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

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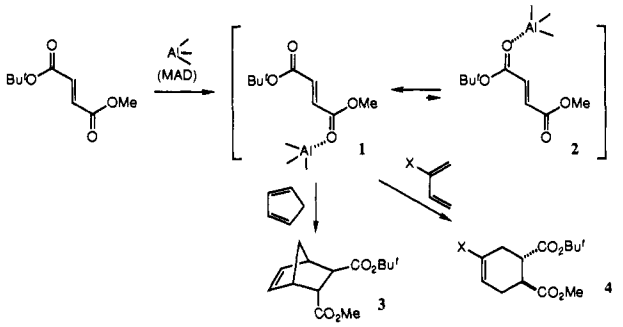
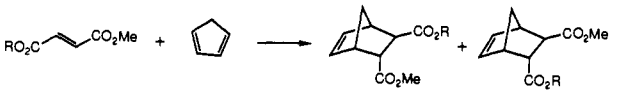
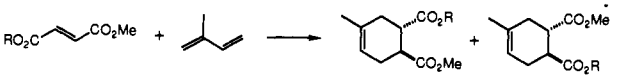
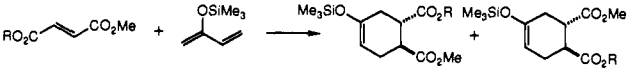
Received October 9, 1991

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

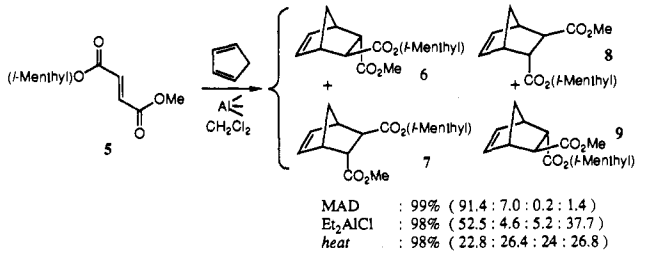
Table I. Diels-Alder Reaction of Unsymmetrical Fummarates[a]

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-

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(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.

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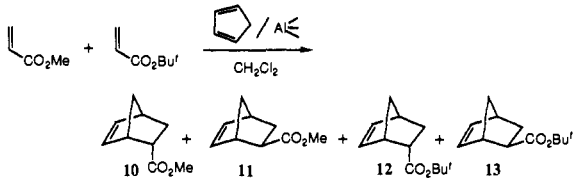
quently, MAD can be utilized both as an effective Lewis acid for endo selectivity and as a stereocontroller for asymmetric induction.

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

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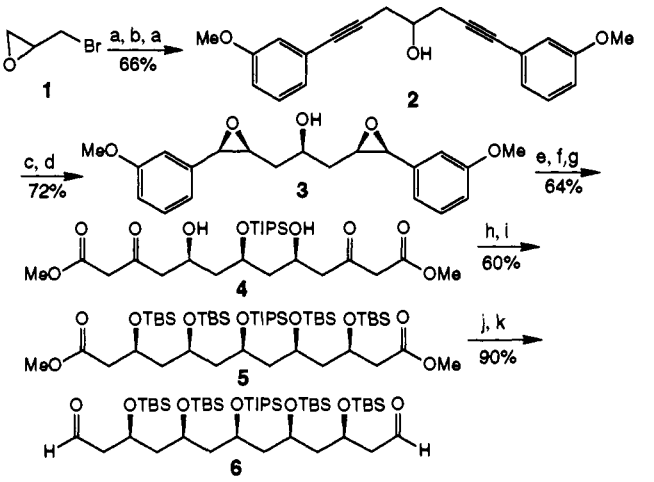
Received September 19, 1991

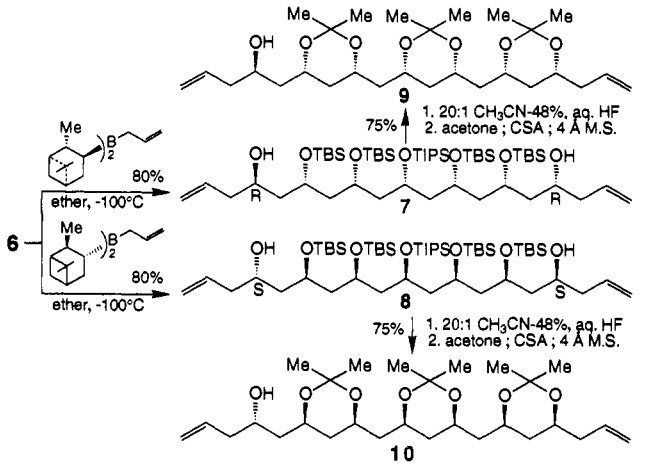
Transformation of meso molecules into chiral, nonracemic products relies mainly on monofunctionalization of the enantiotopic termini by the use of hydrolytic enzymes[1] or some recently developed nonenzymatic chemical reactions,[2] which operate through diastereofacial selective reactions controlled 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, $BF_3{\cdot}OEt_2$, 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

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(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.

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(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.

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