= 2.5 Hz, C_9-H), 2.83-2.94 (m, 2 H, C_{10}-H and C_{12}-H), 2.63 (q, 1 H, J = 7.1 Hz, C_2-H), 2.12-2.22 (m, 1 H, C_{14}-H), 1.22 (s, 3 H, C_{16}-CH_3), 1.06 (d, 3 H, J = 7.1 Hz, C_2-CH_3); MS (FAB, *m*-nitrobenzyl alcohol) m/z 687 (M + Na), 665 (M + H); TLC R_f 0.38 (10% methanol/chloroform).

Adduct 55 sodium salt: oil; IR (CH_2Cl_2) 3400 (br), 3060, 2980, 2940, 2880, 1710, 1580, 1470, 1420, 1380, 1155, 1105, 1050, 1035, 980, 900 cm^{-1}; ^1H NMR ($CHCl_3$, 500 MHz) δ 4.06 (apparent d, 1 H, J_{8-9} = 6.9 Hz, C_9-H), 4.01 (apparent d, 1 H, J = 9.6 Hz, C_7-H or C_{21}-H), 3.71 (apparent d, 1 H, J = 9.5 Hz, C_{13}-H), 3.62 (apparent d, 1 H, J = 8.4 Hz, C_7-H or C_{21}-H), 2.77-2.80 (m, 1 H, C_{12}-H), 2.67-2.72 (m, 1 H, C_{10}-H), 2.54-2.59 (m, 1 H, C_2-H), 2.20-2.26 (m, 1 H, C_{14}-H), 1.22 (s, 3 H, C_{16}-CH_3), 1.16 (d, 3 H, J = 7.1 Hz, C_{10}-CH_3), 1.11 (d, 3 H, J = 7.1 Hz, C_2-CH_3); MS (FAB, *m*-nitrobenzyl alcohol) m/z 687 (M + Na), 665 (M + H); TLC R_f 0.32 (10% methanol/chloroform).

Adduct 56 sodium salt: oil; IR (CH_2Cl_2) 3400 (br), 3060, 2965, 2940, 2880, 1735, 1710, 1590, 1460, 1425, 1375, 1250, 1155, 1105, 1050, 980, 900 cm^{-1}; ^1H NMR ($CHCl_3$, 500 MHz) δ 3.94 (apparent d, 1 H, J = 10.3 Hz, C_{13}-H), 3.91 (apparent d, 1 H, J_{9-10} = 4.7 Hz, C_9-H), 3.66 (apparent d, 1 H, J = 9.5 Hz, C_7-H or C_{21}-H), 3.58 (apparent d, 1 H, J = 8.4 Hz, C_7-H or C_{21}-H), 2.90-2.96 (m, 1 H, C_{10}-H), 2.65-2.75 (m, 2 H, C_2-H and C_{12}-H), 2.06-2.13 (m, 1 H, C_{14}-H), 1.21 (s, 3 H, C_{16}-CH_3), 1.14 (d, 3 H, J = 6.8 Hz, C_{10}-CH_3), 1.11 (d, 3 H, J = 7.2 Hz, C_2-CH_3); MS (FAB, *m*-nitrobenzyl alcohol) m/z 687 (M + Na), 665 (M + H); TLC R_f 0.28 (10% methanol/chloroform).

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Supplementary Material Available: Selected experimental procedures and spectral and analytical data for all reaction products are included (10 pages). Ordering information is given on any current masthead page.

Diene-Dienophile Hydrogen-Bonding Control of Diels-Alder Reactions with Dienes Bearing a Remote Stereogenic Center. Amplification of the Receptor Nature of Dienes by Conformational Tuning Leading to High Diastereofacial Discrimination

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Abstract: The Diels-Alder reactions of 1-(*O*-methylmandeloxy)butadiene and its analogues, bearing a remote stereogenic center, have been studied to elucidate the stereoselective control elements. Several model dienes (**5a-5f**) have been designed to enhance the facial selectivity at room temperature. The design concept of these dienes is based on our proposed perpendicular model (Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1988**, *29*, 5225-5228), which we used to rationalize the diastereofacial preference observed with diene **1**. Our approach to increasing the diastereoselectivity was to enhance the population of the preferred diene rotamer in the ground state as well as in the transition structure. From X-ray structures of the cycloadducts and the reversal of facial selectivity with dienes having a free hydroxy group at the chiral center, we conclude that diene-dienophile coordination through hydrogen bonding plays an important role in promoting chirality transfer. We postulate that facial selectivity is controlled by a balance of two competing forces (stereoelectronics vs hydrogen bonding) on the diene conformation in the transition structure. Conformational tuning at the stereogenic center helped in designing a diene (**5e**), which aims at maximizing the hydrogen-bonding interaction by decreasing the stereoelectronic preference. This diene exhibited high diastereoselectivity with an array of dienophiles at ca. 25 °C, without employing any external catalyst.

Asymmetric control is a challenging problem in organic chemistry.[1] Requirements to achieve enhanced face discrimination involve proper mechanistic understanding and identification of chiral control elements. Approaches to asymmetric induction include use of either covalently bound chiral auxiliary(ies) or of chiral Lewis acid catalysts. In both cases, propagation of chirality is achieved by blocking one prochiral face of a substrate through stereoelectronic contributions of the chiral center. Schematically, this can be categorized as a *repulsive interaction* approach as the incoming reactant preferentially approaches the least hindered substrate face in order to avoid steric congestion with stereogenic groups or ligands. In contrast, enzymes use *attractive interactions*, such as substrate binding through an array of conformationally well defined functionalities, to synthesize enantiomerically pure compounds efficiently under very mild reaction conditions.[2] A key to high asymmetric induction in those cases is the ability of the catalyst to bring the reacting substrates into close proximity.[3] Not surprisingly, in recent years, attempts have been made to design artificial enzymes,[4,5] which aim at binding two reacting species with a nonenzyme receptor to mimic enzyme catalysis.

Recently, during our mechanistic studies on asymmetric Diels-Alder reactions, we discovered such an *attractive interaction*, between the hydroxy group of a remote chiral template placed on a diene and the carbonyl groups of different dienophiles. As a result, high facial selectivity was achieved at ca. 25 °C without employing any external catalyst.[6] Except for allylic positions, the face-discriminating ability of unprotected heteroatom functionalities (such as oxygen or nitrogen atoms) present in chiral

(1) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York and Orlando, FL, 1983-1985; Vol. 1-5.

(2) *Enzymes as Catalysts in Organic Synthesis*; Schneider, M., Ed.; Reidel: Dordrecht, The Netherlands, 1986.

(3) (a) Houk, K. N., Tucker, J. A.; Dorigo, A. E. *Acc. Chem. Res.* **1990**, *23*, 107-113. (b) Bruice, T. C.; Benkovic, S. J. *Bioorganic Mechanisms*; W. A. Benjamin: New York, 1966; Vol. 1, pp 119-211.

(4) For a carbon-carbon bond forming reaction and other leading references to this subject, see: (a) Kelly, T. R.; Zhao, C.; Bridger, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 3744-3745. (b) Kelly, T. R.; Bridger, G. J.; Zhao, C. *J. Am. Chem. Soc.* **1990**, *112*, 8024-8034.

(5) Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245-255.

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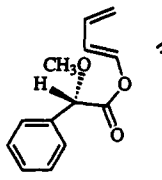
auxiliaries has been ignored by organic chemists in the past, apart from their possible role in conformational preferences. In most asymmetric reactions, the contributions of such groups are generally silenced by masking them with protecting groups. Our work has clearly demonstrated the utility of such unprotected heteroatom functionalities even when they are placed several atoms away from the bond-forming site. Their presence proved to be advantageous in improving the facial selectivity because of their ability to bring about effective coordination (through hydrogen bonding) between reactants. A detailed evaluation of the architectural requirements for efficient interaction between the reacting species is of fundamental concern, as that would lead to design of better chiral receptors. A goal would be receptors compatible with a wide range of substrates, in conrast with a frequent shortcoming of natural receptors such as enzymes[7] or abzymes (antibodies),[8] that they are more or less substrate-specific.

The above-mentioned findings resulted from our continuing search for the improvement of diastereoselectivity in Diels–Alder reactions at room temperature. For quite some time, we have been interested in elucidating the chiral control elements in the asymmetric Diels–Alder reactions of Trost's diene (**1**)[9,10] with different



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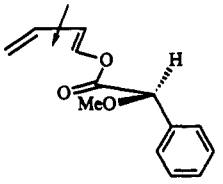

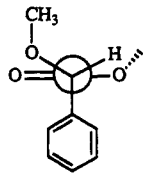

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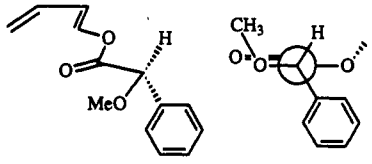
dienophiles.[11] This diene is unique in the sense that even though the stereogenic center remains several atoms away from the actual bond-forming site, it exhibits high diastereoselectivities.[9,12] As we have proposed,[11] the origin of these high selectivities apparently lies in the ability of the diene to adopt a perpendicular conformation (**2**) in the transition structure, a conformation found in X-ray crystal structures of the Diels–Alder adducts.

The essential features of this model are that the dienyl and ester carbonyl groups are coplanar, the C–OMe bond remains proximal to the carbonyl, and the phenyl group adopts a nearly perpendicular orientation. Stereodifferentiation is caused by preferential approach of the dienophile to the less hindered face of the diene, opposite to the phenyl ring. More recently, theoretical calculations by Houk and co-workers indicated that the most populated conformation for the diene **1** is rotamer **3** in the ground state, whereas



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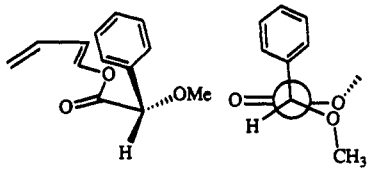


4

4 constitutes the second most stable conformation at about 0.8 kcal/mol higher energy.[13] The predominant conformation **3** resembles our model (**2**), the essential difference between the two being that the calculation favors a C_α–O bond eclipsed with the ester carbonyl, whereas we assigned a gauche (actually about 25° dihedral angle) relationship between those functionalities.

Table I. Diastereoselectivity in the Diels–Alder Reactions of Dienes **1** and **5a–f** with Different Dienophiles at ca. 25 °C

entry	diene	dienophile	solvent	selectivity[a]
1	**5a**	*N*-ethylmaleimide	toluene	5.2:1[b]
2	**1**	*N*-ethylmaleimide	toluene	2.5:1
3	**5b**	*N*-ethylmaleimide	benzene	1.4:1
4	**5b**	*N*-ethylmaleimide	DMF	2.4:1
5	**5c**	*N*-ethylmaleimide	toluene	1:2.5
6	**5c**	*N*-ethylmaleimide	DMF	1.5:1
7	**5d**	*N*-ethylmaleimide	toluene	2.5:1[c]
8	**5e**	*N*-ethylmaleimide	toluene	1:19[b]
9	**5e**	*N*-ethylmaleimide	toluene[d]	1:13.3[b]
10	**5e**	*N*-ethylmaleimide	DMF	1:3.3[b]
11	**5f**	*N*-ethylmaleimide	toluene	1.2:1[c]
12	**5e**	maleic anhydride	toluene	<1:15[e]
13	**5e**	benzoquinone	toluene	1:15.7[b]
14	**5e**	benzoquinone	DMF	1:3.8[b]
15	**5f**	benzoquinone	toluene	no reaction[f]
16	**5e**	naphthoquinone	toluene	1:9[b]
17	**5e**	naphthoquinone	DMF	1:4.3[b]
18	**5e**	tetracyanoethylene	toluene	1:3[b]
19	**5e**	tetracyanoethylene	DMF	no reaction[f]

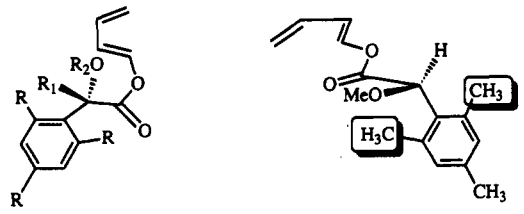
[a] *Si:Re* on (*S*)-diene (cf. A:B in Figure 4). Note that this specifies *relative* facial preference only, since racemic dienes were employed. No exo adducts were observed. [b] By HPLC. [c] By hydrolysis of the TMS group and then HPLC. [d] Molecular sieves (4 Å) added. [e] Estimated from the 250-MHz ^{1}H NMR spectrum. [f] After 4 days, by 250-MHz ^{1}H NMR.

In the course of our attempts to enhance the chirality transfer, we have designed and tested several model dienes. Herein, we describe how conformational preference of the diene in conjunction with intermolecular diene–dienophile coordination can bring about dramatic changes in face selectivity. We also discuss the conditions for maximal binding between reacting substrates, a property that conceptually mimics natural pathways and which, we hope, may trigger design of other asymmetric organic reactions and artificial enzymes.

