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Total synthesis of angelone enabled by a remarkable biomimetic sequence

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ABSTRACT

The natural product angelone was readily accessed with a remarkable biomimetic journey that sequentially features carbonyl formation–elimination, 6π-electrocyclization, visible light-promoted singlet O_2 Diels–Alder reaction, Kornblum–DeLaMare-type peroxide rearrangement, 6π-electrocyclic ring-opening, and conjugative addition–elimination as the key steps. With key intermediates isolated and characterized, this study stands to reveal a rare system in which bio-inspired synthetic strategies were found to mirror experimental realities.

1. Introduction

While pursuing a program aimed at searching for biosynthesis-inspired strategies for rapid constructions of selected natural products uncovered from some important traditional Chinese herbal medical formulations, we have recently become very fascinated with compounds from *Nauclea*, a plant species widely acclaimed for its anti-inflammatory and anti-bacterial utilities.[1] A number of biologically interesting structures from this species have been documented, including notably anglelone (**1**) and indole alkaloids naucleactonin A (**2**), naucleactonin B (**3**), and nauclefoline (**4**) (Fig. 1).[2] In the effort to design efficient and potentially convergent synthetic sequences to these natural products, particular attention was paid to decipher possible inner structural and mechanistic connections that might exist among such skeletal diversities.In this context, as highlighted below in blue in Fig. 1, we were intrigued by the underlying transformations among acyl furan moieties in **1** and **2** and 2*H*-pyran scaffolds in **3** and **4**. We reported herein the success in achieving an unusually efficient synthesis of angleone (**1**) through a remarkable biomimetic sequence designed with insights gained from close inspections on the structural connections among these natural products as well as speculations on their potential mechanistic network.[3] We further showed that this design concept was found indeed to mirror experimental realities through isolation and identification of the key intermediates

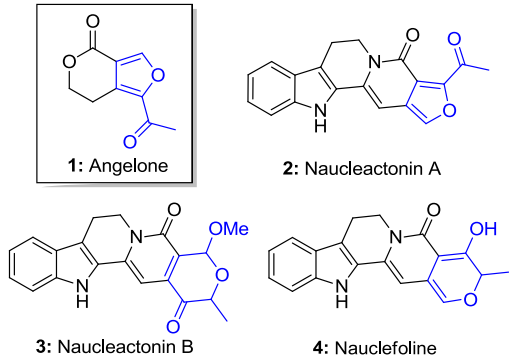

Fig. 1. Bioactive natural products from *Nauclea* species.

involved in this process, which sequentially includes such key events as carbonyl formation–elimination, 6π-electrocyclization, visible light-promoted singlet O_2 Diels–Alder reaction, Kornblum–DeLaMare-type peroxide rearrangement, 6π-electrocyclic ring-opening, and conjugative addition–elimination.

2. Results and discussion

The formal six-to-five-membered ring contraction between structures of **3** and **2** appears to hint on the first critical lesson. Retro-analytically, as outlined in Scheme 1 (with hypothesized intermediates shown in red), we envisioned that **3**'s enolized form **A** would undergo a facile 6π-electrocyclic ring-opening to give

