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Tetrahedron 59 (2003) 6341–6352

TETRAHEDRON

Stereoselectivity, periselectivity, and regioselectivity in the cycloadditions of 8-(*p*-chlorophenyl)-8-azaheptafulvene with cyclopentadiene and fulvenes

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Received 30 December 2002; revised 20 May 2003; accepted 16 June 2003

Dedicated to Professor K. N. Houk, an inspiring teacher and scholar to whom we are very grateful

Abstract—The stereoselectivity, periselectivity, and regioselectivity in the cycloaddition reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene with cyclopentadiene and symmetrical/unsymmetrical fulvenes is described.

1. Introduction

The competition among thermally allowed [4+2], [6+4], and [8+2] cycloaddition reactions has prompted much investigation. It is well known that tropone (**1**) reacts with cyclopentadiene (**2**) stereoselectively and periselectively to give the *exo*-[6+4] cycloadduct **3** (Scheme 1(a)).[1,2] By contrast, Machiguchi et al. reported that tropothione (**4**), a sulphur analog of tropone, reacts with **2** to afford the *endo*-[8+2] cycloadduct **5** (Scheme 1(b)).[3,4] Interestingly, Kitahara and Oda reported that 8,8-dicyanoheptafulvene (**6**), a carbon analog of tropone, reacts with **2** to afford the *exo*-[6+4] cycloadduct **7**, which undergoes a [3,3] sigmatropic shift to yield the [8+2] cycloadduct **8**, which in turn mainly reverts back to starting materials **6** and **2** at higher temperatures, which finally recombine to form the thermodynamically most stable [4+2] cycloadducts **9** (Scheme 1(c)).[5]

Houk et al. reported the periselective formation of 1:1 [6+4] cycloadducts **11a**–**c**, respectively, in the cycloaddition reactions of tropone (**1**) with electron-rich substituted 6-methyl- (**10a**), 6-phenyl- (**10b**), and 6,6-dimethyl- (**10c**) fulvenes, which immediately undergo 1,5-sigmatropic hydrogen shifts to yield the thermodynamically more stable cyclopentadienes **12**, which subsequently undergo a second [6+4] cycloaddition with **1** to form 2:1 cycloadducts **13a**–**c**, respectively (Scheme 2(a)).[6–8] A trace of [4+2] cycloadduct **14c** was also obtained. By contrast, Sasaki et al. reported that tropone (**1**) reacts with more hindered 6,6-diphenylfulvene (**10d**) to afford only [4+2] cycloadduct **14d** instead of the expected [6+4] cycloadduct (Scheme 2(b)).[9] The behaviors of these cycloaddition reactions seem to indicate sensitivity to steric requirements of the exocyclic substituents on the fulvenes. However, in the cycloaddition reactions of tropothione (**4**) with fulvenes **10c** and **10d**, only [8+2] cycloadducts **15c** and **15d** were obtained, respectively (Scheme 2(c)).[10] No [6+4] or [4+2] cycloadduct was isolated. We have reported that electron-deficient 8,8-dicyano- (**6a**: R^1=R^2=CN) and 8,8-bis-(methoxycarbonyl)- (**6b**: R^1=R^2=CO_2Me) heptafulvenes react with 6,6-dimethylfulvene (**10c**: R^3=R^4=Me) and 6,6-diphenylfulvene (**10d**: R^3=R^4=Ph) to give *anti*-endocyclic [8+2], *anti*- and/or *syn*-endocyclic [4+2], and/or *anti*-[6+4] cycloadducts (Scheme 3).[11] We proposed that the *endo* stereochemistry of these reactions is controlled by secondary orbital interactions, and the preferred *anti* regioselectivity (R^1/R^2 vs. R^3/R^4) could be attributed to the steric repulsion between the exocyclic substituents on the heptafulvenes and fulvenes. We have also found that in the unsymmetrical cycloadditions of heptafulvenes with fulvenes, the exocyclic substituent effects exert controlling influence upon the periselectivity and regioselectivity of these cycloadditions (Scheme 3).[12,13]

In this paper, we report the cycloaddition reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**), a nitrogen analog of tropone, with cyclopentadiene (**2**) (Scheme 4) and

Keywords: 8-(*p*-chlorophenyl)-8-azaheptafulvene; fulvenes; cyclopentadiene; stereoselectivity; periselectivity; regioselectivity; [4+2] and [6+4] cycloadditions.

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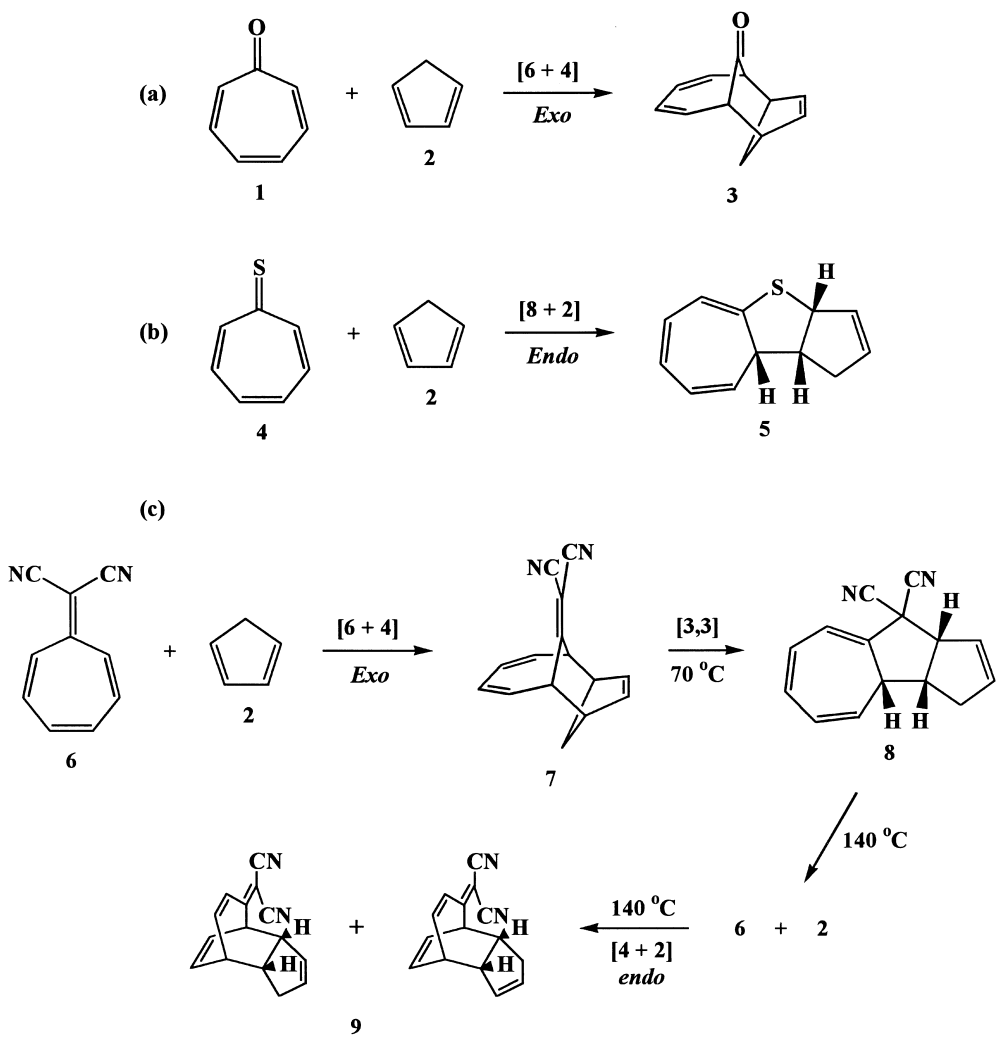
0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4020(03)00994-3



Scheme 1.

symmetrically- and unsymmetrically-substituted fulvenes **10c–f** (Schemes 5–8).

