Unravelling Photochemical Relationships Among Natural Products from *Aplysia dactylomela*

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**ABSTRACT:** Aplydactone (1) is a brominated ladderane sesquiterpenoid that was isolated from the sea hare *Aplysia dactylomela* together with the chamigranes dactylone (2) and 10-epi-dactylone (3). Given the habitat of *A. dactylomela*, it seems likely that 1 is formed from 2 through a photochemical [2 + 2] cycloaddition. Here, we disclose a concise synthesis of 1, 2, and 3 that was guided by excited state theory and relied on several highly stereoselective transformations. Our experiments and calculations confirm the photochemical origin of 1 and explain why it is formed as the sole isomer. Irradiation of 3 with long wavelength UV light resulted in a [2 + 2] cycloaddition that proceeded with opposite regioselectivity. On the basis of this finding, it seems likely that the resulting regioisomer, termed “8-epi-isoplydactone”, could also be found in *A. dactylomela*.

The “spotted sea hare” *Aplysia dactylomela* is a marine mollusk that likes to dwell in tropical seas and feast on algae that produce halogenated terpenoids. ¹⁻³ Several brominated natural products have been isolated from *A. dactylomela* itself (Figure 1). They include dactylone (2)⁴ and its epimer 10-epi-dactylone (3), as well as the chamigranes 4 and 5.⁵ Their most remarkable representative to date, however, is aplydactone (1).⁶ It was isolated by Stonik et al. in 2001 from specimens collected in the shallow waters surrounding Nosy Hara, an island off the coast of Madagascar. Aplydactone possesses an unprecedented tetracyclic skeleton that is highly strained and contains three quaternary stereocenters, which are all embedded in the ladderane substructure.⁷⁻⁹ Given the sea hare’s tropical habitat and the relatively intense solar irradiation it is exposed to, it is reasonable to assume that 2 is converted into aplydactone (1) via a photochemical [2 + 2] cycloaddition. This cycloaddition is noteworthy in several respects. First, Stonik reported that 2 failed to yield 1 under “long-term UV irradiation” and suggested that the formation of 1 may be due to a non-photochemical enzymatic reaction.⁶ Given our experience with natural products whose biosynthesis includes a photochemical step, we suspected that this failure might be due to the experimental conditions chosen.⁹¹⁰ We reasoned that high energy UV light might affect the carbon–bromine bond or lead to other unwanted reactions and that the use of a “biomimetic” light source would be critical. While our studies were ongoing, this was independently verified by Burns and co-workers in their elegant synthesis of 1 and 2.¹¹ Second, the photocycloaddition reaction appears to produce the highly strained [2]-ladderane skeleton in an apparent violation of the “rule of five”.¹²⁻¹³ This rule refers to the observation that intramolecular [2 + 2] reactions (for molecules in the triplet excited state) tend to form regioisomers that contain five-membered rings (Figure 2). In Ciamician’s classic photochemical synthesis of “carvone camphor” from carvone, this was indeed the case.¹⁴ We therefore wondered whether irradiation of 2 at appropriate wavelengths could also yield the less strained “isoaphydactone” (6) and, if not, what the reasons for this might be. Finally, no mention was made whether 10-epi-dactylone (3) was subjected to irradiation as well. We wondered whether 3 would also yield a photocycloaddition product and, if so, whether this product would be 8-epi-aplydactone (7) or its isomer 8-epi-isoplydactone (8), which abides by the rule of five.

To address these questions, we decided to take a two-pronged approach that involved both theory and experiment. We would synthesize both natural products 2 and 3 and then study their photochemical conversions guided by high-level quantum chemical calculations carried out in parallel. These calculations served two purposes: (a) to predict the optimal wavelength with which to irradiate the chamigranes and (b) to rationalize the outcomes of the cycloadditions.

