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Asymmetry induction on the [4C(4π)+3C(2π)] cycloaddition reaction of C2-functionalized furans: influence of the chiral auxiliary nature

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Abstract—The study of the π-facial diastereoselectivity in the [4+3] cycloaddition reaction of thirteen different chiral 2-substituted furans with oxyallyl cations, under sonochemical and/or thermal conditions, is presented. In almost all studied furans, a *cis* diastereoselectivity and a high *endo* diastereoselectivity is observed. Decreasing the distance between the closest stereocenter of the chiral auxiliary and the reactive C2-carbon of the furan ring, increases the π-facial diastereoselectivity, especially by using chiral furyl-sulfoxides. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The [4C(4π)+3C(2π)] cycloaddition reaction[1] between C2-functionalized furans and oxyallyl cations is an elegant and efficient method to synthesize polyfunctionalized cycloheptenes. These systems are added-value structures with applications in the preparation of molecules with pharmacological and/or biological activity.[1,2] These synthons facilitate the straightforward synthesis of molecules having a seven-membered ring (Fig. 1). Moreover, the oxidative cleavage of the carbocycle is also a good method to synthesize, in a stereoselective manner, linear polysubstituted synthons (Fig. 1) that could be transformed into subunits of biologically active natural products such as ionomycin,[3] rifamycin[4] and other antibiotic macrolides, which are usually prepared by reiterated aldol reactions with difficult stereocontrol.

Many of the actual synthetic target molecules having pharmacological interest are chiral, and due to the experimental finding that usually only one of the two enantiomers (eutomer) has the required biological activity, it is of great importance to prepare enantiomerically pure compounds, for economical and safety reasons. The [4+3] cycloaddition reaction is generally used as one of the initial steps of the synthetic pathways, and because the resulting bicyclic cycloadduct has little conformational freedom, this reaction is a very adequate step to induce asymmetry in the overall synthetic process. In addition, in the [4+3] cycloaddition reaction four stereocenters are simultaneously formed, whose relative configuration is determined by mechanistic requirements of the reaction, resulting in a high stereoselectivity.

Surprisingly, in the literature, there are only a few

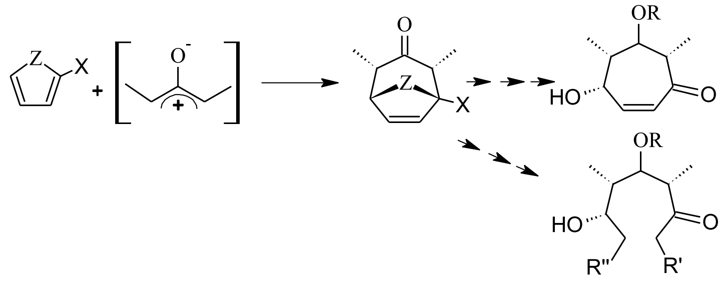

Figure 1. Preparation of useful C_7 synthons by [4+3] cycloaddition reactions.

Keywords: [4+3]-cycloaddition; oxyallyl cation; *syn–anti*; *endo–exo*; π-facial diastereoselectivity; chiral auxiliary; furan.

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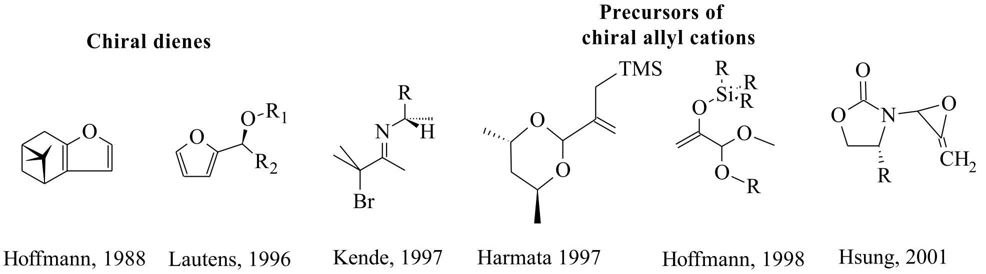


Figure 2. Chiral precursors used in asymmetric [4+3] cycloadditions.

references to the preparation of enantio-enriched cycloheptane synthons via [4+3] asymmetric cycloadditions (Fig. 2). The first reference to the use of chiral substrates in [4+3] cycloadditions is due to Hoffmann[5] who published in 1988 an example of diastereoselective cycloaddition using pinofuran as a chiral diene. In 1996, Lautens[6] published a study on the induction of asymmetry in the [4+3] cycloaddition reactions by using furfural derived substrates such as chiral 2-(1-hydroxy-1-alkyl)-furans. In 1997, Kende[7] published his work on the enantioselectivity of [4+3] cycloadditions induced by chiral 2-amino-allyl cations. The first mention of asymmetric induction in [4+3] cycloaddition reaction using chiral acetals was made by Harmata in 1997.[8a] In 1998, Hoffmann[8b] published the first of a series of works dealing with the asymmetry induction in the [4+3] cycloaddition reaction by using 2-trialkylsilyloxy-1-alkoxy-allyl cations that have at C1 a chiral alkoxy group. Finally, in 2001, Hsung[9] published his work on the use of chiral epoxyallenes as precursors of chiral nitrogen-substituted oxyallyl cations and its use in enantioselective [4+3] cycloadditions (Fig. 2).

On the basis of these precedents, we planned the study of the induction of asymmetry in the [4+3] cycloaddition reaction by using chiral furan derivatives. We introduced on C2 of the furan ring a chiral substituent (in most cases an easily removable chiral auxiliary). We thought this alternative to be promising due to the excellent diastereoselectivity obtained by us in previous work on [4+3] cycloaddition reactions of achiral C2-functionalized furans.[10]

This approach has, a priori, several advantages with respect to other possible methodologies to induce enantioselectivity in this reaction (Fig. 3):

(a) First of all, the insertion of the chiral group to the diene allows, without restrictions, the use of a wide range of methodologies[1,11] to generate oxyallyl cations of different nature, depending on the synthetic necessities, which makes the approach versatile.

(b) The use of C2-functionalized furans results in the formation of cycloadducts having a doubly functionalized bridgehead, which facilitates the opening of the oxygen bridge to afford 3,6-difunctionalized cycloheptanes with controlled and defined relative stereochemistry (Fig. 2). This fact also facilitates the removal and recycling of the chiral auxiliary.

(c) Our previous experience in the reactivity of achiral C2-substituted furans[10] allowed us to select the most adequate diene as substrate in order to get the highest *cis*/*trans* and *endo*/*exo* diastereoselectivities, in such a way that we could obtain almost stereospecifically the *cis*-*endo* diastereoisomeric cycloadducts. This facilitates the study of the π-facial diastereoselectivity ('enantioselectivity' after removal of the chiral auxiliary) because it reduces the number of formed stereoisomers from eight to two.

(d) This methodology allows working with both enantiomers of the chiral auxiliary in order to get stereoselectively one or other of the π-facial diastereomeric cycloadducts.

2. Results and discussion

In the present work, we have synthesized and used as diene substrates in [4+3] cycloaddition reactions 13 chiral C2-functionalized furans, in order to study the influence of the distance between the reactive center, C2, of the furan and the closest stereocenter from the chiral auxiliary. In addition, the influence on the stereoselectivity of the nature of the organic function acting as a linker of the furan and the chiral auxiliary was also studied (Fig. 4).

