Stereocontrolled Synthesis and Cycloaddition of 1,4-Dialkoxy 1,3-Dienes

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An efficient and stereocontrolled access to 1(*Z*),3(*E*)-1,4-dialkoxybutadienes is described that relies on a base-induced conjugated elimination reaction on γ-alkoxy or aryloxy α,β-unsaturated acetals. The dienes have then been applied in [4 + 2] cycloaddition reactions where they demonstrate a good thermal reactivity toward activated dienophiles. Despite the 1,4-competition between oxygenated groups, both regio- and endoselectivities are total. A set of experiments has led to the conclusion that the (1*Z*,3*E*) pattern is responsible for these high stereocontrols. Several chiral alkoxy dienes have also been prepared following the same route. Their thermal cycloaddition with *N*-methylmaleimide leads to corresponding adducts in good yields and with total endoselectivities, but modest diastereoisomeric excess.

Introduction

The versatile Diels−Alder [4 + 2] cycloaddition is an asset in the organic chemist's toolbox because of the simultaneous setting of ring(s), asymmetric centers, and functional groups it triggers.[1] A sustained interest for synthetic routes to functionalized 1,3-dienes[2] is observed in the literature where a special emphasis is put on dienes bearing heteroatom substituents. Henceforth to be ranked among the "classic" building blocks is the most widely used member of this class, 1-methoxy-3[(trimethylsilyl)oxy]butadiene (Danishefsky's diene),[3] which has been given a key part in several elegant routes to natural products[4] and glycals.[5] The corresponding 1,4-dialkoxy dienes have been much less studied, despite a comparably appealing synthetic potential. They are indeed direct [4 + 2] precursors of the 3,6-disubstituted cyclohexenic structure found in conduritols, a new class of glycosidase inhibitors.[6] These cyclohexenes are also powerful synthons[7] and key intermediates in the synthesis of various bioactive compounds[8] such as carbohydrate analogues[9] and cyclitols.[10] Actually, the few papers dealing with 1,4-dialkoxy diene synthesis rely either on a stereospecific, but synthetically rather unpractical, strategy[11] or on a stereouncontrolled approach.[12] Several authors also insist on the mediocre stability of these compounds due to their sensitivity to polymerization and dioxygen.[11b,13,14] The purification and separation of 1,4-dialkoxy dienes are thus described as tedious or even "exceedingly difficult".[11b,12c] Finally, the comparable reactivity of their *E*,*E* and *Z*,*E* isomers further frustrates their applications to cycloadditions since the adducts obtained are a mixture of stereoisomers when the configuration of the dienic precursors is not controlled.[9a,12b,c]

The conjugate elimination of an alcohol molecule from α,β-unsaturated acetals such as ethyl acetal of crotonaldehyde or senecialdehyde has been known for a long time[15] but has received little attention,[16] probably because of the limited functionalization of the dienes originally prepared by this method. We have extended these results to corresponding γ-(arylthio) α,β-unsaturated acetals and obtained 1-(arylthio)-4-methoxy 1,3-dienes with fair to good stereocontrol of the double bonds

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Scheme 1

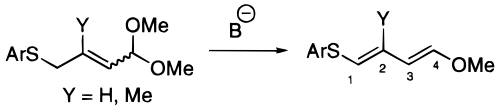
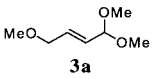
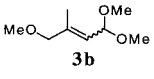
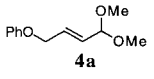
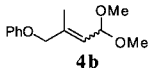
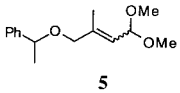
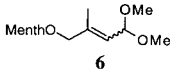
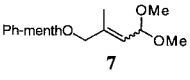


Table 1. Reaction Conditions for the Synthesis of γ-Alkoxy Acetals 3−7

Product	Alcoholate	Reaction conditions	Yield (%)
 **3a**	MeONa, 2.5 eq	MeOH, 50°C, 4 h.	73
 **3b**	MeONa, 2.5 eq	MeOH, 50°C, 20 h.	91
 **4a**	PhONa, 1.2 eq	THF/H_2O, 20°C, 2 h.	69
 **4b**	PhONa, 1.2 eq	THF/H_2O, 20°C, 2 d.	98
 **5**	Ph-CH(Me)-OK, 1.0 eq	THF, 20°C, 1h.	88
 **6**	MenthONa[a], 1.0 eq	THF/HMPA, 70°C, 1 d.	54
 **7**	Ph-menthOK[b], 1.0 eq	THF, 20°C, 6 h.	45

[a] Prepared from (−)-menthol. [b] Prepared from (−)-8-phenylmenthol.

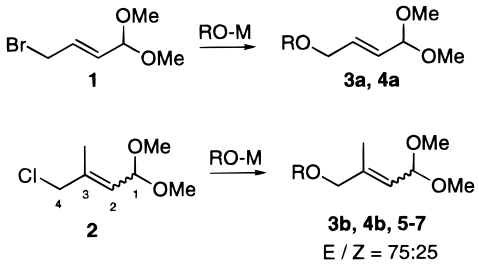
(Scheme 1).[17] When opposed to various classical dienophiles, these sulfurized dienes exhibited a relatively modest reactivity,[17b] probably because of the well-known deactivating effect exerted by sulfur on this type of compound.[18] We thus decided to extend this methodology to the synthesis of 1,4-dialkoxy dienes, expected to be much more reactive compounds,[1,2,19] following the same approach.

The encouraging preliminary results[20] we have obtained prompted us to extend this work to a larger family of γ-oxygenated acetals and to the study of the reactivity of the corresponding dienes.

Results and Discussion

Preparation of Acetals 3−7. The required precursors, viz. the α,β-unsaturated acetals **3**−**7**, can be prepared from γ-bromo acetal **1**, obtained itself in two steps from crotonaldehyde,[17a] or from industrial γ-chloro acetal **2**, a very convenient precursor[21] for the isoprenoid structures (Table 1 and Scheme 2). While **1** is obtained under its pure *E* form, **2** is delivered as a ∼75:25 *E*/*Z* mixture of isomers.

Scheme 2



The γ-alkoxy acetals are prepared by condensation of the corresponding alcoholates onto either the bromo or chloro acetals **1** or **2**. Depending on both the nature of the alcoholate employed and that of the starting acetal, different procedures have been developed that are summarized in Table 1. The γ-alkoxy acetals are obtained from sodium or potassium alcoholates in various solvents. Nucleophilic substitutions on bromo acetal **1** are significantly more rapid than on chloro acetal **2**. However, this latter remains a good substrate provided more drastic conditions (such as addition of 20% HMPA to the THF medium or switching from sodium to potassium alcoholates in pure THF) are employed. The strong basicity of these alcoholates has led us to add slowly the alcoholate in solution to the halo acetal, the reverse procedure leading to a competitive deprotonation reaction (vide infra). Finally, γ-(aryloxy) acetals **4** are simply prepared by vigorous stirring of a heterogeneous mixture of acetals **1** or **2** in THF and aqueous sodium phenolate. The configuration of the double bond in all acetals **3**−**7** is unaltered after substitution: while linear **3a** and **4a** are obtained in their pure *E* form, branched **3b**, **4b**, **5**, and **7** *E*/*Z* configurations vary between 70:30 and 80:20, depending on that of chloro precursor **2**.

Albeit pure enough to be used directly, these acetals can stand a flash chromatography on silica gel. Menthoxy ether **6** tends to decompose slowly, even in the freezer, leading to a mixture of dienes, as discussed below. It still can be chromatographed in the presence of triethylamine in 54% yield.

Synthesis of Dienes 8−15 and 17. The γ-oxygenated acetals prepared above have then been submitted to δ-elimination reactions following different experimental procedures (Schemes 3 and 4). Both *n*-butyllithium (method A) and potassium hexamethyldisilylamide (KHMDS, method B) deprotonate these compounds and trigger the conjugated-elimination reaction. Catalytic amounts of alkyllithium or KHMDS are uneffective since they generate lithium or potassium methylate in the medium and are not basic enough to deprotonate **3**−**7**. The same observation has already been made for the corresponding thioethers.[17] For acetals **3**−**5**, the 1,4-dienol diethers **8**−**11** are selectively recovered in high yields and good stereocontrol, the 1*Z*,3*E* isomer being the major one in all cases (Scheme 3 and Table 2). The configuration of both double bonds could be established either by direct measurement of coupling constants (for butadienoids) or through a set of NOE and NOESY experiments (for isoprenoids).

Let us now consider the case of menthyl derivative **6**. Its treatment by *n*-BuLi leads, as above, to a regioselective δ-elimination of methanol, providing chiral diene **12** (Scheme 4). Here again, **12** is obtained almost exclusively under its 1*Z*,3*E* configuration. Interestingly,

(17) (a) Gaonac'h, O.; Maddaluno, J.; Chauvin, J.; Duhamel, L. *J. Org. Chem.* **1991**, *56*, 4045. (b) Maddaluno, J.; Gaonac'h, O.; Marcual, A.; Toupet, L.; Giessner-Prettre, C. *J. Org. Chem.* **1996**, *61*, 5290.

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(19) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Herhe, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381.

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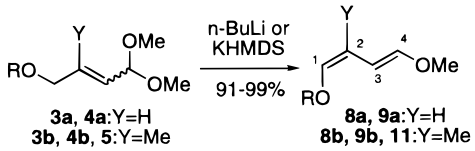
(21) Industrial intermediate from Rhône-Poulenc Chimie.

Table 2. Stereochemical Ratios of Various Iosmers of Dienes 8−15 as a Function of the Elimination Conditions (Methods A−D)

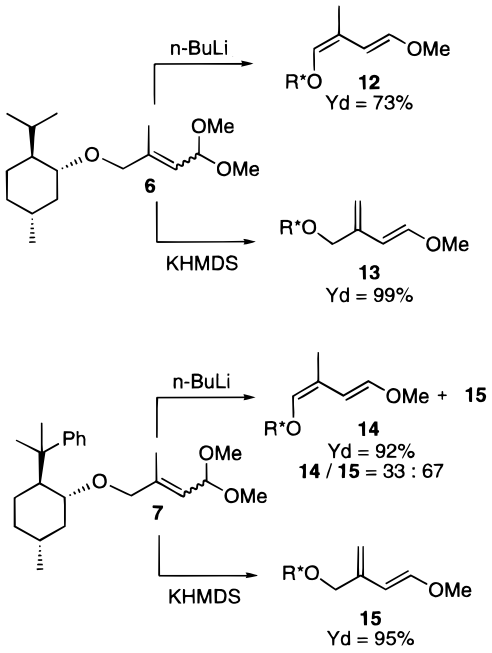
Starting acetal	Vinylic diene	Allylic diene[a]		A[b]	B[c]	C[d]	D[e]
3a	**8a**	-	EE/ZE/ZZ	6:74:20	0:83:17		-
			Yd	95%	98%		
3b	**8b**		EE/ZE[f]	10:90			30:70
			Yd	98%			89%
4a	**9a**	-	EE/EZ/ZE/ZZ	8:0:72:20	0:0:80:20		17:8:56:19
			Yd	93%	97%		99%
4b	**9b**	**10**	**9b / 10**	100:0	100:0	70:30	100:0
			EE/EZ/ZE/ZZ[f]	8:0:92:0	15:0:85:0	10:0:90:0	40:10:40:10
			Yd	91%	99%	82%	94%
5	**11**		EE/ZE[f]	7:93			
			Yd	98%			
6	**12**	**13**	**12 / 13**	100:0	0:100		100 : 0
			EE/ZE[f]	8:92	-		35:65
			Yd	73%	99%		
7	**14**	**15**	**14 / 15**	33:67	0:100		
			ZE[f]	100%	-		
			Yd	92%	95%		

[a] The configuration of the 1,2 double bond is 100% E. [b] *n*-BuLi, −40 °C, THF. [c] KHMDS, rt, THF. [d] DIPEA, TMSOTf, −40 °C then rt, CH_2Cl_2. [e] Thermal cracking. [f] Configuration of the vinylic diene.

Scheme 3



Scheme 4



treatment of **6** by KHMDS (method B) triggers the regioselective deprotonation of the methylene position, this time in sharp contrast with acetals **3** and **4** (Scheme 3). The pure 1*E* "allylic" diene **13** thus obtained is relatively stable and does not need further purification. This is worth emphasizing since **6** gives a 100% selective access to dienes **12** or **13** by a simple base swap (Scheme 4, Table 2). Comparatively, 8-phenylmenthyl derivative **7** is not so easily deprotonated, probably because of the steric hindrance around the allylic positions. It requires the use of a large excess of base and warming the medium to room temperature (BuLi) or to reflux of THF (KHMDS). A mixture of 1*Z*,3*E* vinylic **14** and 1*E* allylic **15** dienes is obtained in a 33:67 ratio with method A, whereas pure **15** is recovered with method B. An achiral set of comparable allylic dienes had been prepared previously,[22] but in relatively modest yields and stereocontrols.

