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π-Facial Diastereoselection in [4+2]-Cycloadditions of 3,4-Epoxy-2-methyleneoxolanes with Oxadienes: A Short Synthesis of Spiroketals.

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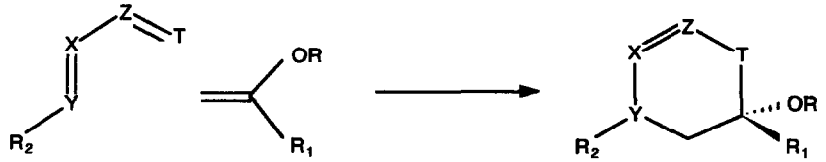
Abstract: Hetero Diels-Alder reaction of oxadienes with 3,4-epoxy-2-methyleneoxolanes gave the corresponding 3,4-epoxy-1,6-dioxaspiro[4, 5]dec-7-enes with high stereoselectivity. Good yields of adducts were obtained in the presence of mild Lewis acids, such as zinc or stannous chloride. The spiroketal adducts have been transformed chemio- and stereospecifically by either hydrogenation, hydride reduction or acid catalyzed isomerization. The stereochemical outcome of the cycloadditions has been investigated. The spiroketal adducts always result from an oxadiene addition anti relative to the allylic epoxy substituent. When the oxadiene is substituted suitably as in crotonaldehyde, we demonstrated that the cycloaddition is totally endo selective relative to the enol ether function. *Ab initio* calculations suggested that 3,4-epoxy-2-methyleneoxolane and 3,4-epoxy-3-methyl-2-methyleneoxolane adopt envelope conformations with the oxygen atom of the oxolane moiety pointing toward the epoxide ring. No significant distortion from planarity was calculated for the exocyclic double bond of these dienophiles.

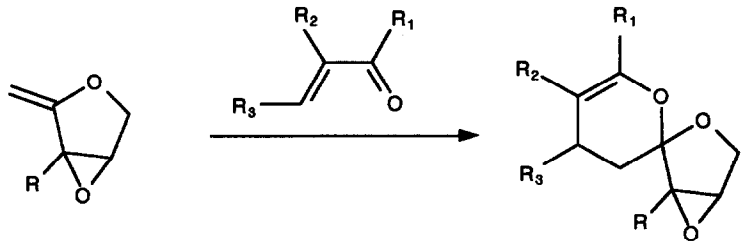
INTRODUCTION

Enol ethers are very reactive species.[1] Among the numerous known reactions of enol ethers, Diels-Alder type cycloadditions provide an unique access to highly functionnalized heterocycles (Scheme 1).[2] Despite the high potentiel in total synthesis of the spirocyclic compounds theoretically available through such cycloadditions, Diels-Alder reactions with α-methylene heterocycles are nearly ignored. Only a few attemps have been reported.[3] This lack of interest is mainly due to the difficulties associated with the formation of α-methylene heterocycles.[4]



Scheme 1

As one of us (P. P.) found recently a mild and easy access to α-methylene heterocycles,[5] we decided to investigate the dienophilic properties of such heterocycles. With spiroketals targets[6] in mind, we first focused on the reaction of 3,4-epoxy-2-methyleneoxolanes with acrolein-like dienes (Scheme 2).[7]



Scheme 2

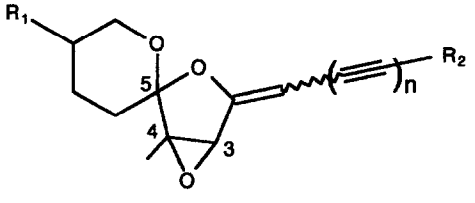
The oxirane substituent in these particular dienophiles would be of interest for the following reasons:

-In the pioneering work of Ireland et al.[3a-c] on [4+2] cycloadditions of 2-methylene oxolane and oxane and a few derivatives with acrolein-like dienes, the main problem encountered was the facile migration of the exocyclic double bond and the poor reactivity of that double bond.[3b] We reasoned that the oxirane ring in 3,4-epoxy-2-methyleneoxolanes could prevent such double bond migration and might enhance the double bond reactivity for electronic reasons.

-An other advantage of the oxirane ring could be taken from its chirality which should impart sufficient perturbation to induce diastereofacial discrimination. We therefore anticipated some face selectivity during the Diels-Alder process.

-The oxirane ring of the expected cycloadducts obtained,[8] as well as the endocyclic enol ether function[1] could be modified under mild conditions These functional groups should therefore offer opportunities for the synthesis of stereodefined spiroketals with complex structures.

Furthermore, the epoxyspiroketal system available through the planned cycloadditions is the central unit of a family of natural products isolated from the plant genus Artemisia (Scheme 3).[9] These cycloadditions could thus become a potential approach to this kind of natural compounds.



3S, 4R, 5S n = 2 $R_1 = H$ $R_2 = Me$

3S, 4R, 5R n = 2 $R_1 = H$ $R_2 = Me$

$R_1 = OAc$ $R_2 = Me$

$R_1 = OPiv$ $R_2 = Me$

Scheme 3

In order to approach some understanding of the role of the oxirane moiety during the cycloaddition process, geometry optimizations of the starting 2-methyleneoxolanes have been calculated by *ab initio* techniques. Prior to the present study, neither experimental nor theoretical evidence was available concerning the role of an allylic oxirane during [4+2] cycloadditions.

RESULTS

Cycloaddition of 3,4-epoxy-2-methyleneoxolanes to oxadienes

The search for optimal cycloaddition conditions was performed with 3,4-epoxy-3-methyl-2-methylene oxolane (**1**), obtained readily from the commercially available *Z*-3-methyl-2-penten-4-yn-1-ol by mcpba epoxidation followed by intramolecular heterocyclization catalyzed by silver ion.[5] The demethylated analogue 3,4-epoxy-2-methyleneoxolane (**2**) was obtained in the same way from the corresponding acetylenic epoxyalcohol[10] prepared from the monoprotected *cis* 2,3-epoxybutan-1,4-diol.[11]

Acrolein, known to be the most reactive oxadiene,[2] was first used as diene. Under the described cycloaddition conditions (neat reagents stirred at room temperature),[3a] the reaction between **1** and acrolein proceeded very slowly. Degradation of the sensitive 3,4-epoxy-2-methyleneoxolane and acrolein polymerization were responsible for modest yields (40-50%, Table 1, entries 1-2). However only one cycloadduct was isolated

Table 1: Cycloaddition of 3,4-epoxy-2-methyleneoxolane to oxadienes [a]

