Pergamon

Tetrahedron, Vol. 53, No. 39, pp. 13427-13448, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00854-5

Experimental and Theoretical Studies on the Diastereoselective Diels-Alder Reactions of Chiral 1-Alkoxy-1,3-butadienes. I: Parent System and 4-Substituted Derivatives

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

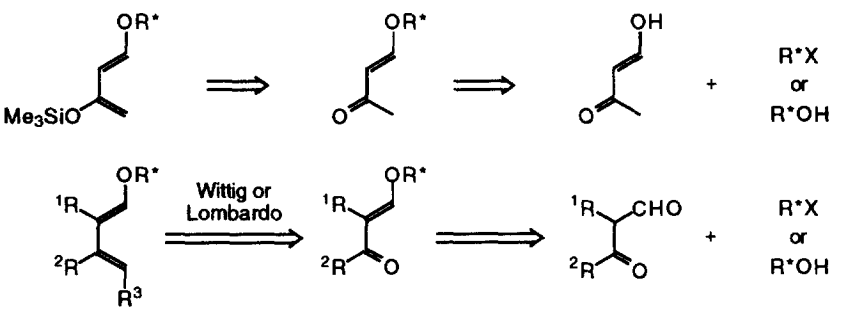
Unitat de Recerca en Síntesi Asimètrica (URSA)

Departament de Química Orgànica, Universitat de Barcelona, c/ Martí i Franquès, 1-11, 08028-Barcelona, Spain

Abstract: Chiral 1-alkoxy-1,3-dienes (parent and 4-substituted) have been prepared from the corresponding chiral alkoxyacetylenes in a stereoselective manner following a 2C + 2C approach. The Diels-Alder reactions of the dienes with maleic anhydride and 4-phenyl-3*H*-1,2,4-triazoline-3,5-dione take place with significant diastereoselectivity. Theoretical calculations on these cycloadditions, performed with the SCF-MO procedure AM1, have been used in the stereochemical assignment of the adducts.

INTRODUCTION

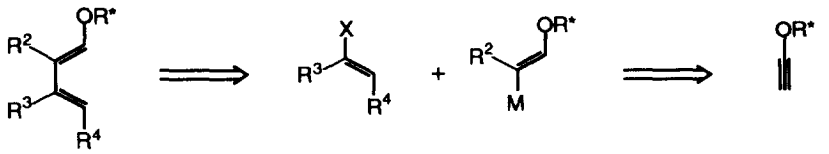
Chiral alkoxybutadienes of several structural types have been employed with success as diene components in diastereoselective Diels-Alder reactions.[1-4] Up to now, the synthesis of these intermediates has generally been based[5] either on enol ether formation from a 3-oxobutyraldehyde equivalent,[2] or has followed a 3C + 1C approach starting from 1,3-dicarbonyl systems,[1d,3] as shown in Scheme 1.



Scheme 1

These approaches, which have allowed the exploration of the diastereoselective Diels-Alder chemistry of the resulting chiral alkoxybutadiene present, however, some serious limitations. On the first place, the bulky chiral substituent has to be introduced either by nucleophilic attack of the chiral alcohol on a sp^2 carbon or, conversely, by reaction of an enolate with a secondary halide. According to that, the incorporation of sterically demanding alcohols into the diene molecules, which is normally key to the achievement of high levels of stereocontrol in the subsequent cycloaddition reactions, can be problematic. Secondly, the 3C + 1C construction scheme, which involves the formation of the distal double bond in the alkoxydiene, is not suitable for certain substitution patterns.

These difficulties could be easily overcome through the implementation of a 2C + 2C construction scheme, as shown in Scheme 2. By this methodology, practically every alkoxy group could be used as a substituent on the 1,3-diene skeketon, since the introduction of bulky alkoxy groups as substituents on triple bonds has practically no limitation.[6] Moreover, simultaneous substitution at C-3 and C-4 (i.e., in vinylcycloalkene systems) could be easily achieved if desired.



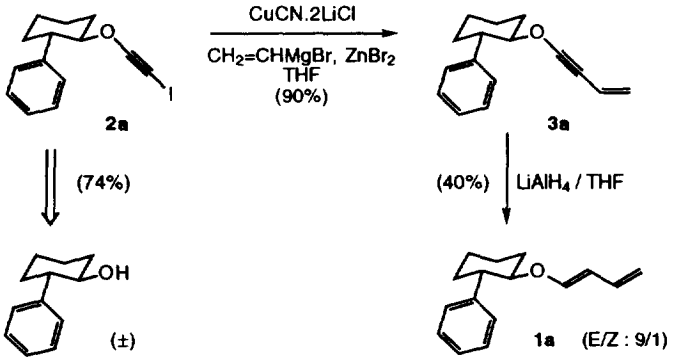
Scheme 2

We wish to report in the present paper the application of this strategy to the synthesis of some chiral 1-alkoxy-1,3-dienes (parent and 4-substituted derivatives) as well as experimental and theoretical results on their diastereoselective Diels-Alder reactions with cyclic dienes. Parallel studies on 3-substituted and 3,4-disubstituted 1-alkoxy-1,3-dienes will be reported separately.[7]

RESULTS AND DISCUSSION

*A) Synthesis and Diels-Alder reactions of (E)-1-[(1SR,2RS)-2-phenylcyclohexyloxy]-1,3-butadiene (**1a**).*

Although several chiral 1-alkoxybutadienes are known,[1] they derive in all cases from sugars and, except in one case,[1d] their syntheses are not stereoselective. To show the validity of the proposed methodology, our initial efforts in this area were directed towards the preparation of **1a** as a representative example of 1-alkoxy-1,3-butadiene. Previous experience on the synthesis of iodoalkoxyacetylenes,[8] and on the stereoselective reduction of acetylene ethers[9] guided the construction of the unsaturated system as an enyne, whose stereoselective reduction would then lead to the target diene as shown in Scheme 3.



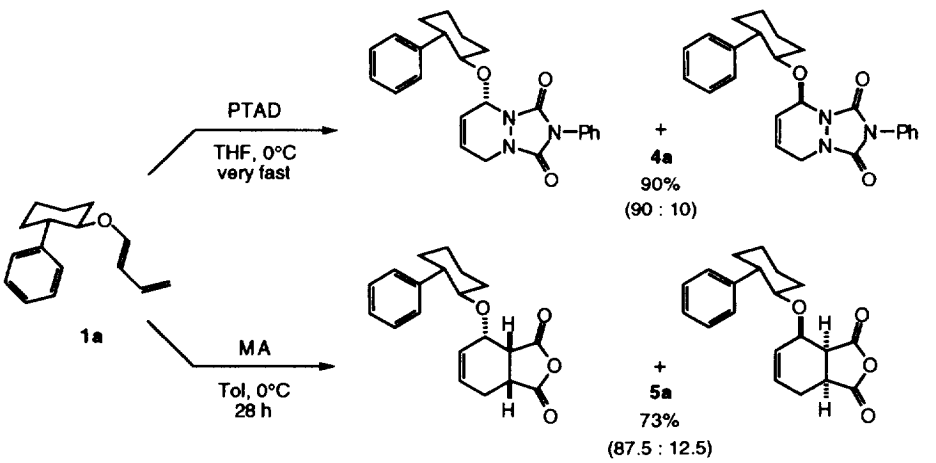
Scheme 3

The known iodoalkoxyacetylene **2a**[8] was conveniently prepared in the present instance in 74% yield through a one-pot sequence from racemic *trans*-2-phenylcyclohexanol.[10] For the construction of the diene skeleton, the preparation of enyne **3a** was first attempted by a copper catalyzed coupling with vinylmagnesium

bromide, but only a trace amount of the desired product could be detected. Much better results were obtained by performing the coupling with bromozinc vinylcianocuprate.[11] In this way, a 90% yield of **3a** could be isolated. The reduction of **3a** was performed with $LiAlH_4$ in THF,[9] and led to **1a** as a 9:1 mixture of the *E* and *Z* stereoisomers. However, the yield of **1a** was only moderate (40%) and the process was accompanied by some decomposition (up to 32% of *trans*-2-phenylcyclohexanol could be recovered from the reaction crude). Some yield improvement could be achieved by performing the reduction with Red-Al in THF[9] (up to 60%), but at the cost of a less satisfactory stereoselectivity. The stereoisomeric dienes could not be separated by column chromatography; however, this is not an important problem for reactivity studies since the *E* stereoisomer undergoes Diels-Alder reaction much faster than the *Z* one.

With **1a** in hands, we next studied its Diels-Alder reactions with the highly reactive dienophiles 4-phenyl-3*H*-1,2,4-triazoline-3,5-dione (PTAD) and maleic anhydride (MA) (Scheme 4). In the case of PTAD, the reaction at 0°C in THF solution turned out to be instantaneous (it could be performed as a titration through the decoloration of the added dienophile) and led to the quantitative formation [from (*E*)-**1a**] of adduct **4a**, as a 90 : 10 mixture of diastereomers (^{13}C NMR and HPLC).[12] The fast reaction recorded in the present case is in sharp contrast with the observation of Breitmaier[4a] in the analogous reaction of the corresponding 2-methyl substituted diene, where more than 6 hours are required for the reaction to proceed.

The reaction of **1a** with MA was considerably slower. In this case, the process at 0°C in toluene required 28 hours for the complete dissappearence of (*E*)-**1a**, although the conversion was greater than 85% after only 7 hours at 0°C. After separation by MPLC of the unreacted *Z* isomer of **1a**, **5a** could be isolated in 73% yield as a 87.5 : 12.5 diastereomeric mixture of *endo* adducts (^1H NMR and HPLC)[12]. The configuration of the major diastereomer of **5a** shown in Scheme 4 was first assigned on the basis of the semiempirical SCF-MO theoretical study on the conformational preferences of diene **1a**[13] described below. The same configuration was assumed for the major diastereomer of **4a**.



Scheme 4

It is worth mentioning that (*E*)-1-(2',3',4',6'-Tetra-*O*-acetyl-β-*D*-glucopyranosyloxy)buta-1,3-diene, the only sugar-derived 1-alkoxybutadiene which has been previously reacted with similar dienophiles (PTAD and N-phenylmaleimide)[1d,4b] is less reactive than **1a**. With respect to diastereoselectivity, it reacts with *N*-

phenylmaleimide to afford a 86 : 14 mixture of *endo* diastereomers, while the reaction with PTAD leads to the corresponding adduct as a single diastereomer.

B) Theoretical calculations on the Diels-Alder reaction of (E)-1-[(1R,2S)-2-phenylcyclohexyloxy]-1,3-butadiene with Maleic Anhydride.

The stereochemical outcome of diastereoselective reactions has been rationalized in many instances on the basis of the conformational preferences of starting materials, with an almost complete disregard of the Curtin-Hammett principle.[14] However, the current development of computational chemistry easily allows the estimation of activation energies in the reactions of individual conformers. This approach can provide a better understanding of diastereoselectivity in cases where the configurations of reaction products are known. Conversely, it can allow a sound stereochemical assignment when product configurations are unknown.

