Asymmetric Catalysis of Diels-Alder Cycloadditions by an MS-Free Binaphthol-Titanium Complex: Dramatic Effect of MS, Linear vs Positive Nonlinear Relationship, and Synthetic Applications

Koichi Mikami,* Yukihiro Motoyama, and Masahiro Terada

Contribution from the Department of Chemical Technology, Tokyo Institute of Technology, Meguro-ku, Tokyo 152, Japan

*Received July 7, 1992**

Abstract: Asymmetric Diels-Alder (D.-A.) reaction of 5-hydroxynaphthoquinone (juglone) with butadienyl acetate catalyzed by the binaphthol-derived chiral titanium (BINOL-Ti) complex **1** proceeds in only 9% ee in the presence of molecular sieves (MS). Remarkably, however, this reaction proceeds in 76-96% ee with BINOL-Ti complex **1** freed from MS to provide the *endo*-adducts useful for the synthesis of anthracyclines and tetracyclines. The solid MS-free BINOL-Ti complex **1** is stable for months at -20 °C. Enhancements in *endo* selectivity and asymmetric induction are observed with the MS-free BINOL-Ti **1** also in the catalyzed D.-A. cycloaddition of methacrolein and glyoxylate with 1,3-dienol ethers and esters. The glyoxylate adducts can be converted to the mevinolin (compactin) intermediates. Surprisingly, the MS-free complex **1** exhibits not only a linear relationship between the ee's of BINOL-Ti **1** and the D.-A. products but also a positive nonlinear effect (asymmetric amplification), depending simply on the mixing manner of (*R*)-**1** with (*S*)-**1** or (±)-**1**.

Introduction

Asymmetric catalysis, particularly of carbon-carbon bond-forming reactions, is one of the most challenging and formidable endeavors in organic synthesis.[1] We have developed an enantioselective carbonyl-ene reaction[2] with glyoxylate (**2**) catalyzed by chiral titanium complexes of type (*R*)-**1**, which are prepared *in situ* from $(i\text{-PrO})_2TiX_2$ and optically pure (*R*)-binaphthol (BINOL) in the presence of molecular sieves 4A (MS).[1f,3] In the course of our study of asymmetric catalytic carbonyl-ene reactions, we found that the use of isoprene as the ene component provides not only the carbonyl-ene product but also the Diels-Alder (D.-A.) product with high enantioselectivity. The D.-A. reaction constitutes an efficient process for six-membered ring formation with the potential to control the absolute and relative stereochemistry at up to all the four newly created chiral centers.[4,5] In this paper, we report a full account[6] on the enantioselective D.-A. cycloaddition of 5-hydroxynaphthoquinone (juglone) (**3a**) or methyl glyoxylate (**2**) with 1,3-dienol ethers and esters (**4**) catalyzed by a chiral BINOL-derived titanium (BINOL-Ti) complex (**1**) which has been freed from the MS (zeolite) involved in the original preparation (Scheme 1).

Diels-Alder Reaction with Juglone

The asymmetric catalytic D.-A. reaction of juglone (**3a**) with butadienyl acetate (**4c**) would provide an efficient entry to the

* Abstract published in *Advance ACS Abstracts*, March 1, 1994.

(1) Reviews: (a) Morrison, J. D. *Asymmetric Synthesis*; Academic Press: New York, 1984; Vol. 3B. (b) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods 1989*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1989; Vol. 5. (c) Bosnich, B. *Asymmetric Catalysis*; Martinus Nijhoff Publishers: Dordrecht, The Netherlands, 1986. (d) Kagan, H. B. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: Oxford, U.K., 1982; Vol. 8. (e) Narasaka, K. *Synthesis* **1991**, 1. Hayashi, Y.; Narasaka, K. *Yuki Gosei Kagaku Kyokaishi* **1990**, *48*, 280. (f) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255. Mikami, K.; Terada, M.; Nakai, T. *Yukagaku* **1990**, *39*, 837.

(2) Reviews on ene reactions: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (b) Mikami, K.; Terada, M.; Shimizu, M.; Nakai, T. *Yuki Gosei Kagaku Kyokaishi* **1990**, *48*, 292. (c) Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 2, p 527, Vol. 5, p 1. (d) Hoffman, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (e) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (f) Taber, D. F. *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer Verlag: Berlin, 1984.

(3) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949; **1989**, *111*, 1940. Mikami, K.; Narisawa, S.; Shimizu, M.; Terada, M. *J. Am. Chem. Soc.* **1992**, *114*, 6566, 9242. Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039.

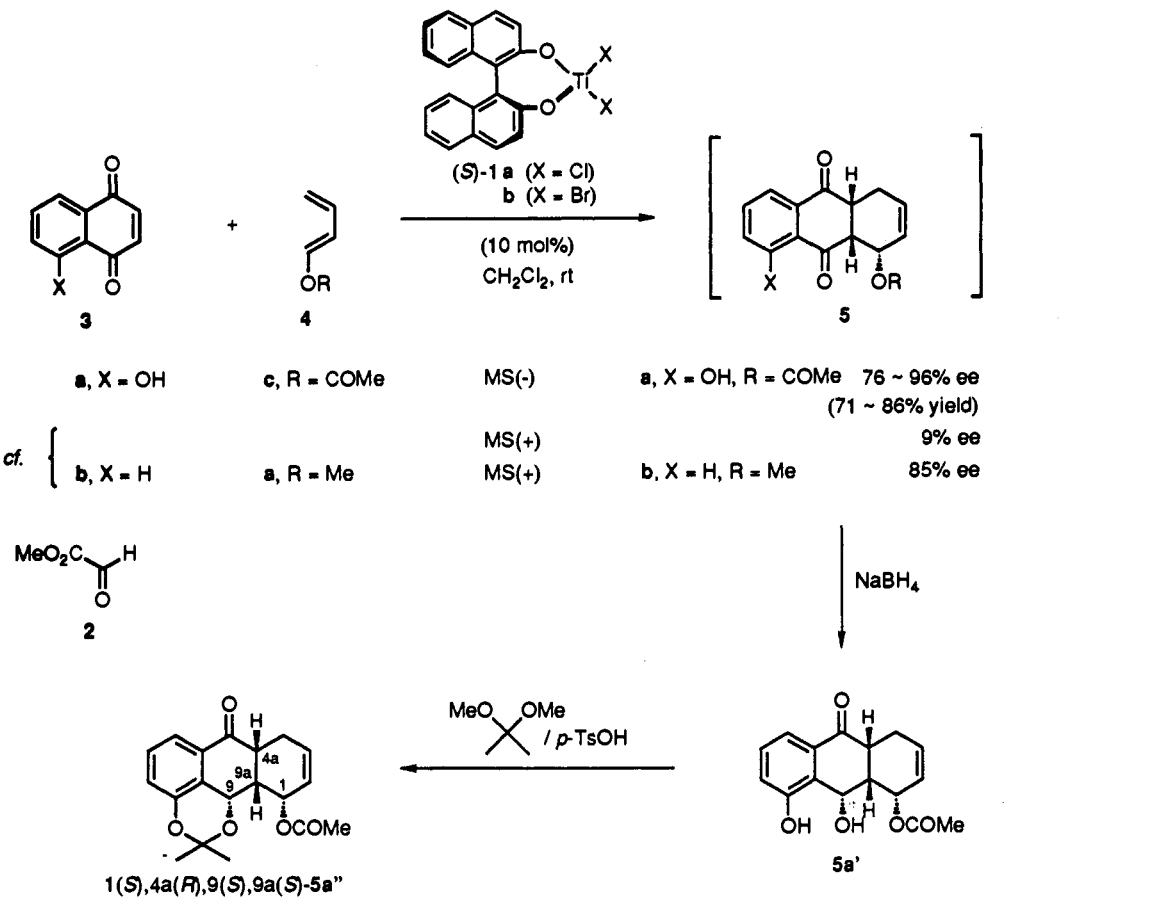
(4) (a) Reviews on asymmetric D.-A. reactions: Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3B. Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 5, p 315. Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; Wiley: New York, 1990. Taschner, M. J. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: London, 1989; Vol. 1. Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. For asymmetric catalytic D.-A. reactions: (b) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340. (c) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481. (d) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (e) Kaufmann, D.; Boese, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545. (f) Rebiere, F.; Riant, O.; Kagan, H. B. *Tetrahedron Asymmetry* **1990**, *1*, 199. (g) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728. (h) Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794. (i) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (j) Kobayashi, S.; Murakami, M.; Harada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 1341. (k) Devine, P. N.; Oh, T. *J. Org. Chem.* **1992**, *57*, 396. (l) Maruoka, K.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938. (m) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814. (n) For a pioneering work on the asymmetric catalysis for the D.-A. reaction using a similar type of chiral Ti complex prepared from the dilithium salt of BINOL and $TiCl_4$ or azeotropic removal of isopropanol from chlorotitanium isopropoxides and BINOL to give, however, lower optical yields: Reetz, M. T.; Kyung, S.-H.; Bolm, C.; Zierke, T. *Chem. Ind.* **1986**, 824. Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954.

(5) (a) Reviews on asymmetric hetero-D.-A. reactions: Bednarski, M. D.; Lyssikatos, J. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 2, p 661. Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. For asymmetric catalytic hetero-D.-A. reactions: (b) Bednarski, M.; Maring, C.; Danishefsky, S. *Tetrahedron Lett.* **1983**, *24*, 3451. (c) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968. (d) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. (e) Togni, A. *Organometallics* **1990**, *9*, 3106. (f) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 1951.

(6) For our preliminary communications of this work, see: Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron Asymmetry* **1991**, *2*, 643. Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1991**, *32*, 935.

0002-7863/94/1516-2812$04.50/0

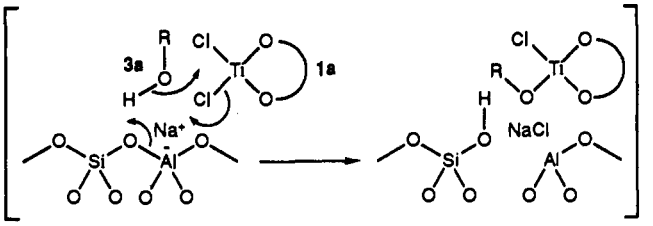
Scheme 1



asymmetric synthesis of anthracycline and tetracycline antibiotics.[7,8] Thus, we examined the reaction of **3a** with **4c** catalyzed by MS(+)-**1a** prepared *in situ* in the presence of MS. Although the reaction proceeded with complete *endo*-selectivity, the enantiomeric enrichment (ee) is only 9% ee as determined by ^{1}H NMR analysis of the corresponding (*R*)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid ((*R*)-MTPA) ester of 9-hydroxy derivative **5a'**, which was prepared by $NaBH_4$ reduction (Scheme 1). The low enantioselectivity (9% ee) is in marked contrast to the 85% ee obtained from the parent naphthoquinone (**3b**) and **4a** under the same reaction conditions. These results indicate that the free hydroxy group of **3a** is responsible for the low ee, suggesting that the hydroxy group of the dienophile might be binding to the titanium in **1a**.

