http://dx.doi.org/10.21577/0103-5053.20180149

J. Braz. Chem. Soc., Vol. 30, No. 1, 19-32, 2019
Printed in Brazil - ©2019 Sociedade Brasileira de Química

Article

Synthesis of Spiro-Pyrrolidinyloxindoles by Oxidative Rearrangement of *N*-Acyltetrahydro-β-carbolines Using an Oxone/Aqueous Acetone Mixture

***Luisa L. Marçal*[a] *and Simon J. Garden*[*,a]**

[a]*Instituto de Química, Universidade Federal do Rio de Janeiro, Centro de Tecnologia, Bloco A, Cidade Universitária, Ilha do Fundão, 21949-909 Rio de Janeiro-RJ, Brazil*

Spiro-pyrrolidinyl-2-oxindoles were prepared by the oxidative rearrangement of N^a-acetyl-1,2,3,4-tetrahydro-β-carbolines (THBC) using dimethyldioxirane generated *in situ*. The N^a-acetyl THBC substrates were obtained by Pictet-Spengler and acyl-Pictet-Spengler reactions of *L*-tryptophan methyl ester, followed by N^a-acetylation. The stereoselectivity of the oxidative rearrangement was evaluated and 2D nuclear magnetic resonance (NMR) was used to determine the stereochemistry of the oxindole products relative to *L*-tryptophan. Density functional theory calculations were consistent with a face selective, substrate controlled, epoxidation of the indolic double bond. The calculations indicated that the resulting epoxide would readily rearrange at room temperature via a concerted ring opening/ring contraction process to give the 3-substituted-2-oxindole.

Keywords: concerted oxidative rearrangement, dimethyl dioxirane, spiropyrrolidinyl-2-oxindole natural products

Introduction

The structural complexity and the biological activity of natural products containing a spiro-cyclic-oxindole ring system,[1,2] such as gelsemine,[3] paraherquamides[4] and spiro-pyrrolidinyloxindoles (for example (Figure 1): horsfiline,[5] coerulescine,[6] elacomine,[7] rhynchophylline,[8] pteropodine,[9] chitosenine,[10,11] alstonisine,[12] spirotryprostatins,[13] and strychnofoline)[14] have attracted a great deal of interest over the past few decades. These and related compounds have been a driving force for the development of synthetic methods for the obtention of spiro-cyclic-oxindoles and the investigation of their biological properties.[15-25]

The intense scientific interest has resulted in the discovery of synthetic spiro-pyrrolidinyloxindoles that are enhancers of the cellular actions of latrunculin B,[26] which interfere with microtubule polymerization,[27] or are potent MDM2 inhibitors[28] with sub-nanomolar inhibitor (K_i) constants that have been advanced through to clinical trials (Figure 1).[29]

Marti and Carreira,[16] as well as Galliford and Scheidt,[1] have classified different generalized synthetic strategies for the synthesis of spiro-pyrrolidinyloxindoles. Amongst the strategies, the oxidative rearrangement of indolic compounds has attracted considerable attention and a diverse range of oxidants can be used to promote the reaction as exemplified by the following recent examples: *t*-BuOCl,[11,30-42] *N*-chlorosuccinimide (NCS),[43] *N*-bromosuccinimide (NBS),[44] dibromo-dimethylhydantoin,[45] oxaziridines,[32,35,46-58] dimethyl dioxirane (DMD),[32,35,47,59-65] trifluoroperacetic acid,[66] *meta*-chloroperoxybenzoic acid (mCPBA),[67] a chiral aspartyl peptide peracid,[68] H_2O_2,[69] selectfluor,[70] XeF_2,[33,71] $Pb(OAc)_4$,[41] OsO_4,[72] or by bioconversion.[73]

In a general manner, the oxidative rearrangement of 2,3-disubstituted indoles to give 3,3-disubstituted-2-oxindoles or 2,2-disubstituted indoxyls occurs via formation of a 3-substituted indolenine derivative (Scheme 1). This intermediate is often isolated or treated *in situ* with acids or bases. The preferential formation of either the 2-oxindole or the indoxyl product depends upon which substituent has a greater propensity to migrate and/or upon the reaction conditions.[30,35-37,74-80]

In contrast, Zhang and Foote[81] reported the formation of *N*-acylindole epoxides at sub-zero temperatures as characterized by nuclear magnetic resonance (NMR) when *N*-acylindole derivatives were oxidized with an isolated acetone solution of DMD. At room temperature, the *N*-acylindole epoxides spontaneously rearranged to 2-oxindole and/or indoxyl derivatives depending upon the nature of the substituents.[81] In a similar fashion, Adam *et al.*[82] found that the 1-acetylcyclopent[2,3]indole

*e-mail: garden@iq.ufrj.br

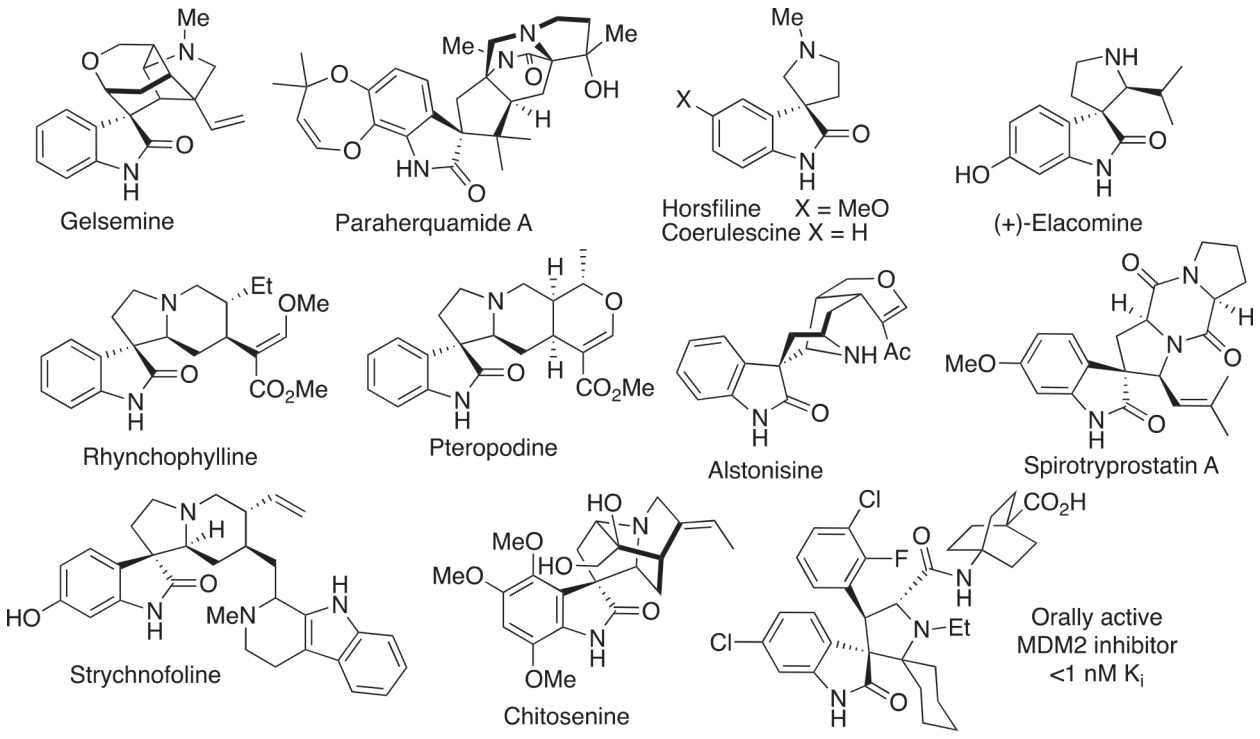
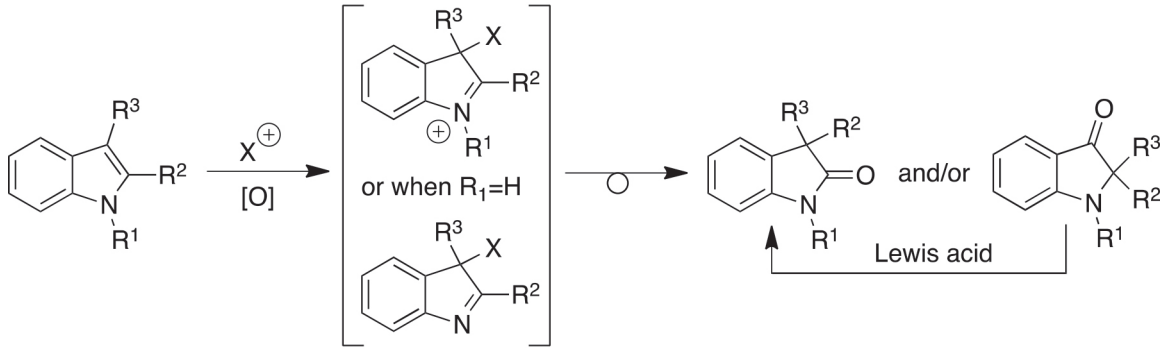


Figure 1. The structures of gelsemine and paraherquamide A and examples of naturally occurring spiro-pyrrolidinyloxindoles and a synthetic MDM2 inhibitor.



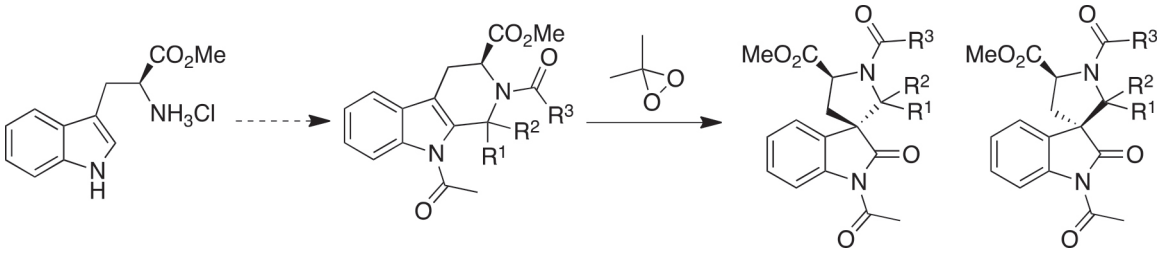
Scheme 1. Oxidation of substituted indoles to give 2-oxindole or indoxyl products.

2,3-epoxide was stable at room temperature for days and they characterized the structure of this compound by single crystal X-ray diffraction.

The present study details the use of DMD, generated *in situ*, for the oxidative rearrangement of N^a-acetyl-1,2,3,4-tetrahydro-β-carbolines (N^a-AcTHBC), prepared from *L*-tryptophan, to give spiro-pyrrolidinyloxindole derivatives without the observed formation of a 3-substituted indolinine derivative (Scheme 2). Initial studies of the oxidation of some acetylated tetrahydro-β-carbolines using DMD were presented few years ago,[83] whilst Martin and co-workers[32,65] and Sarpong and co-workers[59,61] have more recently employed DMD for the oxidative rearrangement of N^a-Boc-hydrocarbazole derivatives as part of a strategy towards the total synthesis of citrinadins and citrinalin B. In developing upon the initial studies we have applied the *in situ* generation of DMD to the oxidative rearrangement of tetrahydrocarboline derivatives (we cannot rule out the possibility that the actual oxidant is in fact an adduct between $KHSO_5$ and acetone, the same adduct which gives rise to DMD). The diastereoselectivity of the rearrangements was qualitatively assessed by the chromatographic separation of the diastereoisomers. The stereochemistry, relative to *L*-tryptophan, was determined from the analysis of the respective nuclear Overhauser effect spectra (NOESY) after assignment of all ^1H and ^{13}C signals using two-dimensional (2D) NMR spectra.

