Pergamon

Tetrahedron 55 (1999) 3959–3986

TETRAHEDRON

Chiral *(E,E)*-1,4-Dialkoxy-1,3-butadienes. 2. Conformational Studies and Diels-Alder Reactions with Symmetric Dienophiles

Marina Virgili, Albert Moyano*, Miquel A. Pericàs*, Antoni Riera

Unitat de Recerca en Síntesi Asimètrica, Departament de Química Orgànica, Universitat de Barcelona, c/ Martí i Franquès, 1-11. 08028-Barcelona, Spain

Received 13 October 1998; revised 4 January 1999; accepted 21 January 1999

Abstract: The first examples of Diels-Alder reactions of chiral, C_2-symmetric *(E,E)*-1,4-dialkoxy-1,3-butadienes are described. The cycloadditions with maleic anhydride lead in all instances to the exclusive formation of the *endo* adducts. C_{2h}-Symmetric dienophiles such as fumaronitrile and diethyl fumarate react with variable diastereoselectivities; best results are obtained with the camphor-derived diene **1d**, whose reaction with diethyl fumarate takes place with complete facial selectivity. A theoretical analysis, using the SCF-MO procedure AM1, of the conformations of the dialkoxydienes has been used to rationalize the steric course of the cycloadditions.

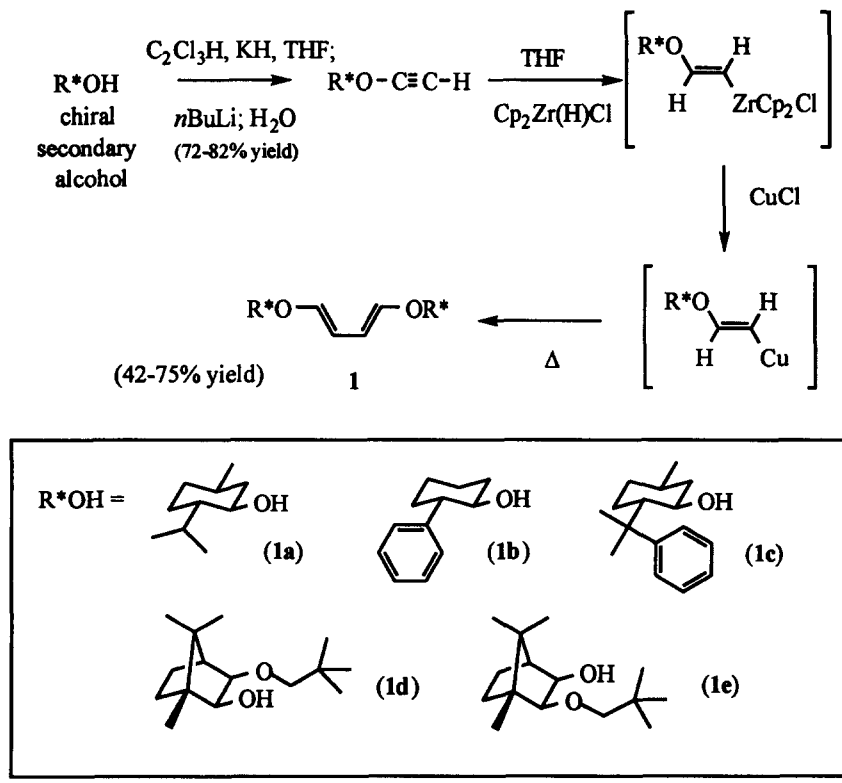
Keywords: *Alkenes; Asymmetric induction; Conformation; Diels-Alder reactions.*

Introduction

In accordance with the central role played by the Diels-Alder reaction in the field of carbocycle synthesis, the development of enantioselective versions of the Diels-Alder and related [4+2] cycloadditions is one of the most thoroughly studied topics in asymmetric synthesis.[1] While several efficient enantioselective Diels-Alder type processes based either on chiral auxiliary-containing dienophiles[2] or chiral catalysts[3,4] are known, the use of chirally-substituted 1,3-dienes for this purpose is less well-established,[5] and the search for enantiopure butadienes displaying high π-facial selectivity upon Diels-Alder cycloadditions is currently being actively pursued.[6,7]

Recently, we have disclosed a practical entry to a previously unknown class of enantiopure dienes bearing chiral groups both at C-1 and at C-4: chiral *(E,E)*-1,4-dialkoxy-1,3-butadienes **1** belonging to the C_2 symmetry point group.[8] As shown in Scheme 1, these dienes can be easily obtained from a variety of chiral secondary alcohols by means of a two-step sequence involving in the first place conversion of the alcohol into an alkoxyethyne[9] followed by one-pot hydrozirconation,[10] Zr(IV) to Cu(I) transmetallation[11] of the resulting alkoxyvinylzirconocene complexes and thermally-induced decomposition of the organocopper intermediate, leading to the regio- and stereoselective dimerization of the alkoxyvinyl moiety.

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00086-1



Scheme 1

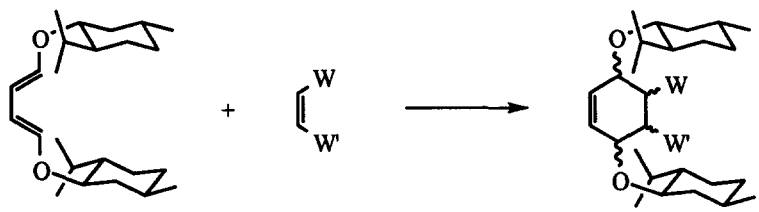
We report in the present paper our initial assays on the Diels-Alder reactivity of this new class of chiral butadienes, a theoretical analysis of the conformational properties of **1a** and **1d** and a study of the cycloadditions of the dienes **1a-e** with representative C_{2v}-symmetric and C_{2h}-symmetric dienophiles. As a result of these studies, we have found that the Diels-Alder reactions of chiral (*E,E*)-1,4-dialkoxy-1,3-butadienes can take place with very high diastereoselectivities.

Results and discussion

1. Diels-Alder reactions of (*E,E*)-1,4-bis(*l*-menthyloxy)-1,3-butadiene

Contrary to other heterosubstituted dienes, the Diels-Alder reactivity of (*E,E*)-1,4-dialkoxy-1,3-butadienes has been scarcely investigated, probably due both to the lack of general, stereoselective synthetic methods to access this type of compound and to their instability (sensitivity to moisture and oxygen and ease of polymerization). In 1980, Sauer, Sustmann and co-workers[12] reported that (*E,E*)-1,4-dimethoxy-1,3-butadiene exhibited at 30°C a reactivity towards maleic anhydride similar to that of 2,3-dimethyl-1,3-butadiene or 2-phenyl-1,3-butadiene, and observed the formation of a blue-colored charge transfer complex with tetracyanoethylene in

methylene chloride at room temperature, which disappeared after some minutes at room temperature, to afford the expected Diels-Alder adduct in 82% yield. The reactivity of (*E,E*)-1,4-dimethoxy-1,3-butadiene with tetracyanoethylene ranked fifth on a series of 26 electron-rich, diversely substituted butadienes, in good accordance to the predictions of frontier molecular orbital theory. Shortly thereafter, Hiranuma and Miller reported additional examples of the cycloaddition of 1,4-dimethoxy-[13] and 1,4-di-*tert*-butoxy-1,3-butadiene[14] with a series of typical dienophiles; however, since these dialkoxybutadienes were obtained in the form of diastereomeric mixtures in which the (*E,E*)-isomer was a minor component (8-10%), it is difficult to draw sound conclusions from these studies.[15] We set out therefore to explore the general Diels-Alder reactivity of (*E,E*)-1,4-bis(*l*-menthyloxy)-1,3-butadiene **1a** (Scheme 2) as a step prior to the study of the diastereoselectivity of the [4+2]-cycloadditions of the chiral dialkoxybutadienes **1a-e** (prepared as previously described;[8] see the experimental section for details) with symmetrical dienophiles. The most relevant results are collected in Table 1.



1a

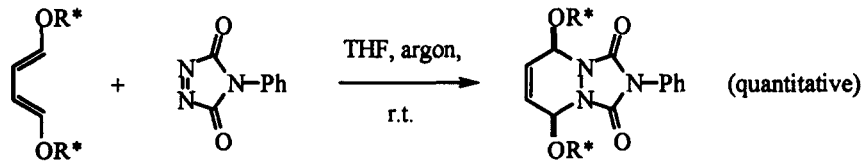
Scheme 2

Table 1: Reactivity of (*E,E*)-1,4-bis(*l*-menthyloxy)-1,3-butadiene (**1a**) with representative dienophiles.

Entry	Dienophile[a] (equivs.)	Solvent, time, temperature	% Yield of cycloadduct
1	PTAD (1)	THF, 2 min, r.t.	100
2	MA (1)	toluene, 3 h, r. t.	trace
3	MA (1)	toluene, 45 min, 60°C	60
4	MA (1)	toluene, 3 h, 95°C	87
5	DEF (1)	toluene, 4 h, r.t.	0
6	DEF (1)	toluene, 14 h, 75°C	7
7	DEF (1)	*m*-xylene, 18 h, 140°C	52
8	CAN (2)	toluene, 3 h, r.t.	0
9	CAN (3)	toluene, 3 h, 70°C	0
10	EA (1)	*m*-xylene, 10 h, 100°C	0
11	EA (40)	–, 10 h, 140°C	74
12	EC (1)	*m*-xylene, 6 h, 140°C	0

a) PTAD = 4-phenyl-3H-1,2,4-triazoline-3,5-dione; MA = maleic anhydride; DEF = diethyl fumarate; CAN = 2-chloroacrylonitrile; EA = ethyl acrylate, EC = ethyl *trans*-cinnamate.

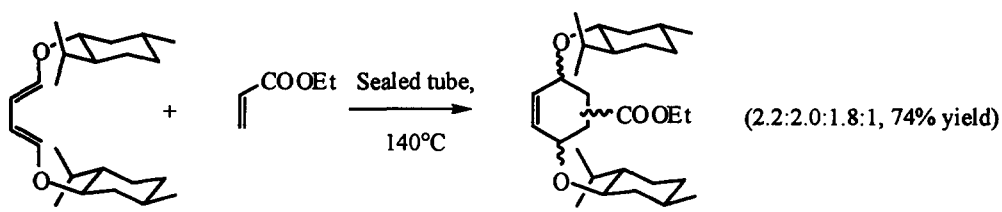
The Diels-Alder reactivity of 1,4-dialkoxybutadiene **1a** proved to be very sensitive to the nature of the dienophile. With the highly reactive 4-phenyl-3H-1,2,4-triazoline-3,5-dione (PTAD), the reaction took place almost instantaneously (as evidenced by the immediate decoloration of the red dienophile solution added to the diene) in tetrahydrofuran at ambient temperature, affording the enantiopure triazolopyridazine **2a** in quantitative yield. A similar behaviour was observed for the other dialkoxydienes **1b-e** (Scheme 3).



1a-e **2a-e**

Scheme 3

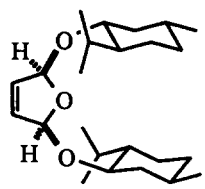
With the remaining dienophiles examined, **1a** reacted at a negligible rate at room temperature (see entries 2, 5 and 8 in Table 1). In the case of maleic anhydride, it was necessary to heat at 95°C for 3 hours in order to observe the complete disappearance of the diene (entry 4), and even more drastic conditions (18 hours in refluxing *m*-xylene) were required for the total reaction of **1a** with 1 molar equivalent of diethyl fumarate (entry 7). An orange-coloured solution was initially formed upon the addition of maleic anhydride to a solution of **1a**, strongly suggesting the formation of a charge-transfer complex.[12] No adduct could be detected from the attempted reactions of **1a** with hydrocarbon solutions of 2-chloroacrylonitrile (entry 9), ethyl acrylate (entry 10), or ethyl (*E*)-cinnamate (entry 12). Only after heating **1a** at 140°C in a sealed tube with an excess of neat ethyl acrylate during 10 hours a 74% yield of a non-separable mixture of the four possible cycloadducts could be isolated (entry 11 and Scheme 4).



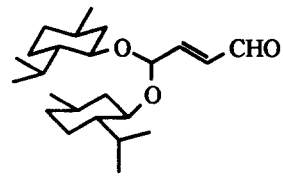
1a

Scheme 4

Except for the case of PTAD, it was necessary to avoid the presence of oxygen in the reaction mixture (reactions run in strictly degassed solvents under pure argon atmosphere) and to add small amounts of *p*-hydroquinone in order to suppress the formation of products arising from the oxidation of the diene, such as the dihydrofuran **3** or the aldehyde **4**. It is also worth noting that all attempts to catalyze the cycloadditions of **1a** by Lewis acids ($ZnCl_2$, $AlEt_2Cl$ or $BF_3{\cdot}Et_2O$) led to the decomposition of the diene, in line with the observations of Hiranuma and Miller.[13,14]



3



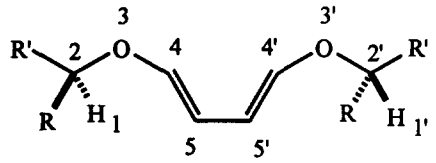
4

In summary, (*E,E*)-1,4-bis(*l*-menthyloxy)-1,3-butadiene **1a** exhibits a good thermal [4+2] reactivity toward activated dienophiles such as maleic anhydride or diethyl fumarate, provided that adequate experimental conditions (exclusion of atmospheric oxygen and use of *p*-hydroquinone as oxidation inhibitor) are employed.

2. Conformational study of (*E,E*)-1,4-bis(*l*-menthyloxy)-1,3-butadiene (1a) and of (*E,E*)-1,4-bis-[(1*R*,2*S*,3*R*,4*S*)-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxy]-1,3-butadiene (1d)

Although a complete rationalization of the stereochemical outcome of the Diels-Alder cycloadditions of the dialkoxydienes **1a-e** would require an analysis not only of the conformational preferences of the starting materials, but also an evaluation of the activation energies in the reaction of each individual conformer with the corresponding dienophile,[16] the size and complexity of the systems involved renders this approach impractical from the point of view of the necessary computational time and resources. We decided therefore, as a preliminary step for a more detailed investigation, to analyse thoroughly the conformational space of two representative 1,4-dialkoxybutadienes: the bis(*l*-menthol) derivative **1a** and the bis(3-*exo*-neopentyloxyisoborneol) derivative **1d**. The employed theoretical procedure was the RHF version of the semiempirical SCF-MO method AM1,[17] which is known to give accurate descriptions of the ground state conformations of a large variety of closed-shell species, as implemented in the MacSpartan Plus[18] package of programs.

The number of stable conformations accessible for a symmetric (*E,E*)-1,4-dialkoxy-1,3-butadiene having alkoxy groups derived from chiral, secondary alcohols is very large. Barring the conformations of the alcohol skeleton, there are three dihedral angles with two limiting conformations and two dihedral angles with three possible limiting conformations (see Figure 1); taking into account the homochirality of the two alkoxy groups, this gives a total maximum number of 42 limiting conformer types. A systematic conformational search around the five relevant dihedral angles (corresponding to rotations around the five single bonds) of the central C-O-CH=CH-CH=CH-O-C core led to the characterisation of 36 stable conformers for **1a** (Table 2), and of 27 stable conformers for **1d** (Table 3). The limiting types to which these conformational minima can be ascribed are designated by a five letter code describing the approximate values of the (4,5,5',4'), (2,3,4,5), (2',3',4',5'), (1,2,3,4), and (1',2',3',4') dihedral angles, respectively (Figure 1).