	Dienophile equivalents	Diene	Conditions solvent	catalyst[b]	Time	Yield[c]	Adduct
1	1-1		neat	-	8d	45 %	
2	1-10		neat	-	11d	52 %	
3	1-3		neat	$Yb(fod)_3$	4d	21%[d]	
4	1-5		$CDCl_3$	-	8d	10 %[d]	
5	1-3		PhH	-	8d	10 %[d]	
6	1-3		PhH	$SnCl_2$	2d	70 %	
7	1-3		PhH	$ZnCl_2$	18h	84 %	
8	1-3		neat	$Yb(fod)_3$	4,5d	17 %[d]	
9	1-3		PhH	$ZnCl_2$	2d	30 %	
10	1-3		THF	$ZnCl_2$	2d	53 %	
11	1-3		THF (60°)	$ZnCl_2$	2h	26 %[e]	
12	1-3		PhH	$ZnCl_2$	2d	37 %	
13	1-3		THF	$ZnCl_2$	3d	63 %[f]	
14	1-3		PhH	$ZnCl_2$	2d	60 %	
15	1-3		THF	$ZnCl_2$	2d	70 %	

a) except when noted, all cycloadditions were run at room temperature; b) the amount of catalyst ranges from 0,05 eq. (Yb) to 0,1-0,2 eq. (Sn, Zn); c) Yields refer to pure adducts isolated after column chromatography; d) **1** was the main product recovered; e) degradation and polymerization occurred; f) the cyclodimer of the oxadiene was also isolated (17%).

from the reaction mixture.[12] ^1H and ^{13}C NMR clearly showed (*vide infra*) the presence of a single adduct. In solvent, polar or not, the cycloaddition was almost suppressed (entries 4-5).

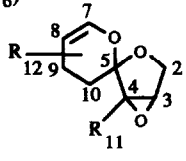
As expected, addition of catalytic amounts of Lewis acid in solvent increased the reaction rate. Since 3,4-epoxy-2-methyleneoxolanes are sensitive compounds, extensive degradation occured with strong Lewis acids. We found zinc chloride (10 to 20 mole %) to be the best compromise between activation and degradation (entries 7). Stannous chloride was almost as effective as zinc chloride (entry 6). Milder catalysts based on lanthanide complexes[13] proved to be ineffective (entries 3 vs 1). With less reactive heterodienes such as crotonaldehyde or methyl vinyl ketone, the same trends were observed, but the yields were lower (entries 8-10). As for acrolein, only one adduct was observed when crotonaldehyde and methyl vinyl ketone were reacted with **1** (entries 8-13). With these less reactive heterodienes, THF proved to be a better solvent than benzene (entry 10 vs 9 and 13 vs 12). This solvent effect could be explained by the greater solubility of zinc chloride in the coordinating solvent (zinc chloride was almost insoluble in benzene). High temperature was deleterious for the reaction. Raising the temperature increased reagent degradation and eventually lowered the cycloaddition yield (entry 11 vs 10).

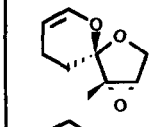
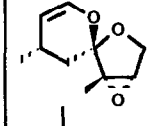
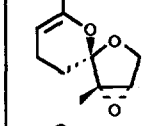
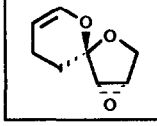
Surprisingly, the non-methylated derivative **2** proved to be slightly less reactive than **1** (entry 14 vs 7). In this case also, the use of THF rather than benzene as solvent allowed for an increase of the yield (entry 15 vs 14).

Structure and stereochemistry of the adducts

The adduct structures were determined by ^1H and ^{13}C NMR. In each case, the presence of only one diastereoisomer was immediately inferred from the NMR spectra. The ^{13}C NMR spectra exhibited signals characteristic of a ketal at 99±5 ppm and of a dihydropyran ring with 2 olefinic carbons at δ_C = 102±5 and 144±4 ppm. The dihydropyran unit was confirmed in the ^1H NMR spectra that displayed 2 vinyl protons at δ_H = 6.2 and 4.6 ppm. The assignments of all proton and carbon signals were obtained by 2D NMR experiments and are displayed in tables 2 and 3.

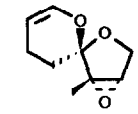
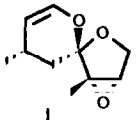
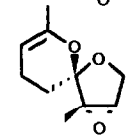
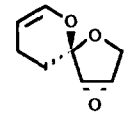
Table 2: ^{1} H NMR signal assignments[a] (δ_H in ppm, internal reference; TMS, solvent: C_6D_6)

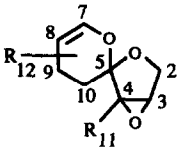


Adduct		Protons											
		H2a	H2e	H3	H4	H7	H8	H9a	H9e	H10a	H10e	H11	H12
	3	3.66	3.60	3.25	-	6.25	4.71	2.32	1.78	1.68	1.98	1.35	-
	4	3.64	3.51	2.92	-	6.21	4.63	-	2.14	2.02	1.83	1.33	1.14
	5	3.68	3.58	3.03	-	-	4.55	2.39	1.82	1.64	2.02	1.38	1.73
	6	3.71	3.52	3.32	3.07	6.24	4.67	2.20	1.78	1.80	2.06	-	-

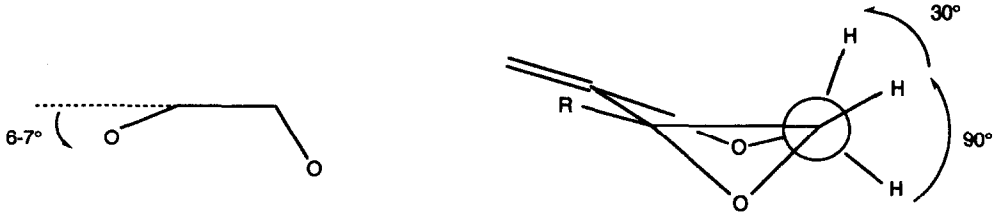
a) the pseudoaxial (a) and pseudoequatorial (e) stereochemistries were deduced from LIS experiments (*vide infra*)

Table 3: ^{13}C NMR signal assignments (δ_C in ppm, internal reference; TMS, solvent: C_6D_6)

Adduct	Carbons									
	C2	C3	C4	C5	C7	C8	C9	C10	C11	C12
 3	65.87	60.30	64.28	103.20	141.10	101.80	16.60	24.31	11.63	-
 4	66.09	60.09	64.77	104.00	140.20	107.50	24.11	31.66	12.03	21.53
 5	65.82	60.46	65.02	94.36	148.00	96.72	17.54	23.96	11.75	20.23
 6	66.77	53.94	57.59	102.70	141.10	101.70	17.38	26.08	-	-

