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Diels–Alder Reactions with Dienes Bearing a Remote Stereogenic Center. Conformational Model for Diastereofacial Selectivity

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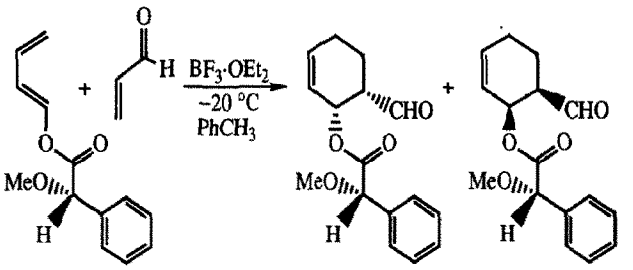
Abstract: In Diels–Alder reactions of 1-acyloxydienes, the 1-*O*-methylmandeloxy group has the distinct advantage of serving dual functions. Not only is it an effective chiral auxiliary for Diels–Alder stereocontrol, but also it provides rather reliable determination of the absolute stereochemistry of the Diels–Alder adduct, via the Dale–Mosher NMR model, subject only to the ability to resolve the proper NMR resonances. Study of the Diels–Alder reactions of such chiral 1-acyloxydienes has led us to a transition structure model which uniquely explains the origin of the observed stereoselectivities and is supported by experimental evidence, including X-ray structures showing the conformations of three Diels–Alder adducts. The model may also have wider applicability in conformational analysis and control of selectivity in other reactions.

Though several chiral dienophiles are now available, further development of diastereofacially selective Diels–Alder reactions with chiral dienes would be very useful.[1] One of the most selective chiral dienes was developed by Trost et al.[2,3] This diene (**1**, eq 1) and its 4-ethyl analogue were found to react with acrolein to



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give at least an 80:20 ratio of the two endo products, with none of the corresponding exo isomers observed. The selectivity was explained by a π-stacked conformation of the diene. Diene **1** was shown to be capable of very high selectivity: >97% was obtained, though only with a special dienophile, juglone. (The phenolic OH of juglone is believed to react with the Lewis acid, forming a rigid complex prior to reaction with the diene.)

If selectivities in excess of 90% could be achieved with typical dienophiles, chiral dienes such as **1** would have considerable synthetic utility, especially since the chiral auxiliary is attached at only one point and is readily removed by ester hydrolysis. Also, because the chiral center is rather remote from the reaction site, the mechanistic origin of the observed selectivity—π-stacking vs. alternative interactions—is of general interest in the ongoing quest for improved means of stereocontrol in organic processes.

The importance of π-stacking in determining product stereochemistry with this and other chiral dienes has been questioned,[4–8] but also supported in one recent case.[9] Consequently, we tested the hexahydrophenyl

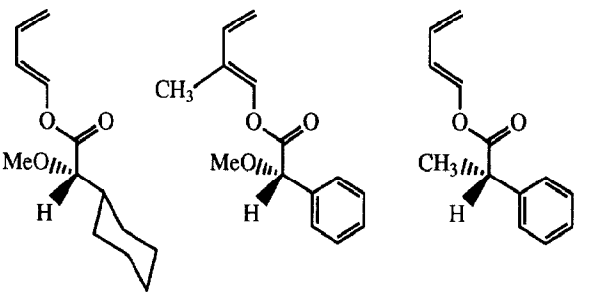
(cyclohexyl) analogue of this diene, sterically similar to phenyl but incapable of π-stacking, and found that it has almost equal facial selectivity with the same directionality. This same hexahydro diene result was also concurrently observed and mentioned in a review footnote[8] prior to our first publication.[10] These results appear to rule out π-stacking as the source of facial selectivity. What, then, might be the source? It was clear that only a very small range of transition structure conformations could give any facial preference whatsoever!

Investigation of the selectivities of acyloxydienes has led us not only to an improvement of the selectivity previously observed with typical dienophiles but also to the development of a working transition structure model.[10] Interestingly, a recent theoretical investigation has provided strong support for the fundamental correctness of our empirical model.[11]

In this paper, we present the results of our extensive investigations of Diels–Alder reactions of acyloxydienes possessing a stereogenic center within the acyloxy group.

Results

Comparison with structural analogues would provide insight into the origin of the facial selectivities of **1**. For this purpose, we have synthesized new dienes *E*-CH_2=CH–CH=CHOCOR* (**2–4**) and determined their selectivities in Diels–Alder additions to several dienophiles, including temperature and solvent effects. The

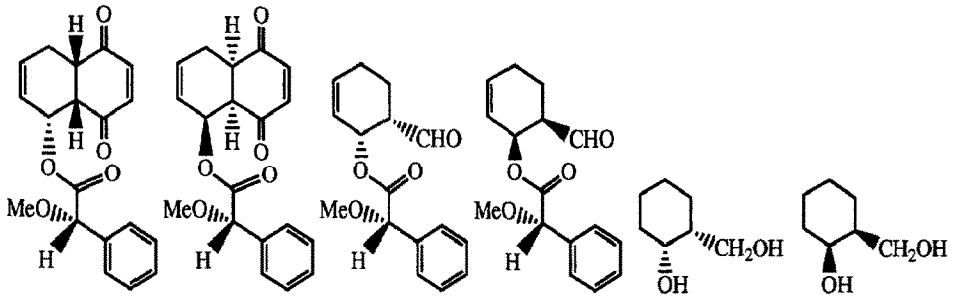


2 **3** **4**

presence of the methyl group in the precursors to **3** gave rise to difficulty in reduction (see Experimental), but, after considerable experimentation, a satisfactory procedure was found. X-ray, degradative, or NMR analyses rigorously established the relative stereochemistry of almost all of our major adducts, thus establishing the preferred face of dienophile attack upon the diene. Diastereofacial selectivities observed for racemic dienes are necessarily equal to those which would be obtained for monochiral dienes. To facilitate preparation of structural analogues, racemic dienes were mainly employed in this work. For brevity, only one enantiomer is drawn. We have, however, also obtained results with optically pure dienes **1** and **2** (vide infra).

Stereochemical Assignments. We have determined the relative stereochemistry of the major Diels–Alder adducts of dienes **1**, **3**, and **4** with benzoquinone and of diene **1** with naphthoquinone by X-ray analysis. Very recently, we have also succeeded in crystallizing the major naphthoquinone adduct of diene **2** and determined its X-ray structure.[12] The relative stereochemistry of the major benzoquinone adduct from diene **2** is assigned by analogy with the X-ray results on the naphthoquinone adducts of **1** and **2**, as well as the major acrolein adduct of **2** (stereochemistry rigorously proven below). *All four dienes* give major adducts having relative stereochemistry corresponding to **5**, in preference to **6**.

Diels–Alder adducts **7** and **8** from **1** have been reported previously.[2,10,13] We have converted the acrolein adducts of *optically pure* (*S*)-dienes **1** and **2** to a mixture of known diols **9** and **10**. The cis stereochemistry of both diols was established by NMR. From the known rotations and configurations of **9** and **10**,[14] the observed



5 6 7 8 9 10

optical rotations of these two diol samples correspond to a 75:25 ratio of diastereomers **7**:**8** from *both* **1** and **2**. This ratio is in close agreement with the result for **1**[12] using a different reduction method. This correlation then confirms the assignment of **7** and **8** as the major and minor products, respectively, for *both* dienes **1** and **2**.

The major adduct of diene **1** with methacrolein is sufficiently stable to permit an X-ray crystal structure, which we have also very recently obtained.[12] The stereochemistry corresponds to **7**.

We employed the reliable ^{1}H NMR model for *O*-methylmandelate esters[2,15,16] to determine the stereochemistries of the adducts of diene **3** with acrolein. This model predicts that the aldehyde H in the analogue of **7** should occur downfield relative to that in the analogue of **8**. The expected shift is observed [^{1}H NMR, 250 MHz, $CDCl_3$, *CHO* δ 9.72 (s) and 9.51 (s), respectively]. Consequently, the stereochemistry of the isomer absorbing at δ 9.72 is assigned as corresponding to **7** and δ 9.51, to **8**. These assignments are confirmed by the shifts observed for the adducts of diene **1** with acrolein, **7** and **8** [*CHO* δ 9.70 (s) and 9.24 (s), respectively], and with methacrolein [*CHO* δ 9.64 (s) and 9.34 (s), respectively], the stereochemistries of which are rigorously assigned by other methods in the preceding two paragraphs.

