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[4+3] Cycloaddition of C-3 substituted furans. Stereoselectivity induced by coordination effects

Ángel M. Montaña [a,*], Pedro M. Grima [b], María Castellví [a,†], Consuelo Batalla [a], Mercè Font-Bardia [c]

[a] Unidad de Química Orgánica Industrial y Aplicada, Departamento de Química Orgánica, Facultad de Química, Universidad de Barcelona, c/Martí i Franquès 1-11, 08028 Barcelona, Spain
[b] Medicinal Chemistry Department, Laboratorios Ferrer Internacional, c/Juan de Sada, 28-32, 08028 Barcelona, Spain
[c] Department of Crystallography, Mineralogy and Mineral Deposits, University of Barcelona, c/Martí Franquès s/n, 08028-Barcelona, Spain

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ABSTRACT

Several C-3 substituted furans with chelating groups have been reacted with 2,3-dibromo-3-pentanone in the presence of a reducing metal, resulting in the formation of [4+3]-cycloadducts with complete *cis–trans* and *endo–exo* diastereoselectivity and in excellent yield. A certain variability of the conversion and reaction yield could be observed, when changing the reaction conditions, but in all cases the stereoselectivity was complete, compared to that of C-3 substituted furans with non-chelating groups. Also, a general method of assignment of stereochemistry of cycloadducts has been established by NMR, considering diagnostic patterns of signals with different multiplicity and chemical shifts depending on the stereochemistry of diastereomeric cycloadducts.

1. Introduction

The [4+3] cycloaddition reaction is a very useful synthetic methodology to prepare, in one step and good yield, polyfunctionalized cycloheptane building blocks with several stereocentres, which can be modified and easily transformed to obtain cyclic and linear precursors for the synthesis of many natural and non-natural products with high added value.[1]

We evaluated in the past the [4+3]-cycloaddition of C-2 functionalized furans in order to prepare cycloadducts having an oxabicyclic structure with an acetalic bridge head, prone to be transformed into a variety of added value molecules,[2] in a diastereoselective and/or enantioselective manner.[3] In those studies we were able to withdraw conclusions on the influence of the stereoelectronic nature of the C-2 substituents on the yield and stereoselectivity of the resulting [4+3]-cycloadducts.

Here, we present the results of our study of the influence of the coordinating nature of C-3 substituted furans on the stereochemical outcome of the [4+3]-cycloaddition reaction of these dienes and an oxyallyl cation as dienophile. With this information we pretend in the future to modulate the reactivity and stereoselectivity of conveniently functionalized C-2 and/or C-3 substituted furans in this type of reactions.

It is well established that the reaction of 3-substituted furans and a symmetric α,α′-disubstituted oxyallyl cation, generated in situ from the corresponding α,α′-dihaloketone with a reducing metal, affords four types of possible stereoisomers, existing as enantiomeric pairs (see Fig. 1). In the case of non-symmetric oxyallyl cations eight possible isomers, existing as enantiomeric pairs, could be formed due to the regiochemistry involved. In this last case the relative proportion of regioisomers is controlled by frontier molecular orbitals (FMO) of the cycloaddends (via primary MO interactions). Thus, the major product results from the relative orientation that favors the maximum HOMO–LUMO overlap of those orbitals with higher coefficients.[4] However, the substituents on the furan system also modulate the regioselectivity of cycloaddition reactions.[5]

In the present work we have worked with the symmetric 1,3-dimethyl-2-oxyallyl cation to simplify the reaction outcome and to obviate the regiochemistry problem. However we will mention, for comparative purposes, some examples found in the literature about the *cis–trans* and *endo–exo* diastereoselectivity in the formation of some regioisomeric cycloadducts from C-3 substituted furans.

* Corresponding author. Tel.: +34 93 402 16 81; fax: +34 93 339 78 78; e-mail address: angel.montana@ub.edu (Á.M. Montaña).
† Present address: Faculty of Science and Technology, University of Twente, P.O. Box 217, 7500 AE Enschede, The Netherlands.

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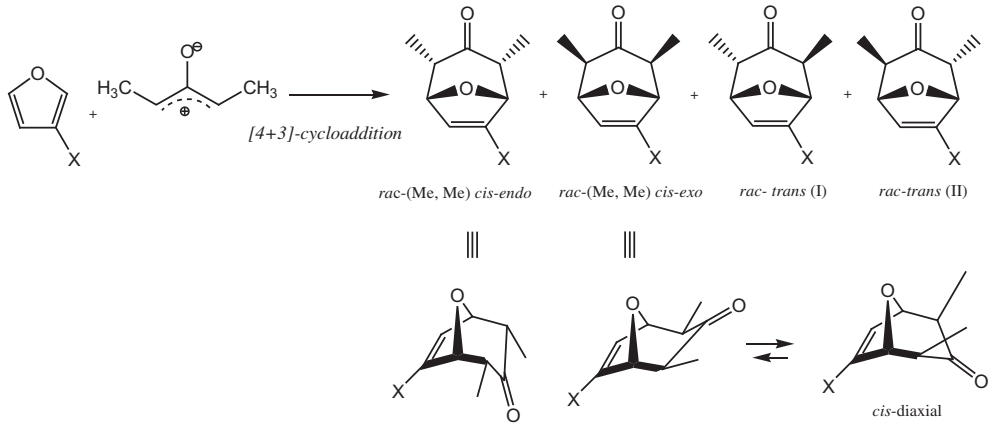


Fig. 1. Stereochemical outcome from the [4+3]-cycloaddition of C3-substituted furans and 1,3-dimethyl-2-oxyallyl cation.

The *cis* stereoselectivity is conditioned and determined by the predominance of the W configuration adopted by the oxyallyl cation in its coupling with the furan diene by a concerted process. The (*Z*,*Z*) or W configuration of the oxyallyl cation is the major one since it is the configuration of lower energy, having the methyl groups far apart from each other. It has been estimated that the population of dienophile molecules having this (*Z*,*Z*) configuration represents the 98% in equilibrium.[6]

The *cis*-diequatorial (*endo*) isomer is formed by a concerted [4C(4π)+3C(2π)] cycloaddition, following a compact late transition state that affords a cycloadduct with both Me groups in equatorial disposition and the 4-piranone ring in a chair-like conformation. The *cis*-diaxial (*exo*) stereoisomer is formed from an extended TS that affords a cycloadduct having the 4-piranone ring in a boat-like conformation. The *trans* isomers come from a stepwise process initiated by an electrophilic attack of the oxyallyl cation to the furan diene, followed by a ring closing. Before closing, the intermediate may modify the conformation of the side chain, re-orientating the methyl groups to decrease the steric interactions, affording the two possible *trans* isomers (see Fig. 2).[1]

The *endo*/*exo* ratio is conditioned by the easiness of the diene–dienophile π-stacking and the minimization of the steric interactions in the approach of diene and dienophile.[7]

The formation of *trans* cycloadducts is conditioned by the facilitation of the stepwise mechanism due to a modification of the electron density of the diene and the electrophilic nature of the oxyallyl cation (rich dienes and highly electrophilic cations facilitate stepwise processes).[7] The inductive and mesomeric effects, if they are activating (+I, +M) or deactivating (−I, −M), will favor the preferential attack on C-2 or C-5 of the furan diene (in the electrophilic addition through the stepwise process) and the resulting intermediates I_1 or I_2 (Fig. 2) will result stabilized or destabilized. On the other hand, apart from these orientating effects, the presence of (+I) groups will favor the stepwise mechanism and (−I) groups will act in the opposite direction, due to the modification of the electron density of the furan ring.[7,8]

Having in mind this background information, we observed in our cycloaddition studies with C-3 substituted furans and also in the results obtained by other authors some trends that we wanted to confirm by the present work.

What one expects, when using C-3 monosubstituted and/or C-3 and C-4 disubstituted furans as dienes in [4+3]-cycloaddition reactions, is an increase of the *exo* or even the *trans* isomers proportion with respect to the furan itself as a diene in the same type of reaction. This was observed by Hoffmann et al.[6] in the reaction of furan and 3,4-dimethylfuran with 1,3-dimethyl-2-oxyallyl cation (see Fig. 3). This is due to the fact that, even though 3,4-dimethylfuran is not highly electron rich it has two methyl groups that hinder a compact approach of the W-configuration of the oxyallyl cation. As a consequence the *trans* isomers are formed in an extent of 21.3%, together with a considerable amount of *cis*-diaxial (*exo*) cycloadduct (33.7%). The formation of the *trans* isomers, via the stepwise process, seems to be favored (respect to furan as substrate) not only by electronic but also by steric factors due to the relative destabilization of the *endo* approach by the compact TS.

In the aforementioned work Hoffmann et al. studied the influence on the reaction outcome (diastereomeric proportions) of several reaction conditions, modifying the reducing metal (and thus the electrophilic nature of the oxyallyl cation, changing the nature of the metallic contra-ion), modifying the solvent and its solvating properties and even the presence of weak Lewis acids.

Also, we found some precedents in the literature that show how not only the steric interactions are important to determine the ratio of *endo*/*exo* isomers, but the chelation or coordination phenomena that could take place between the substituents at C-3 or C-4 and the contra-ion of the oxyallyl cation (dienophile). In these precedents the authors did not take into account this coordination effect because they were discussing other type of factors controlling the regio-, chemo- or p-facial diastereoselectivity of the reaction. However, we consider important to discuss and to unveil these phenomena as responsible for the *cis*/*trans* and *endo*/*exo* selectivity in the [4+3]-cycloaddition reaction. The clarification of this aspect will be important in order to develop more stereoselective processes in the future.

On the other hand, Barbosa et al.[4e,9] and Mann et al.[4c] in their studies on the [4+3]-cycloaddition reaction of mono- di- and trisubstituted furans with symmetric and non-symmetric oxyallyl cations, apart from the regioselectivity observed, which is mainly controlled by primary FMO interactions (diene–dienophile), they isolated in all cases the *endo* isomer as the unique or major product, no matter of the substitution pattern on the furan, especially for those substituents with heteroatoms having coordination capability. Also, Noyori et al.,[4a,10] working with 3-substituted furans with groups of different size and electronic nature (Me, Br, COOEt), obtained isomeric mixtures of [4+3]-cycloadducts. In these mixtures the ratio *endo*/*exo* increased when increasing the coordination capability of the furan substituent with the contra-ion of the oxyallyl cation[4a] (see Fig. 4), as we interpret now. Also, in this original work the authors centered their discussion in the regioselectivity mediated by the FMO interactions but they do not comment or rationalized this *endo*/*exo* variation.

In a more recent study, Hoffmann et al.[11] working on the chemo-regio- and stereoselectivity of the [4+3]-cycloaddition reaction of C-3 substituted furans with oxyallyl cations derived from chiral silyl enol ethers, obtained results that deserve some comments in this

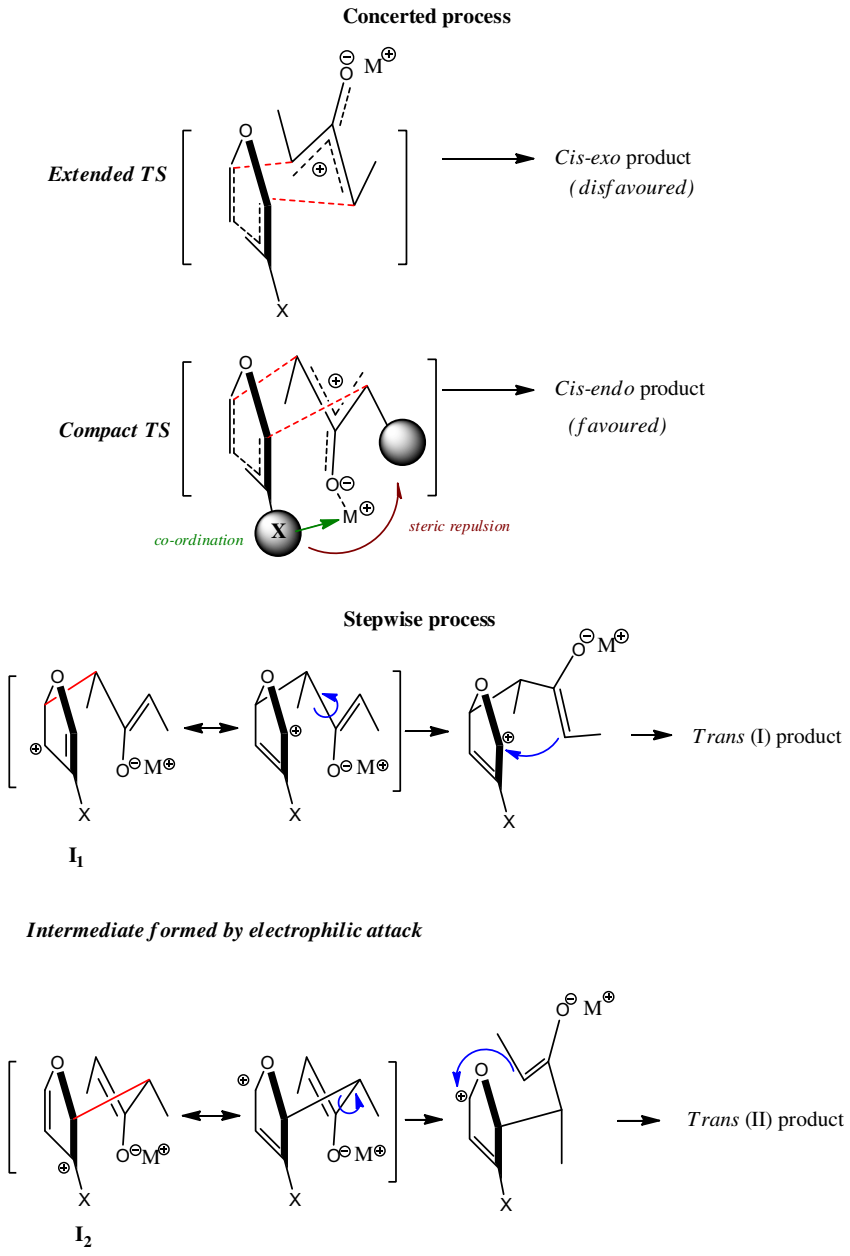


Fig. 2. Formation of *cis* isomers through compact and extended TS in a concerted process. Mechanism of formation of the *trans* isomers by a stepwise reaction.

context. In this work the authors used furans functionalized at C-3 with Br, $SnBu_3$, $SiEt_3$ and S(CO)Ph groups. In this study the chemo-, the regio- and especially the π-facial stereoselectivity were analyzed. This last particular aspect added a great value to this study. In the evaluation of the influence on the selectivity of different substitution patterns of both the oxyallyl cation and the furan diene, the authors worked, among others, with 3-bromofuran and 3,4-dibromofuran as substrates. They experimentally observed an increase of π-facial diastereoselectivity from 7:1 to 17:1 when using 3,4-dibromofuran as substrate instead of 3-bromofuran. In that particular π-facial stereoselectivity the decrease of freedom degrees of both diene and dienophile are important to assure a certain level of selectivity. This was rationalized by the authors when introduced an additional methyl group on the oxyallyl cation, observing an important increase of π-facial diastereoselectivity. They proposed a TS model in which they accounted for the W-configuration of the oxyallyl cation by the introduction of a methyl group on it, as well as the co-ordination of the silicon atom (from the $SiEt_3$ group) to the vicinal oxygen atom of the chiral auxiliary or even the π-staking effect with the aryl group of such chiral auxiliary. However, the authors do not rationalized the important change in stereoselectivity when using 3,4-dibromofurane versus 3-bromofurane (apart from the simplification of the reaction crude, because the regiochemistry problem disappears). In this particular substitution change none of the aforementioned phenomena could be called to justify this important improvement of π-facial selectivity. We think that important chelating effects from the bromine atoms on the silicon atom or even possible halogen bridges[12] could take place.

