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FULL PAPER

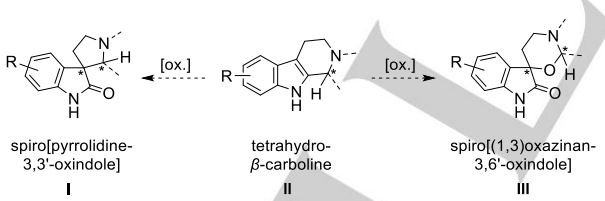
Visible Light Catalytic Photooxygenation of Monoterpene Indole Alkaloids: Access to Spirooxindole-1,3-Oxazines

Thorsten von Drathen,[a] Frank Hoffmann[b] and Malte Brasholz*[c]

Abstract: Few natural oxindole alkaloids possess an exceptional spiro-[(1,3)oxazinan-3,6'-oxindole] core structure, which results from an unusual oxidative indole rearrangement. The *Rauvolfia* alkaloid reserpine can be converted into the spirooxindole-1,3-oxazines dioxyreserpine and trioxyreserpine through efficient visible-light catalytic photooxygenation with anthraquinone photocatalysts. A mechanistic investigation sheds new light on the photooxidative rearrangement of reserpine and related monoterpene indole alkaloids, and the spirooxindole-1,3-oxazine products can be valorized by reductive ring-opening, to obtain *cis*-decahydroisoquinolines as new enantiopure synthetic building blocks as demonstrated for dioxyreserpine.

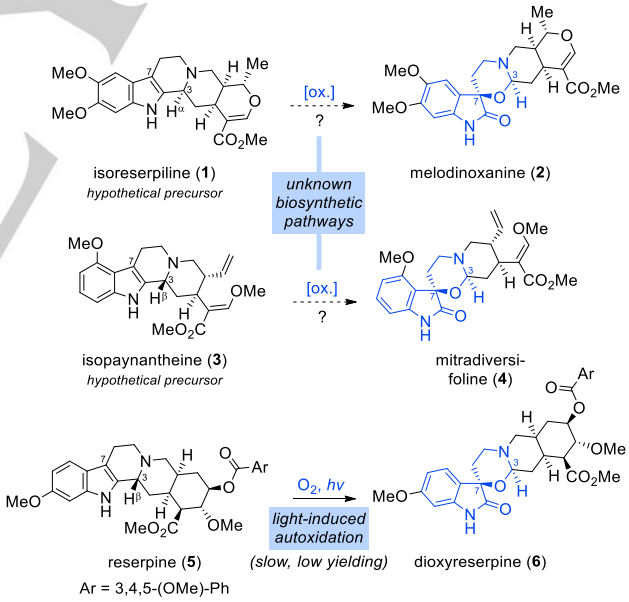
Introduction

Spirocyclic 2-oxindoles constitute an important class of oxygenated indole alkaloids, and many of these natural products possess valuable biological properties such as antihypertensive, analgesic, antitumor, and antiviral activity.[1] The typical core structure encountered in monoterpene spiro-2-oxindoles is the spiro[pyrrolidine-3,3′-oxindole] motif **I** which can biosynthetically[2] and chemically[3] be accessed from a parent tetrahydro-*β*-carboline **II** by oxidation followed by 1,2-rearrangement. However, a few natural spiro-2-oxindoles possess a peculiar spiro-[(1,3)oxazinan-3,6'-oxindole] ring system **III** whose biosynthesis is yet to be elucidated, but putatively proceeds *via* a divergent and unusual oxidative indole rearrangement, with concomitant incorporation of two oxygen atoms into the product structure (Scheme 1).



Scheme 1. Divergent oxidative rearrangements of indole alkaloids.

As the first natural product containing the spirooxindole-1,3-oxazine substructure **III**, melodinoxanine (**2**) was isolated from the stem and leaves of *Melodinus henryi* from Yunnan province in China,[4] and it was speculated that the biosynthetic precursor to **2** is isoreserpiline (**1**) which is also present in *M. henryi* (Scheme 2). Second, mitradiversifoline (**4**) was isolated from *Mitragyna diversifolia* and its putative progenitor is isopaynantheine (**3**), which is a major component in this plant.[5] A third known but synthetic monoterpene spirooxindole-1,3-oxazine is dioxyreserpine (**6**) which has been isolated after the daylight-triggered autoxidation of the *Rauvolfia* alkaloid reserpine (**5**). Awang and co-workers reported in 1990 that when a chloroform solution of **5** was left standing for a prolonged period of time (15 days) under air and in ambient light, product **6** could be isolated in 28% yield at about 50% conversion of **5**, and the structural assignment of **6** was based on NMR spectroscopy.[6]



Scheme 2. Monoterpene spirooxindole-1,3-oxazines **2**, **4**, **6** and their indole alkaloid precursors.