We then tried to put into evidence a possible role for the metallic cation in this somewhat puzzling high 1,2-*Z* selectivity. Acetal **4b** was deprotonated following method A modified by preloading the reaction medium with LiBr or KI. No effect at all could be observed, either on the chemical yield or on the stereoselectivity. The possible role of THF could also be ruled out since slowly adding a commercial solution of *n*-BuLi in hexanes to neat **4b** leads to the same **9b** mixture. Similarly, adding 18-crown-6 (1.7 to 5 equiv with respect to **4b**) to the medium in method B does not alter significantly the stereochemical outcome. No impact of the original configuration of the acetal **4b** double bond on the stereoselectivity of this reaction could be observed either; when treated by *n*-BuLi under similar conditions, both (*E*)- and (*Z*)-**4b**, separated by flash column chromatography, provide **9b** in an identical 1*E*,3*E*/1*Z*,3*E* = 8:92 ratio by contrast with our

(22) Mandai, T.; Osaka, K.; Kawagishi, M.; Kawada, M.; Otera, J. *J. Org. Chem.* **1984**, *49*, 3595.

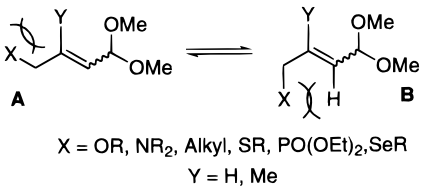
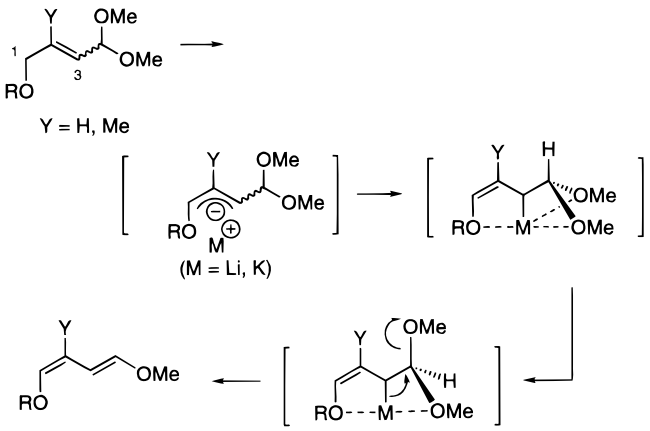


Figure 1. $A^{1,2}$ and $A^{1,3}$ allylic interactions in α,β-unsaturated acetals.

Scheme 5



own finding on corresponding thioethers[17b] and with related works on unsaturated ethers by Schlosser et al.[23]

On a mechanistic point of view, it is worth noting that the stereoselectivity of the deprotonation correlates to the C−Y bond length (Scheme 5): while the sulfinyls (C−S ≈ 1.81 Å), seleninyls (C−Se ≈ 1.98 Å), and phosphonates (C−P ≈ 1.87 Å) provide mainly the *EE* dienes,[24] the ethers (C−O ≈ 1.43 Å), alkyls (C−C ≈ 1.53 Å), and amines (C−N ≈ 1.47 Å) favor the corresponding *ZE* dienes.[25] Such an observation could be explained within the framework of an early transition-state hypothesis, considering that the starting acetal conformation can depend on the C−X bond length (Figure 1). We suppose that long C−X bonds (X = SR, $PO(OEt)_2$, SeR) generate $A^{1,3}$ allylic strains in favor of the A-type conformations, while short C−X bonds (X = OR, NR_2, alkyl) are at the origin of $A^{1,2}$ tensions avoided in B type conformations.

Coming back to the γ-oxygenated acetals **3**−**5**, the very first step of the conjugated elimination reaction is likely to consist of a C^1 deprotonation of the B-type conformer, leading to a delocalized species (ion pair). The mesomeric form placing the metal on C^3 appears favored over its C^1 counterpart since the chelation can involve both the acetal function and the ether's oxygen, thanks to the *Z* double bond (Scheme 5). Such a stabilized allylic lithium compound is supposed to favor some C−M covalency[26] with a partial localization of the double bond.[27] Depending on the metal, this latter chelation by the acetal has been calculated to involve only one oxygen when M is a lithium or both when M is a potassium.[27] If the final β-elimination step takes place in an anti fashion, the antiperiplanar arrangement of one of the methoxy groups with respect to the metal prefigures the 3,4-double bond *E* configuration.

Within this mechanistic framework, the potassium bases appeared of particular interest. A catalytic amount of potassium *tert*-butylate in THF at rt is uneffective on the usual *E*/*Z* mixture of **4b**, but a stoicchiometric amount of this same base leads to a mixture of enol ether **16**, together with allylic diene **10** and a small amount diene **9b** (Scheme 6). Actually, the configuration of the **4b** double bond turns out to be of prime importance this time, for both the ratio and the stereochemistry of the different products. Enol ether **16** is always the main product, but the dominance of the *Z* isomer is dependent on the *E*/*Z* configuration of **4b**. Finally, we resorted to nonmetallic bases. DBU (1.5 equiv, THF, Rfx, 12 h) does not deprotonate **4b**, whereas Schwesinger's *t*-Bu-P4 base (1 equiv, THF, rt, 1h), in which pK_a in THF is reported to be comparable to that of KHMDS,[28] leads to a mixture of enol ether **16** and diene **9b** (Scheme 6), the *Z* isomer still being the major product.

The major (1*Z*) isomer of acetal **16** can be separated by flash column chromatography. It undergoes a β-elimination when treated with *n*-BuLi in conditions similar to method A, leading in 95% yield to diene **9b** in its pure 1*Z*,3*E* configuration (Scheme 7).

Efficient access to enol ethers from acetals by amine-induced alcohol eliminations in the presence of a Lewis acid has also been reported (method C).[29] We have applied Gassman et al.s original procedure to acetal **4b** in an attempt to get the corresponding conjugated elimination. We observe in this case that the methylene and methyl vinylic sites are now competing for deprotonation, leading to **9b** in a 10:90 1*E*,3*E*/1*Z*,3*E* ratio together with pure *E* allylic diene **10** (Scheme 8). At room temperature in methylene chloride, the **9b**/**10** ratio is 70:30. **10** can easily be separated by flash column chromatography since it is relatively more stable than its isomer **9b**.

The A and B deprotonation−elimination procedures can easily be converted to a multigram scale. On the basis of NMR and GC data, dienes **8**−**15** obtained are pure enough to be used as such. These oily compounds are reasonably stable and keep for several days in the freezer under argon in the absence of acidic traces. Interestingly, the elimination reaction on acetals **3b** and **4** also takes place upon heating (method D)[30] or at room temperature for **6**, providing **8b**, **9**, and **12** as a complex mixture of isomers (Scheme 9 and Table 2). The balanced ratio does not seem to be due to a thermal equilibration occurring between the species after the elimination process, as indicated by warming an original 8:92 1*E*,3*E*/1*Z*,3*E* mixture of diene **4b** and recovering it unaltered. Advantage has been taken of the configuration hetero-

(23) Margot, C.; Matsuda, H.; Schlosser, M. *Tetrahedron* **1990**, *46*, 2430.

(24) (a) Sulfinyl: ref 17. (b) Seleninyl: Outurquin, F. Unpublished results. (c) Phosphonyl: ref 20a.

(25) (a) Alkoxy: ref 20a, this work, and: Lançois, D.; Maddaluno, J. *Tetrahedron Lett.* **1998**, *39*, 2335. (b) Alkyl: Deagostino, A. M.; Maddaluno, J.; Mella, M.; Prandi, C.; Venturello, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 881. (c) Amino: Martin, C.; Maddaluno, J.; Duhamel, L. *Tetrahedron Lett.* **1996**, *37*, 8169.

(26) Fraenkel, G.; Qiu, F. *J. Am. Chem. Soc.* **1997**, *119*, 3571.

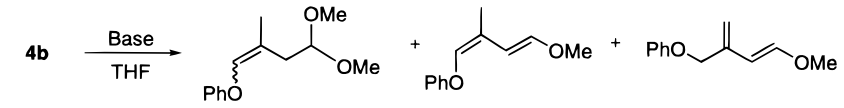
(27) Fossey, J.; Ghigo, G.; Tonachini, G.; Venturello, P. *Tetrahedron* **1997**, *53*, 7937.

(28) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *99*, 1212.

(29) (a) Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1993**, *58*, 1449. (b) Saalfrank, R. W.; Hafner, W.; Markmann, J.; Welch, A.; Peters, K.; von Schnering, H. G. *Z. Naturforsch. B* **1994**, *49*, 389. (c) Dujardin, G. Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1995**, *36*, 1653.

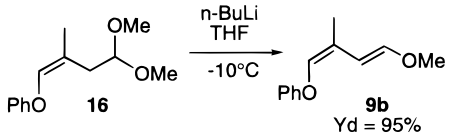
(30) (a) Duhamel, L.; Duhamel, P.; Ancel, J. P. *Tetrahedron Lett.* **1994**, *35*, 1209. (b) De Guigné, C. Ph.D. Thesis, University of Rouen, 1997.

Scheme 6

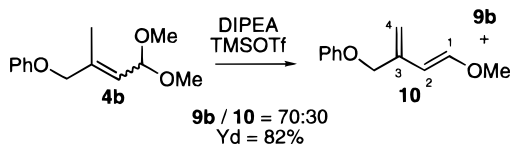


E / Z		16 E / Z	9b 100% ZE	10 100% E
75 : 25	t-BuOK	14 : 49	32	5
100 : 0	t-BuOK	19 : 40	38	3
0 : 100	t-BuOK	0 : 77	13	10
75 : 25	t-Bu-P4	26 : 44	30	0

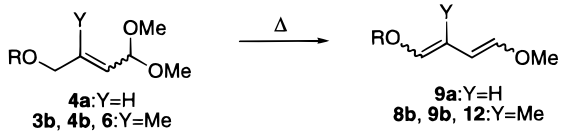
Scheme 7



Scheme 8



Scheme 9



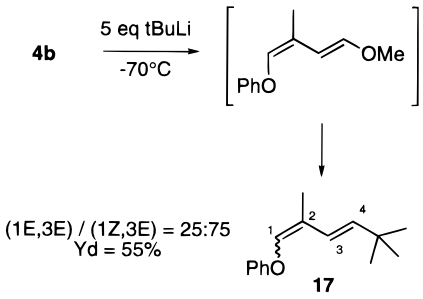
geneity obtained thermally to evaluate the influence of 1*E*,3*E* and 1*Z*,3*E* stereochemistry on diastereoselectivity and regioselectivity in cycloaddition reactions involving these dienes (see below).

Finally, the elimination reaction may also be triggered by catalytic amounts of acids, as reported for the corresponding phenylthio acetals.[31] For instance, a nonneutralized $CDCl_3$ solution of **6** is quantitatively converted into **12** overnight at room temperature. But the 1*E*,3*E*/1*Z*,3*E* ratio is 35:65, in fine agreement with our own previous results in similar conditions.[31] This reaction also takes place on acetal **4b** in the presence of small amounts of an HCl/Et_2O solution with a similar stereoselectivity. Once more, this balanced result does not seem to be due to a postelimination equilibration phenomenum, as checked by placing a 8:92 1*E*,3*E*/1*Z*,3*E* mixture of **6** under the same conditions and recovering it unchanged.

We have previously reported that an excess of alkyllithium reagent or of lithium amide leads, in the case of dienol thioethers, to the chemioselective substitution of the methoxy group by the base itself.[17] We have checked the possible application of this reaction to diene **9b**, keeping in mind that the higher similarity between methoxy and phenoxy groups was likely to jeopardize the chemioselectivity. When **4b** was treated with an excess of *tert*-butyllithium at −70 °C and then room temperature in ether, diene **17**, in which the MeO group had been substituted by a *t*-Bu, was recovered (Scheme 10).

Compound **17** is the only regioisomer obtained; it is isolated in 55% yield after flash chromatography on silica gel. From a configurational point of view, the original

Scheme 10



8:92 1*E*,3*E*/1*Z*,3*E* ratio in **9b** decreases to 25:75 in **17**, still in favor of the same isomer. Thus, it is not the control of the 3,4 double bond, on which the alkyl incorporation occurs, that is affected but the 1,2 bond. When replacing *tert*-butyllithium by *n*-butyllithium, the same regiocontrolled addition−elimination takes place but leads, this time, to a complex mixture of at least three stereoisomers, in agreement with our own previous results on sulfurized dienes.[17] Three main factors may be evoked to justify this total regioselectivity viz. (i) the configuration of the double bond (*E* vs *Z*), (ii) the nature of the leaving group (MeO vs PhO), and (iii) the presence of a methyl group in the 2 position (and not in the 3 position). We have not tried to determine the respective influence of these parameters, but the partial loss in the stereocontrol of diene **17** configuration may occur through an addition−elimination mechanism[32] leading to a lithiated intermediate of poorly controlled geometry.

Cycloadditions with *N*-Methylmaleimide. The papers describing cycloadditions of 1,4-dialkoxybuta-1,3-dienes are scarce.[9a,11a,e,12a−c,33] In those, stereoisomeric mixtures of dienes have been opposed to various dienophiles, leading to several diastereoisomers and hampering a systematic study of the stereoselectivity of these reactions. We decided to investigate successively the reactivity of **8**−**15** with symmetrical (*N*-methylmaleimide) and unsymmetrical (methyl acrylate) dienophiles to probe the regioselectivity and endo/exo selectivities this type of dienes can afford. The eventual diastereoselectivity of the addition on the five different chiral dienes **11**−**15** onto *N*-methylmaleimide was then estimated. Finally, the relative diastereoselectivities provided by the 1*E*,3*E* and 1*Z*,3*E* isomers of **12** could also be ascertained.

Let us first consider 1*Z*,3*E* dienes **9a,b** prepared following method A (Table 2). Refluxing them in toluene with 1.2 equiv of *N*-methylmaleimide (NMM) and small amounts of hydroquinone[33] yields the expected adducts **18a**,**b** in a few hours (Scheme 11).