On the other hand, when working with a C-3 thiobenzoate furan derivative a chelating effect, exerted by the sulfur and/or oxygen atoms of the thiobenzoate substituent of furan, could also be envisioned. This chelating effect may also contribute to interpret the selectivity observed in other study cases carried out by Hoffmann et al. (Fig. 5).[11]

The stereoselection model proposed here involves not only the minimization of interaction between close steric demanding

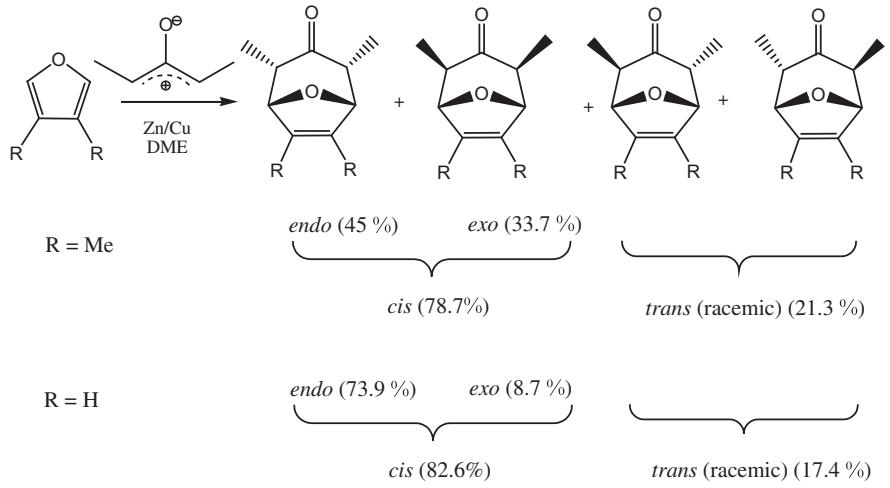


Fig. 3. Variation of the *endo*/*exo*/*trans* ratio with the substitution at C-3 and C-4 of furan in a [4+3]-cycloaddition reaction.[6]

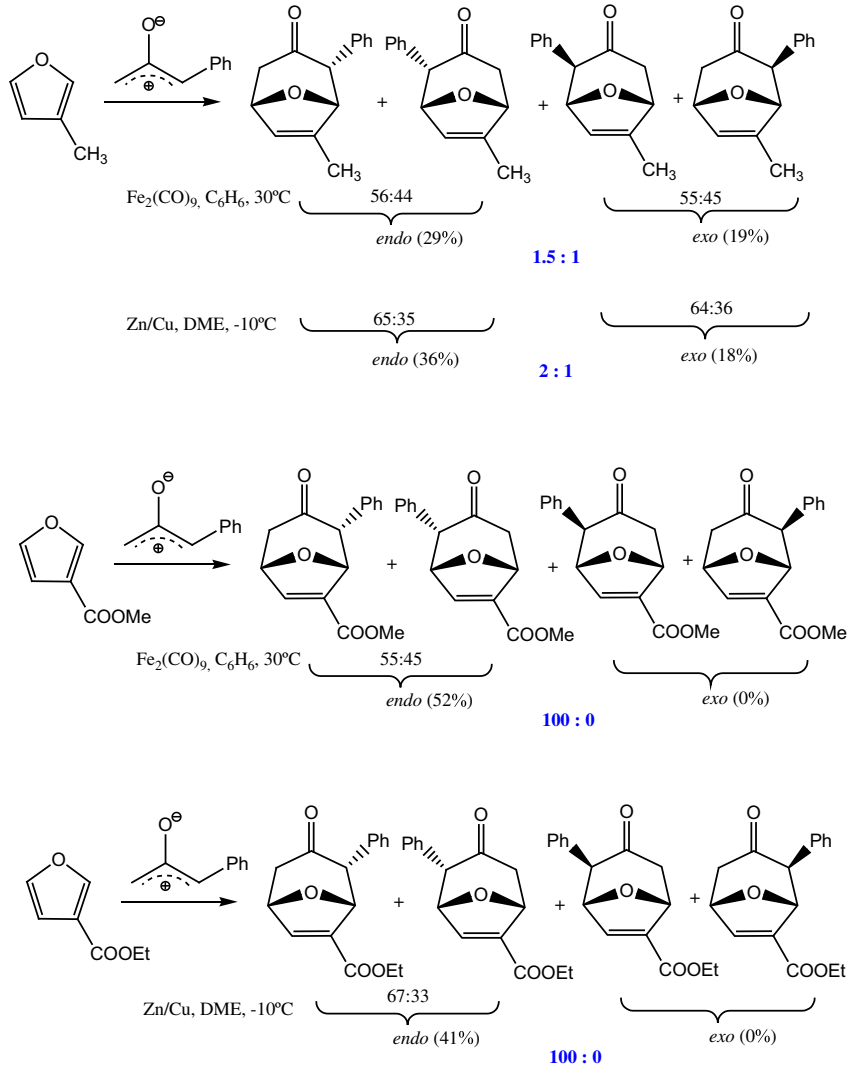


Fig. 4. [4+3]-Cycloaddition of 3-substituted furans with 1-phenyl-2-oxyallyl cation.[4a,10]

groups in the TS, as proposed historically by Hoffmann, but additional coordination effects as described before. New models, interactions and effects have been invoked to explain stereoselectivity in the [4+3] cycloaddition reactions, and in some cases these interactions are more important than the steric hindrance, affording unexpected approaches of reacting subunits in the TS. Some examples could be cited to illustrate these facts: the interaction and approaching model of Harmata and Houk[13] (Fig. 6),

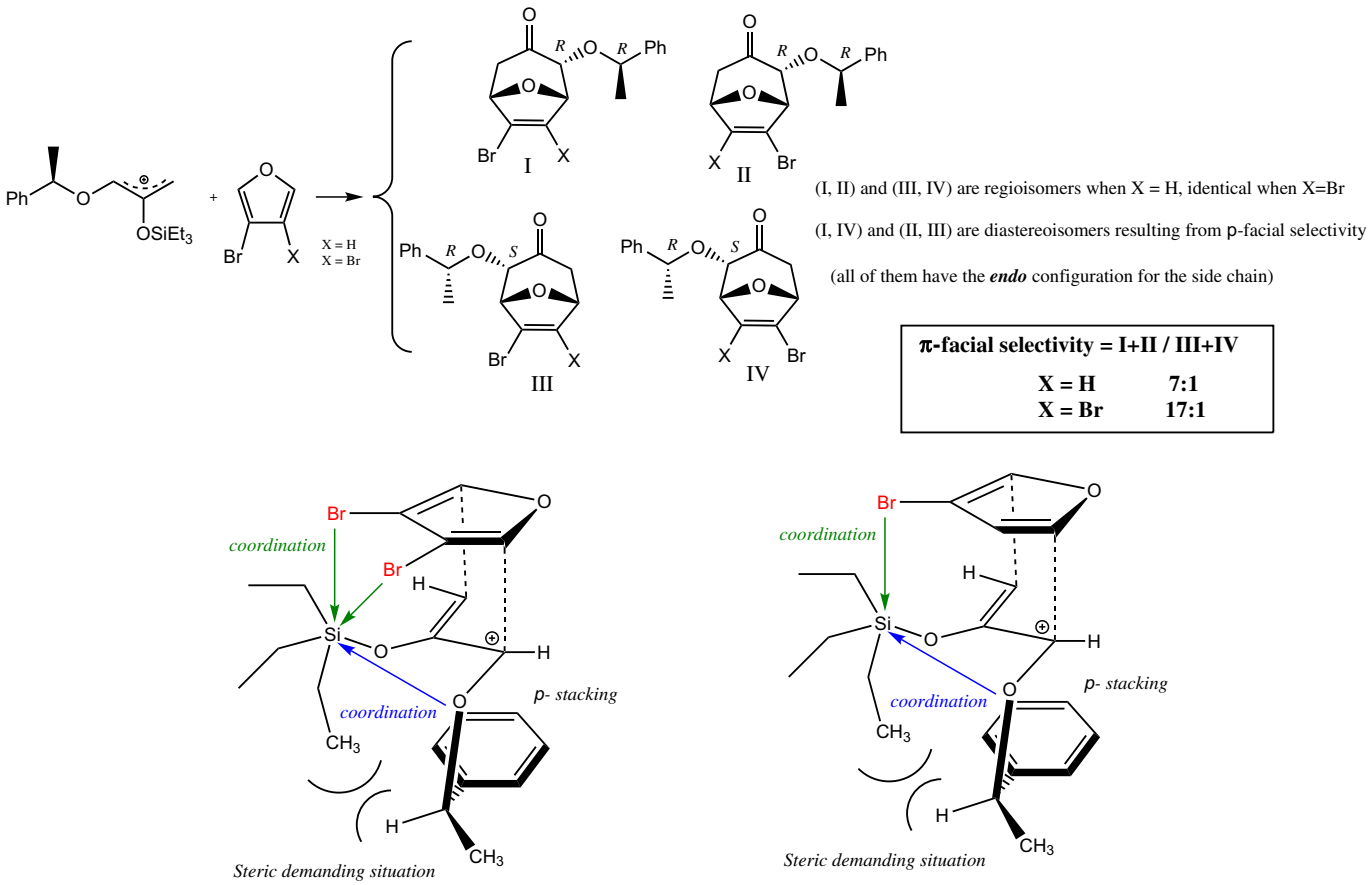


Fig. 5. Possible chelating effects of bromine atoms in the TS model proposed by Hoffmann to explain the π-facial stereoselectivity (from the study case of Ref. 11).

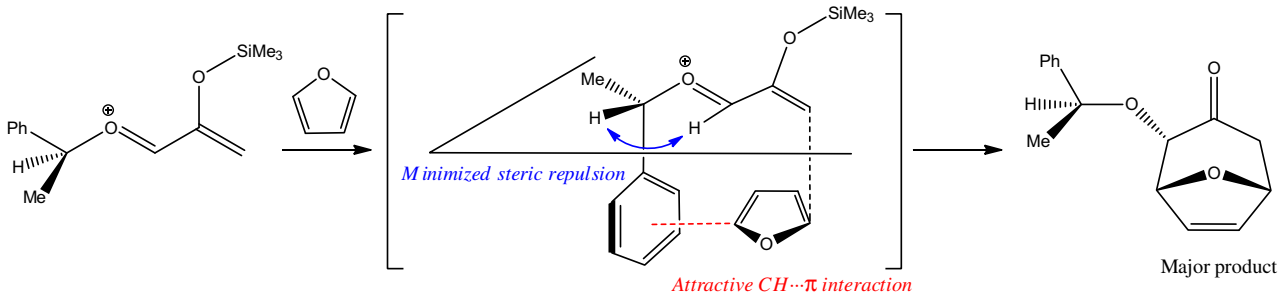


Fig. 6. Example of a new diene–dienophile interaction model proposed by Harmata and Houk to explain stereoselection in [4+3] cycloaddition reactions.

the model of Hsung[14] or the model of Lautens[15] among others. In the stereoselection model proposed by Harmata and Houk, supported by computational calculations, a new attractive CH···π interaction was envisioned, between one CH group at C2 of furan substrate and the π-system of the benzene ring of the side chain of dienophile. This interaction conditioned the coupling of diene and dienophile in an unexpected way, because this approach affords the formation of the major product in a contra-steric and stepwise manner, against the classical approach of Hoffmann (Fig. 5).

These facts should make the researches in this field to reconsider the classical approaching models and to rationalize other type of interactions, different from the simple unstabilizing steric interactions, like, for example, the CH···π interactions proposed by Harmata and Houk or the coordinative effects of a Lewis acid used as a catalyst.