When achiral C2 substituted furans[10] are used, it is possible

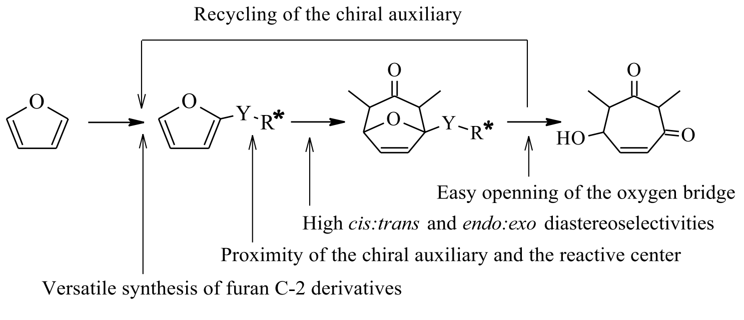


Figure 3. Advantages of the model of induction of asymmetry in the [4+3] cycloaddition reactions by using C2-functionalized furans.

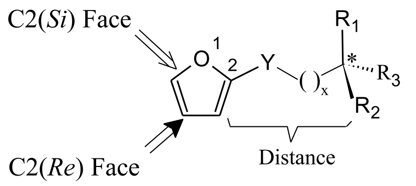


Figure 4. Model of a chiral C2 functionalized furan (the notation of the faces depends on the CIP rules in each case).

to form up to four cycloadducts as racemic diastereoisomers, resulting from the coupling with a symmetrically substituted oxyallyl cation. When using chiral furans, it is possible to obtain up to eight diastereomeric cycloadducts (Fig. 5), due to both faces of the chiral furan are diastereotopic (Fig. 4).

2.1. Influence of the nature of furan dienes on the stereoselectivity

We have synthesized 13 chiral furans by insertion of a chiral group on C2 (Fig. 6). The design and selection of these

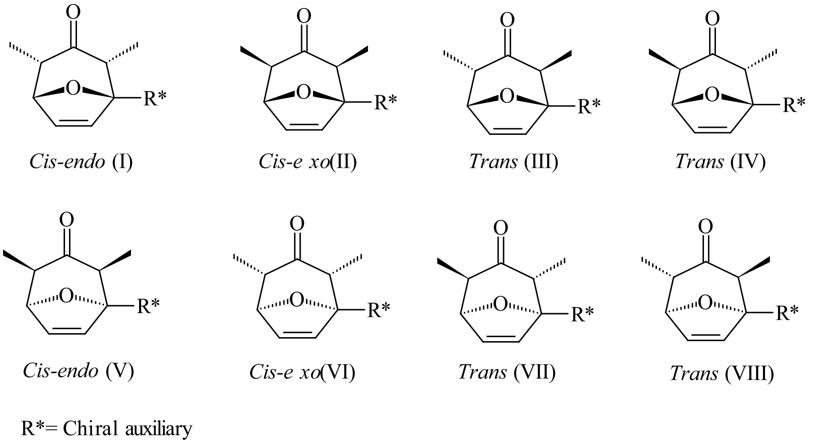


Figure 5. The eight possible diastereomers from the cycloaddition reaction between a symmetrically substituted oxyallyl cation and a C2-substituted chiral furan.

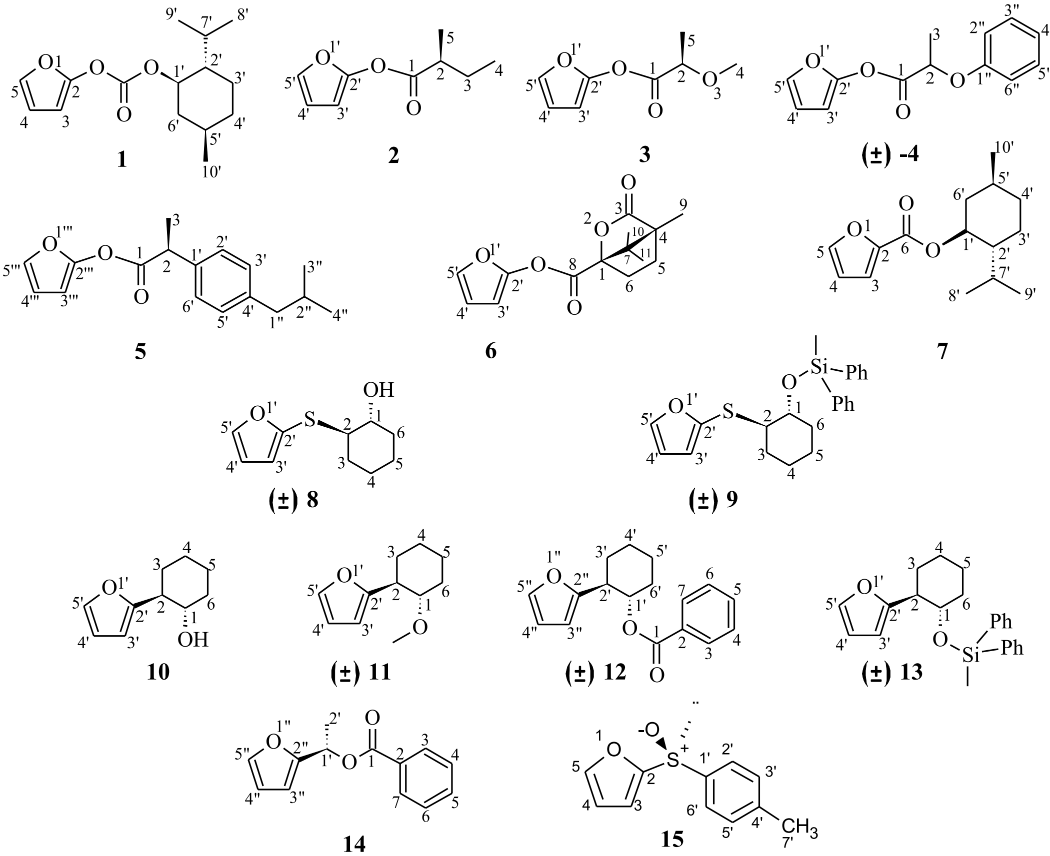


Figure 6. Chiral furan derivatives prepared in the present work.

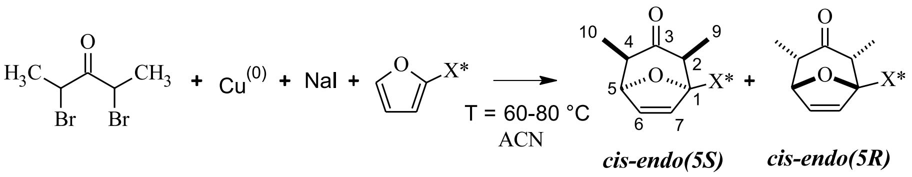


Figure 7. [4+3] Cycloaddition reaction of chiral furans under Hoffmann methodology.

chiral groups was based on the following criteria in order to analyze their influence on the stereodifferentiation of the furan faces: (a) the distance between the insertion and reactive center of the furan derivative and the closest stereocenter of the chiral auxiliary (Fig. 4); (b) the volume and shape of the auxiliary; (c) the stereoelectronic nature of the organic function that acts as a linker between the furan ring and the auxiliary, considering the geometry and the conformational freedom that this function gives to the linker.

The H–C2 of furan is easily removed by a strong base (usually BuLi), which facilitates the preparation of these C2 functionalized furans by attack of the resulting furyl lithium on an electrophilic center of a chiral auxiliary precursor. In most of the cases, we obtained these furan derivatives in enantiopure form, however, in some experiments, racemic furan derivatives were used due to the availability and low cost of racemic precursors. This fact does not distort the study of the stereodifferentiation of both faces of the diene by the chiral group (π-facial diastereoselectivity), but only leads to the formation of the different diastereoisomeric products in racemic form. On the other hand, the values of π-facial diastereoselectivity detected by usual non-chiroptical techniques are identical for both enantiomers of the chiral auxiliary.