We investigated the oxidation of reserpine (**5**) to dioxyreserpine (**6**) and report here a rapid and selective visible light-driven catalytic photooxygenation of **5**, leading to **6** with attractive yield, and we could for the first time unambiguously confirm the proposed structure of **6** by X-ray crystallography. Further, we report that dioxyreserpine (**6**) can be readily converted into a new secondary photooxygenation product which

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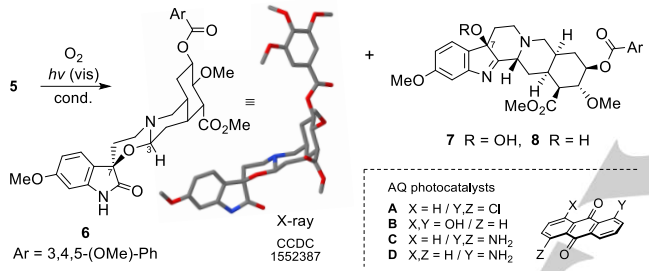
we term *trioxyreserpine*. In addition, we demonstrate that **6** can be chemically dissected to harness its unique *cis*-deca-hydroisoquinoline substructure as a new and valuable chiral building block for organic synthesis. Finally, we present results of a mechanistic study which encompassed the catalytic photooxygenation of the C3-epimer of **6**, isoreserpine, as well as the alkaloid mitragynine from *Mitragyna speciosa*, which led to a refined mechanistic picture.

Results and Discussion

We studied the visible light-induced photooxygenation of reserpine (**5**) under catalyst-free conditions as well as in the presence of various anthraquinone photocatalysts, potent organic photooxidants which we utilized previously in the photocatalytic oxidation of indoles and other heterocycles.[7]

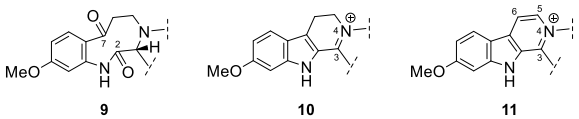
Table 1. Variation of reaction conditions for the visible light photooxygenation of (–)-reserpine (**5**).



entry	solvent (additive)	catalyst	light source (nm)	t [min]	**6/7/8** [%][a]	yield of **6** [%][b]
1	$CHCl_3$	-	CFL (450)	150[c]	52/48/0	37
2	$CHCl_3$	-	CFL (450)	300	50/12/38	29
3	$CHCl_3$	-	CFL (450)	900	57/0/43	17
4	$CHCl_3$	-	CFL (375)	150	42/0/58	23
5	$CHCl_3$	-	LED (460)	150[d]	17/46/37	15
6	MeCN	**A** (5%)	CFL (375)	150	67/0/33	26
7	MeCN	**B** (5%)	CFL (450)	150	100/0/0	26
8	MeCN	**C** (5%)	CFL (450)	150	69/0/31	58
9	MeCN	**D** (5%)	CFL (450)	150	53/0/47	43
10	MeCN	**C** (5%)	LED (460)	150	100/0/0	63
11	MeCN	**C** (3%)	LED (460)	150	100/0/0	63 (60)[e]
12	MeCN	**C** (1%)	LED (460)	150	91/0/9	67 (63)[e]

All reactions were performed with c = 18 µM for substrate **5** and under an atmosphere of O_2. Light sources: CFL = compact fluorescent lamp, 2×18 W, 450±50 nm or 2×18 W, 375±25 nm; LED = blue LED assembly, 10.1 W, 460±15 nm. [a] Ratio determined by ^{1}H NMR analysis. [b] Determined by ^{1}H NMR against CH_2Br_2 standard. [c] Conversion of **5** 93%. [d] Conversion of **5** 83% [e] Isolated yield after chromatography.

During an initial screening, irradiation of solutions of **5** in MeOH, MeCN, THF and HOAC under air and using blue fluorescent lamps resulted in no conversion after 90 min reaction time (which is at least partly due to the poor solubility of **5** in these solvents), but switching to $CHCl_3$, CH_2Cl_2 or $PhCH_3$ produced mixtures of unreacted **5** along with dioxyreserpine (**6**), the known C7 hydroperoxyindolenine **7** as well as the hydroxyindolenine **8** (a sample of which was prepared independently for comparison with **7**, see SI) in varying ratios. As outlined in Table 1, reserpine (**5**) was then irradiated under an atmosphere of O_2 in $CHCl_3$ using compact fluorescent lamps (λ_{max} 450 and 375 nm / 2×18 W each) as well as 460 nm/10 W blue LEDs (entries 1-5; see also Table S1 for additional information). Full conversion was generally observed using CFL lamps and reaction times of 150 min, but prolonged reaction times led to a slow decomposition of product **6** while at the same time, hydroperoxide **7** appeared to have slowly been converted into hydroxyl compound **8** by O-O bond cleavage (entries 1-3). The reaction under blue LED irradiation proceeded more slowly with 83% conversion after 150 min, and with a significant shift of selectivity towards hydroperoxide **7** (entry 5). As we employed the longwave-absorbing 9,10-anthraquinones **A**-**D** as photocatalysts in the reaction, we were pleased to observe a general increase in selectivity in favor of the desired product **6** (entries 6-12). We identified 1,5-diamino-anthraquinone **C** (1,5-AAQ) as the optimal catalyst, and using blue LED irradiation for 150 min with catalyst quantities of 1-3 mol-% in MeCN produced dioxyreserpine (**6**) in isolated yields of 60-63% after chromatography, as a single stereoisomer (entries 11 and 12). Notably, when using 3 mol-% of **C**, the catalyst showed >99.8% absorption of the incident 460 nm light (reserpine **5** shows hardly any absorption in this spectral area, see Figure S3) and product **6** was formed in 90-95% purity as evidenced by ^{1}H-NMR of the crude reaction mixture, which otherwise showed no trace of possible byproducts **7** and **8**. All crude NMR spectra were further carefully examined for the possible presence of the conceivable C2-C7 cleavage product **9** and the previously described anhydronium bases 3,4-dehydroreserspine (**10**) and lumireserpine (**11**),[8] however, compounds **9**-**11** were not detected in any of our experiments including those run under catalytic conditions.



