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Diastereofacial Selectivity in Diels-Alder Cycloadditions of Methyl Acrylate to Facially Differentiated Unsymmetrical Cyclohexa-1,3-dienes

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Abstract: The Diels-Alder cycloadditions of methyl acrylate to the unsymmetrical hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadecadienes **1b-f** proceed with a high degree of π-facial stereoselectivity but only moderate regioselectivity. The results of fixed model transition state calculations, performed in an effort to establish the factors which control selectivity in these cycloadditions, are reported.

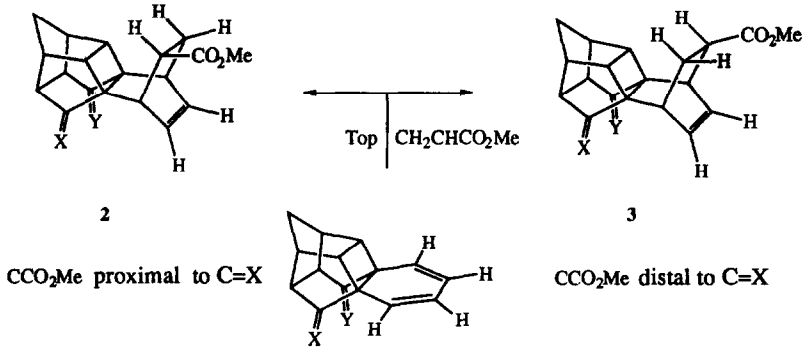
INTRODUCTION

Recent efforts in our laboratories have been concerned with (i) studies of π-facial selectivity in Diels-Alder reactions to facially differentiated 1,3-cyclohexadienes[1] and (ii) the synthesis and chemistry of novel, substituted pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes (PCUs).[2] Understanding those factors that contribute to both stereoselectivity and regioselectivity in Diels-Alder reactions is important in determining how to use and control the reaction in organic synthesis. Our previous studies[1,3] on the reaction of **1a** with symmetrical dienophiles have demonstrated that π-facial selectivity can in general be predicted by molecular mechanics calculations. In an effort to determine if such calculations are also useful in predicting regioselectivity, we have undertaken a study of the Diels-Alder cycloadditions of unsymmetrical dienophiles to facially differentiated and unsymmetrically substituted hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadecadienes **1b-f**.

SYNTHESES OF DIELS-ALDER DIENES

The starting material, **1a**, can be prepared readily in large quantity in two synthetic steps by starting with cyclopentadiene and 1,4-naphthoquinone.[3b,4] Diene **1c**, mp 128-129 °C, was prepared in 90% yield by refluxing a benzene solution of **1a** with excess ethylene glycol in the presence of a catalytic

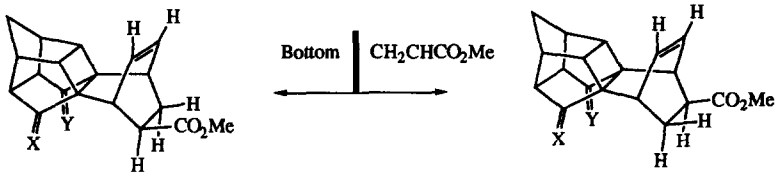
amount of *p*-TsOH.[3b] Subsequent Wolff-Kishner reduction[5] of **1c** afforded **1b** (36%, mp 53 °C). The yield of **1b** was increased to 56% by using the modified Wolff-Kishner reduction procedure developed by Paquette and coworkers.[6] Hydrolysis of **1b** with aqueous oxalic acid produced **1d** quantitatively. Reduction of **1c** and of **1d** with ethanolic $NaBH_4$ afforded **1f** and **1e**, respectively, both in essentially quantitative yield. Structural details of the dienes **1a**[7] and **1c**[8] have been elucidated by X-ray crystallographic studies and show that the diene subunits are planar.



2 **3**

1

a: X = Y = O
b: X = H_2, Y = OCH_2CH_2O
c: X = O, Y = OCH_2CH_2O
d: X = O, Y = H_2
e: X = *endo*-OH Y = H_2
f: X = *endo*-OH, Y = OCH_2CH_2O



4 **5**

RESULTS AND DISCUSSION

The results of the Diels-Alder cycloaddition reactions of dienes **1b-f** with neat methyl acrylate at 75-80 °C are presented in the Table. The structure of seven of the cycloadducts were determined unambiguously by X-ray crystallography, as will be reported elsewhere. The structures of the three remaining adducts were confirmed by NMR methods. In some cases the structures were verified by independent synthesis (see Experimental Section). The cycloadditions of methyl acrylate to **1b-f** proceed in accordance with the known preference for *endo* addition which is also consistent with obvious steric

constraints in this system **1**.[9] Thus four pathways compete. We observed that the cycloadditions take place at the bottom face of the diene π-system. This observation is consistent with earlier results obtained for corresponding Diels-Alder cycloadditions to symmetrical dienes related to **1a**.[1]

Table. Facial and regiochemistry of the addition of methyl acrylate to dienes **1**

Diene	Conditions	Yield (%)[c]	**2**[a] proximal	**3** distal	**4** proximal	**5** distal
1b	68 h	95	0 (0)	0 (0)	30 (69)	70[b] (31)
1c	68 h	72	0 (7)	0 (7)	28[b] (67)	72[b] (18)
1d	80 h	19[d]	0 (0)	0 (0)	70 (90)	30[b] (10)
1e	8 days	43	0 (0)	0 (0)	50[b] (40)	50[b] (60)
1f	7 days	42[e]	0 (0)	0 (0)	33 (32)	66[b] (68)

a experimental (calculated). *b* structure established by single crystal X-ray methods. *c* isolated yield. *d* in crude reaction mixture ca 38%. *e* recovered starting material, 49%.

