Photocycloaddition

Alkene–Arene *meta* Photocycloadditions with a Four-Carbon-Atom Tether: Efficient Approach toward the Polycyclic Ring Systems of Aphidicolin and Stemodinone**

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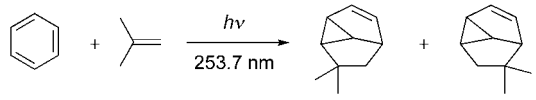
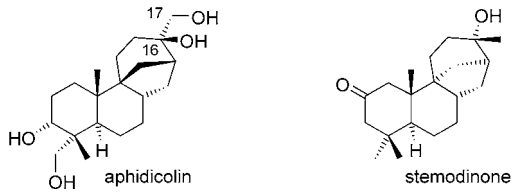
Since its contemporaneous discovery in 1966 by Bryce-Smith, Gilbert, and Orger at Reading, and Wilzbach and Kaplan at Illinois, the photochemical *meta* cycloaddition of alkenes to arenes has provided considerable inspiration for mechanistic and synthetic studies (Scheme 1).[1–4] Extensive experimental and theoretical investigations of this reaction over the ensuing 38 years have greatly advanced the understanding of its mechanism and synthetic potential,[3–5] although much remains to be addressed. In 1969, Morrison and Ferree reported the first example of the intramolecular variant of this reaction.[6]



Scheme 1. Alkene–arene *meta* cycloaddition with characteristic regioisomeric cyclopropane products.[3]

We speculated that use of this reaction might give a rapid entry into the aphidicolin/stemodin ring system and hence facilitate the synthesis of analogue structures.[7] Aphidicolin and its prodrugs, 17-glycinate HCl salt and 16-fluoroaphidicolin, have shown good activity against a range of tumor types,[7] and the use of aphidicolin and its hydroxylated analogues against *leishmanial* parasites has also been discussed.[8]



To apply this reaction to these targets, we had to assess several selectivity issues including the mode of cycloaddition (*ortho*/*meta*), the regio- and stereoselectivity, and the effect of tether length. With regard to the skeleton of aphidicolin (Figure 1), although a *meta* cycloaddition is expected to be the favored mode and while an electron-donating methoxy group can be employed to control the regiochemistry of the addition,[9] a number of studies have emphasized the strong preference for product formation through an *exo* rather than an *endo* exciplex.[3,4] This preference suggests that the biologically potent aphidicolin system might be difficult to access.

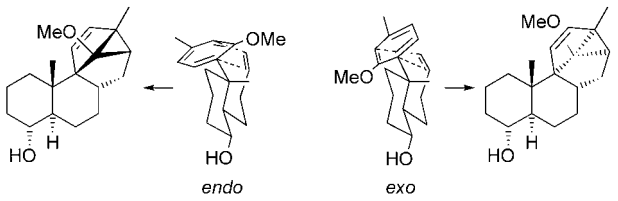


Figure 1. Stereochemical outcome of cycloadditions from *endo* and *exo* exciplexes.

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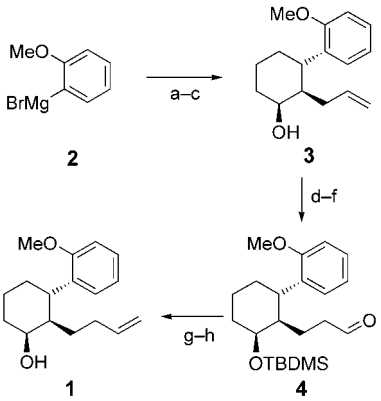
Besides these considerations, simple substrates which feature tethers with four linking units (e.g. CH_2 groups) are reported to have very poor quantum yields (e.g. 6-phenylhex-1-ene, $\varphi < 0.005$,[10] whereas for *cis*-6-phenylhex-2-ene, $\varphi = 0.26$).[6,11] During a study of tandem Norrish Type I intramolecular alkene–arene photocycloaddition reactions, De Keukeleire and He described a highly *exo*-selective reaction that proceeded in 42% yield, whereas DeLong and Wender noted a highly *exo*-selective cycloaddition with 68% yield of product at 60% conversion for four-atom tethers.[12] What appears to distinguish these two examples, which together represent the most efficient cycloadditions of this type, is some restriction of the conformational freedom of the tether. Given that 1) the four-unit tether illustrated in Figure 1 allows the system to adopt a geometry that is suitable for the formation of an *endo* exciplex (favored for most intermolecular cases)[3,4] without undue strain and 2) that the presence of the necessary fused six-membered ring should reduce the conformational freedom of the tether, we felt that such reactions might be successful.

