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# CONFORMATIONAL MODEL FOR ASYMMETRIC DIELS–ALDER REACTIONS WITH CHIRAL DIENES

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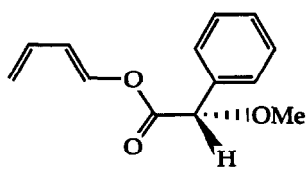
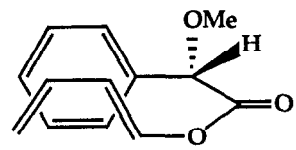
**Abstract:** 1-(*O*-methylmandeloxy)dienes have significant advantages for asymmetric Diels–Alder reactions, and we now show that high (>90%) diastereofacial selectivities can be obtained with these dienes, permitting considerable choice as to dienophile and the presence of additional functionality. We present experimental support, including X-ray structures showing the conformations of three Diels–Alder adducts, for a transition state model which explains the origin of these selectivities. The distinctive characteristics of this model are that the phenyl group is nearly perpendicular to the ester C=O, i.e., the Ph–C–C=O dihedral angle is near 90°, and that the methoxy group is close to the carbonyl oxygen. These features may have wider applications for chiral control by α-chiral ester groups in other types of reactions. Our results should renew interest in the use of chiral 1-acyloxydienes.

Chiral control is one of the most challenging current problems of organic chemistry, and the Diels–Alder reaction can fix several chiral centers simultaneously.[1,2,3,4,5] High selectivities making diastereomer separation unnecessary will greatly enhance synthetic usefulness. Chiral dienophiles are very useful, but chiral dienes, which have been much less studied, could be advantageously employed in many synthetic applications. Acyloxydienes have several merits, including activation of the diene by the OCOR group, giving high regioselectivities and permitting considerable choice as to dienophile and presence of additional functionality, as well as ready subsequent deprotection of the OH group. They have been used, for example, in syntheses of tetracyclines,[6,7,8,9] ibogamine,[10] and bostrycin.[11]

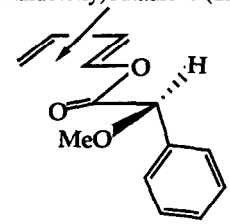
The significant asymmetric induction in Diels–Alder reactions of 1-(*O*-methylmandeloxy)butadiene (**1a**) led to a




**1a**




**2**




**3**

π-stacking model (**2**),[12] but it now turns out that π-stacking cannot be the controlling interaction. For example, **1a** gave a diastereofacial selectivity (df) of 82:18 for the two endo adducts in its Diels–Alder reaction with acrolein using $BF_3$ as catalyst at –20 °C.[12,13,14,15] The configuration of the major product was explained by a π-stacking transition state conformation analogous to **2**, in which the phenyl group blocks the rear face preferentially because the H at the chiral center, rather than the $OCH_3$, then projects toward the diene group.[12] However, saturation of the phenyl ring to give a cyclohexyl group (**1b**) yields the same 82:18 ratio as with phenyl,[16] and we have confirmed that observation. Therefore, π-stacking cannot be controlling the conformation.

1-(*O*-methylmandeloxy)dienes have excellent synthetic potential because both enantiomers of mandelic acid (as well as racemate for model studies) are commercially available. Consequently, we recently initiated a program directed towards exploiting such chiral dienes for synthetically useful stereocontrol and experimentally elucidating the stereo-controlling interactions. In this communication, we report the first characterization of the actual source of stereo-selectivity and the enhancement of diastereofacial selectivities to synthetically useful levels in excess of 90:10.

Specifically, we have made the novel discovery that the **transition states** for Diels–Alder reactions of dienes **1** are best described **not** by conformations related to **2**, but rather by a completely different model (cf. **3**) differing in all three crucial dihedral angles and resembling a perpendicular modification of the **ground state** NMR model of Dale and Mosher.[17,18]

We have also found that it is practical to carry out these reactions at −78 °C and that the enthalpy difference between transition states for attack on the two faces of the diene is sufficient (2.1 kcal $mol^{-1}$ for **1a** + acrolein) to give quite useful levels of selectivity (e.g., in this case, 94:6, with no exo diastereomer detectable).