In addition to "top-bottom" π-facial selectivities, the question of proximal-distal regioselectivity with respect to the C-X functionalities in the dienes must be addressed when considering cycloadditions of unsymmetrical dienophiles to unsymmetrical dienes (e.g., **1b-f**). The results of AM1[10] calculations performed on the dienes **1b-f** show little variation in the energies of the diene HOMO and LUMO. For **1e** and **1f** there is a small variation (*ca.* 0.1eV) depending on the conformation of the OH. The magnitudes of the HOMO coefficients of the diene termini provide the salient frontier orbital interaction which determined the course of the Diels Alder reaction with electron deficient dienophiles. The substituents that are β– to the diene are nearly orthogonal to the diene π-orbitals and therefore are not expected to greatly influence the symmetry of the HOMO. The results of AM1 calculations reveal that the difference between the magnitudes of the coefficients at the termini of the HOMO is not sufficient to permit frontier orbital differentiation of regiochemistry.

Nevertheless some of these reactions display significant regiochemical variation; accordingly, we have performed fixed model MM2 transition state calculations[1b] in an effort to establish the origin of the regiochemistry. The results of these calculations (see Table) successfully account for the π-facial (i.e., top-bottom) selectivity. However, for **1c,** the carbonyl and the ketal moieties provide sufficient hindrance at the transition state that top face attack is predicted to be marginally competitive with bottom face attack, a result that is not observed experimentally. The ability to predict facial selectivity is consistent with previous studies on symmetrical dienes of type **1**.[11]

The addition reactions occur with regioselectivity which can not be explained by a frontier orbital treatment. For example the regiochemistry observed for Diels-Alder reaction of methyl acrylate to **1b**

favours the bottom face product, **5b**, with the CO_2Me group proximal to the ketal functionality. This result is contrary to that which is predicted by the transition state calculations. The calculations overestimate the importance of the steric component as was found to be the case when this methodology was used to predict π-facial selectivity for [4 + 2] cycloadditions to **1c** (*vide infra*). However the experimentally observed preference for **5b** may suggest a long range attractive interaction which is not taken into account by the electrostatic interactions included in the force field terms. For the corresponding cycloaddition to **1c**, the force field does not reproduce the preference for formation of **5c**. Once again, the computational method overestimates the steric repulsion of the ketal moiety. Alternatively, this result may suggest the operation of a long range attractive interaction which is not taken into account by the electrostatic interactions included in the force-field equations.

For the corresponding cycloaddition to **1d**, the observed major product is **4d** in which the CO_2Me group is proximal to the C=O functionality. This preference is reproduced from the molecular mechanics transition state model indicating the absence of significant long range electronic effects. Thus the regiochemistry is accounted for by the steric and torsional factors inherent in the force field model.[12] The corresponding cycloaddition to **1e** proceeds with no regioselection, whereas the computational model predicts a modest preference (60:40) for formation of **5e** in which the CO_2Me group is distal to the hydroxyl group. The absence of a pronounced substituent effect by the OH group on the course of this cycloaddition reaction suggests that hydrogen bonding in the transition state is not a significant factor.

Finally, for the corresponding cycloaddition to **1f**, the major product is the cycloadduct, **5f**, in which the CO_2Me group is proximal to the ketal functionality. This result is reproduced by the transition state calculation. In this case, the force-field is better able to reproduce the steric and electrostatic balance between hydroxyl vs. ketal than was found to be the case for the corresponding balance between CH_2 *vs* ketal (as in **1b**) and between C=O *vs* ketal (as in **1c**).

SUMMARY AND CONCLUSIONS

Diels-Alder cycloadditions of methyl acrylate to the unsymmetrical hexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadecadienes **1b-f** have been studied, and in each case the resulting [4 + 2] cycloadducts have been fully characterised. The addition reactions proceed with a high degree of π-facial stereoselectivity but with only a moderate level of regioselectivity. The observed π-facial selectivity is correctly predicted from BAE distributions of the ensemble of conformations from a conformational search employing a fixed model transition state. However for **1c**, the model predicts that top face addition becomes marginally competitive and this is not reproduced in the experiment. The regioselective trends observed for bottom face addition are predicted similarly from BAE distributions of the ensemble of conformations from a conformational search employing a fixed model transition state. However, the balance of electrostatic vs. steric factors is not well reproduced for the small energy differences involved in the regioselection for the Diels Alder cycloadditions to **1b** and **1c** . Further insight into the subtle blend of steric and electronic factors which influence the regioselectivities of these Diels-Alder reactions awaits detailed theoretical analysis. Computational approaches designed to clarify these points are under way in our respective laboratories.

EXPERIMENTAL

Melting points are uncorrected. Compound **1c** was prepared via acid promoted reaction of **1a** with ethylene glycol.[8] The material thereby obtained displayed mp 132-133 °C (lit.[8] mp 132 °C). High resolution mass spectra were obtained by personnel at the Midwest Centre for Mass Spectrometry, Department of Chemistry, University of Nebraska-Lincoln, Lincoln, NE 68588.