**QUANTUM CHEMICAL ANALYSIS**

The quantum chemical calculations were performed at the CASSCF/CASPT2,¹⁵ CCSD,¹⁶ and DFT/TDDFT¹⁷,¹⁸ level of theory. Since intersystem crossing (ISC) plays a key role in photochemical [2 + 2] cycloadditions,¹⁹ we investigated the singlet as well as the triplet states of dactylone (2). First, the ground state geometry of 2 was optimized and was found to be...
in good agreement with the crystal structure of the isolated natural product\textsuperscript{1} represented by the conformer 2\textit{a} (see Figure 2 and Figure B1, Supporting Information). The other possible chair conformer 2\textit{b} exhibits the bromine in the axial position and is 0.12 eV (11.6 kJ/mol) higher in Gibbs free energy ($\Delta G$), and a barrier of 0.48 eV (46.3 kJ/mol) has to be overcome for the ring-flip to occur (see Figure B2, Supporting Information). Therefore, the conformer 2\textit{a} is the one most populated and will be considered in the following analysis.

The calculated absorption spectrum of 2\textit{a} reveals two strong absorption bands in the UVC region, which cannot be reached by solar irradiation (Figure 3a). Only the weak absorption band of 2\textit{a} in the UVA region, predicted to occur around $\lambda_{\text{max}} = 323$ nm, can be accessed by the solar light.

The calculated absorption band in the UVA region (red bar in Figure 3b) is in good agreement with the experimentally determined spectrum. This absorption band is attributed to the transition from the S\textit{0} to S\textit{1} state and is characterized by an excitation from the lone pair of the oxygen atom to the $\pi$-system of the enone moiety ($n_{\text{O}}\pi^*$) of 2\textit{a} (see Figure 3b) and is therefore completely localized on the enone moiety of 2\textit{a}. The excitation into this band will initiate the photochemical reaction under biomimetic conditions.

The main relaxation pathway from the excited precursor 2\textit{a} to the starting point of the cycloaddition is shown in Figure 4. The calculated spin–orbit coupling and S\textit{1}-triplet energy gaps
reveal that after excitation to the $S_1$ ($n_O\pi^*$) state, a large ISC probability exists for the $S_1$ with the $T_2$ ($\pi\pi^*$) state. Both states run parallel along the initial relaxation coordinate until they reach a low lying $S_1/T_2$ intersection (IS) located in the vicinity of the $S_1$-Min ($S_1/T_2$ IS in Figure 4, see section B.2.3, Supporting Information for details).

Once the $T_2$ ($\pi\pi^*$) state is populated, an energetically close lying conical intersection with the $T_1$ state can be reached ($T_2/T_1$ CoIn in Figure 4). Here, the relaxation path splits into three branches leading to different minima on the $T_1$ potential energy surface. The two minima of $\pi\pi^*$ character ($T_1$-Min2 and $T_1$-Min3 (not shown)) are slightly lower in energy than $T_1$-Min1 with $n\pi^*$ character (see Table B2, Supporting Information). This should lead to their preferred population, which is supported by dynamic simulations of small $\alpha,\beta$-unsaturated enones.\(^{21}\)

At $T_1$-Min2 the hydrogen atom is positioned under the ring plane, which allows the direct attack onto the exo-double bond. Therefore, $T_1$-Min2 represents the starting point of the cycloaddition (see Figure B5, Supporting Information for details).

In principle, there is the possibility of a relaxation from the excited state back to the ground state of $2a$ via internal conversion (IC) or ISC. However, these processes are very unlikely due to the high barriers present for these deactivation pathways for precursor $2a$ (see section B.2.4 and B.2.5, Supporting Information for details).

The first step of the cycloaddition is the formation of a triplet 1,4-diradical (DR) intermediate.\(^{19}\) From the triplet minimum $T_1$-Min2, four different 1,4-diradicals (DR1-DR4) are possible (Figure 5). Once formed, the triplet diradicals (DR) lead to the singlet diradicals (1DR), from which either the cycloadduct can be formed or a relaxation back to the diene can occur. Both diradicals DR1 and DR2 can lead to aplydactone (1) (Figure 5b). In contrast, isoaplydactone (6) can only be formed from the diradical DR3 because for diradical DR4 the second bond formation is prohibited for geometrical reasons.