DIHEDRAL ANGLE NOTATION

(4,5,5',4'): C (*ca.* 0°), T (*ca.* 180°)

(2,3,4,5), (2',3',4',5'): c (*ca.* 0°), t (*ca.* 180°)

(1,2,3,4), (1',2',3',4'): g+ (*ca.* 60°), a (*ca* 180°), g- (*ca.* 240°)

Figure 1

The stable conformations of **1a** are listed, by order of increasing energy, in Table 2. As it can be seen, the energy difference between the most stable *transoid* (T) conformer and the most stable *cisoid* (C) conformer is only 3.55 kJ mol^{-1}, so that the system can readily attain a reactive conformation suitable for [4+2] cycloadditions. The most stable *cisoid* conformers are shown in Figure 2. The fact that the most stable *cisoid* conformer belongs to the Cccg+g+ type is in full agreement with our previous calculations on the related system (*E*)-1-[(1*R*,2*S*)-2-phenylcyclohexyloxy]-1,3-butadiene, which also predict that a Ccg+ conformer as the most stable among the *cisoid* ones.[19]

Table 2. Conformers of (*E,E*)-1,4-bis(*l*-menthyloxy)-1,3-butadiene (**1a**)

Conformer type[a]	Symmetry	Energy[b]	Conformer type[a]	Symmetry	Energy[b]
Tccg+g+	C_2	-597.87	Tttg+g-	C_1	-587.92
Tctg+a	C_1	-594.90	Tctg-g-	C_1	-587.21
Cccg+g+	C_2	-594.31	Cttag+	C_1	-586.91
Tctg+g+	C_1	-593.73	Tctaa	C_1	-586.25
Tttaa	C_2	-592.35	Tttg-g-	C_2	-585.95
Tctg+g-	C_1	-591.68	Cccg-g-	C_2	-585.79
Cctg+a	C_1	-591.55	Cccag+	C_1	-585.58
Tttag+	C_1	-591.14	Tctag+	C_1	-585.07
Tctg-a	C_1	-590.38	Cttag-	C_1	-584.82
Cctg+g+	C_1	-590.38	Cttg+g-	C_1	-583.86
Cccg+g-	C_1	-589.97	Tctag-	C_1	-583.03
Tttg+g+	C_2	-589.92	Cctaa	C_1	-582.86
Tccag+	C_1	-589.21	Cctag+	C_1	-581.52
Tctg-g+	C_1	-589.21	Cccag-	C_1	-580.89
Tttag-	C_1	-589.13	Tccaa	C_2	-580.56
Tccg-g-	C_2	-588.88	Cctag-	C_1	-579.56
Cctg+g-	C_1	-588.29	Cccaa	C_2	-576.59
Cttaa	C_2	-588.21	Cttg+g+	C_2	-574.54

[a] See text and Figure 1. [b] Enthalpies of formation, in kJ mol^{-1}.

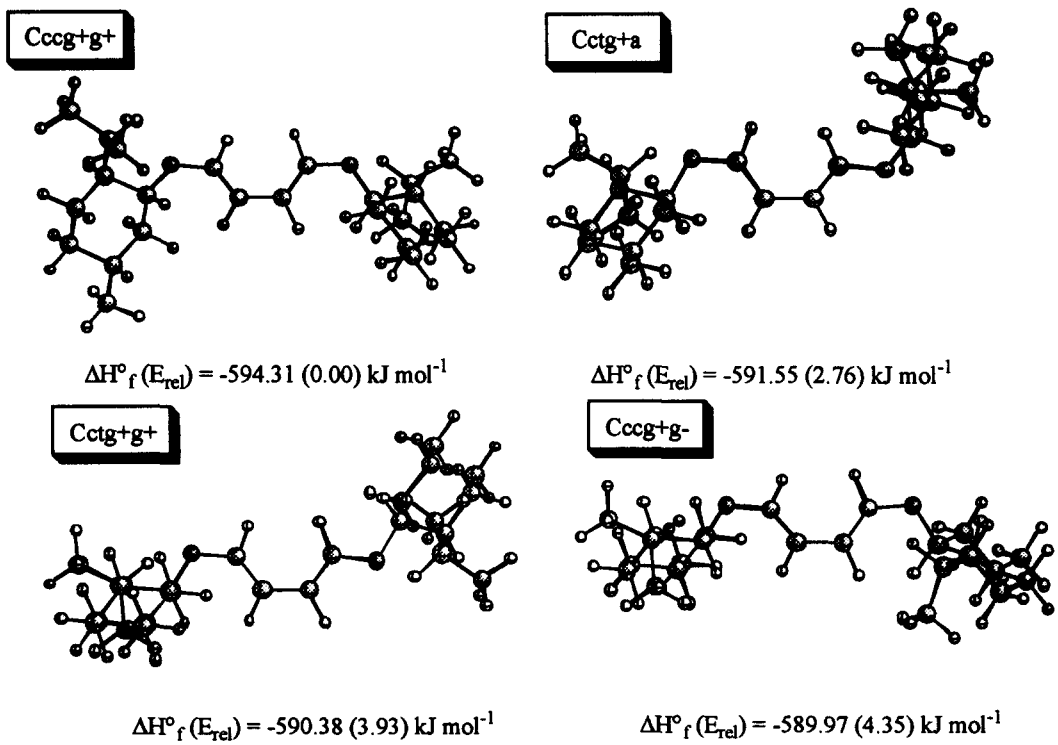


Figure 2. The four more stable *cisoid* conformers of (*E,E*)-1,4-bis(*l*-menthyloxy)-1,3-butadiene (**1a**)

As a result of the exploration of the conformational energy hypersurface of **1d**, 27 conformers could be located (Table 3). The smaller number of stable conformations relative to that of **1a** can be ascribed to the fact that in this case the conformations of the "ca" type –*i.e.*, those having simultaneously a (2,3,4,5) dihedral angle of 0°C and a (1,2,3,4) dihedral angle of around 180°C– are not stable, due to steric reasons. Although there are several conformers of the "ta" type they are *ca.* 21-33 kJ mol^{-1} more unstable than the lowest energy conformers, so that they are expected to be very scarcely populated at the equilibrium. The energy difference between the most stable *transoid* conformer and the most stable *cisoid* conformer of **1d** is 2.72 kJ mol^{-1}, implying that **1d** should be even slightly more reactive towards Diels-Alder dienophiles than **1a**. It is worth noting that, contrary to what is observed in the case of **1a**, **1d** presents two *cisoid* conformers (Cttg+g+ and Cccg+g+) with very similar energies; once again, this fact is in accordance with our calculations on the (*E,E*)-1-alkoxy-1,3-pentadiene derived from 3-*exo*-neopentyloxyisoborneol, which also predict very similar energies for conformers of the Ctg+ and Ccg+ type.[19] The four more stable *cisoid* conformations of **1d** are shown in Figure 3.

Table 3. Conformers of (*E,E*)-1,4-bis[(1*R*,2*S*,3*R*,4*S*)-3-(2,2-dimethylpropoxy)-1,7,7-trimethyl bicyclo[2.2.1]heptyl-2-oxy]-1,3-butadiene (**1d**)

Conformer type[a]	Symmetry	Energy[b]	Conformer type[a]	Symmetry	Energy[b]
Tccg+g+	C_2	-749.01	Tctg-g-	C_1	-739.23
Tctg+g+	C_1	-746.51	Cctg+g-	C_1	-739.07
Tccg+g-	C_1	-746.05	Cttg+g-	C_1	-736.81
Cttg+g+	C_2	-745.88	Cctg-g-	C_1	-736.35
Cccg+g+	C_2	-745.42	Ttg-g-	C_2	-736.18
Tttg+g+	C_2	-744.63	Cttg-g-	C_2	-731.75
Tctg-g+	C_1	-744.42	Tctg+a	C_1	-727.36
Tccg-g-	C_2	-743.12	Tctg-a	C_1	-724.19
Cccg+g-	C_1	-742.41	Cctg+a	C_1	-717.37
Tctg+g-	C_1	-742.03	Cctg-a	C_1	-715.24
Cctg+g+	C_1	-740.78	Cttag+	C_1	-715.07
Cctg-g+	C_1	-740.53	Cttag-	C_1	-710.39
Tttg+g-	C_1	-740.32	Cttaa	C_1	-695.64
Cccg-g-	C_2	-739.94			

[a] See text and Figure 1. [b] Enthalpies of formation, in kJ mol^{-1}.

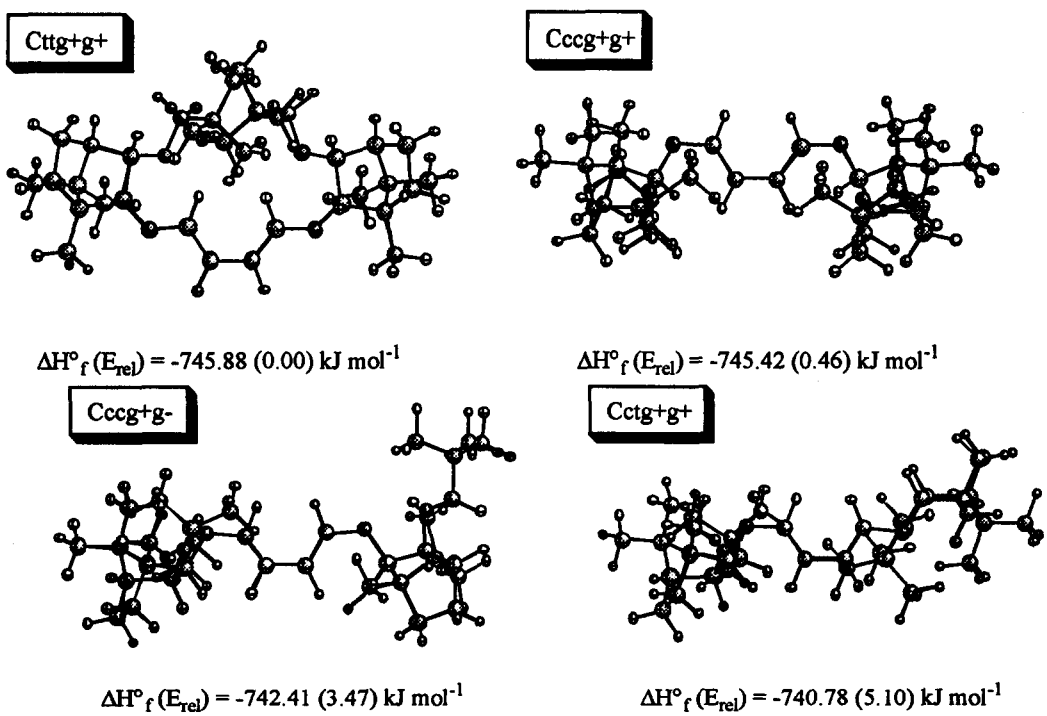
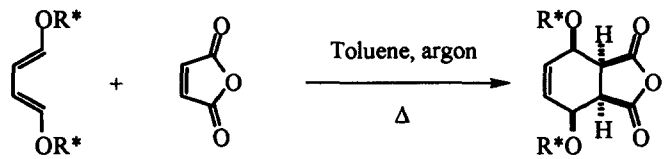


Figure 3. The four more stable *cisoid* conformers of (*E,E*)-1,4-bis[(1*R*,2*S*,3*R*,4*S*)-3-(2,2-dimethylpropoxy)-1,7,7-trimethyl bicyclo[2.2.1]heptyl-2-oxy]-1,3-butadiene (**1d**)

3. Diels-Alder cycloadditions of chiral (*E,E*)-1,4-dialkoxy-1,3-butadienes (1a-e) with maleic anhydride

The cycloadditions of the dialkoxydienes **1b-e** with maleic anhydride (Scheme 5 and Table 4) were run under the experimental conditions described above for **1a**, except for the fact that no *p*-hydroquinone was added to the reaction mixture. We did not observe big differences in reactivity between the dialkoxydienes derived from cyclohexyl alcohols (**1a-c**) and those derived from bornyl alcohols (**1d,e**). The least reactive diene was the bis(8-phenylmenthyloxy)derivative **1c**, which required 10 hours in toluene at 95°C for complete reaction. The yield of the reaction was generally very high, although substantial losses of product were observed upon chromatographic purification of the adducts. In the case of **1d** and **1e**, some hydrolysis of the dienes took place during the reaction, which resulted in the formation of the alcohols.



1a-e **5a-e**

Scheme 5

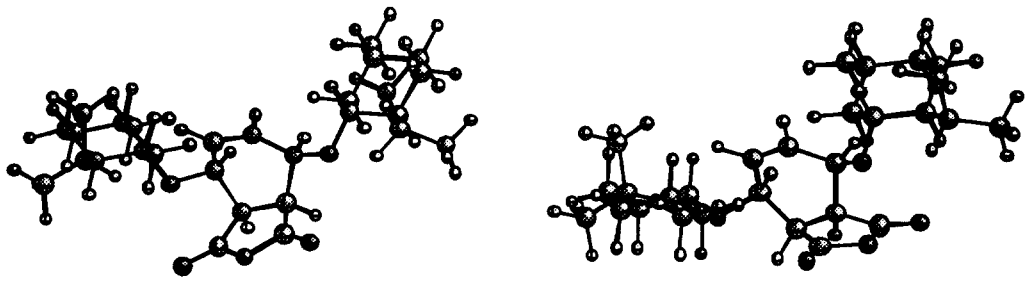
Table 4. Diels-Alder cycloadditions of chiral (*E,E*)-1,4-dialkoxy-1,3-butadienes (**1a-e**) with maleic anhydride

Diene	Solvent, temperature, time	Adduct	Yield(%)
1a	toluene, 95°C, 3 h	**5a**	87
1b	toluene, 80°C, 3 h	**5b**	94[a]
1c	toluene, 95°C, 10 h	**5c**	>95[a], 42[b]
1d	toluene, 80°C, 5 h	**5d**	80[a]
1e	toluene, 80°C, 6 h	**5e**	70[a]

[a] Yield of adduct in the reaction mixture, estimated by ^{1}H NMR spectroscopy.

[b] After chromatographic purification.

With regard to the stereochemical course of the reaction, only one diastereoisomer could be detected (by ^{1}H and ^{13}C NMR spectroscopy) in all instances. In order to ascertain whether the configuration of the adducts was *endo* or *exo*, we performed some selective proton-proton decoupling experiments on the adduct **5a**, which allowed us to establish that the vicinal H-H coupling constant between each pair of allylic and ring-junction protons had a value of *ca.* 6.5 Hz. In the AM1[17] optimized geometry of **5a** (assuming an *endo* configuration), the corresponding dihedral angle measured 46.5-47.0°, a value which is in reasonable agreement, according to the empirical Karplus relationship, with the observed coupling constant. A similar calculation, performed on the *exo* isomer of **5a**, gave a value of *ca.* 149° for the corresponding dihedral angle (see Figure 4). Since this value should correspond to *J* values in the range of 8-10 Hz, we conclude that our dienes react with maleic anhydride in an *endo* fashion, leading to the adducts **5a-e** with the absolute configuration depicted in Scheme 5.

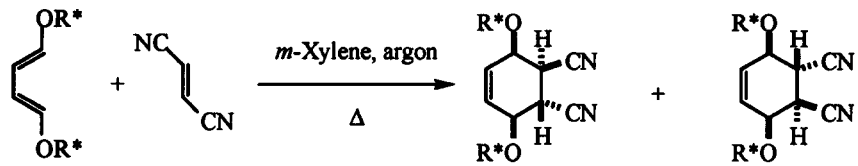


5a (*endo*) ΔH°_{f} = -1081.78 kJ mol^{-1} **5a** (*exo*) ΔH°_{f} = -1101.14 kJ mol^{-1}

Figure 4. Lowest energy conformers (AM1) of the *endo* and *exo* stereoisomers of adduct **5a**.

