

Effect of tether length on endo/exo stereoselectivity in alkene–arene meta-photocycloaddition reactions towards the Aphidocolin/Stemodin scaffolds

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Effect of Tether Length on *endo/exo* Stereoselectivity in Alkene–Arene *meta*-Photocycloaddition Reactions towards the Aphidocolin/Stemodin Scaffolds

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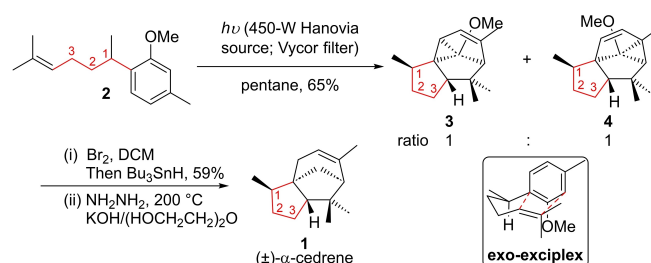
Intramolecular alkene-arene *meta*-photocycloadditions are powerful transformations that use the enhanced reactivity of photoexcited benzene rings to facilitate addition of an alkene 1,3 across donor groups and form complex three-dimensional fused-ring systems from readily accessible starting materials. Intramolecular examples have traditionally been restricted to

three-membered tethers, with cycloaddition resulting from *exo*-conformation. However, by judicious tether design we have demonstrated that a four-membered tether can also proceed in good yield; interestingly, *via* an *endo* exciplex (1.2:1) enabling access to both natural product skeletons and interesting scaffolds for medicinal chemistry research.

Introduction

The alkene-arene *meta*-photocycloaddition represents a hugely powerful transformation resulting in the dearomatisation of the arene ring and the formation of complex fused three-dimension scaffolds.^[1–3] Substantial investigations have been undertaken since its concomitant discovery by Bryce-Smith, Gilbert and Orger at Reading^[4] and Witzbach and Kaplan at Illinois^[5] with a view to taking advantage of the reaction's inherent ability to generate molecular complexity.^[6–10]

In 1969 Morrison and Ferree reported the first example of the intramolecular variant of this alkene-arene *meta*-photocycloaddition reaction^[11] and since then a general rule has emerged that reactions of substrates with a 3-atom tether leads to the reaction taking place with a strong preference for *exo*-stereoselectivity in the products. As shown in Scheme 1, Wender has used this excellent *exo*-selectivity as the key step for the synthesis of (±)- α -cedrene (1).^[12] Irradiation of the three-atom tether 2 (Scheme 1) formed a 1:1 mixture of regioisomers 3 and 4 derived from the *exo* exciplex. Treatment of this



Scheme 1. Alkene-arene *meta*-photocycloaddition with characteristic regioisomeric cyclopropane products, from Wender's synthesis of (±)- α -cedrene.^[12]

mixture with Br_2 , followed by radical debromination and Wolff-Kishner deoxidation provided (±)- α -cedrene (1). A final point of note is that ring opening of the cyclopropane photoproducts^[13] to form the bicyclo[3.2.1]octane ring system is well precedented using diverse reagents such as Pd/C with H_2 , *m*-CPBA, NIS and HCl (aq.) as reviewed by Rodriguez.^[14,15]

However, there are relatively few examples of four-membered tether systems and we were intrigued by the potential to access both the aphidicolin (5) and stemodin (6) ring systems (Figure 1) and hence facilitate the synthesis of analogue structures. Aphidicolin is a potent inhibitor of DNA replication,^[16] it and its prodrugs, 17-glycinat HCl salt and 16-fluoroaphidicolin have shown good activity against a range of tumour types.^[17,18] Stemodin has more limited bioactivity but, more recently, the closely related structure trigoheterone A has shown significant inhibitory effects toward five cancer cell lines (SW480, HL-60, A549, SMMC-7721 and MCF-7) with IC_{50} values similar to cisplatin.^[19,20] The interesting biology and unusual bicyclo[3.2.1]octane ring system have made both structures, and their derivatives, attractive targets for numerous total synthesis that have been thoroughly reviewed elsewhere.^[17,20–22] In considering the application of the alkene-arene *meta*-photocycloaddition reaction to these targets we had to consider

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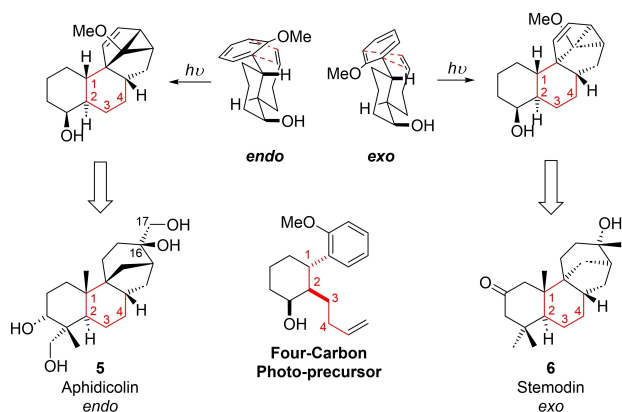


Figure 1. Stereochemical outcome of cycloadditions from *endo* and *exo* exciplexes to form aphidicolin and stemodin scaffolds, respectively.

several selectivity issues, including the mode of cycloaddition (*ortho/meta*), regioselectivity, stereoselectivity and the effect of tether length. If we examine a cycloaddition from which the skeleton of aphidicolin might be derived (Figure 1, left), although a *meta*-photocycloaddition is expected to be the favoured mode (relative to *ortho/para*) and an electron-donating methoxy group can be employed to control the regiochemistry of the addition,^[12] a number of studies have emphasized the strong preference for product formation *via* an *exo* rather than an *endo* exciplex.^[1,6–9] This suggests that the biologically potent aphidicolin system might be difficult to access.