2. Results and discussion

These interesting results and phenomena described in the literature moved us to study the possible influence of the chelating effects on the *endo*/*exo* stereoselectivity exerted by the groups attached to C-3 of furan dienes in [4+3]-cycloaddition reactions. Thus, we prepared C3 substituted furans with groups of different coordination capability, in order to study the *cis*/*trans* and *endo*/*exo* stereoselectivity. We obviated the regioselectivity problems working with the symmetric oxyallyl cation derived from 2,4-dibromo-3-pentanone (**1**) and/or 2,4-diiodo-3-pentanone (**2**).

The cycloaddition of simple furan, **3**, under the same reaction conditions, was used as a reference or standard as well as the previously mentioned results found in the literature from the [4+3]-cycloaddition of differently substituted furans, like, for

example, 3,4-dimethylfuran, **2**, among other study cases. We prepared two furan derivatives having non-coordinating substituents on C-3 and/or C-4: 3-methylfuran, **6** and 3,4-dimethylfuran, **9**. On the other hand, several furan derivatives with a coordinating group attached to C-3 were synthesized (furans **10**–**14**). These furans have one or two coordinating heteroatoms (N, O) separated by a two-bonds linker to the furan ring, in order to facilitate the approach of heteroatoms (having electron lone pairs) to the 'metallic' contra-ion of the oxyallyl dienophile. The hydroxymethyl derivative **12**, with the capability to act as hydrogen bond donor, was prepared in order to evaluate if this phenomenon could condition the freedom degrees of the oxyallyl dienophile and, as a consequence, the stereoselectivity *endo*/*exo*. The use of ester/amide substrates (**11**, **13**) versus the respective alcohol/amine derived functions (**12**, **14**) was considered to evaluate the influence of the different inductive effect of these two kinds of groups on the furan ring and the possible hydrogen bond effects on both the yield and the stereoselectivity. The use of a tertiary amine like **14** was used to evaluate what was the predominant effect: the steric hindrance exerted by the two ethyl groups of the NEt_2 substituent versus the coordinating effect of nitrogen atom through its electron lone pair.

The synthetic pathway to prepare the aforementioned furan derivatives is summarized in Fig. 7 and described in detail in the experimental part.

The results from the [4+3]-cycloaddition reaction of substituted furans and 1,3-dimethyl-2-oxyallyl cation (generated in situ from dihaloketones), under different conditions, are summarized in Table 1. The conversion of furan dienes, the yield of cycloadducts and the *cis*/*trans* and *endo*/*exo* stereoselectivities are quoted.

Looking at the data it is possible to observe how the conversion was complete or very high in most of the evaluated reaction conditions and the yield of cycloadducts was also high. The diastereoselectivity *cis*/*trans* and *cis*–*endo*/*cis*–*exo* was 100:0 for all cases in which furans, having coordinating groups on C-3, were used as substrates (entries 6–11). However, in the standard reaction with furan (entries 1 and 2) and also in the reactions with 3-methylfuran, **6**, (entry 3) and 3,4-dimethylfuran, **9**, (entries 4 and 5), the *cis*/*trans* and *endo*/*exo* selectivity was different from 100:0.

The high yield observed could be explained considering that the substitution on the furan ring is at one bond distance of the C-2 reactive center or at two bonds distance of the C-5 reactive center. Thus, the steric hindrance of the C-3 group should not be very important or determinant to condition the approach diene–dienophile. Other different situation is when a 3,4-disustituted furan is considered. On the other hand, the obtention of similar results no mater of the electronic nature of the groups: electron withdrawing (entries 6–10 and 12–14) or electron donating (entry 15) may be interpreted as the variation of the electron density of furan diene, induced by the evaluated substituents, is not important for the reaction outcome. However, it is well known that increasing the electron density increases the possibility of the stepwise mechanism and consequently the formation of *trans* cycloadducts. Moreover, the evaluation of the possibility of hydrogen bond formation of the hydroxymethyl derivative (entry 11) did not show any relevant result at least for this particular reaction model.

The composition of the reaction crude was studied very carefully by high field ^1H NMR, GC, and GC–MS techniques, determining the conversion of furans and the yield of cycloadducts referred to the converted dienes. All reaction crudes were submitted to column chromatography to isolate the furan starting material and to purify and characterize, physically and spectroscopically, the cycloadducts. The stereochemistry was established after a careful analysis, comparison and correlation of the ^1H and ^{13}C signals (chemical shifts, multiplicity, and coupling constants) of cycloadducts, after an unequivocal assignment of all spectral signals by 1D and 2D NMR experiments (COSY, HETCOR, HMBC, HSQC, etc.), including NOE experiments.

The reaction conditions were modified in order to evaluate the influence on the reaction outcome of parameters, such as: nature of the reducing metal and dihaloketone, reaction temperature, nature of solvent, concentration, presence of NaI, etc. From this comparative study it is possible to appreciate how the use of the system Zn–Cu/dibromoketone–NaI instead of Zn/diiodoketone afforded worse conversion and yield (compare entries 6 vs 8 and 12 vs 13). Other significant result is that the yield may be conditioned by the nature of the metal, maintaining the other reaction parameters constant. Thus, when using Cu (powder, bronze or submicron) in place of Zn the yield decreases a 20–25%. This may be due to the lower electrophilicity of the corresponding oxyallyl cation in the case of using copper (compare entry 8 vs 10 and also 12 vs 14).[7] In all cases de reaction conditions were mild but designed to get short reaction times in order to avoid equilibrations in alpha to the ketone group in cycloadducts or their decomposition, as well as possible side reactions.

The complete *cis*/*trans* stereoselectivity observed could be interpreted by considering that the reaction takes place via a concerted mechanism and due to the reduction of the haloketone affords an oxyallyl cation with a major (*Z*,*Z*) or W configuration.

The observed *endo*/*exo* diastereoselectivity for the C-3 substituted furans resulted, a priori, unexpected according to the results observed in entries 1 to 5. The substitution at C-3 and/or at C-5 of furan may determine a certain degree of steric interaction in the approach of oxyallyl dienophile to the furan diene for a compact TS, as illustrated in Fig. 8. This phenomenon may be the responsible for the stereochemical outcome of the reaction of 3,4-dimethylfurane observed by Hoffmann et al.[6] and also by us in the present work.

In our experiments with furans having coordinating groups on C-3 we expected the appearance of a certain percentage of *cis*-diaxial and *trans* cycloadducts as we observed for furan itself (entries 1 and 2) and also for substrates **6** and **9** (entries 3–5), but we did not observed at all the diastereomers *trans* or *exo*, after a careful analysis of the reaction crude by high field ^1H NMR, GC, and GC–MS techniques. In all cases the only product detected and then isolated was the *cis*-diequatorial or *endo* product. Studying by molecular modeling the *endo* product and performing a conformational analysis we inferred certain proximity in space of the methyl group on C-2 and the group on C-7 of cycloadduct (coming from the substituent of furan precursor). Taking into account this proximity and the Van der Waals radii it is possible to understand that in the late compact TS there would be an unstabilizing interaction between both groups. Why this interaction does not manifest in the evolution to an extended TS or even to a stepwise mechanism? The explanation may be found in a possible chelating or coordinating effect taking place between heteroatoms (N or O, having lone pairs) of the furan substituent and the metallic contra-ion of the oxyallyl dienophile (Fig. 8) (Cu or Zn acting as Lewis acids), which compensates the possible steric interaction, mentioned before, making the compact TS the predominant or unique one.

The assignment of the stereochemistry by NMR in cycloadducts substituted at C-6 turns out to be simpler than that of the functionalized systems on C-1.[16]

As in that case, the substituent at C-6 arranges in space moving away from the quasi-rigid bicyclic structure,[16a] so that it provokes small effects on the chemical shifts of the NMR signals corresponding to the oxabicyclic framework (which is much more affected by the disposition of the other substituents of the rigid structure). Thus, independently of the nature of the substituent at C-6, it is possible to establish a method of general applicability for the assignment of the relative stereochemistry of cycloadducts from a detailed analysis and correlation of ^1H NMR spectra.

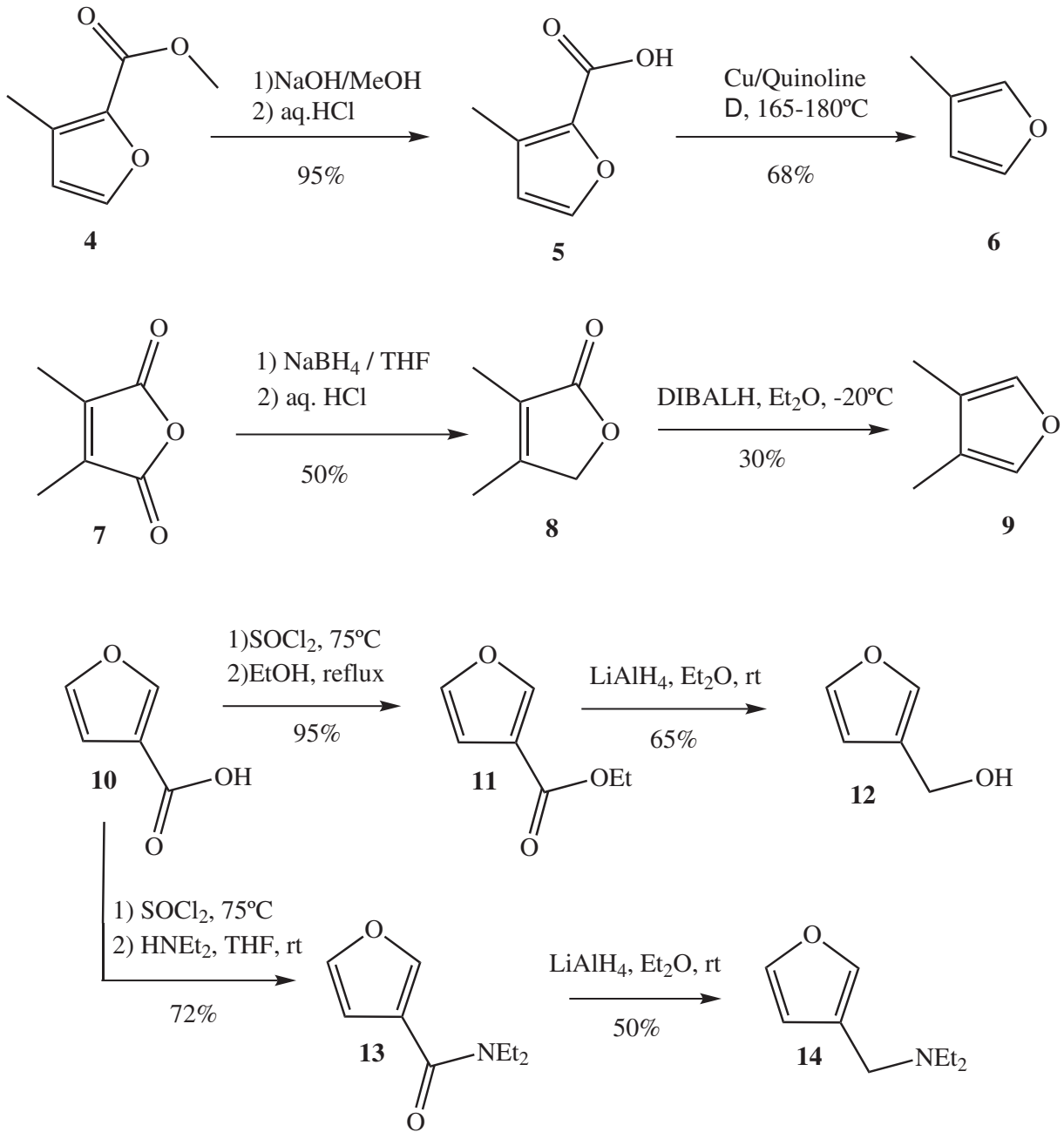


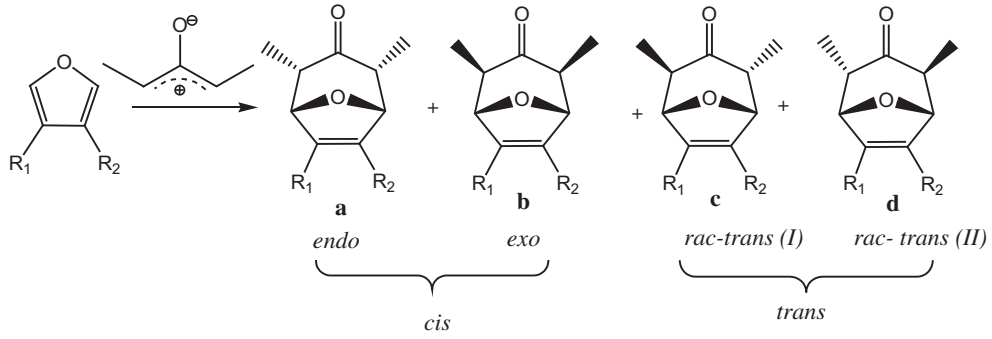
Fig. 7. Synthetic pathways for the C-3 substituted furans used as substrates.

The general trends in the correlation of ^{1}H and ^{13}C NMR spectra of diastereomeric (**a**/**b**) pairs of cycloadducts (**a**=*cis endo*; **b**=*cis exo*) are summarized as follows:

1. The most significant differences in chemical shifts (δ), multiplicity and coupling constants between both diastereoisomers are at the level of H-2, H-4, H-9, and H-10.
2. δ(H-9) and δ(H-10) of major diastereoisomer (**a**) are smaller than the homologous signals in the minor stereoisomer (**b**), which is caused by the different interaction of methyl groups with the bridging oxygen.
3. $J_{2,9}$ (**a**)$<J_{2,9}$ (**b**)$J_{4,10}$ (**a**)$<J_{4,10}$ (**b**)$J_{4,5}$ (**a**)$\neq 0$, normally $4<J_{4,5}<5$ Hz; $J_{4,5}$ (**b**)≈ 0
4. δ(H-2) and δ(H-4) of (**a**) are higher than δ(H-2) and δ(H-4) of (**b**), because of the different interaction of those hydrogen atoms with the bridging oxygen.
5. δ(H-5)(**a**)$>\delta$(H-5)(**b**) by 1,2 shielding effects with Me-(C-4).
6. The main differences in $\delta(^{13}C)$ are observed for carbons: C-1, C-3, C-9, and C-10.
7. δ(C-9) (**a**)$<\delta$(C-9) (**b**) and δ(C-10) (**a**)$<\delta$(C-10) (**b**), due to the γ-*gauche* interactions in the (**a**) diastereoisomer.
8. δ(C-3) (**a**)$<\delta$(C-3) (**b**), caused by electron compression between a sp^3 orbital of the bridging oxygen and a p_z orbital of the C-3 atom.

