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Dialkylated Dihydroazulene / Vinylheptafulvene Derivatives – Synthesis and Switching Properties

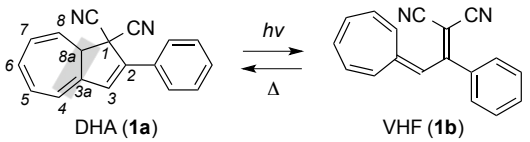
Nickie C. M. Lubrin,[a] Alexandru Vlasceanu,[a] Benjamin N. Frandsen,[a] Anders B. Skov,[a] Martin Drøhse Kilde,[a] Kurt V. Mikkelsen[a] and Mogens Brøndsted Nielsen*[a]

Abstract: Functionalization of molecular photoswitches at specific positions offers a way of tuning their switching properties. The work presented here describes the development of a new protocol towards the synthesis and functionalization of the dihydroazulene/vinylheptafulvene (DHA/VHF) photo-/thermoswitch. The key step is a facile condensation reaction using a functionalized tropone derivative, and the new synthetic method was employed in the regioselective preparation of a novel dimethyl-substituted DHA photoswitch. This compound presents the first accessible derivative incorporating alkyl groups in the seven-membered ring of the system – at positions C5 and C7. From experimental and theoretical kinetics studies on the thermal VHF-to-DHA electrocyclic reaction, the influence of the electron-donating methyl groups was elucidated. In addition, we subjected a small selection of 4,8a-dialkylated compounds to a calculational study to elucidate how steric interactions can alter the relative DHA-VHF stabilities. The synthetic methodology offers access to novel DHA scaffolds and substitution patterns which in turn can lead to systems that can help address the broader questions concerning the potential applicability of the DHA/VHF system in the context of solar-thermal energy storage systems or other photochromic applications.

Introduction

In recent years, the field of molecular photoswitches has benefited from a particular rise in interest and involvement. This can be mainly attributed to the numerous applications that have been envisioned by scientists across all fields of research including chemistry, biochemistry and physics.[1] Due to such widespread attention, several books and reviews have documented the ongoing progress particularly towards the development of organic molecular switches.[2] The foundation of any new technology arising from this field, however, is still dependent on the discovery of new compounds and materials that exhibit desirable properties for their relevant applications. Ultimately, the successful preparation of such innovative materials is grounded on the chemist's synthetic toolbox.

Among other organic molecular photoswitches, the dihydroazulene/vinylheptafulvene (DHA/VHF) photo-/thermoswitch presents an example of one-way (T-type) photochromism. Upon irradiation, DHA (**1a**) undergoes photoisomerization to the meta-stable VHF (**1b**) isomer, which in time thermally reverts to DHA with a simultaneous release of energy (Scheme 1). The system was initially discovered and investigated by Daub and co-workers,[3] and in recent years it has been further tuned by our group in various ways.[4] Summaries of the current progress towards the synthesis and functionalization[4h] as well as the properties and behavior[4i] of the DHA/VHF system have been accounted for in recent reviews



Scheme 1. Photo/thermal switching of the parent DHA (**1a**)/VHF (**1b**) system, also showing the commonly used numbering scheme.

Since their discovery, the synthesis of substituted DHA scaffolds has proceeded through one of two main strategies (Routes **A** and **B**) presented in Scheme 2. Route **A** provides a direct path to the desired DHA scaffold through an [8+2] cycloaddition of 8-methoxyheptafulvene with dicyanoethylenes, from which methanol is subsequently eliminated using P_2O_5.[5] The second general strategy (Route **B**) furnishes DHA in an indirect manner via the corresponding vinylheptafulvene (VHF) intermediate, which is made through the combination of tropylium with a malononitrile derivative (or with the corresponding carbonyl derivative and a subsequent reaction with malononitrile), followed by an oxidation (dehydrogenation).[6] The work presented here outlines Route **C**, which offers particular advantages over the other two.

Although routes **A** and **B** provide the opportunity for facile functionalization at positions 2 and 3 of the DHA scaffold (see Scheme 1), late-stage functionalization of the system at all positions (1-8) has remained limited. The regioselective introduction of substituents on the seven-membered ring has been particularly challenging.[4e, 7] Functionalization of the seven-membered ring has been investigated at both an early synthetic stage (before formation of the DHA scaffold) and at a later one (after DHA formation). The most widely employed late-stage functionalization method exploits the out-of-plane C7-C8 double bond of **1a** which can be selectively brominated (Scheme 3, a).[4c,d,j] The subsequent elimination of HBr is then used to yield a 7-bromo-substituted DHA that can subsequently be subjected to metal-catalyzed cross-coupling reactions.[8]

[a] N. C. M. Lubrin, A. Vlasceanu, B. N. Frandsen, A. B. Skov, M. D. Kilde, Prof. Dr. K. V. Mikkelsen and Prof. Dr. M. B. Nielsen
Department of Chemistry and Center for Exploitation of Solar Energy
University of Copenhagen
Universitetsparken 5, DK-2100 Copenhagen Ø, Denmark
E-mail: mbn@chem.ku.dk
http://chem.ku.dk/research_sections/solarenergy/

