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Enantiomerically Pure Vinylketene Acetals In The Diels-Alder Reaction. Catalysis and Facial Selectivity. [1]

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Abstract. A series of enantiomerically pure vinylketene acetals which function as diastereoselective dienes in the Diels-Alder reaction have been developed. Most selective are (4*R*, 5*R*)-4,5-diphenyl-2-(2-methyl-2-propenidene)-1,3-dioxolane (**8**) and (4*R*, 5*R*)-4,5-diphenyl-2-((*E*)-2-butenidene)-1,3-dioxolane (**9**), which utilize phenyl rings as asymmetric directing groups. It was shown through NOE analysis that the major product obtained from the reaction of diene **9** and *N*-methylmaleimide is due to *Re exo* approach of the dienophile to the diene, with the two *endo* transition states also being manifest in the product mixture in small amounts. The relative order of the transition state energies were determined to be *Re exo* < *Re endo* < *Si endo* < *Si exo*. Both molecular mechanics and π-charge density calculations were used to rationalize the high level of diastereoselectivity observed in the reactions of diene **8** and *N*-methylmaleimide (48:1).

Introduction

The process of forming optically active compounds from the reaction of an enantiomerically pure reagent with an achiral reagent, or achiral reagents with an enantiomerically pure catalyst, defines the field of asymmetric synthesis.[3] One of the premiere synthetic reactions within this field is the Diels-Alder cycloaddition.[4] The attraction of this reaction is that the simultaneous formation of two carbon σ-bonds with a high degree of regio- and stereoselectivity creates the possibility of forming up to four chiral centers in one step.[5] Generally, the asymmetric variant of the Diels-Alder reaction involves the use of an enantiomerically pure dienophile and an achiral diene, and many elegant examples of this protocol exist. Less studied are the reactions utilizing enantiomerically pure dienes, although this variation should also be an extremely powerful tool for the synthesis of complex chiral nonracemic compounds.

In the asymmetric variation, 32 isomers are possible from the formation of 2 σ-bonds and the creation of four contiguous chiral centers. Fortunately for the synthetic chemist, the reaction proceeds with a high degree of specificity for several reasons. First, the molecular orbital symmetry of the interaction of the diene and the dienophile dictates a suprafacial arrangement of the new σ-bonds. Second, regioselectivity is controlled by a generally predictable combination of molecular orbital and electrostatic interactions. Finally, a variety of models that include steric effects, van der Waals interactions, torsional effects, orbital and

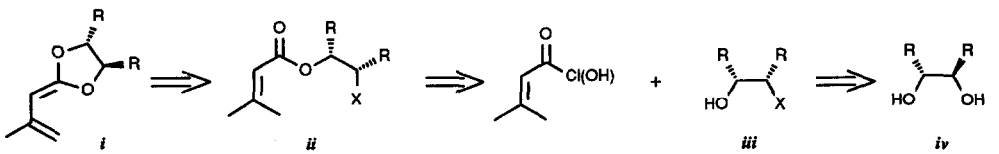
electrostatic interactions have been proposed to explain enantioselectivity.[6]

The initial example of asymmetric induction by way of a Diels-Alder reaction was observed by Korolev from the reaction of menthyl fumarate and butadiene.[7] Almost three decades later the first experiments into the use of chiral nonracemic dienes appeared.[8] David and coworkers utilized sugar derivatives as chiral directing groups to obtain modest diastereoselectivities. Since this initial study, work in this area can be grouped into two categories. The first may be defined as rigid chiral nonracemic dienes.[9,10] These are systems where there is a conformationally fixed relationship between the chiral center(s) and the diene. The second, which is by far the larger of the two,[11-14] consists of enantiomerically pure dienes where the relationship between the diene functionality and the asymmetric center(s) would appear to be conformationally flexible.

Retrosynthetic Analysis to Enantiomerically Pure Vinylketene Acetals

We wished to enter the field of asymmetric Diels-Alder chemistry with an improved source of chiral nonracemic dienes obtained through a short synthetic route. In order to obtain the most generally selective diene; that is, a system that yielded high diastereomeric excesses independent of dienophile type, a rigid system was deemed desirable. This would also allow for *a priori* determination of the major isomer of the reaction. In addition, the enantiomerically pure diene was to be designed around the incorporation of an enantiomerically pure auxiliary. In this way the synthetic flexibility would be increased as the chiral centers of the auxiliary need not be incorporated into the final product, and the auxiliary could be recycled.

The success of Brassard, Danishefsky and others[15] in utilizing vinylketene acetals in Diels-Alder reactions drew our attention to these electron-rich dienes. We also considered the importance of the ketal functionality in asymmetric synthesis.[16] Thus, our analysis led us to consider dienes of type ***i***, as shown below. Note that the dioxolane ring provides a rigid connection between the asymmetric centers and the diene system. The pathway illustrated below allows for the synthesis of the diene from a known source of enantiomerically pure materials via a short synthetic route. This approach was also advantageous due to the large number of chiral vicinal diols of differing steric and electronic qualities available as starting material from the pool of chiral carbon compounds.[17]



i *ii* *iii* *iv*

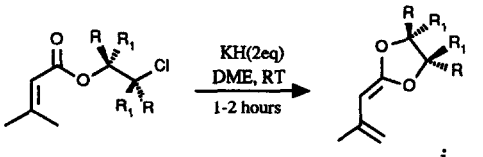
R = alkyl, aryl

The synthesis was designed around two key transformations: the cyclization of β-haloester ***ii*** to dioxolane ***i*** and the synthesis of β-haloalcohols ***iii*** from chiral nonracemic diols of C_2 symmetry ***iv***. Transformations of β-haloesters to 2-ene-1,3-dioxolanes via base-initiated enolate cyclization has been known in the literature since the 1950's.[18] The 5-(enolexo)-exo-tet cyclization has been shown to proceed with complete selectivity for *O*-alkylation.[19] As this reaction proceeds with inversion at the alkylating carbon, the halogenation of the vicinal diol must proceed with inversion if the stereochemical integrity of the auxiliary is to be preserved. The coupling of halohydrin ***iii*** to the appropriate unsaturated acid or acid chloride would not be a problem as several mild methods for this transformation are known. The only limitation is that basic conditions would not be appropriate as this would lead to epoxide formation. At the time this work was initiated two halogenation methods appropriate to the transformation of ***iv*** to ***iii*** were

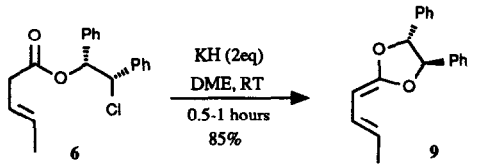
available, but the generality of these methods was not known.[20] We have since prepared a variety of enantiomerically pure β-halohydrins of differing steric and electronic characteristics.[21]

Synthesis of Enantiomerically Pure Vinylketene Acetals

Haloester **1** (Table 1) was synthesized by acid-catalyzed esterification of 3,3-dimethylacrylic acid and 2-chloroethanol in 85% distilled yield. The use of inorganic bases in the cyclization reaction seemed most promising as the by-products and excess base could be removed by Schlenk filtration. This approach was necessary since any excess base remaining in the reaction mixture could not be neutralized due to the documented nucleophilicity of the β-carbon of ketene acetals.[22] While the reaction could be carried out with KH in diethyl ether or THF, the reaction was quite sluggish. Reaction times of 90-96 hours were observed. Use of KH in dimethoxyethane (DME) increased the rate of reaction by two orders of magnitude, allowing for product formation in one to two hours (Table 1).



ii *i*



6 9

Table 1

Ester *ii*	R	R_1	X	Isolated % Yield of *i*
1	H	H	Cl	75
2	CH_3	H	Br	40[a]
3	iPr[b]	H	Br	dec.
4	MM[c]	H	Cl	55[a]
5	H	Ph	Cl	90

(a) Yields based on the isolation of the Diels-Alder product.
(b) *i* Pr = isopropyl. (c) MM = methoxy methyl.

A DCC-mediated[23] coupling protocol was examined for the synthesis of the desired chiral nonracemic esters. While yields of 80-90% were obtained for esters **2-6**, a troublesome aspect of the procedure was the necessary removal of the urea by-product via column chromatography. A superior procedure involved the pyridine-catalyzed esterification of 3,3-dimethylacrylic acid chloride with (1*R*,2*S*)-2-chloro-1,2-diphenylethanol. The reaction proceeds in 80-90% yields after recrystallization with methanol/water. The KH methodology worked well for the cyclization of all esters except for **3**, R = isopropyl. This was not surprising considering that unactivated secondary centers are sluggish under S_N2 conditions. We were also able to synthesize diene **9** from haloester **6** by the methodology described above in 85% yield.

Physical Characteristics of the Vinylketene Acetals.

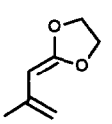
Examination of the physical characteristics of the three isolated vinylketene acetals (**7**, **8** and **9**) gave important conformational and electronic insight. Previous investigators have correlated the shielding of the β-carbon of the ketene acetal system to the amount of *p*-π interaction between the acetal oxygens and ene system.[22e,f] Table 2 compares the ^{13}C NMR and ^{1}H NMR chemical shifts for the ene system of dienes **7-9** and 2-methylene-1,3-dioxolane (**10**) to the average values observed for alkene systems. The large downfield shift in the ^{13}C NMR resonances of the α-carbon indicates its relative electropositive character. The β-carbons have highly shielded resonances to reflect the electronegative characteristics of that carbon. The

shielding of the β-position may also be observed by the shifts of the methylene protons. The relative decrease in the magnitudes of the chemical shift changes of dienes **7-9** versus ene **10** could be due to the delocalization of the electron density throughout the π system. To lend credence to this hypothesis, **7** was hydrolyzed in aqueous NH_4Cl. The reaction was complete in 15 minutes and gave a mixture of conjugated (44%) and nonconjugated (56%) hydroxyesters. Continued stirring for an additional hour did not affect the product distribution. Thus, the formation of the conjugated isomer is a function of the electron density at the terminal carbon of the vinylketene acetal and not due to isomerization of the ester.

The electronic spectra of the dienes were highly informative. The observed 36-38 nm difference of the λ_{max} between γ-substituted dienes **8** and **7** and δ-substituted diene **9** is the difference predicted for *s-cis* and *s-trans* diene systems by Woodward and Fieser.[24] Thus dienes **7** and **8** are thought to be *s-cis* in conformation and are expected to have a greater reaction rate in the Diels-Alder reaction than *s-trans* diene **9**.

Table 3 shows the dependency of the NMR chemical shifts on solvent polarity for compound **8**. Notice that in the less polar solvent, benzene-d_6, the proton and carbon shifts of the β-position are less shielded than in the more polar solvents. Notice also that there are significant changes in the coupling constants between the benzylic protons. An increase in the magnitude of $J_{benzylic}$ indicated an increase in the dihedral angle of these protons and a corresponding flattening of the dioxolane ring. This ring flattening should allow for better orbital interaction between the oxygen *p* orbitals and the diene π system. The observed shielding of the β-position chemical shifts is in agreement with this analysis.