Results and Discussion

Critical to the overall enhancement of diastereoselectivity of this type of Diels–Alder reaction is the conformational preference of the reactants in the transition structure, especially pertinent for the diene, which needs careful investigation and proper substrate design. Our approach to this problem basically starts with attempts to enhance the preferred ground-state diene conformation at room temperature, ultimately to reduce any contributions from the undesired rotamers and thus amplify the face selectivity even without employing any external catalyst. This basic concept of substrate design hinges on the assumption that the diene rotamer preference in the ground state would parallel that in the transition structure. This assumption also enjoys theoretical support: Houk and co-workers[13] concluded for diene **1** that the reactive rotamer in the transition structure is complementary to that of the ground state (viz., **3**). For a successful enhancement of the relative abundance of the perpendicular diene conformation, we planned to assess the role of different factors affecting the conformation of the stereogenic center, such as (a) tuning the stereoelectronics of the chiral center by placement of proper substituents and (b) enhancing hydrogen-bonding interaction. Thus, we have synthesized several model dienes (**5a–f**) (see Experimental Section) in racemic form by a route similar to the methods of Trost[9,10] and Paquette.[14] We have carried out Diels–Alder reactions to test our hypothesis, and the results are recorded in Table I.

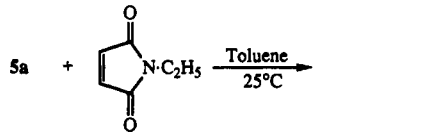
(7) Bonneau, P. R.; Graycar, T. P.; Estell, D. A.; Jones, J. B. *J. Am. Chem. Soc.* **1991**, *113*, 1026–1030 and references therein.
(8) (a) Schultz, P. G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1283–1295. (b) Schultz, P. G. *Acc. Chem. Res.* **1989**, *22*, 287–294.
(9) Trost, B. M.; Godleski, S. A.; Ippen, J. *J. Org. Chem.* **1978**, *43*, 4559–4564.
(10) Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595–7596.
(11) Siegel, C.; Thornton, E. R. *Tetrahedron Lett.* **1988**, *29*, 5225–5228.
(12) Siegel, C., Ph.D. Dissertation in Chemistry, University of Pennsylvania, Philadelphia, PA, 1987.
(13) Tucker, J. A.; Houk, K. N.; Trost, B. M. *J. Am. Chem. Soc.* **1990**, *112*, 5465–5471.
(14) Paquette, L. A.; Ward, J. S.; Boggs, R. A.; Farnham, W. B. *J. Am. Chem. Soc.* **1975**, *97*, 1101–1112.



5 a R = Me, R_1 = H, R_2 = Me
b R = H, R_1 = H, R_2 = H
c R = H, R_1 = Me, R_2 = H
d R = H, R_1 = Me, R_2 = TMS
e R = Me, R_1 = Me, R_2 = H
f R = Me, R_1 = Me, R_2 = TMS

6

Diastereoselectivities were determined from 250- or 500-MHz NMR spectra of the crude reaction mixtures, or by HPLC (reverse-phase, 70:30 methanol–water). The cycloadducts were inseparable by flash chromatography in all of the cases we studied. The major products were purified by crystallization (with a few exceptions, where crystallization was not possible as a result of poor diastereoselectivity). The stereochemistries for the cycloadducts with trimethylsilyl protecting groups were easily correlated by their facile conversion to the corresponding hydroxy compounds. We preferred *N*-ethylmaleimide (NEM) as our representative dienophile for most of our Diels–Alder reactions because of its good reactivity as well as product stability to chromatography (eq 1 is a representative example).



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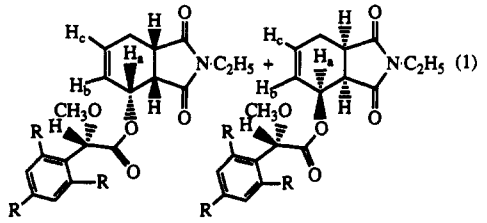


(1)

8 a R = Me
b R = H

9 a R = Me
b R = H

Steric Restriction and Hydrogen-Bonding Strategies. We began our exploration with diene **5a**. The design concept of this substrate was to restrict the conformational mobility of the chiral center. Examination of molecular models indicates that the ortho substituents on the *O*-methylmandelate group almost freeze the phenyl group into a conformation similar to **6**. If the presence of a less populated rotamer similar to **4** for diene **1** causes the formation of the minor adduct, then that could be suppressed for **5a**. With **5a**, by virtue of enhanced population, the reactive rotamer **6** could also be more strongly preferred in the transition structure. The alternate cause for the minor adduct could be approach of the dienophile from the more hindered side (syn to Ph) of the dominant rotamer. Also in that situation, the additional methyl substituents on the phenyl ring would impose more destabilizing steric repulsion (or electrostatic repulsion, as proposed by Houk and co-workers) to the incoming dienophile. As a result, the facial selectivity would be improved.

The Diels–Alder reaction of diene **5a** with *N*-ethylmaleimide (**7**) in toluene proceeded smoothly at ca. 25 °C. The proton NMR spectrum of the crude reaction mixture showed 5.2:1 (**8a**:**9a**) diastereoselectivity (Table I, entry 1), which was also further confirmed by HPLC. The stereochemistry of the major adduct **8a** was unequivocally established by a single-crystal X-ray analysis (Figure 1). The adduct has a Ph—C—C=O dihedral angle of 124.4°. This conformation, if present in the transition structure, places one of the *o*-methyl groups so as to interfere directly with dienophile approach, even though the phenyl group itself is not so nearly perpendicular as in the X-ray structures of Diels–Alder

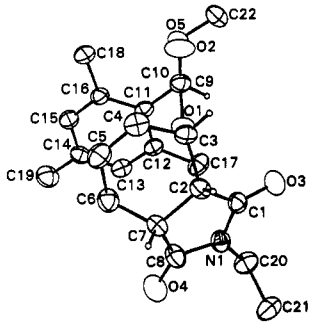
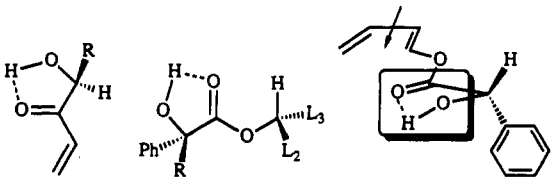


Figure 1. ORTEP diagram of the major cycloadduct (±)-**8a** of diene **5a** with *N*-ethylmaleimide in toluene.

adducts of **1**.[11,12,15] The latter X-ray structures contributed part of our evidence in support of the model **2**.[11] The current observation further generalizes our hypothesis, indicating that *o*-methyl groups can also provide steric interference perpendicular to the plane of the diene group.

Entry 2 (Table I) records the reaction of the Trost diene (**1**) with NEM. The stereochemistry of the major adduct **8b** (eq 1) was directly assigned by comparison of its proton NMR spectrum with that of adduct **8a**. The methine protons H_a for both major and minor cycloadducts in each series have characteristic chemical shifts. The resonance for H_a in minor adducts appears downfield from that in major adducts (δ 0.12 for **9a**, δ 0.08 for **9b**). The methyl group resonance of the *N*-ethyl group also provides a diagnostic chemical shift in all of the cycloadducts with *N*-ethylmaleimide we have examined: The adduct obtained from *Si* face attack (for the *S* configuration of the chiral center) always appears δ 0.05–0.15 downfield from its diastereomer resulting from the *Re* face attack on (*S*)-diene. The methyl resonance of **8b** appears δ 0.1 downfield from **9b**. Moreover, the NMR correlation model[16,17] also corroborates our stereoassignments; the vinylic protons H_b and H_c appear δ 0.15 and 0.17 upfield, respectively, in the major adduct **8b** compared with the minor adduct **9b**. Comparison of the above two Diels–Alder reactions reveals an improvement of stereoselectivity on going from diene **1** to **5a**, from 2.5:1 to 5.2:1, induced by conformational shielding as we predicted.

Our second design concept was analogous to Masamune's design of chiral dienophiles, which demonstrated effective conformational locking of chiral enones **10**[18] to give highly discriminating diastereotopic faces through intramolecular hydrogen bonding.



10 R = cyclohexyl, *t*-butyl

11

12

Additionaly, the Dale–Mosher NMR model postulated eclipsing of the hydroxy group and the carbonyl function as a result of intramolecular hydrogen bonding in mandelate esters **11** (R = H).[16] If such hydrogen bonding could be achieved, it would eliminate the conformational freedom at the chiral center, and the diene would be locked in the desired reactive conformation **12**.

Entry 3 (Table I) records the results of reaction of diene **5b** with NEM. The stereoselectivity (**13**:**14**) dropped to 1.4:1 in benzene. However, the selectivity improved in a polar solvent,

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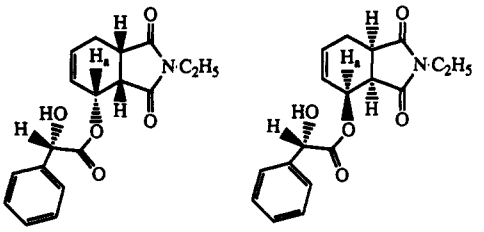
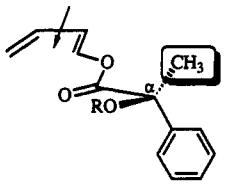
DMF (2.4:1, entry 4). The cycloadducts were not separable; the stereochemistries were assigned by NMR comparison with adducts **8a** and **9a** as described above for **8b** and **9b**: The methyl resonance in **13** appears δ 0.14 downfield from that in **14**. Also, the resonance for H_a in **14** appears δ 0.1 downfield from that in **13**. The poor selectivity for hydroxy diene **5b** might result from diene–dienophile hydrogen bonding. We demonstrate and exploit this feature below.



13 **14**

Influence of α-Substitution at the Chiral Center. Dienes **5c** and **5d** were designed to provide a sensitive test of the dependence of the chiral group conformation on α-substitution of the mandelate chiral auxiliary. Dale and Mosher concluded that their NMR conformational model **12** could be applied to mandelates, MTPA esters, and atrolactates.[16] More recently, Trost et al. have extended this model to *O*-methylmandelates.[17] If all of these esters have similar conformational properties, then all may adopt the approximately perpendicular orientation of the aromatic ring we have observed (as in **2**) in corresponding dienes. Moreover, utilization of atrolactate dienyl esters would be advantageous from a synthetic point of view, as the presence of a quaternary center would prevent any possible racemization of the chiral center during the esterification stage of diene synthesis. Another sensitive test would be the role of a free hydroxy group at the stereogenic center in determining the reactive conformation **15**, in comparison with the effect found with diene **5b**.



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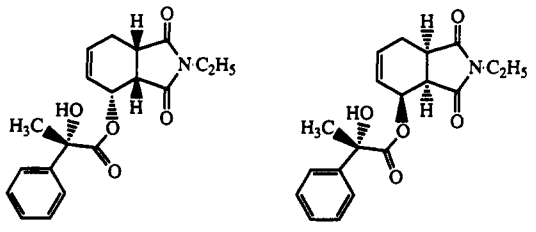
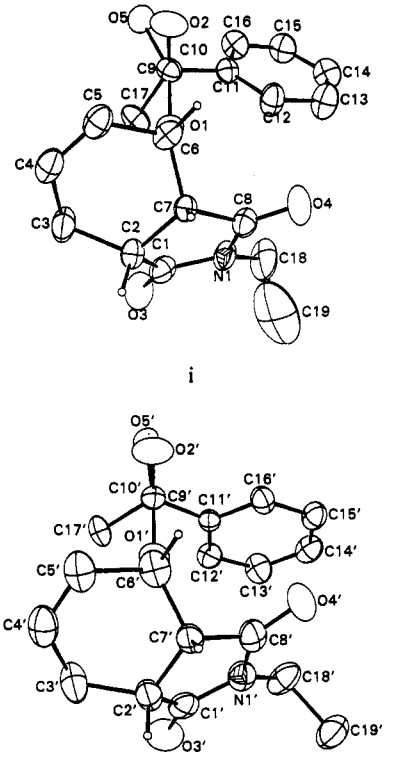
Diels–Alder reactions were carried out for dienes **5c** and **5d** with NEM in toluene (Table I). Entry 5 shows that the atrolactate diene **5c** in toluene gives a remarkable *reversal of facial selectivity* (1:2.5 for **16a**:**17a**) with respect to the dienes we have previously studied. For example, the stereochemistries of major adducts **8a** and **8b** in eq 1 match that of the minor adduct **16a**. Diene **5c** shows a *dramatic solvent effect*: *When the same reaction is carried out in DMF, the selectivity reverses to 1.5:1* (**16a**:**17a**, entry 6).



16a **17a**

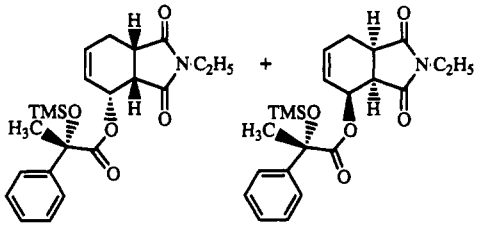
The protected diene **5d** gives the usual sense of selectivity, corresponding to attack on the *Si* face of diene conformation **15**, 2.5:1 (entry 7), for cycloadducts **16b**:**17b**. The magnitude of the diastereoselectivity is comparable with the Trost diene (**1**) at room temperature (entry 2). Cycloadducts **16b** and **17b** were inseparable. The stereochemical relationship between the two series of adducts obtained from **5c** and **5d** in toluene medium (entries 5 and 7) was established by hydrolyzing the adduct silyl ether



i ii

Figure 2. ORTEP diagram of cycloadduct (±)-**17a** of diene **5c** with *N*-ethylmaleimide, showing the two independent rotamers (i and ii).

mixture **16b** and **17b** to the corresponding hydroxy compounds, **16a** and **17a**, respectively (eq 2).



