Thermal and Catalyzed Diels–Alder Reactions with Chiral 2-Substituted-1,3-dienes: Conformational Models for Diastereofacial Selectivity

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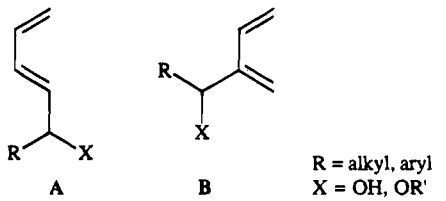
The thermal or BF_3-catalyzed Diels–Alder reactions of chiral 2-substituted-1,3-dienes bearing a hydroxy or a protected hydroxy group at the allylic position with various dienophiles have been studied in order to determine the regio- and stereoselective control elements. Good regio- and facial selectivities were observed in thermal reaction of dienes bearing a free hydroxy group. The stereoselectivity was reversed and strongly lowered when the hydroxy group was protected as an ether. However the regio- as well as the stereoselectivity of the cycloaddition of these diene ethers with α,β-unsaturated aldehydes or ketones are remarkably enhanced by the addition of a Lewis acid since in a few cases a unique isomer was formed. These experimental results have been rationalized and could be explained by conformational preferences of the dienes in the transition state. In particular, the reversal of facial selectivity for dienes having a free hydroxy group has been attributed to a hydrogen bonding interaction between the diene and the dienophile.

The importance held by the Diels–Alder reaction in organic synthesis rests on the generation of six-membered rings with high regio- and stereoselectivity leading to the creation of four contiguous stereogenic centers in one synthetic operation. Among the many aspects of this reaction, the diastereofacial selectivity has recently attracted considerable attention in connection with asymmetric synthesis.[1] The most popular ways to obtain good facial selectivity are either to link the diene[2] or the dienophile[3] to a chiral auxiliary or to chelate the dienophile with a chiral Lewis acid[4] in order to shield one face of the reagent bound to the auxiliary or to the catalyst. Removal of the auxiliary then leads to an enantiomerically enriched adduct. An alternative approach to induce face selectivity is the incorporation in the diene of an allylic stereogenic center. In this case, the adducts are diastereomers since the initial stereogenic center is part of the product. However, if the starting diene is enantiomerically pure, a high diastereofacial selectivity in the cycloaddition will lead to enantiomerically enriched cycloadducts. During the last ten years several reports have shown the role of a heteroatom substitution at the allylic position of 1-substituted-1,3-dienes **A** on the control of facial selectivity.[5] In contrast, very few investigations have been made concerning the influence of a heteroatom substitution at the allylic position of 2-substituted-1,3-dienes **B**. This lack of interest may be due to the poor regioselectivity[6] and diastereoselectivity[7] usually observed in Diels–Alder reactions of such dienes.[8]

In the present work we report the remarkable enhancement of regio- and facial selectivity brought by the presence of a Lewis acid in Diels–Alder reactions of chiral 2-substituted-1,3-butadienes of type **B** (X = OR') with unsaturated ketones or aldehydes.[9]



Results

Preparation of Dienes. The requisite dienes **1-13** were prepared from chloroprene[10] as outlined in Scheme 1. Hydroxy dienes such as **1-5** have been currently

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(1) For interesting reviews see (a) Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876. (b) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 455–501. (c) Carruthers, W. In *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990; pp 61–72.

(2) Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder reaction*; John Wiley and Sons: New York, 1990; pp 39–41 and 56–60.

(3) Review: Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Sheffold, R., Ed.; Springer Verlag: New York, 1986; Vol. 4, pp 262–306.

(4) For a review see: Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

(5) Experimental: (a) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257 and references therein. (b) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, 110, 4625. (c) Kozikowski, A. P.; Jung, S. H.; Springer, J. P. *J. Chem. Soc. Chem. Commun.* **1988**, 167. (d) McDougal, P. G.; Jump, J. M.; Rojas, C.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 3897. (e) Trost, B. M.; Lee, D. C. *J. Org. Chem.* **1989**, *54*, 2274. (f) Fleming, I.; Sarkar, A. K.; Doyle, M. J.; Raithby, P. R. *J. Chem. Soc. Perkin Trans 1* **1989**, 2023. (g) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472. (h) Burnouf, C.; Cristobal-Lopez, J.; Calvo-Flores, F. G.; de Los Angeles Laborde, M.; Olesker, A.; Lukacs, G. *J. Chem. Soc. Chem. Commun.* **1990**, 823. (i) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136. (j) Barluenga, J.; Gonzalez, F. J.; Fustero, S.; Garcia-Granda, S.; Perez-Carreno, E. *J. Org. Chem.* **1991**, *56*, 4459. Theoretical: (k) Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 663. (l) Kaila, N.; Franck, R. W.; Dannenberg, J. J. *J. Org. Chem.* **1989**, *54*, 4206. (m) Coxon, J. M.; Mc Donald, Q. *Tetrahedron Lett.* **1992**, *33*, 651.

(6) (a) Tsuge, O.; Wada, E.; Kanemasa, S.; Sakoh, H. *Chem. Lett.* **1984**, 469. (b) Hosomi, A.; Masunari, T.; Tominaga, Y.; Hojo, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1051.

(7) Brown, P. A.; Bonnert, R. V.; Jenkins, P. R.; Lawrence, N. J.; Selim, M. R. *J. Chem. Soc. Perkin Trans 1* **1991**, 1893.

(8) As this work was in progress the improval of stereoselectivity of Diels–Alder reactions between dienes **B** and *N*-phenylmaleimide using $LiClO_4$–Et_2O as solvent has been reported: Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc. Chem. Commun.* **1992**, 953. In our case, the lower reactivity of the dienophiles (methyl vinyl ketone or acrolein) requires reaction temperatures higher than −20 °C. In these conditions we observed only poor enhancements of regio- or stereoselectivity.

(9) Preliminary communication: Bloch, R.; Chaptal-Gradoz, N. *Tetrahedron Lett.* **1992**, *33*, 6147.

0022-3263/94/1959-4162$04.50/0

Scheme 1

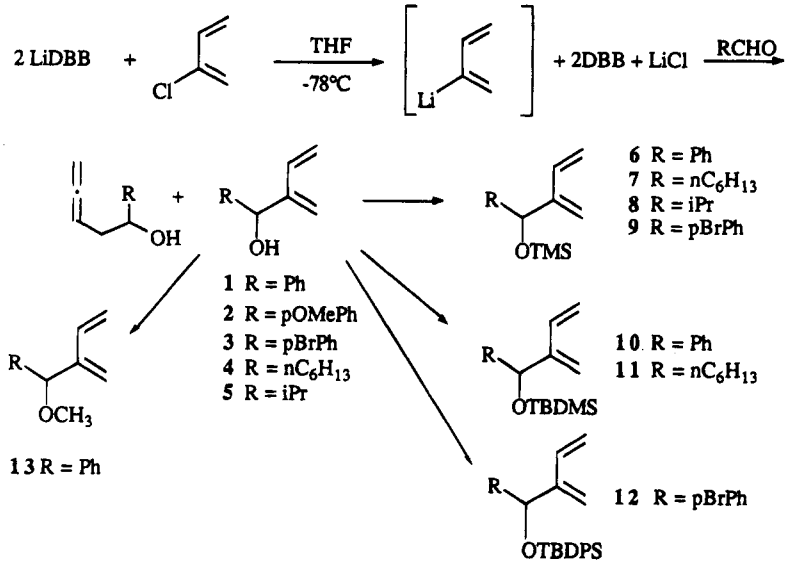


Table 1. Synthesis of Hydroxy Dienes

hydroxy diene	total yield, %	diene/allene
1	84	77/23
2	70	90/10
3	75	75/25
4	73	100/0
5	88	100/0

synthesized by reaction of aldehydes with 2-lithio-1,3-butadiene obtained from chloroprene via 2-(tributylstannyl)-1,3-butadiene.[11] In these conditions, small amounts of hydroxyallenes are also formed with aromatic aldehydes. We have found that 2-lithio-1,3-butadiene can be directly generated from chloroprene and 4,4′-di-*tert*-butylbiphenyl lithium (LiDBB). Hydroxy dienes **1-5** have then been obtained in a one-pot process with better yields and similar diene/allene ratios as shown in Table 1. The hydroxy groups of dienols **1-5** have been protected following conventional methods to afford the corresponding ethers **6-13**.