10



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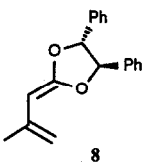

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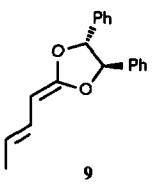

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Table 2

	^{13}C NMR[a]		^{1}H NMR	
Compound	**α**	**β**	**β**	**λ_{max}[b]**
9	159.3	75.1	4.77	242 nm
8	159.8	77.6	4.75	278 nm
7	159.8	76.8	4.51	280 nm
10[c]	164.0	53.5	3.08	
base[d]	128.0		6.00	

(a) NMR shifts are recorded in $CDCl_3$ and reported in δ (ppm). (b) λ_{max} are recorded in ethyl ether. (c) See reference 22e for the the synthesis of **10**. (d) are average values for conjugated HC=R.[24]

Table 3

	^{13}C NMR[a]		^{1}H NMR	
Solvent	**α**	**β**	**β**	**$J_{benzylic}$**
benzene-d_6	159.9	78.5	4.85	6.2 Hz
$CDCl_3$	159.8	77.6	4.75	7.8 Hz
DMSO-d_6	159.3	76.7	4.58	7.2 Hz

(a) NMR shifts reported in δ (ppm).

A Model for the Prediction of the Diastereomeric Outcome of the Diels-Alder Reactions.

An initial hypothesis concerning the steric interaction of the electron-rich chiral nonracemic vinylketene acetal with an electron-poor achiral dienophile such as methyl crotonate was formulated with the aid of space-filling models. This analysis is summarized in Figure 1. *Endo* approach of *s-trans* dienophile to the diene via the "top" face (*v*) gives the adduct ***vi***. Notice that *endo* approach to this face involves steric interaction between the electron withdrawing group Z and the directing group R. By contrast *endo* approach of the *s-trans* dienophile to the "bottom" face (***vii***) of the diene avoids major interactions with the directing group R. Thus, the resulting product distribution should give an excess of product ***viii*** at the expense of ***vi***.

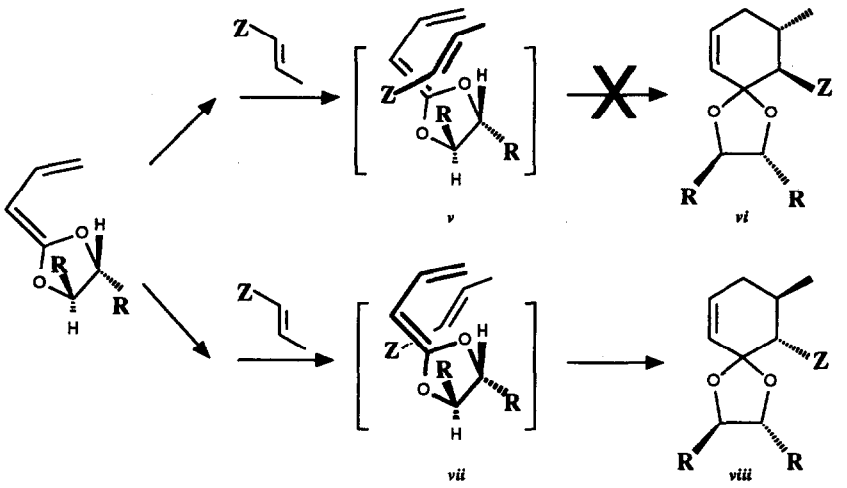
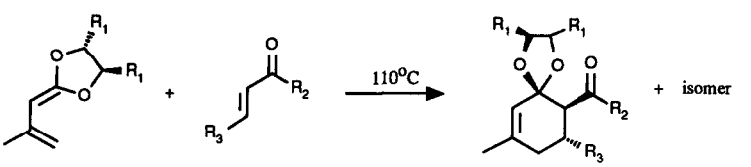


Figure 1

Diels-Alder Reactions with γ-Methyl Substituted Chiral Nonracemic Vinylketene Acetals.

The results of the initial thermal reactions can be found in Table 4. The investigation began with the reaction of achiral diene **7** (entry 1) with methyl crotonate to obtain cycloadduct **11** in good yield. The first enantiomerically pure vinylketene acetal studied was **12**, $R_1 = CH_3$ (entry 2), which was considered a "worst case" substrate due to the small steric demand of the methyl group. The diastereomeric excess observed in the cycloadducts, as determined by both GC and ^1H NMR analysis, was modest (1.4:1). The reaction of diene

Table 4

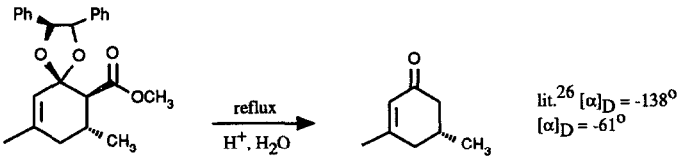


Entry	Diene	Dienophile R_2	Dienophile R_3	Solvent/Time	% Yield	Ratio[a]	Product
1	**7**, $R_1 = H$	OCH_3	CH_3	neat[b]/18 h	85	N/A	**11**
2	**12**, $R_1 = CH_3$	OCH_3	CH_3	toluene/40 h	40[c]	1.4:1	**13**
3	**14**, $R_1 = CH_2OCH_3$	OCH_3	CH_3	toluene/40 h	55[c]	1.3:1	**15**
4	**8**, $R_1 = C_6H_5$	OCH_3	CH_3	toluene/40 h	75	3:1	**16**
5	**8**, $R_1 = C_6H_5$	OCH_3	CH_3	neat/40 h	74	2:1	**16**
6	**8**, $R_1 = C_6H_5$	O*t*Bu	CH_3	neat/40 h	78	2:1	**17**
7	**8**, $R_1 = C_6H_5$	OEt	CO_2Et	neat/40 h	70	2:1	**18**
8	**8**, $R_1 = C_6H_5$	CH_3	H	toluene[b]/40 h	78	1.06:1	**19**

(a) Product distribution was determined by GC and ^1H NMR analysis. (b) Reactions was carried out in a sealed tube. (c) Yields based on the two step transformation from the haloester.

14, R = CH_2OCH_3, and methyl crotonate also displayed minimal selectivity (1.3:1, entry 3).

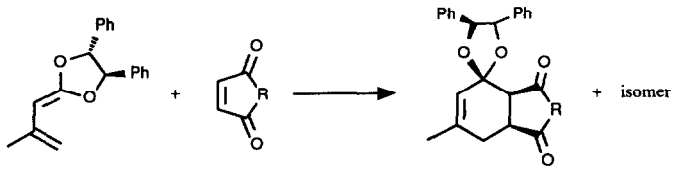
More successful were the reactions involving diene **8**, R = Ph. The larger steric bulk of the phenyl group affects the approach of a dienophile to a greater extent than the smaller methyl and methoxymethyl groups for a given dihedral (R_1-C-C-R_1) angle.[25] The reaction of diene **8** with methyl crotonate gave a 3:1 ratio of diastereomers (entry 4). The stereochemical outcome of the cycloaddition was confirmed by transformation of the product to a compound of known absolute configuration. As shown below, the product mixture obtained in entry 4 was refluxed in 10% HCl to effect deketalization and decarboxylation, yielding 3,5-dimethyl-2-cyclohexenone enriched in the (-) isomer. This allowed the assignment of the asymmetric carbon bearing the methyl group of the major diastereomer as *R*.[26] This result gave us confidence in the model proposed above for the prediction of the stereochemical outcome of reactions involving dienes such as **8**. Entries 5 and 6 illustrate the lack of effect displayed by the R_2 group. Changing the ester from methoxy to *t*-butoxy does not bring any observable change in product distribution. The reaction of diethyl fumarate (entry 7) with diene **8** gives a similar ratio of products, 2:1. The product distribution of the reaction of methyl vinyl ketone and diene **8** shows little diastereoselectivity (entry 8).



16, 3:1 mixture **20**

The results of the reaction of diene **8** with cyclic dienophiles are summarized in Table 5. When maleic anhydride was used as a dienophile poor diastereoselectivities were obtained (entries 1 and 2). Improvement came through the utilization of *N*-substituted maleimides as dienophiles. The cycloadduct of diene **8** and *N*-phenylmaleimide (entry 3) was obtained in nearly quantitative yield and 5.7:1 selectivity. Switching to *N*-methylmaleimide afforded even more gratifying results (entries 4 and 5). When the reaction was carried out at room temperature, the crystalline product was obtained in extremely high yield and diastereomeric purity.

Table 5



Entry	Dienophile	Solvent/Temperature (°C)/Time	% Yield	Ratio	Product
1	R = O	benzene/80/96 h	55[a]	1.2:1	**21**
2	R = O	benzene/25/7 d	56[a]	1.4:1	**21**
3	R = NPh	CH_2Cl_2/25/60 h	96	5.7:1	**22**
4	R = NMe	$CHCl_3$/80/20 h	67	19:1	**23**
5	R = NMe	$CHCl_3$/25/48 h	95	48:1	**23**

(a) Yields are based on isolated diester from hydrolysis and diazomethane treatment of the Diels-Alder reaction mixture.

Various studies were conducted to enhance the reactivity and selectivity of Diels-Alder reactions of **8** with dienophiles less reactive than maleimides. Variations in solvent polarity,[27,28] and Lewis acid catalysis[29]

led to no significant changes in product formation and distribution.

The use of high pressure has been shown to be beneficial in the increase of both yields and stereoselectivity.[30] The effect of pressure on transition state geometry has been studied by Dauben[31] and Jurczak.[32,33] Since the *endo* transition state has a larger negative volume of activation than the *exo* transition state and since the reaction rate is directly proportional to the change in volume, ΔV, the *endo* product is favored by high pressure reaction conditions. However, the use of pressure did not bring about any increase in diastereoselectivity for the reaction of **8** and methyl crotonate over the 3:1 ratio obtained in the thermal reaction.[34] This result was surprising as several investigators have shown that high pressure will affect an increase in selectivity in Diels-Alder cycloadditions.[30,32]

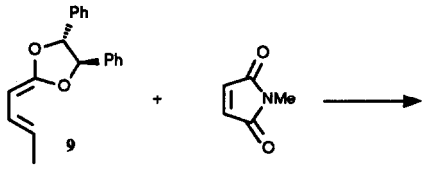
Reactions of δ-Substituted Chiral Nonracemic Vinylketene Acetals.

