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Biomimetic Synthesis

Total Synthesis and Prediction of Ulodione Natural Products Guided by DFT Calculations**

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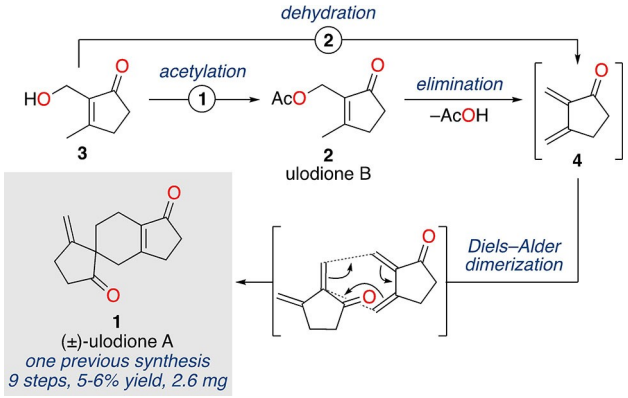
Abstract: A biomimetic synthetic strategy has resulted in a two-step total synthesis of (±)-ulodione A and the prediction of two potential natural products, (±)-ulodiones C and D. This work was guided by computational investigations into the selectivity of a proposed biosynthetic Diels–Alder dimerization, which was then utilized in the chemical synthesis. This work highlights how biosynthetic considerations can both guide the design of efficient synthetic strategies and lead to the anticipation of new natural products.

Introduction

(±)-Ulodione A (**1**) is a racemic natural product isolated from the endolichenic fungus *Ulospora bilgramii* by Lou and co-workers in 2020 (Scheme 1).[1] The structure of (±)-ulodione A (**1**) was determined through NMR and MS studies and confirmed by X-ray crystallography. Our interest in (±)-ulodione A (**1**) stems from its deceptively simple structure and intriguing biogenesis, but there is also interest in this natural product as a selective inhibitor of butyrylcholinesterase (BuChE). Both enantiomers of (±)-ulodione A (**1**) are reported to be micromolar inhibitors of BuChE (IC_{50} ≈ 9 μM), whilst not inhibiting acetylcholinesterase (AChE).[1] Three cholinesterase inhibitors are currently used to reduce symptoms in patients with Alzheimer's disease;[2] donepezil and galantamine are AChE-selective inhibitors, whereas rivastigmine is a non-selective AChE/BuChE inhibitor.[3] It has been proposed that BuChE-selective inhibitors may offer a therapeutic advantage since AChE activity decreases during the progression of Alzheimer's disease whereas BuChE activity is maintained or increases.[4] During the preparation of this manuscript, Hong and co-workers reported the first total synthesis of (±)-ulodione A (**1**).[5] They pursued a transform-based strategy, centered on their ring-expansion rearrangement methodology,[6] which resulted in a 9-step total synthesis (for a full summary, see Supporting Information).

(±)-Ulodione A (**1**) was co-isolated alongside a related natural product, ulodione B (**2**) (Scheme 1).[1] Lou and co-workers proposed that both ulodione A (**1**) and B (**2**) may be derived from the known natural product, 2-hydroxymethyl-3-methylcyclopent-2-enone, **3**.[7] Acetylation gives ulodione B (**2**) (Scheme 1, Pathway 1), whereas de-hydration and Diels–Alder dimerization of the resultant dienone **4** gives (±)-ulodione A (**1**) (Scheme 1, Pathway 2).[1] It is also



Scheme 1. Lou's proposed biosynthetic pathways towards (±)-ulodione A (**1**) and ulodione B (**2**).[1]