We have not been able to separate the hydroxy dienes **1-3** from their allenic impurities so that the mixtures of dienic and allenic alcohols have been used for cycloadditions. However, allenic alcohols, unreactive in the conditions used for the cycloaddition, have been separated easily at this stage from the cycloadducts.

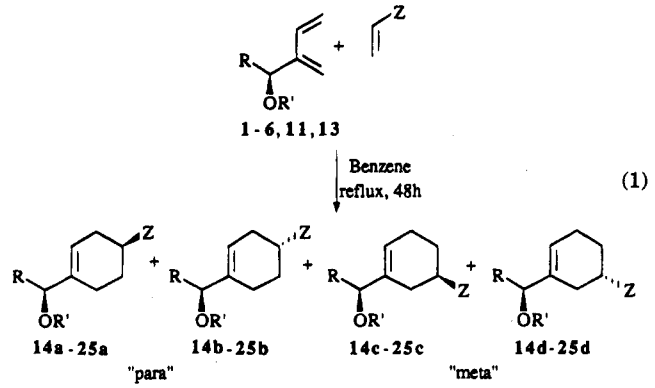
Thermal Cycloadditions of 2-Substituted Dienes. 2-Substituted dienes underwent cycloadditions with various dienophiles at 80 °C to give in each case a mixture of four isomers (see eq 1). Racemic dienes have been used but for clarity only one enantiomer is represented.

We have not been able to separate these isomers by usual chromatography. The proportions of the different isomers are listed in Table 2. The ratios **a+b/c+d** or "para"/"meta" have been determined by capillary gas-liquid chromatography of the ketones obtained after MnO_2 oxidation of the free hydroxy groups (entries 1–8) or by deprotection and oxidation of the released hydroxy groups (entries 9-12). See eq 2 for an example.

Table 2. Thermal Diels–Alder Cycloadditions of 2-Substituted Dienes with Unsymmetrical Dienophiles[a]

entry	diene	dienophile	products	ratio **a+b/c+d**[b]	ratio **a/b**[c]	yield,[d] %
1	**1**	Z = CO_2Me	**14**	69/31	80/20	72
2	**1**	Z = $CONMe_2$	**15**	65/35	80/20	74
3	**1**	Z = COMe	**16**	77/23	80/20	92
4	**2**	Z = COMe	**17**	80/20	80/20	76
5	**3**	Z = COMe	**18**	74/26	70/30	83
6	**4**	Z = CO_2Me	**19**	67/33	80/20	83
7	**4**	Z = COMe	**20**	78/22	80/20	82
8	**5**	Z = COMe	**21**	77/23	75/25	81
9	**11**	Z = CO_2Me	**22**	70/30	45/55	87
10	**6**	Z = COMe	**23**	67/33	45/55	70
11	**11**	Z = COMe	**24**	70/30	45/55	77
12	**13**	Z = COMe	**25**	68/32	25/75	81

[a] The reactions have been carried out in refluxing benzene for 48 h. [b] The ratios **a+b/c+d** have been determined by GLC after oxidation of the hydroxy group. [c] Not accurate values. Ratios evaluated by GLC and/or ^1H NMR and/or ^{13}C NMR. [d] Yields are given with respect to the 1,3-diene for products isolated by column chromatography.



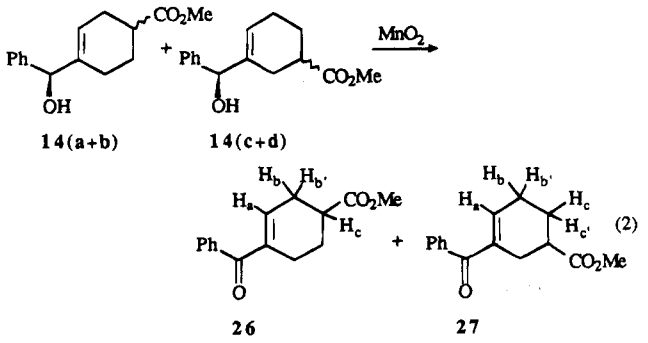
The "para" regiochemistry has been attributed to the major regioisomers on the basis of both literature precedents[12] and predictions of the frontier molecular orbital theory.[13] This "para" structure has been confirmed in the case of **26** by a careful examination of its ^1H NMR spectrum in the presence of a shift reagent Eu(fod)$_3$ used to split and differentiate the signals of all the protons of the molecule. We have found by selective irradiations

(10) Other preparations of such racemic hydroxy dienes: from methyl vinyl ketone: Brown, P. A.; Jenkins, P. R. *Tetrahedron Lett.* **1982**, *23*, 3733; enantiomerically enriched: (a) ref 7; (b) Hatakeyama, S.; Sugawara, K.; Kawamura, M.; Takano, S. *Tetrahedron Lett.* **1991**, *32*, 4509.

(11) Wada, E.; Kanemasa, S.; Fujiwara, I.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1942.

(12) See ref 2, p 49.

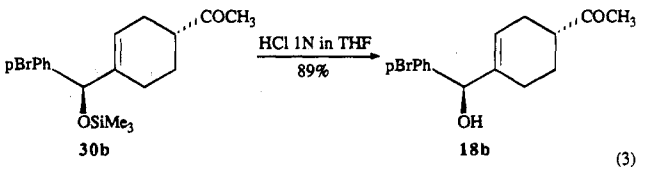
(13) Fleming, I. *Frontier orbitals and organic chemical reactions*; John Wiley and Sons: New York, 1978; pp 121–140.



that in addition to the geminal coupling, protons H_b and $H_{b'}$ are coupled with the olefinic proton H_a and with a single other proton H_c, supporting the "para" position of the carbomethoxy group.

If the proportions of the two minor "meta" stereoisomers **14c-25c** and **14d-25d** have not been established, however the ratios **a/b** of the two major "para" stereomers **14a-25a** and **14b-25b** have been evaluated by capillary GLC when possible and/or by ^1H and ^{13}C NMR of the mixture obtained after purification by column chromatography on silica gel. In general the signals due to the two diastereomers are not well separated so that only approximate values (±5%) have been determined and reported in Table 2.

The relative configurations of the two asymmetric centers have been determined for **18b** (and consequently for **18a**) by desilylation of **30b** (eq 3), the structure of which has been unambiguously established (see below). The stereostructures of the other major cycloadducts **14a-17a** and **19a-21a** were tentatively assigned based on the close similarity of their ^1H and ^{13}C NMR spectra with these of cycloadduct **18a**.

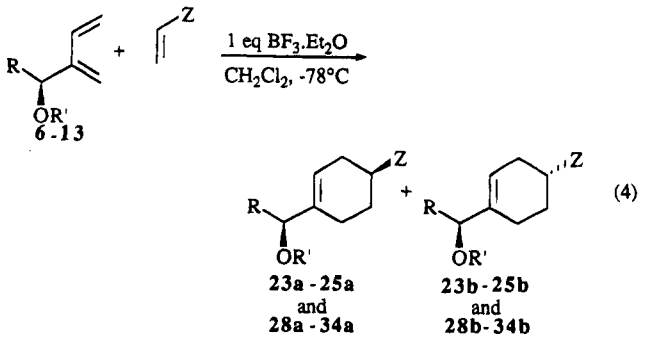


Lewis Acid Catalyzed Cycloadditions of 2-Substituted Dienes 6-13. In an effort to improve the regioselectivity as well as the facial stereoselectivity of the Diels–Alder reactions of dienes **1-13** we decided to try these cycloadditions in the presence of a Lewis acid. It is well known that most of the Diels–Alder reactions are accelerated by the presence of a Lewis acid and that their regio- and stereoselectivities are often increased over the uncatalyzed reaction. However, surprisingly, when we started our work, the influence of a Lewis acid on the facial selectivity of Diels–Alder reaction of dienes **A** or **B** having stereogenic allylic substituents at the C-1 or C-2 positon had to our knowledge never been reported.[8] This lack of information may be the result of the fragility of the dienes in the presence of a Lewis acid. Effectively, we found that hydroxy dienes **1-5** are completely destroyed within 5 min at −78 °C in the presence of Lewis acids. Fortunately, protected dienols **6-13** are not so fragile and are reactive enough to give rise to cycloadditions with unsaturated aldehydes and ketones in the presence of a Lewis acid at −78 °C. A limitation of this reaction is the lack of reactivity of other dienophiles such as α,β-unsaturated esters or amides under these conditions. Several Lewis acids were tried (BF_3, $TiCl_4$, $AlCl_3$, $ZnCl_2$, $TfOSiMe_3$) and the best results, summarized in Table 3, were obtained in the presence of $BF_3{\cdot}Et_2O$ (eq 4).