All the shielding and deshielding effects on the bicycle structure exerted by the different substituents are very useful to establish NMR patterns for the four possible diastereoisomers. Moreover, these systems have the advantage of having hydrogen atoms attached to the bridgeheads (H-1 and H-5), so that, the assignment of stereochemistry turns out to be unequivocal, simply looking at their coupling patterns (see Fig. 9), which are consistent with the

Table 1
Results obtained in the [4C(4π)+3C(2π)] cycloaddition reaction of C-3 substituted furans



Entry	Substitution pattern	Furan	Cycloadduct	Cycloaddition method	Molar ratio: furan:DHK: metal:NaI	Solvent[a]	Reaction temperature (°C)	Time (h)[b]	Conversion of furan (%)[c]	Yield (%)[c]	Ratio *cis*/*trans* (%)[d] **a**+**b**/**c**+**d**	Ratio *cis*–*endo*: *cis*–*exo* (%)[d] **a**:**b**
1	R_1=R_2=H	**3**	**15a–d**	Zn/DIK	1:3:3:0	ACN	0 to rt	2	100	80	99:1	91:8
2	R_1=R_2=H	**3**	**15a–d**	Zn/DIK	240:1:1:0	Furan	0 to rt	2	100	99	99:1	91:8
3	R_1=H R_2=CH_3	**6**	**16a–d**	Zn/DBK/NaI	1:3:3:3	ACN	a) 0 b) rt	1 2	100	60	96:4	69: 31
4	R_1=R_2=CH_3	**9**	**17a–d**	Zn–Cu/DBK	1:0.6:1.2:0	DME	a) −15 b) rt	1.5 0.25	100	61	79:21	57:43
5	R_1=R_2=CH_3	**9**	**17a–d**	Zn/DBK/NaI	1:3:3:3	ACN	a) 0 b) rt	1 2	100	58	93:7	54:46
6	R_1=H; R_2=CO_2Et	**11**	**18a**	Zn–Cu/DBK/NaI	1:3:3:3	ACN	0	1	13	100[e]	100:0	100:0
7	R_1=H; R_2=CO_2Et	**11**	**18a**	Zn–Cu/DBK/NaI	1:3:3:3	ACN	0	4	70	80[e]	100:0	100:0
8	R_1=H; R_2=CO_2Et	**11**	**18a**	Zn/DIK	1:3:3:0	ACN	0	4	90	100[e]	100:0	100:0
9	R_1=H; R_2=CO_2Et	**11**	**18a**	Zn/DIK	1:3:3:0	ACN	25	4	93	95[e]	100:0	100:0
10	R_1=H; R_2=CO_2Et	**11**	**18a**	Cu/DIK	1:3:3:0	ACN	0	4	85	75	100:0	100:0
11	R_1=H; R_2=CH_2OH	**12**	**19a**	Zn/DIK	1:3:3:0	ACN	0	1	100	70	100:0	100:0
12	R_1=H; R_2=$CONEt_2$	**13**	**20a**	Zn/DIK	1:3:3:0	ACN	0	1	100	98	100:0	100:0
13	R_1=H; R_2=$CONEt_2$	**13**	**20a**	Zn–Cu/DBK/NaI	1:3:3:3	ACN	0	1	53	100[e]	100:0	100:0
14	R_1=H; R_2=$CONEt_2$	**13**	**20a**	Cu/DIK	1:3:3:0	ACN	0	4	80	77	100:0	100:0
15	R_1=H; R_2=CH_2NEt_2	**14**	**21a**	Zn/DIK	1:3:3:0	ACN	0	1	100	81	100:0	100:0

[a] Solvent dilution: 1 mL/mmol of furan in all cases, except for entries 4 and 5 in which 0.2 mL/mmol of furan was used and also in entry 2 in which furan was used as a solvent.
[b] Time until constant conversion of furan by GC (In all cases an internal standard and a calibration method have been used).
[c] Yield on isolated product. The non-converted furan derivative was recovered by distillation, when volatile, or by CC when non-volatile.
[d] Determined by 500 MHz ^{1}H NMR, GC and/or GC–MS on the reaction crude.
[e] These figures refer to the chemical selectivity. The substrate under the conditions of entries 6, 7, 8 and 13 was converted in a percentage lower than 100% but was transformed exclusively into the desired final product. No by-products were detected and the unchanged starting material was efficiently recovered by CC and reused.

shifts and coupling constants of the rest of diagnostic hydrogen atoms.

The assignment of the relative configuration established on the basis of ^{1}H NMR correlation has been confirmed by X-ray diffraction analysis on single crystals of cycloadduct **20a** (see Fig. 10 and Table 2).

3. Conclusions

Analyzing the results obtained in experiments of cycloaddition using functionalized furans in the C-3 position, it is possible to withdraw the following conclusions: (a) Neither the steric volume nor the inductive electronic character of substituents on C-3 in the furan substrate have a determinant effect on the reaction yield. (b) A high *cis*/*trans* and *endo*/*exo* diastereoselectivity has been observed for all C-3 substituted furan substrates, compared with the non-substituted furans. In the case of substrates with C-3 substituents having coordinating atoms, able to act as electron donor entities, a *cis*–*endo* stereospecificity was observed and only cycloadducts with this *cis*–*endo* configuration were detected and isolated from the reaction products. This fact induces to think of the existence of coordination effects that favor the coupling diene–dienophile across a compact transition state.

This coordination effect could be taken into consideration by synthetic chemists when designing retrosynthetic pathways and preparing furan substrates for [4+3]-cycloaddition reactions in order to obtain building blocks and intermediates or precursors of added value molecules with a certain stereochemistry, which could be easily derived from that of cycloadducts.

A general method of assignment of stereochemistry has been established by NMR, considering diagnostic patterns of signals with different multiplicity and chemical shifts depending on the stereochemistry of diastereomeric cycloadducts.

4. Experimental section

4.1. General methods

Unless otherwise noted, all reactions were conducted under an atmosphere of dry nitrogen or argon in oven-dried glassware. Raw materials were obtained from commercial suppliers and used as received. All solvents were purified using standard techniques before use: ether, tetrahydrofuran, hexane, and pentane were distilled under nitrogen from sodium/benzophenone. Acetonitrile was distilled under nitrogen from CaH_2. Infrared spectra were recorded on a FT-IR NICOLET 510 spectrophotometer as thin films over NaCl plates. NMR spectra were obtained in $CDCl_3$ on spectrometers at 400 MHz (MERCURY-400) and/or 500 MHz (UNITY-500) for ^{1}H NMR, and at 100 MHz for ^{13}C NMR. For ^{1}H NMR tetramethylsilane was used as internal standard. ^{13}C NMR spectra were referenced to

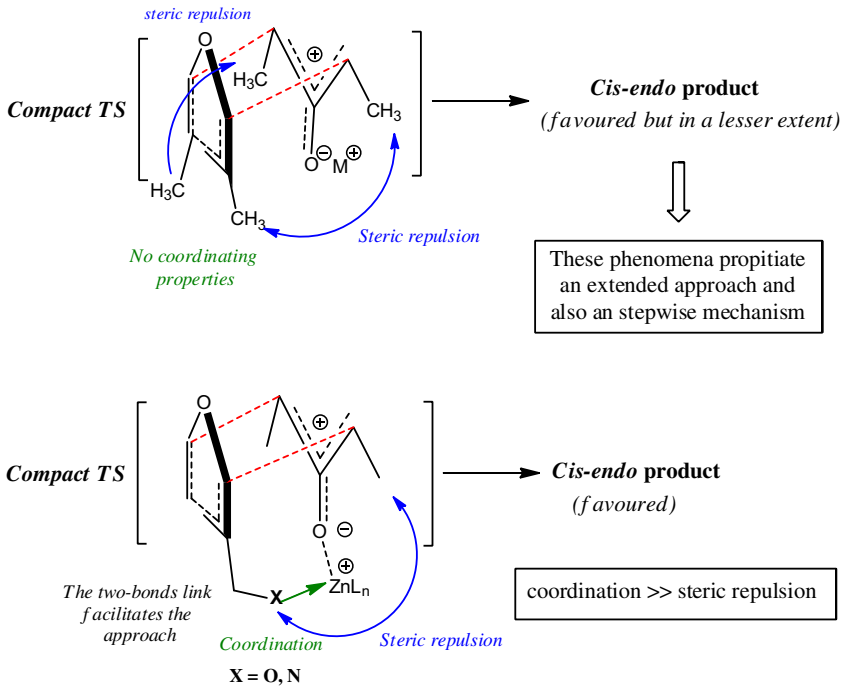


Fig. 8. Different interaction of the furan diene, having coordinating and non-coordinating substituents, with the oxyallyl dienophile.

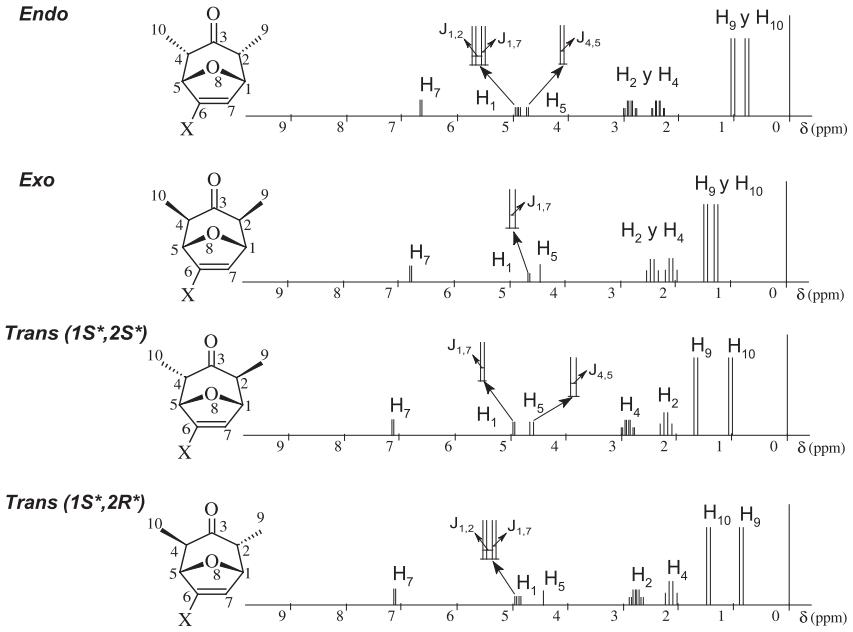


Fig. 9. ^{1}H NMR spectra signal pattern of the four possible diastereoisomers.

the 77.0 ppm resonance of chloroform. When necessary, assignments were established by DEPT, ^{1}H–^{1}H–COSY and HMBC, gHMQC or HSQC ^{13}C–^{1}H correlation experiments. Mass spectra were measured on a HEWLETT-PACKARD 5890 mass spectrometer using the chemical ionization technique and ammonia as ionizing gas. GC analyses were performed on HP-8790 gas chromatograph equipped with a HEWLETT–PACKARD-crosslinked MePhe–Silicone capillary column (L=25 m, Φ=0.2 mm, δ=2.5 μm) using helium as gas carrier and a FID detector (T=250 °C, P_{H_2}=4.2 psi, P_{air}=2.1 psi). The elemental analyses were obtained in a FISONS elemental analyzer, Model Na-1500. The samples were previously pyrolyzed at 1000 °C under oxygen atmosphere and the content of carbon, hydrogen, and nitrogen was determined by evaluation of the combustion gases by gas chromatography using a FID detector.

4.2. Experimental conditions for the X-ray diffraction analysis of a single crystal of cycloadduct 20a

A prismatic crystal (0.1×0.1×0.2 mm) was selected and mounted on a MAR345 diffractometer with image plate detector. Unit-cell parameters were determined from 1418 reflections ($3<\theta<31°$) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation, using φ scan-technique. 4636 reflections were measured in the range

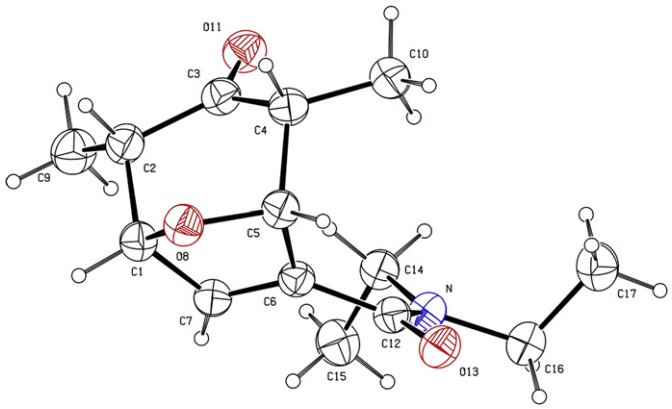


Fig. 10. ORTEP Representation for crystal structure of cycloadduct **20A** with *cis–endo* configuration.