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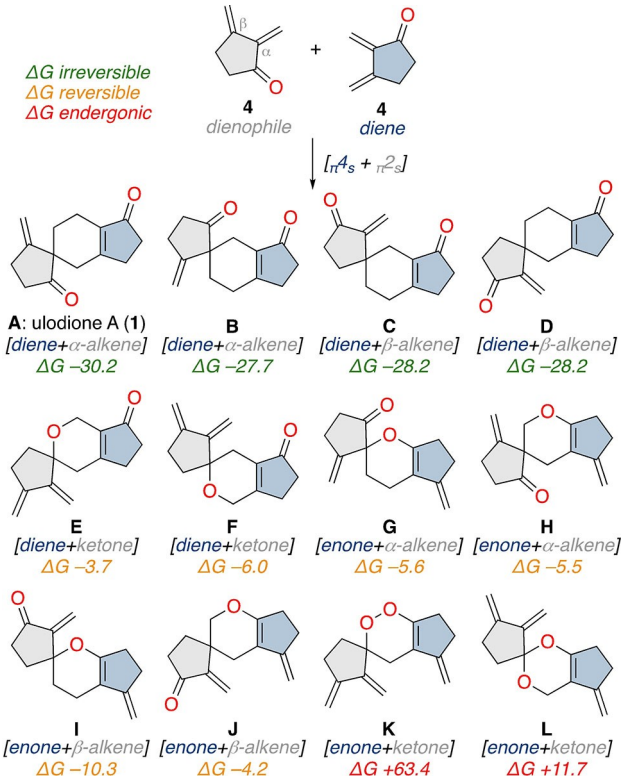
possible that dienone **4** could be derived from ulodione B (**2**) via elimination of AcOH.

Given ulodione A (**1**) is isolated in racemic form,[8] it is likely that the proposed biosynthetic Diels–Alder dimerization of dienone **4** proceeds without direct enzyme participation.[9] This raises a number of questions concerning selectivity. There are 12 isomeric products, **A**–**L**, that could form through a $[_{\pi}4_s+_{\pi}2_s]$ dimerization of dienone **4** (Scheme 2). This is a result of monomer **4** containing two potential diene sites (a diene and enone) and three potential dienophile sites (two alkenes and a ketone), with two possible regioisomeric orientations for each combination (Scheme 2). This raises the question of whether (±)-ulodione A (**1**) is the only natural dimer formed through a highly selective Diels–Alder dimerization, or is there an entire family of related dimers waiting to be discovered?[10]

Results and Discussion

Density functional theory (DFT) calculations, at the PW6B95D3/def2-TZVPP level of theory,[11] were undertaken to investigate the factors that control the reactivity and selectivity of the Diels–Alder dimerization of dienone **4**.[12] The relative change in free energy for each potential product **A**–**L** was first calculated (Scheme 2). The four possible cyclohexene adducts **A**–**D** were found to have ΔG values between −27.7 and −30.2 kcal mol^{-1}, meaning their formation would be essentially irreversible under ambient conditions. Dihydropyrans **E**–**J** on the other hand are more likely to be formed reversibly, with ΔG values between −3.7 and −10.3 kcal mol^{-1}. It was also confirmed that formation of endoperoxide **K** or ketal **L** would be highly unfavorable, with ΔG values of +63.4 and +11.7 kcal mol^{-1}, respectively.