2. Results and discussion

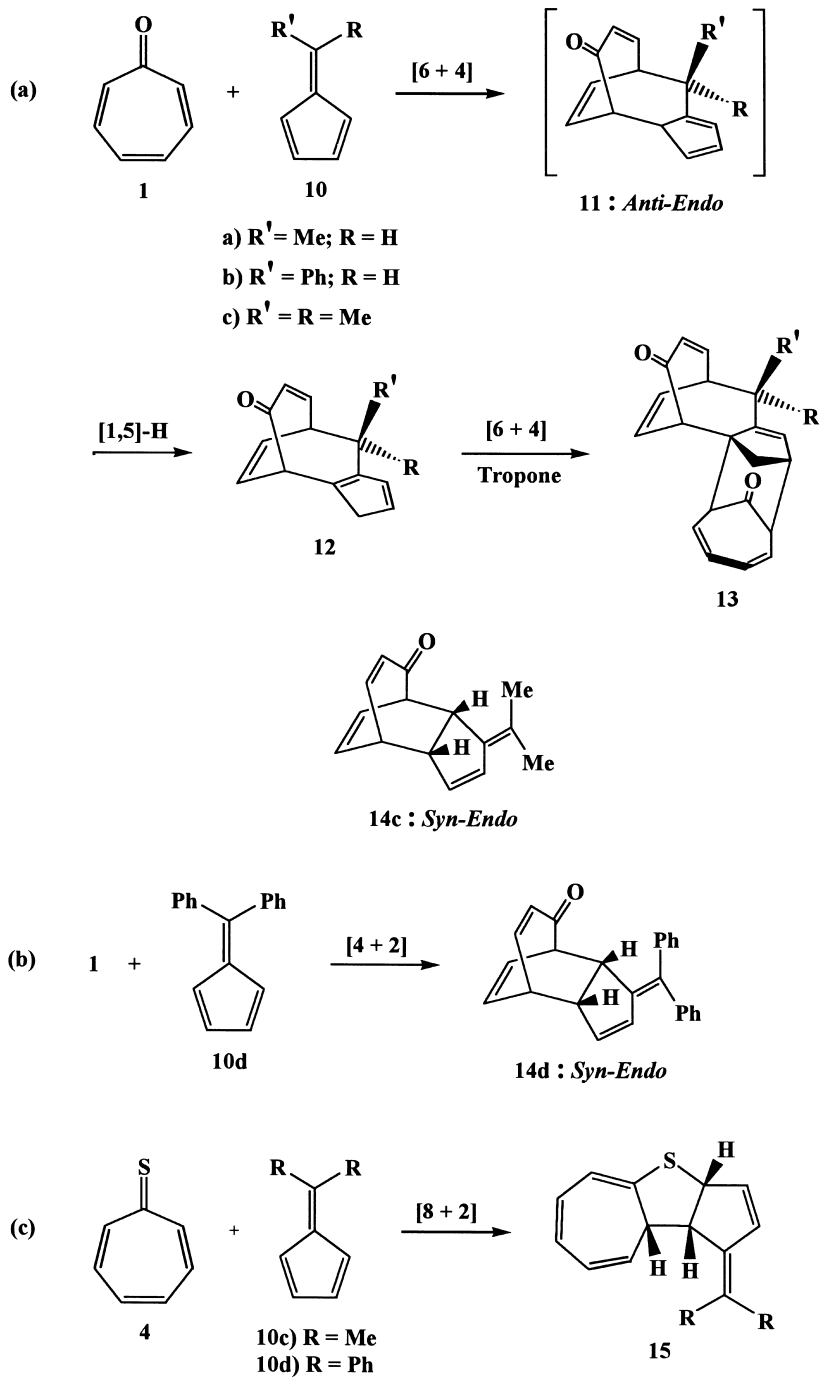
2.1. Reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (16) with cyclopentadiene (2) (Scheme 4)

The reaction of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) with cyclopentadiene (**2**) at room temperature for 24 h gave an *exo*-[6+4] cycloadduct **17** in 35% isolated yield (Scheme 4). The ^{1}H NMR spectrum showed six aliphatic protons, six olefinic protons, and four aromatic protons. The methylene protons resonated at δ 1.37–1.42 (m, H-11) and 2.10 (d, H-11′). The bridgehead protons resonated at δ 2.81–2.83 (m, H-1), 2.98–2.99 (m, H-4), 3.25–3.28 (m, H-10), and 3.34–3.37 (m, H-5). The olefinic protons showed five signals at δ 5.56 (bdd, H-9), 5.81 (dd, H-2), 5.94 (bdd, H-6), 5.98–6.02 (m, H-7 and H-8), and 6.05 (dd, H-3). The aromatic ring protons gave two signals at δ 6.50 (d, 2H, Ph) and 7.15 (d, 2H, Ph′). Extensive analysis of 2D ^{1}H–^{1}H COSY and NOESY spectra of **17** established the structure shown in Figure 1. The NOE correlations in the NOESY spectrum, H-11′ to H-6, H-7, H-8, and H-9, H-11 to H-1, H-2, H-3, and H-4, H-10 to Ph, and Ph to H-10, H-2, and H-9 as shown in Figure 1, confirmed the *exo* stereochemistry of this cycloadduct.

Unfortunately, the attempted hydrolysis reaction of cycloadduct **17** to **3** and [3,3] sigmatropic rearrangement to the expected [8+2] cycloadduct **18** were unsuccessful (Scheme 4), with mainly the starting material **17** being recovered.

2.2. Reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (16) with symmetrically substituted 6,6-dimethylfulvene (10c) (Schemes 5 and 6)

8-(*p*-Chlorophenyl)-8-azaheptafulvene (**16**) reacted sluggishly with 6,6-dimethylfulvene (**10c**) in chloroform at room temperature over 24 h to give an *anti-endo*-[6+4] cycloadduct **20c** in 10% isolated yield (Scheme 5 and Table 1). When the reaction of **16** and **10c** was carried out in refluxing benzene for 12 h, the cycloadduct **20c** was obtained in much higher yield (56%, Scheme 5 and Table 1). Cycloadduct **20c** must arise from an initial [6+4] cycloaddition that forms **19c** followed by a

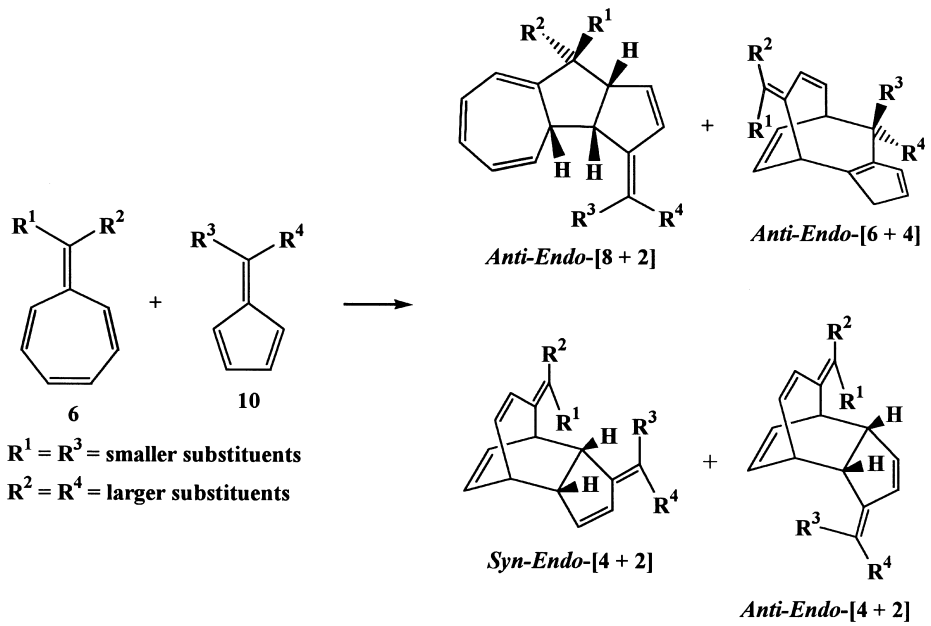


Scheme 2.

1,5-sigmatropic hydrogen shift in the cyclopentadiene moiety.[6–8,11–15] Additional structural evidence for **20c** is the [4+2] cycloaddition reaction of **20c** with DMAD,[6,11–14] which gave **21c**, which in turn afforded ketone **22c** (Scheme 4) upon acid hydrolysis.

