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π-Facial selectivities and proximal/distal regioselectivities in Diels–Alder reactions of unsymmetrical, cage-annulated 1,3-cyclohexadienes

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Abstract—Diels–Alder cycloaddition of hexacyclo[7.5.1.0^{1,6}.0^{6,13}.0^{8,12}.0^{10,14}]pentadeca-2,4-diene-7,15-dione (**1**) to ethyl propiolate proceeds with π-facial selectivity to afford two cycloadducts, **4b** and **5b** (product ratio: **4b/5b**=80:20). Thermal [4+2] cycloaddition of hexacyclo[7.5.2.0^{1,6}.0^{6,13}.0^{8,12}.0^{10,14}]hexadeca-2,4-diene-7,16-dione (**2**) to ethyl propiolate affords two isomeric cycloadducts, i.e. **6c** and **6d** (product ratio: **6c/6d**=40:60). Cycloadducts **6c** and **6d** are formed with a high degree of *endo* π-facial selectivity but with only modest proximal/distal regioselectivity. The corresponding [4+2] cycloaddition of **2** (diene) to dimethyl acetylenedicarboxylate (dienophile) produced a single cycloadduct, **7b**. These observations have been further examined by employing Hartree–Fock relative energies of transition states presumably formed enroute to the various products. Interestingly, filled orbital electrostatic repulsion between the incoming dienophile and the C=O groups in the diene substrate does not appear to be a significant factor that might influence π-facial selection in this [4+2] cycloaddition. Finally, thermal [4+2] cycloaddition of cyclopentadiene (diene) to dienophile **3** proceeded with a high degree of π-facial selectivity to afford a single cycloadduct, **9b**.

1. Introduction

Elucidation of stereoelectronic effects on π-facial diastereoselection in Diels–Alder reactions and control of regioselection in [4+2] cycloadditions to cyclic dienes have received considerable attention from mechanistic and synthetic organic chemists in recent years.[1,2] Constrained, cage-annulated cyclohexa-1,3-dienes (e.g. functionalized hexacyclo[7.5.1.0^{1,6}.0^{6,13}-.0^{8,12}.0^{10,14}]pentadeca-2,4-dienes of the type **1**, Scheme 1) in which conformational ambiguities are minimized have received particular attention as substrates in Diels–Alder reactions of this type.[1,2] The stereoselectivities observed in cycloadducts formed via [4+2] cycloadditions between dienes of the type **1** and a wide variety of olefinic and acetylenic dienophiles have been rationalized in terms of a combination of steric and electronic effects. As part of a continuing program designed to explore the origins of π-facial selectivity and regioselectivity in constrained, cage-annulated cyclohexa-1,3-dienes,[2a,d] we now report the results of experimental and theoretical investigations of Diels–Alder cycloadditions of **1** and a homologous cage-annulated diene (**2**)[3] with ethyl propiolate. In addition, we examined the Diels–Alder reaction of dimethyl acetylenedicarboxlate (DMAD) to **2**. As an extension of these studies, the Diels–Alder reaction of cyclopendiene with **1** was examined.[2d,5] We now report the results of a corresponding study of the thermal [4+2] cycloaddition of cyclopentadiene to 3-carbethoxyl-4-hydroxyhexacyclo[11.2.1.0^{2,12}.0^{5,10}.0^{5,15}0^{10,14}]hexadecane-11-one (**3**, Scheme 2).[4]

2. Experimental results

Diels–Alder reactions of **1** and **2** with ethyl propiolate were performed by refluxing equimolar solutions of the diene and dienophile in toluene for 6 and 5 days, respectively. The former reaction proceeded with π-facial selectivity to afford a mixture of two isomeric cycloadducts, i.e. **4b** and **5b** (Scheme 1; product ratio: **4b/5b**=80:20).

Based on the fact that the corresponding reaction of **1** with methyl propiolate has been reported to proceed with complete π-facial specificity to afford **4a**,[1c] the structure of the major product of Diels–Alder reaction of **1** with ethyl propiolate was assigned structure **4b** (Scheme 1).