In addition to the above considerations, simple substrates that feature tethers with four linking units (e.g. methylene carbons) have been found to have very poor quantum yields (e.g. 6-phenylhex-1-ene, $\phi < 0.005$ ^[23,24] whereas for *cis*-6-phenylhex-2-ene, a 3-carbon tether, $\phi = 0.26$ ^[11]). With regard to these later points, during a study of tandem Norrish Type I-intramolecular alkene-arene photocycloaddition reactions, De Keuleire described a highly *exo*-selective 4-atom tether example in 42% yield,^[25] and Wender and DeLong have noted a similarly highly *exo*-selective cycloaddition in 68% yield at 60% conversion for 4-atom tethers.^[26] More recently, Chen utilised a spiro-fused four-membered tether that adopted a boat-like conformation with exclusive *exo*-selectivity (>65% yield).^[27] What appears to distinguish these examples, which together represent the most efficient cycloadditions of this type, is some restriction of the conformational freedom of the tether,^[28,29] however, excessive steric encumbrance can significantly affect yields.^[30] Given that substrate **8** bearing a 4-unit tether illustrated in Figure 1 allows the system to adopt a geometry suitable for the formation of an *endo* exciplex (favoured for most intermolecular cases)^[1–3,6–9] without undue strain (see Supp. Info.) and that the presence of a fused six-membered ring should reduce the conformational freedom of the tether, we felt that such reactions might be successful. To test the influence of tether length and the inclusion of a six-membered ring in these systems we have synthesised and photolyzed the compounds **7**, **8** and **9** shown in Figure 2.^[31,32]

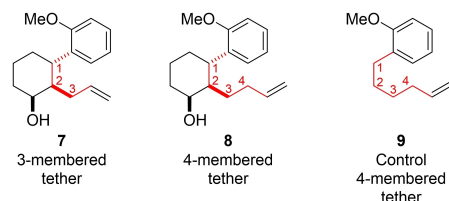


Figure 2. Substrates examined to determine the effect of tether structure on their alkene-arene *meta*-photocycloaddition reactions.

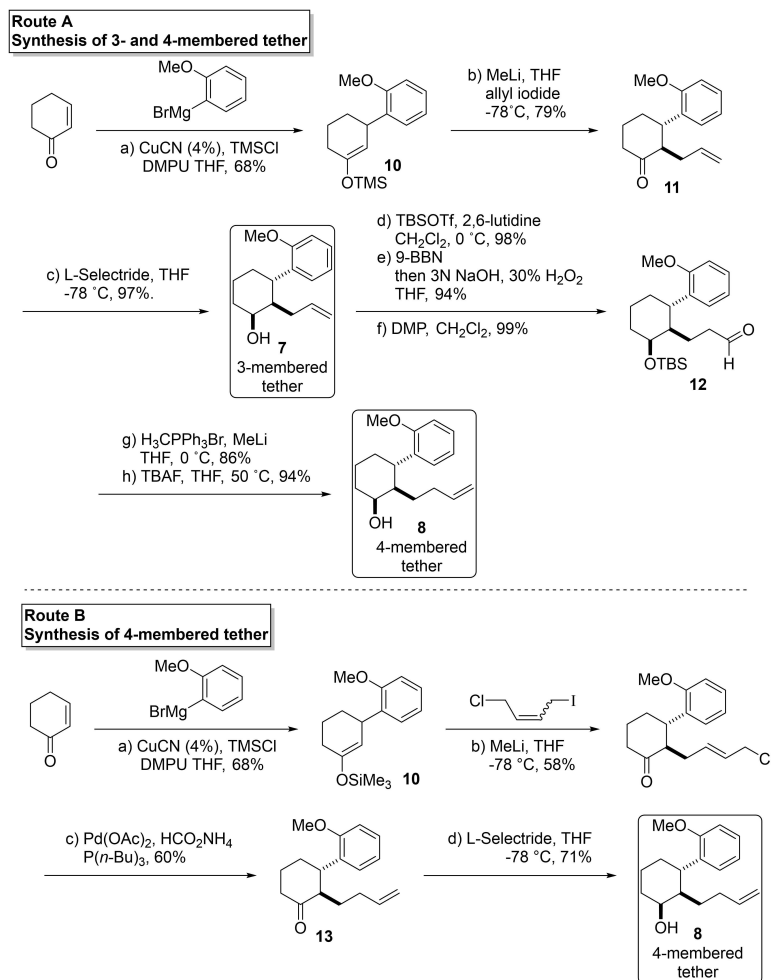
Results and Discussion

In a previous communication^[33] we described the synthesis of **7** and **8** and we now report a comparison of their relative photochemistries, together with a significantly improved synthesis of **8** (Scheme 2, bottom Route B) and full experimental details (see Supp. Info.). The initial synthesis route utilised a TMSCl accelerated, copper-catalysed addition of the Grignard reagent to cyclohexenone that afforded the silyl enol ether **10** in 68% yield (Scheme 2).^[34] This allowed regioselective generation of the lithium enolate from **10** with MeLi followed by alkylation with allyl iodide to provide **11** in 79% yield. To remove any complications from Norrish Type reactions the ketone was stereoselectively reduced with L-Selectride (97%) to give the substrate **7** with a three-membered tether as a crystalline solid.