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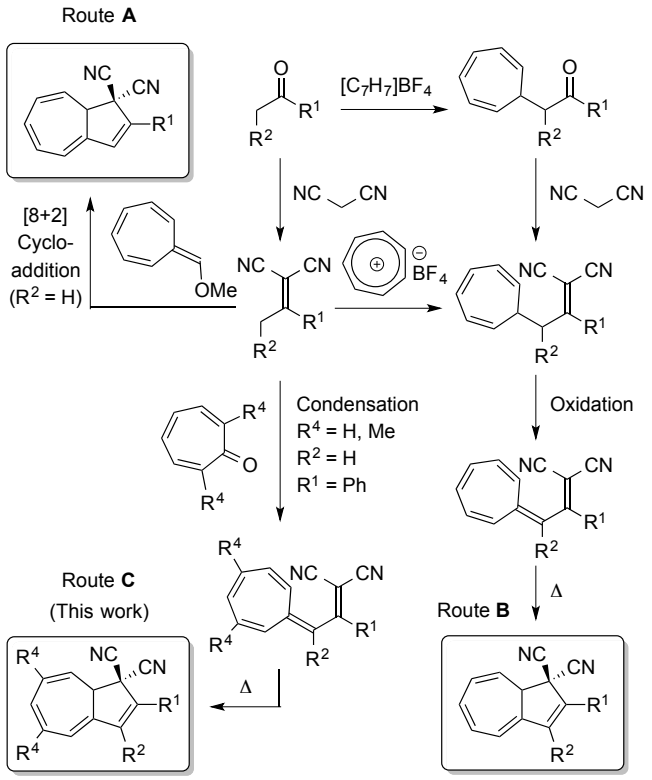
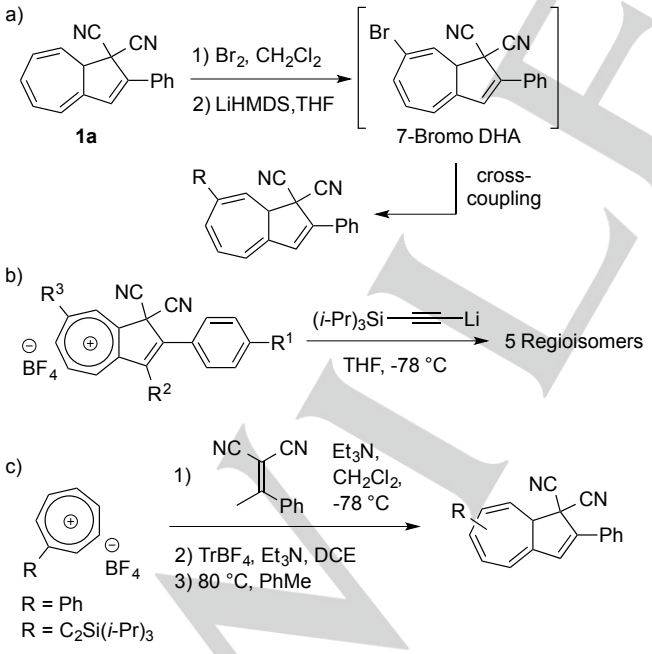


Scheme 2. Established synthetic routes towards functionalized DHA scaffolds (Routes **A** and **B**) in addition to this work (Route **C**). LDA = lithium diisopropylsilylamide.



Scheme 3. Regio- and non-regioselective methods of functionalizing the seven-membered ring. LiHMDS = lithium hexamethyldisalazide; DCE = 1,2-dichloroethane.

In an effort to expand the scope of late-stage functionalization, oxidation of the DHA scaffold to the azulenium cation (Scheme 3, b) was successfully conducted; however, subsequent nucleophilic attack of this system could not be achieved regioselectively, and a low-yielding tautomerization reaction was required to form the photoactive 1,8a-DHA.[7]

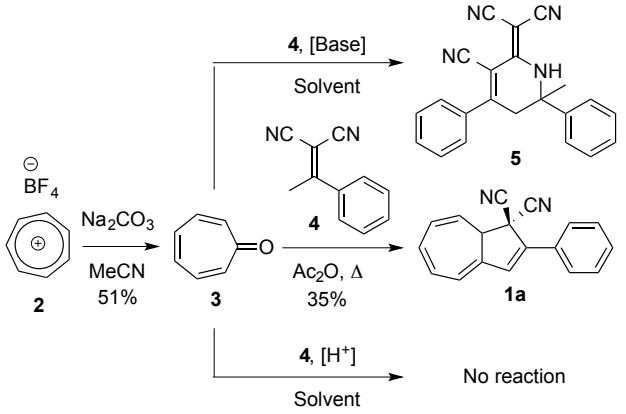
Alternatively, early functionalization of the seven-membered ring has also been attempted by employing substituted tropylium salts as starting materials (Scheme 3, c).[4e] The substituents of these building blocks, however, were not found to be sufficiently directing to result in a regioselective attack of the ring. This method has resulted in product mixtures containing all possible regioisomers, which proved difficult to purify by chromatographic techniques.[4e]

We then rationalized that regioselectivity might be achievable by using a functionalized tropone derivative as the key building block, which in this work led to the development of Route **C** shown in Scheme 2. Provided with access to substituted tropone derivatives, a class of products still under development, the range of accessible DHA products could increase significantly. In addition, the key condensation reaction of Route **C** may be considered a milder alternative to the oxidation step of Route **B**, which has previously been reported to present certain functional-group incompatibilities and low reaction yields.[9] Furthermore, whereas cross-coupling reactions using 7-bromo DHA are limited to the introduction of sp and sp^2 hydrbidized carbon substituents, the method presented here allows for expansion of the substituent scope to include sp^3-hybridized carbon-based R-groups on the seven-membered ring Studies on such derivatives allow for elucidation of the influence of alkyl substitution for the VHF-to-DHA ring closure reaction, while previous studies have focused on direct conjugation effects via aryl or arylethynyl substituents.