Analysis of the NMR spectra of a mixture of juglone (**3a**) and BINOL-Ti dichloride **1a** in the presence of MS indicates that the hydroxy group of juglone binds to titanium, displacing chloride as shown in Scheme 2. No change was observed in the Ti-O*C* of the BINOL-Ti framework at δ 162, nor was the signal for the hydroxy carbon of free BINOL at δ 153 detected. Therefore neither Ti-O bond of **1a** is broken. However, the hydroxy carbon signal of juglone is shifted downfield from δ 161 to 167, indicating that the juglone is binding to titanium. These results suggest

Scheme 2



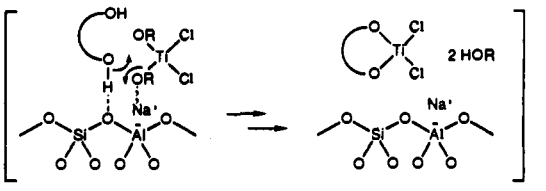
that HCl abstraction could possibly occur by MS (A-type (Na^+) zeolite)[9] from BINOL-$TiCl_2$ and juglone (Scheme 2), rather than the alkoxy-ligand exchange[10] from the cyclic and hence stable BINOL-Ti framework.[11] Indeed, the alkoxy-ligand exchange was observed in the reaction of acyclic (i-PrO)$_2TiCl_2$ with juglone (**3a**) in the presence of MS; the hydroxy carbon signal of **3a** was shifted downfield (δ 165) along with the formation

(7) Reviews on asymmetric synthesis of tetra- and anthracycline antibiotics: Arcamone, F. In *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; Ellis-Horwood: Chichester, U.K., 1978; Vol. 2. Arcamone, F. *Med. Res. Rev.* **1984**, *4*, 153. Broadhurst, M. J.; Hassall, C. H.; Thomas, G. *J. Chem. Ind.* **1985**, *18*, 106. Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790; *Tetrahedron* **1990**, *46*, 291.

(8) For an alternative D.-A. route to the chiral anthracyclinone intermediates by an equimolar use of chiral boron reagent: (a) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510. (b) Maruoka, K.; Sakurai, M.; Fujiwara, J.; Yamamoto, H. *Tetrahedron Lett.* **1986**, 27, 4895. For the asymmetric D.-A. approach using (*S*)-*O*-methylmandeloxy diene in the presence of 1.6 equiv of boron triacetate: (c) Trost, B. M.; O'Krongly, D.; Belletire, J. L. *J. Am. Chem. Soc.* **1980**, *102*, 7595.

(9) (a) Onaka, M.; Izumi, Y. *Yuki Gosei Kagaku Kyokaishi* **1989**, *47*, 233. Izumi, Y.; Urabe, K.; Onaka, M. *Zeolite, Clay, and Heteropoly Acid in Organic Reactions*; Kodansha: Tokyo, 1992. (b) Thomas, J. M.; Theocaris, C. R. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1989; p 249. (c) Dyer, A. *An Introduction to Zeolite Molecular Sieves*; Wiley: New York, 1988.

(10) We have previously reported the catalysis of MS, which would be visualized as shown below, for the alkoxy-ligand exchange reaction in the original preparation of BINOL-Ti complex **1a**.



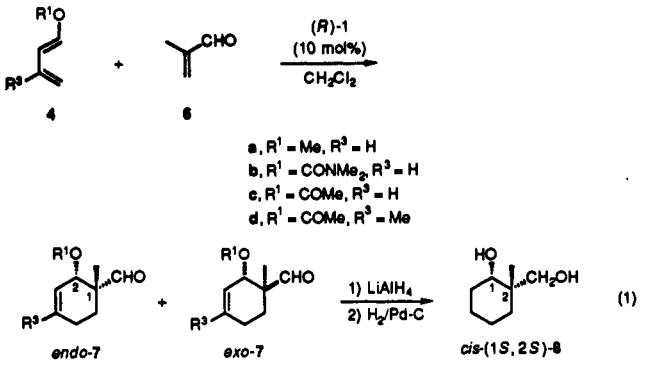
(11) Strain energy calculation using MACROMODEL (version 2.5) shows that the seven-membered dioxatitanacycle is the most stable: Duthaler, R. O.; Hafner, A.; Riediker, M. *Pure Appl. Chem.* **1990**, *62*, 631.

of isopropanol (^{1}H NMR δ 3.81; ^{13}C NMR δ 63.6. *Cf.* $(i\text{-PrO})_2TiCl_2$: ^{1}H NMR δ 4.91; ^{13}C NMR δ 87.6).

Thus, we made the MS-free BINOL–Ti dichloride **1a**, by centrifugation of MS and decanting. Removal of the isopropanol under reduced pressure gave solid MS-free (MS(–)) BINOL–Ti complex **1** that could be stored for months at –20 °C.

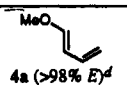
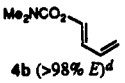
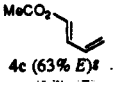
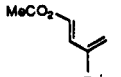
The D.–A. reaction of juglone (**3a**) using this MS-free catalyst affords **5a** in high yield and high optical yield (76–96% ee). The absolute configuration and high enantiomeric purity of the adduct **5a** were determined from the optical rotation of the known compound **5a''**: $[\alpha]^{25}_D$ +371.6° (*c* 0.75, CH_2Cl_2) (lit.[8a] (1*S*,4a*R*,9*S*,9a*S*)-**5a''**: $[\alpha]^{22}_D$ +344° (*c* 1.00, CH_2Cl_2) (>98% ee)). The % ee is, however, somewhat variable and depends sensitively on the catalytic activity of the sample of MS(–)-**1a**, since the uncatalyzed D.–A. reaction of juglone **3a** with **4c** proceeds slowly under these conditions.[12] The increase from 9% ee in the presence of MS to 76–96% ee in the absence of MS is remarkable and supports our hypothesis that MS catalyzes the reaction of juglone with **1a** shown in Scheme 2 to give an intermediate that reacts with low % ee.

Use of MS(–)-**1a** results in enhanced enantioselectivity in the D.–A. reaction of methacrolein (**6**) with the alkoxydiene **4** (Table 1). The methyl ether **4a**, in spite of its higher reactivity, led to the lower chemical yield due to the instability of **4a** under the reaction conditions (entries 1 and 2). The dienylcarbamate **4b**, which is reported to be stable under the Lewis acid conditions,[13] gave the higher chemical yield (entries 3–7). The dibromo catalyst



(1)

Table 1. Asymmetric Catalytic Diels–Alder Reactions Catalyzed by the BINOL–Ti Complex **1**[a]

entry	1 (MS 4A)	diene (4)	conditions	% yield	% *endo*[b]	% ee[c]
1	**1a** (+)		–30 °C, 5 h	43	87	71
2	**1a** (–)	**4a** (>98% *E*)[d]	–30 °C, 2 h	40	93	85
3	**1a** (+)		0 °C, 58 h	82	99.6	86
4	**1a** (+)	**4b** (>98% *E*)[d]	0 °C, 48 h[e]	80	99.4	85
5	**1a** (+)		0 °C, 48 h[f]	67	99.5	85
6	**1b** (+)		0 °C, 58 h	75	99	80
7	**1a** (–)		0 °C, 58 h	64	99	87
8	**1a** (+)		rt, 18 h	69	97	78
9	**1a** (+)		rt, 18 h[e]	81	98	80
10	**1a** (–)	**4c** (63% *E*)[g]	rt, 18 h[e]	63	99	94
11	**1a** (–)[h]	 **4d** (92% *E*)[i]	rt, 20 h[e]	98	89	80

[a] All reactions were carried out using 2.0 mmol of **6**, the indicated amount of **4**, and 0.1 mmol of (*R*)-BINOL–Ti complex **1**. [b] Determined by ^{1}H NMR analysis. [c] Determined by ^{1}H NMR analysis of the corresponding (*R*)-MTPA esters after reduction of **7** with $LiAlH_4$. [d] 1.0 mmol of **4a** or **4b** was used. [e] In toluene. [f] In $CH_2Cl_2/CF_2ClCFCl_2$ = 1:1. [g] 1.6 mmol of **4c** was used. [h] (*S*)-**1a** was used. [i] 1.1 mmol of **4d** was used.

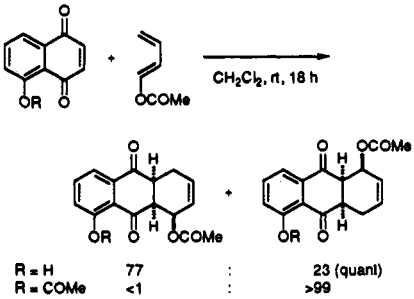
1b affords a slightly lower *endo*-selectivity and enantioselectivity (entry 6). The acetate **4c** with MS(–)-**1a** provides the remarkably enhanced levels of *endo*-selectivity and enantioselectivity (entry 10). The absolute configuration of the *endo*-adduct **7c** was determined to be 1*R*,2*S* after reduction to the known diol (1*S*,2*S*)-*cis*-alcohol **8**: $[\alpha]^{21}_D$ +16.2° (*c* 2.95, $CHCl_3$) (lit.[14] (1*S*,2*S*)-**8**: $[\alpha]^{20}_D$ +3° (*c* 1, CH_2Cl_2)). Thus, the sense of asymmetric induction is exactly the same as was observed for the glyoxylate–ene reaction;[1f,3] (*R*)-**1** provides (1*R*)-**7**. A small solvent effect is observed in the present reaction (entries 3 *vs* 4 and 5, and 8 *vs* 9). Slightly lower enantioselectivity and *endo*-selectivity were observed in the reaction with the 3-methyldiene **4d** (entry 11).