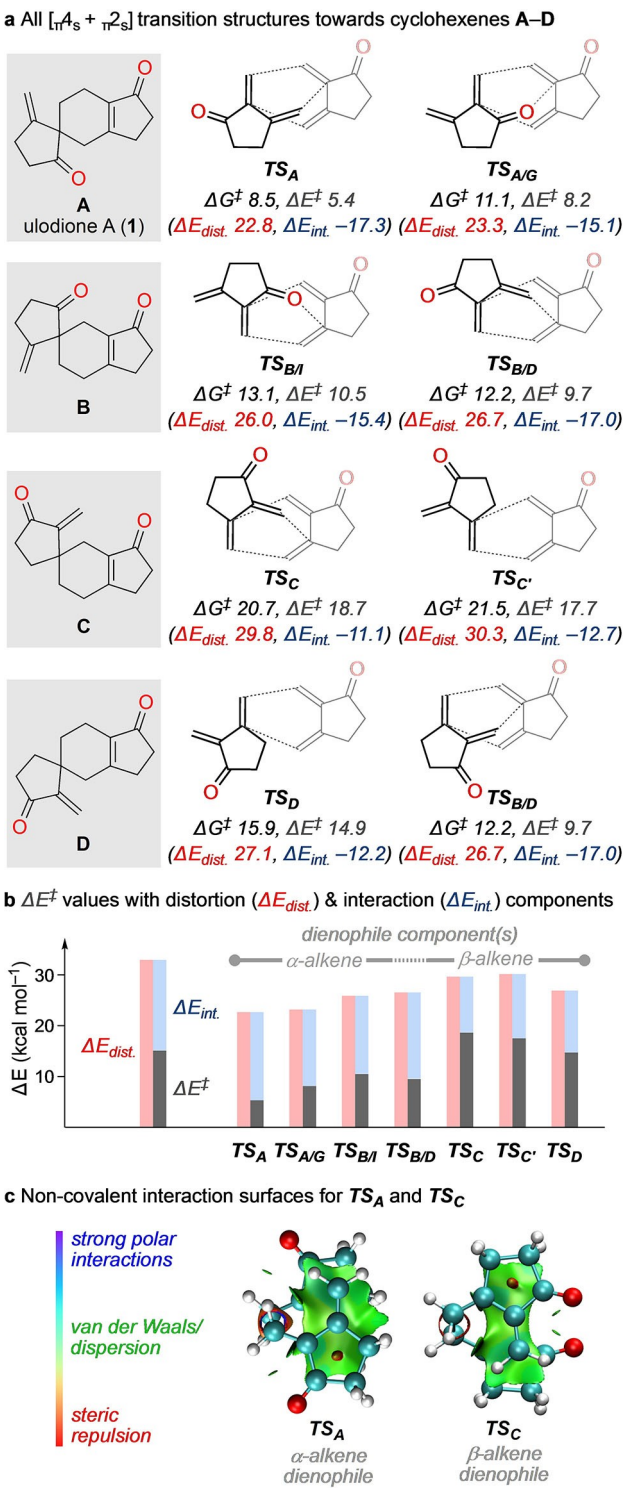
Scheme 2. All possible regioisomers that could form through $[_{\pi}4_s+_{\pi}2_s]$ dimerization of dienone **4**, with their calculated (PW6B95D3/def2-TZVPP) ΔG values (kcal mol^{-1}).

There are two $[_{\pi}4_s+_{\pi}2_s]$ transition states that can lead to the formation of each cyclohexene adduct **A**–**D** (Scheme 3a; ***TS*** label indicates which structures could form, i.e., $\boldsymbol{TS_{X/Y}}$ could lead to structures **X** and **Y**). For example, cyclohexene **A** (i.e., (±)-ulodione A) could form through a C_2-symmetric bis-pericyclic TS ($\boldsymbol{TS_A}$) or through a bifurcating ambimodal TS ($\boldsymbol{TS_{A/G}}$).[8c,13] The calculated barriers were found to be significantly lower for transition states involving the α-alkene as the dienophile, to give cyclohexenes **A** and **B**, compared to when the β-alkene acts as the dienophile, to give cyclohexenes **C** and **D** (Scheme 3a). This can be attributed to lower distortion penalties, better orbital overlap, and more favorable non-covalent interactions (primarily dispersion) when the α-alkene acts as the dienophile (Scheme 3b).[14,15] The differences in dispersion interactions can be visualized in non-covalent interaction surfaces. For example, the non-covalent interaction surfaces for $\boldsymbol{TS_A}$ and $\boldsymbol{TS_C}$, which are representative of when the α-alkene or the β-alkene act as the dienophile, respectively, are shown in Scheme 3c (see Supporting Information for full details).