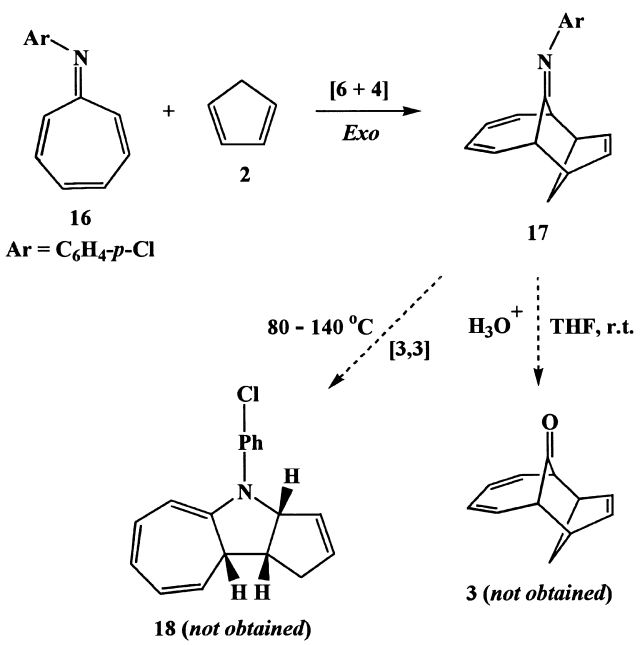
The IR spectrum of cycloadduct **22c** showed characteristic α,β-unsaturated ketone and ester absorptions at 1660 and 1720 cm^{-1}, respectively. The structure was eventually proved by a complete analysis of its ^1H NMR spectra, including 2D $^1H-^1H$ COSY and NOESY techniques (Fig. 2), and comparison of its spectra to those of related compounds.[6,11–14] The ^1H NMR spectrum showed sharp singlets at δ 1.11 and 1.32 (Me′) for the two methyl groups on the saturated carbon, doublets at δ 1.82 and 2.19 for the methylene group (H-5), triplets for H-10, H-8, and H-9 at δ 2.95, 5.87, and 6.25, respectively, broad multiplets for H-4 and H-7 at δ 3.74 and 3.80, respectively, a doublet for H-12 at δ 5.93, a broad doublet for H-3 at δ 6.61, and a doublet of doublets for H-11 at δ 6.84. The appropriate methyl ester resonances at δ 3.70 and 3.80 were also observed. The NOE correlations in the NOESY spectrum, Me′ to H-3, H-10, and H-11 and Me to H-3, H-9, and H-10 as shown in Figure 2, confirmed the stereochemistry for this cycloadduct.

Interestingly, heating a dilute solution of **20c** in refluxing



Scheme 3.

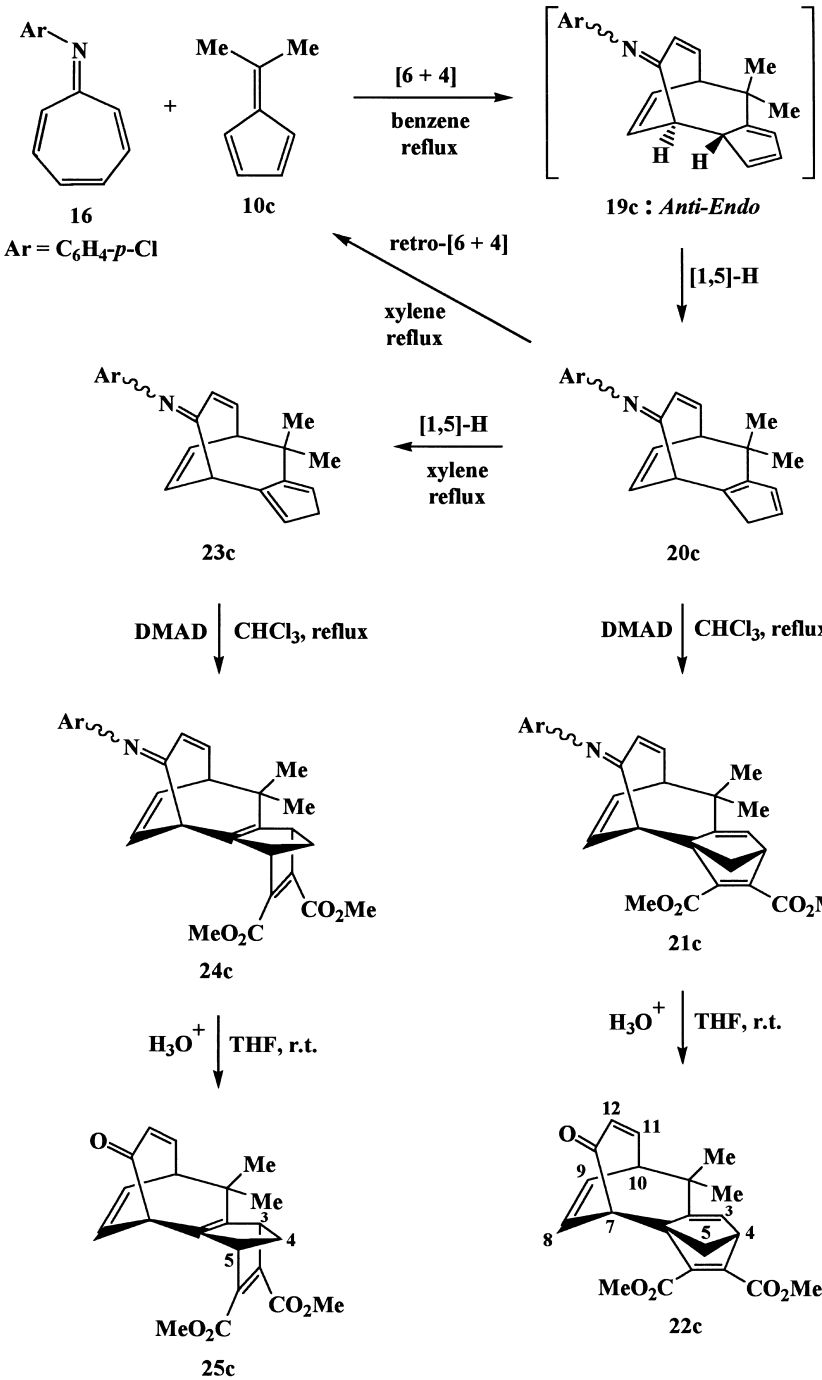
xylene mainly led to a retro-[6+4] cycloaddition reaction of **20c** to starting materials **16** and **10c**, along with minor amounts of another [6+4] cycloadduct, **23c**. Cycloadduct **23c** must arise from a 1,5-sigmatropic hydrogen shift in the cyclopentadiene moiety of **20c**. Additional structural evidence for **23c** is the [4+2] cycloaddition reaction of **23c** with DMAD, which gave **24c**, which in turn afforded ketone **25c** (Scheme 5) upon acid hydrolysis. The structure of **25c** was eventually proved by a complete analysis of its ^{1}H NMR spectra, including 2D ^{1}H–^{1}H COSY and NOESY techniques (Fig. 2), and comparison of its spectra to those of related cycloadduct **22c**. The NOE correlations in the NOESY spectrum, Me′ to H-3, H-10, and H-11, Me to H-3, H-9, and H-10, and H-5 to H-7 as shown in Figure 2, confirmed the stereochemistry for this cycloadduct.



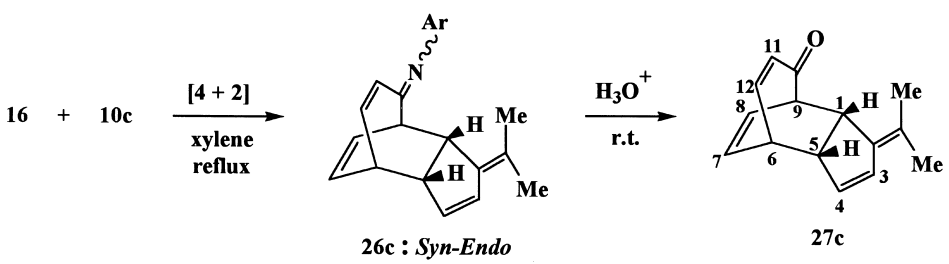
Scheme 4.

