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[6+3] Cycloaddition of pentafulvenes with 3-oxidopyrylium betaine: a novel methodology toward the synthesis of 5–8 fused oxabridged cyclooctanoids

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Abstract—Pentafulvenes undergo a facile [6+3] cycloaddition with 3-oxidopyrylium betaine, generated from the corresponding pyranulose acetate, leading to the formation of 5–8 fused oxabridged cyclooctanoids. The product is formed by a [6+3] cycloaddition, followed by a 1,5-hydrogen shift of the initially formed [6+3] adduct. The reaction was found to be general and a number of fulvenes with a wide range of substituents at the exocyclic double bond, that is, at the C6 position followed a similar reactivity pattern. The [6+3] adduct, a 5–8 fused oxabridged cyclooctanoid, is potentially amenable to a number of synthetic transformations due to the presence of an α,β-unsaturated ketone and cyclopentadiene part. By selecting appropriately substituted fulvene and pyranulose acetates, it is possible to use this methodology for the synthesis of a wide range of 5–8 fused cyclooctanoids. The experimental results have been rationalized on the basis of theoretical calculations.

1. Introduction

The synthesis of cyclooctanoids is of great importance in organic chemistry due to their wide occurrence in many biologically active natural products and synthetic compounds.[1] The interesting biological activities combined with the synthetic challenges have served to make them target molecules in a number of synthetic studies.[2] Some of the interesting cyclooctanoids are shown in Figure 1. Designing efficient, short routes for the stereoselective construction of cyclooctanoids is an interesting challenge in synthetic organic chemistry. Among the various strategies for the synthesis of eight-membered rings,[3] higher order cycloadditions that directly form eight-membered rings[4] are attractive because of their ability to produce complex molecules with extensive functionality in a single step, with good control over the creation of new stereocentres.

Eight-membered rings are notoriously difficult to prepare because of unfavorable entropic and enthalpic effects as well as the propensity for transannular interactions.[5]

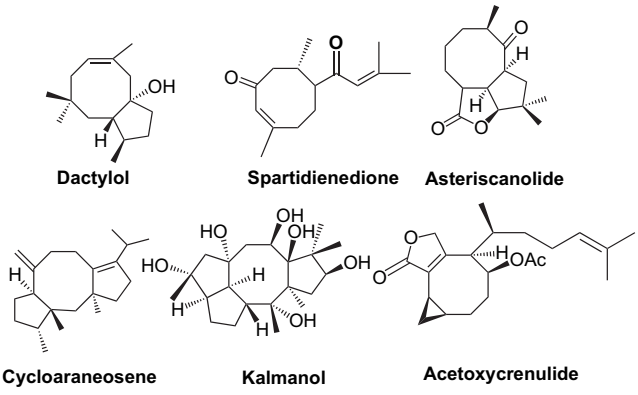

Figure 1. Some of the biologically active cyclooctanoids.

Fragmentation of complex bicyclic systems, metal mediated metathesis, and acyclic ring closures are the commonly used methodologies.[6] [3,3]-Sigmatropic rearrangements of smaller rings to such skeletons have gained popularity because of the high stereoselectivity observed.[6] Transition metal mediated cycloadditions provide another interesting route to cyclooctanoids.[7]

Fulvenes, cyclic molecules with an odd number of carbon atoms in the ring, belong to the category of non-functionalized

Keywords: Fulvenes; Oxidopyrylium betaine; [6+3] Cycloaddition; Oxabridged cyclooctanoids.
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carbon–carbon double bonds.[8] Among various fulvenes, pentafulvenes represent a very attractive structural unit, not only as a model for theoretical studies but also as a valuable building block to access polycyclic cyclopentanoids through a diverse array of cyclizations.[9] The development of efficient and short routes for the stereoselective construction of polycyclic molecules is currently one of the main challenges in synthetic organic chemistry. Pentafulvenes have been the subject of great interest both from synthetic and theoretical points because they exhibit different modes of cycloadditions. In cycloadditions, pentafulvenes can participate as a 2π, 4π, or 6π component[10] and have served as excellent synthons for the synthesis of triquinanes, pyrindines, etc. Investigations from our own laboratory have unraveled the interesting reactivity profile of fulvenes in cycloaddition reactions.[11] Barluenga and co-workers have reported a [6+3] cycloaddition of Fischer carbene complexes[10l] with fulvenes. Recent reports from Hong and co-workers have shown that fulvenes can undergo [6+3] cycloaddition with azomethine ylides leading to the formation of [2]pyrindines [12] and other molecules of biological importance.

3-Oxidopyrylium betaines[13] have been well utilized in the synthesis of cycloheptanoids.[13,14] Hendrickson has reported the generation and cycloaddition of oxidopyrylium betaine with a few electrophilic alkenes leading to oxabicyclo[3.2.1] systems.[14] Later Sammes has demonstrated the utility of oxidopyrylium betaines for the synthesis of oxabicyclic systems by cycloaddition with electron rich and electron deficient alkenes.[13] Wender has exploited the intermolecular cycloaddition of 4-methoxy and 4-silyloxy-3-oxidopyrylium betaines in the construction of phorbol framework.[15] To the best of our knowledge, there is no report on the cycloaddition of pentafulvenes with 3-oxidopyrylium betaines.

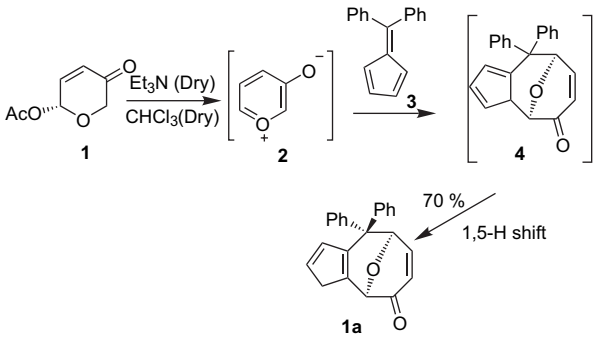
Recently, we have reported a [6+3] cycloaddition of pentafulvenes with 3-oxidopyrylium betaines.[16] We have carried out detailed investigation of the reported reaction with a number of pentafulvenes having wide range of substituents at the exocyclic double bond, that is, at the C6 position. The theoretical calculations were carried out to rationalize the results obtained. The details of our studies are presented in the following section.

2. Results and discussion

2.1. [6+3] Cycloaddition of 6,6-diaryl fulvenes with 3-oxidopyrylium betaine

The fulvenes selected for our studies were synthesized from the corresponding ketone or aldehyde following Little's procedure.[17] The pyranulose acetates,[18] precursors for 3-oxidopyrylium betaines, were synthesized from corresponding furfuryl alcohol by oxidation with *N*-bromosuccinimide followed by protection with acetic anhydride in the presence of pyridine and DMAP.

Our initial experiments involved the reaction of 6,6-diarylfulvene **3** with 3-oxidopyrylium betaine **2**. The reaction proceeded smoothly affording the [6+3] adduct **1a** in 70% yield (Scheme 1).



Scheme 1.