Table 2
Crystal data and structure refinement for **20a**

Empirical formula	$C_{14}H_{21}NO_3$
Formula weight	251.32
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Triclinic, *P*1
Unit cell dimensions	a=9.032(8) Å α=94.74(6)°
	b=9.421(6) Å β=108.64(5)°
	c=10.180(7) Å γ=117.58(4)°
Volume	699.6(9) Å^3
Z	2
Calculated density	1.193 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	272
Crystal size	0.1×0.09×0.08 mm
Theta range for data collection	2.20 to 29.79°.
Limiting indices	$-11\leq h\leq 11$, $-12\leq k\leq 11$, $-13\leq l\leq 12$
Reflections collected/unique	4636/2749 [R(int)=0.0614]
Completeness to theta=25.00	90.7%
Absorption correction	Empirical
Max. and min transmission	0.99 and 0.98
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2749/4/163
Goodness-of-fit on F^2	1.142
Final R indices [$I>2\sigma(I)$]	$R1$=0.0692, $wR2$=0.2041
R indices (all data)	$R1$=0.0872, $wR2$=0.2231
Largest diff. peak and hole	0.197 and −0.301 e Å^{-3}

$2.20\leq\theta\leq29.79$. 2749 of which were non-equivalent by symmetry [Rint(on I)=0.061]. 2132 reflections were assumed as observed applying the condition $I>2\sigma(I)$. Lorentz-polarization and absorption corrections were made.

The structure was solved by Direct methods, using SHELXS computer program and refined by full-matrix least-squares method with SHELX97 computer program,[17] using 4636 reflections, (very negative intensities were not assumed). The function minimized was $\Sigma w\,||Fo|^2-|Fc|^2|^2$, where $w=[\sigma^2(I)+(0.1269P)^2+0.0096P]^{-1}$, and $P=(|Fo|^2+2|Fc|^2)/3$, f, f′ and f″ were taken from International Tables of X-ray Crystallography.[18] All H atoms were computed and refined, using a riding model, with an isotropic temperature factor equal to 1.2 times the equivalent temperature factor of the atom, which are linked. The final R(on F) factor was 0.069, wR(on $|F|^2$)=0.204 and goodness of fit=1.142 for all observed reflections. Number of refined parameters was 163. Max. shift/esd=0.00, Mean shift/esd=0.00. Max. and min. peaks in final difference synthesis was 0.197 and −0.301 e Å^{-3}, respectively.

The main X-ray data are quoted in Table 2. For additional information regarding bond lengths and bond angles for compound **20a**, as well as the hydrogen coordinates and the anisotropic thermal parameters see the CIF file deposited as Supplementary data. The file CCDC-92874 for compound **20a**, contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

4.3. Cycloaddition reaction methodologies

2,4-Dibromo-3-pentanone and 2,4-diiodo-3-pentanone, used as precursors of oxyallyl cation, have been prepared according to procedures described in the literature.[19,20]

In the process of optimization of the [4+3] cycloaddition, several reaction conditions have been used, which are quoted in Table 3.

Table 3
Cycloaddition procedures depending on the used reagents

Reaction procedure	Reducing metal	Dihaloketone	Other reagents
1-Cu	Cu (powder, bronze or submicron)	Dibromoketone	—
2-Cu	Cu (powder, bronze or submicron)	Diiodoketone	—
3-Cu	Cu (powder, bronze or submicron)	Dibromoketone	NaI
4-Cu	Cu (powder, bronze or submicron)	Diiodoketone	NaI
1-Zn	Zn or metallic couples Zn (Metal)	Dibromoketone	—
2-Zn	Zn or metallic couples Zn (Metal)	Diiodoketone	—
3-Zn	Zn or metallic couples Zn (Metal)	Dibromoketone	NaI
4-Zn	Zn or metallic couples Zn (Metal)	Diiodoketone	NaI
5-Zn	Zn or metallic couples Zn (Metal)	Dibromoketone	TMSCl
6-Zn	Zn or metallic couples Zn (Metal)	Diiodoketone	TMSCl

4.3.1. Experimental procedures using copper as reducing agent

4.3.1.1. Experimental procedure 1-Cu: cycloaddition by reduction of a dibromoketone with copper powder. In a double necked flask, fitted with magnetic stirring and nitrogen atmosphere, freshly activated copper (210 mg, 3.32 mmol) was added and suspended in acetonitrile (11 mL). The mixture was cooled down to 0 °C and the furan derivative (300 μL, 4.24 mmol) was added at once using a microsyringe. Then, 2,4-dibromo-3-pentanone (258 mg, 1.06 mmol) was added dropwise. The reaction mixture was homogenized by stirring and maintained at the temperature of work by using a heating/cooling bath with a temperature stabilizing system. The reaction is controlled by both TLC and GC. The reaction is considered finished after observing a constant conversion in successive analyses.

The isolation of products from the reaction mixture, in experiments in which the reducing agent is copper, is carried out in the following way: the mixture was cooled to 0 °C and methylene chloride was added under constant stirring. The mixture was added over a 1:1 mixture of water/ice (30 mL approx.) and it was filtered through a porous sintered plate (filtering plate number 4) under vacuum to remove excess of copper powder. The phases were decanted and the aqueous phase was extracted with methylene chloride until discoloration of the organic phase (4×30 mL) is observed. The organic phases are combined together and washed successively with a 3% water solution of NH_3 (3×20 mL) until no blue color (due to tetraamminecopper(II) complex) was observed in the washing aqueous extracts, followed by ice-water (2×20 mL). Finally, the organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated to dryness, obtaining a product consisting of a unique structure or a mixture of diastereoisomers, depending on the furan substrate. The obtained oil was submitted to a flash column chromatography on silica gel, using mixtures of hexane and ethyl acetate of increasing polarity, eluting by with hexane/ethyl acetate (95:5) and (90:10) (and generally in this order) the *endo*, *trans* and *exo* stereoisomers.

4.3.1.2. Experimental procedure 2-Cu: cycloaddition by reduction of the diiodoketone with copper powder. The melting point of 2,4-diiodo-3-pentanone is close to 0 °C, and in many cases it is not possible the addition of this reagent at working temperature, in the liquid state. Therefore, the procedure of addition was modified in the following way:

In a double necked flask fitted with magnetic stirring and nitrogen atmosphere, freshly activated copper (210 mg, 3.32 mmol) was placed and suspended in acetonitrile (5 mL). The suspension was cooled down to 0 °C and the furan derivative (300 μL, 4.24 mmol) was added at once using a microsyringe. Then, 2,4-diiodo-3-pentanone (360 mg, 1.06 mmol) dissolved in 6 mL of acetonitrile was added dropwise. The total volume of solvent used was the same than in the procedure 1-Cu, so that, the total dilution of the system remains invariable. The work-up and the purification procedure of products is identical to the one described in experimental procedure 1-Cu.

4.3.1.3. Experimental procedure 3-Cu: cycloaddition by reduction of a dibromoketone with copper powder, in the presence of sodium iodide. Basically, this procedure is analogous to the one described in 1-Cu, however, it is worth noting the presence of insoluble salts in the medium, which provoke changes of color in the crude of reaction.

In a double necked flask fitted with magnetic stirring and nitrogen atmosphere, freshly activated copper (210 mg, 3.32 mmol) and sodium iodide (957 mg, 6.36 mmol) were added and suspended in acetonitrile (11 mL). The mixture was cooled down to 0 °C and the furan derivative (300 μL, 4.24 mmol) was added at once using a microsyringe. Then, 2,4-dibromo-3-pentanone (258 mg, 1.06 mmol) was added dropwise. Immediately, a yellowish solid was formed and the reaction mixture became turbid. The mixture got opaque and acquired a brown color. The reaction mixture was homogenized by stirring and maintained at the work temperature by using a heating/cooling bath with a temperature stabilizing system. The reaction was controlled by both TLC and GC. The reaction was considered finished after observing a constant conversion in successive analyses. The isolation of products was performed as described in previous procedures.

4.3.1.4. Experimental procedure 4-Cu: cycloaddition by reduction of the diiodoketones with copper powder in the presence of sodium iodide. Procedure similar to 3-Cu, but using the modification of addition described in 2-Cu.

4.3.2. Experimental procedures using zinc or metallic couples of zinc as reducing agents

4.3.2.1. Experimental procedures 1–4 Zn. In the same way as described for procedures using copper as a reducing agent (procedures 1-Cu to 4-Cu), it is possible to establish four different procedures for the cycloaddition reaction in the presence of zinc powder (procedures 1-Zn to 4-Zn). The only difference among these four procedures is the isolation method of products from the reaction crude. Thus, due to copper salts have not been generated (not even when the reducing agent is a zinc–copper couple), the washing process with an aqueous solution of ammonia is not necessary. Next, two work-up procedures are described for this type of experiments. The first one, has been used in the cases in which the final product is labile and could result altered under an aqueous treatment (during work-up), whereas the second one, has been the procedure chosen in those cases in which the zinc byproducts were so finely divided that they pass through percolation columns.

- *Purification method* 1. Once the reaction was complete, as observed by GC, ethyl acetate (100 mL) was added, in order to stop the progress of the reaction, and it was submitted to percolation across a column packed with a small amount of silica and alumina. Mixtures of ethyl acetate/dichloromethane were used as eluents. Then, the organic phase was concentrated to dryness, and the obtained oil was submitted to flash column chromatography on silica gel, eluting with mixtures of hexane and ethyl acetate of increasing polarity.
- *Purification method* 2. Once the substrate was converted, water was added (5 mL), in order to quench the reaction process, and the solid was filtrated through a porous plate (filter plate number 4). Then, the liquid phase was extracted with methylene chloride (5×15 mL). The organic phases were combined together and washed with brine (2×25 mL), dried with anhydrous $MgSO_4$, and concentrated to dryness. The obtained oil was submitted to flash column chromatography on SiO_2, eluting with mixtures of hexane and ethyl acetate of increasing polarity.

4.3.2.2. Experimental procedure 5-Zn. Cycloaddition by reduction of dibromoketones with Zn and Zn–Cu couple, in the presence of trimethylsilyl chloride.

Only in the case of using zinc (or a couple zinc–copper) as reducing agent, in some experiments trimethylsilyl chloride has been added, in order to accelerate the reaction.[21]

In a two necked flask fitted with magnetic stirring and nitrogen atmosphere, freshly prepared zinc–copper couple (217 mg, 3.32 mmol) was suspended in the used solvent (i.e., acetonitrile, 11 mL). At the working temperature (i.e., 0 °C), furan (300 μL, 4.24 mmol), trimethylsilyl chloride (135 μL, 1.06 mmol) and 2,4-dibromo-3-pentanone (258 mg, 1.06 mmol) were sequentially added using a microsyringe. The reaction mixture was kept in a bath stabilized at working temperature and the course of the reaction was periodically controlled by gas chromatography. The reaction was considered finished after observing a constant conversion in several successive analyses. The work-up and the isolation of product by CC were carried out as described in the previous section.

4.3.2.3. Experimental procedures 6-Zn: cycloaddition by reduction of diiodoketones with Zn in the presence of trimethylsilyl chloride. Procedure similar to 5-Zn, but using the modification described in the 2-Cu addition.

4.4. Synthesis of furan substrates substituted on C-3

4.4.1. Synthesis of 3-methyl-2-furoic acid, ***5****.* Commercial methyl 3-methyl-2-furoate, **4**, (2.0 g, 14.3 mmol) was reacted under reflux with 3.8 mL of 30% sodium hydroxide aqueous solution (28.5 mmol) and 3.6 mL of methanol (88.8 mmol) for 3.5 h. The solvent was removed and the resulting crude mixture was dissolved in 10 mL of water and acidified with concentrated hydrochloric acid until pH 1, and extracted with diethyl ether (4×3 mL). The organic phases were combined together, dried over magnesium sulfate, filtrated, and concentrated to dryness, giving 1.7 g of 3-methyl-2-furoic acid (13.6 mmol, yield 95%). MP: 135 °C (ether). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.40 (3H, s, CH_3), 6.41 (1H, d, $J_{4,5}$=1.6 Hz, H4), 7.52 (1H, d, $J_{5,4}$=1.6 Hz, H5). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 170.2 (COO), 150.1 (C5), 139.9 (C2), 125.3 (C3), 112.0 (C4), 13.3 (Me). IR (film, ν, cm^{-1}): 1102 (st. C–O), 1136 (st. C–O), 1189 (st. C–O), 1488 (def. C–H), 1599 (st. C=C Ar.), 1670 (st. C=O), 2200–3200 (st. O–H). MS (EI, *m*/*z*, %): 126.03 (M^+, 100); 127.03 (7); 109.03 (M^+–OH, 20); 81.03 (40, M^+–CHO_2). EA. Calculated for $C_6H_6O_3$: C (57.14), H (4.80). Found: C (57.11), H (4.83).

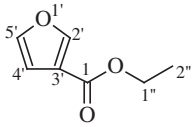
4.4.2. Synthesis of 3-methylfuran, ***6****.*[22] A mixture of 3-methyl-2-furoic acid, **5**, (1.7 g, 13.5 mmol), quinoline (5.7 mL, 27 mmol), and copper powder (0.33 g, 5.2 mmol) was heated in a one-piece microdistillation setup (fitted with a condenser with an ice-water circulating system) during 2.5 h at 165–180 °C. As a result, 0.75 g (9.2 mmol, 68% yield) of 3-methylfuran vapor was condensed in the receiving flask cooled with an ice bath. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.04 (3H, br s, CH_3), 6.23–6.25 (1H, m, H4), 7.19–7.21 (1H, m, H2), 7.32–7.34 (1H, m, H5). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 142.7 (C5), 139.3 (C2), 119.8 (C3), 112.2 (C4), 9.6 (Me). IR (film, ν, cm^{-1}):

1100 (st. C–O), 1130 (st. C–O), 1200 (st. C–O), 1480 (def. C–H), 1588 (st. C=C Ar.). MS (DIP, EI, *m/z*, %): 82.04 (M^+, 100); 83.04 (6). EA. Calculated for C_5H_6O: C (73.15), H (7.37). Found: C (73.10), H (7.41).