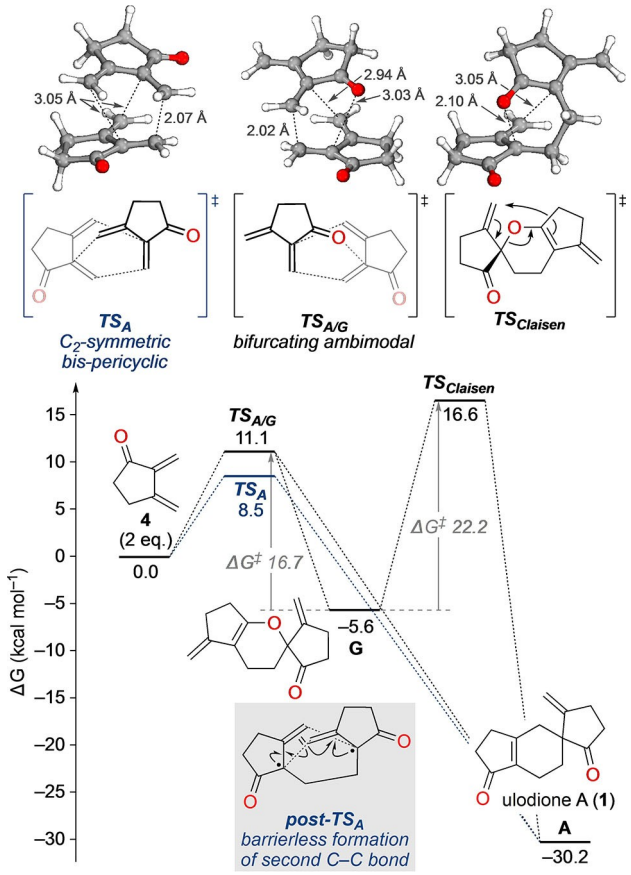
$\boldsymbol{TS_A}$ is calculated to have the lowest barrier for Diels–Alder dimerization of dienone **4** ($\Delta G^{\ddagger}$ 8.5 kcal mol^{-1}). It is a bis-pericyclic TS with C_2-symmetry, wherein the [4+2] and [2+4] cycloaddition pathways have fully merged.[13] Following the TS, the pathway then bifurcates to give the degenerate [4+2] and [2+4] cycloadducts. This is a highly asynchronous TS, with a shorter forming bond between the two terminal alkene carbons (2.07 Å) and two longer forming bonds (3.05 Å), only one of which will eventually form to give (±)-ulodione A (**1**) (Scheme 4). $\boldsymbol{TS_A}$ is calculated to be a closed shell system, but analysis of intrinsic bond orbitals following $\boldsymbol{TS_A}$ indicates that once the first C–C bond is formed the system adopts biradical character leading to barrierless formation of the second C–C bond (Scheme 4; see Supporting Information for full details).[16] The regioselectivity of related Diels–Alder reactions has previously been explained by invoking biradical intermediates, or biradicaloid TSs, with the more stable biradical(oid) correlating to the observed product(s).[17]

$\boldsymbol{TS_{A/G}}$ is only 2.6 kcal mol^{-1} higher in energy than $\boldsymbol{TS_A}$ and is a bifurcating ambimodal TS that can lead to the formation of (±)-ulodione A (**1**) and dihydropyran **G** (Scheme 4). However, even if dihydropyran **G** forms it will readily undergo the retro-Diels–Alder reaction to regenerate dienone **4** ($\Delta G^{\ddagger}$ of 16.7 kcal mol^{-1}). Direct [3,3]-Claisen rearrangement of dihydropyran **G** to give (±)-ulodione A (**1**), on the other hand, was found to have a relatively high barrier ($\Delta G^{\ddagger}$ 22.2 kcal mol^{-1}).