Our initial hope of preparing the higher homologue **8** by alkylation of the lithium enolate derived from **10** with homoallyl iodide was compromised by its low reactivity and a severe allergic reaction to the reagent by a lab member. For our initial route, that would facilitate deuteration (see below), we elected to homologate **7** as shown in Scheme 2 (Route A, top). Protection of the axial alcohol was effected by treatment with TBDMS triflate, then hydroboration of the double bond with 9-BBN followed by a two-step oxidation to afford aldehyde **12** in 91% overall yield. Wittig reaction (86%) and subsequent fluoride-mediated cleavage of the silyl ether (94%) completed the sequence in eight steps from commercial materials. Subsequent work identified a more direct path, Route B (Scheme 2), that begins from the common silyl enol ether **10** and uses a modification of Lautens' procedure^[35] with 1-iodo,4-chloro-but-2-ene^[36] as the alkylation partner. Transfer hydrogenolysis^[37] provided the terminal alkene **13**, which was again reduced stereoselectively to form photo-precursor **8** in only four steps, compared to eight steps *via* Route A.

Comparison of the fluorescence quenching of **7** and **8** with that of their saturated analogues (hydrogenation over 10% Pd/C) revealed the expected strong interaction between the S_1 state of the arene and the alkene in **7** (three-membered tether) and a weaker but still significant quenching interaction for **8** (four-membered example; Figure 3).

We therefore subjected **7** and **8** to photolysis using both a falling film photoreactor and a bespoke flow photosystem at 254 nm (see Supp. Info.). First a degassed 0.8 mM solution of **7** in cyclohexane was irradiated for 1 h in the falling film reactor to give a 87% yield of photoadducts. Three main photo-



Scheme 2. Routes for the formation of the photoprecursors. **Top: Route A:** Synthesis of 7 and eight-step synthesis of 8. **Bottom: Route B:** Four-step synthesis of 8.

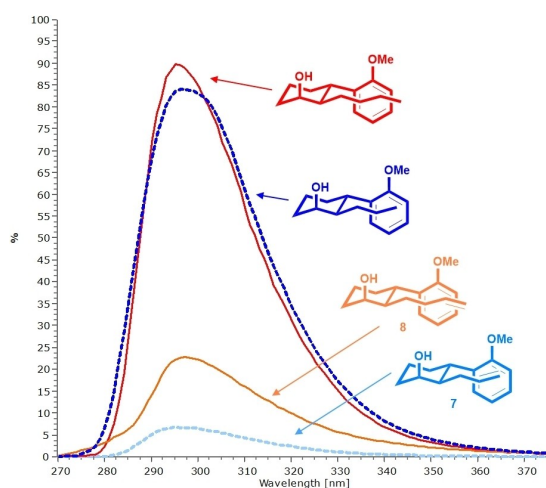
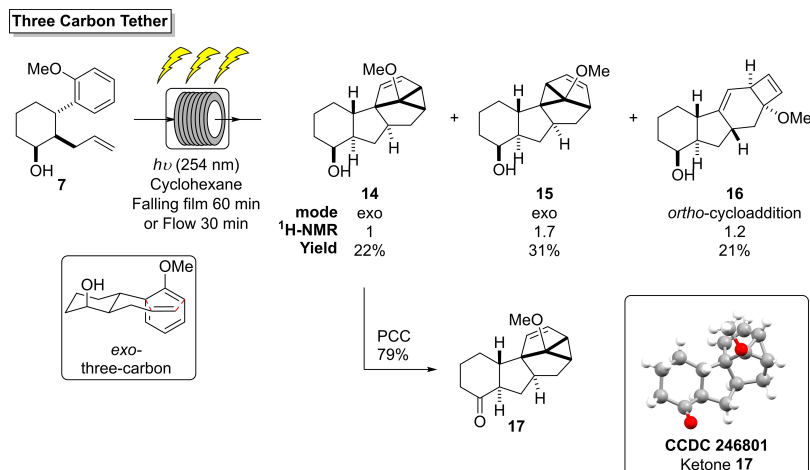


Figure 3. Fluorescence quenching of 7 and 8 upon irradiation of a 4 mM solution in cyclohexane at 267 nm.