One of the reasons to use C2-functionalized furans as substrates is the possibility to open, in an easy and selective manner, the oxygen bridge of the cycloadducts. Further, in our study of the asymmetric induction, it is of interest to analyze the effect of the distance between the first stereocenter of the chiral auxiliary and the reactive center, C2, of the furan derivatives on the stereochemical outcome of the [4+3] cycloaddition reaction. In the case of one-bond distance, the atom directly attached to C2 of furan should be a stereocenter. This is only possible for C2-alkylated furans or for furans attached to chiral heteroatoms like in the case of chiral sulfoxides (Fig. 6).

2.2. Cycloaddition methodologies

Initially we used the cycloaddition methodology based on the generation of the 2-oxyallyl cation by reduction of 2,4-dibromo-3-pentanone with copper, in the presence of sodium iodide, which was described by Hoffmann[12] (Fig. 9). In previous studies,[10] under these conditions, we obtained high *cis*/*trans* and *endo*/*exo* diastereoselectivities. The high *cis* stereoselectivity could be interpreted on the basis of both the preferential adoption of the 'W' configuration by the oxyallyl cation and the concerted mechanism of the cycloaddition reaction. The almost exclusive formation of the *endo* isomers could be due to both the preferential compact (versus extended) approach and the adequate design of the group attached to C2 of the furan substrates.[10] Therefore, under these experimental conditions, it was possible to get the *cis-endo* cycloadducts, almost stereospecifically.

Because the aforementioned Hoffmann methodology implies the use of strong and energetic reaction conditions, we designed a new methodology that requires milder reaction conditions,[13] with the intention of raising both the yield, by decreasing the formation of byproducts, and the π-facial diastereoselectivity, by decreasing the conformational freedom of the reactants. In this new methodology, we generated the oxyallyl cation by reduction of 2,4-diiodo-3-pentanone with zinc–copper couple at lower temperatures under ultrasound sonication.

2.2.1. Diastereoselectivity under the Hoffmann methodology. We have carried out cycloaddition reactions of 13 chiral furans (Fig. 6) under the Hoffmann conditions (Fig. 7)

Table 1. Results from the [4+3] cycloaddition reactions of chiral furans using Hoffmann methodology

Entry	Diene	Cycloadduct	Conversion (%)	Yield (%)	DS[a] *cis*/*trans* (%)	DS[a] *endo*/*exo* (%)	DS[a] π-facial (%)
1	**1**	**16**	66	54	100:0	89:11	51:49
2	**2**	**17**	97	74	100:0	95:5	50:50
3	**3**	**18**	100	66	100:0	94:6	49:51
4	**4**	**19**	96	87	100:0	97:3	48:52
5	**5**	**20**	92	76	100:0	95:5	47:53
6	**6**	**21**	97	12	100:0	100:0	49:51
7	**7**	**22**	83	42	100:0	100:0	45:55
8	**9**	**23**	80	80	100:0	100:0	54:46
9	**13**	**24**	66	53	100:0	100:0	37:63
10	**11**	**25**	69	66	100:0	100:0	63:37
11	**12**	**26**	60	70	100:0	100:0	63:37
12	**14**	**27**	57	38	100:0	100:0	46:54
13	**15**	**28**	55	51[b]	100:0	100:0	73:27

[a] DS: Diastereoselectivity.

[b] Partially reduced to sulfide.

whose results are quoted in Table 1. We have chosen several linking functions to attach the chiral auxiliary to C2 of furan: carbonate, ester, thioether, sulfoxide and cycloalkyl linkers. On the other hand, we have studied the influence on the π-facial diastereoselectivity of one to four bonds distance between C2 of furan and the first stereocenter of the chiral auxiliary.

Table 1 shows that the yields are good in most cases. This parameter has a direct relationship with the stereoelectronic nature of the C2 substituent of furan. These results are consistent with the empirical rules established on the basis of our previous work:[10] electron-donating groups (entries 1–5 and 8) show the best results, followed by the cycloalkyl derivatives (entries 9–12). The furans having electron-withdrawing groups, due to the negative inductive effect on the furan ring, afford lower yields (entry 7). These trends are obviously modulated by the steric interactions of the substituents. Therefore, bulky groups hamper the approach of the dienophile, decreasing the conversion of furans and the yield of cycloadducts.

With respect to the *cis*/*trans* diastereoselectivity, it is possible to observe that, independent of the structure of the furan derivative, all obtained cycloadducts have a relative *cis* configuration for the methyl groups attached to C2 and C4. This could be the consequence of the W configuration adopted by the oxyallyl cation, which depends on the reaction conditions and on the nature of the substituents of the oxyallyl cation. In relation to the *endo*–*exo* diastereoselectivity, the results quoted in Table 2 confirm the empirical rule observed in our previous work[10] that establishes a direct relationship between the size and bulkiness of the C2 substituent of furan and the *endo*/*exo* ratio of the diastereoisomeric cycloadducts. Thus, we observed the almost exclusive formation of the *endo* diastereoisomer. This result could be due to the fact that the extended approach leading to the formation of the *exo* product is destabilized in relation with the compact approach due to the presence of a bulky group on C2 of the diene.

The observed π-facial diastereoselectivity could be rationalized on the basis of four factors: (a) the distance from C2 of furan to the first stereocenter of the chiral auxiliary, (b) the nature of the linker (type of organic function), (c) the size and shape of the chiral auxiliary and (d) the conformational freedom of both the linker and the auxiliary group.

With respect to the effect of the distance on the stereodifferentiation on the faces of the furan ring, we can observe in Table 1 that for long distances the π-facial diastereoselectivity is low or null (see entries 1–6, corresponding to 4 or 3 bonds distance). Even though these results could be expected we designed these 'long distance' chiral dienes in order to account for the possible dipolar interactions and the formation of hydrogen bonds.

When the chiral auxiliary is separated from the furan by one or two bonds (see entries 9–12 and 8, respectively) the π-facial diastereoselectivity increases. The relation between the distance and the π-facial diastereoselectivity is not linear and it depends on other factors as it is commented below (compare, for example, entries 9–11 from Table 2). One effect that should be analyzed is the influence of the volume and shape of the groups attached to the closest stereocenter (C^*). This effect is more important when the $C2{-}C^*$ distance is shorter. Thus, when there is only one bond distance, the increase of the size of substituents attached to the stereocenter, C^*, raises the π-facial diastereoselectivity (compare entries 11 and 12). For long distances, this substitution effect could be observed but to a lesser extent: compare the different furyl esters from entries 2–6 or the three derivatives of 2-furyl-cyclohexanol (entries 10 and 11 versus 9). Finally, another remarkable effect to consider is the nature of the linking function. Thus, comparing entries 2–7 from Table 2, we can observe

Table 2. Results from the [4+3] cycloaddition reactions using mild modified reaction conditions

Entry	Diene	X[a]	M[b]	T[h]	Energy source[d]	Conv. (%)	Yield (%)	DS[e] *cis*/*trans* (%)	DS[e] *endo*/*exo* (%)	DS[e] π-facial (%)
1[f]	**7**	Br	Cu	60	HMS	83	42	100:0	100:0	45:55
2	**7**	I	Zn	0	HMS	41	100	100:0	100:0	45:55
3	**7**	I	Zn	20	HMS	60	100	100:0	100:0	45:55
4	**7**	Br	Cu	20	HMS	50	100	100:0	100:0	45:55
5[f]	**13**	Br	Cu	60	HMS	66	53	100:0	100:0	37:63
6	**13**	I	Cu	0	US	55	100	100:0	100:0	37:63
7[f]	**11**	Br	Cu	60	HMS	69	66	100:0	100:0	63:37
8	**11**	I	Cu	0	US	37	85	100:0	100:0	65:35
9	**11**	I	Zn	0	US	56	100	100:0	100:0	65:35
10[f]	**12**	Br	Cu	60	HMS	60	70	100:0	100:0	63:37
11	**12**	I	Cu	0	US	32	100	100:0	100:0	65:35
12[f]	**14**	Br	Cu	60	HMS	57	38	100:0	100:0	46:54
13	**14**	Br	Zn	20	HMS	40	100	100:0	100:0	46:54
14[f]	**15**	Br	Cu	60	HMS	55	51	100:0	100:0	73:27
15	**15**	Br	Zn	20	HMS	45	100	100:0	100:0	75:25
16	**15**	I	Zn	0	US	36	100	100:0	100:0	77:23
17	**15**	I	Zn	20	US	47	100	100:0	100:0	76:24

[a] Dihaloketone (Fig. 10).