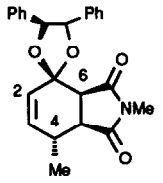
A study of the reactivity of the diene **9** with *N*-methylmaleimide was initiated to probe the *exo*/*endo* ratio of this reaction. We utilized the molecular modeling program of Still[35] in the following manner to obtain the relative energy differences between the four possible transition states of the reaction. First, an MM2 minimized structure for the *s-cis* conformation of diene **9** was obtained. The minimized structure shows a nearly flat dioxolane ring system, with the dihedral angle between the C-1 carbons of the phenyl rings at 128°. The dihedral angle between one of the *ortho* carbons of the phenyl ring and the nearest dioxolane oxygen is 8°. This orientation places the proton of this *ortho* carbon within 5Å of the terminal carbon of the diene system. The transition state energy was calculated by constraining the approach of *N*-methylmaleimide to the minimized diene structure. Bond lengths, bond angles, and carbon pyramidalizations for the carbons involved in the ring forming process were constrained as described by Houk[36] for the reaction of butadiene and acrolein. These transition state parameters were chosen as they approximate the polarized interaction between electron-rich diene **9** and *N*-methylmaleimide. Most importantly, the phenyl rings were not allowed to rotate. Thus the calculations were prejudiced at a geometry that gave maximum steric interaction with the phenyl rings to approximate an early transition state. In fact, space-filling models indicate that rotation of the phenyl rings must occur in concert due to *ortho* proton interactions between the rings. Admittedly, these calculations are crude and the absolute energy values obtained thereof may have little relevance. However, the complexity of the problem ruled out the use of *ab initio* methods. In spite of these limitations, the relative energy values should illustrate the corresponding relative steric interactions encountered in the four transition states.[37]

The relative energies of the calculated transition state geometries are given below their respective products shown in Table 6. *Exo* approach of the dienophile to the *Si* ("top") face of the diene results in the largest steric congestion of the four transition states. The carbonyl group of the dienophile must have a strong interaction with the phenyl ring to attain the proper reaction geometry. Similarly, the vinyl proton of the dienophile interacts with the phenyl ring of the diene during an *endo* approach of the *Si* face. *Endo* approach of the *Re* ("bottom") face of the diene by the dienophile results in interactions between the phenyl directing group and the *N*-methylmaleimide carbonyl group. *Re exo* approach to the diene by the dienophile is devoid of any major steric interactions.

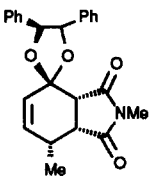
Table 6 summarizes our results from the reactions of diene **9** and *N*-methylmaleimide. We were unable to obtain product formation at room temperature. Contrast this observation with the facile reaction of diene **8** with the same dienophile. This difference in reactivity may be due to the presence of substantial *s-trans* conformer. Yields obtained from the reactions carried out in refluxing $CHCl_3$ were inconsistent, ranging from 5% to 70%. Generally, the yields were between 20-30%; however, the product distributions observed were consistently 78:12:9:0 as determined by GC analysis. Reactions carried out in other solvents were unsuccessful, yielding mostly resinous material.

Table 6

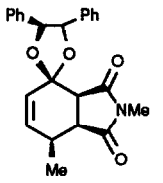




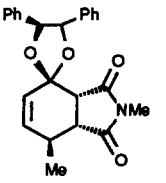
24 *Re exo*



25 *Re endo*



26 *Si endo*



27 *Si exo*

Calculated Transition State Energies

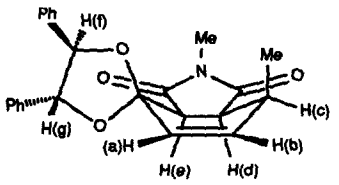
+ 5.47 kcal | + 20.27 kcal | + 24.97 kcal | + 32.66 kcal

Entry	Solvent/Temperature (°C)	%Yield	Ratio 24:25:26:27
1	$CHCl_3$/25	No Reaction	
2	$CHCl_3$/80	5-70	78:12:9:0
3	toluene/110	< 1	N/A
4	CH_3CN/80	Polymer formation	

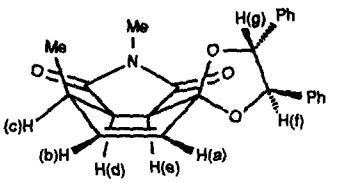
We were able to establish the identity of the major isomer on the basis of NOE analysis. MM2 calculations along with the large coupling constants obtained for the 6-position (9-10 Hz) of the cyclohexene ring establishes that the ring is in a boat conformation. Irradiation of the benzylic resonance at 4.75 ppm (H_g) shows a positive NOE at the methyl doublet (1.29 ppm, 10%) and at the vinyl resonance (6.22 ppm, 4%). These data establish 1) that the methyl on the cyclohexene ring is in an axial position, 2) that the major isomer is one of the four compounds shown in Figure 3, 3) that the benzylic resonance at 4.75 ppm is H_g and not H_f, and 4) that the major isomer is one of the two *Re* adducts. Another NOE observed from the irradiation of vinyl proton H_a provides the final clue as to the structure of the major diastereomer. Along with a positive NOE at the benzylic resonance (4.75 ppm, 12%), a positive NOE is observed from H_a to the *N*-methyl resonance at 3.07 ppm (7%). To observe this signal the maleimide ring must be in a psuedo axial position as seen in the *Re exo* compound. The NOE correlations that establish **24** as the major diastereomer obtained from the reaction of diene **9** and *N*-methylmaleimide are illustrated below.

Additional evidence that the major isomer of the Diels-Alder reaction was **24** came from the coupling constants ($J_{H\text{-}H}$) predicted by MM2 minimization of the products. $J_{H\text{-}H}$ for the protons H_b, H_c and H_d of the cyclohexane ring, Figure 3, are characteristic for *endo* or *exo* addition products. Note that the coupling constants for the major isomer, compound **24**, match those predicted for an *exo* isomer by the MM2 calculations. The predicted coupling constants identify the two minor constituents as *endo* adducts.

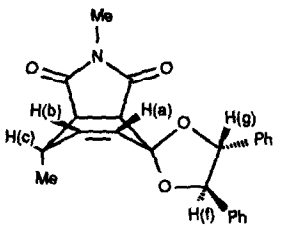
Figure 2



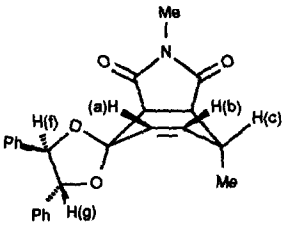
Si endo



Re endo



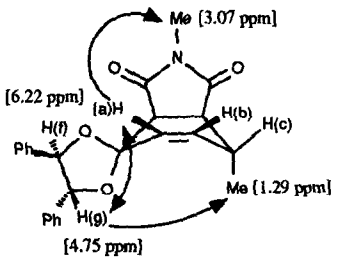
Si exo



Re exo

Predicted[a] J_{H-H}		Observed J_{H-H}	
Endo Product		Minor Products	
J_{bc}	6 Hz	J_{bc}	6.6, 5.1 Hz
J_{cd}	8 Hz	J_{cd}	8.1, 7.6 Hz
J_{de}	12 Hz	J_{de}	10.5, 10.0 Hz
Exo Product		Major Product	
J_{bc}	3 Hz	J_{bc}	2.7 Hz
J_{cd}	9 Hz	J_{cd}	8.1 Hz
J_{de}	11 Hz	J_{de}	9.6 Hz

[a] from MacroModel[35]



24 *Re exo*

Discussion

The results of the reaction of diene **9** with *N*-methylmaleimide prove conclusively that three of the four possible transition states are manifest in the product mixture. These pathways can be identified as the three lowest energy transition states in Table 6. While the magnitude of the energy difference is certainly not correct, there does appear to be a small energy difference between the two *endo* transition states with a larger energy difference between these two and the lowest energy *exo* transition state. These energy differences are reflected by the product distribution obtained from the reaction, 78% (*Re exo*): 12% (*endo*): 9% (*endo*).

As can be seen in Table 6, removal of the C-4 methyl group results in the identity of **24** (*Re exo*) and **26** (*Si endo*). The same is true for **25** (*Re endo*) and **27** (*Si exo*). This redundancy allows for the explanation of several observations gained from the reactions of diene **8**. For example, the lack of increased stereoselectivity in the high pressure reactions of **8** is consistent with the idea that the *Re exo* transition state is dominant. That is, under normal pressure, the *Re exo* transition state is favored over the others. Under high pressure, however, the *endo* transition states are more dominant, and, according to the results in Table 6, the two *endo* transition states are quite similar in energy, resulting in relatively poor diastereoselectivity.

Another interesting observation was the high level of selectivity obtained in the reaction of diene **8** with *N*-methylmaleimide versus the low level of selectivity of **8** with maleic anhydride. One hypothesis would be an intrinsic high *exo* selectivity of *N*-methylmaleimide as compared to the other dienophiles in this study. This also seems likely given the result of the reaction of *N*-methylmaleimide with diene **9** (78% *exo* adduct).

The work of Kakushima and Houk in their investigation of electron-rich butadienes may contribute to our understanding of this phenomenon.[38] These investigators found that two competing secondary overlap effects, closed-shell repulsions and secondary attractive effects, controlled the *exo/endo* selectivity of Diels-Alder reactions with highly electron-rich dienes. Kakushima[38a] demonstrated that large π-charge density interactions between the allylic substituent of the dienophile and the β- and γ-carbons of the diene will result in preferential formation of *exo* Diels-Alder adduct. Hückel calculations show that the π-charge density of the carbonyl carbon of *N*-methylmaleimide (0.844) is much higher than that of maleic anhydride (0.670).[39] Thus, the *exo* selectivity of the *N*-methylmaleimide dienophile may result from closed-shell interactions with the highly electron-rich vinylketene acetals. This allows for the reaction to proceed through the "bottom *exo*" transition state and provide for high levels of selectivity. The low selectivity of maleic anhydride may then be assigned to the dienophile's low π-charge density and its inherently greater *endo* selectivity, which when coupled with the *exo* preference of **8**, affords lower diastereoselectivity.

The predominant *s-trans* conformation of diene **9** leads to the observed problematic reactivity. A bond rotation is required to obtain a conformation favorable to the cycloaddition reaction. This phenomenon, coupled with the zwitterionic characteristics of these compounds, may lead to competing Michael-type reactions, resulting in the production of polymeric material. Silylketene acetals are known to participate in Lewis acid-catalyzed Michael reactions.[40] No such problem exists for diene **8**, probably due to the C-3 methyl group, which restricts rotation around the C-2, C-3 bond.

Conclusions.[41]

We have successfully developed a series of enantiomerically pure vinylketene acetals to act as diastereoselective dienes in the Diels-Alder reaction. Most selective were dienes **8** and **9**, which utilized phenyl rings as asymmetric directing groups. It was shown through NOE analysis that the major product obtained from the reaction of diene **9** and *N*-methylmaleimide was due to *Re exo* approach of the dienophile to the diene. It was demonstrated with the aid of computer modeling and the coupling constants of the minor constituents of this reaction that three of the four possible transition states were contributing to the product distribution. The relative order of the transition state energies were determined to be *Re exo* < *Re endo* < *Si endo* < *Si exo* by computer modeling utilizing MM2 parameters and confirmed by the isolation of the cycloaddition products. The computer model and exclusion shell repulsions were then used to rationalize the high level of selectivity observed with reactions of *N*-methylmaleimide and diene **8** (48:1).