On the occasion, the X-ray crystal structure of **6** could be obtained showing that the initial NMR based structural assignment[6] was in fact correct, including the relative configuration at the C7 and C3 centers of the newly formed 1,3-oxazine ring (CCDC No. 1552387).[9]

While we observed during the catalyst-free photooxygenation of **5** that prolonged reaction times led to decomposition of dioxyreserpine (**6**), traces of a new secondary photooxygenation product were detected in crude NMR spectra when using catalyst **C** and extended reaction times. When pure dioxyreserpine (**6**) was subjected to the typical reaction conditions (3 mol-% catalyst

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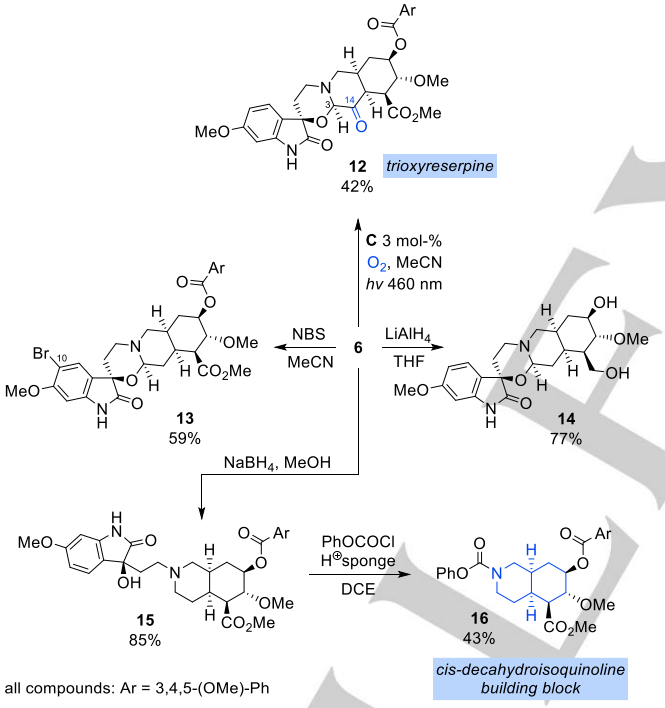
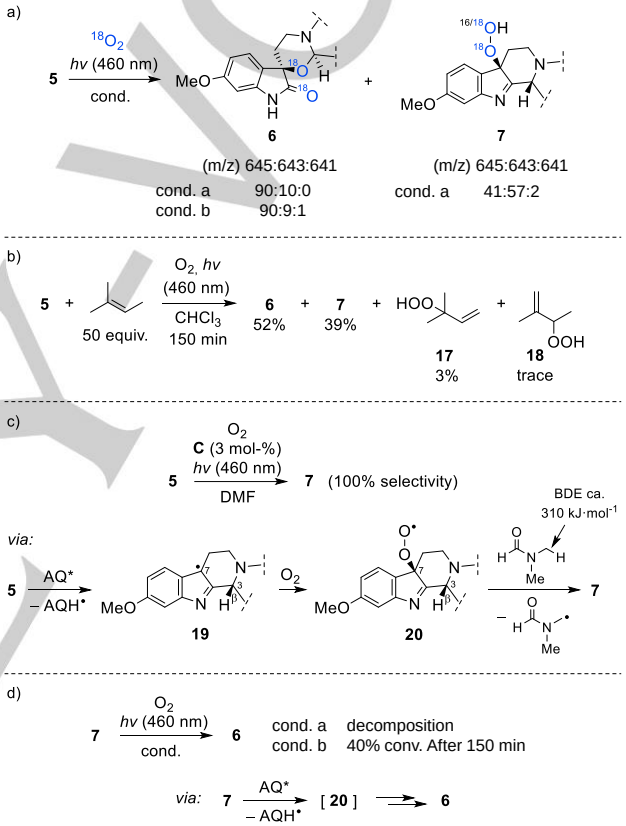
C, O_2, MeCN, blue LED), the new photoproduct could be obtained in 42% yield after 17 h, and it was identified as the C14 ketone which we term *trioxyreserpine* (**12**, Scheme 3). The mechanism of this remarkably regioselective $C_{sp}{}^3$-H oxygenation is currently under investigation; a C3-C14 alkene is a conceivable primary intermediate. Additional new synthetic transformations of dioxyreserpine (**6**) encompass electrophilic bromination with NBS to furnish the C10 bromide **13** in 59% yield, and the reduction of **6** with lithium aluminium hydride which cleaved the aryl and methyl esters to give hydroxymethyl compound **14** in 77% yield. On the other hand, using sodium borohydride in methanol, a reductive opening of the 1,3-oxazine ring could be achieved to give the *N*-alkylated *cis*-decahydroisoquinoline **15** in 85% yield, and we were pleased to find that its *N*-dealkylation could readily be accomplished using phenyl chloroformate and proton sponge,[10] to furnish the *N*-carbamoyl-*cis*-decahydroisoquinoline **16** in 43% yield. Hence, this highly valuable enantiopure synthetic building block could be made accessible by chemical degradation of reserpine (**5**) in three simple and straightforward steps.



Scheme 3. Photooxygenation of dioxyreserpine (**6**) to trioxyreserpine (**12**) and synthesis of enantiopure *cis*-decahydroisoquinoline **16**.