4. Diels-Alder cycloadditions of chiral (*E,E*)-1,4-dialkoxy-1,3-butadienes (1a-e) with dienophiles of C_{2h} symmetry

The results obtained in the cycloaddition of chiral (*E,E*)-1,4-dialkoxy-1,3-butadienes **1a-e** with fumaronitrile (Scheme 6) are summarized in Table 5. The adducts **6a-e** could be isolated in good yields, except for **1e**; in this case, partial decomposition of the starting material took place, leading to recovery of the starting chiral alcohol (24% yield).



1a-e major **6a-e** minor

Scheme 6

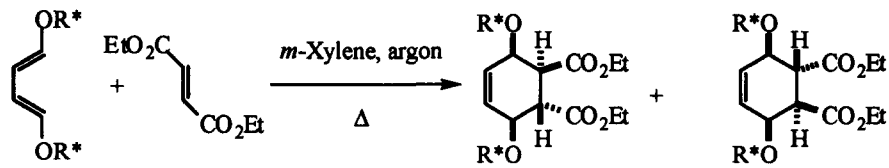
Table 5. Diels-Alder cycloadditions of chiral (*E,E*)-1,4-dialkoxy-1,3-butadienes (**1a-e**) with fumaronitrile

Diene	Solvent, temperature, time	Adduct	Yield(%),[a] d.r.[b,c]
1a	*m*-xylene, 140°C, 5.5 h	**6a**	85, 1.3:1
1b	*m*-xylene, 140°C, 4 h	**6b**	78, 1.45:1
1c	*m*-xylene, 140°C, 22 h	**6c**	59[d], 1.3:1
1d	*m*-xylene, 85°C, 7 h	**6d**	74[e], 2.2:1
1e	*m*-xylene, 80°C, 12 h	**6e**	34, 1:1.5

[a] Yield of isolated adducts, after chromatographic purification.
[b] By ^{13}C NMR spectroacopy. [c] The absolute configurations are tentatively assigned (see text) [d] 17% of starting diene was recovered. [e] 9% of starting diene was recovered.

The effect of the structure of the alkoxy group on the reactivity was much more pronounced than in the case of the cycloadditions with maleic anhydride, the dienes with camphor-derived alkoxy groups (**1d** and **1e**)

being more reactive (reaction temperature 80-85°C) than those (**1a-c**) having cyclohexyl-type alkoxy groups (reaction temperature 140°C). This fact is in accordance with the energy differences between the *cisoid* and the *transoid* sets of conformers described in section 2. In all cases, adducts **6** were obtained in the form of diastereomeric mixtures, not separable by column chromatography (except for **6d** and **6e**). The diastereomeric ratios, determined by ^{13}C NMR spectroscopy, were only moderate, and the best result (2.2:1 d.r.) was observed with diene **1d**. We decided therefore to investigate the use of diethyl fumarate, in order to see if an increase in the steric requirements of the dienophile would lead to higher diastereoselectivities (See Scheme 7 and Table 6).



1a-e major **7a-e** minor

Scheme 7

Table 6. Diels-Alder cycloadditions of chiral (*E,E*)-1,4-dialkoxy-1,3-butadienes (**1a-e**) with diethyl fumarate

Diene	Solvent, temperature, time	Adduct	Yield(%),[a] d.r.[b,c]
1a	*m*-xylene, 140°C, 18 h	**7a**	52[d], 1.2:1
1b	*m*-xylene, 140°C, 20 h	**7b**	56, 1.7:1
1c	*m*-xylene, 140°C, 75 h	**7c**	52[d], 5.5:1
1d	*m*-xylene, 85°C, 48 h	**7d**	63[e], >20:1[f]
1e	*m*-xylene, 80°C, 76 h	**7e**	39[g] 1:10.6

[a] Yield of isolated adducts, after chromatographic purification.
[b] By ^{13}C NMR spectroscopy and HPLC. [c] The absolute configurations are tentatively assigned (see text). [d] 23% of starting diene was recovered. [e] 10% of starting diene was recovered. [f] Only one stereoisomer was detected. [g] 31% of starting diene and 6% of chiral alcohol were recovered.

The reactions with diethyl fumarate were slower than with fumaronitrile, requiring longer reaction times (20-76h) in order to attain conversions higher than 70%. The recovered dienes were almost completely isomerized to the (*E,Z*) diastereomer. As before, the camphor derived dienes **1d** and **1e** were more reactive than **1a-c**. The most significant result was the high degree of stereoselectivity observed in some instances, particularly in the case of **1d**, where only one diastereomer could be detected. The diastereomeric purity of the adduct **7d** was checked by ^{1}H NMR spectroscopy, by ^{13}C NMR spectroscopy and by HPLC. The adduct **7e** was also obtained in high diastereomeric excess (10.6:1 d.r.). As shown in the Table (see also the last entry of Table 5), we assume that the pseudoenantiomeric dienes **1d** and **1e** present opposite facial diastereoselectivities in their reactions with C_{2h}-symmetric dienophiles. A moderate stereoselectivity (5.5:1 d.r.) was observed for **7c**. The diastereomers of both **7c** and **7e** could be partially separated by column chromatography.

Due to the lack of crystallinity of the isolated diastereomers, it has not been possible to determine unambiguously the absolute configurations of the adducts **6a-e** and **7a-e**. However, the analysis of the conformational preferences of dienes **1a** and **1d**, together with the results of our previous calculations on the

cycloadditions of chiral 1-alkoxy-1,3-butadienes,[19] that reveal a significant preference for a Ccg-type conformation of the 1-alkoxy-1,3-diene moiety in the transition states for Diels-Alder reactions,[20] has led us to propose the stereochemical assignments depicted in Schemes 6 and 7.

In the case of the *bis*(*l*-menthyloxy)derivative **1a**, the most stable *cisoid* conformer, that is of the Cccg+g+ type and that belongs to the C_2 symmetry point group, has been assumed to lead to the lowest energy transition states in the Diels-Alder reaction with C_{2h}-symmetric dienophiles. If we extend this assumption to the remaining cyclohexyl-type derivatives **1b** and **1c**, we can easily rationalize the trends observed in the stereoselectivity of their cycloadditions with fumaronitrile and diethyl fumarate. In effect, as depicted in Figure 5, an inspection of the Cccg+g+ conformer shows that the alkoxy groups do not discriminate between the two possible approaches of the dienophile to the diene moiety, at least in the fumaronitrile case. Only for the bulkier dienophile diethyl fumarate (Z = CO_2Et) the (*Si,Re*) ↔ (*Si,Re*) approach becomes relatively hindered (especially in the case of the bis(8-phenylmenthyl) derivative **1c**), so that moderate diastereoselectivities (up to 5.5:1 diastereomeric ratio) are observed.

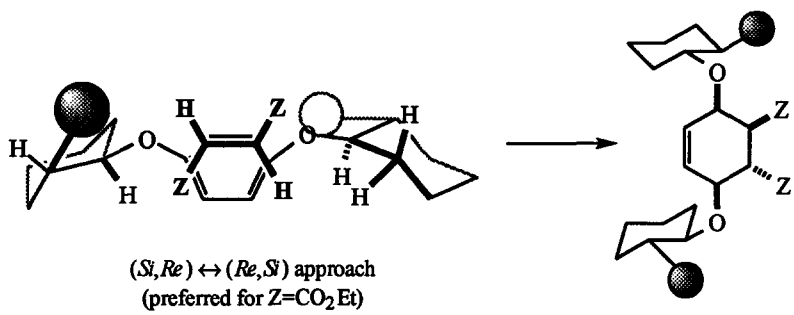


Figure 5. Predicted facial selectivity in the cycloadditions of (*E,E*)-1,4-dialkoxy-1,3-dienes **1a-c** with fumaronitrile (Z = CN) and with diethyl fumarate (Z = CO_2Et).

The small energy difference (0.46 kJ mol^{-1}) calculated between the Cttg+g+ and the Cccg+g+ conformers of the bis(3-*exo*-neopentyloxyisoborneol) derivative **1d** appears at first sight to be in contradiction with the fact that the highest diastereoselectivities have been obtained with this system. However, if we take into account that in the corresponding transition states one should reasonably expect a switch favouring the Cccg+g+ conformer by at least 8 kJ mol^{-1},[19] the significant stereofacial selectivity shown by this diene can also be readily explained. When one examines the arrangement of the camphor-derived alkoxy substituents around the central diene core in conformer Cccg+g+, it is easily seen that, especially in the case of diethyl fumarate, the approach of the

dienophile is severely hindered, except if it takes place in a (*Si,Re*) ↔ (*Re,Si*) fashion. Interestingly enough, this approach could account for the complete diastereoselectivity observed for this reaction (Figure 6). Finally, since the diene **1e** has a pseudoenantiomeric relationship with **1d**, the present analysis would predict a reactive conformation of the Cccg-g- type for this system, which would lead to the opposite (*Si,Re*) ↔ (*Si,Re*) preferred facial selectivity for this system.

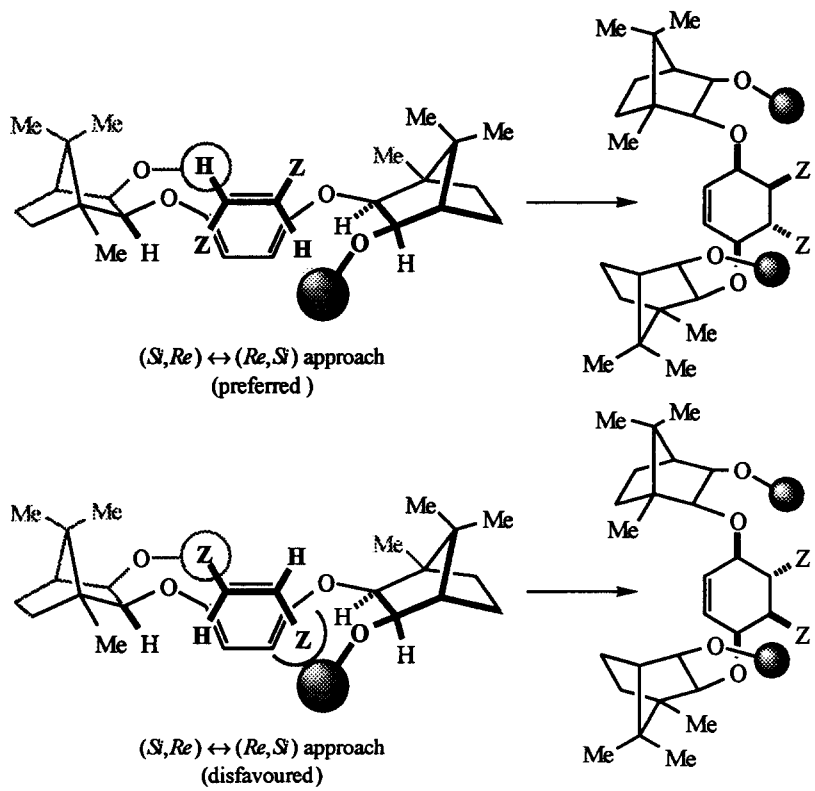


Figure 6. Predicted facial selectivity in the cycloaddition of (*E,E*)-1,4-dialkoxy-1,3-diene **1d** with fumaronitrile (Z = CN) and with diethyl fumarate (Z = CO_2Et)

Conclusions

In summary, we have described for the first time the Diels-Alder reactions of (*E,E*)-1,4-dialkoxy-1,3-dienes **1a-e**, that belong to a new class of C_2-symmetric chiral dienes. A preliminary study, effected with the bis(*l*-menthyloxy) derivative **1a**, has shown that these compounds react instantaneously with PTAD, and that moderate thermal activation is necessary in order to obtain high yields of the cycloadducts with reactive dienophiles such as maleic anhydride or diethyl fumarate. Due to the sensitivity of the dienes, the use of Lewis acids is precluded, and the reactions have to be run under strict argon atmosphere in degassed solvents. The cycloadditions of the dienes with maleic anhydride lead exclusively to the formation of the *endo* cycloadducts.

While the use of fumaronitrile results in low diastereoselectivities, the Diels-Alder reaction with diethyl fumarate takes place with much higher facial selectivities, particularly in the case of the camphor-derived diene **1d**, where only one of the two possible cycloadducts is obtained. The stereochemical course of the reactions has been predicted on the basis of a thorough theoretical analysis, by the AM1 procedure, of the conformational preferences of the dienes, which has allowed an identification of the reactive conformers.

Experimental Section

General Methods

Optical rotations were measured at room temperature (23°C) on a Perkin-Elmer 241 MC polarimeter (Concentration in g/100 ml). Melting points were determined on a Gallenkamp apparatus and have not been corrected. Infrared spectra were recorded on a Perkin-Elmer 681 instrument. ^{1}H-NMR spectra were recorded on Varian Gemini 200, Varian-Unity-300 and Varian-Unity-Plus-300 spectrometers operating at 200 or 300 MHz respectively (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet). ^{13}C-NMR spectra were obtained on the same instruments operating at 50 or 75 MHz respectively. Chemical shifts in $CDCl_3$ are quoted relative to TMS for ^{1}H-NMR and relative to the solvent for ^{13}C-NMR (77.0 ppm for ^{13}C of $CDCl_3$). Coupling constants (*J*) are given in Hz. Carbon multiplicities were assigned by DEPT experiments. Mass spectra were recorded on a Hewlett-Packard 5890 instrument at 70 eV ionising potential; ammonia or methane were used for chemical ionization (CI). High-resolution mass spectra were performed by the "Servicio de Espectrometría de Masas, Universidad de Córdoba". Elemental analyses were performed by the "Servei d'Anàlisis Elementals del CSIC de Barcelona". Column chromatographic separations were carried out using Et_3N pre-treated (2.5% v/v) SiO_2 (70-230 mesh) and chromatographic analyses were performed on a Helwett-Packard 1050 HPLC instrument equipped with a Nucleosil 120 C18 (25 cm) column. THF was distilled under N_2 from sodium benzophenone ketyl prior to use.

Synthesis of (E,E)-1,4-dialkoxy-1,3-butadienes **1a-e**:[8]

(E,E)-1,4-bis(l-menthyloxy)-1,3-butadiene, **1a**: To a stirred suspension of freshly prepared zirconocene hydrochloride[21] (1.44 g, 5.55 mmol) in anhydrous, degassed THF (6 mL), under argon atmosphere, a solution of *l*-menthyloxyethyne[9] (1.00 g, 5.55 mmol) in THF (10 mL) was added dropwise; the resulting mixture was stirred at room temperature for a few min, until the zirconocene hydrochloride dissolved completely; this solution was then transferred via cannula to a stirred suspension of previously purified cuprous chloride (0.60 g, 6.0 mmol) in anhydrous, degassed THF (9 mL). The resulting dark brown mixture was heated at 70°C during 2 h, after which time a bright copper mirror had deposited at the walls of the reaction vessel, together with some black precipitate. After cooling to room temperature, and diluting with hexane (25 mL), the clear supernatant liquid was filtered through a short pad of NEt_3-pretreated (2.5% v/v) silicagel, and the solvents were distilled off at reduced pressure. The resulting crude product was immediately purified by column chromatography on NEt_3-pretreated silicagel (2.5% v/v), eluting with hexane/diethyl ether mixtures, to give 0.74 g (74% yield) of the title compound as a white yellowish solid, and 0.133 g (15% yield) of *l*-menthyl alcohol. (NOTE: Due to the high

sensitivity of the dialkoxydiene, the reaction glassware was washed with aqueous NaOH and oven-dried prior to use).

m. p. 59-60°C. $[\alpha]_D^{23}$ = -18.0 (c=4.5, hexane). IR (NaCl film) ν_{max}: 3030, 2960, 2920, 2870, 1625, 1460, 1380, 1350, 1250, 1185, 1165, 1120, 1060, 1055, 1020, 995, 940, 850 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.76 (d, J=6.9 Hz, 6H), 0.89 (d, J=7.0 Hz, 6H), 0.91 (d, J=6.5 Hz, 6H), 0.75-1.80 (m, 14H), 1.97-2.20 (m, 4H), 3.40 (td, J=11 Hz, J'=4 Hz, 2H), 5.48 (m, 2H), 6.23 (m, 2H) ppm. ^{13}C NMR (50 MHz, C_6D_6) δ: 16.3 (q), 20.9 (q), 22.3 (q), 23.9 (t), 26.2 (d), 31.6 (d), 34.6 (t), 41.6 (t), 48.1 (d), 80.9 (d), 104.9 (d), 145.7 (d) ppm. MS (CI-NH_3) *m/e*: 363 (M+1, 78%), 380 (M+18, 14%), 224 (100%). Anal. Found: C, 79.65; H, 11.70. (Calc. for $C_{24}H_{42}O_2$: C, 79.50; H, 11.68).