[b] Reducing metal.

[c] Inner temperature.

[d] Energy source: HMS=heating and/or magnetic stirring. US=ultrasound.

[e] DS: Diastereoselectivity.

[f] Hoffmann conditions.

that placing the ester function conjugated to the furan ring, we restrict the conformational freedom of the system and the diastereoselectivity raises (up to 10%) with respect to that of the ester functions non-conjugated to the aromatic ring. The high conformational freedom is the responsible of the observed medium to low π-facial diastereoselectivity, which reaches in the most favorable case a value of d.e.=46%.

The experiment involving the 2-(*p*-tolylsulfinyl)-furan requires special mention. Under the Hoffmann experimental conditions, it affords a higher diastereoselectivity than other furans (entry 13). However, the resulting cycloadducts undergo a partial reduction (up to 49%) of the sulfoxide group to thioether, under the aforementioned conditions. It is worth noting that the reduction of the sulfoxide group takes place on the cycloadduct once it is formed and not on the furan precursor, which has been demonstrated by submitting 2-(*p*-tolylsulfinyl)-furan to the same reaction conditions without the presence of 2,4-dibromo-3-pentanone (precursor of the 2-oxyallyl cation). In such cases, the furan derivative remained unchanged after several hours of reaction time. We can rationalize this result by assuming a stabilizing resonance effect between the sulfoxide group and the aromatic furan ring.

2.2.2. Study of the induction of asymmetry in the cycloaddition reaction under mild modified conditions. Due to the high conformational freedom of furan derivatives at the reaction temperature of the previous experiments and the problem of partial reduction of the cycloadducts (in the case of sulfoxide group), we designed new experimental conditions,[13] (Fig. 8) based on the use of 2,4-diiodo-3-pentanone, as precursor of the 1,3-dimethyl-2-oxy-allyl cation and Zn or Zn–Cu couple as reducing agents, at lower temperatures (0–20°C), under ultrasound or magnetic stirring. Under these new reaction conditions, we tried those chiral furan derivatives that showed promising stereodifferentiating properties under the Hoffmann reaction conditions. In Table 2 we have showed, on a comparative way, the experiments carried out under both reaction conditions, the Hoffmann's and the new milder ones, and their corresponding results (yield and diastereoselectivities: *cis*/*trans*, *endo*/*exo* and π-facial).

Looking at Table 2 it is possible to observe that when using the new experimental conditions, the yield is always higher than that obtained by using the more energetic Hoffmann reaction conditions (entries in italics). The yield becomes quantitative when NaI is not used as initiator. The higher observed yields when using lower temperature in the absence of NaI could be due to the increase in chemical selectivity avoiding polymerization reactions of the oxyallyl cation, electrophilic additions to the furan ring or partial reductions of the cycloadducts. However, the conversion of the furan substrates for a given reaction time is lower than in the case of using the Hoffmann reaction conditions.

As in the case of the experiments carried out under the Hoffmann reaction conditions (Table 1), we obtained, with the new milder conditions (Table 2), complete *cis*/*trans* and *endo*/*exo* diastereoselectivities, which confirms that the oxyallyl cations generated by both procedures adopts a preferential W configuration and that the process goes through a concerted mechanism. With respect to the π-facial diastereoselectivity, we observe a slight increase in the stereodifferentiation of the furan faces in the case of dienes **11**, **12** and **15**, while in the case of furans **7**, **13** and **14** the π-facial diastereoselectivity is the same than that observed in the experiments carried out under Hoffmann conditions. This small improvement of 2–3% in the π-facial diastereoselectivity could be interpreted on the basis of the lower reaction temperature (from 60 to 0–20°C) that reduces the conformational freedom at the level of the chiral auxiliary. This allows a better stereodifferentiation of the furan faces and it facilitates the approach of the oxyallyl cation by the less hindered face of the furan ring.

2.3. Assignment of the relative stereochemistry of cycloadducts

When using a symmetric oxyallyl cation and a chiral furan as diene, it is possible to obtain up to eight diastereoisomers (homochiral if an enantiopure diene is used or racemic if the diene is also racemic. See Fig. 5). The differentiation and characterization of these diastereoisomers was carried out by comparative analysis and correlation of their NMR spectra obtained from samples of pure diastereoisomers or from mixtures (in different ratios) of them, when they were non-separable by conventional methods. For this purpose, we followed next protocol:[14]

(a) Unequivocal assignment of the ^1H and ^{13}C NMR signals by 1D and 2D NMR experiments (DEPT, COSY ^1H–^1H, HETCOR ^1H–^{13}C, HMQC, HMBC, TOCSY, etc.).
(b) Conformational analysis by MM3 computational methods in order to find the minimum energy conformation of each diastereoisomer.
(c) Comparative study of the NMR data from all diastereomers. Analysis of significant differences and correlation studies.
(d) Study of the configuration-dependent stereoelectronic effects responsible of significant and diagnostic Δ*J* (Hz)

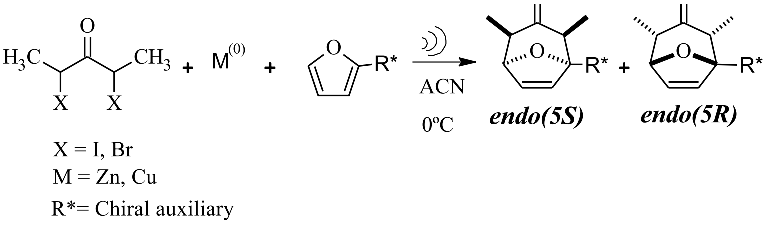
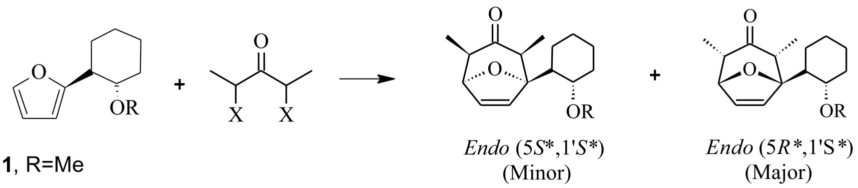


Figure 8. [4+3] Cycloaddition reaction under the mild modified conditions.



Endo (5*S**,1′*S**) (Minor)

Endo (5*R**,1′S*) (Major)

11, R=Me

12, R=OCPh

13, R=$SiPh_2Me$

25, R=Me

26, R=OCPh

24, R=$SiPh_2Me$

Figure 9. *endo* Stereoselectivity in the [4+3] cycloaddition reactions of chiral furans **11**–**13**.

and $\Delta\delta$ (ppm) among diastereomers in their minimum-energy conformations.

(e) Assignment of the relative stereochemistry that should have a consistency with all data and observations from the previous studies.