The mechanistic investigation of the photooxygenation of reserpine (**5**) began with isotope labelling experiments in the presence of $^{18}O_2$, $^{18}OH_2$, D_2O as well as in d_3-MeCN. In the anthraquinone catalyzed reaction, no deuterium incorporation was observed with d_3-MeCN as the reaction solvent or with added D_2O, and also no ^{18}O labelling when $^{18}OH_2$ (5-10 equiv.) was added to the mixture (under $^{16}O_2$ atmosphere), which clearly ruled out any long-lived cationic reaction intermediates.[11] When the photooxygenation of **5** was carried out under an atmosphere of $^{18}O_2$, both the autoxidation reaction in $CHCl_3$ (condition a), and the reaction with catalyst 1,5-AAQ (**C**, 3mol-%) in MeCN (condition b) produced dioxyreserpine (**6**) with ≥90% incorporation of two ^{18}O labels (m/z 645 for doubly labelled $[\mathbf{6}+H]^+$), whereas hydroperoxide **7**, isolable only from the catalyst-free photooxidation, was obtained as a ~1:1 mixture of the singly and doubly ^{18}O-labelled compounds (m/z 645 and 643 for $[\mathbf{7}+H]^+$; Scheme 4a and Figures S4-8). We attribute the latter observation to O-O bond photolysis of hydroperoxide **7** under the reaction conditions followed by oxygen exchange with trace water in the reaction mixture.



Scheme 4. Isotope labelling and control experiments.

Reserpine (**5**) possesses a relatively long-lived triplet state with an energy of ca. 265 kJ/mol[12] and therefore it may self-sensitize singlet oxygen during its autoxidation. In fact, deliberately inducing the singlet oxygenation of **5** with rose bengal or methylene blue gives comparable results (see Table S1). When the catalyst-free oxidation of **5** was performed in the presence of an excess of 2-methyl-2-butene, the allylic hydroperoxides **17** and **18** were produced along with **6** evidencing the presence of $^1O_2$ (Scheme 4b). Substituted anthraquinones (AQs) **A**-**D** are also potential sensitizers of $^1O_2$[13] but at the same time their excited states readily engage in hydrogen abstraction reactions.[14,7b] We propose that the predominant pathway for initiation of the catalytic photooxygenation of **5** is the abstraction of the indole N-H hydrogen atom by the excited state catalyst AQ* to generate a C7

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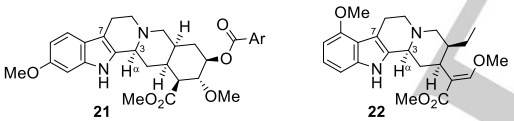
indolyl radical **19**,[7b] which is trapped stereoselectively by O_2 to give the peroxyradical **20** as key intermediate (attack of oxygen occurs from the side of the *β*-positioned C3 hydrogen), and this pathway is supported by several observations. When the photooxygenation of **5** with catalyst **C** was carried out in DMF instead of MeCN, a complete switch of selectivity occurred and hydroperoxide **7** emerged as the only product, which can be attributed to the much stronger hydrogen atom donation ability of DMF (homolytic BDE of 310 kJ/mol compared to 406 kJ/mol for MeCN[15]), causing an immediate trapping of intermediate peroxyradical **20** to give **7** (Scheme 4c). On the other hand, when pure hydroperoxide **7** was subjected to the typical reaction conditions for the photooxygenation of **5** catalyzed by **C** (condition b), **7** was slowly but cleanly converted into dioxyreserpine (**6**), which may be explained by a HAT reaction between **7** and the excited catalyst AQ* to liberate peroxyradical **20** as the key species, to enter the subsequent rearrangement pathway leading to **6** (Scheme 4d). By comparison, irradiation of hydroperoxide **7** in $CHCl_3$ alone (condition a) only led to decomposition of **7**.

Stereochemically, dioxyreserpine (**6**) has the same C7-configuration as hydroperoxide **7** and hydroxyindolenine **8**, while during the rearrangement, a formal inversion occurs at the former *β*-configured C3 of reserpine (**5**). Isopaynantheine (**3**) and mitradiversifoline (**4**) show the identical stereochemical relationship, but isoreserpiline (**1**) is *α*-configured at C3 while melodinoxanine (**2**) has again the same core configuration as **4** and **6**. To clarify the stereochemical course of the photooxygenation, we employed the C3-*α*-epimer of **5**, isoreserpine (**21**), as well as the alkaloid mitragynine (**22**) in the catalytic reaction.



Whereas isoreserpine (**21**) is unreactive under catalyst-free conditions,[6] full conversion was observed in the presence of catalyst **C.** However, in sharp contrast to reserpine (**5**), its epimer **21** reacted very unselectively to give dioxyisoreserpine (**23**) in only ca. 10% yield along with the C7 hydroperoxyindolenine and the C2-C7 cleavage product derived from **21** (see SI section for details). The photooxygenation of mitragynine (**22**) followed the same trend, giving rise to dioxymitragynine (**24**) in 24% yield.

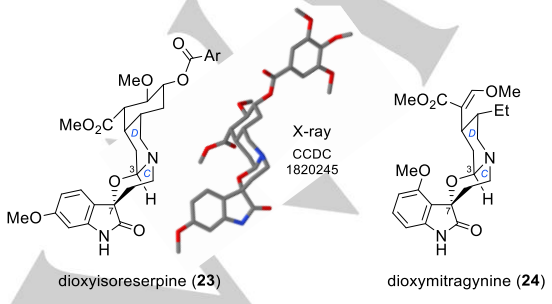


Figure 1. Structures of dioxyisoreserpine (**23**) and dioxymitragynine (**24**).