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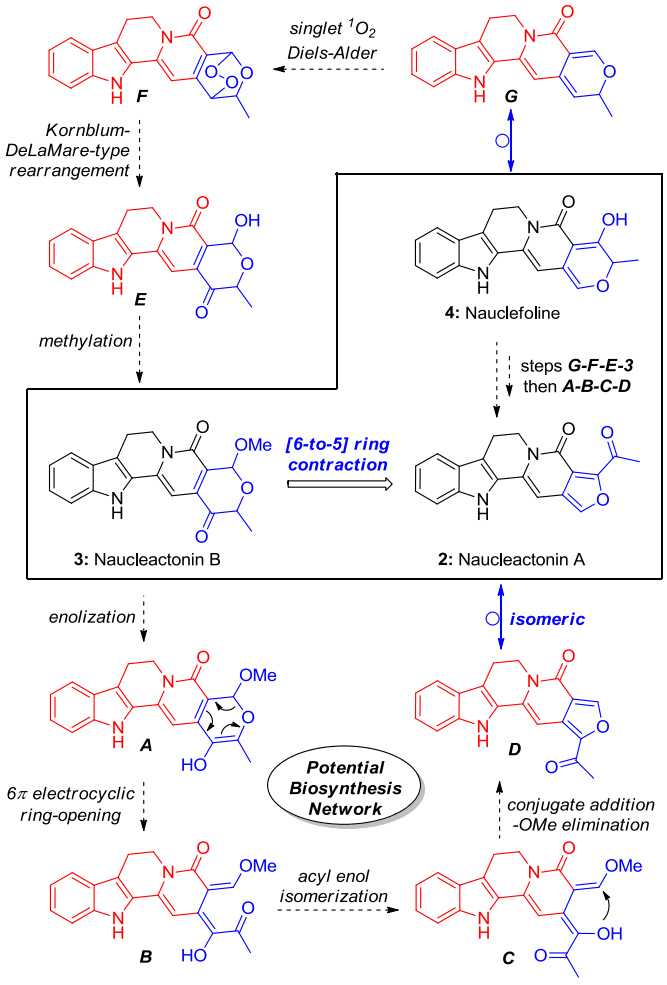
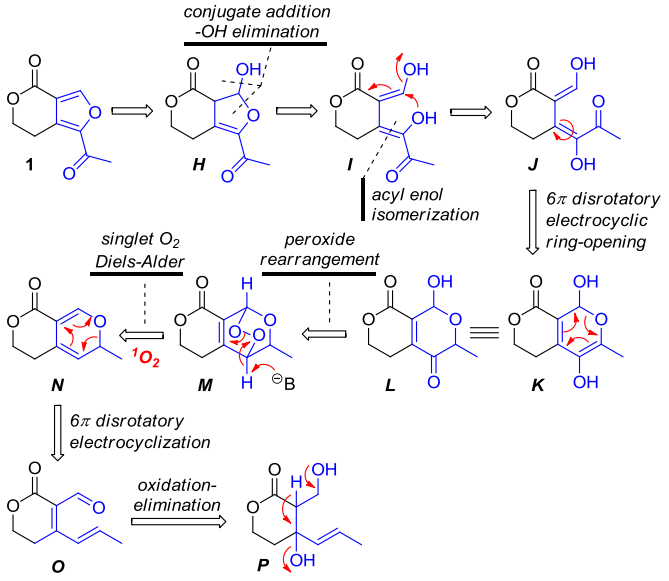


Scheme 1. Hypothesized structural and mechanistic links among indole alkaloids from *Nauclea* species. The structures in red show the assumed intermediates.

intermediate **B**,[4] which, upon in situ isomerization to the geometrically appropriately positioned structure **C**, initiates subsequent intramolecular conjugative addition–OMe elimination events to give an acyl furan-fused indole alkaloid **D** that differs nothing from the natural product **2** but the position of acyl group on the furan ring. Thus, the sequence of **A**–**B**–**C**–**D** loosely illustrates the hypothesized mechanistic pathway connecting **3** with **2**.

Further mechanistic implications arise from structural comparison of **3** to **4**. Biomimetically, a close inspection on their apparent oxygenation–deoxygenation relationship invites consideration on a possible involvement of singlet oxygen ($^1O_2$)-participated pericyclic cycloaddition event (i.e., Diels–Alder reaction).[5] Within this scenario, **3**'s demethylated precursor **E** could thus be derived from a Kornblum–DeLaMare-type rearrangement of the peroxide bridge in the potentially labile Diels–Alder adduct **F**.[5a] Remarkably, the requisite diene **G** herein again was found to correspond to a (dehydroxylated) geometrical analog of the naturally occurring **4**. Taking together, these hypothesized intermediates **A**–**G** seem to reasonably represent the missing elements that might surround the currently known natural products **2**–**4** within a unified mechanistic framework.