The next lowest TS is $\boldsymbol{TS_{B/D}}$ ($\Delta G^{\ddagger}$ 12.2 kcal mol^{-1}), which is another bifurcating ambimodal TS which could potentially lead to the irreversible formation of cyclohexenes **B** and/or **D** (Scheme 5).[13] Semiclassical molecular dynamics simulations initiated from $\boldsymbol{TS_{B/D}}$ were performed.[18] 70 trajectories



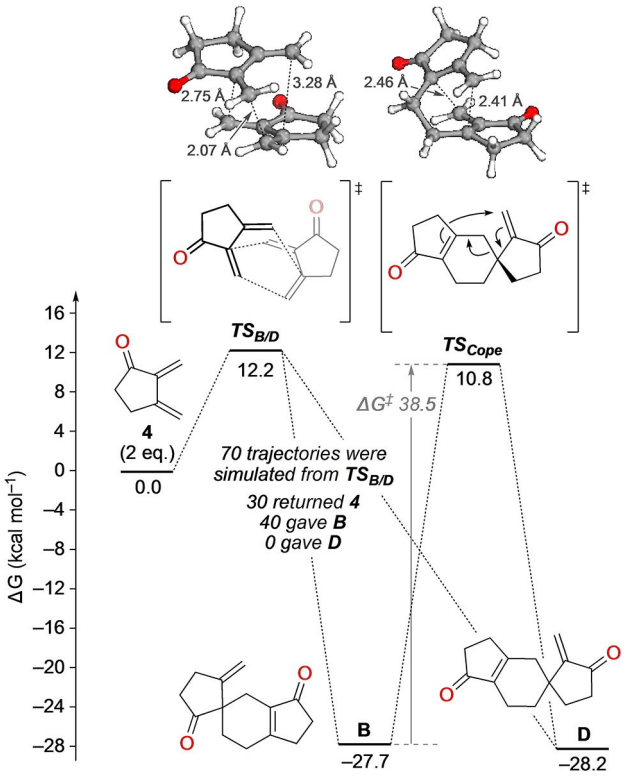
Scheme 3. The $[_{\pi}4_s + _{\pi}2_s]$ transition states for formation of cyclohexene adducts **A**–**D**, with their calculated (PW6B95D3/def2-TZVPP) energy values (kcal mol^{-1}).



Scheme 4. Calculated (PW6B95D3/def2-TZVPP) free energy profile diagram and transition state structures for the formation of (±)-ulodione A (**1**).

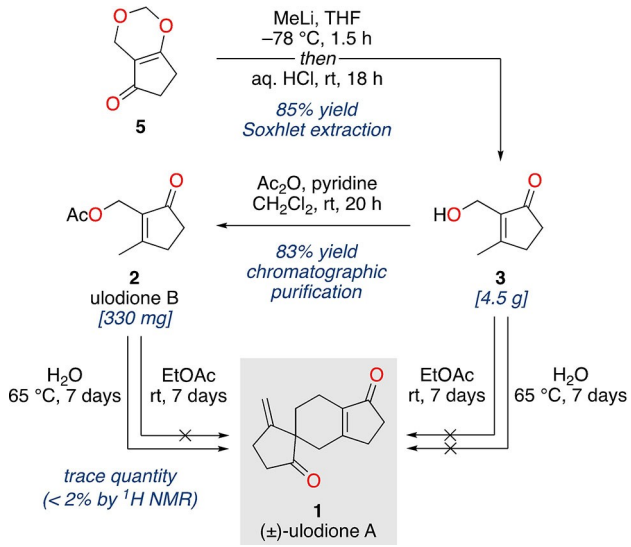
were simulated with randomized initial velocities, with the total kinetic nuclear energy set to the zero-point vibrational energy of ***TS$_{B/D}$***. 30 of these trajectories returned the substrate complex, 40 reached product **B** and none gave **D** (Scheme 5). Therefore, strong dynamic control means product **B** is expected to be the major/sole product formed from ***TS$_{B/D}$***. This is also reflected in the lengths of the two longer forming bonds in ***TS$_{B/D}$*** (2.75 Å vs 3.28 Å). Cyclohexene **D** could still theoretically form from cyclohexene **B** via a [3,3]-Cope rearrangement, but this was found to have a prohibitively high barrier ($\Delta G^{\ddagger}$ 38.5 kcal mol^{-1}) (Scheme 5). Cyclohexene **B** could also form through ***TS$_{B/I}$*** ($\Delta G^{\ddagger}$ 13.1 kcal mol^{-1}), which can also lead to reversible formation of dihydropyran **I** (see Supporting Information for full details).