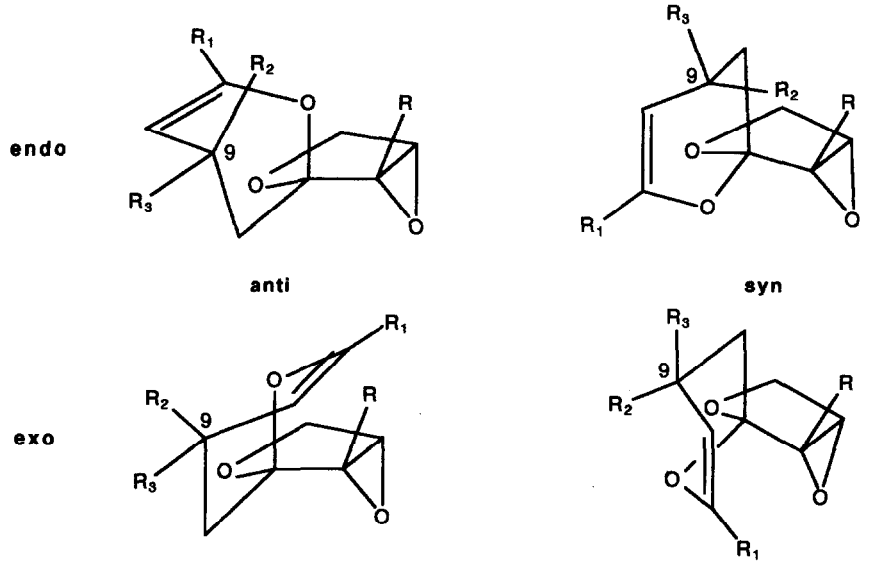


An interesting feature in the NMR spectra of the adducts was the conservation of the particular coupling pattern of the oxirane-oxolane system. In the starting 3,4-epoxy-3-methyl-2-methylene oxolane **1**, the epoxide proton (H3 in the spiroketal numbering) exhibited a very small coupling (1.1 Hz) with only one of the two adjacent protons. From the Karplus equation and from the lowering effect of an electronegative substituent on coupling constants especially effective in antiperiplanar arrangement,[14] the coupling pattern observed indicated a quasi orthogonal arrangement of the two rings with the oxolane oxygen end lying out of the plane toward the oxirane moiety (Scheme 4). This spatial arrangement was confirmed by *ab initio* calculations (*vide infra*).



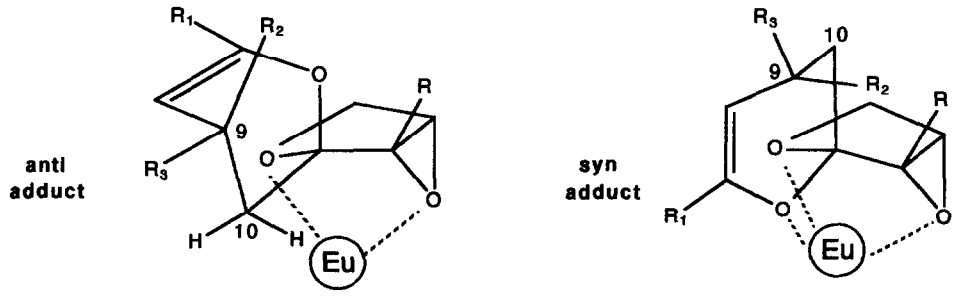
Scheme 4

As the same coupling pattern and almost the same chemicals shifts were observed for all adducts, the relative configuration of the oxolane-oxirane system must have been preserved. The third heterocyclic ring in the adducts could have two orientations, one resulting from an oxadiene addition *anti* relative to the oxirane ring and the other from a *syn* addition (Scheme 5). In these two approaches, exo and endo cycloadditions give the same adduct except when crotonaldehyde is used as oxadiene (Scheme 5, R_2=H, R_3=Me).



Scheme 5: the four possible stereochemical outcomes from the cycloaddition of oxadienes to **1** and **2**

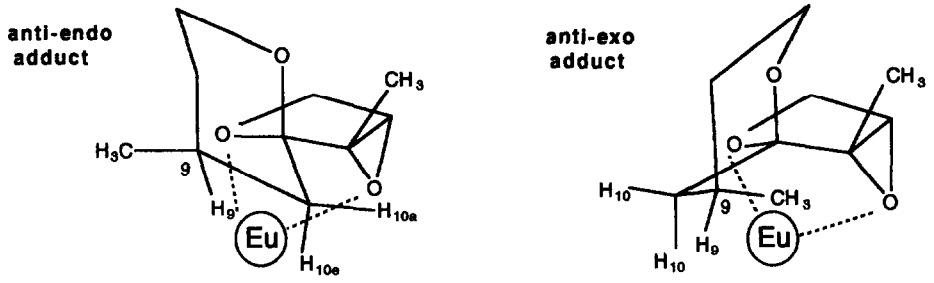
The relative configurations of adducts **3-5** were established by comparative lanthanide-induced shifting (LIS) of their ^{1}H NMR spectra, using increasing amounts of Eu(fod)$_3$. Due to the presence of three oxygen atoms in the adducts, many complexation sites were equally possible *a priori*. We therefore realized preliminary LIS experiments on the starting 3,4-epoxy-3-methyl-2-methyleneoxolane **1**. We found that the europium cation was chelated by both oxygens of the three and five membered rings. This result corroborated well with the conformation of **1** deduced from ^{1}H NMR coupling constants (*vide supra*) and *ab initio* calculations (*vide infra*). In adducts **3-5**, the same chelation was preserved as confirmed by the observation that the largest LIS were associated with the oxolane and oxirane protons. The methylene protons (H10) of the dihydropyran (DHP) ring were also strongly affected, but almost no effect was observed on the vinyl protons. These LIS effects indicated that no complexation occurred with the DHP oxygen atom. These results suggested an *anti* configuration of the adducts where the DHP oxygen center is far from the oxirane moiety (Scheme 6, *anti* diastereoisomer).



Scheme 6: possible Europium complexes for *anti* and *syn* adducts.

We chose crotonaldehyde as an oxadiene to get more insight into the stereochemical course of the cycloaddition. The methyl group in crotonaldehyde can act as a reporter group since the relative configuration of the carbon center bearing that methyl group, C9 in the adduct, depends on the exo or endo approach of the heterodiene (see Scheme 5).

Due to the ring distortion induced by the double bond in **4**, the C9 configuration can not be determined from the ^1H NMR coupling constants. However, ^1H NMR spectra of the saturated analogue **7**, obtained in high yield by Pd/C catalyzed hydrogenation of **4** (see Scheme 8), corresponded to chair conformation of the 6-membered ring and indicated an axial position for the methyl group derived from crotonaldehyde. Indeed, the proton H9, adjacent to this methyl group, exhibited coupling constants, $J_{9e\text{-}10a}$ = 5.5 Hz and $J_{9e\text{-}8a}$ = 5.4 Hz , typical for an equatorial proton (Scheme 7). The relative stereochemistry of the adduct was still unclear since two diastereoisomers can have a conformation with an axial methyl substituent at C9: one resulting from an *endo* mode of addition relative to the oxolane etheral unit, stabilized by two stereoelectronic (anomeric) effects,[15] and one resulting from the *exo* mode of addition, stabilized by only one stereoelectronic effect. We again used LIS experiments to establish the stereochemistry of the adduct. We reasoned that for the *exo* diasteroisomer, europium complexation on the "bottom" face should give rise to appreciable effect on the Me-C9 signal while in the *endo* isomer, this Me-C9 group should remain almost unaffected (Scheme 7).

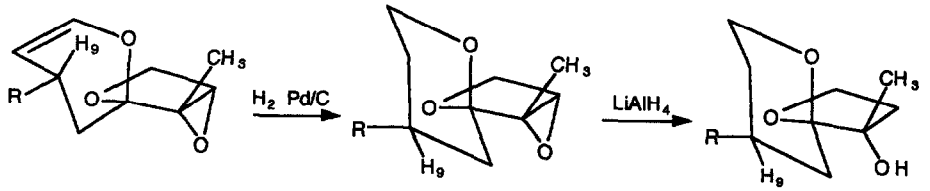


Scheme 7: possible relative conformations of **7**.