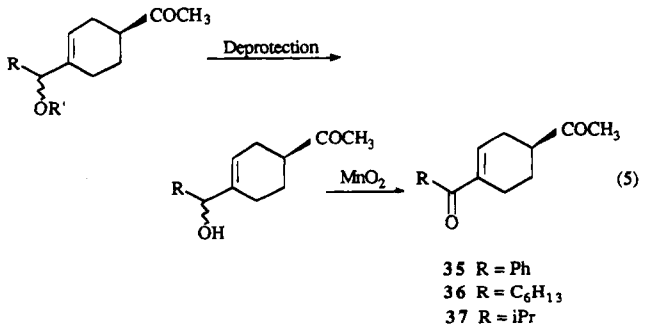
Table 3. Facial Stereoselection of $BF_3{\cdot}Et_2O$-Catalyzed Cycloadditions[a]

entry	diene	dienophile	products	stereoselectivity[b]	yield,[c] %
1	**6**	Z = $COCH_3$	**23b**	>95/5	78
2	**7**	Z = $COCH_3$	**28a + 28b**	81/19	61
3	**8**	Z = $COCH_3$	**29b**	>95/5	66
4	**9**	Z = $COCH_3$	**30b**	>95/5	66
5	**10**	Z = $COCH_3$	**31b**	>95/5[d]	67
6	**11**	Z = $COCH_3$	**24a + 24b**	88/12[d]	66
7	**12**	Z = $COCH_3$	**32b**	>95/5	65
8	**13**	Z = $COCH_3$	**25b**	>95/5	88
9	**6**	Z = CHO	**33a + 33b**	94/6[d]	75
10	**10**	Z = CHO	**34b**	>95/5	40

[a] The reactions have been carried out in methylene chloride at −78 °C for 1 h. [b] A stereoselectivity **b/a** > 95/5 has been assigned when only one diastereomer could be seen by capillary GLC and ^1H NMR and/or ^{13}C NMR. [c] Yields are given for products purified by column chromatography. [d] Very similar stereoselectivities and yields are obtained in these reactions if $BF_3{\cdot}Et_2O$ is replaced by $AlCl_3$.



In most of the experiments a unique cycloadduct was formed as shown by capillary GLC or ^1H and ^{13}C NMR. When two products were observed (entries 2, 6, 8), we proved that they are diastereomers since the suppression of one of the stereogenic centers by oxidation of the deprotected hydroxy group gave rise to a single ketone (eq 5).



The diastereomeric ratios have been determined by capillary GLC or ^1H NMR. The stereochemistry of cycloadducts **23b-25b**, **28b**, **29b**, and **31b-36b** has been determined by comparison of their ^1H and ^{13}C NMR spectra with those of the adduct **30b** whose structure has been established by single-crystal X-ray analysis[14a] (Figure 1).

Discussion

In thermal cycloadditions, as could be predicted by considering the frontier orbitals contributions[13] as well

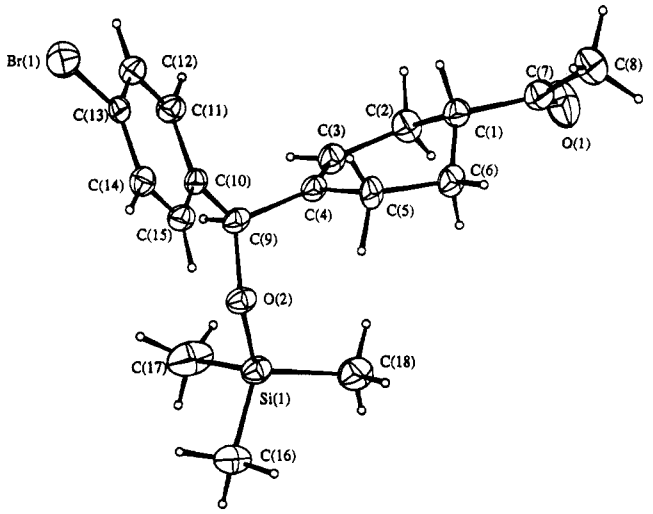


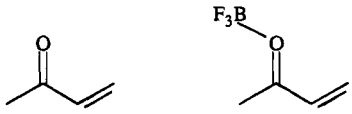
Figure 1. ORTEP representation of the adduct **30b**.

as reported data for others 2-substituted-1,3-dienes,[14b] the regioselectivity in favor of the "para" adducts is not very high and is almost independent of the nature of R and R'. These substituents are effectively too far away to have a significant influence on the orbital coefficients of C_1 and C_4 carbons directly involved in the cycloaddition. The facial stereoselectivity is also independent of R but, in contrast, is directly connected to the presence of a free hydroxy group: the good selectivity observed in this case (Table 2; entries 1-8) practically disappears for dienes containing a masked hydroxy group (Table 2; entries 9-12) suggesting that a hydrogen bond between the diene and the dienophile might play an important role.[15] The regioselectivity as well as the stereoselectivity are considerably enhanced when these cycloadditions are carried out in the presence of a Lewis acid (Table 3). In all cases a totally regioselective cycloaddition giving rise to the "para" regioisomers is observed. This expected very high regioselectivity is well explained by the increased polarization of the LUMO of the C=C double bond of the complexed dienophile.[16] Furthermore an excellent diastereoselectivity, slightly dependent on the steric bulk of the substituent R, is also promoted by the Lewis acid. It is important to notice that the major stereoisomers obtained by thermal cycloaddition of free hydroxy dienes **1-5** have the configuration of the minor stereoisomers obtained by thermal or catalyzed cycloadditions of protected dienes **6-13** so that there is a remarkable reversal of facial selectivity for dienes **B** (X = OH) with respect to dienes **B** (X = OR').

On the basis of literature data and simple molecular mechanic calculations, we have been able to rationalize the facial selectivities of the thermal or catalyzed cycloadditions of dienes **B** (X = OH, OR') with methyl vinyl ketone. We have first established the probable favored conformations of the dienophile and of the diene in the transition state and then we have looked using Dreiding models for the most stable states generated during the endo approach of these entities.

Conformation of the Dienophile. It seems now well established experimentally[17] and theoretically[18] that, in the ground state, transoid conformation of acrolein is favored with respect to the cisoid conformation. Lewis acid complexation does not change the nature of this preferred ground state s-trans conformation of α,β-unsaturated carbonyl compounds.[19] However, Houk has recently shown, by ab initio calculations, that in the endo transition state of the Diels–Alder reaction of butadiene and acrolein[20] or BH_3-complexed acrolein[21] the olefinic aldehyde assumed a s-cis conformation since this conformer is more electrophilic and its geometry leads to better secondary interactions. Experimental support for this cisoid conformation has been reported for the thermal cycloaddition of α,β-unsaturated ketones[22] and the Lewis acid-catalyzed cycloaddition of 2-bromoacrolein.[23]

All these considerations led us to think that in the transition state of the Diels–Alder cycloadditions methyl vinyl ketone adopts the s-cis conformation. Furthermore, in catalyzed reactions, for steric reasons, the Lewis acid complexes the carbonyl group in an anti position.



s-cis s-cis anti

Conformation of the Dienes. The relative energies of ground state conformations of dienes **1**, **6**, and **13** in an s-cis geometry have been established using a molecular modeling program MAD (Allinger MM2 force field).[24] Monte Carlo method has been used and energy minimizations have been made by rotating either one or simultaneously several fragments of the molecule around one or several particular bonds.