Thus, we synthesized and photolyzed compound **1**. Chlorotrimethylsilane-accelerated, copper-catalyzed addition of **2** to cyclohexenone[13] afforded the expected silyl enol ether in 68% yield. Generation of the corresponding lithium enolate, by treatment with methyl lithium, was followed by alkylation with allyl iodide. Then, to avoid any complications from Norrish-type reactions, the ketone was stereoselectively reduced with L-selectride (lithium tri-*sec*-butylborohydride) to give the axial alcohol **3** as a crystalline solid in an overall yield of 77% (Scheme 2).[14]

The initial hope of preparing **1** by alkylation with homoallyl iodide was compromised by its low reactivity and a severe allergic reaction to the reagent by one of us. Thus we elected to homologate **3** as shown in Scheme 2. The axial alcohol was protected by treatment of **3** with *tert*-butyldimethylsilyl (TBDMS) triflate, then hydroboration of the double bond with 9-BBN followed by a two-step oxidation reaction afforded aldehyde **4** in 91% overall yield. A Wittig reaction (86%) and subsequent fluoride-mediated cleavage of the silyl ether (94%) completed the sequence.



Scheme 2. Synthesis of substrate **1**. Reagents and conditions: a) CuCN (4%), TMSCl, DMPU, THF, cyclohex-2-enone, 68%; b) MeLi, THF, allyl iodide, −78°C, 79%; c) L-selectride, THF, −78°C, 97%; d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 98%; e) 9-BBN then NaOH (3 N), 30% H_2O_2, THF, 94%; f) Dess–Martin periodinane, CH_2Cl_2, 99%; g) H_3CPPh_3Br, MeLi, THF, 0°C, 86%; h) TBAF, THF, 50°C, 94%. TMS = trimethylsilyl, DMPU = *N*,*N*′-dimethyl-*N*,*N*′-propylene urea, TBDMS = *tert*-butyldimethylsilyl, 9-BBN = 9-Borabicyclo[3.3.1]nonane, TBAF = tetra-*n*-butylammonium fluoride.

Comparison of the fluorescence quenching of **1** with that of its saturated analogue **5** (formed by quantitative hydrogenation of **1** over 10% Pd/C) revealed a fairly strong interaction between the excited-singlet state S_1 of the arene and the alkene (Figure 2). Therefore, a solution of **1** in

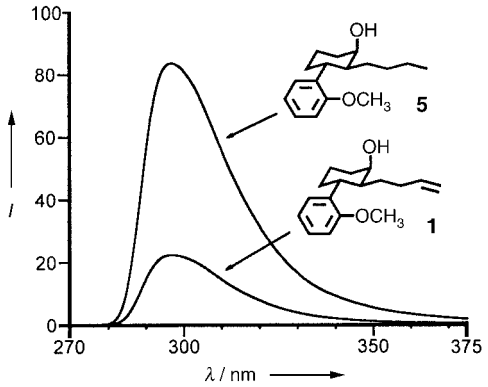
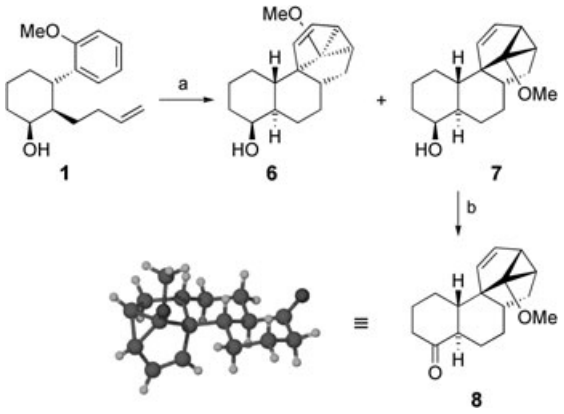