(E,E)-1,4-bis[(1R,2S)-(2-phenylcyclohexyloxy)]-1,3-butadiene, **1b**: The procedure described above for **1a** was followed starting from 0.67 g (3.34 mmol) of (1*R*,2*S*)-(2-phenylcyclohexyloxy)ethyne[9] in 6 mL of THF, 0.86 g (3.34 mmol) of zirconocene hydrochloride in 3 mL of THF, and 0.36 g (3.67 mmol) of CuCl in 4 mL of THF. The reaction required heating at 65°C for 1.5 h and gave, after chromatographic purification (4% diethyl ether/hexane), 0.34 g (50% yield) of **1b** as a colourless solid.

m. p. 95-96°C. $[\alpha]_D^{23}$ = +26.4 (c=3.5, hexane). IR (NaCl film) ν_{max}: 3100, 3075, 3040, 3015, 2940, 2900, 2870, 1630, 1500, 1455, 1380, 1365, 1260, 1230, 1185, 1145, 1110, 1030, 950, 935, 875, 850, 755, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.25-1.92 (m, 14H), 2.13 (m, 2H), 2.59 (td, J=11 Hz, J'=4 Hz, 2H), 3.65 (td, J=11 Hz, J'=4 Hz, 2H), 5.15 (m, 2H), 5.9 (m, 2H), 7.1-7.3 (m, 10H) ppm. ^{13}C NMR (50 MHz, C_6D_6) δ: 25.0 (t), 26.1 (t), 32.9 (t), 34.3 (t), 50.6 (d), 82.8 (d), 104.9 (d), 126.5 (d), 128.0 (d), 128.7 (d), 145.5 (d) ppm. MS (CI-NH_3) *m/e*: 403 (M+1, 20%), 420 (M+18, 100%), 437 (M+35, 1%). Anal. Found: C, 83.49; H, 8.59. (Calc. for $C_{28}H_{34}O_2$: C, 83.54; H, 8.51).

(E,E)-1,4-bis[(1R,2S,5R)-(8-phenylmenthyloxy)]-1,3-butadiene, **1c**: The procedure described above for **1a** was followed starting from 1.0 g (3.9 mmol) of (1*R*,2*S*,5*S*)-(8-phenylmenthyloxy)ethyne[9] in 7 mL of THF, 1.01 g (3.9 mmol) of zirconocene hydrochloride in 4 mL of THF, and 0.43 g (4.29 mmol) of CuCl in 6 mL of THF. The reaction required heating at 65°C for 2 h and gave, after chromatographic purification (1% diethyl ether/hexane), 0.62 g (62% yield) of **1c** as a yellowish semisolid.

$[\alpha]_D^{23}$ = +3.15 (c=3.2, hexane). IR (NaCl film) ν_{max}: 3090, 3065, 3040, 2960, 2930, 2875, 1620, 1495, 1455, 1370, 1245, 1160, 1105, 1050, 1030, 995, 935, 765, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.86 (d, J=6.3 Hz, 6H), 1.33 (s, 6H), 1.40 (s, 6H), 0.70-1.55 (m, 12H), 1.78 (td, J=10 Hz, J'=4 Hz, 2H), 1.98 (m, 2H), 3.46 (td, J=10 Hz, J'=4 Hz, 2H), 5.38 (m, 2H), 6.1 (m, 2H), 7.1-7.3 (m, 10H) ppm. ^{13}C NMR (50 MHz, C_6D_6) δ: 22.0 (q), 24.8 (q), 27.4 (t), 30.3 (q), 31.5 (d), 34.8 (t), 40.8 (s), 42.4 (t), 51.8 (d), 82.2 (d), 105.3 (d), 125.5 (d), 126.4 (d), 128.2 (d), 144.8 (d), 150.7 ppm (s). MS (CI-NH_3) *m/e*: 516 (M+1, 26%), 533 (M+18, 100%).

(E,E)-1,4-bis[(1R,2S,3R,4S)-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxy]-1,3-butadiene, **1d**: The procedure described above for **1a** was followed starting from 0.78 g (2.94 mmol) of (1*R*,2*S*,3*R*,4*S*)-(3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxy)ethyne[9,22] in 5 mL of THF, 0.76 g (2.94 mmol) of zirconocene hydrochloride in 3 mL of THF, and 0.32 g (3.23 mmol) of CuCl in 4 mL of THF. The reaction required heating at 60°C for 1.75 h and gave, after chromatographic purification (hexane), 0.33 g (42% yield) of **1d** as a yellowish solid.

m. p. 45-46°C. $[\alpha]_D^{23}$ = -99.8 (c=2.1, hexane). IR (NaCl film) ν_{max}: 3055, 2950, 2865, 1610, 1480, 1460, 1390, 1360, 1330, 1260, 1140, 1110, 1080, 940, 800 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.77 (s, 6H), 0.86 (s, 18H + 6H), 1.12 (s, 6H), 0.90-1.70 (m, 8H), 1.79 (d, J=5 Hz, 2H), 2.98 (part A of AB system, J=8.0 Hz, 2H), 3.06 (part B of AB system, J=8.0 Hz, 2H), 3.40 (part A of AB system, J=6.7 Hz, 2H), 3.56 (part B of AB system, J=6.7 Hz, 2H), 5.37 (m, 2H), 6.24 (m, 2H) ppm. ^{13}C NMR (50 MHz, C_6D_6) δ: 11.7 (q), 21.2 (q), 21.4 (q), 24.4 (t), 27.2 (q), 32.4 (s), 33.7 (t), 47.0 (s), 49.0 (d), 49.4 (s), 81.4 (t), 85.3 (d), 89.4 (d), 103.5 (d), 148.1 (d) ppm. MS (CI-NH_3) *m/e*: 258 (100%), 532 (M+1, 29%), 549 (M+18, 42%), 565 (M+35, 19%).

(E,E)-1,4-bis[(1R,2S,3R,4S)-2-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-oxy]-1,3-butadiene, **1e**: The procedure described above for **1a** was followed starting from 1.0 g (3.79 mmol) of (1*R*,2*S*,3*R*,4*S*)-(2-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-oxy)ethyne[9,23] in 7 mL of THF, 0.98 g (3.79 mmol) of zirconocene hydrochloride in 4 mL of THF, and 0.41 g (4.16 mmol) of CuCl in 6 mL of THF. The reaction required heating at 65°C for 3.5 h and gave, after chromatographic purification (hexane), 0.47 g (47% yield) of **1e** as a yellowish semisolid.

$[\alpha]_D^{23}$ = -20.9 (c=2.6, hexane). IR (NaCl film) ν_{max}: 3035, 2950, 2880, 1615, 1475, 1460, 1390, 1370, 1360, 1190, 1155, 1115, 940, 850, 800, 770 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.76 (s, 6H), 0.89 (s, 18H + 6H), 1.12 (s, 6H), 0.90-1.80 (m, 8H), 1.81 (d, J=5 Hz, 2H), 2.89 (part A of AB system, J=7.9 Hz, 2H), 3.21 (part A of AB system, J=6.5 Hz, 2H), 3.25 (part B of AB system, J=7.9 Hz, 2H), 3.77 (part B of AB system, J=6.5 Hz, 2H), 5.39 (m, 2H), 6.3 (m, 2H) ppm. ^{13}C NMR (50 MHz, C_6D_6) δ: 11.8 (q), 21.0 (q), 21.2 (q), 24.1 (t), 27.1 (q), 32.7 (s), 33.9 (t), 46.9 (s), 49.6 (d), 49.7 (s), 82.9 (t), 85.7 (d), 88.3 (d), 104.5 (d), 146.4 (d) ppm. MS (CI-NH_3) *m/e*: 258 (100%), 532 (M+1, 5%), 549 (M+18, 9%), 565 (M+35, 15%).

*General procedure for the Diels-Alder cycloadditions of **1a-e** with 4-phenyl-3H-1,2,4-triazoline-3,5-dione*

A THF solution of 4-phenyl-3H-1,2,4-triazoline-3,5-dione (PTAD) (1 eq) was added, under argon, to a THF solution of the dialkoxydiene **1a-e** (1 eq) at room temperature. The reaction was instantaneous in all cases. Evaporation of the solvent at reduced pressure gave the pure adducts **2a-e** in quantitative yield.

(5R,8S)-2-phenyl-5,8-bis-(l-menthyloxy)-5,8-dihydro-[1,2,4]triazolo[1,2-a]pyridazine-1,3-dione, **2a**: The general procedure was followed starting from 50 mg (0.14 mmol) of **1a** in 0.2 mL of THF and 24 mg (0.14 mmol) of PTAD in 0.4 mL of THF.

m. p. 57-58°C. $[\alpha]_D^{23}$ = -70.3 (c=0.9, CH_2Cl_2). IR (NaCl film) ν_{max}: 3060, 2960, 2930, 2870, 1780, 1715, 1605, 1505, 1455, 1420, 1295, 1250, 1155, 1145, 1065, 1050, 920, 880, 765, 720, 690, 645 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.7-2.4 (m, 36H), 3.78 (td, J=10 Hz, J'=5 Hz, 1H), 3.89 (td, J=10 Hz, J'=5 Hz, 1H), 5.84 (dd, J=15 Hz, J'=5 Hz, 2H), 6.25 (m, 2H), 7.35-7.55 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 15.4 (q), 16.0 (q), 21.0 (q), 21.2 (q), 22.2 (q), 22.4 (q), 22.8 (t), 24.6 (d), 25.4 (d), 31.3 (d), 31.7 (d), 34.1 (t), 34.2 (t), 40.3 (t), 42.9 (t), 47.5 (d), 48.7 (d), 73.2 (d), 77.6 (d), 78.0 (d), 80.8 (d), 125.4 (d), 125.5 (d), 128.2 (d), 129.1 (d), 131.4 (s), 149.1 (s), 149.4 (s) ppm. MS (CI-NH_3) *m/e*: 382 (100%), 538 (M+1, 2%), 555 (M+18, 4%). Anal. Found: C, 71.34; H, 8.89; N, 7.87. (Calc. for $C_{32}H_{47}N_3O_4$: C, 71.48; H, 8.81; N, 7.82).

(5R,8S)-2-phenyl-5,8-bis-((1R,2S)-2-phenylcyclohexyloxy)-5,8-dihydro[1,2,4]triazolo[1,2a]pyridazine -1,3-dione, **2b**: The general procedure was followed starting from 25 mg (0.062 mmol) of **1b** in 0.2 mL of THF and 11 mg (0.062 mmol) of PTAD in 0.4 mL of THF.

IR (NaCl film) ν_{max}: 3070, 3040, 2940, 2865, 1780, 1715, 1610, 1510, 1425, 1300, 1255, 1130, 1060, 985, 955, 915, 885, 760, 735, 705, 645 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.8-2.2 (m, 16H), 2.40-2.62 (m, 2H), 3.95-4.18 (m, 2H), 4.77 (d, J=5 Hz, 1H), 5.05 (dd, J=10 Hz, J'=5 Hz, 1H), 5.44 (dd, J=10 Hz, J'=5 Hz, 1H), 5.58 (d, J=5 Hz, 1H), 7.1-7.5 (m, 15H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 24.9 (t), 25.3 (t), 25.8 (t), 33.3 (t), 34.3 (t), 50.2 (d), 52.0 (d), 74.4 (d), 78.6 (d), 80.7 (d), 84.3 (d), 124.3 (d), 125.2 (d), 125.4 (d), 125.9 (d), 126.5 (d), 127.9 (d), 128.3 (d), 129.1 (d), 144.1 (s), 144.2 (s), 149.0 (s), 149.8 (s) ppm. MS (CI-NH_3) *m/e*: 579 (M+1, 1%), 596 (M+18, 100%). HRMS: Calc. for $C_{36}H_{39}N_3O_4$: 577.2940. Found: 577.2892.

(5R,8S)-2-phenyl-5,8-bis-((1R,2S,5R)-8-phenylmenthyloxy)-5,8-dihydro-[1,2,4]triazolo[1,2-a] pyridazine-1,3-dione, **2c**: The general procedure was followed starting from 40 mg (0.078 mmol) of **1c** in 0.2 mL of THF and 14 mg (0.078 mmol) of PTAD in 0.4 mL of THF.

$[\alpha]_D^{23}$ = -34.4 (c=2.0, $CHCl_3$). IR (NaCl film) ν_{max}: 3090, 3060, 3025, 2960, 2920, 2875, 1780, 1715, 1605, 1500, 1420, 1300, 1245, 1165, 1050, 910, 880, 770, 735, 705, 650 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.79 (d, J=6.3 Hz, 3H), 0.86 (d, J=6.3 Hz, 3H), 1.27 (s, 3H), 1.35 (s, 3H), 1.43 (s, 3H), 1.54 (s, 3H), 0.70-2.30 (m, 16H), 3.97 (td, J=10 Hz, J'=4 Hz, 1H), 4.05 (td, J=10 Hz, J'=4 Hz, 1H), 5.40-5.90 (m, 4H), 7.10-7.55 (m, 15H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 21.6 (q), 22.1 (q), 22.2 (q), 27.4 (q), 27.9 (q), 31.3 (d), 31.6 (d), 32.8 (q), 34.5 (t), 34.7 (t), 40.2 (s), 40.8 (t), 41.1 (s), 44.1 (t), 51.7 (d), 51.8 (d), 74.0 (d), 76.7 (d), 79.2 (d), 81.7 (d), 124.9 (d), 125.1 (d), 125.3 (d), 125.6 (d), 125.9 (d), 127.9 (d), 128.0 (d), 128.3 (d), 129.2 (d), 131.2 (s), 149.5 (s), 151.0 (s), 151.6 (s) ppm. MS (CI-NH_3) *m/e*: 250 (100%), 708 (M+18, 3%). HRMS: Calc. for $C_{44}H_{55}N_3O_4$: 689.4193. Found: 689.4153.