Experimental

General Procedures. Nuclear Magnetic Resonance (NMR) spectra were obtained at 300 MHz for protons (^{1}H NMR) and 75 MHz for carbons (^{13}C NMR) on a General Electric GN-300. Signal assignments are reported in δ, parts per million (ppm), from tetramethylsilane in the following format: chemical shift (multiplicity, coupling constants, integration, nuclei assignments). Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Proton chemical shifts were referenced in $CDCl_3$ to the residual $CHCl_3$ signal (7.26 ppm), in benzene-d_6 to the residual benzene-d_5 signal (7.15 ppm), and in DMSO-d_6 to the residual DMSO-d_5 signal (2.49 ppm). Carbon chemical shifts were referenced to the solvent in a similar manner: $CDCl_3$ (77.09 ppm), benzene-d_6 (128.0 ppm), and DMSO-d_6 (39.5 ppm). Low resolution mass spectra (MS) were obtained on a Finnigan 4000 Mass Spectrometer. Sample ionization was initiated by either electron bombardment (EI) or chemical ionization (CI). High resolution mass spectra (HRMS) were obtained at the UC Riverside Analytical Chemistry Instrumentation Facility. Mass spectral data are reported in the following format: MS or HRMS (ionization type), *m/z* = mass

of fragment (mass of parent ion ± assignment of the fragment cleaved or added, % intensity of that spectral line with respect to the base peak). A Nicolet Analytical Instruments 5MX Fourier Transform spectrophotometer was utilized to obtain infrared spectra (IR). Characteristic infrared absorptions are reported in cm^{-1} as well as the solvent used in the solution cell. Melting points were obtained on a Thomas-Hoover instrument and are reported uncorrected. Optical rotations were recorded from a Perkin-Elmer 141 Polarimeter at the sodium D line. Rotations are reported in the following format: $[\alpha]^{25}_{D}$ rotation (concentration in g/100 mL, solvent). Ultraviolet-visible spectra were obtained on a Hitachi 100-80 spectrophotometer. (Solvent), λ_{max} and (extinction coefficient) are reported for all dienes synthesized. Combustion analyses were obtained at Atlantic Microlab, Inc. of Atlanta, Georgia.

All reactions were carried out with oven- or flame-dried glassware under a positive nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on Kieselgel silica 60 F-254 plates or by gas-liquid chromatography (GC) on a Hewlett Packard 5890 gas chromatograph equipped with a flame ionization detector. Diastereomeric ratios were obtained on the above GC utilizing two different columns. Ratios for the Diels-Alder products obtained from the reaction of the chiral diene and *N*-methylmaleimide or *N*-phenylmaleimide were obtained using a methyl silicone, 530 μm wide bore, 5 meter column. All other diastereomeric ratios were obtained utilizing a 25 meter Carbowax capillary column and confirmed by the ^1H NMR of the reaction mixture before chromatography. Flash chromatography was carried out as described by Taber[42] using Merck grade 60, 230-400 mesh silica gel. A Waters Associates Model 6000A high pressure liquid chromatography (HPLC) pump equipped with a Regis "semi-prep" 10 μm, 60Å silica gel, 25 cm x 10 mm i.d. column and a difference refractive index detector were employed for the separation of diastereomers. All aromatic solvents except *o*-nitrotoluene were distilled from sodium before use. Hexanes, ethyl acetate, acetonitrile and CH_2Cl_2 were distilled from CaH_2 when anhydrous conditions were required. $CHCl_3$ was purified by washing with water then dried and distilled from P_2O_5. *o*-Nitrotoluene was also distilled from P_2O_5. All anhydrous ethers were distilled from sodium benzophenone ketyl immediately before their use in a reaction.

3-Methyl-2-butenoic acid, 2-chloroethyl ester (1). 3-Methyl-2-butenoic acid (20.0 g, 0.20 moles) was dissolved in 2-chloroethanol (50 mL) and H_2SO_4 (1 mL). The solution was then heated to reflux overnight. The reaction was quenched with aqueous sodium carbonate and the organic layer dried with $MgSO_4$. Following removal of the excess chloroethanol under vacuum the crude product was purified by distillation, 65-69 °C at 2 mm Hg, 85% yield: ^1H NMR ($CDCl_3$) δ 5.67 (t, 1.2 Hz, 1 H, **H**C=), 4.28 (t, 5.7 Hz, 2 H, $\mathbf{H_2}$CO), 3.64 (t, 5.7 Hz, 2 H, $\mathbf{H_2}$CCl), 2.12 (d, 1.2 Hz, 3 H, $\mathbf{H_3}$C), 1.86 (s, 3 H, $\mathbf{H_3}$C). ^{13}C NMR ($CDCl_3$) δ 166.0, 158.1, 115.4, 63.2, 41.9, 27.5, 20.3. IR ($CDCl_3$) 2951, 1713, 1647 cm^{-1}. MS (CI, isobutane) *m/z* 165 (M^++1, 30%), 163 (M^++1, 100%).

3-Methyl-2-butenoic acid, (2*S*,3*R*)-3-bromo-2-butyl ester (2). Dicyclohexylcarbodiimide (DCC, 1.0 g, 5 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of (2*S*,3*R*)-3-bromo-2-butanol (500 mg, 3.26 mmol), 3,3-dimethylacrylic acid (500 mg, 5 mmol) and DMAP (45 mg) in CH_2Cl_2 (8 mL) at 0 °C. The formation of urea byproduct was observed as a white precipitate before the addition of the DCC was complete. Following the completion of the DCC addition the reaction flask was allowed to warm to ambient temperature and stirred for 24 hours. The reaction was worked up by vacuum filtration of the urea byproduct followed by one wash of 10% HCl (25 mL), two washes of saturated Na_2CO_3 (25 mL) and one wash of brine solution (25 mL). The organic layer was dried with $MgSO_4$ and the CH_2Cl_2 removed by rotary evaporation. The resulting heterogeneous oil was triturated twice with hexanes and a bulb to bulb distillation (85-90 °C, 1 mm Hg) was performed on the resulting oil to give clean ester (656 mg, 86% yield): $[\alpha]^{25}_{D}$ = -18.6° (c = 2.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 5.73 (t, 1.2 Hz, 1 H, **H**C=), 4.98 (m, 1 H, **H**CO), 4.25 (m, 1 H, **H**CBr), 2.21 (s, 3 H, $\mathbf{H_3}$CC=), 1.96 (d, 1.2 Hz, 3 H, $\mathbf{H_3}$CC=), 1.69 (d, 6.9 Hz, 3 H, $\mathbf{H_3}$CCH), 1.35 (d, 6.9 Hz, 3 H, $\mathbf{H_3}$CCH). ^{13}C NMR ($CDCl_3$) δ 171.8, 159.7, 115.7, 72.1, 52.2, 27.7, 21.8, 20.5, 16.7. IR ($CDCl_3$) 2917, 1717, 1649

cm^{-1}. MS (70 eV) *m/z* 132 (M^+- 3-methylbutenoate, 1.0%), 130 (M^+- 3-methylbutenoate, 1.1%).

3-Methyl-2-butenoic acid, (3*S*,4*R*)-2,5-dimethyl-4-bromo-3-hexyl ester (3). Dicyclohexylcarbodiimide (DCC, 600 mg, 2.9 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a mixture of 3,3-dimethylacrylic acid (300 mg, 3.0 mmol), DMAP (30 mg) and (3*S*,4*R*)-2,5-dimethyl-4-bromo-3-hexanol (380 mg, 1.8 mmol) in 5 mL CH_2Cl_2 at 0 °C. The reaction was carried out as stated above. A yield of 457 mg (87%) was obtained after a bulb to bulb distillation (90-95 °C, 0.75 mm Hg): $[\alpha]^{25}_D$ = -43.5° (c = 2.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 5.72 (m, 1 H, **HC**=), 4.80 (dd, 7.5, 3.3 Hz, 1 H, **HCO**), 4.35 (dd, 7.0, 3.3 Hz, 1 H, **HCBr**), 2.16 (d, 1.2 Hz, 3 H, $\mathbf{H_3}$CC=), 2.05 (m, 1 H, **HCCH**$_3$), 1.90 (d, 1.2 Hz, 3 H, $\mathbf{H_3}$CC=), 1.58 (m, 1 H, **HCCH**$_3$), 0.98-0.87 (m, 12 H, $\mathbf{H_3}$CCH). ^{13}C NMR ($CDCl_3$) δ 166.5, 157.6, 115.8, 76.6, 62.3, 31.1, 29.2, 27.5, 19.4, 18.3, 18.1. IR ($CDCl_3$) 2974, 1721, 1648 cm^{-1}. MS (70 eV), *m/z* 194 (M^+-3-methylbutenoate, 1.0%), 192 (M^+-3-methylbutenoate, 1.1%). MS (CI, isobutane) m/z 293 (M^++1, 2.1%), 291 (M^++1, 2.2%).

3-Methyl-2-butenoic acid, (2*S*,3*R*)-1,4-dimethoxy-3-chloro-2-butyl ester (4). Dicyclohexylcarbodiimide (DCC, 1.0 g, 5 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of (2*S*,3*R*)-1,4-dimethoxy-3-chloro-2-butanol (490 mg, 2.98 mmol), 3,3-dimethylacrylic acid (500 mg, 5 mmol) and DMAP (45 mg) in CH_2Cl_2 (8 mL) at 0 °C. The reaction was carried out as stated above. The product was isolated as an oil by column chromatography utilizing 10% Et_2O in hexanes as the elutant (625 mg, 84% yield): $[\alpha]^{25}_D$ = +17.0° (c = 8.3, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 5.68 (m, 1 H, **HC**=), 5.23 (m, 1 H, **HCO**), 4.26 (m, 1 H, **HCCl**), 3.77 (d, 5.2 Hz, 2 H, $\mathbf{H_2}$CO), 3.62 (d, 5.2 Hz, 2 H, $\mathbf{H_2}$CO), 3.42 (s, 3 H, $\mathbf{H_3}$CO), 3.39 (s, 3 H, $\mathbf{H_3}$CO), 2.17 (d, 1.2 Hz, 3 H, $\mathbf{H_3}$CC=), 2.08 (d, 1.2 Hz, 3 H, $\mathbf{H_3}$CC=). ^{13}C NMR ($CDCl_3$) δ 171.6, 158.5, 115.9, 73.9, 73.2, 71.7, 59.4, 59.3, 59.2, 27.7, 21.1. IR ($CDCl_3$) 2986, 2974, 1720, 1648, 1456 cm^{-1}. MS (CI, isobutane), *m/z* 252 (M^++1, 0.5%), 250 (M^++1, 1.5%).

