Dynamic Equilibria in the Products of Intramolecular Buchner Additions of Diazoketones to Aryl Rings Bearing Methoxy Substituents

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Rhodium carboxylate catalyzed aromatic addition reactions of a range of diazoketones bearing methoxy-substituted aryl rings have been explored. While the existence of norcaradiene−cycloheptatriene equilibria in related compounds is well established, the aromatic addition products in this study display more complex dynamic equilibria due to conjugation with the methoxy group; the experimental evidence for this is discussed in detail. In the azulenone products **21**−**26** derived from *p*-methoxy-substituted diazoketones **14**−**16**, the diastereomers interconvert via a spiro intermediate **39**. A related mechanistic process in the azulenones **43**−**46** derived from the *o*-methoxy-substituted diazoketones **17**, **18** interconverts regioisomers, explaining the conflicting reports for the regioselectivity of the cyclization of diazoketone **1**. With the *m*-methoxy-substituted diazoketone **19**, involvement of the methoxy group through a different pathway results in fragmentation of the azulenone to form the tetralone **47**. With the azulenones **21**−**26** exclusive trapping of the norcaradiene associated with the less thermodynamically stable diastereomers in a cycloadduct with *N*-phenylmaleimide is observed. Due to the presence of the activating methoxy substituent on the aromatic ring, the aromatic addition reactions of the diazoketones studied were not very sensitive to the nature of the rhodium catalyst.

Introduction

The intramolecular Buchner reaction of diazoketones has attracted considerable attention in recent years.[1] As part of an ongoing investigation of stereocontrol in this transformation,[2] we extended our study to reactions with substituted benzene derivatives to determine the effect of substituents on the aromatic ring on both the efficiency and stereocontrol in the cyclization. The activating methoxy group was among the substituents selected for investigation.[3] The influence of the methoxy substituent on the efficiency of the cyclization and regio- and stereoselectivity and its effect on the position of equilibrium between the resulting norcaradiene (NCD) and cycloheptatriene (CHT) tautomers were of particular interest. The presence of methoxy substituents has been shown to strongly affect the relative stability of NCD and CHT tautomers.[3g]

During the course of this study, rearrangements in the resulting methoxy-substituted norcaradiene derivatives were uncovered. In addition to the intrinsic mechanistic interest in the dynamic equilibria observed, these results explained the conflicting results that have been reported for cyclization of 1-diazo-4-(2-methoxyphenyl)butan-2-one **1**.[4,5] The original description[4] of the cyclization of diazoketone **1** reported that the azulenone **2** formed was that which corresponded to the cyclization toward the methoxy substituent, which on treatment with TFA produced the tetralone **3**. However, in 1993, Cordi et al.[5] reported that the tetralone isolated was the regioisomeric compound **5** and therefore assigned structure **4** to the azulenone (Scheme 1). A recent report of related work conducted independently by Manitto et al.[6] is consistent with our observations.

Results and Discussion

A series of diazoketones **13**−**19** bearing methoxy substituents on the aryl ring was prepared under standard

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(1) For a comprehensive review of intramolecular addition of diazoketones to aromatic systems, see: *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Doyle, M. P., McKervey, M. A., Ye, T., Eds.; Wiley: New York, 1998; pp 298−336.

(2) Maguire, A. R.; Buckley, N. R.; O'Leary, P.; Ferguson, G. *Chem. Commun.* **1996**, 2595. Maguire, A. R.; Buckley, N. R.; O'Leary, P.; Ferguson, G. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4077.

(3) For examples of intramolecular diazoketone additions to methoxy substituted aromatic derivatives, see: (a) Ledon, H.; Cannic, G.; Linstrumelle, G.; Julia, S. *Tetrahedron Lett.* **1970**, 3971. (b) Ledon, H.; Linstrumelle, G.; Julia, S. *Tetrahedron* **1973**, *29*, 3609. (c) Pirrung, M. C.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 8162. (d) Manitto, P.; Monti, D.; Zanzola, S.; Speranza, G. *J. Org. Chem.* **1997**, *62*, 6658. (e) Mander, L. N. *Synlett* **1991**, 134. (f) Mander, L. N.; Wells, A. P. *Tetrahedron Lett.* **1997**, *38*, 5709. (g) Morris, J. C.; Mander, L. N.; Hockless, D. C. R. *Synthesis* **1998**, 455. (h) Zhan, H.; Appels, D. C.; Hockless, D. C. R.; Mander, L. N. *Tetrahedron Lett.* **1998**, *39*, 6577. (i) Matsumoto, M.; Shiono, T.; Mutoh, H.; Amano, M.; Arimitsu, S. *J. Chem. Soc., Chem. Commun.* **1995**, 101. (j) Doyle, M. P.; Protopopova, M. N.; Peterson, C. S.; Vitale, J. P.; McKervey, M. A.; Fernandez Garcia, C. *J. Am. Chem. Soc.* **1996**, *118*, 7865.

(4) Kennedy, M.; McKervey, M. A.; Maguire, A. R.; Tuladhar, S. M.; Twohig, M. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1047.

(5) Cordi, A. A.; Lacoste, J.-M.; Hennig, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3.

(6) Manitto, P.; Monti, D.; Zanzola, S.; Speranza, G. *Chem. Commun.* **1999**, 543.

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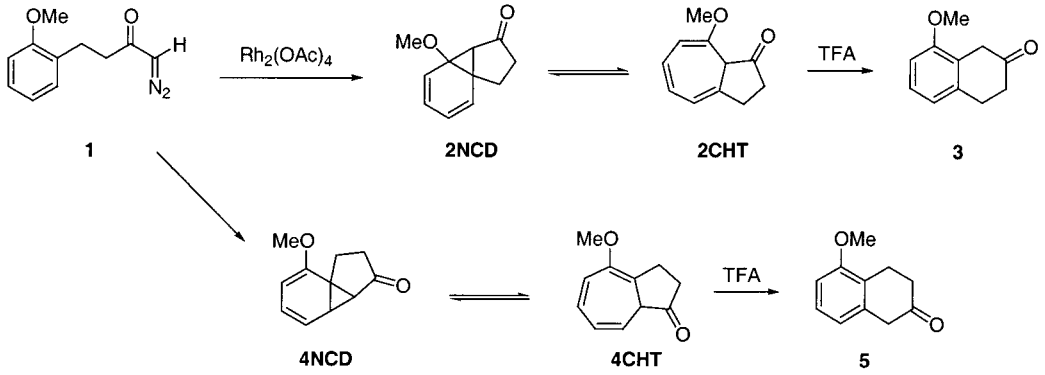
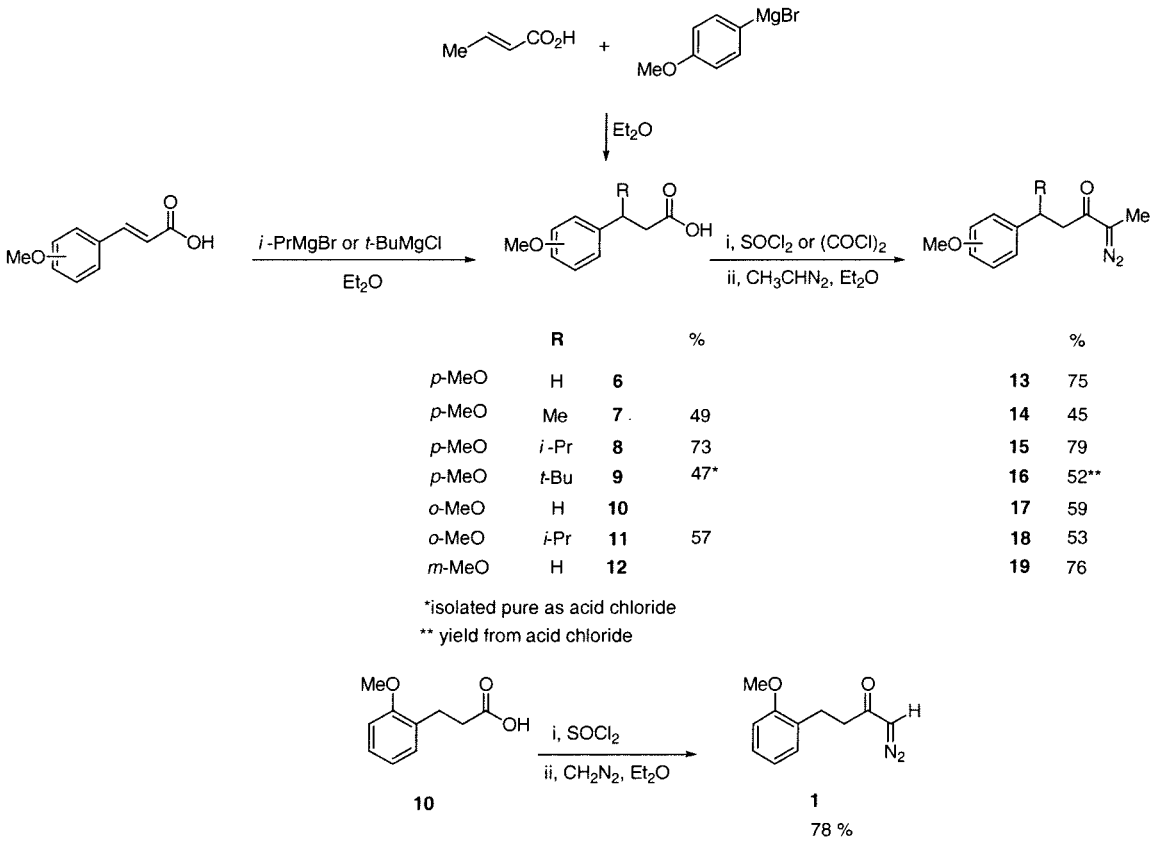
Scheme 1



Scheme 2



	R		%		%
p-MeO	H	**6**		**13**	75
p-MeO	Me	**7**	49	**14**	45
p-MeO	*i*-Pr	**8**	73	**15**	79
p-MeO	*t*-Bu	**9**	47*	**16**	52**
o-MeO	H	**10**		**17**	59
o-MeO	*i*-Pr	**11**	57	**18**	53
m-MeO	H	**12**		**19**	76

*isolated pure as acid chloride
** yield from acid chloride

10 **1** 78 %

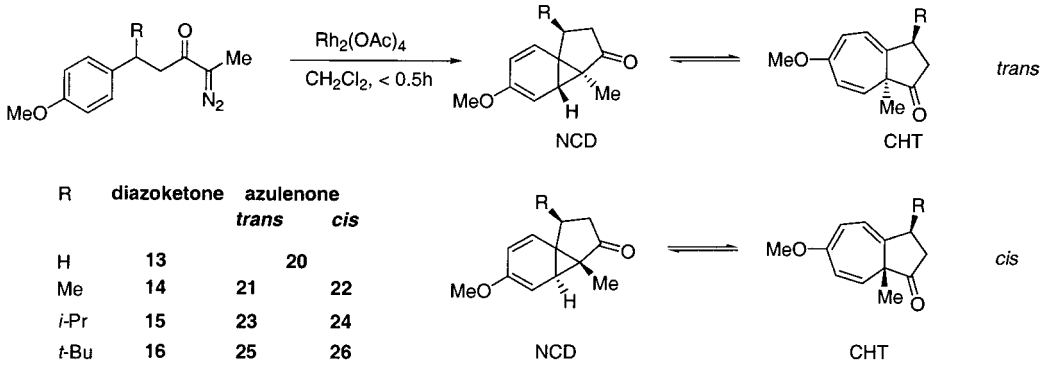
conditions from the analogous carboxylic acids **6**−**12** as outlined in Scheme 2 by initial formation of the acid chlorides and then treatment with an excess of diazoethane. The precursor carboxylic acids **6**, **10**, and **12** are commercially available, while **7**−**9** and **11** were synthesized as summarized in Scheme 2. The derivatives **13**−**19** were selected for investigation to determine the influence of the position of the methoxy substituent and side-chain substituents on the rhodium acetate catalyzed cyclization. Following the Cordi report, the terminal diazoketone **1** was added to the study. Pure samples of each of the diazoketones were obtained by chromatographic purification and could be stored in a freezer for several months without decomposition.

Rhodium acetate catalyzed decompositions of the 4-methoxy-substituted derivatives **13**−**16** were explored initially (Scheme 3 and Table 1). All reactions were conducted with <1 mol % of $Rh_2(OAc)_4$ in refluxing dichloromethane unless otherwise stated, and in general were very rapid, with the diazoketone decomposition complete once the addition was finished. Cyclization of the diazoketone **13** without any side-chain substituent produced the azulenone **20** in good yield.