In each case, we found two s-cis conformations I and II of very similar energy in which the phenyl group is perpendicular to the diene plane and the OR' group is in a syn or anti position with respect to the adjacent double bond. The other conformations III to VI are much higher in energy.

It has been reported by Franck [5a] that, for Diels–Alder reactions of dienes **A**, the stereoselectivity can be predicted in most of the cases by assuming that the conformation of the ground states of the dienes are reflected in the transition states of the reaction. Fur-

(14) (a) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (b) See for example: Hosomi, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1980**, *21*, 355 and references therein.

(15) The control of the facial selectivity in Diels–Alder reactions of 1-(*O*-methylmandeloxy)butadiene through hydrogen bonding has been recently reported: (a) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1990**, *112*, 6743. (b) Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630.

(16) Reference 13, p 163.

(17) Blom, C. E.; Grassi, G.; Bauder, A. *J. Am. Chem. Soc.* **1984**, *106*, 7427.

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(19) (a) Reetz, M. T.; Hüllmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405. (b) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1992**, *57*, 1370. (c) Honeychuck, R. V.; Bonnesen, P. V.; Farahi, J.; Hersh, W. H. *J. Org. Chem.* **1987**, *52*, 5293. (d) Bonnesen, P. V.; Pruckett, C. L.; Honeychuck, R. V.; Hersh, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 6070. (e) Corey, E. J.; Loh, T. P.; Sanshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945.

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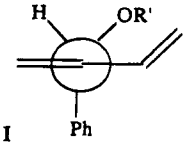
(21) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127.

(22) Stammer, B.; Berlage, U.; Kindermann, R.; Kaiser, M.; Günther, B.; Sheldrick, W. S.; Welzel, P.; Roth, W. R. *J. Org. Chem.* **1992**, *57*, 6566.

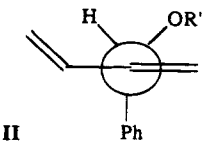
(23) Corey, E. J.; Loh, T. P. *J. Am. Chem. Soc.* **1991**, *113*, 8966.

(24) MAD (Molecular Advanced Design) version 2.0 is available from Oxford Molecular, Ecole Polytechnique, Palaiseau, France.



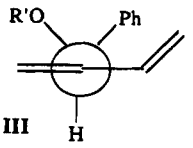
I

R' = H, $SiMe_3$, CH_3 0.00



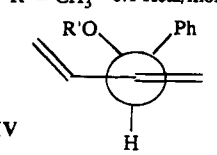
II

R' = H 0.2 Kcal/mol
R' = $SiMe_3$ 0.1 Kcal/mol
R' = CH_3 0.1 Kcal/mol



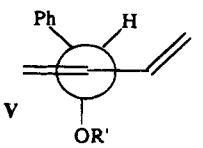
III

R' = H 1.3 Kcal/mol
R' = $SiMe_3$ 5.9 Kcal/mol
R' = CH_3 3.0 Kcal/mol



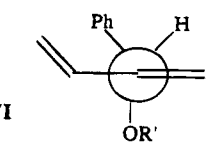
IV

R' = H 2.1 Kcal/mol
R' = $SiMe_3$ 4.7 Kcal/mol
R' = CH_3 3.2 Kcal/mol



V

R' = H 7.8 Kcal/mol
R' = $SiMe_3$ 15.7 Kcal/mol
R' = CH_3 13.3 Kcal/mol



VI

R' = H 3.6 Kcal/mol
R' = $SiMe_3$ 11.6 Kcal/mol
R' = CH_3 13.0 Kcal/mol

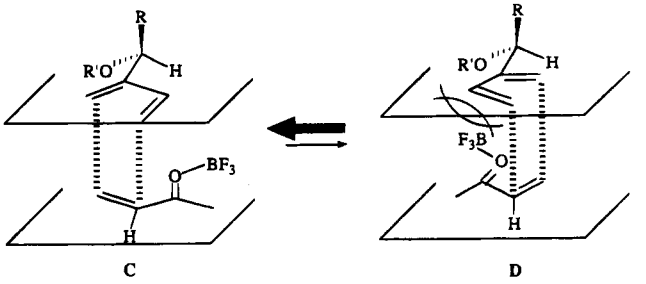
thermore, in agreement with proposed perpendicular models for electrophilic attack on chiral allyl systems,[25] in order to minimize electron withdrawal from the diene by the carbon–heteroatom σ^* orbital, the heteroatom must keep a position near the plane of the dienyl moiety such as in I, II, III, IV. Finally according to the "Cieplak effect",[26] recent calculations have shown that the transition states of Diels–Alder reactions are also stabilized by σ electron donation into the vacant σ^* orbital associated with the forming bond.[5m] For dienes **B** the best stabilization will occur if the most electron rich C–C σ bonds is in an anti position, perpendicular to the diene such as in I and II. All these observations led us to consider that the two most reactive conformers of dienes **B** must be also the two most stable ground states conformers I and II.

Transition state models of Diels–Alder reactions involving dienes **B** have then been built considering an endo approach of the dienophile in its s-cis conformation onto the less hindered and more nucleophilic face of the conformations I and II of the diene, that is to say syn to the heteroatom and anti to the alkyl or aryl groups. The relative stability of the transition state models which reflects the π-facial selectivity can be rationalized as shown below.

Diels–Alder Reactions of Dienic Ethers. (a) Catalyzed Reactions. The two transition state models constructed following the above considerations are depicted by **C** and **D**.

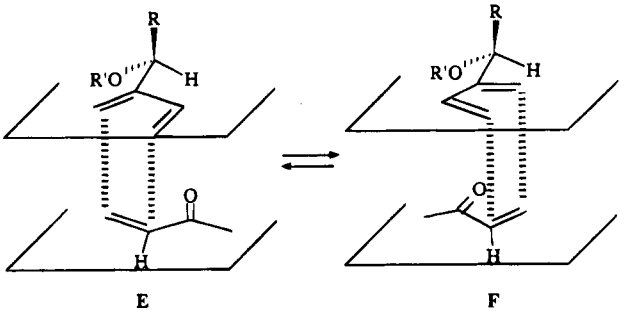
A careful examination of the Dreiding models indicates for **D** a severe steric interaction between the hydroxy protective group R′ and the coordinated Lewis acid. This interaction is reflected by a difference in energy for the models **C** and **D** which entails the excellent diastereoselective excesses reported in Table 3.

(b) Thermal Reactions. Two transition structures **E** and **F**, very similar to **C** and **D**, can be drawn for the



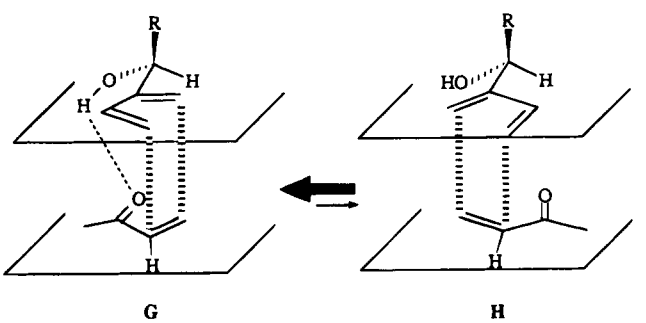
C D

thermal reactions, but here, there is no more great steric interaction in one or the other model so that the two transition states must be of very similar energy, explaining the poor facial selectivity experimentally found.



E F

Diels–Alder Reactions of Dienes Bearing a Free Hydroxy Group. The two competing transition state models postulated to rationalize the stereochemistry of the thermal cycloadditions of dienes **1-5** are represented by **G** and **H**. In the transition structure **G**, the conformation of the diene allows intermolecular coordination of the hydroxy hydrogen with the carbonyl group of the dienophile. The hydrogen bonding interaction stabilizes **G** with respect to **H** so that the major cycloadduct arises from **G**, explaining the surprising reversal of facial selectivity observed with protected or unprotected dienols, respectively.