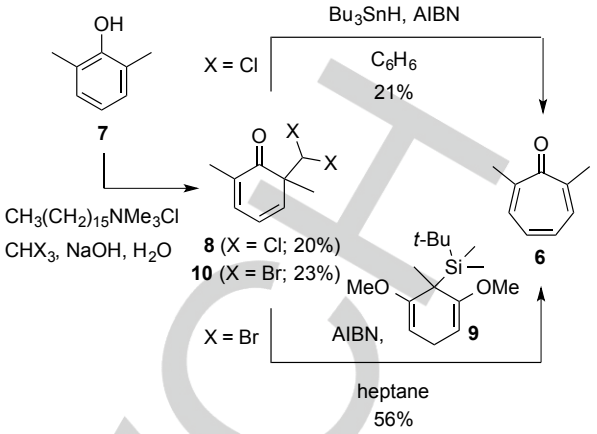
Results and Discussion

Synthesis. In this work, synthetic Route **C** is explored primarily with a focus on the regioselective functionalization of the DHA scaffold. Although seemingly trivial starting materials, the synthesis of tropones has not been very thoroughly explored in literature. The lack of detailed investigation into this class of compounds has perhaps been due, in part, to the relatively uncommon occurrence of 7-membered, all-carbon atom rings in natural products.[10]

Via a disproportionation reaction of tropylium tetrafluoroborate (**2**), the synthesis of tropone **3** could be accomplished according to a procedure by Reingold and DiNardo (Scheme 4).[11] As chromatographic methods result in product loss, partial purification of the crude tropone could be achieved by extraction with hot heptane (see SI). The optimal conditions for a condensation reaction between tropone **2** and dicyanoethylene derivative **4** were first investigated towards the synthesis of parent DHA **1a** by varying the temperature, solvent, reaction time, and catalysts (Scheme 4). Investigations were initially carried out to determine the effect of either acid, base, or Lewis acid catalysis on the success of the condensation reaction (see SI for details).



Scheme 4. Conditions for the synthesis of **1a** via Route **C** (see SI).



Scheme 5. Synthesis of 2,7-dimethyltropone **6**. AIBN = azabisisobutyronitrile.

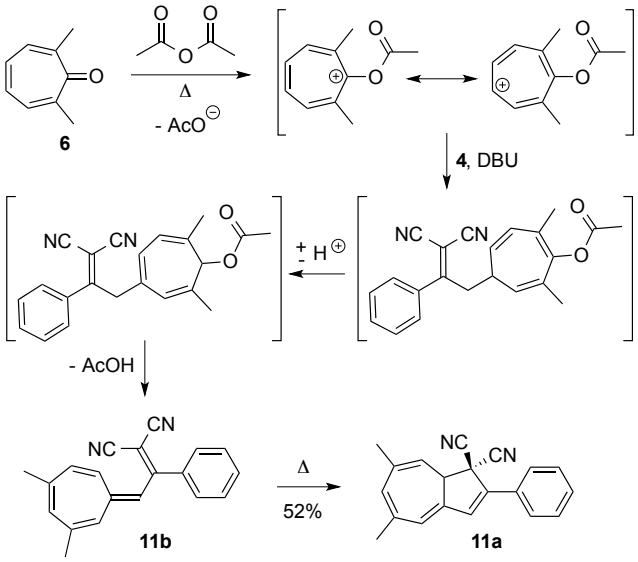
Over the course of the screening, basic aldol-type conditions were consistently observed to promote crotononitrile dimerization yielding byproduct **5** instead of the intended condensation with the ketone, which was not observed to any degree. This is perhaps unsurprising as such reactivity has been previously reported in literature.[12] In an acidic reaction medium on the other hand, crotononitrile dimerization could be avoided completely; however, no reactivity of the substrates could be observed at all, even under forcing conditions (MW, 200 °C; MW = microwave heating). Conducting the reaction in a buffered system under Knoevenagel-like conditions was also unsuccessful in achieving any reactivity between the starting materials. Tropone activation using a variety of Lewis acids was also attempted but this too did not show any trace of the desired reactivity. The reaction towards **1a** was, however, found to proceed in the presence of acid anhydrides (Table S1, SI). Gratifyingly, using acetic anhydride as solvent, a yield of 35% was achieved of **1a**.

To test the regioselectivity of the newly developed method, the synthesis of 2,7-dimethyl-tropone **6** was first undertaken according to a method reported by Barbier *et al.*[13] (Scheme 5) for similar transformations. In the first step, dichlorocarbene is generated *in situ* and undergoes a directed addition to 2,6-dimethylphenol **7** at the *ortho* position to the OH group to form product **8**. Although initial attack by the carbene at the *para* position could also be expected, no such byproduct or any other major products could be isolated upon chromatographic purification, indicating that the low yield is likely due to decomposition. Finally, compound **8** was subjected to a ring expansion to form **6** in a yield of 21% using tributyltin hydride and azabisisobutyronitrile (AIBN).

Although this method is satisfactory in yielding the desired 2,7-dimethyltropone, the low yielding reactions as well as the hazardous and toxic reagents employed in the ring expansion could be circumvented. Recent work by Studer *et al.*[14] reports that various silylated 1,4-cyclohexadienes such as **9** can be employed as superior tin hydride substitutes in a variety of radical chain reductions. These conditions, however, were found to be more successful on bromo- or iodo-functionalized starting materials, and so the synthesis of 2,7-dimethyltropone **6** was instead achieved in a yield of 56% through the dibromo derivative **10** (Scheme 5).

The condensation between dimethyltropone **6** and dicyanoethene derivative **4** was then successfully conducted, providing the DHA **11a** via VHF **11b** (Scheme 6). Further optimization revealed that the addition of DBU to the reaction mixture was advantageous. Nucleophilic attack at the tropone ring is not observed to occur at the carbonyl carbon (C1) but rather, it can be inferred that the attack must take place at C4 as the product **11a** was isolated. The mechanism of this condensation is thus hypothesized to occur as described in Scheme 6. It is thought that the steric effects of the methyl groups flanking the carbonyl carbon are sufficient to disfavor attack at this position or at C3. The new synthetic protocol thus allowed the isolation of one regioisomeric product in high yield (52%) in contrast to the previous method of using a functionalized tropylium ion as substrate.

Finally, Wittig and Horner-Wadsworth-Emmons olefinations were also attempted towards the synthesis of VHF **1b**, but none of these attempts turned out successful (see SI).