Analysis of the ^{1}H NMR spectra of the crude product mixtures from reactions of the methyl and isopropyl substituted diazoketones **14** and **15** showed that both the cis and trans diastereomers were formed in 3−5:1 ratio with the trans isomers **21** and **23** predominating in each case. Following chromatographic purification on silica gel, the ratio of azulenones observed changed only slightly with the trans isomers **21** and **23** still predominating. As the azulenone products exist as rapidly equilibrating norcaradiene−cycloheptatriene tautomers for which time-averaged signals are observed, the ^{1}H NMR characteristics are very informative as to the nature of the products, especially the position of NCD-CHT equilibria,[7]

(7) Hannemann, K. *Angew. Chem., Int. Ed. Engl.* **1987**, *27*, 284.

Scheme 3



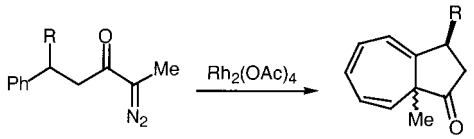
R	diazoketone	azulenone *trans*	azulenone *cis*
H	**13**	**20**	
Me	**14**	**21**	**22**
i-Pr	**15**	**23**	**24**
t-Bu	**16**	**25**	**26**

Table 1. Rhodium Acetate Catalyzed Cyclization of 4-Methoxyphenyl-Substituted Diazoketones 13−16

R	diazoketone	*T* (°C)	azulenone trans	azulenone cis	dr (crude)[a] trans/cis	yield[b] (%)	dr (purified)[a] trans/cis
H	**13**	Δ	**20**			80	
Me	**14**	Δ	**21**	**22**	3:1	82	4:1
		0			4.6:1	51	4:1
Pr^i	**15**	Δ	**23**	**24**	3:1	77	9:1[c]
		0			>98:2	63	4:1
Bu^t	**16**	Δ	**25**	**26**	98:2	72	>98:2[d] 95:5[d]

[a] Diastereomeric ratios determined by ^{1}H NMR spectroscopy of the crude product and the product following chromatography on silica gel. [b] Yields reported for the azulenones following purification by chromatography on silica gel. [c] This sample was stored in the freezer prior to recording the ^{1}H NMR spectrum; accordingly, the ratio had shifted from the thermodynamic ratio of 4:1 to 9:1. [d] The sample isolated directly from chromatography consisted of **25** only; however, on holding in $CDCl_3$ for 2−3 days, equilibration to the thermodynamic ratio 95:5 was observed.

Table 2. Diastereoselection in $Rh_2(OAc)_4$ Cyclization of β-Substituted Diazoketones[a]



diazoketone	R	azulenone	yield[b] (%)	trans/cis[c]
27	Me	**33**	87	89:11
28	Et	**34**	80	96:4
29	Pr	**35**	74	97:3
30	Pr^i	**36**	74	> 98:2
31	Bu	**37**	70	98:2
32	Bu^t	**38**	72	> 98:2

[a] The data for cyclization of diazoketones **28**−**32** is described in detail in ref 2. [b] Yield of azulenones isolated following chromatography on silica gel. [c] Diastereomeric ratios in the crude product mixtures estimated by ^{1}H NMR spectroscopy; chromatographic separation of the diastereomers is possible.

and furthermore, the signals for the cis and trans isomers are well distinguished, allowing ready estimation of the isomeric ratios. The signals ($CDCl_3$, 20 °C) for the C(8)H in the trans isomers **21** and **23** appear at 3.47 and 3.69 (J = 7.3 Hz) while those of the cis isomers **22** and **24** appear at 4.51 and 4.68 (J = 9.5 Hz), respectively. Therefore, the position of equilibrium in the trans isomers favors the NCD tautomer to a greater extent than in the cis isomers.

As we have already reported,[2] $Rh_2(OAc)_4$-catalyzed cyclization of related diazoketones **28**−**32** onto phenyl rings without any substituents is highly diastereoselective (see Table 2). Further to our earlier report, we have investigated reaction of the methyl-substituted diazoketone **27**. Significantly, in the context of this work, the diastereoselection observed when the β-substituent is a methyl group is notably lower at 89:11 compared to that observed with other alkyl groups, and indeed, a distinct trend of increased diastereoselection as the β-substituent is increased in size from Me to Et, Pr, Bu can be distinguished. With branched alkyl side chains, Pr^i and Bu^t, only a single diastereomer can be detected in the crude product mixtures.

Our initial interpretation of the results of cyclization of the 4-methoxyphenyl-substituted diazoketones **14** and **15** (Table 1) was that introduction of the activating methoxy group to the aromatic system decreased the diastereoselection compared to those observed with unsubstituted phenyl rings (Table 2) resulting in the observed mixtures of diastereomers. However, when the rhodium(II) acetate catalyzed cyclization of the diazoketone **15** was conducted at 0 °C, the reaction was marginally slower, the efficiency of cyclization reduced somewhat, but critically the ^{1}H NMR spectrum of the crude product ratio showed the presence of the trans isomer **23** only. Following chromatographic purification on silica gel, however, a diastereomeric mixture of **23** and **24** in a similar ratio to that observed before (4:1) was obtained. Thus, it seems that the trans isomer **23** is the kinetic product of the cyclization and that this can then equilibrate with the cis isomer **24**; the thermodynamic ratio of **23**/**24** at room temperature appears to be 4:1. In contrast, with the methyl-substituted diazoketone **14**, the crude product of the cyclization conducted at 0 °C contained the cis isomer in a ratio comparable to that found after chromatography. This suggests that either cyclization of **14** is less stereoselective than that of **15** or equilibration of the methyl-substituted product **21**/**22** is more rapid than that of the isopropyl derivative **23**/**24**. More likely, both factors are involved. This difference is presumably due to the decreased steric demands of the methyl substituent compared to the isopropyl group. As outlined above (Table 2), the diastereoselection in the cyclization of β-methyl-substituted derivatives is lower than those observed with the larger isopropyl substituent at this position. However, we were never able to fractionate the two isomers **21** and **22** on silica gel or in any other manner, whereas **23** and **24**, the isopropyl-substituted derivatives, could be separated chromatographically and then monitored as they returned to the equilibrium mixture. Therefore, the rate of equilibration is apparently faster for the methyl-substituted derivatives than for the isopropyl-substituted derivatives, and in fact, we have

Scheme 4

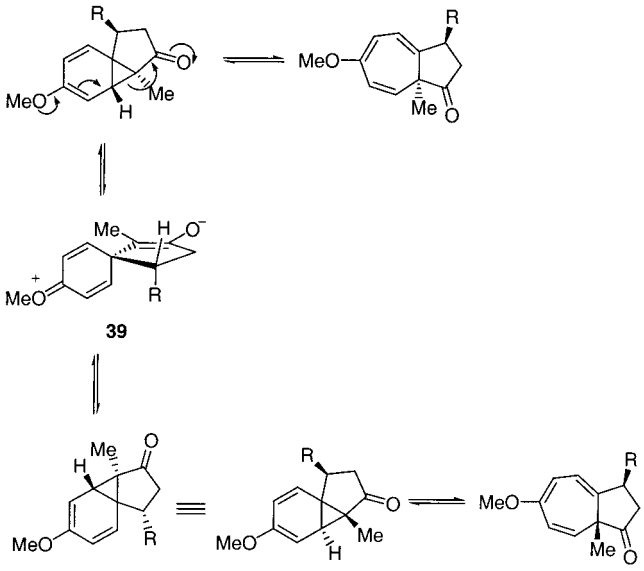


Table 3. Equilibration of the *trans*-Azulenone 23 with the Cis Diastereomer 24

conditions	diastereomeric ratio[a] **23**:**24**
cyclization at 0 °C	> 98:2
7 days at 20 °C	~7:1
18 h on silica gel (dry)	~4:1
18h in EtOAc/hexane mixture (1:9) with silica gel	~4:1
18h in refluxing EtOAc	2.5:1

[a] Diastereomeric ratios determined by integration of ^{1}H NMR spectra.

never isolated a sample of **21** and **22** at other than the thermodynamic ratio. Interestingly, the thermodynamic ratio at 20 °C for both systems is the same at 4:1 trans/cis.

The mechanism envisaged for the interconversion of **21** and **22**, and also **23** and **24**, is illustrated in Scheme 4. The electron-donating methoxy group triggers opening of the cyclopropane ring to form a spiro enol or enolate intermediate **39** that on reclosure can form either the cis or trans isomer. On silica gel, acidic catalysis of this process results in rapid formation of the thermodynamic ratio of cis and trans isomers. To confirm this proposal, the following experiments were conducted:

(a) Interconversion of a pure sample of the trans isomer **23** (formed by conducting the rhodium acetate catalyzed cyclization at 0 °C) on storage at room temperature for 7 days, exposure to silica gel, either dry or in solution (hexane/ethyl acetate 9:1, the chromatography eluant used), and on heating (refluxing ethyl acetate for 18 h) was observed as shown in Table 3. A thermodynamic ratio of 4:1 for **23**:**24** at room temperature is again indicated from each of these experiments. The experiment involving heating in ethyl acetate is discussed further in (c).

(b) A sample of the azulenone which contained predominantly the cis isomer **24** was isolated by chromatography (ratio **23**:**24** 1:11.5). Within 21 h at room temperature in $CDCl_3$, the ratio had altered to 1:6.2, and after 190 h a ratio of 4:1, the thermodynamic ratio, was observed.

(c) Variable-temperature ^{1}H and ^{13}C NMR studies of **21**/**22** and **23**/**24** showed that as the temperature is lowered the position of equilibrium shifts in favor of the trans isomer in each case. At 218 K, the ratio of trans/cis observed in each case was ~6:1, compared to 4:1 at 298 K. We did not establish if this is the thermodynamic ratio at this temperature; the rate of equilibration of the isopropyl derivatives **23**/**24** in particular is rather slow, and therefore, the position of equilibrium may not have been attained while recording these NMR spectra.

Furthermore, samples of the isopropyl-substituted azulenone **23**/**24,** which were stored in a freezer, on occasion showed ratios of trans/cis greater than the equilibrium ratio of 4:1, e.g., 9:1 (see Table 1), again indicating that the position of equilibrium is temperature sensitive. With the isopropyl derivative, the rate of equilibration is relatively slow, with the result that NMR spectra of samples that are not at the position of thermodynamic equilibrium can be recorded. With the methyl-substituted derivative, the rate of interconversion of **21** and **22** is much more rapid, so alteration of the diastereomeric ratio following storage in the freezer was not observed.

The sample of **23** that had been heated in ethyl acetate (Table 3) showed a ratio of **23**/**24** of 2.5:1, indicating that as the temperature is increased the position of equilibrium shifts even further toward **24**; again, the rate of equilibration is sufficiently slow that, even though the NMR spectrum was recorded at room temperature in $CDCl_3$, the sample had not yet returned to the thermodynamic ratio for this temperature of 4:1.

(d) Resolution of ^{1}H NMR signals for the bridgehead methyl groups of the two enantiomers of the azulenones formed in this work through addition of $Eu(hfc)_3$ as chiral shift reagent is generally readily achieved, e.g., with azulenones **33**−**38** and **23**/**24**. However, in the case of the azulenone **20** resolution of the signals for the two enantiomers was not possible. This observation is explained by the dynamic behavior illustrated in Scheme 4; when R = H the two enantiomers of **20** are interconverted via the spiro enolate intermediate **39**. Thus, the azulenone **20** is nonresolvable. Furthermore, the rate of this interconversion is likely to be enhanced by the addition of $Eu(hfc)_3$. In contrast, with the substituted derivatives, e.g., **23**/**24**, the dynamic equilibrium converts only the diastereoisomers, not the enantiomers of each component, and therefore, on addition of $Eu(hfc)_3$, signals for the bridgehead methyl groups of the two enantiomers of **23** were clearly distinguished.