(31) Gaonac'h, O.; Maddaluno, J.; Plé, G.; Duhamel, L. *Tetrahedron Lett.* **1992**, *33*, 2473.

(32) For the addition of alkyllithium on olefins, see inter alia: (a) Glaze, W. H.; Jones, P. C. *Chem. Commun.* **1969**, 1434. (b) Wei, X.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1996**, 187.

(33) Broekhuis, A. A.; Scheeren, J. W.; Nivard, R. J. F. *Rec. J. R. Neth. Chem. Soc.* **1980**, *99*, 6.

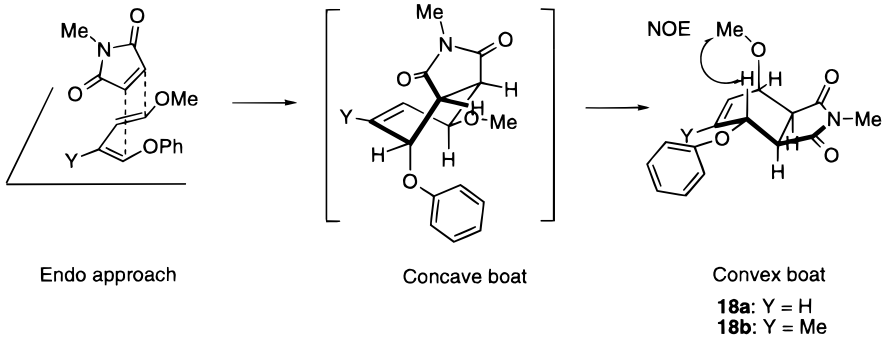
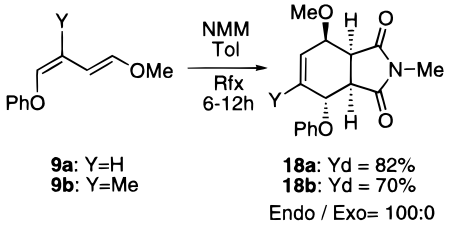


Figure 2. Conformations of bicycles **18**.

Scheme 11



After flash chromatography, **18a,b** are recovered in reasonable yields. The standard thermal conditions applied to perform these reactions indicate the unfavorable 1*Z*,3*E* configuration of dienes **9** can be overcome by their high reactivity in direct demand Diels−Alder additions. As indicated in Scheme 11, the stereoisomers derive from pure endo approaches, in fine agreement with comparable situations.[17b,34] NMR coupling constants as well as a NOESY experiment further indicate these bicyclic structures to adopt a convex boat-type folding (Figure 2).

The trans relationship between methoxy and phenoxy groups, imposed by the 1*Z*,3*E* configuration of the original diene, puts the methoxy in an axial position and the phenoxy in an equatorial one. This could be confirmed in the case of **18b** by a single-crystal X-ray analysis (Figure 3). The preference of such flexible systems as **18** for convex conformations has been discussed lately.[17b] It is worth noticing, however, that while the convex-boat flipping appears favorable to both **18a** and **18b** (three equatorial vs one axial substituents) it generates, for **18b**, an unfavorable allylic $A^{1,2}$ strain between the vinylic methyl and equatorial allylic phenoxy groups.

For further synthetic applications, the incorporation of a chiral appendage onto those structures might be of interest, albeit only a limited number of chiral dienes have proved to act as efficient inductors in cycloaddition reactions.[35] We decided to evaluate the diastereoselectivity that a *Z*-borne α-methylbenzyloxy, a menthyloxy, or a phenylmenthyloxy group could induce in Diels−Alder reactions. The availability of both 1*Z*,3*E* and 1*E*,3*E* isomers by the four methods presented above allows the evaluation of the influence of the double bond configuration on the relative reactivities and selectivities

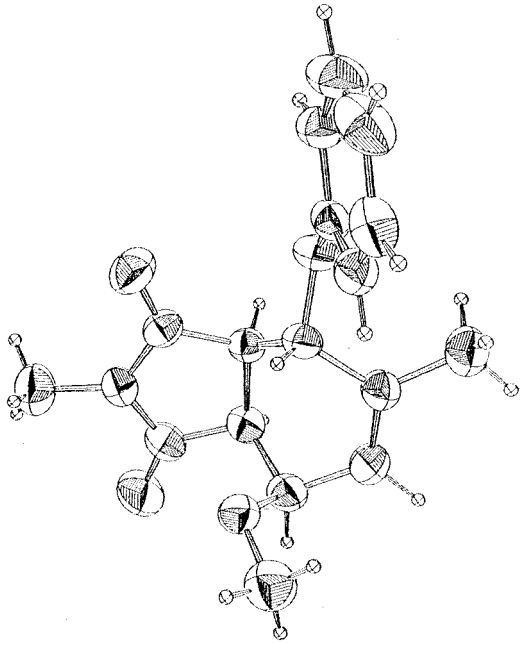


Figure 3. ORTEP representation of adduct **18b**.

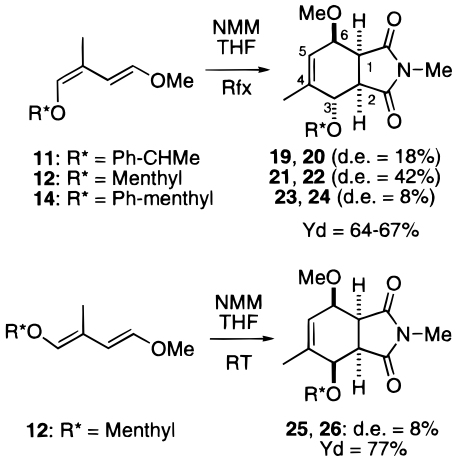
of these isomers. Let us first discuss the case of 1*Z*,3*E* isomers **11**, **12**, and **14**. Those have been prepared from acetals **5**, **6**, and **7**, following method A. For consistency with the above results, the retained dienophile is once more NMM. The reaction takes place at reflux of THF and the adducts **19**−**24**, derived from dienes **11**, **12**, and **14**, are obtained as a mixture of two isomers in each case (Scheme 12). Strong similarities between NMR spectra of these adducts and **18** indicate they all derive from pure endo approaches. Therefore, the stereoheterogeneity in **19**/**20**, **21**/**22**, and **23**/**24** should stem from the control of centers 1, 2, 3, and 6 relative to those of the chiral moieties. The de measured directly on the crude spectra are rather low, and the highest figure (42%) is obtained in the case of the menthyl derivatives **21** and **22**.[36] Although phenylmenthyl was anticipated to behave as a better inductor, the de for **23**/**24** is dramatically low. Both diastereoisomers of α-methylbenzyloxy and menthyloxy derivatives **19**/**20** and **21**/**22** were isolated by flash column chromatography in respectable yields, whereas purification of the phenylmenthoxy adducts **23**/**24** has not been achieved because of a limited supply of starting material. The absolute configuration of the major diastereoisomers has not been determined. We thought that these modest

(34) Danishefsky, S.; Yan, C. F.; Singh, R. K.; Gammill, R. B.; McCurry, P. M.; Fritsch, N.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 7001.

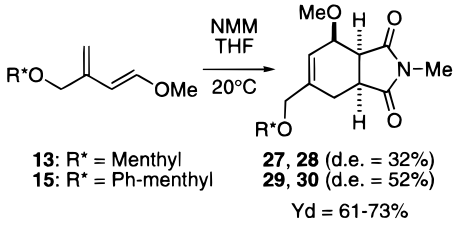
(35) See, for instance: (a) Krohn, K. *Organic Synhesis Highlights*; Verlag Chemie: Weinhein, 1990. (b) Winterfeld, E. *Chem. Rev.* **1993**, *93*, 827. (c) Gawley, R. E.; Aubey, J. *Principles of Asymmetric Synthesis*; Pergamon Press: Oxford, 1996.

(36) Interestingly, **12** adds also to TCNE at −78 °C in $CDCl_3$ and exhibits a 50% de from NMR data.

Scheme 12



Scheme 13

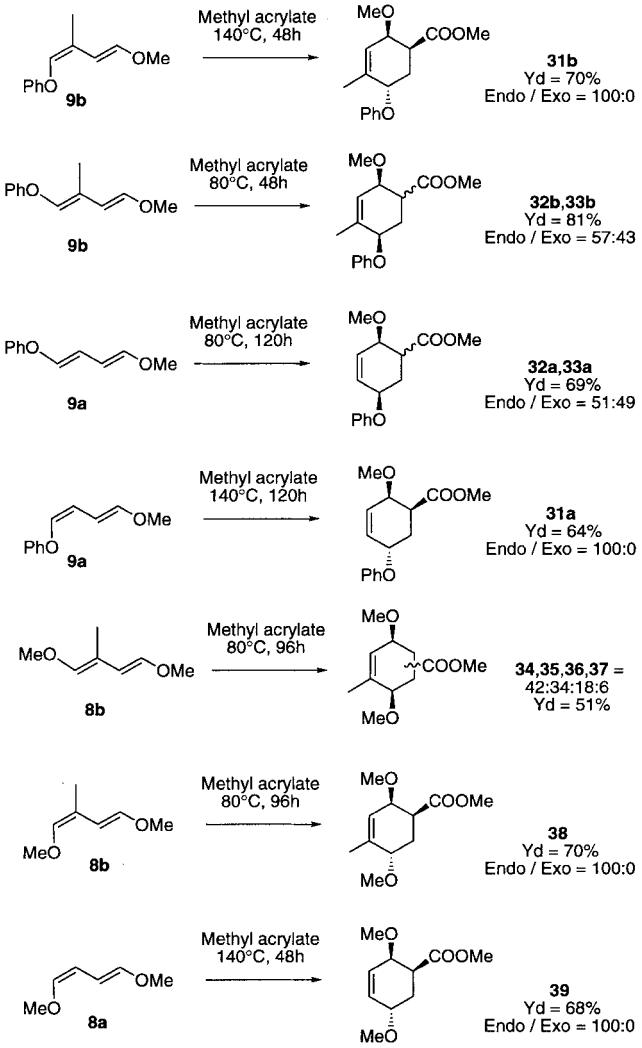


results could, in part, be ascribed to the thermal activation conditions; we thus performed the reaction between **11** and NMM in methylene chloride at 20 °C under high pressure (13 kbar). Disappointingly enough, the **21**/**22** ratio remained the same.

We finally decided to check the influence of the double-bond configuration by reacting the 1*E*,3*E* isomer of menthyl diene **12**. When working with a 35:65 1*E*,3*E*/1*Z*,3*E* mixture, the selective addition of the 1*E*,3*E* isomer reaches completion in 1 day at room temperature in THF. Two diastereoisomers **25** and **26** are also obtained in a low 8% de this time, a frustrating result in regard to those obtained with 2-methyl-1(*E*)-menthoxybuta-1,3-diene,[17b,37] but very related to values by Pericas and collaborators.[38] When heated to reflux for 2 days, the cycloaddition of remaining (1*Z*,3*E*)-**12** is obtained as above with 42% de, and the four adducts are purified by flash column chromatography. The *EE* isomer is, as expected, more reactive than the *ZE* isomer, but the induction exerted by the menthoxy moiety is much weaker in the former case. Therefore, 1*Z*,3*E* dienes can increase the efficiency of a chiral group provided this latter is borne by the *Z* double bond.

At this stage, it was worth considering the reactivity of the allylic dienes **13** and **15**. We retained NMM to evaluate the reactivity, the endo selectivity, and the diastereoselectivity (induced by the chiral alkoxymethyl group in the 3 position) this family of dienes could afford. Actually, the addition takes place at rt in THF in a few minutes to a few hours, leading in both **13** and **15** cases to a mixture of two isomers only, **27**/**28** and **29**/**30**, respectively (Scheme 13). The flash chromatography purification of these adducts, followed by NMR analysis, indicates that all these additions take place through an

Scheme 14



endo-type approach, the diastereoisomery steming from the relative control of the newly formed asymmetric centers with respect to those of the chiral moiety. When the chiral moiety is a menthyl group (diene **13**), the de measured on the crude **27**/**28** mixture is 32%. With a phenylmenthyl moiety (diene **15**), it reaches 52% for **29**/**30**.

Cycloadditions with Methyl Acrylate. Both endo and regioselectivities are difficult to predict when methyl acrylate is used as a dienophile. This latter is indeed known for its modest endo performances,[39] while the competing influences of the oxygenated groups in its 1 and 4 positions should endorse diene **9b** with a weak electronic polarization.[2b,19,40] Warming **9b** with methyl acrylate in toluene in a sealed tube (140 °C) with a trace amount of hydroquinone leads to the cyclic adduct **31b** in 2 days (Scheme 14). It may be recovered, after absorption of the partly polymerized reaction medium, on silica gel followed by flash chromatography, in 71% yield. A GC/MS and NMR study indicates a single isomer to be obtained following a regio- and endo-controlled approach. The same three factors evoked above, viz. configuration of the double bond, nature of the alkoxy/

(37) Rotscheid, K.; Breitmaier, E. *Synthesis* **1989**, 836.
(38) Virgili, P.; Pericàs, M. A.; Moyano, A.; Riera, A. *Tetrahedron* **1997**, *53*, 13427.
(39) Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 17.
(40) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.

aryloxy group, and presence of a vinylic methyl substituent, can contribute to this selectivity and have been probed separately through the set of experiments presented in Scheme 14.