Scheme 6. Mechanistic proposal for the condensation reaction between 2,7-dimethyltropone **6** and the dicyanoethene derivative **4** leading to 5,7-dimethyl DHA **11a**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Optical Properties and Switching Studies. The UV-Vis absorption spectrum of DHA **11a** is shown in Figure 1. It exhibits a characteristic absorption at λ_{max} 338 nm, blueshifted relative to that of **1a** (λ_{max} 353 nm[6e]). Upon irradiation, the DHA is converted to VHF **11b** with a characteristic absorption at λ_{max} 500 nm, redshifted relative to that of VHF **1b** (λ_{max} 470 nm[6e]). In time, **11b** undergoes a thermal ring closure to form **11a**, and we determined a half-life of 36 min (MeCN, 25 °C), whereas that from **1b** to **1a** has been previously determined as 218 min.[6e] The significantly shorter half-life of **11b** is considered to be due to the electron-donating character of the methyl substituents as electron-donating groups at the seven-membered ring are known to enhance the thermal back reaction (TBR).[4g] As with most systems previously investigated,[4c,d] VHF **11b** exhibits two sites of possible ring closure, accessible via double bond isomerization that may occur both upon irradiation and thermally (Scheme 7), which can lead to the 6,8-disubstituted DHA/VHF system **12a**/**12b**. This isomerization is evident by the fact that the UV-Vis absorption spectrum after one cycle is not identical to that of DHA **11a** as the solution now also contains DHA **12a**. Thus, after one cycle the DHA absorption spectrum presents a new absorption maximum at 327 nm, assigned to **12a**, as well as a shoulder at the original 338 nm (**11a**). The different absorption properties of the two DHA isomers **11a** and **12a** are further supported by calculations (*vide infra*), and the isomeric mixture was also confirmed by NMR spectroscopic studies (SI, Figure S4).

The decay in VHF absorption at 500 nm could be fitted by one exponential function. In consequence, the two VHFs **11b** and **12b** seem to undergo the TBR at similar rates. We achieve a half-life of 36 min, which is a factor of six smaller than that of **1b** (218 min). Figure 2 shows the differences in half-lives for the TBR of various VHF derivatives, containing different substituents on the seven-membered ring.[4c,d, 6e] Interestingly, we see that the presence of two methyl groups has a much stronger influence than expanding the π-conjugated system by a phenyl substituent. Incorporation of an inductively electron-withdrawing bromo substituent has the opposite effect on the half-life, increasing it by a factor of four.

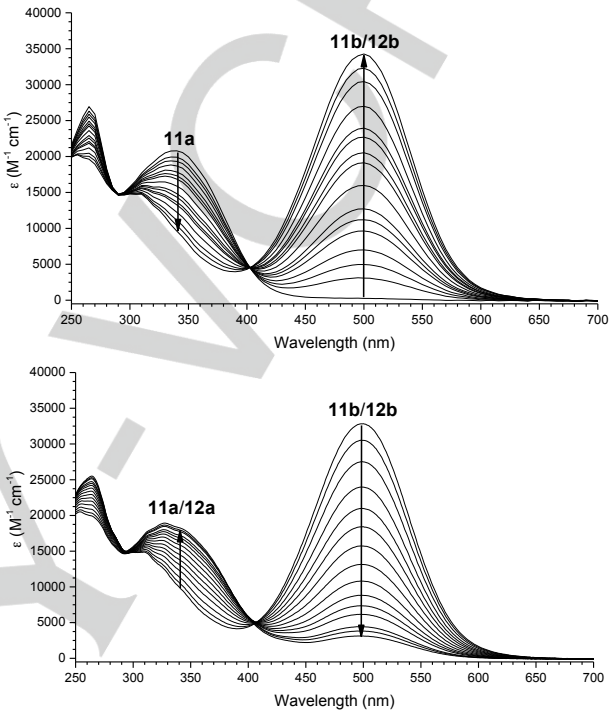


Figure 1. UV-Vis absorption spectra of **11a** showing conversion to **11b** (in equilibrium with **12b**) by irradiation at 338 nm (top) and thermal conversion of **11b**/**12b** into **11a**/**12a** over time at 25 °C in MeCN (bottom).

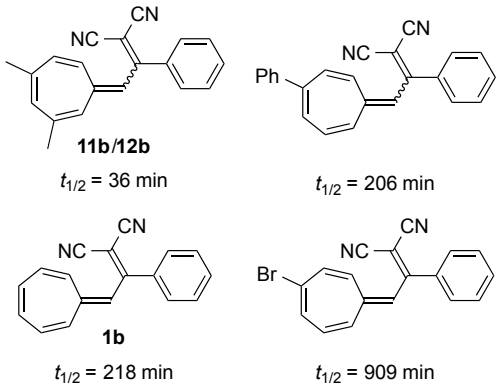
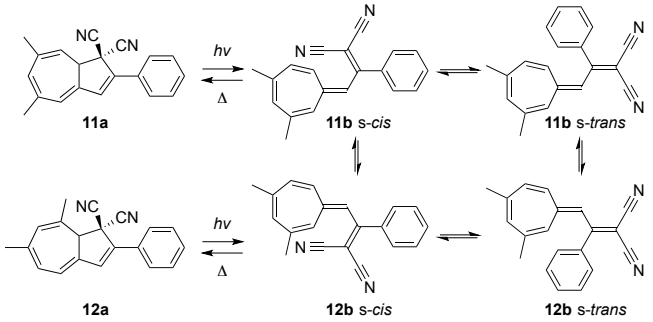


Figure 2. Differences in half-lives between VHF derivatives, based on electron donating or withdrawing substituents on the seven-membered ring (measured in MeCN at 25 °C; this work and references [4c,d, 6e]).



Scheme 7. One ring opening/closure cycle provides a mixture of DHA isomers **11a**/**12a**. The VHFs **11b**/**12b** correspond to *E*/*Z* isomers.

The electronic excitation (UV-Vis) spectra of the two DHA species were computationally modeled (CAM-B3LYP/6-311+G(d,p) using the IEFPCM method for solvent modeling) and are shown to accurately reflect the experimental observations (Figure 3). Thus, partial isomerization from **11a** to **12a** is supported by a sligthly blueshifted absorption of the latter.