When the reaction of **16** and **10c** was carried out in refluxing xylene for 5 h, the *syn-endo*-[4+2] cycloadduct **26c** and *anti-endo*-[6+4] cycloadduct **20c** were obtained in a ratio of 2.4:1 in 60% isolated yield (Scheme 6 and Table 1). A trace of the [6+4] cycloadduct **23c** was also obtained. With longer reaction time (7 h), **26c** was formed as the main product. Additional structural evidence for **26c** is acid hydrolysis of **26c** affords the corresponding ketone **27c**. Traces of the [6+4] cycloadducts **22c/25c** (after DMAD and H_3O^+) were also isolated. The IR spectrum of cycloadduct **27c** showed a characteristic α,β-unsaturated ketone absorption at 1660 cm^{-1}. The structure was eventually proved by a complete analysis of its ^{1}H NMR spectra, including 2D ^{1}H–^{1}H COSY and NOESY techniques (Fig. 2), and comparison of its spectra to those of related compounds.[6,11–14] The ^{1}H NMR spectrum showed sharp singlets at δ 1.73 and 1.78 (Me′) for the two methyl groups on the unsaturated carbon, doublets at δ 3.22 and 5.74 for H-1 and H-11, respectively, triplets for H-6, H-7, and H-8 at δ 3.38, 6.22, and 5.97, respectively, doublet of doublets for H-3 and H-12 at δ 6.39 and 7.10, respectively, and broad multiplets for H-4 and H-5/H-9 at δ 5.55 and 3.60, respectively. The small coupling constants between H-1 and H-9 and between H-5 and H-6 are compatible only with an *endo* stereochemistry for this cycloadduct.[11–18] H-5 was coupled to H-1, H-3, H-4, and H-6, respectively, indicating a *syn* regiochemistry. The NOE correlations in the NOESY spectrum, Me′ to H-1 and H-9, Me to H-3, and H-4 to H-6, as shown in Figure 2, further confirmed the stereochemistry for this cycloadduct.

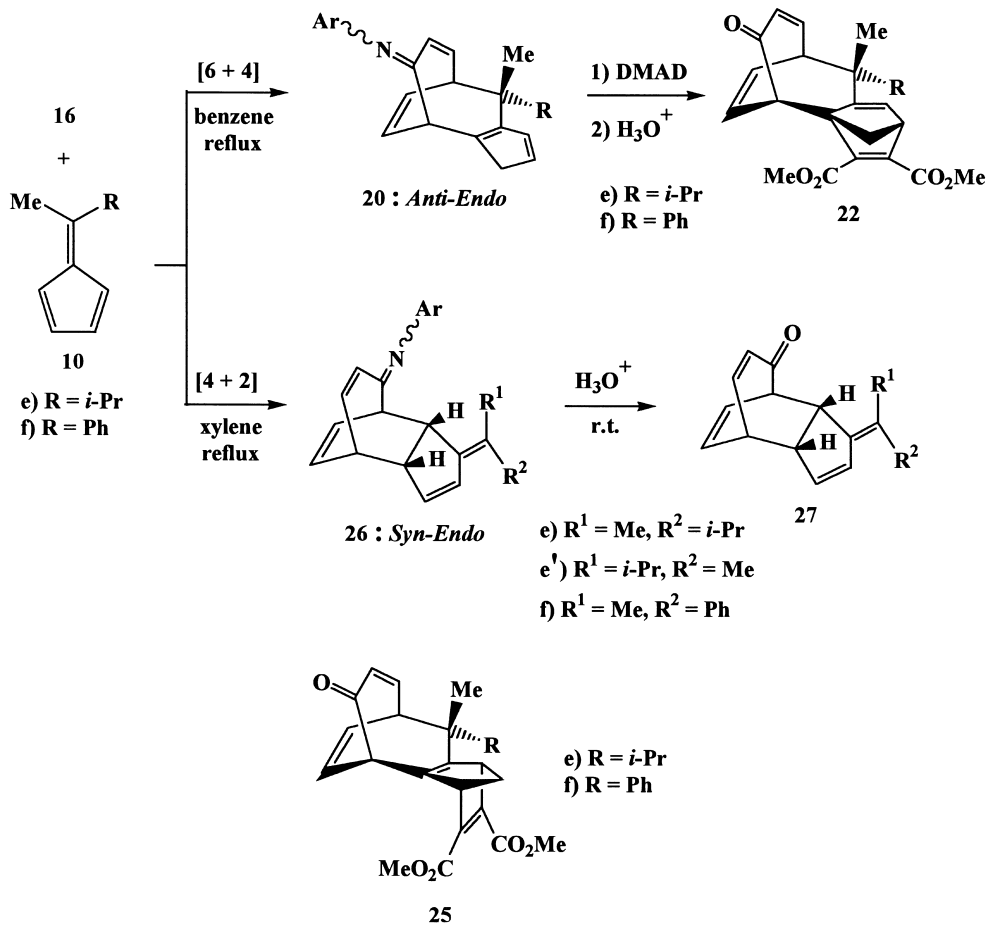
The present results show that the [6+4] cycloadduct **20c**, although formed under mild conditions, mainly reverted back to starting materials **16** and **10c** at higher temperatures and in turn recombined to form the thermodynamically



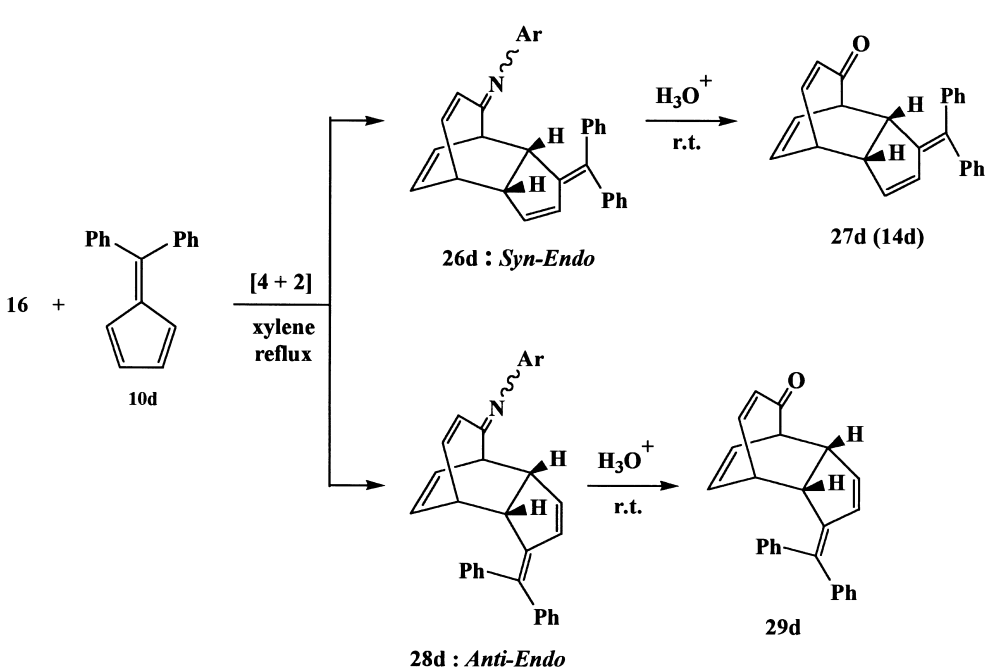
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

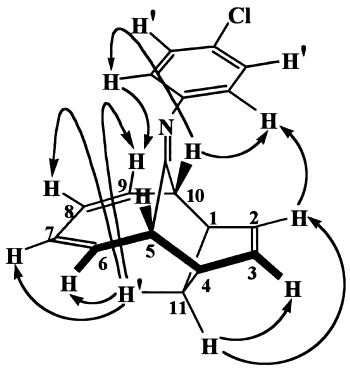


Figure 1. Structure of compound **17** and NOE correlations.

more stable [4+2] cycloadduct **26c**. The [6+4] cycloaddition reactions took place with exclusive *endo* diastereoselectivity and *anti* regioselectivity. However, the [4+2] cycloaddition reactions took place with exclusive *endo* diastereoselectivity and *syn* regioselectivity.