3-[2'-(1',3'-Dioxolano)]hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene (1b). A mixture of **1c** (525 mg, 1.96 mmol), K_2CO_3 (3.3 g, 0.024 mol), diethylene glycol (30 mL) and anhydrous hydrazine (3.0 mL, 94 mmol) was heated to 140-160 °C for 3 h[6]. The temperature of the reaction mixture then was raised gradually during 1 h by distilling off low-boiling components until the temperature of the reaction mixture reached 220 °C. The reaction mixture was heated at 220 °C for 4 h and then allowed to cool gradually to room temperature. The resulting mixture was stirred at room temperature for 15 h and then poured into water (150 mL). The resulting suspension was extracted with CH_2Cl_2 (4 x 30 mL), and the combined organic layers were washed with brine (1 x 50 mL). The organic layer was dried ($MgSO_4$) and filtered, and the filtrate was concentrated *in vacuo* (40 °C, 15 mm Hg). The residue, a brown oil (632 mg) was purified via column chromatography on silica gel (45 g) by using a 0.5-10% EtOAc-hexane to 1:10 EtOAc-hexane gradient elution scheme. Pure **1b** (278 mg, 56%) was thereby obtained as a colourless microcrystalline solid: mp 53 °C; IR (KBr) 2800 (m), 1470 (w), 1330 (m), 1165 cm-1 (m); ^{1}H NMR ($CDCl_3$): δ 1.03 (dd, J = 2.8, 11.9 Hz, 1 H), 1.09 (d, J = 10.2 Hz, 1 H), 1.57 (d, J = 10.6 Hz, 1 H), 2.01-2.22 (m, 1 H), 2.33-2.58 (m, 3 H), 2.66-2.90 (m, 2H), 3.72-4.12 (m, 4 H), 5.38 (d, J = 9.5 Hz, 1 H), 5.51 (d, J = 9.6 Hz, 1 H), 5.70 (dd, J = 5.5, 9.5 Hz, 1 H), 5.82 (dd, J = 5.5, 9.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$): δ 33.61 (t), 35.92 (t), 43.41 (d), 44.79 (d), 47.05 (s), 48.74 (d), 48.90 (d), 49.63 (s), 54.37 (d), 56.07 (d), 64.45 (t), 66.58 (t), 116.8 (s), 121.4 (d), 124.2 (2 C, d), 130.4 (d). Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.27; H, 7.19. Found: C, 80.31; H, 7.09.

Hexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene-3-one (1d). To a suspension of silica gel (10 g) in CH_2Cl_2 (50 ml) was added saturated aqueous oxalic acid[13] (1 mL), and the resulting mixture was stirred vigorously at 25 °C for 15 minutes. A solution of **1c**[8] (235 mg, 0.93 mmol) in CH_2Cl_2 (8 mL) then was added, and the resulting mixture was stirred at room temperature for 21 h. Solid $NaHCO_3$ (1.5 g) was added, and the resulting mixture was stirred for 10 minutes. The reaction mixture was then filtered, and the residue was washed with CH_2Cl_2 (3 x 30 mL).The combined organic extracts were dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo* (25 °C, 15 mm Hg), thereby affording **1d** (291 mg, *ca.* 100%) as a colourless oil : IR ($CHCl_3$): 3028 (w), 2960 (sh, s), 2866 (m), 1734 cm^{-1} (sh, s); ^{1}H NMR ($CDCl_3$) δ 1.29 [d(*AB*), *J* = 10.0, 13.0 Hz, 1 H], 1.38 (*AB*, *J* = 10.5 Hz, 1 H), 1.66 (d, *J* = 13.0 Hz, 1 H), 1.78 (br d, *J* = 10.5 Hz, 1 H), 2.42 (ddd, *J* = 2.0, 4.5, 9.5 Hz, 1 H), 2.58-2.83 (m, 3 H), 2.90 (ddd, *J* = 2.0, 5.5, 8.5 Hz, 1 H), 3.12 (ddd, *J* = 1.5, 5.5, 8.5 Hz, 1 H), 5.35 (br d, *J* = 10.0 Hz, 2 H), 5.72 (dd, *J* = 5.5, 10.0 Hz, 1 H), 5.89 (br dd, *J* = 5.5, 10.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 36.44 (t), 37.58 (t), 43.46 (d), 48.60 (d), 49.34 (d), 50.26 (s), 50.80 (d), 50.91 (s), 53.16 (d), 57.25 (d), 121.1 (d), 122.2 (d), 125.0 (d), 128.4 (d), 218.8 (s). Anal. Calcd for $C_{15}H_{14}O$: M_r^+ = 210.1045. Found (high-resolution mass spectrometry): M_r^+ = 210.1042.

***endo*-10-Hydroxyhexacyclo[10.2.1.0^{2,11}.0^{4,9}.0^{4,14}.0^{9,13}]pentadeca-5,7-diene (1e).** To a cooled (0 °C, external ice-water bath) solution of **1d** (44 mg, 0.21 mmol) in EtOH (5 mL) was added with stirring

solid $NaBH_4$ (210 mg, 5.55 mmol) in one portion. The resulting mixture was stirred for 22 h, during which time the external ice-water bath gradually warmed to ambient temperature. Water (50 mL) and brine (30 mL) were then added sequentially, and the resulting aqueous suspension was extracted with CH_2Cl_2 (4 x 15 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and filtered, and the filtrate was concentrated *in vacuo*. Compound **1d** (75 mg, *ca.* 100%) was thereby obtained as a colourless oil which gradually thickened to form a gummy, semisolid mass when allowed to stand for several days at room temperature. Several attempts to recrystallise this material from hexane or from CH_3OH were unsuccessful; IR (KBr) 3400 (br, s), 2950 (s), 2850 (m), 1600 cm^{-1} (sh, w); ^1H NMR ($CDCl_3$): δ 0.90-1.08 (m, 2 H), 1.50-1.80 (m, 2 H), 2.20-2.48 (m, 3 H), 2.56 (d, J = 12.0 Hz, 1 H), 2.65 (m, 1 H), 2.80 (m, 1 H), 3.64 (br s, 1 H), 5.28 (br d, J = 9.5 Hz, 1 H), 5.38 (br d, J = 9.5 Hz, 1 H), 5.66 (br dd, J = 6.0, 10.5 Hz, 1 H), 5.85 (br dd, J = 6.0, 10.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 32.98 (t), 34.84 (t), 42.40 (d), 42.56 (d), 45.80 (d), 46.25 (s), 47.61 (s), 47.75 (d), 54.16 (d), 55.85 (d), 77.82 (d), 120.7 (d), 124.6 (d), 127.5 (d), 130.7 (d).Anal. Calcd for $C_{15}H_{16}O$: M_r^+ = 212.1201. Found (high-resolution mass spectrometry): M_r^+ = 212.1197.