The above NMR analysis establishes the stereochemistry at C-3 (the cyclohexene ring carbon bearing the ester group) relative to the *O*-methylmandelate chiral auxiliary, but not at C-4; hence, it does not in itself distinguish between endo and exo products. However, the stereochemical assignments established above, by X-ray or by reduction to **9** and **10**, have shown the major isomer to be endo in all cases, *including* the adduct of diene **3** with benzoquinone. Both the major and minor adducts have been shown to be endo for three reactions of acrolein, with dienes **1** and **2** (above) and **4** (below), by ^{1}H NMR of the diol reduction products **9**/**10**. In addition, the major adduct of **1** with methacrolein is shown by X-ray analysis (above) to be endo. Because all of these Diels–Alder reactions are with very similar dienes and well known endo-selective dienophiles,[17,18] the acrolein adduct of **3** is reliably assigned as endo.

The acrolein adducts from (racemic) diene **4** were both shown to have endo configurations **7** and **8** by the following experiments. After conversion of a crude product mixture to the racemic diol (**9**/**10**), only *cis* diol could be observed by ^{1}H NMR compared with authentic samples of *cis*- and *trans*-diols. This evidence does not prove the relative stereochemistry in relation to the chiral auxiliary; however, the major product is assigned relative stereochemistry corresponding to **7** based on (a) the similarity of this reaction to all the others assigned above, and (b) the X-ray structure we have described above for the major *benzoquinone* adduct of **4**, which does in fact correspond to **7**.

Diastereofacial Selectivities. Selectivity ratios were determined in each case by integration of ^{1}H NMR spectra of the crude products. The specific resonances integrated for each product pair are given in the Experimental section. Results for the reactions of dienes **1**–**4** at +20, −20, and −78 °C are given in Table I. Acrolein

Table I. Diastereofacial Selectivities for the Diels–Alder Reactions of Dienes **1**–**4**[a]

Diene	Solvent	Temp, °C	Product Ratio for Dienophiles[b]			
			Acrolein	Methacrolein	Benzoquinone	Naphthoquinone
1	toluene	+20			81:19[c]	
	CH_2Cl_2	+20			80:20[c]	
	toluene	−20	82:18	92:8	94:6	
	CH_2Cl_2	−20	82:18		92:8	85:15
	toluene	−78	93:7		96:4	
	CH_2Cl_2	−78	94:6	98:2	96:4	
2	toluene	+20			68:32[c]	
	toluene	−20	79:21		90:10	
	CH_2Cl_2	−20	74:26		90:10	
	toluene	−78	93:7		94:6	
	CH_2Cl_2	−78	89:11		92:8	
3	toluene	+20			83:17[c]	
	CH_2Cl_2	+20			83:17[c]	
	CH_2Cl_2	−78	97:3		96:4	
4	toluene	+20			77:23[c]	
	toluene	−20	84:16		91:9	
	CH_2Cl_2	−20	76:24		80:20	
	toluene	−78	93:7		92:8	
	CH_2Cl_2	−78	85:15		82:18	

[a]Reactions were run with $BF_3{\cdot}OEt_2$ (15–30 mol %) catalysis except as otherwise noted. [b]Mean ratio of **7**:**8** or (analogue of **7**):(analogue of **8**) for acroleins; ratio of **5**:**6** or (analogue of **5**):(analogue of **6**) for quinones. Ratios were determined by ^1H NMR analysis of the crude reaction mixture. Most reactions were repeated 3 times or more (all at least twice). [c]Uncatalyzed reaction.

does not react at +20 °C. We mainly investigated acrolein and benzoquinone as representative dienophiles; for comparison, we also briefly examined methacrolein and naphthoquinone.

We have uncovered conditions which improve upon both selectivities and reaction times. Previously, diene **1** was allowed to react with acrolein at −20 °C with 15 mol % of $BF_3{\cdot}OEt_2$ over 2 days. The present work shows that these reactions are complete at −20 °C in 3–4 h (by ^1H NMR analysis) and that, with 30 mol % of $BF_3{\cdot}OEt_2$ at −78 °C, the reaction is still complete within 4 h. Not only are these reaction times much shorter and thus more convenient than previously reported, but also there is a dramatic improvement in selectivity at the lower temperature. When the reaction temperature is changed from −20 to −78 °C, there is a significant increase in the ratio for reaction of both dienes **1** and **2** with acrolein.

Diene **1** gives high selectivities in its reaction with methacrolein. However, monosubstituted dienophiles other than acrolein were found to be either nonselective or nonreactive with diene **1**. Methyl vinyl ketone reacted with diene **1** under the same conditions but the adduct isomers (not identified) were obtained in near 1:1 ratio at both −20 and −78 °C (at −20 °C, 45:55; at −78 °C, 65:35). Diene **1** was found to be unreactive with methyl acrylate, acrylonitrile, or ethyl methacrylate under the same conditions (24 h; no product detected by ^1H NMR). A preliminary investigation into the possibility of using other Lewis acid catalysts led only to the

conclusion that $BF_3{\cdot}OEt_2$ is the catalyst of choice for these reactions. Et_2AlCl, BCl_3, $ZnCl_2$, $TiCl_4$ and TiF_4 were all found to give lower selectivities in the acrolein reaction with these 1-acyloxydienes at −20 °C.

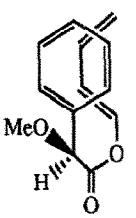
The similarity of the ratios obtained for all four dienes is striking. Three dienes, **1**, **2**, and **4**, all have the same selectivity within experimental error (93:7) in their reactions with acrolein in toluene at −78 °C. These three dienes also exhibit similar selectivities at −20 °C in toluene. Diene **3** is somewhat more selective (97:3) at −78 °C in CH_2Cl_2. The only major difference in selectivity between these dienes is seen in CH_2Cl_2 at −78 °C where both **2** and **4** give lower ratios than **1** or **3**. The similarity of selectivities is even more striking with benzoquinone. Except for the reaction of diene **4** with benzoquinone in CH_2Cl_2, the average of all the $BF_3{\cdot}OEt_2$-catalyzed product ratios of these Diels–Alder reactions with benzoquinone is 93:7 (± 2.4). This consistency extends through different dienes, different solvents, *and* different temperatures! Surprisingly, these ratios are also within experimental error of those achieved with acrolein in toluene at −78 °C. A major difference exists between the reactions of benzoquinone and those of acrolein, however: the temperature dependence of the selectivity is smaller for benzoquinone.

Discussion

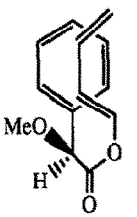
This work shows that diastereofacial selectivities in excess of 90% can be obtained in asymmetric Diels–Alder reactions of chiral dienes such as 1-(*O*-methylmandeloxy)-1,3-butadiene (**1**). Results with structurally modified chiral dienes rule out the previous phenyl–diene π-stacking model as the origin of the observed selectivities. Our data indicate a distinctive conformational preference—with the Ph–C_α–C=O dihedral angle near 90° and the methoxy syn to the C=O in the transition structure—as the source of facial differentiation. X-ray structures of several Diels–Alder adducts show just such conformations! Transition structures need not, of course, reflect ground state preferences, but these crystal structures strongly support the hypothesis that the adduct conformational preference seen by X-ray is indeed favored in the transition structure. These results point to the desirability of further studies on the conformational preferences of α-chiral esters and their role in mechanism and stereocontrol of the Diels–Alder as well as other classes of reactions.