In summary, DFT calculations indicate that (±)-ulodione A (**1**) will be the major product formed through a spontaneous (i.e., non-enzyme mediated) dimerization of dienone **4**. It is also likely that cyclohexene **B** will form as a minor product and thus may represent an as-yet-undiscovered natural product. It is highly unlikely, however, that cyclohexenes **C** or **D** would be observed in a spontaneous dimerization of dienone **4**, as ***TS$_{C}$***, ***TS$_{C'}$***, and ***TS$_{D}$*** are all significantly higher in energy than ***TS$_{A}$***, ***TS$_{A/G}$***, ***TS$_{B/D}$*** and ***TS$_{B/I}$*** ($\Delta G^{\ddagger}$ 15.9–21.5 vs 8.5–13.1 kcal mol^{-1}) (Scheme 3). Therefore, we decided to pursue a biomimetic synthesis of (±)-ulodione A (**1**), to both investigate the chemical feasibility of the proposed biosynthetic pathway and to concurrently search for cyclohexene **B** as a potential natural product.[10]



Scheme 5. Calculated (PW6B95D3/def2-TZVPP) free energy profile diagram and transition state structures for the formation of cyclohexenes **B** and **D**.

The known natural product, and proposed biosynthetic intermediate, hydroxy-enone **3** was synthesized on a multigram scale and without need for chromatographic purification (Scheme 6).[19] Stork–Danheiser transposition of commercially available vinylogous ester **5** was achieved through addition of methyl lithium followed by treatment with hydrochloric acid to give hydroxy-enone **3** in 85% yield, following Soxhlet extraction. Ulodione B (**2**) was then easily accessed via acetylation of hydroxy-enone **3** under standard conditions in 83% yield (Scheme 6).

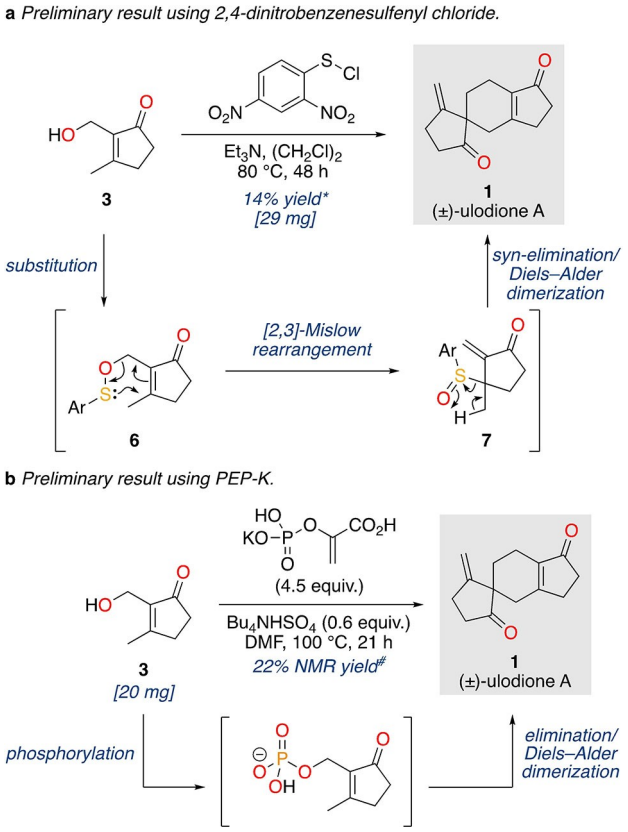


Scheme 6. Synthesis of proposed biosynthetic intermediate **3** and ulodione B (**2**).