Results and Discussion

Initially, the oxidation of the indole derivatives **4**-**7** using DMD generated *in situ* from $NaHCO_3$ and oxone

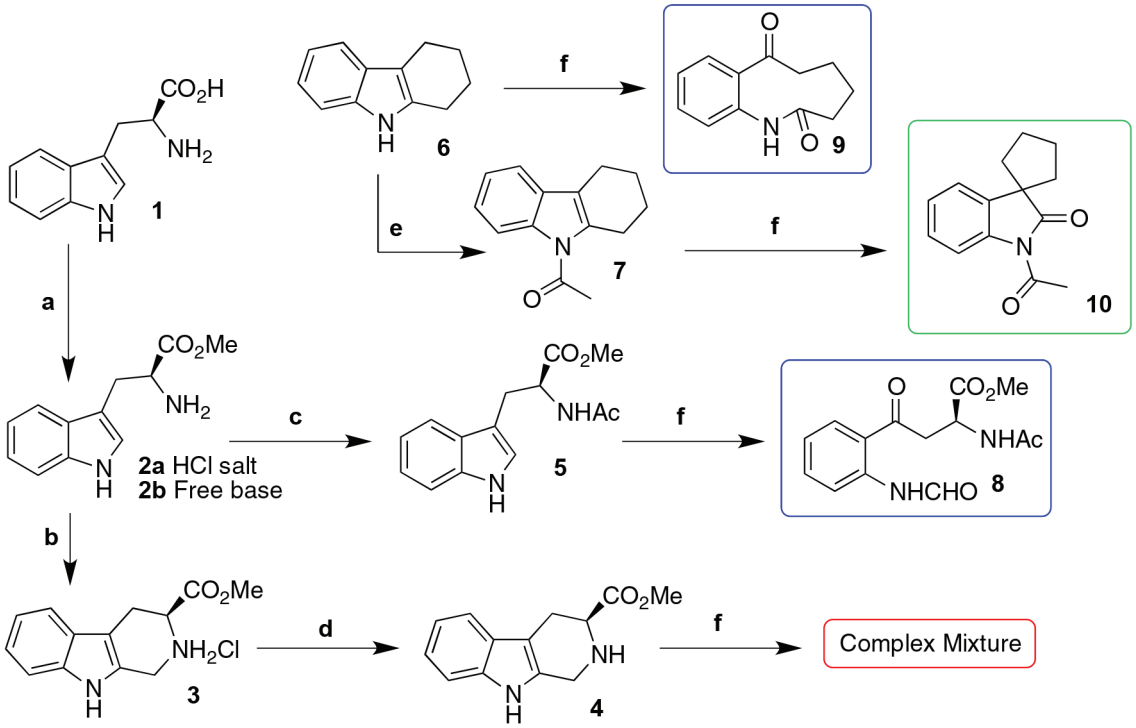


Scheme 2. Synthesis of spiro-pyrrolidinyloxindoles by oxidative rearrangement of *N*-AcTHBCs, derived from *L*-tryptophan methyl ester, using DMD.

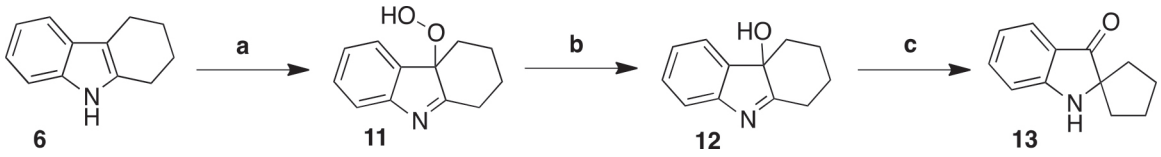
in H_2O/acetone (1/1 v/v) was investigated (Scheme 3).[84] Whereas the oxidation of **4** gave a complex mixture, the oxidation of **5** readily provided the *N*-formylkynurenine derivative **8** (60%) and the oxidation of **6** gave the tetrahydrobenzazonine-2,7-dione **9** (63%). These reactions were performed using one mole equivalent of oxone, which resulted in complete substrate consumption. The reactions were not optimized.

The indole ring cleavage product **8** has been previously obtained by superoxide oxidation,[85] or by metalloporphyrin catalyzed oxidation in 32% yield[86] and, more recently, as a product from ozonolysis of **5**,[87] whilst **9** has been obtained in a quantitative yield by the periodate oxidation of **6**.[88] In addition to the indole ring cleavage product **9**, substrate **6** can give rise to a spiro-cyclopentyl-1,2'-indol-3'-one (**13**, Scheme 4).[89] On the other hand, the oxidation of **7** readily gave the *N*-acetyl-spiro-cyclopentyl-1,3'-indol-2'-one (**10**) as observed by Zhang and Foote.[81] The 2-oxindole[90] and the isomeric 3-oxindole products are readily distinguished by their different physical and spectroscopic properties where the ^{13}C chemical shifts ($CDCl_3$) of the respective carbonyl groups are 184.6[91] and 205.2 ppm.[89]

The contrasting reactivity of the substrates **6** and **7**, and the complex product mixture obtained on oxidation of **4**, reveals that the *N*-acetyl group modulates the reactivity of the indolic substrates in favor of 2-oxindole product formation. Therefore, the tetrahydro-β-carboline (THBC) **4** was transformed into the N^a,N^b-diacetyl THBC (**14**) by heating in a mixture of Ac_2O/AcCl (Scheme 5). Treatment of **14** with DMD, generated *in situ*, resulted in the formation of a mixture of products. Thin layer chromatography (TLC) analysis revealed the presence of two pairs of products that were subsequently separated and characterized as pairs of diastereoisomeric spiropyrrolidinyl-(N^a-acetyl)-(**15a/b**, the apolar fraction) and spiropyrrolidinyl-(N^a-H)-oxindoles (**16a/b**, the polar fraction). Subsequently,



Scheme 3. Synthesis and oxidation of indole derivatives **4**-**7** with DMD. (a) MeOH, $SOCl_2$, reflux (quantitative yield (QY)); (b) CH_2O, TFA, MeOH, reflux (QY); (c) Ac_2O, NaOAc (97%); (d) aqueous NH_4OH (97%); (e) Ac_2O, AcCl, Δ, 3 h (83%); (f) oxone, $NaHCO_3$, H_2O, acetone.



Scheme 4. Synthesis of spiro-cyclopentyl-1,2'-indol-3'-one (**13**).[89] (a) Rose Bengal, O_2, AcOH, hv (90% yield); (b) 10% aqueous Na_2SO_3 (89%); (c) 10% methanolic H_2SO_4 (98%).

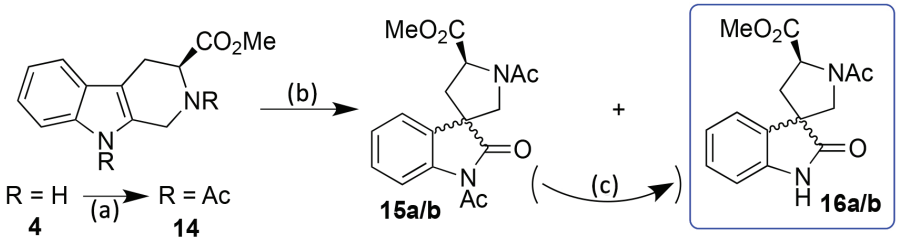
upon repeating the oxidation reaction, and in order to simplify the characterization and quantification of the diastereoisomers, the product mixture was N^a-deacetylated by briefly refluxing in MeOH to which a catalytic quantity of *p*TSA (*p*-toluenesulfonic acid) had been added. This resulted in the exclusive formation of the more polar pair of diastereoisomeric (N^a-H)-oxindoles **16a/b** as a 1:1 mixture (^{1}H NMR) (Scheme 5).

The mixture was chromatographically separated and the diastereoisomers (the least polar diastereoisomer **16a** and the more polar **16b**) were individually characterized. 2D NMR experiments were used to assign the ^{1}H and ^{13}C signals. The 2-oxindole substructure was confirmed by: (*i*) the ^{13}C shift of the oxindole carbonyl groups (177.2 and 180.7 ppm for **16a** and **16b**, respectively); (*ii*) the heteronuclear multiple bond correlation (HMBC) spectrum revealed that the methylene groups (C8 and C11, for atom numbering, see Figure 2) of the spiro-pyrrolidine ring fragment were ^3J coupled with C3a, the quaternary aromatic carbon bonded to spiro-C3 of the oxindole fragment, revealing that both methylene groups were bonded to the spiro-C3 center. The stereochemistry, relative to *L*-tryptophan, was determined by 2D NOESY. In the case of **16a**, H4 of the oxindole nucleus revealed through space dipolar couplings with specific hydrogens (H8b, H11b and H9) of the spiro-pyrrolidine group. The more deshielded hydrogens, H8a and H11a, of the respective methylene groups (C8 and C11) revealed a strong nOe correlation between them, consistent with the respective C–H bonds occupying pseudo-axial positions of an envelope conformation of the spiropyrrolidine group, where the spiro-C3 of the oxindole nucleus is the envelope flap (Figure 2). The distinction between H4 and H7 of the oxindole nucleus was ratified by the observation of an nOe correlation between H7 and the NH group. Notably, the N^b-acetyl group of the spiro-pyrrolidinyl group gave rise to two conformers in a 5:1 ratio for **16a** and a 3:1 ratio for **16b**, as determined by integration of the oxindole NH signals. An nOe interaction of the acetyl methyl group with the hydrogens H11a and H11b of the more deshielded methylene group of the pyrrolidine ring allowed distinction of the conformer structures (Figure 2).

In a similar fashion, a 2D NOESY experiment allowed the stereochemical definition of the diastereoisomer **16b** (*S*,*S*). The hydrogens H4 and H7 were readily defined from their respective nOe dipolar couplings, where H7 revealed a coupling with the NH group and H4 revealed couplings with H8b and H11. In the case of **16b**, the hydrogens H11a and H11b are magnetically equivalent and gave rise to a singlet (δ 3.92 ppm) in the ^{1}H NMR spectrum. Additionally, the hydrogens H8a and H8b revealed nOe correlations with the hydrogens H11 and the hydrogen H9 with H11 (Figure 2).

With the aim of further exploring the oxidative rearrangement of THBC derivatives, a small group of *N*-AcTHBCs was prepared from *L*-tryptophan methyl ester hydrochloride salt (**2a**), the structures are given in Figure 3. The synthetic methodology for their preparation is detailed in the Supplementary Information (SI) section.

Initially, *trans*-**21** was oxidized in an analogous fashion to the oxidation of **14** (Scheme 5). TLC analysis of the reaction revealed four products. However, GC-MS (gas chromatography-mass spectrometry) analysis revealed two pairs of diastereoisomers, the *N*-acetyloxindoles with molecular ions *m/z* 342 (60%, 4:1 ratio) and the N^a-H oxindoles with molecular ions *m/z* 300 (30%, 2:1 ratio), as well as two unidentified minor products (with molecular ions *m/z* 314, 10% total area).