In the presence instance, we decided to analyze not only the conformational preferences of the (1*R*,2*S*) enantiomer of **1a**, but also to evaluate the activation energies in the reactions of all of the individual conformers of the diene with MA in order to perform the stereochemical assignment of the major stereoisomer of **5a** and, by analogy, of **4a**. The theoretical procedure employed has been the RHF version of the semi-empirical SCF-MO procedure AM1,[15] which is known to provide an accurate description of the ground state conformation of closed-shell species, as well as a good estimate of activation energies of Diels-Alder reactions,[16] as implemented in the MacSpartan Plus[17] package of programs.

A systematic conformational search around the two C-O bonds in **1a** led to the characterization of the four distinct *cisoid* conformers shown in Figure 1.

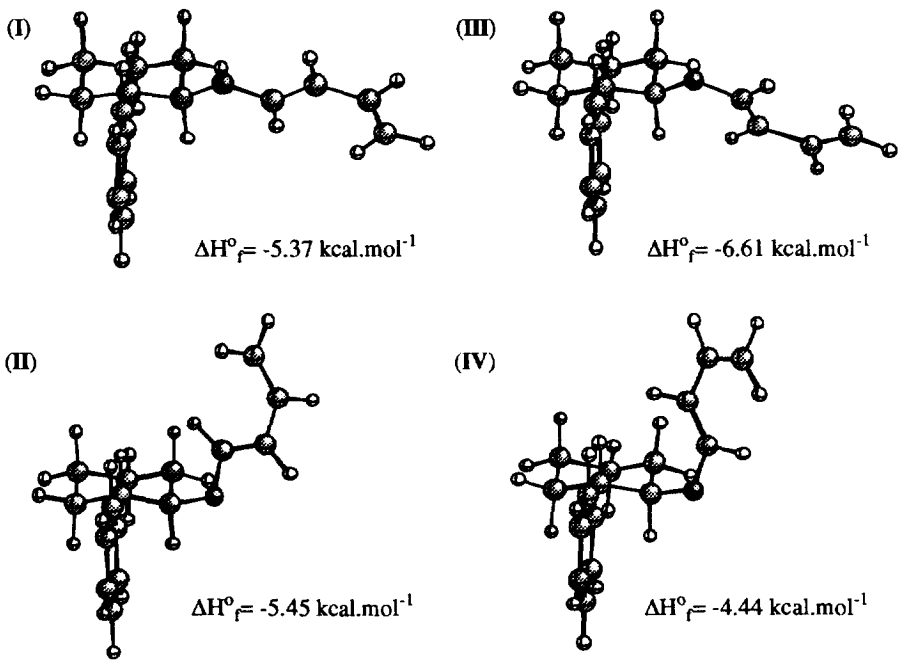
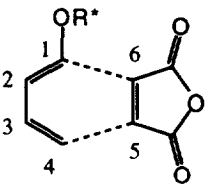


Figure 1. *Cisoid* conformers of (*E*)-1-[(1*R*,2*S*)-2-phenylcyclohexyloxy]-1,3-butadiene

Conformers **I** and **II** are of the *s-trans* type with respect to the enol ether moiety, whereas conformers **III** and **IV** are of the *s-cis* type. When the steric bias of these conformers is analyzed, it is suggested that the most stable ones (**III** and **II**) will preferentially react through the C1-*re* face of the diene, whereas the less stable ones (**I** and **IV**) will in turn react through the C1-*si* face. According to this criteria, the major diastereomer arising from the reaction (**5a**) would possess the configuration depicted in Scheme 4.

To get a deeper insight on the origin of the diastereoselectivity in these processes, the location of the transition states corresponding to the *endo* interaction of MA with both diastereotopic faces of the diene in conformations **I-IV** was undertaken. As a result of this search, all eight possible transition structures were located and characterized as such. The results of this study are summarized in Table 1. The atom numbering is referred to the following general structure:



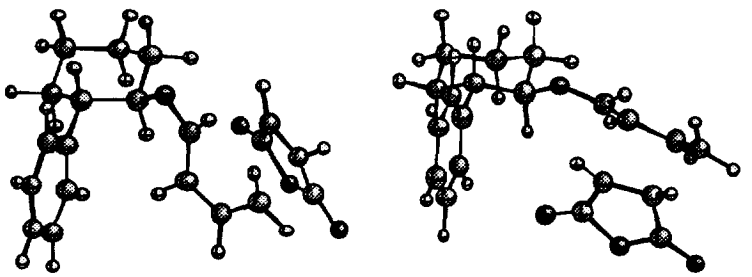
For every particular reaction mode, the activation energy has been calculated from the heats of formation of the corresponding transition state, starting conformer of the diene, and maleic anhydride. Moreover, a "Curtin-Hammett relative energy", calculated by taking into account both the activation energy and the differences in stability between conformers **I-IV**, is given for every reaction mode. As a general trend, it should be noted that the cycloaddition is predicted to be slightly asynchronous, the formation of the C4-C5 bond being more advanced than that of the C1-C6 bond in all transition states.[18]

Table 1. Transition states in the Diels-Alder reaction of **1a** with maleic anhydride

Starting conformer	Reacting face	Distance 1-6 [Å]	Distance 4-5 [Å]	Imaginary frequency [cm^{-1}]	Activation Energy [$kcal.mol^{-1}$]	Curtin-Hammett relative energy [$kcal.mol^{-1}$]
I	C1-*re*	2.256	2.086	817.8	21.71	2.87
	C1-*si*	2.318	2.067	779.7	20.39	1.54
II	C1-*re*	2.304	2.066	799.7	21.08	2.15
	C1-*si*	2.251	2.085	824.7	21.90	2.97
III	C1-*re*	2.329	2.051	778.7	20.09	0.00
	C1-*si*	2.300	2.048	792.4	20.34	0.25
IV	C1-*re*	2.333	2.042	788.1	23.88	5.96
	C1-*si*	2.350	2.023	795.8	20.30	2.38

When the complementary diastereomeric approaches to each alkoxydiene conformer are considered, it is found in all cases that the approach from the less hindered face leads to the most favourable transition state. However, the predicted energy differences, which are key to the diastereoselectivity of the reaction, are smaller than expected from a qualitative point of view. Thus, in the case of the most stable conformer **III**, this difference amounts only 0.25 kcal.mol^{-1}. Conversely, in the case of the less stable conformer **IV** an important diastereofacial discrimination (3.58 kcal.mol^{-1}) is predicted.

An explanation to this behaviour can be found in the fact that the most stable conformers of alkoxydiene **1a** are precisely those in which the diene moiety lies in a sterically free region. Thus, unfavourable steric interactions along the reaction path can be easily relieved through small rotations around the C-O bonds. In any case, according to the present theoretical calculations, the diastereoselectivity of the reaction would be largely determined by the difference in activation energy between the C1-*re* and the C1-*si* attacks on conformer **III**. The corresponding transition states are represented in Figure 2. Interestingly, the configuration of the major stereoisomer of **5a** derived from the present analysis, i.e., that arising from the C1-*re* attack on conformer **III**, is coincident with that derived from the analysis of the conformational preferences of **1a**.[13]



C1-*re* attack ΔH°_{f}= -62.87 kcal.mol^{-1}

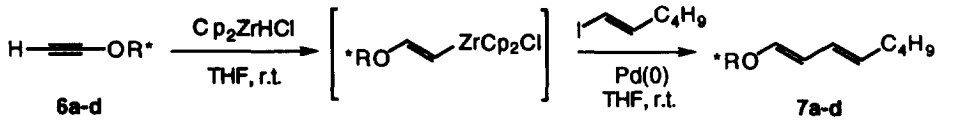
C1-*si* attack ΔH°_{f}= -62.62 kcal.mol^{-1}

Figure 2. Most favourable transition states in the reaction of **1a** with maleic anhydride

*C) Synthesis and Diels-Alder Reactions of Chiral (1*E,3E*)-1-Alkoxy-1,3-octadienes, **7a-d**.*

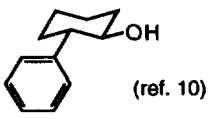
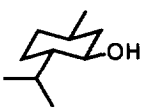
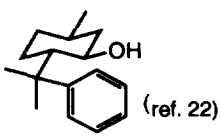
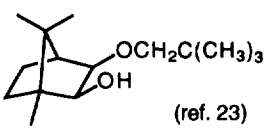
In view of the difficulties encountered in the reduction of **3a**, access to (*E,E*)-4-substituted-1-alkoxydienes was planned through a Pd(0) catalyzed cross-coupling of two stereochemically defined and electronically complementary olefin fragments. A vinylzirconocene was selected as the nucleophilic fragment, since the completely regio- and stereoselective hydrozirconation of ethoxyacetylene has been reported by Negishi,[19] and the resulting (*E*)-ethoxyvinylzirconocene chloride has shown to efficiently undergo nickel(0) catalyzed cross-coupling with aryl and vinyl iodides.[19,20] Guided also by these precedents, a vinyl iodide was selected as the electrophilic fragment. In the present instance, readily available (*E*)-1-iodo-1-hexene has been used in all the studied coupling reactions. Moreover, to ensure stereochemical control, Pd(0) has been the employed catalyst.[21]

Gratifyingly, alkoxyacetylenes **6a-d**[6b] underwent a completely regio- and stereoselective hydrozirconation when treated with freshly prepared Cp_2ZrHCl in THF at room temperature (Scheme 5). When the resulting alkoxyvinylzirconocene chloride solutions were treated with (*E*)-1-iodo-1-hexene in the presence of a catalytic amount of Pd(0), the target (*E,E*)-1-alkoxy-1,3-octadienes **7a-d** were formed as summarized in Table 2.



Scheme 5

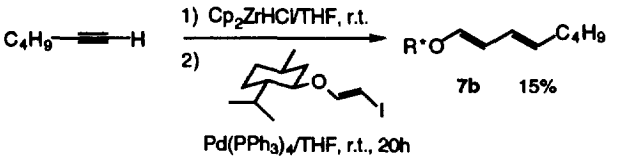
Table 2. Synthesis of (*E,E*)-1-Alkoxy-1,3-octadienes by Hydrozirconation/ Cross-coupling[a] of Acetylenic Ethers

R*OH	Starting alkoxyacetylene	Catalyst	Reaction time [h]	Product	Yield [%]
 (ref. 10)	**6a**	$Pd(PPh_3)_2$	5	**7a**	38
	**6b**	$Pd(PPh_3)_4$	2	**7b**	39
 (ref. 22)	**6c**	$Pd(PPh_3)_2$	6	**7c**	52
 (ref. 23)	**6d**	$Pd(PPh_3)_2$	5	**7d**	50

[a]1.2 equivalents of (*E*)-1-Iodo-1-hexene were used in all experiments. [b]Reaction time refers to the cross-coupling stage.