3-Methyl-2-butenoic acid, (1*R*,2*S*)-2-chloro-1,2-diphenylethyl ester (5). (1*R*,2*S*)-2-Chloro-1,2-diphenylethanol (4.0 g, 13 mmol), CH_2Cl_2 (35 mL), and 3,3-dimethylacrylic acid chloride (3.2 g, 2 eq.) were placed in a round bottom flask blanketed with an atmosphere of N_2 and cooled to 0 °C. Pyridine (1.5 mL) was then added dropwise with stirring. After the addition was complete the solution was allowed to warm to room temperature and stirred for an additional 8 hours. The solution was washed with 1N HCl (2 x 30 mL), water (30 mL), saturated Na_2CO_3 (3 x 30 mL). The organic layer was dried with $MgSO_4$ and the solvent removed by evaporation. The crude product was recrystallized with methanol/water to give a white solid (89% yield). This ester may also be synthesized by the DCC procedure described above. Isolation by column chromatography using 2.5% EtOAc in hexanes as the mobile phase gives the compound in 78% yield: mp 75-76 °C. $[\alpha]^{25}_D$ = +22.1° (c = 3.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.28-7.35 (m, 10 H), 6.19 (d, 6.3 Hz, 1 H, **CHPh**), 5.65 (br s, 1 H, =**CH**), 5.18 (d, 6.3 Hz, 1 H, **CHPh**), 2.07 (s, 3 H, $\mathbf{CH_3}$), 1.86 (s, 3 H, $\mathbf{CH_3}$). ^{13}C NMR ($CDCl_3$) δ 165.4, 158.8, 137.2, 136.6, 128.7, 128.4, 128.3, 127.8, 115.4, 78.2, 64.6, 27.5, 20.4. IR ($CDCl_3$) 3160, 2932, 1721, 1649, 1468 cm^{-1}. MS (70 eV) *m/z* 217 (M^+- 3-methylbutenoate, 2.5%), 215 (M^+-3-methylbutenoate, 7.5%). Anal. calcd for $C_{19}H_{19}ClO_2$: C, 72.49; H, 6.08. Found: C, 72.36; H, 6.04.

(*E*)-4-Methyl-2-butenoic acid, (1*R*,2*S*)-2-chloro-1,2-diphenylethyl ester (6). Dicyclohexylcarbodiimide (DCC, 1.0 g, 5 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of (1*R*,2*S*)-2-chloro-1,2-diphenylethanol (750 mg, 3.23 mmol), (*E*)-3-pentenoic acid (500 mg, 5 mmol) and DMAP (45 mg) in CH_2Cl_2 (8 mL) at 0 °C. The reaction was manipulated as described above. The pure oil (900 mg, 89% yield) was obtained by utilizing 2.5% Et_2O in hexanes as the elutant in column chromatography: $[\alpha]^{25}_D$ = +21.0° (c = 2.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.34-7.20 (m, 10 H), 6.18 (d, 6.9 Hz, 1 H, **HCO**), 5.44 (m, 1 H, **HC**=), 5.33 (m, 1 H, **HC**=), 5.14 (d, 6.9 Hz, 1 H, **HCCl**), 2.90 (d, 6.6 Hz, 2 H, $\mathbf{H_2}$C), 1.63 (dd, 6.3, 1.2 Hz, 3 H, $\mathbf{H_3}$C). ^{13}C NMR ($CDCl_3$) δ 170.5, 137.3, 136.6, 129.7, 128.7, 128.4, 128.3, 127.8, 122.1, 78.1, 64.2, 38.0, 18.0. IR ($CDCl_3$) 3038, 2919, 1811, 1732, 1645 cm^{-1}. MS (CI, isobutane) *m/z* 317 (M^++1, 0.2%), 315 (M^++1, 0.6%). Anal. calcd for $C_{19}H_{19}ClO_2$: C, 72.49; H, 6.08. Found: C, 72.24; H,

6.02.

Diene Synthesis, General Procedure. A round bottom flask was charged with 2 equivalents KH (380 mg, 8.0 mmol), dimethoxyethane (DME, 50 mL) and a N_2 atmosphere. A solution of the haloester (4.0 mmol) in DME (5 mL) was then added dropwise at 0 °C with stirring. Stirring was maintained for an additional two hours at ambient temperature and the solvent removed under vacuum after Schlenk filtration. Kugelrhor distillation at reduced pressure gave the purified product in 65-90% yields. The product was stored as a solution in benzene at -33 °C under a N_2 atmosphere.

2-(2-Methyl-2-propenidene)-1,3-dioxolane (7). 3-Methyl-2-butenoic acid, 2-chloroethyl ester was treated with KH as stated above. Distilled yield, 65-75%, 43 °C at 2 mm Hg: ^{1}H NMR ($CDCl_3$) δ 4.72 (d, 2.4 Hz, 1 H, =CH_2), 4.52 (dq, 2.4, 1.2 Hz, 1 H, =CH_2), 4.51 (s, 1 H, =CH), 4.32 (t, 7.5 Hz, 2 H, CH_2), 4.18 (t, 7.5 Hz, 2 H, CH_2), 1.92 (br s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$) δ 159.6, 139.6, 107.1, 76.8, 66.9, 64.7, 23.2. IR ($CDCl_3$) 3093, 3041, 2964, 2924, 1683, 1479, 1454 cm^{-1}. λ_{max} (Et_2O), 280.0 nm (14800).

(4*R*,5*R*)-4,5-Diphenyl-2-(2-methyl-2-propenidene)-1,3-dioxolane (8). 3-Methyl-2-butenoic acid, (1*R*,2*S*)-2-chloro-1,2-diphenylethyl ester was treated with KH as described above. Distilled yield, 80-90%, 150 °C at 1 mm Hg: $[\alpha]^{25}_D$ = +189° (c = 2.3, benzene). ^{1}H NMR ($CDCl_3$) δ 7.41-7.29 (m, 10 H), 5.22 (d, 7.8 Hz, 1 H, HCPh), 5.05 (d, 7.8 Hz, 1 H, HCPh), 4.83 (d, 2.1 Hz, 1 H, H_2C=), 4.75 (s, 1 H, HC=), 4.61 (dq, 2.1, 1.2 Hz, 1 H, H_2C=), 2.03 (br s, 3 H, H_3C). (DMSO-d_6) δ 7.40-7.31 (m, 10 H), 5.51 (d, 7.2 Hz, 1 H), 5.33 (d, 7.2 Hz, 1 H), 4.68 (d, 1.8 Hz, 1 H), 4.58 (s, 1 H), 4.47 (d, 1.8 Hz, 1 H), 1.89 (s, 3 H). (benzene-d_6) δ 7.17-6.96 (m, 10 H), 5.15 (s, 1 H), 5.13 (d, 6.3 Hz, 1 H), 4.87 (s, 1 H), 4.85 (s, 1 H), 4.70 (d, 6.3 Hz, 1 H), 2.23 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 159.8, 139.6, 136.0, 135.8, 129.2, 129.0, 128.8, 128.4, 126.5, 126.3, 108.0, 87.1, 85.1, 77.6, 23.3. (DMSO-d_6) d 159.3, 138.5, 137.1, 135.4, 131.3, 129.1, 128.8, 128.4, 128.2, 107.7, 85.5, 83.5, 76.7, 22.9. (benzene-d_6) δ 159.9, 139.9, 138.0, 137.5, 128.9, 128.2, 128.0, 127.5, 127.3, 108.5, 87.2, 85.2, 78.5, 23.5. IR ($CDCl_3$) 3158, 3092, 3044, 3038, 2964, 2924, 1682, 1480, 1454 cm^{-1}. λ_{max} (Et_20), 278.6 nm (14600).

(4*R*,5*R*)-4,5-Diphenyl-2-((*E*)-2-butenidene)-1,3-dioxolane (9). (*E*)-4-Methyl-2-butenoic acid, (1*R*,2*S*)-2-chloro-1,2-diphenylethyl ester was treated with KH as described above. Distilled yield, 75-85%, 150 °C at 0.15 mm Hg. $[\alpha]^{25}_D$ = +198° (c = 2.2, benzene). ^{1}H NMR ($CDCl_3$) δ 7.44-7.11 (m, 10 H), 6.26 (dd, 15.3, 11.1 Hz, 1 H, =CHCH), 5.42 (dq, 15.3, 6.6 Hz, 1 H, =$CHCH_3$), 5.16 (d, 7.5 Hz, 1 H, CHPh), 5.11 (d, 7.5 Hz, 1 H, CHPh), 4.77 (d, 11.1 Hz, 1 H, =CHCH), 1.76 (dd, 6.6, 1.2 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$) δ 159.3, 137.4, 137.2, 135.9, 129.2, 129.0, 128.7, 128.4, 126.5, 119.9, 86.4, 86.0, 75.1, 18.5. IR ($CDCl_3$) 3158, 3092, 3044, 3040, 2964, 2924, 1683, 1479, 1450 cm^{-1}. λ_{max} (Et_2O) = 244.0 nm (22100).

Hydrolysis of 2-(2-methyl-2-propenidene)-1,3-dioxolane (7). Diene 7 (100 mg) was subjected to saturated NH_4Cl (3 mL) for 5 minutes. The solution was extracted with Et_2O (2 x 5 mL) and the organic layer dried with $NaSO_4$. Removal of the solvent by rotary evaporation gave 110 mg (99%) of a mixture of conjugated (44%) and unconjugated (56%) hydroxy esters.

3-Methyl-2-butenoic acid, 2-hydroxyethyl ester: ^{1}H NMR ($CDCl_3$) δ 5.66 (s, 1 H, HC=), 4.16 (t, 4.9 Hz, 2 H, H_2CO), 3.76 (t, 2 H, 4.9 Hz, H_2COH), 2.78 (br s, 1 H, HO), 2.11, (s, 3 H, H_3C), 1.85 (s, 3 H, H_3C). ^{13}C NMR ($CDCl_3$) δ 167.0, 157.9, 115.6, 65.2, 60.9, 27.5, 20.3. IR ($CDCl_3$) 3441, 2951, 1713, 1647 cm^{-1}. MS (CI, isobutane), *m/z* 145 (M^++1, 100%).

3-Methyl-3-butenoic acid, 2-hydroxyethyl ester: ^{1}H NMR ($CDCl_3$) δ 4.87 (s, 1 H, H_2C=), 4.80 (s, 1 H, H_2C=), 4.16 (t, 4.9 Hz, 2 H, H_2CO), 3.76 (t, 2 H, 4.9 Hz, H_2COH), 3.03 (br s, 2 H, H_2C), 1.76 (s, 3 H, H_3C). ^{13}C NMR ($CDCl_3$) δ 171.9, 138.4, 114.9, 66.2, 61.2, 43.3, 22.5. IR ($CDCl_3$) 3441, 2951, 1735, 1649 cm^{-1}. MS (CI, isobutane), *m/z* 145 (M^++1, 100%).