2.3. Reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (16) with unsymmetrically substituted 6-isopropyl-6-methylfulvene (10e) and 6-methyl-6-phenylfulvene (10f) and symmetrically substituted 6,6-diphenylfulvene (10d) (Schemes 7 and 8)

The reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) with unsymmetrically substituted fulvenes **10e** and **10f** in refluxing benzene afforded only the *anti-endo*-[6+4] cycloadducts **20e** and **20f** in 51 and 45% yields, respectively (Scheme 7 and Table 1). Additional structural evidence for **20e** and **20f** are the [4+2] cycloaddition reactions of **20e** and **20f** with DMAD, which gave **21e** and **21f**, which in turn afforded ketones **22e** and **22f**, respectively upon acid hydrolysis.

When **16** was reacted with fulvene **10e** in refluxing xylene for 5 h, the *syn-endo*-[4+2] cycloadducts **26e** and **26e′** and the *anti-endo*-[6+4] cycloadduct **20e** were obtained in a ratio of 4:1 in 50% isolated yield (Scheme 7 and Table 1). Similarly, **16** reacted with more hindered fulvene **10f** in

Table 1. Cycloaddition reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) with fulvenes **10c–f**

Reactants 16+10x X	Solvent	Temp	Time (h)	Adduct (ratio)	Yield (%)
c	Chloroform	Room temperature	24	**20c**	10
	Benzene	Reflux	12	**20c**	56
	Xylene	Reflux	5	**26c**+**20c** (2.4:1)+**23c** (trace)	60
	Xylene	Reflux	7	**26c**+**20c** (trace)+**23c** (trace)	65
e	Benzene	Reflux	5	**20e**	51
	Xylene	Reflux	5	**26e/e′**+**20e** (4:1)+**25e** (trace)	50
	Xylene	Reflux	7	**26e**+**26e′** (1.4:1)[a]+**20e** (trace)+**25e** (trace)	60
f	Benzene	Reflux	5	**20f**	45
	Xylene	Reflux	3	**26f**+**20f** (3.3:1)+**25f** (trace)	60
	Xylene	Reflux	7	**26f**+**20f** (trace) +**25f** (trace)	62
d	Xylene	Reflux	7	**26d**+**28d** (1:1.5)	48

[a] Ratio of adducts was estimated from ^{1}H NMR data in the inseparable mixture of adducts.

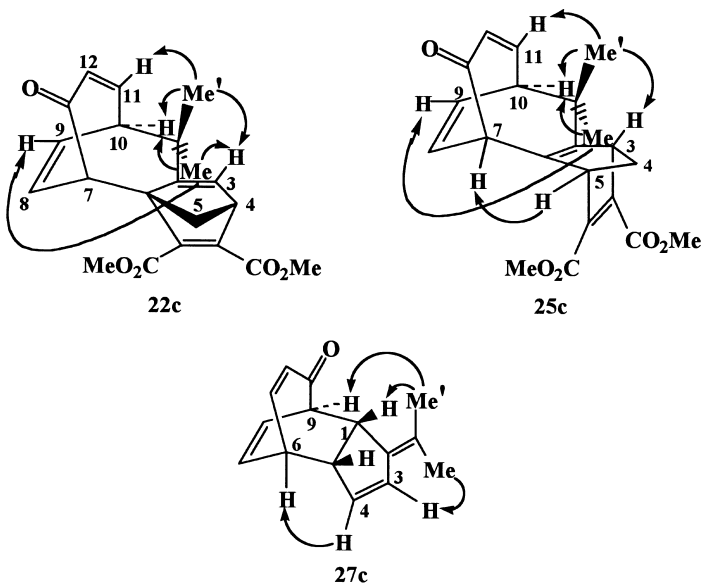


Figure 2. Structure of compound **22c**, **25c**, and **27c** and NOE correlations.

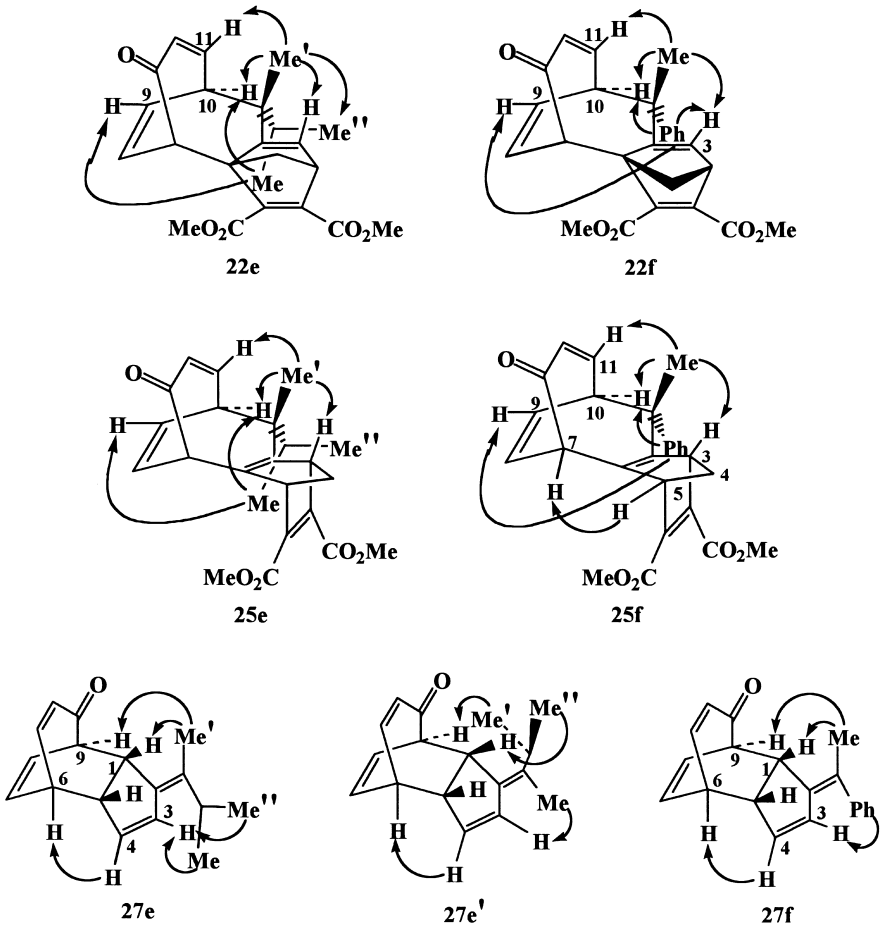


Figure 3. Structure of compound **22e**,**f**, **25e**,**f**, and **27e**,**e**′,**f** and NOE correlations.

refluxing xylene for 5 h, the *syn-endo*-[4+2] cycloadducts **26f** and *anti-endo*-[6+4] cycloadduct **20f** were obtained in a ratio of 3.3:1 in 60% isolated yield (Scheme 7 and Table 1). A trace of the [6+4] cycloadducts **25e/25f** (after DMAD and H_3O^+) was also isolated. With longer reaction time (7 h), **26e/26e**′ (1.4:1 mixture of inseparable regioisomers) and **26f** were formed as the main products in 60 and 62% yields, respectively. Additional structural evidence for **26e**, **26e**′, is that their acid hydrolysis affords the corresponding ketones **27e**,**27e**′ and **27f**, respectively.

In contrast to the reactions of **16** and **10c**,**10e**, and **10f**, the reaction of **16** with more hindered 6,6-diphenylfulvene (**10d**) in refluxing xylene afforded the *syn-endo*- (**26d**) and *anti-endo*- (**28d**) [4+2] cycloadducts in a ratio of 1:1.5 in 48% isolated yield (Scheme 8 and Table 1). No [6+4] cycloadduct was observed. Additional structural evidence for **26d** and **28d** is acid hydrolysis of **26d** and **28d** affords the corresponding ketones **14d** and **29d**, respectively. The structure of these cycloadducts were eventually proved by complete analysis of their ^{1}H NMR spectra, including 2D ^{1}H–^{1}H COSY and NOESY techniques (Figs. 3 and 4), and comparison of their spectra to those of related cycloadducts **22c**, **25c**, and **27c**.