Scheme 5. Synthesis of spiro-pyrrolidinyloxindoles **15** and **16** by DMD oxidation of N^a,N^b-diacetyl-THBC **14**. (a) Ac_2O/AcCl, Δ, 4 h (71% yield); (b) oxone, $NaHCO_3$, H_2O, acetone, 30 min, r.t.; (c) MeOH, cat. *p*TSA (10 mol%) (87%, 1:1 **16a/b**).

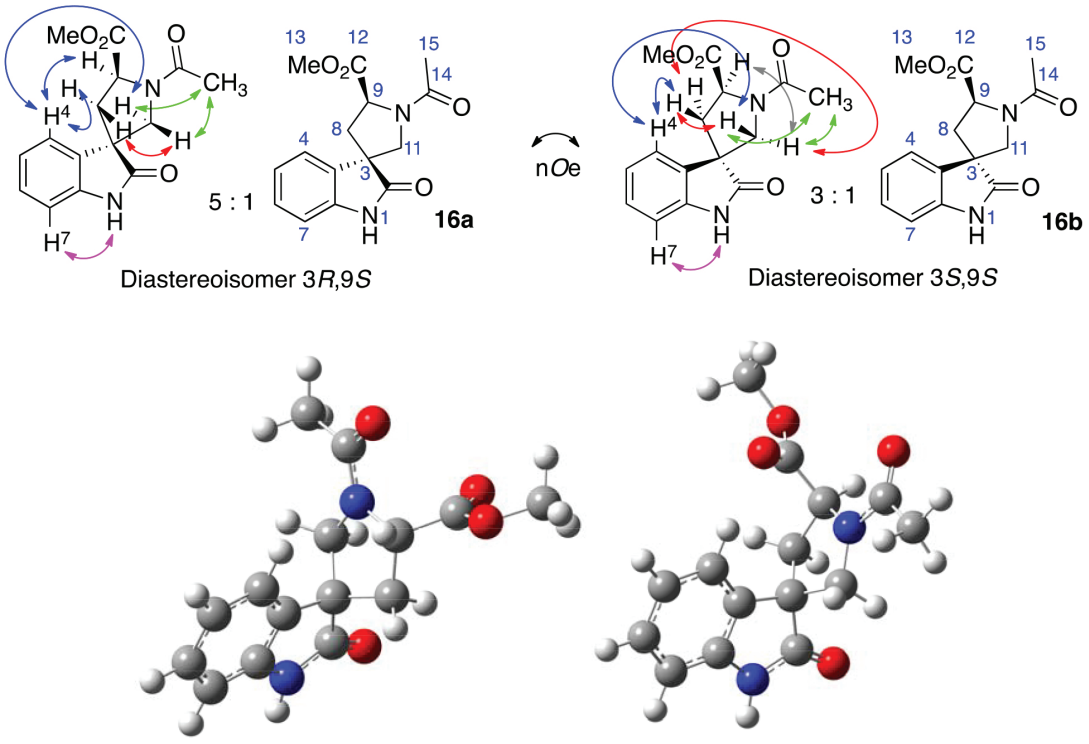


Figure 2. The stereochemistry of the diastereoisomers (**16a**-*R*,*S* on the left and **16b**-*S*,*S* on the right), relative to *L*-tryptophan, as determined by nOe interactions as well as the respective amide conformer populations for each diastereoisomer and DFT [B3LYP//6-31+G(d,p)] calculated minimum energy conformers of the diastereoisomers.

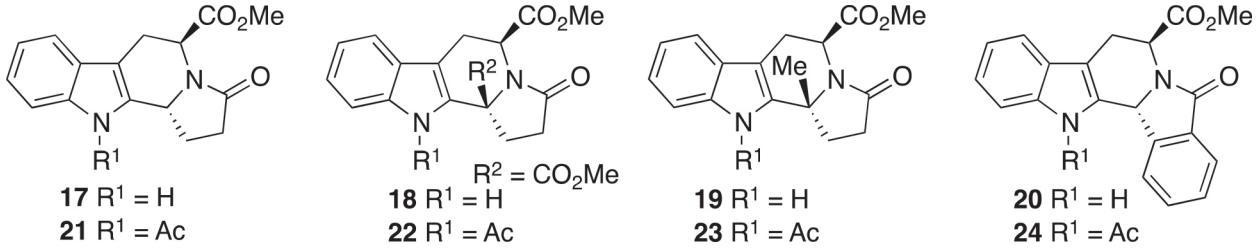
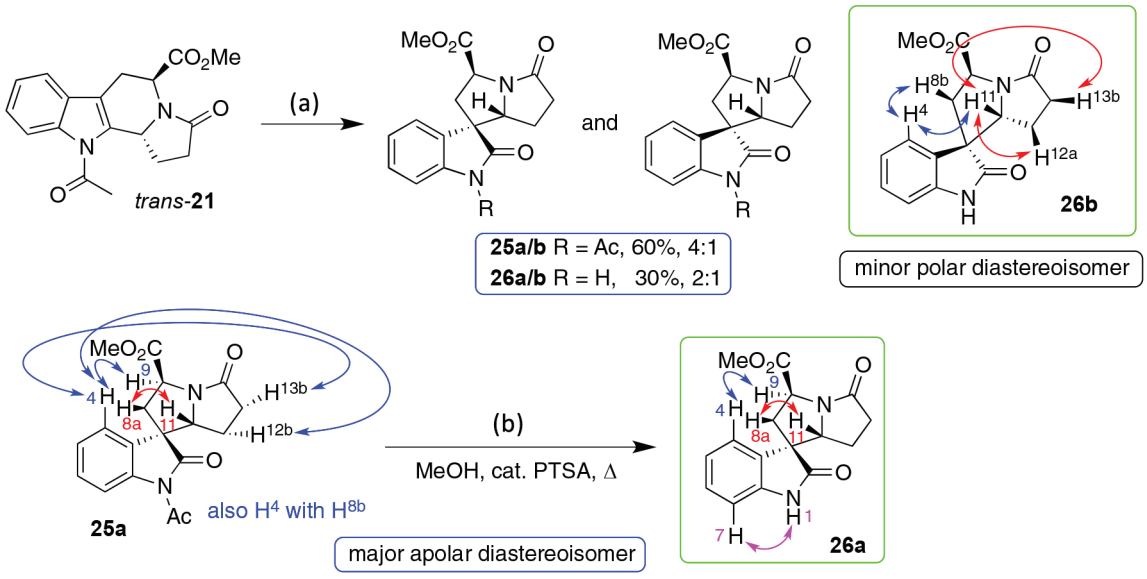


Figure 3. N^a-Acetyl tetrahydro-β-carboline derivatives (N^a-AcTHBC's) used to further investigate the oxidative rearrangement.

The principal apolar N^a-acetyloxindole diastereoisomer (**25a**) could be partially separated from the product mixture and was recrystallized from EtOAc. The structure was characterized by 2D NMR and the NOESY method was used to determine the relative stereochemistry based upon *L*-tryptophan (Scheme 6 and SI). N^a-Deacetylation of **25a** in MeOH with a catalytic quantity of *p*TSA gave the respective apolar N^a-H oxindole (**26a**) as determined by comparative TLC with the oxidation product mixture. As expected, determination of the relative stereochemistry of the N^a-H oxindole (**26a**) revealed this to be the same as the N^a-acetyl diastereoisomer **25a** (Scheme 6). This finding confirmed that epimerization of spiro-C3a, due to a retro-Mannich reaction of the spiro-pyrrolidinyl ring, was not observed to occur under the conditions used for N^a-deacetylation.

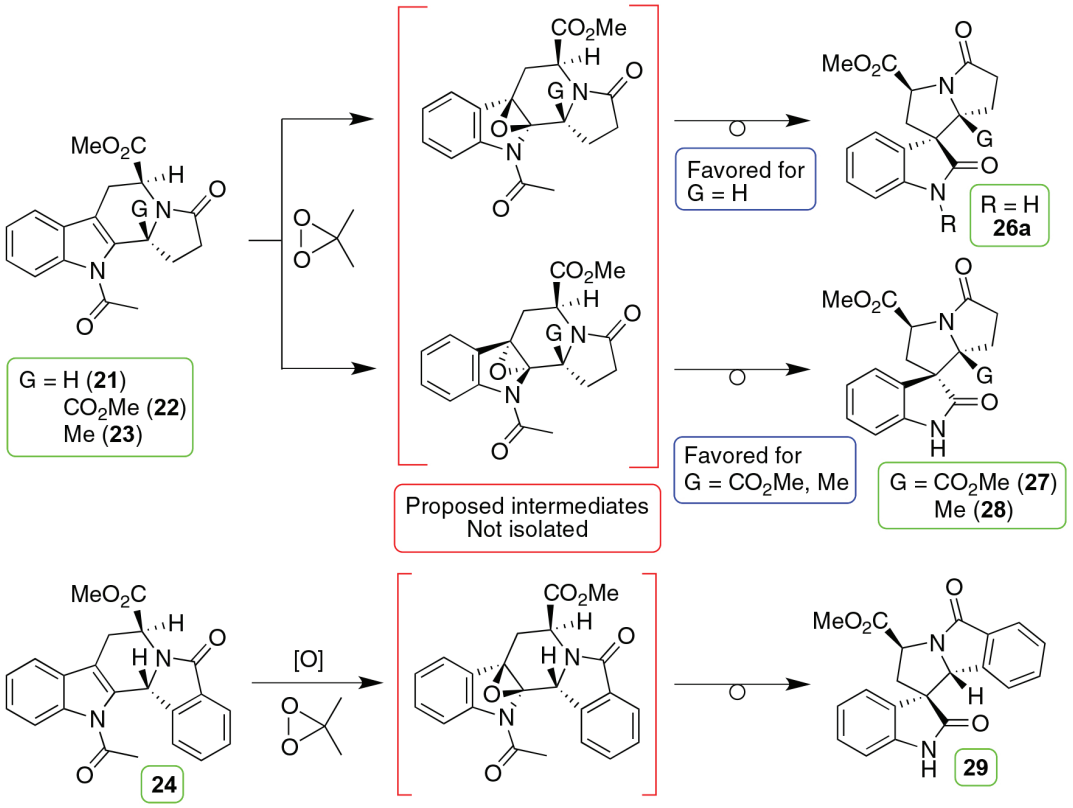
Based upon the observation that the N^a-H oxindoles **16a/b** (Scheme 5), obtained from the oxidation of the N^a,N^b-diacetyl THBC **14**, could be more readily separated, the oxidized product mixture (**25a/b//26a/b**) was N^a-deacetylated to give **26a/b**. However, the chromatographic separation of the N^a-H diastereoisomers **26a/b** proved to be more challenging. The polar N^a-H diastereoisomer **26b** was partially separated from the N^a-deacetylated mixture. The product was characterized by 2D NMR and the use of NOESY confirmed the inversion of the C3 spiro center, relative to the C9 and C11 asymmetric carbons (Scheme 6 and SI).