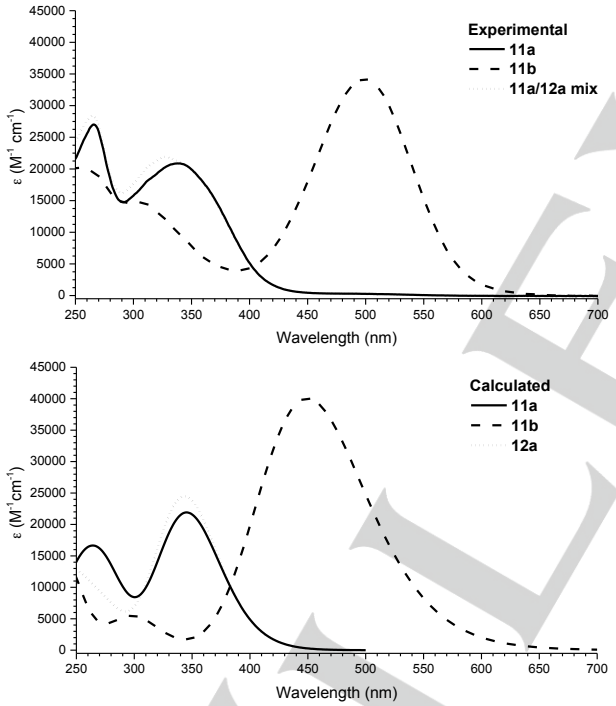
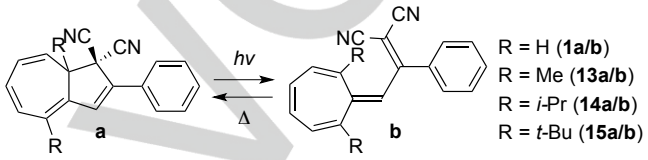


Figure 3. Top: Experimental UV-Vis absorption spectra of **11a**, **11b**, and an isomeric mixture of **11a**/**12a** obtained after exposing **11a** to a light/heat cycle; Bottom: Calculated UV-Vis absorption spectra of 5,7-dimethyl DHA **11a**, VHF **11b** and 6,8-dimethyl DHA isomer **12a**. Both experimental and theoretical spectra were obtained at 25 °C in MeCN.

Computational Study. A theoretical investigation of substituted systems **11a**/**11b**, **12a**/**12b**, as well as the 4,8a-dialkylated systems **13**-**15a**/**b** (Scheme 8) in comparison with **1a**/**1b** was then conducted in order to estimate DHA-VHF Gibbs free energy differences (ΔG) and back reaction barriers ($\Delta G^{‡}$). Compounds **13a**/**b** represent the isomeric couple to **11a**/**b** that would have formed from nucleophilic attack instead at the carbonyl of the tropone. For the calculations, the DFT method and basis set M06-2X/6-311+g(d) were employed, again using the IEFPCM solvent model, which have previously been shown to provide accurate results for the parent **1a**/**1b** system.[15] Photochemical ring opening of DHA (**a**) initially results in the formation of *s-cis* VHF ($\mathbf{b}_{s\text{-}cis}$),[16] which exists in thermal equilibrium with the more stable *s-trans* VHF ($\mathbf{b}_{s\text{-}trans}$). Thus, both conformers should be considered when estimating thermal ring closure rates. A representation of the composite reaction coordinate ($\mathbf{b}_{s\text{-}cis}$ → **a** and $\mathbf{b}_{s\text{-}cis}$ ↔ $\mathbf{b}_{s\text{-}trans}$) for the ground state isomerization reactions of the systems considered here is depicted in Figure 4.



Scheme 8. Various DHA/VHF systems subjected to a computational study.

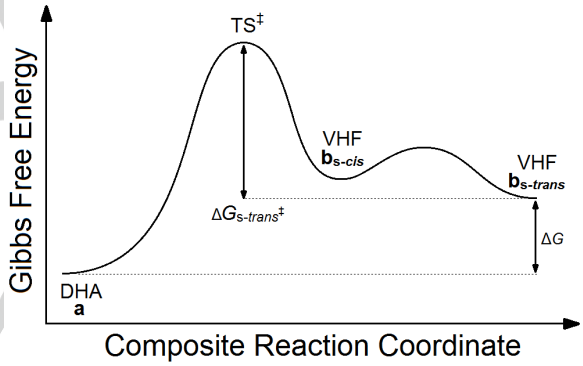


Figure 4. Schematic representation of the composite reaction coordinate ($\mathbf{b}_{s\text{-}cis}$ → **a** and $\mathbf{b}_{s\text{-}cis}$ ↔ $\mathbf{b}_{s\text{-}trans}$) for the ground state isomerization reactions of the systems considered here.

In theory, a model for the thermal ring closure from VHF ($\mathbf{b}_{s\text{-}cis}$↔$\mathbf{b}_{s\text{-}trans}$) to DHA (**a**) can be constructed in at least two ways, both employing the Eyring equation to estimate reaction rates (k_{calc}). The first considers the $\mathbf{b}_{s\text{-}cis}$ conformer as the starting point and the free energy of activation ($\Delta G_{s\text{-}cis}^{‡}$) to the transition state connecting $\mathbf{b}_{s\text{-}cis}$ to **a**. For all systems studied here, two transition states were identified, yet only the one exhibiting the lowest energy is reported. In the calculation of an accurate reaction rate constant from $\mathbf{b}_{s\text{-}cis}$ to **a**, the pre-equilibrium, $\mathbf{b}_{s\text{-}cis}$↔$\mathbf{b}_{s\text{-}trans}$, can be accounted for by factoring $K/(K+1)$ into the rate equation, where $K = [\mathbf{b}_{s\text{-}cis}]/[\mathbf{b}_{s\text{-}trans}]$. This factor reflects the limited amount of $\mathbf{b}_{s\text{-}cis}$ present, and thereby the contribution of the pre-equilibrium on the reaction rate from $\mathbf{b}_{s\text{-}cis}$ to **a**. The rate equation describing this approach is derived in the SI. An alternative approach considers $\mathbf{b}_{s\text{-}trans}$ as the starting point and $\Delta G_{s\text{-}trans}^{‡}$ as the free energy of activation. One advantage of this method is that it requires no knowledge of the