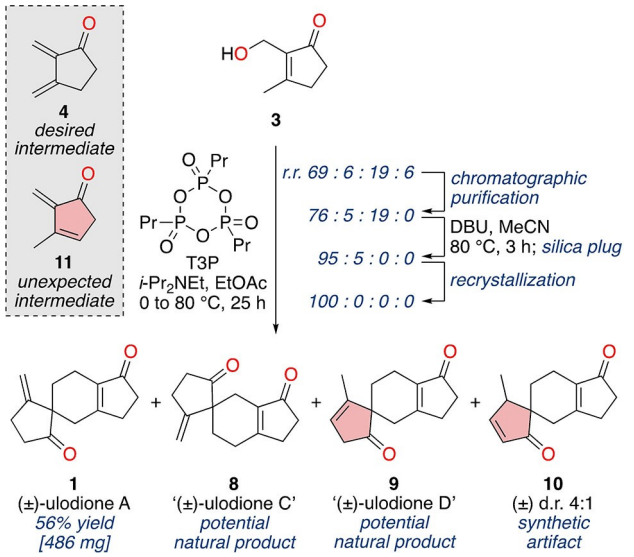
In an attempt to emulate the process by which (±)-ulodione A (**1**) was isolated from the mycelium of *Ulospora bilgramii*,[1] hydroxy-enone **3** and ulodione B (**2**) were both separately dissolved in EtOAc and left for several days under ambient conditions (Scheme 6). There was no detectable change in these samples by ^{1}H-NMR spectroscopy, supporting the notion that (±)-ulodione A (**1**) is a bona fide natural product and not an artifact of the isolation process.[20] Hydroxy-enone **3** and ulodione B (**2**) were also exposed to aqueous reaction conditions to probe whether (±)-ulodione A (**1**) might form spontaneously from these potential biosynthetic precursors in water. There was no detectable formation of (±)-ulodione A (**1**) when hydroxy-enone **3** was dissolved in water, even after prolonged heating. However, when ulodione B (**2**) was heated in water at 65 °C for 7 days trace quantities of (±)-ulodione A (**1**) could be detected (<2% by ^{1}H-NMR analysis), alongside significant hydrolysis to give hydroxy-enone **3** and acetic acid. Despite these tantalizing observations, it was clear that to achieve an efficient and practical synthesis of (±)-ulodione A (**1**) a more rational design of reaction conditions was required. Attempts to identify other conditions for the efficient elimination of AcOH from ulodione B (**2**) were unsuccessful.[21] Our attention, therefore, turned to the dehydration of hydroxy-enone **3**.[22]

After an initial screen of conditions to dehydrate hydroxy-enone **3**, we encountered success using sulfur and phosphorus reagents (Scheme 7).[23,24] In 1982, Reich and Wollowitz reported the conversion of allylic alcohols to 1,3-dienes using 2,4-dinitrobenzenesulfenyl chloride and NEt_3.[23] When hydroxy-enone **3** was treated to these conditions (±)-ulodione A (**1**) could be isolated, albeit in modest yield and on a relatively small scale (Scheme 7a). It is proposed that allylic sulfenate ester **6** undergoes [2,3]-Mislow rearrangement to give allylic sulfoxide **7** followed by *syn*-elimination and Diels–Alder dimerization to give (±)-ulodione A (**1**).[23] Unfortunately, attempts to scale-up this reaction and improve the yield were unsuccessful. Kanai, Yamatsugu and co-workers recently reported a chemoselective method for phosphorylation of alcohols using potassium phosphoenolpyruvate (PEP-K) and catalytic NBu_4HSO_4.[24] We hoped that under these conditions hydroxy-enone **3** would be phosphorylated and undergo elimination and Diels–Alder dimerization to give (±)-ulodione A (**1**). Analysis of the crude product, from a small test-scale reaction, indicated a 22% NMR yield of (±)-ulodione A (**1**) (Scheme 7b), but attempts to improve upon this result were also unsuccessful.