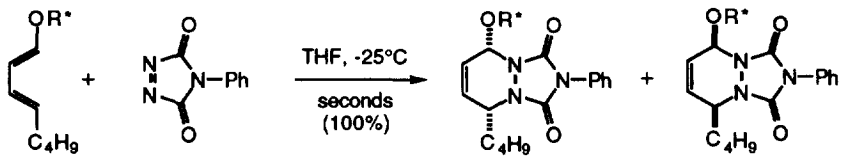
Best results in the coupling reaction were recorded working with a 20% molar excess of (*E*)-1-Iodo-1-hexene. For the less sterically demanding **6b**, $Pd(PPh_3)_4$ was employed as the catalyst; in all other cases, the more active $Pd(PPh_3)_2$, generated by DIBALH reduction of $Cl_2Pd(PPh_3)_2$, was required in order to improve reaction rates. Although the reactions took place in a clean manner, leading stereospecifically to the target *E,E* dienes **7a-d**, the recorded yields present a limit near 50%. Unavoidable decomposition of the intermediate zirconaolefins appears to be in the origin of this behaviour since variable amounts (20-40%) of the starting chiral alcohols were recovered as by-products.[24]

In an attempt to circumvent these difficulties, the reverse strategy involving hydrozirconation of 1-hexyne and cross-coupling with with an (*E*)-1-alkoxy-2-iodoethene (arising from the iodinolysis of the corresponding alkoxyvinylzirconocene chloride) was studied in the case of **7b** (Scheme 6). The cross-coupling turned out to be considerably slower, and **7b** was obtained in a modest 15% yield.



Scheme 6

The cycloadditions of **7a-d** with PTAD were next studied. As in the case of **1a**, the reactions turned out to be instantaneous, being performed in the present instance at -25°C in THF solution. The adducts **8a-d** could be isolated in quantitative yield as diastereomeric mixtures, as indicated in Scheme 7.



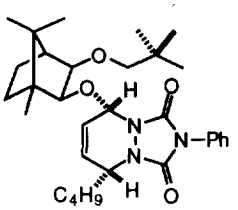
Entry	Diastereoselectivity[a]
a	94.5 : 5.5
b	50 : 50
c	85.0 : 15.0
d	94.5 : 5.5

[a]By ^1H NMR, ^{13}C NMR and HPLC

Scheme 7

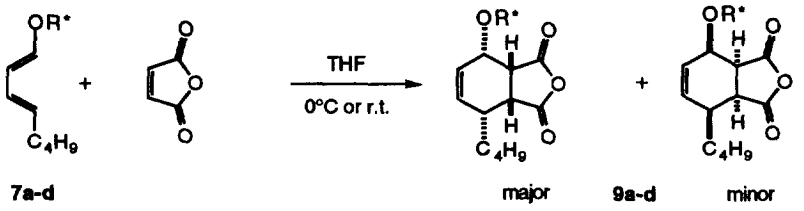
As it can be seen from the results in Scheme 7, *l*-menthol (entry **b**) is completely unefficient as a chiral controller in this cycloaddition. The situation is notably better for 8-phenylmenthol (entry **c**), and the best results are obtained with *trans*-2-phenylcyclohexanol (entry **a**) and 3-*exo*-neopentyloxyisoborneol (entry **d**). With these two auxiliaries, diastereomeric excesses of *ca.* 90% are achieved

It is worth mentioning that the diastereomers of **8d** can be readily separated by column chromatography, the major one being isolated in diastereomerically pure form in 77% yield. The absolute stereochemistry depicted in structure **8d** has been tentatively assigned on the basis of the theoretical calculations described in the next section of the manuscript.



8d (major)

The reactions of **7a-d** with MA were initially studied in THF solution. In this solvent, the processes were considerably slower than the reactions with PTAD, requiring for completion up to 55 h at room temperature. The reaction products were directly isolated in conveniently pure form and high yield by simple evaporation of the reaction mixture. However, attempts to further purify the adducts by column chromatography were accompanied by very important yield losses. Relevant information on these reactions is summarized in Scheme 8 and Table 3.



7a-d **9a-d**

Scheme 8

Table 3. Diels-Alder reactions of dienes **7a-d** with maleic anhydride

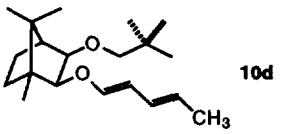
Diene	Reaction conditions	Adduct	Yield [%]	Diastereoselectivity
7a	room temp., 48 h, THF	**9a**	100(crude)	93.5 : 6.5[a]
	room temp., 36 h, toluene			91.5 : 8.5[a]
	room temp., 48 h, CH_3CN			92.5 : 7.5[a]
7b	room temp., 48 h, THF	**9b**	100(crude)	58.0 : 42.0[b]
7c	room temp., 55 h, THF	**9c**	100(crude)	78.0 : 22.0[b]
			33(SiO_2)	
7d	0°C, 46 h, THF	**9d**	100(crude)	83.5 : 16.5[b]
	0°C, 72 h, CH_3CN			94.5 : 5.5[b]

[a]By ^{13}C NMR and HPLC. [b]By ^{1}H and ^{13}C NMR

The observed diastereoselectivities follow trends similar to those in the reaction with PTAD, being somewhat lower in the present case. *trans*-2-Phenylcyclohexanol behaves as the best auxiliary for the reactions performed in THF. When comparing both series of reactions (PTAD *vs.* MA), the rather low diastereoselectivity recorded in the reaction of **7d** with MA was surprising. In an attempt to improve it, the effect of solvent polarity was analyzed in the cases of **7a** and **7d**. Whereas the diastereoselectivity of the cycloaddition of **7a** with MA appears to be independent of solvent polarity, a dramatic increase in diastereoselectivity (up to 22% in diastereomeric excess) is observed when the cycloaddition of **7d** is performed in acetonitrile. This is indicative of rather polar diastereomeric transition states whose differential stabilization is proportional to solvent polarity.

D) Theoretical calculations on the Diels-Alder reaction of (E,E)*-1-[(1*R,2S,*3*R,*4*S)*-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptyl-2-oxy]-1,3-pentadiene (**10d**) with maleic anhydride.*

The very high diastereoselectivities achieved in the reaction of **7d** with MA in acetonitrile prompted us to undertake a theoretical investigation on the conformational behaviour of the slightly simplified model **10d**, where the linear *n*-butyl substituent has been substituted by a methyl group, and on its energetically viable reaction modes with MA. As in the case of the reactions of **1a**, the calculations have been performed with the SCF-MO semi-empirical procedure AM1.[14]



10d

First of all, the conformational energy hypersurface of **10d** was explored. The structures and heats of formation of the four most stable conformers are depicted in Figure 3.

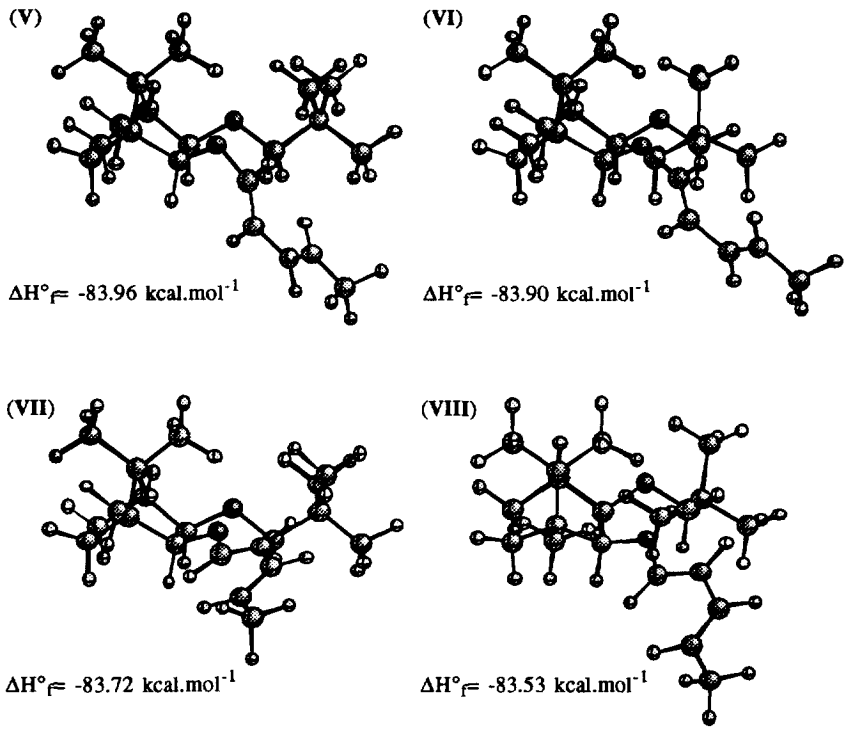


Figure 3. Low energy conformers of **10d**.

Inspection of Figure 3 reveals that the energies of all these conformers are very similar, falling in a range of only 0.4 kcal.mol^{-1}. Among these structures, **V** and **VI**, which are slightly more stable, correspond to *s-cis* conformers (with respect to the enol ether moiety) and appear to offer for reaction the C1-*si* face of the diene. The only difference between **V** and **VI** lies on the orientation of the neopentyloxy group. On the other hand **VII** and

VIII correspond to *s-trans* conformers; they differ from one another in the same aspect than **V** and **VI** and show a more sterically free C1-*re* face.

It is worth noting that, probably due to the presence of the isopropylidene bridge, all these conformers are characterized by a H-C(sp^3)-O-C(sp^2) dihedral angle of *ca.* 0° at the alcohol-diene junction. The presence of the corresponding conformers with a dihedral angle value of *ca.* 180°, which we had previously located for the *trans*-2-phenylcyclohexanol containing diene **1a**, was thoroughly investigated; however, we only could locate in this region of the potential energy hypersurface a single *s-trans* conformer, 5.2 kcal.mol^{-1} above the less stable one in Figure 3. It is thus clear that this conformer has no significance from the point of view of the reactivity of **10d**.

The calculated energy differences between conformers **V-VIII** do not seem sufficiently high as to account for the observed diastereoselectivity in the reaction of **7d** with MA, since all four conformers should be almost equally populated at the equilibrium. Moreover, the prediction of diastereofacial selectivity based on the simple inspection of these conformers is not evident. To clarify this point, a systematic search of the transition states corresponding to the *endo* interaction of MA with the C1-*re* and C1-*si* faces of conformers **V-VIII** was performed. As a result, only four distinct transition structures could be located and characterized. Their relevant data have been summarized in Table 4, where the atom numbering employed in Table 1 has been maintained.

Table 4. Transition states in the Diels-Alder reaction of **10d** with maleic anhydride

Starting conformer	Reacting face	Distance 1-6 [Å]	Distance 4-5 [Å]	Imaginary frequency [cm^{-1}]	Activation Energy [kcal.mol^{-1}]	Curtin-Hammett relative energy [kcal.mol^{-1}]
V	C1-*re*	2.273	2.071	789.9	21.01	0.00
VI	C1-*si*	2.164	2.143	848.9	26.23	5.28
VII	C1-*si*	2.265	2.083	796.5	22.71	1.94
VIII	C1-*re*	2.155	2.159	840.6	25.43	4.85

As it can be seen, the diastereoselectivity of the reaction appears to be governed by the difference between the C1-*re* attack on the *s-cis* conformer **V** and the C1-*si* attack on the *s-trans* conformer **VII**. The structures of the transition states corresponding to these approaches are presented in Figure 4.