Similar to the reaction of **16** and **10c**, these [6+4] cycloaddition reactions took place with exclusive *endo* diastereoselectivity and *anti* regioselectivity. The most important result of the present work is the finding that the exocyclic substituents of the fulvenes exert great influence on the periselectivity between the two reaction sides. In all cases with the unsymmetrically 6,6-disubstituted fulvenes, **10e** and **10f**, these [6+4] cycloaddition reactions took place exclusively on the side that is *anti* to the larger exocyclic substituent of the fulvenes. This periselectivity can be explained by comparing the various transition states involved in the cycloadditions. The only possible transition-state geometry (*anti-endo*) for these cycloaddition reactions is shown in Figure 5. Careful examination of this

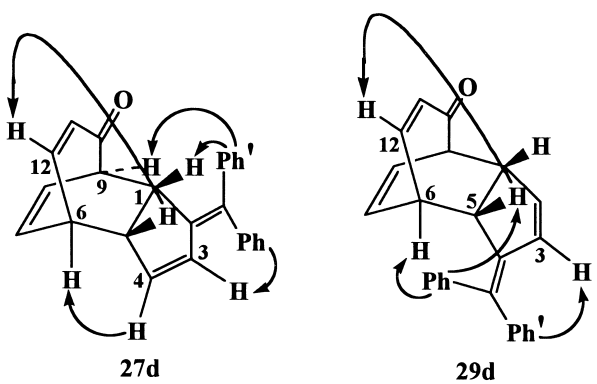


Figure 4. Structure of compound **27d**, and **29d**, and NOE correlations.

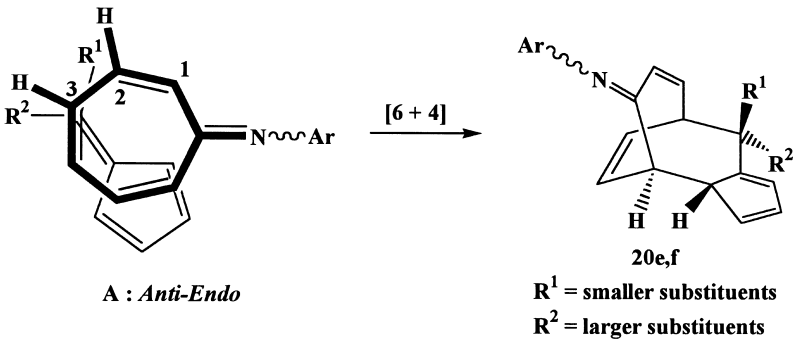


Figure 5. *Anti-endo* transition state, **A**, of the [6+4] cycloaddition reactions.

transition state suggests that possible steric repulsion mainly results from the proximity of the R^1 group of of the fulvene to the C-2 and C-3 methine groups of the 8-azaheptafulvene. Thus, transition state **A**, with the smaller R^1 substituent is more favorable and leads to the formation of cycloadducts **20e** and **20f**.

The present results also show that the [4+2] cycloaddition reactions of **16** with **10e** and **10f** took place preferentially and exclusively, on the endocyclic double bond that is *anti* to the larger exocyclic substituent of the fulvene. This periselectivity can be explained by comparing the various transition states involved in the cycloadditions. The possible transition-state geometries (*endo*) for these cycloaddition reactions are shown in Figure 6. Examination of these transition states indicates that steric repulsion results from the proximity of the R^1 group of the fulvene to the C-1 methine group of the 8-azaheptafulvene. Thus, transition

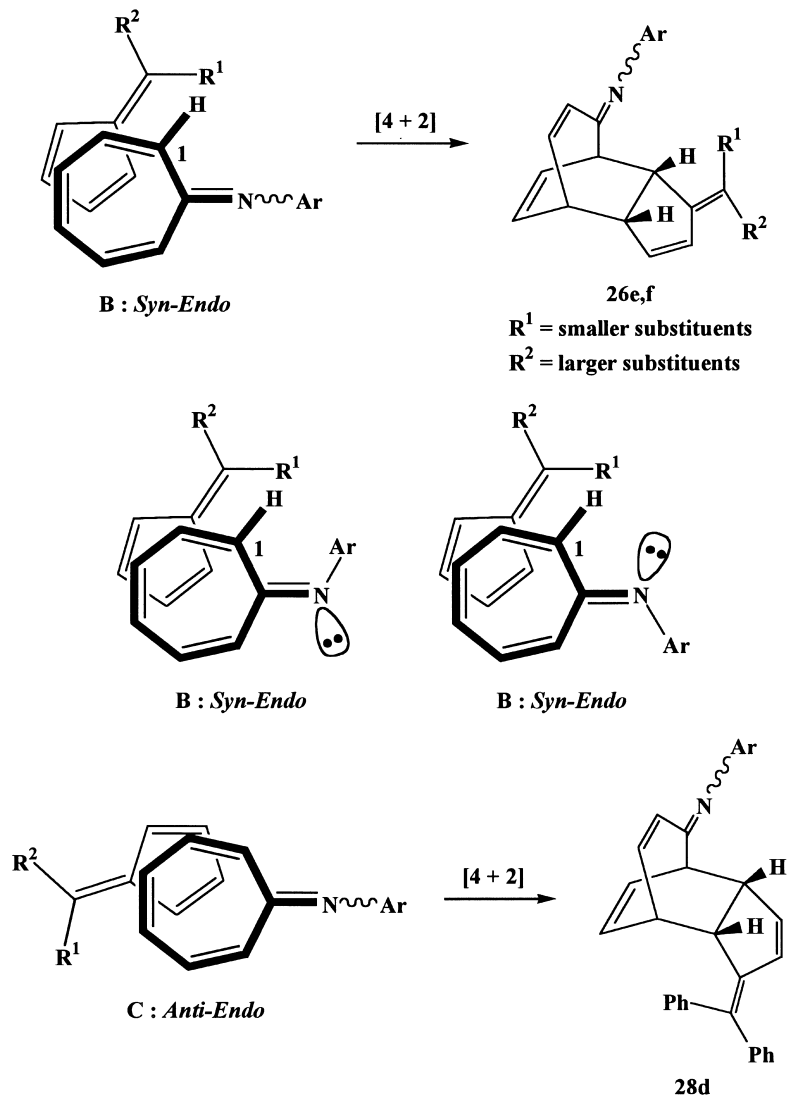


Figure 6. *Endo* transition states of the *syn*-[4+2] (**B**) and *anti*-[4+2] (**C**) cycloaddition reactions.

state **B** is more favorable and leads to the formation of cycloadducts **26e**. Increasing steric bulk of the larger one of the two exocyclic substituents on the fulvenes should cause higher periselectivity, and thus the reaction of fulvene **10f** with **16** took place exclusively on the endocyclic double bond that is *anti* to the larger exocyclic substituent of the fulvene to give the cycloadduct **26f**. As Table 1 indicates, the [4+2] cycloaddition reactions of fulvenes **10c**,**10e** and **10f** with **16**, proceed with exclusively *syn* regioselectivity. With a secondary steric repulsion from the proximity of the R^1 group of the fulvene to the exocyclic Ar group and/or nonbonded electron-pairs on the nitrogen of the 8-azaheptafulvene in transition state **B**, a nonbonded interaction which is absent in **C**, fulvene **10d**, with two bulky exocyclic substituents, that destabilize the *syn* transition state **B**, reacted with **16** preferentially to give the *anti*-[4+2] cycloadduct **28d**.

All these results show that the exocyclic substituent effects exert controlling influence upon the periselectivity and regioselectivity of these cycloadditions.

3. Experimental

3.1. General

^{1}H NMR spectra were determined on either a Varian Mercury-200 or a Bruker DMX-500 spectrometer and chemical shifts are reported as δ values in ppm relative to TMS (δ=0.00) as the internal standard and $CDCl_3$ as the solvent. Infrared (IR) spectra were determined on a Perkin–Elmer 1600 FT-IR spectrometer. Mass spectra were determined on a VG Platform Electrospray mass spectrometer. High resolution mass spectra (HRMS) were determined on a FINNIGAN MAT 95S mass spectrometer. All reagents were of reagent grade and were purified prior to use. All reactions were performed under an inert atomsphere of nitrogen. The preparations of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**)[19] and fulvenes **10c**–**f**[20,21] were by literature procedures.