In continuation of the investigation, the N^a-acetyl derivatives (**22**-**24**) were oxidized in an analogous fashion and the crude products were subsequently N^a-deacetylated in methanolic HCl. The crude product was separated into two fractions using a Chromatotron (Harrison Research). The apolar component was generally found to be (by NMR analysis) a mixture of compounds whereas



Scheme 6. The oxidative rearrangement of *trans*-**21**. The observed nOe interactions for the apolar N^a-acetyl **25a** and N^a-H **26a** oxindoles as well as the polar N^a-H oxindole **26b** are indicated. (a) Oxone, $NaHCO_3$, acetone/H_2O; (b) MeOH, cat. *p*TSA, Δ. Complete atomic numbering of the structures is given with the respective 2D NMR interpretations in the SI section.

the polar, principal, component was found to be essentially a single diastereoisomer in the case of the products **27** (80% yield) and **28** (67% yield), and an estimated 5:1 mixture in the case of **29** (75% yield). The structures of the isolated polar products were characterized by 2D NMR and the relative stereochemistry was determined by the use of NOESY experiments (full details are given in the SI section). Scheme 7 summarizes the results and reveals how the substrate structure sterically influences the outcome of the oxidation reaction. Compound **27**



Scheme 7. Summary of the substrate stereochemical influence upon favored product structure in the oxidative rearrangement of the N^a-acetyl-pyrrolidinyltetrahydro-β-carbolines.

was recently reported by Schendera *et al.*[80] They obtained this compound via a 1,2-rearrangement of the 3-hydroxyindolenine. The spectroscopic data and the stereochemical assignments are equivalent. On the other hand, Bathula *et al.*[45] obtained what they claimed to be a mixture of diastereoisomers of **28** when they oxidized **19** (N^a-H substrate for preparation of the N^a-Ac derivative **23**, Figure 3) with dibromodimethylhydantoin (DBDMH) in AcOH/tetrahydrofuran (THF)/H_2O.

Based upon the studies of Zhang and Foote[81] and Adam *et al.*,[82] the oxidation of the N^a-acetylindole derivatives is proposed to occur through the formation of an epoxide intermediate that undergoes spontaneous rearrangement, below room temperature, to give the respective spiropyrrolidine-2-oxindole. With this in mind, density functional theory (DFT) calculations were used to investigate the interaction of DMD with N^a-acetyltetrahydrocarboline (**7**). Figure 4 portrays the Gibbs free energy (ΔG) for stationary points and the total electronic energy for the intrinsic reaction coordinate for oxygen atom transfer from DMD to **7**. Interestingly, for the gas phase calculation, as DMD approaches the indolic double bond, the oxygen atom transfer for the lowest energy transition state regioselectively occurs at C2. Following this, as the reaction coordinate relaxes, the indolic C3–C2–O angle closes to give the epoxide of **7** as the product.[92] The inclusion of an implicit solvation model (IEFPCM, solvent = water) in the calculation resulted in the smooth transfer of the oxygen atom to both C2 and C3 simultaneously, directly yielding the epoxide intermediate.

In a similar fashion, the reaction of DMD with **23** was calculated. The calculations revealed the differences in the energetics for oxygen atom transfer to the two faces (*cis* to the methyl and methyl carboxylate substituents or *trans* with respect to the same substituents) of the indolic double bond. The energetic change (ΔH and ΔG) upon conversion of a van der Waals complex of DMD with **23** via the transition state for oxygen atom transfer to the van der Waals complex of epoxide and acetone is graphically portrayed in Figure 5 (*cis* oxygen atom transfer is represented as coordinate A and *trans* oxygen atom transfer as coordinate B). The nature of the transition state was observed to be dependent upon the face to which the oxygen atom was being transferred. The sterically congested *cis* face resulted in oxygen atom transfer to C3 of the indolic double bond, where the adjacent methylene group is unsubstituted. On the other hand, the less congested *trans* face resulted in oxygen atom transfer to C2. The inclusion of an implicit solvation model gave similar results. For both intrinsic reaction coordinates, post transition state relaxation resulted in the formation of the respective epoxides. Notably, $\Delta\Delta G^{\ddagger}$ for the reaction coordinates was 2.45 kcal mol^{-1} (equivalent to a diastereoisomeric ratio of 98.5:1.5) and the inclusion of implicit solvation reduced this activation barrier to 1.84 kcal mol^{-1} (diastereoisomer ratio of 95.7:4.3). The facts that the epoxidation reaction is considerably exothermic (ca. 50 kcal mol^{-1}) and that the equilibrium for the epoxidation reaction is completely displaced in favor of the epoxide would imply that the observed diastereoselectivity for the formation of the 2-oxindole products is controlled by formation of the respective epoxides.

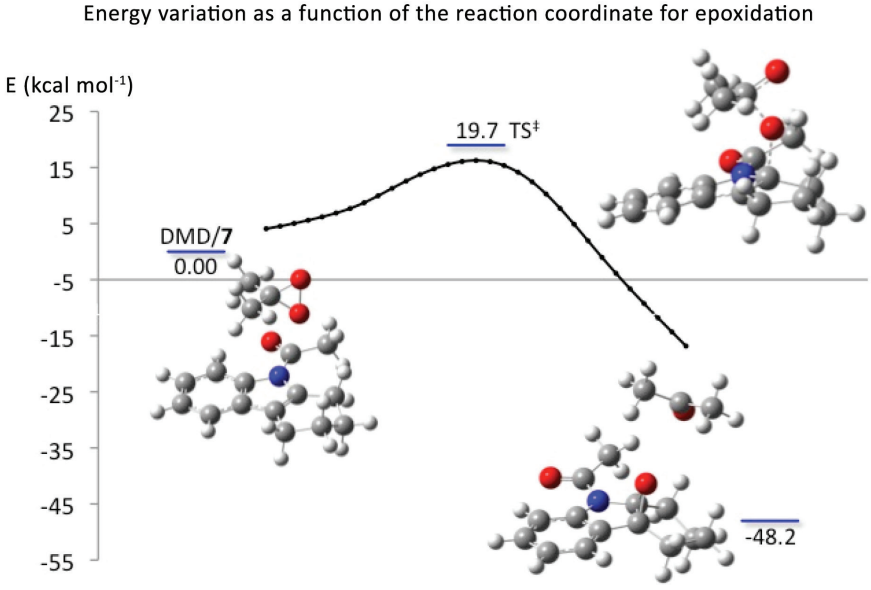


Figure 4. DFT (B3LYP//6-31+G(d)) calculated total electronic energy for the intrinsic reaction coordinate (—) for oxygen atom transfer from DMD to **7** and the Gibbs free energies (and structures) for the stationary points (—) of the reaction coordinate relative to the van der Waals complex DMD/**7**.

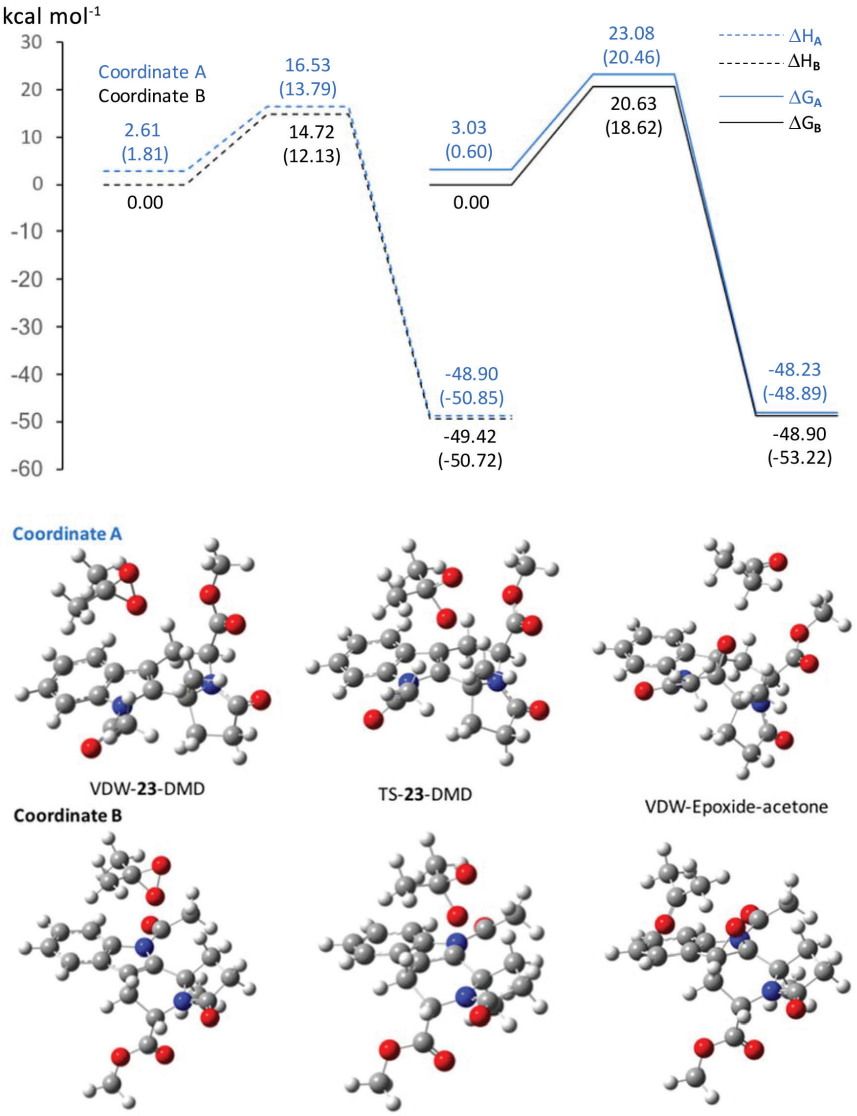


Figure 5. DFT (B3LYP//6-31+G(d)) calculated energies (ΔH and ΔG, values in parenthesis correspond to values calculated with implicit solvation, IEFPCM = water) and structures for stationary points for the epoxidation of **23** by DMD.

Adam *et al.*[82] proposed that rearrangement of the indole epoxides occurs by heterolysis of an epoxide C–O bond to generate a zwitterionic intermediate. Heterolysis of the C3–O epoxide bond would give rise to a benzylic cation 2-alkoxide zwitterion. A 1,2-alkyl group shift (Wagner-Meerwein rearrangement) from C2 to C3 would result in the respective 3-alkyl-2-oxindole. A polar protic reaction medium might be expected to stabilize a zwitterionic intermediate, although a concerted epoxide ring opening/alkyl group migration is not ruled out.

Attempts to locate both transition state for ring opening of the epoxide of **7** and minimum energy zwitterionic intermediate, with or without implicit solvation, were unsuccessful (B3LYP/6-31+G(d), IEFPCM = water). However, a transition state for the 1,2-alkyl group migration was located and this was used as a starting point for an intrinsic reaction coordinate calculation (IRC). The IRC calculation endpoints resembled a zwitterionic intermediate and the 2-oxindole product. Optimization of the IRC calculation endpoints resulted in the epoxide of **7** and the 2-oxindole **10** as minimum energy stationary points to either side of the transition state for the 1,2-alkyl group migration. The result is consistent with a concerted ring opening/ring contraction process. The Gibbs activation free energy ($\Delta G^{\ddagger}$) and enthalpy of activation ($\Delta H^{\ddagger}$) for the concerted process are 16.19 and 16.66 kcal mol^{-1}, respectively (Figure 6).