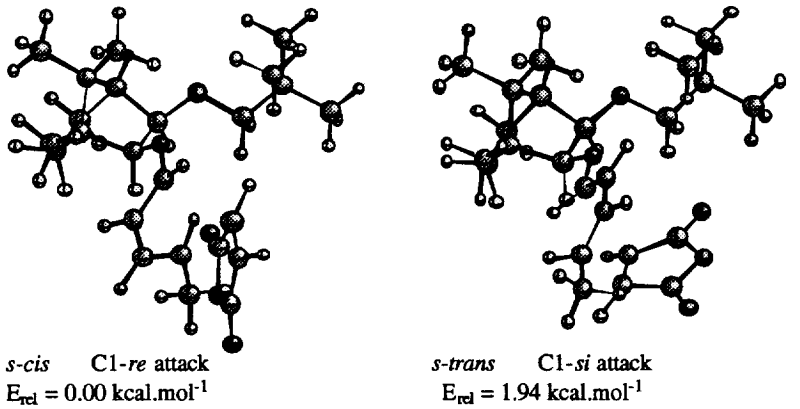


Figure 4. Most favourable transition states in the reaction of **10d** with maleic anhydride

The most energetically favourable approach is a C1-*re* attack on a *s-cis* conformer (**V** or **VII**). The stereochemistries of the major diastereomers arising from the reactions of **7d** with PTAD and MA have been assigned by analogy (Schemes 7 and 8).

From the geometric point of view, it is important to realize that all four transition structures are characterized by a significant change in the conformation of the diene moiety, which tends to be parallel to the basis plane of the bicyclo[2.2.1]heptane system. Thus, contrary to common qualitative thinking, the "chiral wall" responsible for diastereoselectivity in the reactions where 3-*exo*-neopentyloxyisoborneol is employed as a chiral auxiliary is not simply constituted by the neopentyloxy group; rather, the isopropylidene bridge, the neopentyloxy group and the bridgehead methyl substituent appear to be simultaneously responsible for the observed diastereoselectivity (Figure 5).

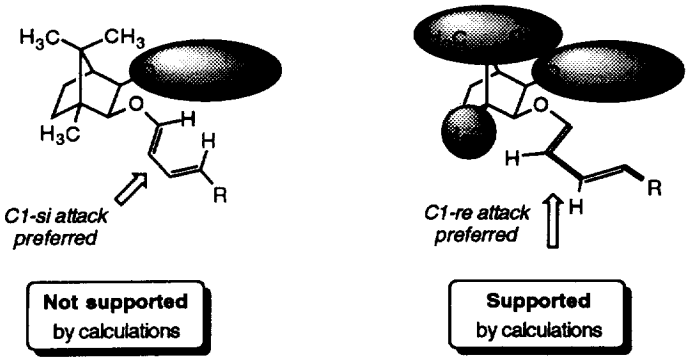


Figure 5. Predicted facial selectivity in the cycloadditions of 1-(3-neopentyloxyisobornyloxy)-1,3-butadienes

In this respect, it is important to realize that opposite conclusions can be reached on the preferred reacting face of a given diene conformer depending on the consideration of either the geometry of the isolated diene or the analysis of the lowest energy transition states in the cycloaddition. Due to the different quality of these predictions, it is strongly recommended that the second approach be followed whenever possible.

CONCLUSIONS

In summary, we have developed two different procedures for the stereoselective synthesis of chiral 1-alkoxy-1,3-dienes from alkoxyacetylenes. By these methods, we have prepared the first non-sugar-derived chiral (*E*)-1-alkoxy-1,3-butadiene **1a**, as well as a family of (*E,E*)-1-alkoxy-1,3-octadienes (**7a-d**). Whereas the Diels-Alder chemistry of chiral 1-alkoxy-1,3-butadienes derived from sugars has been previously studied at some extent, the corresponding 4-alkyl substituted derivatives were up to now unknown. Among these last substances, those bearing a 3-*exo*-neopentyloxyisobornyloxy- or a *trans*-2-phenylcyclohexyloxy- chiral auxiliary undergo Diels-Alder reaction with PTAD or MA with optimal facial selectivity. In comparison with 2-alkyl substituted dienes, the presence of an alkyl substituent at C-4 exerts a highly beneficial effect on diastereoselectivity, although reactivity is slightly diminished. We have also performed a complete theoretical analysis by the AM1 procedure of the cycloadditions of (*E*)-1-[(1*R*,2*S*)-2-phenylcyclohexyloxy]-1,3-butadiene, (**1a**) and (*E,E*)-1-[(1*R*,2*S*,3*R*,4*S*)-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptyl-2-oxy]-1,3-pentadiene (**10d**) with MA. This kind of analysis, which can be nowadays performed at an affordable computational cost, allows a much safer prediction of diastereoselectivity and/or stereochemical assignment than the mere conformational analysis of the chiral substrate.

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 and b=broad). ^{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). Elemental analyses were performed by the "Servei d'Anàlisis Elementals del CSIC de Barcelona". Medium pressure liquid chromatography (MPLC) separations were performed using Fluka Silica gel 100 (C_{18}-Reversed phase), eluting with acetonitrile/water mixtures; 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.

*(±)-1-(*trans*-2-Phenylcyclohexyloxy)-2-iodoethyne, 2a*

To a suspension of 2.33 g (20.32 mmol) of KH (35 wt. % dispersion in mineral oil) in 20 mL of THF were added, under N_2, 1.76 g (10 mmol) of (±)-*trans*-2-phenylcyclohexanol dissolved in 20 mL of THF. When the release of hydrogen was over (approx. 1 hour), the suspension was cooled at -50°C and 1.31 g (10 mmol) of trichloroethylene dissolved in 12 mL de THF were added. The mixture was allowed to warm up to room temperature and stirred for 1 hour. The mixture was then cooled at -78°C and 15 mL (24 mmol) of *n*-BuLi (1.6 M

in hexanes) were added *via* syringe. The mixture was allowed to reach -40°C and stirred for 30 minutes. It was then cooled to -50°C and 3.81 g (15 mmol) of I_2 dissolved in 15 mL of THF were added. The mixture was then allowed to warm up to 0°C, stirred for 1 hour and poured over a mixture of a saturated NH_4Cl solution, ice and hexane. The aqueous layer was extracted three times with hexane and the combined organic extracts were washed with aqueous $Na_2S_2O_3$ to remove excess iodine and then with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by chromatography using hexane/Et_2O as eluent to give 2.37 g (74%) of **2a** as a yellow solid. IR (film) 3070, 3040, 2940, 2860, 2210, 1590, 1450, 1260, 1190, 1170, 1150, 1000, 930, 700 cm^{-1}. ^{1}H-NMR (200 MHz) δ= 7.4-7.1 (m, 5H), 4.16 (td, J= 10.6 Hz, J'= 4.5 Hz, 1H), 2.74 (td, J= 11.3 Hz, J'= 4.1 Hz, 1H), 2.5-2.3 (m, 1H), 2.05-1.2 (m, 7H).

*(±)-1-(*trans*-2-phenylcyclohexyloxy)-3-buten-1-yne, 3a*

CuCN (89 mg, 1 mmol) and LiCl (85 mg, 2 mmol), previously dried for 4h at 150°C in a vacuum oven, were suspended, under N_2, in 1 mL of THF. The mixture was stirred at room temperature until complete dissolution. In a separate flask, 225 mg (1 mmol) of $ZnBr_2$ (previously dried for 4h at 150°C in a vacuum oven) were dissolved under N_2 in 0.5 mL of THF. The solution was cooled to 0°C, and 1 mL (1 mmol) of a 1M solution of H_2C=CH-MgBr in THF was added, whereupon a white precipitate appeared. The mixture was stirred for 35-40 minutes at 0°C. This suspension was added *via* cannula to the CuCN.2LiCl cooled at -10°C, the formation of a black precipitate being observed. The mixture was stirred for 35 minutes at 0°C; then cooled to -78°C, and a solution of 100 mg (0.31 mmol) of **2a** in 1 mL of THF was added. The mixture was allowed to warm up to -50°C over 90 minutes and stirred at that temperature for another 90 minutes. Then, it was poured over a mixture of saturated NH_4Cl solution, ice and ether, and the aqueous layer was extracted three times with ether. The combined organic extracts were washed with a saturated NH_4Cl solution and then with brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by chromatography eluting with hexane to give 63 mg (90%) of **3a** as a colourless oil that crystallized on standing at -18°C. IR (film) 3100, 3070, 3040, 3010, 2940, 2860, 2250, 1630, 1610, 1500, 1450, 1420, 1260, 1230, 1055, 1000, 930, 900, 870, 820, 755, 700 cm^{-1}. ^{1}H-NMR (200 MHz) δ= 7.4-7.2 (m, 5H), 5.71 (dd, J= 17.4 Hz, J'= 10.7 Hz, $1H_{olef}$), 5.35 (dd, J= 17.4 Hz, J'= 2.5 Hz, $1H_{olef}$), 5.20 (dd, J= 10.7 Hz, J'= 2.5 Hz, $1H_{olef}$), 4.15 (td, J= 11 Hz, J'= 4 Hz, $1H_{\alpha\text{-}O}$), 2.77 (td, J= 12 Hz, J'= 3.5 Hz, $1H_{\alpha\text{-}Ph}$), 2.5-1.2 (m, 8H). ^{13}C-NMR (50 MHz) δ= 142.4 (Cq), 128.4 (2CH), 127.5 (2CH), 126.7 (CH), 122.6 (CH), 117.3 (CH), 90.1 (Cq), 89.8 (CH), 86.5 (Cq), 49.1 (CH), 33.8 (CH_2), 31.1 (CH_2), 25.6 (CH_2), 24.7 (CH_2). MS (DIP-EI) m/z= 226 (M^+, 1%), 159 (36%), 117 (14%), 91 (100%).

*(±)-(*E*)-1-(*trans*-2-Phenylcyclohexyloxy)-1,3-butadiene, 1a.*

To a suspension of 34 mg (0.88 mmol) of $LiAlH_4$ in 2 mL of THF under N_2, was added at room temperature a solution of 100 mg (0.44 mmol) of **3a** in 2 mL of THF. The reaction mixture was stirred for 7 h and quenched by the successive addition of 0.034 mL of water, 0.034 mL of 15% NaOH and 3x0.034 mL of water. The mixture was stirred for 30 minutes at room temperature, the solids were filtered and washed with ether, the filtrate was dried over Na_2SO_4 and the solvents removed *in vacuo*. The crude product was submitted to column chromatography eluting with hexane to give 25 mg (32% recovery) of *trans*-2-phenylcyclohexanol and 41 mg (40%) of **1a** as a white solid in the form of a 9:1 mixture of the *E* and *Z* stereoisomers, according to ^{1}H-NMR spectroscopy. IR (film) 3080, 3035, 2935, 2860, 1650, 1600, 1445, 1175, 1120, 990, 905, 870, 750,

695 cm^{-1}. ^{1}H-NMR (200 MHz) δ= 7.35-7.10 (m, 5H), 6.19 (d, J= 12.1 Hz, $1H_{olef}$), 6.04 (dt, J= 16.8 Hz, J'= 10.3 Hz, $1H_{olef}$), 5.46 (dd, J= 12.1 Hz, J'= 10.3 Hz, $1H_{olef}$), 4.86 (dd, J= 16.8 Hz, J'= 1.8 Hz, $1H_{olef}$), 4.69 (dd, J= 10.3 Hz, J'= 1.8 Hz, $1H_{olef}$), 3.80 (m, $1H_{\alpha\text{-}O}$), 2.67 (td, J= 11 Hz, J'= 4 Hz, $1H_{\alpha\text{-}Ph}$), 2.30-1.30 (m, 8H).