3.2. Cycloaddition reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (16) with cyclopentadiene (2)

A solution of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) (215 mg, 1.00 mmol) in 25 mL of freshly distilled cyclopentadiene (**2**) was stirred at room temperature for 24 h afforded a yellow oil. Purification by silica gel flash chromatography, using 5% EtOAc in *n*-hexane as eluant, gave **17** (98 mg, 35%) as a yellowish oil: ^{1}H NMR δ 1.37–1.42 (m, 1H, H-11), 2.10 (d, 1H, *J*=11.2 Hz, Me), 2.81–2.83 (m, 1H, H-1), 2.98–2.99 (m, 1H, H-4), 3.25–3.28 (m, 1H, H-10), 3.34–3.37 (m, 1H, H-5), 5.56 (bdd, 1H, *J*=7.4, 11.5 Hz, H-9), 5.81 (dd, 1H, *J*=2.5, 5.6 Hz, H-2), 5.94 (bdd, 1H, *J*=7.4, 11.5 Hz, H-6), 5.98–6.02 (m, 2H, H-7-8), 6.05 (dd, 1H, *J*=2.5, 5.6 Hz, H-3), 6.50 (d, 2H, *J*=8.5 Hz, Ph), 7.15 (d, 2H, *J*=8.6 Hz, Ph′); ν_{max} (KBr): 2940, 1659, 1587, 1483, 1340, 1192 cm^{-1}; MS *m*/*z* 281 (M^+); HRMS: calcd for $C_{18}H_{16}ClN$: 281.0972; found: 281.0983.

3.3. Attempted hydrolysis of cycloadduct 17

A solution of **17** (20 mg) in 10 mL of THF, 5 mL of water, and 3 mL of 37% HCl was vigorously stirred at room temperature for 24 h. The mixture was concentrated in vacuo and extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by silica gel flash chromatography, using 5% EtOAc in *n*-hexane as eluant, gave mainly the starting material **17**. No hydrolyzed cycloadduct **3** was obtained.

3.4. Attempted thermolysis of [6+4] cycloadduct 17

The attempted thermolysis of **17** (20 mg) in 30 mL of refluxing benzene or xylene for 24 h did not proceed; mainly the starting material **17** was recovered. No [3,3] sigmatropic rearranged [8+2] cycloadduct **18** was obtained.

3.5. General procedure for cycloaddition reactions of 8-(*p*-chlorophenyl)-8-azaheptafulvene (16) with fulvenes 2c–f

A solution containing 1.0 mmol of 8-(*p*-chlorophenyl)-8-azaheptafulvene (**16**) and 1.1 mmol of fulvenes **10c**–**f** in 6 mL of solvent was stirred (the solvents and the reaction conditions are all indicated in Table 1). After evaporation of the excess solvent under reduced pressure, the crude mixture was subjected to silica gel flash chromatography with 5–15% EtOAc in n-hexane as the eluant to give a complex mixture. A solution of this complex mixture and excess DMAD in 6 mL of chloroform was stirred under reflux for 7 h to afforded a yellow oil. Column chromatography, using 20% EtOAc in n-hexane as eluant to give the [6+4] cycloadducts **21** and **24** and the [4+2] cycloadducts **26** and **28**. Then, same procedure as in **17**, acid hydrolysis to give the corresponding ketone **22**, **25**, **27**, and **29**, respectively. IR spectra data for cycloadducts (cm^{-1}): 1720–1725 (*O*=*C*ROMe); 1655–1665 (*O*=*C*RR′). Other data, ^{1}H NMR, MS; HRMS for:

3.5.1. Compound 22c. ^{1}H NMR δ 1.11 (s, 3H, Me′), 1.32 (s, 3H, Me), 1.82 (d, 1H, *J*=6.6 Hz, H-5), 2.19 (d, 1H, *J*=6.6 Hz, H-5), 2.95 (t, 1H, *J*=8.5 Hz, H-10), 3.70 (s, 3H, $-CO_2Me$), 3.73–3.75 (m, 1H, H-4), 3.78–3.81 (m, 4H, H-7, $-CO_2Me$), 5.87 (t, 1H, *J*=9.1 Hz, H-8), 5.93 (d, 1H, *J*=11.8 Hz, H-12), 6.25 (bt, 1H, *J*=9.5 Hz, H-9), 6.61 (bd, 1H, *J*=3.4 Hz, H-3), 6.84 (dd, 1H, *J*=11.8, 8.5 Hz, H-11); MS *m*/*z*354 (M^+); HRMS: calcd for $C_{21}H_{22}O_5$: 354.1467; found: 354.1453.

3.5.2. Compound 25c. ^{1}H NMR δ 1.04 (s, 3H, Me′), 1.32 (s, 3H, Me), 2.05 (bd, 1H, *J*=6.7 Hz, H-4), 2.16 (bd, 1H, *J*=6.7 Hz, H-4), 2.99 (t, 1H, *J*=8.3 Hz, H-10), 3.62 (bs, 1H, H-5), 3.72 (s, 3H, $-CO_2Me$), 3.74 (s, 3H, $-CO_2Me$), 3.87 (bd, 1H, *J*=8.3 Hz, H-7), 3.89 (bs, 1H, H-3), 5.74 (d, 1H, *J*=11.9 Hz, H-12), 6.09 (t, 1H, *J*=8.3 Hz, H-8), 6.22 (bt, 1H, *J*=8.3 Hz, H-9), 6.53 (dd, 1H, *J*=8.3, 11.9 Hz, H-11); MS *m*/*z* 354 (M^+); HRMS: calcd for $C_{21}H_{22}O_5$: 354.1467; found: 354.1457.

3.5.3. Compound 27c. ^{1}H NMR δ 1.73 (s, 3H, Me), 1.78 (s,

3H, Me′), 3.22 (bd, 1H, *J*=7.5 Hz, H-1), 3.38 (bt, 1H, *J*=7.8 Hz, H-6), 3.59–3.61 (m, 2H, H-5, H-9), 5.54–5.56 (m, 1H, H-4), 5.74 (d, 1H, *J*=10.9 Hz, H-11), 5.97 (t, 1H, *J*=7.8 Hz, H-8), 6.22 (t, 1H, *J*=7.8 Hz, H-7), 6.39 (dd, 1H, *J*=2.1, 5.7 Hz, H-3), 7.10 (dd, 1H, *J*=8.7, 10.9 Hz, H-12); MS *m*/*z*212 (M^+); HRMS: calcd for $C_{15}H_{16}O$: 212.1201; found: 212.1195.

3.5.4. Compound 22e. ^{1}H NMR δ 0.49 (d, 3H, *J*=6.8 Hz, –CHMe*Me″*), 0.86 (d, 3H, *J*=6.8 Hz, –CH*Me*Me″), 1.07 (s, 3H, Me′), 1.83 (d, 1H, *J*=6.7 Hz, H-5), 1.86–1.93 (m, 1H, –C*H*MeMe″), 2.16 (d, 1H, *J*=6.7 Hz, H-5), 3.19 (t, 1H, *J*=8.3 Hz, H-10), 3.70 (s, 3H, $-CO_2Me$), 3.74–3.77 (m, 4H, H-7, $-CO_2Me$), 5.88 (t, 1H, *J*=8.7 Hz, H-8), 5.93 (d, 1H, *J*=11.9 Hz, H-12), 6.24 (bt, 1H, *J*=8.7 Hz, H-9), 6.49 (bs, 1H, H-3), 6.81 (dd, 1H, *J*=8.5, 11.9 Hz, H-11); MS *m*/*z*382 (M^+); HRMS: calcd for $C_{23}H_{26}O_5$: 382.1780; found: 382.1771.

