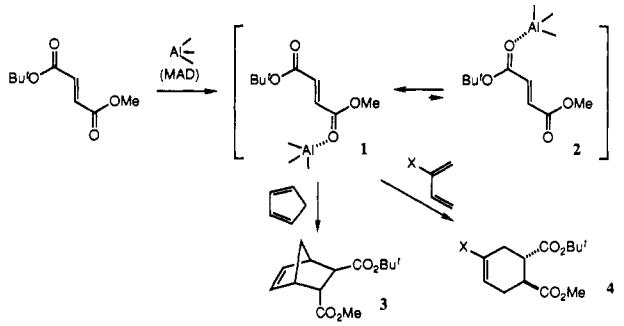
Discrimination of Two Different Ester Carbonyls with Methylaluminum Bis(2,6-di-*tert*-butyl-4-methylphenoxide): Application to the Regiocontrolled and Stereocontrolled Diels-Alder Reaction of Unsymmetrical Fumarates

Keiji Maruoka, Susumu Saito, and Hisashi Yamamoto*

Department of Applied Chemistry, Nagoya University Chikusa, Nagoya 464-01, Japan

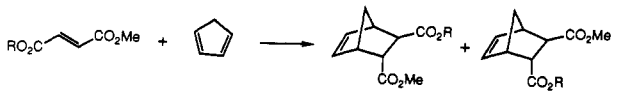
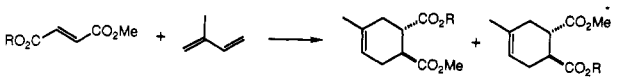
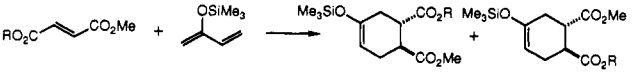
Received October 9, 1991

The Diels-Alder reaction is undoubtedly the best known and most thoroughly investigated of all cycloaddition reactions because of sustained interest in its mechanism and its exceptionally broad application to regio- and stereodefined synthesis.[1] In particular, the greater comprehension of the steric and electronic effects governing this reaction has led to the utilization of specifically functionalized dienes and dienophiles to produce hitherto unattainable substitution patterns regio- and stereoselectively, thereby expanding its utility in complex natural product synthesis. Reported herein is the remarkably high regio- and stereochemical control in the Diels-Alder reaction of unsymmetrical fumarates based on the discrimination of two different fumarate carbonyls by selective complexation with the exceptionally bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD).[2]



Reaction of *tert*-butyl methyl fumarate with 1.1 equiv of MAD in CH_2Cl_2 at −78 °C gave rise to the organoaluminum-fumarate complex **1** exclusively, the structure of which was rigorously established by low-temperature ^{13}C NMR spectroscopy.[3] The Diels-Alder reaction of complex **1** with cyclopentadiene at −78 °C resulted in stereoselective formation of the cycloadduct **3** (86% yield) almost exclusively.[4] In addition, treatment of complex **1** with 2-substituted 1,3-butadiene (X = Me, $OSiMe_3$) afforded cycloadduct **4** (X = Me, $OSiMe_3$) with high regioselectivity.[5] In marked contrast, the cycloadditions with Et_2AlCl as an ordinary Lewis acid were found to have a total lack of selectivity. These and other examples are listed in Table I. Several characteristic features of the reaction have been noted. Good to excellent selectivity is observed by pairing *tert*-butyl ester with methyl ester. Even ethyl and methyl esters can be discriminated moderately

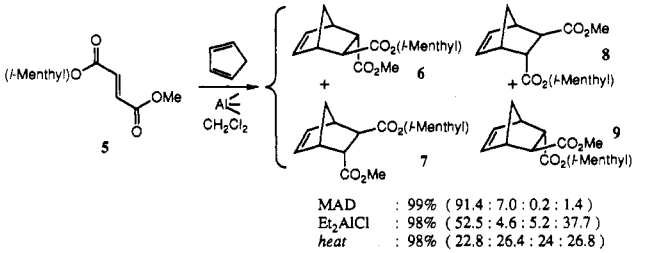
Table I. Diels-Alder Reaction of Unsymmetrical Fummarates[a]

entry	fumarate	Lewis acid	conditns (°C, h)	yield,[b] % (ratio)[c]
				