16b **17b**

$$\xrightarrow[\text{ca. 25 °C}]{\text{MeOH/H}^+} \textbf{16a} + \textbf{17a} \qquad (2)$$

Examination of the ^{1}H NMR after hydrolysis showed that the major compound in the adduct mixture of one is the minor compound of the other and vice versa. The stereochemistries of adducts **16a** and **17a** were established by X-ray structure determination (Figures 2 and 3).

The X-ray structures also provide interesting information regarding conformation. Firstly, adduct **17a** has two independent conformations in the unit cell as shown in Figure 2. In both of the adducts, **16a** and **17a**, the phenyl group remains nearly perpendicular to the carbonyl plane; the Ph—C—C=O dihedral angles are 91.2°, 112.7°, and 94.5° for the two rotamers of **17a** and for **16a**, respectively. The hydroxy oxygen is syn to the carbonyl group of the atrolactate ester. *More strikingly, in spite of a nearly eclipsing relation between the hydroxyl oxygen at the chiral center and the ester carbonyl group, intermolecular hydrogen bonding is observed between the hydroxy group of one adduct and the amide carbonyl group of another.* The OH···O=C H···O distance is 1.846, 1.802, and 1.937 Å; the O—H···O angle is 149.06°, 155.06°, and 157.86° for the two independent conformations of **17a** and for **16a**, respectively.

The crystal structure for **16a** (Figure 3) shows a representative example of this intermolecular hydrogen bonding. In the unit cell, two molecules bind each other in a head-to-tail fashion.[19] It may

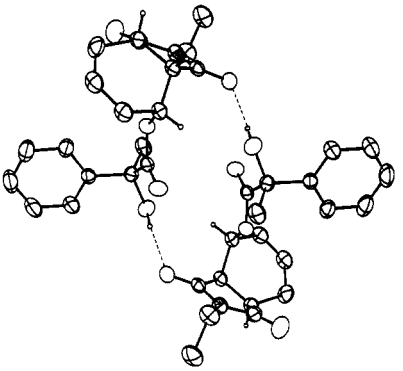


Figure 3. ORTEP diagram of cycloadduct (±)-**16a** of diene **5c** with *N*-ethylmaleimide, showing the intermolecular hydrogen bonding between two enantiomeric, but otherwise identical, molecules in a head-to-tail fashion (shown by dotted lines). As shown, the left structure has *S* configuration of the chiral auxiliary, the right structure, *R*.

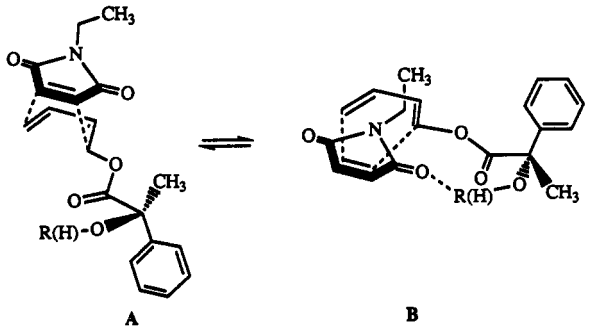


Figure 4. The two endo transition structures for reaction of diene **5c** or **5d** with *N*-ethylmaleimide.

be argued that X-ray structures do not necessarily correspond to solution structures,[20] but the consistency among the present structures as well as the reversal of selectivity for the atrolactate dienyl ester **5c** reveals that the *free hydroxy group does not form an intramolecular hydrogen bond in the dienyl ester* **5c**, *at least in the transition structure.*

Another important observation concerns exo–endo stereochemistries of the cycloadducts. In some of our previous work as well as certain of our present results, we have assumed that both the minor and major adducts result from endo attack of the dienophile. The X-ray structures for the adducts **16a** and **17a**, which represent the major and minor adducts for two sets of reactions (entries 5 and 7), indeed further confirm that both are endo.

Reversal of Facial Selectivity by Hydrogen Bonding. To explain this surprising stereochemical reversal for the dienes **5c** and **5d** in toluene, we reasoned that the hydroxy hydrogen might be coordinating with the dienophile carbonyl, which is a potential hydrogen bond acceptor, rather than the ester carbonyl. Such an interaction between the two reactants would necessarily alter the facial selectivity. It seems that the perpendicular conformation for the mandelate or atrolactate dienes (conformations **12** and **15**, respectively, or analogous Houk rotamers) does not contribute predominantly to the transition structures. Rather, a conformation analogous to **4** (Houk's second most stable rotamer) might be favored. We postulate two competing transition structures to rationalize the stereochemical properties of the dienes having a free hydroxy functionality (A and B, Figure 4).

Figure 4 shows the proposed endo transition structures for the atrolactate dienes **5c** and **5d**, with the two principal reactive diene rotameric forms in effective equilibrium. The stereoelectronically favored diene rotamer in A is similar to perpendicular rotamer **2** or analogous Houk rotamer **3**; the favored direction of attack is at the top face. In transition structure B, the dienophile attacks from the bottom face of the diene, which adopts a stereoelectronically less favored rotameric form but permits intermolecular coordination of the hydroxy hydrogen with the carbonyl group of the dienophile. The hydrogen-bonding interaction stabilizes B sufficiently to cause it to be the major reaction pathway, rather than A. This stabilization can be pictured in two equivalent ways: (1) the hydrogen bonding causes the reaction to be in effect an intramolecular Diels–Alder reaction of the diene–dienophile hydrogen bonded complex, or (2) the presence of the additional hydrogen bond within an intermolecular Diels–Alder transition structure lowers the free energy of B relative to A. Primarily, the product distribution is controlled by the above two diene rotamers, and the relative populations of their transition structures, B vs A, are ultimately governed by *a delicate balance of two competing forces (stereoelectronics vs hydrogen bonding) on the conformational preference at the chiral center.*

Interestingly, there is a recent report of reversal of face selectivity for another diene having a conformationally flexible hydroxy allylic substituent, with two different dienophiles, acrolein and *N*-phenylmaleimide.[21] Hydrogen bonding was proposed to rationalize the observed stereochemical difference in the case of acrolein, such that diene–dienophile hydrogen bonding controls the facial selectivity. In earlier work on dipolar cycloaddition reactions, theoretical calculation has also indicated that an allylic dipolarophile adopts two different reactive conformations for the protected and unprotected hydroxy functionalities, respectively, to allow hydrogen bonding between the dipolarophile and the nitrile oxide in the latter case.[22] When these arguments are translated to the present system, they also support our hypothesis.

The possible role of hydrogen bonding in controlling diastereoselective reactions is not new. It has been shown by several researchers in the past that such bonding at allylic positions can bring about dramatic changes in facial selectivity in different reactions.[23] More recently, Curran has ingeniously set up conditions to maximize this interaction by making the donor hydrogen atom more acidic.[23a] In Diels–Alder reactions also, chiral dienes substituted at an allylic position with conformationally locked, unprotected hydroxy groups show reversal of facial selectivities as opposed to the case when the hydroxy group is protected. These reversals have been rationalized in terms of hydrogen bonding.[24,25] In most of the work in this area, proximal hydrogen bond donors control the diastereoselectivities, and very little is known about the role of such functionalities when they are placed far away from any bond-forming site. *Our current observations are fascinating in that the hydrogen bond donor–acceptor relationship can be maintained in the transition structure, even when several bonds intervene between the participating groups.*

Design of a Highly Effective Diene Acting as a Receptor for Dienophiles. Now the question is whether the diene–dienophile interaction can be maximized to give complete facial discrimination. *We hypothesized that, in order to achieve a significant*

(19) The intermolecular hydrogen-bonding pattern is more complex in the case of **17a**: One molecule binds to another, the hydroxy hydrogen of one being hydrogen-bonded to an amide carbonyl group of the other, forming a polymeric chain.

(20) Similar arguments have been advanced in the case of triamides. See: (a) Dado, G. P.; Desper, J. M.; Gellman, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 8630–8632. Also see: (b) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–126.

(21) Trost, B. M.; Lee, D. C. *J. Org. Chem.* **1989**, *54*, 2271–2274.

(22) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880–3882.

(23) For leading references on dipolar cycloaddition reactions, see: (a) Curran, D. P.; Choi, S.-M.; Gothe, S. A.; Lin, F.-t. *J. Org. Chem.* **1990**, *55*, 3710–3712. (b) Caramella, P.; Cellerino, G. *Tetrahedron Lett.* **1974**, 229–232. (c) Caramella, P.; Albini, F. M.; Vitali, D.; Rondan, N. G.; Wu, Y.-D.; Schwartz, T. R.; Houk, K. N. *Tetrahedron Lett.* **1984**, *25*, 1875–1878. (d) Burdisso, M.; Gandolfi, R.; Pevarello, P.; Rastelli, A. *Tetrahedron Lett.* **1987**, *28*, 1225–1228. (e) Dal Bola, L.; De Amici, M.; De Micheli, C.; Gandolfi, R.; Houk, K. N. *Tetrahedron Lett.* **1989**, *30*, 807–810. (f) Curran, D. P.; Gothe, S. A. *Tetrahedron* **1988**, *44*, 3945–3952. For leading references on electrophilic addition reactions, see: (g) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650–663 and references therein.

(24) (a) Tripathy, R. Ph.D. Thesis, City University of New York, NY, 1989. (b) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472–8478.

(25) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625–4633.

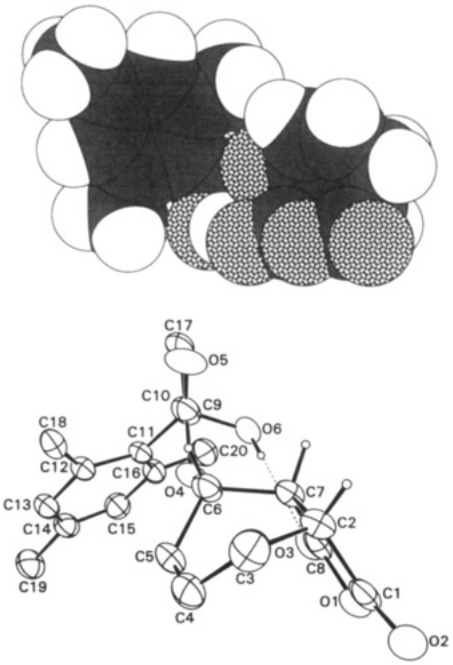


Figure 5. ORTEP diagram of the major cycloadduct (±)-**19c** of diene **5e** with maleic anhydride in toluene, showing the hydrogen bonding (dotted line) between the α-OH function and a carbonyl O of the dienophile moiety. Also shown is a space-filling model of this X-ray structure, which emphasizes the pocket-like environment of the hydrogen bond.

enhancement in the facial selectivity, the balance of opposing forces on the diene conformation should be interrupted. In principle, this can be done in two ways, either by decreasing the stereoelectronic preference of the diene or by increasing the coordination ability of the hydroxyl group. The magnitude of coordination appears to be very much dependent on the flexibility of the hydroxy function, as the more rigidified hydroxy group in the atrolactate diene **5c** provides better selectivity than the mandelate **5b** (a selectivity of 1.4:1 for diene **5b** and 1:2.5 in the case of diene **5c**, Table I, entries 3 and 5).

We therefore designed a potential diene receptor on the basis of the information gained from the above experiments. Diene **5e**, apart from all the rigidifying elements (i.e., the ortho substituents on the Ph ring and the C_α–Me group), was equipped with a free hydroxy hydrogen that is disposed to interact with the carbonyl group of the dienophiles. This final design meets all of the criteria and achieves remarkably high diastereoselectivity in Diels–Alder reactions at 25 °C, *without employing any Lewis acid catalyst* (Table I).

Apart from NEM, the diene shows high selectivities with different dienophiles such as maleic anhydride, benzoquinone, and naphthoquinone (entries 8, 12, 13, and 16, respectively). Most reactions showed a dramatic solvent effect (entries 10, 14, 17, and 19) when the polar solvent DMF was employed. We consider the solvent effect as a probe of hydrogen bonding: In a polar solvent like DMF, the hydroxy group becomes solvated, and the effect of hydrogen bonding is interrupted. The solvation of the hydroxy function acts like a protecting group[26] and thus favors a transition structure analogous to A (Figure 4). Moreover, the protected diene **1** shows little solvent dependence with a wide variety of solvents.[15] Analogous solvent effects have been observed and interpreted in terms of H bonding in Diels–Alder reactions of other dienes bearing an allylic heteroatom.[24,25]

In order to test the possibility that the presence of a small amount of water present in toluene might be responsible for the minor adduct formation, a reaction was carried out with the receptor diene **5e** with NEM in toluene in the presence of 4-Å molecular sieves.[27] However, there was a slight decrease in the facial selectivity (entry 9).