Compound **1d** was further characterised via conversion into its corresponding 3,5-dinitrobenzoate derivative. Thus, to a solution of **1d** (88 mg, 0.42 mmol), in CH_2Cl_2 (4 mL) and pyridine (1 mL) was added 3,5-dinitrobenzoyl chloride (120 mg, excess) in one portion. The resulting mixture was stirred at room temperature for 2 h. The reaction mixture then was poured into 3% aqueous HCl (100 mL), and the resulting aqueous suspension was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extracts were washed successively with brine (50 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue, an orange oil (120 mg), was purified via column chromatography on silica gel (10 g) by using at 1-4% EtOAc-hexane gradient elution scheme. The 3,5-dinitrobenzoate derivative of **1d** was thereby obtained as a yellow oil (60 mg, 35%) which solidified upon trituration with hexane. Recrystallisation of the solid material thereby obtained from EtOAc-hexane afforded the pure derivative (40 mg, 24%) as a yellow microcrystalline solid: mp 170-172 °C; IR (film) 3100 (w), 2957 (m), 1724 (sh, s), 1622 (sh, w), 1546 (sh, s), 1452 (sh, w), 1345 (sh, s), 1274 (sh, s), 1159 (sh, m), 723 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 0.90 (m, 1 H), 1.11 (br d, J = 11.0 Hz, 1 H), 1.67 (br d, J = 11.0 Hz, 1 H), 2.31 (br d, J = 12.0 Hz, 1 H), 2.42-2.66 (m, 4 H), 2.77 (m, 1 H), 2.91 (m, 1 H), 5.03 (d, J = 3.5 Hz, 1 H), 5.36 (br d, J = 9.5 Hz, 1 H), 5.46 (d, J = 9.5 Hz, 1 H), 5.73 (m, 2 H), 9.09 (d, J = 2.3 Hz, 2 H), 9.19 (*t*, J = 2.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 33.18 (t), 35.75 (t), 42.46 (d), 42.73 (d), 44.30 (d), 46.15 (s), 47.14 (s), 47.85 (d) 53.23 (d), 55.82 (d), 80.29 (d), 121.1 (d), 122.2 (d), 124.2 (d), 126.1 (d), 129.4 (d), 129.7 (d), 134.34 (s), 148.7 (s), 162.7 (s). Anal. Calcd for $C_{22}H_{18}N_2O_6$: C, 65.02; H, 4.46. Found: C, 64.95; H, 4.71.

3-[2'-(1',3'-Dioxolano)]-*endo*-10-hydroxyhexacyclo[10.2.1.$0^{2,11}$.$0^{4,9}$.$0^{4,14}$.$0^{9,13}$]pentadeca-5,7-diene (1f). To a solution of **1c** (1.8 g, 6.7 mmol) and $CeCl_3 \cdot 7H_2O$ (5.00 g, 13.4 mmol) in MeOH (60 mL) was added portionwise with vigorous stirring powdered $NaBH_4$ (504 mg, 13.3 mmol).[14] After the addition of the reducing agent had been completed, the reaction mixture was stirred at ambient temperature for 2 h. The reaction was quenched via addition of water (20 mL), and the resulting aqueous suspension was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The solid residue (1.465 g, 81%) was recrystallised from MeOH to afford pure **1f** as a colourless microcrystalline solid: mp 79-80 °C; IR (KBr) 3430 (br,s), 1580 cm^{-1} (m);

^{1}H NMR ($CDCl_3$) δ 1.02 (*AB*, J_{AB} = 11.0 Hz, 1 H); 1.55 (*AB*, J_{AB} = 11.0 Hz, 1 H); 2.23 (ddd, *J* = 1.5, 4.0, 9.5 Hz, 1 H); 2.35-2.53 (m, 2 H), 2.59 (m, 1 H), 2.72 [dd(*AB*), *J* = 1.8, 5.0, 9.0 Hz, 1 H], 2.84 [dd(*AB*), *J* = 1.8, 5.0, 9.0 Hz, 1 H], 3.47 (dd, *J* = 3.8, 12.5 Hz, collapses to a d, *J* = 3 Hz, upon H-D exchange with D_2O, 1 H); 3.86-4.12 (m, 4 H); 5.35 (d, *J* = 12.5 Hz, peak disappears upon H-D exchange with D_2O, 1 H); 5.41-5.55 (m, 2 H); 5.86 dt, *J* = 3.0, 11.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 32.71 (t), 42.91 (d), 44.51 (d), 46.91 (d), 47.23 (d), 47.95 (s), 48.25 (s), 52.97 (d), 53.85 (d), 64.35 (t), 66.13 (t), 75.90 (d), 115.1 (s), 122.5 (d), 122.9 (d), 124.0 (d), 128.3 (d). Anal. Calcd for $C_{17}H_{18}O_3$: M^+ 270.1256. Found (high-resolution mass spectrometry): M+ 270.1250; Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.31. H, 6.61.