We have first investigated the effect of the double-bond configuration preparing diene **9b** (1*E*,3*E*) by method D, which provides a mixture containing 40% of this isomer. At reflux of methyl acrylate (80 °C), it reacts almost selectively to afford two stereoisomers corresponding to the endo and exo adducts **32b**/**33b** (in a 57:43 ratio) of the same regioisomer. Therefore, and in the frame of this regiocontrolled approach, the *Z* configuration of diene **9b** seems to be essential to the endo/exo selectivity. Next were the origins of the regiodirectivity. To evaluate the pure phenoxy vs methoxy effect, we prepared butadienic **9a** (1*E*,3*E*) following method D, which provides 17% of this isomer. Its higher reactivity leads to a reasonable recovery of the corresponding adducts **32a**/**33a**. Once again, a lack of endocontrol is observed while the regiocontrol remains total. This result indicates that the methoxy group imposes its regiodirection over the phenoxy one, a difference that may originate from the decreased contribution of the PhO oxygen lone pair to the dienic system due to its involvement in the phenyl ring conjugation. A related example of regiocompetition has been reported recently.[41] Thus, the vinylic methyl group is not necessary to the regiocontrol. In addition, a total endocontrol is recovered for **31a** when switching from (1*E*,3*E*)- to (1*Z*,3*E*)-**9a** and confirming the essential role of the *ZE* configuration.

To supress the methoxy vs phenoxy effect, we then prepared the 1,4-dimethoxybutadienes **8a** and isoprenes **8b**. Particularly, in diene **8b** (1*E*,3*E*), the pure effect of the vinylic methyl group is at work, leading to four isomers **34**, **35**, **36**, and **37** in a 42:34:18:6 ratio. These compounds were purified but could not be separated by flash column chromatography. The GC/MS and NMR analysis on the mixture indicate that they correspond to the combination of the regio and endo-exo approaches. Therefore, the methyl substituent is unable to account for the total regiocontrol observed in the case of **9b**,[42] and the (1*E*,3*E*) configuration leads once more to a mixture of endo and exo isomers. By contrast, the (1*Z*,3*E*)-**8b** isomer selectively gives access to adduct **38**. Finally, 1*Z*,3*E* diene **8a** provides the pure *Z* vs *E* configurational effect on the regioselectivity. Only one isomer, **39**, is detected that derives from a pure endo and regiocontrolled approach. Hence, the *ZE* configuration is sufficient to steady both controls.

Two effects can be proposed to link endo selectivities and *ZE* configuration. First, strong steric repulsions may arise in the exo-type approach between the *Z*-borne alkoxy group of the diene and the ester moiety of the acrylate (Figure 4), whereas these interactions are avoided in the endo approach. Second, the exo approach puts the polar groups of both diene and dienophile in the same half-space while the endo mode corresponds to a better overall balance for the system.[43]

The orbitalar control of the Diels−Alder reaction implies that the HOMO coefficients rule its regioselectivity. We have thus undertaken a set of AM1 semiempirical calculations for both *EE* and *ZE* isomers of dienes **8** and **9**, and the results qualitatively account for the observed orientations. The coefficients corresponding to the C_1 atomic orbital in the s-cis conformer's HOMO are indeed systematically larger than that for C_4, favoring the overlap between C_1 and acrylate β-carbon (Table 3). This trend is amplified in isoprenoid **9b**, probably because of the vinylic methyl contribution. Comparing the *EE* to the *ZE* isomers clearly shows that the *Z* double bond reinforces the 1,4-orbital disymmetry. The origin of the decreased electronic contribution of the *Z*-borne alkoxy group may be accounted for on a steric basis, considering that the oxygen substituent is probably pushed off the diene plane in the s-cis reactive conformer, preventing the fine alignment of oxygen p-orbitals with those of the sp^2 carbons of the diene (Figure 5). The *E*-borne 4-methoxy group should therefore be better conjugated than its 1-*Z* counterpart. Steric considerations can be added to

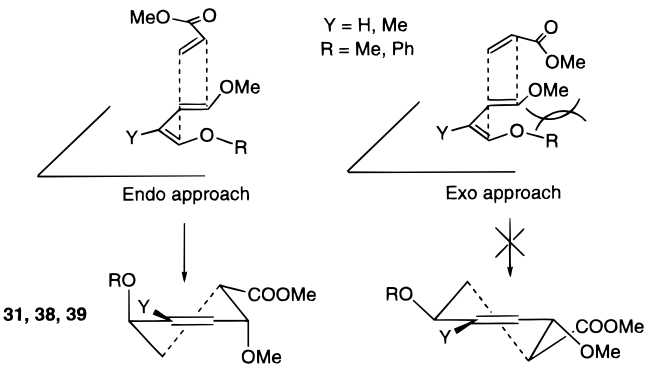
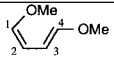
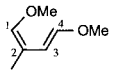
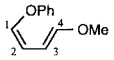
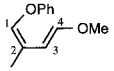
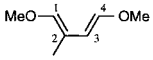
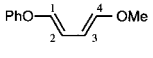
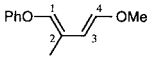


Figure 4. Endo and exo approaches of methyl acrylate onto (1*Z*,3*E*) dienes **8** and **9**.

Table 3. AM1 Coefficients for the HOMO of s-Cis (*ZE*)- and (*EE*)-1,4-Dialkoxybutadienes 8 and 9

		C_1	C_2	C_3	C_4	$\Delta C_{1,4}$
8a (ZE)		-0.471	-0.404	0.453	0.439	0.032
8b (ZE)		-0.489	-0.420	0.419	0.418	0.071
9a (ZE)		-0.444	-0.375	0.434	0.410	0.034
9b (ZE)		-0.447	-0.380	0.403	0.386	0.061
8b (EE)		-0.447	-0.427	0.381	0.404	0.043
9a (EE)		-0.413	-0.390	0.391	0.395	0.017
9b (EE)		-0.410	-0.390	0.357	0.368	0.042

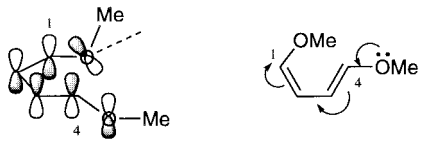


Figure 5. Electronic origin of (*ZE*) diene polarization.

(41) Olsen, R. K.; Feng, X.; Campbell, M.; Shao, R. L.; Math, S. K. *J. Org. Chem.* **1995**, *60*, 6025.

(42) Isoprene itself is known for its modest regiodirectivity toward methyl acrylate (Inukai, T.; Kojima, T. *J. Org. Chem.* **1971**, *36*, 924), and the case of diene **8b** opposed to juglone derivatives has also been discussed in the literature (see ref 12a).

(43) We thank Dr. André Guingant (CNRS/Université de Nantes) for suggesting this hypothesis.

these electronic factors, the approach of the bulkiest extremity of the diene, i.e., the *Z* 1,2-double bond, by the less cumbersome side of the dienophile, i.e., the methylene group, making much more sense than the other way around.

From a conformational point of view, all the above cyclohexenic structures adopt half-chair topologies, in which the ester function is equatorial. Therefore, the two "para" ether moieties adopt either an axial/axial or an axial/equatorial orientation, depending on their syn/anti relationship. This could be established on the basis of NMR and confirmed in a very similar case by X-ray crystallography.[44]

Concluding Remarks

The results we present indicate a fairly large set of 1,4-dialkoxy-1,3-butadienes to be obtainable by the conjugate elimination reactions. The dienes are obtained in good yields and mostly in their 1*Z*,3*E* configurations. Instead of being a drawback in terms of reactivity, the *Z* double bond turns out to be at the origin of total regio- and endoselectivities. These compounds give a simple and convergent access to trans-1,4-disubstituted cyclohexenic structures, which have received a great deal of attention lately. Further extensions of this work are currently in progress (hetero Diels−Alder, tandem additions on bis-dienic structures, ...) and will be presented in forthcoming papers.

Experimental Section

General Aspects. ^{1}H and ^{13}C NMR spectra have been taken in deuteriochloroform or deuteriobenzene on 200 and 300 MHz FT-spectrometers; coupling constants (*J*) are given in Hz. Gas chromatography analyses have been performed on a high-resolution DB-1-type column (30 m, 0.25 mm i.d., 0.25 μm coating). GC/MS analyses have been performed on an instrument equipped with the same column. Transmission IR spectra have been recorded from NaCl cells. The silica gel used for flash chromatography was 230−400 mesh. All reagents were of reagent grade and were used as such or distilled prior to use.

Preparation of Acetals 3−7. (2*E*)-1,1,4-Trimethoxybut-2-ene (3a). Under an atmosphere of argon, a suspension of sodium methylate (4.38 g, 81.1 mmol, 2.5 equiv) in methanol (30 mL) was added to a solution of (2*E*)-bromo acetal **1** (6.29 g, 32.4 mmol, 1.0 equiv) in methanol (20 mL), and the mixture was refluxed for 4 h and then cooled to room temperature. Water and ethylic ether (20 mL) were then added, the organic phase was separated, the aqueous layer was extracted twice with ethylic ether, and the organic fractions were dried on anhydrous magnesium sulfate. The (2*E*)-acetal **3a** was obtained after evaporation of the solvents and flash chromatography over silica gel using petroleum ether/ethylic ether = 90:10 as eluent as a pale yellow oil: 3.45 g (73% yield); IR (neat) 1731, 1457, 1380, 1263 cm^{-1}; MS (EI, 70 eV) *m*/*z* 146 ($M^{\bullet+}$, 1), 114 (64), 75 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.26 (6H, s), 3.29 (3H, s), 3.80 (2H, d, J = 5.0), 4.74 (1H, d, J = 4.5), 5.62 (1H, dd, J = 6.4, 4.5), 5.86 (1H, dt, J = 16.4, 5.0); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 56.1, 60.1, 74.4, 104.9, 131.2, 133.6.

(2*E*)- and (2*Z*)-3-Methyl-1,1,4-trimethoxybut-2-ene (3b). From the same procedure as above, starting from chloro acetal **2** 2*E*/2*Z* = 75:25 (5.0 g, 30.4 mmol, 1.0 equiv) and refluxing for 20 h, 4.4 g pale yellow oil of acetal **3b** 2*E*/2*Z* = 75:25 was obtained after evaporation of the solvents (91% yield) and could eventually be flash chromatographed on silica gel using petroleum ether/ethyl acetate = 90:10 as eluent: IR (neat) 1450 cm^{-1}; MS (EI, 0 eV), 2*E* isomer, *m*/*z* 128 ($M^{\bullet+}$ − 32, 30), 85 (64), 55 (100), 2*Z*-isomer, *m*/*z* 128 ($M^{\bullet+}$ − 32, 39), 85 (82), 55 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2*E* isomer, 1.71 (3H, s), 3.30 (3H, s), 3.33 (6H, s), 3.81 (2H, s), 5.03 (1H, d, J = 6.4), 5.49 (1H, d, J = 6.4); 2*Z* isomer, 1.75 (3H, s), 3.30 (3H, s), 3.33 (6H, s), 3.95 (2H, s), 5.06 (1H, d, J = 6.4), 5.40 (1H, d, J = 6.4); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 2*E* isomer, 13.2, 50.7, 56.5, 76.3, 99.0, 123;2, 137.2; 2*Z* isomer, 20.0, 50.7, 56.5, 70.0, 96.5, 125.1, 137.7.

(2*E*)-1,1-Dimethoxy-4-phenoxybut-2-ene (4a). A reaction vessel was charged with phenol (2.72 g, 28.8 mmol, 1.2 equiv) and a solution of NaOH (40 mL, 0.75 M, 30.0 mmol, 1.25 equiv) and was stirred for 15 min. A solution of (2*E*)-bromo acetal **1** (4.66 g, 24.0 mmol, 1.0 equiv) in THF (20 mL) was added and allowed to react at 20 °C for 2 h. Ethyl acetate (60 mL) was then added, the organic phase was separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic fractions were first concentrated and then rediluted in ethyl acetate and washed with NaOH (9 M). The organic fraction was finally dried ($MgSO_4$) and the solvent evaporated. The resulting yellow oil was the (2*E*)-acetal **4a** (3.44 g, 69% yield), which could be flash chromatographed on silica gel using petroleum ether/ethyl acetate = 90:10 to give a pale yellow oil: IR (neat) 1601, 1500, 1458, 1377, 1353 cm^{-1}; MS (CI, NH_3) *m*/*z* 226 (M + 18, 18), 194 (100), 177 (78); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.30 (6H, s), 4.55 (2H, d, J = 5.0), 4.82 (1H, d, J = 4.5), 5.83 (1H, dd, J = 16.4, 4.5), 6.10 (1H, dt, J = 16.4, 5.0), 6.75−7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 52.6, 67.1, 102.0, 114.6, 120.8, 129.1, 129.4, 129.7, 158.3.