The small activation energies for both epoxidation and rearrangement, combined with the exothermicity of each step, result in a rapid room temperature reaction consistent with the short experimental reaction times and the absence of any observable intermediate.

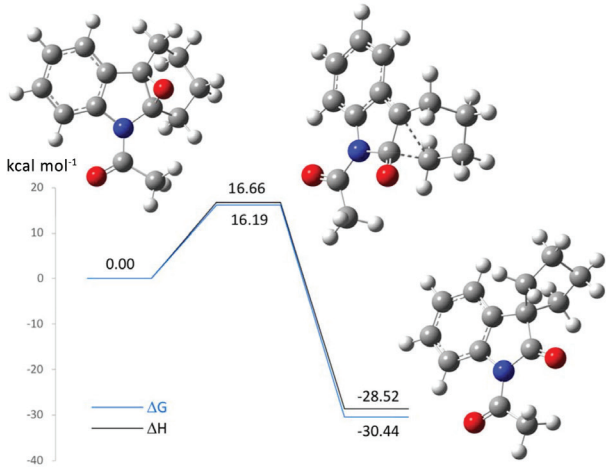


Figure 6. Relative energies (in kcal mol^{-1}) for stationary points along the reaction coordinate for 2-oxindole **10** formation from the epoxide of **7** (B3LYP//6-31+G(d) IEFPCM = water).

Conclusions

The oxidation of *N*-H-indole derivatives (**5** and **6**) using DMD generated *in situ* resulted in the cleavage of the indole ring as exemplified by the products **8** and **9**, whereas the oxidation of the THBC **4** gave a complex mixture of products. *N*-Acetylation of **6** and **4**, to give **7** and **14**, respectively, followed by oxidation with DMD cleanly resulted in the formation of the oxindoles **10** and the mixture of spiro-diastereoisomers N^a-acetyl **15a/b** and N^a-H **16a/b** in good yields (where **15** was transformed into **16** by N^a-deacetylation). The oxidative rearrangement was further explored with a small set of N^a-acetyl pyrrolidinyltetrahydro-β-carbolines (**21**-**24**). DMD oxidation stereoselectively gave the respective spiropyrrolidinyl-2-oxindole products without the observation of the formation of isolable hydroxyindolenine intermediates. The oxindole products were spectroscopically characterized and the stereoselectivity of the oxidative rearrangement reaction was qualitatively assessed from ratios of isolated products or by the use of GC-MS and or NMR. The stereochemistry, relative to *L*-tryptophan, of the oxindole products was determined by NOESY. The configuration of the spiro-center of the principal spiro-pyrrolidinyloxindole diastereoisomer was found to be substrate structure dependent.

DFT calculations of the intrinsic reaction coordinate for oxygen atom transfer from DMD to **7** were found to result in the formation of an intermediate epoxide, consistent with experimental results reported by Zhang and Foote.[81] A similar analysis of the epoxidation of **23** by DMD revealed a face selective epoxidation of the indolic double bond consistent with the experimental isolation of a single 2-oxindole diastereoisomer resulting from the oxidative rearrangement of the diastereoselectively formed epoxide intermediate. A DFT study using implicit solvation for rearrangement of epoxide-**7** to give **10** located a single transition state, characterized as a 1,2-alkyl group migration as a consequence of heterolysis of an epoxide C–O bond, and therefore a concerted epoxide ring opening/ring contraction process to give **10**.

Experimental

General

All commercial reagents were used as received. The products of the reactions were purified using a Chromatotron (Harrison Research, silica gel 60 PF_{254} with gypsum). Thin layer chromatography (TLC) was used to monitor the reactions (silica gel 60, 0.2 mm). NMR spectra were acquired using Bruker spectrometers (200, 300 and 500 MHz). The ^{1}H NMR data are given as the chemical shift δ (ppm), number of protons, multiplicity and the respective coupling constant(s) J (Hz). The ^{13}C NMR assignments (where given) are based upon distortionless enhancement by polarization transfer (DEPT) and/or interpretation of 2D spectra. The NMR spectra in $CDCl_3$ are referenced as residual $CHCl_3$ in ^{1}H NMR spectra (7.26 ppm) and as natural abundance ^{13}C (77.16 ppm) unless otherwise indicated. FTIR-ATR (Fourier transform infrared spectroscopy-attenuated total reflectance) spectra were recorded with a Nicolet Magna spectrometer. High-resolution mass spectra (HRMS) were obtained with a QTOF (Micromass) spectrometer. GC-MS analyses were performed with a Shimadzu (QP2010S) gas chromatograph coupled to a mass sensitive detector using an Agilent DB-5 column (30 m) and helium as carrier gas. Ionization was achieved by electron impact (70 eV). DFT calculations were performed using Gaussian 09C.[93] Procedures for the preparation of the substrates are given in the SI section.

General procedure for the oxidation reactions using dimethyl dioxirane generated *in situ*

Reactions were generally conducted on a scale of 1 to 10 mmol of the indolic substrate. The following procedure is representative. The substrate (10 mmol) was solubilized in aqueous acetone (50:45 mL) to which was added $NaHCO_3$ (3.4 equiv., 34 mmol). Subsequently, Oxone® (10 mmol) was added in portions during a period of 10 min at room temperature. CO_2 evolution was noted. After 30-60 min, TLC analysis of the reaction revealed the complete consumption of the respective substrate and the formation of the products. The reaction was diluted with aqueous NaCl solution (10%, 70 mL) and extracted

with CH_2Cl_2 (4 × 50 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product as an oil, which solidified with time. The crude products were N^a-deacetylated (see "N^a-Deacetylation of the oxidatively rearranged diastereoisomeric mixtures" section) unless otherwise stated. The substrates, methyl *N*-acetyltryptophan ester (**5**) and tetrahydrocarbazol (**6**), gave products resulting from oxidative cleavage of the indolic double bond (**8** and **9**, respectively). DMD oxidation of the substrate **7** gave the oxindole **10** in 83-92% yield, N^a-deacetylated product was not quantified.[81] The crude products were purified using a Chromatotron (eluent: hexane:EtOAc, 3:1).

Methyl (*S*)-2-acetamido-4-(2-formamidophenyl)-4-oxobutanoate (**8**)[85]

Yield 60%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.34 (1H, s), 8.71 (1H, d, *J* 8 Hz), 8.44 (1H, s), 7.91 (1H, d, *J* 8 Hz), 7.57 (1H, t, *J* 8 Hz), 7.16 (1H, t, *J* 8 Hz), 6.62 (1H, s), 3.78-3.70 (5H, m), 2.00 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$, ref. 77.0 ppm) δ 201.8, 171.6, 170.1, 159.9, 139.9, 135.8, 130.9, 123.2, 121.61, 120.9, 52.7, 48.1, 41.7, 22.9.

3,4,5,6-Tetrahydro-1*H*-benzo[*b*]azonine-2,7-dione (**9**)[88]

Yield 63%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.39 (1H, s), 7.56-7.35 (3H, m), 7.24-7.20 (1H, m), 2.84 (2H, bs), 2.19 (2H, bs), 1.83 (4H, bs); ^{13}C NMR (50 MHz, $CDCl_3$, ref. 77.0 ppm) δ 206.0, 176.7, 138.9, 134.6, 132.0, 128.5, 128.3, 127.8, 41.2, 32.2, 24.6, 24.4.

(3*R*,3'*S*,7'a*R*) 3'-Methyl N^a-acetyl 1,2,2',3',6',7'-hexahydro-2,5'-dioxo-spiro[3*H*-indole-3,1'-[1*H*]pyrrolizine]-3'(5'*H*)-carboxylate (**25a**)

From **21** (1.113 g, 3.4 mmol), the crude product was obtained as a mixture (1.121 g) of the N^a-acetyl (**25a/b**) and *N*-H (**26a/b**) diastereoisomers. The principal apolar N^a-acetyl diastereoisomer **25a** could be partially separated from the mixture chromatographically on silica using a CH_2Cl_2/EtOAc gradient (0-30%). Initial fractions gave **25a** (0.173 g from 0.550 g of the crude mixture), which was recrystallized from EtOAc, mp 213-4 °C. Posterior fractions were mixtures.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (1H, d, *J* 8.0 Hz), 7.32 (1H, dd, *J* 8.0, 7.6 Hz), 7.15 (1H, t, *J* 7.6 Hz), 6.79 (1H, d, *J* 7.6 Hz), 4.73 (1H, t, *J* 8.8 Hz), 4.47 (1H, dd, *J* 8.5, 4.7 Hz), 3.75 (3H, s), 2.80 (1H, dd, *J* 13.5, 8.8 Hz), 2.64 (dd, *J* 13.5, 8.8 Hz), 2.61 (3H, s), 2.56-2.62 (1H, m), 2.15 (1H, ddd, *J* 17.5, 10.8, 4.1 Hz), 2.07-1.96 (1H, m), 1.24-1.05 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3 (CO), 175.6 (CO), 171.0 (CO), 170.6 (CO), 139.9 (C), 129.6 (CH), 128.0 (C), 126.2 (CH), 122.9 (CH), 117.2 (CH), 70.0 (CH), 56.8 (C), 54.9 (CH), 53.0 (CH_3), 43.2 (CH_2), 33.1 (CH_2), 26.9 (CH_3), 18.9 (CH_2). Mass spectrum (electrospray ionization, ESI(+)) *m/z* $C_{18}H_{18}N_2O_5$ $[M + Na]^+$ calcd. 365.1108, obs. 365.1099.

N^a-Deacetylation of the oxidatively rearranged diastereoisomeric mixtures

The N^a-acetyl 1,2,3,4-tetrahydro-β-carbolines (**14** and **21**-**24**) gave mixtures of N^a-H and N^a-acetyl diastereoisomeric 2-oxindole products. Therefore, the product mixture was hydrolyzed to give the deacetylated N^a-H oxindole diastereoisomers. The crude diastereoisomeric mixture from the oxidative rearrangement reaction was heated for a period of 40 min in MeOH (10 mL) to which a few drops of AcCl (or 10 mol% of *p*TSA in relation to the substrate) had been added. TLC confirmed the complete transformation of the *N*-acetyloxindole diastereoisomers into the deacetylated *N*-H oxindole diastereoisomers. The reaction mixture was concentrated by evaporating the volatiles under reduced pressure, and the crude products were partitioned between aqueous 10% $NaHCO_3$ and EtOAc. The organic phase was separated, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude products were purified using the Chromatotron (eluent: hexane:EtOAc, 3:1 unless otherwise indicated).

Methyl (5'*S*)-1'-acetyl-2-oxo-1*H*-spiro[indole-3,3'-pyrrolidine]-5'-carboxylate (**16a/b**)

Yield 87% (**16a**:**16b**, 1:1).