Compared to spirooxindole oxazines **2**, **4** and **6**, dioxyisoreserpine (**23**) and dioxymitragynine (**24**) show a double inverted configuration at the C3 and C7 stereocenters as evident from NMR analysis in solution and the X-ray crystal structure of **23** (Figure 1, CCDC No. 1820245),[9] which proved that **23** and **24** were formed *via* the same mechanism as **6**, beginning with a stereoselective attack of oxygen from the side of the C3-*α*-hydrogen. However, the formation of the new oxazine ring occurred in such fashion that the C and D rings in **23** and **24** are *cis*-fused, causing the compounds to suffer from sterically highly unfavorable 1,3-diaxial interactions, and thus explaining the poor yield and selectivity observed in the photooxygenation of C3-*α*-configured substrates **21** and **22**. At the same time, this result strongly suggests that if isoreserpiline (**1**, Scheme 1) is the true biosynthetic precursor to melodinoxanine (**2**), it must undergo isomerization to its *β*-configured epimer reserpiline prior to oxidation, possibly under acid catalysis.[16]

Any plausible mechanism for the rearrangement occurring during the photooxygenation of tetrahydro-*β*-carboline alkaloids leading to the spiro-[(1,3)oxazinan-3,6'-oxindole] ring system **III** but not to the 'regular' spiro[pyrrolidine-3,3′-oxindole] motif **I** must account for the key observations made during this study. *N*-Methyl reserpine did not undergo the analogous rearrangement under catalytic or catalyst-free conditions, confirming the necessity of an unprotected indole nitrogen. Apart from byproducts **7** and **8**, no other reaction intermediates could be detected in the photooxygenation of reserpine (**5**), and the attempted nucleophilic trapping of possible radical cationic or cationic intermediates failed. This points towards a rapid reaction sequence involving radical or possibly even carbene intermediates, and further it renders a previous proposal of the biosynthetic intermediacy of the 'regular' spiro-2-oxindole structure **I** on the way to spirooxazines **III** highly unlikely.[5] Further, a previously assumed dioxetane intermediate[4,6] seems not to be involved at least in the case of reserpine (**5**), since no trace of keto amide **9** could be detected and the clean stereochemical inversion at C3 can be explained only with difficulty in this scenario, which at the same time involves an unlikely simultaneous homolytic cleavage of the O-O and C2-C3 bonds. On the other hand, the observation of the C2-C7 cleavage product in the photooxygenation of isoreserpine (**21**) clearly shows that mechanistic branching must occur after the initial radical oxygenation step.

A proposed overall reaction mechanism is depicted in Scheme 5, for the case of C3-*β*-configuration as found in reserpine (**5**). The catalytic photooxygenation is initiated by hydrogen abstraction from indole precursor **II** by excited catalyst AQ* followed by stereoselective radical oxygenation with O_2 (*vide supra*).[7b] The resulting peroxyradical **20'** is less stable than its C7 epimer derived from *α*-configured **II** due to *cis*-fused C and D rings,[16] however, its peroxy group is properly oriented to engage in an intramolecular 1,5-hydrogen atom transfer (HAT), to give a stabilized and strain-relieved allylic radical **25**. Subsequent HAT to **25** generates a reactive dienamine **26** which is epoxidized, followed by ring-opening of epoxide **27** to the zwitterion **28**. At this stage, the key scission of the C2-C3 bond occurs and we propose that intermediate **28** rearranges to give the cyclic (alkyl)(amino) carbene **29**,[17] which undergoes final ring-closure by proton

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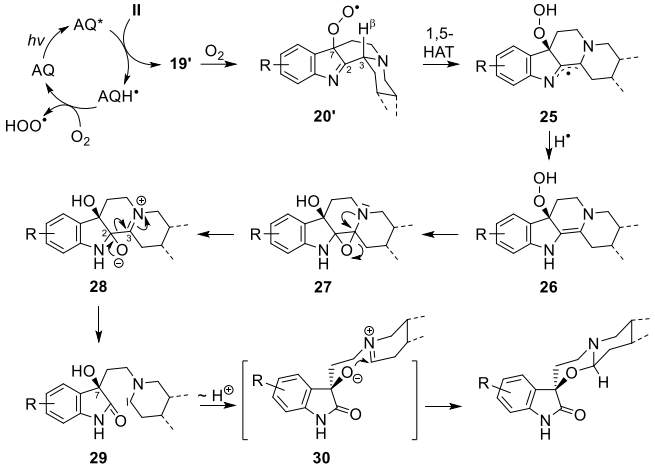
transfer[18] and nucleophilic trapping of the iminium ion through the chair-like transition structure **30**, to yield the final product with the observed stereochemistry. Alternatively, carbene **29** may react *via* direct OH-insertion[19] with the C7-hydroxy group.



Scheme 5. Proposed mechanism for the catalytic photooxygenation of C3-*β*-configured tetrahydro-*β*-carbolines.

Conclusions

In summary, we developed efficient catalytic photooxygenation procedures to access the valuable spirooxindole-1,3-oxazines dioxyreserpine (**6**) and trioxyreserpine (**12**) from their parent indole alkaloid reserpine (**5**). Dioxyreserpine (**6**) could be valorized by reductive ring-opening and *N*-dealkylation to harness its *cis*-decahydroisoquinoline core structure **16** as a new enantiopure building block. The mechanistic investigation of the photooxygenation of **5** compared to its C3-epimer **21** as well as mitragynine (**22**) allowed to develop a new mechanistic hypothesis for their unusual photooxidative rearrangements, with implications that may enhance the understanding of the biosynthesis of related natural spirooxindole-1,3-oxazines.