Keywords: electrostatic repulsion; cycloadduct; π-facial selection.
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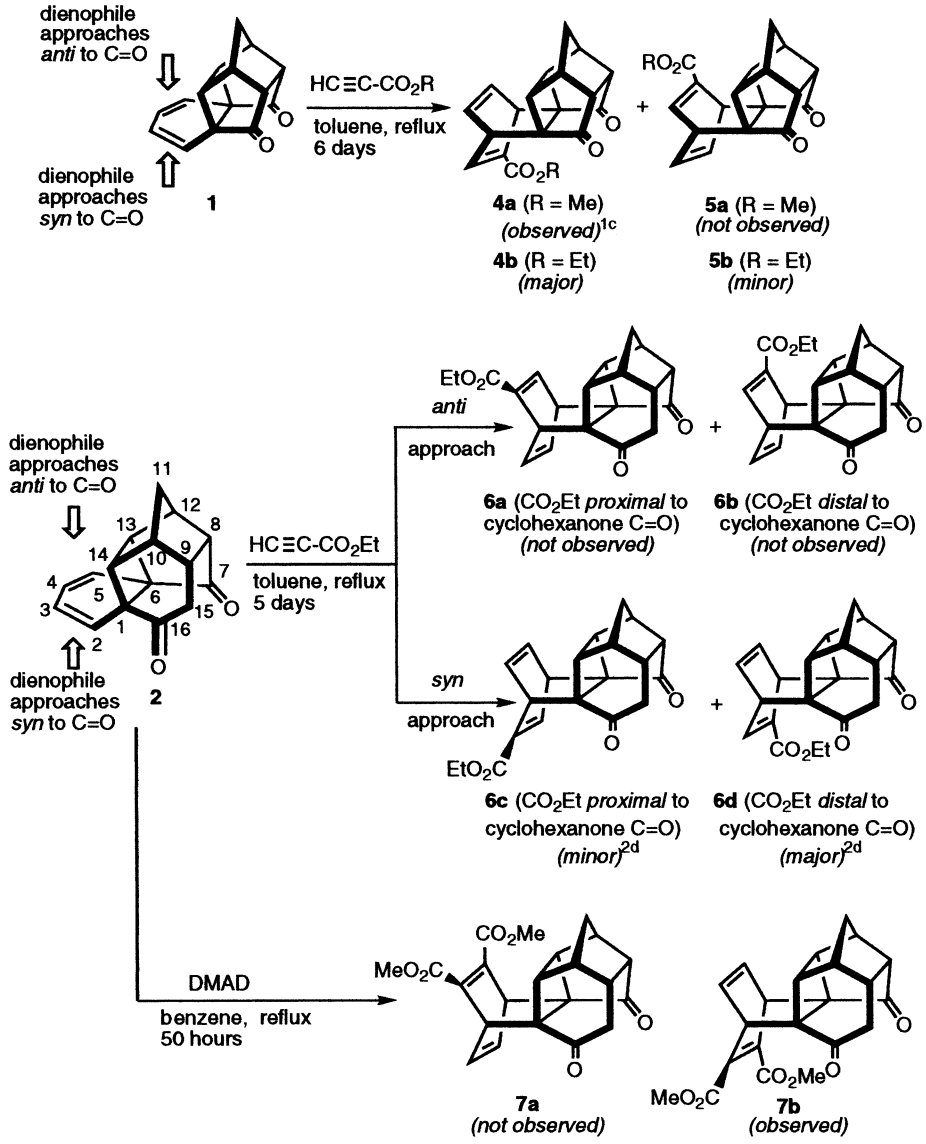


Scheme 1.