Methyl (3*R*,5'*S*)-1'-acetyl-2-oxo-1*H*-spiro[indole-3,3'-pyrrolidine]-5'-carboxylate (**16a**)

IR (ATR) ν / cm^{-1} 3292, 3093, 2882, 1744, 1717, 1619, 1487, 1472, 1442, 1366, 1267, 1200, 1177, 1108, 1036, 887, 867, 779, 758; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.21 (1H, s), 7.27 (1H, td, *J* 1.5, 7.6 Hz), 7.15-7.05 (2H, m), 6.99 (1H, d, *J* 7.8 Hz), 4.86 (1H, t, *J* 9.5 Hz), 4.05 (1H, d, *J* 10.1 Hz), 3.77 (3H, s), 3.67 (1H, dd, ^4J_W 1.5, 10.1 Hz), 2.56 (1H, dd, *J* 9.5, 12.8 Hz), 2.40 (1H, ddd, ^4J_W 1.5, 8.1, 12.8 Hz), 2.10 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.3 (CO), 171.7 (CO), 169.7 (CO), 140.2 (C), 132.9 (C), 129.0 (CH), 123.4 (CH), 122.3 (CH), 110.7 (CH), 58.5 (CH), 56.4 (CH_2), 53.4 (C), 52.6 (OCH_3), 39.2 (CH_2), 22.4 (CH_3). Mass spectrum (ESI(+)) *m/z* $C_{15}H_{16}N_2O_4$ $[M + Na]^+$ calcd. 311.1003, obs. 311.0993; $[2M + Na]^+$ calcd. 599.2113, obs. 599.2103.

Methyl (3*S*,5'*S*)-1'-acetyl-2-oxo-1*H*-spiro[indole-3,3'-pyrrolidine]-5'-carboxylate (**16b**)

IR (ATR) ν / cm^{-1} 3230, 3068, 3021, 2950, 2867, 1763, 1723, 1621, 1467, 1452, 1439, 1404, 1336, 1261, 1189,

1176, 1150, 1104, 768, 759, 708; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.29 (1H, s), 7.30 (1H, dd, *J* 1.1, 7.7 Hz), 7.25 (1H, td, *J* 1.1, 7.7 Hz), 7.05 (1H, td, *J* 1.1, 7.7 Hz), 6.95 (1H, d, *J* 7.7 Hz), 4.93 (1H, t, *J* 8.3 Hz), 3.92 (2H, s), 3.77 (3H, s), 2.66 (1H, dd, *J* 8.3, 13.3 Hz), 2.30 (1H, dd, *J* 8.3, 13.3 Hz), 2.10 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.9 (CO), 172.6 (CO), 169.5 (CO), 141.2 (C), 129.2 (CH), 129.1 (C), 123.3 (CH), 123.1 (CH), 110.5 (CH), 58.9 (CH), 55.7 (CH), 52.9 (C), 52.5 (OCH_3), 39.0 (CH_2), 22.4 (CH_3). Mass spectrum (ESI(+)) *m/z* $C_{15}H_{16}N_2O_4$ $[M + Na]^+$ calcd. 311.1003, obs. 311.0999; $[2M + Na]^+$ calcd. 599.2113, obs. 599.2113.

(3'*S*,7'a*R*) 3'-Methyl 1,2,2',3',6',7'-hexahydro-2,5'-dioxo-spiro[3*H*-indole-3,1'-[1*H*]pyrrolizine]-3'(5'*H*)-carboxylate (**26a/b**)

A part of the crude product mixture of **25a/b** and **26a/b** (0.550 g) was hydrolyzed to give a mixture of **26a/b**. This was chromatographically separated using CH_2Cl_2:EtOAc (9:1 v/v) to give the apolar **26a** (347 mg) and the polar **26b** (131 mg).

Apolar (3*R*,3'*S*,7'a*R*) 3'-methyl 1,2,2',3',6',7'-hexahydro-2,5'-dioxo-spiro[3*H*-indole-3,1'-[1*H*]pyrrolizine]-3'(5'*H*)-carboxylate (**26a**)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (1H, s, NH), 7.28 (1H, td, *J* 7.7, 1.1 Hz), 7.04 (1H, td, *J* 7.6, 1.0 Hz), 6.99 (1H, d, *J* 7.8 Hz), 6.86 (1H, dd, *J* 7.6, 1.1 Hz), 4.80 (1H, t, *J* 8.8 Hz), 4.53 (1H, dd, *J* 8.5, 4.7 Hz), 2.82 (1H, dd, *J* 13.3, 9.1 Hz), 2.73-2.61 (m, 2H), 2.25 (1H, ddd, *J* 17.6, 11.0, 4.2 Hz), 2.08 (1H, dddt, *J* 17.1, 8.7, 7.0, 4.4 Hz), 1.26 (1H, dddd, *J* 13.7, 11.0, 7.6, 4.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3 (CO), 176.0 (CO), 171.3 (CO), 140.8 (C), 129.3 (C), 129.2 (CH), 123.5 (CH), 123.5 (CH), 110.7 (CH), 69.1 (CH), 56.9 (C), 54.9 (CH), 52.9 (CH_3), 41.9 (CH_2), 33.1 (CH_2), 18.9 (CH_2). Mass spectrum (ESI(+)) *m/z* $C_{16}H_{16}N_2O_4$ $[M + Na]^+$ calcd. 323.1002, obs. 323.0989.

Polar (3*S*,3'*S*,7'a*R*) 3'-methyl 1,2,2',3',6',7'-hexahydro-2,5'-dioxo-spiro[3*H*-indole-3,1'-[1*H*]pyrrolizine]-3'(5'*H*)-carboxylate (**26b**)

IR (ATR) ν / cm^{-1} 3209, 3041, 3000, 2944, 1703, 1669, 1619, 1472, 1466, 1432, 1288, 1234, 1183, 756; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.12 (1H, s), 7.28-7.24 (1H, m), 7.22 (1H, dd, *J* 7.5, 1.1 Hz), 7.07 (1H, td, *J* 7.6, 0.9 Hz), 6.98 (1H, d, *J* 7.8 Hz), 4.92 (1H, t, *J* 8.4 Hz), 4.45 (1H, dd, *J* 8.7, 4.3 Hz), 3.80 (3H, s), 2.84 (1H, dd, *J* 13.7, 8.5 Hz), 2.70-2.60 (1H, m), 2.58-2.49 (2H, m), 2.19-2.08 (1H, m), 1.80-1.68 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1 (CO), 177.4 (CO), 172.4 (CO), 141.4 (C), 129.3 (CH), 127.2 (C), 123.1 (CH), 122.9 (CH), 110.7 (CH), 69.1 (CH), 55.8 (C), 55.7 (CH), 52.8 (CH_3), 41.4 (CH_2), 32.6 (CH_2), 19.6 (CH_2). Mass spectrum (ESI(+)) *m/z* $C_{16}H_{16}N_2O_4$ $[M + Na]^+$ calcd. 323.1002, obs. 323.0997.

(3*S*,3'*S*,7'a*R*) 3',7'a-Dimethyl 1,2,2',3',6',7'-hexahydro-2,5'-dioxo-spiro[3*H*-indole-3,1'-[1*H*]pyrrolizine]-3',7'a(5'*H*)-dicarboxylate (**27**)

A single diastereoisomer was isolated in 80% yield. IR (ATR) ν / cm^{-1} 3244, 2956, 2926, 2854, 1721, 1713, 1699, 1620, 1472, 1438, 1333, 1232, 1192, 1078, 756; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (1H, s), 7.24 (1H, td, *J* 7.6, 1.3 Hz), 7.05-6.97 (2H, m), 6.86 (1H, d, *J* 7.4 Hz), 5.01 (1H, t, *J* 8.4 Hz), 3.80 (3H, s), 3.75 (3H, s), 3.01 (1H, dd, *J* 7.9, 13.8 Hz), 2.71 (1H, dd, *J* 8.9, 13.8 Hz), 2.75-2.60 (2H, m), 2.52-2.47 (1H, m), 2.06-2.02 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4 (CO), 177.6 (CO), 171.6 (CO), 171.0 (CO), 141.7 (C), 129.8 (CH), 124.6 (C), 123.8 (CH), 122.8 (CH), 110.9 (CH), 78.1 (C), 58.9 (C), 56.9 (CH), 52.7 (CH_3), 52.5 (CH_3), 38.6 (CH_2), 32.4 (CH_2), 23.7 (CH_2). Mass spectrum (ESI(+)) *m/z* $C_{18}H_{18}N_2O_6$ $[M + Na]^+$ calcd. 381.1062, obs. 381.1057.

(3*S*,3'*S*,7'a*R*) 3'-Methyl 1,2,2',3',6',7'-hexahydro-7'a-methyl-2,5'-dioxo-spiro[3*H*-indole-3,1'-[1*H*]pyrrolizine]-3'(5'*H*)-carboxylate (**28**)

A single diastereoisomer was isolated in 67% yield. IR (ATR) ν / cm^{-1} 3250, 2983, 2958, 2926, 1709, 1680, 1666, 1619, 1472, 1435, 1334, 1241, 1178, 1110, 754; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.69 (1H, s), 7.35-7.15 (2H, m), 7.04 (1H, t, *J* 7.6 Hz), 6.94 (1H, d, *J* 7.6 Hz), 4.88 (1H, t, *J* 8.7 Hz), 3.79 (3H, s), 2.80-2.65 (3H, m), 2.47 (1H, ddd, *J* 3.7, 11.1, 17.5 Hz), 2.10-1.90 (1H, m), 1.85-1.60 (1H, m), 1.58 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.6 (CO), 177.0 (CO), 172.7 (CO), 141.8 (C), 129.3 (CH), 126.4 (C), 125.7 (CH), 122.6 (CH), 110.5 (CH), 72.6 (C), 59.2 (C), 54.6 (CH), 52.7 (OCH_3), 39.6 (CH_2), 33.0 (CH_2), 29.2 (CH_2), 26.5 (CH_3). Mass spectrum (ESI(+)) *m/z* $C_{17}H_{18}N_2O_4$ $[M + Na]^+$ calcd. 337.1211, obs. 337.1158; $[2M + Na]^+$ calcd. 651.2525, obs. 651.2425.

(3*R*,3'*S*,7'a*R*) 3'-Methyl 1,2,2',3'-tetrahydro-2,5'-dioxo-spiro[3*H*-indole-3,1'-benzo[6',7'][1*H*]pyrrolizine]-3'(5'*H*)-carboxylate (**29**)

Yield 75% (approximately 5:1 ratio of diastereoisomers); IR (ATR) ν / cm^{-1} 3263, 2953, 2923, 2848, 1744, 1724, 1681, 1472, 1370, 1307, 1174, 757, 723. Data for the principal isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (1H, s), 7.73 (1H, d, *J* 7.4 Hz), 7.31 (1H, t, *J* 7.4 Hz), 7.28 (1H, d, *J* 7.4 Hz), 7.03 (1H, d, *J* 7.4 Hz), 7.02 (1H, t, *J* 7.6 Hz), 6.82 (1H, d, *J* 7.6 Hz), 6.69 (1H, t, *J* 7.6 Hz), 6.48 (1H, d, *J* 7.6 Hz), 5.42

(1H, s), 4.98 (1H, dd, *J* 8.5, 9.5 Hz), 3.86 (3H, s), 3.19 (1H, dd, *J* 9.5, 13.3 Hz), 2.90 (1H, dd, *J* 8.5, 13.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0 (CO), 171.4 (CO), 170.9 (CO), 141.8 (C), 139.7 (C), 133.6 (C), 132.5 (CH), 129.2 (CH), 128.8 (CH), 128.6 (C), 124.2 (CH), 123.3 (CH), 123.2 (CH), 122.1 (CH), 110.3 (CH), 71.0 (CH), 55.4 (C), 55.0 (CH), 53.0 (OCH_3), 43.9 (CH_2). Mass spectrum (ESI(+)) *m/z* $C_{20}H_{16}N_2O_4$ $[M + Na]^+$ calcd. 371.1007, obs. 371.1002. $[2M + Na]^+$ calcd. 719.2117, obs. 719.2112.

