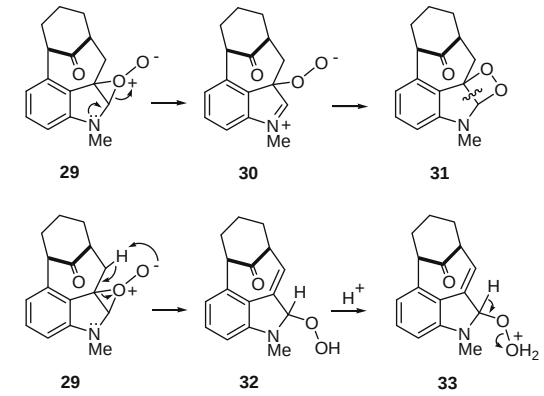


Scheme 6. Further examples of indole oxidation.

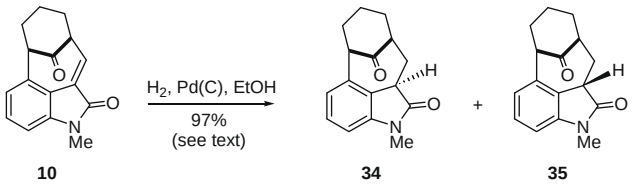
an intermediate or transition state (TS) resembling a perepoxide is involved.[13] Rationalisation of our results via a perepoxide intermediate **29** is illustrated in Scheme 7.

According to precedent, involvement of the nitrogen lone pair would lead to zwitterion **30** and then to dioxetane **31**, which is the accepted precursor to C2–C3 cleavage products. Instead, our system undergoes rapid rearrangement to the 'ene' type allylic hydroperoxide product **32**, which then undergoes acid-catalysed dehydration to give the observed products. Although this can be visualised in terms of competing pathways for intermediate **29,** it can also be considered that the favourable alignment of the allylic (in the indole) C–H in a transition state resembling **29** facilitates collapse towards **32** in a concerted process.

We can rationalise the formation of oxindoles in conformationally constrained systems such as hapalindole A, and our welwistatin models if we consider that alignment of a neighbouring hydrogen in a stereoelectronically favourable orientation is required for collapse of intermediate (or related TS) **29** towards ene product **32**. From X-ray data,[7b,10] both hapalindole A (**6**) and bridged ketoindole **9** possess an allylic hydrogen orientated approximately perpendicular to the plane of the indole, which arrangement should be roughly preserved in the perepoxide intermediate (or TS resembling it) and should be favourable for transformation towards **32**. In contrast, in compounds closely related to 12-*epi*-hapalindole E (**3**), such as hapalindole D,[7b] the allylic hydrogen is twisted to an angle of around 48° with respect to the indole plane, which will make allylic hydrogen abstraction geometrically more difficult, and stereoelectronically less favourable for processing towards **32**.[14]



Scheme 7. Rationale for the results.



Scheme 8. Hydrogenation to give oxindole epimers.

Finally, we were interested to see if we could access saturated oxindoles related to welwitindolinones **1** and **2**, and to this end we hydrogenated unsaturated oxindole **10** under standard conditions, Scheme 8.

Interestingly, this reaction gave a mixture of the epimeric indoles **34** and **35** (ratios between 1:1 and 1:2), the former compound having the correct stereochemistry for welwistatin, but unfortunately the mixture was difficult to separate. We also established that treatment of oxindole **35** with pTSA in THF at 50 °C gives similar mixtures of **34** and **35**, with ratios around 1:2. Thus, acid-mediated equilibration of oxindoles in the welwistatin series appears possible, which has significant implications for synthetic routes proceeding via oxidation of bridged indole intermediates. This type of equilibration may also explain the co-existence of pseudo-epimers **1** and **2** in the natural series. It is to be hoped that more elaborate intermediates may provide an improved bias for the welwistatin stereochemistry.

In summary, we have demonstrated for the first time that the indole to α,β-unsaturated oxindole transformation can be carried out in synthetically useful yields. The apparent limitation of this process to particular, conformationally constrained, indoles having a correctly orientated C–H attached to C-3 casts further doubt on the likelihood of Moore's intermediate **4** being a viable biosynthetic intermediate.

Typical procedure for the singlet oxygen reaction; preparation of oxindole 14

An oven-dried 5 mL round-bottomed flask was purged with argon and charged with the substrate **13** (10 mg, 0.030 mmol), *meso*-tetraphenylporphyrin (cat. <1 mg), dry CH_2Cl_2 (2 mL) and pTSA (8.7 mg, 0.046 mmol, 1.5 equiv). Oxygen from a balloon was bubbled through the solution for 2 min. The flask was subsequently plunged into an ice bath, and the solution was irradiated (300 W lamp) for 2 × 1 h. The resultant solution was concentrated under reduced pressure, and the residue was purified *via* column chromatography [light petroleum/ethyl acetate (80:20)] to give the desired product **14** (7.7 mg, 74%); R_f = 0.13 [light petroleum/ethyl acetate (80:20)]; mp 213–215 °C; found: C, 80.29; H, 6.10; N, 3.98; $C_{23}H_{21}NO_2$ requires C, 80.44; H, 6.16; N, 4.08; IR ($CHCl_3$) ν_{max} 2940, 1704, 1658, 1608, 1462, 1370, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.63 (m, 1H), 1.89-1.99 (m, 2H), 2.01–2.09 (m, 2H), 2.14 (m, 1H), 3.17 (d, J = 13.9 Hz, 1H), 3.23 (s, 3H), 3.29 (d, J = 13.9 Hz, 1H), 3.97 (dm, J = 5.8 Hz, 1H), 6.69 (dd, J = 7.8, 0.6 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.82 (s, 1H), 7.24–7.35 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9 (CH_2), 26.3 (CH_3), 37.2 (CH_2), 38.5 (CH_2), 41.8 (CH_2), 57.1 (C), 57.3 (CH), 106.5 (CH), 120.0 (C), 122.3 (CH), 126.8 (CH), 128.4 (CH), 129.4 (C), 130.9 (CH), 131.6 (CH), 134.8 (C), 136.7 (C), 137.2 (CH), 143.3 (C), 166.9

(C), 208.5 (C); HRMS (ESI) *m/z* 344.1645 $[M+H]^+$, $[C_{23}H_{22}NO_2]^+$ requires 344.1645.

Acknowledgements

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Supplementary data

Experimental procedures, characterisation data, and ^1H and ^{13}C NMR spectra for new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.061.

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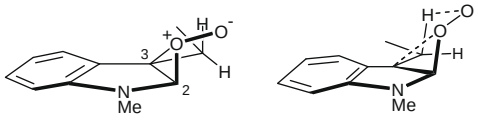
14. Consideration of the geometry of the putative perepoxide, having an *exo*-orientated oxide group, suggests that removal of an orthogonal (with respect to the indole ring) hydrogen is preferred, as in (i). This can also be appreciated considering the pseudo-chair arrangement possible in a transition state in which the C-3 to oxygen link is extended, shown as (ii) (not all making/breaking bonds shown as dashed, and charges omitted, for clarity)



(i) (ii)

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