(e) Reaction of the azulenones **21**/**22** and **23**/**24** with *N*-phenylmaleimide in refluxing ethyl acetate resulted in formation of cycloadducts **40** and **41** as single diastereomers (see Scheme 5); X-ray crystallographic analysis (Figure S1, Supporting Information) of the cycloadduct **40** formed from the methyl-substituted azulenone mixture **21**/**22** established that the relative stereochemistry of the methyl substituents is cis; i.e., the cycloadduct is formed selectively from the norcaradiene tautomer of the minor diastereomer **22** present in the equilibrating mixture. As the yield of the cycloadducts is greater than that which would be possible if the minor diastereomer only in the mixtures reacted, this provides further evidence for the dynamic equilibration of the cis and trans isomers. By analogy, the cycloadduct **41** from the isopropyl substituted azulenone **23**/**24** is assigned the same relative stereochemistry. Evidently, approach of the dienophile, through transition state **A** (Figure 1), is easier in the less hindered cis isomers **22** and **24** than in the

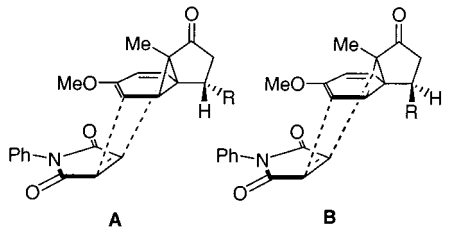
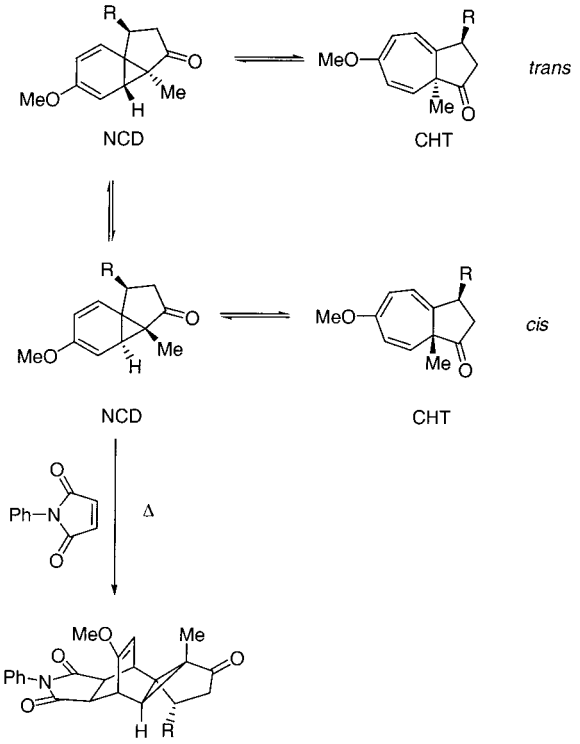


Figure 1. Stereoselectivity of cycloaddition.

Scheme 5



R	azulenones	solvent	time	adducts	%
Me	**21/22**	EtOAc	16h	**40**	45
i-Pr	**23/24**	EtOAc	16h	**41**	32
t-Bu	**25/26**	EtOAc	16h	**42**	0
t-Bu	**25/26**	CH_2Cl_2	31d	**42**	21 + 33% **25/26**
t-Bu	**25/26**	$CHCl_3$	6d	**42**	76

trans isomers **21** and **23** in which the alkyl substituent hinders approach of the dienophile as shown in transition state **B**.

Interestingly, when the *tert*-butyl-substituted diazoketone **16** was investigated, its behavior was quite different from that of the methyl- or isopropyl-substituted derivatives **14** and **15** (Table 1). The crude product of the rhodium acetate catalyzed cyclization typically had a diastereomeric ratio of **25/26** of 98:2, and following purification on silica gel, the product was isolated with a dr of >98:2; i.e., **26** could not be observed in the ^{1}H NMR spectrum. On holding for 2−3 days either neat or in $CDCl_3$, the ratio altered slightly to **25**:**26** 95:5. When the azulenone **25/26** was treated with *N*-phenylmaleimide in refluxing ethyl acetate under identical conditions used to form the cycloadducts **40** and **41** from **21/22** and **23/24** respectively (Scheme 5), there was no evidence of formation of a cycloadduct.

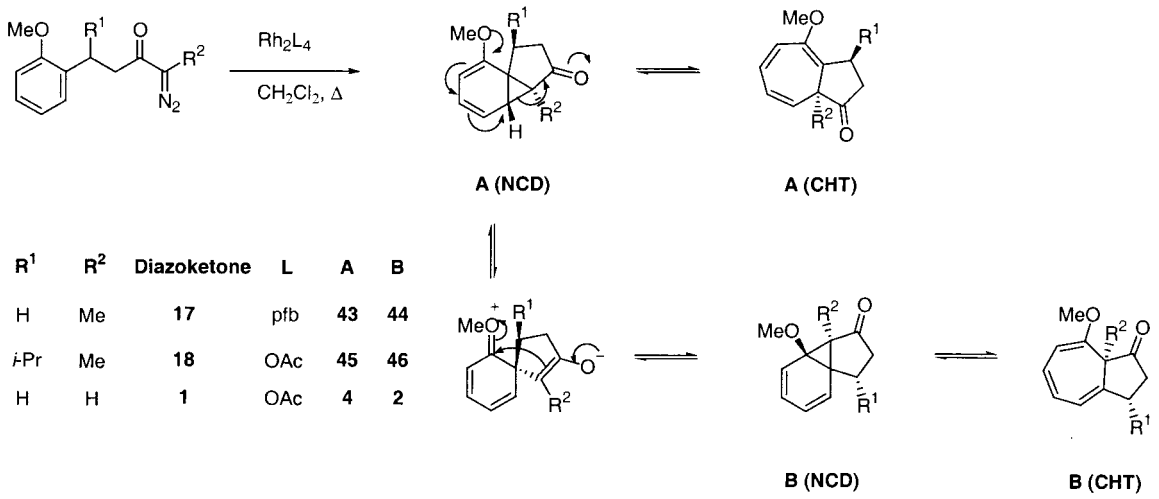
On the basis of these preliminary observations, it was not clear whether the dynamic behavior that had been observed with **21/22** and **23/24** was also occurring in **25/26**. The altered ratio of **25/26** on purification by chromatography is consistent with interconversion of **25** and **26** on silica gel, but in this case resulting in isolation of **25** exclusively or separation of two isomers **25** and **26**, which do not interconvert. The formation of **25** as the exclusive product following chromatography is very different from the behavior of **21/22** and **23/24** where the thermodynamic ratio is ∼4:1 at 20 °C. Furthermore, as the cycloadducts **40** and **41** were formed from the minor cis isomers **22** and **24**, the fact that **25/26** did not produce a cycloadduct could indicate that in this case dynamic interconversion between the isomers is not possible, and with a maximum of 5% of the cis isomer **26** present (NMR studies in $CDCl_3$ at 20 °C) then the cycloadduct is not formed to a detectable extent. Therefore, this system was explored further, and firm evidence for dynamic interconversion of **25** and **26** was obtained as outlined below.

(a) A sample of the azulenone **25** in which **26** could not be detected was obtained following chromatographic purification (i.e., dr **25**/**26** > 98:2). Monitoring of this sample in $CDCl_3$ over 5 days showed that the dr of **25**/**26** gradually altered to 95:5, indicating that interconversion takes place slowly and that the position of thermodynamic equilibrium in this solvent at 20 °C is dr **25**/**26** 19:1. Evidently, the sterically demanding *tert*-butyl substituent alters the conformation of the product and, as a result, the relative stability of the isomers, with the trans isomer **25** more favored than in the derivatives **21/22** and **23/24** with the smaller substituents.

(b) The isolation of the trans azulenone **25** as a single diastereomer following chromatography (hexane/ethyl acetate), together with the fact that no cycloaddduct could be formed in refluxing ethyl acetate, led us to propose that **25** and **26** undergo interconversion in the same manner as **21/22** and **23/24** as illustrated in Scheme 4, but that in ethyl acetate the position of equilibrium of **25/26** favors **25** exclusively with none of **26** present. To test this proposal, a sample of the azulenone **25/26** with a dr of 98:2 (estimated by ^{1}H NMR in $CDCl_3$ at 20 °C) was divided in three portions. The first was stirred with silica gel in CH_2Cl_2, the second was stirred with silica gel in EtOAc and the third portion was stirred in EtOAc, each for 2h. Each of the samples was filtered, concentrated and redissolved in $CDCl_3$ for ^{1}H NMR spectroscopy; the first sample had a dr of ∼95:5, while the two samples that had been in contact with EtOAc consisted of **25** only. These experiments confirmed that in ethyl acetate the position of equilibrium is such that only **25** is present. They also explain why only **25** was isolated following chromatography, as during evaporation of the eluent the sample of **25** would be in solution in ethyl acetate as the more volatile hexane was removed. In dichloromethane or chloroform, the thermodynamic ratio of **25/26** is 95:5 at 20 °C. Interestingly, the rate of interconversion of **25** and **26** is sufficiently slow that the samples that had been in contact with ethyl acetate consisted of **25** only, even after they had been concentrated and redissolved in $CDCl_3$.

(c) The failure to form a cycloadduct from **25/26** on refluxing with *N*-phenylmaleimide in ethyl acetate could now be rationalized—the cycloadducts **40** and **41** formed from the cis isomers of the azulenones **22** and **24** only. However, in ethyl acetate the cis isomer **26** is not present,

Scheme 6



R1	R2	Diazoketone	L	A	B
H	Me	17	pfb	43	44
i-Pr	Me	18	OAc	45	46
H	H	1	OAc	4	2

and therefore, cycloaddition is not observed. To confirm this, the azulenone **25/26** (dr ~98:2 estimated by ^{1}H NMR in $CDCl_3$ at 20 °C) was heated in dichloromethane with *N*-phenylmaleimide for 31 days with NMR monitoring; 33% of **25/26** was recovered together with 21% of the cycloadduct **42** (Scheme 5). As the cycloaddition was inefficient in refluxing dichloromethane, the reaction was repeated in refluxing chloroform; following 6 days at the higher reaction temperature, only the cycloadduct could be detected in the ^{1}H NMR spectrum of the crude product with none of the azulenone **25/26** remaining. Chromatographic purification resulted in isolation of the analytically pure cycloadduct **42** in 76% yield. X-ray crystallography (Figure S2, Supporting Information) confirmed that the relative stereochemistry of this cycloadduct was identical to that of **40** confirming that the cycloaddition occurred to the minor cis isomer **26** even though only 5% of this is present at equilibrium.

The slow cycloaddition in refluxing dichloromethane had two possible reasons, first that the rate of cycloaddition to **26** was slow at this temperature and second that the rate of interconversion of **25** to **26** was limiting. The latter possibility was ruled out: following 3 days, a sample of the reaction mixture was withdrawn. The ^{1}H NMR spectrum indicated that **25** and **26** were present in ~94:6 ratio; i.e., thermodynamic equilibrium had been attained.

Thus, dynamic interconversion of the azulenones **25/26**, mechanistically identical to the behavior of **21/22** and **23/24**, was confirmed; however, the bulky *tert*-butyl group influences both the position of equilibrium (**25** exists exclusively in ethyl acetate, and is more favored in chloroform or dichloromethane, dr **25/26** 19:1 cf. 4:1 for **21/22** and **23/24**) and the rate of interconversion. As the substituent decreases in size the rate of the interconversion increases, with interconversion of **21/22** occurring so quickly that they were never observed at anything other than the thermodynamic ratio, while **23/24** and **25/26** bearing the larger isopropyl and *tert*-butyl substituents interconvert more slowly, and NMR spectra at ratios other than the thermodynamic equilibrium could be recorded.

Having established that the 6-methoxyazulenones **21/22** and **23/24** could be interconverted via the spiro intermediate **39**, we commenced investigation of $Rh_2(OAc)_4$-catalyzed cyclization of diazoketones **17**−**19** bearing 2- and 3-methoxyphenyl substituents, envisaging similar dynamic behavior for the products from the 2-substituted derivatives **17** and **18** but not the 3-substituted compound **19**. Cordi et al.[5] had described cyclization of 1-diazo-4-(2-methoxyphenyl)butan-2-one **1** and reported regiochemistry opposite to that which had been earlier described as shown in Scheme 1.[4] On the basis of our results, we immediately recognized that the source of these conflicting reports was most likely due to a dynamic equilibrium between norcaradienes as illustrated in Scheme 6 and therefore expanded our study to include the terminal diazoketone **1** also.

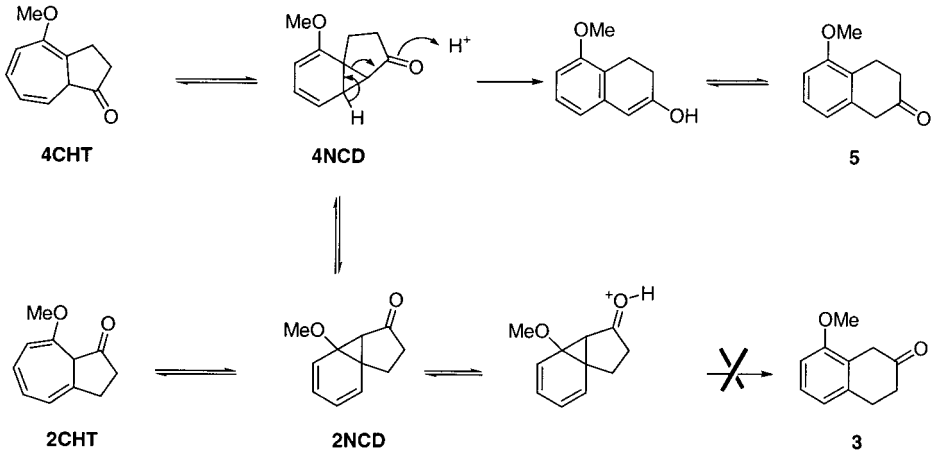
Table 4. Rhodium Carboxylate Catalyzed Cyclization of 2-Methoxyphenyl-Substituted Diazoketones

SM	R1	R2	*T* (°C)	catalyst	A	B	crude ratio[a] A/B	purified ratio[a] A/B	yield[b] (%)
17	H	Me	0	$Rh_2(pfb)_4$	**43**	**44**	9:1		
			Δ	$Rh_2(pfb)_4$	**43**	**44**	2.3:1	2:1	58
18	Pr^i	Me	Δ	$Rh_2(OAc)_4$	**45**	**46**	4:1	3:1	58
								>96:4[c]	
1	H	H	Δ	$Rh_2(OAc)_4$	**4**	**2**	1:2.3		~95[d]
			0				2:1[e]		

[a] Ratios determined by integration of ^{1}H NMR spectra (MeO signals) of both the crude product mixtures and the products following purification by chromatography on silica gel. [b] Yields following chromatographic purification [c] The ratio of isomers had changed after storage in the freezer at −20 °C for 1 year; no noticeable decomposition of the azulenone was observed. [d] This sample was not purified as the ^{1}H NMR spectrum of the crude product was very clean; yield estimated by ^{1}H NMR spectroscopy of the crude product [e] This is the result reported by Manitto et al.[6] after these experiments. The rhodium acetate catalyzed cyclization was in this case conducted at 0 °C, and therefore, the ratio of the kinetic isomer **4** is higher than in our experiment conducted at reflux in DCM where the amount of the thermodynamic isomer **2** is increased.