High Stereoselectivities. From a synthetic standpoint, we have found that the selectivity observed[2] at −20 °C with acrolein as the dienophile can be significantly improved by lowering the reaction temperature to −78 °C. If the acrolein reaction of diene **1** is run in toluene at −78 °C with 30 mol % of $BF_3{\cdot}OEt_2$, a 3.4-fold increase in the selectivity is obtained without affecting the reaction time. Essentially complete endo selectivity and facial selectivities greater than 90% are normally observed. In the best cases, selectivities of 97–98% can be achieved. The benzoquinone and methacrolein adducts are easily purified by recrystallization to give diastereomeric purities of greater than 98%.

Selectivity Without π-Stacking. The selectivity of diene **1** was reasonably explained using a π-stacking model.[2] In this model, overlap of the orbitals of the phenyl ring with the diene would lead to two dynamically equilibrating intramolecular complexes, **11** and **12**, in which the phenyl ring is placed in a plane above or



11



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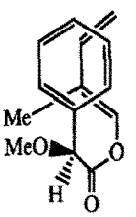


13

below the plane of the diene. Complex **11** would be more stable than **12** because of steric repulsion between the methoxy and the diene in **12**. The dienophile would preferentially approach the face opposite the phenyl ring in **11** to give the preferred product.

The similarity of the selectivity of dienes **1** and **2** (Table I) is in contradiction with the π-stacking model. Diene **2**, in which a cyclohexyl group replaces the phenyl ring, is incapable of π-stacking. Its selectivity must be caused by some other preferred conformation in the transition structure. It is most unlikely that two different types of transition structure conformation for **1** and **2** would accidently lead to selectivities so similar, and in some cases the same, under the variety of conditions observed. It is more reasonable to conclude that both dienes are reacting through similar transition structures which do not involve π-stacking.

The similarity of the selectivities of dienes **1** and **3** is also inconsistent with the π-stacking model. It is clear from molecular models that **3** could achieve a conformation like **11** (cf. **13**) only at very high energy cost. There would be a severe steric repulsion between the carbonyl and/or the chiral center and the diene's 2-methyl group. Therefore, the *especially high* selectivities observed with diene **3** must have a different origin than π-stacking. Because of the similar ratios observed for dienes **1** and **3**, it is reasonable to conclude that diene **1** is also, like **3**, reacting through a transition structure in which π-stacking is not the controlling factor.

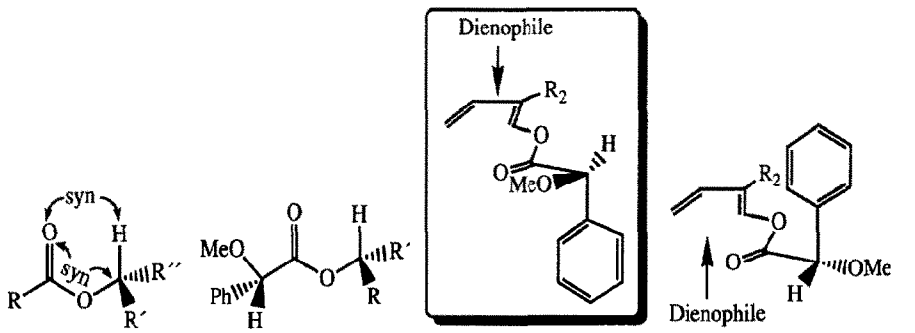
In the π-stacking model, the repulsion between the diene and the α-methoxy group at the chiral center is responsible for the lower stability of **12** relative to **11**. We have tested this point, too, by means of diene **4**, in which the α-methoxy group is replaced by methyl. The bulkier α-methyl group should destabilize **12** relative to **11** still more than α-methoxy, thus increasing the selectivity of **4** compared with **1**. The observed selectivities of **4** are in fact similar to or lower than those of **1** (Table I). Hence, the selectivities of diene **4** are indicated not to be controlled by π-stacking. Since the π-stacking interaction in **11** should be little affected by substitution of methyl for methoxy, the lack of π-stacking control with **4** provides additional, though indirect, evidence that the selectivities of **1** are also not controlled by π-stacking.

The Perpendicular Model. Because the chiral center is three atoms away from the diene unit, possible interactions which might give high facial selectivities, instead of 50:50, are severely limited. The similarities in selectivities already noted suggested that a single type of transition structure might be common to all, or most, of our substrates. We recognized that such a model must involve some preferred conformation of the diene in the transition structure. Indeed, a conformation similar to probable preferred conformations of the ground state dienes uniquely explains our data. These Diels–Alder reactions are expected to proceed by a concerted mechanism, with transition structure geometry intermediate between reactants and product. Hence, it is quite reasonable that conformational preferences of the starting diene should be preserved to a significant extent in the transition structure. Quite remarkably, this conformational model is *the only one which can be found which provides any significant interaction between the chiral center and the approaching dienophile!* Without such interaction, the facial selectivities would necessarily approach 50:50.

Esters are well known to prefer planar, syn conformations with a hydrogen of the alkyl group also syn to the carbonyl (cf. **14**).[11,19] The conformational preference about the chiral center remains to be defined. The model developed by Dale and Mosher[16] and very successfully used by Trost, et al.[15] to explain the relative ^1H NMR shifts of diastereomeric *O*-methylmandelate esters not only adopts the expected ester conformation but also postulates a preferred conformation of the ester in which the methoxy group is preferentially eclipsed with the carbonyl oxygen as shown in **15**. These authors have not suggested a reason for the eclipsed preference of the α-alkoxy group, but it may be steric: on steric grounds, the OMe, being larger than H, should prefer the

region of the larger C_α–C=O angle rather than the smaller C_α–C–O angle. Molecular models suggest little interaction between the chiral center and the approaching dienophile unless the bulky phenyl ring (the C_α–Ph bond) is oriented nearly perpendicular to the plane defined by the diene moiety, but a slight rotation from the perfectly eclipsed methoxy group to a more staggered conformation nicely explains the observed selectivity.

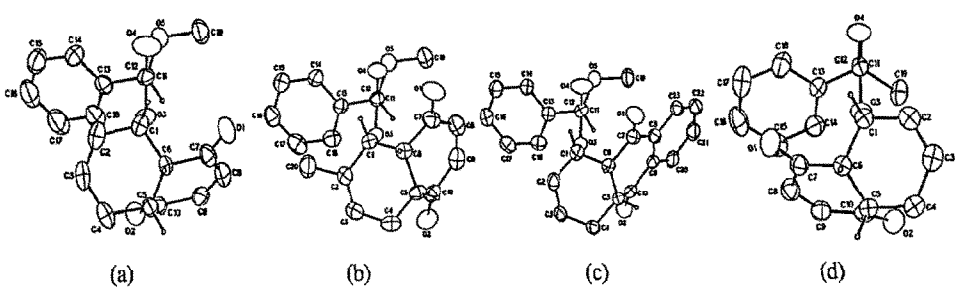
This **"perpendicular model"** is pictured as **16**. According to the model, conformation **16** is favored over **17**. In **16**, the bottom face the diene is blocked by the phenyl group, and the dienophile must predominantly



14 **15** **16** **17**

attack the top face, opposite to the phenyl. If the preference for **16** over **17** also prevails in the transition structure, this model predicts the correct, observed relative stereochemistry of the major Diels–Alder adducts. The minor products could be arising from disfavored attack on the same diene face as the phenyl ring in a transition structure corresponding to **16** and/or from attack opposite to the phenyl in the minor conformation **17**.

The X-ray structures obtained for the products in this study strongly support such a preferred conformation. The three X-ray structures, of the adducts of dienes **1** and **3** with benzoquinone and of diene **1** with naphthoquinone, all have the phenyl ring in a position nearly perpendicular to the carbonyl plane. The experimental dihedral angles between the carbonyl and C–Ph, i. e., the Ph–C_α–C=O dihedral angles, are 98.5, 100.8 and 95.5° (mean 98.3 ± 2.7°), respectively. As can be seen in Figure 1, the methoxy group is closer to a staggered



(a) (b) (c) (d)

Figure 1. ORTEP drawings for the X-ray crystal structures, viewed along the O_2C–C_α bond, showing conformational preferences, including for (a)–(c), the nearly perpendicular orientation of the phenyl group supporting the "perpendicular model": major adducts from (a) benzoquinone–diene **1**, (b) benzoquinone–diene **3**, (c) naphthoquinone–diene **1**, and (d) benzoquinone–diene **4**.

arrangement than eclipsed with respect to the carbonyl oxygen. A staggered, syn methoxy group has also been found in an X-ray structure for an *O*-methylmandelate ester.[15] Conformations found in crystal structures do not necessarily reflect the conformations of these compounds in solution, of course. However, the consistency of the observed conformations for several *O*-methylmandelate esters is highly suggestive that the same conformation is also preferred in solution.