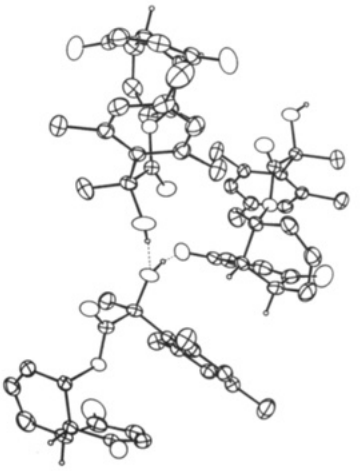
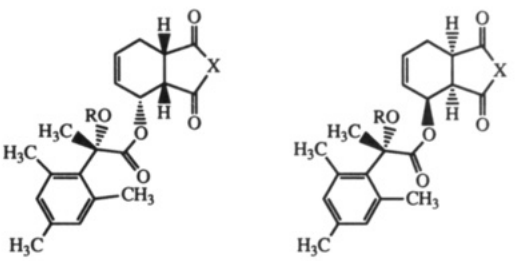


Figure 6. ORTEP diagram of the major cycloadduct (±)-**19d** of diene **5e** with benzoquinone, showing the two independent rotamers that are linked through intermolecular hydrogen bonding (shown by dotted lines). Out of three rotamers shown here, the right-most one has *R* configuration of the chiral auxiliary, the other two, *S*, and the right-most and bottom rotamers are identical except for being enantiomeric.

The contribution that a hydroxy hydrogen makes to the overall facial selectivity of this system can be seen by comparison of the results from a related diene in which the hydroxy group has been protected with a trimethylsilyl group. Reactions of the protected diene **5f** (entries 11 and 15) are extremely slow, but some reaction occurs with *N*-ethylmaleimide (entry 11). The magnitude of the facial selectivity decreases drastically.

From each cycloadduct mixture (**18a–18e** and **19a–19e**, **20**, and **21**), the predominant products **19a–19e** and **21** were purified by crystallization. While the stereochemistries of the major adducts **19a–19e** and **21** were determined by X-ray crystallography or chemical conversion (with one exception, the naphthoquinone adduct **19e**, where the stereochemistry was correlated by NMR), the stereochemistries for the minor adducts **18a–18e** and **20** have been assumed by comparison with related adducts of known endo stereochemistry (**16a,b**, **17a,b**; refs 11 and 15). For the silyl adducts **18b** and **19b**, the stereochemical relationship with adducts **18a** and **19a**, respectively, was established by hydrolysis.



18 **19**

a	X = NEt,	R = H
b	X = NEt,	R = TMS
c	X = O,	R = H
d	X = CH=CH,	R = H
e	X = C_6H_4,	R = H

The X-ray structures also provide striking evidence for the postulated hydrogen bonding. In two cases, cycloadducts **19a** and **19c**, the X-ray structures deviate from the earlier trend. Figure 5 *shows one representative example. The X-ray structures of adducts* ***19a*** *and* ***19c*** *show OH···O=C(dienophile) H···O distances of 1.839 and 2.234* Å (*O—H···O angles 159.6, 168.7°*), *characteristic of hydrogen bonding, the α-CH_3 eclipsing the ester C=O, and the phenyl anti to the dienophile moiety.* The

(26) The steric bulk of solvated hydroxy groups differs from solvent to solvent. See ref 25, footnote 34, and Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983; pp 5–6.

(27) The presence of molecular sieves is reported to enhance asymmetric induction in Lewis acid mediated Diels–Alder reactions. See: Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345.

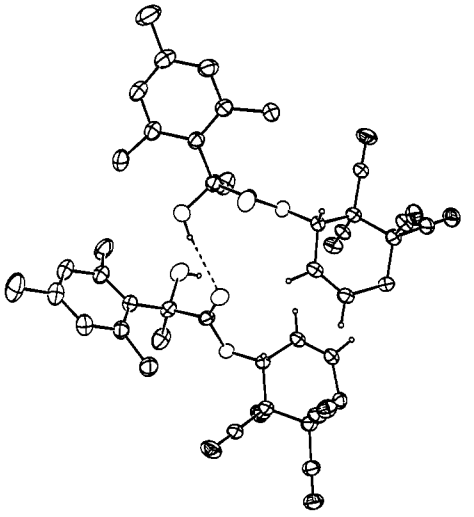


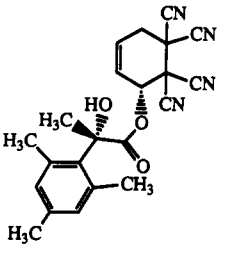
Figure 7. ORTEP diagram of the major cycloadduct (±)-**21** of diene **5e** with tetracyanoethylene, showing the two enantiomeric, but otherwise identical, rotamers that are linked through intermolecular hydrogen bonding (shown by dotted line). As shown, the upper structure has *S* configuration of the chiral auxiliary, the lower structure, *R*.

space-filling model of the X-ray structure of **19c** (Figure 5) shows how the hydrogen bond is located in a "recognition pocket" bounded by the other diene component groups.

Figure 6 shows the X-ray structure of the benzoquinone adduct **19d**, which lacks intramolecular hydrogen bonding analogous to **19a** and **19c** and rather shows an interesting intermolecular hydrogen-bonding pattern. The unit cell has two independent conformations, and in both of them (Ph—C—C=O dihedral angles 136.3° and 138.5°, respectively), the hydroxy group remains close to the ester carbonyl. The rotamers differ from each other in their hydrogen-bonding pattern. As shown in Figure 6, while one rotamer forms a polymeric chain of hydrogen bonds between the hydroxy hydrogen and the enone carbonyl of another identical conformer (two are shown in Figure 6), the hydroxy hydrogen of the second independent rotamer forms a hydrogen bond with the oxygen atom of the hydroxy group of the first. (H···O(carbonyl) distance 1.966 Å, O–H···O(carbonyl) angle 157.3°, H···O(hydroxy) distance 1.923 Å, O–H···O(hydroxy) angle 172.9°). The hydrogen-bonding pattern implies that, in the adduct **19d**, it is probably the conformational puckering of the six-membered enone ring which causes the absence of intramolecular hydrogen bonding of the type we have observed for cycloadducts **19a**[6] and **19c** (Figure 5). The ring carbonyl groups are twisted with respect to the plane of the benzoquinone moiety of the cycloadduct **19d** as a result of conformational preference, thus making them inaccessible for intramolecular hydrogen bonding without added energy cost. For the maleic anhydride or NEM adducts **19a** and **19c**, the rigid five-membered rings leave the carbonyls not twisted out of the plane of the ring. A typical distance measurement in adducts **19c** and **19d** supports our reasoning. The distances between the chiral carbon atom and its nearest enone carbonyl are 4.554 and 4.935 Å (two rotamers) for the cycloadduct **19d**, while the analogous distance in the adduct **19c** is considerably shorter (4.002 Å).

In the reaction of diene **5e** with benzoquinone, the selectivity is high, and the major adduct has the stereochemistry predicted by diene–dienophile hydrogen bonding. The data thus indicate that the diene–dienophile hydrogen-bonding interaction still controls the facial selectivity. This result is actually quite plausible, since the transition structure, especially if relatively early, will have considerable residual dienophilic π character. The presence of π character should keep the carbonyl groups in-plane, to allow hydrogen bonding like that for **19a**[6] and **19c**. Later, after rehybridization of the reacting dienophile double bond is more complete, the carbonyl groups would adopt the twist form characteristic of the product, so that the hydrogen-bonding interaction would be disrupted.

The last two entries in Table I record the reaction with tetracyanoethylene, which was employed to test the hydrogen-bonding hypothesis further. If diene–dienophile hydrogen bonding is indeed present in the favorable transition structures, as indicated by our data with carbonyl-activated dienophiles, it should be precluded with TCNE. Since the nitrogen lone electron pair is directed far from the OH group in any plausible transition structure, the stereocontrol and rate-accelerating effects would be absent. The poor diastereoselectivity (entry 18) and virtually no reaction in DMF (entry 19) are nicely consistent with this prediction. The X-ray structure (Figure 7) shows that the distance between the chiral carbon and the nearest nitrile nitrogen is 5.100 Å, still longer than the corresponding distance in other series of adducts as stated earlier. The X-ray structure shows polymeric intermolecular hydrogen bonding between the hydroxyl hydrogen of one molecule and the ester carbonyl of the other (OH···O=C(ester) H···O distance 2.196 Å, O—H···O angle 156.6°).



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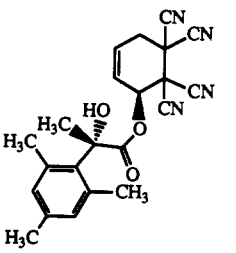


21

Conclusion

The overall conclusion from our work is that a free hydroxy function from a remote position on the sterogenic center can indeed control the diastereoselectivity in Diels–Alder reactions by providing effective coordination between the reactants. Our method mimics natural processes in the sense of excluding the need for low temperature or external additives such as a Lewis acid. We have used conformational tuning to design better receptor dienes by studying the nature of the forces that control the facial selectivity. The facial selectivity is basically controlled by two competing forces: While the stereoelectronics of the diene conformation favors one face, the diene–dienophile coordination through hydrogen bonding favors the opposite face of the diene. Conformational refinement through proper choice of substituents on the stereogenic center can retard the stereoelectronic effects to enhance hydrogen bonding. As a result, high diastereoselectivity can be achieved. We hope that the concept of controlling facial selectivity through hydrogen bonding can be applied to other reactions. It will be extremely advantageous in systems where the stereoelectronics and hydrogen bonding can act together in the same direction.

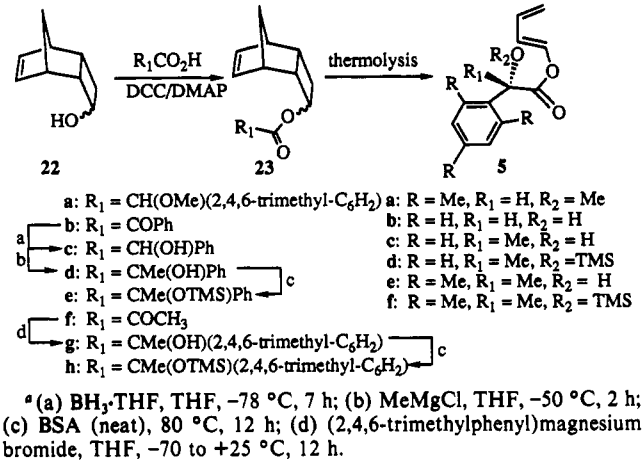
Experimental Section

Materials and Methods. All solvents and reagents were of reagent grade or better, and purified by standard methods.[28] Unless stated otherwise, all nonaqueous reactions were conducted under argon with oven-dried glassware that was flame-dried under a stream of argon. Melting points were determined on a Thomas–Hoover melting point apparatus and are reported uncorrected. ^1H and ^{13}C NMR (proton-decoupled) data are on the δ scale (parts per million relative to internal Me_4Si), and coupling constants are in hertz. Flash chromatography was carried out by using the procedure of Still et al.[29] Eluant compositions follow each column description. Fractions were analyzed by TLC with either fluorescence or stain (2.3% ethanolic phosphomolybdic acid or $KMnO_4$ solution) visualization.

General Synthetic Approach to Dienes 5a–f. These racemic chiral dienes were prepared according to the combined procedures of Trost[9] et al. and Paquette[14] et al. by thermolysis of the 3-(acyloxy)tricyclo-[4.2.1.$0^{2,5}$]non-7-ene prepared from the alcohol precursor as shown in Scheme I. Compounds are racemic mixtures, though for brevity only one enantiomer is shown. The free hydroxy groups at the chiral centers of dienes **5b**, **5c**, and **5e** were introduced in two steps. (i) Esterification[30]

(28) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: Oxford, 1980.
(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

Scheme I[a]



[a](a) BH_3·THF, THF, −78 °C, 7 h; (b) MeMgCl, THF, −50 °C, 2 h; (c) BSA (neat), 80 °C, 12 h; (d) (2,4,6-trimethylphenyl)magnesium bromide, THF, −70 to +25 °C, 12 h.

of either benzoylformic acid ($C_6H_5COCOOH$) or pyruvic acid ($CH_3COCOOH$) with tricyclic alcohol **22** furnished esters **23b** and **23f**, respectively. (ii) BH_3·THF reduction or Grignard reaction of those two esters gave the required diene precursors **23c**, **23d**, and **23g**, which on thermolysis furnished dienes **5b**, **5c**, and **5e**, respectively. The trimethylsilyl-protected dienes **5d** and **5f** were prepared by thermolysis of the protected precursors **23e** and **23h**, which were in turn prepared from **23d** and **23g** by treatment with $MeC[{=}NSiMe_3]OSiMe_3$ (BSA), as in Scheme I.