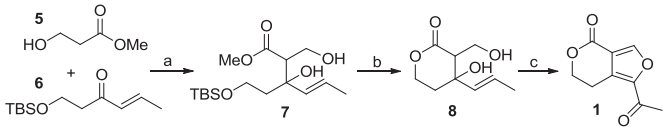
From the above analysis it is transparent that the acyl furan characterizes a critical ending structure that concludes the multiple ring conversions and eventual contraction events. Therefore, with these hypotheses in mind, we set out to examine their experimental feasibility on the platform of angleone structure. Our synthetic plan carrying this bio-inspired spirit was briefly illustrated in Scheme 2.



Scheme 2. Biomimetic hypothesis-inspired disconnections.

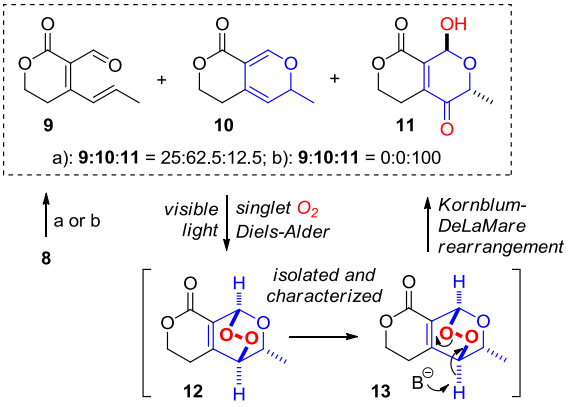
We envisioned that angelone (**1**) may be derived from the intermediates **H** and **I** through a conjugate addition–OH elimination process. The inter-conversion of the requisite (*Z*)-acyl enol geometry in **I** from the (*E*)-geometry in **J** should be readily facilitated by in situ tautomerization. **J** represents a reasonable 6π-disrotatory electrocyclic ring-opening product of hydroxyketone **L** proceeded though its enol form **K**.[6] Subsequently, the key events connecting **L** and its de-oxygenated precursor diene **N** would be a singlet O_2-participated Diels–Alder reaction followed by a base-promoted Kornblum–DeLaMare peroxide rearrangement in **M**.[7] Structure **N** may again be accessed by a concerted 6π-electrocyclization process from unsaturated aldehyde **O**.[6] Finally, the requisite unsaturation in **O** could be furnished via a carbonyl formation–dehydration protocol from a diol **P**. We anticipated that, should this retro-synthetic design to some extent reflect the biomimetic pathways hypothesized in Scheme 1, such sequential events would well likely be orchestrated into a facile process.

Indeed, as summarized in Scheme 3, a three-pot practical synthesis of angelone was readily achieved from the conceived diol precursor **8**, which was in turn prepared in high yield from condensing directly hydroxyl methyl ester **5** and α,β-unsaturated ketone **6** and subsequent lactonization of the resultant intermediate **7**. Compound **8** has proved to be uniquely positioned for initiating the cascade process: when it was activated by Dess–Martin periodinane reagent, at room temperature the concentrated crude product was directly mixed with Rose Bengal sensitizer in CH_2Cl_2 and was irradiated by visible light (120 W fluorescent lamp) under an oxygen balloon atmosphere, thus formed intermediate again without any isolation was subjected to the action of Et_2NH in CH_2Cl_2. Angelone was isolated in a remarkable 47% yield over these manipulations. The synthetic sample was found to be spectroscopically fully identical to the natural product.



Scheme 3. Three-pot synthesis of angleone. Reagents and conditions: (a) LDA, THF, −78 °C, 2 h, 81%. (b) (i) PPTS, MeOH, rt, 3 h; (ii) toluene, reflux, 72 h, 91% over two steps. (c) (i) Dess–Martin periodinane, CH_2Cl_2, rt, 30 min, no isolation; (ii) Rose Bengal, O_2 balloon (1 atm), visible light, CH_2Cl_2, rt, 4 h, no isolation; (iii) Et_2NH, THF, rt, 15 h, 47% yield over the three steps.