In our three X-ray structures of adducts from dienes **1** and **3**, the phenyl ring also has its face toward the CO_2 group, i. e., the ring plane is nearly perpendicular to the plane defined by $C_{1Ph}C_{\alpha}C_{carboxy}$ ($C_{11}C_{12}C_{13}$, Figure 1), thus beautifully rationalizing the Dale–Mosher NMR model. The shielded group in these diastereomeric esters is positioned clearly in a shielding region above the phenyl π system. If it proves to be general, this perpendicular phenyl orientation adds still more confidence in the use of *O*-methylmandelate esters for determination of absolute configuration.

Conformations and Selectivities. As just described, the perpendicular model consistently explains the experimental facial selectivities in the Diels–Alder reactions we have investigated. Mechanistic/conformational conclusions can be drawn from our experiments, which were designed to probe the origins of the observed differences in selectivity. The following conclusions can be drawn from the presently available data.

(1) It is striking that our facial selectivities (Table I) fall into two distinct classes. Excepting only diene **4** in CH_2Cl_2 and the dienophile methacrolein, which are special cases, all of the selectivity ratios at −78 °C have a mean value of 17.2, corresponding to 94.5:5.5. As discussed below, diene **4** is special in having an α-methyl rather than α-methoxy, and methacrolein has an α-methyl group believed to give additional steric interactions. With the exception of diene **4** in CH_2Cl_2, all the BF_3-catalyzed reactions of *benzoquinone* give a mean ratio of 15.1, corresponding to 93.8:6.2. Considering the variety of variables—different dienes, different temperatures, and different solvents—the near constancy of these ratios seems highly significant. The other striking result is that essentially all the other selectivities are also nearly constant, but lower. (Diene **2** at +20 °C gives a still lower ratio, probably because cyclohexyl C-1 is tetrahedral: the small C-1 H can be oriented so as to reduce steric hindrance as compared with phenyl). Excluding that one item, all the other reactions give a mean ratio of 4.3, corresponding to 81.2:18.8. The selectivities divide cleanly into two distinct classes, centered around selectivity ratios of ca. 17 and ca. 4. It is difficult to imagine that these striking results could be fortuitous.

(2) A change of solvent from toluene to CH_2Cl_2 was studied for two reasons. First, toluene might be interfering with the π-stacking interaction by complexing in some way with the diene to the exclusion of the phenyl in the chiral ester group. Second, the conformational preference indicated by our results might involve dipole–dipole interactions; if so, a change of solvent should alter those interactions. For the α-methoxy dienes (**1–3**), the selectivities are nearly independent of solvent. Therefore, these solvent effects are not significant, and the origin of the selectivities is indeed indicated to lie in transition structure conformational preferences.

(3) The stereochemistry of complexation of the Lewis acid catalyst in the transition structure is a significant mechanistic issue. The BF_3-complexed carbonyl of benzoquinone is expected to be adjacent to the ester-substituted end of the diene; however, reaction could still take place at either C=C of benzoquinone—syn or anti to the BF_3. We therefore determined the selectivity for naphthoquinone, in which the *peri*-hydrogen of the benzo group should force the BF_3 to be preferentially syn to the reacting C=C. The selectivity with diene **1** is near 4 for naphthoquinone, but near 17 for benzoquinone (−20 °C). Naphthoquinone is unreactive under our conditions at −78 °C. The best interpretation is that benzoquinone reacts with BF_3 oriented anti, not syn, and that the anti BF_3 must be interacting with the chiral ester group in such a way as to increase the facial selectivity compared with a syn BF_3.

(4) With benzoquinone, the BF_3-catalyzed selectivities fall near 17, but near 4 for the uncatalyzed reaction at +20 °C. Since both −20 and −78 °C give similar results, it is probable that the difference at +20 °C is not a temperature effect but is the result of the absence of BF_3. This would be consistent with the conclusion from naphthoquinone, that the BF_3 interacts with the chiral ester group.

(5) Based on the results discussed above, it appears that the crucial difference between the classes of facial selectivity, near 4 and near 17, is the absence or presence, respectively, of interactions involving the Lewis acid BF_3 complexed to the dienophile. Selectivity near 4 would result from the bare CH=CH–C=O skeleton present in all of the dienophiles so far studied. Addition of extra groups causing still larger interactions would increase the selectivity. In particular, anti-complexed BF_3 gives essentially no repulsive interaction upon dienophile approach to the less hindered face of **16**, but models indicate a repulsive α-methoxy–BF_3 interaction upon approach to the less hindered face of **17**, which could increase the selectivity ratio to the range of 17. MO calculations have revealed a greater degree of asynchronicity in the model BH_3-catalyzed reaction of acrolein with butadiene; however, it still appears that the major difference controlling facial selectivities in our reactions is the presence or absence of interactions between the complexed BF_3 and the chiral center.[20]

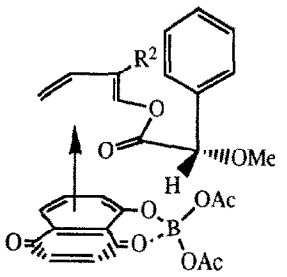
(6) Acrolein, in its BF_3-catalyzed reaction with **1**, gives a facial selectivity near 17 at −78 °C, but only near 4 at −20 °C. In contrast with the quinones, acrolein is not locked into an s-trans C=C–C=O conformation. A transition structure involving the s-cis conformation of acrolein cannot be ruled out at present: the repulsive α-methoxy–BF_3 interaction expected with s-trans, in analogy with benzoquinone, would be absent with s-cis. The lower reaction temperature could lower the population of the s-cis transition structure and thus at least partially account for the dramatic increase in selectivity. However, the similarity of the selectivity of acrolein at −20 °C to the group which falls near 4 makes this mechanism unlikely, since an s-cis acrolein conformation would not be expected to exhibit the same selectivity as the quinones, which must react as s-trans.

On the other hand, there is evidence that the s-cis and s-trans forms as well as syn and anti BF_3 complexes of methyl vinyl ketone are present in substantial amounts.[21,22] The nonselectivity of methyl vinyl ketone (nearly 1:1, see Results section) can therefore be explained by the predominance of transition structures containing more reactive s-cis or syn, s-trans conformations.

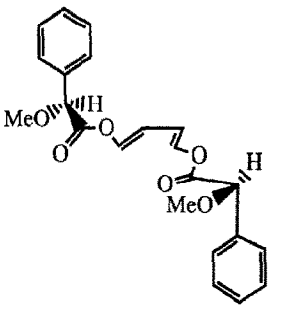
(7) Methacrolein gives selectivities near 17 at both −20 and −78 °C. Its selectivity at −78 °C is the *highest* we have observed. Its α-methyl group is seen from models to have a repulsive interaction with the ester C=O oxygen in both **16** and **17**. Apparently, this interaction is sufficient to alter the transition structure, possibly by causing the ester group to rotate slightly out of conjugation with the diene system, which would increase the repulsive α-methoxy–BF_3 interaction in **17** [cf. (5) above] and thus strengthen the preference for **16**.