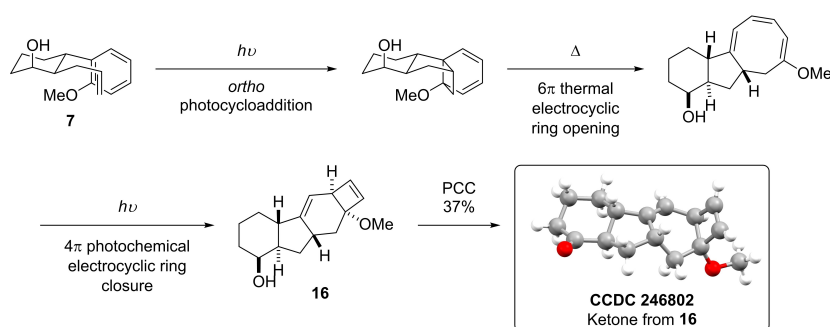
products **14:15:16** (1:1.7:1.2; ¹H-NMR) were isolated (74%) in a ratio of 1:1.4:1 accompanied by a small amount of a mixture of two other *meta*-cycloadducts (3.4:1.0; ¹H-NMR) which we

were unable to separate and identify (Scheme 3). When we used the 10 mL flow photochemical reactor coupled with a 25 W germicide lamp, similar to our previous publication,^[38] we found that a residence time of 30 min resulted in a very similar reaction outcome. A clear advantage of continuous flow photochemistry^[39–41] is that scalability can be simply achieved by running the system for longer – a process that is not possible using the batch-wise falling-film reactor.

The *meta*-adducts **14** and **15** are postulated to have formed from a common *exo*-exciplex arising from a reactive conformation of **7** shown in Scheme 3, bottom left. Addition of the alkene has occurred in the predicted manner across the electron-donating methoxy group and given rise to the characteristic regioisomeric cyclopropanes typical of this class of reactions. Although it is known that these types of isomer can undergo photochemical vinylcyclopropane-cyclopentene interconversion/rearrangement we did not observe much variation in the ratio of the two *meta*-products **14** and **15** in our studies.^[24,42] Furthermore, upon oxidation of **14** with pyridinium chlorochromate (PCC, 79%) we were able to solve a single crystal X-ray structure of ketone **17** providing us with further confidence for our assignment.^[43]



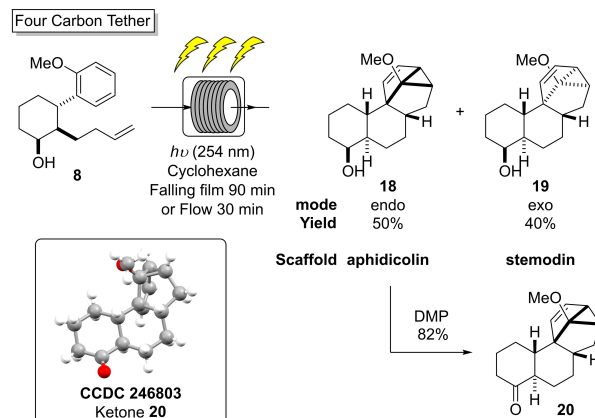
Scheme 3. Photolysis of the 3-membered tether 7..

Scheme 4. Possible *exo* conformation of 7 leading to an *ortho*-photocycloaddition and subsequent rearrangement to give 16.

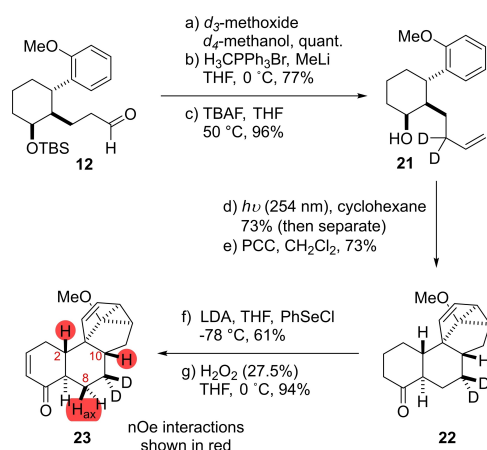
A significant amount of tetracycle 16 was also seen. Such compounds have previously been found to arise from both S_1 [44–50] and T_1 [51–54] states of benzene derivatives, however, in this case it is most likely that the S_1 state is implicated. Of particular interest is the stereochemistry at C-3 of 16 as it is opposite to that seen in the two *meta*-adducts. The simplest, though by no means only, interpretation of this result is *ortho* addition arises from a different reactive (*exo*) conformation of 7 depicted in Figure 1 followed by a tandem thermal 6 π -electrocyclic ring opening then 4 π -photochemical electrocyclic ring closure (Scheme 4).

By contrast, photolysis of a 0.4 mM solution of substrate 8, bearing a four-membered tether, in cyclohexane using the falling film system for 90 minutes or 30 minutes in flow afforded a 1.2:1.0 mixture of mainly two photoadducts, 18 and 19, in a remarkable 90% yield (Scheme 5). The structure of the major product 18 was solved by a single crystal X-ray structure of the ketone derivative 20, and shown to arise from an *endo* conformation and it also possesses the correct relative stereochemistry for aphidicolin.