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

A solution of the dienophile (1 eq) was added, under N_2, to a solution of **1a** (1 eq) at 0°C. When all the *E* stereoisomer had reacted, the mixture was purified by MPLC, eluting with acetonitrile/water, without previous removal of the solvent employed in the reaction.

*(±)-2-phenyl-5-(*trans*-2-phenylcyclohexyloxy)-5,8-dihydro-[1,2,4]triazolo[1,2-a]pyridazine-1,3-dione*, **4a**

The general procedure was followed starting from a sample of **1a** containing 59 mg (0.257 mmol) of the *E* stereoisomer in 0.25 mL of THF and 45 mg (0.257 mmol) of 4-phenyl-3H-1,2,4-triazoline-3,5-dione (PTAD) in 0.25 mL of THF. The reaction was instantaneous and gave, after purification, 104 mg (100%) of **4a** as a white solid in the form of a 90 : 10 diastereomeric mixture (80% d.e.) according to ^{13}C-NMR and HPLC. Major adduct: IR (film) 3080, 3040, 2945, 2870, 1785, 1730, 1610, 1510, 1420, 1290, 1250, 1140, 1060, 1000, 950, 880, 760, 705, 620 cm^{-1}. ^{1}H-NMR (200 MHz) δ= 7.5-7.2 (m, 10H), 5.8-5.7 (m, $1H_{olef}$), 5.1 (m, $1H_{\alpha\text{-}O/N}$), 4.75 (m, $1H_{olef}$), 4.32/3.81 (AB, J= 17 Hz, 2H, cyclic CH_2), 4.15 (td, $1H_{\alpha\text{-}O}$), 2.5 (td, $1H_{\alpha\text{-}Ph}$), 2.1-1.2 (m, 8H). ^{13}C-NMR (50 MHz) δ= 153.0 (Cq), 151.8 (Cq), 144.1 (Cq), 131.0 (Cq), 129.2 (2CH), 128.5 (2CH), 128.2 (3CH), 126.8 (CH), 125.5 (2CH), 123.0 (CH), 122.9 (CH), 86.8 (CH), 80.1 (CH), 52.7 (CH), 43.7 (CH_2), 34.5 (CH_2), 33.5 (CH_2), 25.7 (CH_2), 25.3 (CH_2). MS (DIP-CI-NH_3) m/z= 421 (M+18, 100%), 404 (M+1, 7%), 228 (27%).

*(±)-*cis*-3-(*trans*-2-Phenylcyclohexyloxy)cyclohex-4-ene-1,2-dicarboxylic anhydride*, **5a**

The general procedure was followed starting from from a sample of **1a** containing 56 mg (0.244 mmol) of the *E* stereoisomerof **1a** in 0.3 mL of toluene and 29 mg (0.3 mmol) of maleic anhydride in 0.3 mL of toluene. The reaction mixture, which became yellow, was stirred for 28 h at 0°C, the reaction progress being followed by HPLC (Nucleosil 120 C18 column, 25 cm; eluent: CH_3CN/H_2O 70/30). After purification, 58 mg (73%) of **5a** were obtained as a 86 : 14 diastereomeric mixture (72% d.e.) according to ^{1}H-NMR, ^{13}C-NMR and HPLC. Major adduct: IR (KBr) 3080, 3040, 2940, 2870, 1870, 1790, 1650 (weak), 1610 (weak), 1450, 1230, 1070, 1040, 930, 760, 710 cm^{-1}. ^{1}H-NMR (200 MHz) δ= 7.40-7.00 (m, 5H), 5.87-5.65 (m, $2H_{olef}$), 4.45 (m, $1H_{\alpha\text{-}O}$), 3.40-1.10 (m, 14H). ^{13}C-NMR (50 MHz) δ= 173.9 (Cq), 172.0 (Cq), 144.4 (Cq), 132.8 (CH), 128.1 (2CH), 127.9 (2CH), 126.1 (CH), 125.5 (CH), 78.8 (CH), 64.5 (CH), 50.7 (CH), 46.3 (CH), 35.8 (CH), 33.5 (CH_2), 30.6 (CH_2), 25.8 (CH_2), 24.7 (CH_2), 20.5 (CH_2). MS (DIP-CI-NH_3) m/z= 361 (M+35, 10%), 344 (M+18, 100%).

General procedure for the preparation of (E,E)*-1-alkoxy-1,3-octadienes*, **7**

The starting alkoxyacetylene **6** (1 eq) dissolved in THF was added *via* syringe, under a strict argon atmosphere, to a suspension of freshly prepared[25] Cp_2ZrHCl in THF at room temperature. The suspension was stirred until it became a clear solution (colour ranging from orange to green). This solution was added *via* cannula to a suspension or solution of 0.05-0.1 eq of Pd catalyst ($Pd(PPh_3)_4$ or $Pd(PPh_3)_2$) in THF, under a strict argon

atmosphere, and 1.2 eq of (*E*)-1-iodohexene dissolved in THF were then added. The mixture was stirred at room temperature and the reaction progress was followed by TLC. When the reaction was complete, the mixture was diluted with hexane and filtered through Celite or SiO_2/Et_3N 2.5% v/v to remove Pd and Zr salts. Solvents were removed *in vacuo* and the crude product was immediately purified by chromatography eluting with hexane or hexane/ether mixtures.

*(±)-(*E,E*)-1-(*trans*-2-Phenylcyclohexyloxy)-1,3-octadiene*, **7a**

The above procedure was followed starting from 240 mg (1.2 mmol) of **6a** in 0.5 mL of THF, 309 mg (1.2 mmol) of Cp_2ZrHCl in 0.5 mL of THF, 84 mg (0.12 mmol) of $Cl_2Pd(PPh_3)_2$ and 0.24 mL (0.24 mmol) of DIBAH (1M in hexane) in 0.2 mL of THF, and 302 mg (1.44 mmol) of (*E*)-1-iodohexene in 0.4 mL of THF. The reaction was complete after 5 h. After purifying the crude by chromatography, eluting with 95:5 hexane/ether, 131 mg (38%) of **7a** were obtained as a yellow oil that crystallized on standing at 4°C. IR (film) 3070, 3040, 2940, 2860, 1670, 1630, 1455, 1175, 1100, 1045, 975, 760, 705 cm^{-1}. ^{1}H-NMR (300 MHz, C_6D_6) δ= 7.22-7.05 (m, 5H), 6.04 (d, J= 12.3 Hz, $1H_{olef\ \alpha\text{-}O}$), 5.79 (ddt, J= 15 Hz, J'= 10.5 Hz, J"= 0.15 Hz, $1H_{olef}$), 5.64 (dd, J= 10.5 Hz, J'= 12.3 Hz, $1H_{olef}$), 5.31 (dt, J= 15 Hz, J'= 7.5 Hz, $1H_{olef\ \alpha\text{-}butyl}$), 3.57 (td, J= 10.5 Hz, J'= 4.2 Hz, $1H_{\alpha\text{-}O}$), 2.56 (ddd, J= 12.3 Hz, J'= 10.2 Hz, J"= 3.9 Hz, $1H_{\alpha\text{-}Ph}$), 2.10-0.82 (m, 17H). ^{13}C-NMR (75 MHz, C_6D_6) δ= 148.4 (CH), 144.1 (Cq), 128.6 (2CH), 128.2 (CH), 128.0 (2CH), 127.0 (CH), 126.6 (CH), 108.4 (CH), 83.0 (CH), 50.6 (CH), 34.1 (CH_2), 32.9 (CH_2), 32.8 (CH_2), 32.3 (CH_2), 26.2 (CH_2), 25.0 (CH_2), 22.5 (CH_2), 14.2 (CH_3). MS (DIP-EI) m/z= 284 (M^+, 0.7%), 159 (8.5%), 115 (19%), 91 (100%).

*(*E,E*)-1-(1-Menthyloxy)-1,3-octadiene*, **7b**.

The general procedure was followed starting from 225 mg (1.25 mmol) of **6b** in 0.5 mL of THF, 324 mg (1.25 mmol) of Cp_2ZrHCl in 0.5 mL of THF, 144 mg (0.125 mmol) of $Pd(PPh_3)_4$ in 0.3 mL of THF and 315 mg (1.5 mmol) of (*E*)-1-iodohexene in 0.4 mL of THF. The reaction took 3 h to completion. After purification, 128 mg (39%) of **7b** were obtained as a colourless oil. $[\alpha]_D^{23}$= -20.3 (c= 2.23 in hexane). IR (film) 3030, 2960, 2930, 2875, 1660, 1625, 1450, 1175, 1145, 1090, 970 cm^{-1}. ^{1}H-NMR (200 MHz) δ= 6.38 (d, J= 12.5 Hz, $1H_{olef\ \alpha\text{-}O}$), 5.89 (dd, J= 15 Hz, J'= 10 Hz, $1H_{olef}$), 5.59 (dd, J= 12.5 Hz, J'= 10 Hz, $1H_{olef}$), 5.42 (dt, J= 15 Hz, J'= 7.5 Hz, $1H_{olef\ \alpha\text{-}butyl}$), 3.45 (td, J= 10 Hz, J'= 4 Hz, $1H_{\alpha\text{-}O}$), 2.20-0.80 (m, 18H), 0.91 (d, J= 6.2 Hz, 3H), 0.89 (d, J= 7.4 Hz, 3H), 0.76 (d, J= 7 Hz, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$) δ= 148.1 (CH), 128.7 (CH), 126.0 (CH), 107.8 (CH), 81.0 (CH), 47.7 (CH), 41.2 (CH_2), 34.3 (CH_2), 32.5 (CH_2), 31.9 (CH_2), 31.5 (CH), 25.8 (CH), 23.4 (CH_2), 22.2 (CH_2), 22.1 (CH_3), 20.7 (CH_3), 16.3 (CH_3), 14.0 (CH_3). MS (DIP-CI-CH_4) m/z= 265 (M+1, 45%), 264 (M^+, 53%), 139 (100%).