The LIS results are displayed graphically in Figure 1 using the Bouquant's coordinates.[16] Large europium effects were observed for the protons of oxirane and oxolane rings and also for H10, especially H10e. The methyl group at C9 was almost unaffected and only sufferred from a slight shift with a magnitude comparable to the least affected H7 and H8 protons. Therefore these LIS values are in agreement with a C9 configuration resulting from an *anti-endo* mode of addition (Scheme 7). This was confirmed by the structure of the products of reduction of **3** and **4**.

Modification of the adducts

Catalytic hydrogenation in methanol of adducts **3** and **4** gave the saturated 3,4-epoxyspiro[4-5] bicyclodecanes **7** and **8**, respectively, in high yield. These compounds can be further reduced by lithium aluminium hydride into **9** and **10**, respectively. In both cases, the oxirane ring was cleanly and regiospecifically opened at the less hindered position (Scheme 8). ^1H and ^{13}C NMR clearly established the conservation of the spiroketal system. In the case of **10**, 2D NMR and decoupling experiments confirmed the axial position of the methyl group at C9, thus confirming the relative configuration of adduct **4**.



3, R=H
4, R=Me

7, R=H
8, R=Me

9, R=H
10, R=Me

Scheme 8

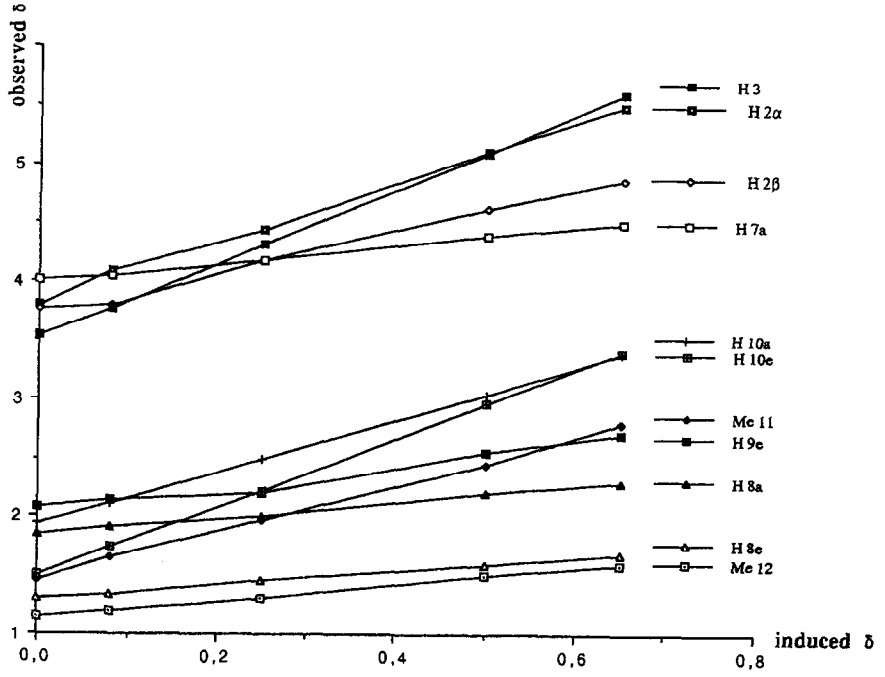
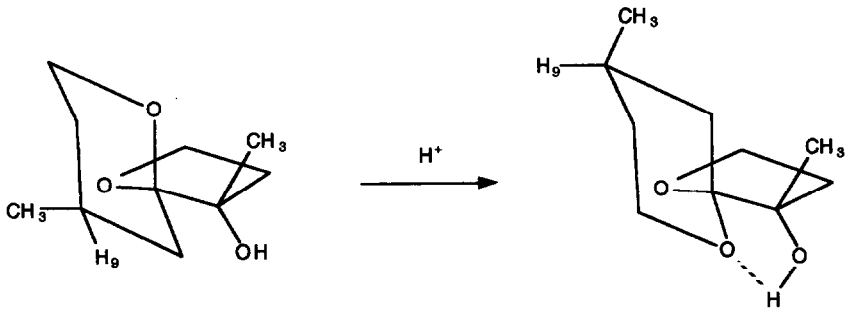


Figure 1: LIS values obtained with **10**, plotted as observed shifts against induced shifts, with H7e as the reference proton (see ref [16] for definitions)

Under slightly acidic conditions (CF_3COOH-0.01 equiv.-in PhH), we found that the spiroketal alcohol **10** was isomerized to a less polar alcohol **11** (Rf 0.78 in petroleum ether-ethyl acetate 90-10, compared to Rf 0.68 for **10**). NMR spectra showed the conservation of the spiroketal structure, the major modification was due to the methyl group at C9 which was now equatorial. IR spectra of this isomeric alcohol at various

concentrations established the presence of an intramolecularly bonded OH group. These results demonstrated that traces of acid are able to catalyze equilibration of the spiroketal alcohol **10**. This equilibration is driven toward the most stable alcohol stabilized by intramolecular hydrogen bonding (Scheme 9). Precedents for such isomerisation have been reported for instance in a synthesis of monensin and analogues.[17] Similar behaviour was also observed in dispiroketal systems such as naracin.[18]



10 **11**

Scheme 9.

DISCUSSION

The cycloadditions of 2-methylene-3,4-epoxyoxolanes with oxadienes showed a total preference for an addition *anti* relative to the allylic epoxy substituent. When the oxadiene is substituted as in crotonaldehyde, the cycloaddition course is totally *endo* selective relative to the enol ether function. *Endo* stereochemical course is a common feature in Diels-Alder reactions (Alder rule) which is attributed to secondary orbitals overlaps.[19] The lone pair orbitals in oxadienes usually reinforce secondary orbitals interactions and thus the *endo* selectivity.[2,20] Unfortunately, no comparison concerning the mode of cycloaddition can be drawn from the cycloadditions of α-methylene heterocycles reported so far,[3a,c,e] since the oxadienes used in these cases did not bear an appropriate substituent. Nevertheless, *endo* modes are usually preferred in [4+2] cycloadditions involving endocyclic enolethers as dienophiles.[21] Our work thus demonstrated that 2-methylene-3,4-epoxyoxolanes follow the general *endo* rule with high selectivity.

Isomerization experiments as well as molecular mechanic calculations have shown that the compounds we obtained always correspond to the most stable isomers. Due to its Lewis acid properties, the zinc catalyst we used might have catalyzed an *in situ* isomerization to the most stable spiroketal. However, since the same adducts were obtained without catalyst (see Table 1), this equilibrating role of the catalyst appeared unlikely. The very high facial selectivity observed can, therefore, be attributed to a kinetic control due to the asymmetric nature of the dienophile.