Supplementary Information

Supplementary data are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgments

The authors thank FAPERJ, CAPES and CNPq for financial support and the mass spectrometry facilities at IPPN and CEMBIO (UFRJ) for the HRMS.

References

1. Galliford, C. V.; Scheidt, K. A.; *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.
2. Yu, B.; Yu, D. Q.; Liu, H. M.; *Eur. J. Med. Chem.* **2015**, *97*, 673.
3. Lin, H.; Danishefsky, S. J.; *Angew. Chem., Int. Ed.* **2003**, *42*, 36.
4. Williams, R. M.; Cox, R. J.; *Acc. Chem. Res.* **2003**, *36*, 127.
5. Jossang, A.; Jossang, P.; Hadi, H. A.; Sevenet, T.; Bodo, B.; *J. Org. Chem.* **1991**, *56*, 6527.
6. Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Vit, I.; Willing, R. I.; *Phytochemistry* **1998**, *48*, 437.
7. Pellegrini, C.; Weber, M.; Borschberg, H.-J.; *Helv. Chim. Acta* **1996**, *79*, 151.
8. Kang, T.-H.; Murakami, Y.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H.; Matsumoto, K.; *Life Sci.* **2004**, *76*, 331; Kang, T.-H.; Murakami, Y.; Matsumoto, K.; Takayama, H.; Kitajima, M.; Aimi, N.; Watanabe, H.; *Eur. J. Pharmacol.* **2002**, *455*, 27; Trager, W. F.; Lee, C. M.; Phillipson, J. D.; Haddock, R. E.; Dwuma-Badu, D.; Beckett, A. H.; *Tetrahedron* **1968**, *24*, 523.
9. Yeoh, G. B.; Chan, K. C.; Morsingh, F.; *Tetrahedron Lett.* **1966**, 931; Chan, K. C.; Morsingh, F.; Yeoh, G. B.; *J. Chem. Soc. C* **1966**, 2245; Bacher, N.; Tiefenthaler, M.; Sturm, S.; Stuppner, H.; Ausserlechner, M. J.; Kofler, R.; Konwalinka, G.; *Br. J. Haematol.* **2006**, *132*, 615; Paniagua-Perez, R.; Madrigal-Bujaidar, E.; Molina-Jasso, D.; Reyes-Cadena, S.; Alvarez-Gonzalez, I.; Sanchez-Chapul, L.; Perez-Gallaga, J.; *Basic Clin. Pharmacol. Toxicol.* **2009**, *104*, 222.
10. Sakai, S.; Aimi, N.; Yamaguchi, K.; Ohhira, H.; Hori, K.; Haginiwa, J.; *Tetrahedron Lett.* **1975**, 715.
11. Fonseca, G. O.; Wang, Z.-J.; Namjoshi, O. A.; Deschamps, J. R.; Cook, J. M.; *Tetrahedron Lett.* **2015**, *56*, 3052.
12. Wong, W.-H.; Lim, P.-B.; Chuah, C.-H.; *Phytochemistry* **1996**, *41*, 313; Elderfield, R. C.; Gilman, R. E.; *Phytochemistry* **1972**, *11*, 339.
13. Cui, C. B.; Kakeya, H.; Osada, H.; *J. Antibiot.* **1996**, *49*, 832; Cui, C.-B.; Kakeya, H.; Osada, H.; *Tetrahedron* **1996**, *52*, 12651; Afiyatullov, S. S.; Zhuravleva, O. I.; Chaikina, E. L.; Anisimov, M. M.; *Chem. Nat. Compd.* **2012**, *48*, 95.
14. Lerchner, A.; Carreira, E. M.; *Chem. - Eur. J.* **2006**, *12*, 8208; Bassleer, R.; Depauw-Gillet, M. C.; Massart, B.; Marnette, J. M.; Wiliquet, P.; Caprasse, M.; Angenot, L.; *Planta Med.* **1982**, *45*, 123; Dideberg, O.; Lamotte-Brasseur, J.; Dupont, L.; Campsteyn, H.; Vermeire, M.; Angenot, L.; *Acta Crystallogr., Sect. B* **1977**, *B33*, 1796.
15. da Silva, J. F. M.; Garden, S. J.; Pinto, A. C.; *J. Braz. Chem. Soc.* **2001**, *12*, 273.
16. Marti, C.; Carreira, E. M.; *Eur. J. Org. Chem.* **2003**, 2209.
17. Zhou, F.; Liu, Y.-L.; Zhou, J.; *Adv. Synth. Catal.* **2010**, *352*, 1381.
18. Singh, G. S.; Desta, Z. Y.; *Chem. Rev.* **2012**, *112*, 6104.
19. Dalpozzo, R.; Bartoli, G.; Bencivenni, G.; *Chem. Soc. Rev.* **2012**, *41*, 7247.
20. Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K.; *Org. Biomol. Chem.* **2012**, *10*, 5165.
21. Hong, L.; Wang, R.; *Adv. Synth. Catal.* **2013**, *355*, 1023.
22. Cheng, D. J.; Ishihara, Y.; Tan, B.; Barbas, C. F.; *ACS Catal.* **2014**, *4*, 743.
23. Chen, L.; Yin, X. P.; Wang, C. H.; Zhou, J.; *Org. Biomol. Chem.* **2014**, *12*, 6033.
24. Santos, M. M. M.; *Tetrahedron* **2014**, *70*, 9735.
25. Dalpozzo, R.; *Adv. Synth. Catal.* **2017**, *359*, 1772.
26. Lo, M. M. C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L.; *J. Am. Chem. Soc.* **2004**, *126*, 16077.
27. Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schuermann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H.; *Nat. Chem.* **2010**, *2*, 735.
28. Lu, Y.; Nikolovska-Coleska, Z.; Fang, X.; Gao, W.; Shangary, S.; Qiu, S.; Qin, D.; Wang, S.; *J. Med. Chem.* **2006**, *49*, 3759; Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, S.; *J. Med. Chem.* **2006**, *49*, 3432; Ding, K.; Wang, G.; Deschamps, J. R.; Parrish, D. A.; Wang, S.; *Tetrahedron Lett.* **2005**, *46*, 5949; Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qiu, S.; Ding, Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Tomita, Y.; Parrish, D. A.; Deschamps, J. R.; Wang, S.; *J. Am. Chem. Soc.* **2005**, *127*, 10130.
29. Zhao, Y.; Yu, S.; Sun, W.; Liu, L.; Lu, J.; McEachern, D.; Shargary, S.; Bernard, D.; Li, X.; Zhao, T.; Zou, P.; Sun, D.; Wang, S.; *J. Med. Chem.* **2013**, *56*, 5553; Zhao, Y.; Liu, L.; Sun, W.; Lu, J.; McEachern, D.; Li, X.; Yu, S.; Bernard, D.;

Ochsenbein, P.; Ferey, V.; Carry, J.-C.; Deschamps, J. R.; Sun, D.; Wang, S.; *J. Am. Chem. Soc.* **2013**, *135*, 7223; Aguilar, A.; Sun, W.; Liu, L.; Lu, J.; McEachern, D.; Bernard, D.; Deschamps, J. R.; Wang, S.; *J. Med. Chem.* **2014**, *57*, 10486; Zhao, Y.; Aguilar, A.; Bernard, D.; Wang, S.; *J. Med. Chem.* **2015**, *58*, 1038; Gollner, A.; Rudolph, D.; Arnhof, H.; Bauer, M.; Blake, S. M.; Boehmelt, G.; Cockroft, X. L.; Dahmann, G.; Ettmayer, P.; Gerstberger, T.; Karolyi-Oezguer, J.; Kessler, D.; Kofink, C.; Ramharter, J.; Rinnenthal, J.; Savchenko, A.; Schnitzer, R.; Weinstabl, H.; Weyer-Czernilofsky, U.; Wunberg, T.; McConnell, D. B.; *J. Med. Chem.* **2016**, *59*, 10147; Aguilar, A.; Lu, J.; Liu, L.; Du, D.; Bernard, D.; McEachern, D.; Przybranowski, S.; Li, X.; Luo, R.; Wen, B.; Sun, D.; Wang, H.; Wen, J.; Wang, G.; Zhai, Y.; Guo, M.; Yang, D.; Wang, S.; *J. Med. Chem.* **2017**, *60*, 2819.