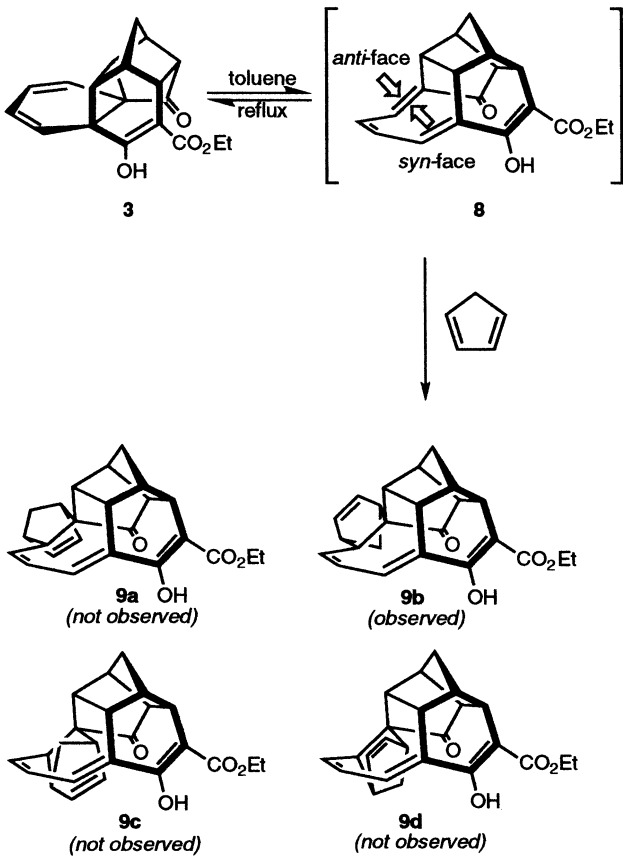
This conclusion is reinforced by the results of quantum chemical calculations (vide infra). It should be noted that the products **4a**, **4b**, (**5a**) and **5b** are obtained as racemic mixtures.

The corresponding reaction of **2** with ethyl propiolate proved to be π-facially specific. Thus, [4+2] cycloaddition proceeds via exclusive approach of the dienophile toward the *endo*face of the diene moiety to afford only two of four possible isomeric cycloadducts (i.e. **6c** and **6d**, Scheme 1). However, in contrast to the observed *syn* π-facial specificity, the *proximal*/*distal* selectivity of this cycloaddition reaction was modest (product ratio: **6c**/**6d**=40:60). The structures of the two cycloadducts thereby obtained (**6c** and **6d**) were established unequivocally by application of single crystal X-ray crystallographic methods (vide infra).

Thermal reaction of **2** with DMAD proceeds with a high degree of π-facial selectivity to afford a single [4+2] cycloadduct, **7b** (35% yield, Scheme 1). The cycloaddition occurs via preferential attack of the dienophile upon the '*syn*-face' of the diene π-system. This cycloaddition proceeds in accordance with the Alder–Stein rule.[6] The observed preferential mode of approach of the dienophile upon the *syn*-face of the diene moiety is closely analogous to the previously observed facial selectivity that accompanies Diels–Alder cycloadditions of cyclic and acyclic dienophiles to **1**.[1c–e,j,4b,7]

Compound **3** was heated with cyclopentadiene to promote thermal [4+2] cycloaddition. A single 1:1 cycloadduct, **9b** (Scheme 2), was isolated from this reaction in 80% yield. The structure of **9b** was established unequivocally via application of X-ray crystallographic methods.

Interestingly, cycloadduct **9b** appears to have been formed in a manner that is closely analogous to the corresponding [4+2] cycloaddition of cyclopentadiene to **1**.[5] Thus, under the conditions employed to promote reaction, disrotatory six-electon electrocyclic ring opening of **3** occurs to afford **8**, which subsequently is trapped in situ by cyclopentadiene to produce **9b**. The [4+2] cycloaddition



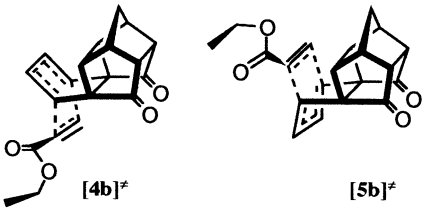
Scheme 2.

proceeds selectively; preferential attack of cyclopentadiene (diene) occurs at only one of the three C=C double bonds in the hexatriene π-system in **8** (dienophile). The diene also proceeds via exclusive attack upon the '*anti*-face' of the dienophile π-system (see Scheme 2), thereby affording the corresponding *endo* cycloadduct, **9b**, in a manner, once again, that is consistent with predictions based upon consideration of the familiar Alder–Stein rule.[6]

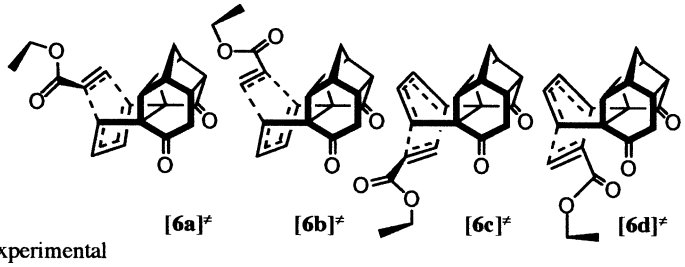
3. Results of quantum chemical calculations