Hetero-Diels–Alder Reaction with Glyoxylate

Use of MS-free complex **1** also improves the *endo*-selectivity and enantioselectivity in the hetero-D.–A. reactions of glyoxylate **2** even with methoxydienes, which proceed smoothly to give the 2,6-*cis*(*endo*)-adduct **9** with high enantioselectivity (Table 2). The absolute configuration at C-6 of the adduct **9a** with methoxydiene **4a** (entry 1) was determined to be *R* in both *cis*- and *trans*-**9a** after conversion of the isomeric mixture to *trans*-**9a** with $ZnCl_2$ followed by reduction to the (2*R*,6*R*)-*trans*-alcohol **10**: $[\alpha]^{20}_D$ –119.9° (*c* 1.07, benzene) (lit.[15] (2*S*,6*S*)-**10**: $[\alpha]^{20}_D$ +127.7° (*c* 4.3, benzene)). Thus, the sense of asymmetric induction is exactly the same as observed for the glyoxylate–ene[1f,3] and D.–A. reactions; (*R*)-**1** provides (6*R*)-**9**. No epimerization was observed at C-2 after prolonged reaction (entry 2). The dibromo catalyst **1b** affords a higher *cis*-selectivity but slightly lower enantiomeric excess, particularly in the *trans*-adduct **9a** (entry 3). An enhanced (96% ee) enantioselectivity was obtained along with the increased (88%) *cis*-selectivity, when the MS-free dichloride **1a** was used (entry 4). High optical yields were also obtained with 4-methyl-1-methoxydiene with or without a 2-methyl substituent (**4e** and **4f**) (entries 6 and 8). However, a lower optical yield was obtained with 3-methyldiene **4g** (entry 9), because the hetero-D.–A. reaction with **4g** proceeded even in the absence of the Lewis acid catalyst (entry 10).

The hetero-D.–A. adduct **9a** obtained using (*S*)-**1a** is a useful intermediate for the synthesis of not only monosaccarides[16] but also the lactone portion (**12**) in mevinolin or compactin, coenzyme A reductase inhibitors[17–19] (Scheme 3). Reduction and benzyl-

(12) (a) Kelly, T. R.; Ananthasubramanian, L.; Borah, K.; Gillard, J. W.; Goerner, R. N., Jr.; King, P. F.; Lyding, J. M.; Tsang, W.-G.; Vaya, J. *Tetrahedron* **1984**, *40*, 4569. (b) Kelly, T. R.; Parekh, N. D. *J. Org. Chem.* **1982**, *47*, 5009. (c) Kelly, T. R.; Montury, M. *Tetrahedron Lett.* **1978**, 4311. Furthermore, regioisomeric product was, however, obtained in the attempted reaction with the acetate of **3a** in quantitative yield after 88 h.



(13) D.–A. reaction with the dienylcarbamate and the transformation of the D.–A. adduct to (±)-hernandulcin: De Cusati, P. F.; Olofson, R. A. *Tetrahedron Lett.* **1990**, *31*, 1405, 1409.

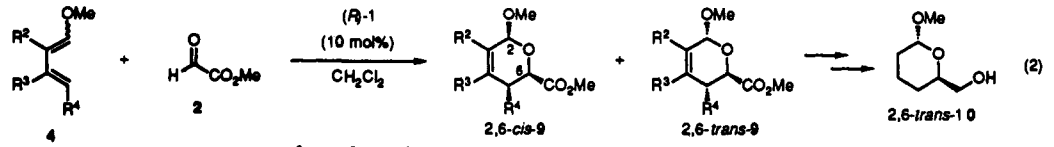
(14) Lubineau, A.; Queneau, Y. *J. Org. Chem.* **1987**, *52*, 1001.

(15) Jurczak, J.; Bauer, T.; Filipek, S.; Tkacz, M.; Zygo, K. *J. Chem. Soc., Chem. Commun.* **1983**, 540.

(16) Konowal, A.; Jurczak, J.; Zamojski, A. *Tetrahedron* **1976**, *32*, 2957. Also see the review: Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15.

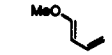
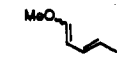
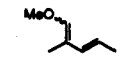
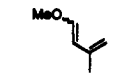
(17) Isolation and activity: Endo, A. *J. Med. Chem.* **1985**, *28*, 401.

(18) The lactone portion is responsible for their biological activity: Stokker, G. E.; Hoffmann, W. F.; Alberts, A. W.; Cragoe, E. J., Jr.; Deana, A. A.; Gilfillan, J. L.; Huff, J. W.; Novello, F. C.; Prugh, J. D.; Smith, R. L.; Willard, A. K. *J. Med. Chem.* **1985**, *28*, 347.



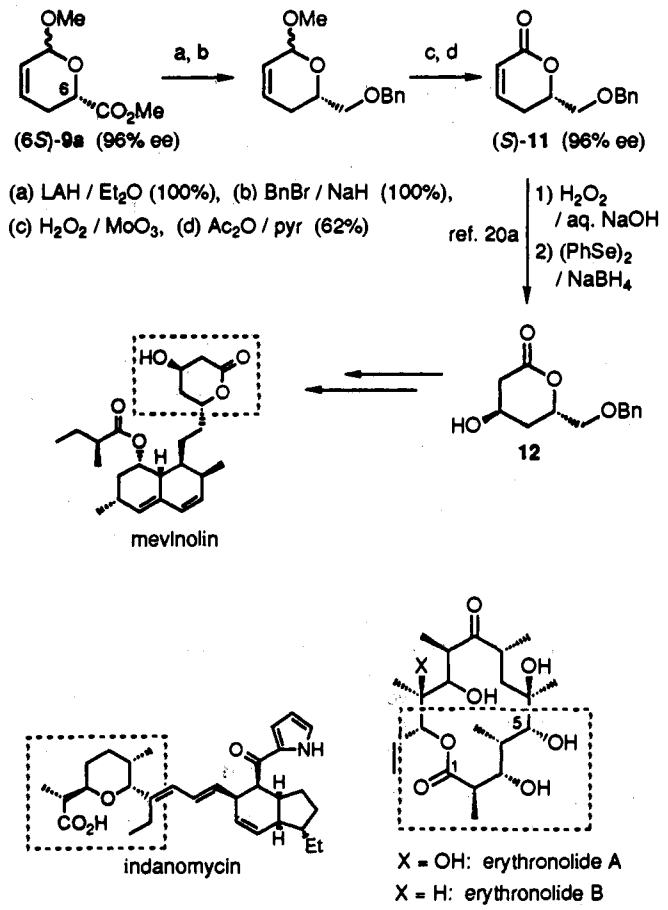
a: $R^2 = H, R^3 = H, R^4 = H$
e: $R^2 = H, R^3 = H, R^4 = Me$
f: $R^2 = Me, R^3 = H, R^4 = Me$
g: $R^2 = H, R^3 = Me, R^4 = H$

Table 2. Asymmetric Catalytic Hetero-Diels–Alder Reactions Catalyzed by the BINOL–Ti Complex 1[a]

entry	1 (MS 4A)	diene (4)	conditions	% yield	2,6-*cis*-9[b] (% ee)[c]	2,6-*trans*-9[b] (% ee)[c]
1	1a (+)		−30 °C, 10 min	56	78 (94% ee)	22 (>90% ee)
2	1a (+)		−30 °C, 48 h	77	78 (94% ee)	22 (>90% ee)
3	1b (+)	4a (>98% *E*)[d]	−30 °C, 1 h	88	84 (92% ee)	16 (50% ee)
4	1a (−)		−30 °C, 1 h	78	88 (96% ee)	12 (>90% ee)
5	1a (+)		−10 °C, 1 h	63	97 (90% ee)	3
6	1a (−)		−30 °C, 1 h	58	>98 (93% ee)	<2
		4e (40% 1*E*,3*E*)[e]				
7	1a (+)		−30 °C, 1 h	18	98 (88% ee)	2
8	1a (−)		−30 °C, 1 h	32	>98 (>95% ee)	<2
		4f (50% 1*E*,3*E*)[e]				
9	1a (−)		−30 °C, 1 h	51	92 (71% ee)	8 (10% ee)
10[f]			−30 °C, 3 h	63	85	15
		4g (67% *E*)[g]				

[a] All reactions were carried out using 1.0 mmol of **2**, the indicated amount of **4**, and 0.1 mmol of (*R*)-BINOL–Ti complex **1**. [b] The 2,6-*cis*/*trans* ratio was determined by ^{1}H NMR analysis. [c] Determined by LIS-^{1}H NMR analysis using (+)-Eu(dppm)$_3$ as a chiral shift reagent. [d] 1.5 mmol of **4a** was used. [e] 2.5 mmol of **4e** or **f** was used. [f] The reaction was run in the absence of BINOL–Ti complex. [g] 2.0 mmol of **4g** was used.

Scheme 3



ation of ester **9** followed by MoO_3-catalyzed oxidation and decomposition of the peroxide gave the α,β-unsaturated lactone **11** in 62% overall yield along with 96% ee: $[\alpha]^{23}_D$ −110.2° (*c* 0.69, $CHCl_3$) (lit.[20a] $[\alpha]^{24}_D$ −115.1° (*c* 1.0, $CHCl_3$)). Since the conversion of **11** to **12** has been reported,[20a] this process provides a practical asymmetric synthesis of lactone **12**.

The D.–A. adducts **9e** and **9f** can in principle be transformed to the left-wing portion of ionophore antibiotic indanomycin (X-14547A)[21] and the C_1–C_5 portion of the macrolide antibiotic erythromycin,[22,23] respectively.

Linearity *vs* Positive Nonlinearity

A surprisingly interesting phenomenon in the asymmetric catalytic D.–A. reaction is that the MS-free complex MS(−)-**1**

(19) (a) Review on the syntheses: Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, *42*, 4909. (b) Wovkulich, P. M.; Tang, P. C.; Chadha, N. K.; Batcho, A. D.; Barrish, J. C.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1989**, *111*, 2596. (c) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599. (d) Clive, D. L. J.; Keshava Murthy, K. S.; Wee, A. G. H.; Siva Prasad, J.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018. (e) Askin, D.; Verhoeven, T. R.; Liu, T. M.-H.; Shinkai, I. *J. Org. Chem.* **1991**, *56*, 4929.

(20) (a) Takano, S.; Shimazaki, Y.; Sekiguchi, Y.; Ogasawara, K. *Synthesis* **1989**, 539. Bauer, T.; Kozak, J.; Chapuis, C.; Jurczak, J. *J. Chem. Soc., Chem. Commun.* **1990**, 1178. For the asymmetric synthesis of the lactone portion, see also: (b) Sletzinger, N.; Verhoeven, T. R.; Volante, R. P.; McNamara, J. M.; Corley, E. G.; Liu, T. M.-H. *Tetrahedron Lett.* **1985**, *26*, 2951. (c) Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett.* **1987**, *28*, 1385. (d) Roth, B. D.; Roark, W. H. *Tetrahedron Lett.* **1988**, *29*, 1255. (e) Johnson, W. S.; Kelson, A. B.; Elliott, J. D. *Tetrahedron Lett.* **1988**, *29*, 3757. (f) David, C.; Gesson, J. P.; Jacquesy, J. C. *Tetrahedron Lett.* **1989**, *30*, 6015. (g) Boquel, P.; Chapleur, Y. *Tetrahedron Lett.* **1990**, *31*, 1869. (h) Reddy, G. B.; Minami, T.; Hanamoto, T.; Hiyama, T. *J. Org. Chem.* **1991**, *56*, 5752.