The product **1a** was characterized on the basis of spectroscopic data. The IR spectrum showed characteristic absorptions at 1691 cm^{-1}, indicating the presence of an α,β-unsaturated carbonyl, and at 1077 cm^{-1} indicative of the ether linkage. In the ^1H NMR spectrum, the two protons at C1 appeared as a singlet at δ 3.06 ppm. Two bridgehead protons resonated as a singlet and doublet at δ 4.88 and 5.36 ppm, respectively. The protons at C5 and C6 appeared as a doublet and double doublet at δ 5.76 and 5.99 ppm, respectively. ^{13}C NMR spectroscopy showed a characteristic signal for a carbonyl group at δ 194.5 ppm. The bridgehead carbons appeared at δ 76.6 and 74.9 ppm. Unambiguous evidence for the structure and stereochemistry of the product was obtained by single crystal X-ray analysis[16] (Fig. 2). The product **1a** is formed by a [6+3] cycloaddition followed by a 1,5-hydrogen shift.

Similar reactivity was observed with different 6,6-diaryl fulvenes and the results are summarized in Table 1. 6,6-Diaryl fulvenes afforded [6+3] adducts on reaction with 3-oxidopyrylium betaines in good to excellent yield.

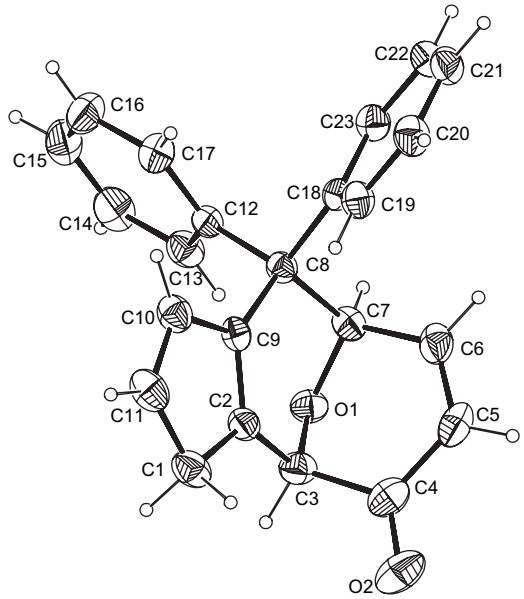
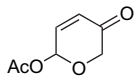
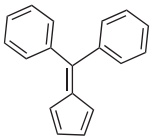
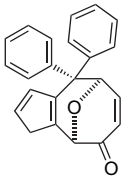
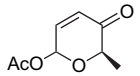
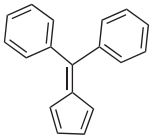
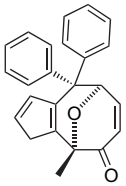
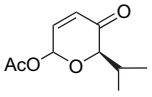
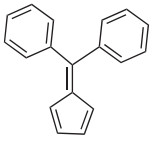
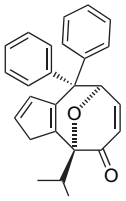
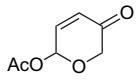
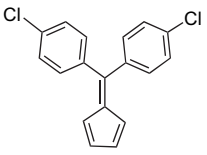
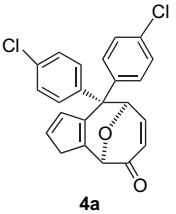


Figure 2. ORTEP plot for X-ray crystal structure of **1a**.

Table 1. [6+3] Cycloaddition of 6,6-diaryl fulvenes with 3-oxidopyrylium betaines

Entry	Pyranulose acetate	Fulvene	Product	Yield [%]
1			 **1a**	70
2			 **2a**	62
3			 **3a**	53
4			 **4a**	57

Reaction conditions: fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

2.2. [6+3] Cycloaddition of 6,6-dimethyl fulvene with 3-oxidopyrylium betaines

6,6-Dimethyl fulvene showed a similar reactivity pattern and the results are summarized in Table 2. The unsubstituted 3-oxidopyrylium betaine **2** on reaction with 6,6-dimethyl fulvene afforded [6+3] adduct in 83% yield. 2-Methyl and 2-isopropyl substituted 3-oxidopyrylium betaine also afforded [6+3] adducts in good yield.

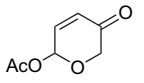
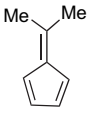
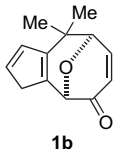
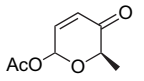
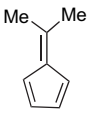
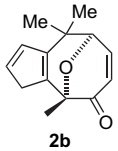
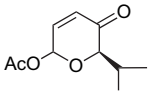
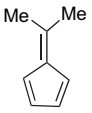
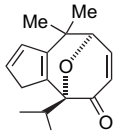
2.3. [6+3] Cycloaddition of cycloalkyl fulvenes with 3-oxidopyrylium betaines

Cycloalkyl fulvenes (6,6-pentamethylene, hexamethylene, and heptamethylene fulvenes), prepared from the corresponding cyclic ketones, also followed a similar reaction pathway and the results obtained with various substituted betaines are summarized in Table 3.

2.4. [6+3] Cycloaddition of 6-alkyl,6-aryl fulvenes and 6-aryl fulvenes with 3-oxidopyrylium betaines

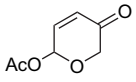
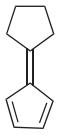
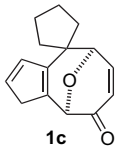
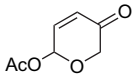
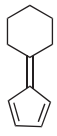
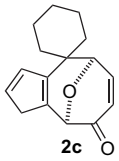
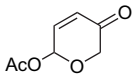
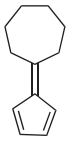
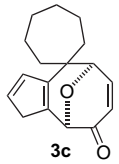
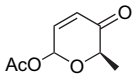
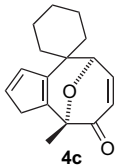
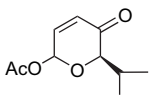
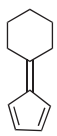
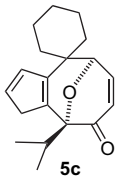
6-Alkyl,6-aryl fulvenes and 6-aryl fulvenes also underwent smooth [6+3] cycloaddition leading to the functionalized 5–8 fused cyclooctanoids in good to excellent yield. The results are summarized in Tables 4 and 5.