Due to the poor dispersal of resonances, especially in the high-field/aliphatic region (15 protons), we were initially unable to directly assign the structure and stereochemistry of 18 by NMR techniques. Taking advantage of the homologation sequence we had initially used to prepare 8 (Route A), the

Scheme 5. Four-membered *endo*-selective intramolecular photochemical cycloaddition of 8.

aldehyde 12 was dideuterated using d_3 -sodium methoxide in d_4 -methanol then converted to 21 as described above (Scheme 5). Photolysis followed by oxidation with PCC [55] afforded ketone 22 which on desaturation, to form enone 23 by the Sharpless-Reich protocol, [56,57] allowed the relative stereochemistry at C-10 to be established by nOe with irradiation of H-2 and H-8 (axial) showing a significant enhancement at H-10 (Scheme 6). Deuteration for spectral simplification has been



Scheme 6. Synthetic sequence to aid in the structural assignment of **14** featuring deuteration and desaturation to simplify the ^1H -NMR spectrum.

commonly used in systems with repeating units such as proteins^[58,59] and nucleic acids,^[60] but our combined deuteration and desaturation protocol, in effect removing six of the 15 protons, is an underused approach for the structural determination of small molecules and offers an alternative approach for when single crystal X-ray techniques are impractical.

Thus, in contrast to the photolysis of three-membered tether **7**, four-membered **8** exhibited a rare high regioselectivity of cyclopropane formation,^[6,61–63] with the minor product **19** arising from the conformation analogous to the *exo* arrangement shown in Figure 1 and proceeding *via* an *exo* exciplex to give a relative stereochemistry appropriate for the stemodin ring system (Scheme 5). As described, we have a stereo-divergent route for the synthesis of both aphidocolin (*endo*) and stemodin (*exo*) ring systems, with reasonable selectivity (1.2:1) for the aphidocolin scaffold. By comparison, the interesting report of Chen on synthetic studies toward the skeleton of lancifodilactone **F** showed a strong preference for *exo* selectivity.^[27] Further studies will explore the influence of additional substituents on this stereoselectivity.

As a final demonstration that careful consideration of the identity of the tether is required, the linear control compound **9** (Figure 2) was prepared according to the procedure of Fuhrer^[64,65] and subjected to photolysis under the standard conditions. Monitoring of the reaction by ^1H -NMR showed an initial build-up of two main *meta*-adducts followed by a rapid deterioration of the product mixture with formation of many products. Polymer formation has been reported for some other inefficient photocycloadditions.^[66]

Conclusions

In summary, we have carried out intramolecular alkene-arene *meta*-photocycloaddition reactions on two homologous substrates **7** and **8** possessing three- and four-membered tethers, respectively, and have observed a high-yielding reaction in each case. As was precedented, the shorter three-membered

homologue **7** reacted *via* *exo* exciplexes but of most interest the higher four-membered homologue **8** shows a reasonable preference (1.2:1, chemical yield) for the *endo* arrangement, the first such intramolecular example to do so. Taken together with the previously described *exo*-favoured 4-atom tether examples,^[25–27] these results show that, with careful design of the tether, the restriction of using three linking unit tethers in this type of reaction is no longer valid. The key photochemical step has been performed in a continuous flow manner (residence time 30 minutes), providing the possibility for scaling up/out.^[40,67] Furthermore, we have demonstrated that the observation of intramolecular fluorescence quenching (Figure 3) can provide a robust initial guide to the success of these systems under photolysis. We have an effective 3-component modular synthesis (enone, arene and alkene) holding the promise of a rapid entry into the aphidicolin/stemodin ring systems and thence to afford biologically active analogues. A single photochemical step produces three C–C bonds, three rings and five stereocentres without the use of a chemical reagent. The final photoproducts (**18** and **19**) themselves offer much further promise of diversification possessing ‘spring-loaded’ ring-fused vinyl cyclopropanes. Finally, the observation of preferential *exo* selectivity in the case of lancifodilactone **F**^[27] suggests that, in addition to tether length, steric factors are also likely to be significant in determining stereoselectivity; further studies on this point are in progress.

Experimental Section

Photolysis of the 3-Carbon Tether Substrate (**7**)

Falling film: A 8.3 mM solution of (\pm) (*1S*, *2R*, *3S*)-2-allyl-3-(2'-methoxyphenyl)cyclohexanol (**7**) was prepared by dissolving 0.204 g (0.83 mmol) of the substrate in cyclohexane (100 ml). The flask was connected to a condenser and placed inside a thin-film photoreactor containing a low-pressure mercury arc lamp. The photoreactor pump was initiated and the system was completely de-gassed by bubbling nitrogen through the solution for 1 hour. After this time the flow of nitrogen was stopped and the lamp was switched on. After 1 hour of photoreaction TLC and NMR indicated that no more starting material remained and that four major photoproducts appeared to have formed. The reaction mixture was transferred to a separate flask before the system was thoroughly washed through with cyclohexane (4x50 ml). All the washings were collected together and concentrated *in vacuo* to give a crude yellow oil. The three major products were separated from all the reaction by-products and then purified using flash column chromatography by gradually increasing the solvent polarity (95:5 \rightarrow 90:10 \rightarrow 85:15 petroleum ether [40–60]/ethyl acetate).