(2*E*)- and (2*Z*)-1,1-Dimethoxy-3-methyl-4-phenoxybut-2-ene (4b). The same procedure as above was followed starting from chloro acetal **2** 2*E*/2*Z* = 75:25 (10.09 g, 61.3 mmol, 1.0 equiv) in THF (50 mL), using 4.0 equiv of phenol and 4.5 equiv of NaOH (0.75 M) and stirring at 20 °C for 2 days. The yield was 13.38 g (98%) of a 2*E*/2*Z* = 75:25 mixture of **4b**, which can eventually be flash chromatographed on silica gel using petroleum ether/ethyl acetate = 80:20 as eluent to give a pale yellow oil: IR (neat) 1682, 1601, 1499 cm^{-1}; MS (EI, 70 eV) *m*/*z* 222 ($M^{\bullet+}$, 9), 190 (100); HRMS analysis (EI, $C_{13}H_{18}O_3$ = 222.1256), found 222.1255; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2*E* isomer, 1.83 (3H, s), 3.32 (6H, s), 4.43 (2H, s), 5.12 (1H, d, J = 5.9), 5.65 (1H, d, J = 5.9), 6.85−7.35 (5H, m); 2*Z* isomer, 1.90 (3H, s), 3.32 (6H, s), 4.57 (2H, s), 5.14 (1H, d, J = 5.9), 5.50 (1H, d, J = 5.9), 6.85−7.35 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 2*E* isomer, 14.1, 52.0, 72.0, 99.7, 114.6, 120.7, 123.9, 129.2, 137.0, 158.4; 2*Z* isomer, 20.7, 52.0, 66.5, 99.3, 115.1, 119.8, 125.7, 129.2, 137.7, 158.4. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.12; H, 8.45.

(2*E*)- and (2*Z*)-1,1-Dimethoxy-3-methyl-4-[(α-methylbenzyl)oxy]but-2-ene (5). A suspension of potassium hydride (1.79 g, 44.1 mmol, 1.1 equiv) in anhydrous THF (10 mL) was added via syringe and under argon to a solution of racemic α-methylbenzyl alcohol (4.89 g, 40.1 mmol, 1.0 equiv) in THF (20 mL). The reaction mixture was stirred at room temperature until 977 mL of hydrogen was recovered. The resulting alcoholate was added dropwise to a solution of chloro acetal **2** 2*E*/2*Z* = 75:25 (6.60 g, 40.1 mmol, 1.0 equiv) in THF (20 mL) at 0 °C and the solution warmed to room temperature for 1 h. The mixture was then quenched carefully at 0 °C with 20 mL of water, and the organic phase was separated, washed with saturated aqueous sodium hydrogenocarbonate solution, and concentrated. The resulting yellow oil was poured into ethyl acetate and dried over anhydrous magnesium sulfate and the solvent evaporated. The crude product was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate = 90:10 as eluent to give a 75:25 mixture of 2*E* and 2*Z* acetal **5**: 8.82 g (88% yield); colorless oil; IR (neat) 1681, 1450, 1372, 1208 cm^{-1}; MS (EI, 20 eV) *m*/*z* 218 ($M^{\bullet+}$ − 32, 8), 105 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2*E* isomer, 1.42 (3H, d, J = 6.5), 1.70 (3H, s), 3.29 (6H, s), 3.66, 3.80 (2H, $2d_{AB}$, J = 12.7), 4.40 (1H, q, J = 6.5), 5.05 (1H, d, J = 6.4), 5.50 (1H, d, J = 6.4), 7.29 (5H, m); 2*Z* isomer, 1.42 (3H, d, J = 6.5), 1.82 (3H, s), 3.29 (6H, s), 3.81, 3.91 (2H, $2d_{AB}$, J = 11.8), 4.38 (1H, q, J = 6.5), 4.81 (1H, d, J = 6.6), 5.38

(44) Guillam, A.; Toupet, L.; Maddaluno, J. To be published.

(1H, d, $J = 6.6$), 7.29 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 2*E* isomer, 14.1, 23.8, 52.0, 72.5, 76.7, 99.7, 123.0, 125.9, 127.1, 128.1, 138.2, 143.5, 2*Z* isomer, 20.9, 23.5, 52.0, 66.5, 76.7, 99.1, 125.4, 125.9, 127.1, 128.1, 138.4, 143.5.

(2*E*)- and (2*Z*)-1,1-Dimethoxy-4-menthoxy-3-methylbut-2-ene (6). A solution of L-(−)-menthol (3.32 g, 21.3 mmol, 1.0 equiv) in anhydrous THF (10 mL) was added via syringe and under argon to a suspension of sodium hydride (614 mg, 25.6 mmol, 1.2 equiv) in THF (5 mL). The reaction mixture was then stirred at room temperature until 512 mL of hydrogen evolved. HMPA was added (4 mL), followed by chloroacetal **2** 2*E*/2*Z* = 75:25 (3.30 g, 20.1 mmol, 1.0 equiv) in THF (5 mL), and the resulting solution was warmed to reflux for 24 h. The mixture was then quenched carefully at 0 °C with 2 mL of water and the organic phase separated, washed with a solution of saturated aqueous sodium hydrogenocarbonate, and concentrated. The resulting yellow oil was poured into ethyl acetate and dried on anhydrous magnesium sulfate, and the solvent was evaporated. The crude product was finally purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate/triethylamine = 95:4:1 as eluent to give a 75:25 mixture of 2*E* and 2*Z* acetal **6**: 3.27 g (54% yield); colorless oil; IR (neat) 1662, 1456, 1368, 1342 cm^{-1}; MS (EI, 70 eV) *m*/*z* 284 ($M^{\bullet+}$, 1), 252 (17), 114 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2*E* isomer, 0.70 (3H, d, $J = 6.9$), 0.83 (3H, d, $J = 6.9$), 0.86 (3H, d, $J = 6.9$), 1.70 (3H, s), 0.65−1.05, 1.10−1.40, 1.50−1.65, 1.95−2.35 (9H, 4m), 3.05 (1H, td, J = 11.0, 4.5), 3.26 (6H, s), 3.75, 3.95 (2H, $2d_{AB}$, $J = 12.5$), 5.02 (1H, d, $J = 6.7$), 5.48 (1H, d, $J = 6.7$); 2*Z* isomer, 0.70 (3H, d, $J = 6.9$), 0.83 (3H, d, $J = 6.9$), 0.86 (3H, d, $J = 6.9$), 1.77 (3H, s), 0.65−1.05, 1.10−1.40, 1.50−1.65, 1.95−2.35 (9H, 4m), 3.05 (1H, td, 11.0, 4.5), 3.26 (6H, s), 3.85, 4.13 (2H, $2d_{AB}$, $J = 12.5$), 5.05 (1H, d, $J = 6.7$), 5.32 (1H, d, $J = 6.7$); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 2*E* isomer, 14.4, 15.9, 20.7, 22.1, 23.0, 25.2, 31.3, 34.3, 40.1, 48.1, 51.9, 73.1, 78.6, 99.9, 123.0, 139.1, 2*Z* isomer, 15.9, 20.7, 21.0, 22.1, 23.0, 25.2, 31.3, 34.3, 40.1, 48.1, 51.9, 66.6, 78.6, 99.4, 124.6, 139.1.

(2*E*)- and (2*Z*)-1,1-Dimethoxy-3-methyl-4-(phenylmenthoxy)but-2-ene (7). See the Supporting Information.

General Procedures for the Synthesis of Dienes 8−15. For the preparation of dienes **8**−**15**, the γ-oxygenated acetals described above were used in their 2*E* configuration in the case of **3a** and **4a** and in their 2*E*/2*Z* = 75:25 configuration in the case of **3b**, **4b**, and **5**−**7**. The identification as well as the measurement of the ratio of different dienic stereoisomers obtained were performed by ^{1}H NMR, GC, and GC/MS analysis. Four methods A−D have been employed for the preparation of vinylic and allylic dienes.

Method A. Under an atmosphere of argon, a solution of *n*-BuLi in hexane (1.35 mL, 2.0 M, 2.70 mmol, 1.2 equiv) was added to a solution of γ-oxygenated acetal (2.25 mmol, 1.0 equiv) in anhydrous THF (3 mL) at −40 °C. After a few seconds, the solution turned deep purple and was stirred for 15 min at this temperature. It was then quenched with 1 mL of water, the organic phase was separated, and the aqueous layer was extracted twice with ethyl acetate or ethylic ether. The combined solvents were evaporated, and the resulting red-yellow oil was rediluted in ethyl acetate or ethylic ether, dried ($MgSO_4$), and concentrated to give the crude product.

Method B. Under an atmosphere of argon, a solution of potassium bis(trimethylsilyl)amide (KHMDS, 671 mg, 3.37 mmol, 1.5 equiv) in THF (5 mL) was added at 20 °C to neat γ-oxygenated acetal (2.25 mmol, 1.0 equiv). The slowly turning purple solution was stirred for 1 h at room temperature and then quenched at 0 °C with 1 mL of water. The rest of the procedure was similar to method A.

Method C. A reaction vessel was swept with argon and charged with γ-oxygenated acetal (2.25 mmol, 1.0 equiv), diisopropylethylamine (DIPEA, 873 mg, 6.75 mmol, 3.0 equiv), and CH_2Cl_2 (5 mL). After the solution was cooled to −40 °C, trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1.30 mL, 1.5 g, 6.75 mmol, 3.0 equiv) was added dropwise via syringe to the cold solution with stirring. The resulting yellow mixture was allowed to warm to room temperature and subsequently stirred at this same temperature for 3 h. The resulting purple solution was quenched by the addition of aqueous NaOH solution (0.25 mL, 1.0 M, 0.25 mmol, 0.11 equiv), diluted with 10 mL of petroleum ether, and refrigerated overnight to precipitate the trialkylammonium triflate salt. The organic phase was then separated, the aqueous layer was extracted twice with petroleum ether, and the combined solvents were dried (Na_2CO_3) and concentrated to give the crude product.

Method D. Neat γ-oxygenated acetal (5.0 mmol, 1.0 equiv) was warmed to 120 °C in a round-bottom flask equipped with a condenser under argon, until methanol reflux and a progressive dark coloration of the medium were observed. The crude product was obtained after evaporation of the methanol.

(1*Z*,3*E*)- and (1*Z*,3*Z*)-1,4-Dimethoxybuta-1,3-diene (8a). Method A. Starting from acetal **3a** (330 mg, 2.25 mmol) and using ethylic ether for the extractions, 243 mg (95% yield) of crude product **8a** was obtained as an oily mixture of isomers 1*E*,3*E*/1*Z*,3*E*/1*Z*,3*Z* = 6:74:20. **Method B.** Starting from acetal **3a** (330 mg, 2.25 mmol), 251 mg (98% yield) of crude product **8a** was obtained as a 83:17 mixture of 1*Z*,3*E*/1*Z*,3*Z* isomers: IR (neat) 1610, 1467, 1380, 1330, 1211 cm^{-1}; MS (EI, 70 eV) 1*E*,3*E* isomer, *m*/*z* 114 ($M^{\bullet+}$, 49), 71 (100); 1*Z*,3*E* isomer, *m*/*z* 114 ($M^{\bullet+}$, 71), 71 (100); 1*Z*,3*Z* isomer, *m*/*z* 114 ($M^{\bullet+}$, 73), 71 (100); ^{1}H NMR (200 MHz, C_6D_6) δ (ppm) 1*Z*,3*E* isomer, 3.17 (6H, s), 4.96 (1H, dd, $J = 10.8, 6.1$), 5.56 (1H, d, $J = 6.1$), 6.06 (1H, dd, $J = 12.4, 10.8$), 6.57 (1H, d, $J = 12.4$); (1*Z*,3*Z* isomer, 3.15 (6H, s), 5.60 (2H, d, $J = 6.1$), 5.75 (2H, m); ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 1*Z*,3*E* isomer, 54.9, 58.7, 98.7, 103.1, 143.4, 148.4; 1*Z*,3*Z* isomer, 54.9, 100.1, 144.7.

(1*E*,3*E*)- and (1*Z*,3*E*)-1,4-Dimethoxy-2-methylbuta-1,3-diene (8b). Method A. Starting from acetal **3b** (360 mg, 2.25 mmol) and using ethylic ether for the extractions, the crude product obtained was an oily 10:90 mixture of 1*E*,3*E*/1*Z*,3*E* isomers **8b**, 282 mg (98% yield). **Method D.** Starting from acetal **3b** (360 mg, 2.25 mmol), the crude product was obtained as 256 mg (89% yield) of a 30:70 mixture of 1*E*,3*E* and 1*Z*,3*E* isomers **8b**: IR (neat) 1618, 1456, 1380, 1336, 1210 cm^{-1}; MS (EI, 70 eV) 1*E*,3*E* isomer, *m*/*z* 128 ($M^{\bullet+}$, 100); 1*Z*,3*E* isomer, *m*/*z* 128 ($M^{\bullet+}$, 100); HRMS analysis (EI, $C_7H_{12}O_2$ = 128.0837), found 128.0833; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1*E*,3*E* isomer, 1.60 (3H, s), 3.50 (6H, s), 5.39 (1H, d, $J = 12.6$), 5.89 (1H, s), 6.31 (1H, d, $J = 12.6$); 1*Z*,3*E* isomer, 1.54 (3H, s), 3.50 (6H, s), 5.64 (1H, s), 5.87 (1H, d, $J = 13.0$), 6.44 (1H, d, $J = 13.0$); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 1*E*,3*E* isomer, 20.6, 55.7, 101.0, 143.8, 144.7; 1*Z*,3*E* isomer, 13.7, 55.4, 58.9, 100.6, 109.0, 141.4, 148.5.