Synthesis of compound 11. The Diels-Alder reaction of diene 7 and methyl crotonate. A glass tube was charged with achiral diene 7 (300 mg), K_2CO_3 (50 mg) and methyl crotonate (2 mL). The tube was degassed, sealed and heated to 110 °C for 18 hours. The liquid was removed from the reaction flask and the

excess crotonate removed at reduced pressure, 1mm Hg. Flash chromatography of the resulting oil with 15% EtOAc in hexanes as the mobile phase gave the cycloadduct (434 mg, 85% yield): ^{1}H NMR ($CDCl_3$) δ 5.29 (d, 1.2 Hz, 1 H, **HC**=), 3.92 (m, 2 H, $\mathbf{H_2}$CO), 3.72 (m, 2 H, $\mathbf{H_2}$CO), 3.68 (s, 3 H, $\mathbf{H_3}$CO), 2.55 (d, 12.0 Hz, 1 H, **HCC**=O), 2.29 (m, 1 H, **HCCH**$_3$), 2.10 (dd, 18.0, 4.8 Hz, 1 H, $\mathbf{H_2}$CC=), 1.68 (m, 1 H, $\mathbf{H_2}$CC=), 1.66 (s, 3 H, $\mathbf{H_3}$CC=), 0.94 (d, 6.6 Hz, 3 H, $\mathbf{H_3}$CCH). ^{13}C NMR ($CDCl_3$) δ 172.1, 138.9, 122.3, 107.0, 65.2, 64.8, 55.8, 51.7, 38.1, 29.9, 22.9, 19.7. IR ($CDCl_3$) 3028, 2979, 1732, 1666, 1456, 1437 cm^{-1}. MS (CI, isobutane), *m/z* 227 (M^++1, 0.5%), 195 (M^+-OCH_3, 2.1%).

Synthesis of compound 13. The Diels-Alder reaction of (4*S*,5*S*)-4,5-dimethyl-2-(2-methyl-2-propenidene)-1,3-dioxolane (12) and methyl crotonate. 3-Methyl-2-butenoic acid, (2*S*,3*R*)-3-bromo-2-butyl ester (450 mg, 1.9 mmol) in DME (1 mL) was added dropwise to a round-bottom flask charged with KH (289 mg, 7.22 mmol) and DME (5 mL). After one hour at room temperature the reaction was observed to be complete by TLC. The solution was then filtered and the solvent removed as stated in the general diene synthesis procedure. The crude product was then added to a solution of toluene (5 mL) and methyl crotonate (0.5 mL) and brought to reflux for 80 hours. Upon cooling, excess solvent was removed under vacuum, 2 mm Hg, at ambient temperature. The cycloadduct (193 mg, 40% yield) was isolated as a mixture of two diastereomers, 1.4:1, by flash chromatography utilizing 10% Et_2O in hexanes as the elutant.

Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 5.38 (s, 1 H, **HC**=), 3.69 (s, 3 H, $\mathbf{H_3}$CO), 3.48 (m, 1 H, **HCO**), 3.35 (m, 1 H, **HCO**), 2.58 (d, 12 Hz, 1 H, **HCCO**$_2$), 2.28 (m, 1 H, **HCCH**$_3$), 2.11 (dd, 14.4, 3.9 Hz, 2 H, $\mathbf{H_2}$CC=), 1.71 (m, 1 H, $\mathbf{H_2}$CC=), 1.67 (s, 3 H, $\mathbf{H_3}$CC=), 1.22 (d, 6.8 Hz, 3 H, $\mathbf{H_3}$C), 1.19 (d, 6.9 Hz, 3 H, $\mathbf{H_3}$C), 0.96 (d, 3.9 Hz, 3 H, $\mathbf{H_3}$C). ^{13}C NMR ($CDCl_3$) δ 172.0, 139.1, 123.7, 105.9, 78.9, 77.8, 57.1, 51.5, 37.9, 29.7, 23.1, 20.0, 17.4, 16.4. IR ($CDCl_3$) 3028, 2958, 2931, 1733, 1667, 1454 cm^{-1}. MS (CI, isobutane), *m/z* 255 (M^++1, 0.5%), 223 (M^+-OCH_3, 2.1%).

Distinguishing resonances for the minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 5.30 (s, 1 H, **HC**=), 2.50 (d, 12 Hz, 1 H, **HCCO**$_2$), 1.66 (s, 3 H, $\mathbf{H_3}$CC=), 1.20 (d, 6.8 Hz, 3 H, $\mathbf{H_3}$C), 1.17 (d, 6.9 Hz, 3 H, $\mathbf{H_3}$C), 0.95 (d, 3.9 Hz, 3 H, $\mathbf{H_3}$C). ^{13}C NMR ($CDCl_3$) δ 172.2, 138.2, 123.7, 106.2, 78.9, 77.8, 56.3, 51.4, 38.4, 29.6, 22.9, 19.7, 17.0, 16.1.

Synthesis of compound 15. The Diels-Alder reaction of (4*S*,5*S*)-4,5-[di-(methoxymethyl)]-2-(2-methyl-2-propenidene)-1,3-dioxolane (14) and methyl crotonate. 3-Methyl-2-butenoic acid, (2*S*,3*R*)-1,4-dimethoxy-3-chloro-2-butyl ester (430 mg, 1.7 mmol) in DME (1 mL) was added dropwise to a round-bottom flask charged with KH (287 mg, 7.14 mmol) and DME (5 mL). After one hour at room temperature the reaction was observed to be complete by TLC. The solution was then filtered and the solvent removed as stated in the general diene synthesis procedure. The crude product was then added to a solution of toluene (5 mL) and methyl crotonate (0.5 mL) and brought to reflux for 80 hours. Upon cooling, the excess solvent was removed under vacuum, 2 mm Hg. The cycloadduct (293 mg, 55% yield) was isolated by flash chromatography as a mixture of two diastereomers, 1.3:1, when eluted with 40% Et_2O in hexanes.

Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 5.38 (s, 1 H, **HC**=), 4.04 (m, 1 H, **HCO**), 3.74 (m, 1 H, **HCO**), 3.65 (s, 3 H, $\mathbf{H_3}$CO$_2$C), 3.60 (m, 1 H, **HCO**), 3.51-3.38 (m, 3 H, **HCO**), 3.33 (s, 3 H, $\mathbf{H_3}$CO), 3.29 (s, 3 H, $\mathbf{H_3}$CO), 2.57 (d, 12.3 Hz, 1 H, **HCCO**$_2$), 2.24 (m, 1 H, **HCCH**$_3$), 1.99 (dd, 18.0, 5.4 Hz, 1 H, $\mathbf{H_2}$CC=), 1.65 (m, 1 H, $\mathbf{H_2}$CC=), 1.62 (s, 3 H, $\mathbf{H_3}$CC=), 0.91 (d, 6.0 Hz, 3 H, $\mathbf{H_3}$CCH). ^{13}C NMR ($CDCl_3$) δ 171.5, 138.9, 123.1, 107.5, 78.1, 77.1, 72.7, 72.5, 59.4, 56.4, 51.4, 37.9, 29.4, 23.0, 20.0. IR ($CDCl_3$) 3028, 2979, 1732, 1667, 1457, 1437 cm^{-1}. MS (CI, isobutane), *m/z* 315 (M^++1, 0.3%), 283 (M^+-OCH_3, 0.5%).

Characteristic resonances for the minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 5.28 (s, 1 H, **HCC**=), 3.32 (s, 3 H, $\mathbf{H_3}$CO), 3.29 (s, 3 H, $\mathbf{H_3}$CO), 2.52 (d, 13.2 Hz, 1 H, **HCCO**$_2$), 1.61 (s, 3 H, $\mathbf{H_3}$CC=), 0.89 (d, 6.0 Hz, 3 H, $\mathbf{H_3}$CCH). ^{13}C NMR ($CDCl_3$) δ 171.9, 138.2, 123.1, 107.7, 77.4, 76.8, 59.4, 56.1, 51.3, 38.3, 29.7, 22.8, 19.6.

Synthesis of compound 16. The Diels-Alder reaction of diene 8 and methyl crotonate. Diene **8** (50

mg, 0.18 mmol) and methyl crotonate (90 mg, 5 eq) were placed in a round-bottom flask with 1 mL of the appropriate solvent. BSA (50 μL, proton scavenger) and BHT (5 mg, radical scavenger) were also added. After the listed reaction time at 110 °C had elapsed, a small sample was retained for GLC analysis and the solvent removed under reduced pressure, 1 mm Hg. The cycloadduct was isolated by flash chromatography utilizing 6% Et_2O in hexanes as the elutant. Results: neat, 40 hours reaction time, diasteriomeric ratio 2:1, 74% yield; toluene, 40 hours reaction time, diasteriomeric ratio 3:1, 70%; *o*-dichlorobenzene, 60 hours reaction time, diasteriomeric ratio 2:1, 65%; *o*-nitrotoluene, 60 hours reaction time, diasteriomeric ratio 4:1, 62%; acetonitrile, 80 hours reaction time, diasteriomeric ratio 3.3:1, 62%.

Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.39-7.20 (m, 10 H), 5.83 (s, 1H, **H**C=), 4.81 (d, 8.7 Hz, 1 H, **H**CPh), 4.60 (d, 8.7 Hz, 1 H, **H**CPh), 3.83 (s, 3 H, H_3CO), 2.87 (d, 12.3Hz, 1 H, **H**CCO_2), 2.50 (m, 1 H, **H**CCH_3), 2.21 (dd, 18.3, 4.8 Hz, H_2CC=), 1.86 (m, 1 H, H_2CC=), 1.81 (s, 3 H, H_3CC=), 1.09 (d, 6.3 Hz, 3 H, H_3CCH). ^{13}C NMR ($CDCl_3$) δ 171.9, 140.0, 136.7, 135.6, 129.3, 128.9, 128.5, 128.1, 127.3, 127.0, 126.8, 126.7, 125.2, 123.0, 106.9, 85.9, 85.4, 56.5, 51.9, 38.2, 29.6, 23.3, 20.1. IR ($CDCl_3$) 3156, 3069, 3036, 2959, 2930, 1819, 1792, 1738, 1658, 1454 cm^{-1}. MS (CI, isobutane) *m/z* 379 (M^++1, 0.5%), 347 (M^+-OCH_3, 1.8%). Anal. calcd for $C_{24}H_{26}O_4$: C, 75.96; H, 7.17. Found: C, 75.76; H, 7.10.

Distinguishing resonances for the minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 5.68 (s, 1 H, **H**C=), 4.79 (d, 8.4 Hz, 1 H, **H**CPh), 4.49 (d, 8.4 Hz, 1 H, **H**CPh), 3.82 (s, 3 H, H_3CO), 2.86 (d, 12.3Hz, 1 H, **H**CCO_2), 1.06 (d, 6.3 Hz, 3 H, H_3CCH). ^{13}C NMR ($CDCl_3$) δ 172.3, 139.0, 135.7, 107.5, 85.8, 84.8, 56.4, 51.8, 38.6, 29.9, 23.1, 19.7.