Diels-Alder Reaction of 1b with Methyl Acrylate. To a solution of **1b** (500 mg, 1.9 mmol) in methyl acrylate (10 mL, excess) was added hydroquinone (220 mg), and the resulting mixture was refluxed under argon for 68 h. The progress of the reaction was monitored via ^{1}H NMR spectroscopy performed on aliquots which were withdrawn periodically from the reaction mixture. After all of the starting material (**1b**) had reacted, the reaction mixture was cooled to ambient temperature and then was concentrated *in vacuo* to remove excess methyl acrylate. Analysis of the ^{1}H NMR spectrum of the residue indicated the presence of two Diels-Alder cycloadducts (ratio 30:70). The residue was purified via column chromatography on silica gel by eluting with 10% EtOAc-hexane. A mixture of **4b** and **5b** (482 mg, 72%) was thereby obtained. Fractional recrystallisation of this mixture from EtOAc-hexane afforded the major isomer, **5b**, as a colourless microcrystalline solid: mp 116 °C; IR (KBr) 2946 (s), 2854 (s), 1726 (m), 1448 (w), 1306 (m), 1196 (m), 1140 (m), 1035 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.02 (dd, J = 3.3, 11.6 Hz, 1 H), 1.13 (d, *J* = 9.9 Hz, 1 H), 1.52 (s, 1 H), 1.66-1.81 (m, 2 H), 1.92-2.00 (m, 2 H), 2.00-2.14 (m, 2 H), 2.20-2.32 (m, 2 H), 2.32-2.47 (m, 2 H), 3.04 (dt, *J* = 1.2, 6.4 Hz, 1 H), 3.14 (ddd, *J* = 3.0, 4.9, 9.5 Hz, 1 H), 3.63 (s, 3 H), 2.84-3.99 (m, 4 H), 6.27 (dt, *J* = 1.2, 6.4 Hz, 1 H), 6.46 (dt, *J* = 1.4, 8.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.13 (t), 31.46 (t), 33.57 (d), 35.59 (t), 36.34 (d), 37.50 (d), 41.82 (d), 42.87 (d), 43.09 (d), 44.60 (d), 47.17 (d), 48.11 (d), 50.08 (s), 50.40 (s), 51.52 (q), 63.42 (t), 65.38 (t), 116.9 (s), 131.7 (d), 135.8 (d), 176.5 (s). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.10; H, 7.11. Found: C, 73.91; H, 7.28. The structure of **5b** was also established unequivocally via application of X-ray crystallographic methods.

The remaining mother liquor was concentrated and the residue was repeatedly recrystallised from EtOAc-hexane. Pure **4b** was thereby obtained as a colourless microcrystalline solid: mp 82-83 °C; IR (film) 2950 (s), 2855 (s), 1722 (m), 1629 (m), 1448 (m), 1300 (m), 1260 (m), 1145 (m), 1035 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.05 (dd, *J* = 3.0, 11.2 Hz, 1 H), 1.11 (d, *J* = 11.0 Hz, 1 H), 1.37 (dq, *J* = 2.6, 5.7 Hz, 1 H), 1.48-1.59 (m, 1 H), 1.89-2.18 (m, 5 H), 2.22-2.45 (m, 3 H), 2.55-2.79 (m, 3 H), 2.61 (s, 3 H), 3.75-3.95 (m, 4 H), 6.28 (t, *J* = 7.4 Hz, 1 H), 6.45 (t, *J* = 7.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.43 (t), 30.87 (t), 31.52 (t), 35.63 (t), 39.09 (d), 39.23 (d), 42.02 (d), 43.08 (d), 43.25 (d), 44.25 (d), 47.20 (d), 48.18 (d), 49.82 (s), 50.96 (s), 51.58 (q), 63.47 (t), 65.40 (t), 117.0 (s), 131.9 (d), 135.8 (d), 176.5 (s). Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.10; H, 7.11. Found: C, 74.28; H, 7.33.

Diels Alder Reaction of 1c with Methyl Acrylate. To a solution of **1c** (70 mg, 0.26 mmol) in methyl acrylate (15 mL, excess) was added hydroquinone (100 mg), and the resulting mixture was refluxed under argon for 68 h. The progress of the reaction was monitored via ^{1}H NMR spectroscopy performed on aliquots which were withdrawn periodically from the reaction mixture. After all of the starting material (**1c**) had reacted, the reaction mixture was cooled to ambient temperature and then was concentrated *in*

vacuo to remove excess methyl acrylate. Analysis of the ^{1}H NMR spectrum of the residue indicated the presence of two Diels-Alder cycloadducts (ratio 28:72). The residue was purified via column chromatography on silica gel by using 10% EtOAc-hexane as eluent. A mixture of **4c** and **5d** (88 mg, 95%) was thereby obtained. Fractional recrystallisation of this mixture from EtOAc-hexane afforded the major isomer, **5c**, as a colourless microcrystalline solid: mp 159 °C; IR (KBr) 1695 (s), 1295 (w), 1190 (m), 1160 (m), 1120 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.44 (*AB*, J_{AB} = 11.0 Hz, 1 H), 1.62-1.77 (m, 2 H), 2.00-2.23 (m, 2 H), 2.32-2.45 (m, 2 H), 2.45-2.74 (m, 4 H), 2.99 (dt, *J* = 3.5, 9.8 Hz, 1 H), 3.13 (ddd, *J* = 1.5, 2.6, 6.3 Hz, 1 H), 3.60 (s, 3 H), 2.84-4.05 (m, 4 H), 6.31 (dt, *J* = 1.3, 7.4 Hz, 1 H), 6.43 (dt, *J* = 1.3, 7.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.40 (t), 29.69 (d), 33.94 (d), 37.39 (d), 38.98 (t), 40.14 (d), 41.94 (d), 43.23 (d), 44.47 (d), 50.49 (s), 51.63 (d), 51.82 (q), 52.30 (s), 54.75 (d), 65.06 (t), 65.49 (t), 113.7 (s), 132.4 (d), 134.8 (d), 175.9 (s), 214.5 (s). Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.19; H, 6.21. Found: C, 71.15; H, 6.46.