(5R,8S)-5,8-bis-[(1R,2S,3R,4S)-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxy]-2-phenyl-5,8-dihydro-[1,2,4]triazolo[1,2-a]pyridazine-1,3-dione, **2d**: The general procedure was followed starting from 30 mg (0.057 mmol) of **1d** in 0.2 mL of THF and 10 mg (0.057 mmol) of PTAD in 0.4 mL of THF.

m. p. 158-159°C. $[\alpha]_D^{23}$ = -92.4 (c=1.96, $CHCl_3$). IR (NaCl film) ν_{max}: 3060, 3020, 2950, 2875, 1780, 1720, 1605, 1500, 1475, 1415, 1360, 1285, 1135, 1100, 1055, 1020, 925, 880, 765, 735 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.77 (s, 6H), 0.88 (s, 3H), 0.92 (s, 3H), 0.95 (s, 18H), 1.12 (s, 3H), 1.14 (s, 3H), 0.80-1.90 (m, 10H), 3.00 (part A of AB system, J=9.0 Hz, 1H), 3.13 (part B of AB system, J=9.0 Hz, 1H), 3.08 (part A of AB system, J=9.0 Hz, 1H), 3.09 (part A of AB system, J=7.5 Hz, 1H), 3.29 (part B of AB system, J=9.0 Hz, 1H), 3.29 (part A of AB system, J=7.5 Hz, 1H), 3.92 (part B of AB system, J=7.5 Hz, 1H), 4.13 (part B of AB system, J=7.5 Hz, 1H), 5.89 (m, 2H), 6.10 (dd, J=11 Hz, J'=4 Hz, 1H), 6.27 (dd, J=11 Hz, J'=4.5 Hz, 1H), 7.30-7.60 (m, 5H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 11.7 (q), 11.8 (q), 20.8 (q), 21.0 (q), 21.1 (q), 21.2 (q), 23.9 (t), 27.1 (q), 32.0 (s), 32.2 (s), 33.7 (t), 46.9 (s), 47.0 (s), 47.1 (d), 47.6 (d), 48.9 (s), 49.2 (s), 76.4 (d), 80.0 (d), 80.3 (t), 80.6 (t), 84.6 (d), 84.8 (d), 85.6 (d), 86.1 (d), 125.4 (d), 125.6 (d), 128.0 (d), 129.1 (d), 131.4 (s), 150.5 (s), 151.3 (s) ppm. MS (CI-NH_3) *m/e*: 707 (M+1, 1%), 724 (M+18, 100%). HRMS: Calc. for $C_{34}H_{58}O_4$ (M-$C_8H_5N_3O_2$): 530.4335. Found: 530.4347.

(5R,8S)-5,8-bis-[(1R,2S,3R,4S)-2-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-oxy]-2-phenyl-5,8-dihydro-[1,2,4]triazolo[1,2-a]pyridazine-1,3-dione, **2e**: The general procedure was followed starting from 32 mg (0.060 mmol) of **1e** in 0.2 mL of THF and 11 mg (0.060 mmol) of PTAD in 0.4 mL of THF.

$[\alpha]_D^{23}$ = +17.5 (c=0.45, $CHCl_3$). IR (NaCl film) ν_{max}: 3060, 3020, 2950, 2860, 1770, 1720, 1600, 1500, 1475, 1455, 1415, 1360, 1285, 1240, 1130, 1120, 1105, 1075, 1055, 1030, 910, 875, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.73 (s, 3H), 0.79 (s, 3H), 0.89 (s, 3H), 0.90 (s, 9H), 0.93 (s, 3H), 0.94 (s, 9H), 1.11 (s, 3H), 1.17 (s, 3H), 1.0-2.02 (m, 10H), 2.86 (part A of AB system, J=7.8 Hz, 1H), 3.24 (part A of AB system, J=6.9 Hz, 1H), 3.25 (part A of AB system, J=8.4 Hz, 1H), 3.31 (part B of AB system, J=8.4 Hz, 1H), 3.40 (part A of AB system, J=6.6 Hz, 1H), 3.43 (part B of AB system, J=7.8 Hz, 1H), 4.05 (part B of AB system, J=6.9 Hz, 1H), 4.15 (part B of AB system, J=6.6 Hz, 1H), 5.80 (dd, J=5.6 Hz, J'=5.6 Hz, 2H), 6.00 (dd, J=10.4 Hz, J'=4.2 Hz, 1H), 6.18 (dd, J=10.5 Hz, J'=4.5 Hz, 1H), 7.33-7.59 (m, 5H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (q), 11.8 (q), 20.8 (q), 20.9 (q), 21.2 (q), 24.1 (t), 24.5 (t), 27.0 (q), 27.1 (q), 32.4 (s), 32.6 (s), 33.3 (t), 33.6 (t), 46.5 (s), 47.0 (s), 48.0 (d), 49.8 (s), 50.2 (s), 50.5 (d), 75.6 (d), 76.6 (d), 81.5 (d), 82.4 (t), 82.7 (d), 83.2 (t), 87.9 (d), 88.8 (d), 125.2 (d), 125.3 (d), 125.6 (d), 128.2 (d), 129.2 (d), 131.3 (s), 150.7 (s), 151.3 (s) ppm. MS (CI-NH_3) *m/e*: 707 (M+1, 2%), 724 (M+18, 100%). HRMS: Calc. for $C_{34}H_{58}O_4$ (M-$C_8H_5N_3O_2$): 530.4335. Found: 530.4334.

General procedure for the Diels-Alder cycloadditions of 1a-e with maleic anhydride

A degassed toluene solution containing 1 eq of the dialkoxydiene **1a-e** and 1 eq of maleic anhydride (freshly recrystallized from benzene) was heated, under strict Ar athmosphere, at 80-95°C for 3-10 h. The progress of the reaction was monitored by TLC. Removal of the solvent at reduced pressure gave the cycloadducts **5a-e**, that could be further purified, albeit with significant product loss, by chromatography.

(1R,2S,3R,6S)-3,6-bis-(l-menthyloxy)cyclohex-4-en-1,2-dicarboxylic acid anhydride, **5a**: The general procedure was followed starting from 30 mg (0.083 mmol) of **1a**, 8 mg (0.083 mmol) of maleic anhydride, and 0.6 mL of anhydrous, degassed toluene. The reaction required heating at 95°C for 3 h and gave 33 mg (87% yield) of **5a** as a pure, colourless solid.

m. p. 160.5-161.0°C. $[\alpha]_D^{23}$ = -119.7 (c=1.43, $CHCl_3$). IR (KBr) ν_{max}: 3045, 2940, 2910, 2860, 1860, 1790, 1620 (w), 1450, 1370, 1300, 1255, 1210, 1180, 1110, 1055, 1015, 950, 940, 920, 850, 755, 745, 655 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.74 (d, J=6.5 Hz, 3H), 0.77 (d, J=6.5 Hz, 3H), 0.8-1.7 (m, 26H), 1.95-2.15 (m, 2H), 2.31 (m, 1H), 2.46 (m, 1H), 3.22 (td, J=10 Hz, J'=4 Hz, 1H), 3.27 (td, J=10 Hz, J'=4 Hz, 1H), 3.48 (m, 2H), 4.20 (m, 2H), 6.05 (m, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 15.8 (q), 15.9 (q), 21.2 (q), 22.3 (q), 22.8 (t), 22.9 (t), 24.6 (d), 24.7 (d), 31.6 (d), 34.2 (t), 34.3 (t), 40.2 (t), 41.3 (t), 44.3 (d), 44.9 (d), 47.9 (d), 48.0 (d), 68.1 (d), 69.5 (d), 79.2 (d), 80.7 (d), 130.6 (d), 133.4 (d), 168.4 (s), 168.7 (s) ppm. MS (CI-NH_3) *m/e*: 461 (M+1, 20%), 478 (M+18, 100%). Anal. Found: C, 72.92; H, 9.72. (Calc. for $C_{28}H_{44}O_5$: C, 73.01; H, 9.63).

(1R,2S,3R,6S)-3,6-bis-((1R,2S)-2-phenylcyclohexyloxy)cyclohex-4-en-1,2-dicarboxylic acid anhydride, **5b**: The general procedure was followed starting from 26 mg (0.065 mmol) of **1b**, 7 mg (0.065

mmol) of maleic anhydride, and 0.6 mL of anhydrous, degassed toluene. The reaction required heating at 80°C for 3 h and gave 31 mg (94% yield) of **5b** as a colourless solid.

m. p. 134-135°C. $[\alpha]_D^{23}$ = -22.9 (c=0.90, $CHCl_3$). IR (NaCl film) ν_{max}: 3065, 3035, 2930, 2860, 1865, 1790, 1610, 1495, 1450, 1365, 1300, 1255, 1190, 1105, 1055, 930, 905, 755, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.25-2.7 (m, 19H), 2.90-3.33 (m, 5H), 4.96 (m, 1H), 5.57 (m, 1H), 7.15-7.3 (m, 10H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 25.1 (t), 25.6 (t), 25.7 (t), 32.7 (t), 32.8 (t), 32.9 (t), 33.9 (t), 43.7 (d), 44.2 (d), 51.0 (d), 51.1 (d), 70.3 (d), 71.8 (d), 84.1 (d), 85.5 (d), 126.3 (d), 128.0 (d), 128.1 (d), 130.7 (d), 131.7 (d), 144.1 (s), 144.4 (s), 168.2 (s) ppm. MS (CI-NH_3) *m/e*: 518 (M+18, 100%). HRMS: Calc. for $C_{32}H_{37}O_5$ (M+H): 501.2641. Found: 501.2649.

(1R,2S,3R,6S)-3,6-bis-((1R,2S,5R)-8-phenylmenthyloxy)cyclohex-4-en-1,2-dicarboxylic acid anhydride, **5c**: The general procedure was followed starting from 64 mg (0.124 mmol) of **1c**, 12 mg (0.124 mmol) of maleic anhydride, and 0.2 mL of anhydrous, degassed toluene. The reaction required heating at 95°C for 10 h and gave, after chromatographic purification (preparative TLC, hexane/ethyl acetate 5/1), 32 mg (42% yield) of **5c** as a colourless oil.

IR (NaCl film) ν_{max}: 3090, 3060, 3020, 2975, 2920, 2880, 1885, 1790, 1605, 1495, 1455, 1375, 1195, 1105, 1060, 955, 855, 770, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.90 (d, J=6.3 Hz, 3H), 0.91 (d, J=6.3 Hz, 3H), 1.26 (s, 3H), 1.34 (s, 3H), 1.39 (s, 3H), 1.40 (s, 3H), 0.80-2.26 (m, 16H), 3.17 (dd, J=9.1 Hz, J'=5.5 Hz, 1H), 3.28 (dd, J=8.6 Hz, J'=5.6 Hz, 1H), 3.38 (td, J=9.9 Hz, J'=3.6 Hz, 1H), 3.42 (td, J=9.9 Hz, J'=3.6 Hz, 1H), 3.81 (m, 1H), 3.98 (m, 1H), 5.66 (dt, J=9.9 Hz, J'=2.4 Hz, 1H), 5.82 (m, 1H), 7.10-7.41 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.1 (q), 22.2 (q), 24.8 (q), 25.7 (q), 27.3 (t), 29.1 (q), 29.7 (t), 30.2 (q), 31.4 (d), 31.5 (d), 34.3 (t), 34.6 (t), 40.4 (s), 40.5 (s), 40.6 (t), 41.7 (t), 44.8 (d), 44.9 (d), 51.5 (d), 52.0 (d), 68.8 (d), 70.2 (d), 80.9 (d), 81.8 (d), 125.0 (d), 125.1 (d), 125.9 (d), 126.0 (d), 127.7 (d), 127.9 (d), 129.5 (d), 133.7 (d), 151.3 (s), 151.5 (s), 167.9 (s), 168.7 (s) ppm. MS (CI-NH_3) *m/e*: 250 (100%), 630 (M+18, 8%).

(1R,2S,3R,6S)-3,6-bis-[(1R,2S,3R,4S)-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxy]cyclohex-4-en-1,2-dicarboxylic acid anhydride, **5d**: The general procedure was followed starting from 37 mg (0.070 mmol) of **1d**, 7 mg (0.070 mmol) of maleic anhydride, and 0.3 mL of anhydrous, degassed toluene. The reaction required heating at 80°C for 5 h and gave a mixture of the cycloadduct **5d** (80% yield) and (1*R*,2*S*,3*R*,4*S*)-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (20% yield, estimated by NMR). (NOTE: Due to the high sensitivity of the dialkoxydiene, the reaction glassware was washed with aqueous NaOH and oven-dried prior to use).

IR (NaCl film) ν_{max}: 3030, 2950, 2870, 1860, 1785, 1480, 1460, 1390, 1360, 1190, 1140, 1105, 1060, 950, 940, 740 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.79 (s, 6H), 0.85 (s, 9H), 0.92 (s, 9H), 0.94 (s, 3H), 0.99 (s, 3H), 1.15 (s, 3H), 1.21 (s, 3H), 0.80-1.90 (m, 10H), 2.80-3.65 (m, 10H), 4.19 (m, 1H), 4.38 (m, 1H), 5.95-6.10 (m, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 11.4 (q), 11.7 (q), 20.5 (q), 20.6 (q), 21.2 (q), 21.3 (q), 24.0 (t), 24.1 (t), 26.7 (q), 27.0 (q), 27.1 (q), 32.0 (s), 32.1 (s), 33.6 (t), 34.0 (t), 40.8 (d), 45.0 (d), 46.7 (d), 46.9 (d), 49.0 (s), 49.2 (s), 70.8 (d), 71.6 (d), 80.5 (t), 80.6 (t), 84.6 (d), 85.4 (d), 85.7 (d), 85.9 (d), 129.9 (d), 132.6 (d), 168.3 (s), 168.6 (s) ppm. MS (CI-NH_3) *m/e*: 629 (M+1, 44%), 646 (M+18, 100%).

(1R,2S,3R,6S)-3,6-bis-[(1R,2S,3R,4S)-2-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-oxy]cyclohex-4-en-1,2-dicarboxylic acid anhydride, **5e**: The general procedure was followed starting from 52 mg (0.098 mmol) of **1e**, 10 mg (0.098 mmol) of maleic anhydride, and 0.4 mL of anhydrous, degassed toluene. The reaction required heating at 80°C for 6 h and gave a mixture of the cycloadduct **5e** (70% yield) and (1*R*,2*S*,3*R*,4*S*)-2-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-ol (30% yield, estimated by NMR). (NOTE: Due to the high sensitivity of the dialkoxydiene, the reaction glassware was washed with aqueous NaOH and oven-dried prior to use).

IR (NaCl film) ν_{max}: 3020, 2950, 2870, 1850, 1785, 1475, 1455, 1390, 1360, 1180, 1150, 1110, 1070, 1010, 950, 795, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.78 (s, 6H), 0.89 (s, 9H), 0.90 (s, 9H), 0.87 (s, 3H), 0.93 (s, 3H), 1.16 (s, 3H), 1.18 (s, 3H), 1.0-1.90 (m, 10H), 2.93 (d, J=7.5 Hz, 1H), 3.05 (d, J=7.5 Hz, 1H), 3.2-3.3 (m, 3H), 3.49 (d, J=7.5 Hz, 1H), 3.65 (m, 2H), 3.81 (d, J=6.8 Hz, 1H), 3.85 (d, J=6.5 Hz, 1H), 4.18 (m, 2H), 5.95 (m, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 11.6 (q), 11.8 (q), 20.5 (q), 20.7 (q), 21.0 (q), 21.2 (q), 24.2 (t), 24.4 (t), 26.9 (q), 32.3 (s), 32.4 (s), 33.5 (t), 33.6 (t), 42.1 (d), 42.9 (d), 46.6 (d), 49.3 (d), 49.5 (s), 49.9 (s), 69.2 (d), 71.4 (d), 82.3 (d), 82.5 (t), 83.2 (t), 83.7 (d), 88.0 (d), 88.8 (d), 130.9 (d), 131.5 (d), 168.1 (s), 168.3 (s) ppm. MS (CI-NH_3) *m/e*: 258 (100%), 629 (M+1, 6%), 646 (M+18, 40%). HRMS: Calc. for $C_{38}H_{60}O_7$: 628.4339. Found: 628.4288.