reactive conformer and thus avoids any such assumptions that would otherwise restrict the reaction coordinate to pass through the $\mathbf{b}_{s\text{-}cis}$ minimum. This approach can be commonly refered to as a lowest conformer transition state theory (LC-TST) [17] and works best when this conformer is predominant, at which point it also converges with the pre-equilibrium method (SI, Figure S5). The rate equation describing this approach is also derived in the SI.

The relative stabilities of VHF conformers $\mathbf{b}_{s\text{-}cis}$ and $\mathbf{b}_{s\text{-}trans}$, which on average exhibit an energy difference of approx. 10 kJ mol^{-1}, translate to a preference of nearly 99% towards the $\mathbf{b}_{s\text{-}trans}$ conformation. Although only the pre-equilibrium approach has the correct behavior for k when K is variable, the LC-TST method is presented here as a reasonable approximation. Theoretical estimates of the reaction rate constants (k_{calc}) based on both methods are listed in Table 1. The pre-equilibrium approach yields a rate constant for the conversion of **1b**, which is close to the experimental one, while the LC-TST method comes within approx. a factor of 2 of this. Experimentally, it was not possible to differentiate between the rates of ring closure of **11b** and **12b**, and the overall rate constant was found to be 3.18 x 10^{-4} s^{-1}, being six times that of **1b**. In line with the experimental results, the calculations do indeed predict a faster TBR of **11b** and **12b** relative to that of **1b**, but both methods seem to underestimate the influence of the methyl groups. With respect to the Gibbs free energy difference between s-*trans* VHF and DHA isomers, the calculations predict VHF **12b** (s-*trans*) to be slightly more stable than DHA **12a**.

Computational investigations on systems **13**-**15a/b** (so far synthetically elusive compounds) show that increasing steric bulk at the positions of ring closure (C4 and C8a) destabilizes the DHA isomer relative to the VHF (Table 1). In fact, VHF **15b** (s-*trans*) is significantly more stable than DHA **15a**. With increasing bulkiness of the alkyl substituent, we observe an increase in the C8a–C(alkyl) bond length. This increase is more significant for the DHA species (**a**) than for the VHF species (**b**): 1.537 Å (**13a**) -> 1.580 Å (**14a**) -> 1.594 Å (**15a**) *versus* 1.509 Å (**13b**) -> 1.522 Å (**14b**) -> 1.540 Å (**15b**). The conformational distortion resulting from increasing steric bulk at the 4 and 8a positions can also be clearly observed in the calculated UV-Vis absorption spectra of s-*trans* VHF isomers **13b**, **14b**, and **15b** (Figure 5). Here, a corresponding decrease in intensity and blueshift of the characteristic VHF absorption band is observed with increasing steric bulk.

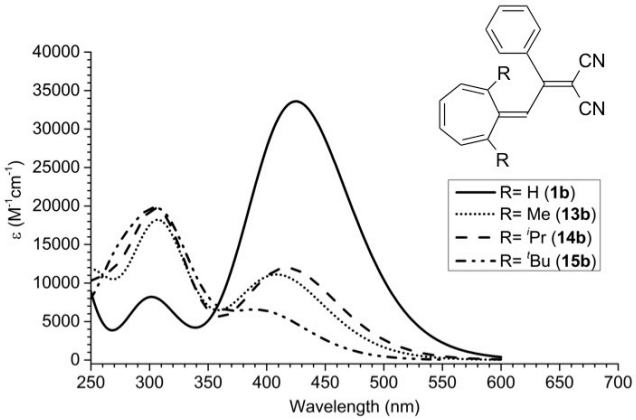


Figure 5. Calculated UV-Vis absorption spectra (CAM-B3LYP/6-311+G(d,p) using the IEFPCM solvent model) of s-*trans* VHF isomers **13**-**15b** at 25 °C in MeCN.

Table 1. Gibbs free energy differences (ΔG, energy difference between s-*trans* VHF and DHA) and VHF-to-DHA rate constants calculated for **1a/b** as well as **11**-**15a/b** at 25 °C in MeCN using the M06-2X/6-311+g(d) method and the IEFPCM solvent model with acetonitrile. Harmonic frequencies and default approximations in Gaussian 09 were used.

System	ΔG [kJ mol^{-1}]	k_{calc}[a] [10^{-4} s^{-1}]	k_{calc}[b] [10^{-4} s^{-1}]	k_{exp}[c] [10^{-4} s^{-1}]
1a/**1b**	16	0.58	0.28	0.54
11a/**11b**	9	1.39	0.62	3.18
12a/**12b**	-3	0.77	0.41	3.18
13a/**13b**	18	0.41	0.21	-
14a/**14b**	-2	-	-	-
15a/**15b**	-21	-	-	-

[a] Calculated using the pre-equilibrium approach described in the SI. [b] Calculated using the lowest conformer transition state theory (LC-TST) described in the SI. [c] Experimental rate constants.