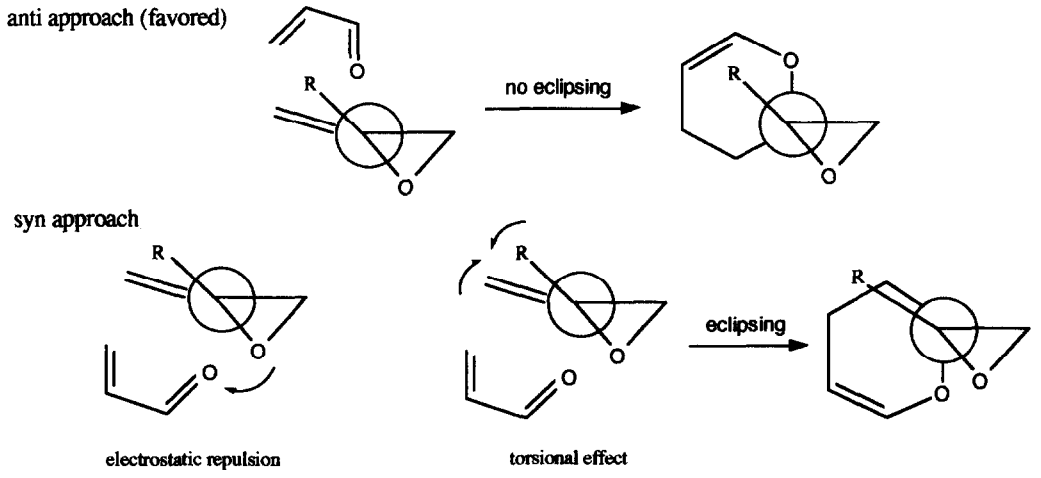
Asymmetric versions of the Diels-Alder reaction, with either asymmetric dienophiles or asymmetric dienes, are now widely used in organic synthesis.[22] A single stereogenic center in an allylic position of either a dienophile or a diene is known to exert a directing effect on diastereofacial selectivity. If a heteroatom is included in this allylic stereocenter, the directing effect is even more pronounced. Despite numerous experimental[23, 24] and theoretical[25] studies, the exact factors responsible for such diastereofacial selection are still imperfectly understood.

The complete diastereofacial selectivity observed in the cycloadditions of 2-methylene-3,4-epoxyoxolanes described here could be controlled by (Scheme 10):

- the anisotropy of the exocyclic methylene group, which can be expressed by the bending of the double bond,[26] *i. e.* a stereochemical control by the electronic structure of the dienophile;

-the staggering around forming bonds in the transition state as described by Houk and coworkers for related systems,[27] *i. e.* a stereochemical control by transition state structure;

-repulsive interactions between the oxygen atom of the approaching oxadiene and the epoxide oxygen atom, *i. e.* a stereochemical control by long range intermolecular recognition forces.



Scheme 10

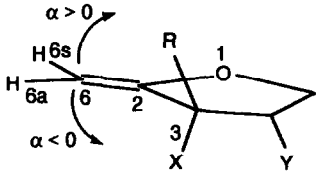
Geometries of the dienophiles

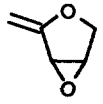
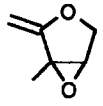
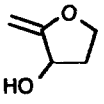
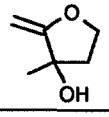
Due to the number and the size of the molecules studied, only the minimal basis set STO-3G was used in our *ab initio* molecular orbital calculations. This basis set successfully predicts double bond bending in bicyclic systems[28] although it usually gives angle values lower than the experimental ones.[29] The geometry of the 2-methylene-3,4-epoxyoxolanes **1** and **2** was fully optimized. To clarify the effect of the three membered rings and heteroatoms on the postulated bending of the exocyclic double bond, the analogues **12**, **13** and **14**, **15** were also calculated in which the epoxy group was replaced by a cyclopropyl and an hydroxyl group respectively (see Table 4). Calculated values of the angle α between the plane defined by the atoms O_1-C_2-C_3 and the double bond, of the angle β defined as the dihedral angle between the H_{6s}-C_6-C_2 plane and the H_{6a}-C_6-C_2 plane, and of the angle γ defined as the dihedral angle between the O_1-C_2-C_6 plane and the C_6-C_2-C_3 plane are reported in Table 4. A negative value for angle α corresponds to a double bond bending toward the three-membered ring or the hydroxyl group.

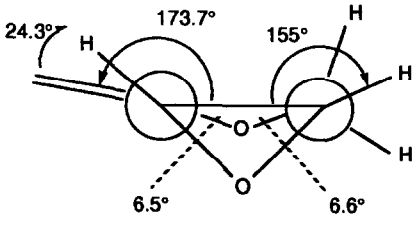
The results of Table 4 show a very small bending of the exocyclic double bond compared with the more pronounced bending of the norbornene double bond.[29] Therefore we cannot attribute the high face differentiation observed to the non-planarity of the exocyclic double bond in dienophiles **1** and **2**.

These calculations also suggest that the important changes in the geometry of the oxolane ring due to the nature of the 3,4-group (epoxide, cyclopropyl or hydroxyl group) do not affect significantly the degree of bending of the exocyclic double bond. Only slight angle modifications occur when the hydrogen atom in position 3 was replaced by a bulkier methyl group (Schemes 11 and 12). Interestingly, the oxolanes **1**, **2**, **12-15** were calculated to adopt envelope conformations in which the oxygen atom of the oxolane moiety is poiting toward the three-membered ring (**1**, **2**, **12-13**) or the alcoholic moiety (**14**, **15**).

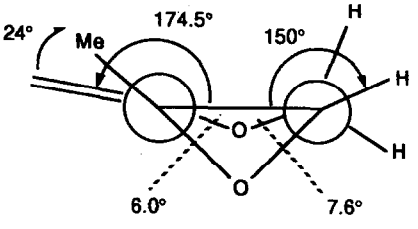
Table 4: calculated angles of the exocyclic double bond in 2-methyleneoxolanes



		α	β (H–C–H)	γ (O^1–C^2–C^3)
1		0.2	179.7	179.8
2		0.4	179.6	179.5
12		0.6	179.6	179.0
13		0.7	179.9	178.1
14		- 0.6	179.9	179.9
15		- 0.1	179.9	179.8

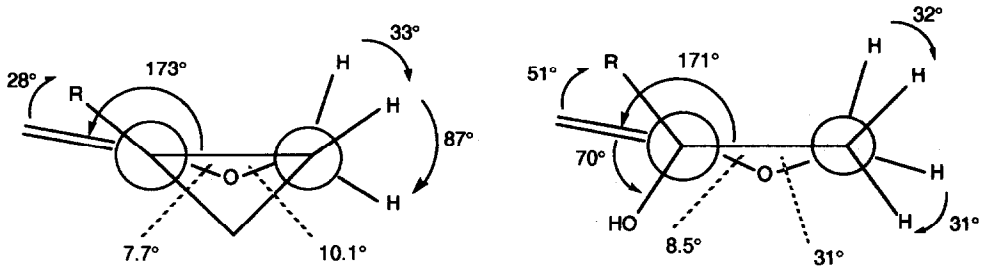


2



1

Scheme 11



R=H 12
R=Me 13

R=H 14
R=Me 15

Scheme 12

This study leaves us with the hypothesis that the *anti* selectivity observed for the [4+2] cycloadditions of oxadienes to **1** and **2** is due to the fact that this mode of reaction suffer less than the *syn* approach from electrostatic repulsion between the oxadienes and the oxygen centres of both the epoxide and oxolane moiety.[30] An alternative explanation could be that the *anti* approach avoids eclipsing in the transition state that cannot be avoided in a *syn* mode of addition.[29]