General procedure for the Diels-Alder cycloadditions of ***1a-e*** *with fumaronitrile*

A degassed *m*-xylene solution containing 1 eq of the dialkoxydiene **1a-e**, 1 eq of fumaronitrile and hydroquinone (*ca.* 20% molar amount) was heated, under strict argon atmosphere, at 80-140°C for 2-22 h. The progress of the reaction was monitored by TLC. Removal of the solvent at reduced pressure and chromatographic purification (triethylamine-pretreated silica gel [2.5% v/v], eluting with hexane/diethyl ether mixtures of increasing polarity) gave the cycloadducts **6a-e**.

(1R,2R,3R,6S)- and *(1S,2S,3S,6R)- 3,6-bis-(l-menthyloxy)cyclohex-4-en-1,2-dicarbonitrile,* **6a**: The general procedure was followed starting from 30 mg (0.083 mmol) of **1a**, 7 mg (0.083 mmol) of fumaronitrile, 2 mg of hydroquinone and 0.8 mL of anhydrous, degassed *m*-xylene. The reaction required heating at 140°C for 5.5 h and gave, after chromatographic purification (4/1 hexane/diethyl ether), 31 mg (85% yield) of **6a** (1.3:1 diastereomer mixture) as a colourless solid.

IR (KBr) ν_{max}: 2960, 2920, 2855, 2260, 1455, 1390, 1370, 1315, 1180, 1100, 1065, 950, 920, 760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.70-2.45 (m, 36H), 3.01-3.67 (m, 4H), 4.10-4.20 (m, 2H), 5.78-5.95 (m, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) Major diastereomer. δ: 16.0 (q), 16.1 (q), 21.1 (q), 21.4 (q), 22.3 (q), 22.4 (q), 22.8 (t), 22.9 (t), 24.8 (d), 25.1 (d), 31.4 (d), 31.5 (d), 32.3 (d), 34.2 (t), 34.6 (d), 40.2 (t), 42.0 (t), 48.1 (d), 48.7 (d), 66.7 (d), 71.5 (d), 77.6 (d), 80.2 (d), 116.3 (s), 116.4 (s), 127.9 (d), 129.1 (d) ppm. Minor diastereomer. δ: 15.9 (q), 16.2 (q), 21.0 (q), 21.3 (q), 22.3 (q), 22.4 (q), 22.8 (t), 22.9 (t), 24.7 (d), 24.8 (d), 31.3 (d), 31.4 (d), 31.9 (d), 32.3 (d), 34.2 (t), 35.7 (d), 40.0 (t), 41.6 (t), 48.0 (d), 48.5 (d), 64.7 (d), 72.5 (d), 78.3 (d), 80.6 (d), 118.2 (s), 118.6 (s), 125.7 (d), 132.2 (d) ppm. MS (CI-NH_3) *m/e*: 458 (M+18, 100%), 475 (M+35, 2%). Anal. Found: C, 76.18; H, 10.14; N, 6.24. (Calc. for $C_{28}H_{44}N_2O_2$: C, 76.32; H, 10.06, N, 6.36).

(1R,2R,3R,6S)- and *(1S,2S,3S,6R)-3,6-bis-((1R,2S)-2-phenylcyclohexyloxy)cyclohex-4-en-1,2-dicarbonitrile,* **6b**: The general procedure was followed starting from 30 mg (0.075 mmol) of **1b**, 6 mg (0.075 mmol) of fumaronitrile, 2 mg of hydroquinone and 0.4 mL of anhydrous, degassed *m*-xylene. The reaction required heating at 140°C for 4 h and gave, after chromatographic purification (6/1 hexane/diethyl ether), 28 mg (78% yield) of **6b** (1.45:1 diastereomer mixture) as a colourless solid.

IR (NaCl film) ν_{max}: 3095, 3075, 3045, 2940, 2870, 2265, 1610, 1495, 1455, 1310, 1270, 1180, 960, 760, 740, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.20-2.72 (m, 20H), 3.42-3.65 (m, 4H), 4.69 (dd, J=10.5 Hz, J'=2.1 Hz, 1H, minor diastereomer), 4.74 (ddd, J=10.5 Hz, J'=4.8 Hz, J"=1.8 Hz, 1H, major diastereomer), 5.23 (ddd, J=10.5 Hz, J'=2.4 Hz, J"=1.5 Hz, 1H, minor diastereomer), 5.40 (ddd, J=10.5 Hz, J'=4.5 Hz, J"=1.5 Hz, 1H, major diastereomer), 7.14-7.35 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) Major diastereomer. δ: 24.8 (t), 25.1 (t), 25.6 (t), 25.7 (t), 31.7 (d), 32.6 (t), 33.2 (t), 33.4 (d), 33.4 (t), 33.5 (t), 51.2 (d), 51.8 (d), 66.0 (d), 75.0 (d), 81.8 (d), 85.4 (d), 84.1 (d), 116.0 (s), 118.3 (s), 126.1 (d), 126.2 (d), 126.6 (d), 128.0 (d), 128.1 (d), 129.7 (d), 143.5 (s), 144.1 (s) ppm. Minor diastereomer. δ: 24.8 (t), 25.1 (t), 25.6 (t), 25.7 (t), 31.0 (d), 33.2 (t), 33.4 (t), 33.5 (t), 33.9 (t), 34.4 (d), 50.9 (d), 51.9 (d), 68.9 (d), 72.3 (d), 82.5 (d), 84.6 (d), 116.5 (s), 118.0 (s), 126.4 (d), 126.5 (d), 126.6 (d), 128.1 (d), 128.3 (d), 129.8 (d), 143.6 (s), 143.8 (s) ppm MS (CI-NH_3) *m/e*: 498 (M+18, 100%). Anal. Found: C, 80.07; H, 7.59; N, 5.76. (Calc. for $C_{32}H_{36}N_2O_2$: C, 79.97; H, 7.55, N, 5.83).

(1R,2R,3R,6S)- and *(1S,2S,3S,6R)-3,6-bis-((1R,2S,5R)-8-phenylmenthyloxy)cyclohex-4-en-1,2-dicarbonitrile,* **6c**: The general procedure was followed starting from 60 mg (0.117 mmol) of **1c**, 9 mg (0.117 mmol) of fumaronitrile, 2 mg of hydroquinone, and 0.6 mL of anhydrous, degassed *m*-xylene. The reaction required heating at 140°C for 22 h and gave, after chromatographic purification (4/1 hexane/diethyl ether), 41 mg (59% yield) of **6c** (1.3:1 diastereomer mixture) as a colourless dense oil. 10 mg (17% yield) of the starting diene could also be recovered.

IR (NaCl film) ν_{max}: 3090, 3060, 2960, 2920, 2870, 2250, 1600, 1490, 1450, 1370, 1320, 1180, 1090, 1050, 905, 760, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88-0.98 (m, 6H), 1.22 (s, 3H, minor diastereomer), 1.32 (s, 3H, minor diastereomer), 1.36 (s, 3H, major diastereomer), 1.41 (s, 3H, major diastereomer), 1.42 (s, 3H, minor diastereomer), 1.48 (s, 6H, major diastereomer), 1.51 (s, 3H, minor diastereomer), 0.70-2.20 (m, 16H), 2.73-3.03 (m, 2H), 3.39 (td, J=10.3 Hz, J'=3.3 Hz, 1H, minor diastereomer), 3.45 (td, J=10.2 Hz, J'=3.6 Hz, 1H, major diastereomer), 3.65 (td, J=10.3 Hz, J'=3.3 Hz, 1H, minor diastereomer), 3.81 (td, J=10.2 Hz, J'=3.6 Hz, 1H, major diastereomer), 3.96-4.20 (m, 2H), 5.58 (dd, J=10.4 Hz, J'=1.5 Hz, 1H, minor diastereomer), 5.64 (dd, J=10.4 Hz, J'=3.0 Hz, 1H, minor diastereomer), 5.76 (dd, J=10.5 Hz, J'=1.8 Hz, 1H, major diastereomer), 5.86 (ddd, J=10.4 Hz, J'=4 Hz, J"=1.5 Hz, 1H, major diastereomer), 7.10-7.41 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) Major diastereomer. δ: 22.1 (q), 23.3 (q), 25.1 (q), 27.1 (t), 27.2 (t), 29.4 (q), 31.3 (d), 31.5 (d), 34.5 (d), 34.6 (t), 35.6 (d), 39.7 (d), 39.7 (s), 39.8 (t), 40.7 (s), 41.7 (t), 51.3 (d), 52.3 (d), 62.9 (d), 71.6 (d), 78.0 (d), 81.8 (d), 116.1 (s), 119.1 (s), 124.9 (d), 125.1 (d), 125.3 (d), 125.5 (d), 125.8 (d), 127.9 (d), 128.0 (d), 132.7 (d), 151.5 (s), 151.9 (s) ppm. Minor diastereomer. δ: 22.0 (q), 22.2 (q), 24.0 (q), 24.5 (q), 26.5 (t), 27.4 (t), 29.1 (q), 30.3 (q), 31.3 (d), 31.7 (d), 34.5 (d), 34.6 (t), 35.6 (d), 39.9 (t), 40.3 (s), 40.6 (s), 42.4 (t), 51.7 (d), 52.0 (d), 66.3 (d), 69.4 (d), 77.7 (d), 80.9 (d), 117.1 (s), 118.2 (s), 124.6 (d), 125.5 (d), 125.8 (d), 127.8 (d), 127.9 (d), 128.0 (d), 151.1 (s), 152.4 (s) MS (CI-NH_3) *m/e*: 250 (100%), 610 (M+18, 26%).

(1R,2R,3R,6S)- and *(1S,2S,3S,6R)-3,6-bis-[(1R,2S,3R,4S)-3-(2,2-dimethylpropoxy)-1,7,7-trimethyl bicyclo[2.2.1]heptan-2-oxy]cyclohex-4-en-1,2-dicarbonitrile,* **6d**: The general procedure was followed starting from 53 mg (0.10 mmol) of **1d**, 8 mg (0.10 mmol) of fumaronitrile, 2 mg of hydroquinone and 0.4 mL of anhydrous, degassed *m*-xylene. The reaction required heating at 85°C for 7 h and gave, after chromatographic purification (15/1 hexane/diethyl ether) 24 mg of the major diastereomer of **6d** as a colorless oil; 14 mg of a 1:1 mixture of the two diastereomers of **6d**; 7 mg of the minor diastereomer of **6d** as a colorless solid; and 5 mg (9% recovery) of the starting diene **1d**. The overall yield for **6d** was 74%, and the diastereoselectivity 2.2:1. (NOTE: Due to the high sensitivity of the dialkoxydiene, the reaction glassware was washed with aqueous NaOH and oven-dried prior to use).

Major diastereomer: $[\alpha]_D^{23}$ = -70.0 (c=1.3, $CHCl_3$). IR (NaCl film) ν_{max}: 3050, 3020, 2950, 2860, 2250, 1475, 1460, 1390, 1360, 1140, 1100, 1075, 960, 920, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.76 (s, 3H), 0.78 (s, 3H), 0.90 (s, 9H), 0.91 (s, 3H), 0.95 (s, 9H), 0.98 (s, 3H), 1.11 (s, 6H), 0.80-1.70 (m, 8H), 1.86 (d, J=5 Hz, 1H), 1.90 (d, J=5 Hz, 1H), 2.98 (part A of AB system, J=8.7 Hz, 1H), 3.11 (part A of AB system, J=8.4 Hz, 1H), 3.17 (dd, J=8.7 Hz, J'=3.9 Hz, 1H), 3.21 (part B of AB system, J=8.4 Hz, 1H), 3.24 (part B of AB system, J=8.7 Hz, 1H), 3.44 (part A of AB system, J=6.9 Hz, 1H), 3.47 (part A of AB system, J=6.6 Hz, 1H), 3.51 (dd, J=8.7 Hz, J'=6.3 Hz, 1H), 3.54 (part B of AB system, J=6.9 Hz, 1H), 3.79 (part B of AB system, J=6.6 Hz, 1H), 4.09 (m, 1H), 4.31 (m, 1H), 5.90 (ddd, J=10.5 Hz, J'=2.7 Hz, J"=1.5 Hz, 1H), 6.08 (ddd, J=10.5 Hz, J'=3.3 Hz, J"=1.8 Hz, 1H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 11.7 (q), 11.8 (q), 20.6 (q), 20.8 (q), 21.2 (q), 21.3 (q), 24.0 (t), 24.1 (t), 27.0 (q), 27.1 (q), 31.1 (d), 32.0 (s), 32.1 (s), 32.7 (d), 33.6 (t), 33.7 (t), 46.7 (s), 46.8 (s), 47.0 (d), 47.1 (d), 49.2 (s), 49.3 (s), 69.4 (d), 74.6 (d), 80.5 (t), 80.9 (t), 85.6 (d), 85.9 (d), 87.4 (d), 89.4 (d), 116.5 (s), 118.2 (s), 127.1 (d), 129.3 (d) ppm. MS (CI-NH_3) *m/e*: 609 (M+1, 3%), 626 (M+18, 100%). HRMS: Calc. for $C_{38}H_{60}N_2O_4$: 608.4553. Found: 608.4543.

Minor diastereomer: m.p. 192-194°C. $[\alpha]_D^{23}$ = -100.0 (c=0.47, $CHCl_3$). IR (NaCl film) ν_{max}: 3050, 2950, 2860, 2250, 1480, 1460, 1395, 1365, 1140, 1110, 1075, 1055, 920 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.77 (s, 6H), 0.88 (s, 3H), 0.89 (s, 9H), 0.94 (s, 9H), 0.95 (s, 3H), 1.10 (s, 3H), 1.16 (s, 3H), 0.80-1.66 (m, 8H), 1.86 (d, J=5 Hz, 1H), 1.89 (d, J=5 Hz, 1H), 3.06 (dd, J=10.3 Hz, J'=3.3 Hz, 1H), 2.97 (part A of AB system, J=8.4 Hz, 1H), 3.08 (part A of AB system, J=8.4 Hz, 1H), 3.20 (part B of AB system, J=8.4 Hz, 1H), 3.23 (part B of AB system, J=8.4 Hz, 1H), 3.35 (dd, J=10.3 Hz, J'=8.0 Hz, 1H), 3.44 (part A of AB system, J=6.9 Hz, 1H), 3.45 (part A of AB system, J=6.9 Hz, 1H), 3.58 (part B of AB system, J=6.9 Hz, 1H), 3.82 (part B of AB system, J=6.9 Hz, 1H), 4.16 (m, 1H), 4.36 (t, J=3.6 Hz, 1H), 5.94 (ddd, J=10.5 Hz, J'=4.2 Hz, J"=1.8 Hz, 1H), 6.10 (dd, J=10.5 Hz, J'=2.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.6 (q), 11.7 (q), 20.6 (q), 20.8 (q), 21.2 (q), 21.3 (q), 24.0 (t), 24.1 (t), 27.0 (q), 27.1 (q), 30.3 (s), 31.2 (s), 32.0 (d), 33.7 (t), 33.8 (t), 34.2 (d), 46.7 (s), 46.8 (s), 47.0 (s), 47.1 (s), 49.2 (d), 49.3 (d), 68.7 (d), 74.8 (d), 80.7 (t), 80.8 (t), 85.7 (d), 85.9 (d), 86.7 (d), 88.4 (d), 116.2 (s), 119.1 (s), 125.3 (d), 132.1 (d) ppm. MS (CI-NH_3) *m/e*: 626 (M+18, 100%). HRMS: Calc. for $C_{38}H_{60}N_2O_4$: 608.4553. Found: 608.4528.