Experimental Section

Dioxyreserpine (6): In a 10 mL crimp cap vial, (−)-reserpine (**5**; 22.0 mg; 36.1 µmol) was suspended in 2.0 mL of a freshly prepared stock solution of 1,5-AAQ (**C**) in dry MeCN (0.13 mg/mL equivalent of 0.54 µmol/mL) to give a 18 mM solution of **5** containing 3 mol-% of catalyst. The vial was sealed and O_2 was briefly bubbled through the reaction mixture *via* cannula, then an O_2-balloon was fitted to the cannula. The reaction mixture was stirred rapidly with irradiation inside a blue LED assembly (10.1 W, 294 lm, 460±15 nm) at ambient temperature for 150 min, whereupon the mixture turned homogeneous. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, petroleum ether/ethyl acetate 1:0→1:3) to give 14.6 mg (63%) of dioxyreserpine (**6**) as a pale yellow solid.

***R*f** = 0.60 (EtOAc); **m.p.** 150 °C; **[α]D** = −60.0°, c 0.50, $CHCl_3$ (lit. −78.8°, c 0.10, $CHCl_3$).[6] **^{1}H NMR ($CDCl_3$, 400 MHz):** δ = 1.44 (td, *J* = 3.5, 12.7 Hz, 1 H, 14-H^a), 1.72 (m$_c$, 1 H, 14-H^b), 1.80 (td, *J* = 1.7, 13.8 Hz, 1 H, 6-H^a), 1.97-2.02 (m, 2 H, 19-H^a, 20-H), 2.26-2.42 (m, 3 H, 19-H^b, 6-H^b, 15-H), 2.54 (dd, *J* = 2.7, 11.7 Hz, 1 H, 21-H^a), 2.64-2.76 (m, 3 H, 5-H^a, 16-H, 21-H^b), 3.03 (m$_c$, 1 H, 5-H^b), 3.50 (s, 3 H, 33-H), 3.67 (s, 3 H, 34-H), 3.79 (s, 3 H, 35-H), 3.82-3.89 (m, 2 H, 17-H, 18-H), 3.92 (s, 3 H, 31-H), 3.93 (s, 6 H, 30-H, 32-H), 4.59 (dd, *J* = 3.2, 9.7 Hz, 1 H, 3-H), 4.99-5.08 (m, 1 H, 18-H), 6.37 (d, *J* = 2.2 Hz, 1 H, 12-H), 6.52 (dd, *J* = 2.2, 8.2 Hz, 1 H, 10-H, 7.26 (d, *J* = 8.2 Hz, 1 H, 9-H), 7.34 (s, 2 H, 25-H, 29-H) ppm. **^{13}C NMR ($CDCl_3$, 150 MHz):** δ = 29.3 (t, C14), 30.3 (t, C19), 31.8 (t, C6), 34.0 (d, C20), 36.1 (d, C15), 47.9 (t, C5), 51.7 (d, C16), 51.8 (q, C34), 55.6 (q, C35), 56.3 (q, C30, C32), 57.3 (t, C21), 60.86 (q, C33), 60.93 (q, C31), 74.4 (s, C7), 77.8 (d, C17), 78.1 (d, C18), 87.0 (d, C3), 97.2 (d, C12), 106.8 (d, C25, C29), 107.4 (d, C10), 122.7 (s, C8), 125.2 (d, C9), 125.4 (s, C24), 141.1 (s, C13), 142.3 (s, C27), 153.0 (s, C26, C28), 161.3 (s, C11), 165.4 (s, C23), 171.8 (s, C22), 178.1 (s, C2) ppm. **IR:** $\tilde{\nu}$ = 3355 (N-H), 2955, 2920, 2850 (C-H), 1715 (C=O), 1660, 1630, 1460, 760 cm^{-1}. **HRMS (ESI):** m/z $[M+H]^+$ calc. for $[C_{33}H_{41}N_2O_{11}]^+$ 641.2705, found 641.2772.

Trioxyreserpine (12): In a 10 mL crimp cap vial, dioxyreserpine (**6**; 35.4 mg; 55.3 µmol) was dissolved in 3.0 mL of a freshly prepared stock solution of 1,5-AAQ (**C**) in dry MeCN (0.13 mg/mL equivalent of 0.54 µmol/mL) to give a 18 mM solution of **6** containing 3 mol-% of catalyst. The vial was sealed and O_2 was briefly bubbled through the reaction mixture *via* cannula, then an O_2-balloon was fitted to the cannula. The reaction mixture was stirred rapidly with irradiation inside a blue LED assembly (10.1 W, 294 lm, 460±15 nm) at ambient temperature for 17 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (silica gel, EtOAc/$CHCl_3$ 1:1) to give 15.3 mg (42%) of trioxyreserpine (**12**) as a colorless resin.