1	R = *t*-Bu	MAD	−78, 1	86 (99:1)
2		MAD[d]	−78, 1	93 (99:1)
3		Et_2AlCl	−78, 1	65 (46:54)
4		heat[d]	80, 5	89 (48:52)
5	R = *i*-Pr	MAD	−78, 1	90 (89:11)
6		Et_2AlCl	−78, 1	87 (45:55)
7	R = Et	MAD	−78, 4	66 (71:29)
8		MAD[d]	−78, 2.5	98 (71:29)
9		Et_2AlCl	−78, 1	89 (48:52)
				
10	R = *t*-Bu	MAD	−20, 130	51 (86:14)
11		MAD[d]	−20, 99	60 (80:20)
12		Et_2AlCl	−20, 24	52 (56:44)
13		heat[d]	120, 11	49 (44:56)
14	R = *i*-Pr	MAD	0, 3; 25, 9	79 (52:48)
15		Et_2AlCl	0, 2	34 (41:59)
				
16	R = *t*-Bu	MAD	−20, 50	48 (99:1)
17		MAD[d]	−20, 72	56 (83:17)
18		Et_2AlCl	−20, 42.5	19 (56:44)
19		heat[d]	120, 10	46 (52:48)

[a] Unless otherwise noted, the Diels-Alder reaction of fumarate with diene was carried out with 1.1-2 equiv of Lewis acid in CH_2Cl_2. [b] Isolated yield. [c] Determined by capillary GLC and/or 500-MHz ^1H NMR analysis. [d] In toluene.

with MAD (entries 7 and 8). Dichloromethane solvent produces higher regioselectivity than nonpolar toluene (entries 10 and 16 vs 11 and 17). Use of excess MAD (2-3 equiv) for the cycloadditions gives similar results in yield and selectivity. Various cycloadducts from *tert*-butyl methyl fumarate are synthetically quite useful, since either the *tert*-butyl or methyl ester can be selectively cleaved under acidic or basic conditions.[6] For example, treatment of cycloadduct **4** (X = Me) with CF_3CO_2H in CH_2Cl_2 at room temperature gave the methoxycarbonyl acid in 99% yield, whereas basic hydrolysis of **4** (X = Me) with K_2CO_3 in MeOH at 60 °C afforded the *tert*-butoxycarbonyl acid in 76% yield.

Another striking feature of the present MAD-mediated chemistry is the asymmetric Diels-Alder reaction of *l*-menthyl methyl fumarate (**5**).[7] For example, the asymmetric Diels-Alder reaction of **5** with cyclopentadiene (2 equiv) in CH_2Cl_2 at −78 °C under the influence of MAD gave stereoisomeric cycloadducts **6-9** in a ratio of 91.4:7.0:0.2:1.4. This means that the cycloaddition proceeds in 86% de with an *endo*/*exo*-methoxycarbonyl ratio of



98.4:1.6.[8] In contrast, Et_2AlCl-catalyzed cycloaddition under similar conditions gave 80% de with endo:exo = 57:43. Conse-

(1) Recent reviews: (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: New York, 1990. (b) Fringuelli, F.; Taticchi, A.; Wenkert, E. *Org. Prep. Proced. Int.* **1990**, *22*, 131. (c) Okamura, W. H.; Cuetin, M. L. *Synlett.* **1990**, 1. (d) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987. (e) Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873.

(2) Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588.

(3) The 125-MHz ^{13}C NMR measurement of *tert*-butyl methyl fumarate-MAD complex **1** in $CDCl_3$ at −50 °C showed that the original signal of methoxycarbonyl at δ 165.7 shifted downfield to δ 173.3, whereas the signal of *tert*-butoxycarbonyl appeared at δ 162.0 compared to the original peak at δ 164.0. Further addition of an additional 1 equiv of MAD resulted in the shift of the methoxycarbonyl and *tert*-butoxycarbonyl signals at δ 173.3 and 162.0 to δ 171.3 and 169.8, respectively.

(4) The stereochemistry of this and isomeric cycloadducts was established by iodolactonization of these adducts.

(5) The regiochemistry of **4** (X = Me) was determined by its iodolactonization, in which only γ-lactone was formed.

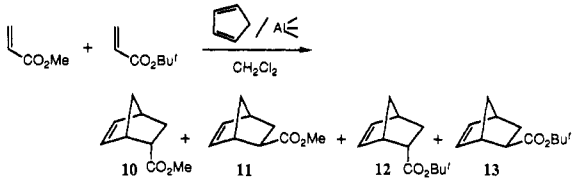
(6) Greene, T. W. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1981.