(1R,2R,3R,6S)- and *(1S,2S,3S,6R)-3,6-bis-[(1R,2S,3R,4S)-2-(2,2-dimethylpropoxy)-1,7,7-trimethyl bicyclo[2.2.1]heptan-3-oxy]cyclohex-4-en-1,2-dicarbonitrile,* **6e**: The general procedure was followed starting from 61 mg (0.115 mmol) of **1e**, 9 mg (0.115 mmol) of fumaronitrile, 2 mg of hydroquinone and 0.4 mL of

anhydrous, degassed *m*-xylene. The reaction required heating at 80°C for 12 h and gave, after chromatographic purification (6/1 hexane/diethyl ether) 2 mg of the minor diastereomer of **6e** as a colorless solid, 17 mg of a 1:1.5 mixture of the two diastereomers of **6e** and 5 mg of the major diastereomer of **6e** as a colorless solid. The overall yield for **6e** was 34%, and the diastereoselectivity 1.5:1. (NOTE: Due to the high sensitivity of the dialkoxydiene, the reaction glassware was washed with aqueous NaOH and oven-dried prior to use).

Major diastereomer: m.p. 158-159°C. $[\alpha]_D^{23}$ = -8.4 (c=0.31, $CHCl_3$). IR (NaCl film) ν_{max}: 3040, 2960, 2880, 2260, 1510, 1480, 1465, 1395, 1365, 1220, 1150, 1120, 1100, 1020, 800, 745 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.77 (s, 3H), 0.79 (s, 3H), 0.85 (s, 9H), 0.88 (s, 3H), 0.89 (s, 3H), 0.92 (s, 9H), 1.08 (s, 3H), 1.18 (s, 3H), 0.80-1.92 (m, 10H), 2.85 (part A of AB system, J=7.8 Hz, 1H), 3.00 (part A of AB system, J=8.1 Hz, 1H), 3.01 (dd, J=12.1 Hz, J'=3.0 Hz, 1H), 3.19 (part A of AB system, J=6.9 Hz, 1H), 3.22 (part B of AB system, J=7.8 Hz, 1H), 3.28 (part A of AB system, J=6.6 Hz, 1H), 3.30 (dd, J=16.2 Hz, J'=9.3 Hz, 1H), 3.52 (part B of AB system, J=8.1 Hz, 1H), 3.63 (part B of AB system, J=6.9 Hz, 1H), 3.85 (part B of AB system, J=6.6 Hz, 1H), 4.07 (d, J=9.3 Hz, 1H), 4.15 (t, J=3.0 Hz, 1H), 5.91 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.5 (q), 11.6 (q), 20.7 (q), 21.0 (q), 21.1 (q), 21.2 (q), 23.9 (t), 24.0 (t), 26.9 (q), 27.0 (q), 31.7 (d), 32.4 (s), 32.5 (s), 33.4 (t), 33.7 (t), 35.0 (d), 46.6 (s), 46.8 (s), 48.7 (d), 49.5 (s), 49.6 (s), 49.8 (d), 68.8 (d), 73.6 (d), 77.0 (d), 82.8 (t), 83.5 (t), 84.4 (d), 87.5 (d), 88.3 (d), 116.5 (s), 118.2 (s), 126.8 (d), 129.1 (d) ppm. HRMS: Calc. for $C_{38}H_{60}N_2O_4$: 608.4553. Found: 608.4535.

Minor diastereomer: $[\alpha]_D^{23}$ = -80.8 (c=0.20, $CHCl_3$). IR (NaCl film) ν_{max}: 3060, 2960, 2880, 2260, 1475, 1465, 1390, 1365, 1265, 1150, 1135, 1120, 1015, 795, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.77 (s, 3H), 0.78 (s, 3H), 0.89 (s, 6H), 0.90 (s, 18H), 1.13 (s, 3H), 1.19 (s, 3H), 0.80-1.96 (m, 10H), 2.88 (part A of AB system, J=8.1 Hz, 1H), 2.98 (part A of AB system, J=8.1 Hz, 1H), 3.12 (dd, J=11.1 Hz, J'=3.3 Hz, 1H), 3.19 (part A of AB system, J=6.6 Hz, 1H), 3.25 (dd, J=11.4 Hz, J'=8.7 Hz, 1H), 3.26 (part B of AB system, J=8.1 Hz, 1H), 3.29 (part A of AB system, J=6.6 Hz, 1H), 3.44 (part B of AB system, J=8.1 Hz, 1H), 3.67 (part B of AB system, J=6.6 Hz, 1H), 3.85 (part B of AB system, J=6.6 Hz, 1H), 4.18 (d, J=9.3 Hz, 1H), 4.20 (m, 1H), 5.95 (m, 2H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) δ: 11.6 (q), 11.7 (q), 20.8 (q), 21.0 (q), 21.1 (q), 21.2 (q), 24.0 (t), 24.2 (t), 26.9 (q), 27.0 (q), 31.9 (d), 32.5 (s), 32.6 (s), 33.5 (t), 33.6 (t), 34.6 (d), 46.7 (s), 46.8 (s), 48.7 (d), 49.2 (d), 49.5 (s), 49.8 (s), 68.0 (d), 75.0 (d), 82.9 (t), 83.3 (t), 84.8 (d), 87.5 (d), 88.5 (d), 88.9 (d), 116.4 (s), 118.2 (s), 125.9 (d), 131.6 (d) ppm. MS (CI-NH_3) *m/e*: 522 (100%), 610 (M+1, 33%). HRMS: Calc. for $C_{38}H_{60}N_2O_4$: 608.4553. Found: 608.4530.

General procedure for the Diels-Alder cycloadditions of ***1a-e*** *with diethyl fumarate*

A degassed *m*-xylene solution containing 1 eq of the dialkoxydiene **1a-e**, 1 eq of diethyl fumarate and hydroquinone (*ca.* 20% molar amount) was heated, under strict argon atmosphere, at 80-140°C for 18-76 h. The progress of the reaction was monitored by TLC. Removal of the solvent at reduced pressure and chromatographic purification (triethylamine-pretreated silica gel [2.5% v/v], eluting with hexane/diethyl ether mixtures of increasing polarity) gave the cycloadducts **7a-e**.

(1R,2R,3R,6S)- and *(1S,2S,3S,6R)-3,6-bis-(l-menthyloxy)cyclohex-4-en-1,2-dicarboxylic acid diethyl ester*, **7a**: The general procedure was followed starting from 30 mg (0.083 mmol) of **1a**, 14 mg (0.083 mmol) of diethyl fumarate, 2 mg of hydroquinone and 0.8 mL of anhydrous, degassed *m*-xylene. The reaction required

heating at 140°C for 18 h and gave, after chromatographic purification (24/1 hexane/diethyl ether), 23 mg (52% yield) of **7a** (1.2:1 diastereomer mixture) as a colourless oil.

IR (NaCl film) ν_{max}: 3030, 2940, 2920, 2860, 1720, 1445, 1365, 1305, 1290, 1260, 1175, 1055, 1030, 910 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.65 (d, J=6.9 Hz, 3H, major diastereomer), 0.68 (d, J=7 Hz, 3H, minor diastereomer), 0.75 (d, J=7 Hz, 3H, minor diastereomer), 0.80 (d, J=6.9 Hz, 3H, major diastereomer), 1.21 (t, J=6.5 Hz, 3H, minor diastereomer), 1.23 (t, J=6.3 Hz, 3H, major diastereomer), 1.28 (t, J=6.5 Hz, 3H, minor diastereomer), 1.29 (t, J=6.3 Hz, 3H, major diastereomer), 0.80-1.64 (m, 26H), 1.80-2.32 (m, 4H), 2.84-3.20 (m, 4H), 3.94-4.27 (m, 6H), 5.72-5.90 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) Major diastereomer. δ: 13.9 (q), 14.2 (q), 15.9 (q), 16.1 (q), 21.2 (q), 21.4 (q), 22.3 (q), 22.4 (q), 22.8 (t), 22.9 (t), 24.3 (d), 24.6 (d), 31.4 (d), 31.5 (d), 34.2 (t), 34.3 (t), 40.4 (t), 42.8 (t), 44.2 (d), 47.9 (d), 48.0 (d), 48.7 (d), 66.7 (d), 60.6 (t), 60.7 (t), 69.2 (d), 74.9 (d), 77.4 (d), 78.5 (d), 127.8 (d), 130.8 (d), 170.8 (s), 175.2 (s) ppm. Minor diastereomer. δ: 13.9 (q), 14.0 (q), 15.9 (q), 16.1 (q), 21.1 (q), 21.5 (q), 22.3 (q), 22.4 (q), 22.9 (t), 23.0 (t), 24.5 (d), 24.6 (d), 31.5 (d), 31.6 (d), 34.3 (t), 34.4 (t), 40.0 (t), 43.0 (t), 44.1 (d), 48.0 (d), 48.3 (d), 48.8 (d), 60.7 (t), 66.5 (d), 75.6 (d), 77.4 (d), 79.6 (d), 125.4 (d), 133.5 (d), 170.7 (s), 175.4 (s) ppm. MS (CI-NH_3) *m/e*: 535 (M+1, 19%), 552 (M+18, 100%). HRMS: Calc. for $C_{32}H_{55}O_6$ (M+H): 535.3999. Found: 535.3969.

(1R,2R,3R,6S)- and *(1S,2S,3S,6R)-3,6-bis-((1R,2S)-2-phenylcyclohexyloxy)cyclohex-4-en-1,2-dicarboxylic acid diethyl ester,* **7b**: The general procedure was followed starting from 30 mg (0.075 mmol) of **1b**, 13 mg (0.075 mmol) of diethyl fumarate, 2 mg of hydroquinone and 0.4 mL of anhydrous, degassed *m*-xylene. The reaction required heating at 140°C for 20 h and gave, after chromatographic purification (11.5/1 hexane/diethyl ether), 24 mg (56% yield) of **7b** (1.7:1 diastereomer mixture) as a colourless oil.

IR (NaCl film) ν_{max}: 3090, 3075, 3040, 2990, 2940, 2870, 1750, 1735, 1610, 1495, 1455, 1400, 1380, 1305, 1275, 1190, 1075, 970, 865, 760, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.00 (t, J=7.2 Hz, 3H, minor diastereomer), 1.19 (t, J=7.2 Hz, 3H, major diastereomer), 1.23 (t, J=7.2 Hz, 3H, major diastereomer), 1.31 (t, J=7.2 Hz, 3H, minor diastereomer), 1.20-2.14 (m, 16H), 2.34-2.80 (m, 4H), 3.16-4.22 (m, 6H), 4.69 (dd, J=10.2 Hz, J'=2.0 Hz, 1H, minor diastereomer), 4.80-4.88 (m, 2H, major diastereomer), 5.40 (ddd, J=10.2 Hz, J'=4.8 Hz, J"=2.0 Hz, 1H, minor diastereomer), 7.10-7.32 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) Major diastereomer. δ: 14.0 (q), 14.1 (q), 25.0 (t), 25.1 (t), 25.7 (t), 25.8 (t), 32.8 (t), 33.4 (t), 33.8 (t), 34.6 (t), 43.2 (d), 47.9 (d), 51.0 (d), 51.3 (d), 60.4 (t), 60.5 (t), 69.9 (d), 75.9 (d), 78.4 (d), 82.0 (d), 125.6 (d), 125.9 (d), 126.2 (d), 127.7 (d), 127.9 (d), 128.0 (d), 128.2 (d), 130.7 (d), 144.5 (s), 144.6 (s), 171.0 (s), 174.3 (s) ppm. Minor diastereomer. δ: 13.9 (q), 14.3 (q), 25.0 (t), 25.1 (t), 25.7 (t), 25.8 (t), 33.0 (t), 33.2 (t), 33.7 (t), 34.0 (t), 44.2 (d), 47.6 (d), 50.6 (d), 51.3 (d), 60.2 (t), 60.5 (t), 68.6 (d), 77.5 (d), 79.4 (d), 82.0 (d), 125.8 (d), 126.0 (d), 126.2 (d), 127.9 (d), 128.0 (d), 128.2 (d), 131.7 (d), 144.6 (s), 144.7 (s), 170.0 (s), 175.5 (s) ppm. MS (CI-NH_3) *m/e*: 575 (M+1, 2%), 592 (M+18, 100%). HRMS: Calc. for $C_{36}H_{47}O_6$ (M+H): 575.3373. Found: 575.3367.

(1R,2R,3R,6S)- and *(1S,2S,3S,6R)-3,6-bis-((1R,2S,5R)-8-phenylmenthyloxy)cyclohex-4-en-1,2-dicarboxylic acid diethyl ester,* **7c**: The general procedure was followed starting from 85 mg (0.165 mmol) of **1c**, 28 mg (0.165 mmol) of diethyl fumarate, 2 mg of hydroquinone, and 0.4 mL of anhydrous, degassed *m*-xylene. The reaction required heating at 140°C for 75 h and gave, after chromatographic purification (24/1 hexane/diethyl ether), 41 mg of the major diastereomer of **7c** as a colourless solid and 18 mg of a 1:1 mixture of

the two diastereomers of **7c**. 20 mg (23% yield) of the starting diene could also be recovered. The overall yield for **7c** was 52%, and the diastereoselectivity 5.5:1.

Major diastereomer: m.p. 43-45°C. $[\alpha]_D^{23}$ = -62.4 (c=1.39, $CHCl_3$). IR (NaCl film) ν_{max}: 3090, 3060, 2960, 2920, 2880, 1750, 1730, 1605, 1495, 1450, 1375, 1275, 1235, 1190, 1140, 1100, 1060, 980, 940, 910, 860, 770, 740, 705 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.86 (d, J=6.2 Hz, 6H), 1.29 (s, 6H), 1.29 (t, J=7.0 Hz, 3H), 1.34 (t, J=7.0 Hz, 3H), 1.45 (s, 3H), 1.46 (s, 3H), 0.60-2.30 (m, 16H), 2.95 (dd, J=12.5 Hz, J'=3.5 Hz, 1H), 3.15 (dd, J=12.5 Hz, J'=9.0 Hz, 1H), 3.40 (td, J=10.0 Hz, J'=3.5 Hz, 1H), 3.65 (td, J=10.0 Hz, J'=3.5 Hz, 1H), 4.00-4.45 (m, 6H), 5.82 (d, J=10.0 Hz, 1H), 6.00 (dd, J=10.0 Hz, J'=3.5 Hz, 1H), 7.05-7.35 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9 (q), 14.1 (q), 21.1 (q), 22.1 (q), 22.2 (q), 22.3 (q), 27.5 (t), 27.6 (t), 31.4 (d), 31.9 (q), 34.6 (t), 34.8 (t), 40.1 (t), 40.8 (s), 41.0 (s), 41.4 (t), 44.2 (d), 48.3 (d), 52.1 (d), 52.7 (d), 60.6 (t), 60.9 (t), 65.1 (d), 73.2 (d), 76.5 (d), 79.8 (d), 121.7 (s), 124.4 (d), 124.8 (d), 124.9 (d), 125.6 (d), 125.8 (d), 127.8 (d), 134.5 (d), 152.2 (s), 170.6 (s), 176.1 (s) ppm. MS (CI-NH_3) *m/e*: 351 (100%), 704 (M+18, 2%). HRMS: Calc. for $C_{36}H_{50}O_2$ (M-$C_8H_{12}O_4$): 514.3811. Found: 514.3801.