CONCLUSION

The above results constitute, to the best of our knowledge, the first experimental evidences of [4+2] cycloadditions between 2-methylene-3,4-epoxyoxolanes and heterodienes. With acrolein-like dienes, the expected adducts, 3,4-epoxy-1,6-dioxaspiro[4,5]dec-7-enes, were obtained in good yields in the presence of mild Lewis acid catalysts such as zinc or stannous chloride. The α-methylene heterocycles behave as efficient dienophiles when appropriately substituted, in opposition with previous results.[3b-d] The presence of an allylic substituent brings forward enough stability to the exocyclic double bond and allows for that double bond to react. [31]

The allylic epoxy substituent in the 3,4-epoxy-2-methyleneoxolanes investigated here renders these dienophiles dissymmetric in nature and is responsible for the exceptionally high *anti* face selectivity observed in these particular dienophiles during hetero Diels-Alder reactions.

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EXPERIMENTAL SECTION

General remarks: Melting points are uncorrected. IR spectra were recorded on a Philips SP3-300 infra-red spectrophotometer. NMR spectra were recorded with a Bruker AC-300 spectrometer at 300 MHz for ^1H and 75.5 MHz for ^{13}C or with a Bruker AC-250 spectrometer at 250 MHz for ^1H and 62.9 MHz for ^{13}C. ^1H NMR chemical shifts are expressed in parts per million downfield relative to internal tetramethylsilane ($\delta = 0$). Splitting patterns are assigned as: s, singlet; d, doublet; t, triplet; q, quartet; sext, sextet, m, multiplet. ^{13}C NMR are recorded using the central peak of the $CDCl_3$ signal as the internal standard ($\delta = 77.00$) or the central peak of the C_6D_6 signal as the internal standard ($\delta = 128.00$). Mass spectra were recorded on a JEOL D300 mass spectrometer at 70 ev. All reactions were monitored by thin-layer chromatography using 0.25 mm E. Merck silica gel plates (60 F_{254}). Flash column chromatography was performed on silica gel Merck 60 (particle size 0.040-0.063 mm). THF was distilled from Na/benzophenone; and C_6H_6 were distilled from CaH_2.

General procedure for the cycloadditions of 3,4-epoxy-2-methyleneoxolanes with oxadienes:

To a stirred solution of 3,4-epoxy-2-methyleneoxolane **1**, **2** (9.6 mmol, 1 eq.) in benzene or THF (8 ml), were successively added at room temperature the oxadiene (28.8 mmol, 3 eq.) and zinc chloride (262 mg, 1.9 mmol, 0.2 eq.). The mixture was stirred at room temperature until TLC (Petroleum Ether, PE, - Ethyl Acetate, EA, 90-10) showed the disappearance of the starting 3,4-epoxy-2-methyleneoxolanes (see Table 1, for specific details). Water was then added and the phases separated. The aqueous layer was further extracted three times with methylene chloride. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

The unsaturated epoxy spiroketals so obtained proved to be sensitive at room temperature but could be kept for months in a freezer (-20°).

NMR data were collected in Tables 2 and 3.

rel-(3*S*, *4S*, *5R*)-3, 4-epoxy-4-methyl-1, 6-dioxaspiro[4, 5]dec-7-ene: 3

colourless oil. TLC R_f 0.60 (PE-EA : 90-10); IR (thin film) 1640, 1400, 1255, 1210, 1120, 1070, 1035, 860, 820, 800 cm^{-1}; ^1H NMR (C_6D_6) δ : 1.35 (3H, s), 1.68 (H10, ddd, J = 12.5, 12.5, 6.0 Hz), 1.78 (H9, ddddd, J = 16.5, 6.3, 6.0, 1.6, 1.4 Hz), 1.98 (H10, dddd, J = 12.5, 6.3, 1.6, 1.4 Hz), 2.32 (H9, ddddd, J = 16.5, 12.5, 5.6, 2.6, 1.6 Hz), 3.02 (H3, s), 3.60 (H2, d, J = 10.2 Hz), 3.65 (H2, d, J = 10.2 Hz), 4.71 (H8, dddd, J = 6.0, 5.6, 1.6, 1.4 Hz), 6.25 (H7, ddd, J = 6.0, 2.6, 1.4 Hz); ^{13}C NMR (C_6D_6) δ 11.63, 16.60, 24.31, 60.30, 64.28, 65.87, 101.75, 103.79, 141.12; mass spectrum, m/e (intensity) 168 (M^+, 50), 151 (38), 113 (51), 112 (66), 100 (58), 69(100), 55 (88);. Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found : C, 64.14; H, 7.11.

rel-(3*S*, *4S*, *5R*, *9S*)-3, 4-epoxy-4, 9-dimethyl-1, 6-dioxaspiro[4, 5]dec-7-ene: 4

colourless oil. TLC R_f 0.63 (PE-EA : 90-10); IR (thin film) 1635, 1215, 1210, 1170, 1110, 1170, 1030, 970, 920, 880, 850 cm^{-1}; ^1H NMR (C_6D_6) δ : 1.14 (3H, d, J = 7.0), 1.33 (3H, s), 1.83 (H10, ddd, J = 13.0, 3.8, 1.1 Hz), 2.02 (H10, dd, J = 13.0, 7.0 Hz), 2.14 (H9, qdddd, J = 7.0, 7.0, 3.8, 4.0, 1.7 Hz), 2.92 (H3, s), 3.51 (H2, d, J = 10.1 Hz), 3.64 (H2, d, J = 10.1 Hz), 4.63 (H8, ddd, J = 6.3, 4.0, 1.1 Hz), 6.21 (H7, dd, J = 6.3, 1.7 Hz); ^{13}C NMR (C_6D_6) δ 12.03, 21.35, 24.11, 31.66, 60.09, 64.77, 66.09, 103.95, 107.47,

140.16; mass spectrum, m/e (intensity) 182 (M^+, 32), 167 (18), 112 (85), 97 (25), 83 (23), 69(100), 55 (45);. Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found : C, 65.97; H, 7.90.