The results of these studies, summarized in Table 4, support the proposed dynamic equilibria between regioisomeric structures as illustrated in Scheme 6. Rhodium acetate catalyzed cyclization of diazoketone **17** proved rather inefficient. However, rhodium perfluorobutyrate catalyzed decomposition of the 2-methoxy-substituted diazoketone **17**, without any side-chain substituent, displayed in the ^{1}H NMR spectra of the crude product a mixture of the two possible regioisomers **43** and **44**. When the cyclization was conducted at 0 °C, **43** and **44** were recovered in a 9:1 ratio, while at reflux the ratio was 2.3:

Scheme 7



1, with the principal product in each case corresponding to cyclization away from the methoxy group. Rhodium acetate catalyzed cyclization of the analogous diazoketone bearing an isopropyl substituent on the side chain **18** was more efficient and again produced a mixture of regioisomers **45** and **46**, but this time in a ratio of 4:1, with the same regioisomer **A** predominating. However, both compounds displayed altered ratios of regioisomers on exposure to silica gel during chromatography resulting in thermodynamic ratios of 2:1 (**43**/**44**) and 3:1 (**45**/**46**). Furthermore, when the sample of **45** and **46** (3:1) was stored in the freezer at −20 °C for 1 year, the ratio altered to >96:4 as shown by ^{1}H NMR spectroscopy with no significant level of decomposition of the azulenone evident over this period. Therefore, with these two azulenones the kinetic isomer is **A**, i.e., **43** and **45**, corresponding to cyclization away from the methoxy substituent, and this is also the thermodynamically favored isomer at 20 °C, with the equilibrium shifting even more toward **A** on storage at −20 °C.

In light of the report by Cordi et al.,[5] we decided to look at the cyclization of diazoketone **1** as we believed that equilibration of the regioisomeric azulenones **4** and **2** via the mechanism outlined in Scheme 6 explains the conflicting reports outlined in Scheme 1.[4,5] When the $Rh_2(OAc)_4$-catalyzed cyclization of **1** was conducted at reflux and the ^{1}H NMR spectra recorded as soon as possible once the reaction was complete, the crude product contained a mixture of regioisomers **4** and **2** in a 1:2.3 ratio. Treatment of an ether solution of this sample of **4** and **2** with TFA for 10 min resulted in isomerization to a 3:97 ratio, indicating that conversion to the thermodynamically more stable isomer **2** was catalyzed by the acid. These results are in agreement with the result subsequently described by Manitto et al.[6] with a ratio of **4**/**2** of 2:1 when the cyclization was conducted at 0 °C. As described by Manitto et al.[6] **4** disappears and is gradually converted to the thermodynamic isomer **2**. Therefore, when the cyclization was conducted at reflux the equilibration of the initially formed kinetic isomer **4** to the thermodynamic isomer **2** proceeded more rapidly. With this compound, the thermodynamically favored isomer **2** is regioisomer **B**, opposite to that observed when there is a bridgehead methyl substituent where **43** and **45**, i.e. regioisomer **A**, were thermodynamically preferred. These results confirm McKervey's original assignment[4] of the product of cyclization of diazoketone **1** as azulenone **2**, the product formed by apparent cyclization toward the methoxy group, but in fact derived by rearrangement of the kinetic product **4**. Thus, the directive effect of the *o*-methoxy group on the carbenoid cyclization, away from the substituent, is the same as that reported with other substituents such as methyl at the ortho position.

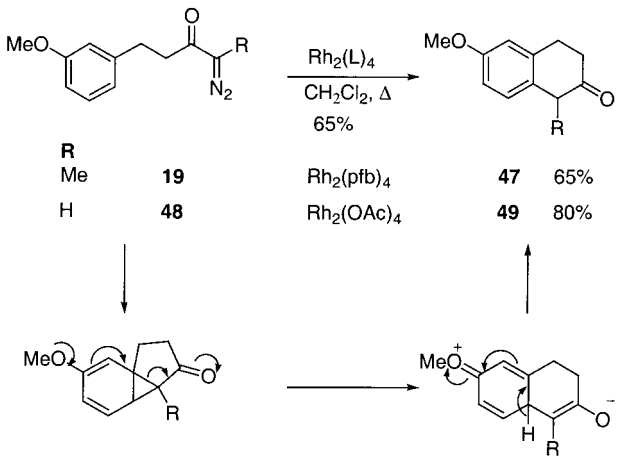
However, the tetralone formed when the azulenone **2**, or a mixture of **4** and **2**, is treated with trifluoroacetic acid is the 8-methoxy-2-tetralone **5** as described by Cordi et al,[5] derived from the kinetic product of the cyclization **4** as mechanistically the norcaradiene tautomer of **2** is not readily rearomatized to form tetralone **3** (see Scheme 7). The formation of tetralone **5** from the azulenone **2** even when the rearrangement of **4** to **2** is essentially complete by NMR spectroscopy, provides evidence for the existence of a dynamic equilibrium between the two regioisomers **4** and **2**. The sample of the tetralone **5** which we generated during the course of this research by treatment of the azulenones **2** and **4** with TFA in dichloromethane had identical spectroscopic characteristics to those reported by Cordi et al.[5]

NMR spectroscopic analysis of the azulenone products is particularly informative; two tautomers, NCD and CHT, are possible for each isomer and furthermore the position of this NCD-CHT equilibrium is very sensitive to the nature and position of the substituents on the compound;[3g,7] for example, **45** exists almost entirely as the NCD tautomer. The rate of tautomerisation is fast on the NMR time scale while interconversion via the spiro intermediates of the diastereomers for the 6-methoxy azulenones **21**−**24** and the regioisomers for the 4/8-methoxy azulenones **43**−**46**, **2**, **4** is slow. Therefore, distinct time-averaged signals for the NCD/CHT tautomers of each of the diastereomers/regioisomers are observed in each case.

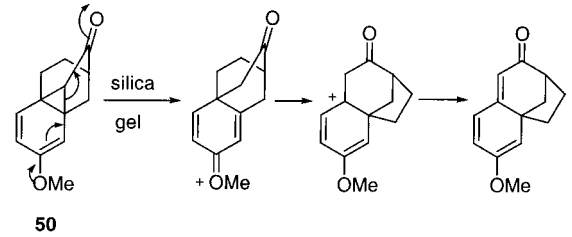
The azulenones synthesized in this work were relatively stable compounds that could be purified on silica gel and stored in a freezer for extended periods without any significant level of decomposition.

At this point, on the basis of our results, we had demonstrated that the origin of the controversy[4,5] in the regioselectivity of cyclization of the methoxy-substituted diazoketone **1** was due to the dynamic equilibrium via a spiro intermediate as illustrated in Scheme 6. The interconversion of the cis and trans isomers of the 6-substituted azulenones supports this mechanism. Further evidence supporting this mechanistic interpretation was secured when the 3-methoxyphenyl-substituted diazoketone **19** was examined. On treatment with rhodium-

Scheme 8



Scheme 9



(II) perfluorobutyrate in refluxing dichloromethane, only the tetralone **47** was observed in agreement with McKervey's report[4] that the tetralone **49** was formed directly from the terminal diazoketone **48** (Scheme 8). Therefore, as illustrated in Scheme 8, the 5-methoxy group triggers an alternative fragmentation of the cyclopropane ring of the norcaradiene intermediate resulting in formation of the tetralone. Interestingly, there was no evidence in the cyclization of **19** of a regioisomeric product; McKervey[4] also reported the formation of a single tetralone from **48**.

Following the completion of this work, a report of a related study by Manitto et al.[6] appeared which is in agreement with our results. Involvement of a methoxy substituent in cleavage of norcaradienes is precedented; Mander et al.[3g] have proposed the mechanism illustrated in Scheme 9 to explain the instability of norcaradiene **50** on exposure to silica gel. Moriarty et al.[8] have also reported related rearrangements in intermediates generated by reaction of iodonium ylides with methoxy substituted aromatic rings.

It is well established that variation of the ligand on rhodium carboxylate and carboxamide catalysts can have a significant effect on the reactivity of carbenoids formed from the catalysts; chemo-, regio-, and stereoselectivity can be altered by variation of the ligand.[1,9] While the aromatic addition reaction would be expected to be catalyzed more efficiently by catalysts such as $Rh_2(tfa)_4$ and $Rh_2(pfb)_4$ which form highly electrophilic carbenoids and less efficiently by $Rh_2(cap)_4$ compared to $Rh_2(OAc)_4$, in practice it was observed that the activating effect of the methoxy group overcame to a large extent the electronic effect of the catalysts. Rhodium(II) caprolactam was noticeably less efficient in the cyclization of diazoketones **13**−**15** typically producing the azulenones in 50−60% yield. Use of this catalyst with the diazoketones **1**, **17**, and **18** was not explored. Also, cyclization of diazoketone **17** was notably more efficient with the more electron-withdrawing ligands in the catalysts $Rh_2(pfb)_4$ and $Rh_2(mand)_4$ than with $Rh_2(OAc)_4$. However, other than these two observations the efficiency of the diazoketone cyclizations was not very sensitive to the nature of the catalyst ligand. In particular the outcome of the cyclization of the *tert*-butyl substituted diazoketone **16** was very insensitive to the catalyst employed, with good yields (64−82%) observed in each case even with $Rh_2(cap)_4$ (79%). Interpretation of the influence of the catalyst on the selectivity of the cyclizations, diastereoselectivity with the 4-methoxy and regioselectivity with the 2-methoxy derivatives, was difficult due to the dynamic equilibria discussed above which result in product ratios which are more dependent on the history of the sample in terms of age, reaction temperature, temperature of storage etc. than on the kinetic properties of the catalyst.

In conclusion, rhodium(II)-catalyzed cyclizations of diazoketones to aromatic rings bearing methoxy substituents proceed efficiently; the activating effect of the methoxy substituent overcomes to a large extent the electronic effect of the ligands on the catalyst and results in relatively minor catalyst sensitivity. Interesting dynamic equilibria are observed in the cyclization products via rearrangements of the methoxy substituted norcaradienes. These observations explain the conflicting results reported for the regioselectivity of cyclization of diazoketone **1**.[4,5,6]

Experimental Section

All reactions were carried out under an inert atmosphere of nitrogen. Infrared (IR) spectra were obtained as films on NaCl plates or as KBr disks, and wavelengths (ν) are reported in cm^{-1}. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ (270 and 67.8 MHz, respectively) unless indicated otherwise. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Flash chromatography was conducted using the indicated solvent mixture and Merck silica gel 60 (0.040−0.063 mm). Thin-layer chromatography (TLC) was carried out on silica gel coated aluminum sheets (Merck silica gel F_{254}). Melting points are uncorrected. All solvents were rountinely dried and distilled prior to use. Ether refers to diethyl ether. All extractions were usually followed by water and saturated NaCl aqueous solution washings, $MgSO_4$ drying, filtration, and evaporation. Diazoethane and diazomethane solutions in ether were freshly prepared prior to use and were distilled unless otherwise stated. All commercially available reagents were used as received unless otherwise stated. Thionyl chloride was distilled first from quinoline and then from linseed oil.[10] Rhodium acetate was obtained from Johnson Matthey. Other rhodium catalysts were prepared according to standard procedures.[11] In the cases of the minor diastereomers of the *azulenones* spectral characteristics reported are those which were easily distinguished from those due to the major diastereomer. While acids **6**, **10**, and **12** are commercially available, these were prepared for this work by hydrogenation of the analogous cinnamic acid derivatives.