G H

Recent reports on the role of hydrogen bonding in controlling the diastereoselectivity of Diels–Alder reactions of hydroxy dienes[5b,e,15] support our postulations.

Conclusion

The diastereoselectivity of Diels–Alder reactions of 2-substituted-1,3-dienes bearing a free hydroxy or a protected hydroxy group at the allylic position can be controlled by hydrogen bonding or by addition of a Lewis acid, respectively. The experimental results have been rationalized and explained by conformational preferences of the diene in the transition state. For the first time complete regio- and stereoselectivity have been observed in the cycloadditions of chiral 2-substituted-1,3-buta-

(25) Houk, K. N.; Moses, S. R.; Wu, Y. D.; Rondan, D. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880.
(26) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

dienes with α,β-unsaturated ketones or aldehydes opening a new way for the obtention of stereochemically defined polyfunctional cyclohexenes.

Experimental Section[27]

General Procedure for the Synthesis of Dienes 1-5. To a solution of 4,4'-di-*tert*-butylbiphenyl (DBB) (13.30 g, 50 mmol) in 100 mL of dry THF kept under argon were added small chips of lithium (316 mg, 45 mmol). The mixture was sonicated for 3 h at 10–15 °C in a cleaning bath. The cleaning bath was replaced by a cold dry ice–acetone bath, and chloroprene (1.85 mL, 20 mmol) was added dropwise at −78 °C. The mixture was stirred for 15 min, the required aldehyde (20 mmol) was added, and stirring was continued for an additional 30 min. The mixture was then quenched with saturated aqueous NH_4Cl (25 mL), extracted with ether (3 × 80 mL), and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the crude product was submitted to flash chromatography (hexane/ether 90/10) to give DBB (12 g) and the pure diene (**4**, **5**) or a mixture with its allenic isomer (**1**, **2**, **3**). Dienols **1** and **4** are known compounds.[11]

2-Methylidene-1-(*p*-methoxyphenyl)-but-3-en-1-ol (2). Obtained as a mixture with the isomeric allene (ratio 90/10): yield 70%; IR (neat) 3400, 3010, 2960, 2940, 2840, 1615, 1595, 1250, 1035 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.92 (d, J = 3.9 Hz, 1H), 3.81 (s, 3H), 5.08 (d, J = 11.5 Hz, 1H), 5.20 (d, J = 17.4 Hz, 1H), 5.28 and 5.35 (2s, 2H), 5.45 (s, 1H), 6.33 (dd, J = 11.5, 17.4 Hz, 1H), 6.85 (d, J = 9.2 Hz, 2H), 7.33 (d, J = 9.2 Hz, 2H).

2-Methylidene-1-(*p*-bromophenyl)-but-3-en-1-ol (3). Obtained as a mixture with the isomeric allene (ratio 75/25): yield 75%; IR (neat) 3360, 3100, 1950, 1600, 1490, 1070, 1010 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.96 (d, J = 4.2 Hz, 1H), 5.08 (d, J = 10.9 Hz, 1H), 5.23 (d, J = 17.9 Hz, 1H), 5.35 and 5.40 (2s, 2H), 5.46 (d, J = 4.2 Hz, 1H), 6.31 (dd, J = 10.9, 17.9 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.4 Hz, 2H); MS m/z (rel intensity) 240 (M^+, 5), 238 (M^+, 5), 187 (49), 185 (81), 159 (38), 131 (28), 78 (52), 77 (100).

2-Methyl-4-methylidenehex-5-en-3-ol (5): clear oil; yield 88%; IR (neat) 3430, 3095, 2980, 2890, 1600, 1470, 900 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.94 (d, J = 6.6 Hz, 6H), 1.51 (d, J = 4 Hz, 1H), 1.91 (m, 1H), 4.14 (m, 1H), 5.11 (d, J = 11 Hz, 1H), 5.18 and 5.21 (2s, 2H), 5.35 (d, J = 17.4 Hz, 1H), 6.34 (dd, J = 11, 17.4 Hz, 1H); MS m/z (rel intensity) 126 (M^+, 2), 84 (20), 83 (100), 68 (11), 55 (61).

General Procedure for the Synthesis of Silyl Ethers 6-11. To a stirred solution of the dienol (1 mmol) in CH_2Cl_2 (6 mL) kept at 0 °C under argon were added dropwise, successively, triethylamine (2.2 mmol) and trimethylsilyl triflate (or *tert*-butyldimethylsilyl triflate) (1.8 mmol). The mixture was allowed to warm to room temperature and stirring was continued for an additional 30 min. The solution was diluted with ether (20 mL) and poured into a cold solution of $NaHCO_3$. After extraction with ether (2 × 10 mL), the organic phase was washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was submitted to chromatographic separation on silica gel (hexane).

2-Methylidene-1-phenyl-1-[(trimethylsilyl)oxy]but-3-ene (6). Obtained as a mixture with the isomeric allene: yield 93%; IR (neat) 3095, 3015, 2960, 2860, 1960, 1595, 1250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.11 (s, 9H), 5.01 (d, J = 11.3 Hz, 1H), 5.27 (d, J = 17.6 Hz, 1H), 5.30 and 5.40 (2s, 3H), 6.25 (dd, J = 11.3, 17.6 Hz, 1H), 7.20–7.52 (m, 5H); MS m/z (rel intensity) 232 (M^+, 22), 179 (74), 142 (16), 128 (16), 75 (21), 73 (100).

3-Methylidene-4-[(trimethylsilyl)oxy]dec-1-ene (7): clear oil; yield 76%; IR (neat) 2960, 2870, 1600, 1260 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.1 (s, 9H), 0.89 (m, 3H), 1.20–1.35 (m, 8H), 1.4–1.6 (m, 2H), 4.32 (dd, J = 4.5, 8.4 Hz, 1H), 5.07 (d, J = 11.2 Hz, 1H), 5.10 and 5.19 (2s, 2H), 5.30 (d, J = 18.0 Hz, 1H), 6.33 (dd, J = 11.2, 18.0 Hz, 1H); MS m/z (rel intensity) 240 (M^+, 0.5), 225 (7), 156 (31), 155 (100), 73 (57).

5-Methyl-3-methylidene-4-[(trimethylsilyl)oxy]hex-1-ene (8): pale yellow oil; yield 77%; IR (neat) 2970, 2940, 2880, 1605, 1260 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 9H), 0.85 (d, J = 6.7 Hz, 6H), 1.80 (m, 1H), 4.00 (d, J = 5.4 Hz, 1H), 5.05 (d, J = 11.6 Hz, 1H), 5.10 and 5.15 (2s, 2H), 5.33 (d, J = 18.0 Hz, 1H), 6.31 (dd, J = 11.6, 18.0 Hz, 1H).

2-Methylidene-1-(*p*-bromophenyl)-1-[(trimethylsilyl)-oxy]but-3-ene (9). Obtained as a mixture with the isomeric allene: yield 88%; IR (neat) 3095, 2960, 1960, 1600, 1490, 1250, 1010, 890, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.11 (s, 9H), 5.00 (d, J = 11.3 Hz, 1H), 5.23 (d, J = 17.9 Hz, 1H), 5.29, 5.33 and 5.37 (3s, 3H), 6.22 (dd, J = 11.3, 17.9 Hz, 1H), 7.15–7.30 (m, 2H), 7.40–7.50 (m, 2H); MS m/z (rel intensity) 312 (M^+, 5), 310 (M^+, 5), 259 (65), 257 (66), 142 (16), 141 (18), 75 (16), 73 (100).

2-Methylidene-1-phenyl-1-[(*tert*-butyldimethylsilyl)-oxy]but-3-ene (10). Obtained as a mixture with the isomeric allene: yield 81%; IR (neat) 3095, 3015, 2960, 2940, 2860, 1960, 1590, 1250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.0 and 0.10 (2s, 6H), 0.92 (s, 9H), 5.00 (d, J = 11.2 Hz, 1H), 5.28 (s, 1H), 5.32 (d, J = 18 Hz, 1H), 5.38 and 5.42 (2s, 2H), 6.22 (dd, J = 11.2, 18.0 Hz, 1H), 7.2–7.4 (m, 5H); MS m/z (rel intensity) 218 (27), 217 (100), 143 (19), 128 (30), 115 (23), 75 (83), 73 (56).