(1*E*,3*E*)-, (1*E*,3*Z*)-, (1*Z*,3*E*)-, and (1*Z*,3*Z*)-4-Methoxy-1-phenoxybuta-1,3-diene (9a). Method A. Starting from acetal **4a** (469 mg, 2.25 mmol) and using ethyl acetate for the extractions, the crude product **9a** (368 mg, 93% yield) was obtained as an oily mixture of 1*E*,3*E*/1*Z*,3*E*/1*Z*,3*Z* isomers (8:72:20). **Method B.** Starting from acetal **4a** (469 mg, 2.25 mmol), the crude product was an 80:20 mixture of 1*Z*,3*E*/1*Z*,3*Z* isomers **9a**, 384 mg (97% yield). **Method D.** Starting from acetal **4a** (1.04 g, 5.0 mmol), the crude product **9a** (871 mg, 99% yield) was a mixture of the 1*E*,3*E*/1*E*,3*Z*/1*Z*,3*E*/1*Z*,3*Z* isomers (17:8:56:19): IR (neat) 1618, 1585 cm^{-1}; MS (EI, 70 eV) 1*E*,3*E* isomer, *m*/*z* 176 ($M^{\bullet+}$, 100); 1*E*,3*Z* isomer, *m*/*z* 176 ($M^{\bullet+}$, 100); 1*Z*,3*E* isomer, *m*/*z* 176 ($M^{\bullet+}$, 100); 1*Z*,3*Z* isomer, *m*/*z* 176 ($M^{\bullet+}$, 100); ^{1}H NMR (200 MHz, $CDCl_3$) attribution of the chemical shifts to the protons of the different isomers has been made possible by a set of homodecoupling experiments: δ (ppm) 1*E*,3*E* isomer, 3.66 (3H, s), 5.47 (1H, t, $J = 12.4$), 5.91 (1H, t, $J = 12.4$), 6.53 (1H, t, $J = 12.4$), 6.59 (1H, d, $J = 12.4$), 7.00−7.40 (5H, m); 1*Z*,3*E* isomer, 3.63 (3H, s), 5.39 (1H, dd, J = 12.4, 6.1), 5.92 (1H, t, $J = 12.2$), 6.25 (1H, d, $J = 6.1$), 6.68 (1H, d, $J = 12.4$), 7.00−7.40 (5H, m); 1*Z*,3*Z* isomer, 3.60 (3H, s), 5.51 (1H, dd, $J = 11.3, 6.1$), 5.78 (1H, dd, $J = 11.3, 6.1$), 5.96 (1H, d, $J = 6.1$), 6.28 (1H, d, $J = 6.1$), 7.00−7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 1*Z*,3*E* isomer, 56.0, 97.8, 108.8, 116.2, 122.4, 129.4, 137.3, 150.0, 157.4.

(1*E*,3*E*)-, (1*E*,3*Z*)-, (1*Z*,3*E*)-, and (1*Z*,3*Z*)-4-Methoxy-2-methyl-1-phenoxybuta-1,3-diene (9b). Method A. Starting from acetal **4b** (500 mg, 2.25 mmol), the crude product **9b** (389 mg, 91% yield) was obtained as an 8:92 mixture of the 1*E*,3*E* and 1*Z*,3*E* isomers. Starting this time from pure 1*Z*

acetal **16** (see below, 500 mg, 2.25 mmol) and working at −10 °C in THF for the deprotonation, diene **9b** (406 mg, 95% yield) was obtained under its pure 1*Z*,3*E* configuration. **Method B.** Starting from acetal **4b** (500 mg, 2.25 mmol), the crude product was obtained as a 15:85 mixture of 1*E*,3*E* and 1*Z*,3*E* isomers **9b**, 423 mg (99% yield). **Method D.** Starting from acetal **4b** (1.11 g, 5.0 mmol), 893 mg (94% yield) of crude product **9b** was obtained as a 40:10:40:10 mixture of 1*E*,3*E*, 1*E*,3*Z*, 1*Z*,3*E*, and 1*Z*,3*Z* isomers: IR (neat) 1618, 1590, 1488, 1384, 136, 1230 cm^{-1}; MS (EI, 70 eV) *m*/*z* 190 ($M^{\bullet+}$, 100); HRMS analysis (EI, $C_{12}H_{14}O_2$ = 190.0994), found 190.0995; ^1H NMR (200 MHz, C_6D_6) δ (ppm) 1*E*,3*E* isomer, 1.78 (3H, s), 3.14 (3H, s), 5.55 (1H, d, *J* = 12.9), 6.32 (1H, s), 6.50 (1H, d, *J* = 12.9), 6.80−7.25 (5H, m); 1*Z*,3*E* isomer, 1.54 (3H, s), 3.14 (3H, s), 6.01 (1H, s), 6.32 (1H, d, *J* = 13.1), 6.62 (1H, d, *J* = 13.1), 6.80−7.25 (5H, m); NOE experiments showed that irradiation at δ 6.01 resulted in enhancement at δ 1.54, and irradiation at δ 1.54 resulted in enhancements at both δ 6.01 and 6.62; ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 1*E*,3*E* isomer, 14.1, 55.7, 104.6, 111.8, 115.2, 119.9, 129.4, 137.5, 146.8, 156.5; 1*Z*,3*E* isomer, 14.1, 55.1, 100.3, 115.8, 116.0, 122.1, 129.4, 135.2, 148.3, 157.8. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.41; H, 7.83.

(1*E*)-1-Methoxy-3-(phenoxymethylene)buta-1,3-diene (10). Method C. Starting from acetal **4b** (500 mg, 2.25 mmol), 350 mg (82% yield) of crude product was obtained as a 70:30 mixture of vinylic **9b** and allylic **10** dienes. While **9b** was a 1*E*,3*E*/1*Z*,3*E* = 10:90 mixture, **10** was pure *E*. **10** was separated by flash column chromatography on silica gel using petroleum ether/ethyl acetate = 95:5 as eluent to give a colorless oil: IR (neat) 1618, 1590 cm^{-1}; MS (EI, 70 eV) *m*/*z* 190 ($M^{\bullet+}$, 100); HRMS analysis (EI, $C_{12}H_{14}O_2$ = 190.0994), found 190.0992; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.61 (3H, s), 4.62 (2H, s), 5.06 (2H, s), 5.59 (1H, d, *J* = 13.1), 6.80 (1H, d, *J* = 13.1), 6.90−7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 56.0, 68.8, 104.5, 112.8, 114.7, 120.8, 129.3, 139.0, 149.2, 158.4.

(1*E*,3*E*)- and (1*Z*,3*E*)-4-Methoxy-2-methyl-1-[(α-methylbenzyl)oxy]buta-1,3-diene (11). Method A. Starting from acetal **5** (563 mg, 2.25 mmol), the yield was 480 mg of the crude product **11** (98%), which was an oily mixture of the 1*E*,3*E* and 1*Z*,3*E* isomers (7:93): IR (neat) 1611, 1456, 1375, 1338, 1210 cm^{-1}; MS (CI, CH_4) *m*/*z* 219 (M + 1, 94), 218 (100); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 1*E*,3*E* isomer, 1.52 (3H, d, *J* = 6.5), 1.76 (3H, s), 3.48 (3H, s), 4.43 (1H, q, *J* = 6.5), 5.51 (1H, d, *J* = 12.8), 5.97 (1H, s), 6.35 (1H, d, *J* = 12.8), 7.15−7.45 (5H, m); 1*Z*,3*E* isomer, 1.52 (3H, d, *J* = 6.5), 1.58 (3H, s), 3.60 (3H, s), 4.74 (1H, q, *J* = 6.5), 5.74 (1H, s), 6.13 (1H, d, *J* = 12.8), 6.49 (1H, d, *J* = 12.8), 7.15−7.45 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 1*Z*,3*E* isomer, 14.6, 23.7, 56.1, 79.3, 101.6, 109.8, 125.8, 127.4, 128.4, 139.3, 143.4, 146.9.

(1*E*,3*E*)- and (1*Z*,3*E*)-1-Menthoxy-4-methoxy-2-methylbuta-1,3-diene (12). Method A. Starting from acetal **6** (640 mg, 2.25 mmol), 414 mg of the pure vinylic compound **12** (73%) was obtained as an oily 8:92 mixture of 1*E*,3*E* and 1*Z*,3*E* isomers. **Method D.** Starting from neat acetal **6**, the dark coloration appeared at room temperature in 6 days, leading to a 35:65 mixture of 1*E*,3*E*/1*Z*,3*E* dienes **12**: IR (neat) 1618, 1458, 1371, 1334, 1210 cm^{-1}; MS (EI, 70 eV) *m*/*z* 252 ($M^{\bullet+}$, 14), 114 (100); HRMS analysis (EI, $C_{16}H_{28}O_2$ = 252.2089), found 252.2077; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 1*E*,3*E* isomer, 0.75 (3H, d, *J* = 6.9), 0.87 (6H, 2d, *J* = 6.9), 1.66 (3H, s), 0.70−1.12, 1.25−1.50, 1.52−1.85, 1.90−2.30 (9H, 4m), 3.32 (1H, td, *J* = 11.0, 4.5), 3.57 (3H, s), 5.44 (1H, d, *J* = 12.9), 6.06 (1H, s), 6.32 (1H, d, *J* = 12.9); 1*Z*,3*E* isomer, 0.75 (3H, d, *J* = 6.9), 0.87 (6H, 2d, *J* = 6.9), 1.58 (3H, s), 0.70−1.12, 1.25−1.50, 1.52−1.85, 1.90−2.30 (9H, 4m), 3.32 (1H, td, *J* = 11.0, 4.5), 3.57 (3H, s), 5.77 (1H, s), 5.97 (1H, d, *J* = 12.9), 6.43 (1H, d, *J* = 12.9); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 1*Z*,3*E* isomer, 14.5, 16.2, 20.5, 21.9, 23.4, 25.7, 31.4, 34.2, 41.4, 47.6, 56.0, 81.2, 101.7, 108.6, 139.7, 146.2.

(1*E*)-1-Methoxy-3-(menthoxymethylene)buta-1,3-diene (13). Method B. Starting from acetal **6** (640 mg, 2.25 mmol), 561 mg of a yellow oil, which was the pure allylic isomer **13** (99% yield) in its 1*E* configuration, was obtained; IR (neat) 1642, 1456, 1360, 1211 cm^{-1}; MS (EI, 70 eV) *m*/*z* 252 ($M^{\bullet+}$, 100); HRMS analysis (EI, $C_{16}H_{28}O_2$ = 252.2089), found 252.2088; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.69 (3H, d, *J* = 6.9), 0.84 (3H, *J* = 6.9), 0.88 (3H, d, *J* = 6.9), 0.65−1.05, 1.10−1.40, 1.50−1.65, 2.00−2.32 (9H, 4m), 3.05 (1H, td, *J* = 10.5, 4.0), 3.52 (3H, s), 3.90, 4.16 (2H, $2d_{AB}$, *J* = 11.6), 4.87 (2H, s), 5.45 (1H, d, *J* = 13.0), 6.74 (1H, d, *J* = 13.0); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 15.7, 20.8, 22.1, 22.9, 25.0, 31.3, 34.4, 39.8, 48.1, 55.9, 67.0, 77.8, 104.9, 112.1, 140.7, 149.2.

(1*Z*,3*E*)-4-Methoxy-2-methyl-1-(phenylmenthoxy)buta-1,3-diene (14) and (1*E*)-1-Methoxy-3-[(phenylmenthoxy)-methyl]buta-1,3-diene (15). Method A. Starting from acetal **7** (500 mg, 1.39 mmol), the deprotonation was done this time in ethylic ether and required 5.0 equiv of *n*-BuLi and warming to room temperature for 1 h. The yield was 420 mg of the crude product (92%), which was an oily 33:67 mixture of vinylic 1*Z*,3*E* isomer **14** and allylic 1*E* isomer **15**. **Method B.** Starting from acetal **7** (150 mg, 0.42 mmol), the deprotonation required 5.0 equiv of KHMDS and warming to reflux of THF followed by stirring at 20 °C for 12 h. The yield was 127 mg in pure 1*E* allylic diene **15** (95%). Vinylic diene **14**: ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.84 (3H, d, *J* = 6.4), 1.33 (3H, s), 1.41 (3H, s), 1.58 (3H, s), 0.60−1.00, 1.10−1.50, 1.60−1.85 (8H, 4m), 3.10 (1H, m), 3.55 (3H, s), 5.63 (1H, s), 5.82 (1H, d, *J* = 12.8), 6.40 (1H, d, *J* = 12.8), 7.00−7.40 (5H, m). Allylic diene **15**: IR (neat) 1644, 1601, 1456, 1368, 1210 cm^{-1}; MS (EI, 70 eV) *m*/*z* 328 ($M^{\bullet+}$, 57), 214 (73), 131 (85), 99 (100); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.84 (3H, d, *J* = 6.4), 1.33 (3H, s), 1.41 (3H, s), 0.60−1.00, 1.10−1.50, 1.60−1.85, 1.95−2.15 (8H, 4m), 3.10 (1H, m), 3.57 (3H, s), 3.76, 4.11 (2H, $2d_{AB}$, *J* = 12.5), 4.87 (2H, s), 5.47 (1H, d, *J* = 12.8), 6.66 (1H, d, *J* = 12.8), 7.00−7.40 (5H, m); ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 21.8, 24.7, 27.3, 30.3, 31.2, 34.7, 40.3, 46.4, 53.2, 55.0, 68.4, 80.8, 105.1, 110.6, 124.5, 125.9, 127.5, 141.3, 148.7, 150.4.