3-(4′-Methoxyphenyl)butanoic Acid (7). A suspension of but-2-enoic acid (4.00 g, 4.65×10^{-2} mol) in ether (50 mL) was

(8) Moriarty, R. M.; May, E. J.; Prakash, O. *Tetrahedron Lett.* **1997**, *38*, 4333.

(9) Miah, S.; Slawin, A. M. Z.; Moody, C. J.; Sheehan, S. M.; Marino, J. P., Jr.; Semones, M. A.; Padwa, A.; Richards, I. C. *Tetrahedron* **1996**, *52*, 2489; Padwa, A.; Austin, D. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1797.

(10) Vogel, A. *Textbook of Practical Organic Chemistry*; Longman: London, 1978.

(11) (a) Doyle, M. P.; Westrum, L. J.; Walthius, W. N. E.; Sie, M. M.; Boone, W. P.; Bagheri, V.; Pearson, M. M. *J. Am. Chem. Soc.* **1993**, *115*, 958. (b) Drago, R. S.; Long, R. F.; Cosmano, R. *Inorg. Chem.* **1982**, *21*, 2196.

added over 10 min to a solution of 4-methoxyphenylmagnesium bromide [freshly prepared from magnesium (3.35 g, 1.38×10^{-1} mol), 4-bromoanisole (26.10 g, 1.40×10^{-1}mol), and iodine (catalytic amount)] in ether (140 mL) at 0 °C. The reaction mixture was stirred for 1 h while slowly returning to room temperature and was then brought to reflux for 6 h. The reaction mixture was then cooled to 0 °C and poured carefully onto hydrochloric acid (120 mL, 10%) in ice (150 g). After extraction with ether, the residue was purified by flash chromatography with gradient ethyl acetate−hexane as eluant to give the *acid* **7** (4.42 g, 49%) as a white solid: mp 67−69 °C (lit.[12] mp 67−68 °C); IR (KBr) 3600−2400, 1712, 1614 cm^{-1}; ^1H NMR δ 1.29 (d, $J = 7$ Hz, 3H), 2.47−2.69 (m, 2H), 3.14−3.20 (m, 1H), 3.78 (s, 3H), 6.79−6.88 (m, 2H), 7.09−7.20 (m, 2H); ^{13}C NMR δ 22.00, 35.44, 42.83, 55.26, 114.03, 127.64, 137.65, 158.26, 178.11. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.20; H, 7.32.

3-(4′-Methoxyphenyl)-4-methylpentanoic Acid (8). 4′-Methoxycinnamic acid (3.00 g, 1.69×10^{-2} mol) was added portionwise over 30 min to a solution of isopropylmagnesium bromide [freshly prepared from magnesium (1.37 g, 5.62×10^{-2} mol), 2-propyl bromide (6.92 g, 5.62×10^{-2} mol), and iodine (catalytic amount)] in ether (100 mL) at 0 °C. The reaction mixture was stirred for 1 h while slowly returning to room temperature and was then brought to reflux for 1 h. The reaction mixture was then cooled to 0 °C and poured carefully onto hydrochloric acid (50 mL, 10%) in ice (50 g). After extraction with ether and the usual workup, the residue was purified by flash chromatography with gradient ethyl acetate−hexane as eluant to give the *acid* **8** (2.75 g, 73%) as a white solid: mp 82−86 °C; IR (KBr) 3650−2400, 1705, 1612 cm^{-1}; ^1H NMR δ 0.67 (d, $J = 7$ Hz, 3H), 0.85 (d, $J = 7$ Hz, 3H), 1.68−1.85 (m, 1H), 2.44−2.58 (m, 1H), 2.65−2.84 (m, 2H), 3.71 (s, 3H), 6.70−6.81 (m, 2H), 6.96−7.06 (m, 2H); ^{13}C NMR δ 20.08, 20.59, 33.19, 38.32, 47.71, 55.17, 113.43, 129.12, 134.64, 158.17, 178.76. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.47; H, 8.29.

3-(4′-Methoxyphenyl)-4,4-dimethylpentanoic Acid (9). This was prepared following the procedure described for **8** from 3-(4′-methoxyphenyl)propenoic acid (2.00 g, 1.12×10^{-2} mol) and *tert*-butylmagnesium chloride in ether (2 M, 16.8 mL, 3.36×10^{-2} mol). The reaction was refluxed for 3 h. The crude *acid* was isolated in 86% yield (2.27 g), which was pure enough to use without further purification. Recrystallization of a small portion of the crude product from ethanol gave an analytically pure sample of the *acid* **9** as a white solid: mp 126−127 °C (lit.[13] mp 131−132 °C); IR (KBr) 3680−3030, 1711, 1610 cm^{-1}; ^1H NMR δ 0.85 (s, 9H), 2.66 (dd, $J = 15$, 11 Hz, 1H), 2.77 (dd, $J = 16$, 4 Hz, 1H), 2.87 (dd, $J = 11$, 4 Hz, 1H), 3.78 (s, 3H), 6.78 (d, $J = 9$ Hz, 2H), 7.05 (d, $J = 9$ Hz, 2H); ^{13}C NMR δ 27.83, 33.73, 35.54, 51.02, 55.11, 113.01, 130.09, 133.31, 158.05, 179.01; EIMS *m*/*z* (rel int) 236 (M^+, 15), 221 (8), 179 (base), 137 (90). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.47. Found: C, 71.41; H, 8.22.

3-(2′-Methoxyphenyl)-4-methylpentanoic Acid (11). This was prepared following the procedure described for **8** from 3-(2′-methoxyphenyl)propenoic acid (1.96 g, 1.10×10^{-2} mol) and isopropylmagnesium bromide [freshly prepared from magnesium (0.94 g, 3.84×10^{-2} mol), 2-propyl bromide (4.73 g, 3.84×10^{-2} mol) and iodine (catalytic amount)] in ether (100 mL). Purification by flash chromatography with gradient ethyl acetate−hexane as eluant gave the *acid* **11** (1.39 g, 57%) as a white solid: IR (KBr) 3650−2400, 1711, 1602 cm^{-1}; ^1H NMR δ 0.76 (d, $J = 7$ Hz, 3H), 0.92 (d, $J = 7$ Hz, 3H), 1.87−2.06 (m, 1H), 2.58−2.82 (m, 2H), 3.23−3.35 (m,1H), 3.78 (s, 3H), 6.79−6.92 (m, 2H), 7.03−7.22 (m, 2H); ^{13}C NMR δ 20.52, 20.78, 31.92, 36.98, 42.26, 55.21, 110.91, 120.32, 127.25, 128.72, 131.43, 157.58, 179.55. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.31; H, 8.08. Evidence was seen in the ^1H NMR for 9% of an isomeric compound, which is presumably similar to those products observed by Mestres et al.[14]

2-Diazo-5-(4′-methoxyphenyl)pentan-3-one (13). 3-(4′-Methoxyphenyl)propanoyl chloride [prepared from 3-(4′-methoxyphenyl)propanoic acid **6** (0.46 g, 2.55×10^{-3} mol) and freshly distilled thionyl chloride (15 mL) and purified by bulb to bulb distillation (110 °C at 0.3 mmHg): IR (film) 1797, 1613 cm^{-1}] (0.44 g, 2.22×10^{-3} mol), in ether (10 mL), was added dropwise over 20 min to an ethereal diazoethane solution [prepared from *N*-ethyl-*N*-nitrosourea (7.15 g, 6.11×10^{-2} mol)],[15] at −20 °C while stirring under nitrogen. The solution was allowed to slowly return to room temperature while stirring for 3h. The ether and residual diazoethane were evaporated under reduced pressure at room temperature, using a rotary evaporator fitted with an acetic acid trap. Purification by chromatography, using ethyl acetate−hexane (5:95) as eluant, gave the *diazoketone* **13** (0.42 g, 75%) as a yellow oil: IR (film) 2071, 1634 cm^{-1}; ^1H NMR δ 1.92 (br s, 3H), 2.72 (br t, $J = 7$ Hz, 2H), 2.90 (br t, $J = 8$ Hz, 2H), 3.77 (s, 3H), 6.77−6.88 (m, 2H), 7.04−7.19 (m, 2H); ^{13}C NMR δ 8.03, 29.70, 39.72, 55.25, 62.20, 113.96, 129.32, 132.84, 158.13, 193.63; HRMS (EI) calcd for $C_{12}H_{14}N_2O_2$ 218.1055 (M^+) found 218.1063; EIMS *m*/*z* (rel int) 218 (M^+, 3), 190 (20), 175 (18), 134 (21), 121 (base). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.13; H, 6.61; N, 13.04. Found: C, 66.13; H, 6.47; N, 12.83.

2-Diazo-5-(4′-methoxyphenyl)hexan-3-one (14). This was prepared following the procedure described for **13**, using 3-(4′-methoxyphenyl)butanoyl chloride [prepared from 3-(4′-methoxyphenyl)butanoic acid **7** (3.00 g, 1.55×10^{-2} mol) and freshly distilled thionyl chloride (20 mL)] and purified by bulb-to-bulb distillation (100 °C, at 0.5 mmHg): IR (film) 1798, 1613 cm^{-1}] (1.09 g, 8.94×10^{-3} mol), in ether (20 mL) and ethereal diazoethane [prepared from *N*-ethyl-*N*-nitrosourea (10.00 g, 8.55×10^{-2} mol)].[15] Purification by chromatography, using ethyl acetate−hexane (3:97) as eluant, gave the *diazoketone* **14** (1.60 g, 45%) as a yellow oil: IR (film) 2065, 1634 cm^{-1}; ^1H NMR δ 1.28 (d, $J = 7$ Hz, 3H), 1.83 (br s, 3H), 2.52−2.79 (m, 2H), 3.22−3.39 (m, 1H), 3.78 (s, 3H), 6.76−6.92 (m, 2H), 7.06−7.22 (m, 2H); ^{13}C NMR δ 7.98, 21.61, 35.77, 46.38, 55.18, 62.53, 113.86, 127.61, 137.84, 158.10, 193.50; EIMS *m*/*z* (rel int) 233 ($M^+ + 1$, 27), 204 (35), 189 (41), 135 (base). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.38; H, 7.20; N, 12.30.

2-Diazo-5-(4′-methoxyphenyl)-6-methylheptan-3-one (15). Oxalyl chloride (0.83 mL, 9.51×10^{-3} mol) was added dropwise over 5 min to 3-(4′-methoxyphenyl)-4-methylpentanoic acid **8** (1.93 g, 8.69×10^{-3} mol) in ether (15 mL) with stirring at 0 °C. The solution was allowed to slowly return to room temperature with stirring for 18 h. The solvent and residual reagent were removed under reduced pressure to give the *acyl chloride*, which was used without further purification. An ethereal diazoethane solution[15] was prepared from *N*-ethyl-*N*-nitrosourea (10.16 g, 8.68×10^{-2} mol) and cooled to −20 °C. The crude acyl chloride in ether (20 mL) was added dropwise over 20 min to the stirring diazoethane solution. The solution was then allowed to return to room temperature with stirring for 4 h. The ether and residual diazoethane were evaporated under reduced pressure, using a rotary evaporator fitted with an acetic acid trap. Purification by chromatography, using ethyl acetate−hexane (2:98) as eluant gave the *diazoketone* **15** (1.78 g, 79%) as a yellow oil: IR (film) 2072, 1632 cm^{-1}; ^1H NMR δ 0.73 (d, $J = 7$ Hz, 3H), 0.96 (d, $J = 7$ Hz, 3H), 1.69−1.92 (m, 4H), 2.68−2.82 (m, 2H), 2.83−2.97 (m, 1H), 3.78 (s, 3H), 6.74−6.87 (m, 2H), 7.00−7.15 (m, 2H); ^{13}C NMR δ 8.02, 20.58, 20.87, 33.01, 41.76, 48.29, 55.13, 62.77, 113.34, 128.98, 135.02, 158.03, 193.89; EIMS *m*/*z* (rel int) 288 ($M^+ + N_2$, 12), 261 ($M^+ + 1$, 10), 232 ($M^+ - N_2$, 33), 217 (20), 189 (base). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76. Found: C, 69.19; H, 8.12; N, 9.45.

2-Diazo-5-(4′-methoxyphenyl)-6,6-dimethylheptan-3-one (16). This was prepared following a similar procedure to

(12) Fort, A. W.; Leary, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 2494.

(13) Antoniadou-Vyza, A.; Foscolos, G. B.; Costakis, E. *Chem. Chron.* **1985**, *14*, 79; *Chem. Abstr.* **1986**, *105*, 60354q.

(14) (a) Aurell, M. J.; Mestres, R.; Munoz, E. *Tetrahedron Lett.* **1998**, *39*, 6351. (b) Aurell, M. J.; Banuls, M. J.; Mestres, R.; Munoz, E. *Tetrahedron* **1999**, *55*, 831.