30. David, N.; Pasceri, R.; Kitson, R. R. A.; Pradal, A.; Moody, C. J.; *Chem. - Eur. J.* **2016**, *22*, 10867.
31. Suetsugu, S.; Tsukano, C.; Takemoto, Y.; *Eur. J. Org. Chem.* **2016**, *2016*, 108.
32. Bian, Z.; Marvin, C. C.; Pettersson, M.; Martin, S. F.; *J. Am. Chem. Soc.* **2014**, *136*, 14184.
33. Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S.; *J. Am. Chem. Soc.* **2008**, *130*, 17938.
34. Yang, J.; Wearing, X. Z.; Le Quesne, P. W.; Deschamps, J. R.; Cook, J. M.; *J. Nat. Prod.* **2008**, *71*, 1431.
35. Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A.; *Org. Lett.* **2008**, *10*, 4009.
36. Poriel, C.; Lachia, M.; Wilson, C.; Davies, J. R.; Moody, C. J.; *J. Org. Chem.* **2007**, *72*, 2978.
37. Lachia, M.; Poriel, C.; Slawin, A. M. Z.; Moody, C. J.; *Chem. Commun.* **2007**, 286.
38. Deiters, A.; Pettersson, M.; Martin, S. F.; *J. Org. Chem.* **2006**, *71*, 6547.
39. Baran, P. S.; Richter, J. M.; *J. Am. Chem. Soc.* **2005**, *127*, 15394.
40. Williams, R. M.; Cao, J.; Tsujishima, H.; Cox, R. J.; *J. Am. Chem. Soc.* **2003**, *125*, 12172.
41. Takayama, H.; Fujiwara, R.; Kasai, Y.; Kitajima, M.; Aimi, N.; *Org. Lett.* **2003**, *5*, 2967.
42. Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F.; *J. Am. Chem. Soc.* **2001**, *123*, 8003.
43. Powell, N. A.; Kohrt, J. T.; Filipski, K. J.; Kaufman, M.; Sheehan, D.; Edmunds, J. E.; Delaney, A.; Wang, Y.; Bourbonais, F.; Lee, D.-Y.; Schwende, F.; Sun, F.; McConnell, P.; Catana, C.; Chen, H.; Ohren, J.; Perrin, L. A.; *Bioorg. Med. Chem. Lett.* **2012**, *22*, 190.
44. Chen, L.; Xie, J.; Song, H.; Liu, Y.; Gu, Y.; Wang, L.; Wang, Q.; *J. Agric. Food Chem.* **2016**, *64*, 6508; Li, Z.; Li, Z.; Lin, Y.; Meng, Z.; Ding, G.; Cao, L.; Li, N.; Liu, W.; Xiao, W.; Wu, X.; Xu, J.; *Chem. Biol. Drug Des.* **2015**, *86*, 523; Efremov, I. V.; Vajdos, F. F.; Borzilleri, K. A.; Capetta, S.; Chen, H.; Dorff, P. H.; Dutra, J. K.; Goldstein, S. W.; Mansour, M.; McColl, A.; Noell, S.; Oborski, C. E.; O'Connell, T. N.; O'Sullivan, T. J.; Pandit, J.; Wang, H.; Wei, B.; Withka, J. M.; *J. Med. Chem.* **2012**, *55*, 9069; Pumphrey, A. L.; Dong, H.; Driver, T. G.; *Angew. Chem., Int. Ed.* **2012**, *51*, 5920; Nagata, K.; Ishikawa, H.; Tanaka, A.; Miyazaki, M.; Kanemitsu, T.; Itoh, T.; *Heterocycles* **2010**, *81*, 1791; White, J. D.; Li, Y.; Ihle, D. C.; *J. Org. Chem.* **2010**, *75*, 3569; Hart, D. J.; Oba, G.; *Tetrahedron Lett.* **2007**, *48*, 7069; Walker, S. J.; Hart, D. J.; *Tetrahedron Lett.* **2007**, *48*, 6214; Li, C.; Chan, C.; Heimann, A. C.; Danishefsky, S. J.; *Angew. Chem., Int. Ed.* **2007**, *46*, 1444.
45. Bathula, C.; Dangi, P.; Hati, S.; Agarwal, R.; Munshi, P.; Singh, A.; Singh, S.; Sen, S.; *New J. Chem.* **2015**, *39*, 9281.
46. Zhang, B.; Zheng, W.; Wang, X.; Sun, D.; Li, C.; *Angew. Chem., Int. Ed.* **2016**, *55*, 10435.
47. Mercado-Marin, E. V.; Garcia-Reynaga, P.; Romminger, S.; Pimenta, E. F.; Romney, D. K.; Lodewyk, M. W.; Williams, D. E.; Andersen, R. J.; Miller, S. J.; Tantillo, D. J.; Berlinck, R. G. S.; Sarpong, R.; *Nature* **2014**, *509*, 318.
48. Han, S.; Morrison, K. C.; Hergenrother, P. J.; Movassaghi, M.; *J. Org. Chem.* **2014**, *79*, 473.
49. Bian, Z.; Marvin, C. C.; Martin, S. F.; *J. Am. Chem. Soc.* **2013**, *135*, 10886.
50. Qi, X.; Bao, H.; Tambar, U. K.; *J. Am. Chem. Soc.* **2011**, *133*, 10050.
51. Finefield, J. M.; Williams, R. M.; *J. Org. Chem.* **2010**, *75*, 2785.
52. Miller, K. A.; Tsukamoto, S.; Williams, R. M.; *Nat. Chem.* **2009**, *1*, 63.
53. Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M.; *Angew. Chem., Int. Ed.* **2008**, *47*, 3573.
54. Greshock, T. J.; Williams, R. M.; *Org. Lett.* **2007**, *9*, 4255.
55. Greshock, T. J.; Grubbs, A. W.; Williams, R. M.; *Tetrahedron* **2007**, *63*, 6124.
56. Artman III, G. D.; Grubbs, A. W.; Williams, R. M.; *J. Am. Chem. Soc.* **2007**, *129*, 6336.
57. Greshock, T. J.; Grubbs, A. W.; Tsukamoto, S.; Williams, R. M.; *Angew. Chem., Int. Ed.* **2007**, *46*, 2262.
58. Grubbs, A. W.; Artman III, G. D.; Tsukamoto, S.; Williams, R. M.; *Angew. Chem., Int. Ed.* **2007**, *46*, 2257.
59. Mercado-Marin, E. V.; Sarpong, R.; *Chem. Sci.* **2015**, *6*, 5048.
60. Umehara, A.; Ueda, H.; Tokuyama, H.; *Org. Lett.* **2014**, *16*, 2526.
61. Mundal, D. A.; Sarpong, R.; *Org. Lett.* **2013**, *15*, 4952.
62. Liu, S.; Hao, X.-J.; *Tetrahedron Lett.* **2011**, *52*, 5640.
63. Guo, C.; Song, J.; Luo, S.-W.; Gong, L.-Z.; *Angew. Chem., Int. Ed.* **2010**, *49*, 5558.
64. Suarez-Castillo, O. R.; Melendez-Rodriguez, M.; Contreras-Martinez, Y. M. A.; Alvarez-Hernandez, A.; Morales-Rios, M. S.; Joseph-Nathan, P.; *Nat. Prod. Commun.* **2009**, *4*, 797.
65. Pettersson, M.; Knueppel, D.; Martin, S. F.; *Org. Lett.* **2007**, *9*, 4623.

66. Guerrero, C. A.; Sorensen, E. J.; *Org. Lett.* **2011**, *13*, 5164.
67. Medeiros, M. R.; Schaus, S. E.; Porco Jr., J. A.; *Org. Lett.* **2011**, *13*, 4012.
68. Kolundzic, F.; Noshi, M. N.; Tjandra, M.; Movassaghi, M.; Miller, S. J.; *J. Am. Chem. Soc.* **2011**, *133*, 9104.
69. Sun, M.; Hao, X.-Y.; Liu, S.; Hao, X.-J.; *Tetrahedron Lett.* **2013**, *54*, 692.
70. Jiang, X.; Yang, J.; Zhang, F.; Yu, P.; Yi, P.; Sun, Y.; Wang, Y.; *Org. Lett.* **2016**, *18*, 3154.
71. Baran, P. S.; Maimone, T. J.; Richter, J. M.; *Nature* **2007**, *446*, 404.
72. Wearing, X. Z.; Cook, J. M.; *Org. Lett.* **2002**, *4*, 4237.
73. Kato, H.; Nakahara, T.; Yamaguchi, M.; Kagiyama, I.; Finefield, J. M.; Sunderhaus, J. D.; Sherman, D. H.; Williams, R. M.; Tsukamoto, S.; *Tetrahedron Lett.* **2015**, *56*, 247; Sunderhaus, J. D.; McAfoos, T. J.; Finefield, J. M.; Kato, H.; Li, S.; Tsukamoto, S.; Sherman, D. H.; Williams, R. M.; *Org. Lett.* **2013**, *15*, 22; Li, S.; Finefield, J. M.; Sunderhaus, J. D.; McAfoos, T. J.; Williams, R. M.; Sherman, D. H.; *J. Am. Chem. Soc.* **2012**, *134*, 788; Kato, H.; Nakamura, Y.; Finefield, J. M.; Umaoka, H.; Nakahara, T.; Williams, R. M.; Tsukamoto, S.; *Tetrahedron Lett.* **2011**, *52*, 6923; Finefield, J. M.; Greshock, T. J.; Sherman, D. H.; Tsukamoto, S.; Williams, R. M.; *Tetrahedron Lett.* **2011**, *52*, 1987.
74. Patrick, J. B.; Witkop, B.; *J. Am. Chem. Soc.* **1950**, *72*, 633.
75. Witkop, B.; Patrick, J. B.; *J. Am. Chem. Soc.* **1953**, *75*, 2572.
76. Williams, R. M.; Glinka, T.; Kwast, E.; *Tetrahedron Lett.* **1989**, *30*, 5575.
77. Williams, R. M.; Glinka, T.; Kwast, E.; Coffman, H.; Stille, J. K.; *J. Am. Chem. Soc.* **1990**, *112*, 808.
78. Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M.; *J. Am. Chem. Soc.* **1996**, *118*, 557.
79. Williams, R. M.; Cao, J.; Tsujishima, H.; *Angew. Chem., Int. Ed.* **2000**, *39*, 2540.
80. Schendera, E.; Lerch, S.; von Drathen, T.; Unkel, L.-N.; Brasholz, M.; *Eur. J. Org. Chem.* **2017**, *2017*, 3134.
81. Zhang, X.; Foote, C. S.; *J. Am. Chem. Soc.* **1993**, *115*, 8867.
82. Adam, W.; Ahrweiler, M.; Peters, K.; Schmiedeskamp, B.; *J. Org. Chem.* **1994**, *59*, 2733.
83. Garden, S. J.; 10th Brazilian Meeting on Organic Synthesis (BMOS); São Pedro, São Paulo, 2003; Marçal, L. L.; Garden, S. J.; *The Oxidation of Indole Derivatives Using Dimethyl Dioxirane*; 15th Brazilian Meeting on Organic Synthesis (BMOS), Campos do Jordão, São Paulo, 2013.
84. Murray, R. W.; Jeyaraman, R.; *J. Org. Chem.* **1985**, *50*, 2847; Adam, W.; Bialas, J.; Hadjiarapoglou, L.; *Chem. Ber.* **1991**, *124*, 2377; Brik, M. E.; *Tetrahedron Lett.* **1995**, *36*, 5519; Ferrer, M.; Gilbert, M.; Sanchez-Baeza, F.; Messeguer, A.; *Tetrahedron Lett.* **1996**, *37*, 3585; Gibert, M.; Ferrer, M.; Sanchez-Baeza, F.; Messeguer, A.; *Tetrahedron* **1997**, *53*, 8643; Frohn, M.; Wang, Z.-X.; Shi, Y.; *J. Org. Chem.* **1998**, *63*, 6425; Zeller, K.-P.; Kowallik, M.; Haiss, P.; *Org. Biomol. Chem.* **2005**, *3*, 2310; Cheshev, P.; Marra, A.; Dondoni, A.; *Carbohydr. Res.* **2006**, *341*, 2714; Mikula, H.; Svatunek, D.; Lumpi, D.; Gloecklhofer, F.; Hametner, C.; Froehlich, J.; *Org. Process Res. Dev.* **2013**, *17*, 313.
85. Fang, X.; Jin, F.; Jin, H.; von Sonntag, C.; *J. Chem. Soc., Perkin Trans. 2* **1998**, 259.
86. Sagawa, T.; Ohkubo, K.; *J. Mol. Catal. A: Chem.* **1996**, *113*, 269.
87. Goeschen, C.; Wibowo, N.; White, J. M.; Wille, U.; *Org. Biomol. Chem.* **2011**, *9*, 3380.
88. Dolby, L. J.; Booth, D. L.; *J. Am. Chem. Soc.* **1966**, *88*, 1049.
89. Mateo, C. A.; Urrutia, A.; Rodriguez, J. G.; Fonseca, I.; Cano, F. H.; *J. Org. Chem.* **1996**, *61*, 810.
90. Garden, S. J.; Correa, M. B.; Pinto, A. C.; *Tetrahedron Lett.* **2003**, *44*, 7617.
91. Hsieh, J.-C.; Cheng, A.-Y.; Fu, J.-H.; Kang, T.-W.; *Org. Biomol. Chem.* **2012**, *10*, 6404.
92. For previous theoretical studies of dioxirane reactivity with olefins see: Bach, R. D.; Andres, J. L.; Owensby, A. L.; Schlegel, H. B.; McDouall, J. J. W.; *J. Am. Chem. Soc.* **1992**, *114*, 7207; Jenson, C.; Liu, J.; Houk, K. N.; Jorgensen, W. L.; *J. Am. Chem. Soc.* **1997**, *119*, 12982.
93. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J.; *Gaussian 09, Revision C*; Gaussian, Inc., Wallingford, CT, 2016.

Submitted: May 16, 2018
Published online: August 9, 2018