(8) The strong parallel between the selectivities for diene **4** in toluene and those for dienes **1–3** indicates that **4** is subject to the same controlling factors as **1–3**. Since **4** has a nonpolar α-methyl group at the chiral center instead of the polar α-methoxy present in **1–3**, these results indicate that polar interactions involving the methoxy group are not responsible for selectivity in **1–3** and are more consistent with a steric origin. However, there is a notable difference in CH_2Cl_2: at *both* −20 and −78 °C, and with *both* acrolein and benzoquinone, the selectivity ratios fall near 4. Since both acrolein and benzoquinone are involved, this solvent effect is indicated to be a characteristic of the diene (**4**), not of the dienophile. More data are necessary to isolate the origin of this toluene/CH_2Cl_2 solvent effect with **4**, but one indication that **4** does not parallel **1–3** in every respect is the X-ray structure of its adduct with benzoquinone (Figure 1d). In the crystal, the conformation about the chiral center is not the perpendicular one characteristic of the α-methoxy dienes **1–3**, but has the α-hydrogen eclipsed with the ester C=O, closer to **17** than **16**. Nonetheless, the adducts do have the same stereochemical sense as those for **1–3**, indicating that, in *solution*, the *transition structures* corresponding to **16** are still preferred.

(9) The high (>97:3) selectivity in the boron triacetate mediated reaction of diene **1** with juglone[2] can be explained, as this reaction almost certainly involves the formation of the boron ester (cf. **18**).[23,24] This ester



18



19

has an acetate group oriented such that it should provide more steric hindrance than BF_3 in benzoquinone.

(10) The reported nonreactivity of diene **19**[2] can be explained using the perpendicular model. If both ester groups adopt the perpendicular conformation, the two phenyl groups would block both faces of the diene and therefore slow down any Diels–Alder reaction. This nonreactivity of **19** provides added evidence that the minor products from dienes like **1** do not arise from attack on the diene face syn to the phenyl group; if they did, one would expect **19** to produce significant amounts of adduct via syn attack (e. g., for a reaction giving a selectivity near 4 with **1**, such as that with acrolein at −20 °C, reaction should occur at about 20% of the rate of **1** on each of the two equivalent faces of **19**, for an overall rate about 40% of that of **1**).

Conclusion

We conclude that the **perpendicular model** proposed is a good working hypothesis for predicting diastereofacial selectivity in Diels–Alder reactions of dienes like **1**. With this model, it is now possible to rationally design new chiral 1-acyloxydienes with improved diastereofacial selectivity.

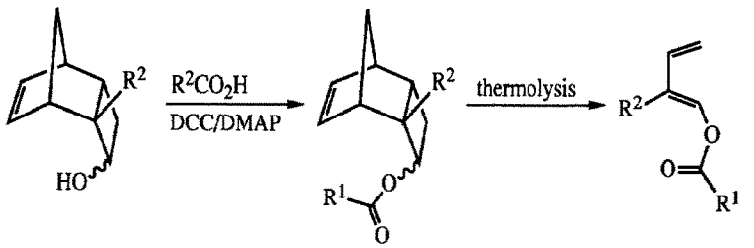
Experimental

Materials and Methods. All solvents and reagents were of reagent grade or better, purified by standard methods.[25] Unless stated otherwise, all nonaqueous reactions and distillations were conducted under argon with oven-dried glassware (160 °C) that was flame-dried under a stream of argon. High resolution chemical-ionization mass spectra (CI MS) were obtained by the University of Pennsylvania Mass Spectrometry Center of the Chemistry Department. Single-crystal X-ray structure determination was performed by Dr. P. Carroll of the University of Pennsylvania X-ray Crystallography Laboratory. Flash column chromatography (FCC) was carried out by the procedure of Still et al.[26] Eluant compositions follow each column description. Rotary evaporation refers to removal of volatile components, including solvent, under water aspirator pressure at ≤30 °C.

Synthesis of (±)-(*E*)-1-(2-Methoxy-2-phenylacetoxy)-1,3-butadiene (1), (±)-(*E*)-1-(2-Methoxy-2-cyclohexylacetoxy)-1,3-butadiene (2), (±)-(*E*)-1-(2-Methoxy-2-phenylacetoxy)-2-methyl-1,3-butadiene (3), and (±)-(*E*)-1-(2-phenylpropionoxy)-1,3-butadiene (4). Racemic chiral dienes **1**–**4** were prepared by a combination of previous procedures, culminating in thermolysis of the 3-acyloxytricyclo[4.2.1.$0^{2,5}$]non-7-ene **21** prepared from the alcohol precursor **20** as shown.[27–31] Monochiral (*S*)-**1** and (*S*)-**2** were also prepared by the same method, using optically pure (*S*)-2-methoxy-2-phenylacetic acid and (*S*)-mandelic acid, respectively. Compounds are racemic mixtures unless otherwise stated, even though only one enantiomer is shown.

The known alcohol **20a** was prepared according to precedent;[27,28] **20b** was prepared by a combination of prior procedures, from the known 4-hydroxy-2-*exo*-methyl-*endo*-tricyclo[4.2.1.$0^{2,5}$]non-7-en-3-one via tosylation.[27,28,32,33] The ketone 2-*exo*-methyl-*endo*-tricyclo[4.2.1.$0^{2,5}$]non-7-en-3-one was prepared by reductive

elimination of the tosylate by a procedure used for a similar α-acetoxyketone.[28] The chromous chloride reductive elimination procedure used in the preparation of **20a** was found to be unsuccessful with this tosylate.



20 **a**: $R^2 = H$
b: $R^2 = CH_3$

21 **a**: $R^1 = CH(OMe)Ph$, $R^2 = H$
b: $R^1 = CH(OMe)C_6H_{11}$, $R^2 = H$
c: $R^1 = CH(OMe)Ph$, $R^2 = CH_3$
d: $R^1 = CH(Me)Ph$, $R^2 = H$

General Procedure for Formation of Dienes 1–4. Flash vacuum pyrolysis of esters **21a–d** to form the corresponding dienes was accomplished with a home-made apparatus similar to that previously described,[27] except that the pyrolysis tube and oven were replaced with a heated fractionating column. The temperature of this heated fractionating column was controlled by a variable transformer which was calibrated to achieve the desired temperature (ca. 450 °C). A Kugelrohr oven and glassware comprised the remainder of the apparatus. The diene precursor **21** (1–6 mmol) was placed in the distilling flask, which was connected to the apparatus under vacuum (0.5–1.0 mmHg). After allowing the pyrolysis tube to reach a temperature of ca. 450 °C, the distilling oven was slowly warmed from ca. 25 °C to 250 °C while the receiving flask was cooled with a gentle stream of air. The diene precursor began to distill into the pyrolysis tube at a temperature of 125–150 °C. After the pyrolysis was complete, the apparatus was allowed to cool to ca. 25 °C, and the diene was collected using diethyl ether washes. The solvent was removed and the residue was placed under vacuum for at least 2 h. The diene could be purified by flash chromatography, but the crude diene was normally used in subsequent reactions within 2 days. The purity of the crude diene was ≥ 95% by ^1H NMR analysis in most cases.

(±)-(*E*)-1-(2-Methoxy-2-phenylacetoxy)-1,3-butadiene (1). Pyrolysis of **21a** yielded 98%; FCC (2:8 diethyl ether:hexanes) gave 85% of a clear oil, **1**. IR (CCl_4) 3060, 2905, 2890, 1775 (s), 1660, 1100–1245 (br), 995, 930, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.5–7.3 (m, 6 H), 6.25 (m, 1 H), 6.05 (dd, J = 11.8, 11.4, 1 H), 5.20 (dd, J = 17.6, 1.4, 1 H), 5.09 (dd, J = 10.2, 1.4, 1 H), 4.84 (s, 1 H), 3.43 (s, 3 H); ^1H NMR decoupling: irradiation at δ 7.3 collapsed 6.25 to d, J = 11.0 , irradiation at δ 6.25 collapsed 5.20 and 5.09 to 2 d, J = 1.4; ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 167.6, 138.2, 135.4, 131.2, 129.0, 128.8, 127.3, 117.9, 117.1, 82.2, 57.2. CI MS: *m/e* 236.1280 $(M + NH_4)^+$. Calcd for $C_{13}H_{18}NO_3$: *m/e* 236.1287.