Our results are shown in Table I, which illustrates the stereochemical results for Diels–Alder reactions with three representative dienophiles and with three dienes designed to provide information about the controlling interactions. Not only does cyclohexyl in place of phenyl (**1a** vs. **1b**) give the same diastereofacial selectivity (df) at −20 °C, but it also gives nearly as high a selectivity at −78 °C, indicating little or no contribution of π-stacking (**2**) to the df. To determine whether ester conformations *resembling* **2** might still be controlling, we synthesized the 2-methyl diene **1c**, which sterically precludes conformations anywhere near **2**. In fact, **1c** gives equal or **higher** df than **1a** (with dienophiles **4b** and **4a**, respectively) and thus requires that an entirely different conformation is controlling the df.

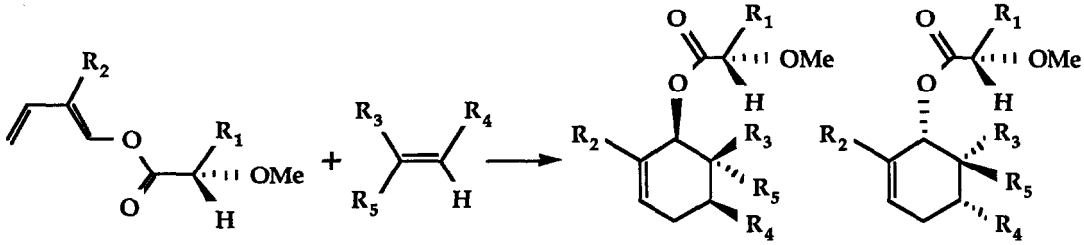
Moreover, with benzoquinone it is possible to carry out Diels–Alder reaction in the absence of the $BF_3$ catalyst with only modest reduction of the stereoselectivity, indicating that there is interaction of the chiral center of the diene with the dienophile (presumably the s-trans C=O group) and not just with the complexed $BF_3$.

Essentially the only transition state model consistent with these data and capable of giving **any** interaction of an approaching dienophile with the chiral center is one similar to **3**, with the bulky phenyl group nearly perpendicular to the approximate plane defined by the diene moiety in the transition state. In this case, attack on the diene face opposite the phenyl group should be strongly preferred. The selectivity would be determined by the relative populations of transition states having the phenyl group above or below the diene plane. All other plausible conformations, even simply rotating the phenyl group to a 120° dihedral angle, completely remove any steric preference for diastereofacially selective approach of the dienophile to the diene.

This model is similar to the Dale–Mosher model for NMR of secondary *O*-methylmandelate esters,[17,18] but a more stringent requirement is essential—the perpendicularity of the phenyl group noted above, without which there would appear to be no significant interaction of the dienophile with the chiral center (and thus a 50:50 df). This model, where the phenyl group, and not the methoxy, is perpendicular, bears a formal resemblance to the "staggered, inside methoxy" effect postulated for cycloaddition involving a quite different structural type.[19,20,21,22]

Finally, though we do not yet have a crystalline diene, we have obtained X-ray structures for **three** of our adducts, those from diene **1a** with benzoquinone (Figure 1) and naphthoquinone and that from diene **1c** with benzoquinone. Strikingly, all three have the phenyl group nearly perpendicular to the ester O=C–O plane (Ph–C–C=O dihedral angles 99.2°, 95.4°, and 101°, respectively)![23] In fact, these X-ray results almost uniquely agree with all of the conclusions from our other data above, i.e., that the phenyl group needs to be nearly perpendicular to the diene in order to interact with an approaching dienophile, that the ester group should be in its favored syn conformation, and that the results with **1c** indicate an s-trans conformation (not s-cis) about the ester O–diene bond. Of course, crystal structures of adducts may not exactly reflect preferences at transition states in solution, but the extensive agreement with our other data strongly suggests that conformations close to those in our X-ray data are indeed preferred in these transition states.