4.4.3. Synthesis of 3,4-dimethyl-2-butenolide, ***8****.*[23] A mixture of $NaBH_4$ (0.60 g, 15.9 mmol) in anhydrous THF (3 mL) was stirred and cooled in an ice bath while 2.0 g (15.9 mmol) of 2,3-dimethylmaleic anhydride, **7**, dissolved in 19.3 mL of THF anhydrous was added slowly. The ice bath was removed and the stirring was continued for 1.5 h. The solution was cooled in an ice bath and acidified with 2 M aqueous HCl down to pH 5–6. The resulting mixture was concentrated, dissolved in 30 mL of water and extracted three times with 10 mL of diethyl ether. The organic phases were combined, dried over anhydrous magnesium sulfate, and concentrated to dryness, affording 0.90 g (8.0 mmol) of 2,3-dimethyl-2-butenolide (yield 50%). ^{1}H NMR (300 MHz; $CDCl_3$; δ, ppm) 1.83 (3H, br s, CH_3), 2.02 (3H, br s, CH_3), 4.63 (2H, q, $J_{5,7}$=0.8 Hz, H5). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 175.7 (C2), 157.1 (C4), 122.8 (C3), 73.4 (C5), 15.0 (C7), 9.2 (C6). IR (film, ν, cm^{-1}) 1031 (st. C–O), 1081 (st. C–O), 1456 (def. C–H), 1684 (st. C=C), 1751 (st. C=O), 2927 (st. C–H). GC (50 °C, 1 min, 5 °C/min, 250 °C, 10 min) t_R=7.8 min. MS (DIP, EI, *m/z*, %): 112.05 (M^+, 100); 113.04 (8); 97.03 (M^+–Me, 30); 68.06 (M^+–CO_2, 15). EA. Calculated for $C_6H_8O_2$: C (64.27), H (7.19). Found: C (64.29), H (7.22).

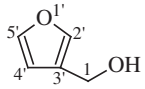
4.4.4. Synthesis of 3,4-dimethylfuran, ***9****.*[24] 3,4-Dimethyl-2-butenolide (0.79 g, 7.0 mmol), **8**, dissolved in dry ether (15 mL) was stirred and cooled to −20 °C in a 25 mL flask, fitted with magnetic stirring and argon atmosphere. To this solution, diisobutylaluminum hydride (6.4 mL, 7.9 mmol from a 25% w/w solution in hexane) was added slowly, avoiding the temperature to increase. Once the addition was complete, the mixture was allowed to stir at −20 °C for 1 h before quenching the reaction with 5 mL of 10% aqueous H_2SO_4. After warming to ambient temperature, the aqueous and organic phases were separated. The aqueous phase was extracted with ether (3×10 mL) and the ether extracts were combined with the organic phase, washed with brine (2×10 mL) and 5% $NaHCO_3$ solution (2×10 mL) and dried over $MgSO_4$ and filtered. The solvents of the resulting mixture were removed by controlled simple distillation in a one-piece distillation setup and then by a Kugelrohr distillation apparatus at atmospheric pressure (oven temperature 42–54 °C, for the removal of solvents; oven temperature 91–100 °C, for the distillation of 3,4-dimethylfuran). 0.21 g (2.2 mmol) of the product was obtained in this way (yield 30%). ^{1}H NMR (400 MHz; $CDCl_3$; δ, ppm) 1.95 (6H, d, $J_{2,6}$=$J_{5,7}$=0.4 Hz, CH_3, H6 and H7), 7.14 (2H, q, $J_{2,6}$=$J_{5,7}$=0.4 Hz, H2 and H5). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 138.3 (C2, C5), 121.3 (C3, C4), 8.7 (Me). GC (35 °C, 1 min, 20 °C/min, 250 °C, 10 min) t_R=1.6 min. MS (DIP, EI, *m/z*, %): 96.06 (M^+, 100); 97.06 (5); 81.03 (M^+–Me, 25). EA. Calculated for C_6H_8O: C (74.97), H (8.39). Found: C (75.01), H (8.37).

4.4.5. Synthesis of ethyl 3-furoate, ***11****.*



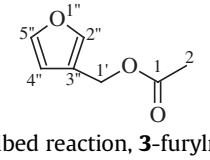
In a two-necked oven dried 50 mL flask, fitted with magnetic stirring and nitrogen atmosphere, 3-furoic acid (2 g, 17 mmol) was placed at room temperature and thionyl chloride (12.9 mL, 177 mmol) was added through the condenser. Then, the mixture was warmed up to reflux, maintaining this temperature for 4 h in order to get complete conversion of 3-furoic acid into 3-furoyl chloride. The excess of thionyl chloride was separated by distillation. Next, ethanol (10.3 mL, 177 mmol) was added to the resulting residue and the solution was warmed up to reflux. After 1 h, as verified by gas chromatography, the acid chloride acid disappeared and converted into ethyl 3-furoate. Diethyl ether (100 mL) was added to the reaction mixture and it was successively extracted with an aqueous saturated solution of $NaHCO_3$ (2×25 mL) and water (2×25 mL). The aqueous phases were extracted with diethyl ether (2×25 mL) and all the organic phases were combined together and dried with anhydrous $MgSO_4$. The solvent was evaporated under vacuum affording pure ethyl 3-furoate (2.34 g, yield=95%) as a lightly yellowish oil. IR (film, ν, cm^{-1}): 3080, 3000, 2975, 2960, 1730 (C=O, st), 1580, 1520, 1410, 1370, 1315, 1170, 1080, 1030, 1010. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.35 (3H, t, J=7.0 Hz, H2″), 4.30 (2H, d, J=7.0 Hz, H1″), 6.737 (1H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H4′), 7.41 (1H, dd, J_1=1.8 Hz, J_2=0.4 Hz, H5′), 8.00 (1H, dd, J_1=1.8 Hz, J_2=0.2 Hz, H2′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 14.3 (C2″), 60.4 (C1″), 109.7 (C4′), 119.5 (C3′), 143.5 (C5′), 147.5 (C2′), 163.0 (C1). MS [DIP-EI, 70 eV, 150 °C, *m/z* (%)]: 140 (1, M), 111 (42, M–C_2H_5), 95 (17, M–C_2H_5O). GC (50 °C, 1 min, 10 °C/min, 250 °C, 15 min): t_R=8.1 min. EA. Calculated for $C_7H_8O_3$: C (59.99%), H (5.75%). Found: C (60.01%), H (5.73%).

4.4.6. Synthesis of 3-furylmethanol, ***12****.*



A suspension of $LiAlH_4$ (516 mg, 13 mmol) in dry diethyl ether (10 mL) was placed in an oven-dried two-necked flask, fitted with a condenser, magnetic stirring and nitrogen atmosphere. Then, a solution of ethyl 3-furoate (2 g, 13.6 mmol) in dry diethyl ether (10 mL) was added, at room temperature. Immediately, generation of H_2 was observed. The reaction mixture was kept under these conditions for 45 min (control by gas chromatography). The excess of hydride was quenched by adding ethyl acetate (50 mL). Then, the reaction mixture was washed with water (5×20 mL). The aqueous phase was extracted with ethyl acetate (2×20 mL) and all organic phases were combined together, dried with anhydrous $MgSO_4$, and concentrated to dryness. The residue was submitted to a flash column chromatography (SiO_2, eluting it with mixtures of hexane and ethyl acetate of increasing polarity) obtaining, with hexane/ethyl acetate (8:2), 3-furylmethanol (850 mg, yield=65%) as a transparent oil. The resulting product was very volatile, so, the process of concentration in the rotary evaporator must be carried out at 0 °C or by simple distillation. IR (film, ν, cm^{-1}): 3350 (H–O, st), 3080, 2980, 1610, 1520, 1460, 1400, 1160, 1030, 970, 880. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 4.55 (2H, s, H1), 6.43 (1H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H4′), 7.40 (2H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H2′ and H5′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 56.6 (C1), 109.7 (C4′), 125.0 (C3′), 139.8 (C2′), 143.3 (C5′). MS [GC–MS (CI), NH_3, 70 eV, 150 °C, *m/z*, (%)]: 132 (100, M+N_2H_6), 115 (14, M+NH_3), 98 (13, M^+). GC (50 °C, 1 min, 10 °C/min, 250 °C, 15 min): t_R=5.6 min. TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.55 (black color, developed with anisaldehyde–H_2SO_4 reagent). EA. Calculated for $C_5H_6O_3$: C (61.22%), H (6.16%). Found: C (61.19%), H (6.20%).

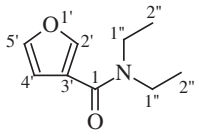
4.4.7. Isolation of 3-furylmethyl acetate, ***12′****.*



In the before-described reaction, **3**-furylmethyl acetate was obtained as a by-product and it was isolated by flash column chromatography (SiO_2, eluting with mixtures of hexane and ethyl acetate of ethyl of increasing polarity), affording with hexane/ethyl acetate (95:5) 410 mg (yield=10%) of this acetylated product as a yellowish oil. IR (film, ν, cm^{-1}): 3080, 2980, 1750 (C=O, st), 1510, 1460, 1380, 1370, 1240, 1170, 1030, 960. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 2.07

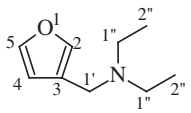
(3H, s, H2), 4.98 (2H, s, H1′), 6.43 (1H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H4″), 7.40 (1H, t, J=1.8 Hz, H5″), 7.47 (1H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H2″). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 170.3 (C1), 142.7 (C5″), 139.4 (C2″), 118.5 (C3″), 110.7 (C4″), 57.6 (C1′), 20.8 (C2). MS [GC–MS (CI), NH_3, 70 eV, 150 °C, *m*/*z*, (%)]: 174 (40, M+N_2H_6), 158 (100, M1+NH_4), 140 (11, M^+). GC (50 °C, 1 min, 10 °C/min, 250 °C, 15 min): t_R=7.96 min. TLC (SiO_2, hexane/ethyl acetate, 8:2): R_f=0.60 55 (black color, developed with anisaldehyde–H_2SO_4 reagent). EA. Calculated for $C_7H_8O_3$: C (59.99%), H (5.75%). Found: C (59.98%), H (5.77%).

4.4.8. Synthesis of N,N-diethyl-3-furamide, ***13****.*[25]



In a two-necked oven dried 50 mL flask, fitted with magnetic stirring and nitrogen atmosphere, 3-furoic acid (5 g, 44.3 mmol) was placed at room temperature and thionyl chloride (12.9 mL, 177 mmol) was added through the condenser. Then, the mixture was heated up to reflux, maintaining this temperature for 4 h in order to get complete conversion of 3-furoic acid into 3-furoyl chloride. The excess of thionyl chloride was separated by simple distillation. In another flask, a solution of diethylamine (13.88 mL, 133 mmol) in dry tetrahydrofuran (10 mL) is prepared. Over this solution, the crude 3-furoyl chloride of the previous step dissolved in dry tetrahydrofuran (2×10 mL) was added, at 0 °C and dropwise. Then, the reaction mixture was kept at room temperature for 19 h, observing the formation of a white solid (diethylammonium chloride). The reaction mixture was concentrated to dryness and the resulting crude oil was diluted with diethyl ether (100 mL) and washed with water (50 mL). The aqueous (basic) phase was acidified with concentrated hydrochloric acid (up to pH <4) and it was extracted with ethyl acetate (3×100 mL). All organic phases were combined, dried with anhydrous $MgSO_4$, filtered, and concentrated under vacuum in a rotary evaporator, affording pure product (5.86 g, yield=72%) as a colorless oil, which does not need further purification. IR (film, ν, cm^{-1}): 3060, 2990, 2970, 1630 (amide I), 1510 (amide II), 1420, 1390, 1370, 1320, 1300, 1220, 1160, 1120, 1070, 1020. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.21 (6H, t, J=7.0 Hz, H2″), 3.47 (4H, q, J=7.0 Hz, H1″), 6.58 (1H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H4′), 7.40 (1H, t, J=1.8 Hz, H5′), 7.69 (1H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H2′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 13.80 (C2″), 41.69 (C1″), 90.22 (C3′), 110.17 (C4′), 142.64 (C5′), 142.68 (C2′), 164.09 (C1). MS [GC–MS (CI), NH_3, 70 eV, 150 °C, *m*/*z*, (%)]: 185 (100, M+NH_4), 168 (79 (M+H^+)). GC (50 °C, 1 min, 10 °C/min, 250 °C, 15 min): t_R=13.84 min. CCF (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.46 (developed with anisaldehyde–H_2SO_4 reagent). EA. Calculated for $C_9H_{13}NO_3$: C (64.65%), H (7.84%). Found: C (64.67%), H (7.81%).