Up to this point, we were only able to establish the relative stereochemistry. In most cases, we worked with enantiopure chiral auxiliaries, and we should be able to determine the absolute stereochemistry (because we have as a stereochemical marker the inserted chiral auxiliary of known absolute stereochemistry). However, it was not possible to get crystals suitable for X-ray diffraction studies.

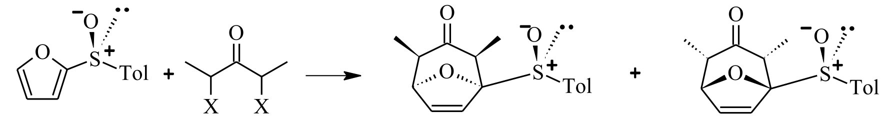
The assignment of the relative *cis*/*trans* and *endo*/*exo* stereochemistry was possible by the analysis of the influence exerted on the chemical shifts δ (ppm) by the stereoelectronic effects (coulomb interactions, shielding and deshielding effects) among the substituents of the oxabicycle,[14] which is facilitated by the conformational rigidity of the bicyclic system. These assignments are corroborated by the comparative analysis of the coupling patterns between vicinal hydrogens on all formed diastereoisomers. This model of assignment has proven to be of general applicability to all studied cycloadducts, irrespective of the nature of the chiral auxiliary, because the influence that the auxiliary has on the chemical shifts of the hydrogens and carbon atoms of the oxabicyclic moiety is very low compared to the influence among the atoms and other substituents of the oxabicycle itself.

The assignment of stereochemistry to the diastereoisomers (for example: *endo* (5*R*,1′*S*) and *endo* (5*S*,1′*S*)) resulting from the attack through both faces of the furan ring (π-facial diastereoselectivity) cannot be carried out on the basis of a unique model of general applicability. Each case should be individually studied, because the variations of the chemicals shifts of the involved hydrogens and carbon atoms depend on the nature of the chiral auxiliary. Thus, it is possible to distinguish two cases:

(a) Cycloadducts with a chiral center far away from the oxabicyclic system. In this case, the stereoelectronic interaction of the chirality-inducing group with the rest of the molecule is very low and the shielding and deshielding effects are very difficult to rationalize. For this reason, in many of these cases, it was not possible to do the assignment of the stereochemistry (i.e. *endo* (5*R*) or *endo* (5*S*)) of the cycloadducts. In these cases, the *endo* diastereoisomers are identified as *endo* A and *endo* B (without using the CIP notation). The notation A, B corresponds to the order of elution of both diastereoisomers in gas chromatography (R_t *endo A*$<$$R_t$ *endo B*).

(b) Cycloadducts with a chiral center close to the oxabicyclic system and with bulky groups near the first stereocenter (products **24**–**28**). In this case, it is possible that the stereochemical assignment of each model because the interaction of the auxiliary with the oxabicyclic moiety of the molecule is more intense, which allows a more reliable interpretation of the shielding and deshielding effects in NMR spectra. On the other hand, the conformational freedom is lower, in such a way that the aforementioned effects could be rationalized on the basis of the most stable conformation of one or other of both ‘π-facial’ diastereoisomers. These diastereoisomers are named in this work as *endo* (5*R*) or *endo* (5*S*) depending upon the stereochemistry postulated in each case. These are tentative reasonable assignments of the configuration, which should be confirmed by X-ray diffraction analyses when reliable crystals became available.

In the case of cycloadducts **24**–**26** derived from the *trans*-cyclohexyloxy-furans (**11**–**13**), an exhaustive correlation study of their spectroscopic properties and also molecular modeling studies,[15] based on MM3 computational methods, permitted us to postulate that the diene–dienophile



15

28, *Endo* (5*S*, S_S) (Minor)

28, *Endo* (5*R*, S_S) (Major)

Figure 10. *endo* Stereoselectivity in the [4+3] cycloaddition reaction of chiral furan **15**.

approach takes place preferment by the C2(*Si*) face of the chiral furan derivative, through late transition states (resembling the products). Thus, we obtained the stereoisomer *endo* ($5R^*$,1′*S*) as the major one and the *endo* ($5S^*$,1′*S*) as the minor one (Fig. 9).

The NMR analysis of the cycloadducts derived from 2-(*p*-tolylsulfinyl)-furan indicates the preferential approach between the furan and the oxyallyl cation takes place by the C2(*Re*) face (same face than in the previous case, but the notation changes according to the CIP rules), leading to the *endo* ($5R,S_S$) diastereoisomer as the major one and to the cycloadduct *endo* ($5S,S_S$) as the minor one (Fig. 10).

3. Conclusions

The results obtained from the experiments carried out following both cycloaddition methodologies (Hoffmann's and the milder modified one) allowed us to draw interesting conclusions that represent a first step in the induction of asymmetry in the [4+3] cycloaddition reactions mediated by chiral C2-functionalized furans. We have obtained in this work excellent *cis*/*trans* and *endo*/*exo* diastereoselectivities and from null to moderate (d.e.=30% from furans **11–13**) or promising (d.e.=54% in the case of furan **15**) π-facial diastereoselectivities. In addition, we have opened the possibility, by designing the chiral auxiliary, of obtaining an oxabicycle with *endo* (5*R*) or *endo* (5*S*) stereochemistry.

In addition, we observed that both, the length and functional nature of the linker between the furan ring and the chiral auxiliary and, the bulkiness, substitution pattern and shape of the auxiliary group itself have high influence on the π-facial diastereoselectivity and a very low influence on the *cis*/*trans* and *endo*/*exo* diastereoselectivities. At the same time, we appreciated the influence of the conformational freedom of the diene-chiral auxiliary system on the π-facial diastereoselectivity, effect that has important consequences at low temperature.

Now, we are actively working in our laboratory in order to improve the conversion of substrates and the π-facial diastereoselectivity in the [4+3] cycloaddition reactions of chiral C2-functionalized furans on two fronts: (a) working at very low temperatures but using high frequency ultrasound as an energy source; (b) modifying the structure of the chiral auxiliary and the nature of the linker in order to decrease the conformational freedom of the system. Simultaneously, we are trying to optimize the isolation and purification methods of cycloadducts and to obtain crystals of cycloadducts suitable for X-ray analysis.

4. Experimental

4.1. General methods

Unless otherwise noted, all reactions were conducted under an atmosphere of dry argon in oven-dried glassware. All solvents were purified before use: ether, tetrahydrofuran, benzene, hexane and pentane were distilled under nitrogen from sodium/benzophenone. Methylene chloride, acetonitrile and propionitrile were distilled under nitrogen from CaH_2. Infrared spectra were recorded on a FT-IR NICOLET 510 spectrophotometer as thin films or as solutions. NMR spectra were carried out in deuterated chloroform at 200 MHz (GEMINI-200), 300 MHz (UNITY-300) and/or 500 MHz (UNITY-500) for ^{1}H NMR, and at 50 and 75.43 MHz for ^{13}C NMR. For ^{1}H NMR, tetramethylsilane was used as internal standard. ^{13}C NMR spectra were referenced to the δ 77.0 ppm resonance of chloroform. Mass spectra were measured on a HEWLETT–PACKARD 5890 mass spectrometer using electron impact or/and chemical ionization. Melting points were measured on a GALLENKAMP equipment. GC analyses were performed on HP-8790 gas chromatograph equipped with a HEWLETT–PACKARD *cross-linked* MePh–silicone capillary column (L=25 m, $\varnothing$=0.2 mm, ϑ=0.25 μm) using Helium as a carrier gas and a FID detector (T=250°C, Pressure (H_2)=4.2 psi, Pressure (air)=2.1 psi). GC analyses were carried out under different temperature/time conditions, indicated at each compound as: initial temperature (°C), initial time (min), rate (°C/min), final temperature (°C), final time (min). Elementary analyses were obtained with a FISIONS Na 1500 apparatus, analyzing combustion gases by gas chromatography and using a thermal conductivity detector. The optical activity analyses were carried out on a PERKIN–ELMER 241 MC polarimeter, at room temperature.