(21) (a) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440. (b) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Feving, J. M. *Tetrahedron* **1986**, *42*, 2787. (c) Danishefsky, S. J.; DeNinno, S.; Lartey, P. *J. Am. Chem. Soc.* **1987**, *109*, 2082.

(22) Reviews: (a) Masamune, S.; McCarthy, P. A. in *Macrolide Antibiotics. Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic: Orlando, FL, 1984; Chapter 4. (b) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. (c) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489. (d) Boeckman, R. H.; Goldstein, M. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New York, 1988; Vol. 7, p 1.

(23) Burke, S. D.; Schoenen, F. J.; Murtiashaw, C. W. *Tetrahedron Lett.* **1986**, *27*, 449.

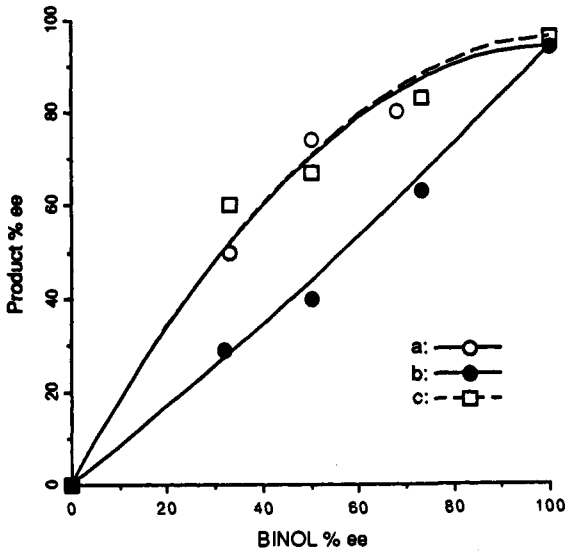


Figure 1. (a) D.–A. reaction catalyzed by (*R*)-**1a** and (±)-**1a** mixture. (b) D.–A. reaction catalyzed by (*R*)-**1a** and (*S*)-**1a** mixture. (c) Hetero-D.–A. reaction catalyzed by (*R*)-**1a** and (±)-**1a** mixture.

Table 3. Hetero-Diels–Alder Reaction Catalyzed by the Mixture of (*R*)- and (±)-MS-Free BINOL–Ti Complexes (**1a**)

4	dienophiles	**1a** (*x*% ee)	conditions	% yield	% *endo*	% ee[a]
4c	**6**	33	rt, 18 h	54	99	50
4c	**6**	50	rt, 18 h	50	99	74
4c	**6**	68	rt, 18 h	69	99	80
4c	**6**	100	rt, 18 h	63	99	94
4c	**6**	32[b]	rt, 18 h	42	98	29
4c	**6**	50[b]	rt, 18 h	62	99	40
4c	**6**	73[b]	rt, 18 h	51	98	63
4a	**2**	33	−30 °C, 1 h	43	72	60
4a	**2**	50	−30 °C, 1 h	50	77	67
4a	**2**	73	−30 °C, 1 h	60	86	83
4a	**2**	100	−30 °C, 1 h	78	88	96

[a] Refer to the major *endo*-isomer. [b] Catalyzed by the mixture of (*R*)- and (*S*)-MS-free BINOL–Ti complexes (**1a**).

exhibits not only a linear relationship between the ee's of BINOL–Ti (**1**) and the D.–A. products but also an asymmetric amplification (positive nonlinear effect: (+)-NLE),[24] depending simply on the mixing manner of (*R*)-**1** with (*S*)-**1** or (±)-**1** (Figure 1, Table 3). A convex deviation ((+)-NLE) from the linear relationship between the ee's of MS(−)–**1** and the D.–A. product *endo*-**7c** (eq 1) was obtained through a wide range of ee values of MS(−)–**1** (10 mol % scale, 25 mM solution), prepared by mixing (*R*)-**1** and (±)-**1** (Figure 1a). As expected, the catalytic activity (initial reaction rate) by the MS(−)–(*R*)-**1** derived from 100% ee (*R*)-BINOL is *ca.* 5 times greater than that of MS(−)–(±)-**1** derived from 0% ee BINOL under the same reaction conditions using 10 mol % (25 mM) of MS(−)–**1** (Figure 2). A similar level of asymmetric amplification was also observed in the hetero-D.–A. reaction of **4a** with glyoxylate **2** (eq 2) by mixing (*R*)-**1** with (±)-**1** (Figure 1c).

In sharp contrast, a linear relationship between the ee's of BINOL–Ti (**1**) and the extent of the asymmetric induction in the D.–A. cycloaddition of **4c** with **6** (eq 1) was found by the use of MS(-)-**1** solution, prepared by mixing (*R*)-**1** but, in this case, with (*S*)-**1** (Figure 1b). These results imply that, in the absence

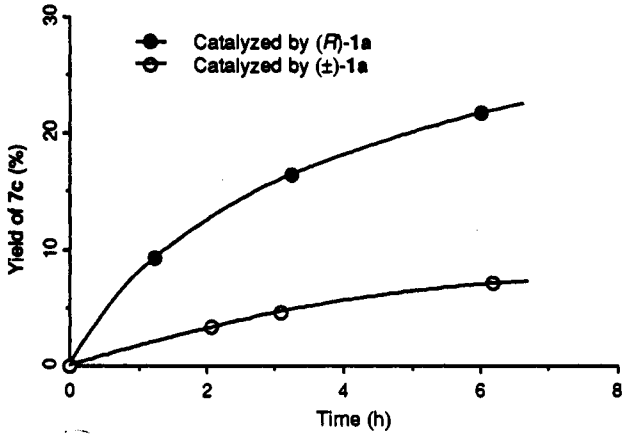


Figure 2. Kinetic studies.

of MS, there is little possibility for the distribution between the dimers (*R*)(*R*)-(**1**)$_2$ and (*S*)(*S*)-(**1**)$_2$ to give the more stable and hence catalytically less active (*R*)(*S*)-(**1**)$_2$ (Scheme 4). Indeed,

Scheme 4

$$(R)(R)\text{-}\mathbf{1}_2 + (S)(S)\text{-}\mathbf{1}_2 \xrightarrow[\text{MS(-)}]{} (R)\text{-}\mathbf{1} + (S)\text{-}\mathbf{1} \xrightarrow[\text{MS(-)}]{} (R)(S)\text{-}\mathbf{1}_2$$

MS(−)–**1**, prepared from 52% ee BINOL in the presence of MS, exhibits the asymmetric amplification between the ee's of MS-(−)–**1** and the D.–A. products (76% ee *endo*-**7c**).

Mechanistic Considerations

The observed *cis(endo)*-selectivity in the hetero-D.–A. reactions provides mechanistic insight into the complex between glyoxylate **2** and the chiral titanium catalyst **1**. Of the two transition states leading to the *cis*-product **9a**, the *syn–endo* transition state **A** should be less favorable because of the steric repulsion in the sterically demanding titanium complex. Thus, the titanium catalyst **1** would be complexed in an *anti* (monodentate) fashion and the hetero-D.–A. reaction could proceed through the *endo*-orientation **B**.

Furthermore, the sense of asymmetric induction in the D.–A. reactions with enal **6** (1*R* by (*R*)-**1**) is exactly the same as observed in the glyoxylate–ene[1f,3] and hetero-D.–A. reactions with glyoxylate. Since the enal **6** possesses the *transoid* conformation[25] and the titanium catalyst **1** should be complexed to the enal **6** in an *anti* fashion,[25a] the reaction could occur with the *transoid–anti* complex of **1** and **6** (**C**).

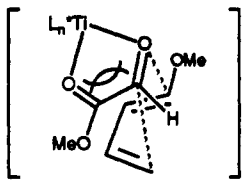
In summary, these observations demonstrate that the MS-free BINOL–Ti catalyst MS(−)–**1** is effective for the π-facial selection not only over the complexed carbonyl group but also over the olefinic group attached to the complexed carbonyl group.

Experimental Section

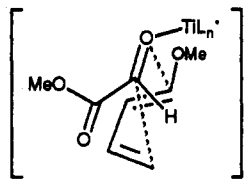
General Methods. Juglone (**3a**), (*E*)-1-methoxy-1,3-butadiene (**4a**), 1-acetoxy-1,3-butadiene (**4c**), and molecular sieves 4A (activated powder) were purchased from Aldrich Chemical Co. (*R*)-(+)- and (*S*)-(−)–1,1′-bi-2-naphthol were purchased from Wako Pure Chemical Ltd. Melting points and boiling points were uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a Varian EM390 (90 MHz), GEMINI 200 (200 MHz) or 300 (300 MHz), and JEOL FX-90Q (90 MHz) or GSX-500 (500 MHz) spectrometers. Chemical shifts of ^{1}H NMR were described in parts per million downfield from tetramethylsilane as an internal standard (δ = 0) in $CDCl_3$, unless otherwise noted. Chemical shifts of ^{13}C NMR

(24) Reviews: Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. Wynberg, H. *Chimia* **1989**, *11*, 150. (a) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353. (b) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877. (c) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (d) Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **1989**, 1581. (e) Mikami, K.; Terada, M. *Tetrahedron* **1992**, *48*, 5671.

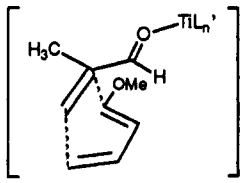
(25) (a) Corey, E. J.; Loh, T.-P.; Sarshar, S.; Azimioara, M. *Tetrahedron Lett.* **1992**, *33*, 6945. (b) Shambayatti, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256. (c) Birney, D. M.; Houk, K. N. *J. Am. Chem. Soc.* **1990**, *112*, 4127. (d) Oelichmann, H.-J.; Bougeard, D.; Schrader, B. *Angew. Chem. Suppl.* **1982**, 1404. (e) Montaudo, G.; Librando, V.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365.



syn-endo (A)



anti-endo (B)



anti-endo (C)

were expressed in parts per million in $CDCl_3$ as an internal standard (δ = 77.1), unless otherwise noted. IR spectra were measured on a JASCO FT/IR-5000 spectrometer. Optical rotations were measured on a JASCO DIP-140. Mass spectra were obtained with a JEOL JMS-300 or AX-500. Analytical thin-layer chromatography (TLC) was performed on glass plates and aluminium sheets precoated with silica gel (Merck, Kieselgel 60 F_{254}, layer thickness 0.25 and 0.2 mm, respectively). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. All experiments were carried out under argon atmosphere. Tetrahydrofuran, diethylether, benzene, and toluene were distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane and hexane were freshly distilled from CaH_2.