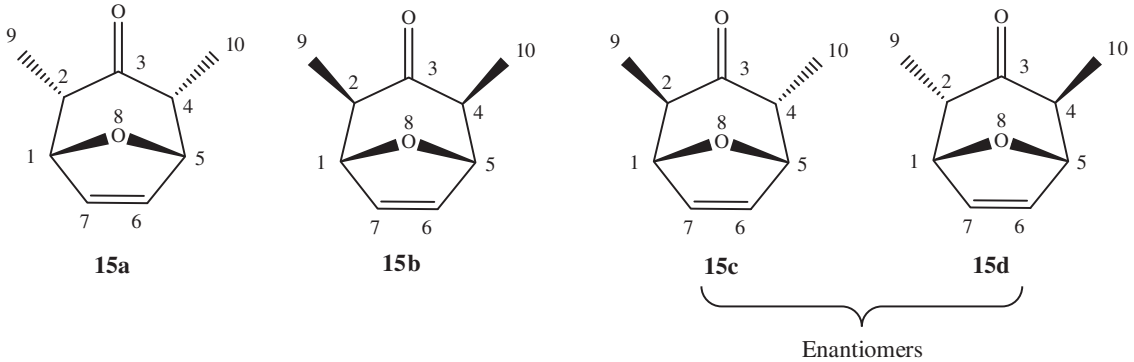
4.4.9. Synthesis of N,N-diethyl-3-furylmethylamine, ***14****.*



A suspension of $LiAlH_4$ (796 mg, 21 mmol) in dry diethyl ether (7 mL) was placed in an oven-dried two-necked flask, fitted with a condenser, magnetic stirring and nitrogen atmosphere. Then, a solution of *N,N*-diethyl-3-furamide (4 g, 21 mmol) in dry diethyl ether (10 mL) was added, at room temperature. Immediately, generation of H_2 was observed. The reaction mixture was stirred under reflux of solvent for 15 h. The excess of hydride was quenched by adding ethyl acetate (50 mL). The solid was separated by filtration through a Büchner funnel and washed with ether (100 mL) and brine (5×20 mL). The aqueous phase was extracted with ethyl acetate (2×20 mL) and all organic phases were combined together, dried with anhydrous $MgSO_4$, and concentrated to dryness, obtaining pure product (1.78 g, yield=50%), which does not need further purification. IR (film, ν, cm^{-1}): 3040, 2990, 2980, 2800, 1510, 1450, 1400, 1200, 1150, 1030, 880. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.06 (6H, t, J=7.0 Hz, H2″), 2.51 (4H, q, J=7.0 Hz, H1″), 3.49 (2H, s, H1′), 6.37 (H1, d, J=0.8 Hz, H4), 7.32 (1H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H2), 7.37 (1H, t, J=1.8 Hz, H5). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 11.84 (C2″), 46.46 (C1″), 46.90 (C1′), 111.38 (C4), 121.80 (C3), 140.49 (C2), 142.65 (C5). MS [GC–MS (CI), NH_3, 70 eV, 150 °C, *m*/*z*, (%)]: 154 (100, M+H^+). EA. Calculated for $C_9H_{15}NO$: C (70.55%), H (9.87%). Found: C (70.57%), H (9.85%).

4.5. Synthesis of cycloadducts. Physical and spectroscopic characterization

4.5.1. Synthesis of 2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one.



In the cycloaddition reactions in which a mixture of cycloadducts **15a**–**d** are formed, the diastereoisomers **15a**, **15b** and **15cd** can be separated by successive flash column chromatographies on silica gel, eluting with mixtures of hexane and ethyl acetate of increasing polarity. The elution order is **15a**, then **15cd** and finally **15b**, by using hexane/ethyl acetate 95:5 and 90:10 as eluents. The assignment of configuration has been carried out on the basis of ^{1}H NMR and ^{13}C NMR correlations by 1D and 2D experiments (COSY, HMBC, HSQC, HETCOR, etc.).

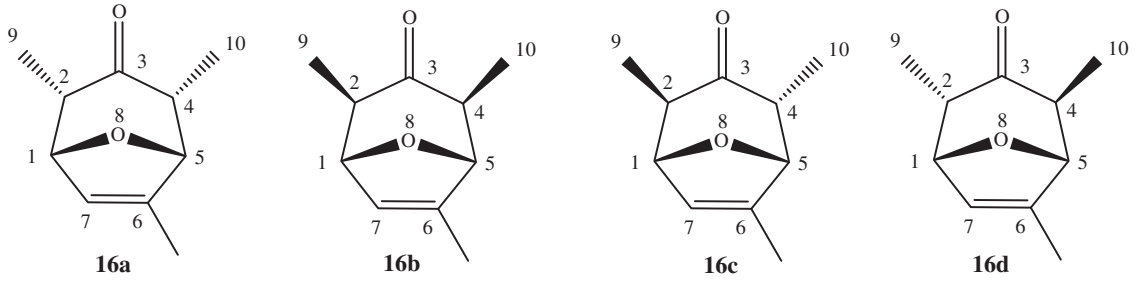
Isomer **15a**: IR (KBr, ν, cm^{-1}): 3080, 2974, 2950, 2885, 1715 (C=O, st), 1590 (C=C, st), 1460–1450 (C–C, δ), 1380 (C–H, δ), 1340, 1160, 1085, 920. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.97 (6H, d, J=7.0 Hz, H9 and H10), 2.80 (2H, dq, J_1=7.0 Hz, J_2=4.4 Hz, H2 and H4), 4.85 (2H, d, J=4.4 Hz, H1 and H5), 6.34 (2H, s, H6 and H7). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 10.0 (C9 and C10), 50.3 (C2 and C4), 82.6 (C1 and C5), 133.5 (C6 and C7), 208.9 (C3). MS [GC–MS (CI), NH_3, 70 eV, 150 °C, *m*/*z*, (%)]: 187 (100, M+N_2H_5), 170 (82, M+NH_4), 153 (2, M+H), 152

(1, M^+). EA. Calculated for $C_9H_{12}O_2$: C (71.03%), H (7.95%). Found: C (71.42%), H (8.02%). GC (50 °C, 1 min, 10 °C/min, 250 °C, 1 min): t_R=11.80 min.

Isomer **15b**: IR (KBr, ν, cm^{-1}): 3080, 2960, 2925, 1885, 1715 (C=O, st), 1630 (C=C, st), 1450, 1375, 1320, 1240, 1175, 1085, 1040, 960, 815. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.36 (6H, d, J=7.5 Hz, H9 and H10), 2.28 (2H, q, J=7.5 Hz, H2 and H4), 4.65 (2H, s, H1 and H5), 6.27 (2H, s, H6 and H7). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 17.7 (C9 and C10), 49.8 (C2 and C4), 81.9 (C1 and C5), 133.6 (C6 and C7), 213.7 (C3). MS [GC–MS (CI), NH_3, 70 eV, 150 °C, *m*/*z*, (%)]: 187 (100, M+N_2H_5), 170 (30, M+NH_4), 153 (52, M+H), 152 (5, M^+). EA. Calculated for $C_9H_{12}O_2$: C (71.03%), H (7.95%). Found: C (71.21%), H (7.86%). GC (50 °C, 1 min, 10 °C/min, 250 °C, 1 min): t_R=11.46 min.

Isomers **15cd** (*racemic mixture*): IR (KBr, ν, cm^{-1}): 3060, 2965, 2945, 2885, 1707 (C=O, st), 1600 (C=C, st), 1460, 1450, 1370, 1240, 1165, 1085, 920. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.96 (3H, d, J=7.0 Hz, H9), 1.35 (3H, d, J=7.2 Hz, H10), 2.36 (1H, q, J=7.2 Hz, H4), 2.85 (1H, dq, J_1=7.0 Hz, J_2=4.4 Hz, H2), 4.67 (1H, s, H1), 4.80 (1H, d, J=4.4 Hz, H5), 6.31 (1H, d, J=2.0 Hz, H6) 6.33 (1H, d, J=2.0 Hz, H7). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 10.1 (C9), 16.1 (C10), 48.6 (C4), 50.3 (C2), 81.9 (C5), 82.9 (C1), 132.0 (C6), 135.1 (C7), 213.7 (C3). MS [GC–MS (CI), NH_3, 70 eV, 150 °C, *m*/*z*, (%)]: 187 (100, M+N_2H_5), 170 (85, M+NH_4), 153 (2, M+H). EA. Calculated for $C_9H_{12}O_2$: C (71.03%), H (7.95%). Found: C (71.10%), H (7.99%). GC (50 °C, 1 min, 10 °C/min, 250 °C, 1 min): t_R=11.61 min.

4.5.2. Synthesis of 2,4,6-trimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one.



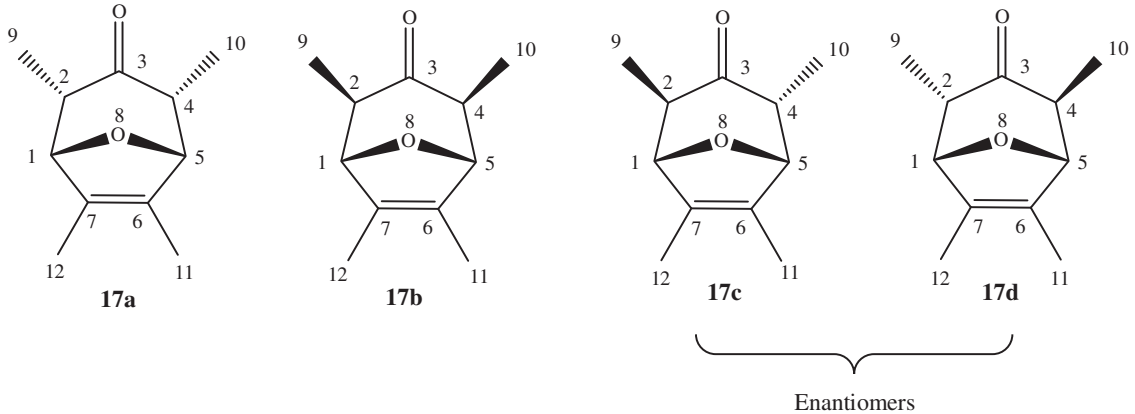
Diastereoisomers were separated after successive flash column chromatographies on silica gel, eluting with mixtures of hexane and diethyl ether of increasing polarity.

4.5.2.1. cis-Diequatorial Isomer, ***16a***. IR (film, ν, cm^{-1}): 999 (st. C–O), 1053 (st. C–O), 1151 (st. C–O), 1448 (def. C–H), 1644 (st. C=C), 1706 (st. C=O), 2935 (st. C–H). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.94 (3H, d, $J_{4,10}$=7.5 Hz, H10), 1.04 (3H, d, $J_{2,9}$=7.5 Hz, H9), 1.85 (3H, br s, H11), 2.79 (1H, dq, $J_{4,5}$=4.5 Hz, $J_{4,10}$=7.5 Hz, H4), 2.90 (1H, dq, $J_{1,2}$=4.5 Hz, $J_{2,9}$=7.5 Hz, H2), 4.57 (1H, d, $J_{4,5}$=4.5 Hz, H5), 4.73 (1H, br.d, $J_{1,2}$=4.5 Hz, H1), 5.86–5.88 (1H, m, H7). ^{13}C NMR (400 MHz; $CDCl_3$; δ, ppm): 10.1, 10.3 (C9, C10), 15.2 (C11), 48.8 (C4), 51.0 (C2), 83.4 (C5), 85.7 (C1), 126.6 (C7), 145.1 (C6), 209.5 (C3). MS [GC–CI–NH_3, t_R=8.08 min, 70 eV, 200 °C, $CHCl_3$, *m*/*z* (%)]: 184 (14, M+NH_4), 167 (100, M+H), 166 (36, M), 109 (8, M–C_3H_5O), 95 (12, M–C_4H_7O). EA. Calculated for $C_{10}H_{14}O_2$: C (72.26), H (8.49%). Found: C (72.29), H (8.51%). GC (35 °C, 1 min, 20 °C/min, 250 °C, 10 min): t_R=6.4 min.

cis-Diaxial isomer, **16b**: IR (film, ν, cm^{-1}): 1005 (st. C–O), 1060 (st. C–O), 1149 (st. C–O), 1450 (def. C–H), 1648 (st. C=C), 1705 (st. C=O), 2940 (st. C–H). ^1H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.33 (3H, d, $J_{10,4}$=7.5 Hz, H10), 1.36 (3H, d, $J_{2,9}$=7.5 Hz, H9), 1.79 (3H, br s, H11), 2.22 (1H, q, $J_{10,4}$=7.5 Hz, H4), 2.34 (1H, q, $J_{2,9}$=7.5 Hz, H2), 4.31 (1H, s, H5), 4.56 (1H, s, H1), 5.78–5.80 (1H, m, H7). ^{13}C NMR (400 MHz; $CDCl_3$; δ, ppm) 12.8 (C11), 17.8, 18.0 (C9, C10), 49.1 (C4), 50.3 (C2), 82.7 (C5), 85.0 (C1), 127.3 (C7), 143.9 (C6), 214.3 (C3). MS [GC–CI–NH_3, t_R=7.80 min, 70 eV, 200 °C, $CHCl_3$, *m*/*z* (%)]: 184 (40, M+NH_4), 167 (100, M+H), 166 (92, M), 109 (12, M–C_3H_5O), 95 (26, M–C_4H_7O). EA. Calculated for $C_{10}H_{14}O_2$: C (72.26), H (8.49%). Found: C (72.31), H (8.47%). GC (35 °C, 1 min, 20 °C/min, 250 °C, 10 min): t_R=6.1 min.

trans Diastereoisomers, **16c**,**d**. Only isomer **16d** has been formed or detected in very small amount. Isomer **16c** was not formed or if formed it has been in such a small amount that it was not detected by high field ^1H NMR, GC and GC–MS on the reaction crude mixture. IR (film, ν, cm^{-1}): 998 (st. C–O), 1058 (st. C–O), 1155 (st. C–O), 1449 (def. C–H), 1650 (st. C=C), 1707 (st. C=O), 2938 (st. C–H). ^1H NMR (500 MHz; $CDCl_3$; δ, ppm): 0.82 (3H, d, J=7.5 Hz, H9), 1.23 (3H, d, J=7.5 Hz, H10), 1.82 (3H, s, H11), 2.37–2.47 (4H, m, H4), 2.50–2.61 (1H, m, H2), 4.35 (1H, s, H5), 4.71 (1H, brd, $J_{1,2}$=4.5 Hz, H1), 5.82–5.84 (1H, m, H7). MS [GC–CI–NH_3, t_R=8.50 min, 70 eV, 200 °C, $CHCl_3$, *m*/*z* (%),]: 184 (45, M+NH_4), 167 (100, M+H), 166 (90, M), 109 (8, M–C_3H_5O), 95 (20, M–C_4H_7O). EA. Calculated for $C_{10}H_{14}O_2$: C (72.26), H (8.49%). Found: C (72.23), H (8.52%). GC (35 °C, 1 min, 20 °C/min, 250 °C, 10 min): t_R=5.9 min.