*(*E,E*)-1-((1*R*,2*S*,5*R*)-8-Phenylmenthyloxy)-1,3-octadiene*, **7c**

The general procedure was followed starting from 256 mg (1 mmol) of **6c** in 0.5 mL of THF, 258 mg (1 mmol) of Cp_2ZrHCl in 0.5 mL of THF, 72 mg (0.1 mmol) of $Cl_2Pd(PPh_3)_2$ and 0.2 mL (0.2 mmol) of DIBAH (1M in hexane) in 0.2 mL of THF and 252 mg (1.2 mmol) of (*E*)-1-iodohexene in 0.4 mL of THF. The reaction was complete after 6 h. After purification, 176 mg (52%) of **7c** were obtained as a colourless oil. $[\alpha]_D^{23}$= -10.5 (c= 0.6 in hexane). IR (film) 3080, 3055, 3020, 2950, 2920, 2870, 1660, 1625, 1450, 1370, 1180, 1155, 1095, 970, 765, 700 cm^{-1}. ^{1}H-NMR (200 MHz, C_6D_6) δ= 7.45-7.15 (m, 5H), 6.24 (d, J= 12.4 Hz, $1H_{olef}$),

6.14 (m, $1H_{olef}$), 5.90 (m, $1H_{olef}$), 5.56 (dt, J= 14.7 Hz, J'= 6.9 Hz, $1H_{olef}$), 3.44 (m, $1H_{\alpha\text{-}O}$), 2.30-0.60 (m, 26H). ^{13}C-NMR (75 MHz) δ= 150.5 (Cq), 147.1 (CH), 128.6 (CH), 127.8 (2CH), 126.1 (CH), 126.0 (2CH), 125.1 (CH), 108.0 (CH), 82.1 (CH), 51.3 (CH), 41.9 (CH_2), 40.5 (Cq), 34.6 (CH_2), 32.5 (CH_2), 31.9 (CH_2), 31.5 (CH), 29.4 (CH_3), 27.1 (CH_2), 24.8 (CH_3), 22.3 (CH_2), 21.8 (CH_3), 14.0 (CH_3). MS (DIP-CI-CH_4) m/z= 369 (M+29, 2%), 341 (M+1, 46%), 215 (100%).

(E,E)-1-[(1R,2S,3R,4S)-3-(2,2-Dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]heptyl-2-oxy]-1,3-octadiene, **7d**

The general procedure was followed starting from 318 mg (1.2 mmol) of **6d** in 0.5 mL of THF, 309 mg (1.2 mmol) of Cp_2ZrHCl in 0.5 mL of THF, 84 mg (0.12 mmol) of $Cl_2Pd(PPh_3)_2$ and 0.24 mL (0.24 mmol) of DIBAH (1M in hexane) in 0.3 mL of THF and 302 mg (1.44 mmol) of (*E*)-1-iodohexene in 0.4 mL of THF. The reaction was complete after 5 h. After purification, 210 mg (50%) of **7d** were obtained as a colourless oil. $[\alpha]_D^{23}$= -89.2 (c= 1.7 in hexane). IR (film) 3050, 3025, 2940, 2870, 1655, 1620, 1475, 1460, 1390, 1360, 1175, 1110, 970 cm^{-1}. ^{1}H-NMR (300 MHz, C_6D_6) δ= 6.39 (d, J= 12 Hz, $1H_{olef}$), 6.00 (dd, J= 15 Hz, J'= 10.5 Hz, $1H_{olef}$), 5.73 (m, $1H_{olef}$), 5.46 (dt, J= 15 Hz, J'= 6.9 Hz, $1H_{olef}$), 3.48/3.20 (AB, J= 6.6 Hz, 2H), 3.02/2.93 (AB, J= 8.1 Hz, 2H), 2.12-0.70 (m, 14H), 1.38 (s, 3H), 0.99 (s, 9H), 0.98 (s, 3H) 0.75 (s, 3H). ^{13}C-NMR (75 MHz, C_6D_6) δ= 150.8 (CH), 127.8 (CH), 127.4 (CH), 107.2 (CH), 88.7 (CH), 85.3 (CH), 81.4 (CH_2), 49.2 (Cq), 48.7 (CH), 47.1 (Cq), 33.8 (CH_2), 33.0 (CH_2), 32.4 (CH_2), 32.3 (Cq), 27.0 (CH_3), 24.3 (CH_2), 22.5 (CH_2), 21.3 (CH_3), 21.0 (CH_3), 14.2 (CH_3), 11.7 (CH_3). MS (DIP-CI-CH_4) m/z= 377 (M+29, 25%), 349 (M+1, 18%), 223 (81%).

General procedure for the Diels-Alder cycloadditions of (E,E)- 1-alkoxy-1,3-octadienes, 7, with PTAD

A solution of the dienophile (1 eq) in THF (cooled to -25°C) was added, under argon, to a solution of **7** (1 eq) in THF at -25°C. The reaction was instantaneous (the red colour of the dienophile solution immediately disappeared as it was being added). The solvent was removed *in vacuo* to give the desired cycloadduct in quantitative yield and in pure form.

(±)-cis-5-Butyl-2-phenyl-8-(trans-2-phenylcyclohexyloxy)-5,8-dihydro-[1,2,4]triazolo[1,2-a]pyridazine-1,3-dione, 8a

The above procedure was followed starting from 29 mg (0.102 mmol) of **7a**, 18 mg (0.102 mmol) of PTAD and 0.5 mL of THF to give 47 mg (100%) of **8a** as a solid in the form of a 94.5 : 5.5 mixture of diastereomers (89% d.e.) according to ^{13}C-NMR and HPLC Major adduct: IR (KBr) 3060, 3030, 2930, 2860, 1775, 1715, 1600, 1500, 1415, 1055, 760, 700, 685 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3CN) δ= 7.54-7.12 (m, 10H), 5.70-5.64 (m, $1H_{olef}$), 5.04-4.97 (m, $1H_{olef}$ + $1H_{\alpha\text{-}O/N}$), 4.26 (m, $1H_{\alpha\text{-}N}$), 4.05 (td, J= 10.5 Hz, J'= 4.5 Hz, $1H_{\alpha\text{-}O}$), 2.46 (m, $1H_{\alpha\text{-}Ph}$), 2.06-1.20 (m, 14H), 0.90 (t, J= 6.9 Hz, 3H). ^{13}C-NMR (75 MHz, CD_3CN) δ= 153.7 (Cq), 151.2 (Cq), 145.3 (Cq), 132.6 (Cq), 129.9 (2CH), 129.8 (CH), 129.3 (2CH), 129.1 (CH), 129.1 (2CH), 127.4 (CH), 127.2 (2CH), 122.6 (CH), 84.9 (CH), 78.6 (CH), 56.7 (CH), 52.9 (CH), 35.1 (CH_2), 34.2 (CH_2), 33.3 (CH_2), 26.6 (CH_2), 26.4 (CH_2), 25.9 (CH_2), 23.3 (CH_2), 14.2 (CH_3). MS (DIP-EI) m/z= 459 (M^+, 1%), 284 (22%), 159 (26%), 91 (100%).

cis-5-Butyl-2-phenyl-8-(l-menthyloxy)-5,8-dihydro-[1,2,4]triazolo[1,2-a]pyridazine-1,3-dione, 8b

The general procedure was followed starting from 32 mg (0.121 mmol) of **7b** in 0.3 mL of THF and 21 mg (0.121 mmol) of PTAD in 0.3 mL of THF to give 53 mg (100%) of **8b** as an oil in the form of a 50 : 50 diastereomeric mixture according to ^{1}H and ^{13}C-NMR. Diastereomeric mixture: IR (film) 3050, 2960, 2920, 2860, 1750, 1710, 1605, 1500, 1420, 1290, 1240, 1160, 1140, 1050, 875, 765, 640 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3CN) δ= 7.60-7.40 (m, 2 x 5H), 6.19-5.73 (m, 2 x $2H_{olef}$ + 2 x $1H_{\alpha\text{-}O/N}$), 4.51 (m, 2 x $1H_{\alpha\text{-}N/butyl}$), 3.71/3.70 (td, J= 10.3 Hz, J'= 4.8 Hz and J= 10.3 Hz, J'= 4.2 Hz, 2 x $1H_{\alpha\text{-}O}$), 2.40-0.70 (m, 2 x 27H). ^{13}C-NMR (75 MHz, CD_3CN) δ= 154.0/153.9 (Cq), 151.0/150.8 (Cq), 132.7 (2 x Cq), 130.6/130.3 (CH), 130.0 (2 x 2CH), 129.1 (2 x CH), 127.1 (2 x 2CH), 123.6/123.0 (CH), 79.3/78.0 (CH), 76.8/73.6 (CH), 57.2 (2 x CH), 49.9/49.0 (CH), 43.4/41.2 (CH_2), 35.0/34.9 (CH_2), 33.9/33.5 (CH_2), 32.5/32.2 (CH), 26.8/26.7 (CH_2), 26.2/26.1 (CH), 23.9/23.9 (CH_2), 23.4/23.4 (CH_2), 22.6 (2 x CH_3), 21.5/21.3 (CH_3), 16.6/16.3 (CH_3), 14.4/14.3 (CH_3). MS (DIP-CI-CH_4) m/z= 468 (M+29, 10%), 440 (M+1, 27%), 439 (M, 86%), 284 (100%).

cis-5-Butyl-2-phenyl-8-[(1R,2S,5R)-8-phenylmenthyloxy]-5,8-dihydro-[1,2,4]triazolo[1,2-a]-pyridazine-1,3-dione, 8c.

The general procedure was followed starting from 40 mg (0.118 mmol) of **7c**, 21 mg (0.118 mmol) of PTAD and 0.5 mL of THF, to give 61 mg (100%) of **8c** as a solid in the form of a 85 : 15 mixture of diastereomers (70% d.e.) according to ^{1}H-NMR, ^{13}C-NMR and HPLC Major diastereomer: IR (film) 3055, 2960, 2920, 2870, 1775, 1720, 1605, 1505, 1420, 1055, 770, 705 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3CN) δ= 7.60-7.15 (m, 10H), 6.00-5.52 (m, $2H_{olef}$ + $1H_{\alpha\text{-}O/N}$), 4.43 (m, $1H_{\alpha\text{-}N}$), 3.90 (td, J= 10.3 Hz, J'= 4.2 Hz, $1H_{\alpha\text{-}O}$), 2.15-0.80 (m, 17H), 1.46 (s, 3H), 1.32 (s, 3H), 0.87 (d, J= 6.6 Hz, 3H). ^{13}C-NMR (75 MHz, CD_3CN) δ= 154.0 (Cq), 150.7 (Cq), 132.7 (2Cq), 130.2 (CH), 130.0 (2CH), 129.2 (CH), 128.8 (2CH), 127.2 (2CH), 126.5 (2CH), 125.9 (CH), 122.9 (CH), 80.1 (CH), 75.7 (CH), 57.2 (CH), 53.0 (CH), 44.2 (CH_2), 40.9 (Cq), 35.2 (CH_2), 33.8 (CH_2), 32.4 (CH), 28.0 (CH_3), 28.0 (CH_2), 27.5 (CH_3), 26.9 (CH_2), 23.3 (CH_2), 22.4 (CH_3), 14.3 (CH_3). MS (DIP-CI-CH_4) m/z= 516 (M+1, 15%), 284 (25%), 215 (100%).

cis-5-Butyl-8-[(1R,2S,3R,4S)-3-(2,2-dimethylpropoxy)-1,7,7-trimethylbicyclo[2.2.1]hepyl-2-oxy]-2-phenyl-5,8-dihydro[1,2,4]triazolo[1,2-a]pyridazine-1,3-dione, 8d.