(±)-3-[2-Methoxy-2-(2,4,6-trimethylphenyl)acetoxy]-*endo*-tricyclo-[4.2.1.0^{2,5}]non-7-ene (23a). Esterification was carried out according to a literature procedure.[30] A mixture of (±)-2-methoxy-2-(2,4,6-trimethylphenyl)acetic acid[31] (913 mg, 4.38 mmol), alcohol **22** (727 mg, 5.34 mmol), 1,3-dicyclohexylcarbodiimide (DCC, 1.22 g, 5.96 mmol), 4-(dimethylamino)pyridine (DMAP, 70 mg, catalytic), and CH_2Cl_2 (35 mL) was stirred at ca. 25 °C for 24–36 h with monitoring by TLC. The reaction was worked up by filtration of the dicyclohexylurea. The filtrate was washed with H_2O (50 mL) three times, 5% acetic acid (50 mL) three times, and finally H_2O (50 mL) three times. The organic layer was dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (4:1 hexanes–EtOAc) and yielded **23a** (1.08 g, 76%) as a clear, colorless oil. IR ($CHCl_3$): 3020, 2980, 2935, 1740, 1610 (vw), 1190, 1135, 1110, 995 cm^{-1}. ^{1}H NMR analysis showed that the product was a mixture of two diastereomers in a 1:1 ratio, which were not separated since they lead to the same diene upon thermolysis. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.85 and 6.83 (2 s, 2 H, aromatic *H*), 5.86 and 5.79 (2 m, 1 H, C=C*H*), 5.32 (m, 0.5 H, *H*C=C), 5.2–4.7 (m, 2.5 H, *H*C=C, C*H*O$_2$C, C*H*OMe), 3.3 and 3.29 (2 s, 3 H, CH_3O), 3.2–0.9 (series of overlapping m and s, 17 H, C*H*C-*H*C=CC*H*C*H*, 2 CH_2 and 3 ArCH_3). Chemical ionization (CI) mass spectrum (MS) (*m/e*): 344.2201 (M + NH_4)$^+$, calcd for $C_{21}H_{30}NO_3$ 344.2226.

3-(2-Oxo-2-phenylacetoxy)-*endo*-tricyclo[4.2.1.0^{2,5}]non-7-ene (23b). To a solution of alcohol **22** (905 mg, 6.65 mmol), DCC (2 g, 9.7 mmol), DMAP (100 mg, catalytic), and CH_2Cl_2 (30 mL) was added dropwise a solution of benzoylformic acid (1.24 g, 8.26 mmol) in CH_2Cl_2 (10 mL) at ca. 25 °C over a period of 15 min. After stirring for 1 h, the reaction was worked up by filtration of the dicyclohexylurea. The filtrate was washed with H_2O (50 mL) three times, 5% acetic acid (50 mL) three times, and finally H_2O (50 mL) three times. The organic layer was dried ($MgSO_4$), and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (4:6 diethyl ether–hexanes) and gave **23b** (1.47 g, 82%) as a colorless syrup. IR ($CHCl_3$): 3080, 3040, 2990, 2975, 2875, 1730, 1690, 1600, 1455, 1340, 1320, 1300, 1240, 1195, 1175 (s), 1025, 985, 850, 815 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97–7.45 (3 m, 5 H, aromatic *H*), 6.21 (m, 1 H, C=C*H*), 6.12 (m, 1 H, *H*C=C), 5.14 (dd, appears as q, *J* = 6.6, 1 H, C*H*O$_2$C), 3.2 (m, 1 H, C*H*CHC=CCHCH), 3.03 and 2.84 (2 br s, 1 H each, CHC*H*C=CC*H*CH), 2.6–2.4 (m, 2 H, CHCHC=CCHC*H*), CH_aH$_b$), 1.73 (m, 1 H, CH$_a$*H*$_b$), 1.51 (d, *J* = 8.2, 1 H, CH_aH$_b$), 1.08 (d, *J* = 8.1, 1 H, CH$_a$*H*$_b$), CI MS (*m/e*) 286.1475 (M + NH_4)$^+$, calcd for $C_{17}H_{20}NO_3$ 286.1443.

(±)-3-(2-Hydroxy-2-phenylacetoxy)-*endo*-tricyclo[4.2.1.0^{2,5}]non-7-ene (23c). To a solution of **23b** (792 mg, 2.95 mmol) in dry THF (30 mL) was added, dropwise at −78 °C, a solution of BH_3·THF (1 M in THF) complex (3.5 mL, 3.5 mmol) over a period of 30 min. After the reaction mixture was stirred at −78 °C for 4 h, additional BH_3·THF (1 mL, 1 mmol) was added, and the mixture was stirred at −78 °C for 3 h. After quenching with 10% aqueous $NaHCO_3$ (15 mL), the mixture was brought to ca. 25 °C and extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (30 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvent gave an oil that was purified by flash chromatography (2:1 hexanes–EtOAc) to yield **23c** (744 mg, 93%) as a syrup. The purified product crystallizes in the freezer. Mp range: 62–74 °C. IR ($CHCl_3$): 3530, 3080, 3045, 2985, 2960, 2880, 1725, 1490, 1445, 1420, 1340, 1250, 1185, 1110, 1065, 1025, 900, 850, 810 cm^{-1}. ^{1}H NMR analysis showed that the product was a mixture of two diastereomers in a 3:2 ratio. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.5–7.3 (m, 5 H, aromatic *H*), 5.92 and 5.86 (2 m, 1 H, C=C*H*), 5.65 and 5.09 (2 m, 1 H, *H*C=C), 5.04 and 5.02 (2 s, 1 H, C*H*OH), 4.96–4.86 (2 m, 1 H, C*H*O$_2$C), 3.5 (2 br s, 1 H, O*H*), 3.2–2.3 (series of 6 m, 4 H, C*H*C*H*C=CC*H*C*H*), 1.6–0.9 (m, 4 H, 2CH_2). CI MS (*m/e*) 288.1632 (M + NH_4)$^+$, calcd for $C_{17}H_{22}NO_3$ 288.1600.

(±)-3-(2-Hydroxy-2-methyl-2-phenylacetoxy)-*endo*-tricyclo-[4.2.1.0^{2,5}]non-7-ene (23d). To a solution of **23b** (2.61 g, 9.73 mmol) in THF (50 mL) was added, dropwise at −50 °C, a solution of methylmagnesium chloride (3 M in THF, 3.33 mL, 10 mmol) over a period of 20 min. After the reaction mixture was stirred at −50 °C for 2 h, aqueous NH_4Cl (50%, 20 mL) was added slowly. The mixture was allowed to warm to ca. 25 °C and extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. Evaporation of solvent gave an oil that was purified by flash chromatography (4:1 hexanes–EtOAc) to yield **23d** (1.73 g, 66%) as a colorless syrup that crystallizes in the freezer. Mp range: 46–68 °C. IR ($CHCl_3$): 3590, 3530, 3080, 3000, 2960, 2935, 2880, 1715, 1600 (vw), 1490, 1445, 1420, 1375, 1340, 1310, 1255, 1140, 1065, 1020, 990, 980, 940, 905, 870, 815 cm^{-1}. ^{1}H NMR analysis showed that the product was a mixture of two diastereomers in a 3:2 ratio. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55–7.3 (m, 5 H, aromatic *H*), 5.97 (m, 1 H, C=C*H*), 5.72 and 5.43 (2 m, 1 H, *H*C=C), 4.9 (m, 1 H, C*H*O$_2$C), 3.8 and 3.65 (2 s, 1 H, O*H*), 3.1–2.3 (series of 5 m, 4 H, C*H*C*H*C=CC*H*C*H*), 1.76 and 1.75 (2 s, 3 H, CCH_3), 1.6–0.95 (m, 4 H, 2 CH_2). CI MS (*m/e*): 302.1797 (M + NH_4)$^+$, calcd for $C_{18}H_{24}NO_3$ 302.1756.

(±)-3-[2-Methyl-2-[(trimethylsilyl)oxy]-2-phenylacetoxy]-*endo*-tricyclo[4.2.1.0^{2,5}]non-7-ene (23e). A mixture of **23d** (412 mg, 1.45 mmol) in BSA (0.8 mL, neat) was stirred overnight at 80 °C. The product was purified by flash chromatography (9:1 hexanes–EtOAc) to give **23e** (396 mg, 76%) as a colorless oil. IR ($CHCl_3$): 3080, 3030, 2980, 2860, 2820, 1720, 1595 (vw), 1490, 1445, 1420, 1370, 1340, 1250, 1210, 1165, 1120 (br), 1060, 1025, 995, 860, 840, 760 (br) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.5–7.3 (m, 5 H, aromatic *H*), 5.92 and 5.77 (m, 1 H, C=C*H*), 5.53 and 5.42 (2 m, 1 H, *H*C=C), 4.85 (m, 1 H, C*H*O$_2$C), 3.05–2.2 (series of 4 m, 4 H, C*H*C*H*C=CC*H*C*H*), 1.76 (s, 3 H, CCH_3), 1.6–0.9 (m, 4 H, 2 CH_2), 0.11 (s, 9 H, 3 SiCH_3). CI MS (*m/e*): 357.1895 (M + H)$^+$, calcd for $C_{21}H_{29}O_3Si$ 357.1886.

3-(2-Oxopropionoxy)-*endo*-tricyclo[4.2.1.0^{2,5}]non-7-ene (23f). This compound was prepared according to the procedure for **23b**, except for the use of pyruvic acid ($CH_3COCOOH$) in place of benzoylformic acid. The crude product was purified by flash chromatography (3:1 hexanes–EtOAc) to give **23f** (2.78 g, 80%) as a volatile, colorless oil. IR ($CHCl_3$): 3030, 2970, 2880, 1725 (br), 1650, 1450, 1415, 1370, 1295, 970, 850, 810 cm^{-1}. ^{1}H NMR showed the presence of 10–15% impurity; **23f** was subjected to the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.18 (m, 1 H, C*H*=CH), 6.09 (m, 1 H, C*H*=CH), 4.90 (m, 1 H, C*H*O$_2$C), 3.1–2.3 (series of 5 m and 2 s, 7 H, C*H*C*H*-C=CC*H*C*H*, CH_3), 2.2–1.0 (m, 4 H, 2 CH_2). CI MS (*m/e*): 224.1297 (M + NH_4)$^+$, calcd for $C_{12}H_{18}NO_3$ 224.1287.

(±)-3-[2-Hydroxy-2-methyl-2-(2,4,6-trimethylphenyl)acetoxy]-*endo*-tricyclo[4.2.1.0^{2,5}]non-7-ene (23g). To a solution of **23f** (1.21 g, 5.87 mmol) in THF (30 mL) was added, dropwise at −70 °C, a solution of (2,4,6-trimethylphenyl)magnesium bromide (1 M in THF, 8 mL, 8 mmol) over a period of 15 min. The reaction mixture was allowed to warm slowly to ca. 25 °C and stirred for ca. 12 h. Workup as described for the preparation of **23d** gave the crude product, which was purified by column chromatography (eluting first with CH_2Cl_2, followed by increasing percent of EtOAc) to give **23g** (76% yield) as a gummy solid. IR ($CHCl_3$): 3590, 3080, 2980, 2960, 2880, 1735 (s), 1715, 1610, 1445, 1420, 1370, 1340, 1255, 1215, 1125 (br), 1055, 1030, 990, 975, 850, 755 (br) cm^{-1}. ^{1}H NMR showed the product to be a mixture of two diastereomers in the ratio of 3:2. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 (s, 2 H, aromatic *H*), 5.99 (m, 1 H, C=C*H*), 5.72 and 5.64 (2 m, 1 H, *H*C=C), 5.0–4.9 (m, 1 H, C*H*O$_2$C), 3.2–2.2 (series of 5 m and 3 s, 14 H, C*H*C*H*C=CC*H*C*H*, 3 ArCH_3, O*H*), 1.74 and 1.73 (2 s, 3 H, CCH_3),

(30) The procedure of Hassner and Alexanian was followed: Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475–4478.

(31) Groβ, H.; Freiberg, J. *Chem. Ber.* **1966**, *99*, 3260–3267.

1.6–1.0 (3 m, 4 H, 2 CH_2). CI MS (m/e) 344.2202 $(M + NH_4)^+$, calcd for $C_{21}H_{30}NO_3$ 344.2226.

(±)-3-[2-Methyl-2-(2,4,6-trimethylphenyl)-2-[(trimethylsilyl)oxy]-acetoxy]-*endo*-tricyclo[4.2.1.0^{2,5}]non-7-ene (23h). Trimethylsilylation of **23g** (331 mg, 1.02 mmol) gave compound **23h**, using the preparation and purification procedures described above for **23e** (yield 261 mg, 65%). IR ($CHCl_3$): 3035, 3015, 2970, 2860, 2820, 1725, 1610, 1450, 1370, 1340, 1255, 1200, 1130, 1060, 1030, 860, 845 (br) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.80 (s, 2 H, aromatic *H*), 5.94 (m, 1 H, C=C*H*), 5.58 (m, 1 H, *H*C=C), 5.16–5.04 (m, 1 H, CHO_2C), 3.2–2.1 (series of 5 m and 2 s, 13 H, C*H*C*H*C=CC*H*C*H*, 3 ArCH_3), 1.81 and 1.80 (2 s, 3 H, CCH_3), 1.65–1.01 (3 m, 4 H, 2 CH_2), 0.11 and 0.10 (2 s, 9 H, 3 SiCH_3). CI MS (m/e): 416.2569 $(M + NH_4)^+$, calcd for $C_{24}H_{38}NO_3Si$ 416.2621.

General Procedure for Synthesis of Dienes 5a–f. Thermolysis of esters **23a**, **23c**, **23d**, **23e**, **23g**, and **23h** to form the corresponding dienes was accomplished according to our previous method,[11] which is similar to that described by Trost et al.[9] 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 that was calibrated to achieve the desired temperature range (ca. 450–500 °C). A Kugelrohr oven and glassware (Aldrich) comprised the remainder of the apparatus. A general procedure is as follows. A distilling flask containing the diene precursor **23a**, **23c**, **23d**, **23e**, **23g**, or **23h** (0.5–2 mmol) was connected to the apparatus under vacuum (0.5–1.0 mmHg). After the pyrolysis tube reached a temperature of ca. 450–500 °C, the distilling oven was slowly warmed from ca. 25 to 250 °C while the receiving flask was cooled with a gentle stream of air. After distillation and pyrolysis were complete, the apparatus was allowed to cool to ca. 25 °C. The diene was collected in a round-bottom flask by using diethyl ether washes, the solvent was removed, and the residue was placed under vacuum for at least 2 h. In most cases, the crude dienes were pure enough for the Diels–Alder reactions. The dienes could also be purified by flash chromatography.