Preparation of 1,3-Dienes: (*E*)-1,3-Butadien-1-yl *N*,*N*-Dimethylcarbamate (4b). To a solution of *t*-BuOK (6.5 g, 57.9 mmol) in tetrahydrofuran (100 mL) was added a solution of crotonaldehyde (3.75 g, 53.5 mmol) in tetrahydrofuran (10 mL) over 20 min at −78 °C. Once the yellow enolate was formed, a solution of *N*,*N*-dimethylcarbamoyl chloride (6.4 g, 59.5 mmol) in tetrahydrofuran (7 mL) was added into the mixture, which turned red and viscous. After adding the half volume of the solution, removal of the cold bath facilitated stirring. When the mixture reached room temperature, it was quenched with crushed ice and extracted three times with ether (totally 150 mL). The combined organic layer was washed with brine (50 mL), dried over $MgSO_4$, and distilled to obtain pure (*E*)-1,3-butadien-1-yl *N*,*N*-dimethylcarbamate (**4b**), 5.21 g (69%), as a clear liquid: bp 69–71 °C/5 mmHg; IR (neat) 3558, 3076, 2940, 1727, 1661, 1485, 1450, 1392, 1168, 998 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.96 (s, 3H), 2.98 (s, 3H), 5.01 (dd, J = 9.5, 1.0 Hz, 1H), 5.14 (ddd, J = 17.0, 1.0 Hz, 1H), 5.97 (ddd, J = 12.5, 11.0, 1.0 Hz, 1H), 6.28 (ddd, J = 17.0, 11.0, 9.5 Hz, 1H), 7.34 (d, J = 12.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.0, 36.6, 113.9, 115.6, 132.2, 140.6, 153.5.

1-Acetoxy-3-methyl-1,3-butadiene (4d). The title compound was prepared according to the literature procedure.[26]

General Procedure for the Preparation of Methoxy 1,3-Diene 4: 1-Methoxy-1,3-pentadiene (4e) (1*E*,3*E*/1*Z*,3*E* = 4:6 Mixture). To a suspension of *t*-BuOK (22.8 g, 200 mmol) in ether (350 mL) was added (methoxymethyl)triphenylphosphonium chloride (72 g, 150 mmol) over 5 min at 0 °C. The resultant reddish suspension was stirred for 1 h at 0 °C, and a tetrahydrofuran (50 mL) solution of freshly distilled crotonaldehyde (12.4 mL, 150 mmol) was then added. The reaction mixture was warmed to room temperature and stirred for 30 min. The resultant solution was poured into brine (50 mL) and pentane (100 mL). Triphenylphosphine oxide was filtered off through a pad of Celite. The filtrate was extracted twice with a pentane/ether (1:1) mixture (totally 100 mL). The combined organic layer was washed with brine (50 mL) and dried over $MgSO_4$. After careful distillation under atmospheric pressure, the residue was distilled under reduced pressure to give 1-methoxy-1,3-pentadiene (**4e**) in 62% yield (9.1 g) (1*E*,3*E*/1*Z*,3*E* = 4:6): bp 75–85 °C/250 mmHg; IR (neat) 1660, 1620, 1460, 1110, 970, 920 cm^{-1}. (1*E*,3*E*)-**4e**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.71 (m, 3H), 3.56 (s, 3H), 5.49 (m, 1H), 5.51 (m, 1H), 5.89 (m, 1H), 6.84 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.1, 59.9, 105.9, 123.5, 127.2, 149.4. (1*Z*,3*E*)-**4e**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.74 (m, 3H), 3.63 (s, 3H), 5.01 (m, 1H), 5.56 (m, 1H), 5.76 (m, 1H), 6.34 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.2, 54.6, 107.1, 124.1, 125.7, 145.3.

1-Methoxy-2-methyl-1,3-pentadiene (4f) (1*E*,3*E*/1*Z*,3*E* = 1:1 Mixture): bp 85–88 °C/71 mmHg; IR (neat) 1690, 1630, 1450, 1380, 1140, 1100, 980, 870 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.62 (bs, 3H), 1.69 (bs, 3H), 1.73 (m, 3H), 1.81 (m, 3H), 3.60 (s, 3H), 3.62 (s, 3H), 5.45 (dq, J = 15.4, 6.6 Hz, 1H), 5.55 (ddq, J = 15.8, 0.8, 6.6 Hz, 1H), 5.90 (m, 1H), 5.95 (m, 1H), 6.03 (m, 1H), 6.56 (m, 1H).

1-Methoxy-3-methyl-1,3-butadiene (4g) (*E*/*Z* = 2:1 Mixture): bp 78–82 °C/250 mmHg; IR (neat) 1640, 1610, 1460, 1210, 1160, 1130, 1100, 930, 870 cm^{-1}. (*E*)-**4g**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.81 (m, 3H), 3.59 (s, 3H), 4.69 (m, 1H), 4.77 (m, 1H), 5.64 (d, J = 12.8 Hz, 1H), 6.58 (d, J = 12.8 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.1, 56.5, 108.7, 111.9, 140.1, 149.4. (*Z*)-**4g**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.95 (m, 3H), 3.63 (s, 3H), 4.77 (m, 1H), 4.81 (d, J = 7.0 Hz, 1H), 4.99 (m, 1H), 5.87 (d, J = 7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.4, 60.5, 108.1, 113.5, 140.6, 147.8.

Preparation of MS-Free BINOL–Ti Complex (MS(−)-1a). A 200-mL three-necked, round-bottomed flask equipped with a magnetic stirring bar and argon inlet was charged with powdered molecular sieves 4A (15.0 g), (*R*)-(+)-binaphthol (859 mg, 3.00 mmol), and 90 mL of dichloromethane. After the mixture was stirred for 20 min at ambient temperature, diisopropoxytitanium dichloride (711 mg, 3.00 mmol) was added into the resulting suspension in one portion. At this point, the reaction mixture became a red-brown suspension. After being stirred for 1 h at that temperature, the resultant suspension was transferred with a cannula to a centrifugating tube capped with a rubber septum. By centrifugation at 4000 rpm for 20 min, molecular sieves were sedimented. The resultant supernatant was transferred with a cannula to a 200-mL two-necked, round-bottomed flask equipped with a distillation apparatus and magnetic stirring bar. The stirred mixture was evaporated at 0 °C under reduced pressure to give a deep reddish residue. The resulting residue was suspended by adding 50 mL of pentane. The suspension was stirred for 20 min, and pentane was then decanted with a syringe. The resulting precipitate was vacuum-dried to give the binaphthol–titanium complex in 90–95% yield and used as a catalyst.[27]

General Procedure for the Diels–Alder Reaction Catalyzed by the MS-Free BINOL–Ti Complex. The MS-free BINOL–Ti complex (MS(−)-**1a**) (43 mg, 0.1 mmol) was dissolved in toluene (3 mL). Freshly distilled methacrolein (**6**) (140 mg, 2 mmol) and a solution of freshly distilled 1-acetoxy-1,3-butadiene (**4c**) (178 mg, 1.6 mmol) (*E*/*Z* = 63:37) in toluene (1 mL) were added into the catalyst solution at room temperature. After being stirred for 18 h at that temperature, the resultant mixture was diluted with ether (5 mL) and quenched by the addition of saturated $NaHCO_3$ (10 mL). The solution was filtered through a pad of Celite and Florisil, and the filtrate was extracted three times with ether (totally 15 mL). The combined organic layer was washed with brine. The extract was then dried over $MgSO_4$ and evaporated under reduced pressure. Separation by silica gel chromatography (hexane/ethyl acetate = 5:1) gave 2-acetoxy-1-methyl-3-cyclohexenecarbaldehyde (**7c**) in 63% yield.

2-Methoxy-1-methyl-3-cyclohexenecarbaldehyde (7a): $[\alpha]^{21}_D$ +116.0° (*c* 0.98, $CHCl_3$) (93:7 *endo*/*exo* mixture, 85% ee 1*R*,2*S*); IR (neat) 3412, 2936, 1707, 1460, 1367, 1093, 721 cm^{-1}; HRMS for $C_9H_{14}O_2$ calcd 154.0994, found 154.0983. *endo*-**7a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.50–1.62 (m, 1H), 1.92–2.25 (m, 3H), 3.39 (s, 3H), 3.64 (bs, 1H), 5.87–5.99 (m, 2H), 9.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0, 22.3, 25.6, 48.5, 57.2, 79.0, 124.1, 131.3, 205.7. *exo*-**7a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.40–2.30 (m, 4H), 3.37 (s, 3H), 3.98 (bs, 1H), 5.80 (bs, 2H), 9.59 (s, 1H).

2-[(*N*,*N*-Dimethylcarbamoyl)oxy]-1-methyl-3-cyclohexenecarbaldehyde (7b): $[\alpha]^{25}_D$ +165.3° (*c* 1.72, $CHCl_3$) (99.4:0.6 *endo*/*exo* mixture, 85% ee 1*R*,2*S*); IR (neat) 3220, 2940, 1707, 1493, 1450, 1394, 1243, 1191, 1048, 942, 770 cm^{-1}; HRMS for $C_{11}H_{17}NO_3$ calcd 211.1209, found 211.1236. *endo*-**7b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.66 (dt, J = 13.5, 5.9 Hz, 1H), 1.96 (dt, J = 13.5, 6.8 Hz, 1H), 2.08–2.28 (m, 2H), 2.83 (s, 3H), 2.91 (s, 3H), 5.19 (bs, 1H), 5.84 (ddt, J = 10.1, 3.7, 1.9 Hz, 1H), 5.94 (ddt, J = 10.1, 1.0, 3.5 Hz, 1H), 9.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 21.7, 25.5, 35.5, 36.1, 47.7, 72.4, 124.4, 131.4, 155.4, 204.1. *exo*-**7b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.50–1.60 (m, 1H), 1.80–1.95 (m, 1H), 2.10–2.30 (m, 2H), 2.83 (s, 3H), 2.89 (s, 3H), 5.48 (bs, 1H), 5.68–5.76 (m, 1H), 5.81–5.89 (m, 1H), 9.52 (s, 1H).

2-Acetoxy-1-methyl-3-cyclohexenecarbaldehyde (7c): $[\alpha]^{25}_D$ +239.3° (*c* 0.83, $CHCl_3$) (99:1 *endo*/*exo* mixture, 94% ee 1*R*,2*S*); IR (neat) 3442, 2940, 1717, 1435, 1375, 1236, 1019, 729 cm^{-1}; HRMS for $C_{10}H_{14}O$ calcd 182.0943, found 182.0922. *endo*-**7c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ

(26) Banks, R. E.; Miller, J. A.; Nunn, M. J.; Stanley, P.; Weakley, T. J. R.; Ullah, Z. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1096.