As noted above, Diels–Alder cycloaddition of diene **1** with ethyl propiolate proceeds with some degree of *syn* π-facial selectivity to afford two [4+2] cycloadducts, i.e. **4b** and **5b**. Single-point energy calculations have been performed at the Hartree–Fock level of theory with the 3-21G basis set on AM1[8] and PM3[9] optimized geometries for transition states $[\mathbf{4b}]^{\neq}$ and $[\mathbf{5b}]^{\neq}$, which lead presumably to the formation of **4b** and **5b**, respectively. The results thereby obtained, shown in Table 1, indicate a clear energetic preference for approach by the dienophile (ethyl propiolate) toward the *syn* face of diene **1**. This observation is in qualitative agreement with experiment. Insight into the nature of thermal cycloaddition of **2** to ethyl propiolate is also provided by the computational results. Inspection of the HF/3-21G//AM1 results shown in Table 1 indicate that all four calculated transition states (i.e. $[\mathbf{6a}]^{\neq}$–$[\mathbf{6d}]^{\neq}$) are in qualitative agreement with experiment. The computational results indicate a clear kinetic preference for approach by the dienophile (ethyl propiolate) toward the *syn* face of diene **2**. However, no clear preference is indicated for the mode of *syn* π-facial approach by the dienophile that results in formation of **6d**

Table 1. Calculated relative transition state energies (kcal mol^{-1}) for various modes of Diels–Alder cycloaddition of ethyl propiolate to dienes **1** and **2**



	$[\mathbf{4b}]^{\neq}$	$[\mathbf{5b}]^{\neq}$
Experimental product ratio	80	20
HF/3-21G//PM3	0.0	3.8
HF/3-21G//AM1	0.0	4.7



	$[\mathbf{6a}]^{\neq}$	$[\mathbf{6b}]^{\neq}$	$[\mathbf{6c}]^{\neq}$	$[\mathbf{6d}]^{\neq}$
Experimental product ratio	- -	- -	40	60
HF/3-21G//PM3	7.7	6.1	0.0	2.9
HF/3-21G//AM1	9.2	8.7	0.9	0.0

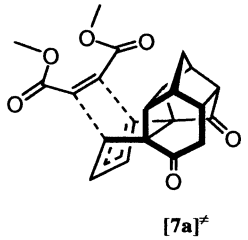
(via transition state $[\mathbf{6d}]^{\neq}$) as the major cycloadduct.[2d] Although the relative energies obtained by using PM3 optimized geometries succeed in predicting that the (unobserved) cycloadducts **6a** and **6b** are unlikely to be formed as products of this reaction, the HF/3-21G//PM3 methodology nevertheless fails to predict that **6d** is minimally preferred kinetically vis-à-vis **6c**.

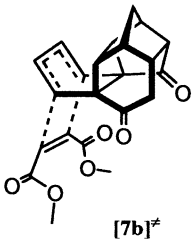
Calculated (HF/3-21G//AM1) relative energies obtained for Diels–Alder reactions that proceed via transition states $[\mathbf{6a}]^{\neq}$–$[\mathbf{6d}]^{\neq}$ have been published previously.[2d] However, the results that appear in Table 1 differ significantly from the corresponding, previously published (HF/3-21G//AM1) relative energies. In fact, the earlier semi-empirical results were obtained by using SPARTAN (version 5.0), and the single-point calculations were obtained by using a former version of Gaussian that is now known to have been improperly compiled in-house for the computer that ran the executable version of the code. The results presented in Table 1 are intended to correct those errors.[2d]

Calculated relative transition state energies for [4+2] cycloaddition of DMAD to **2** appear in Table 2. In this case, predictions based upon the computational results agree qualitatively with the experimentally observed cycloaddition pathway, which proceeds via approach of the dienophile upon the *syn* face of diene **2**, thereby affording **7b**.