(±)-(*E*)-1-[2-Methoxy-2-(2,4,6-trimethylphenyl)acetoxy]-1,3-butadiene (5a). Diene precursor **23a** (660 mg, 2.02 mmol) was pyrolyzed to yield diene **5a** (538 mg, 96%), which was purified by flash chromatography (1:4 diethyl ether–hexanes) to give a clear oil (462 mg, 82%). IR ($CHCl_3$): 3060 (br), 2915, 2810, 1760 (s), 1660, 1610, 1450, 1230 (br), 1160 (br), 1110, 995, 925 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.4 (d, J = 12.1, 1 H, CHO_2C), 6.83 (s, 2 H, aromatic *H*), 6.21 (m, 1 H, C*H*=CH_2), 5.95 (dd, J = 12.1, 11.2, 1 H, C*H*=CO), 5.26 (s, 1 H, C*H*OMe), 5.14 (dd, J = 16.9, 0.6, 1 H, C$H_{cis}H_{trans}$=CH), 5.05 (dd, J = 10.3, 0.6, 1 H, CH$_{cis}H_{trans}$=CH), 3.36 (s, 3 H, OCH_3), 2.36 (s, 6 H, 2 ArCH_3), 2.24 (s, 3 H, ArCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 168.2 (*C*=O), 138.2, 137.6, 131.3, 130.2, 129.8, 129.0, 117.5, 116.8, (aromatic *C* and *C*=*C*C=*C*, 2 equiv), 77.6 (*C*OMe), 56.9 (O*C*H$_3$), 20.8, 20.1 (3 *C*H$_3$). CI MS (m/e): 278.1737 $(M + NH_4)^+$, calcd for $C_{16}H_{24}NO_3$ 278.1756.

(±)-(*E*)-1-(2-Hydroxy-2-phenylacetoxy)-1,3-butadiene (5b). Diene precursor **23c** (730 mg, 2.70 mmol) was pyrolyzed to give diene **5b** as a white solid (yield 454 mg, 82%). ^{1}H NMR of the crude diene showed it to be 95% pure; it was directly used for Diels–Alder reactions. A portion was crystallized from pentane in the freezer to furnish white needles. Mp: 43–44 °C. IR ($CHCl_3$): 3540 (br), 3035, 2995, 2920, 1740 (s), 1660, 1600 (w), 1380, 1245 (br), 1170, 1050, 930 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42–7.23 (m, 6 H, aromatic *H* and C*H*O$_2$C), 6.21 (m, 1 H, C*H*=CH$_2$), 6.04 (dd, J = 11.4, 11.2, 1 H, C*H*=CO), 5.24 (s, 1 H, C*H*OH), 5.20 (dd, J = 16.9, 0.66, 1 H, CH_{cis}H$_{trans}$=CH), 5.09 (dd, J = 10.22, 0.66, 1 H, CH$_{cis}H_{trans}$=CH), 3.3 (br s, 1 H, O*H*). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.6 (*C*=O), 138.1, 137.4, 130.9, 128.8, 128.7, 126.6, 118.3, 117.6 (aromatic *C* and *C*=*C*-*C*=*C*, 2 equiv), 72.8 (*C*OH). CI MS (m/e): 222.1116 $(M + NH_4)^+$, calcd for $C_{12}H_{16}NO_3$ 222.1130.

(±)-(*E*)-1-(2-Hydroxy-2-methyl-2-phenylacetoxy)-1,3-butadiene (5c). Diene precursor **23d** (437 mg, 1.53 mmol) was pyrolyzed to yield a light yellow oil (271 mg, 81%). The crude diene was purified by flash chromatography (2:3 diethyl ether–hexanes) to yield **5c** (234 mg, 70%) as a syrup. IR ($CHCl_3$): 3545 (br), 3100, 3080, 2995, 2960, 1740 (s), 1660, 1600 (w), 1490, 1440, 1410, 1380, 1240 (br), 1145, 1110, 990 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55–7.28 (m, 6 H, aromatic *H* and C*H*O$_2$C), 6.24 (m, 1 H, C*H*=CH$_2$), 6.09 (dd, J = 11.8, 11.6, 1 H, C*H*=CO), 5.22 (dd, J = 16.2, 0.6, 1 H, CH_{cis}H$_{trans}$=CH), 5.11 (dd, J = 9.6, 0.6, 1 H, CH$_{cis}H_{trans}$=CH), 3.6 (br s, 1 H, O*H*), 1.8 (s, 3 H, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): 172.4 (*C*=O), 141.9, 138.4, 130.9, 128.4, 128.0, 125.0, 118.2, 117.5 (aromatic *C* and *C*=*C*C=*C*, 2 equiv), 75.7 (*C*OH), 26.3 (*C*H$_3$). CI MS (m/e): 236.1289 $(M + NH_4)^+$, calcd for $C_{13}H_{18}NO_3$ 236.1287.

(±)-(*E*)-1-[2-Methyl-2-[(trimethylsilyl)oxy]-2-phenylacetoxy]-1,3-butadiene (5d). Diene precursor **23e** (214 mg, 0.60 mmol) was pyrolyzed to yield a colorless oil (164 mg, 94%). Diene **5d** was pure enough (>95% from ^{1}H NMR) to be directly used for Diels–Alder reaction. IR ($CHCl_3$): 3100, 3080, 2980, 2895, 1740 (s), 1655, 1600 (vw), 1490, 1440, 1410, 1370, 1250 (br), 1160 (br), 1110, 995, 860, 840 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.5–7.26 (m, 6 H, aromatic *H* and C*H*O$_2$C), 6.23 (m, 1 H, C*H*=CH$_2$), 6.03 (dd, J = 11.9, 11.5, 1 H, C*H*=CO), 5.18 (dd, J = 16.9, 0.6, 1 H, CH_{cis}H$_{trans}$=CH), 5.07 (dd, J = 10.3, 0.6, 1 H, CH$_{cis}H_{trans}$=CH), 1.84 (s, 3 H, CH_3), 0.16 (s, 9 H, 3 SiCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 171.2 (*C*=O), 143.2, 138.7, 131.4, 128.2, 127.7, 125.0, 117.5, 116.8 (aromatic *C* and *C*=*C*C=*C*, 2 equiv), 78.4 (*C*OSi), 27.9 (*C*H$_3$), 1.7 (3 SiCH_3). CI MS (m/e): 275.1079 $(M - CH_3)^+$, calcd for $C_{15}H_{19}O_3Si$ 275.1103.

(±)-(*E*)-1-[2-Hydroxy-2-(2,4,6-trimethylphenyl)propionoxy]-1,3-butadiene (5e). Diene precursor **23g** (648 mg, 1.98 mmol) was pyrolyzed to yield a light yellow syrup (424 mg, 82%). The crude diene was purified by flash chromatography (3:2 hexanes–diethyl ether) to yield **5e** (371 mg, 72%) as a syrup that solidified in the freezer. IR ($CHCl_3$): 3575 (br), 3035, 3018, 2925, 2858, 1753, 1658, 1610 (w), 1454, 1419, 1379, 1217, 1201, 1120 (br), 995, 925 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, J = 12.6, 1 H, CHO_2C), 6.8 (s, 2 H, aromatic *H*), 6.26 (m, 1 H, C*H*=CH$_2$), 6.04 (dd, J = 12.3, 11.1, 1 H, C*H*=CO), 5.17 (dd, J = 16.9, 0.7, 1 H, CH_{cis}H$_{trans}$=CH), 5.09 (dd, J = 10.9, 0.6, 1 H, CH$_{cis}H_{trans}$=CH), 2.6 (br s, 1 H, O*H*), 2.33 (s, 6 H, 2 ArCH_3), 2.23 (s, 3 H, ArCH_3), 1.77 (s, 3 H, CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 171.6 (*C*=O), 138.6, 136.8, 136.0, 135.5, 131.4, 131.3, 117.9, 117.4, (aromatic *C* and *C*=*C*C=*C*, 2 equiv), 79.0 (*C*OH), 24.3, 22.2, 20.5 (4 *C*H$_3$, 1 equiv). CI MS (m/e): 278.1717 $(M + NH_4)^+$, calcd for $C_{16}H_{24}NO_3$ 278.1756.

(±)-(*E*)-1-[2-Methyl-2-(2,4,6-trimethylphenyl)-2-[(trimethylsilyl)-oxy]acetoxy]-1,3-butadiene (5f). Diene precursor **23h** (230 mg, 0.57 mmol) was pyrolyzed to yield a colorless oil (184 mg, 96%). Diene **5f** was >95% pure (by ^{1}H NMR); it was directly used for Diels–Alder reaction without further purification. IR ($CHCl_3$): 3020, 2980, 1740 (s), 1655, 1610 (w), 1490, 1410, 1370, 1250, 1115, 920, 850, 840 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, J = 12.3, 1 H, CHO_2C), 6.78 (s, 2 H, aromatic *H*), 6.28 (m, 1 H, C*H*=CH$_2$), 6.04 (dd, J = 12.2, 11.2, 1 H, C*H*=CO), 5.17 (dd, J = 16.9, 0.7, 1 H, CH_{cis}H$_{trans}$=CH), 5.08 (dd, J = 10.3, 0.6, 1 H, CH$_{cis}H_{trans}$=CH), 2.29 (s, 6 H, 2 ArCH_3), 2.22 (s, 3 H, ArCH_3), 1.81 (s, 3 H, CH_3), 0.15 (s, 9 H, 3 SiCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 171.0 (*C*=O), 138.7, 137.2, 136.0, 135.0, 131.6, 131.3, 117.5, 117.3 (aromatic *C* and *C*=*C*C=*C*, 2 equiv), 80.7 (*C*OSi), 26.3, 22.5, 20.4 (4 *C*H$_3$, 1 equiv), 1.66 (3 SiCH_3). CI MS (m/e): 350.2147 $(M + NH_4)^+$, calcd for $C_{19}H_{32}NO_3Si$ 350.2151.

General Procedure for Diels–Alder Reactions. A solution of the diene (ca. 1 equiv) and the dienophile (ca. 1.5 equiv) in 3–5 mL (per mmol) of dry toluene or benzene or dimethylformamide was stirred for 1–5 days at ca. 25 °C. The reaction was worked up by removing solvent under rotary evaporation and drying under high vacuum. For the reactions in DMF, the crude reaction mixture was poured into water (10 mL), extracted with EtOAc (2 × 15 mL), washed with brine, and dried over $MgSO_4$. Evaporation of the solvent furnished the crude product. For the adducts with *N*-ethylmaleimide, the products were purified by preparative TLC (PTLC) to remove excess dienophile. The major adducts were purified by crystallization.

Cycloaddition of 5a with *N*-Ethylmaleimide. Diels–Alder reaction in toluene gave a ratio of racemic diastereomeric products **8a**:**9a** of 84:16, determined by HPLC (reverse-phase, 70:30 methanol–water, t_R (min) = 9.15 for **9a**, 10.35 for **8a**). The crude products on PTLC (65:35 hexanes–EtOAc) gave purified cycloadducts (71%); on crystallization (hexanes–EtOAc), **8a** (170 mg, 56%, ≥99% diastereomerically pure) was recovered. Crystals of **8a** for X-ray diffraction were obtained by a further recrystallization from methanol–water. Mp: 120–121 °C. IR ($CHCl_3$): 3025, 2965, 1750, 1705, 1605 (vw), 1440, 1405, 1380, 1355, 1245, 1125 (br), 995, 910 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.76 (s, 2 H, aromatic *H*), 5.98 and 5.92 (2 m, 2 H, CH=C*H*CHO$_2$C and C*H*=CHCHO$_2$C), 5.42 (dd (appears as t), J = 5.3, 5.0, 1 H, C*H*O$_2$C), 5.14 (s, 1 H, C*H*OMe), 3.49 (m, 2 H, CH_2CH$_3$), 3.33 (s, 3 H, CH_3O), 3.25 (dd, J = 9.7, 5.9, 1 H, COC*H*CHO$_2$C), 2.92 (m, 1 H, COC*H*CH$_2$), 2.25–2.1 (2 s and 1 m, 10 H, CH_aH$_b$C=C, 3 ArCH_3), 1.82 (m, 1 H, CH$_a$H$_b$C=C), 1.11 (t, J = 7.2, 3 H, CH$_2$CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 178.4, 175.0 (2 NC=O), 170.26 (CO_2), 137.9, 137.2, 131.4, 129.7, 129.6, 127.7 (aromatic and olefinic *C*; 2 equiv), 77.5 (*C*OMe), 66.4 (*C*HO$_2$C), 57.1 (*C*H$_3$O), 42.7, 37.0 (CO*C*HCHO), 33.6, 21.9, 20.8, 20.0, 13.4 (*C*H$_2$CH$_3$, CH$_2$*C*=C, 3 *C*H$_3$). CI MS (m/e): 403.2288 $(M + NH_4)^+$, calcd for $C_{22}H_{31}N_2O_5$ 403.2233. The stereochemistry of **8a** was determined by X-ray analysis (Figure 1).