Minor diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ: 0.60-2.24 (m, 40H), 2.89 (dd, J=12.3 Hz, J'=3.4 Hz, 1H), 3.02 (dd, J=12.3 Hz, J'=9.3 Hz, 1H), 3.39 (td, J=10.0 Hz, J'=3.3 Hz, 1H), 3.47 (td, J=10.0 Hz, J'=3.3 Hz, 1H), 4.04-4.48 (m, 6H), 5.82-5.94 (m, 2H), 7.07-7.30 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9 (q), 14.4 (q), 22.0 (q), 22.1 (q), 22.2 (q), 23.1 (q), 27.5 (t), 27.6 (t), 31.1 (q), 31.3 (d), 31.5 (d), 31.8 (q), 34.5 (t), 34.9 (t), 39.8 (t), 40.6 (s), 40.8 (s), 42.8 (t), 44.3 (d), 47.9 (d), 52.3 (d), 52.7 (d), 60.4 (t), 60.8 (t), 67.8 (d), 71.9 (d), 76.2 (d), 79.3 (d), 124.4 (d), 124.9 (d), 125.0 (d), 125.6 (d), 126.0 (d), 127.8 (d), 127.9 (d), 129.6 (d), 151.4 (s), 151.9 (s), 171.0 (s), 175.0 (s) ppm.

(1R,2R,3R,6S)-3,6-bis-[(1R,2S,3R,4S)-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-oxy]cyclohex-4-en-1,2-dicarboxylic acid diethyl ester, **7d**: The general procedure was followed starting from 30 mg (0.057 mmol) of **1d**, 10 mg (0.057 mmol) of diethyl fumarate, 2 mg of hydroquinone and 0.2 mL of anhydrous, degassed *m*-xylene. The reaction required heating at 85°C for 48 h and gave, after chromatographic purification (98/2 hexane/diethyl ether) 25 mg (63% yield) of **7d** (single diastereomer) as a colorless oil, and 3 mg (10% recovery) of the starting diene **1d**. (NOTE: Due to the high sensitivity of the dialkoxydiene, the reaction glassware was washed with aqueous NaOH and oven-dried prior to use).

$[\alpha]_D^{23}$ = -35.0 (c=0.85, $CHCl_3$). IR (NaCl film) ν_{max}: 3040, 2950, 2870, 1730, 1475, 1460, 1375, 1260, 1220, 1180, 1140, 1100, 1055, 855, 795, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.73 (s, 3H), 0.74 (s, 3H), 0.84 (s, 3H), 0.90 (s, 9H), 0.91 (s, 3H), 0.93 (s, 9H), 1.05 (s, 3H), 1.08 (s, 3H), 1.25 (t, J=7.5 Hz, 3H), 1.30 (t, J=7.5 Hz, 3H), 0.80-1.60 (m, 8H), 1.79 (d, J=5 Hz, 1H), 1.81 (d, J=5 Hz, 1H), 2.86 (dd, J=11.8 Hz, J'=3.5 Hz, 1H), 3.06 (part A of AB system, J=8.7 Hz, 1H), 3.07 (part A of AB system, J=8.1 Hz, 1H), 3.12 (part B of AB system, J=8.1 Hz, 1H), 3.15 (dd, J=11.5 Hz, J'=8.7 Hz, 1H), 3.16 (part B of AB system, J=8.7 Hz, 1H), 3.23 (part A of AB system, J=6.6 Hz, 1H), 3.32 (part A of AB system, J=6.9 Hz, 1H), 3.35 (part B of AB system, J=6.9 Hz, 1H), 3.48 (part B of AB system, J=6.6 Hz, 1H), 4.06-4.20 (m, 4H), 4.29 (m, 1H), 4.44 (m, 1H), 5.95 (dd, J=10.4 Hz, J'=2.0 Hz, 1H), 6.11 (ddd, J=10.4 Hz, J'=5.0 Hz, J"=2.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.6 (q), 12.1 (q), 13.9 (q), 14.0 (q), 20.7 (q), 20.9 (q), 21.1 (q), 21.2 (q), 24.0 (t), 24.1 (t), 27.0 (q), 27.2 (q), 32.1 (s), 34.0 (t), 43.9 (d), 46.5 (s), 46.6 (s), 47.0 (d), 47.4 (d), 47.8 (d), 49.2 (s), 49.4 (s), 60.5 (t), 60.6 (t), 71.6 (d), 76.2 (d), 80.9 (t), 81.1 (t), 84.1

(d), 86.1 (d), 87.5 (d), 128.7 (d), 129.1 (d), 171.6 (s), 175.4 (s) ppm. MS (CI-NH3) *m/e*: 703 (M+1, 5%), 720 (M+18, 100%). HRMS: Calc. for $C_{42}H_{71}O_8$ (M+H): 703.5149. Found: 703.5096.

(1R,2R,3R,6S)- and *(1S,2S,3S,6R)-3,6-bis-[(1R,2S,3R,4S)-2-(2,2-dimethylpropoxy)-1,7,7-trimethyl bicyclo[2.2.1]heptan-3-oxy]cyclohex-4-en-1,2-dicarboxylic acid diethyl ester,* **7e**: The general procedure was followed starting from 57 mg (0.107 mmol) of **1e**, 18 mg (0.107 mmol) of diethyl fumarate, 2 mg of hydroquinone and 0.6 mL of anhydrous, degassed *m*-xylene. The reaction required heating at 80°C for 76 h and gave, after chromatographic purification (24/1 hexane/diethyl ether) 25 mg of the major diastereomer of **7e** as a colourless oil, 3 mg of a 1:1 mixture of the two diastereomers of **7e** and 1 mg of the minor diastereomer of **7e**. 18 mg (31% recovery) of the starting diene could also be isolated. The overall yield for **7e** was 39%, and the diastereoselectivity 10.6:1. (NOTE: Due to the high sensitivity of the dialkoxydiene, the reaction glassware was washed with aqueous NaOH and oven-dried prior to use).

Major diastereomer: $[\alpha]_D^{23}$ = -101.7 (c=1.08, $CHCl_3$). IR (NaCl film) ν_{max}: 3030, 2950, 2870, 1730, 1480, 1460, 1370, 1300, 1270, 1230, 1185, 1150, 1100, 1080, 1030, 930, 910, 900, 860, 800, 745, 710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.74 (s, 3H), 0.76 (s, 3H), 0.85 (s, 3H), 0.86 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.01 (s, 3H), 1.16 (s, 3H), 1.22 (t, J=7.2 Hz, 3H), 1.31 (t, J=7.2 Hz, 3H), 0.9-1.82 (m, 10H), 2.71 (part A of AB system, J=8.1 Hz, 1H), 2.82 (part A of AB system, J=8.1 Hz, 1H), 2.93 (dd, J=12.1 Hz, J'=3.9 Hz, 1H), 3.04 (dd, J=12.0 Hz, J'=9.6 Hz, 1H), 3.08 (part A of AB system, J=6.6 Hz, 1H), 3.09 (part A of AB system, J=6.6 Hz, 1H), 3.44 (part B of AB system, J=8.1 Hz, 1H), 3.45 (part B of AB system, J=6.6 Hz, 1H), 3.56 (part B of AB system, J=8.1 Hz, 1H), 3.56 (part B of AB system, J=6.6 Hz, 1H), 3.96-4.30 (m, 4H), 4.18 (d, J=9.6 Hz, 1H), 4.36 (m, 1H), 5.91 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.7 (q), 13.9 (q), 14.2 (q), 20.5 (q), 21.2 (q), 21.3 (q), 21.4 (q), 24.3 (t), 24.4 (t), 27.0 (q), 32.5 (s), 32.6 (s), 33.5 (t), 33.7 (t), 44.0 (d), 46.3 (s), 46.4 (s), 46.9 (d), 47.9 (d), 48.5 (d), 49.4 (s), 49.5 (s), 60.6 (t), 68.3 (d), 77.3 (d), 82.4 (d), 82.5 (t), 82.9 (t), 86.2 (d), 88.4 (d), 89.0 (d), 125.2 (d), 134.7 (d), 170.3 (s), 175.7 (s) ppm. HRMS: Calc. for $C_{42}H_{71}O_8$ (M+H): 703.5149. Found: 703.5108.

Minor diastereomer: IR (NaCl film) ν_{max}: 3040, 2960, 2870, 1735, 1480, 1455, 1380, 1275, 1235, 1190, 1155, 1125, 1100, 1085, 805, 705 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.73 (s, 3H), 0.76 (s, 3H), 0.86 (s, 9H), 0.91 (s, 9H), 1.06 (s, 3H), 1.08 (s, 3H), 0.80-1.80 (m, 22H), 2.69 (part A of AB system, J=8.2 Hz, 1H), 2.78 (part A of AB system, J=8.2 Hz, 1H), 3.05 (part A of AB system, J=6.8 Hz, 1H), 3.12 (part A of AB system, J=6.8 Hz, 1H), 3.22 (part B of AB system, J=8.2 Hz, 1H), 3.41 (part B of AB system, J=8.2 Hz, 1H), 3.52 (part B of AB system, J=6.8 Hz, 1H), 3.61 (part B of AB system, J=6.8 Hz, 1H), 4.00-4.37 (m, 6H), 5.86 (ddd, J=9.7 Hz, J'=4.8 Hz, J"=1.9 Hz, 1H), 5.95 (d J=9.7 Hz, 1H) ppm.

Acknowledgments: Financial support from CIRIT-CICYT (QFN93-4407) is gratefully acknowledged. Marina Virgili is grateful to CIRIT for a pre-doctoral fellowship.

References and Notes

1. Reviews: (a) Jurczak, J.; Bauer, T.; Chapuis, C. "Intermolecular [4+2] Cycloadditions", in: Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds., *Methods of Organic Chemistry (Houben-Weyl). Stereoselective Synthesis, Workbench Edition E21 vol. 5*, Georg Thieme Verlag, Stuttgart-New York: 1996, pp. 2735-2871. (b) Paquette, L. A. "Asymmetric Cycloaddition Reactions", in: Morrison, J. D., Ed., *Asymmetric Synthesis, vol. 3*, Academic Press, Orlando, Fl.: 1984, pp. 455-501.

2. For a review, see: (a) Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969-2004. Recent references: (b) Bauer, T.; Chapuis, C.; Jezewski, A.; Kozak, J.; Jurczak, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1391-1404. (c) Ikeda, I.; Honda, K.; Osawa, E.; Shiro, M.; Aso, M.; Kanematsu, K. *J. Org. Chem.* **1996**, *61*, 2031-2037. (d) Loupy, A.; Monteux, D. *Tetrahedron Lett.* **1996**, *37*, 7023-7026. (e) Le, T. X.; Bussolari, J. C.; Murray, W. V. *Tetrahedron Lett.* **1997**, *38*, 3849-3852. (f) Kitagawa, O.; Izawa, H.; Taguchi, T.; Shiro, M. *Tetrahedron Lett.* **1997**, *38*, 4447-4450. (g) Powers, T. S.; Jiang, W.; Su, J.; Wulff, W. D.; Waltermire, B. E.; Rheingold, A. L. *J. Am. Chem. Soc.* **1997**, *119*, 6438-6439.

3. Reviews: (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York: 1995, pp. 537-553. (b) Togni, A.; Venanzi, L. M. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 497. (c) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007-1019. (d) Maruoka, K.; Yamamoto, H. "Asymmetric Reactions with Chiral Lewis Acid Catalysts", in: Ojima, I., Ed., *Catalytic Asymmetric Synthesis*, VCH, New-York-Weinheim: 1993, pp. 413-440. (e) Oh, T.; Reilly, M. *Org. Prep. Proced. Int.* **1994**, *26*, 129-158. (f) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763-784.

4. For some recent references, see: (a) Corey, E. J.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 5755-5758. (b) Naraku, G.; Hori, K.; Ito, Y. N.; Katsuki, T. *Tetrahedron Lett.* **1997**, *38*, 8231-8232. (c) Schaus, S. E.; Branalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403-405. (d) Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaks, J.; Wada, E.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 6454-6455. (e) Evans, D. A.; Shaughmessy, E. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 3193-3194. (f) Hayashi, Y.; Rhode, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502-5503. (g) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 3049-3050. (h) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357-7360. (i) Otto, S.; Boccaletti, G.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238-4239. And references cited therein.

5. Fringuelli, F.; Taticchi, A. *Dienes in the Diels-Alder Reaction*; John Wiley, New York: 1990.

6. Recent references on 1,3-butadienes with chiral substituents at C-1: (a) Carreño, M. C.; Cid, M. B.; García Ruano, J. L.; Santos, M. *Tetrahedron Lett.* **1998**, *39*, 1405-1408. (b) Carreño, M. C.; Cid, M. B.; García Ruano, J. L.; Santos, M. *Tetrahedron: Asymmetry* **1997**, *8*, 2093-2097. (c) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1997**, *119*, 7165-7166. (d) Hu, Y.-J.; Huang, X.-D.; Yao, Z.-J.; Wu, Y.-L. *J. Org. Chem.* **1998**, *63*, 2456-2461. (e) Adam, W.; Güthlein, M.; Peters, E.-M.; Peters, K.; Wirth, T. *J. Am. Chem. Soc.* **1998**, *120*, 4091-4093. See also: (f) Abas, A.; Beddoes, R. L.; Conway, J. C.; Quayle, P.; Urch, C. J. *Synlett* **1995**, 1264-1266.

7. Recent references on 1,3-butadienes with chiral substituents at C-2: (a) Fernández de la Pradilla, R.; Martínez, M. V.; Montero, C.; Viso, A. *Tetrahedron Lett.* **1997**, *38*, 7773-7776. (b) Fernández de la

Pradilla, R.; Montero, C.; Viso, A. *Chem. Commun.* **1998**, 409-410. (c) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1997**, *62*, 6746-6753. (d) Barluenga, J.; Tomás, M.; López, L. A.; Suárez-Sobrino, S. *Synthesis* **1997**, 967-974. (e) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C.; Fernández, M.; Cabal, M.-P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805-811. (f) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Giannetto, P.; Jones, D. N. *J. Org. Chem.* **1997**, *62*, 4376-4384.

8. Virgili, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 6921-6924.
9. Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919-2922.
10. Negishi, E.; Van Horn, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 3168-3170.
11. Yoshifuji, M.; Loots, M. J.; Schwartz, J. *Tetrahedron Lett.* **1977**, *18*, 1303-1306.
12. Rücker, C.; Lang, D.; Sauer, J.; Friege, H.; Sustmann, R. *Chem. Ber.* **1980**, *113*, 1663-1690.
13. Hiranuma, H.; Miller, S. I. *J. Org. Chem.* **1982**, *47*, 5083-5088.
14. Hiranuma, H.; Miller, S. I. *J. Org. Chem.* **1983**, *48*, 3096-3102.
15. While this manuscript was in preparation, a paper dealing with the [4+2] cycloaddition reactions of several (1*Z*,3*E*)-1,4-dialkoxy-1,3-butadienes with activated dienophiles (*N*-methylmaleimide and methyl acrylate) appeared in the literature: Guillam, A.; Toupet, L.; Maddaluno, J. *J. Org. Chem.* **1998**, *63*, 5110-5122.
16. Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*, John Wiley, New York: 1994, pp. 647-655.
17. Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909.
18. MacSpartan Plus, version 1.0, Wavefunction, Inc., 18041 Von Karman, Suite 1370, Irvine, CA.
19. Virgili, M.; Pericàs, M. A.; Moyano, A.; Riera, A. *Tetrahedron* **1997**,*39*, 13427-13448.
20. For a recent report on conformational switches in transition states of cycloadditions to enol ethers, see: Liu, J.; Niwayama, S.; You, Y.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 1064-1073.
21. Buchwald, S. L.; La Maire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895.
22. For the preparation of (1*R*,2*S*,3*R*,4*S*)-(3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol, see: Verdaguer, X.; Marchueta, I.; Tormo, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *Helv. Chim. Acta* **1998**, *81*, 78-84.
23. For the preparation of (1*R*,2*S*,3*R*,4*S*)-2-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptan-3-ol, see: Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, H. *Helv. Chim. Acta* **1985**, *68*, 2100-2114.