(15) Arndt, F. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 461.

that described for the preparation of **13**, using 3-(4′-methoxyphenyl)-4,4-dimethylpentanoyl chloride [prepared from crude 3-(4′-methoxyphenyl)-4,4-dimethylpentanoic acid **9** (25.86 g, 1.09×10^{-1} mol) and thionyl chloride (80 mL)] and purified by fractional distillation (122 °C, at 0.035 mmHg) to give the *acid chloride* [14.15 g, 47% from 3-(4′-methoxyphenyl)propenoic acid: IR (film) 1803, 1611 cm^{-1}] (7.10 g, 2.79×10^{-2} mol) in ether (100 mL) and ethereal diazoethane [prepared from *N*-ethyl-*N*-nitrosourea (26.11 g, 2.38×10^{-1} mol) and not distilled but dried twice over KOH].[15] Purification by chromatography, using ethyl acetate−hexane (1:4) as eluant, gave the *diazoketone* **16** (3.99 g, 52% from acid chloride) as a yellow solid: mp 78−79 °C; IR (film) 2071, 1631 cm^{-1}; ^1H NMR (300 MHz) δ 0.88 (s, 9H), 1.76 (br s, 3H), 2.73 (br d, $J = 13$ Hz, 1H), 2.85−3.07 (m, 2H), 3.78 (s, 3H), 6.79 (d, $J = 9$ Hz, 2H),7.06 (d, $J = 9$ Hz, 2H); ^{13}C NMR (75.47 MHz) δ 8.06, 27.97, 33.87, 38.44, 51.53. 55.06, 113.06, 129.92, 133.70, 157.94, 194.07; EIMS *m*/*z* (rel int) 274 (M^+, 1), 246 (22), 189 (43). Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.02; N, 10.20. Found: C, 70.56; H, 8.31; N, 10.03.

2-Diazo-5-(2′-methoxyphenyl)pentan-3-one (17). This was prepared following the procedure described for **15** using 3-(2′-methoxyphenyl)propanoic acid **10** (3.31 g, 1.84×10^{-2} mol) in ether (50 mL), oxalyl chloride (1.87 mL, 2.14×10^{-2} mol), and ethereal diazoethane [prepared from from *N*-ethyl-*N*-nitrosourea (18.34 g, 1.57×10^{-1} mol)].[15] Purification by chromatography, using ethyl acetate−hexane (5:95) as eluant, gave the *diazoketone* **17** (2.37 g, 59%) as a low melting yellow solid: mp 38−39 °C dec; IR (KBr) 2070, 1632 cm^{-1}; ^1H NMR δ 1.92 (br s, 3H), 2.74 (br t, $J = 8$ Hz, 2H), 2.94 (br t, $J = 7$ Hz, 2H), 3.80 (s, 3H), 6.79−6.93 (m, 2H), 7.08−7.29 (m, 2H); ^{13}C NMR δ 8.04, 26.50, 37.91, 55.09, 62.15, 110.19, 120.48, 127.59, 128.84, 130.14, 157.44, 194.42. HRMS (EI) calculated for $C_{12}H_{14}N_2O_2$ 218.1055 (M^+) found 218.1158; EIMS *m*/*z* (rel int) 246 ($M^+ + N_2$, 4), 218 (M^+, 8), 190 (1), 175 (47), 162 (47), 121 (40). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.83. Found: C, 65.91; H, 6.62; N, 12.79.

2-Diazo-5-(2′-methoxyphenyl)-6-methylheptan-3-one (18). This was prepared following the procedure described for **15** using 3-(2′-methoxyphenyl)-4-methylpentanoic acid **11** (2.00 g, 9.01×10^{-3} mol) in ether (15 mL), oxalyl chloride (1.00 mL, 1.15×10^{-2} mol), and ethereal diazoethane [prepared from from *N*-ethyl-*N*-nitrosourea (10.53 g, 9.00×10^{-2} mol)].[15] Purification by chromatography, using ethyl acetate−hexane (5:95) as eluant gave the *diazoketone* **18** (1.24 g, 53%) as a yellow oil: IR (film) 2071, 1634 cm^{-1}; ^1H NMR 0.72 (d, $J = 7$ Hz, 3H), 0.97 (d, $J = 7$ Hz, 3H), 1.76 (br s, 3H), 1.91−2.13 (m, 1H), 2.69−2.85 (m, 1H), 2.86−3.05 (m, 1H), 3.18−3.36 (br m, 1H), 3.80 (s, 3H), 6.77−6.94 (m, 2H), 6.99−7.24 (m, 2H); ^{13}C NMR δ 8.08, 20.38, 20.76, 31.82, 40.62, 44.27, 55.20, 62.59, 110.63, 120.22, 127.13, 129.28, 131.24, 157.46, 194.29; EIMS *m*/*z* (rel int) 288 ($M^+ + N_2$, <1), 260 (M^+, <1), 232 ($M^+ - N_2$, 20), 217 (13), 189 (100). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76. Found: C, 68.93; H, 7.39; N, 10.31.

2-Diazo-5-(3′-methoxyphenyl)pentan-3-one (19). This was prepared following the procedure described for **15** using 3-(3′-methoxyphenyl)propanoic acid **12** (3.03 g, 1.68×10^{-2} mol) in ether (15 mL), oxalyl chloride (2.57 mL, 2.95×10^{-2} mol), and ethereal diazoethane [prepared from *N*-ethyl-*N*-nitrosourea (18.44 g, 1.68×10^{-1} mol)].[15] Purification by chromatography, using ethyl acetate−hexane (5:95) as eluant, gave the *diazoketone* **19** (2.78 g, 76%) as a yellow oil: IR (film) 2070, 1634 cm^{-1}; ^1H NMR δ 1.93 (br s, 3H), 2.75 (br t, $J = 7$ Hz, 2H), 2.94 (br t, $J = 8$ Hz, 2H), 3.79 (s, 3H), 6.68−6.84 (m, 3H), 7.14−7.28 (m, 1H); ^{13}C NMR δ 8.16, 30.86, 39.44, 55.19, 62.20, 111.70, 114.25, 120.76, 129.41, 142.51, 159.87, 193.43; EIMS *m*/*z* (rel int) 220 ($M^+ + 2$, 5), 204 (1), 180 (<1), 161 (3), 91 (30). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.83. Found: C, 65.80; H, 6.79; N, 11.29.

2-Diazo-5-phenylheptan-3-one (27). This was prepared following the procedure described for **13**, using 3-phenylbutanoyl chloride [prepared from 3-phenylbutanoic acid (1.00 g, 6.09×10^{-3} mol) and thionyl chloride (4.42 mL) and purified by bulb-to-bulb distillation (75 °C, at 0.1 mmHg): IR (film) 1800 cm^{-1}] (0.930 g, 5.10×10^{-3} mol 84%) in ether (20 mL) and ethereal diazoethane [prepared from *N*-ethyl-*N*-nitrosourea (5.54 g, 5.04×10^{-2} mol)].[15] Purification by chromatography, using ethyl acetate−hexane (1:4) as eluant, gave the *diazoketone* **27** (0.755 g, 62% from acid) as a yellow oil: IR (film) 2069, 1633 cm^{-1}; ^1H NMR (300 MHz) δ 1.31 (d, $J = 7$ Hz, 3H), 1.88 (br s, 3H), 2.57−2.80 (m, 2H), 3.28−3.43 (m, 1H), 7.15−7.32 (m, 5H); ^{13}C NMR δ 8.13, 21.37, 36.48, 46.20, 62.35, 126.34, 126.87, 128.12, 145.87, 193.21; EIMS *m*/*z* (rel int) 174 ($M^+ - N_2$, 22), 159 (28), 132 (base), 105 (98). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.29; H, 6.93; N, 13.86. Found: C, 71.33; H, 7.18; N, 13.56.

1-Diazo-4-(2′-methoxyphenyl)butan-2-one (1).[4] This was prepared in a manner similar to that described for **13**, using 3-(2′-methoxyphenyl)propanoyl chloride [prepared from 3-(2′-methoxyphenyl)propanoic acid **10** (0.84 g, 4.67×10^{-3} mol) and freshly distilled thionyl chloride (10 mL) and purified by bulb-to-bulb distillation (100 °C, at 0.5 mmHg): IR (film) 1798 cm^{-1}] (0.86 g, 4.33×10^{-3} mol) in ether (20 mL) and ethereal diazomethane [prepared from Diazald (8.00 g, 3.73×10^{-2} mol)].[10] Purification by chromatography, using ethyl acetate−hexane (2:98) as eluant, gave the *diazoketone* **1** (0.74 g, 78%) as a yellow oil: IR (film) 2105, 1644 cm^{-1}; ^1H NMR δ 2.54−2.72 (br m, 2H), 2.93 (t, $J = 8$ Hz, 2H), 5.20 (br s, 1H), 6.77−6.93 (m, 2H), 7.10−7.28 (m, 2H); ^{13}C NMR δ 26.46, 40.98, 54.62, 55.49, 110.60, 120.82, 127.89, 129.18, 130.28, 157.73, 194.93.

3,8a-Dihydro-6-methoxy-8a-methylazulen-1(2*H*)-one (20). 2-Diazo-5-(4′-methoxyphenyl)pentan-3-one **13** (100 mg, 4.59×10^{-4} mol) in CH_2Cl_2 (100 mL) was added dropwise over 1 h to a refluxing solution of rhodium(II) acetate (0.5 mg) in CH_2Cl_2 (100 mL). The reaction was monitored by TLC and was complete once the diazoketone had been added. Evaporation of the solvent at reduced pressure gave the crude product as a yellow oil. A ^1H NMR spectrum was recorded to determine the efficiency of the cyclization (88%) (percent of azulenone by comparison to aromatic byproducts). Purification by flash chromatography, with gradient ethyl acetate−hexane as eluant, gave the *azulenone* **20** (70 mg, 80%) as a colorless oil: IR (film) 1745, 1710, 1645, 1577 cm^{-1}; ^1H NMR δ 0.81 (s, 3H), 2.16−2.60 (m, 4H), 3.61 (s, 3H), 4.00 (br d, $J = 7.8$ Hz, 1H), 5.49 (dd, $J = 8$, 2 Hz, 1H), 5.79 (dd, $J = 7$, 2 Hz, 1H), 6.07 (d, $J = 8$ Hz, 1H); ^{13}C NMR δ 11.28, 27.11, 34.28, 54.58, ~85 (br), 108.68, 111.56, 123.87, 129.29, 156.58, 219.07; HRMS (EI) calcd for $C_{12}H_{14}O_2$ 190.0994 (M^+), found 190.0998; EIMS *m*/*z* (rel int) 190 (M^+, base), 175 (52), 162 (68), 147 (95), 133 (55). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.77; H, 7.40. Found: C, 75.35; H, 7.52. No resolution of signals for enantiomers was seen in a ^1H NMR chiral shift study using (+)-Eu(hfc)$_3$. It was difficult to obtain **20** completely free of aromatic impurities.

***trans*-(3*R**,8a*R**)-3,8a-Dihydro-6-methoxy-3,8a-dimethylazulen-1(2*H*)-one (21) and *cis*-(3*R**,8a*S**)-3,8a-dihydro-6-methoxy-3,8a-dimethylazulen-1(2*H*)-one (22).** This was prepared following the procedure described for **20** from 2-diazo-5-(4′-methoxyphenyl)pentan-3-one **14** (100 mg, 4.31×10^{-4} mol) and rhodium(II) acetate (0.5 mg). An ^1H NMR spectrum was recorded to determine the efficiency of the cyclization (91%) and the diastereomeric ratio of the *azulenones* formed: diastereomeric ratio, *trans*-**21**/*cis*-**22**, 76:24 [by comparison of the ^1H NMR integration for C(8)*H* cis and C(7)-*H* trans]. Purification by flash chromatography, with gradient ethyl acetate−hexane as eluant, gave a mixture of the diastereomers of the *azulenones* **21**, **22** (72 mg, 82%) as a colorless oil. The diastereomeric ratio was estimated as *trans*-**21**/*cis*-**22**, 80:20: IR (film) 1745, 1712, 1646 cm^{-1}.