Table 2. [6+3] Cycloaddition of 6,6-dimethyl fulvene with 3-oxidopyrylium betaines

Entry	Pyranulose acetate	Fulvene	Product	Yield [%]
1			 **1b**	83
2			 **2b**	79
3			 **3b**	68

Reaction conditions: fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

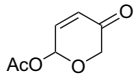
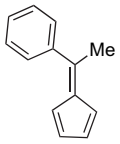
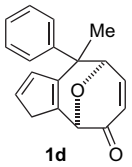
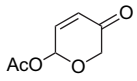
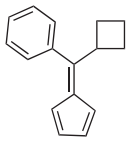
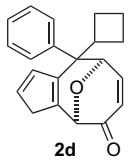
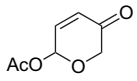
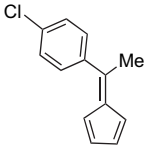
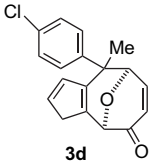
Table 3. [6+3] Cycloaddition of cycloalkyl fulvenes with 3-oxidopyrylium betaines

Entry	Pyranulose acetate	Fulvene	Product	Yield [%]
1			 **1c**	70
2			 **2c**	60
3			 **3c**	58
4			 **4c**	59
5			 **5c**	52

Reaction conditions: fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

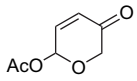
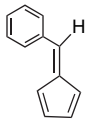
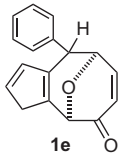
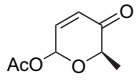
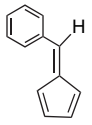
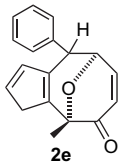
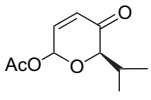
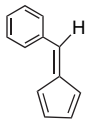
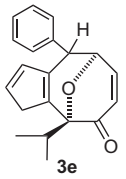
From the results summarized in Tables 1–5, it is clear that pentafulvenes undergo facile [6+3] cycloaddition with 3-oxidopyrylium betaines leading to the regioselective formation of 5–8 fused cyclooctanoids in good to excellent

Table 4. [6+3] Cycloaddition of 6-alkyl,6-aryl fulvenes with 3-oxidopyrylium betaines

Entry	Pyranulose acetate	Fulvene	Product	Yield [%]
1			 **1d**	67
2			 **2d**	54
3			 **3d**	50

Reaction conditions: fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

Table 5. [6+3] Cycloaddition of 6-aryl fulvenes with 3-oxidopyrylium betaines

Entry	Pyranulose acetate	Fulvene	Product	Yield [%]
1			 **1e**	65
2			 **2e**	50
3			 **3e**	45

Reaction conditions: fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

yield. The reaction is applicable to a wide range of fulvenes with substituents at C6 position, i.e., at the exocyclic double bond.

The adducts obtained may be transformed to fused eight-membered rings, which is the main structural skeleton of a number of natural products such as dactylol, asteriscanolide, cycloaraneosene, kalmanol, etc (Fig. 1). A survey of the literature showed that some of the naturally occurring oxabridged cyclooctanoids possess interesting biological activity such as cytotoxicity and anti-HIV activity (Fig. 3).[19] The presence of an α,β-unsaturated ketone, an oxabridge and the cyclopentadiene functionality makes these adducts

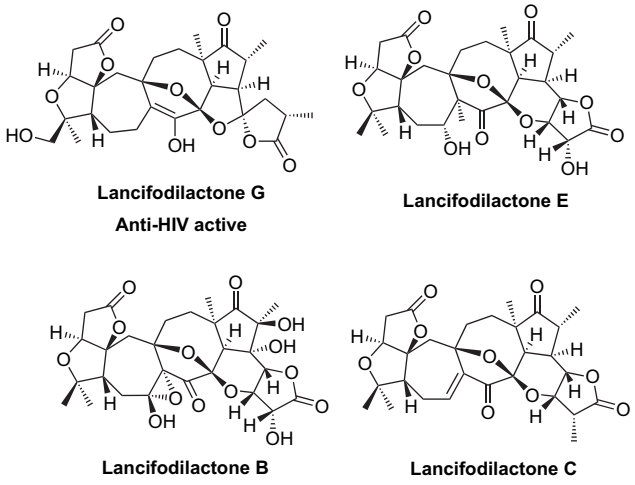


Figure 3. Examples of oxabridged cyclooctanoid natural products.

amenable to a number of synthetic transformations. It is presumed that by using appropriately functionalized fulvenes and oxidopyrylium betaines, the present methodology can be utilized in the synthesis of fused oxabridged cyclooctanoid natural products.

We have carried out theoretical calculations to rationalize the results obtained and are discussed in the following section.

3. Theoretical calculations

All the molecular geometries were optimized at the DFT level by using the Becke's three-parameter exchange functional (B3)[20,21] in conjunction with the Lee–Yang–Parr correlation functional (LYP)[22] as implemented in the Gaussian 03 suite of programs.[23] For H, C, and O, 6-31G(d) basis functions were selected.[24] Normal coordinate analysis has been performed for all stationary points to characterize the transition states and minimum structures. The calculated Gibbs' free energy changes were used throughout the text for discussing the energetics.

Several modes of cycloaddition reactions between fulvene and 3-oxidopyrylium betaine can be envisioned. At first, using unsubstituted fulvene and the 3-oxidopyrylium betaine shown in Figure 4, we have investigated the 18 different possible cycloaddition products. The structure and energetics of these cycloadducts are depicted in Figure 5.

The optimized geometry of fulvene shows two localized double bonds of length 1.353 Å each in the ring and another one of 1.344 Å in the *exo* position (Fig. 4a). The *exo* double bond is more localized than the ring double bonds, which is consistent with the experimental geometry.[25] In the case of 3-oxidopyrylium betaine, the C2–C3 and C3–C4 bonds are significantly longer than other bonds (Fig. 4b) as well as a typical C–C aromatic bond (1.400 Å), which means that the schematic structure given in Figure 4c is quite suitable for this molecule. The dotted lines represent a 6π electron conjugation, which includes two electrons from ring oxygen as in the case of furan molecule. However, compared to furan where the C–O bond lengths are 1.369 Å,[26] the bonding around the ring oxygen in the oxidopyrylium betaine

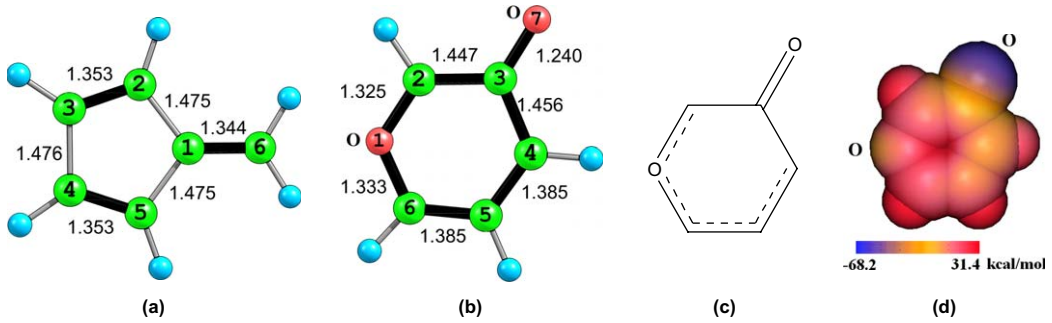


Figure 4. Optimized structure of (a) fulvene and (b) 3-oxidopyrylium betaine. (c) Schematic structure of 3-oxidopyrylium betaine and (d) MESP painted on the van der Waals' surface of betaine. Bond lengths in Å. See text for details.