rel-(3*S*, 4*S*, 5*R*)-3, 4-epoxy-4, 7-dimethyl-1,6-dioxaspiro[4, 5]dec-7-ene: 5
colourless oil. TLC R_f 0.58 (PE-EA : 90-10); IR (thin film) 1640, 1250, 1140, 1070, 1030, 960, 870, 850, 800 cm^{-1}; ^1H NMR (C_6D_6) δ : 1.38 (3H, s), 1.64 (H10, ddd, J = 12.5, 12.5, 6.0 Hz), 1.73 (3H, ddd, J = 1.1, 1.0, 1.0), 1.82 (H9, dddq, J = 16.5, 6.2, 6.0, 1.0 Hz), 2.02 (H10, dddd, J = 12.5, 6.2, 1.8, 1.3 Hz), 2.39 (H9, ddddq, J = 16.5, 12.5, 5.4, 1.8, 1.0 Hz), 3.02 (H3, s), 3.58 (H2, d, J = 10.5 Hz), 3.68 (H2, d, J = 10.5 Hz), 4.50 (H8, dddq, J = 5.4, 1.3, 1.1, 1.0 Hz); ^{13}C NMR (C_6D_6) δ 11.75, 17.54, 20.23, 23.98, 60.46, 65.02, 65.82, 94.36, 96.72, 147.96; mass spectrum, m/e (intensity) 182 (M^+, 32), 167 (28), 112 (80), 97 (20), 83 (28), 69(100), 55 (55);. Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found : C, 65.96; H, 7.85.

rel-(3*S*, 4*S*, 5*R*)-3, 4-epoxy-1, 6-dioxaspiro[4, 5]dec-7-ene: 6
colourless oil. TLC R_f 0.52 (PE-EA : 90-10); IR (thin film) 1640, 1400, 1255, 1210, 1120, 1100, 1070, 1020, 860, 820, 800 cm^{-1}; ^1H NMR (C_6D_6) δ : 1.77 (H10, ddd, J = 12.5, 12.5, 6.0 Hz), 1.80 (H9, ddddd, J = 17.0, 6.0, 3.0, 2.5, 1.5 Hz), 2.06 (H10, dddd, J = 12.5, 4.5, 3.0, 1.5 Hz), 2.20 (H9, ddddd, J = 17.0, 12.5, 5.4, 4.5, 2.1 Hz), 3.07 (H3, d, J = 3.0 Hz), 3.32 (H4, d, J = 3.0), 3.51 (H2, d, J = 10.5 Hz), 3.71 (H2, d, J = 10.5 Hz), 4.67 (H8, dddd, J = 6.0, 5.4, 2.5, 1.5 Hz), 6.24 (H7, ddd, J = 6.0, 2.1, 1.5 Hz); ^{13}C NMR (C_6D_6) δ 17.38, 26.08, 53.94, 57.59, 66.77, 101.66, 102.70, 141.12; mass spectrum, m/e (intensity) 154 (M^+, 40), 113 (50), 112 (61), 100 (62), 69(100), 55 (81);. Anal. Calcd. for $C_8H_{10}O_3$: C, 62.33; H, 6.54. Found : C, 62.44; H, 6.66.

Hydrogenation of the cycloadducts 3, 4:

At room temperature, a stirred solution of 3, 4-epoxy-1, 6-dioxaspiro-[4, 5]-dec-7-ene (1.19 mmol, 1 eq.) in methanol (4 ml), was saturated with hydrogen by bubbling hydrogen gas. Then, palladium on charcoal (20 mg,) was introduced. The resulting suspension was vigorously stirred under hydrogen atmosphere (balloon). After 1 h, the mixture was filtrated through a short pad of Celite and concentrated *in vacuo*. The hardly pure product was further purified by flash column chromatography.

rel-(3*S*, 4*S*, 5*S*)-3, 4-epoxy-4-methyl-1, 6-dioxaspiro[4, 5]decane: 7
98%, as a colourless oil. TLC R_f 0.53 (PE-EA : 90-10); IR (thin film) 1440, 1400, 1370, 1200, 1190, 1130, 1080, 1010, 970, 920, 880, 855, 810, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ : 1.39 (3H, s), 1.41-1.76 (6H, m), 3.46 (H3, s), 3.58 (H7, ddd, J = 11.5, 4.0, 2.5 Hz), 3.68 (H2, d, J = 10.2 Hz), 3.75 (H7, ddd, J = 11.5, 11.0, 3.2 Hz), 3.79 (H2, d, J = 10.2 Hz); ^{13}C NMR ($CDCl_3$) δ 11.38, 18.97, 25.28, 27.35, 59.85, 61.73, 65.02, 65.30, 102.92; mass spectrum, m/e (intensity) 171 (M^+ +1, 0.4), 170 (M^+, 0.4), 155 (4), 115 (15), 104 (72), 55 (100);. Anal. Calcd. for $C_9H_{14}O_3$: C, 63.53; H, 8.23. Found : C, 63.64; H, 8.51.

rel-(3*S*, 4*S*, 5*S*, 9*R*)-3, 4-epoxy-4, 9-dimethyl-1, 6-dioxaspiro[4, 5]decane: 8
86%, as a colourless oil. TLC R_f 0.52 (PE-EA : 90-10); IR (thin film) 1455, 1425, 1370, 1340, 1250, 1200, 1170, 1150, 1130, 1080, 1030, 975, 920, 860, 840, 790 cm^{-1}; ^1H NMR (C_6D_6) δ : 1.16 (3H, d, J =

7.0), 1.29 (H8, ddddd, J = 13.1, 3.0, 2.5, 2.0,1.5 Hz), 1.49 (3H, s), 1.50 (H10, ddd, J = 13.5, 3.5, 1.5 Hz), 1.87 (H8, dddd, J = 13.1, 12.0, 5.4, 5.4 Hz), 1.95 (H10, dd, J = 13.5, 5.5 Hz), 2.07 (H9, qdddd, J = 7.0, 5.5, 5.4, 3.5, 2.0 Hz), 3.51 (H3, s), 3.58 (H7, ddd, J = 11.5, 5.4, 2.5 Hz), 3.76 (H2, d, J = 10.4 Hz), 3.89 (H2, d, J = 10.4 Hz), 3.97 (H7, ddd, J = 12.0, 11.5, 3.0 Hz); ^{13}C NMR (C_6D_6) δ 12.04, 19.70, 24.09, 30.96, 32.57, 57.79, 59.78, 65.44, 65.87, 103.85; mass spectrum, m/e (intensity) 185 (M^+ +1, 0.5), 184 (M^+, 0.5), 169 (2.9), 149 (5.7), 115 (79), 55 (100);. Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found : C, 65.13; H, 8.68.