(27) ^{1}H NMR analysis of the titanium complex indicates the presence of *i*-PrOH in the form of $(C_{20}H_{12}O_2TiCl_2)_2$·*i*-PrOH.

1.08 (s, 3H), 1.66 (dt, J = 13.2, 5.6 Hz, 1H), 1.98 (dt, J = 13.2, 6.8 Hz, 1H), 2.05 (s, 3H), 2.08–2.28 (m, 2H), 5.26–5.31 (m, 1H), 5.78 (ddt, J = 9.9, 3.8, 2.0 Hz, 1H), 5.97 (ddt, J = 9.9, 3.6, 1.1 Hz, 1H), 9.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 20.7, 21.8, 25.5, 47.4, 71.7, 123.4, 132.1, 170.3, 203.9. ***exo*-7c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.55–1.65 (m, 1H), 1.80–2.20 (m, 1H), 2.07 (s, 3H), 5.57 (bs, 1H), 5.66–5.74 (m, 1H), 5.86–5.94 (m, 1H), 9.49 (s, 1H).

2-Acetoxy-1,4-dimethyl-3-cyclohexenecarbaldehyde (7d): $[\alpha]^{22}_D$ −151.0° (c 1.00, $CHCl_3$) (89:11 *endo*/*exo* mixture, 80% ee 1*S*,2*R*); IR (neat) 3588, 2920, 2364, 1734, 1448, 1375, 1238, 1021 cm^{-1}. ***endo*-7d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.72 (s, 3H), 2.02 (s, 3H), 1.60–2.10 (m, 4H), 5.21–5.26 (m, 1H), 5.47–5.54 (m, 1H), 9.64 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.6, 21.1, 23.2, 25.6, 26.8, 47.5, 72.6, 118.2, 140.9, 170.6, 204.3. ***exo*-7d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 3H), 1.60–2.18 (m, 4H), 1.69 (s, 3H), 2.05 (s, 3H), 5.43–5.58 (m, 2H), 9.46 (s, 1H).

Determination of the Enantioselectivity of the Diels–Alder Products (7a–d). The enantioselectivity of the Diels–Alder products (**7a–d**) was determined by ^{1}H NMR analysis of the corresponding (*R*)-MTPA esters of 6-(hydroxymethyl)-2-cyclohexene derivatives which were obtained by the reduction of **7a–d** with lithium aluminium hydride.

Reduction of the Diels–Alder Products: (1*S*,6*S*)-6-(Hydroxymethyl)-6-methyl-2-cyclohexenol. To a suspension of lithium aluminium hydride (105 mg) in ether (4 mL) was added an ether (1 mL) solution of 2-acetoxy-1-methyl-3-cyclohexenecarbaldehyde (**7c**) (115 mg, 0.63 mmol) at 0 °C. After the mixture was stirred for 2 h at room temperature, saturated Na_2SO_4 was carefully added to the reaction mixture. Vigorous stirring was continued until white precipitate was observed. The solution was filtered and evaporated under reduced pressure. Purification by silica gel chromatography (ether) gave 6-(hydroxymethyl)-6-methyl-2-cyclohexenol in 81% yield: $[\alpha]^{29}_D$ +104.1° (c 0.95, $CHCl_3$) (99:1 *cis*/*trans* mixture, 94% ee); IR (neat) 3370, 2930, 1727, 1653, 1435, 1377, 1243, 1021, 758 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.25 (dt, J = 13.2, 5.1 Hz, 1H), 1.71 (dt, J = 13.2, 7.6 Hz, 1H), 2.02–2.11 (m, 2H), 2.34 (bs, 2H), 3.51 (d, J = 11.0 Hz, 1H), 3.66 (d, J = 11.0 Hz, 1H), 3.89 (dd, J = 4.2, 0.7 Hz, 1H), 5.76 (ddt, J = 9.9, 4.2, 2.1 Hz, 1H), 5.86 (ddt, J = 9.9, 0.7, 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 22.3, 26.4, 37.2, 70.2, 72.3, 127.8, 130.2.

(1*S*,6*S*)-1-Methoxy-6-(hydroxymethyl)-6-methyl-2-cyclohexene: $[\alpha]^{21}_D$ +115.5° (c 0.91, $CHCl_3$) (93:7 *cis*/*trans* mixture, 85% ee); IR (neat) 3450, 2180, 1647, 1093 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3H), 1.29 (dt, J = 13.5, 5.0 Hz, 1H), 1.79 (dt, J = 13.5, 6.9 Hz, 1H), 2.02–2.12 (m, 2H), 3.42 (s, 3H), 3.44–3.50 (m, 2H), 3.61 (d, J = 11.0 Hz, 1H), 5.82–5.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 22.5, 27.6, 37.2, 57.0, 70.1, 82.9, 124.3, 130.9.

(1*R*,6*R*)-6-(Hydroxymethyl)-3,6-dimethyl-2-cyclohexenol: $[\alpha]^{24}_D$ −55.1° (c 1.10, $CHCl_3$) (89:11 *cis*/*trans* mixture, 80% ee); IR (neat) 3292, 2922, 1435, 1379, 1021, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.17–1.28 (m, 1H), 1.70 (bs, 3H), 1.70–1.82 (m, 1H), 1.94–2.02 (m, 2H), 2.27 (bs, 2H), 3.51 (d, J = 11.0 Hz, 1H), 3.60 (d, J = 11.0 Hz, 1H), 3.85 (dm, J = 4.6 Hz, 1H), 5.49 (dq, J = 4.6, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8, 23.4, 26.3, 27.3, 36.9, 70.6, 73.0, 122.3, 138.6.

Determination of the Absolute Stereochemistry of 7b and 7c. The absolute stereochemistry of **7b** and **7c** was determined after conversion to **8** via two-step standard operations.

Hydrogenation of 6-(Hydroxymethyl)-6-methyl-2-cyclohexenol: (1*S*,2*S*)-2-(Hydroxymethyl)-2-methylcyclohexanol (8). 6-(Hydroxymethyl)-6-methyl-2-cyclohexenol (57 mg, 0.40 mmol) obtained as above and was reduced at room temperature in the presence of 5% Pd-C (5 mg) in ethanol (2.5 mL) under a H_2 atmosphere. The resultant solution was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure. Purification by silica gel chromatography (ether) gave 2-(hydroxymethyl)-2-methylcyclohexanol (**8**) in 99% yield: $[\alpha]^{21}_D$ + 16.2° (c 2.95, $CHCl_3$) (99:1 *cis*/*trans* mixture, 94% ee) (lit.[14] $[\alpha]^{20}_D$ +3° (c 1, CH_2Cl_2) (20% ee 1*S*,2*S*)); IR (neat) 3288, 2938, 1742, 1454, 1377, 1245, 1048, 733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.05–1.15 (m, 1H), 1.30–1.50 (m, 3H), 1.55–1.85 (m, 4H), 3.14 (bs, 2H), 3.40 (d, J = 11.0 Hz, 1H), 3.61 (dd, J = 7.4, 3.4 Hz, 1H), 3.88 (d, J = 11.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.1, 22.3, 22.5, 30.5, 32.2, 38.1, 69.9, 77.0.

NMR Studies on the Effect of MS. To a suspension of activated powder molecular sieves 4A (250 mg) in CD_2Cl_2 (1.5 mL) was added diisopropoxytitanium dichloride (12 mg, 0.05 mmol) and (*R*)-(+)-binaphthol (15 mg, 0.05 mmol) at room temperature under an argon atmosphere. After the resulting suspension was stirred for 1 h at room temperature, juglone (**3a**) (18 mg, 0.10 mmol) was added as one portion. After being stirred for 2 h at that temperature, the resultant suspension was transferred with a cannula to a centrifuging tube capped with a rubber septum. With centrifugation at 4000 rpm for 20 min, molecular sieves were sedimented. The resultant supernatant was placed with a syringe in a well-dried 5-mm NMR tube, replacing argon. All FID collections at the appropriate timing were stored on a floppy diskette.

Diels–Alder Reaction of Juglone with 1-Acetoxy-1,3-butadiene: 8-Hydroxy-1-acetoxy-1(*S*),4,4a(*R*),9a(*R*)-tetrahydroanthraquinone (5a). To a solution of MS-free (*S*)-BINOL–Ti complex (0.1 mmol) and juglone (**3a**) (174 mg, 1 mmol) in dichloromethane (3 mL) was added a solution of freshly distilled 1-acetoxy-1,3-butadiene (**4c**) (356 mg, 3.18 mmol) (*E*/*Z* = 63:37) in dichloromethane (1 mL) at room temperature. The solution was stirred for 19 h at that temperature. The resultant mixture was used for the next reduction due to the instability of **5a**.

8,9-Dihydroxy-1-acetoxy-10-oxo-1(*S*),4,4a(*R*),9(*S*),9a(*S*),10-hexahydroanthracene (5a′). To the reaction mixture obtained above was added toluene (5.6 mL) and methanol (3.1 mL). After the mixture was cooled to 0 °C, $NaBH_4$ (40 mg, 1.06 mmol) was added into the mixture in portions over 5 min. After being stirred for 15 min at that temperature, the mixture was diluted with ether (10 mL) and quenched by the addition of 0.35 N $NaHSO_4$ (10 mL). The solution was filtered through a pad of Celite and Florisil, and the filtrate was extracted three times with ether (totally 30 mL). The combined organic layer was washed twice with brine (totally 30 mL). The extract was then dried over $MgSO_4$ and evaporated under reduced pressure. Separation by silica gel chromatography (hexane/ethyl acetate = 3:1) gave 8,9-dihydroxy-1-acetoxy-10-oxo-1(*S*),4,4a(*R*),9(*S*),9a(*S*),10-hexahydroanthracene (**5a′**) in 86% yield (96% ee): mp 173–174 °C; $[\alpha]^{25.5}_D$ +200.8° (c 0.60, $CHCl_3$); IR (KBr) 3400, 2854, 1736, 1700, 1460, 1375, 1257, 1019, 708 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 2.29 (dddm, J = 19.0, 6.9, 2.6 Hz, 1H), 2.94–3.03 (m, 2H), 3.31 (dd, J = 19.0, 4.7 Hz, 1H), 5.49 (dd, J = 6.0, 3.0 Hz, 1H), 5.50 (d, J = 12.0 Hz, 1H), 5.60 (dd, J = 12.0, 5.5 Hz, 1H), 5.72 (ddm, J = 9.9, 6.6 Hz, 1H), 6.15 (ddd, J = 9.9, 4.7, 2.6 Hz, 1H), 7.08 (dd, J = 8.1, 1.3 Hz, 1H), 7.25 (dd, J = 8.1, 7.7 Hz, 1H), 7.56 (dd, J = 7.7, 1.3 Hz, 1H), 9.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 23.4, 42.4, 44.9, 64.7, 69.7, 117.7, 121.9, 122.2, 125.4, 129.1, 133.0, 136.4, 156.9, 174.5, 195.4.