***R*f** = 0.30 (EtOAc/$CHCl_3$ 1:1); **[α]D** = −69.4°, c 0.16, $CHCl_3$. **^{1}H NMR ($CDCl_3$, 600 MHz):** δ = 1.79 (td, *J* = 2.2, 13.9 Hz, 1 H, 6-H^a), 1.91 (dd, *J* = 12.4, 13.0 Hz, 1 H, 19-H^a), 2.07 (m$_c$, 1 H, 19-H^b), 2.33 (dt, *J* = 4.9, 13.9 Hz, 1 H, 6-H^b), 2.44 (m$_c$, 1 H, 20-H), 2.53 (dd, *J* = 5.2, 10.3 Hz, 1 H, 16-H), 2.82-2.88 (m, 2 H, 5-H^{eq}, 21-H^{eq}), 3.10 (dd, *J* = 3.0, 12.3 Hz, 1 H, 21-H^{ax}), 3.36 (m$_c$, 1 H, 5-H^{ax}), 3.48-3.52 (m, 1 H, 15-H), 3.63 (s, 3 H, 33-H), 3.68 (s, 3 H, 34-H), 3.65 (s, 3 H, 34-H), 3.76 (s, 3 H, 35-H), 3.92 (s, 3 H, 31-H), 3.94 (s, 6 H, 30-H, 32-H), 4.06 (dd, *J* = 9.3, 10.3 Hz, 1 H, 17-H), 4.99 (ddd, *J* = 5.0, 9.3, 12.2 Hz, 1 H, 18-H), 5.31 (s, 1 H, 3-H), 6.28 (d, *J* = 2.2 Hz, 1 H, 12-H), 6.52 (dd, *J* = 2.2, 8.2 Hz, 1 H, 10-H), 7.25 (d, *J* = 8.2 Hz, 1 H, 9-H), 7.33 (s, 3 H, 25-H, 29-H, N-H) ppm. **^{13}C NMR ($CDCl_3$, 150 MHz):** δ = 31.3 (t, C6), 31.6 (t, C19), 35.9 (d, C20), 46.5 (d, C-16), 48.2 (t, C5), 51.0 (d, C15), 51.9 (q, C34), 55.5 (q, C-35), 55.8 (t, C21), 56.3 (q, C30, C32), 60.8 (q, C33), 60.9 (q, C31), 74.7 (s, C7), 77.1 (d, C17), 78.1 (d, C18), 87.8 (d, C3), 97.1 (d, C12), 106.8 (d, C25, C29), 107.4 (d, C10), 121.7 (s, C8), 125.2 (s, C24), 125.6 (d, C9), 141.3 (s, C13), 142.3 (s, C27), 153.0 (s, C26, C28), 161.5 (s, C11), 165.4 (s, C23), 171.2 (s, C22), 177.4 (s, C2), 200.9 (s, C14) ppm. **IR:** $\tilde{\nu}$ = 3305 (N-H), 2940, 2840 (C-H), 1715 (C=O), 1635, 1590, 1505, 1335, 1250, 1155, 755 cm^{-1}. **HRMS (ESI):** m/z $[M+H]^+$ calc. for $[C_{33}H_{39}N_2O_{12}]^+$ 655.2498, found 655.2508.

***N*-Alkyl-*cis*-decahydroisoquinoline 15:** Dioxyreserpine (**6,** 108 mg, 169 µmol) was dissolved in MeOH (27 mL) under N_2 and the solution was cooled to 0 °C. Sodium borohydride (63.9 mg, 169 µmol, 10.0 eq.) was added, and the mixture was allowed to warm to r.t. and stirred overnight. The mixture was diluted with H_2O, extracted with EtOAc (3×), dried over $MgSO_4$, filtered and concentrated. The crude mixture was then purified by column chromatography (silica gel, PET/ethyl acetate 1:1→0:1) to give 92.3 mg (85%) **15** as a colorless film.

***R*f** = 0.38 (EtOAc); **[α]D** = −41.0°, c 0.58, $CHCl_3$. **^{1}H NMR ($CDCl_3$, 500 MHz):** δ = 1.26-1.33 (m, 1 H, 8-H^a), 1.34-1.40 (m, 1 H, 4-H^a), 1.63 (br s, 1

H, OH), 1.81 (ddd, *J* = 2.9, 6.0, 14.6 Hz, 1H, 2'-H^a), 1.86-2.00 (m, 3 H, 4-H^b, 2'-H^b, 3-H^a), 2.02-2.15 (m, 3 H, 4a-H, 8a-H, 8-H^b), 2.22 (d, *J* = 11.5 Hz, 1 H, 1-H^a), 2.54 (m$_c$, 1 H, 1'-H^a), 2.73 (dd, *J* = 4.5, 11.0 Hz, 1 H, 5-H), 3.10 (d, *J* = 11.5 Hz, 1 H, 1-H^b), 3.16 (m$_c$, 1 H, 1'-H^b), 3.32-3.38 (m, 1 H, 3-H^b), 3.49 (s, 3 H, C6-OMe), 3.74 (s, 3 H, CO_2Me), 3.76 (s, 3 H, C6''-OMe), 3.79 (dd, *J* = 9.5, 11.0 Hz, 1 H, 6-H), 3.88 (s, 3 H, Ar-OMe), 3.89 (s, 6 H, Ar-OMe), 4.98-5.06 (m, 1 H, 7-H), 6.38 (d, *J* = 2.2 Hz, 1 H, 7''-H), 6.51 (dd, *J* = 2.2, 8.3 Hz, 1 H, 5''-H), 7.16 (d, *J* = 8.3 Hz, 1 H, 4''-H), 7.28 (s, 2 H, Ar-H), 7.70 (s, 1 H, NH) ppm. **^{13}C NMR ($CDCl_3$, 100 MHz):** δ = 23.3 (t, C4), 29.7 (t, C8), 32.1 (t, C-2'), , 34.7 (d, C8a), 37.1 (d, C4a), 51.7 (q, CO_2Me), 52.1 (d, C5), 53.7 (t, C1'), 54.5 (t, C3), 55.5 (q, C6''-OMe), 56.2 (q, Ar-OMe), 57.9 (t, C1), 60.89 (q, Ar-OMe), 60.92 (q, C6-OMe), 77.2 (s, C3''), 77.9 (2 d, C6, C7), 97.5 (C7''), 106.97 (d, Ar), 107.05 (d, C5''), 124.3 (s, C3a''), 124.8 (d, C4''), 125.2 (s, Ar), 140.9 (s, C7a''), 142.3 (s, Ar), 152.9 (s, Ar), 160.8 (s, C6''), 165.5 (s, OCOAr), 172.1 (s, CO_2Me), 180.5 (s, C2'') ppm. **IR:** $\tilde{\nu}$ = 3310 (OH), 2940, 2840 (C-H), 1715 (C=O), 1630, 1590, 1505, 1250, 1125, 725 cm^{-1}. **HRMS (ESI):** m/z $[M+H]^+$ calc. for $[C_{33}H_{43}N_2O_{11}]^+$ 643.2861, found 643.2955.