Spectral details for *trans*-**21**: ^1H NMR δ 0.75 (s, 3H), 1.08 (d, $J = 6$ Hz, 3H), 1.84 (dd, $J = 18$, 9 Hz, 1H), 2.46 (dd, $J = 18$, 9 Hz, 1H), 2.67−2.87 (m, 1H), 3.47 (d, $J = 7.3$ Hz, 1H), 3.61 (s, 3H), 5.29 (dd, $J = 7$, 2 Hz, 1H), 5.92 (dd, $J = 9$, 2 Hz, 1H), 6.04 (d, $J = 9$ Hz, 1H); ^{13}C NMR δ 9.08, 18.84, 33.54, 42.07, 54.58, 66.95, 102.98, 116.42, 124.93, 156.43, 217.76. Spectral details for *cis*-**22**: ^1H NMR δ 0.86 (s, 3H), 1.28 (d, $J = 6$ Hz, 3H), 2.08−2.18 (m, 1H), 2.45−2.59 (m, 1H), 3.62 (s, 3H), 4.51 (d, $J = 9.5$ Hz, 1H), 5.66 (dd, $J = 10$, 2 Hz, 1H), 5.78 (dd, $J = 8$, 2 Hz, 1H), 6.21 (dd, $J = 8,1$ Hz, 1H); ^{13}C NMR δ 13.94, 21.63, 33.25, 43.68, 54.58, 108.79, 113.80, 120.40,

127.77, 156.43; HRMS (EI) calcd for $C_{13}H_{16}O_2$ 204.1150 (M^+) found 204.1152; EIMS *m/z* (rel int) 204 (M^+, 82), 189 (84), 176 (20), 162 (80), 134 (base).

***trans*-(3*R**,8a*S**)-3,8a-Dihydro-3-isopropyl-6-methoxy-8a-methylazulen-1(2*H*)-one (23) and *cis*-(3*R**,8a*R**)-3,8a-dihydro-3-isopropyl-6-methoxy-8a-methylazulen-1(2*H*)-one (24).** This was prepared following the procedure described for **20**, from 2-diazo-5-(4′-methoxyphenyl)-6-methylheptan-3-one **15** (100 mg, 3.85×10^{-4} mol) and rhodium(II) acetate (0.5 mg). The efficiency of the cyclization (>90%) and the diastereomeric ratio of the *azulenones* formed were estimated: diastereomeric ratio, trans **23**: *cis* **24**, 76:24. Purification by flash chromatography, with gradient ethyl acetate−hexane as eluant, gave a mixture of the diastereomers of the *azulenones* **23**, **24** (69 mg, 77%) as a colorless oil. The diastereomeric ratio was estimated as *trans*-**23**/*cis*-**24**, 90:10: IR (film) 1746, 1711, 1645 cm^{-1}.

Spectral details for *trans*-**23**: ^1H NMR δ 0.76 (s, 3H), 0.80 (d, $J = 7$, 3H), 0.90 (d, $J = 7$ Hz, 3H), 1.58−1.73 (m, 1H), 1.99 (dd, $J = 17$, 7 Hz, 1H), 2.30−2.63 (m, 2H), 3.61 (s, 3H), 3.69 (br d, $J = 7.3$ Hz, 1H), 5.34 (br dd, $J = 8$, 2 Hz, 1H), 5.85 (dd, $J = 9$, 2 Hz, 1H), 6.06 (d, $J = 9$ Hz, 1H); ^{13}C NMR δ 9.69, 19.13, 20.93, 32.37, 37.89, 45.41, 54.58, 70−74 (br), 104.05, 114.02, 126.18, 156.58, 217.73. Spectral details for *cis*-**24**: ^1H NMR δ 0.84 (s, 3H), 0.88 (d, $J = 7$ Hz, 3H), 0.98 (d, $J = 7$ Hz, 3H), 3.62 (s, 3H), 4.68 (br d, $J = 9.5$ Hz, 1H), 5.72−5.79 (m, 2H), 6.15 (dd, $J = 8$, 2 Hz, 1H); ^{13}C NMR δ 13.67, 16.80, 21.13, 29.77, 37.38, 44.86, 55.03, 106.89, 113.38, 120.40, 129.07, 156.58, 219.50; HRMS (EI) calcd for $C_{15}H_{20}O_2$ 232.1463 (M^+) found 232.1462; EIMS *m/z* (rel int) 232 (M^+, 13), 217 (17), 189 (16), 175 (17), 161 (76), 134 (base). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.32; H, 8.83.

***trans*-(3*R**,8a*S**)-3,8a-Dihydro-3-*tert*-butyl-6-methoxy-8a-methylazulen-1(2*H*)-one (25) and *cis*-(3*R**,8a*R**)-3,8a-Dihydro-3-*tert*-butyl-6-methoxy-8a-methylazulen-1(2*H*)-one (26).** This was prepared following the procedure described for **20**, from 2-diazo-5-(4′-methoxyphenyl)-6,6-dimethylheptan-3-one **16** (102 mg, 3.71×10^{-4} mol) and rhodium(II) acetate (0.5 mg). The efficiency of the cyclization (90%) and the diastereomeric ratio of the *azulenones* formed were estimated: diastereomeric ratio, *trans*-**25**/*cis*-**26**, 98:2. Purification by flash chromatography, with gradient ethyl acetate−hexane as eluant, gave a mixture of the diastereomers of the *azulenones* **25**, **26** (66 mg, 72%) as a colorless oil. The diastereomeric ratio was estimated as *trans*-**25**/*cis*-**26**, >98:2: IR (film) 1746, 1713, 1645 cm^{-1}.

Spectral details for *trans*-**25**: ^1H NMR (300 MHz) δ 0.74 (s, 3H), 0.86 (s, 9H), 2.18 (dd, $J = 18$, 8 Hz, 1H), 2.43 (dd, $J = 18$, 9 Hz, 1H), 2.61 (dd, $J = 9$, 8 Hz, 1H), 3.62 (s, 3H), 3.75−3.87 (br d, 1H), 5.34 (d, $J = 8$ Hz, 1H), 5.85 (dd, $J = 9$, 2 Hz, 1H), 6.10 (d, $J = 9$ Hz, 1H); ^{13}C NMR (75.47 MHz) δ 9.22, 27.81, 33.83, 36.84, 49.54, 54.53, 102.59, 114.35, 122.15, 156.70, 217.75. Selected spectral details for *cis*-**26**: ^1H δ 0.98 (s, 9H), 3.76 (s, 3H), 5.26 (d, $J = 11$ Hz, 1H), 5.72−5.76 (m, 1H), 5.99−6.04 (m, 1H), 6.31 (d, $J = 7$ Hz, 1H); EIMS *m/z* (rel int) 246 (M^+, 50), 231 (32), 189 (55), 105 (base). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.72; H, 9.08.

***trans*-(3*R**,8a*R**)-3,8a-Dihydro-3,8a-dimethylazulen-1(2*H*)-one and *cis*-(3*R**,8a*S**)-3,8a-dihydro-3,8a-dimethylazulen-1(2*H*)-one (33).** This was prepared following the procedure described for **20** from 2-diazo-5-phenylhexan-3-one **27** (100 mg, 4.95×10^{-4} mol) and rhodium(II) acetate (0.5 mg). A ^1H NMR spectrum was recorded to determine the efficiency of the cyclization (~86%) and the diastereomeric ratio of the *azulenones* **33** formed: diastereomeric ratio, trans/cis 8:1. Purification by flash chromatography, with gradient ethyl acetate−hexane as eluant, gave a mixture of the diastereomers of the *azulenones* **33** (75 mg, 87%) as a colorless oil. The diastereomeric ratio was estimated as trans/cis, 7:1: IR (film) 1748, 1715 cm^{-1}.

Spectral details for *trans*-**33**: ^1H NMR δ 0.72 (s, 3H), 1.10 (d, $J = 7$ Hz, 3H), 1.90 (dd, $J = 18$, 9 Hz, 1H), 2.52 (dd, $J = 18$, 9 Hz, 1H), 2.78−2.97 (m, 1H), 3.75 (d, $J = 7$ Hz, 1H), 6.05−6.19 (m, 2H), 6.25−6.42 (m, 2H); ^{13}C NMR δ10.62, 19.53, 34.03, 42.74, 122.94, 125.20, 126.68, 127.80, 218.21. Spectral details for *cis*-**33**: ^1H NMR δ 0.82 (s, 3H), 1.31 (d, $J = 7$ Hz, 3H), 4.69 (d, $J = 7$ Hz, 1H); EIMS *m/z* (rel int) 174 (M^+, 30), 159 (22), 131 (75), 44 (base). Anal. Calcd for $C_{12}H_{14}O$: C, 82.76; H, 8.05. Found: C, 82.40; H, 8.36.

Diels−Alder Adduct (40). A solution of *trans*-(3*R**,8a*R**)-3,8a-dihydro-6-methoxy-3,8a-dimethylazulen-1(2*H*)-one **21**, *cis*-(3*R**,8a*S**)-3,8a-dihydro-6-methoxy-3,8a-dimethylazulen-1(2*H*)-one **22** (**21**/**22** 4:1) (121 mg, 5.93×10^{-4} mol), and *N*-phenylmaleimide (103 mg, 5.93×10^{-4} mol) in ethyl acetate (5 mL) was refluxed for 16 h. The solvent was removed under reduced pressure. Excess dienophile and aromatic impurities were removed by trituration with ether. Recrystallization from ethanol−dichloromethane gave the *adduct* **40** (101 mg, 45%) as a colorless solid: mp 189−191 °C; IR (KBr) 1710, 1649 cm^{-1}; ^1H NMR δ 1.18 (d, $J = 7$ Hz, 3H), 1.23 (s, 3H), 1.35 (d, $J = 4$ Hz, 1H), 1.77−1.93 (m, 1H), 2.33−2.49 (m, 2H), 3.22 (dd, $J = 8$, 4 Hz, 1H), 3.37 (dd, $J = 8$, 4 Hz, 1H), 3.42−3.53 (4H, m), 3.77 (dd, $J = 8$, 3 Hz, 1H), 4.68 (dd, $J = 7$, 3 Hz, 1H), 7.09−7.23 (m, 2H), 7.33−7.54 (m, 3H); ^{13}C NMR δ 8.91, 20.11, 30.11, 31.41, 33.76, 38.62, 39.15, 42.14, 44.63, 45.22, 46.92, 55.03, 92.47, 126.26, 128.64, 129.16, 131.84, 156.92, 175.66, 177.00, 213.56; HRMS (EI) calcd for $C_{23}H_{23}NO_4$ 377.1627 (M^+) found 377.1626; EIMS *m/z* (rel int) 377 (M^+, base), 362 (7), 255 (18), 230 (15), 204 (20), 189 (30). Anal. Calcd for $C_{23}H_{23}NO_4$: C, 73.19; H, 6.14; N 3.71. Found: C, 73.55; H, 5.88; N, 3.61.

Crystal for X-ray crystallography grown from ethanol−dichloromethane.

Diels−Alder Adduct (41). This was prepared following the procedure outlined for the preparation of **40** from *trans*-(3*R**,-8a*S**)-3,8a-dihydro-3-isopropyl-6-methoxy-8a-methylazulen-1(2*H*)-one **23**, *cis*-(3*R**,8a*R**)-3,8a-dihydro-3-isopropyl-6-methoxy-8a-methylazulen-1(2*H*)-one **24** (**23**/**24** 80:20) (69 mg, 2.97×10^{-4} mol) and *N*-phenylmaleimide (52 mg, 2.99×10^{-4} mol) in ethyl acetate (5 mL). Recrystallization from ethanol−dichloromethane gave the *adduct* **41** (38 mg, 32%) as a colorless solid: mp 229−230 °C; IR (KBr) 1713, 1651 cm^{-1}; ^1H NMR δ 0.68 (d, $J = 7$ Hz, 3H), 0.94 (d, $J = 7$ Hz, 3H), 1.18 (d, $J = 4$ Hz, 1H), 1.23 (s, 3H), 2.04−2.22 (m, 2H), 2.25−2.42 (m, 2H), 3.21 (dd, $J = 8$, 4 Hz, 1H), 3.36 (dd, $J = 8$, 4 Hz, 1H), 3.42−3.57 (4H, m), 3.75 (dd, $J = 7$, 3 Hz, 1H), 4.68 (dd, $J = 7$, 4 Hz, 1H), 7.10−7.22 (m, 2H), 7.33−7.54 (m, 3H); ^{13}C NMR δ 8.72, 14.71, 20.56, 28.21, 30.12, 33.45, 34.20, 38.53, 39.87, 40.70, 44.11, 44.51, 45.02, 54.87, 92.26, 126.20, 128.47, 129.02, 131.92, 157.07, 175.42, 176.88, 213.77; HRMS (EI) calcd for $C_{25}H_{27}NO_4$ 405.1940 (M^+), found 405.1941; EIMS *m/z* (rel int) 405 (M^+, 1), 362 (1), 327 (1), 173 (base). Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.06; H, 6.70; N, 3.60. Found: C, 73.97; H, 6.98; N, 3.60.