3-Methylidene-4-[(*tert*-butyldimethylsilyl)oxy]dec-1-ene (11): clear oil; yield 86%; IR (neat) 3095, 2960, 2940, 2860, 1595, 1250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.0 and 0.05 (2s, 6H), 0.85–0.95 (m, 12H), 1.20–1.40 (m, 8H), 1.45–1.60 (m, 2H), 4.34 (t, J = 5.4 Hz, 1H), 5.06 (d, J = 11.2 Hz, 1H), 5.09 and 5.17 (2s, 2H), 5.30 (d, J = 18 Hz, 1H), 6.30 (dd, J = 11.2, 18 Hz, 1H); MS m/z (rel intensity) 226 (15), 223 (64), 75 (100), 73 (41).

2-Methylidene-1-(*p*-bromophenyl)-1-[(*tert*-butyldi-phenylsilyl)oxy]but-3-ene (12). To a solution of a mixture of diene **9** and the isomeric allene (150 mg, 0.63 mmol) in dimethylformamide (6 mL) was added imidazole (282 mg, 4.14 mmol) and diphenyl-*tert*-butylsilyl chloride (538 mL, 2.07 mmol). The mixture was stirred at 65 °C for 48 h, diluted with ether (30 mL), and washed with water (4 × 10 mL). The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (SiO_2, hexane/ether 95/5) gave 269 mg (90%) of a mixture of **12** and its isomeric allene: IR (neat) 3080, 3060, 2985, 2940, 2870, 1595, 1490, 1430 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (s, 9H), 4.93 (d, J = 11.2 Hz, 1H), 5.10 (d, J = 17.7 Hz, 1H), 5.21, 5.28 and 5.45 (3s, 3H), 6.16 (dd, J = 11.2, 17.7 Hz, 1H), 7.03–7.12 (m, 2H), 7.20–7.50 (m, 10H), 7.60–7.70 (m, 2H); CIMS (NH_3) m/z (rel intensity) 496 and 494 (MNH_4^+, 28), 479 and 477 (MH^+, 16), 223 (100), 221 (99), 196 (38).

2-Methylidene-1-methoxy-1-phenylbut-3-ene (13). To a suspension of NaH (168 mg, 7 mmol) in dry THF (6 mL) was added a mixture of diene **1** and its allenic isomer (966 mg, 6 mmol). The mixture was stirred at 20 °C for 1 h, at 50 °C for an additional 1 h, and cooled to 0 °C. Then methyl iodide (777 μL, 12 mmol) was added at 0 °C, and the mixture was allowed to warm to room temperature and poured on water (20 mL) and Et_2O (20 mL). The aqueous layer was extracted with ether (3 × 15 mL) and the organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane) to afford 760 mg (72.5%) of a mixture of **13** and the corresponding allene: IR (neat) 3090, 3020, 2980, 2930, 2820, 1950, 1590, 1450, 1100, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.38 (s, 3H), 4.90 (s, 1H), 5.05 (d, J = 11.4 Hz, 1H), 5.33 (d, J = 17.9 Hz, 1H), 5.35 and 5.38 (2s, 2H), 6.31 (dd, J = 11.4, 17.9 Hz, 1H), 7.22–7.43 (m, 5H); MS m/z (rel intensity) 174 (M^+, 8), 122 (83), 121 (100), 92 (20), 91 (16), 78 (25), 77 (28).

General Procedure for Thermal Cycloadditions. A solution of the diene (1 mmol) and the dienophile (2 mmol) in benzene (5 mL) was stirred at 80 °C for 48 h. After addition of ether (25 mL), the solution was washed with brine (2 × 10 mL) and dried over $MgSO_4$. The solution was concentrated in vacuo and the cycloadducts were purified and separated from the unreactive allene when present by column chroma-

(27) For a general description of experimental parameters see Bloch, R.; Bortolussi, M.; Girard, C.; Seck, M. *Tetrahedron* **1992**, *48*, 453.

tography on silica gel (hexane/ether). The mixtures of isomers were then analyzed by capillary GLC and ^1H and ^{13}C NMR.

General Procedure for Catalyzed Cycloadditions. A solution of distilled $BF_3{\cdot}Et_2O$ (1.1 mmol) and freshly distilled dienophile (1.1 mmol) in CH_2Cl_2 (3 mL) was stirred at −30 °C under argon for 20 min. To the mixture cooled to −78 °C was added a solution of the diene (1 mmol) in CH_2Cl_2 (3 mL) and stirring was continued for an additional 40 min. The mixture was quenched successively with Et_3N (1.1 mmol) and water (2 mL) and diluted with ether (20 mL). The organic layer was washed with brine (2 × 10 mL) and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/ether 90/10).

(1*R,1′*R**)-4-[1′-[(Trimethylsilyl)oxy]benzyl]cyclohex-3-enyl Methyl Ketone (23b).** Obtained by catalyzed cycloaddition between the diene **6** and methyl vinyl ketone: colorless oil; yield 78%; IR (neat) 3095, 3060, 3025, 2960, 2840, 1715, 1670, 1600, 1250, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.10 (s, 9H), 1.38−1.58 (m, 1H), 1.63−1.85 (m, 1H), 1.89−2.03 (m, 1H), 2.04−2.17 (m, 1H), 2.15 (s, 3H), 2.20−2.30 (m, 2H), 2.43−2.59 (m, 1H), 5.10 (s, 1H), 5.27 (bs, 1H), 7.20−7.38 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ −0.1, 22.8, 24.6, 26.7, 27.9, 47.4, 78.1, 121.4, 126, 126.7, 127.8, 140.3, 143.0, 211.2; MS *m*/*z* (rel intensity) 302 (M^+, 2), 212 (16), 169 (100), 91 (11), 75 (17), 73 (40). Anal. Calcd for $C_{18}H_{26}O_2Si$: C, 71.47; H, 8.66. Found: C, 71.59; H, 8.30.

(1*R,1′*R**) and (1*S**,1′*R**)-4-[1′-[(*tert*-Butyldimethylsilyl)oxy]heptyl]cyclohex-3-enyl Methyl Ketones 24a and 24b.** Obtained by catalyzed cycloaddition between the diene **11** and methyl vinyl ketone: yield 66%; ratio **24a/24b** = 12/88. Spectral data of **24b**: IR (neat) 2960, 2935, 2860, 1720, 1250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ −0.03 and 0.03 (2s, 6H), 0.84−0.91(m, 12H), 1.18−1.35 (m, 8H), 1.37−1.60 (m, 3H), 1.83−2.10 (m, 2H), 2.10−2.32 (m, 6H), 2.44−2.61 (m, 1H), 3.93 (t, J = 5.6 Hz, 1H), 5.55 (bs, 1H); MS *m*/*z* (rel intensity) 295 (M^+ − tBu, 8), 220 (10), 93 (25), 91 (15), 75 (100).

(1*R,1′*R**)-4-[1′-Methoxybenzyl]cyclohex-3-enyl Methyl Ketone (25b).** Obtained by catalyzed cycloaddition between the diene **13** and methyl vinyl ketone: colorless oil; yield 88%; IR (neat) 3095, 3060, 3020, 2980, 2930, 1715, 1680, 1600, 1090, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.43−1.61 (m, 1H), 1.70−1.88 (m, 1H), 1.90−2.12 (m, 2H), 2.14 (s, 3H), 2.21−2.30 (m, 2H), 2.45−2.60 (m, 1H), 3.30 (s, 3H), 4.57 (s, 1H), 5.85 (bs, 1H), 7.25−7.38 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.0, 24.6, 26.7, 27.9, 47.3, 56.3, 86.9, 123.3, 126.4, 127.2, 128.05, 137.8, 140.6, 211.1; MS *m*/*z* (rel intensity) 244 (M^+, 1), 213 (17), 212 (30), 170 (61), 169 (100), 141 (18), 121 (20), 91 (35). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.25; H, 7.98.