The general procedure was followed starting from 43 mg (0.124 mmol) of **7d**, 22 mg (0.124 mmol) of PTAD and 0.7 mL of THF to give 65 mg (100%) of **8d** as a solid in the form of a 94.5 : 5.5 mixture of diastereomers (89% d.e.) according to ^{1}H-NMR, ^{13}C-NMR and HPLC. The crude product was purified by column chromatography on SiO_2, eluting with hexane/ether 85:15, to give 50 mg (77%) of the major diastereomer. White crystals, m.p. 43-45°C. $[\alpha]_D^{23}$= -15.8 (c= 1.71 in CH_3CN). IR (film) 3060, 3040, 2950, 2860, 1775, 1715, 1605, 1500, 1415, 1290, 1140, 1100, 1055, 1025, 765, 690 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3CN) δ= 7.55-7.40 (m, 5H), 6.14 (ddd, J= 10.2 Hz, J'= 4.8 Hz, J''= 1.8 Hz, $1H_{olef}$), 5.96 (dd, J= 10.2 Hz, J'= 3.1 Hz, $1H_{olef}$), 5.85 (dd, J= 4.8 Hz, J'= 1.2 Hz, $1H_{\alpha\text{-}O/N}$), 4.52 (m, $1H_{\alpha\text{-}N}$), 3.99/3.54 (AB, J= 6.6 Hz, 2H), 3.29/3.11 (AB, J= 8.4 Hz, 2H), 2.28-0.88 (m, 14H), 1.10 (s, 3H), 0.96 (s, 9H), 0.85 (s, 3H), 0.77 (s, 3H). ^{13}C-NMR (75 MHz, CD_3CN) δ= 153.4 (Cq), 151.5 (Cq), 132.9 (Cq), 130.1 (CH), 129.9 (2CH), 129.0 (CH), 127.2 (2CH), 123.4 (CH), 86.8 (CH), 86.2 (CH), 81.2 (CH_2), 76.9 (CH), 55.5 (CH), 49.5 (Cq), 48.3 (CH), 47.5 (Cq), 34.5 (CH_2), 34.1 (CH_2), 32.6 (Cq), 27.2 (CH_3), 26.8 (CH_2), 24.5 (CH_2), 23.4 (CH_2), 21.5 (CH_3), 21.3 (CH_3), 14.4 (CH_3), 12.1 (CH_3). MS (DIP-CI-CH_4) m/z= 564 (M+41, 9%), 552 (M+29,

27%), 524 (M+1, 38%), 342 (37%), 312 (7%), 284 (100%). Elemental analysis: Calculated for $C_{31}H_{45}N_3O_4$: C 71.10%, H 8.66%, N 8.02%; found: C 71.44%, H 8.99%, N 7.80%.

General procedure for the Diels-Alder cycloadditions of (E,E)- *1-alkoxy-1,3-octadienes, 7, with MA*

A solution of the dienophile (1.0-1.2 eq) in THF was added, under argon, to a solution of the diene (1 eq) in THF at 0°C. The mixture was then allowed to warm up to room temperature and was stirred until complete dissappearance of the diene (TLC). The solvent was then removed *in vacuo* to give the desired cycloadduct.

(±)-(r-1,c-2,c-3,c-6)-3-Butyl-6-(trans-2-phenylcyclohexyloxy)-4-cyclohexene-1,2-dicarboxylic anhydride, **9a**.

The above procedure was followed starting from 42 mg (0.148 mmol) of **7a**, 17 mg (0.177 mmol) of maleic anhydride and 0.4 mL of THF. The reaction took 48 h to completion and gave 56 mg (100%) of crude **9a** as a white solid in the form of a 93.5 : 6.5 mixture of diastereomers according to ^{1}H-NMR and HPLC. Major diastereomer: IR (KBr) 3060, 3020, 2920, 2850, 1850, 1775, 1605, 1440, 1260, 1175, 1145, 1115, 1090, 1070, 1035, 950, 750, 700 cm^{-1}. ^{1}H-NMR (300 MHz) δ= 7.40-7.15 (m, 5H), 5.49 (ddd, J= 9.5 Hz, J'= 3.8 Hz, J"= 2.1 Hz, $1H_{olef}$), 5.24 (dt, J= 9.9 Hz, J'= 3 Hz, $1H_{olef}$), 3.75 (m, $1H_{\alpha\text{-}O/C=C}$), 3.40 (td, J= 10.5 Hz, J'= 4.5 Hz, $1H_{\alpha\text{-}O}$), 3.35-3.13 (m, $2H_{\alpha\text{-}CO}$), 2.58 (m, $1H_{\alpha\text{-}Ph}$), 2.30-1.20 (m, 15H), 0.90 (t, J= 6.9 Hz, 3H). ^{13}C-NMR (75 MHz) δ= 170.8 (Cq), 169.2 (Cq), 144.0 (Cq), 132.4 (CH), 130.1 (CH), 128.1 (2CH), 128.0 (2CH), 126.3 (CH), 83.0 (CH), 70.2 (CH), 51.0 (CH), 45.6 (CH), 42.5 (CH), 34.4 (CH), 32.9 (CH_2), 32.6 (CH_2), 30.5 (CH_2), 30.0 (CH_2), 25.7 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 14.0 (CH_3). MS (DIP-EI) m/z= 354 (1%), 284 (2%), 223 (3%), 175 (41%), 159 (27%), 157 (79%), 129 (30%), 91 (100%).

The same experiment was ran in different solvents. Using acetonitrile, the reaction took 48 h to completion and gave **9a** as a 92.5 : 7.5 diastereomeric mixture according to ^{1}H-NMR and HPLC. In toluene, the reaction took 36 h to completion, **9a** being obtained as a 91.5 : 8.5 mixture of diastereomers according to ^{1}H-NMR and HPLC.

(r-1,c-2,c-3,c-6)-3-Butyl-6-(1-menthyloxy)-4-cyclohexene-1,2-dicarboxylic anhydride, **9b**.

The general procedure was followed starting from 51 mg (0.193 mmol) of **7b** in 0.2 mL of THF and 21 mg (0.20 mmol) of maleic anhydride in 0.3 mL of THF. The reaction took 48 h to completion, and gave 71 mg (100%) of crude **9b** as a solid in the form of a 58 : 42 mixture of diastereomers according to ^{1}H-NMR and ^{13}C-NMR. Major diastereomer: IR (KBr) 3040, 2960, 2940, 2870, 1855, 1785, 1460, 1380, 1260, 1180, 1115, 1095, 1045, 960, 945 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3CN) δ= 6.02-5.76 (m, $2H_{olef}$), 4.21 (m, $1H_{\alpha\text{-}O}$), 3.54 (dd, J= 9.3 Hz, J'= 6.6 Hz, $1H_{\alpha\text{-}CO}$), 3.47-3.39 (m, $1H_{\alpha\text{-}CO}$), 3.29 (td, J= 10.3 Hz, J'= 3.9 Hz, $1H_{\alpha\text{-}O}$), 2.50-0.80 (m, 25H), 0.77 (d, J= 6.9 Hz, 3H). ^{13}C-NMR (75 MHz, CD_3CN) δ= 173.1 (Cq), 171.2 (Cq), 133.5 (CH), 133.7 (CH), 80.6 (CH), 71.5 (CH), 49.5 (CH), 46.9 (CH), 43.8 (CH), 42.3 (CH_2), 35.4 (CH), 35.1 (CH_2), 32.2 (CH), 31.6 (CH_2), 30.7 (CH_2), 25.4 (CH), 23.5 (CH_2), 23.3 (CH_2), 22.6 (CH_3), 21.5 (CH_3), 16.1 (CH_3), 14.3 (CH_3). MS (DIP-CI-CH_4) m/z= 363 (M+1, 100%), 225 (59%), 139 (7%).

(r-1,c-2,c-3,c-6)-3-Butyl-6-[(1R,2S,5R)-8-phenylmenthyloxy]-4-cyclohexene-1,2-dicarboxylic anhydride, **9c**.

The general procedure was followed starting from 53 mg (0.156 mmol) of **7c**, 17 mg (0.17 mmol) of maleic anhydride and 0.5 mL of THF. The reaction took 55 h to completion, an gave 69 mg (100%) of **9c** as an oil (that crystallized on standing at 4°C) in the form of a 78 : 22 mixture of diastereomers according to ^{1}H-NMR and ^{13}C-NMR. Purification of the crude product by column chromatography on SiO_2, eluting with hexane/ether

85:15, gave 23 mg (33%) of **9c** as the same diastereomeric mixture. Major diastereomer: IR (film) 3085, 3055, 3020, 2960, 2920, 2870, 1855, 1780, 1640, 1605, 1500, 1460, 1375, 1255, 1195, 1100, 1040, 945, 850, 770, 705 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3CN) δ= 7.42-7.15 (m, 5H), 5.91 (dt, J= 9.9 Hz, J'= 2.7 Hz, $1H_{olef}$), 5.79 (dt, J= 9.9 Hz, J'= 2.7 Hz, $1H_{olef}$), 4.24 (m, $1H_{\alpha\text{-}O}$), 3.68-3.38 (m, $2H_{\alpha\text{-}CO}$ + $1H_{\alpha\text{-}O}$), 2.40-0.70 (m, 15H), 1.43 (s, 3H), 1.36 (s, 3H), 0.98 (t, 3H), 0.92 (d, J= 6.6 Hz, 3H). ^{13}C-RMN (75 MHz, CD_3CN) δ= 172.9 (Cq), 170.6 (Cq), 152.5 (Cq), 133.3 (CH), 132.1 (CH), 128.7 (2CH), 126.7 (2CH), 125.9 (CH), 81.6 (CH), 70.8 (CH), 52.8 (CH), 47.7 (CH), 44.2 (CH), 42.1 (CH_2), 41.3 (Cq), 35.4 (CH), 35.2 (CH_2), 32.1 (CH), 31.3 (CH_2), 31.3 (CH_3), 30.6 (CH_2), 28.2 (CH_2), 24.2 (CH_3), 23.2 (CH_2), 22.43 (CH_3), 14.2 (CH_3). MS (DIP-CI-CH_4) m/z= 479 (M+41, 6%), 467 (M+29, 6%), 439 (M+1, 6%), 265 (12%), 253 (23%), 243 (8%), 225 (91%), 215 (100%).