The remaining mother liquor was concentrated *in vacuo*, and the residue was recrystallised from EtOAc-hexane. The minor product, **4c**, was thereby obtained as a colourless microcrystalline solid: mp 166-167 °C; IR (KBr) 1695 (s), 1295 (m), 1190 (s), 1160 (m), 1120 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.32 (ddd, *J* = 2.6, 6.2, 12.5 Hz, 1 H), 1.44 (*AB*, J_{AB} = 11.0 Hz, 1 H), 1.72 (*AB*, J_{AB} = 11.0 Hz, 1 H), 1.98-2.30 (m, 2 H), 2.32-2.79 (m, 6 H), 3.17-3.30 (m, 2 H), 3.62 (s, 3 H), 3.88-4.06 (m, 4 H), 6.31 (t, *J* = 6.8 Hz, 1 H), 6.49 (t, *J* = 6.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.84 (t), 32.31 (d), 33.10 (d), 37.79 (d), 39.24 (t), 40.40 (d), 42.53 (d), 49.05 (d), 45.47 (d), 51.13 (s), 51.54 (q), 52.27 (d), 52.62 (s), 55.20 (d), 65.60 (t), 65.97 (t), 114.3 (s), 131.9 (d), 136.7 (d), 175.9 (s), 212.8 (s). Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.19; H, 6.21. Found: C, 71.26; H, 6.48. The structures of **4c** and **5c** were established unequivocally via application of X-ray crystallographic methods.

Diels-Alder Reaction of 1d with Methyl Acrylate. A mixture of **1d** (268 mg, 1.28 mmol) and methyl acrylate (4 mL) was heated to 75-80 °C for 80 h. The reaction mixture was concentrated *in vacuo* (40 °C, 1 mm Hg), and the residue was purified by column chromatography on silica gel (10 g) by using a 1-10% EtOAc-hexane gradient elution scheme. The first chromatography fraction afforded a mixture of **4d** and **5d** (71 mg, 19%) as a colourless solid, mp 121-123 °C. Analysis of the integrated ^{1}H NMR spectrum of this material indicated that a mixture of two Diels-Alder cycloadducts had been obtained (product ratio 30:70). Repeated attempts to separate this mixture by fractional recrystallisation were not successful.

The identity of each isomer was established by independent synthesis. Thus, to a suspension of silica gel (15 g) in CH_2Cl_2 (30 mL) was added saturated aqueous oxalic acid (1.5 mL), and the resulting mixture was stirred vigorously at 25 °C for 10 minutes. A solution of **5b** (610 mg, 1.79 mmol) in CH_2Cl_2 (6 mL) was then added, and the resulting mixture was stirred at room temperature for 48 h. Solid $NaHCO_3$ (2.7 g) was added, the resulting mixture was filtered, and the residue was washed with CH_2Cl_2 (4 x 15 mL).The combined organic extracts were concentrated *in vacuo* (40 °C, 15 mm Hg), thereby affording a colourless oil (284 mg, 54%) which slowly crystallised upon trituration with hexane (10 ml). Recrystallisation of this material from hexane afforded pure **4d** as a colourless microcrystalline solid: mp 133-134 °C; IR (film) 2966 (s), 1724 (sh, s), 1195 cm^{-1} (sh, m); ^{1}H NMR ($CDCl_3$) δ 1.42 (br d, *J* = 11.0 Hz, 2 H), 1.50-1.69 (m, 3 H), 1.76 (br d, *J* = 11.0 Hz, 1 H), 2.12-2.22 (m, 1 H), 2.24-2.38 (m, 2 H), 2.45-2.58 (m, 3 H), 2.71-2.82 (m, 1 H), 2.99 (br dt, *J* = 2.8, 6.5 Hz, 1 H), 3.23 (ddd, *J* = 2.5, 5.5, 9.8 Hz, 1 H), 3.62 (s, 3 H), 6.28 (br t, *J* = 7.0 Hz, 1 H), 6.45 (br t, *J* = 70 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.41 (t), 32.53

(d), 33.80 (t), 36.37 (d), 36.78 (d), 38.33 (t), 39.94 (d), 42.17 (d), 45.96 (d), 48.08 (d), 48.55 (d), 51.70 (q), 52.78 (s), 53.02 (d), 55.14 (s), 131.3 (d), 135.5 (d), 175.9 (s), 220.8 (s). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.85; H, 6.56. The ^1H and ^{13}C NMR spectral data thus obtained for **4d** correspond to those of the major isomer formed via Diels-Alder cycloaddition of **1d** with methyl acrylate. Independent verification of the structure of **4d** was obtained via its $NaBH_4$ promoted reduction to afford **4e**, the structure of which was established unequivocally via application of X-ray crystallographic methods.