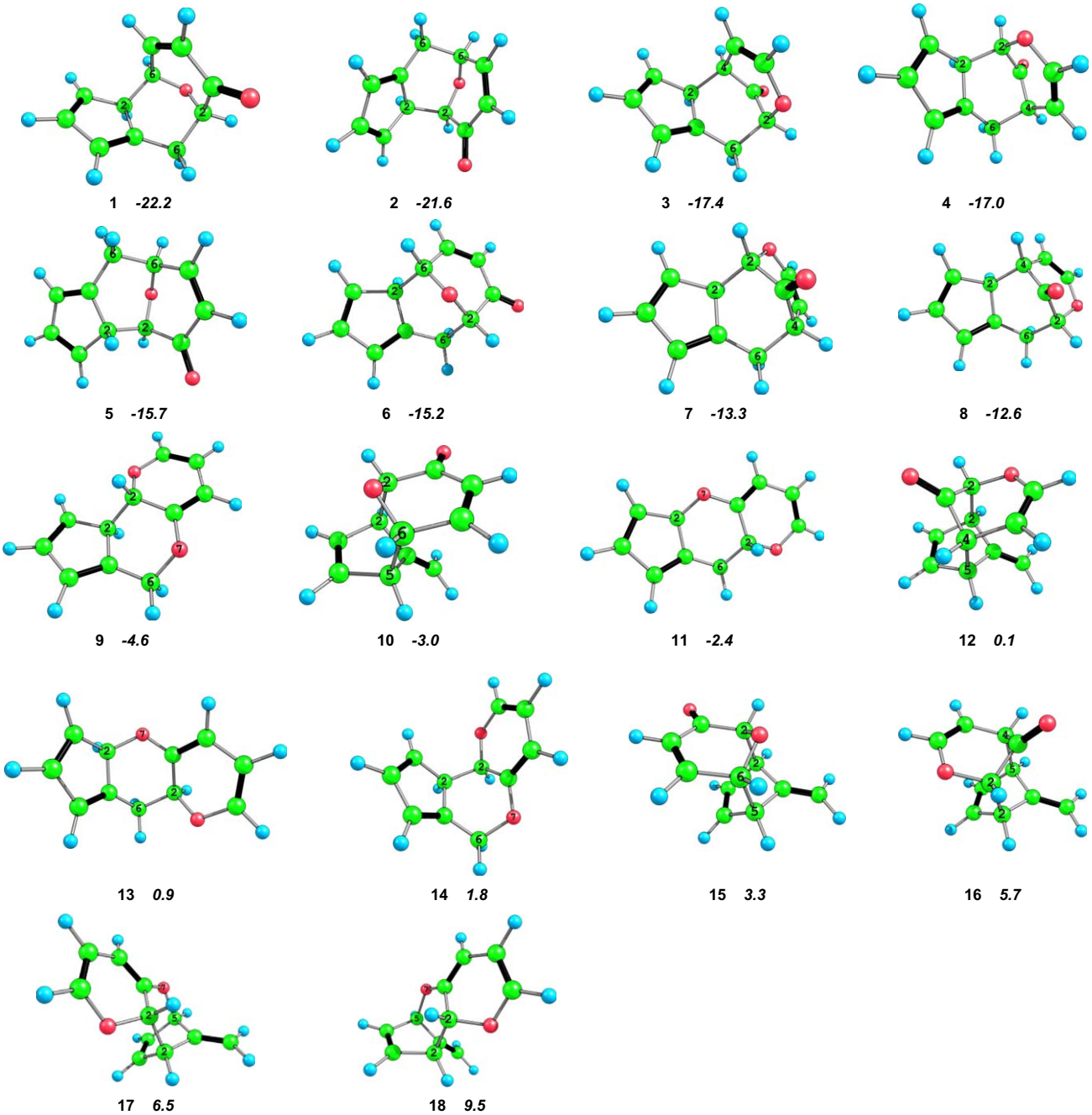


Figure 5. Optimized geometries of various cycloadducts (values in italics are relative free energy in kcal/mol). The sum of the free energies of fulvene and 3-oxidopyrylium betaine is taken as 0.0 kcal/mol.

is stronger. The molecular electrostatic potential (MESP) analysis was carried out on the oxidopyrylium betaine to understand its π-electron distribution.[27] It is found that the negative MESP is centered around the carbonyl oxygen and no negative MESP is observed over the ring region (Fig. 4d). This suggests a zwitterionic structure for this molecule wherein the carbonyl oxygen and the ring oxygen would bear the negative and positive charges, respectively.

Among the 18 cycloadducts given in Figure 5, the structures **1**, **2**, **5**, and **6** are formed as a result of [6+3] cycloaddition in which the atoms C2 and C6 of both fulvene and 3-oxidopyrylium betaine are reacted. Compound **1** is formed from *endo*-cycloaddition giving rise to $C2_{(fulvene)}$–$C6_{(betaine)}$ and $C6_{(fulvene)}$–$C2_{(betaine)}$ bond formations while **2**, also an *endo*-cycloaddition product is formed by the $C2_{(fulvene)}$–$C2_{(betaine)}$ and $C6_{(fulvene)}$–$C6_{(betaine)}$ bond formations. Similarly, **5** and **6** are obtained by the *exo*-cycloadditions. Clearly, the *endo*-cycloaddition products are more stable than *exo*- and all other cycloaddition products. The transition states (TSs) **TS1** and **TS2** are also located for the cycloaddition corresponding to the formation of **1** and **2**, respectively (Fig. 6). A relative free energy of 19.1 kcal/mol is obtained for **TS1** while it is 7.4 kcal/mol for **TS2**. This suggests that compound **2** is the most favored product in cycloaddition step of the reaction. It may be noted that in the experiment, predominantly only one product is formed and in the case of the reaction of 6,6-diphenyl fulvene, the X-ray structure of the product is also available (Fig. 2). This product can be considered as formed from **2** (except for the substituent phenyl groups) when it undergoes a 1,5-hydrogen shift of the H atom, which was originally bonded to the C2 atom of fulvene. For the 1,5-hydrogen shift starting from **2**, a TS **TS3** is also located which gives an activation barrier of 16.7 kcal/mol for it (Fig. 6). Thus, the theoretical study using the unsubstituted systems strongly support the stereoselective formation of the product shown in Figure 2. Since in the calculation **1** is 0.6 kcal/mol more stable than **2**, we expect that in the experiment the stereoelectronic effect exerted by the phenyl groups may give additional stability to the cycloadduct **2** than **1**. In order to understand this substituent effect, further modeling study is carried out for the reaction of 6,6-diphenyl fulvene and the 3-oxidopyrylium betaine.

The optimized geometry of the cycloadducts **19** and **20** which are similar to **1** and **2**, respectively, are presented in Figure 7. Interestingly, **20** is more stable than **19** by 1.9 kcal/mol and as noted in the previous paragraph, this can be attributed to the stereoelectronic effect of the phenyl groups. The TSs **TS4** and **TS5** are also located for the formation of **19** and **20**, respectively. **TS5** is 11.7 kcal/mol lower in energy than **TS4**, which further confirms the stereoselective formation of **20**. Moreover, the activation barrier of 22.2 kcal/mol obtained from **TS5** for the [6+3] cycloaddition is quite reasonable for a feasible reaction as compared to a higher activation barrier of 33.9 kcal/mol obtained from **TS4**. It may be noted that the steric effect is in favor of the less stable TS **TS4** because a closer approach of the reactants is found in this TS as compared to **TS5**. Therefore, the higher stability of **TS5** and the corresponding product **20** can be attributed mainly to the electronic effect. The same conclusion can be obtained even from the unsubstituted systems as one can see a higher stability of 11.7 kcal/mol for **TS2** than **TS1**. This difference should come mainly from the electronic effect because the steric effect is nearly the same or negligible in both the TSs. Also obtained is a TS **TS6** for the 1,5-hydrogen shift starting from **20** and the corresponding product **21** (Fig. 7). The activation energy of 26.6 kcal/mol is predicted for this step of the reaction.