4.2. Synthesis of chiral furan derivatives

4.2.1. (1′*R*,2′*S*,5′*R*)-2-[(2-Isopropyl-5-methyl-1-cyclohexyloxy)-carbonyloxy]furan,[16] (1). Under argon atmosphere and at −23°C, γ-crotonolactone (388 mg, 4.57 mmol) was dissolved in dry acetonitrile (1 mL). Then, at this temperature, freshly distilled (from potassium hydroxide) triethylamine (554 mg, 5.48 mmol) was added. The color of the reaction mixture changed from white to pale red, then, a solution of (−)-menthyl-chloroformiate (1 g, 4.57 mmol) in dry acetonitrile (4 mL) was added dropwise. The reaction mixture was kept at 0°C for 1 h, and then it was stirred for additional 14 h at room temperature. The product was isolated by distilling off the solvent and by suspending the residue in dry diethyl ether (25 mL) and filtering out the formed $NEt_3H^+Cl^-$. The organic layer was washed with water (3×50 mL) and brine (1×50 mL), dried over anh. $MgSO_4$, filtered and concentrated to dryness. The product was purified by distillation under 8 mmHg and at a temperature between 150 and 200°C, on a Kugelrohr apparatus, affording 1.032 g of a colorless oil (Conv.=100%, Yield=64%). IR (film, ν, cm^{-1}): 2960, 2940, 2920, 1740 (C=O, st), 1600, 1570, 1410, 1210, 1160. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.82 (3H, d, J=6.9 Hz, H10′), 0.92 (3H, d, J=7 Hz, H8′ or H9′), 0.94 (3H, d, J=6.4 Hz, H8′ or H9′), 1.15–1.25 (2H, m, 1H3′ and 1H6′), 1.42–1.47 (2H, m, H7′ and H2′), 1.68–1.72 (2H, m, H3′ and H4′), 1.95–2.04 (1H, m, H5′), 2.12–2.17 (1H, m, 1H6′), 4.61 (1H, dt, J_1=10.8 Hz, J_2=4.5 Hz, H1′), 5.87 (1H, dd, J_1=3.3 Hz, J_2=1.1 Hz, H3), 6.35 (1H, dd, J_1=2.1 Hz, J_2=3.4 Hz, H4), 7.05 (1H, dd, J_1=2.2 Hz, J_2=1.1 Hz, H5). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 16.7 (C10′), 20.6 and 22.0 (C9′ and C8′), 23.2 (C3′), 26.1 (C5′), 31.2 (C7′), 33.9 (C4′), 40.2 (C6′), 46.8 (C2′), 80.6 (C1′), 92.0 (C3), 111.5 (C4), 136.6 (C5), 151.1 (CO_3), 151.2 (C2). MS

[GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 301 (10, M+N_2H_7), 285 (18, M+1+NH_4), 284 (100, M+NH_4). Anal. calcd for $C_{15}H_{22}O_4$: C, 67.63; H, 8.33. Found: C, 67.49; H, 8.51%. $[\alpha]_D^{23}=-43.2$ (c=1.5, $CHCl_3$). GC (100°C, 1 min, 10°C/min, 250°C, 1 min): R_t=14.4 min. TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.58.

4.3. Synthesis of 2-furyl esters[17]

At −23°C and under argon atmosphere, γ-crotonolactone (1 equiv.) was dissolved in dry acetonitrile (1 mL, distilled from calcium hydride). Then, triethylamine (1.2 equiv., freshly distilled from potassium hydroxide) was added. The mixture turned into a pale red color, then, a solution of the acid chloride derivative (1 equiv., synthesized according to the literature[18]), in dry acetonitrile, was added dropwise under efficient magnetic stirring. The reaction mixture was maintained at 0°C for 1 h, and then was stirred at room temperature, until constant conversion. The crude mixture was concentrated to dryness in a rotary evaporator, without heating. Diethyl ether was added (25 mL) and the resulting suspension filtered to remove $NEt_3H^+Cl^-$. The organic solution was washed with water (3×50 mL) and brine (1×50 mL), dried over anh. $MgSO_4$ and concentrated to dryness without heating. The product was purified by distillation in a Kugelrohr apparatus, under the conditions adequate for each compound.

4.3.1. (*S*)-2-Furyl 2-methyl-butanoate (2). Colorless oil synthesized following the procedure described above, starting from (*S*)-2-methyl-butanoyl chloride (432 mg, 3.58 mmol) and obtaining 168 mg (Yield=11%, Conv.=73%). IR (film, ν, cm^{-1}): 3160, 2973, 2940, 2880, 1780 (C=O, st), 1645, 1512, 1462, 1388, 1238, 1202, 1171, 1086, 1038. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.97 (3H, t, J=7.4 Hz, H4), 1.21 (3H, d, J=7 Hz, H5), 1.56–1.86 (2H, m, H3), 2.48 (1H, dq, J_1=6.9 Hz, J_2=7 Hz, H2), 5.86 (1H, dd, J_1=1.0 Hz, J_2=3.3 Hz, H3′), 6.35 (1H, dd, J_1=2.2 Hz, J_2=3.3 Hz, H4′), 7.05 (1H, dd, J_1=2.2 Hz, J_2=1.0 Hz, H5′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 11.8 (C4), 16.3 (C5), 26.6 (C3), 41.3 (C2), 92.6 (C3′), 111.6 (C4′), 135.7 (C5′), 159.5 (C2′), 173.0 (C1). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 221 (9, M+N_3H_{11}), 204 (45, M+N_2H_8), 186 (14, M+NH_4), 169 (1, M+1). Anal. calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.11; H, 7.25%. GC (100°C, 1 min, 10°C/min, 250°C, 1 min): R_t=5.76 min. TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.66.

4.3.2. (*R*)-2-Furyl 2-methoxy-propanoate (3). It was synthesized following the aforementioned procedure, from (*S*)-2-methoxypropanoyl chloride (915 mg, 7.47 mmol), obtaining the product as a colorless oil (230 mg, Yield=18%, Conv.=68%). IR (film, ν, cm^{-1}): 3158, 3138, 2992, 2940, 2834, 1779 (C=O, st), 1611 (C=C, st), 1512, 1485, 1458, 1385, 1238, 1157, 1124, 1094, 1061, 1011, 951, 879, 725. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.55 (3H, t, J=7 Hz, H3), 3.47 (3H, s, H4), 4.09 (1H, q, J=7 Hz, H2), 5.93 (1H, dd, J_1=1.0 Hz, J_2=3.1 Hz, H3′), 6.36 (1H, dd, J_1=2.2 Hz, J_2=3.2 Hz, H4′), 7.06 (1H, dd, J_1=2.2 Hz, J_2=1.0 Hz, H5′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 18.3 (C3), 57.9 (C4), 75.9 (C2), 92.4 (C3′), 111.2 (C4′), 135.4 (C5′), 150.5 (C2′), 169 (C1). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]:171 (1, M+1), 122 (5, M+NH_4−$C_4H_3O^+$), 103 (7, M−$C_4H_3O^+$), 102 (100). Anal. calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.38; H, 6.01%. GC (100°C, 1 min, 10°C/min, 250°C, 1 min): R_t=5.74 min. TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.72.