Figure 2. Fluorescence quenching of **1** and **5** in cyclohexane (4 mM) upon irradiation at $\lambda = 267$ nm.

cyclohexane (0.45 mM) was photolyzed in a falling-film photoreactor[15] at $\lambda = 253.7$ nm for 1.5 h. Such photolysis afforded a 1.0:1.2 mixture of two main photoadducts **6** and **7** in a remarkable 90% yield (Scheme 3). The structure of the

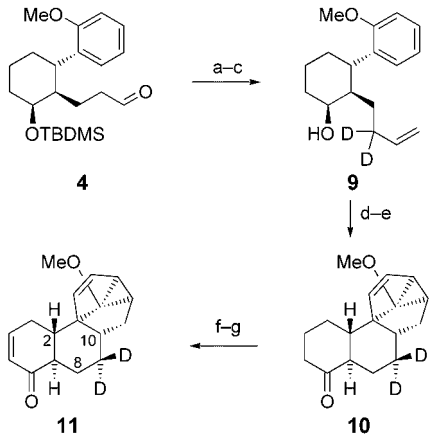


Scheme 3. *Endo*-selective intramolecular photochemical cycloaddition of **1**. Reagents and conditions: a) *hν* ($\lambda = 253.7$ nm), cyclohexane, 90% (**6**:**7**, 1.0:1.2); b) Dess–Martin periodinane, CH_2Cl_2, 81%.

major product **7** was solved by a single-crystal X-ray structure of the ketone derivative **8** and shown to arise from an *endo* conformation analogous to that shown in Figure 1.[16] The product **7** also exhibits the correct relative stereochemistry for aphidicolin.

Owing to the poor dispersal of resonances, we were unable to directly assign the structure and stereochemistry of **6** by NMR spectroscopic techniques. Taking advantage of the

homologation sequence we had developed to prepare **1** (Scheme 2), the aldehyde **4** was dideuterated by using sodium deuteromethoxide in deuterated methanol and then converted into **9** as shown in Scheme 4. Photolysis of **9** followed



Scheme 4. Structural assignment of **6**. Reagents and conditions: a) sodium [D_3]methoxide, [D_4]MeOH; b) H_3CPPh_3Br, MeLi, THF, 0 °C, 77%; c) TBAF, THF, 50 °C, 96%; d) *hν* ($\lambda = 253.7$ nm), cyclohexane, 73% (then separate); e) PCC, CH_2Cl_2, 73%; f) LDA, THF, PhSeCl, −78 °C, 61%; g) H_2O_2 (27.5%), THF, 0 °C, 94%. PCC = pyridinium chlorochromate, LDA = lithium diisopropylamide.

by oxidation of the product with pyridinium chlorochromate[17] afforded ketone **10**, which on desaturation to **11** by the Sharpless–Reich protocol[18] allowed the relative stereochemistry at C-10 to be established by NOE measurements with irradiation of H-2 and H-8(axial) that showed a significant enhancement at H-10 (Scheme 4). Thus, **1** exhibited a rare high regioselectivity of cyclopropane formation[3,19] to give **6** starting from a conformation that is analogous to the *exo* arrangement shown in Figure 1 and proceeding by an *exo* exciplex to give a relative stereochemistry that is appropriate for the stemodinone ring system (Scheme 3).

In summary, an intramolecular alkene–arene *meta* photocycloaddition has been carried out on **1** in a high yielding reaction despite the presence of a four-carbon-atom tether. Furthermore, this is a unique example of such a reaction proceeding with a preference for an *endo* exciplex in an intramolecular case. Taken with De Keukeleire's and Wender's examples, these results show that with careful design of the tether, the restriction of three-linking-unit tethers in this type of reaction is no longer valid. The products of these reactions hold promise of a rapid entry into the aphidicolin/stemodinone ring systems and to yield biologically active analogues.

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