(1*R,1′*R**) and (1*S**,1′*R**)-4-[1′-[(Trimethylsilyl)oxy]heptyl]cyclohex-3-enyl Methyl Ketones 28a and 28b.** Obtained by catalyzed cycloaddition between the diene **7** and methyl vinyl ketone: yield 61%; Ratio **28a/28b** = 19/81. Spectral data of **28b**: IR (neat) 2960, 2930, 2860, 1715, 1670, 1250, 840 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 9H), 0.9 (t, J = 6.7 Hz, 3H), 1.10−1.35 (m, 8H), 1.40−1.70 (m, 3H), 1.83−2.13 (m, 2H), 2.15−2.34 (m, 6H), 2.48−2.62 (m, 1H), 3.91 (t, J = 6.7 Hz, 1H), 5.57 (bs, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 0.08, 14.0, 22.42, 22.58, 24.8, 25.9, 26.7, 29.1, 31.8, 36.0, 37.9, 47.7, 77.0, 120.5, 140.2, 211.3; MS *m*/*z* (rel intensity) 310 (M^+, 2), 226 (18), 225 (100), 220 (20), 177 (32), 93 (53), 75 (36), 73 (74). Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.61; H, 11.03. Found: C, 69.30; H, 11.01.

(1*S,1′*R**)-4-[2′-Methyl-1′-[(trimethylsilyl)oxy]propyl]cyclohex-3-enyl Methyl Ketone 29b.** Obtained by catalyzed cycloadditon between the diene **8** and methyl vinyl ketone: colorless oil; yield 66%; IR (neat) 2960, 2870, 1715, 1670, 1250 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.07 (s, 9H), 0.72 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H), 1.40−1.55 (m, 1H), 1.67 (m, 1H), 1.80−1.99 (m, 1H), 2.0−2.1 (m, 1H), 2.13−2.37 (m, 6H), 2.47−2.58 (m, 1H), 3.48 (d, J = 9.3 Hz, 1H), 5.53 (bs, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ −0.1, 18.9, 19.1, 22.2, 24.7, 26.6, 27.8, 31.4, 47.5, 83.2, 121.7, 139.1, 211.0; MS *m*/*z* (rel intensity) 268 (M^+, 0.3), 226 (17), 225 (100), 93 (46), 75 (31), 73 (85). Anal. Calcd for $C_{15}H_{28}O_2Si$: C, 67.10; H, 10.51. Found: C, 67.28; H, 10.33.

(1*R,1′*R**)-4-[1′-[(Trimethylsilyl)oxy]-*p*-bromobenzyl]cyclohex-3-enyl Methyl Ketone (30b).** Obtained by catalyzed cycloaddition between diene **9** and methyl vinyl ketone: colorless solid; mp 56 °C; IR (neat) 3080, 3060, 3005, 2940, 2860, 1740, 1595, 1250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.1 (s, 9H), 1.36−1.59 (m, 1H), 1.6−1.8 (m, 1H), 1.87−2.0 (m, 1H), 2.02−2.31 (m, 6H), 2.4−2.6 (m, 1H), 5.06 (s, 1H), 5.75 (bs, 1H), 7.2 (d, J = 8.1 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 0.6, 23.1, 23.6, 27.4, 28.0, 47.5, 78.6, 121.5, 122.9, 128.6, 131.8, 140.6, 143.3, 209.1; MS *m*/*z* (rel intensity) 382 and 380 (M^+, 1.5), 292 (18), 290 (18), 249 (54), 247 (55), 168 (45), 75 (100), 73 (86). Anal. Calcd for $C_{18}H_{25}BrO_2Si$: C, 56.67; H, 6.60; Br, 20.95. Found: C, 56.76; H, 6.38; Br, 21.18.

(1*R,1′*R**)-4-[1′-[(*tert*-Butyldimethylsilyl)oxy]benzyl]cyclohex-3-enyl Methyl Ketone (31b).** Obtained by catalyzed cycloaddition between the diene **10** and methyl vinyl ketone: colorless oil; yield 67%; IR (neat) 3095, 3060, 3030, 2940, 2860, 1715, 1605, 1250, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0 and 0.07 (2s, 6H), 0.9 (s, 9H), 1.38−1.55 (m, 1H), 1.6−1.78 (m, 1H), 1.88−2.0 (m, 1H), 2.08−2.2 (m, 1H), 2.15 (s, 3H); 2.2−2.3 (m, 2H), 2.42−2.57 (m, 1H), 5.11 (s, 1H), 5.28 (bs, 1H), 7.2−7.38 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ −5.1, −4.9, 22.4, 24.6, 25.8, 26.7, 27.7, 47.3, 78.3, 121.05, 125.8, 126.6, 127.7, 140.6, 143.3, 210.7; MS *m*/*z* (rel intensity) 287 (M^+ − tBu, 32), 169 (18), 91 (22), 75 (100). Anal. Calcd for $C_{21}H_{32}O_2Si$: C, 73.20; H, 9.36. Found: C, 73.19; H, 9.43.

(1*R,1′*R**)-4-[1′-[(*tert*-Butyldiphenylsilyl)oxy]-*p*-bromobenzyl]cyclohex-3-enyl Methyl Ketone (32b).** Obtained by catalyzed cycloaddition between the diene **12** and methyl vinyl ketone: colorless oil; yield 65%; IR (neat) 3080, 3060, 2940, 2860, 1740, 1595, 1430 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.2−1.4 (m, 1H), 1.47−1.63 (m, 1H), 1.8−2.4 (m, 8H), 5.04 (s, 1H), 5.4 (bs, 1H), 7.13−7.23 (m, 2H), 7.23−7.34 (m, 2H), 7.34−7.46 (m, 6H), 7.46−7.53 (m, 2H), 7.61−7.68 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 16.0, 22.8, 25.1, 27.3, 27.7, 28.0, 47.4, 79.7, 121.5, 123.2, 128.4, 131.9, 139.4, 143.1, 209.2; CI MS (NH_3) *m*/*z* (rel intensity) 566 and 564 (MNH_4^+, 37), 310 (22), 308 (22), 293 (100), 291 (95), 213 (41).

(1*R,1′*S**) and (1*R**,1′*R**)-4-[1′-[(Trimethylsilyl)oxy]benzyl]cyclohex-3-enecarboxaldehydes 33a and 33b.** Obtained by catalyzed cycloaddition between the diene **6** and acrolein. Ratio **33a/33b** = 6/94. The aldehydes, very unstable, have not been obtained in pure form but always accompanied with the allene (estimated yield by ^1H NMR: 75%). Spectral data for **33b**: IR (neat) 3095, 3060, 3025, 2960, 1725, 1605, 1250, 840 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.1 (s, 9H), 1.15−1.35 (m, 2H), 1.35−1.6 (m, 2H), 1.6−1.85 (m, 1H), 1.85−2.1 (m, 2H), 5.03 (s, 1H), 5.56 (bs, 1H), 7.03−7.28 (m, 3H), 7.33−7.41 (m, 2H), 9.21 (s, 1H); MS *m*/*z* (rel intensity) 288 (M^+, 15), 259 (15), 198 (19), 179 (24), 169 (23), 91 (20), 75 (32), 73 (100).

(1*R,1′*R**)-4-[1′-[(*tert*-Butyldimethylsilyl)oxy]benzyl]cyclohex-3-enecarboxaldehyde (34b).** Obtained by catalyzed cycloaddition between the diene **10** and acrolein. Unstable colorless oil: yield 40%; IR (neat) 3095, 3060, 3025, 2960, 2930, 2860, 1730, 1600, 1260 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ −0.02 (s, 3H), 0.05 (s, 3H), 0.9 (s, 9H), 1.45−1.62 (m, 1H), 1.62−1.79 (m, 1H), 1.90−2.02 (m, 2H), 2.08−2.2 (m, 1H), 2.26−2.34 (m, 2H), 2.35−2.50 (m, 1H), 5.10 (s, 1H), 5.8 (bs, 1H), 7.18−7.35 (m, 5H), 9.69 (s, 1H); MS *m*/*z* (rel intensity) 273 (M^+ − tBu, 32), 143 (15), 91 (33), 75 (100), 73 (33).