Deketalization and decarboxylation of the Diels-Alder product 16. The 3:1 diastereomeric mixture of cycloadduct **16** (50 mg) was refluxed for 3 hours in 2 mL of 10% HCl. The reaction mixture was extracted with Et_2O (3 x 3 mL) and the organic layer dried with Na_2SO_4. Evaporation of the solvent followed by flash chromatography (10% Et_2O in pentanes) gave (*R*)-3,5-dimethyl-2-cyclohexenone **20** (11 mg, 68% yield). $[\alpha]^{25}_D$ = -61° (c = 0.5, $CHCl_3$). Reported[26]: $[\alpha]^{25}_D$ = -138° (c = 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 5.85 (s, 1 H), 2.53 (dd, 17.0, 9.3 Hz, 1 H), 2.35-2.09 (m, 3 H), 2.01 (s, 3 H), 1.08 (d, 6.9 Hz, 3 H).

Synthesis of compound 16. The high pressure Diels-Alder reaction of diene 8 and methyl crotonate. Diene **8** (100 mg, 0.36 mmol) and methyl crotonate (2.5 eq) and 1 mL of the appropriate solvent were placed in a polyethylene reaction vessel. The reaction vessel was then submitted to 6.8 kbar of pressure for 60 hours at ambient temperatures. After solvent removal by evaporation, flash chromatography of the resulting oil as described above gave compound **16**. Results: Reaction 1; neat, no product observed. Reaction 2; Et_2O, 83% yield, 3:1 ratio of diastereomers. Reaction 3; $CHCl_3$, 80% yield, 3:1 ratio of diastereomers.

Synthesis of compound 17. The Diels-Alder reaction of Diene 8 and (*E*)-*t*-butyl crotonate. Diene **8** (245 mg, 0.88 mmol) and *t*-butyl crotonate (2 mL) were placed in a round-bottom flask with BSA (50 μL) and BHT (5 mg). After 40 hours at 110 °C, a small sample was retained for GLC analysis and the solvent removed under reduced pressure, 1 mm Hg. The cycloadduct was isolated by flash chromatography utilizing 6% Et_2O in hexanes as the elutant (370 mg, 78% yield, diasteriomeric ratio 2:1).

Major diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.39-7.20 (m, 10 H), 5.82 (s, 1 H, **H**C=), 4.80 (d, 8.7 Hz, 1 H, **H**CPh), 4.64 (d, 8.7 Hz, 1 H, **H**CPh), 2.74 (d, 11.4 Hz, 1 H, **H**CCO_2), 2.48 (m, 1 H, **H**CCH_3), 2.18 (dd, 18.0, 5.1 Hz, 1 H, H_2CC=), 1.82 (m, 1 H, H_2CC=), 1.78 (s, 3 H, H_3C), 1.52 (s, 9 H, *t*-butyl), 1.10 (d, 6.6 Hz, 3 H, H_3CCH). ^{13}C NMR ($CDCl_3$) δ 170.9, 142.5, 139.8, 136.8, 129.4, 128.9, 128.5, 128.3, 127.4, 127.3, 127.1, 126.8, 125.2, 106.8, 85.8, 85.3, 85.0, 56.9, 38.2, 29.9, 28.4, 23.2, 19.8. IR ($CDCl_3$) 3069, 2998, 2886, 1738, 1655, 1497, 1454 cm^{-1}. MS (CI, isbutane) *m/z* 397 (M^++1, 0.5%), 307 (M^+-O*t*-Bu, 1.1%). Anal. calcd for $C_{27}H_{32}O_4$: C, 76.93; H, 7.87. Found: C, 76.79; H, 7.90.

Distinguishing resonances of the minor diastereomer: ^{1}H NMR ($CDCl_3$) δ 5.66 (s, 1 H, **H**CC=), 4.82 (d, 8.7 Hz, 1 H, **H**CPh), 4.59 (d, 8.7 Hz, 1 H, **H**CPh), 2.72 (d, 12.3 Hz, 1 H, **H**CCO_2), 2.14 (dd, 17.7, 4.9 Hz,

1 H, H_2CC=), 1.63 (s, 3 H, H_3C), 1.53 (s, 9 H, *t*-butyl), 1.07 (d, 7.5 Hz, 3 H, H_3CCH). ^{13}C NMR ($CDCl_3$) δ 171.0, 140.9, 135.6, 107.4, 57.3, 38.6, 30.4, 28.3, 23.1, 19.6.

Synthesis of compound 18. Diels-Alder reaction of diene 8 and diethyl fumarate. 3-Methyl-2-butenoic acid, (1*R*,2*S*)-2-chloro-1,2-diphenylethyl ester (374 mg, 1.19 mmol) in DME (1 mL) was added dropwise to a round-bottom flask charged with KH (100 mg, 2.5 eq) and DME (5 mL). After one hour of stirring at room temperature the reaction was observed to be complete by TLC. The solution was filtered and the solvent removed as stated in the general diene synthesis procedure. The crude product was added to diethyl fumarate (2 mL) and brought to reflux for 40 hours. Upon cooling, the excess solvent was removed under vacuum, 1 mm Hg, at ambient temperature. The cycloadduct (375 mg, 70% yield) was isolated as a mixture of two diastereomers, 2:1, by flash chromatography utilizing 20% Et_2O in hexanes as the elutant.

Major diasteromer: ^1H NMR ($CDCl_3$) δ 7.58 (d, 7.8 Hz, 1 H), 7.40-7.09 (m, 9 H), 5.87 (s, 1 H, HC=), 5.04 (d, 8.7 Hz, 1 H, HCPh), 4.90 (d, 8.7 Hz, 1 H, HCPh), 4.25 (q, 7.2 Hz, 2 H, CH_2CH_3), 4.06 (q, 7.2 Hz, 2 H, CH_2CH_3), 3.76 (m, 2 H, $HCCO_2$), 2.22 (dd, 19.0, 4.5 Hz, 1 H, H_2CC=), 1.94 (dd, 19.0, 8.7 Hz, 1 H, H_2CC=), 1.48 (s, 3 H, H_3CC=), 1.15-1.01 (m, 6 H, H_3C). ^{13}C NMR ($CDCl_3$) δ 174.1, 171.1, 138.2, 136.6, 135.4, 128.5, 126.9, 126.8, 126.6, 123.8, 106.4, 86.0, 85.4, 61.2, 60.9, 51.1, 41.2, 32.9, 23.0, 14.3. IR ($CDCl_3$) 3154, 3071, 2955, 2899, 1782, 1713, 1599, 1566 cm^{-1}. MS (CI, isobutane) *m/z* 451 (M^++1, 0.5%), 405 (M^+-OEt, 1.2%).

Distinguishing resonances of the minor isomer: ^1H NMR ($CDCl_3$) δ 5.69 (s, 1 H, HC=), 4.94 (d, 8.7 Hz, 1 H, HCPh), 4.82 (d, 8.7 Hz, 1 H, HCPh), 1.46 (s, 3 H, H_3CC=). ^{13}C NMR ($CDCl_3$) δ 173.9, 170.8, 137.3, 136.5, 123.3, 106.0, 85.9, 84.9, 66.1, 50.8, 41.4, 33.0, 22.9.

Synthesis of compound 19. The Diels-Alder reaction of diene 8 and methyl vinyl ketone. Diene **8** (245 mg, 0.88 mmol) and methyl vinyl ketone (3 eq.) were placed in a round-bottom flask with BSA (50 μL), BHT (5 mg) and toluene (1 mL). After 18 hours at 110 °C, a small sample was retained for GLC analysis and the solvent removed under reduced pressure, 1 mm Hg. The cycloadduct was isolated by flash chromatography utilizing 8% Et_2O in hexanes as the elutant (306 mg, 78% yield, diasteriomeric ratio 1.06:1).

Major diastereomer: ^1H NMR ($CDCl_3$) δ 7.34-7.13 (m, 10 H), 5.81 (s, 1H, HC=), 4.83 (d, 8.7 Hz, 1 H, HCPh), 4.67 (d, 8.7 Hz, 1 H, HCPh), 3.16 (dd, 10.2, 3.3 Hz, 1 H, HCC=O), 2.41 (s, 3 H, CH_3), 2.21-1.91 (m, 4 H), 1.81 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$) δ 206.4, 141.1, 136.7, 135.4, 128.6, 126.9, 126.7, 123.3, 107.3, 85.5, 85.2, 55.4, 31.6, 29.3, 23.7, 23.4. IR ($CDCl_3$) 3156, 3069, 3036, 2959, 1713, 1454 cm^{-1}. MS (CI, isobutane) *m/z* 349 (M^++1, 0.35%), 153 (base).

Distinguishing resonances for the minor diastereomer: ^1H NMR ($CDCl_3$) δ 5.70 (d, 0.9 Hz, 1H, HC=), 4.84 (d, 8.7 Hz, 1 H, HCPh), 4.55 (d, 8.7 Hz, 1 H, HCPh), 3.08 (dd, 11.7, 3.3 Hz, 1 H, HCC=O), 2.38 (s, 3 H, CH_3). ^{13}C NMR ($CDCl_3$) δ 206.0, 140.1, 135.7, 123.3, 85.3, 84.7, 55.5, 31.0, 28.8, 23.3.

Synthesis of compound 21. The Diels-Alder reaction of diene 8 and maleic anhydride. Diene **8** (100 mg, 0.36 mmol) and maleic anhydride (300 mg) were combined with benzene (2 mL). The solution was brought to reflux for 4 days, then cooled to room temperature. Saturated NH_4Cl (5 mL) was then added to the mixture and the solution stirred for 2 hours. The layers were separated and the aqueous layer extracted with $CHCl_3$ (2 x 5 mL). The combined organic layers were dried with $MgSO_4$ and the solvent removed in vacuo. The crude mixture was redissolved into THF (5 mL) and treated with diazomethane at 0 °C. Flash chromatography (15% EtOAc in hexanes) of the resulting oil gave the bismethylester (83 mg, 55% yield) as a 55:45 mixture of diastereomers.

Diene **8** (100 mg, 0.36 mmol) and maleic anhydride (300 mg) were combined with benzene (2 mL) and stirred at room temperature for 7 days. The reaction was then manipulated as described above (85 mg, 56% yield), 59:41 ratio of diastereomers.

Major diastereomer: ^1H NMR ($CDCl_3$) δ 7.33-7.18 (m, 10 H), 5.60 (s, 1 H, HC=), 4.82 (d, 8.4 Hz, 1 H,

HCPh), 4.70 (d, 8.4 Hz, HCPh), 3.77 (s, 3 H, H_3CO), 3.73 (s, 3 H, H_3CO), 3.51 (d, 3.9 Hz, 1 H, $HCCO_2$), 3.30 (m, 1 H, $HCCO_2$), 2.78 (dd, 18.0, 13.5 Hz, 1 H, H_2CC=), 2.30 (dd, 18.0, 6.0 Hz, 1 H, H_2CC=), 1.89 (s, 3 H, H_3CC=). ^{13}C NMR ($CDCl_3$) δ 173.4, 170.5, 140.9, 135.7, 135.1, 128.6, 128.4, 128.2, 127.3, 127.2, 126.8, 126.7, 121.0, 106.5, 86.2, 85.1, 52.2, 51.8, 50.0, 40.8, 29.6, 23.2. IR ($CDCl_3$) 3154, 3071, 2956, 2899, 1777, 1711, 1598, 1566 cm^{-1}. MS (CI, isobutane) *m/z* 423 (M^++ 1, 0.4%), 391 (M^+- OCH3, 0.6%).