The quantum chemical calculations reveal that both diradical pathways leading to aplydactone (1)—DR2 and especially DR1—are associated with smaller barriers than the DR3 pathway leading to isoaplydactone (6) (see section B.2.6, SI). Thus, the formation of 1 should be strongly favored over the formation of the “rule of five” product 6.

Overall, the theoretical results predict that an optical excitation to the singlet $S_1$ ($n_O\pi^*$) state of dactylone ($2$) should allow for the photochemical and biomimetic synthesis of aplydactone (1).

### SYNTHESIS OF DACTYLONE AND 10-EPIDACTYLONE

With these results in hand, we endeavored to validate the photochemical cycloaddition hypothesis and sought a stereoselective synthesis of dactylone (2). We reasoned that both dactylone (2) and 10-epi-dactylone (3) could be synthesized from the natural product 10-bromo-β-chamigrene (9)\(^3\) via an allylic oxidation (Figure 6). Remarkably, the Burns and Snyder
Our synthesis began with a copper mediated conjugate addition of trimethylsilylmethyl magnesium chloride, which served as a masked methyl group, followed by trapping with trimethylsilyl chloride. This afforded silyl ene ether 13 in excellent yield and as the only stereoisomer (Figure 7). Exposure of 13 to Li2CO3 and Eschenmoser’s salt, followed by treatment with m-CPBA, then afforded exocyclic enone 14 in good yield.

With a reliable route to 14 in hand, we turned our attention to the key Diels–Alder reaction to introduce the spiroundecane scaffold. Unfortunately, 14 was found to be either unreactive toward isoprene or unstable in the presence of several Lewis acids. Reacting 14 with 4 equiv of isoprene and 1.5 equiv of BCl3 converted 14 into the desired spirocyclic ketone 15 in moderate yield but as a single diastereoisomer.

However, this reaction was not scalable and difficult to reproduce. We therefore turned to high pressure chemistry, which had previously served us well in cycloadditions. After extensive optimization, we found that reacting 14 in the presence of 6 equiv of isoprene and 0.2 equiv of ZnBr2 under 6 kbar of pressure afforded the silylated spiroundecane 15 in good yield and on a gram scale. The structure of 15 was confirmed by crystallography of the deprotected adduct 16 (see Supporting Information). The presence of the trimethylsilyl group was critical for the high level of diastereoselectivity in the Diels–Alder reaction. The steric bulk of the silane forces both large substituents of 14 to reside in an axial position, blocking the top face of the dienophile (see X-ray in Figure 7).

At this stage, we needed to introduce the exocyclic methylene on the C7 position, remove the silyl groups, and convert the C10 hydroxyl into an alkyl bromide to arrive at 9. The sterically hindered C7 carbonyl of 15 was found to be unreactive toward several standard methenylation conditions, including Tebbe, Petasis, Lombardo, Peterson, Wittig, and Kauflmann olefinations. However, we were finally able to overcome this obstacle by heating spirocycle 15 with the...
Both the Diels–Alder reaction and the olefination could be performed in a one-pot procedure (see Supporting Information for details). Compound 17 could then be desilylated to afford 18 in nearly quantitative yield. Presumably, the removal of the TMS group involved a rare 1,4-Brook-rearrangement.\(^{33}\) Interestingly, the implementation of the TMS-methylene as a “traceless” directing group to improve diastereoselectivity appears to have little precedence in the literature.\(^{34}\)