Several aspects of this tandem synthesis merit attention. First, when diol **8** was treated by the Dess–Martin periodinane reagent with exposure to both air and visible light source, the desired oxidation–OH elimination appeared to be efficiently effected and three products, α,β,δ,γ-unsaturated aldehyde **9**, its electrocylized form vinyl ether **10**, and hydroxylketone **11** were isolated in the ratio of 25:62.5:12.5 with a combined yield of 89% (Scheme 4). The equilibrium between **9** and **10**, apparently due to the activation of 6π system by the ester carbonyl group, was found to be readily establishable at room temperature with a ratio of 1:4. Controlled experiments showed that **11** was not formed when light was absent, implying strongly the operation of a singlet O_2-participated reaction pathway. Indeed, when an efficient photochemical sensitizer Rose Bengal was purposefully added under a balloon oxygen atmosphere, **9** and **10** were smoothly converted in situ into **11**, which was exclusively isolated in 63% yield; and when a known singlet O_2 quencher 1,4-diazabicyclo[2.2.2]octane (DABCO) was present (ca. 0.1 M concentration), the formation of **11** was again inhibited. It is thus important to note that the generation of singlet O_2 species in the original reaction condition leading to a mixture of **9**–**11** products in the absence of any externally added sensitizer, in agreement with literature findings on relevant systems,[8] should be attributed to the outcome of visible light-induced self-sensitizations of **9** or/and **10**.

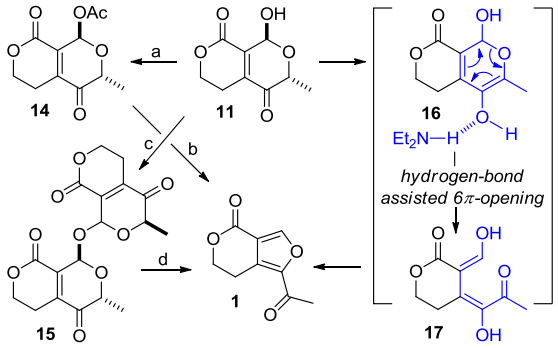


Scheme 4. Isolations and identifications of key intermediates **9**–**12**. Reagents and conditions: (a) Dess–Martin periodinane, CH_2Cl_2, 30 min, then exposed to air under visible light, 30 min, 89%. (b) Dess–Martin periodinane, CH_2Cl_2, 30 min, then exposed to visible light under O_2 balloon, 8 h, 63%.

Within a mechanistic scenario involving singlet O_2 intermediate in this system, the formation of **11** could most reasonably be rationalized via a Diels–Alder cycloaddition on the *s-cis* configured 1,3-diene followed by a Kornblum–DeLaMare peroxide rearrangement (i.e., structures **12** and **13**). Fortunately, when pure **9** and **10** were allowed to react with O_2 under the sensitization of Rose Bengal, an *endo*-peroxide Diels–Alder adduct **12** was isolated and characterized, thus directly corroborating such a [4+2] reaction pathway.

The base-promoted conversion of **12** into **11** (by acetate anion[5a] present in the Dess–Martin oxidation residues) was remarkably facile and clean, and it was found to progress even in neat form, albeit with a slower rate, presumably due to additional driving force arising from the release of ring strain incurred by the bridged peroxide acetal moiety.

The mechanistic course involved in the transformation of **11** into the final angleone product is another issue deserving attention. An intriguing observation we made was that it was a secondary amine Et_2NH, but not tertiary amines, such as Et_3N and DBU, that was most effective in bringing about the desired conversion, suggesting that simple base-mediated pathways, such as enolate formation and 1,2-elimination events initiated from deprotonation of the α-carbonyl hydrogen are unlikely to be operating (Scheme 5). Furthermore, two hydroxyl-protected forms of **11**, i.e., acetate **14** and dimer **15**, were separately prepared and subjected to the action of Et_2NH, and both were found to give angleone in good yields (70% and 85%, respectively), thus rendering those hydroxyl group-directed events, such as carbonyl nucleophilic addition pathway unreasonable. Collectively, we believe that the uncovered reactivity could be most economically explained by the stabilization of the enol tautomer of **11** via an N–H–O hydrogen bond (i.e., structure **16**),[9] thereby considerably enhancing its propensity toward 6π-electrocyclic ring-opening. Thus formed labile acyl enol species **17** then underwent isomerization and conjugate addition–OH elimination processes to give angelone.