Fraction 3 contained (\pm) (*1S*, *2S*, *6S*, *7R*, *9S*, *11S*, *12R*, *15R*)-15-methoxypentacyclo[10.2.1.0^{1,9}.0^{2,7}.0^{11,15}]pentadec-13-en-6-ol (**14**) as a pure colourless oil (0.044 g, 21%). Fraction 2 contained (\pm) (*1S*, *3S*, *5R*, *6S*, *10S*, *11S*, *12R*, *15R*)-15-methoxypentacyclo[10.2.1.0^{3,11}.0^{5,10}.0^{11,15}]pentadec-13-en-6-ol (**15**) as a pure colourless oil (0.063 g, 31%). Fraction 1 contained (\pm) (*1S*, *3S*, *5R*, *6S*, *10S*, *13R*)-1-methoxytetracyclo[11.2.0^{1,13}.0^{3,11}.0^{5,10}]pentadec-11,14-dien-6-ol (**16**) as a pure cream coloured solid (0.044 g, 22%).

Flow Photochemistry Continuous Flow / One Pass Manner: The flask containing a 4 mM solution of (\pm) (*1S*, *2R*, *3S*)-2-allyl-3-(2'-

methoxyphenyl)cyclo-hexanol (7) in cyclohexane was connected to the flow system by threading the input tube through a red rubber septa and the output went into the collection flask. The flow system using consists of a Vapourtec peristaltic pump, and a 10 mL reactor placed around a 25 W germicide lamp inside a light box with a gentle flow of compressed air for cooling (not essential). The reaction mixture was degassed by bubbling N₂ for 20 minutes and then a balloon was used to keep the flask under a positive pressure of N₂. As the ATOI/Actual Time Of Irradiation for this 10 mL reactor system was known (30 minutes), the reaction was then performed in a continuous manner with a residence time of 30 minutes by flowing at 0.3 mL/min (10 mL/30 minutes).

Photolysis of the 4-Carbon Tether Substrate (8)

A 4.5 mM solution of (±) (1*S*, 2*R*, 3*S*)-2-but-3'-enyl-3-(2''-methoxyphenyl)cyclo-hexanol (8) (0.118 g, 0.45 mmol) in cyclohexane (100 ml) was irradiated for 1.5 hours until TLC and NMR spectroscopy indicated that no more starting material remained. Analysis also suggested that two major products had formed. All the washings from the thin film photoreactor were collected together and concentrated *in vacuo* to give a crude yellow oil. The two main photoproducts were separated from all the reaction by-products and then purified using flash column chromatography by gradually increasing the solvent polarity (95:5→90:10→85:15 petroleum ether [40–60]/diethyl ether).

Fraction 1 contained (±) (1*R*, 2*S*, 6*S*, 7*R*, 10*S*, 12*R*, 13*S*, 16*S*)-16-methoxypentacyclo[11.2.1.0^{1,10}.0^{2,7}.0^{12,16}]hexadec-14-en-6-ol (19) as a pure colourless oil (0.048 g, 40%). Fraction 2 contained (±) (1*S*, 2*S*, 6*S*, 7*R*, 10*S*, 12*S*, 13*R*, 16*R*)-16-methoxypentacyclo[11.2.1.0^{1,10}.0^{2,7}.0^{12,16}]hexadec-14-en-6-ol (18) as a pure solid (0.059 g, 50%).

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Conflict of Interests

The authors declare no conflict of interest.

Keywords: meta-Photocycloaddition · Photochemistry · Aphidicolin · Stemodin · Continuous flow