(7) Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* **1984**, *106*, 3806.

0002-7863/92/1514-1089$03.00/0

quently, MAD can be utilized both as an effective Lewis acid for endo selectivity and as a stereocontroller for asymmetric induction.

Furthermore, chemoselective Diels–Alder reaction of a mixture of *tert*-butyl and methyl acrylates with cyclopentadiene appears feasible in the presence of MAD. Here, only small amounts of the *tert*-butyl acrylate–cyclopentadiene endo adduct **12** were detected (ratio of **10**–**13**, 94:3:3:0), indicating the virtually complete discrimination of two different acrylate carbonyls with MAD.



MAD	: 95% (94 : 3 : 3 : 0)
Et_2AlCl	: 72% (32 : 1 : 67 : 0)
heat	: 88% (43 : 20 : 28 : 9)

In conclusion, the exceptionally bulky MAD, in addition to its Lewis acidic character, has been proven to play a crucial role in synthetically promising discrimination of two different fumarate carbonyls, thereby achieving remarkably high regioselectivity, endo selectivity, and diastereoselectivity in the Diels–Alder reactions of unsymmetrical fumarates hitherto not observable with ordinary Lewis acids. This methodology not only provides a conceptually new mode of carbonyl discrimination but also meets versatile synthetic demands due to continuous, yet extensive developments of stereoselective Diels–Alder reactions in organic synthesis.

(8) The absolute configuration of the cycloadducts **6**–**9** was correlated to the known (5*S*,6*S*)-5,6-bis(hydroxymethyl)-2-norbornene: Horton, D.; Machinami, T. *J. Chem. Soc., Chem. Commun.* **1981**, 88.

Enantiospecific Synthesis via Sequential Diastereofacial and Diastereotopic Group Selective Reactions: Enantiodivergent Synthesis of *syn*-1,3-Polyols

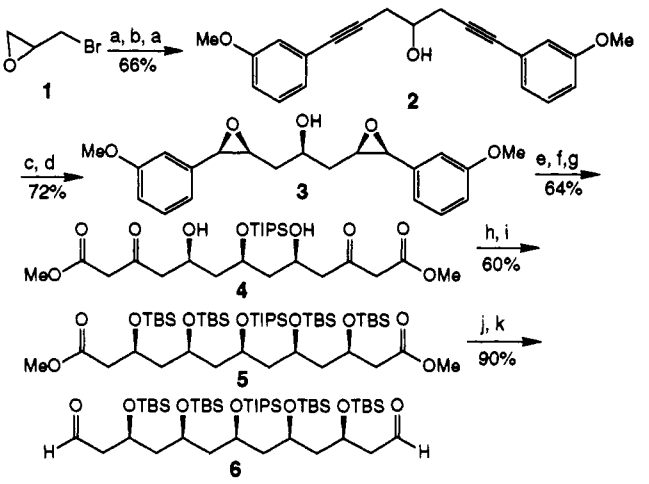
Zhaoyin Wang* and Denis Deschênes

Merck Frosst Centre for Therapeutic Research, P.O. Box 1005 Pointe Claire/Dorval, Québec, Canada H9R 4P8

Received September 19, 1991

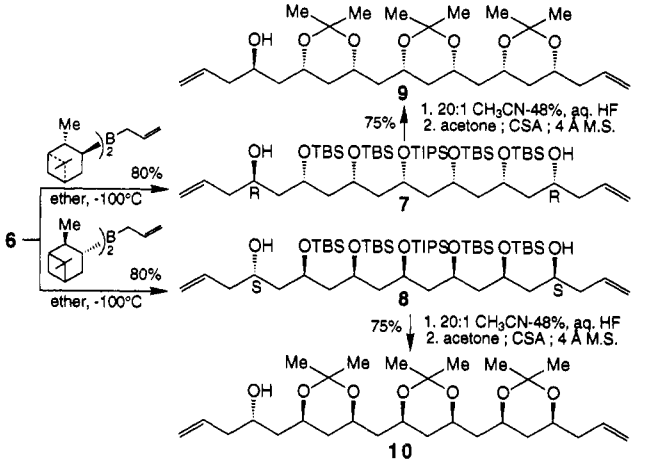
Transformation of meso molecules into chiral, nonracemic products relies mainly on monofunctionalization of the enantiotopic termini by the use of hydrolytic enzymes[1] or some recently developed nonenzymatic chemical reactions,[2] which operate through diastereofacial selective reactions controlled by *both* substrate and reagent. Herein, we describe a different approach via two simultaneous *exclusively* reagent-controlled diastereofacial selective reactions at both termini and subsequent terminal differentiation via a diastereotopic group selective reaction.[3] This strategy has been applied to an enatiodivergent synthesis of *syn*-1,3-polyol chains from a meso precursor.