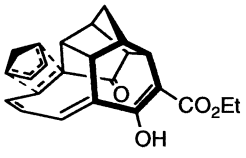
The computational results obtained for [4+2] cycloaddition of cyclopentadiene to **8** are also shown in Table 2. Only transition states $[\mathbf{9a}]^{\neq}$ and $[\mathbf{9b}]^{\neq}$, which correspond to *anti* facial attack of cyclopentadiene upon the dienophile, could be located. This result reflects the fact that the triene moiety in **8** is perturbed from its expected planar geometry by the cage system, as is the case in **3**, with the result that the triene is puckered and the π-orbitals of the dieneophile in **8** point 'inward' (*syn*-face) and 'outward' (*anti*-face). As illustrated in Scheme 2, in order to form **9c** or **9d**, cyclopentadiene must orient itself inside the triene moeity of the 11-membered ring in **8**. As a consequence, approach by cyclopentadiene toward the *syn* face of the dienophile is sterically hindered. Examination of the computational results for the energetics of transition states $[\mathbf{9a}]^{\neq}$ vs $[\mathbf{9b}]^{\neq}$ reveals that all treatments are consistent with kinetically preferred formation of **9b**.

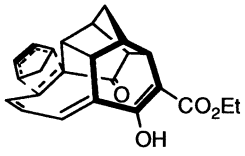
Table 2. Calculated relative transition state energies (kcal mol^{-1}) for various modes of Diels–Alder cycloaddition of cyclopentadiene to diene **3** and DMAD to diene **2**





	$[\mathbf{7a}]^{\neq}$	$[\mathbf{7b}]^{\neq}$
HF/3-21G//PM3	2.1	0.0
HF/3-21G//AM1	3.3	0.0





	$[\mathbf{9a}]^{\neq}$	$[\mathbf{9b}]^{\neq}$
HF/3-21G//PM3	7.0	0.0
HF/3-21G//AM1	3.6	0.0

4. Summary and conclusions

Diels–Alder cycloaddition of diene **1** with ethyl propiolate proceeds with a high degree of *syn* π-facial selectivity to afford two [4+2] cycloadducts, i.e. **4b** and **5b** (product ratio: **4b/5b**=80:20). The corresponding cycloaddition of diene **2** with ethyl propiolate proceeds with a high degree of *syn* π-facial selectivity but with only modest proximal/distal regioselectivity. Diels–Alder cycloaddition of **2** with DMAD proceeds with exclusive addition to the *syn* face to afford **7b**. Cyclopentadiene reacts with **8**, a reaction intermediate that is produced via thermal electrocyclic ring-opening of **3**, via exclusive approach toward the *anti* face of **8** to produce **9b**. In this example, approach by cyclopentadiene toward the *syn* face of **8** is hindered due to the conformational effects of ring strain imposed by the cage in **8** upon the conjugated triene system. The relative energies obtained from Hartree–Fock single-point calculations with the 3-21G basis set and geometries that correspond to transition state optimizations performed with AM1 correctly model the formation of the experimentally observed Diels–Alder cycloadducts. The results based on PM3 geometry optimizations were slightly less successful.

5. Experimental

5.1. General

Melting points are uncorrected. Proton and ^{13}C NMR spectra were obtained at 200 MHz by using a Varian Gemini-200 FT-NMR spectrometer. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

5.1.1. Thermal reaction of 1 with ethyl propiolate. To a solution of diketone **1** (250 mg, 1.11 mmol) in toluene (20 mL) was added ethyl propiolate (164 mg, 1.67 mmol), and the resulting solution was refluxed for 6 days. The reaction mixture was allowed to cool to ambient temperature and then was concentrated in vacuo. The residue was further purified via flash column chromatography on silica gel by eluting with 20% EtOAc/hexane. Pure **5b** (50 mg, 15%) was thereby obtained as a colorless microcrystalline solid: mp 139–141°C; IR ($CHCl_3$) 2974 (m), 1741 (s), 1701 (s), 1253 (s), 1082 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J=6.9 Hz, 3H), 1.94 (dd, J_{AB}=10.0 Hz, 2H), 2.42–2.71 (m, 5H), 2.90 (s, 1H), 3.61 (t, J=5.2 Hz, 1H), 4.02–4.35 (m, 3H). 6.52 (t, J=6.2 Hz, 1H), 6.63 (t, J=6.2 Hz, 1H), 7.50 (d, J=6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3 (q), 37.1 (d), 37.7 (d), 39.9

(d), 40.2 (d), 41.7 (t), 43.9 (d), 44.0 (d), 53.9 (d), 54.3 (d), 60.3 (s), 60.7 (t), 61.2 (s), 132.9 (d), 134.4 (d), 139.9 (s), 144.8 (d), 164.7 (s), 210.6 (s), 210.8 (s). Anal. calcd for $C_{20}H_{18}O_4$: C, 74.52: H, 5.63. Found: C, 74.36; H, 5.70.