***cis*-Decahydroisoquinoline 16:** *N*-Alkyl-*cis*-decahydroisoquinoline **15** (29.5 mg, 45.9 µmol) was dissolved in DCE (2 mL) under N_2 and the solution was cooled to 0 °C. A solution of proton sponge (30.0 mg, 140 µmol, 3.05 eq.) and phenyl chloroformate (11.8 µL, 94.2 µmol, 2.05 eq.) in DCE (3 mL) was added dropwise. The mixture was stirred at r.t. for 1 h and 2.5 h at 100 °C. The solvent was removed under reduced pressure, the residue was diluted with water and extracted with EtOAc (3×). The combined organic layers were washed with cold 1 M HCl (3×), H_2O (3×), brine (3×) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude mixture was purified by column chromatography (silica gel, PET/ethyl acetate 1:0→1:1) to give 11.0 mg (43%) **16** as a colorless film.

R_f = 0.35 (PET/EtOAc 1:1); **$[\alpha]_D$** = −30.3°, c 0.46, $CHCl_3$. **^{1}H NMR ($CDCl_3$, 600 MHz):** δ = 1.36-1.46 (m, 4-H^a), 1.79-1.98 (m, 2 H, 4-H^b, 8-H^a), 2.04-2.14 (m, 2 H, 8-H^b, 8a-H), 2.23-2.32 (m, 1 H, 4a-H), 2.77 (dd, *J* = 4.7, 10.8 Hz, 1 H, 5-H), 2.75,* 2.89* (2 t, *J* = 12.0 Hz, 1 H, 3-H^a), 3.03,* 3.19* (2 d, *J* = 12.5 Hz, 1 H, 1-H^a), 3.52 (s, 3 H, CH-OMe), 3.76 (s, 3 H, CO_2Me), 3.80-3.89 (m, 1 H, 6-H), 3.92, 3.93 (2 s, 9 H, Ar-OMe), 4.13-4.25 (m, 1 H, 1-H^b), 4.33-4.46 (m, 1 H, 3-H^b), 5.02-5.13 (m, 1 H, 7-H), 6.99-7.12 (m, 2 H, Ph) 7.14-7.21 (m, 1 H, Ph) 7.27-7.37 (m, 4 H, Ar, Ph) ppm. *Signals marked show rotamer splitting. **^{13}C NMR ($CDCl_3$, 150 MHz):** δ = 22.5 (t, C4), 28.8 (t, C8), 34.4 (d, C8a), 37.2 (d, C4a), 44.3 (t, C3), 48.9 (t, C1), 51.9 (q, CO_2Me), 52.1 (d, C5), 56.3 (q, Ar-OMe), 61.0 (q, Ar-OMe, CH-OMe), 77.5 (d, C7), 77.7 (d, C6), 106.9 (d, Ar), 121.6 (d, Ph), 125.1 (s, Ar), 125.3 (d, Ph), 129.2 (d, Ph), 142.4 (s, Ar), 151.2 (s, Ph), 153.0 (s, Ar), 154.0 (s, NCO), 165.4 (s, OCOAr), 171.8 (s, CO_2Me) ppm. **IR:** $\tilde{\nu}$ = 2940, 2840 (C-H), 1710 (C=O), 1590, 1505, 1250, 1210, 725 cm^{-1}. **HRMS (ESI):** m/z $[M+H]^+$ calc. for $[C_{29}H_{36}NO_{10}]^+$ 558.2334, found 558.2347.

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Keywords: alkaloids • indoles • photooxygenation • rearrangements

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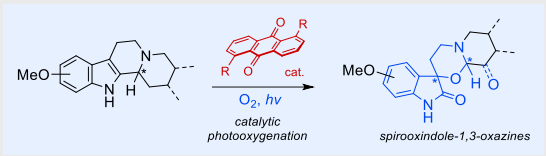

*Thorsten von Drathen, Frank Hoffmann, Malte Brasholz**

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Visible Light Catalytic Photooxygenation of Monoterpene Indole Alkaloids: Access to Spirooxindole-1,3-Oxazines

Photooxidative rearrangement: Few natural oxindole alkaloids possess an exceptional spirooxindole-1,3-oxazine core structure, which results from an unusual oxidative indole rearrangement. The *Rauvolfia* alkaloid reserpine can be converted into the photoproducts dioxyreserpine and trioxyreserpine through efficient visible-light catalytic photooxygenation with anthraquinone photocatalysts.