4. Conclusion

In conclusion, we have unraveled a novel reactivity pattern of pentafulvenes with 3-oxidopyrylium betaines. It offers a useful methodology for the synthesis of 5–8 fused cyclooctanoids. The theoretical studies have confirmed a highly stereospecific *endo*-cycloaddition giving rise to $C2_{(fulvene)}$–$C2_{(betaine)}$ and $C6_{(fulvene)}$–$C6_{(betaine)}$ bond formations. The intermediate product thus formed (**20**) undergoes a facile 1,5-hydrogen shift at the five-membered ring of fulvene unit to yield the cyclooctanoid system **21** (Fig. 6), which is in complete agreement with the X-ray structure of the product reported in Figure 2. The reaction was found to be general and a number of fulvenes with a wide range of substituents at the exocyclic double bond, that is, at the C6 position followed similar reactivity pattern. The [6+3] adduct, a 5–8 fused oxabridged cyclooctanoid, is potentially amenable to a number of synthetic transformations due to the presence of an α,β-unsaturated ketone and cyclopentadiene part. By selecting appropriately substituted fulvene and pyranulose acetate, it is possible to use this methodology for the synthesis of a wide range of 5–8 fused cyclooctanoids.

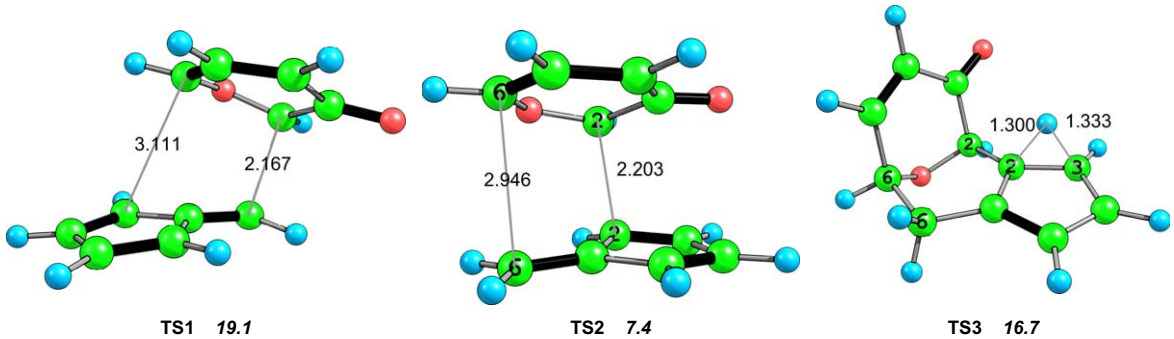


Figure 6. Optimized geometries of transition states. **TS1** and **TS2** are for the formation of **1** and **2**, respectively, and **TS3** for the 1,5-hydrogen shift. The sum of the free energies of fulvene and oxidopyrylium betaine is taken as 0.0 kcal/mol.

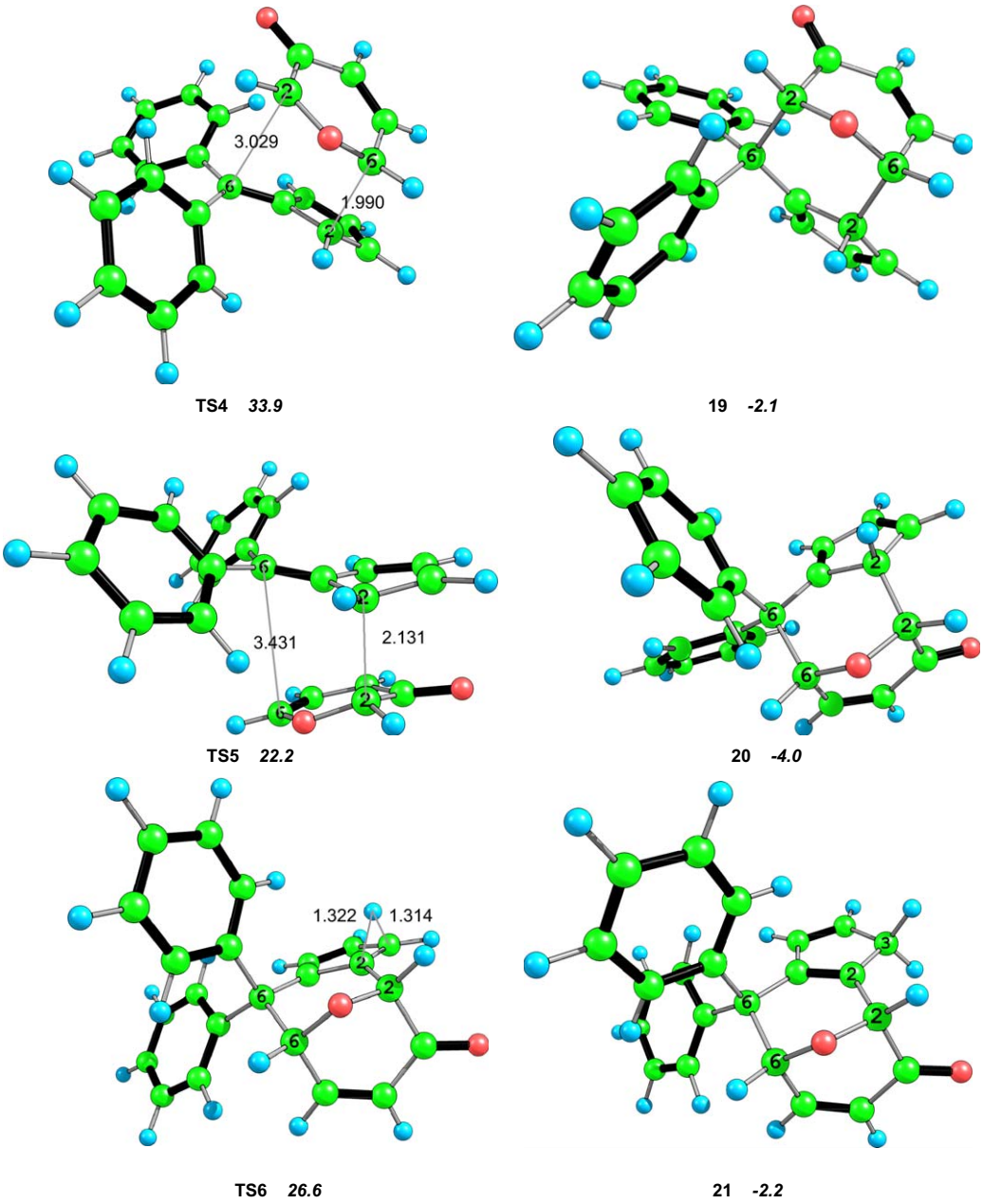


Figure 7. Optimized geometries of the TSs (**TS4** and **TS5**) and products (**19** and **20**) for [6+3] cycloaddition as well as the TS (**TS6**) and product (**21**) for 1,5-hydrogen shift. Relative free energy values with respect to the sum of the free energies of 6,6-diphenyl fulvene and 3-oxidopyrylium betaine are given in italics.