(±)-(*E*)-1-(2-Cyclohexyl-2-methoxyacetoxy)-1,3-butadiene (2). Pyrolysis of **21b** yielded 95%; FCC (1:9 diethyl ether:hexanes) gave 78% of a clear oil, **2**. IR (CCl_4) 3085, 2920, 2850, 1760 (s), 1660, 1455, 1230 (br), 1140 (br), 1090, 995, 925, 905 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.47 (d, J = 12.2, 1 H), 6.3–6.1 (m, 2 H), 5.24 (dd, J = 17.6, 1.3, 1 H), 5.12 (dd, J = 10.0, 1.3, 1 H), 3.60 (d, J = 5.3, 1 H), 3.38 (s, 3 H), 1.9–1.0 (m, 11 H); ^{13}C NMR (125.8, $CDCl_3$) δ 169.6, 138.1, 131.4, 117.7, 116.8, 85.2, 58.6, 41.08, 28.9, 27.9, 26.1, 26.0, 25.9. CI MS: *m/e* 242.1733 $(M + NH_4)^+$. Calcd for $C_{13}H_{24}NO_3$: *m/e* 242.1756.

(±)-(*E*)-1-(2-Methoxy-2-phenylacetoxy)-2-methyl-1,3-butadiene (3). Pyrolysis of **21c** and FCC (2:8 diethyl ether:hexanes) gave 43.5% of a clear oil, **3**. IR (CCl_4) 3100, 3000, 2925, 2825, 1785 (s), 1660, 1465, 1160 (br), 1000, 910, 850 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.5–7.3 (m, 5 H), 7.24 (br s, 1 H), 6.29 (dd,

J = 17.3, 10.7, 1 H), 5.20 (br d, J = 17.3, 1 H), 5.09 (br d, J = 10.7, 1 H), 4.88 (s, 1 H), 3.46 (s, 3 H), 1.72 (br s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 167.5, 135.6, 135.4, 135.0, 128.9, 128.7, 127.2, 122.0, 113.4, 82.3, 57.4, 9.4. CI MS: *m/e* 250.1453 $(M + NH_4)^+$. Calcd for $C_{14}H_{20}NO_3$: *m/e* 250.1443.

(±)-(*E*)-1-(2-Phenylpropionoxy)-1,3-butadiene (4). Pyrolysis of **21d** and FCC (1:9 diethyl ether:hexanes) gave 83% of a clear oil, **4**. IR (CCl_4) 3030, 2930, 2880, 1770 (s), 1670, 1460, 1380, 1335, 1150, 1000, 930, 905 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4–7.2 (m, 6 H), 6.3–6.0 (m, 2 H), 5.18 (dd, J = 17.2, 1.2, 1 H), 5.06 (dd, J = 10.2, 1.2, 1 H), 3.79 (q, J = 7.2, 1 H), 1.54 (d, J = 7.2, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.3, 139.6, 138.8, 131.6, 128.7, 128.2, 127.5, 117.2, 116.3, 45.3, 18.3. CI MS: *m/e* 220.1345 $(M + NH_4)^+$. Calcd for $C_{13}H_{18}NO_2$: *m/e* 220.1337.

General Procedure for the Diels–Alder Reactions of Dienes 1–4. All glassware was dried in an oven (160 °C, 12 h) and allowed to cool in a desiccator. All reactions were run under argon.

Method A [for solid dienophiles (e. g., benzoquinone, naphthoquinone)]: The dienophile (purified by sublimation; ca. 1.5 equiv) was dried as a solution in CH_2Cl_2 or toluene (ca. 0.1 M) with molecular sieves for 2–3 h. To the diene (dried under vacuum for 2 h; 1.0 equiv) in ca. 1 mL of solvent at −78 or −20 °C was added this dienophile solution by cannula. After stirring for ca. 10 min at the indicated temperature, $BF_3{\cdot}OEt_2$ (15–20 mol % with respect to the diene) was added, and the reaction was stirred for 3–4 h. The reaction was worked up by adding it to a dilute aqueous $NaHCO_3$ and CH_2Cl_2 mixture. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with saturated $NaHCO_3$ and saturated NaCl. After drying (Na_2SO_4), the solvent was removed by rotary evaporation and the residue was placed under vacuum (ca. 0.5 mmHg).

Method B [for liquid dienophiles (e. g., acrolein, methacrolein]: To the diene (dried under vacuum ca. 2 h) in CH_2Cl_2 or toluene (freshly distilled, 0.2 M) at −78 or −20 °C was added the dienophile (freshly distilled, 2 equiv). After stirring for ca. 10 min at −78 or −20 °C, $BF_3{\cdot}OEt_2$ (15–20 mol % at −20 °C or 30–35 mol % at −78 °C, with respect to the diene) was added and the solution was stirred at the indicated temperature for 3–5 h. These reactions were worked up as in method A.

Representative reactions employing Methods A and B are given below.

Cycloaddition of (±)-(*E*)-1-(2-Methoxy-2-phenylacetoxy)-1,3-butadiene (1) with 1,4-Benzoquinone. At −78 °C in CH_2Cl_2, the ratio of the racemic diastereomeric products **5**:**6** was 96:4 ± 0.6 by ^{1}H NMR analysis of the crude product [C*H*OMe δ **5** = 4.53 (s), **6** = 4.47 (s)]. Recrystallization gave 77% of white needles, **5** (≥99% diastereomerically pure), mp 111.5–112.5 °C. IR (CCl_4) 3050, 2950, 2835, 1790, 1745, 1690 (s), 1550 (br), 1240, 1170, 1020, 1000 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5 H), 6.79 (d, J = 10.3, 1 H), 6.60 (dd, J = 10.3, 0.8, 1 H), 5.94 (ddd, J = 10.1, 4.4, 2.6, 1 H), 5.83 (dm, J = 10, 1 H), 5.37 (dd (appears as t), J = 4.4, 4.0, 1 H), 4.53 (s, 1 H), 3.45–3.25 (m, 2 H), 3.31 (s, 3 H), 3.02 (br dd, J = 19.2, 4.4, 1 H), 2.1 (dm, J = 19, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 197.6, 196.2, 169.4, 141.9, 140.1, 135.5, 131.8, 128.6, 128.5, 126.1, 122.1, 82.4, 67.2, 57.4, 49.4, 42.0, 21.3. CI MS: *m/e* 344.1546 $(M + NH_4)^+$. Calcd for $C_{19}H_{22}NO_5$: *m/e* 344.1498. The relative stereochemistry of (racemic) **5** was determined by X-ray analysis (Figure 1a).

Cycloaddition of (±)-(*E*)-1-(2-Methoxy-2-phenylacetoxy)-1,3-butadiene (1) with 1,4-Naphthoquinone. At −20 °C in CH_2Cl_2, the ratio of racemic product diastereomers corresponding to **5**:**6** was 85:15 by ^{1}H NMR analysis of the crude product [C*H*OMe δ (analogue of **5**) = 3.79 (s), (analogue of **6**) = 4.08 (s)]. Recrystallization gave 71% of the analogue of **5** as white needles (≥98% diastereomerically pure), mp 118–120 °C. IR (CCl_4) 3040, 3000, 2930, 2865, 1760 (s), 1700 (br), 1600, 1460, 1340, 1295, 1255, 1210, 1170, 1110, 1000,

920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.1 and 7.8 (2 m, 4 H), 7.2 and 6.86 (2 m, 5 H), 6.02 (ddd, J = 10.1, 4.7, 2.6, 1 H), 5.82 (ddd, J = 10.1, 5.0, 2.5, 1 H), 5.46 (dd (appears as t), J = 4.5, 4.2, 1 H), 3.79 (s, 1 H), 3.51 (m, 2 H), 3.21 (dd, J = 18.8, 4.7, 1 H), 3.00 (s, 3 H), 2.2 (dm, J = 19, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 195.7, 195.1, 169.2, 136.9, 135.4, 135.2, 134.82, 133.3, 132.1, 128.4, 128.3, 126.8, 126.4, 126.1, 122.1, 81.9, 67.2, 57.1, 50.2, 42.5, 21.9. CI MS: *m/e* 394.1633 $(M + NH_4)^+$. Calcd for $C_{23}H_{24}NO_5$: *m/e* 394.1654. The relative stereochemistry of this (racemic) adduct was determined by X-ray analysis (Figure 1b).