4.3.3. (±)-2-Furyl 2-phenoxy-propanoate (4). The ester **4** was prepared following the previously described procedure, starting from (±)-2-phenoxypropanoyl chloride (140 mg, 0.76 mmol). The crude product was purified by ball-to-ball distillation, resulting in a colorless oil (111 mg) (Yield=13%, Conv.=100%). The low yield was due to a partial thermal decomposition of the product during distillation. IR (film, ν, cm^{-1}): 3080, 2995, 2940, 1770 (C=O, st), 1600 (C=C, st), 1490, 1380, 1240, 1094, 970, 825. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.76 (3H, d, J=6.7 Hz, H3), 4.92 (1H, q, J=6.7 Hz, H2), 5.92 (1H, dd, J_1=1.4 Hz, J_2=2.3 Hz, H3′), 6.36 (1H, dd, J_1=2.3 Hz, J_2=2.4 Hz, H4′), 6.85–6.95 (3H, m, H2″, H4′ and H6′), 7.15–7.30 (2H, m, H3″ and H5″), 7.35 (1H, dd, J_1=2.4 Hz, J_2=1.4 Hz, H5′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 14.9 (C3), 78.3 (C2), 109 (C3′, C4′), 114.8 (C2″, C6″), 118.9 (C4″), 129.4 (C3″, C5″), 142.7 (C2′, C5′), 158.3 (C1″), 170.1 (C1). MS [DIP-EI, 70 eV, 150°C, *m/z*, (%)]: 232 (29, M), 165 (24, M−C_4H_3O), 149 (25, M−$C_4H_3O_2$), 155 (51, M−C_6H_5), 83 (100, $C_4H_3O_2{}^+$). Anal. calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.30; H, 5.42%. GC (100°C, 1 min, 10°C/min, 250°C, 1 min): R_t=21.1 min. TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.6.

4.3.4. 2-Furyl (*S*)-2-(4-isobutyl-1-phenyl)-propanoate (5). It was prepared following the general procedure described above, starting from (*S*)-2-(4-isobutyl-1-phenyl)-propanoyl chloride (950 mg, 4.01 mmol) obtaining 835 mg of a crude oily product that was purified by ball-to-ball distillation (Yield=42%, Conv.=100%). Distillation should be carried out under very low pressure to avoid the thermal decomposition of the product. IR (film, ν, cm^{-1}): 2956, 2927, 1775 (C=O, st), 1604, 1512, 1466, 1383, 1238, 1063, 1034, 1018. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.9 (6H, d, J=6.6 Hz, H3″ and H4″), 1.59 (3H, d, J=7.4 Hz, H3), 1.80–1.88 (2H, m, H2″), 2.45 (2H, d, J=7.2 Hz, H1″), 3.84 (1H, q, J=7 Hz, H2), 5.84 (1H, d, J=3.4 Hz, H3‴), 6.34 (1H, dd, J_1=5.6 Hz, J_2=3.4 Hz, H4‴), 7.02–7.10 (3H, m, H3′, H5′ and H5‴), 7.20–7.25 (2H, m, H2′ and H6′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 16.5 (C3), 21.4 (C3″, C4″), 30.1 (C2″), 38.9 (C2), 44.3 (C1″), 109.3 (C3‴, C4‴), 128.7 (C2′, C6′), 129.8 (C3′, C5′), 131.5 (C1′), 140.2 (C4′), 143.8 (C2‴, C5‴), 170.6 (C1). MS [DIP-EI, 70 eV, 150°C, *m/z*, (%)]:273 (1, M), 206 (4, M−C_4H_3O), 161 (24, M−111). Anal. calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.89; H, 7.35%. GC (100°C, 1 min, 10°C/min, 250°C, 1 min): R_t=16.0 min. TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.68.

4.3.5. 2-Furyl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxilate (6). It was prepared following the aforementioned general procedure, starting from commercially available (1*S*)-camphanic chloride (483 mg, 2.23 mmol), obtaining 383 mg of the product, as a colorless oil (Yield=52%, Conv.=61%). IR (film, ν, cm^{-1}): 3160, 2980, 2950, 2890, 1800 (C=O, st), 1750 (C=O, st), 1613, 1510, 1449, 1383, 1227, 1097, 933. ^{1}H

NMR (200 MHz, $CDCl_3$, δ, ppm): 1.07 (3H, s, H9), 1.14 (3H, s, H10 or H11), 1.16 (3H, s, H10 or H11), 1.75–2.52 (4H, m, H5 and H6), 5.99 (1H, d, J=2.1 Hz, H3′), 6.39 (1H, t, J=2.1 Hz, H4′), 7.09 (1H, d, J=2.1 Hz, H5′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 9.2 (C9), 16.1 and 16.2 (C10 and C11), 28.4 (C5), 30.2 (C6), 54.3 and 54.4 (C4 and C7), 90.0 (C1), 92.5 (C3′), 110.7 (C4′), 135.2 (C5′), 160.1 (C2′), 170.0 (C8), 176.7 (C3). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 299 (11, M+N_2H_7), 282 (57, M+NH_4), 233 (26), 216 (100), 181 (11). Anal. calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.58; H, 6.15%. $[\alpha]_D^{23}=-18.9$ (c=0.8, $CHCl_3$). GC (100°C, 1 min, 10°C/min, 250°C, 1 min): R_t=15.9 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.78.

4.3.6. (1*S*,2*R*,5*S*)-1-(2-Isopropyl-5-methyl)-cyclohexyl 2-furoate (7). Under nitrogen atmosphere, 2-furoyl chloride (1.72 g, 14 mmol) and triethylamine (1.1 mL, 8 mmol) were dissolved in dry tetrahydrofuran (5 mL). Then, a catalytic amount of DMAP (10 mg) was added at once. A solution of (+)-menthol (1.26 g, 8 mmol) in dry tetrahydrofuran (7 mL) was added dropwise at room temperature. The reaction was magnetically stirred for 7 h, up to constant conversion by GC analysis. The formed triethylammonium hydrochloride was separated by filtration, and the organic layer percolated through a short column of aluminum oxide. The product was finally purified by flash column chromatographic (SiO_2, hexane/ethyl acetate), obtaining 1.91 g of a colorless oil (Yield=89%, Conv.=100%). IR (film, ν, cm^{-1}): 3141, 2956, 2930, 2871, 1721 (C═O, st), 1582, 1474, 1393, 1231, 1180, 1122, 1011, 960, 883, 764. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.8 (3H, d, J=7 Hz, H10′), 0.91 (3H, d, J=7 Hz, H8′ or H9′), 0.92 (3H, d, J=6.4 Hz, H8′ or H9′), 1.08–1.14 (2H, m, 1H3′ and 1H6′), 1.49–1.56 (2H, m, H7′ and H2′), 1.68–1.74 (2H, m, 1H3′ and 1H4′), 1.90–1.96 (1H, m, H5′), 2.03–2.10 (1H, m, 1H6′), 4.92 (1H, dt, J_1=10.8 Hz, J_2=4.4 Hz, H1′), 6.50 (1H, dd, J_1=3.4 Hz, J_2=1.6 Hz, H4), 7.15 (1H, dd, J_1=3.6 Hz, J_2=0.8 Hz, H3), 7.57 (1H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H5). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 16.4 (C10′), 20.6 and 21.9 (C9′ and C8′), 23.6 (C3′), 26.5 (C5′), 31.3 (C7′), 34.1 (C4′), 40.9 (C6′), 47.2 (C2′), 74.8 (C1′), 111.6 (C3), 117.4 (C4), 145.06 (C2), 149.9 (C5), 158.3 (C6). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 285 (5, M+N_2H_7), 268 (100, M+NH_4), 251 (7, M+1). Anal. calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.54; H, 8.72%. $[\alpha]_D^{23}=-72.7$ (c=4.3, $CHCl_3$). GC (100°C, 1 min, 10°C/min, 250°C, 1 min): R_t=19.7 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.5.