Conclusions

A new method for the synthesis of the DHA scaffold was developed (Route **C**), which avoids an occasionally problematic oxidation step by replacing it with a rather simple condensation reaction employing tropone as a starting material. This method was successfully employed in a novel regioselective functionalization of the seven-membered ring using 2,7-dimethyltropone as substrate, whose synthesis was moderately optimized. This led to the synthesis of a novel DHA/VHF system (**11a**/**11b**), which was found to exhibit a significantly faster VHF-to-DHA thermal ring closure than the parent system (**1a**/**1b**). The faster ring closure of **11b** was mirrored in a calculational study although this study did not provide as large a rate enhancement as observed experimentally. By placing bulky alkyl groups at positions C4 and C8a, calculations reveal that the relative DHA-VHF stabilities can be reversed, rendering VHF more stable than DHA. In all, this work has shown for the first time the influence of alkyl substitution in the seven-membered ring of the DHA/VHF system. The work has also shown that DFT calculations provide

important guidelines for the design of alkyl-substituted derivatives with specific switching and optical properties.

Experimental Section

Synthesis and Standard Characterization – General Information. C_6H_6 was distilled over Na. All commercially available reagents were purchased from Sigma Aldrich and used as received. 2-(1-Phenylethylidene)malononitrile **4** was synthesized according to literature procedure.[6e] All light-sensitive compounds, reactions and manipulations were shielded from light by either conducting the procedures in a dimly lit room or by masking the glassware and equipment with aluminum foil. Purification of products carried out by flash column chromatography was conducted using Davisil® LC60A (60 Å pore size; 43-60 µm particle size) silica. For dry column vacuum chromatography, SilicaFlash G60 (15-40 µm particle size, 400-800 mesh) silica was employed. Nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Ultrashield Plus 500 (^{1}H at 500 MHz, ^{13}C at 126 MHz) equipped with a non-inverse cryo-probe or a 500 MHz Varian spectrometer (^{1}H at 500 MHz) equipped with a penta-probe/broad-band probe. Chemical shift values are provided relative to residual solvent references for ^{1}H and ^{13}C-NMR spectra. Infrared spectroscopy (IR) data were acquired on a Bruker Alpha FT-IR spectrometer, equipped with ALPHA's Platinum ATR single reflection diamond ATR module. Samples were loaded directly or by evaporation from a suitable solvent. IR absorptions are reported in units of wavenumbers (cm^{-1}); intensities are reported as s = strong; m = medium; w = weak. Mass spectra were recorded on a Bruker Solarix ESI-MALDI-FT-ICR instrument equipped with a 7 T magnet (prior to the experiments, the instrument was calibrated using sodium trifluoroacetate (NaTFA) cluster ions). Thin layer chromatography (TLC) was conducted using commercially available, precoated plates (silica 60) with fluorescence indicator. With respect to the DHA compounds, TLC was carried out in the absence of light; a color change from yellow to red upon exposure to UV light indicates a conversion to VHF. All melting points are uncorrected.

2-Phenylazulene-1,1(8a*H*)-dicarbonitrile (1a). To a solution of 2-(1-phenylethylidene)malononitrile **4** (218 mg, 1.30 mmol) in acetic anhydride (8 mL) was added tropone **3** (125 mg, 1.18 mmol) under an N_2 atmosphere, and the mixture was heated to reflux overnight (16 h). The reaction mixture was then cooled to rt and diluted with toluene (50 mL) to assist acetic anhydride evaporation as an azeotrope under reduced pressure. The residue was purified by flash column chromatography (SiO_2, toluene) to yield title product **1a** as a crystalline yellow solid (105 mg, 35%). Characterization data are consistent with those reported in literature.[6e]

6-(Dichloromethyl)-2,6-dimethylcyclohexa-2,4-dien-1-one (8). Modified literature procedure.[13] To a solution of 2,6-dimethylphenol **7** (20.0 g, 164 mmol) in $CHCl_3$ (44.0 mL, 549 mmol) was added a 25% aqueous solution of cetyltrimethylammonium chloride (0.541 mL, 0.423 mmol), and the reaction mixture was heated to 50 °C in an ambient atmosphere. To this, a solution of NaOH (50.4 g, 1.26 mol) in H_2O (115 mL) was added over 1 h under mechanical stirring and the mixture stirred at this temperature for a further 4 h. The reaction mixture was then diluted with H_2O (250 mL) and extracted with Et_2O (3 x 200 mL). The organic fractions were combined and washed with H_2O (2 x 200 mL) and brine (2 x 200 mL), dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 4% EtOAc/heptane) to yield title compound **8** as a pale yellow oil (6.88 g, 20%). TLC R_f= 0.33 (20% EtOAc/heptane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 – 6.87 (m, 1H), 6.58 – 6.54 (m, 1H), 6.40 (dd, *J* = 9.7, 6.1 Hz, 1H), 6.09 (s, 1H), 1.91 (s, 3H), 1.30 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.92, 138.40, 137.86, 133.25, 123.74, 77.51, 57.70, 24.40, 15.48 ppm. HRMS (ESI, *m*/*z*) found 205.01850 $[M+H]^+$, calc. $(C_9H_{11}Cl_2O)^+$: 205.01815 $[M+H]^+$.

6-(Dibromomethyl)-2,6-dimethylcyclohexa-2,4-dien-1-one (10). To a solution of 2,6-dimethylphenol **7** (20.0 g, 164 mmol) in $CHBr_3$ (47.0 mL, 537 mmol) was added a 25% aqueous solution of cetyltrimethylammonium chloride (0.541 mL, 0.423 mmol), and the reaction mixture was heated to 50 °C under an ambient atmosphere. To this, a solution of NaOH (50.4 g, 1.26 mol) in H_2O (115 mL) was added over 30 min under mechanical stirring, and the mixture was stirred at this temperature for a further 4 h. The reaction was then quenched with H_2O (250 mL) and extracted with Et_2O (3 x 200 mL). The organic fractions were combined and washed with H_2O (2 x 200 mL) and brine (2 x 200 mL), dried over $MgSO_4$, filtered, and the solvent was removed *in vacuo*. The residue was purified by dry column vacuum chromatography (SiO_2, 0-50% $CHCl_3$/heptane, 2% increments, 150 mL fractions, then 100% $CHCl_3$) to yield title compound **10** as a pale yellow oil (11.2 g, 23%). TLC R_f= 0.37 (20% EtOAc/heptane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 – 6.87 (m, 1H), 6.60 – 6.57 (m, 1H), 6.41 (dd, *J* = 9.7, 6.1 Hz, 1H), 5.97 (s, 1H), 1.92 (s, 3H), 1.29 (s, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.65, 139.54, 138.40, 133.38, 123.51, 57.25, 51.01, 25.91, 15.50 ppm. HRMS (ESI, *m*/*z*) found: 314.89903 $[M+Na]^+$, calc. $(C_9H_{10}Br_2ONa)^+$: 314.89906 $[M+Na]^+$; found: 292.91714 $[M+H]^+$, calc. $(C_9H_{11}Br_2O)^+$: 292.91712 $[M+H]^+$.