Next, we turned to the introduction of the requisite C10 bromide from the corresponding hydroxy group. The steric hindrance of neopentyl alcohols makes them unsuitable toward C–O bond activation/nucleophilic displacement and is a notoriously difficult challenge in halogenation chemistry.\(^{35}\) In our previous non-biomimetic synthesis of aplydactone, we faced a similar challenge which we overcame with a late stage addition of the bromine source (see Figure B16, Supporting Information). The minor product 24 could arise via axial attack onto 23a, which we calculated to have an activation barrier of 25.6 kJ/mol. This is consistent with selectivities for equatorial vs axial attack reported in the literature\(^{28}\) and matches the observed diastereomeric ratio of 93:7. Alternatively, the minor isomer 24 could arise from equatorial attack onto the radical conformer 23b. However, we calculated that the activation barrier for the necessary ring inversion is 43.4 kJ/mol. This means that the unimolecular ring-flip is considerably slower than the bimolecular bromine transfer at the given concentrations and temperature and that the observed diastereoselectivity is solely due to the preferences of conformer 23a (see Figure B15, Supporting Information for details).

For the final stage of the synthesis, we sought to access dactylone (2) and 10-epi-dactylone (3) by exploiting the inherent pseudo-symmetry of 9. By implementing divergent oxidation strategies, it was possible to either “retain” or “invert” the stereocenter at C6 relative to the C10 bromide (Figure 9).\(^{38,39}\) Starting with 9, a catalytic Upjohn dihydroxylation proceeded with exclusive regio- and diastereoselectivity, providing 25 in nearly quantitative yield. Diol 25 could then be oxidized with IBX followed by dehydration with SOCl\(_2\) and pyridine, affording dactylone (2) in 66% yield over two steps. Very recently, this natural product was also reached by Snyder using a similar oxidative end game.\(^{22}\) Conversely, 10-epi-dactylone (3) could be obtained from 9 by an allylic oxidation using SeO\(_2\), which provided allylic alcohol 22 in moderate yield, followed by further oxidation with an excess of MnO\(_2\), consistent with the reaction sequence reported by Burns and co-workers.\(^{11}\) Using this strategy, we were able to reach both 2 and 3 in the racemic series from a single precursor, viz. chamigrane 9.

### PHOTOCHEMICAL [2 + 2] CYCLOADDITION OF DACTYLONE AND 10-EPI-DACTYLONE

With ample quantities of dactylone (2) and 10-epi-dactylone (3) in hand, we then proceeded to investigate their photochemistry.

![Figure 9. Synthesis of aplydactone and 8-epi-isoplydactone by stereodivergent synthesis and selective irradiation.](image-url)

Nysted/Utimoto reagent\(^{32}\) in the presence of TiCl\(_4\) which cleanly provided the desired exocyclic alkene 17 in good yield. For the explanation for this favorable outcome is shown in Figure 8. Attack of the methyl radical generated by thermal decomposition of hyponitrite 20 onto thiocarbamate 19 gives intermediary radical 22, which undergoes fragmentation to afford the secondary radical 23a. A fast bimolecular reaction with the bromine source 21 via an equatorial attack then gives the observed major product 9. This equatorial attack has a very low calculated activation barrier of 19.1 kJ/mol (see Figure B16, Supporting Information). The minor product 24 could arise via axial attack onto 23a, which we calculated to have an activation barrier of 25.6 kJ/mol. This is consistent with selectivities for equatorial vs axial attack reported in the literature\(^{28}\) and matches the observed diastereomeric ratio of 93:7. Alternatively, the minor isomer 24 could arise from equatorial attack onto the radical conformer 23b. However, we calculated that the activation barrier for the necessary ring inversion is 43.4 kJ/mol. This means that the unimolecular ring-flip is considerably slower than the bimolecular bromine transfer at the given concentrations and temperature and that the observed diastereoselectivity is solely due to the preferences of conformer 23a (see Figure B15, Supporting Information for details).