Cycloaddition of 1 with *N*-Ethylmaleimide. Diels–Alder reaction in toluene gave a ratio of racemic diastereomeric products **8b**:**9b** of 72:28, determined by ^{1}H NMR analysis of the crude product (250 MHz, $CDCl_3$, CHO_2C, δ(**8b**) = 5.40, δ(**9b**) = 5.48). The products were not further separated. IR ($CHCl_3$): 3005, 2965, 2845, 1755, 1705, 1445,

1405, 1380, 1355, 1225, 1135, 1115, 995 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.4–7.2 (m, 5 H, aromatic *H*), 6.15 and 6.03 (2 m, 0.3 H each, CH=C*H*CHO$_2$C and C*H*=CHCHO$_2$C), 5.98 and 5.88 (2 m, 0.7 H each, CH=C*H*CHO$_2$C and C*H*=CHCHO$_2$C), 5.48 (dd, (appears as t), J = 5.24, 5.21, 0.3 H, C*H*O$_2$C), 5.40 (dd (appears as t), J = 5.2, 5.1, 0.7 H, C*H*O$_2$C), 4.64 (s, 1 H, C*H*OMe), 3.54 (m, 2 H, CH_2CH$_3$), 3.39 (s, 0.7 H, CH_3O), 3.33 (s, 0.3 H, CH_3O), 3.28 (dd, 0.7 H, J = 9.7, 5.8, COC*H*CHO$_2$C), 3.13 (dd, 0.3 H, J = 9.8, 5.2, COC*H*CHO$_2$C) 3.0 (m, 1 H, COC*H*CH$_2$), 2.38 (m, 0.3 H, CH_aH$_b$C=C), 2.36 (dm, J = 16.6, 0.3 H, CH$_a$*H*$_b$C=C), 2.24 (ddd, J = 16.4, 8.7, 5.5, 0.7 H, CH_aH$_b$C=C), 2.04 (dm, J = 16.5, 0.7 H, CH$_a$*H*$_b$=C), 1.18 (t, J = 7.2, 0.7 H, CH$_2$C*H*$_3$), 1.08 (t, J = 7.2, 0.3 H, CH$_2$C*H*$_3$). CI MS (*m/e*): 361.1741 (M + NH$_4$)$^+$, calcd for $C_{19}H_{25}N_2O_5$ 361.1763.

Cycloaddition of 5b with *N*-Ethylmaleimide. Diels–Alder reactions in benzene and dimethylformamide gave diastereomeric ratios **13**:**14** of 58:42 and 71:29, respectively, determined by ^1H NMR analysis of the crude product (500 MHz, $CDCl_3$, C*H*O$_2$C, δ(**13**) = 5.44, δ(**14**) = 5.54). The crude cycloadducts from benzene were purified by PTLC (1:1 hexanes–EtOAc) to yield 84% of adduct mixture **13**–**14**, which could not be further separated by crystallization. IR ($CHCl_3$): 3545, 3000, 2890, 1740, 1705, 1520 (br), 1440, 1400, 1380, 1350, 1215, 1110, 1060, 760 (br) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.4–7.2 (m, 5 H, aromatic *H*), 6.11 (m, 0.8 H, C*H*=C*H*CHO$_2$C), 5.99 (dddd, J = 9.5, 4.8, 2.6, 1.0, 0.6 H, CH=C*H*CHO$_2$C), 5.89 (ddd, J = 9.6, 5.7, 3.9, 0.6 H, C*H*=CHCHO$_2$C), 5.54 (m, 0.4 H, C*H*O$_2$C), 5.44 (dd (appears as t), J = 5.2, 5.1, 0.6 H, C*H*O$_2$C), 5.07 and 5.05 (2 s, 1 H, C*H*OH), 3.56 (q, J = 7.2, 1.2 H, CH_2CH$_3$), 3.45 (br s, 0.4 H, O*H*), 3.26–3.19 (m, 1.6 H, COC*H*-CHO$_2$C, O*H*), 3.11–2.93 (m, 1.4 H, COC*H*CH$_2$, CH_2CH$_3$), 2.50 (m, 0.8 H, CH_aH$_b$C=C), 2.22 (ddd, J = 16.6, 8.9, 5.7, 0.6 H, CH_aH$_b$C=C), 1.86 (dm, J = 16.6, 0.6 H, CH$_a$*H*$_b$C=C), 1.19 (t, J = 7.2, 0.6 H, CH$_2$C*H*$_3$), 0.95 (t, J = 7.2, 0.3 H, CH$_2$C*H*$_3$). CI MS (*m/e*): 347.1633 (M + NH$_4$)$^+$, calcd for $C_{18}H_{23}N_2O_5$ 347.1607.

Cycloaddition of 5c with *N*-Ethylmaleimide. Diels–Alder reactions in toluene and dimethylformamide gave diastereomeric ratios **16a**:**17a** of 29:71 and 60:40, respectively, determined by ^1H NMR analysis of the purified product mixture (500 MHz, $CDCl_3$, C*H*O$_2$C, δ(**16a**) = 5.44, δ(**17a**) = 5.49). The crude cycloadducts from toluene were purified by PTLC (1:1 hexanes–EtOAc) to yield adduct mixture **16a**–**17a** (112.6 mg, 88%). Recrystallization from acetone–water (3 times) gave adduct **17a** as a colorless solid (55 mg, 43%). Mp: 101–103 °C. ^1H NMR showed the presence of 10–15% of the minor adduct **16a**. Crystals suitable for X-ray analysis were selected under a microscope. IR ($CHCl_3$): 3560 (br), 3040, 3000, 2950, 1770, 1730, 1700, 1595 (vw), 1490, 1440, 1400, 1375, 1350, 1225 (br), 1130 (br), 1065, 990, 910, 820 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.5–7.2 (m, 5 H, aromatic *H*), 6.05 (m, 2 H, C*H*=C*H*CHO$_2$C), 5.49 (m, 1 H, C*H*O$_2$C), 3.75 (br s, 1 H, O*H*), 3.45–3.25 (m, 3 H, CH_2CH$_3$, COC*H*CHO$_2$C), 3.05 (m, 1 H, COC*H*CH$_2$), 2.51 (dm, J = 18.1, 1 H, CH_aH$_b$C=C), 2.42 (m, 1 H, CH$_a$*H*$_b$C=C), 1.75 and 1.69 (2 s, 3 H, CCH_3), 1.03 (t, J = 7.2, 3 H, CH$_2$C*H*$_3$). CI MS (*m/e*): 326.1383 (M – OH)$^+$, calcd for $C_{19}H_{20}NO_4$ 326.1392. The stereochemistry of **17a** was determined by X-ray analysis (Figure 2).

Cycloaddition of 5d with *N*-Ethylmaleimide. Diels–Alder reactions were carried out in toluene. The ratio of adducts **16b**:**17b** was roughly estimated from the ^1H NMR (500 MHz) spectrum of the crude reaction mixture (~70:30), as there was no baseline separation of peaks for major and minor adducts. The ratio was determined after the hydrolysis of the reaction mixture to the corresponding hydroxy adducts **16a** and **17a**, respectively. The crude product was purified by PTLC (65:35 hexanes–EtOAc). The cycloadducts were inseparable; the mixture was obtained as a colorless syrup (yield 174 mg, 80%). IR ($CHCl_3$): 3080, 3040, 3000, 2980, 2920, 2270, 1780, 1745, 1710, 1600 (vw), 1490, 1440, 1400, 1375, 1350, 1250, 1225, 1110 (br), 1070, 990, 860, 840, 760 (br) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.4–7.2 (m, 5 H, aromatic *H*), 6.22 and 6.1–5.95 (m, 0.3 H, and m, 1.7 H, respectively, C*H*=C*H*CHO$_2$C), 5.41 (m, 1 H, C*H*O$_2$C), 3.6–3.3 (m, 2 H, CH_2CH$_3$), 3.17 (dd, J = 9.9, 5.3, 0.7 H, COC*H*CHO$_2$C), 3.17 (dd, J = 10.4, 4.9, 0.3 H, COC*H*CHO$_2$C), 3.00 (m, 1 H, COC*H*CH$_2$), 2.48–2.3 (m, 1 H, CH_aH$_b$C=C), 2.15–1.95 (m, 1 H, CH$_a$*H*$_b$C=C), 1.14 (t, J = 7.2, 2.1 H, CH$_2$C*H*$_3$), 1.08 (t, J = 7.2, 0.9 H, CH$_2$C*H*$_3$), 0.15 (2 s, 9 H, 3 SiC*H*$_3$). CI MS (*m/e*): 433.2194 (M + NH$_4$)$^+$, calcd for $C_{22}H_{33}N_2O_5Si$ 433.2159.

Hydrolysis of Trimethylsilyl Adduct Mixture 16b–17b. To a solution of the adduct mixture **16b**–**17b** (110 mg, 0.26 mmol) in MeOH (3 mL) was added 1–2 drops of a saturated aqueous solution of oxalic acid, and the reaction mixture was stirred for 1 h at ca. 25 °C. Excess MeOH was removed under rotary evaporation, and the crude product mixture was purified by PTLC (1:1 hexanes–EtOAc) to furnish a white solid (82 mg, 90%). The ^1H NMR (500 MHz, $CDCl_3$) of the mixture showed the presence of **16a**:**17a** in a ratio of 71:29 (two sets of peaks used: CH$_2$C*H*$_3$ δ(**16a**) = 1.17, δ(**17a**) = 1.03; C*H*O$_2$C δ(**16a**) = 5.44, δ(**17a**) = 5.49). Repeated recrystallization (methanol–water) gave major product **16a** as a colorless solid (≥99% diastereomerically pure). Mp: 120–121 °C. IR ($CHCl_3$): 3540 (br) 3000, 2955, 1780, 1720, 1700, 1440, 1400, 1370, 1350, 1220 (br), 1210 (br), 990 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.4–7.2 (m, 5 H, aromatic *H*), 6.01 and 5.95 (2 m, 1 H each, CH=C*H*CHO$_2$C and C*H*=CHCHO$_2$C), 5.44 (dd (appears as t), J = 5.2, 5.0, 1 H, C*H*O$_2$C), 3.72 (br s, 1 H, O*H*), 3.55 (q, J = 7.2, 2 H, CH_2CH$_3$), 3.25 (dd, J = 9.8, 5.6, 1 H, COC*H*CHO$_2$C), 3.04 (ddd, J = 9.7, 8.9, 6.5, 1 H, COC*H*CH$_2$), 2.31 (ddd, J = 16.5, 8.8, 5.7, CH_aH$_b$C=C), 2.06 (dm, J = 16.5, 1 H, CH$_a$*H*$_b$C=C), 1.17 (t, J = 7.2, 3 H, CH$_2$C*H*$_3$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 178.6, 174.9, 174.7 (*C*O), 142.1, 132, 128.3, 127.9, 126.7, 125.2 (aromatic and olefinic *C*, 2 equiv), 75.3 (*C*O-H), 67.7 (*C*HO$_2$C), 42.9, 36.7 (COC*H*C*H*CO), 33.8, 25.9, 22, 13.1 (*C*H$_2$C=C, *C*H$_2$, 2 *C*H$_3$). CI MS (*m/e*): 361.1729 (M + NH$_4$)$^+$, calcd for $C_{19}H_{25}N_2O_5$ 361.1763. The stereochemistry of **16a** was determined by X-ray analysis (Figure 3).