Continued elution of the chromatography column afforded a second cycloadduct, i.e. **4b** (220 mg, 61.5%), as a colorless microcrystalline solid: mp 179–180°C; IR ($CHCl_3$) 2980 (s), 1739 (s), 1710 (s), 1261 (s), 1084 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, J=7.3 Hz, 3H), 1.87 (dd, J=11.6 Hz, 2H), 2.54 (m, 5H), 2.8 (s, 1H), 3.62 (t, J=5.2 Hz, 1H), 4.01–4.22 (m, 3H). 6.43 (t, J=6.2 Hz, 1H), 6.56 (t, J=6.2 Hz, 1H), 7.32 (d, J=7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 36.9 (d), 37.9 (d), 39.9 (d), 40.0 (d), 41.7 (t), 43.9 (d), 44.0 (d), 54.2 (d, 2 C), 60.3 (s), 61.2 (s), 61.8 (t), 133.7 (d), 135.2 (d), 139.3 (s), 144.1 (d), 164.0 (s), 210.8 (s), 211.0 (s). Anal. calcd for $C_{20}H_{18}O_4$: C, 74.52: H, 5.63. Found C, 74.58; H, 5.73.

5.1.2. Thermal reaction of 2 with ethyl propiolate. To a solution of **2** (300 mg, 1.26 mmol) in toluene (20 mL) was added ethyl propiolate (200 mg, 1.89 mmol), and the resulting solution was refluxed for 5 days. The reaction mixture was allowed to cool to ambient temperature and then was concentrated in vacuo. The residue, a colorless solid (350 mg), was further purified via column chromatography on silica gel by eluting with 1:7 EtOAc/hexane. Pure **6d** (200 mg, 47.2%) was thereby obtained as a colorless microcrystalline solid: mp 202–203°C; IR ($CHCl_3$) 2966 (m), 1712 (s), 1698 (s), 1244 (s), 1234 (m), 1087 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, J=7.5 Hz, 3H), 1.62 (*A*B, J_{AB}=10.0 Hz, 1H), 1.81 (A*B*, J_{AB}=10.0 Hz, 1H), 2.24–2.89 (m, 9H), 3.94–4.32 (m, 3H). 6.45 (t, J=6.3 Hz, 1H), 6.84 (t, J=6.3 Hz, 1H), 7.53 (d, J=5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.7 (q), 39.1 (d), 39.6 (t), 40.5 (t), 40.6 (d), 41.4 (d), 42.2 (d), 43.3 (d), 43.6 (d), 44.3 (d), 54.6 (d), 60.8 (t), 63.8 (s), 64.2 (s), 131.8 (d), 136.3 (s), 141.5 (d), 149.9 (d), 164.9 (s), 210.8 (s), 216.7 (s). Anal. calcd for $C_2{}^1H_{20}O_4$: C, 74.98: H, 5.99. Found: C, 74.84; H, 6.25. The structure of **6d** was established unequivocally via application of X-ray crystallographic methods (vide infra).

Continued elution of the chromatography column afforded a second cycloadduct, i.e. **6c** (150 mg, 35.5%), as a colorless microcrystalline solid: mp 198°C; IR ($CHCl_3$) 2988 (m), 2962 (m), 1724 (s), 1707 (s), 1246 (s), 1219 (s), 1087 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, J=7.5 Hz, 3H), 1.59 (*A*B, J_{AB}=10.0 Hz, 1H), 1.78 (A*B*, J_{AB}=10.0 Hz, 1H), 2.23–2.82 (m, 9H), 4.19–4.37 (m, 3H), 6.59–6.66 (m, 2H), 7.17 (d, J=6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) 14.8 (q), 39.6 (d), 39.7 (t), 40.5 (t), 40.7 (d), 41.4 (d), 41.7 (d), 42.5 (d), 43.8 (d), 44.7 (d), 54.5 (d), 60.8 (t), 63.4 (s), 64.9 (s), 139.6 (d), 140.2 (d), 140.8 (d), 145.1 (s), 164.9 (s), 210.3 (s), 217.3 (s). Anal. calcd for $C_{21}H_{20}O_4$: C, 74.98: H, 5.99. Found: C, 75.12; H, 6.16. The structure of **6c** was established unequivocally via application of X-ray crystallographic methods (vide infra).