Scheme I[a]



[a] (a) 2-MeOPhCCLi, BF_3·OEt_2, THF, −78 °C; (b) powdered KOH, Et_2O; (c) H_2, Ni_2B, EtOH (aqueous); (d) VO(O*i*-Pr)$_3$ (catalytic), *t*-BuOOH, CH_2Cl_2; (e) TIPSOTf, Et_3N, CH_2Cl_2; (f) Li, NH_3 (liquid), THF, *t*-BuOH; (g) O_3, MeOH, −78 °C, then PPh_3; (h) $MeOBEt_2$, $NaBH_4$, THF/MeOH, −78 °C; (i) TBSOTf, Et_3N, CH_2Cl_2; (j) $LiEt_3BH$, THF, 0 °C; (k) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N.

Scheme II



The two-directional synthesis of a *meso-syn*-1,3-polyol[4,5] is depicted in Scheme I. Achiral carbinol **2** was prepared by sequential homologations of epibromohydrin with lithium 3-methoxyphenylacetylide.[6] Controlled hydrogenation of **2**,[7] followed by stereoselective epoxidation[8] afforded bisepoxide **3** with diastereofacial selectivity of 15:1.[9] Silylation of **3**, followed by dissolving metal–ammonia reduction[10] and ozonolysis, revealed

(1) Jones, J. B. In Asymmetric Synthesis; Morrison, J. D., Ed.; Academic Press: New York, 1985; pp 309–339. For recent examples, see: Johnson, C. R.; Golebiowski, A.; McGill, T. K.; Steensma, D. H. *Tetrahedron Lett.* **1991**, *32*, 2597.

(2) (a) Bertz, S. H. *Tetrahedron Lett.* **1983**, *24*, 5577. (b) Bertz, S. H. *J. Chem. Soc., Chem. Commun.* **1984**, 218. (c) Nagao, Y.; Inoue, T.; Hashimoto, K.; Hagiwara, Y.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1419. (d) Fuji, K.; Node, M.; Terada, S.; Murata, M.; Nagasawa, H.; Taga, T.; Machida, K. *J. Am. Chem. Soc.* **1985**, *107*, 6404. (e) Takano, S.; Sakurai, K.; Hatakeyama, S. *J. Chem. Soc., Chem. Commun.* **1985**, 1759. (f) Whitesell, J. K.; Allen, D. E. *J. Org. Chem.* **1985**, *50*, 3025. (g) Jäger, V.; Schröter, D.; Häfele, B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 87. (h) Dokuzovic, Z.; Roberts, N. K.; Sawyer, J. F.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1986**, *108*, 2034. (i) Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718. (j) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525. (k) Aubé, J.; Burgett, P. M.; Wang, Y. *Tetrahedron Lett.* **1988**, *29*, 151. (l) Tamao, K.; Tohma, T.; Inui, N.; Naayama, O.; Ito, Y. *Tetrahedron Lett.* **1990**, *31*, 7333. (m) Harada, T.; Wada, I.; Uchimura, J.; Inoue, A.; Tanaka, S.; Oku, A. *Tetrahedron Lett.* **1991**, *32*, 1219.

(3) (a) Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738. (b) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303. (c) Schreiber, S. L.; Wang, Z.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 4085. (d) Schreiber, S. L.; Sammakia, T.; Uehling, D. E. *J. Org. Chem.* **1989**, *54*, 15.

(4) For a discussion of the two-directional chain synthesis strategy, see: Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563.

(5) For a recent review of synthesis of 1,3-polyols, see: Oishi, T.; Nakata, T. *Synthesis* **1990**, 635.

(6) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(7) Brown, C. A.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 1003.

(8) Mihelich, E. D.; Daniels, K.; Eickhoff, D. *J. Am. Chem. Soc.* **1981**, *103*, 7690.

(9) The ratio is based on the pure major product and combination of the undesired minor isomers isolated by silica gel chromatography as determined by weight.

(10) (a) Flisak, J. R.; Hall, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 7299. (b) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, *56*, 741.

0002-7863/92/1514-1090$03.00/0