Hydride reduction of the cycloadducts 3, 4:

To a stirred solution of 3, 4-epoxy-1, 6-dioxaspiro-[4, 5]-decane (2 mmol, 1 eq.) in diethylether (3 ml), was added dropwise at room temperature, a commercial solution of lithium aluminium hydride(2.9 mmol, 1.45 eq,). The resulting solution was vigorously stirred overnight under argon atmosphere. The excess of hydride was destroyed by successive addition of silica and water (400µl). After stirring for 30 mn, the mixture was filtrated through a short pad of Celite and concentrated *in vacuo*. The hardly pure product was further purified by flash column chromatography.

rel-(*4S, 5S*)- 4-hydroxy-4-methyl-1, 6-dioxaspiro[4, 5]decane: 9

98%, as a colourless oil. TLC R_f 0.50 (PE-EA : 60-40); IR (thin film) 3460, 1460, 1440, 1365, 1210, 1160, 1120, 1070, 1040, 1005, 975, 950, 940, 900, 890, 820 cm^{-1}; ^{1}H NMR (C_6D_6) δ : 1.25 (H8, ddddd, J = 13.5, 4.0, 2.8, 1.5, 1.0 Hz), 1.36 (3H, s), 1.43 (H8, dddd, J = 13.5, 13.0, 12.5, 2.8 Hz), 1.46 (H10, ddd, J = 14.0, 13.0, 4.8 Hz), 1.58 (H9, dddd, J = 14.0, 4.8, 3.0, 1.5 Hz), 1.67 (H3, ddd, J = 12.5, 8.0, 3.5 Hz), 1.89 (H10, dddd, J = 14.0, 4.1, 3.0, 1.0 Hz), 1.91 (H9, ddddd, J = 14.0, 13.0, 13.0, 4.1, 4.0 Hz), 2.13 (H3, ddd, J = 12.5, 9.7, 8.0), 3.55 (H7, dddd, J = 11.0, 4.8, 1.5, 1.5 Hz), 3.73 (H2, ddd, J = 9.7, 8.0, 3.5 Hz), 3.83 (H2, ddd, J = 8.0, 8.0, 8.0 Hz), 3.84 (H7, ddd, J = 12.5, 11.0, 2.8 Hz); ^{13}C NMR (C_6D_6) δ 18.75, 19.26, 24.41, 25.27, 37.43, 59.68, 62.25, 79.12, 105.28; mass spectrum, m/e (intensity) 173 (M^+ +1, 5), 155 (38), 137 (11), 101 (100), 72 (100), 69(91), 55 (48);. Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found : C, 62.28; H, 9.43.

rel-(*4S, 5S, 9R*)-4-hydroxy-4, 9-dimethyl-1, 6-dioxaspiro[4, 5]decane: 10

78%, as a white solid, mp: 67°. TLC R_f 0.60 (PE-EA : 60-40); IR (CH_2Cl_2) 3560, 3500, 1460, 1370, 1340, 1180, 1140, 1100, 1060, 1020, 1000, 980, 960, 930, 910, 850 cm^{-1}; ^{1}H NMR (C_6D_6) δ : 1.10 (H8, ddddd, J = 13.5, 2.8, 2.2, 2.0, 1.0 Hz), 1.17(OH), 1.32 (3H, d, J = 7.0 Hz), 1.38 (3H, s), 1.62 (H3, ddd, J = 12.5, 8.0, 3.5 Hz), 1.65 (H10, ddd, J = 14.0, 3.0, 1.0 Hz), 1.72 (H8, dddd, J = 13.5, 12.2, 5.5, 5.0 Hz), 1.79 (H10, dd, J = 14.0, 6.0 Hz), 1.97 (H9, qdddd, J = 7.0, 6.0, 5.0, 3.0, ~2.0 Hz), 2.11 (H3, ddd, J = 12.5, 9.7, 8.0 Hz), 3.48 (H7, ddd, J = 11.2, 5.5, 2.2), 3.79 (H2, ddd, J = 9.7, 8.2, 3.5 Hz), 3.80 (H2, ddd, J = 8.2, 8.0, 8.0 Hz), 4.00 (H7, ddd, J = 12.2, 11.2, 2.8); ^{13}C NMR (C_6D_6) δ 19.98, 20.28, 24.46, 30.76, 31.39, 37.91, 56.86, 63.63, 81.41, 106.75; mass spectrum, m/e (intensity) 187 (M^+ +1, 4), 169 (20), 141(15), 115 (100), 99 (32), 97(40), 73 (100), 69 (100), 55 (53);. Anal. Calcd. for $C_{10}H_{14}O_3$: C, 64.48; H, 9.74. Found : C, 64.43; H, 9.57.

Acid catalyzed isomerization of the 4-hydroxy-4, 9-dimethyl-1, 6-dioxaspiro[4, 5]decane:

The hydroxy spiroketal **10** (150 mg, 0.81 mmol, 1 eq.) was dissolved in benzene (5 ml) or in C_6D_6 (in this case, the reaction was run on a 15 mg, scale). Trifluoroacetic acid (10µl, 0.13mmol, 0.15 eq.; 3µl, 38 µmol, 0.5 eq. for the 15 mg scale reaction) was then added. The reaction was monitored either by TLC (R_f 0.68 for the starting **10** compared to R_f 0.78 for the newly formed **11**, in PE-EA : 80-20) or by NMR. After 30mn to 1h, the solvent and the acid were pumped off, yielding a chromatographically pure product.

rel-(*4S, 5R, 9R*)-4-hydroxy-4, 9-dimethyl-1, 6-dioxaspiro[4, 5]decane: 11

99%, as a white solid, mp: 51°. TLC R_f 0.78 (PE-EA : 80-20); IR (CH_2Cl_2) 3560, 1450, 1360, 1340, 1205, 1190, 1160, 1130, 1070, 1000, 980, 920, 850 cm^{-1}; ^1H NMR (C_6D_6) δ : 0.80 (3H, d, J = 6.5), 1.02 (H8, dddd, J = 12.5, 12.0, 12.0, 4.8 Hz), 1.22 (3H, d, J = 1.0 Hz), 1.23 (H10, dd, J = 12.8, 12.0 Hz), 1.24 (H8, ddddd, J = 12.5, 4.0, 2.4, 1.8, 1.5 Hz), 1.59 (H10, ddd, J = 12.80, 4.0, 1.8 Hz), 1.70 (H3, ddd, J = 11.8, 8.0, 3.5 Hz), 1.96 (H9, ddqdd, J = 12.0, 12.0, 6.5, 4.0, 4.0 Hz), 2.13 (H3, dddq, J = 11.8, 10.0, 8.2, 1.0 Hz), 3.57 (H2, ddd, J = 8.5, 8.2, 8.0 Hz), 3.58 (H7, ddd, J = 11.0, 4.8, 1.5 Hz), 3.74 (H2, ddd, J = 10.0, 8.5, 3.5 Hz), 3.84 (H7, ddd, J = 12.0, 11.0, 2.40 Hz) ; ^{13}C NMR (C_6D_6) δ 22.15, 22.56, 26.42, 33.95, 35.86, 38.63, 61.48, 63.59, 78.96, 103.3; mass spectrum, m/e (intensity) 187 (M^++1, 4), 169 (18), 141(10), 115 (100), 99 (25), 97 (40), 73 (100), 69 (100), 55 (56);. Anal. Calcd. for $C_{10}H_{14}O_3$: C, 64.48; H, 9.74. Found : C, 64.14; H, 9.81.

Ab initio calculations were performed with the program Gaussian-82[32] on a Cray 1S Supercomputer, Gaussian-86[33] on a NAX XL60 computer, Gaussian-90[34] on a Cray 2 Supercomputer and IRIS 4D-320 and 4D-35 workstations. The geometries were fully optimized with respect to all bond lengths, bond angles and dihedral angles with the Berny method using standard convergence criteria.[35]

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