Further work to utilize this methodology toward the synthesis of biologically active oxabridged cyclooctanoids is in progress and will be reported in due course.

5. Experimental

5.1. General

All reactions were carried out in oven-dried glasswares under an atmosphere of argon. Progress of reactions was monitored by thin layer chromatography (Silica gel 60 F_{254}, 0.25 mm, Merck) and purification was effected using silica gel column chromatography. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Brücker DPX-300 MHz spectrometer. Chemical shifts (δ) were reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constants (J) are reported in Hertz (Hz). IR spectra were recorded on a Bomem MB Series FTIR spectrophotometer. Melting points were recorded on a Buchi melting point apparatus and are uncorrected. Fulvenes were prepared according to the literature procedure.[17] Pyranulose acetates,[18] precursors for 3-oxidopyrylium betaines, were prepared from corresponding furfuryl alcohol by oxidation with *N*-bromosuccinimide followed by protection with acetic anhydride in presence of pyridine and DMAP. Commercial grade solvents were distilled prior

to use. Triethylamine, chloroform and diethyl ether were dried as per the standard procedures.

5.1.1. Details of a typical experiment are as follows. Diphenyl fulvene (100 mg, 0.43 mmol), pyranulose acetate (81 mg, 0.52 mmol) and dry triethylamine (52 mg, 0.52 mmol) were taken in anhydrous chloroform and stirred at 50 °C in a Schlenk tube for 6 h under nitrogen. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 5% ethyl acetate/hexane mixture as eluent to afford the product as a pale yellow crystalline solid (98 mg, 70%). The product **1a** was recrystallized from dichloromethane/hexane mixture.

5.2. Spectroscopic data for new compounds

5.2.1. Compound 1a. Yield 70%, pale yellow crystalline solid. Mp 173–175 °C. R_f 0.50 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3062, 2928, 1691, 1598, 1443, 1376, 1247, 1160, 1077, 1036, 943 cm^{-1}. ^1H NMR: δ 3.06 (s, 2H), 4.88 (s, 1H), 5.36 (d, 1H, J=4.3 Hz), 5.76 (d, 1H, J=10.4 Hz), 5.99 (dd, 1H, J_1=4.3, J_2=10.4 Hz), 6.44 (d, 1H, J=5.3 Hz), 6.56 (d, 1H, J=5.3 Hz), 7.00–7.54 (m, 10H). ^{13}C NMR: δ 194.5, 148.5, 145.8, 142.3, 141.4, 133.9, 132.9, 132.3, 129.3, 129.0, 128.6, 128.4, 128.3, 128.2, 127.3, 126.4, 123.2, 76.6, 74.9, 52.7, 40.7. HRMS (EI): m/z calcd for $C_{23}H_{18}O_2$: 326.1307. Found: (M^+) 326.1323. Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.37; H, 5.41.

5.2.2. Compound 2a. Yield 62%, pale yellow crystalline solid. Mp 213–215 °C. R_f 0.48 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3061, 2929, 1692, 1596, 1491, 1446, 1262, 1157, 1069, 1024, 947 cm^{-1}. ^1H NMR: δ 1.56 (s, 3H), 2.98 (s, 2H), 5.35 (d, 1H, J=4.2 Hz), 5.73 (d, 1H, J=10.3 Hz), 5.94 (dd, 1H, J_1=4.2, J_2=10.3 Hz), 6.42 (d, 1H, J=5.1 Hz), 6.55 (d, 1H, J=5.2 Hz), 7.00–7.57 (m, 10H). ^{13}C NMR: δ 196.1, 148.3, 146.2, 142.5, 141.4, 137.9, 132.9, 132.5, 129.5, 129.2, 128.8, 128.5, 128.3, 128.3, 128.2, 127.2, 126.4, 123.3, 79.6, 75.8, 52.6, 39.9, 20.4. HRMS (EI): m/z calcd for $C_{24}H_{20}O_2$: 340.1463. Found: (M^+) 340.1490.

5.2.3. Compound 3a. Yield 53%, pale yellow solid. Mp 193–195 °C. R_f 0.43 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2918, 2851, 1687, 1460, 1383, 1209, 1176, 1069, 900, 760 cm^{-1}. ^1H NMR: δ 0.70 (d, 3H, J=6.8 Hz), 0.99 (d, 3H, J=6.6 Hz), 2.58–2.68 (m, 1H), 2.95 (s, 2H), 5.38 (d, 1H, J=4.3 Hz), 5.75 (d, 1H, J=10.3 Hz), 5.95 (dd, 1H, J_1=4.3, J_2=10.3 Hz), 6.43 (d, 1H, J=5.3 Hz), 6.52 (d, 1H, J=5.3 Hz), 6.96–7.56 (m, 10H). ^{13}C NMR: δ 196.2, 147.8, 146.1, 142.7, 142.1, 137.1, 132.9, 132.3, 129.0, 128.4, 128.3, 128.1, 128.0, 127.9, 126.9, 126.1, 124.3, 84.8, 75.2, 39.4, 30.8, 16.3, 16.1. HRMS (EI): m/z calcd for $C_{26}H_{24}O_2$: 368.1776. Found: (M^+) 368.1773.

5.2.4. Compound 4a. Yield 57%, pale yellow viscous liquid. R_f 0.71 (7:3 hexane/EtOAc) IR (KBr) ν_{max}: 2956, 2927, 1691, 1495, 1379, 1252, 1098, 1074, 1015, 906 cm^{-1}. ^1H NMR: δ 3.07 (s, 2H), 4.88 (s, 1H), 5.28 (d, 1H, J=4.3 Hz), 5.79 (d, 1H, J=10.4 Hz), 6.02 (dd, 1H, J_1=4.3 Hz, J_2=10.4 Hz), 6.47 (s, 2H), 6.89–7.47 (m, 8H). ^{13}C NMR: δ 193.9, 147.6, 143.9, 140.5, 140.3, 134.4, 133.8, 133.6, 132.7, 131.5, 130.5, 130.3, 129.7, 128.9, 128.7, 128.6, 123.5, 74.7, 51.8, 40.8. HRMS (EI): m/z calcd for $C_{23}H_{16}O_2Cl_2$: 394.0527. Found: (M^+) 394.0509.