(1*E*)- and (1*Z*)-4,4-Dimethoxy-2-methyl-1-phenoxybut-1-ene (16). Using *t*-BuOK. A solution of potassium *tert*-butylate (740 mg, 6.6 mmol, 1.1 equiv) in THF (10 mL) was added under argon to a solution of acetal **4b** (1.33 g, 6.0 mmol, 1.0 equiv) in THF (10 mL). This slowly turning purple mixture was stirred at room temperature for 20 h and then quenched carefully with 20 mL of water. Ethyl acetate was added, and the organic fraction was separated and concentrated. The resulting yellow oil was then rediluted in ethyl acetate and dried ($MgSO_4$). After elimination of the solvent, a mixture of several compounds was obtained. Its ratio (as determined by ^1H NMR analysis) depended on the conformation of the starting acetal **4b**. While pure 2*E* isomer **4b** led to a 19:40:38:3 mixture of 1*E* acetal **16**, 1*Z* acetal **16**, 1*Z*,3*E* vinylic diene **9b**, and 1*E* allylic diene **10**, pure 2*Z* isomer **4b** gave a 0:77:13:10 ratio of the same products. In this latter case, acetal **16** of the 1*Z* configuration was isolated after flash column chromatography as 812 mg of a colorless oil (61% yield). **Using *t*-BuP4.** A solution of *t*-BuP4 in hexane (0.45 mL, 1.0 M, 1.0 equiv) was added, under argon and at 20 °C, to 100 mg of acetal **4b** 1*E*/1*Z* = 75:25 in 1 mL of THF. After being stirred at 20 °C for 1 h, 3 mL of ethyl ether was added to the resulting purple solution, and the organic solution was separated from an oily residue. After evaporation, 67 mg (70% yield) of a yellow oil containing acetal **16** (1*E*,1*Z*) and diene **9b** (1*Z*,3*E*) as a 26:44:30 mixture was obtained. Acetal **16**: IR (neat) 1*Z*,3*E* isomer, 1680, 1593, 1491, 1375, 1288 cm^{-1}; MS (EI, 70 eV) *m*/*z* 222 ($M^{\bullet+}$, 5), 190 (8), 75 (100); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 1*E* isomer, 1.74 (3H, s), 2.28 (2H, d, *J* = 5.9), 3.35 (6H, s), 4.49 (1H, t, *J* = 5.9), 6.30 (1H, s), 6.95−7.35 (5H, m); 1*Z* isomer, 1.74 (3H, s), 2.53 (2H, d, *J* = 5.9), 3.32 (3H, s), 4.57 (1H, t, *J* = 5.9), 6.28 (1H, s), 6.95−7.32 (5H, m); a NOESY experiment showed a cross-peak between the ethylenic proton at δ 6.28 and the vinylic methyl at δ 1.74; ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 1*Z* isomer, 17.8, 32.4, 52.5, 102.9, 115.8, 116.2, 122.0, 129.3, 137.0, 157.4.

(1*E*,3*E*)- and (1*Z*,3*E*)-1-Phenoxy-2,5,5-trimethylhexa-1,3-diene (17). 4.5 mL of *t*-BuLi in pentane (2.5 M, 11.25 mmol, 5.0 equiv) were added under argon to a solution of acetal **4b** (500 mg, 2.25 mmol, 1.0 equiv) in anhydrous ethyl ether (5 mL) at −70 °C. After 15 min at this temperature, the purple solution was warmed to room temperature for 24 h and then quenched at 0 °C with 3 mL of water. The organic phase was separated and the aqueous layer extracted twice with ethyl ether. The combined organic fractions were dried ($MgSO_4$) and the solvents evaporated. The resulting reddish oil was a 25:75 mixture of 1*E*,3*E* and 1*Z*,3*E* isomers of diene **17** (from NMR data). The 1*Z*,3*E* isomer was isolated after flash column chromatography on silica gel using petroleum ether/ethyl acetate = 95:5 as eluent to give 267 mg of a colorless oil (55% yield): IR (neat) 1*Z*,3*E* isomer 1609, 1494, 1241 cm^{-1}; MS (EI, 70 eV) *m*/*z* 216 ($M^{\bullet+}$, 68), 201 (17), 123 (97), 107 (100); HRMS analysis (EI, $C_{15}H_{20}O$ = 216.1514), found 216.1504; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 1*E*,3*E* isomer, 1.08 (9H, s), 1.77 (3H, s), 5.75 (1H, d, J = 12.9), 6.20 (1H, s), 6.60 (1H, d, J = 15.5), 6.80−7.10 (5H, m); 1*Z*,3*E* isomer, 1.08 (9H, s), 1.77 (3H, s), 5.72 (1H, d, J = 15.5), 6.28 (1H, s), 6.65 (1H, d, J = 15.5), 6.80−7.10 (5H, m); NOE experiments on the 1*Z*,3*E* isomer showed that irradiation at δ 6.28 resulted in enhancement at δ 1.77, irradiation at δ 5.72 resulted in enhancement at δ 1.77, and irradiation at δ 1.77 resulted in enhancements at both δ 5.72 and 6.28; ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 1*Z*,3*E* isomer, 14.6, 30.1, 33.3, 116.3, 117.8, 119.0, 122.3, 129.4, 137.3, 141.3, 157.5.

General Procedure for the Cycloaddition Reactions of Vinylic and Allylic Dienes with *N*-Methylmaleimide. The solvents (anhydrous THF or toluene), the temperature, and the length of the reaction were dependent on the starting diene. Under an atmosphere of argon, neat *N*-methylmaleimide (2.4 mmol, 1.2 equiv) and 100 mg of hydroquinone was added to a solution of diene (2.0 mmol, 1.0 equiv) in the solvent (20 mL). This resulting mixture was stirred at a selected temperature until the starting reactive dienes completely disappeared. The solvent was then evaporated and the crude product purified by flash column chromatography on silica gel using a 80:20 petroleum ether/ethyl acetate mixture as eluent for adducts derived from vinylic dienes. A 60:40 ratio was retained for those derived from allylic dienes.

***N*-Methyl-7,9-dioxo-5-methoxy-2-phenoxy-8-azabicyclo-[4.3.0]non-3-ene (18a).** Starting from 1*E*,3*E*/1*Z*,3*E*/1*Z*,3*Z* = 8:72:20 diene **9a** prepared following method A (352 mg, 2.0 mmol) and refluxing for 6 h in toluene, 339 mg of adduct **18a** was isolated as a colorless oil. This adduct was derived from the 1*Z*,3*E* diene (59% yield, 82% conversion of this isomer): IR (neat) 1706, 1599, 1496, 1230 cm^{-1}; MS (CI, t-BuH) *m*/*z* 288 (M + 1, 100); HRMS analysis (EI, $C_{16}H_{17}NO_4$ = 287.1158), found 287.1170; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.97 (3H, s), 3.13 (1H, dd, J = 9.6, 4.6), 3.25 (3H, s), 3.33 (1H, dd, J = 9.6, 3.5), 4.30 (1H, m), 5.21 (1H, d, J = 4.9), 6.20 (2s, 2H), 6.75−7.40 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 24.6, 43.0, 44.3, 56.6, 69.6, 70.7, 116.2, 121.6, 129.5, 133.4, 134.0, 156.9, 176.0, 177.7.

***N*-Methyl-7,9-dioxo-5-methoxy-3-methyl-2-phenoxy-8-azabicyclo[4.3.0]non-3-ene (18b).** Starting from 1*E*,3*E*/1*Z*,3*E* = 8:92 diene **9b** prepared following method A (380 mg, 2.0 mmol) and refluxing for 12 h in toluene, 385 mg of white solid **18b** was isolated (64% yield), which was derived from the 1*Z*,3*E* isomer of **9b** (70% conversion of this diene). After recrystallization in Et_2O: mp 108−110 °C; IR (neat) 1706, 1600, 1490, 1431, 1266 cm^{-1}; MS (EI, 70 eV) *m*/*z* 301 ($M^{\bullet+}$, 17), 208 (79), 176 (41), 123 (100); HRMS analysis (EI, $C_{17}H_{19}NO_4$ = 301.1314), found 301.1313; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.85 (3H, s), 2.94 (3H, s), 3.22 (1H, dd, J = 9.1, 5.5), 3.32 (3H, s), 3.35 (1H, dd, J = 9.1, 4.0), 4.31 (1H, t, J = 5.5), 5.18 (1H, d, J = 4.0), 5.85 (1H, d, J = 5.5), 6.90−7.35 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 20.3, 24.5, 42.3, 44.4, 56.8, 71.8, 72.5, 116.1, 121.6, 125.2, 129.5, 139.9, 157.6, 175.6, 177.2. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.77; H, 6.31; N, 4.65. Found: C, 67.92; H, 6.73; N, 4.73.

***N*-Methyl-7,9-dioxo-5-methoxy-3-methyl-2-(α-methylbenzyloxy)-8-azabicyclo[4.3.0]non-3-enes (19) and (20).** See the Supporting Information.

***N*-Methyl-7,9-dioxo-2-menthoxy-5-methoxy-3-methyl-8-azabicyclo[4.3.0]non-3-enes (21) and (22).** See the Supporting Information.

***N*-Methyl-7,9-dioxo-5-methoxy-3-methyl-2-(phenylmenthoxy)-8-azabicyclo[4.3.0]non-3-enes (23) and (24).** See the Supporting Information.

***N*-Methyl-7,9-dioxo-2-menthoxy-5-methoxy-3-methyl-8-azabicyclo[4.3.0]non-3-enes (25) and (26).** A 35:65 mixture of 1*E*,3*E* and 1*Z*,3*E* dienes **12**, prepared following method D (437 mg, 2.0 mmol), in THF was first stirred at 20 °C for 1 day. The selective cycloaddition of the 1*E*,3*E* isomer was observed leading to a mixture of two stereoisomers **25**, **26** in 35% NMR yield and with 8% diastereoisomeric excess. This solution was then warmed to reflux for 4 days, putting the 1*Z*,3*E* isomer into reaction. After flash chromatography, the expected adducts **21** and **22** (described above) were isolated (de = 42%) as well as the two new adducts **25** and **26** derived from diene 1*E*,3*E*. This yielded 545 mg of a colorless oil (77% yield): IR (neat) 1704, 1434, 1382, 1284 cm^{-1}; MS (CI, CH_4) *m*/*z* 392 (M + 29, 81), 364 (M + 1, 65), 332 (49), 294 (38), 266 (100); HRMS analysis (EI, $C_{21}H_{33}NO_4$ = 363.2410), found 363.2412; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm), **25**, 0.74 (3H, d, J = 6.9), 0.93 (6H, d, J = 6.9), 1.80 (3H, s), 0.65−1.45, 1.50−1.75, 1.90−2.70 (9H, 3m), 2.90 (3H, s), 3.00−3.33 (3H, m), 3.44 (3H, s), 4.05 (2H, m), 5.57 (1H, m); **26**, 0.68 (3H, d, J = 6.9), 0.83 (3H, d, J = 6.9), 0.91 (3H, d, J = 6.9), 1.83 (3H, s), 0.65−1.45, 1.50−1.75, 1.90−2.70 (9H, 3m), 2.92 (3H, s), 3.00−3.33 (3H, m), 3.44 (3H, s), 4.01 (1H, m), 4.13 (1H, t, J = 5.5), 5.66 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) **25**, 15.8, 21.3, 21.6, 22.3, 22.8, 24.2, 24.5, 30.6, 34.4, 40.9, 42.3, 43.4, 48.4, 56.7, 72.0, 73.3, 79.2, 122.6, 141.1, 175.3, 176.3; **26**, 15.8, 21.1, 22.2, 22.6, 22.8, 24.2, 24.7, 31.5, 34.4, 40.9, 42.3, 43.9, 48.4, 57.2, 72.0, 72.7, 77.4, 123.3, 141.1, 176.3, 177.9.

***N*-Methyl-7,9-dioxo-4-(menthoxymethyl)-2-methoxy-8-azabicyclo[4.3.0]non-3-enes (27) and (28).** Stirring (1*E*) allylic diene **13**, prepared following method B (437 mg, 2.0 mmol), for 10 min in THF, a mixture of diastereoisomers **27** and **28** was obtained with a 32% de (measured by quantitative ^{13}C NMR and HPLC on the crude product), leading to 530 mg of a colorless oil after purification (73% yield): IR (neat) 1704, 1438, 1387, 1285 cm^{-1}; MS (EI, 70 eV) *m*/*z* 363 ($M^{\bullet+}$, 9), 225 (92), 92 (100); HRMS analysis (EI, $C_{21}H_{33}NO_4$ = 363.2410), found 363.2412; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) **27**, 0.65−1.06, 1.10−1.45, 1.50−1.80, 1.95−2.30, 2.40−2.60 (20H, 5m), 2.92 (3H, s), 2.90−3.15 (3H, m), 3.17 (3H, s), 3.75, 4.06 (2H, $2d_{AB}$, J = 14.0), 4.20 (1H, t, J = 3.9), 5.98 (1H, d, J = 4.1); **28**, 0.65−1.06, 1.10−1.45, 1.50−1.80, 1.95−2.30, 2.40−2.60 (20H, 5m), 2.92 (3H, s), 2.90−3.15 (3H, m), 3.17 (3H, s), 3.81, 4.02 (2H, $2d_{AB}$, J = 14.0), 4.20 (1H, t, J = 3.9), 5.98 (1H, d, J = 4.1); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) **27**, 16.1, 20.8, 22.2, 23.2, 23.6, 24.5, 25.5, 31.4, 34.3, 37.2, 40.2, 42.4, 48.1, 56.5, 71.0, 72.0, 79.5, 122.8, 141.7, 176.7, 179.8; **28**, 16.1, 20.8, 22.2, 23.2, 23.6, 24.5, 25.5, 31.4, 34.3, 37.2, 40.2, 42.4, 48.1, 56.5, 70.7, 72.0, 79.1, 122.4, 141.7, 176.7, 179.8.