4.5.3. Synthesis of 2,4,6,7-tetramethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one.

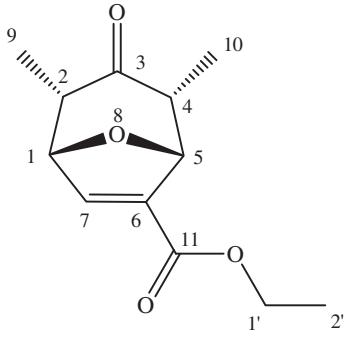


cis-Diequatorial isomer, **17a**: IR (ATR, ν, cm^{-1}): 1028 (st. C–O), 1152 (st. C–O), 1223 (st. C–O), 1456 (def. C–H), 1653 (st. C=C), 1709 (st. C=O), 2876 (st. C–H), 2933 (st. C–H), 2972 (st. C–H), 3418 (harmonic C=O). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.02 (6H d, CH_3; $J_{2,9}$=$J_{4,10}$=7.3 Hz, H9 and H10), 1.71 (6H, s, H11 and H12), 2.88 (2H, dq, $J_{1,2}$=$J_{4,5}$=4.0 Hz, H2 and H4), 4.55 (2H, d, $J_{1,2}$=$J_{4,5}$=4.0 Hz, H1 and H5). ^{13}C NMR (100 MHz; $CDCl_3$; δ, ppm): 10.1 (C9, C10), 12.5 (C11, C12), 50.8 (C2, C4), 87.0 (C1, C5), 134.8 (C6, C7), 209.7 (C3). MS [GC–CI–NH_3, 70 eV, 200 °C, $CHCl_3$, *m*/*z* (%)]: 182 (19, M+H), 181 (100, M), 123 (4, M–C_3H_5O), 109 (4, M–C_4H_7O). EA. Calculated for $C_{11}H_{16}O_2$: C (73.30), H (8.95%). Found: C (73.33), H (8.98%). GC (35 °C, 1 min, 20 °C/min, 250 °C, 10 min) t_R=7.0 min.

cis-Diaxial isomer, **17b**: IR (ATR, ν, cm^{-1}) 1030 (st. C–O), 1150 (st. C–O), 1225 (st. C–O), 1460 (def. C–H), 1655 (st. C=C), 1710 (st. C=O), 2901 (st. C–H), 2935 (st. C–H), 2980 (st. C–H), 3420 (harmonic C=O). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 1.35 (6H, d, $J_{2,9}$=$J_{4,10}$=7.5 Hz, H9 and H10), 1.65 (6H, s, H11 and H12), 2.27 (2H, q, $J_{2,9}$=$J_{4,10}$=7.5 Hz, H2 and H4), 4.32 (2H, s, H1 and H5). ^{13}C NMR (100 MHz; $CDCl_3$; δ, ppm): 10.1 (C11, C12), 17.8 (C9, C10), 47.7 (C2, C4), 86.1 (C1, C5), 135.7 (C6, C7), 214.5 (C3). MS [GC–CI–NH_3, 70 eV, 200 °C, $CHCl_3$, *m*/*z* (%)]: 199 (2, M+NH_4), 181 (84, M+H), 180 (100, M), 123 (6, M–C_3H_5O), 109 (5, M–C_4H_7O). EA. Calculated for $C_{11}H_{16}O_2$: C (73.30), H (8.95%). Found: C (73.28), H (8.89%). GC (35 °C, 1 min, 20 °C/min, 250 °C, 10 min): t_R=6.6 min.

trans Isomers, **17c**,**d** (*racemic mixture*): IR (ATR, ν, cm^{-1}) 1029 (st. C–O), 1155 (st. C–O), 1220 (st. C–O), 1458 (def. C–H), 1651 (st. C=C), 1708 (st. C=O), 2890 (st. C–H), 2930 (st. C–H), 2978 (st. C–H). ^{1}H NMR (500 MHz, C_5D_5N, δ, ppm): 1.01 (3H, d, $J_{4,10}$=7.5 Hz, H10), 1.35 (9H, d, $J_{2,9}$=7.5 Hz, H9), 1.66 (3H, s, H11), 1.75 (3H, s, H12), 2.32–2.39 (2H, q, $J_{4,10}$=7.5 Hz, $J_{2,9}$=7.5 Hz, H2 and H4), 4.47–4.49 (2H, m, H1 and H5). MS [GC–CI–NH_3, 70 eV, 200 °C, $CHCl_3$, *m*/*z* (%)]: 181 (70, M+H), 180 (100, M), 123 (4, M–C_3H_5O), 120 (3, M+NH_4), 109 (5, M–C_4H_7O). EA. Calculated for $C_{11}H_{16}O_2$: C (73.30), H (8.95%). Found: C (73.35), H (8.90%). GC (35 °C, 1 min, 20 °C/min, 250 °C, 10 min): t_R=6.4 min.

4.5.4. Synthesis of ethyl (1R,2S*,4R*,5R*)-2,4-dimethyl-8-oxabicyclo [3.2.1]oct-6-en-3-oxo-6-carboxilate,* ***18a****.*

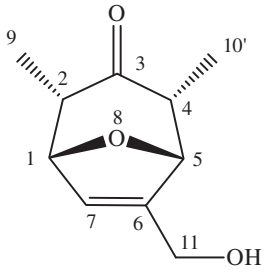


(*cis-endo* isomer)

Product **18a** has been prepared from furan **11** under different reaction conditions, which are quoted in Table 1 (see also the General methods section for the synthetic procedures).

Isomer cis–endo: IR (film, ν, cm^{-1}): 2977, 2938, 2878, 1715 (C=O, st),1458, 1379, 1277, 1250, 1001, 1032, 933. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.00 (3H, d, *J*=7.4 Hz, H9), 1.01 (3H, d, *J*=7.4 Hz, H10), 1.28 (3H, t, *J*=7.4 Hz, H2′), 2.93 (2H, m, H2 and H4), 4.21 (2H, m, H1′), 4.97 (1H, dd, J_1=5.2 Hz, J_2=1.8 Hz, H1), 5.11 (1H, d, *J*=4.4 Hz, H5), 7.16 (1H, d, *J*=1.8 Hz, H7). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 10.02 (C9), 10.5 (C10), 14.1 (C2′), 50.2 (C2), 50.9 (C4), 60.9 (C1′), 82.0 (C1), 83.9 (C5), 140.8 (C6), 143.4 (C7), 168.2 (C11), 209.2 (C3). MS [GC–MS (CI), NH_3, 70 eV, 150 °C, *m*/*z*, (%)]: 242 (100, M+NH_4), (225 (2, M+H)). EA. Calculated for $C_{10}H_{16}O_4$: C (64.27%), H (7.19%). Found: C (64.50%), H (7.12%). GC (50 °C, 1 min, 10 °C/min, 290 °C, 15 min): 12.03 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.20 (developed with vanillin–sulfuric acid reagent).

4.5.5. Synthesis of (1R,2S*,4R*,5R*)-6-hidroximethyl-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one,* ***19a****.*



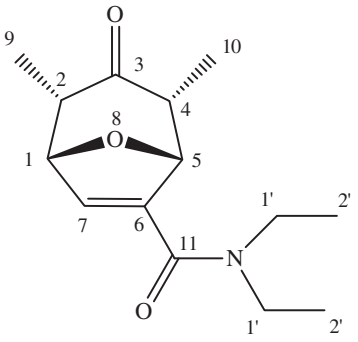
(*cis-endo* isomer)

The experimental method 2-Zn was used to prepare compound **19a** from furan **12**, but modified by stirring at 0 °C (see the General methods section for experimental details).

Results: Yield=70%. Diastereoselectivity: *cis*/*trans*=100:0, *endo*/*exo*=100:0.

Isomer cis–endo: IR (film, ν, cm^{-1}): 3448 (O–H, st), 2932, 1734 (C=O, st), 1684, 1653, 1559, 1456, 1375, 1150, 1051, 928. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.96 (3H, d, *J*=7.0 Hz, H9), 1.03 (3H, d, *J*=7.0 Hz, H10), 2.88 (2H, m, H2 and H4), 4.21 (2H, d, *J*=12 Hz, H11), 4.31 (1H, dd, J_1=5.0 Hz, J_2=1.8 Hz, H1), 4.81 (1H, d, *J*=4.4 Hz, H5), 6.16 (1H, d, *J*=1.8 Hz, H7). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 10.5 (C9), 10.9 (C10), 47.3 (C4), 50.8 (C2), 64.3 (C11), 80.2 (C5), 87.4 (C1), 127.3 (C7), 148.1 (C6), 210.2 (C3). MS [GC–MS (CI), NH_3, 70 eV, 150 °C, *m*/*z*, (%)]: 200.1 (100, M+NH_4), 183.2 (5, M+H), 164 (30, M–OH). EA. Calculated for $C_{10}H_{14}O_3$: C (65.91%), H (7.74%). Found: C (65.87%), H (7.79%). CCF (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.26 (blue color developed with anisaldehyde–sulfuric acid reagent).

4.5.6. Synthesis of (1R,2S*,4R*,5R*)-N,N-diethyl-2,4-dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-6-carboxamide,* ***20a****.*



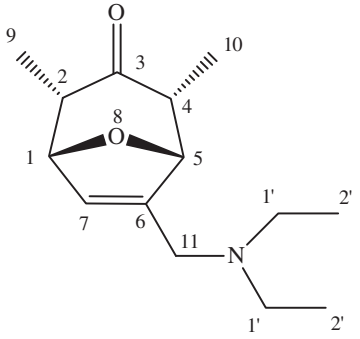
(*cis-endo* isomer)

Product **20a** has been prepared from furan **13**, under different reaction conditions, which are quoted in Table 1 (see also the General methods section for the synthetic procedures).

Isomer cis–endo: IR (film, ν, cm^{-1}): 2980, 2920, 1700 (C=O, st), 1460, 1430, 1350, 1310, 1210, 1090, 1030, 930. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.93 (3H, d, *J*=7.2 Hz, H9), 1.10 (3H, d, *J*=7.2 Hz, H10), 1.14 (6H, br t, *J*=7.0 Hz, H2′ and H2″), 2.93 (2H, dq, J_1=4.4 Hz, J_2=7.0 Hz, H2 and H4), 3.20 (4H, m, H1′ and H1″), 4.96 (1H, dd, J_1=4.4 Hz, J_2=1.8 Hz, H1), 5.19 (1H, d, *J*=4.4 Hz, H5), 6.68 (1H, d, *J*=1.8 Hz, H7). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 9.4 (C9), 10.4 (C10), 12,3 and 14.5 (C2′ and/or C2″), 42.6 and 39.6 (C1′ and/or C1″), 50.6 (C2), 50.9 (C4), 84.2 (C1), 84.7 (C5), 131.4 (C7), 142.1 (C6), 163.1

(C11), 208.7 (C3). MS [GC–MS (CI), NH_3, 70 eV, 150 °C, *m*/*z*, (%)]: 269 (45, M+NH_4), 262 (100, M+H). EA. Calculated for $C_{14}H_{21}NO_3$: C (66.91%), H (8.42%). Found: C (67.04%), H (8.25%). GC (50 °C, 1 min, 10 °C/min, 290 °C, 15 min): 15.78 min. TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.17 (blue color developed with anisaldehyde–sulfuric acid reagent).

4.5.7. Synthesis of (1R,2S*,4R*,5R*)-6-(N,N-diethylaminomethyl)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one,* ***21a****.*



(*cis-endo* isomer)

Compound **21a** has been prepared according to the experimental method 2-Zn, under stirring at 0 °C (see the General methods section for experimental details).

Results: Yield=81%. Diastereoselectivity: *cis*/*trans*=100:0, *endo*/*exo*=100:0.

Isomer cis–endo: IR (film, ν, cm^{-1}): 2950,2800, 2750, 1725 (C=O, st), 1460, 1445, 1380, 1200, 1150, 1040, 925. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.94 (3H, d, *J*=6.8 Hz, H9), 0.98 (6H, t, *J*=7.2 Hz, H2′ and H2″), 1.04 (3H, d, *J*=7.4 Hz, H10), 2.40 and 2.56 (4H, m, H1′ and H1″), 2.80 (1H, dq, J_1=4.7 Hz, J_2=7.0 Hz, H4), 2.91 (1H, dq, J_1=4.6 Hz, J_2=7.0 Hz, H2), 3.02 and 3.21 (2H, d, *J*=14, H11), 4.78 (1H, brd, *J*=4.4 Hz, H5), 4.80 (1H, d, *J*=4.8 Hz, H1), 6.06 (1H, br s, H6). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 9.7 (C9), 10.1 (C10), 11.7 (C2′ and C2″), 47.0 (C1′ and C1″), 47.1 (C2), 51.0 (C4), 52.2 (C11), 83.1 (C1), 83.3 (C5), 127.8 (C6), 148.5 (C7), 209.4 (C3). MS [GC–MS (CI), NH_3, 70 eV, 150 °C, *m*/*z*, (%)]: 238 (97, M+H), 237 (14, M^+). EA. Calculated for $C_{14}H_{23}NO_2$: C (70.85%), H (9.77%). Found: C (70.65%), H (6.69%). TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.08 (blue color developed with anisaldehyde–sulfuric acid reagent).

Acknowledgements

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Supplementary data

Digital copies of IR and ^{1}H- and ^{13}C NMR spectra of compounds described in this work are available on line from the publisher.

The main X-ray data for compound **20a** are quoted in Table 2 of this paper. The CIF file has been deposited as Supplementary data with The Cambridge Crystallographic Data Centre as file CCDC-92874, which contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. For additional information regarding bond lengths and bond angles for compound **20a**, as well as the hydrogen coordinates and the anisotropic thermal parameters see also Tables 4–7 of the Supplementary data available on line from the publisher. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.09.070.

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