Diels−Alder Adduct (42). A solution of *trans*-(3*R**,8a*S**)-3,8a-dihydro-3-*tert*-butyl-6-methoxy-8a-methylazulen-1(2*H*)-one **25**, *cis*-(3*R**,8a*R**)-3,8a-dihydro-3-*tert*-butyl-6-methoxy-8a-methyl azulen-1(2*H*)-one **26**, **25**/**26** >98:2 (86 mg, 3.49×10^{-4} mol), and *N*-phenylmaleimide (121 mg, 6.97×10^{-4} mol) in chloroform (1 mL) was refluxed for 6 days. The solvent was removed under reduced pressure. Purification by flash chromatography, with gradient ethyl acetate−hexane as eluant gave the *adduct* **42** (111 mg, 76%) as a colorless solid: mp 98−100 °C dec; IR (KBr) 1775, 1714, 1655 cm^{-1}; ^1H NMR (300 MHz) δ 1.07 (s, 9H), 1.21−1.26 (m, 4H), 2.18−2.26 (m, 3H), 3.24 (dd, $J = 8$, 3 Hz, 1H), 3.43−3.51 (m, 5H), 4.18 (dd, $J = 7$, 3 Hz, 1H), 4.65 (dd, $J = 8$, 3 Hz, 1H), 7.15 (d, $J = 7$ Hz, 2H), 7.33−7.49 (m, 3H); ^{13}C NMR (75.47 MHz) δ 8.91, 28.81, 32.07, 34.28, 35.62, 37.41, 38.02, 40.09, 44.30, 45.05, 46.37, 55.01, 92.53, 126.17, 128.60, 129.13, 131.74, 156.86, 175.77, 176.94, 214.20; EIMS *m/z* (rel int) 419 (M^+, 25), 362 (20), 256 (18), 215 (20), 57 (base). Anal. Calcd for $C_{26}H_{29}NO_4$: C, 74.44; H, 6.97; N, 3.34. Found: C, 74.33; H, 6.70; N, 3.90.

Crystal for X-ray crystallography grown from ethanol−dichloromethane.

3,8a-Dihydro-4-methoxy-8a-methylazulen-1(2*H*)-one (43) and 3,8a-Dihydro-8-methoxy-8a-methylazulen-1(2*H*)-one (44). (a) This was prepared following the procedure described for **20**, from 2-diazo-5-(2′-methoxyphenyl)pentan-3-one **17** (100 mg, 4.59×10^{-4} mol) and rhodium(II) perfluorobutyrate (0.5 mg). The efficiency of the cyclization (80%) and the ratio of

the *azulenones* formed were estimated: **43**/**44** 70:30 (by comparison of the ^{1}H NMR integration for OC*H*$_3$ **43** and **44**). Purification by flash chromatography, with gradient ethyl acetate−hexane as eluant, gave the *azulenones* **43**, **44** (51 mg, 58%) as a colorless oil. The ratio of the two *azulenones* was estimated as **43**/**44** 63:37: IR (film) 1753 (w), 1714 cm^{-1}.

(b) This reaction was conducted as above except the reaction temperature was 0 °C. The efficiency of the cyclization (83%) and the ratio of the *azulenones* formed were estimated: **43**:**44** 90:10 and the crude sample was subjected to further spectroscopic examination.

The spectral details of the two isomers were assigned as follows. The assignment for **43** was obtained from the NMR spectra of the crude product, of the reaction carried out at 0 °C and stored in the freezer subsequently, in which this product was dominant (90%). The assignment for **44** was obtained from the NMR spectra of the purified products (reaction at reflux), ratio **43**/**44** 63:37 by subtraction of the previously identified signals for **43**.

Spectral details for **43**: ^{1}H NMR δ 0.71 (s, 3H), 1.83−2.33 (m, 3H), 2.57 (d, J = 5.1 Hz, 1H), 2.62−2.79 (m, 1H), 3.66 (s, 3H), 5.27 (d, J = 6.8 Hz, 1H), 5.58 (dd, J = 9.2, 5.1, 1H), 6.17 (dd, J = 8.6, 6.5 Hz, 1H); ^{13}C NMR δ 5.05, 22.14, 24.84, 31.51, 40.38, 45.76, 55.25, 94.27, 114.88, 126.21, 156.17, 217.27. Selected spectral details for **44**: ^{1}H NMR δ 0.76 (s, 3H), 2.45−2.56 (m, 4H), 3.56 (s, 3H), 5.48 (d, J = 5 Hz, 1H), 6.25−6.35 (m, 3H); ^{13}C NMR δ 12.92, 27.04, 37.89, 56.61, 96.93, 120.97, 122.47, 124.73, 157.49; HRMS (EI) calcd for $C_{12}H_{14}O_2$ 190.0994 (M^+) found 190.0995; EIMS *m*/*z* (rel int) 190 (M^+, 34), 148 (52), 121 (62), 91 (base). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.77; H, 7.40. Found C, 75.41; H, 7.62.

***trans*-(3*R**,8a*S**)-3,8a-Dihydro-3-isopropyl-4-methoxy-8a-methylazulen-1(2*H*)-one (45) and *cis*-(3*R**,8a*R**)-3,8a-Dihydro-isopropyl-8-methoxy-8a-methylazulen-1(2*H*)-one (46).** This was prepared following the procedure described for **20**, from 2-diazo-5-(2′-methoxyphenyl)-6-methyl-heptan-3-one **18** (100 mg, 3.85 × 10^{-4} mol) and rhodium(II) acetate (0.5 mg). The efficiency of the cyclization (90%) and the ratio of the *azulenones* formed were estimated: **45**/**46** 80:20. Purification by flash chromatography, with gradient ethyl acetate−hexane as eluant, gave the *azulenones* **45**, **46** (52 mg, 58%) as a colorless oil. The ratio of the two *azulenones* was estimated as **45**/**46**, 74:26: IR (film) 1714 cm^{-1}. The sample was stored in the freezer (∼−20 °C) for 1 year, and the ^{1}H and ^{13}C NMR were again recorded. The ratio of the two *azulenones* was estimated as **45**:**46**, >96:4. The spectral characteristics for **45** have been obtained from these spectra and those of **46** from the original ca. 3:1 mixture. Spectral details for **45**: ^{1}H NMR δ 0.69 (s, 3H), 0.85 (d, J = 7, 3H), 0.86 (d, J = 7, 3H), 1.44−1.61 (m, 1H), 1.81 (dd, J = 18, 9 Hz, 1H), 2.33 (dd, J = 18, 10 Hz, 1H), 2.61 (d, J = 5.1 Hz, 1H), 2.70−2.88 (m, 2H), 3.65 (s, 3H), 5.22 (d, J = 6.8 Hz, 1H), 5.57 (dd, J = 9.3, 5.1 Hz, 1H), 6.15 (dd, J = 9.1, 6.7 Hz, 1H); ^{13}C NMR δ 4.92, 20.64, 21.09, 25.51, 32.33, 37.23, 37.60, 40.71, 47.52, 57.80, 93.85, 114.46, 126.29, 157.07, 216.96. Spectral details for **46**: ^{1}H NMR δ 0.76 (s, 3H), 0.90 (d, J = 7, 3H), 0.98 (d, J = 7, 3H), 3.56 (s, 3H), 5.43−5.52 (m, 1H), 6.25−6.35 (m, 3H); ^{13}C NMR δ 13.00, 18.20, 33.31, 41.41, 47.20, 56.70, 97.10, 122.51, 122.53, 124.60; HRMS (EI) calcd for $C_{15}H_{20}O_2$ 232.1463 (M^+), found 232.1465; EIMS *m*/*z* (rel int) 232 (M^+, 73), 215 (27), 189 (18), 162 (69), 119 (74), 84 (base). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.62; H, 8.65.

8-Methoxy-3,8a-dihydroazulen-1(2*H*)-one (2) and 4-Methoxy-3,8a-dihydroazulen-1(2*H*)-one (4).[4−6] This was prepared following the procedure described for **20**, from 1-diazo-4-(2′-methoxyphenyl)-butan-2-one **1** (100 mg, 4.90 × 10^{-4} mol) and rhodium(II) acetate (0.5 mg). The ratio of the *azulenones* formed was estimated: **2**/**4** 2.3:1. The crude product, a clear oil, was sufficiently pure to use without chromatography. Spectral details for the major regioisomer **2**: ^{1}H NMR δ 2.50−2.71 (m, 3H), 2.81−3.01 (br t, J = 9, 2H), 3.59 (s, 3H), 5.41 (d, J = 6, 1H), 6.09−6.22 (m, 1H), 6.26−6.42 (m, 2H); ^{13}C NMR δ 27.00, 38.92, 53.73, 56.37, 96.97, 120.95, 124.31, 126.52, 132.67, 145.76, 213.82. Spectral details for the minor regioisomer **4**: ^{1}H NMR δ 1.33 (br s, 1H), 2.04−2.37 (m, 2H), 3.40 (br s, 1H), 3.66 (s, 3H), 5.50 (d, J = 6, 1H), 5.90 (dd, J = 8, 6, 1H); ^{13}C NMR δ 27.87, 33.76, 55.01, 104.34, 110.12, 120.05, 126.38, 216.14.

An ether (15 mL) solution of the crude reaction mixture (15 mg) was treated with 1 drop of trifluoroacetic acid for 10 min. The solution was then washed with sodium hydrogen carbonate (10%, 10 mL) and worked up in the normal manner. A ^{1}H NMR spectrum was recorded which indicated that the product of the reaction was the *azulenones* **2**, **4** in the ratio **2**/**4** 97:3.

3,4-Dihydro-5-methoxynaphthalene-2(1*H*)-one (5).[4−6] A dichloromethane (15 mL) solution of the crude reaction mixture of **2** and **4** (15 mg) was treated with 1 drop of trifluoroacetic acid for 10 min, washed with aqueous sodium hydrogen carbonate, and worked up in the normal manner to give **5** (15 mg, 100%) as a clear oil: ^{1}H NMR δ 2.51 (t, J = 7, 2H), 3.08 (t, J = 7, 2H), 3.56 (s, 1H), 3.85 (s, 3H), 6.75 (dd, J = 14, 7, 2H), 7.18 (dd, J = 7, 7, 1H).

3,4-Dihydro-1-methyl-6-methoxynaphthalene-2(1*H*)-one (47). 2-Diazo-5-(3′-methoxyphenyl)pentan-3-one **19** (100 mg, 4.59 × 10^{-4} mol) in CH_2Cl_2 (100 mL) was added dropwise over 1 h to a refluxing solution of rhodium(II) perfluorobutyrate (0.5 mg) in CH_2Cl_2 (150 mL). Evaporation of the solvent at reduced pressure gave the product as a yellow oil. A ^{1}H NMR spectrum of the crude product was recorded to determine the efficiency of the reaction and indicated the absence of the *azulenone*. Purification by flash chromatography, with gradient ethyl acetate−hexane as eluant, gave the *tetralone* **47** (57 mg, 65%) as a colorless oil: IR (film) 1714, 1609 cm^{-1}; ^{1}H NMR δ 1.45 (d, J = 7, 3H), 2.42−2.70 (m, 2H), 2.93−3.16 (m, 2H), 3.47 (q, J = 7, 1H), 3.81 (s, 3H), 6.72−6.85 (m, 2H), 7.06−7.17 (m, 1H); ^{13}C NMR δ 14.65, 28.38, 37.58, 46.74, 55.36, 112.38, 113.33, 128.27, 130.20, 138.01, 158.53, 212.27.

Crystal data for **40**: $C_{23}H_{23}NO_4$, 377.42, colorless hexagonal plate 0.42 × 0.27 × 0.16 mm, monoclinic, $P2_1/c$, a = 10.0820(16) Å, b = 18.328(3) Å, c = 10.455(3) Å, β = 95.164(16)°, U = 1924.1(6) Å^3, Z = 4, T = 293 K, θ_{max} = 24.92°, Nonius MACH-3 diffractometer, Mo Kα radiation (λ = 0.710 73 Å), R (on F, 1563 reflections with $I > 2(\sigma)I$) = 0.068, $wR2$ (on F^2, all 3368 unique reflections) = 0.174, gof (F^2) = 1.13, 256 parameters.

Crystal data for **42**: $C_{26}H_{29}NO_4$, 419.50, colorless column 0.30 × 0.12 × 0.10 mm, monoclinic, $P2_1/c$, a = 8.8062(7) Å, b = 22.772(2) Å, c = 10.9663(9) Å, β = 95.080(2)°, U = 2190.5(3) Å^3, Z = 4, T = 150 K, θ_{max} = 28.65°, Bruker SMART1000 diffractometer, Mo Kα radiation (λ = 0.710 73 Å), R (on F, 3093 reflections with $I > 2(\sigma)I$) = 0.041, $wR2$ (on F^2, all 5139 unique reflections) = 0.093, gof (F^2) = 0.874, 285 parameters.

The X-ray data for compounds **40** and **42** have been deposited with the Cambridge Crystallographic Data Centre. The data can be obtained, upon request, from the Director, Cambridge Crystallographic Data Centre. The deposition numbers are CCDC 162992 and 162993.

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Supporting Information Available: Detailed spectral assignments for each of the compounds. ORTEP diagrams (Figures S1−2) for **40** and **42**, and NMR spectra for **15**, **16**, **18**−**20**, **21/22**, **42,** and **47**. This material is available free of charge via the Internet at http://pubs.acs.org.

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