5.2.5. Compound 1b. Yield 83%, pale yellow solid. Mp 110–112 °C. R_f 0.45 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2963, 2917, 1702, 1468, 1379, 1243, 1159, 1069, 896, 769 cm^{-1}. ^1H NMR: δ 1.13 (s, 3H), 1.43 (s, 3H), 2.79–3.07 (m, 2H), 4.29 (d, 1H, J=4.1 Hz), 4.74 (s, 1H), 5.92 (d, 1H, J=10.2 Hz), 6.32 (d, 1H, J=4.2 Hz), 6.41 (s, 1H), 6.97 (dd, 1H, J_1=4.1 Hz, J_2=10.2 Hz). ^{13}C NMR: δ 193.0, 147.4, 133.9, 131.5, 129.9, 129.7, 123.9, 77.0, 76.5, 40.5, 39.2, 29.3, 22.7. HRMS (EI): m/z calcd for $C_{13}H_{14}O_2$: 202.0994. Found: (M^+) 202.0999. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.18; H, 7.35.

5.2.6. Compound 2b. Yield 79%, pale yellow solid. Mp 124–126 °C. R_f 0.51 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2963, 2937, 1687, 1442, 1370, 1206, 1172, 1059, 902, 770 cm^{-1}. ^1H NMR: δ 1.13 (s, 3H), 1.39 (s, 3H), 1.48 (s, 3H), 2.75–3.04 (m, 2H), 4.31 (d, 1H, J=4.2 Hz), 5.88 (d, 1H, J=10.3 Hz), 6.28 (s, 1H), 6.39 (d, 1H, J=10.7 Hz), 6.91 (dd, 1H, J_1=4.2 Hz, J_2=10.3 Hz). ^{13}C NMR: δ 196.4, 147.1, 133.9, 130.1, 124.1, 123.9, 123.7, 76.9, 76.1, 39.7, 38.4, 29.7, 22.7, 19.2. HRMS (EI): m/z calcd for $C_{14}H_{16}O_2$: 216.1150. Found: (M^+) 216.1122.

5.2.7. Compound 3b. Yield 68%, pale yellow solid. Mp 178–180 °C. R_f 0.56 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2963, 2937, 1687, 1442, 1370, 1206, 1172, 1059, 902, 770 cm^{-1}. ^1H NMR: δ 0.78 (d, 3H, J=6.6 Hz), 0.88 (d, 3H, J=6.6 Hz), 1.22 (s, 3H), 1.41 (s, 3H), 2.64–2.97 (m, 3H), 4.25 (d, 1H, J=4.2 Hz), 5.81 (d, 1H, J=10.3 Hz), 6.21 (s, 1H), 6.29–6.36 (m, 1H), 6.80–6.85 (dd, 1H, J_1=4.2, J_2=10.3 Hz). ^{13}C NMR: δ 196.4, 146.8, 134.0, 131.4, 129.9, 125.3, 125.0, 85.1, 76.6, 39.5, 37.7, 30.9, 29.8, 23.6, 16.4, 16.3. HRMS (EI): m/z calcd for $C_{16}H_{20}O_2$: 244.1463. Found: (M^+) 244.1469.

5.2.8. Compound 1c. Yield 70%, pale yellow viscous liquid. R_f 0.53 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3067, 2953, 1702, 1620, 1455, 1377, 1157, 1128, 1067, 980, 940 cm^{-1}. ^1H NMR: δ 0.88–1.26 (m, 8H), 2.89–2.99 (m, 2H), 4.34 (d, 1H, J=4.1 Hz), 4.73 (s, 1H), 5.91 (d, 1H, J=10.4 Hz), 6.36 (d, 1H, J=5.2 Hz), 6.42 (d, 1H, J=5.2 Hz), 6.93 (dd, 1H, J_1=4.1, J_2=10.4 Hz). ^{13}C NMR: δ 194.9, 146.8, 133.9, 130.5, 129.7, 123.8, 77.2, 74.5, 40.7, 32.9, 31.6, 26.0, 24.5. HRMS (EI): m/z calcd for $C_{15}H_{16}O_2$: 228.1150. Found: (M^+) 228.1133.

5.2.9. Compound 2c. Yield 60%, pale yellow solid. Mp 125–127 °C. R_f 0.50 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3070, 2933, 1691, 1612, 1454, 1378, 1245, 1157, 1067, 996, 943 cm^{-1}. ^1H NMR: δ 1.25–1.79 (m, 10H), 2.81–3.07 (m, 2H), 4.71 (s, 1H), 4.84–4.87 (m, 1H), 5.94 (d, 1H, J=10.5 Hz), 6.29–6.34 (m, 1H), 6.39–6.47 (m, 1H), 6.96–7.06 (m, 1H). ^{13}C NMR: δ 194.9, 147.2, 133.8, 130.2, 129.5, 123.8, 123.7, 76.5, 70.4, 40.6, 39.7, 36.4, 31.7, 25.7, 22.2, 22.1. HRMS (EI): m/z calcd for $C_{16}H_{18}O_2$: 242.1307. Found: (M^+) 242.1321. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49; O, 13.21. Found: C, 79.69; H, 4.08.

5.2.10. Compound 3c. Yield 58%, pale yellow viscous liquid. R_f 0.69 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2928, 2856, 1697, 1459, 1377, 1248, 1161, 1068, 924, 733 cm^{-1}. ^1H NMR: δ 1.29–1.81 (m, 12H), 2.89–3.07 (m, 2H), 4.71 (s, 1H), 4.84–4.87 (m, 1H), 5.94 (d, 1H, J=10.5 Hz), 6.28–6.34 (m, 1H), 6.39–6.48 (m, 1H), 6.97–7.07 (m, 1H). ^{13}C NMR: δ 193.4, 147.7, 133.9, 131.2, 130.7, 124.0, 123.8, 77.3, 76.3, 43.7, 40.1, 38.7, 34.2, 31.3, 30.5, 23.9, 23.6. HRMS (EI): m/z calcd for $C_{17}H_{20}O_2$: 256.1463. Found: (M^+) 256.1451.

5.2.11. Compound 4c. Yield 59%, pale yellow viscous liquid. R_f 0.59 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3066, 2932, 2859, 1691, 1621, 1453, 1370, 1257, 1174, 1057, 938, 900 cm^{-1}. ^1H NMR: δ 1.35–1.70 (m, 13H), 2.84–3.05 (m, 2H), 4.89 (d, 1H, J=4.3 Hz), 5.90 (d, 1H, J=10.3 Hz), 6.40–6.46 (m, 2H), 6.97 (dd, 1H, J_1=4.3, J_2=10.3 Hz). ^{13}C NMR: δ 196.2, 148.0, 146.9, 133.6, 130.9, 130.4, 124.1, 76.5, 71.9, 40.3, 35.1, 33.2, 31.7, 26.3, 22.6, 22.3, 21.8. HRMS (EI): m/z calcd for $C_{17}H_{20}O_2$: 256.1463. Found: (M^+) 256.1467.