- [1] T. Gaich, in *Compr. Org. Synth. II*, Elsevier, **2014**, pp. 703–731.
- [2] R. Remy, C. G. Bochet, *Chem. Rev.* **2016**, *116*, 9816–9849.
- [3] P. A. Wender, R. Ternansky, M. DeLong, S. Singh, A. Olivero, K. Rice, *Pure Appl. Chem.* **1990**, *62*, 1597–1602.
- [4] D. Bryce-Smith, A. Gilbert, B. H. Orger, *Chem. Commun. (London)* **1966**, 512–514.
- [5] K. E. Wilzbach, L. Kaplan, *J. Am. Chem. Soc.* **1966**, *88*, 2066–2067.
- [6] J. Cornelisse, *Chem. Rev.* **1993**, *93*, 615–669.
- [7] N. Hoffmann, *Synthesis* **2004**, 481–495.
- [8] D. Chappell, A. T. Russell, *Org. Biomol. Chem.* **2006**, *4*, 4409–4430.
- [9] T. Gaich, J. Mulzer, *J. Am. Chem. Soc.* **2009**, *131*, 452–453.
- [10] S. Clifford, M. J. Bearpark, F. Bernardi, M. Olivucci, M. A. Robb, B. R. Smith, *J. Am. Chem. Soc.* **1996**, *118*, 7353–7360.
- [11] H. Morrison, W. I. Ferree, *J. Chem. Soc. D* **1969**, 268–269.
- [12] P. A. Wender, J. J. Howbert, *J. Am. Chem. Soc.* **1981**, *103*, 688–690.
- [13] M. Meazza, H. Guo, R. Rios, *Org. Biomol. Chem.* **2017**, *15*, 2479–2490.
- [14] M. Pisset, Y. Coquerel, J. Rodriguez, *Chem. Rev.* **2013**, *113*, 525–595.
- [15] M. Kovac, M. Anderluh, J. Vercouillie, D. Guilloteau, P. Emond, S. Mavel, *J. Fluorine Chem.* **2013**, *147*, 5–9.
- [16] A. G. Baranovskiy, N. D. Babayeva, Y. Suwa, J. Gu, Y. I. Pavlov, T. H. Tahirov, *Nucleic Acids Res.* **2014**, *42*, 14013–14021.
- [17] M. Toyota, M. Ihara, *Tetrahedron* **1999**, *55*, 5641–5679.
- [18] M. Toyota, M. Sasaki, M. Ihara, *Org. Lett.* **2003**, *5*, 1193–1195.
- [19] D. A. Leonard, H. W. Chen, *J. Biol. Chem.* **1984**, *259*, 4904–4909.
- [20] S. Chen, T. Chen, G. Liu, X. Wang, G. Zhu, Y. Liu, S. Fu, B. Liu, *Org. Biomol. Chem.* **2019**, *17*, 4711–4714.
- [21] J. R. Hanson, *J. Chem. Res.* **2018**, *42*, 395–401.
- [22] F. Leonelli, L. M. Migneco, A. Valletta, R. Marini Bettolo, *Molecules* **2021**, *26*, 2761.
- [23] W. Ferree, J. B. Grutzner, H. Morrison, *J. Am. Chem. Soc.* **1971**, *93*, 5502–5512.
- [24] H. A. Neijenesch, E. J. Ridderikhoff, C. A. Ramsteijn, J. Cornelisse, *J. Photochem. Photobiol. A* **1989**, *48*, 317–336.
- [25] D. De Keukeleire, S. He, *J. Chem. Soc. Chem. Commun.* **1992**, 419–420.
- [26] P. A. Wender, M. A. DeLong, *Tetrahedron Lett.* **1990**, *31*, 5429–5432.
- [27] Q. Wang, C. Chen, *Org. Lett.* **2008**, *10*, 1223–1226.
- [28] C. S. Penkett, P. J. Brann, J. A. Woolford, R. J. Kahan, *Chem. Commun.* **2013**, 49, 1106.
- [29] C. S. Penkett, P. W. Byrne, B. J. Teobald, B. Rola, A. Ozanne, P. B. Hitchcock, *Tetrahedron* **2004**, *60*, 2771–2784.
- [30] T. R. Hoye, *Tetrahedron Lett.* **1981**, *22*, 2523–2526.
- [31] H. M. Barentsen, E. G. Talman, D. P. Piet, J. Cornelisse, *Tetrahedron* **1995**, *51*, 7469–7494.
- [32] H. M. Barentsen, A. B. Sieval, J. Cornelisse, *Tetrahedron* **1995**, *51*, 7495–7520.
- [33] J. W. Boyd, N. Greaves, J. Kettle, A. T. Russell, J. W. Steed, *Angew. Chem. Int. Ed.* **2005**, *44*, 944–946.
- [34] S. Yoo, K. Y. Yi, *Synlett* **1990**, 697–699.
- [35] G. Hughes, M. Lautens, J. Wu, *Synlett* **2000**, 835–837.
- [36] J. Robertson, H. W. Lam, S. Abazi, S. Roseblade, R. K. Lush, *Tetrahedron* **2000**, *56*, 8959–8965.
- [37] J. Tsuji, T. Mandai, *Synthesis* **1996**, 1–24.
- [38] J. S. Babra, A. T. Russell, C. D. Smith, Y. Zhang, *Tetrahedron* **2018**, *74*, 5351–5357.
- [39] C. Sambigao, T. Noël, *Trends Chem.* **2020**, *2*, 92–106.
- [40] T. H. Rehm, *Chem. A Eur. J.* **2020**, *26*, 16952–16974.
- [41] D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, *116*, 10276–10341.
- [42] P. A. Wender, G. B. Dreyer, *Tetrahedron* **1981**, *37*, 4445–4450.
- [43] Deposition Numbers **CCDC-246801** (17), **CCDC-246802** (ketone of 16) and **CCDC-246803** (20) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.
- [44] K. B. Cosstick, M. G. B. Drew, A. Gilbert, *J. Chem. Soc. Chem. Commun.* **1987**, 1867–1868.
- [45] J. Mani, S. Schüttel, C. Zhang, P. Bigler, C. Müller, R. Keese, *Helv. Chim. Acta* **1989**, *72*, 487–495.
- [46] C. Zhang, D. Bourgin, R. Keese, *Tetrahedron* **1991**, *47*, 3059–3074.
- [47] S. Y. Al-Qaradawi, K. B. Cosstick, A. Gilbert, *J. Chem. Soc. Perkin Trans. 1* **1992**, 1145–1148.