Cycloaddition of 5e with *N*-Ethylmaleimide. Diels–Alder reactions in toluene, in toluene in the presence of 4-Å molecular sieves, and in DMF gave diastereomeric ratios **18a**:**19a** of 5:95, 7:93, and 23:77, respectively, determined by HPLC (reverse-phase, 70:30 methanol–water, t_R (min) = 9.21 for **18a**, 11.12 for **19a**). The crude products from toluene were purified by PTLC (65:35 hexane–EtOAc), and the purified cycloadducts (126 mg, 89%) on crystallization (hexanes–EtOAc) gave **19a** (108 mg, 76%, ≥99% diastereomerically pure). Crystals of **19a** for X-ray diffraction were obtained by recrystallization from acetone–water. Mp: 148–149 °C. IR ($CHCl_3$): 3500 (br), 2995, 1750, 1695, 1450, 1400, 1350, 1210, 1130, 1105 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.77 (s, 2 H, aromatic *H*), 5.92 and 5.82 (m and dm, J = 9.7, respectively, 1 H each, CH=C*H*CHO$_2$C and C*H*=CHCHO$_2$C), 5.53 (m, 1 H, C*H*O$_2$C), 4.65 (s, 1 H, O*H*), 3.43 (dd, J = 9.2, 7.1, 1 H, COC*H*CHO$_2$C), 3.38 (q, J = 7.2, 2 H, CH_2CH$_3$), 3.08 (ddd, J = 9.2, 7.2, 2.9, 1 H, COC*H*CH$_2$), 2.65 (ddd, J = 15.9, 6.3, 3.0, 1 H, CH_aH$_b$C=C), 2.34 (s, 6 H, 2 ArCH_3), 2.25 (m, 1 H, CH$_a$*H*$_b$C=C), 2.21 (s, 3 H, ArCH_3), 1.70 (s, 3 H, CCH_3), 1.02 (t, J = 7.2, 3 H, CH$_2$C*H*$_3$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 178.5, 176.2, 172.7 (ester and amide *C*=O), 136.7, 136.1, 135.3, 131.0, 128.6, 128.4 (aromatic and olefinic *C*, 2 equiv), 79.1 (*C*OH), 67.2 (*C*H-O$_2$C), 42.1 (N*C*H$_2$), 37.8, 34.0 (CO*C*H*C*HCO), 24.1, 23.4, 22.2, 20.5, 12.8 (*C*H$_2$C=C, 5 *C*H$_3$, 2 equiv). CI MS (*m/e*): 403.2241 (M + NH$_4$)$^+$, calcd for $C_{22}H_{31}N_2O_5$ 403.2233. The stereochemistry of **19a** was determined by X-ray analysis.[6]

Cycloaddition of 5f with *N*-Ethylmaleimide. Diels–Alder reaction in toluene was extremely slow. The ratio of adducts **18b**:**19b** was determined after hydrolysis of the inseparable cycloadducts to the corresponding adduct alcohol mixture **18a** and **19a**. The crude product mixture was purified by PTLC (1:1 hexanes–EtOAc), giving a syrup (33 mg, 49%). Unreacted diene was also recovered (15.5 mg, 0.46 mmol). IR ($CHCl_3$): 3040, 2980 (br), 2260, 1780, 1730, 1705, 1610 (w), 1450, 1400, 1375, 1350, 1250, 1215, 1130, 1115, 1055, 1015, 990, 855, 840, 760 (br) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.72 and 6.69 (2 s, 2 H, aromatic *H*), 6.32 and 6.17 (2 m, 1 H each, CH=C*H*CHO$_2$C and C*H*=CHCHO$_2$C), 5.32 (m, 1 H, C*H*O$_2$C), 3.2 (m, 1 H, CH_aH$_b$CH$_3$), 3.05–3.3 (m, 3 H, CH$_a$*H*$_b$CH$_3$, COC*H*CHO$_2$C), 2.55–2.15 (3 m and 4 s, 11 H, CH_aH$_b$C=C, ArCH_3), 1.74 (s, 3 H, CCH_3), 0.98 (t, J = 7.2, 1.5 H, CH$_2$C*H*$_3$), 0.89 (t, J = 7.2, 1.5 H, CH$_2$C*H*$_3$), 0.10 (s, 9 H, 3 SiC*H*$_3$). CI MS (*m/e*): 475.2611 (M + NH$_4$)$^+$, calcd for $C_{25}H_{39}N_2O_5Si$ 475.2628.

Hydrolysis of Trimethylsilyl Adduct Mixture 18b–19b. The adduct mixture **18b**–**19b** (30 mg, 0.072 mmol) was hydrolyzed and purified as described above for hydrolysis of the adduct mixture **16b**–**17b** (yield 22 mg, 89%). The ^1H NMR (500 MHz, $CDCl_3$) of the mixture showed the presence of **16a** and **17a**, and the diastereomeric ratio **16a**:**17a** was found to be 54:46, determined by HPLC (reverse-phase, 70:30 methanol–water). The mixture was not further separated.

Cycloaddition of 5e with Maleic Anydride. Diels–Alder reaction in toluene gave a diastereomeric ratio **18c**:**19c** of <6:94, as approximately estimated by ^1H NMR analysis of the crude product mixture (250 MHz, $CDCl_3$, CCH_3, δ(**18c**) = 1.62, δ(**19c**) = 1.52). The crude cycloadduct mixture was recrystallized from hexanes–EtOAc to yield colorless crystals of **19c** (50 mg, 77%, ≥99% diastereomerically pure). Mp: 141.5–142 °C. IR ($CHCl_3$): 3525, 3020, 2923, 2854, 1855, 1782 (br), 1749, 1612, 1539, 1444, 1419, 1379, 1344, 1217, 1088, 985 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.77 (s, 2 H, aromatic *H*), 6.08 and 6.04 (m and dm, J = 9.8, respectively, 1 H each, CH=C*H*CHO$_2$C and C*H*=CHCHO$_2$C), 5.51 (m, 1 H, C*H*O$_2$C), 3.60 (dd, J = 10.1, 6.3, 1 H, COC*H*CHO$_2$C), 3.41 (ddd, J = 10.1, 8.6, 3.3, 1 H, COC*H*CH$_2$), 3.31 (s, 1 H, O*H*), 2.68 (ddd, J = 16.4, 8.3, 4.6, 1 H, CH_aH$_b$C=C), 2.38 (m, 1 H, CH$_a$*H*$_b$C=C), 2.30 (s, 6 H, 2 ArCH_3), 2.22 (s, 3 H, ArCH_3), 1.52 (s, 3 H, CCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 172.7, 172.6, 170.0 (ester and anhydride *C*=O), 136.5, 135.9, 135.2, 131.2, 130.2, 127.3

(aromatic and olefinic C, 2 equiv), 79.3 (COH), 65.6 (CHO_2C), 43.4, 37.7 (COCHCHCO), 23.9, 22.6, 22.1, 20.4 ($CH_2C{=}C$, 4 CH_3, 1 equiv). CI MS (m/e): 376.1784 $(M + NH_4)^+$, calcd for $C_{20}H_{26}NO_6$ 376.1760. The stereochemistry of **19c** was determined by X-ray analysis (Figure 5).

Cycloaddition of 5e with 1,4-Benzoquinone. Diels-Alder reactions in toluene and dimethylformamide gave diastereomeric ratios **18d**:**19d** of 6:94 and 21:79, respectively, determined by HPLC (reverse-phase, 70:30 methanol-water, t_R (min) = 5.65 for **18d**, 6.83 for **19d**). The crude product from toluene was recrystallized from hexanes-EtOAc to yield colorless needles of **19d** (114.4 mg, 72%, ≥97% diastereomerically pure). Mp: 159-160 °C. IR ($CHCl_3$): 3540 (br), 3010, 2925, 1735, 1705, 1680, 1610 (w), 1420, 1110, 1015 (br), 750 (br) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.77 (s, 2 H, aromatic *H*), 6.0 (m, 3 H, COC*H*=C-HCO, $CH_2CH{=}CHCH$), 5.88 (dd, J = 10.2, 0.8, 1 H, COCH=C*H*CO), 5.25 (dd, J = 4.0, 3.5, 1 H, CHO_2C), 3.24 (m, 1 H, COC*H*CHO_2C), 3.15 (dd, J = 7.4, 6.7, 1 H, COC*H*CH_2), 3.01 (br dd, J = 19.0, 1.1, 1 H, $CH_aH_bC{=}C$), 2.9 (br s, 1 H, O*H*), 2.22 (s, 9 H, 3 $ArCH_3$), 2.08 (br dd, J = 19.3, 7.6, 1 H, $CH_aH_bC{=}C$), 1.66 (s, 3 H, CH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 197.9, 196.5 (C=O), 175.9 (CO_2), 140.7, 138.9, 137.3, 136.7, 134.2, 132.3, 131.6, 121.7 (aromatic and olefinic C, 2 equiv), 77.9 (COH), 68.5 (CHO_2C), 48.9, 41.9 (COC-H-CHCO), 28.7, 22.8, 21.3, 20.4 ($CH_2C{=}C$, 4 CH_3, 1 equiv). CI MS (m/e): 386.1963 $(M + NH_4)^+$, calcd for $C_{22}H_{28}NO_5$ 386.1967. The stereochemistry of the major product **19d** was determined by X-ray analysis (Figure 6).

Cycloaddition of 5e with 1,4-Naphthoquinone. Diels-Alder reactions in toluene and dimethylformamide gave diastereomeric ratios **18e**:**19e** of 10:90 and 19:81, respectively, determined by HPLC (reverse-phase, 70:30 methanol-water, t_R (min) = 19.82 for **13e**, 14.77 for **19e**). The crude product mixture from toluene was recrystallized from methanol to yield pale yellow needles of **19e** (59 mg, 70%, ≥98% diastereomerically pure). Mp: 192-193 °C. The crystals were not suitable for X-ray analysis. IR ($CHCl_3$): 3580, 3040, 1740, 1700 (br), 1590, 1430, 1335, 1255, 1255, 1210, 1110 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.94 (dd, J = 8.6, 0.5, 1 H, benzo *H*), 7.6 (m, 1 H, benzo *H*), 7.53 (d, J = 3.9, 2 H, benzo *H*), 6.58 (s, 2 H, Ar*H*), 6.15 and 6.13 (AB pattern with additional splitting, $J_{AB} \approx 10.5$, 2 H, C*H*=C*H*), 5.46 (br s, 1 H, CHO_2C), 3.51 (dd, J = 6.1, 4.5, 1 H, COC*H*CHO_2C), 3.51 (dd (appears as t), J = 6.5, 6.4, 1 H, COC*H*CH_2), 3.9 (br d, J = 17.9, 1 H, $CH_aH_bC{=}C$), 2.21 (m overlapping s, 4 H, $ArCH_3$ and $CH_aH_bC{=}C$), 1.95 (s, 6 H, 2 $ArCH_3$), 1.65 (br s, 1 H, O*H*), 1.24 (s, 3 H, CCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 195.7, 194.8 (C=O), 173.8 (CO_2), 136.3, 136.0, 135.2, 134.8, 134.3, 133.1, 132.5, 131.2, 126.2, 125.9, 122.2, 106.6 (aromatic and olefinic C, 2 equiv), 78.7 (COH), 68.9 (CHO_2C), 49.7, 42.5 (COCHC-HCO), 24.1, 22.0, 20.5 ($CH_2C{=}C$ and 4 CH_3, 2 equiv). CI MS (m/e): 436.2083 $(M + NH_4)^+$, calcd for $C_{26}H_{30}NO_5$ 436.2124. The stereochemistry for **19e** was assigned by correlation with another naphthoquinone adduct.[11]

Cycloaddition of 5e with Tetracyanoethylene. Diels-Alder reaction in toluene gave a diastereomeric ratio **20**:**21** of 25:75, determined by HPLC (reverse-phase, 70:30 methanol-water, t_R (min) = 12.96 for **20**, and 14.51 for **21**). In dimethylformamide, there was virtually no reaction after stirring for 4 days. The crude product from toluene was recrystallized from methanol to yield pure white needles of **21** (32.7 mg, 63%, ≥99% diastereomerically pure). Mp: 213-214 °C. IR ($CHCl_3$): 3580, 3025, 2985, 2950, 1755, 1445, 1430, 1375, 1325, 1135, 1120, 995 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 6.80 (s, 2 H, aromatic *H*), 6.08 (ddd, J = 10.6, 3.7, 1.5, 1 H, one of C*H*=C*H*), 5.99 (ddd, J = 4.8, 1.7, 1.7, 1 H, CHO_2C), 5.95 (ddd, J = 10.6, 2.1, 1.0, 1 H, one of C*H*=C*H*), 3.22 and 3.15 (AB pattern of 2 dm, J = 18.8, 2 H, $CH_aH_bC{=}C$), 2.65 (s, 1 H, O*H*), 2.34 (s, 6 H, 2 $ArCH_3$), 2.21 (s, 3 H, $ArCH_3$), 1.54 (s, 3 H, CCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 172.3 (ester C=O), 137.1, 135.1, 134.8, 131.6, 125.2, 122.6, 110.0, 109.9, 108.5, 107.8 (aromatic, cyano, and olefinic C, 2 equiv), 79.6 (COH), 67.4 (CHO_2C), 42.3, 36.8, 32.3, 24.7, 22.4, 20.4, (NCCHCHCN, $CH_2C{=}C$ and 4 CH_3, 1 equiv). CI MS (m/e): 406.1908, $(M + NH_4)^+$, calcd for $C_{22}H_{24}N_5O_3$ 406.1879. The stereochemistry of **21** was determined by X-ray analysis (Figure 7).

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Supplementary Material Available: Crystal structure determination summaries and tables of refined atomic positional and thermal parameters and bond distances and angles for the six Diels-Alder adducts **8a**, **16a**, **17a**, **19c**, **19d**, and **21** (64 pages). Ordering information is given on any current masthead page.

Hydrogen Bonding and Molecular Recognition: Synthetic, Complexation, and Structural Studies on Barbiturate Binding to an Artificial Receptor

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Abstract: A series of synthetic receptors with strong selectivity for the barbiturate family of drugs has been prepared. The receptor design is based on two 2,6-diaminopyridine groups linked through an isophthalic acid spacer. X-ray crystallographic, ^1H NMR spectroscopic, and substrate binding studies confirm that six hydrogen bonds are formed between the receptor and its substrate. The strongest binding ($K_a \approx 10^5$ M^{-1}) is seen to those substrates containing the complementary barbituric acid core. Systematic deletion of hydrogen-bonding sites from the receptor and substrate allows an assessment of the contribution of individual binding sites to complexation.

Introduction

The development of *artificial receptors* for neutral molecules is an important challenge in modern bio-organic chemistry.[1] In addition to a compatibility of shape and size, effective molecular recognition requires a precise alignment of binding groups on the receptor with complementary regions on the substrate. In several recent reports,[2,3] one or more hydrogen-bonding sites have been incorporated into artificial receptors to provide both orientation

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