Distinguishing resonances for the minor diastereomer: ^1H NMR ($CDCl_3$) δ 5.67 (s, 1 H, HC=), 5.02 (d, 8.7 Hz, 1 H, HCPh), 4.92 (d, 8.7 Hz, HCPh), 3.76 (s, 3 H, H_3CO), 3.65 (s, 3 H, H_3CO), 1.91 (s, 3 H, H_3CC=).

Synthesis of compound 22. The Diels-Alder reaction of diene 8 and *N*-phenylmaleimide. Diene **8** (100 mg, 0.36 mmol) and *N*-phenylmaleimide (500 mg) were combined with 1 mL of the appropriate solvent and BSA (50 μL). The solution was stirred at room temperature for the indicated time. Upon completion of the reaction the solvent was removed in vacuo and the product obtained by flash chromatograpy (18% EtOAc in hexanes). Results: toluene, 5 days reaction time, 5:1 diasteromeric ratio, 88% yield; *o*-dichlorobenzene, 5 days reaction time, 5:1 diasteromeric ratio, 85% yield; *o*-nitrotoluene, 72 hours reaction time, 5.5:1 diasteromeric ratio, 83% yield; $CHCl_3$, 40 hours reaction time, 6:1 diasteromeric ratio, 92% yield; CH_3CN, 12 hours reaction time, 12:1 diasteromeric ratio, 94% yield.

Major diastereomer: ^1H NMR ($CDCl_3$) δ 7.50-7.40 (m, 3 H), 7.32-7.15 (m, 12 H), 6.04 (s, 1 H, HC=), 5.12 (d, 9.0 Hz, 1 H, HCPh), 4.70 (d, 9.0 Hz, 1 H, HCPh), 3.61 (d, 9.5 Hz, 1 H, HCC=O), 3.47 (dt, 9.5, 9.5, 6.5 Hz, 1 H, HCC=O), 2.72 (dd, 17.0, 6.5 Hz, 1 H, H_2C), 2.57 (dd, 17.0, 9.5 Hz, 1 H, H_2C), 1.92 (s, 3 H, H_3C). ^{13}C NMR ($CDCl_3$) δ 178.1, 174.6, 141.2, 136.5, 134.9, 129.1, 128.8, 128.7, 128.5, 127.7, 127.0,126.6, 126.1, 125.1, 105.4, 86.1, 85.3, 49.4, 38.3, 26.9, 23.4. IR ($CDCl_3$) 3156, 3071, 3036, 2951, 2916, 1794, 1714, 1659, 1467 cm^{-1}. MS (EI, 70 eV) 451 (M^+, 0.6%). Anal. calcd for $C_{29}H_{25}NO_4$: C, 77.14; H, 5.58. Found: C, 77.01; H, 5.66.

Characteristic resonances for the minor diastereomer: ^1H NMR ($CDCl_3$) δ 5.87 (s, 1 H, HC=), 4.81 (d, 9.0 Hz, 1 H, HCPh), 4.76 (d, 9.0 Hz, 1 H, HCPh), 1.94 (s, 3 H, H_3C).

Synthesis of compound 23. The Diels-Alder reaction of diene 8 and *N*-methylmaleimide. Diene **8** (100 mg, 0.36 mmol) and *N*-methylmaleimide (400 mg, 5 eq) were added to a round-bottom flask containing $CHCl_3$ (2 mL). The reaction was brought to reflux for 24 hours. After the reaction was complete the solution was cooled to room temperature and the solvent removed in vacuo. Column chromatography (20% EtOAc in hexanes) of the crude solid gave the cycloadduct (94 mg, 67% yield, 95:5 ratio of diastereomers).

Diene **8** (100 mg, 0.36 mmol) and *N*-methylmaleimide (400 mg, 5 eq) were added to a round-bottom flask containing CH_2Cl_2 (2 mL). After 7 days of stirring the reaction was manipulated as described above (133 mg, 95 %, 98:2 ratio of diastereomers). Enantiomerically pure compound was obtained from $CHCl_3$/hexanes recrystallization.

Major diastereomer: mp 150.0-151.5 °C. $[\alpha]^{25}_D$ = +105° (c = 2.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.31-7.20 (m, 10 H), 6.00 (d, 0.9 Hz, 1 H, HC=), 5.08 (d, 8.7 Hz, 1 H, HCPh), 4.65 (d, 8.7 Hz, 1 H, HCPh), 3.46 (d, 9.9 Hz, 1 H, $HCCO_2$), 3.25 (dd, 16.2, 8.4 Hz, 1 H, $HCCO_2$), 3.08 (s, 3 H, H_3CN), 2.54 (s, 1 H), 2.51 (br s, 1 H), 1.88 (s, 3 H, H_3C). ^{13}C NMR ($CDCl_3$) δ 179.2, 175.6, 141.4, 136.5, 135.3, 128.7, 128.5, 128.3, 127.4, 126.7, 126.3, 105.3, 86.1, 85.5, 49.4, 38.2, 27.1, 24.9, 23.4. IR ($CDCl_3$) 3160, 3071, 3036, 2951, 2916, 1777, 1713, 1659 cm^{-1}. HRMS (EI, 70 eV), calcd for $C_{24}H_{23}O_4N$ 389.1628, Found 389.1636. Anal. calcd : C, 74.02; H, 5.95. Found: C, 73.89; H, 6.03.

Characteristic resonances for the minor diastereomer: ^1H NMR ($CDCl_3$), δ 5.84 (br s, 1 H, HC=), 4.72 (d, 8.7 Hz, 1 H, HCPh), 4.72 (d, 8.7 Hz, 1 H, HCPh), 3.05 (s, 3 H, H_3CN), 1.90 (s, 3 H, H_3C).

Synthesis of compounds 24, 25 and 26. The Diels-Alder reaction of diene 9 and *N*-methylmaleimide. Diene **9** (400 mg, 1.4 mmol) and *N*-methylmaleimide (800 mg, 5 eq) were added to a round-bottom flask containing $CHCl_3$ (2 mL), BSA (50 μl), and BHT (5 mg). The reaction was brought to reflux for 24 hours. The solution was then cooled to room temperature and the solvent removed by

evaporation. Column chromatography (20% EtOAc in hexanes) of the crude solid gave the cycloadduct (114 mg, 21% yield, 78:12:9 ratio of diastereomers) as a mixture of isomers **24**, **25**, **26**. Yields obtained from this reaction were not reproducible as they ranged from 5-70%. Substituting toluene or CH_3CN for the solvent gave yields of 1% and 0%, respectively. A white resinous material was isolated from these reactions that accounted for much of the mass yield. The ratio of diastereomers was consistant between reactions. The diastereomers were separated by HPLC utilizing 18% EtOAc in hexanes as the mobile phase.

Major isomer **24**: $[\alpha]^{25}_D$ = -28° (c = 1.2, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.33-7.22 (m, 10 H), 6.22 (m, 2 H, **HC**=), 5.08 (d, 8.7 Hz, 1 H, **HCPh**), 4.75 (d, 8.7 Hz, 1 H, **HCPh**), 3.58 (d, 9.6 Hz, 1 H, **HCC**=O), 3.27 (dd, 9.6, 8.1 Hz, **HCC**=O), 3.07 (s, 3 H, $\mathbf{H_3}$CN), 3.01 (ddt, 8.1, 7.2, 2.7 Hz, 1 H, **HCCH**$_3$), 1.29 (d, 7.2 Hz, 3 H, $\mathbf{H_3}$C). ^{13}C NMR ($CDCl_3$) δ 177.4, 174.9, 138.7, 136.2, 135.4, 131.4, 128.5, 127.2, 126.8, 103.8, 86.5, 85.1, 50.7, 42.5, 28.5, 24.9, 17.3. IR ($CDCl_3$) 3156, 3038, 2931, 1776, 1703, 1459 cm^{-1}. MS (CI, isobutane) *m/z* 390 (M^++1, 8.7%), 194 (100%). Anal. calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95. Found: C, 73.89; H, 6.03.

Minor isomer (12 %): $[\alpha]^{25}_D$ = +63° (c = 3.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.52 (m, 2 H), 7.37 (m, 3 H), 7.27 (m, 3 H), 6.32 (dd, 9.9, 6.6 Hz, 1 H, **HC**=), 6.08 (d, 9.9 Hz, 1 H, **HC**=), 5.01 (d, 8.7 Hz, 1 H, **HCPh**), 4.70 (d, 8.7 Hz, 1 H, **HCPh**), 3.62 (d, 10.5 Hz, 1 H, **HCC**=O), 3.33 (dd, 10.5, 8.1 Hz, **HCC**=O), 3.04 (s, 3 H, $\mathbf{H_3}$CN), 3.00 (m, 1 H, **HCCH**$_3$), 1.23 (d, 7.2 Hz, 3 H, $\mathbf{H_3}$C). ^{13}C NMR ($CDCl_3$) δ 177.6, 174.8, 137.2, 136.8, 135.3, 130.6, 128.8, 128.6, 128.4, 127.8, 126.3, 104.0, 86.5, 86.2, 49.4, 42.2, 28.2, 24.8, 17.3. IR ($CDCl_3$), 3154, 2976, 2907, 1817, 1794, 1777, 1703, 1647, 1456 cm^{-1}. MS (CI, isobutane) *m/z* 390 (M^++1, 6.3%), 194 (100%).

Minor isomer (9%): $[\alpha]^{25}_D$ = +3.2° (c = 2.5, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.06-6.95 (m, 10 H), 6.30 (dd, 9.6, 5.1 Hz, 1 H, **HC**=), 6.24 (dd, 9.6, 1.2 Hz, 1 H, **HC**=), 5.87 (d, 7.4 Hz, 1 H, **HCPh**), 5.73 (d, 7.4 Hz, 1 H, **HCPh**), 3.62 (d, 10.0 Hz, 1 H, **HCC**=O), 3.24 (dd, 10.0, 7.6 Hz, **HCC**=O), 3.01 (s, 3 H, $\mathbf{H_3}$CN), 3.01 (m, 1 H, **HCCH**$_3$), 1.38 (d, 7.5 Hz, 3 H, $\mathbf{H_3}$C). ^{13}C NMR ($CDCl_3$) δ 177.4, 174.5, 139.8, 136.3, 135.4, 129.9, 127.7, 127.6, 127.3, 127.0, 107.5, 82.9, 81.8, 50.8, 44.2, 28.7, 25.0, 17.3. IR ($CDCl_3$) 3156, 2960, 2917, 1813, 1792, 1701, 1654, 1561 cm^{-1}. MS (CI, isobutane) *m/z* 390 (M^++1, 6.4%), 194 (100%).

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