Figure 8. Stereoselectivity of the radical bromination of 19.
Using a Rayonet photoreactor, we irradiated dactylone at different wavelengths. When 2 was exposed to 300 nm UVB light, we observed rapid degradation and found only minor quantities of aplydactone in the crude product mixture. However, irradiation with 350 nm light (UVA) over a period of 24 h led to the complete conversion of dactylone (2) into aplydactone (1). The wavelength dependence and quantitative conversion of 2 to 1 corroborate results recently disclosed by the Burns lab.11 Finally, we found that exposure of 2 to Munich sunlight converted it to aplydactone over a period of 6 days in good agreement with Burns and co-workers.11

Our calculations show why the choice of a light source was so critical (Figure 10). Upon irradiation with 350 nm light (blue arrow, Figure 10), the majority of the S1 population undergoes energetically favorable ISC leading to the formation of aplydactone. However, 300 nm irradiation (purple arrow, Figure 10) deposits more energy (0.6 eV) into the system. Now a larger fraction of the excited molecules can reach the conical intersection of the S1 with the S2 state (S2/S1 CoIn, Figure 10). The S2 state is characterized by an excitation from the lone pair of the bromine to the antibonding σ*-orbital of the carbon–bromine bond (nBrσ*). At the Franck–Condon (FC) region, the S2 state is too high in energy to be reached by direct excitation under our reaction conditions (see Figure 10 and Table B1, Supporting Information). However, an elongation of the carbon–bromine bond stabilizes this state and leads to the conical intersection with the S1 state which is located 0.23 eV above the resonant S0–S1 transition and can therefore be accessed through the 300 nm excitation (see Table B3, Supporting Information). The population of the nBrσ* state leads to a minimum on the S1 potential energy surface (S1-Min (nBrσ*)) and to the homolytic cleavage of the carbon–bromine bond. The separated radical pair can then cause unwanted side reactions, resulting in the observed substrate degradation.

When 10-epi-dactylone (3) was irradiated with 350 nm light, 3 was converted to the [2 + 2] product 8, termed “8-epi-isoplydactone”, as the sole product in 97% yield. The conversion of 3 to 8 was complete in 3 h and is significantly faster than the conversion of 2 to 1. We were unable to detect the presence of 8-epi-aplydactone (7), which we had obtained in our previous nonbiomimetic synthesis.36

Again, our experimental results could be rationalized with excited state computations. Analogous to dactylone (2), for 10-epi-dactylone (3) the excitation to the S1 state of the preferred conformer 3b leads to a triplet minimum T1-Min2 (see section B.3, Supporting Information for details). From here, four different 1,4-diradicals (DR1-DR4) are possible as well (Figure 11). In the case of 3, the calculations reveal that the formation of 8-epi-isoplydactone (8) via the two diradical pathways DR3 and DR4 is preferred over the formation of 8-epi-aplydactone (7) through the diradical pathway DR2 (see section B.3.4, Supporting Information).

Figure 10. Schematic illustration of the homolytic cleavage of the carbon–bromine bond via the S2/S1 conical intersection after excitation to the S1 state of 2a. The bromine–carbon distances at the relevant optimized geometries are shown.

Figure 11. (a) Intercarbon distances for the reaction pathways leading to 8-epi-aplydactone (7) and 8-epi-isoplydactone (8) at the triplet minimum T1-Min2 of 3b. (b) Optimized geometries of the four triplet diradicals (3DR) possible from T1-Min2.
Taken together, our results demonstrate the powerful influence of the C10 bromide on the reaction outcome for 2 and 3. In both cases, the C10 bromide prefers the equatorial position and controls the conformation of the molecule in the ground state (2a and 3b in Figure 2). For dacltylone, the conformer 2a leads to the preferred formation of aplydacltyone (1). In contrast, for 10-epi-dacltylone (3) the conformer 3b favors the formation of “8-epi-isoplydacltyone”.

The configuration at C10 thus determines the conformation and controls the regioselectivity of the photochemical reaction. The facility with which 3 is converted into 8 and the biomimetic irradiation used suggests that “8-epi-isoplydacltyone” may also occur naturally in A. dactylomela. If this can be confirmed, it would be another case of natural product prediction through synthesis.5,23,40–44

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available on free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.6b00293.

Procedures for the synthesis of all compounds and characterization data, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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