Scheme 5. Hydrogen bond-assisted 6π-electrocyclic ring-opening. Reagents and conditions: (a) AcCl, Et_3N, CH_2Cl_2, rt, 30 min, 92%; (b) Et_2NH, THF, rt, 8 h, 70%; (c) BF_3, CH_2Cl_2, rt, 3 h, 87%; (d) Et_2NH, THF, rt, 24 h, 85%.

3. Conclusion

In summary, through inspection of the structures of four interesting natural products from *Nauclea* species plants, i.e., angelone, indole alkaloids naucleactonin A and B, and nauclefoline, and speculation on their potential inner mechanistic links, we were able to devise and execute a remarkable biomimetic process leading to the total synthesis of angleone that sequentially features carbonyl formation–elimination, 6π-electrocyclization, visible light-promoted singlet O_2 Diels–Alder reaction, Kornblum–DeLaMare-type peroxide rearrangement, 6π-electrocyclic ring-opening, and conjugative addition–elimination as the key steps. With key intermediates isolated and characterized, the study stands to reveal a rare system in which bio-inspired synthetic strategies were found to fully mirror experimental realities. Our current efforts are directed toward expanding this core technology to the convergent syntheses of a range of these structurally correlated natural products and will be reported in due course.

4. Experimental

4.1. General experimental

Reagents were purchased at the highest commercial quality from Acros and Aldrich and used without further purification unless otherwise noted. Silica gel (ZCX-II, 200–300 mesh) used for flash column chromatography was purchased from Qing Dao Ocean Chemical Industry Co. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III (300 MHz or 500 MHz) spectrometers and are internally referenced to residual solvent signals (note: $CDCl_3$ referenced at δ 7.26 ppm for ^1H and δ 77.1 ppm for ^{13}C). Data for ^1H NMR are reported as follows: chemical shift (δ parts per million), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, dd=doublet of doublets, ddd=doublet of doublet of doublets, and m=multiplet), integration, coupling constant (hertz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). High resolution mass spectrometric (HRMS) data were obtained using Bruker Apex IV RTMS.

4.2. Synthesis of angelone

To a solution of the alcohol **8** (93 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) was added $NaHCO_3$ (84 mg, 1.0 mmol) and DMP (250 mg, 0.6 mmol) in one portion. The mixture was stirred for 30 min at room temperature, diluted with CH_2Cl_2 (10 mL), and then quenched with saturated aqueous $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (5 mL). The product was extracted with CH_2Cl_2 (6×10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude material was directly mixed with Rose Bengal sensitizer (10 mg) and irradiated by visible light (regular 120 W fluorescence lighting bulb) under an oxygen balloon atmosphere (1 atm) for 4 h. Then Et_2NH (100 mg, 1.50 mmol) was added, and the mixture was stirred at room temperature for another 15 h. The solvent was removed in vacuo, and the residue was purified with flash column chromatography (silica gel, hexane /:EtOAc=2:l) to afford **1** (42 mg, 47% yield) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.14 (s, 1H), 4.53 (t, J=6.1 Hz, 2H), 3.21 (t, J=6.1 Hz, 2H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=188.2, 160.7, 148.1, 147.5, 128.3, 117.7, 68.4, 26.7, 21.3; HRMS (ESI): calcd for $C_9H_9O_4^+$, [M+H$^+$] 181.0501, found 181.0498.

Acknowledgements

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Supplementary data

Detailed experimental procedures, compound characterization data, and copies of ^{1}H and ^{13}C NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.03.076.

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