**Table I.** Diastereofacial Selectivities in Diels–Alder Reactions of Chiral Dienes 1[a]



1a $R_1$ = Ph, $R_2$ = H
1b $R_1$ = c-$C_6H_{11}$, $R_2$ = H
1c $R_1$ = Ph, $R_2$ = $CH_3$

4a $R_3$ = CHO, $R_4$, $R_5$ = H
4b $R_3$, $R_4$ = –CO–CH=CH–CO–, $R_5$ = H
4c $R_3$ = CHO, $R_4$ = H, $R_5$ = $CH_3$

5 6

| Diene | Dienophile | Temperature, °C | Catalyst (mol %) | Product Ratio 5:6[b] |
|---|---|---|---|---|
| **1a** | $CH_2$=CH–CHO (**4a**) | –20 | $BF_3$·$Et_2O$ (15) | 82:18 |
| **1a** | $CH_2$=CH–CHO (**4a**) | –78 | $BF_3$·$Et_2O$ (30) | 94:6 |
| **1b** | $CH_2$=CH–CHO (**4a**) | –78 | $BF_3$·$Et_2O$ (30) | 89:11 |
| **1c** | $CH_2$=CH–CHO (**4a**) | –78 | $BF_3$·$Et_2O$ (30) | 97:3 |
| **1a** | Benzoquinone (**4b**) | –78 | $BF_3$·$Et_2O$ (15) | 96:4 |
| **1a** | Benzoquinone (**4b**) | +20 | None | 80:20 |
| **1b** | Benzoquinone (**4b**) | –78 | $BF_3$·$Et_2O$ (15) | 92:8 |
| **1c** | Benzoquinone (**4b**) | –78 | $BF_3$·$Et_2O$ (15) | 96:4 |
| **1a** | $CH_2$=C($CH_3$)–CHO (**4c**) | –78 | $BF_3$·$Et_2O$ (30) | 98:2 |

[a] Reactions were run using racemic dienes **1**, in $CH_2Cl_2$, and were complete in 4–5 h. Yields ranged from 46–94% and are not optimized. Dienes **1** and products **5**, **6** were fully characterized: for the acrolein adducts of **1a** and **1b**, by preparation of optically active dienes and reduction of the adduct mixture to *cis*-2-hydroxymethylcyclohexanol and measurement of optical rotation as in the lit. study[12] of **1a**, giving $[\alpha]_D^{26} = -18.5°$ (*c* 0.014, $H_2O$) from **1a**, $[\alpha]_D^{26} = -18.2°$ (*c* 0.016, $H_2O$) from **1b**, lit.[12] $[\alpha]_D^{23} = -17.7°$ (*c* 0.01, $H_2O$) from **1a**; for the benzoquinone adducts of **1a** and **1c**, by X-ray crystallographic analysis, and for the others, by NMR using the highly reliable Dale–Mosher model.[17,18] No exo adducts were detected. [b] Ratios were determined by integration of the 250 MHz $^1H$ NMR spectrum of the crude product mixture and comparison with authentic product spectra.

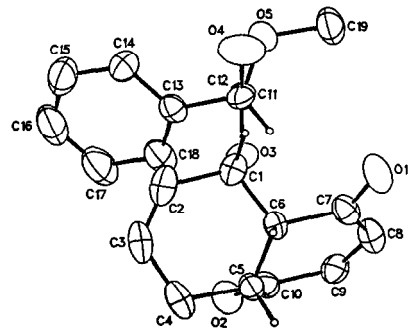



**Figure 1.** Structure of adduct **5** from **1a** and **4b**, viewed along the CO–CH(OMe)Ph bond.

In all three of our X-ray structures and a related one,[18,23] the phenyl group also has its **face toward the O=C–O group**, i.e., the ring plane is nearly perpendicular to the plane defined by $C_{1Ph}$–$C_\alpha$–$CO_2$ ($C_{11}$–$C_{12}$–$C_{13}$, Figure 1), thus beautifully rationalizing the Dale–Mosher NMR shielding model—the shielded group would be positioned in a clearly shielding region[24] directly above the phenyl $\pi$ system. If it proves to be general, this perpendicular phenyl orientation adds still more confidence in the use of *O*-methylmandelate esters for determinations of absolute configuration. It is tempting to suggest that this phenyl orientation may involve a $HOMO_{Ph}$–$LUMO_{C=O}$ interaction.

We conclude that this "**perpendicular model**" is a good working hypothesis for predicting diastereofacial selectivity in Diels–Alder reactions of dienes like **1**. The high selectivities we have achieved should be synthetically useful and suggest further definition and development of the synthetic potential of such dienes. The implication of these results is that the ester conformational properties are playing the crucial role in determining diastereofacial selectivity here, independently of direct interaction with the diene moiety. Therefore, extensions of this transition state conformational model to reactions other than the Diels–Alder seem likely to be rewarding.

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