General Procedure for the Deprotection of Trimethylsilyl Ethers. To a solution of the trimethylsilyl ether (1 mmol) in THF (2 mL) was added a 1 M aqueous solution of HCl (50 μL, 0.05 mmol). The mixture was stirred for 30 min and the solvent removed under reduced pressure. The residue was diluted with ether (10 mL) and water (2 mL) and the aqueous phase was extracted with ether (5 mL). The organic phase was dried ($MgSO_4$) and concentrated and the product was purified by chromatography on silica gel (hexane/ether 40/60).

(1*R,1′*R**)-4-[1′-Hydroxybenzyl]cyclohex-3-enyl Methyl Ketone (16b).** Obtained by deprotection of **23b**: colorless

oil; yield 87%; IR (neat) 3420, 3095, 3060, 3020, 2930, 2840, 1705, 1600, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.43–1.61 (m, 1H), 1.76–2.18 (m, 7H), 2.23–2.42 (m, 2H), 2.47–2.61 (m, 1H), 5.14 (bs, 1H), 5.90 (bs, 1H), 7.26–7.39 (m, 5H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.6, 25.3, 27.3, 28.0, 47.5, 78.3, 122.3, 127.1, 127.8, 128.8, 140.7, 143.8, 210.4; MS *m/z* (rel intensity) 230 (M^+, 0.3), 212 (16), 170 (16), 169 (100), 141 (20), 105 (21), 91 (26), 77 (19). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.87. Found: C, 78.13; H, 7.87.

(1*R,1′*R**)-4-[1′-Hydroxy-*p*-bromobenzyl]cyclohex-3-enyl Methyl Ketone (18b).** Obtained by deprotection of **30b**: colorless oil; yield 89%; IR (neat) 3410, 2930, 1710, 1600, 1490 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 1.08 (d, J = 3.1 Hz, 1H), 1.19–1.35 (m, 1H), 1.35–1.5 (m, 1H), 1.5–1.6 (m, 1H), 1.64 (s, 3H), 1.78–2.0 (m, 2H), 2.04–2.23 (m, 1H), 4.63(bs, 1H), 5.46 (bs, 1H), 7.00 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H); ^{13}C NMR (50.3 MHz, C_6D_6) δ 23.2, 25.2, 27.1, 28.1, 47.3, 77.6, 121.7, 122.9, 128.8, 131.9, 140.2, 142.7, 210.5; MS *m/z* (rel intensity) 249 (26), 247 (27), 169 (26), 168 (100), 167 (44), 165 (21), 153 (17), 77 (15).

(1*R,1′*R**) and (1*S**,1′*R**)-4-[1′-Hydroxyheptyl]cyclohex-3-enyl Methyl Ketones 20a and 20b.** Obtained by deprotection of **28a** + **28b** as a mixture of stereomers: ratio **20a/20b** = 19/81; yield 80%. Spectral data for **28b**: IR (neat) 3405, 2980, 2930, 2860, 1715, 1350, 1160 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.9(t, J = 6.3 Hz, 3H), 1.15–1.45 (m, 9H), 1.45–1.63 (m, 3H), 1.9–2.16 (m, 2H), 2.16–2.34 (m, 6H), 2.5–2.7 (m, 1H), 3.95–4.05 (m, 1H), 5.18 (bs, 1H); MS *m/z* (rel intensity) 220 (M^+ − 18, 17), 177 (41), 107 (20), 93 (100), 91 (29).

(1*S,1*R**)-4-[2′-Methyl-1′-hydroxypropyl]cyclohex-3-enyl Methyl Ketone (21b).** Obtained by deprotection of **29b**: colorless oil; yield 76%; IR (neat) 3450, 2960, 2930, 2870, 1710 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 0.78 (d, J = 6.3 Hz, 3H), 0.96 (bs, 1H), 1.07 (d, J = 6.3 Hz, 3H), 1.29–1.46 (m, 1H), 1.52–1.77 (m, 6H), 1.83–2.03 (m, 1H), 2.04–2.19 (m, 3H), 3.34 (d, J = 7.9 Hz, 1H), 5.36 (bs, 1H); ^{13}C NMR (50.3 MHz, C_6D_6) δ 19.6, 20.2, 23.3, 25.5, 27.3, 28.1, 31.8, 47.9, 82.6, 122.6, 140.4, 210.2; MS *m/z* (rel intensity) 178 (M^+ − 18, 15), 135 (33), 93 (56), 91 (23), 79 (39), 77 (21), 43 (100). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.27; H, 10.61.

General Procedure for Oxidation. In a suspension of activated MnO_2 (2 g) in dry CH_2Cl_2 (10 mL) was added in one portion the allylic alcohol (1 mmol). The mixture was stirred at room temperature for 4 h and then filtered on a bed of Celite. The solid was washed with CH_2Cl_2 (3 × 5 mL) and the filtrate was dried over $MgSO_4$. The solvent was then removed under reduce pressure and the residue was purified by chromatography on silica gel (hexane/ether = 60/40).

4-Acetylcyclohex-1-enyl Phenyl Ketone (35). Obtained by oxidation of alcohol **16b**: colorless oil; yield 90%; IR (neat) 3040, 3005, 2940, 2840, 1710, 1640, 1605 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.6–1.8 (m, 1H), 2.11–2.2 (m, 1H), 2.2–2.4 (m, 4H), 2.4–2.57 (m, 2H), 2.57–2.64 (m, 1H), 2.64–2.8 (m, 1H), 6.6 (m, 1H), 7.37–7.6 (m, 3H), 7.6–7.7 (m, 2H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.4, 24.4, 27.0, 27.9, 46.2, 128.0, 129.0, 131.4, 137.8, 138.2, 141.9, 197.3, 210.1; MS *m/z* (rel intensity) 228 (M^+, 7), 185 (69), 106 (21), 105 (79), 77 (100). Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.91; H, 7.06. Found: C, 78.84; H, 7.19.

4-Acetylcyclohex-1-enyl Hexyl Ketone (36). Obtained by oxidation of alcohols **20a** + **20b**: colorless oil; yield 65%; IR (neat) 2960, 2930, 2860, 1715, 1670, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.9 (t, J = 6.4 Hz, 3H), 1.2–1.38 (m, 6H), 1.48–1.68 (m, 3H), 2.01–2.36 (m, 5H), 2.36–2.70 (m, 6H), 6.91 (bs, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.0, 22.5, 22.8, 24.6, 24.7, 27.1, 29.0, 31.6, 37.1, 38.0, 46.3, 137.4, 138.5, 201.1, 210.4. Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.2. Found: C, 76.14; H, 10.47.

4-Acetylcyclohex-1-enyl Isopropyl Ketone (37). Obtained by oxidation of alcohol **21b**: colorless oil; yield 73%; IR (neat) 2970, 2940, 2880, 1715, 1670, 1640 cm^{-1}; ^1H NMR (200 MHz, C_6D_6) δ 1.04 (d, J = 7.6 Hz, 3H), 1.06 (d, J = 7.6 Hz, 3H), 1.09–1.29 (m, 1H), 1.49–1.59 (m, 1H), 1.69 (s, 3H), 1.72–1.97 (m, 2H), 1.97–2.37 (m, 2H), 2.37–2.56 (m, 1H), 2.89 (heptuplet, J = 7.6 Hz, 1H), 6.33 (bs, 1H); ^{13}C NMR (50.3 MHz, C_6D_6) δ 20.2, 23.9, 25.2, 27.6, 27.9, 34.1, 46.5, 137.2, 137.9, 203.9, 208.7; MS *m/z* (rel intensity) 194 (M^+, 3), 151 (25), 79 (20), 43 (100). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 73.91; H, 9.66.

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Supplementary Material Available: Copies of ^1H NMR spectra of **2**, **3**, **5–13**, **18b**, **24b**, **32b**, **34b** and copies of ^{13}C NMR spectra of **18b** and **32b** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.