The best results we achieved, in terms of yield and scalability, involved the use of propanephosphonic acid anhydride (T3P) and *i*-Pr_2NEt; conditions originally developed by Meudt, Scherer, and Böhm for the dehydration of allylic alcohols (Scheme 8).[25] In our largest scale reaction, a gram of hydroxy-enone **3** was treated to a slight excess of



Scheme 7. Preliminary small-scale and low-yielding syntheses of (±)-ulodione A (**1**). [*] Re-analysis of the ^{1}H-NMR spectrum of the crude reaction product revealed a small quantity of (±)-ulodione C (**8**) was present (**1**:**8**, ≈93:7). [#] Re-analysis of the ^{1}H-NMR spectrum of the crude reaction product revealed small quantities of (±)-ulodione C (**8**) and D (**9**) were present (**1**:**8**:**9**, 67:9:24) (see below).



Scheme 8. Synthesis of (±)-ulodione A (**1**) via a bioinspired domino dehydration/Diels–Alder reaction sequence.

T3P and *i*-Pr$_2$NEt in EtOAc at 0 °C before being heated to 80 °C overnight. This gave a mixture of (±)-ulodione A (**1**), cyclohexene **B** (**8**), and two unexpected alkene-site regioisomers, **9** and **10**. Analytically pure samples of each product (**1**, **8**–**10**) were obtained using HPLC (see Supporting Information for full details). An optimized process was then developed to separate (±)-ulodione A (**1**) from this mixture of products (Scheme 8). First, column chromatography was used to separate (±)-ulodione A (**1**), **8**, and **9** from the diastereomeric mixture of bis-enone **10**. Subsequent treatment of the mixture of (±)-ulodione A (**1**), **8**, and **9** with DBU resulted in full consumption of **9**, presumably through selective deprotonation of the skipped enone functionality. A small quantity of bis-enone **10** formed through this process was then easily removed via filtration through a short plug of silica to give a mixture of (±)-ulodione A (**1**) and **8**. Finally, recrystallization delivered almost half a gram of analytically pure (±)-ulodione A (**1**) in 56 % isolated yield.

Subsequent re-analysis of the ^{1}H-NMR spectra from our earlier syntheses of (±)-ulodione A (**1**) using 2,4-dinitrobenzenesulfenyl chloride or PEP-K, as the dehydrating reagent, revealed cyclohexene **B** (**8**) was also formed as a minor product in both these reactions (Scheme 7). Isomer **9** was also observed when using PEP-K, but not when using 2,4-dinitrobenzenesulfenyl chloride. Thus, our computational and synthetic results both indicate that cyclohexene **B** (**8**) is likely to be an as-yet-undiscovered natural product which, if later identified, we suggest should be named (±)-ulodione C (**8**). We propose that the unexpected alkene-site regioisomer **9** is formed through a crossed-Diels–Alder reaction between the intended dienone intermediate **4** and a regioisomeric dienone **11** (Scheme 8), which could form through a non-selective dehydration process. Thus, depending on how selective the biosynthesis of dienone **4** is, it is also possible that isomer **9** might be a natural product, which if later identified as such should be named (±)-ulodione D (**9**). Bis-enone **10**, on the other hand, can simply form via alkene isomerization of (±)-ulodione D (**9**) and so is perhaps better characterized as an artifact of synthesis.

Conclusion

In summary, our combined computational and synthetic investigations have provided new insights into the selectivity of Lou's proposed biosynthetic Diels–Alder dimerization towards (±)-ulodione A (**1**) (Scheme 1).[1] This has resulted in the shortest reported total synthesis of (±)-ulodione A (**1**) (2 steps, 48 % overall yield, 486 mg prepared; cf. previous 9-step synthesis, 5–6 % overall yield, 2.6 mg prepared).[5] The short and practical nature of this synthesis is facilitating ongoing SAR studies in our laboratory. We have also identified "(±)-ulodione C" (**8**) and "(±)-ulodione D" (**9**) as potential natural products, which we hope will motivate further isolation efforts focused on *Ulospora bilgramii*.[8]

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Biomimetic Synthesis · Cycloaddition · Density Functional Calculations · Dimerization · Total Synthesis

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