5.1.3. Control experiment. A solution of isomerically pure **6d** (30 mg, mp 201–203°C) in toluene-d_8 (1.5 mL) was placed in a 5 mL round-bottom flask. The flask was fitted with a small water-jacketed condenser, and the solution was refluxed for 5 days. The solution was allowed to cool, and its proton and ^{13}C NMR spectra were obtained. These spectra were found to be identical in all respects to the corresponding spectra of the sample of isomerically pure **6d** that had been used for the control experiment. The solution was concentrated in vacuo; the mp of the residue thereby obtained was found to be 200–203°C. The fact that **6d** survives prolonged heating unchanged attests to the thermal stability of **6d** under conditions that essentially duplicate the thermal reaction of **2** with ethyl propiolate by which **6c** and **6d** were synthesized.

5.1.4. Thermal reaction of 2 with DMAD. A solution of **2** (120 mg, 0.50 mmol) and DMAD (100 mg, 0.70 mmol) in dry benzene (10 mL) was refluxed for 50 h. At that time, TLC analysis of the reaction mixture revealed the absence of unreacted **2**. The reaction mixture was concentrated *in vacuo*, and the residue was purified via fractional recrystallization from $CHCl_3$/hexane. Pure **7b** (67 mg, 35%) was thereby obtained as a colorless, microcrystalline solid: mp 247–248°C; IR (KBr) 2962 (m), 1714 (s), 1639 (m), 1602 (m), 1423 (m), 1259 (m), 1055 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (*A*B, J_{AB}=10.6 Hz, 1H), 1.77 (A*B*, J_{AB}=10.6 Hz, 1H), 2.25–2.85 (m, 8H), 3.72 (s, 3H), 3.75 (s, 3H), 3.86–3.90 (m, 1H), 4.20–4.30 (m, 1H), 6.50–6.65 (m, 1H), 6.67–6.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 38.8 (t), 39.8 (d), 40.1 (t), 40.6 (d), 40.9 (d), 41.4 (d), 43.3 (d), 44.0 (d), 44.1 (d), 52.0 (d), 52.1 (s), 54.0 (s), 62.0 (s), 63.2 (s), 132.4 (d), 140.1 (s), 140.2 (d), 147.8 (s), 165.5 (s), 165.9 (s), 209.3 (s), 215.0 (s). Anal. calcd for $C_{22}H_{20}O_6$: C, 69.46; H, 5.30. Found C, 69.25; H, 5.46. The structure of **7b** was established unequivocally via application of X-ray crystallographic methods.[11]

5.1.5. Thermal reaction of 3 with cyclopentadiene. A solution of **3**[4] (600 mg, 1.93 mmol) and freshly cracked cyclopentadiene[12] (190 mg, 2.87 mmol) in dry toluene (20 mL) was refluxed for 24 h. The reaction mixture was allowed to cool gradually to ambient temperature and then was concentrated in vacuo. The residue was purified via column chromatography on silica gel by eluting with 1:6 EtOAc/hexane. Pure **9b** (550 mg, 80%) was thereby obtained as a colorless microcrystalline solid: mp 143–144°C; IR (KBr) 2964 (s), 1732 (s), 1651 (s), 1412 (w), 1303 (w), 1259 (m), 1095 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21–1.39 (m, 5H), 1.59–1.81 (m, 3H), 2.16–2.34 (m, 2H), 2.54–3.23 (m, 7H), 4.19–4.27 (q, J=7.5 Hz, 2H), 5.22–5.24 (br s, 1H), 6.02 (d, 1H), 6.23–6.44 (m, 2H), 6.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.8 (q), 36.3 (t), 41.4 (d), 41.6 (d), 43.4 (s), 44.1 (d), 44.5 (d), 46.0 (d), 47.3 (s), 49.1 (d), 53.6 (d), 55.4 (d), 61.0 (s), 71.0 (t), 98.9 (s), 130.8 (d), 135.7 (d), 136.2 (d), 136.5 (d), 138.6 (d), 140.4 (s), 164.6 (s), 172.0 (s), 220.2 (s). Anal. calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.46; H, 6.49. The structure of **9b** was established unequivocally via application of X-ray crystallographic methods (vide infra).