3.5.5. Compound 25e. ^{1}H NMR δ 0.92 (s, 3H, Me′), 0.95 (d, 3H, *J*=6.9 Hz, –CH*Me*Me″), 1.02 (d, 3H, *J*=6.9 Hz, –CHMe*Me″*), 2.10–2.15 (m, 3H, H-4, –C*H*MeMe″), 3.19 (t, 1H, *J*=8.3 Hz, H-10), 3.62 (bs, 1H, H-5), 3.72 (s, 3H, $-CO_2Me$), 3.73 (s, 3H, $-CO_2Me$), 3.85–3.88 (m, 2H, H-3, H-7), 5.68 (d, 1H, *J*=11.9 Hz, H-12), 6.03 (t, 1H, *J*=8.9 Hz, H-8), 6.17 (t, 1H, *J*=9.1 Hz, H-9), 6.43 (dd, 1H, *J*=8.5, 11.9 Hz, H-11); MS *m*/*z* 382 (M^+); HRMS: calcd for $C_{23}H_{26}O_5$: 382.1780; found: 382.1765.

3.5.6. Compound 27e. ^{1}H NMR δ 0.92–0.98 (m, 6H, –CH*MeMe″*), 1.67 (s, 3H, Me′), 2.79–2.85 (m, 1H, –C*H*MeMe″), 3.19 (bd, 1H, *J*=7.5 Hz, H-1), 3.37 (bt, 1H, *J*=7.8 Hz, H-6), 3.56–3.58 (m, 2H, H-5, H-9), 5.52–5.54 (m, 1H, H-4), 5.76 (d, 1H, *J*=10.9 Hz, H-11), 5.95–6.01 (m, 1H, H-8), 6.21 (t, 1H, *J*=7.8 Hz, H-7), 6.46 (dd, 1H, *J*=2.0, 5.7 Hz, H-3), 7.10 (dd, 1H, *J*=8.7, 10.9 Hz, H-12); MS *m*/*z* 240 (M^+); HRMS: calcd for $C_{17}H_{20}O$: 240.1514; found: 240.1504.

3.5.7. Compound 27e′. ^{1}H NMR δ 0.92–0.98 (m, 3H, –CHMe*Me″*), 1.07 (d, 3H, *J*=6.8 Hz, –CH*Me′*Me), 1.61 (s, 3H, Me), 2.71–2.77 (m, 1H, –C*H*Me′Me″), 3.25 (bd, 1H, *J*=7.5 Hz, H-1), 3.37 (bt, 1H, *J*=7.8 Hz, H-6), 3.56–3.58 (m, 2H, H-5) 3.50 (d, 1H, *J*=7.4 Hz, H-9), 5.55–5.57 (m, 1H, H-4), 5.76 (d, 1H, *J*=10.9 Hz, H-11), 5.95–6.01 (m, 1H, H-8), 6.21 (t, 1H, *J*=7.8 Hz, H-7), 6.38 (dd, 1H, *J*=2.1, 5.7 Hz, H-3), 7.10 (dd, 1H, *J*=8.7, 10.9 Hz, H-12); MS *m*/*z* 240 (M^+); HRMS: calcd for $C_{17}H_{20}O$: 240.1514; found: 240.1504.

3.5.8. Compound 22f. ^{1}H NMR δ 1.59 (s, 3H, Me), 2.01 (d, 1H, *J*=6.8 Hz, H-5), 2.31 (d, 1H, *J*=6.8 Hz, H-5), 3.56 (s, 3H, $-CO_2Me$), 3.79 (m, 3H, $-CO_2Me$), 3.81–3.85 (m, 2H, H-4, H-10), 3.92 (d, 1H, *J*=8.3 Hz, H-7), 5.68 (t, 1H, *J*=9.5 Hz, H-8), 5.87 (bt, 1H, *J*=9.5 Hz, H-9), 6.04 (d, 1H, *J*=11.5 Hz, H-12), 6.86 (bd, 1H, *J*=2.8 Hz, H-3), 6.96 (dd, 1H, *J*=8.5, 11.5 Hz, H-11), 7.04–7.06 (m, 2H, Ph), 7.11–7.13 (m, 1H, Ph), 7.15–7.18 (m, 2H, Ph); MS *m*/*z*416 (M^+); HRMS: calcd for $C_{26}H_{24}O_5$: 416.1624; found: 416.1629.

3.5.9. Compound 25f. ^{1}H NMR δ 1.40 (s, 3H, Me), 2.22 (bd, 1H, *J*=6.9 Hz, H-4), 2.36 (bd, 1H, *J*=6.9 Hz, H-4), 3.30 (t, 1H, *J*=8.6 Hz, H-10), 3.70 (bs, 4H, H-3, $-CO_2Me$), 3.76 (bs, 4H, H-5, $-CO_2Me$), 3.98 (bd, 1H, *J*=8.3 Hz, H-7), 5.64 (t, 1H, *J*=8.2 Hz, H-9), 5.81 (d, 1H, *J*=11.9 Hz, H-12), 6.02 (t, 1H, *J*=8.3 Hz, H-8), 6.61 (dd, 1H, *J*=8.5, 11.9 Hz, H-11), 7.21–7.22 (m, 1H, Ph), 7.28–7.31 (m, 2H, Ph), 7.37–7.39 (m, 2H, Ph); MS *m*/*z* 416 (M^+); HRMS: calcd for $C_{26}H_{24}O_5$: 416.1624; found: 416.1629.

3.5.10. Compound 27f. ^{1}H NMR δ 2.14 (s, 3H, Me), 3.37–3.41 (m, 2H, H-1, H-6), 3.64 (bd, 1H, *J*=7.1 Hz, H-5), 3.76 (bd, 1H, *J*=7.4 Hz, H-9), 5.58–5.59 (m, 1H, H-4), 5.80 (d, 1H, *J*=11.0 Hz, H-11), 6.04 (t, 1H, *J*=7.4 Hz, H-8), 6.24–6.27 (m, 2H, H-3, H-7), 7.10 (dd, 1H, *J*=8.6, 11.0 Hz, H-12), 7.13–7.17 (m, 3H, Ph), 7.26–7.30 (m, 2H, Ph); MS *m*/*z*274 (M^+); HRMS: calcd for $C_{20}H_{18}O$: 274.1358; found: 274.1351.

3.5.11. Compound 27d. ^{1}H NMR δ 3.26–3.31 (m, 2H, H-6, H-9), 3.60–3.63 (m, 1H, H-5), 3.80 (bd, 1H, *J*=7.1 Hz, H-1), 5.64 (bd, 1H, *J*=10.9 Hz, H-11), 5.81 (dd, 1H, *J*=2.4, 5.7 Hz, H-4), 5.96 (t, 1H, *J*=7.9 Hz, H-8), 6.27 (t, 1H, *J*=7.9 Hz, H-7), 6.38 (dd, 1H, *J*=2.4, 5.7 Hz, H-3), 7.04 (dd, 1H, *J*=8.7, 10.9 Hz, H-12); 7.07–7.18 (m, 5H, Ph), 7.18–7.34 (m, 5H, Ph′); MS *m*/*z* 336 (M^+); HRMS: calcd for $C_{25}H_{20}O$: 336.1514; found: 336.1502.

3.5.12. Compound 29d. ^{1}H NMR δ 3.02 (t, 1H, *J*=7.9 Hz, H-6), 3.45–3.48 (m, 2H, H-1, H-9), 3.62 (bd, 1H, *J*=7.4 Hz, H-5), 5.66 (dd, 1H, *J*=11.0 Hz, H-11), 5.91 (dd, 1H, *J*=2.5, 5.6 Hz, H-2), 5.98 (t, 1H, *J*=7.9 Hz, H-8), 6.27 (t, 1H, *J*=7.9 Hz, H-7), 6.34 (dd, 1H, *J*=1.6, 5.6 Hz, H-3), 6.70 (dd, 1H, *J*=7.9, 11.0 Hz, H-12); 7.09–7.25 (m, 5H, Ph′), 7.25–7.40 (m, 5H, Ph); MS *m*/*z* 336 (M^+); HRMS: calcd for $C_{25}H_{20}O$: 336.1514; found: 336.1501.

Acknowledgements

We are grateful to the National Science Council of the Republic of China for financial support of this research.

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