Determination of the Absolute Stereochemistry of 5a. The absolute stereochemistry was deduced from the optical rotation after conversion to **5a″**.

1-Acetoxy-8,9-(isopropylidenedioxy)-10-oxo-1(*S*),4,4a(*R*),9(*S*),9a-(*S*),10-hexahydroanthracene (5a″). A crystalline of *p*-toluenesulphonic acid monohydride was added to a solution of 8,9-dihydroxy-1-acetoxy-10-oxo-1(*S*),4,4a(*R*),9(*S*),9a(*S*),10-hexahydroanthracene (**5a′**) (28 mg, 0.097 mmol) and 2,2-dimethoxypropane (0.1 mL) in dimethylformamide (1 mL). After the reaction mixture was stirred for 28 h at room temperature, the reaction was quenched by addition of saturated $NaHCO_3$ (5 mL) and the mixture extracted three times with ether (totally 15 mL). The combined organic layer was washed twice with brine (totally 10 mL). The extract was then dried over $MgSO_4$ and evaporated under reduced pressure. Purification by silica gel chromatography (hexane/ethyl acetate = 3:1) gave 1-acetoxy-8,9-(isopropylidenedioxy)-10-oxo-1(*S*),4,4a(*R*),9(*S*),9a(*S*),10-hexahydroanthracene (**5a″**) in 97% yield: mp 200–201 °C; $[\alpha]^{25}_D$ +371.6° (c 0.75, CH_2Cl_2) (96% ee) (lit.[8a] $[\alpha]^{22}_D$ +344° (c 1.0, CH_2Cl_2) (>98% ee 1(*S*),4a(*R*),9(*S*),9a(*S*))); IR (KBr) 3400, 1738, 1678, 1636, 1278, 1236 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.59 (s, 3H), 1.64 (s, 3H), 2.25 (dm, J = 18.7 Hz, 1H), 2.95–3.09 (m, 2H), 3.32 (dd, J = 18.7, 4.9 Hz, 1H), 5.42 (d, J = 5.8 Hz, 1H), 5.52–5.58 (m, 1H), 5.71 (dm, J = 10.0 Hz, 1H), 5.97 (ddd, J = 10.0, 4.9, 2.3 Hz, 1H), 6.97 (d, J = 7.8 Hz, 1H), 7.23 (dd, J = 7.8, 7.1 Hz, 1H), 7.60 (d, J = 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 23.4, 28.3, 42.1, 63.3, 65.9, 101.2, 118.1, 120.8, 123.8, 125.0, 127.9, 130.9, 131.6, 150.2, 169.4, 195.5.

Hetero-Diels–Alder Reaction Catalyzed by the MS-Free BINOL–Ti Complex. The hetero-Diels–Alder reaction was carried out in dichloromethane according to the general procedure for the Diels–Alder reaction.

6-Carbomethoxy-2-methoxy-5,6-dihydro-2*H*-pyran (9a): IR (neat) 2360, 1740, 1660, 1440, 1400, 1050, 960, 820, 720 cm^{-1}; HRMS for $C_8H_{12}O_4$ calcd 172.0735, found 172.0723. ***cis*-9a**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.3–2.6 (m, 1H), 3.49 (s, 3H), 3.77 (s, 3H), 4.41 (t, J = 6.0 Hz, 1H), 5.03 (m, 1H), 5.69 (m, 1H), 6.04 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.0, 52.2, 55.7, 69.6, 97.4, 126.4, 128.1, 171.9; capillary GC (ULBON HR-20M, column temperature 100 °C, detection FID) t_R of *cis*-isomer 31.3 min and *trans*-isomer 27.0 min. ***trans*-9a**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.3–2.4 (m, 1H), 3.46 (s, 3H), 3.81 (s, 3H), 4.52 (dd,

J = 7.4, 8.4 Hz, 1H), 4.99 (m, 1H), 5.77 (m, 1H), 6.04 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.5, 52.4, 55.8, 65.9, 96.1, 125.7, 127.7, 172.2.

6-Carbomethoxy-5,6-dihydro-2-methoxy-5-methyl-2*H*-pyran (9e). 2,5-*cis*-5,6-*cis*-9e: $[\alpha]^{23}_D$ +112.8° (*c* 0.88, $CHCl_3$) (93% ee); IR (neat) 2940, 1740, 1440, 1030, 910, 780, 710 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.04 (d, J = 6.8 Hz, 3H), 2.52 (m, 1H), 3.53 (s, 3H), 3.79 (s, 3H), 4.43 (d, J = 3.6 Hz, 1H), 5.16 (m, 1H), 5.62 (m, 1H), 6.02 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.8, 31.7, 52.1, 55.3, 74.2, 99.4, 126.4, 135.2, 170.8; MS for $C_9H_{14}O_4$ calcd 186.0892, found 186.

2,5-*cis*-5,6-*trans*-9e: IR (neat) 2940, 1740, 1440, 1030, 910, 780, 710 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.05 (d, J = 7.2 Hz, 3H), 2.55 (m, 1H), 3.45 (s, 3H), 3.82 (s, 3H), 4.09 (d, J = 10.4 Hz, 1H), 4.95 (m, 1H), 5.73 (m, 1H), 5.81 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.3, 32.0, 52.4, 55.8, 72.9, 95.6, 124.4, 134.9, 170.8; MS for $C_9H_{14}O_4$ calcd 186.0892, found 186.

6-Carbomethoxy-5,6-dihydro-3,5-dimethyl-2-methoxy-2*H*-pyran (9f). 2,5-*cis*-5,6-*cis*-9f: $[\alpha]^{29}_D$ +80.8° (*c* 1.07, $CHCl_3$) (>95% ee); IR (neat) 1750, 1450, 1380, 1210, 1130, 1080, 930 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.01 (d, J = 7.0 Hz, 3H), 1.66 (m, 3H), 2.46 (m, 1H), 3.48 (s, 3H), 3.78 (s, 3H), 4.38 (d, J = 3.5 Hz, 1H), 5.04 (m, 1H), 5.73 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.8, 17.5, 31.8, 52.1, 54.5, 74.4, 101.3, 130.1, 132.9, 171.0; MS for $C_{10}H_{16}O_4$ calcd 200.1049, found 200. **2,5-*cis*-5,6-*trans*-9f:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.02 (d, J = 7.1 Hz, 3H), 1.72 (m, 3H), 2.51 (m, 1H), 3.46 (s, 3H), 3.81 (s, 3H), 4.03 (d, J = 10.5 Hz, 1H), 4.73 (m, 1H), 5.43 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.6, 18.8, 32.4, 52.3, 56.1, 72.9, 98.8, 128.9, 131.7, 171.9; MS for $C_{10}H_{16}O_4$ calcd 200.1049, found 200.

6-Carbomethoxy-5,6-dihydro-2-methoxy-4-methyl-2*H*-pyran (9g). 2,6-*cis*-9g: $[\alpha]^{23}_D$ +42.9° (*c* 1.00, $CHCl_3$) (*cis*/*trans* = 92:8 mixture, 71% ee for 2,6-*cis* isomer); IR (neat) (*cis*/*trans* mixture) 1740, 1440, 1220, 1080, 1060, 1020, 950, 750 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.78 (m, 3H), 2.25 (m, 1H), 2.40 (m, 1H), 3.48 (s, 3H), 3.77 (s, 3H), 4.39 (dd, J = 5.5, 6.0 Hz, 1H), 5.00 (m, 1H), 5.42 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.8, 30.7, 52.4, 55.6, 69.7, 97.9, 120.4, 136.7, 172.3; MS for $C_9H_{14}O_4$ calcd 186.0892, found 186. **2,6-*trans*-9g:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.77 (m, 3H), 2.15 (m, 1H), 2.30 (m, 1H), 3.45 (s, 3H), 3.80 (s, 3H), 4.53 (dd, J = 4.4, 11.0 Hz, 1H), 4.99 (m, 1H), 5.50 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.7, 32.2, 52.4, 55.7, 66.3, 96.6, 119.9, 136.7, 172.3; MS for $C_9H_{14}O_4$ calcd 186.0892, found 186.

Determination of Relative Stereochemistry of 6-Carbomethoxy-5,6-dihydro-2-methoxy-5-methyl-2*H*-pyran (9e). Relative stereochemistry was determined on the basis of ^{1}H NMR analysis (coupling constants) after conversion to tetrahydropyrans as follows.

Hydrogenation of the Hetero-Diels–Alder Products: 6-Carbomethoxy-3,4,5,6-tetrahydro-2-methoxy-5-methyl-2*H*-pyran. A solution of dihydropyran (9e) in ethanol (5 mL) was stirred for 1 day at room temperature in the presence of PtO_2 (5 mg) under a H_2 atmosphere. The solution was then filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to give tetrahydropyran in 95% yield.

2,5-*cis*-5,6-*cis*-6-Carbomethoxy-3,4,5,6-tetrahydro-2-methoxy-5-methyl-2*H*-pyran: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, J = 6.9 Hz, 3H), 1.5–1.8 (m, 5H), 3.48 (s, 3H), 3.72 (s, 3H), 4.15 (d, J = 2.8 Hz, 1H), 4.29 (dd, J = 2.3, 8.7 Hz, 1H); IR (neat) 2940, 1760, 1440, 1130, 910, 830 cm^{-1}.

2,5-*cis*-5,6-*trans*-6-Carbomethoxy-3,4,5,6-tetrahydro-2-methoxy-5-methyl-2*H*-pyran: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (d, J = 6.9 Hz, 3H), 1.5–1.8 (m, 5H), 3.32 (s, 3H), 3.73 (s, 3H), 3.94 (d, J = 10.5 Hz, 1H), 4.75 (dd, J = 0.8, 2.3 Hz, 1H); IR (neat) 2940, 1760, 1440, 1130, 910, 830 cm^{-1}.

Determination of the Absolute Stereochemistry. The absolute configuration of 6-carbomethoxy-5,6-dihydro-2-methoxy-2*H*-pyran was determined after conversion to *trans*-3,4,5,6-tetrahydro-6-(hydroxymethyl)-2-methoxy-2*H*-pyran (**10**). Other hetero-Diels–Alder products were assigned by the similarity in shift pattern seen in the LIS-NMR analysis using (+)-Eu(dppm)$_3$.