(r-1,c-2,c-3,c-6)-3-Butyl-6-[(1R,2S,3R,4S)-3-(2,2-dimethyl-propoxy)-1,7,7-trimethylbicyclo[2.2.1]heptyl-2-oxy]-4-cyclohexene-1,2-dicarboxylic anhydride, 9d.

The general procedure was followed starting from 51 mg (0.147 mmol) of **7d**, 16 mg (0.162 mmol) of maleic anhydride and 0.4 mL of THF. The reaction took 46 h to completion (reaction progress was very slow during the last 20 h), and gave 59 mg (90%) of **9d** as an oil in the form of a 83.5 : 16.5 mixture of diastereomers according to ^{1}H and ^{13}C-NMR. Major diastereomer: IR (film) 3040, 2940, 2860, 1850, 1775, 1690, 1630, 1455, 1390, 1360, 1190, 1140, 1100, 940 cm^{-1}. ^{1}H-NMR (300 MHz) δ= 5.96 (dt, J= 9.6 Hz, J'= 3.0 Hz, $1H_{olef}$), 5.71 (dt, J= 9.6 Hz, J'= 3.0 Hz, $1H_{olef}$), 4.41 (m, $1H_{\alpha\text{-}O}$), 3.84 (dd, J= 9 Hz, J'= 7.8 Hz, $1H_{\alpha\text{-}CO}$), 3.73/3.47 (AB, J= 6.9 Hz, 2H), 3.40 (dd, J= 9.15 Hz, J'= 6.0 Hz, $1H_{\alpha\text{-}CO}$), 3.25/2.92 (AB, J= 8.4 Hz, 2H), 2.20-0.80 (m, 15H), 1.15 (s, 3H), 0.95 (s, 3H), 0.83 (s, 9H), 0.79 (s, 3H). ^{13}C-NMR (75 MHz) δ= 173.3 (Cq), 170.6 (Cq), 134.3 (CH), 132.2 (CH), 86.3 (CH), 85.8 (CH), 81.1 (CH_2), 73.5 (CH), 49.7 (Cq), 47.8 (CH), 47.5 (Cq), 45.1 (CH), 43.8 (CH), 35.9 (CH), 34.7 (CH_2), 32.5 (Cq), 31.3 (CH_2), 30.7 (CH_2), 27.1 (CH_3), 24.5 (CH_2), 23.1 (CH_2), 21.6 (CH_3), 21.3 (CH_3), 14.3 (CH_3), 12.0 (CH_3). MS (DIP-CI-CH_4) m/z= 487 (M+41, 3%), 475 (M+29, 5%), 447 (M+1, 100%).

The same experiment was ran in acetonitrile at 0°C. The reaction took 72 h to completion (reaction progress was very slow during the last 20 h) and gave **9d** as a 94.5 : 5.5 mixture of diastereomers (89% d.e.) as determined by ^{1}H and ^{13}C-NMR.

ACKNOWLEDGEMENTS

Financial support from CIRIT-CICYT (QFN93-4407), from CIRIT (GRQ93-1083, SGR96-13) and from DGICYT (PB95-0265) is gratefully acknowledged. Marina Virgili thanks CIRIT for a fellowship.

REFERENCES AND NOTES

1. For sugar-derived 1-alkoxy-1,3-butadienes, see: a) David, S.; Lubineau, A.; Thieffry, A. *Tetrahedron* **1978**, *34*, 299-304. b) David, S.; Eustache, J.; Lubineau, A. *J. Chem. Soc., Perkin Trans. I* **1979**, 1795-1798. c) Lubineau, A.; Queneau, Y. *J. Org. Chem.* **1987**, *52*, 1001-1007. d) Larsen, D.S.; Stoodley, R.J. *J. Chem. Soc. Perkin Trans. I* **1989**, 1841-1852.

2. For 1-alkoxy-3-trimethylsiloxy-1,3-butadienes, see: a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968-6969. b) Gupta, R.C.; Harland, P.A.; Stoodley, R.J. *J. Chem. Soc, Chem. Commun.* **1983**, 754-756. c) Danishefsky, S.; Bednarski, M.; Izawa, T.; Maring, C. *J. Org. Chem.* **1984**, *49*, 2290-2292. d) Gupta, R.C.; Harland, P.A.; Stoodley, R.J. *Tetrahedron* **1984**, *40*, 4657-4567. e) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060-7067. f) Gupta, R.C; Raynor, C.M.; Stoodley, R.J.; Slawin, A.M.Z.; Williams, D.J. *J. Chem. Soc. Perkin Trans. I* **1988**, 1773-1785. g) Gupta, R.C; Larsen, R.J.; Stoodley, R.J.; Slawin, A.M.Z.; Williams, D.J. *J. Chem. Soc. Perkin Trans. I* **1989**, 739-749. h) Larsen, D.S.; Stoodley, R.J. *J. Chem. Soc. Perkin Trans. I* **1990**, 1339-1352. i) Beagley, B.; Larsen, D.S.; Pritchard, R.G.; Stoodley, R.J. *J. Chem. Soc. Perkin Trans. I* **1990**, 3113-3127. j) Lowe, R.F.; Stoodley, R.J. *Tetrahedron Lett.* **1994**, *35*, 6351-6354.

3. For 2-methyl substituted 1-alkoxy-1,3-butadienes, see: a) Thiem, R.; Rotscheidt, K.; Breitmaier, E. *Synthesis* **1989**, 836-843. b) Rieger, R.; Breitmaier, E. *Synthesis* **1990**, 697-701. c) Lehmler, H.-J.; Nieger, M.; Breitmaier, E. *Synthesis* **1996**, 105-110.

4 For other types of substituted 1-alkoxy-1,3-butadienes, see reference 1d, as well as: a) Aspinall, I.H.; Cowley, P.M.; Mitchell, G.; Stoodley, R.J. *J. Chem. Soc, Chem. Commun.* **1993**, 1179-1180. b) Aspinall, I.H.; Cowley, P.M.; Stoodley, R.J. *Tetrahedron Lett.* **1994**, *35*, 3397-3400. c) Cowley, P.M.; Stoodley, R.J. *Tetrahedron Lett.* **1994**, *35*, 7853-7856.

5. For an exception, see ref. 1a-c.

6. Alkoxyacetylenes containing very bulky alkoxy groups are readily available from either ethyl vinyl ether or trichloroethylene: a) M.A. Pericàs, F. Serratosa, E. Valentí. *Tetrahedron* **1987**, *43*, 2311-2316. b) A. Moyano, F. Charbonnier, A.E. Greene. *J. Org. Chem.* **1987**, *52*, 2919-2922.

7. Virgili, M.; Moyano, A.; Pericàs, M.A.; Riera, A., Manuscript in preparation.

8. Castro, J.; Sörensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericàs, M.A.; Greene, A.E. *J. Am. Chem. Soc.* **1990**, *112*, 9388-9389.

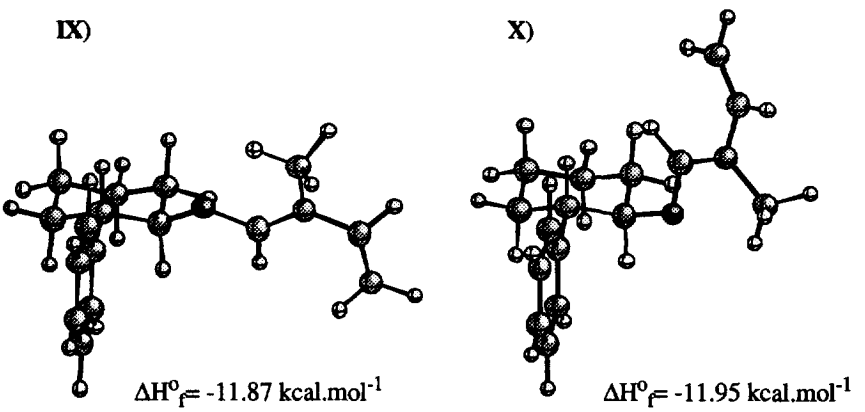
9. Solà, Ll.; Castro, J.; Moyano, A.; Pericàs, M.A.; Riera, A. *Tetrahedron Lett.* **1992**, *33*, 2863-2366.

10. Schwartz, A.; Madan, P.; Whitesell, J.K.; Lawrence, R.M. *Org. Synth.* **1990**, *69*, 1-9.

11. Sörensen, H.; Greene, A.E. *Tetrahedron Lett.* **1990**, *31*, 7597-7598.

12. A 84 : 16 mixture of diastereomers was obtained according to ^{1}H-NMR, ^{13}C-NMR and HPLC when the reaction was performed at room temperature

13. Breitmaier,[3a] on the basis of NOE experiments, has assumed that the analogous 2-methyl substituted diene preferentially exists in solution as a *s-trans* conformer and has subsequently assigned the configuration of the major diastereomers arising from the Diels-Alder reaction with MA and PTAD by assuming an endo attack to the more sterically free face of the diene in that conformer. We have now found that an AM1 based theoretical conformational analysis supports this hypothesis. However, the small value of the calculated energy differences between conformer **X** (*s-trans*) and conformer **IX** (*s-cis*) suggests the convenience of a more detailed analysis.



14. For a discussion of the Curtin-Hammett principle, see: Eliel, E.L.; Wilen, S.H.; Mander, L.N. Stereochemistry of Organic Compounds; John Wiley & Sons: New York, 1994; pp. 647-655.

15. Dewar, M.J.S.; Zoebisch, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909.

16. Dewar, M.J.S.; Olivella, S.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1986**, *108*, 5771-5779.

17. MacSpartan Plus, version 1.0, Wavefunction, Inc., 18401 Von Karman, Suite 370, Irvine, California, 92612.

18. For a recent theoretical account on the Diels-Alder reactions of (*E*)-1-amino- and (*E*)-1-hydroxy-1,3-butadiene with cyanoetylenes, see: Sustmann, R.; Sicking, W. *J. Am. Chem. Soc.* **1996**, *118*, 12562-12571.

19. Negishi, E.; Van Horn, D.E. *J. Am. Chem. Soc.* **1977**, *99*, 3168-3170.

20. Hegedus, L.S.; Toro, J.L.; Miles, W.H.; Harrington, P.J. *J. Org. Chem.* **1987**, *52*, 3319-3322.

21. Okukado, N.; Van Horn, D.E.; Klima, W.L.; Negishi, E. *Tetrahedron Lett.* **1978**, *19*, 1027-1030.

22. Ort, O. *Org. Synth.* **1987**, *62*, 203-214.

23. Oppolzer, W.; Chapuis, C.; Dao, G.M.; Reichlin, D.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4781-4784.

24. A controlled decomposition of the vinylcopper reagent generated from these zirconaolefins affords (*E,E*)-1,4-dialkoxy-1,3-butadienes: Virgili, M.; Moyano, A.; Pericàs, M.A.; Riera, A. Submitted for publication.

25. Buchwald, S.L.; LaMaire, S.J.; Nielsen, R.B.; Watson, B.T.; King, S.M. *Tetrahedron Lett.* **1987**, *34*, 3895-3898.

(*Received in UK* 1 *July* 1997; *accepted* 24 *July* 1997)