The structure of the corresponding minor isomer formed via Diels-Alder reaction of **1d** with methyl acrylate (i.e., **5d**) was established similarly. Thus, a mixture of **4b** and **5b** which had been obtained previously via Diels-Alder cycloaddition of **1b** to methyl acrylate (*vide supra*) was subjected to hydrolysis by using the procedure described above for the synthesis of **4d** from **5b**. Careful fractional crystallisation of the mixture of **4d** and **5d** thereby obtained from hexane followed by final fractional recrystallisation from EtOAc afforded pure **5d** as a colourless microcrystalline solid: mp 143.5-145 °C; IR (film) 2955 (s), 1728 (sh, s), 1180 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.42 (br d, J = 10.8 Hz, 1 H), 1.43 (d, J = 2.5 Hz, 2 H), 1.59 (ddd, J = 3.5, 5.0, 13.8 Hz, 1 H), 1.75 (br d, J = 10.8 Hz, 1 H), 2.15 (ddd, J = 1.8, 5.5, 8.0 Hz, 1 H), 2.21-2.41 (m, 3 H), 2.44-2.68 (m, 4 H), 2.72-2.88 (m, 1 H), 2.88 (ddd, J = 1.5, 2.5, 6.5 Hz, 1 H), 3.61 (s, 3 H), 6.29 (ddd, J = 1.5, 6.2, 8.0 Hz, 1 H), 6.42 (ddd, J = 1.5, 6.5, 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 23.63 (t), 29.89 (d), 33.87 (t), 38.34 (t), 38.84 (d), 39.21 (d), 40.36 (d), 42.16 (d), 45.64 (d), 48.06 (d), 48.37 (d), 51.75 (q), 52.77 (s), 52.94 (d), 55.10 (s), 132.0 (d), 134.8 (d), 175.6 (s), 220.5 (s). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00 H, 6.80. Found; C, 77.02; H, 6.65. The structure of **5d** was established unequivocally via application of X-ray crystallographic methods. The ^1H and ^{13}C NMR spectral data thus obtained for **5d** correspond to those of the minor isomer formed via Diels-Alder cycloaddition of **1d** with methyl acrylate.

Diels-Alder Reaction of 1e with Methyl Acrylate. A mixture of **1e** (536 mg, 2.53 mmol), methyl acrylate (40 ml) and hydroquinone (150 mg) was stirred at room temperature under argon at 70-80 °C for 5 days. The reaction mixture was then concentrated *in vacuo* (60 °C, 15 mm Hg), and the residue was purified via column chromatography on silica gel (23 g) by using a 3-20% EtOAc-hexane gradient elution scheme. The first chromatography fraction afforded an oil (278 mg) which was not further characterised. The second chromatography fraction afforded a colourless microcrystalline solid (326 mg, 43%), mp 141-155 °C. Analysis of the ^1H NMR spectrum of this material suggested that it consisted of a mixture of two Diels-Alder adducts (ratio *ca.* 1:1, determined via integration of the ^1H NMR spectrum). Repeated fractional recrystallisation of this material from hexane followed by final fractional recrystallisation from EtOAc afforded isomerically pure **5e** as a colourless microcrystalline solid: mp 182-184 °C; IR (film) 3531 (m), 2950 (s), 2854 (w), 1716 (sh, s), 1433 (w), 1351 (w), 1226 (w), 1175 (s), 1038 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 1.03 (br d, J = 10.0 Hz, 1 H), 1.07 (dd, J = 3.0, 11.5 Hz, 1 H), 1.39 (br s, 1 H), 1.46 (ddd, J = 2.5, 6.0, 12.5 Hz, 1 H), 1.54 (br d, J = 10.0 Hz, 1 H), 1.78 (ddd, J = 1.5, 5.5, 8.0 Hz, 1 H), 1.97 (ddd, J = 1.5, 5.5, 7.0 Hz, 1 H), 2.07 (m, 1 H), 2.14-2.26 (m, 2 H), 2.27 (br d, J = 11.5 Hz, 1 H), 2.31-2.50 (mc, 3 H), 2.74 (m, 2 H), 3.62 (s, 3 H), 3.88 (d, J = 3.2 Hz, 1 H), 6.27 (br t, J = 7.3 Hz, 1 H), 6.47 (br t, J = 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.65 (t), 31.47 (t), 35.67 (t), 36.05 (d), 39.16 (d), 39.67 (d), 40.52 (d), 42.01 (d), 43.74 (d), 44.21 (d), 46.79 (d), 47.68 (d), 48.23 (s), 50.95 (s), 51.59 (q), 77.33 (d), 131.7 (d), 136.1 (d), 176.6 (s). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.23; H, 7.43. The structure of **5e** was established unequivocally via application of X-ray crystallographic methods.

Further fractional recrystallisation from hexane of the remaining hexane-based mother liquor eventually afforded **4e** as a colourless microcrystalline solid: mp 155-157 °C; IR (film) 3491 (s), 2950 (s), 1716 (s), 1195 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.02 (dd, *J* = 3.5, 11.5 Hz, 1 H), 1.03 (d, br, *J* = 9.5 Hz, 1 H), 1.39-1.46 (m, 1 H), 1.54 (d, *J* = 9.5 Hz, 1 H), 1.69 (ddd, *J* = 3.5, 4.5, 13.0 Hz, 1 H), 1.79 (dd, br, *J* = 2.5, 9.5 Hz, 1 H), 1.82-1.98 (m, 1 H), 2.08 (m, 1 H), 2.14-2.30 (m, 2 H), 2.22 (d, *J* = 11.0 Hz, 1 H), 2.33-2.46 (m, 2 H), 2.86 (d, br, *J* = 6.5 Hz, 1 H), 3.49 (ddd, J = 2.8, 4.5, 9.8 Hz, 1 H), 3.61 (s, 3 H,), 3.93 (br s, 1 H), 6.27 (ddd, *J* = 1.5, 6.5, 8.0 Hz, 1 H), 6.42 (ddd, *J* = 1.5, 6.5, 8.0 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 25.36 (t), 31.47 (t), 35.66 (t), 36.67 (d), 37.79 (d), 38.74 (d), 40.38 (d), 41.98 (d), 43.24 (d), 44.61 (d), 46.85 (d), 47.80 (d), 48.44 (s), 50.24 (s), 51.53 (q), 77.26 (d), 132.2 (d), 135.6 (d), 176.83 (s). Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.56; H, 7.09. The structure of **4e** was established unequivocally via application of X-ray crystallographic methods.