5,6-Dihydro-6-(hydroxymethyl)-2-methoxy-2*H*-pyran. The obtained *cis*/*trans* mixture of 6-carbomethoxy-5,6-dihydro-2-methoxy-2*H*-pyran (100 mg, 94% ee for *cis*, >90% ee for *trans*, *cis*/*trans* = 78:22) was isomerized to *trans* major dihydropyran. To a solution of the dihydropyran in dichloromethane (1 mL) was added a solution of $ZnCl_2$ (10 mg) in dichloromethane (3 mL) at −15 °C. After the mixture was stirred for 2 h, the reaction was quenched with saturated $NaHCO_3$. The mixture was extracted twice with ether and washed with brine. The organic layer was evaporated under reduced pressure to give the 95% *trans* major dihydropyran. The crude material was used for the next steps without purification. To a suspension of lithium aluminium hydride (100 mg) in ether (3 mL) was added an ether (1 mL) solution of 6-carbomethoxy-5,6-dihydro-2-methoxy-2*H*-pyran (*cis*/*trans* = 5:95) at 0 °C. After the reaction mixture was stirred for 1 h at room temperature, saturated Na_2SO_4 was added carefully. Vigorous stirring was continued until white precipitate was observed. Decantation and evaporation gave 5,6-dihydro-6-(hydroxymethyl)-2-methoxy-2*H*-pyran. The crude dihydropyran was converted to tetrahydropyran without purification.

***cis*-5,6-Dihydro-6-(hydroxymethyl)-2-methoxy-2*H*-pyran:** IR (neat) (*cis*/*trans* mixture) 3380, 2890, 1660, 1400, 1100, 1050, 965 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.0–2.2 (m, 2H), 2.75 (br, 1H), 3.57 (s, 3H), 3.68 (m, 2H), 3.94 (m, 1H), 5.08 (bs, 1H), 5.66 (m, 1H), 6.01 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 25.9, 55.4, 65.6, 72.6, 97.7, 126.7, 129.0.

***trans*-5,6-Dihydro-6-(hydroxymethyl)-2-methoxy-2*H*-pyran:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.0–2.2 (m, 2H), 2.53 (br, 1H), 3.44 (s, 3H), 3.68 (m, 2H), 4.00 (m, 1H), 4.91 (bs, 1H), 5.75 (m, 1H), 6.03 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.1, 55.4, 65.3, 67.2, 95.9, 125.6, 128.2.

3,4,5,6-Tetrahydro-6-(hydroxymethyl)-2-methoxy-2*H*-pyran (10). A solution of 5,6-dihydro-6-(hydroxymethyl)-2-methoxy-2*H*-pyran (140 mg, 0.97 mmol) in ethanol (5 mL) was stirred for 1 day at room temperature in the presence of PtO_2 (5 mg) under a H_2 atmosphere. The solution was then filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to give 3,4,5,6-tetrahydro-6-(hydroxymethyl)-2-methoxy-2*H*-pyran (*cis*/*trans* = 5:95). Purification by silica gel column chromatography gave the pure *trans*-tetrahydropyran **10** in 65% yield from the *cis*/*trans* mixture of 6-carbomethoxy-5,6-dihydro-2-methoxy-2*H*-pyran (**9a**). ***trans*-10:** $[\alpha]^{20}_D$ −119.9° (*c* 1.07, benzene) (96% ee) (lit.[14] $[\alpha]^{20}_D$ +129.7° (*c* 4.3, benzene) (2*S*, 6*S*)); IR (neat) (*cis*/*trans* mixture) 3440, 1660, 1400, 1100, 1050 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2–2.0 (m, 6H), 2.6 (br, 1H), 3.37 (s, 3H), 3.5–3.6 (m, 3H), 4.76 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5, 26.7, 29.7, 54.6, 66.3, 69.5, 98.6. ***cis*-10:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2–2.0 (m, 6H), 2.6 (br, 1H), 3.51 (s, 3H), 3.5–3.6 (m, 3H), 4.37 (dd, J = 1.8, 9.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 26.4, 31.1, 56.3, 65.9, 76.8, 103.7.

Determination of the Enantioselectivity of the Hetero-Diels–Alder Products: ^{1}H NMR Shift Analysis (LIS-NMR Analysis). (+)-Eu(dppm)$_3$ was used as a chiral NMR shift reagent (30% w/v CCl_2FCClF_2 solution). A 15-μL sample of the hetero-Diels–Alder product was dissolved in $CDCl_3$ (0.4 mL) and transferred to an NMR tube. A 5-μL portion of (+)-Eu(dppm)$_3$ (30% w/v CCl_2FCClF_2 solution) was added to the α-methoxy ester sample. The mixture was shaken well, and the ^{1}H NMR spectrum was recorded. Additional shift reagent solutions were added in 5-μL portions until the methyl ether and methyl ester resonances showed baseline resolution of those from the two enantiomers. Totally 20–60 μL of the shift reagent solution should be required to achieve the desired shift.

Synthesis of the Lactone Portion of Compactin. In this reaction, the chiral titanium catalyst derived from (*S*)-BINOL was used to prepare the lactone with the desired absolute configuration.

5,6-Dihydro-6-(hydroxymethyl)-2-methoxy-2*H*-pyran was prepared as described above.

6-((Benzyloxy)methyl)-5,6-dihydro-2-methoxy-2*H*-pyran. To a suspension of sodium hydride (2 mmol) (stripped by dry hexane before used) in tetrahydrofuran (5 mL) was added a tetrahydrofuran (1 mL) solution of 5,6-dihydro-6-(hydroxymethyl)-2-methoxy-2*H*-pyran (1.5 mmol, 216 mg (*cis*/*trans* = 87:13)) at room temperature. After being refluxed for 2 h, the reaction mixture was cooled to room temperature and benzyl bromide (268 μL, 2.0 mmol) was added. The resultant mixture was refluxed for 30 min and poured into water (10 mL) and ice (*ca.* 5 g). Usual workup followed by column chromatography gave the benzyl ether in quantitative yield (*cis*/*trans* = 87:13): IR (neat) 2930, 1660, 1190, 1120, 960, 740, 700 cm^{-1}; HRMS for $C_{14}H_{18}O_3$ calcd 234.1256, found 234.1260. ***cis*-6-((benzyloxy)methyl)-5,6-dihydro-2-methoxy-2*H*-pyran:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.0–2.2 (m, 2H), 3.48 (s, 3H), 3.6 (m, 2H), 4.05 (m, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 5.05 (m, 1H), 5.66 (m, 1H), 5.96 (m, 1H), 7.3 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.9, 55.4, 71.2, 72.6, 73.6, 97.7, 127.2, 127.9, 128.0, 128.6, 128.7, 138.7. ***trans*-6-((benzyloxy)methyl)-5,6-dihydro-2-methoxy-2*H*-pyran:** ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.9–2.3 (m, 2H), 3.44 (s, 3H), 3.6 (m, 2H), 4.1 (m, 1H), 4.58 (s, 2H), 4.91 (m, 1H), 5.75 (m, 1H), 6.00 (m, 1H), 7.3 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 55.3, 65.8, 73.5, 96.0, 125.7, 127.9, 128.0, 128.7, 129.0, 138.7.

6-((Benzyloxy)methyl)-5,6-dihydro-2*H*-pyran-2-one (11). A mixture of 5,6-dihydro-6-((benzyloxy)methyl)-2-methoxy-2*H*-pyran (*cis*/*trans* = 87:13) (135 mg, 0.5 mmol), MoO_3 (15 mg), and 30% H_2O_2 (5 mL) was stirred at room temperature for 16 h. The reaction was then complete. The product was extracted with chloroform. The extract was dried over

$MgSO_4$ and concentrated, and the crude oily product (120 mg) was obtained. A mixture of crude peroxide and acetic anhydride/pyridine (1:4 mixture) was kept overnight at room temperature and then concentrated under reduced pressure. The crude product was purified by silica gel chromatography with a hexane/ether (9:1) mixture to give the pure lactone **11** in 62% yield without any loss of enantiomeric purity: $[\alpha]^{23}_D$ −110.2° (*c* 0.69, $CHCl_3$) (lit.[19a] $[\alpha]^{24}_D$ −115.1° (*c* 1.0 $CHCl_3$) (6*S*)); IR (neat) 2920, 1720, 1250, 1055, 820, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.40 (m, 1H), 2.55 (m, 1H), 3.69 (d, *J* = 5.8 Hz, 1H), 4.5–4.7 (m, 3H), 6.02 (ddd, *J* = 1.2, 3.8, 10.8 Hz, 1H), 6.90 (ddd, *J* = 2.6, 5.8, 10.8 Hz, 1H), 7.3 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.3, 71.0, 73.8, 76.8, 121.5, 128.1, 128.2, 128.8, 138.0, 145.5, 164.3; HRMS for $C_8H_{12}O_4$ calcd 172.0735, found 172.0723.

Linear *vs* Positive Nonlinear Effects. A. Preparation of Catalyst Solution. 1. Mixing of (*R*)- and (*S*)-MS-Free BINOL–Ti Complexes. The catalyst solution (50% ee) was prepared as follows. (*R*)- (33 mg) and (*S*)-MS-free (11 mg) BINOL–Ti complex (**1a**) (totally 44 mg, 0.1 mmol) were dissolved in 3 mL of toluene, and the Diels–Alder reaction was carried out as described above.

2. Mixing of (*R*)- and (±)-MS-Free BINOL–Ti Complexes. The catalyst solution (*x*% ee: *y* mg/44 mg × 100) was prepared as described above using (*R*)- (*y* mg) and (±)-MS-free (*z* mg) BINOL–Ti complex (**1a**) (totally 44 mg, 0.1 mmol: *y* mg + *z* mg = 44 mg) (Table 3).

B. Kinetic Studies. To a solution of (*R*)- or (±)-MS-free BINOL–Ti complex (11 mg, 0.025 mmol) in an NMR tube at room temperature were transferred methacrolein (**6**) (35 mg, 0.25 mmol) and 1-acetoxy-1,3-butadiene (**4c**) (44.5 mg, 0.40 mmol) in toluene-d_8 (1 mL), and ^1H NMR spectra were recorded. The spectra showed a decrease in integration at δ 7.62 (vinylic proton of **4c**) along with an increase in integration at δ 9.75 (aldehydic proton of **7c**) (Figure 2).

Acknowledgment. We are grateful to Professor Barry B. Snider of Brandeis University for his comments and useful discussions.