***N*-Methyl-7,9-dioxo-2-methoxy-4-[(phenylmenthoxy)-methyl]-8-azabicyclo[4.3.0]non-3-enes (29) and (30).** See the Supporting Information.

General Procedure for the Cycloaddition Reactions of 1*E*,3*E* or 1*Z*,3*E* Dienes with Methyl Acrylate. Under an atmosphere of argon, 100 mg of hydroquinone was added to a solution of diene (2.0 or 4.0 mmol, 1.0 equiv) in a mixture of toluene (5 mL) and methyl acrylate (15 mL). The reaction conditions were dependent on the configuration of the starting diene: 1*E*,3*E* isomers were reacted at reflux of methyl acrylate (80 °C) in a round-bottom flask equipped with a condenser, whereas 1*Z*,3*E* were put in sealed tubes and warmed to 140 °C for several days. After NMR and GC control of the mixture, the polymers of methyl acrylate were adsorbed on silica gel, the solvents were removed, and the crude product was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate = 80:20 or 90:10 as eluent.

3-Methoxy-4-(methoxycarbonyl)-1-methyl-6-phenoxycyclohex-1-ene (31b). Cycloaddition of 1*Z*,3*E* Isomer. Warming 380 mg (2.0 mmol) of 1*E*,3*E*/1*Z*,3*E* = 8:92 diene **9b**, prepared following method A, at 140 °C for 2 days, 465 mg of a single stereoisomer **31b**, derived from the 1*Z*,3*E* isomer, was

isolated as a white solid (64% yield, 70% with respect to the 1*Z*,3*E* diene). A recristallization was done in petroleum ether/ethyl acetate = 70:30. The same reaction was also performed in anhydrous methanol under high pressure (13 kbar), using 4 equiv of methyl acrylate and leading in 4 days to the same adduct **31b** with a comparable yield: mp 77−78 °C; IR (neat) 1739, 1596, 1491, 1221 cm^{-1}; MS (EI, 70 eV) *m*/*z* 276 ($M^{\bullet+}$, 4), 245 (8), 183 (100), 123 (81); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.85 (3H, s), 2.10 (1H, td, J = 13.8, 4.8), 2.28 (1H, ddd, J = 13.8, 4.0, 2.2), 2.96 (1H, dt, J = 13.6, 4.8), 3.36 (3H, s), 3.70 (3H, s), 4.04 (1H, t, J = 4.7), 4.61 (1H, m), 5.97 (1H, d, J = 5.5), 6.80−7.35 (5H, m); ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 21.1, 24.7, 40.6, 51.2, 56.7, 73.0 116.0, 121.2, 124.2, 129.9, 137.6, 158.7, 172.6. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.24; H, 7.20.

3-Methoxy-4-(methoxycarbonyl)-1-methyl-6-phenoxycyclohex-1-enes (32b) and (33b). Cycloaddition of 1*E*,3*E* Isomer. Warming 760 mg (4.0 mmol) of a 40:10:40:10 mixture of 1*E*,3*E*/1*E*,3*Z*/1*Z*,3*E*/1*Z*,3*Z* **9b** isomers, prepared following method D, at 80 °C for 2 days, led to an almost quantitative consumption of the 1*E*,3*E* diene, while other isomers remained nearly unreactive in these conditions. Two adducts were thus obtained as a 57:43 mixture of *endo*-**32b** and *exo*-**33b** diastereoisomers, corresponding to a regiocontrolled cycloaddition of 1*E*,3*E* diene and leading to 353 mg of colorless oil after purification (32% yield, 81% corresponding to 1*E*,3*E* diene): IR (neat) 1740, 1597, 1494, 1234 cm^{-1}; MS (EI, 70 eV) *m*/*z* 276 ($M^{\bullet+}$, 1), 183 (47), 123 (100); HRMS analysis (EI, $C_{16}H_{20}O_4$ = 276.1362), found 276.1365; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) **32b**, 1.82 (3H, s), 2.08 (1H, q, J = 13.5), 2.40 (1H, ddd, J = 12.4, 5.4, 2.6), 2.66 (1H dt, J = 13.1, 2.9), 3.35 (3H, s), 3.69 (3H, s), 3.99 (1H, m), 4.64 (1H, dd, J = 10.9, 5.5), 5.87 (1H, dm, J = 5.1), 6.75−7.20 (5H, m); **33b**, 1.82 (3H, s), 2.03 (1H, td, J = 13.9, 3.3), 2.22 (1H, dt, J = 13.9, 3.3), 2.87 (1H, ddd, J = 12.4, 9.1, 3.3), 3.39 (3H, s), 3.67 (3H, s), 4.01 (1H, d, J = 7.3), 4.53 (1H, m), 5.76 (1H, m), 6.75−7.20 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) **32b**, 19.4, 24.0, 43.7, 51.8, 57.0, 72.6, 75.8, 115.9, 121.1, 122.6, 129.6, 141.2, 158.2, 172.3; **33b**, 20.4, 29.0, 41.1, 51.7, 55.9, 72.1, 76.7, 115.8, 121.0, 125.8, 129.4, 134.9, 158.1, 174.8. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.34; H, 7.43.

3-Methoxy-4-(methoxycarbonyl)-6-phenoxycyclohex-1-enes (32a) and (33a). Cycloaddition of 1*E*,3*E* Isomer. Warming 740 mg (4.0 mmol) of a 17:8:56:19 mixture of 1*E*,3*E*/1*E*,3*Z*/1*Z*,3*E*/1*Z*,3*Z* **9a** isomers, prepared following method D, at 80 °C for 5 days, led to an almost quantitative consumption of the 1*E*,3*E* diene, while 1*Z*,3*E* and 1*E*,3*Z* isomers remained nearly unreactive under these conditions. Two adducts were thus obtained as a 51:49 mixture of *endo*-**32a** and *exo*-**33a** diastereoisomers, corresponding to a regiocontrolled cycloaddition of 1*E*,3*E* diene and leading to 126 mg of colorless oil after purification (12% yield, 69% corresponding to 1*E*,3*E* diene): IR (neat) 1734, 1595, 1497, 1292 cm^{-1}; MS (EI, 70 eV) *m*/*z* 262 ($M^{\bullet+}$, 7), 231 (6), 169 (100); HRMS analysis (EI, $C_{15}H_{18}O_4$ = 262.1205), found 262.1197; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) **32a**, 1.96 (1H, dt, J = 13.6, 12.9), 2.37 (1H, ddd, J = 12.8, 6.0, 2.7), 2.70 (1H, ddd, J = 13.6, 4.0, 2.8), 3.39 (3H, s), 3.72 (3H, s), 4.03 (1H, t, J = 4.5), 4.80 (1H, m), 6.08 (2H, m), 6.75−7.40 (5H, m); **33a**, 1.98 (1H, td, J = 11.2, 4.3), 2.22 (1H, dt, J = 13.0, 3.4), 2.97 (1H, ddd, J = 12.0, 8.9, 3.4), 3.32 (3H, s), 3.74 (3H, s), 4.13 (1H, d, J = 8.9), 4.76 (1H, m), 6.00 (2H, m), 6.75−7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) **32a**, 25.1, 43.3, 51.8, 57.3, 67.7, 72.5, 115.8, 121.2, 126.8, 129.0, 131.1, 157.3, 172.1; **33a**, 29.2, 41.2, 51.8, 56.1, 72.0, 77.5, 115.8, 121.2, 126.8, 129.0, 134.1, 157.3, 174.6.

3-Methoxy-4-(methoxycarbonyl)-6-phenoxycyclohex-1-ene (31a). Cycloaddition of 1*Z*,3*E* Isomer. Warming 352 mg (2.0 mmol) of a 1*Z*,3*E*/1*Z*,3*Z* = 80:20 mixture of diene **9a**, prepared following method B, at 140 °C for 5 days, led to 267 mg of a single diastereoisomer **31a** isolated as a colorless oil and derived from the 1*Z*,3*E* diene (51% yield, 64% with respect to the 1*Z*,3*E* diene): IR (neat) 1743, 1599, 1496,1234 cm^{-1}; MS (EI, 70 eV) *m*/*z* 262 ($M^{\bullet+}$, 19), 231 (17), 169 (100); HRMS analysis (EI, $C_{15}H_{18}O_4$ = 262.1205), found 262.1205; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.17 (1H, td, J = 10.9, 4.4), 2.24 (1H, dm, J = 10.9), 3.06 (1H, dt, J = 11.3, 4.5), 3.37 (3H, s), 3.70 (3H, s), 4.07 (1H, t, J = 4.4), 4.85 (1H, dd, J = 4.5, 2.3), 6.11 (1H, dd, J = 10.0, 5.1), 6.24 (1H, dd, J = 10.0, 4.6), 6.75−7.40 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 24.3, 40.3, 51.5, 57.3, 66.3, 72.1, 115.5, 120.9, 128.8, 129.1, 129.4, 157.2, 172.9.

3,6-Dimethoxy-4-(methoxycarbonyl)-1-methylcyclohex-1-enes (34), (35), (36), and (37). Cycloaddition of 1*E*,3*E* Isomer. Warming 512 mg (4.0 mmol) of a 30:70 mixture of 1*E*,3*E*/1*Z*,3*E* diene **8b**, prepared following method D, at 80 °C for 4 days, led to complete cycloaddition of both 1*E*,3*E* and 1*Z*,3*E* dienes, providing a mixture of five cycloadducts, as determined from NMR and GC/MS analysis on the crude product. Four of them, **34**/**35**/**36**/**37** = 42:34:18:6, were derived from 1*E*,3*E* diene, the last one, **38**, being derived from the 1*Z*,3*E* diene **8b** (as clearly identified by cycloaddition of this nearly pure isomer in the same conditions, see below). These compounds were purified but not separated by flash column chromatography, leading to 436 mg of colorless oil (51% yield): IR (neat) 1740, 1433 cm^{-1}; MS (EI, 70 eV), isomer **34**, *m*/*z* 182 ($M^{\bullet+}$ − 32, 10), 123 (100); isomer **35**, *m*/*z* 214 ($M^{\bullet+}$, 100), 182 (8), 123 (45), 91 (100); isomer **36**, *m*/*z* 182 (4), 123 (320), 91 (100); isomer **37**, *m*/*z* 182 (15), 123 (17), 91 (100).

3,6-Dimethoxy-4-(methoxycarbonyl)-1-methylcyclohex-1-ene (38). Cycloaddition of 1*Z*,3*E* Isomer. Same conditions as above, starting from a 10:90 mixture of 1*E*,3*E* and 1*Z*,3*E* isomers of **8b** (256 mg, 2.0 mmol), prepared following method A, led to a single adduct **38**, corresponding to the 1*Z*,3*E* isomer of **8b**. It has been isolated by flash column chromatography as 270 mg (63% yield, 70% with respect to the 1*Z*,3*E* diene) of a colorless oil: IR (neat) 1740, 1433, 1288, 1197 cm^{-1}; MS (EI, 70 eV) *m*/*z* 182 ($M^{\bullet+}$ − 32, 45), 123 (100); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.76 (3H, s), 1.85 (1H, td, J = 13.2, 4.0), 2.15 (1H, dm, J = 13.2), 2.78 (1H, dt, J = 13.2, 3.2), 3.29 (3H, s), 3.33 (3H, s), 3.46 (1H, m), 3.67 (3H, s), 3.90 (1H, t, J = 4.4), 5.77 (1H, d, J = 4.4); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 21.0, 22.6, 39.6, 51.3, 57.0, 57.3, 72.7, 77.5, 122.4, 138.4, 173.4. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.37; H, 8.74.

3,6-Dimethoxy-4-(methoxycarbonyl)cyclohex-1-ene (39). Cycloaddition of 1*Z*,3*E* Isomer. Warming 228 mg (2.0 mmol) of a 83:17 mixture of 1*Z*,3*E* and 1*Z*,3*Z* isomers of **8a**, prepared following method A, at 140 °C for 2 days, led to the selective consumption of the 1*Z*,3*E* isomer, providing a single cycloadduct **39**, whereas the 1*Z*,3*Z* isomer remained unreactive in these conditions. **39** was isolated after flash column chromatography as a colorless oil: 226 mg (52% yield, 68% corresponding to 1*Z*,3*E* diene); IR (neat) 1738, 1435, 1289, 1194 cm^{-1}; MS (EI, 70 eV) *m*/*z* 200 ($M^{\bullet+}$, 100); ^1H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.93 (1H, td, J = 12.4, 4.1), 2.03 (1H, td J = 12.4; 2.6), 2.88 (1H, dt, J = 12.4, 3.8), 3.30 (6H, s), 3.66 (3H, s), 3.73 (1H, td, J = 4.1, 2.4), 3.95 (1H, t, J = 4.2), 6.02 (1H, dd, J = 10.1, 4.4), 6.10 (1H, dd, J = 10.1, 4.3); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 23.6, 40.2, 51.6, 56.5, 57;3, 71.8, 72.3, 128.1, 129.9, 173.6. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05. Found: C, 58.14; H, 7.82.

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Supporting Information Available: Experimental details and spectral descriptions for compounds **7**, **19**−**24**, **29**, and **30**, main crystallographical parameters for adduct **18b**, and NMR spectra of various compounds (36 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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