Cycloaddition of (±)-(*E*)-1-(2-Methoxy-2-phenylacetoxy)-1,3-butadiene (1) with Acrolein. At −78 °C in CH_2Cl_2, the ratio of racemic product diastereomers **7**:**8** was 93:7 ± 1 by ^1H NMR analysis of crude product [C*H*O δ **7** = 9.70 (s), **8** = 9.24 (s)]. The crude product could not be purified because of its rapid decomposition. The Diels–Alder adducts of dienes **1**–**4** are all subject to decomposition, the acrolein adducts being the least stable. A ^1H NMR yield (trichloroethylene standard, $CDCl_3$) was determined to be 48%. The stereochemistries of **7** and **8** were determined from literature ^1H NMR analyses and conversion to known diols (vide infra).[2,13]

(±)-(3*RS*,4*RS*)-4-Hydroxymethylcyclohexen-3-yl (2*SR*)-2-Methoxy-2-phenylacetate. The crude product (**7** and **8**) was reduced to the alcohol with $NH_3{\cdot}BH_3$ in diethyl ether/H_2O;[34] FCC (1:1 ethyl acetate: hexanes) gave 38.5% (overall yield from the two steps, Diels–Alder and reduction) of a clear oil. IR (neat) 3460, 3040 (br), 2930, 2840, 1734, 1190, 1140, 1000, 900, 875, 735 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.5–7.3 (m, 5 H), 6.02 (br ddd, J = 9.7, 4.6, 2.7, 1 H), 5.98 (dm, J = 9.7, 1 H), 5.38 (dd (appears as t), J = 4.06, 4.11, 1 H), 4.80 (s, 1 H), 3.43 (s, 3 H), 3.5–3.3 (m, 2 H), 2.44 (dd, J = 5.3, 8.4, 1 H), 2.1–1.8 (m, 3 H), 1.5–1.3 (m, 2 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 171.6, 136.2, 134.4, 128.7, 128.6, 126.9, 123.5, 82.8, 68.5, 63.3, 57.4, 40.7, 25.2, 19.9. CI MS: *m/e* 294.1723 $(M + NH_4)^+$. Calcd for $C_{16}H_{24}NO_4$: *m/e* 294.1705.

The crude product from Diels–Alder reaction in toluene at −20 °C with monochiral (*S*)-diene **1** was reduced to a mixture of diols **9** and **10** by a literature method,[13] $[\alpha]_D^{26} = -18.5°$ (c = 0.014, H_2O).

Cycloaddition of (±)-(*E*)-1-(2-Methoxy-2-phenylacetoxy)-1,3-butadiene (1) with Methacrolein. At −78 °C in CH_2Cl_2, the ratio of racemic product diastereomers corresponding to **7**:**8** was 97.8:2.8 ± 0.2 by ^1H NMR analysis of the crude product [C*H*O δ (analogue of **7**) = 9.64 (s), (analogue of **8**) = 9.34 (s)]. Recrystallization gave 73% of the analogue of **7** as white needles (contains ≤0.5% of the analogue of **8**), mp 68–70 °C. IR (KBr) 3050, 3000, 2980, 2950, 2860, 2760, 1755 (s), 1720 (s), 1490, 1460, 1400, 1380, 1330, 1270, 1185, 1115, 1005, 980, 910 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.64 (s, 1 H), 7.3–7.1 (m, 5 H), 5.88 and 5.55 (2 dm, J = 10.0, 2 H), 5.33 (br d, J = 1.9, 1 H), 4.74 (s, 1 H), 3.40 (s, 3 H), 2.2–2.1 (m, 2 H), 2.0–1.6 (m, 2 H), 1.04 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 203.8, 171.6, 135.9, 132.7, 128.7, 128.5, 126.9, 123.1, 82.4, 73.0, 57.3, 47.7, 26.1, 22.0, 17.9. CI MS: *m/e* 306.1668 $(M + NH_4)^+$. Calcd for $C_{17}H_{24}NO_4$: *m/e* 306.1705. The relative stereochemistry of this (racemic) adduct has been determined by X-ray analysis.[12]

Cycloaddition of (±)-(*E*)-1-(2-Cyclohexyl-2-methoxyacetoxy)-1,3-butadiene (2) with 1,4-Benzoquinone. At −78 °C in CH_2Cl_2, the ratio of racemic product diastereomers corresponding to **5**:**6** was 93:7 ± 0.6 by ^1H NMR analysis of the crude product [CH_3O δ (analogue of **5**) = 3.05 (s), (analogue of **6**) = 2.98 (s)]. Recrystallization gave 74% of the analogue of **5** as white needles (≥99% diastereomerically pure), mp 101–103 °C. IR (CCl_4) 3035, 2955, 2860, 1760, 1735, 1710, 1690 (s), 1265, 1240, 1180, 1135, 1005, 935, 830 (br) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.92 (d, J = 10.3, 1 H), 6.72 (dd, J = 10.3, 0.6, 1 H), 6.02 (m, 2 H), 5.39 (dd (appears as t), J = 3.6, 3.3, 1 H), 3.36 (m, 2 H), 3.28 (d, J = 4.9, 1 H), 3.18 (s, 3 H), 3.10 (br dd, J = 20.0, 3.0, 1 H), 2.17 (br dd, J = 19.6, 6.7, 1 H), 1.8–1.0 (m, 11 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 198.0, 196.5, 171.1, 142.1, 140.4, 131.7, 122.6, 85.3, 66.9, 58.4, 49.3, 42.1, 41.1, 28.6, 27.7, 26.0, 25.8, 21.3. CI MS: *m/e*

350.1980 $(M + NH_4)^+$. Calcd for $C_{19}H_{28}NO_5$: *m/e* 350.1967. The relative stereochemistry of this (racemic) adduct was assigned by analogy with our recent X-ray structure of the major naphthoquinone adduct of this same diene (**2**),[12] with the major acrolein adduct of **2**, the stereochemistry of which is rigorously proven (vide infra), and with the X-ray structure of the naphthoquinone adduct of diene **1** (vide supra).

Cycloaddition of (±)-(*E*)-1-(2-Cyclohexyl-2-methoxyacetoxy)-1,3-butadiene (2) with Acrolein. At −78 °C in CH_2Cl_2, the ratio of racemic product diastereomers corresponding to **7**:**8** was 89:11 ± 2 by ^1H NMR analysis of the crude product [in C_6D_6, *CHO* δ (analogue of **7**) = 9.47 (s), (analogue of **8**) = 9.43 (s)]. The crude product could not be purified because of its rapid decomposition. A ^1H NMR yield (trichloroethylene standard, $CDCl_3$) was determined to be 76%. The stereochemistries of the analogues of **7** and **8** were determined by conversion to the known diols (vide infra).[2,13]

(±)-(3*RS*,4*RS*)-4-Hydroxymethylcyclohexen-3-yl (2*SR*)-2-Cyclohexyl-2-methoxyacetate. The crude product above was reduced to the alcohol with $NH_3{\cdot}BH_3$ in diethyl ether/H_2O as described above for **7** and **8**. FCC (1:1 ethyl acetate:hexanes) gave 54% (overall yield from the two steps) of a clear oil. IR (neat) 3450 (br), 3025, 2925, 2860, 1725 (s), 1450, 1265, 1185, 1105, 1040, 985, 900, 875 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.05 (m, 1 H), 5.83 (m, 1 H), 5.44 (dd (appears as t), J = 4.4, 4.2, 1 H), 3.54 (m, 3 H), 3.36 (s, 3 H), 2.65 (br s, 1 H), 2.3–1.9 (m, 3 H), 1.8–1.1 (m, 13 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 173.1, 134.2, 123.7, 85.6, 68.0, 63.5, 58.4, 41.2, 40.6, 28.9, 28.0, 26.1, 26.0, 25.9, 25.2, 19.9. CI MS: *m/e* 300.2202 $(M + NH_4)^+$. Calcd for $C_{16}H_{30}NO_4$: *m/e* 300.2175.