5.2.12. Compound 5c. Yield 52%, pale yellow viscous liquid. R_f 0.61 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2933, 2861, 1681, 1537, 1454, 1259, 1259, 1184, 1069, 749 cm^{-1}. ^1H NMR: δ 0.79 (d, 3H, J=6.8 Hz), 0.93 (d, 3H, J=6.6 Hz), 1.25–1.59 (m, 10H), 2.55–2.59 (m, 1H), 2.86–3.07 (m, 2H), 4.87–4.90 (m, 1H), 5.89 (d, 1H, J=10.3 Hz), 6.27 (s, 1H), 6.40–6.42 (m, 1H), 6.91–6.95 (m, 1H). ^{13}C NMR: δ 196.9, 146.5, 133.6, 131.4, 130.2, 129.1, 125.2, 70.5, 39.5, 35.1, 32.9, 31.4, 25.6, 22.2, 21.9, 16.3, 15.9. HRMS (EI): m/z calcd for $C_{19}H_{24}O_2$: 284.1776. Found: (M^+) 284.1776.

5.2.13. Compound 1d. Yield 67%, pale yellow viscous liquid. R_f 0.51 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3063, 2927, 1693, 1602, 1490, 1370, 1240, 1116, 1072, 991, 940 cm^{-1}. ^1H NMR: δ 1.84 (s, 3H), 3.12 (s, 2H), 4.51 (dd, 1H, J_1=0.9, J_2=4.3 Hz), 4.83 (s, 1H), 5.78 (d, 1H, J=10.5 Hz), 6.08 (dd, 1H, J_1=4.3, J_2=10.5 Hz), 6.27 (d, 1H, J=5.3 Hz), 6.46 (d, 1H, J=5.3 Hz), 7.17–7.33 (m, 5H). ^{13}C NMR: δ 194.5, 148.6, 143.9, 140.9, 133.4, 133.0, 131.8, 128.7, 128.4, 127.9, 127.5, 127.2, 122.9, 77.4, 76.6, 44.5, 40.9, 26.5. HRMS (EI): m/z calcd for $C_{18}H_{16}O_2$: 264.1150. Found: (M^+) 264.1156.

5.2.14. Compound 2d. Yield 54%, pale yellow solid. Mp 55–57 °C. R_f 0.56 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2963, 2937, 1687, 1442, 1370, 1206, 1172, 1059, 902, 770 cm^{-1}. ^1H NMR: δ 1.11–1.41 (m, 7H), 3.07–3.27 (m, 2H), 4.58 (d, 1H, J=4.1 Hz), 4.78 (s, 1H), 5.73 (d, 1H, J=10.3 Hz), 6.00 (dd, 1H, J_1=4.1, J_2=10.3 Hz), 6.38 (d, 1H, J=4.9 Hz), 6.49 (d, 1H, J=4.9 Hz), 7.13–7.28 (m, 5H). ^{13}C NMR: δ 194.4, 148.8, 139.6, 139.5, 133.5, 131.9, 128.5, 127.9, 126.9, 122.8, 77.8, 76.4, 59.5, 45.3, 38.1, 31.2, 29.6, 26.6. HRMS (EI): m/z calcd for $C_{21}H_{20}O_2$: 304.1463. Found: (M^+) 304.1487.

5.2.15. Compound 3d. Yield 50%, pale yellow viscous liquid. R_f 0.37 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2963, 2937, 1687, 1442, 1370, 1206, 1172, 1059, 902, 770 cm^{-1}. ^1H NMR: δ 1.82 (s, 3H), 3.12 (s, 2H), 4.47 (d, 1H, J=4.2 Hz), 4.83 (s, 1H), 5.80 (d, 1H, J=10.3 Hz), 6.11 (dd, 1H, J_1=4.2, J_2=10.3 Hz), 6.20 (d, 1H, J=5.3 Hz), 6.47 (d, 1H, J=4.9 Hz), 7.10–7.29 (m, 4H). ^{13}C NMR: δ 194.0, 148.7, 134.3, 132.2, 129.8, 129.7, 124.0, 123.7, 121.4, 121.1, 78.3, 76.4, 41.7, 30.6, 27.3. HRMS (EI): m/z calcd for $C_{18}H_{15}ClO_2$: 298.0761. Found: (M^+) 298.0788.

5.2.16. Compound 1e. Yield 65%, pale yellow crystalline solid. Mp. 99–101 °C. R_f 0.49 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3065, 2928, 1692, 1605, 1492, 1377, 1248, 1154, 1069, 995, 944 cm^{-1}. ^1H NMR: δ 2.82–3.21 (m, 2H), 3.57 (d, 1H, J=8.7 Hz), 4.69 (d, 1H, J=4.0 Hz), 4.93 (s, 1H), 5.96 (d, 1H, J=10.4 Hz), 6.19 (d, 1H, J=5.2 Hz), 6.42 (d, 1H, J=4.8 Hz), 7.06 (dd, 1H, J_1=4.0, J_2=10.4 Hz), 7.14–7.30 (m, 5H). ^{13}C NMR: δ 194.9, 146.9, 133.8, 132.6, 129.6, 128.9, 128.8, 127.9, 127.2, 123.9, 123.7, 76.6, 73.7, 42.9, 40.6. HRMS (EI): m/z calcd for $C_{17}H_{14}O_2$: 250.0994. Found: (M^+) 250.0991.

5.2.17. Compound 2e. Yield 50%, pale yellow viscous liquid. R_f 0.52 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2928, 2851, 1694, 1460, 1388, 1249, 1176, 1072, 909, 749 cm^{-1}. ^1H NMR: δ 1.26 (s, 3H), 2.86–3.03 (m, 2H), 4.28–4.34 (m, 1H), 4.90–4.95 (m, 1H), 5.92 (d, 1H, J=10.3 Hz), 6.12 (d, 1H, J=5.3 Hz), 6.34–6.40 (m, 1H), 6.39–6.43 (m, 1H), 7.00–7.28 (m, 5H). ^{13}C NMR: δ 196.9, 146.9, 134.2, 132.8, 132.6, 129.6, 128.9, 128.8, 127.9, 127.2, 123.8, 123.7, 76.3, 74.0, 44.9, 40.5, 20.6. HRMS (EI): m/z calcd for $C_{18}H_{16}O_2$: 264.1150. Found: (M^+) 264.1164.

5.2.18. Compound 3e. Yield 45%, pale yellow viscous liquid. R_f 0.47 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2969, 2928, 1692, 1460, 1388, 1249, 1176, 1074, 909, 749 cm^{-1}. ^1H NMR: δ 0.86 (d, 3H, J=7.0 Hz), 0.96 (d, 3H, J=6.6 Hz), 2.66–2.73 (m, 1H), 2.97–3.05 (m, 2H), 4.35–4.38 (m, 1H), 4.94–4.98 (m, 1H), 5.93 (d, 1H, J=10.3 Hz), 6.14 (d, 1H, J_1=5.3 Hz), 6.31–6.36 (m, 1H), 6.39–6.43 (m, 1H), 7.05–7.33 (m, 5H). ^{13}C NMR: δ 196.2, 147.8, 146.1, 142.7, 137.1, 132.9, 132.3, 129.0, 128.4, 128.3, 128.1 127.9, 126.9, 126.1, 124.3, 84.8, 75.2, 39.4, 30.8. HRMS (EI): m/z calcd for $C_{20}H_{20}O_2$: 292.1463. Found: (M^+) 292.1464.

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