2,7-Dimethylcyclohepta-2,4,6-trien-1-one (6). *Method using substrate **8**;* modified literature procedure.[13] To a solution of **8** (3.00 g, 14.6 mmol) in dry C_6H_6 (294 mL) under N_2 atmosphere was added AIBN (0.241 g, 1.47 mmol) in one portion followed by tributyltin hydride (9.89 mL, 36.7 mmol) via slow addition. The temperature was slowly raised to 80 °C and the reaction mixture stirred for 14 h. The reaction mixture was then cooled to rt and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 4% EtOAc/heptane) to yield title compound **6** as a pale yellow oil (0.41 g, 21%). TLC R_f= 0.40 (20% EtOAc/heptane). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 6.91 – 6.85 (m, 2H), 2.32 (d, *J* = 0.8 Hz, 6H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.66, 149.60, 134.84, 131.93, 23.76 ppm. HRMS (ESI, *m*/*z*) found: 157.06246 $[M+Na]^+$, calc. $(C_9H1_{10}ONa)^+$: 157.06239 $[M+Na]^+$. *Method using substrate **10**.* A solution of **10** (2.00 g, 6.80 mmol), AIBN (0.112 g, 0.682 mmol) and *tert*-butyl(2,6-dimethoxy-1-methylcyclohexa-2,5-dien-1-yl)dimethylsilane (2.37 g, 8.83 mmol) in heptane (75 mL) was heated to reflux and stirred overnight (14 h) under an N_2 atmosphere. The mixture was then cooled to rt and stirred for another 24 h. The reaction mixture was then concentrated *in vacuo* and the residue purified by flash column chromatography (SiO_2, 10% EtOAc/heptane) to yield title compound **6** as a pale yellow oil (0.51 g, 56%).

5,7-Dimethyl-2-phenylazulene-1,1(8a*H*)-dicarbonitrile (11a). A solution of dimethyltropone **6** (66 mg, 0.49 mmol), 2-(1-phenylethylidene)malononitrile **4** (126 mg, 0.749 mmol) and DBU (7 µL, 0.047 mmol) in Ac_2O (4 mL) was heated to reflux for 4 h under an N_2 atmosphere. The reaction mixture was then cooled to rt and diluted with toluene (20 mL) to assist acetic anhydride evaporation as an azeotrope under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), washed with 2M $NaOH_{(aq)}$ (15 mL), dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 20% heptane/toluene) to yield the title compound **11a** as a yellow film (73 mg, 52%). TLC R_f = 0.34 (40% heptane/toluene). M.p. 51-53 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.71 (m, 2H), 7.49 – 7.45 (m, 2H), 7.44 – 7.40 (m, 1H), 6.82 (s, 1H), 6.20 (br s, 1H), 6.12 (br s, 1H), 5.52 (br d, *J* = 3.3 Hz, 1H), 3.71 (ddd, *J* = 3.3, 1.9, 1.7 Hz, 1H), 2.06 (d, *J* = 1.0 Hz, 3H), 1.93 (dd, *J* = 1.6, 1.5 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.44, 139.44, 139.18, 135.66, 132.02, 131.59, 130.76, 130.05, 129.36, 126.41, 123.50, 115.54, 114.71, 113.10, 50.50, 45.13,

24.74, 22.90 ppm. IR (thin film): 3064w, 3030w, 2978m, 2917m, 2855m, 2246w, 2207w, 1726w, 1674m, 1637w, 1570w, 1496s, 1446s, 1438s, 1406m, 1379m, 1359m, 1343m, 1302m, 1276m, 1245m, 1213m cm^{-1}. HRMS (ESI, *m*/*z*) found: 285.13961 $[M+H]^+$, calc. $(C_{20}H_{17}N_2)^+$: 285.13862 $[M+H]^+$.

For synthesis optimizations, switching studies, NMR spectra, and calculational studies, see SI.

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Keywords: condensation • electrocyclic reactions • olefination • radical reactions • tropone

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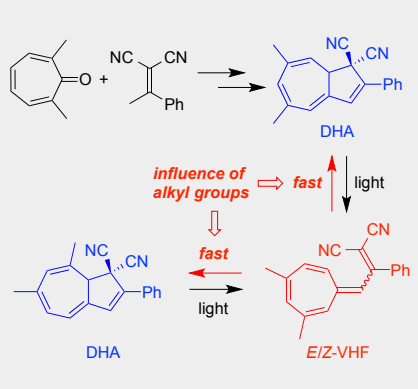
FULL PAPER

We here present a novel regioselective synthesis of a dimethyl-substituted dihydroazulene (DHA) photoswitch by employing a functionalized tropone as substrate. Photoisomerization results in isomeric vinylheptafulvenes (VHFs), which undergo electrocyclic ring closures significantly faster than the unsubstituted derivative, revealing the influence of electron-donating methyl substituents.



Molecular Switches

*Nickie C. M. Lubrin, Alexandru Vlasceanu, Benjamin N. Frandsen, Anders B. Skov, Martin Drøhse Kilde, Kurt V. Mikkelsen, Mogens Brøndsted Nielsen**

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Dialkylated Dihydroazulene / Vinylheptafulvene Derivatives – Synthesis and Switching Properties