5.2. X-Ray structure determination of 6d (Cambridge Crystallographic Data Centre Deposition Number 164911)

X-Ray data on compound **6d** were collected at 213 K on a Bruker SMARTTM 1000 CCD-based diffractometer. A total of 1321 frames were collected at a scan width of 0.3° and an exposure time of 10 s/frame. The frames were

Table 3. X-Ray data collection and processing parameters for **6c**, **6d** and **9b**

Compound	**6c**	**6d**	**9b**
Formula	$C_{21}H_{20}O_4$	$C_{21}H_{20}O_4$	$C_{24}H_{24}O_4$
Size (mm)	$0.22\times0.24\times0.26$	$1.2\times0.18\times0.14$	$0.09\times0.22\times0.31$
Space group	*C*2/*c*	*Pna*2(1)	$P2_1/n$
a (Å)	23.761 (3)	17.4352 (17)	7.8006 (8)
b (Å)	7.8436 (8)	7.5688 (7)	12.7681 (9)
c (Å)	17.549 (2)	24.600 (2)	18.530 (1)
(α (°)	90	90	90
β (°)	102.40 (2)	90	97.019 (9)
γ (°)	90	90	90
V (Å^3)	3194.3 (7)	3246.3 (5)	1831.7 (2)
Z-value	8	8	4
D_{calc} (g cm^{-3})	1.399	1.377	1.365
μ (cm^{-1})	0.90	0.189	0.86
T (K)	293	213	293
$2\theta_{max}$ (°)	44	56.54	44
Total reflections	2184	18349	2563
Unique reflections	2088	6478	2375
R_{int}	0.055	0.0655	0.017
$I\geq3\sigma(I)$	1063	6478[a]	1614
Parameters	145	454	253
R, R_w	0.0672; 0.0676	0.0614; 0.1457	0.038; 0.040
$(\Delta/\sigma)_{max}$	<0.04	≤0.01	<0.01
ρ_{max}; ρ_{min} (eÅ^{-3})	0.31; −0.21	0.262; −0.235	0.17; −0.16

[a] Number of reflections $\geq2\sigma(I)$.

processed with the SAINT software package[13] by using a narrow-frame integration algorithm, and the structure was solved and refined by using SHELXTL.[14] An empirical absorption correction was applied. Pertinent crystal, data collection and refinement parameters are given in Table 1.

5.3. X-Ray structure determination of 6c and 9b (Cambridge Crystallographic Data Centre Deposition Numbers 167383 and 167382, respectively)

Crystal and data collection and solution details are given in Table 3. Standard procedures in our laboratory (S.G.B.) have been described previously.[15] Data were collected on an Enraf-Nonius CAD-4 diffractometer equipped with graphite-monochromated MoKα radiation (λ=0.71073 Å) and corrected for Lorentz and polarization effects and absorption (Ψ scans, correction from 0.83 to 0.99). The structures were solved by using direct methods (*SIR*)[16] and difference Fourier syntheses and were subjected to full-matrix least-squares refinement.[17] Disorder of the ethyl group was observed in **6c**; refinement of occupancy factors revealed this to be in a ratio of 3:2. In **9b**, all non-hydrogen atoms were treated with anisotropic thermal parameters, while in **6c**, only the ester group was refined in this fashion due to the paucity of data. Hydrogen atoms were located from difference maps and included in the model in idealized positions (where possible) [d_{C-H}=0.95≈, $U(H)$=1.3 U_{eq}(attached atom)] and were not refined. Scattering factors were taken from the usual source.[18] No variation of $w(F_0-F_c)$ vs F_0 or (sin θ/λ) was observed.

5.4. Computational methods

Geometry optimizations were executed separately by applying the AM1[8] and PM3[9] semi-empirical methods in Gaussian 98[10] to obtain all of the transition states reported herein. Second derivative vibrational frequency analyses were performed on stationary points to verify they are saddle points of order 1. Single-point Hartee–Fock level calculations were subsequently performed on these extrema with the 3-21G basis set.

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