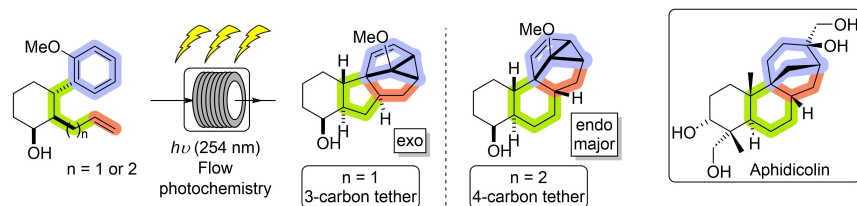
- [48] D. C. Blakemore, A. Gilbert, *J. Chem. Soc. Perkin Trans. 1* **1992**, 2265–2270.
- [49] D. De Keukeleire, S.-L. He, D. Blakemore, A. Gilbert, *J. Photochem. Photobiol. A* **1994**, 80, 233–240.
- [50] A. G. Avent, P. W. Byrne, C. S. Penkett, *Org. Lett.* **1999**, 1, 2073–2075.
- [51] P. J. Wagner, M. Sakamoto, *J. Am. Chem. Soc.* **1992**, 114, 7298–7299.
- [52] P. J. Wagner, R. P. Smart, *Tetrahedron Lett.* **1995**, 36, 5135–5138.
- [53] P. J. Wagner, K. Nahm, *J. Am. Chem. Soc.* **1987**, 109, 4404–4405.
- [54] P. J. Wagner, C. Kung-Lung, *Tetrahedron Lett.* **1993**, 34, 907–910.
- [55] E. J. Corey, J. W. Suggs, *Tetrahedron Lett.* **1975**, 16, 2647–2650.
- [56] H. J. Reich, I. L. Reich, J. M. Renga, *J. Am. Chem. Soc.* **1973**, 95, 5813–5815.
- [57] K. B. Sharpless, R. F. Lauer, A. Y. Teranishi, *J. Am. Chem. Soc.* **1973**, 95, 6137–6139.
- [58] D. M. LeMaster, *Annu. Rev. Biophys. Biophys. Chem.* **1990**, 19, 243–266.
- [59] M. Sattler, S. W. Fesik, *Structure* **1996**, 4, 1245–1249.
- [60] C. K. Brush, M. P. Stone, T. M. Harris, *Biochemistry* **1988**, 27, 115–122.
- [61] D. M. Amey, A. Gilbert, D. T. Jones, *J. Chem. Soc. Perkin Trans. 2* **1998**, 213–218.
- [62] P. A. Wender, T. W. Von Geldern, B. H. Levine, *J. Am. Chem. Soc.* **1988**, 110, 4858–4860.
- [63] D. C. Blakemore, A. Gilbert, *Tetrahedron Lett.* **1995**, 36, 2307–2310.
- [64] W. Fuhrer, F. Ostermayer, M. Zimmermann, M. Meier, H. Mueller, *J. Med. Chem.* **1984**, 27, 831–836.
- [65] J. L. Kelley, J. A. Linn, J. W. T. Selway, *J. Med. Chem.* **1989**, 32, 1757–1763.
- [66] G. C. R. Ellis-Davies, A. Gilbert, P. Heath, J. C. Lane, J. V. Warrington, D. L. Westover, *J. Chem. Soc. Perkin Trans. 2* **1984**, 1833–1841.
- [67] D. Cambié, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.* **2016**, 116, 10276–10341.
- [68] K. V. Baker, J. M. Brown, N. Hughes, A. J. Skarnulis, A. Sexton, *J. Org. Chem.* **1991**, 56, 698–703.
- [69] P. Pracht, F. Bohle, S. Grimme, *Phys. Chem. Chem. Phys.* **2020**, 22, 7169–7192.
- [70] F. Neese, F. Wennmohs, U. Becker, C. Riplinger, *J. Chem. Phys.* **2020**, 152, 224108.
- [71] M. D. Hanwell, D. E. Curtis, D. C. Lonie, T. Vandermeersch, E. Zurek, G. R. Hutchison, *J. Cheminf.* **2012**, 4, 17.
- [72] C. Bannwarth, S. Ehlert, S. Grimme, *J. Chem. Theory Comput.* **2019**, 15, 1652–1671.
- [73] D. Qiu, P. S. Shenkin, F. P. Hollinger, W. C. Still, *J. Phys. Chem. A* **1997**, 101, 3005–3014.
- [74] A. D. Becke, *J. Chem. Phys.* **1992**, 96, 2155–2160.
- [75] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, 37, 785–789.
- [76] F. Weigend, R. Ahlrichs, *Phys. Chem. Chem. Phys.* **2005**, 7, 3297–3305.
- [77] F. Weigend, *Phys. Chem. Chem. Phys.* **2006**, 8, 1057–1065.
- [78] B. Helmich-Paris, B. de Souza, F. Neese, R. Izsák, *J. Chem. Phys.* **2021**, 155, 104–109.
- [79] S. Grimme, S. Ehrlich, L. Goerigk, *J. Comput. Chem.* **2011**, 32, 1456–1465.
- [80] S. Grimme, J. Antony, S. Ehrlich, H. Krieg, *J. Chem. Phys.* **2010**, 132, 154104.
- [81] V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, 102, 1995–2001.
- [82] B. H. Lipshutz, B. Frieman, *Tetrahedron* **2004**, 60, 1309–1316.

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Intramolecular alkene-arene *meta*-photocycloaddition reactions are powerful '*reagentless*' transformations that form complex three-dimensional fused-ring systems from readily accessible starting materials. By judicious

tether design in combination with continuous flow it is demonstrated that substrates with a four-membered tether can also undergo *meta*-photocycloaddition in good yield, enabling access to natural product skeletons.

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Effect of Tether Length on *endo/exo* Stereoselectivity in Alkene–Arene *meta*-Photocycloaddition Reactions towards the Aphidocolin/Stemodin Scaffolds