The crude product from Diels–Alder reaction in toluene at −20 °C with monochiral (*S*)-diene **2** was reduced to a mixture of diols **9** and **10** by a literature method,[13] $[\alpha]_D^{26} = -18.2°$ (c = 0.016, H_2O).

Cycloaddition of (±)-(*E*)-1-(2-Methoxy-2-phenylacetoxy)-2-methyl-1,3-butadiene (3) with 1,4-Benzoquinone. At −78 °C in CH_2Cl_2, the ratio of racemic product diastereomers corresponding to **5**:**6** was 96:4 by ^1H NMR analysis of the crude product [*CH*OMe δ (analogue of **5**) = 4.52 (s), (analogue of **6**) = 4.50 (s)]. Recrystallization gave 55% of the analogue of **5** as white needles (98% diastereomerically pure), mp 155.5–157 °C. IR (CH_2Cl_2) 3050, 2985, 2845, 1760 (s), 1695 (s), 1430, 1250, 1175, 1125, 1010, 945, 770 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5 H), 6.73 (d, J = 10.3, 1 H), 6.53 (dd, J = 10.3, 0.9, 1 H), 5.57 (m, 1 H), 5.48 (d, J = 3.9, 1 H), 4.52 (s, 1 H), 3.4–3.2 (m, 2 H), 3.34 (s, 3 H), 2.98 and 2.10 (2 dm (AB pattern), J = 19, 2 H), 1.30 (br s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 197.6, 196.8, 169.6, 141.7, 140.1, 135.5, 129.9, 128.5, 126.5, 126.9, 125.7, 82.3, 69.4, 57.4, 50.9, 42.1, 21.6, 20.4. CI MS: *m/e* 358.1622 $(M + NH_4)^+$. Calcd for $C_{20}H_{24}NO_5$: *m/e* 358.1654. The relative stereochemistry of this (racemic) adduct was determined by X-ray analysis (Figure 1c).

Cycloaddition of (±)-(*E*)-1-(2-Methoxy-2-phenylacetoxy)-2-methyl-1,3-butadiene (3) with Acrolein. At −78 °C in CH_2Cl_2, the ratio of racemic product diastereomers corresponding to **7**:**8** was 97:3 by ^1H NMR analysis of the crude product [*CHO* δ (analogue of **7**) = 9.72 (s), (analogue of **8**) = 9.51 (s)]. The crude product could not be purified because of its rapid decomposition. A ^1H NMR yield (trichloroethylene standard, $CDCl_3$) was determined to be 94%. The relative stereochemistries of the (racemic) analogues of **7** and **8** were established by application of the Dale–Mosher NMR correlation (see Results section).[15,16]

(±)-(5*RS*,6*SR*)-5-Hydroxymethyl-1-methylcyclohexen-6-yl (2*SR*)-2-Methoxy-2-phenylacetate. The crude product above was reduced to the alcohol with $NH_3{\cdot}BH_3$ in diethyl ether/H_2O as described above for **7** and **8**. FCC (1:1 ethyl acetate:hexanes gave 49% of a white solid, mp 89.5–91 °C. IR (CCl_4) 3555, 3045, 2940, 2890, 1735 (s), 1655, 1465, 1210, 1185, 1135, 1090, 1015, 916 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.5–7.3

(m, 5 H), 5.65 (br s, 1 H), 5.25 (d, J = 2.9, 1 H), 4.80 (s, 1 H), 3.44 (s, 3 H), 3.45–3.15 (m, 2 H), 2.94 (dd, J = 10.1, 4.1, 1 H), 2.1–1.8 (m, 3 H), 1.4–1.2 (m, 2 H), 1.29 (d, J = 1.7, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.8, 136.1, 130.1, 128.9, 128.6, 127.0, 82.7, 71.9, 63.0, 57.4 42.0, 25.2, 20.6, 19.9. CI MS: *m/e* 308.1834 $(M + NH_4)^+$. Calcd for $C_{17}H_{26}NO_4$: *m/e* 308.1862.

Cycloaddition of (±)-(*E*)-1-(2-Phenylpropionoxy)-1,3-butadiene (4) with 1,4-Benzoquinone. At −78 °C in toluene, the ratio of racemic product diastereomers corresponding to **5**:**6** was 91.5:8.5 ± 0.6 by ^{1}H NMR analysis of the crude product [COC*H*=CHCO δ (analogue of **5**) = 6.41 (dd, J = 10.3, 0.9), (analogue of **6**) = 6.32 (d, J = 10.3)]. Recrystallization gave 74% of the analogue of **5** as white needles (≥97% diastereomerically pure), mp 91–92.5 °C. IR (CCl_4) 3000, 2930, 2855, 1755, 1735, 1705, 1685, 1550, 1240, 1020 (br), 1000, 815, 720 (br) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.0 (m, 5 H), 6.58 (d, J = 10.3, 1 H), 6.41 (dd , J = 10.3, 0.9, 1 H), 5.91 (m, 2 H), 5.32 (dd (appears as t), J = 4.7, 4.1, 1 H), 3.53 (q, J = 7.25, 1 H), 3.3–3.2 (m, 2 H), 3.01 (br dd, J = 19.2, 3.9, 1 H), 2.1 (dm, J = 19, 1 H), 1.37 (d, J = 7.3, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 197.9, 196.4, 173.0, 141.7, 139.9, 139.3, 131.3, 128.5, 127.4, 127.1, 122.6, 66.7, 49.5, 45.3, 42.1, 21.3, 17.4. CI MS: *m/e* 328.1542 $(M + NH_4)^+$. Calcd for $C_{19}H_{22}NO_4$: *m/e* 328.1549. The relative stereochemistry of this (racemic) adduct was determined by X-ray analysis (Figure 1d).

Cycloaddition of (±)-(*E*)-1-(2-Phenylpropionoxy)-1,3-butadiene (4) with Acrolein. At −78 °C in CH_2Cl_2, the ratio of racemic product diastereomers corresponding to **7** and **8** was 85:15 ± 0.6 by ^{1}H NMR analysis of the crude product [C*H*O δ (analogue of **7**) = 9.68 (s), (analogue of **8**) = 9.34 (s)]. The crude product could not be purified because of its rapid decomposition. A ^{1}H NMR yield (trichloroethylene standard, $CDCl_3$) was determined to be 60%. Both of these (racemic) products were shown to be endo isomers by conversion to a known diol, as described below.

(3*RS*,4*RS*)-4-Hydroxymethylcyclohexen-3-yl (2*SR*)-2-Phenylpropionate. The crude product above was reduced to the alcohol with $NH_3{\cdot}BH_3$ in diethyl ether/H_2O as described above for **7** and **8**. FCC (4:6 ethyl acetate:hexanes) gave 46% (overall yield from the two steps) of a clear oil. IR (neat) 3465 (br), 3040, 2940, 2880, 2835, 1730 (s), 1455, 1210, 1175, 1035, 995, 910, 880 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5 H), 5.90 (m, 1 H), 5.72 (m, 1 H), 5.34 (dd (appears as t), J = 4.0, 3.9, 1 H), 3.77 (q, J = 7.2, 1 H), 3.42 (dd, J = 11.6, 5.2, 1 H), 3.28 (dd, J = 11.6, 9.3, 1 H), 2.2–1.8 (m, 4 H), 1.54 (d, J = 7.2, 3 H), 1.6–1.3 (m, 2 H). CI MS: *m/e* 278.1719 $(M + NH_4)^+$. Calcd for $C_{16}H_{24}NO_3$: *m/e* 278.1756. The crude product from racemic diene **4** was reduced to a mixture of diols **9** and **10** by a literature method.[13] Comparison of the ^{1}H NMR spectrum of these diol products with the NMR spectra of authentic samples of both *cis*- and *trans*-2-(hydroxymethyl)cyclohexanols showed that only the *cis*, and none of the *trans*, product could be detected.

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