In addition, the lower melting of the two isomers produced via Diels-Alder cycloaddition of **1e** to methyl acrylate (i.e., **4e**) was synthesised independently via $NaBH_4$ reduction of **4d**. Thus, to a cooled (0 °C, external ice-water bath) solution of **4d** (284 mg, 0.94 mmol) in CH_2Cl_2 (10 mL) and EtOH (10 mL) was added with stirring solid $NaBH_4$ (200 mg, 5.29 mmol) in one portion. The resulting mixture was stirred at 0 °C for 3.5 h, at which time water (30 mL) was added followed by dropwise addition of 5% aqueous HCl until the acidity of the aqueous mixture remained below pH 4. The resulting mixture then was extracted with CH_2Cl_2 (3 x 20 ml), and the combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4) and filtered, and the filtrate was concentrated *in vacuo*. The residue was recrystallised from EtOAc-hexane to afford pure **4e** (113 mg, 40%) as a colourless microcrystalline solid: mp 156-157 °C. The ^1H NMR spectrum of this material was identical in all respects with that of **4e** which had previously been obtained via Diels-Alder reaction of **1e** with methyl acrylate.

Diels-Alder Reaction of 1f with Methyl Acrylate. A mixture of **1f** (1.03 g, 3.82 mmol), methyl acrylate (60 mL, excess) and hydroquinone (20 mg) was heated to 70-80 °C for 7 days. The reaction mixture then was concentrated *in vacuo* (60 °C, 15 mm Hg), and the residual brown oil was purified via column chromatography on silica gel by using a 10-33% EtOAc-hexane gradient elution scheme. The first chromatography fraction afforded recovered **1f** (510 mg, 49%). The second fraction afforded a colourless oil (569 mg, 42%). Analysis of the ^1H NMR spectrum of this material suggested that it consisted of a mixture of two Diels-Alder adducts (ratio *ca.* 2:1, determined via integration of the ^1H NMR spectrum). Continued column chromatographic purification of this material afforded a colourless microcrystalline solid. Fractional recrystallisation of this material from EtOAc-hexane afforded the major product, **5f**, as a colourless microcrystalline solid: mp 126-128 °C; IR (KBr) 3444 (s), 2944 (s), 1725 (sh, m), 1443 (sh, m), 1200 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.02 (d, *J* = 10.5 Hz, 1 H), 1.47 (d, *J* = 11.5 Hz, 1H), 1.50-1.64 (m, 1 H), 1.86-1.96 (m, 1 H), 2.00-2.10 (m, 1 H), 2.15-2.27 (m, 2 H), 2.32-2.45 (m, 2 H), 2.48-2.66 (m, 2 H), 3.04-3.16 (m, 2 H), 3.60 (s, 3 H), 3.63 (dd, *J* = 2.8, 12.0 Hz, 1 H), 3.95-4.09 (m, 4 H), 4.90 (d, J = 12.5 Hz, 1 H), 6.25 (br t, *J* = 7.3 Hz, 1 H), 6.48 (br t, *J* = 7.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$): δ 24.21 (t), 33.76 (d), 34.95 (t), 35.99 (d), 37.52 (d), 41.12 (d), 42.30 (d), 43.44 (d), 43.54 (d), 47.78 (d), 48.79(d), 48.88 (s), 49.09 (s), 51.61 (q), 63.89 (t), 65.68 (t), 75.32 (d), 116.2 (s), 131.3 (d), 136.5(d), 176.4 (s). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.79; H, 6.45. The structure of **5f** was established unequivocally via application of X-ray crystallographic methods.

The remaining mother liquor was concentrated, and the residue was recrystallised by repeated fractional crystallisation from EtOAc-hexane. Pure **4f** (minor product) was thereby obtained as a colourless microcrystalline solid: mp 98-100 °C; IR (film) 3437 (m), 2920 (s), 1736 (s), 1438 (m), 1194 cm^{-1} (s); ^1H NMR ($CDCl_3$): δ 1.01 (d, br, J = 10.5 Hz, 1 H), 1.43-1.60 (m, 2 H), 1.88-2.14 (m, 3 H), 2.16-2.25 (m, 2 H), 2.30-2.46 (m, 2 H), 2.66-2.85 (m, 1 H), 2.99 (dt, J = 1.8, 6.0 Hz, 1H), 3.60 (s, 3 H), 3.60-3.70 (m, 2 H), 5.04 (d, J = 12.5 Hz, 1 H), 6.25-6.47 (m, 2 H); ^{13}C NMR ($CDCl_3$): δ 24.77 (t), 31.02 (d), 34.96 (t), 37.14 (d), 38.29 (d), 40.98 (d), 42.36 (d), 43.11 (d), 43.74 (d), 47.73 (d), 48.76 (d), 48.95 (s), 51.48 (s), 51.51 (q), 63.84 (t), 65.58 (t), 75.26 (d), 116.3 (s), 132.8 (d), 135.2 (d), 176.6 (s). Anal. Calcd for $C_{21}H_{24}O_5$: C, 70.77; H, 6.79. Found: C, 70.84; H, 6.58. The structure of **4f** was established unequivocally via application of X-ray crystallographic methods.

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