4.3.7. (±)-*trans*-2-(2-Furyl-thioxy)-cyclohexan-1-ol (8).[19] Under nitrogen atmosphere, a 2.5 M BuLi solution in hexane (2.7 mL, 6.73 mmol) was added dropwise at room temperature to a solution of freshly distilled furan (468 mg, 6.73 mmol) in diethyl ether (15 mL). The reaction mixture was magnetically stirred for 2 h at room temperature and then warmed at 35°C for 30 min, observing the formation of a pale yellow solid. Under nitrogen atmosphere, solid sulphur (216 mg, 6.73 mmol) was added portion wise during 15 min. The reaction mixture was stirred for 3 h at room temperature. Then, it was cooled down to 0°C, and cyclohexene oxide (667 mg, 6.73 mmol) was added dropwise during 30 min. The reaction was kept at room temperature for 13 h. The product was purified by selective extraction: adding diethyl ether (15 mL) and washing the organic layer with water (3×30 mL). The organic layer was concentrated to dryness affording pure product as a pale yellow oil (830 mg, Yield=63%, Conv.=80%). IR (film, ν, cm^{-1}): 3424 (H–O, st), 3110, 2934, 2859, 1540 (C═C, st), 1449, 1358, 1261, 1215, 1150, 1063, 1005, 960, 881, 742. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.21–1.29 (4H, m, H5 and H4), 1.61–1.73 (2H, m, H3), 2.04–2.13 (2H, m, H6), 2.53 (1H, td, J_1=10.7 Hz, J_2=4 Hz, H2), 2.64 (1H, br s, O*H*), 3.25 (1H, td, J_1=9.8 Hz, J_2=4.4 Hz, H1), 6.41 (1H, dd, J_1=3.4 Hz, J_2=1.8 Hz, H4′), 6.59 (1H, dd, J_1=3.4 Hz, J_2=1 Hz, H3′), 7.53 (1H, dd, J_1=1.8 Hz, J_2=1 Hz, H5′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 24.4 (C5), 26.1 (C4), 32.5 (C3), 33.7 (C6), 56.7 (C2), 72.2 (C1), 111.6 (C4′), 119.6 (C3′), 142.6 (C2′), 146.2 (C5′). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 233 (9, M+N_2H_7), 216 (100, M+NH_4), 1996 (31, M+1). Anal. calcd for $C_{10}H_{14}O_2S$: C, 60.57; H, 7.12; S, 16.17%. Found: C, 60.49; H, 7.05; S, 16.11%. GC (50°C, 1 min, 10°C/min, 250°C, 1 min): R_t=17.25 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.40.

4.3.8. (±)-*trans*-[2-(2-Furylthioxy)-1-cyclohexyloxy] methyl diphenyl silane (9).[20] Under nitrogen atmosphere and at room temperature, (±)-*trans*-2-(2-furylthio)-cyclohexan-1-ol (480 mg, 2.22 mmol) and imidazole (362 mg, 5.33 mmol) were dissolved in dry dimethylformamide (2 mL). Under stirring and at room temperature, diphenylmethylchlorosilane (623 mg, 2.66 mmol) was added dropwise. Then, the reaction mixture was stirred for 1 h and then water (10 mL) was added at once. The mixture was extracted with hexane (4×30 mL). The organic layer was washed with water (20 mL) and brine (20 mL). Finally, it was dried over anh. Na_2SO_4 and the solvent evaporated to dryness, obtaining pure product, as a pale yellow oil (740 mg, Yield=85%, Conv.=100%). IR (film, ν, cm^{-1}): 3069, 3030, 2936, 2859, 1653, 1589, 1459, 1368, 1259, 1150, 1119, 1022, 1005, 904, 877. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.7 (3H, s, Si–C$H_{3>}$), 1.25–1.55 (4H, m, H5 and H4), 1.45–1.65 (2H, m, H3), 1.87–1.96 (2H, m, H6), 2.95 (1H, td, J_1=8.4 Hz, J_2=4 Hz, H2), 3.67 (1H, td, J_1=8.4 Hz, J_2=4 Hz, H1), 6.32 (1H, dd, J_1=3.4 Hz, J_2=1.8 Hz, H4′), 6.38 (1H, dd, J_1=3.4 Hz, J_2=0.8 Hz, H3′), 7.26–7.38 (6H, m, H_{meta}, H_{para}), 7.44 1H, (dd, J_1=1.8 Hz, J_2=0.8 Hz, H5′), 7.55–7.69 (4H, m, H_{ortho}). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): −2.21 (Si–CH_3), 23.3 (C5), 24.6 (C4), 30.9 (C3), 34.5 (C6), 54.3 (C2), 73.7 (C1), 111.2 (C4′), 118.4 (C3′), 127.7 (C_{meta}), 129.6 (C_{para}), 133.9 (C_{ortho}), 134.5 (C_{ipso}), 141.5 (C2′), 145.5 (C5′). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 429 (27, M+N_2H_7), 428 (73, M+N_2H_6), 413 (27, M+NH_4), 412 (72, M+NH_3), 395 (21, M+1), 329 (22, M), 317 (51, M−Ph), 295 (8, $C_6H_8OSiMePh_2$), 214 (33, $HOSiMePh_2$), 181 (100, M−$OSiMePh_2$). Anal. calcd for $C_{23}H_{26}O_2SSi$: C, 70.01; H, 6.64; S, 8.13. Found: C, 70.12; H, 6.60; S, 8.09%. GC (50°C, 1 min, 10°C/min, 290°C, 1 min): R_t=31.3 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.5.

4.3.9. (±)-*trans*-2-(2-Furyl)-cyclohexan-1-ol (10). Under nitrogen atmosphere, a solution of 2.5 M BuLi in hexane (2.72 mL, 6.73 mmol) was diluted with dry diethyl ether

(5 mL). At room temperature, freshly distilled furan (468 mg, 6.73 mmol) was added dropwise. The mixture was stirred at room temperature for 2 h and then warmed up to 35°C for an additional 1.5 h, observing the formation of 2-furyl lithium as a pale yellow solid. Then, the reaction mixture was cooled down to 0°C and cyclohexene oxide (667 mg, 6.73 mmol) was added dropwise along 30 min. Finally, the reaction mixture was stirred overnight at room temperature. The product was purified by selective extraction: addition of water (100 mL) and that extraction with diethyl ether (3×30 mL). The organic layer was dried over anh. Na_2SO_4, filtered and concentrated to dryness, obtaining 369 mg of pure product as a colorless oil (Yield=35%, Conv.=48%). IR (film, ν, cm^{-1}): 3411 (H–O, st), 3100, 2932, 2859, 1593, 1451, 1150, 1061, 1011, 976, 922. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.35–2.1 (8H, m, H3, H4, H5 and H6), 2.56 (1H, ddd, J_1=10 Hz, J_2=3.6 Hz, J_3=13 Hz, H2), 3.60 (1H, td, J_1=10 Hz, J_2=4.4 Hz, H1), 6.12 (1H, dd, J_1=3.4 Hz, J_2=0.8 Hz, H3′), 6.32 (1H, dd, J_1=3.4 Hz, J_2=2 Hz, H4′), 7.34 (1H, dd, J_1=2 Hz, J_2=0.8 Hz, H5′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 24.5 (C5), 25.3 (C4), 29.9 (C3), 34.1 (C6), 45.7 (C2), 72.9 (C1), 105.3 (C3′), 110.1 (C4′), 141.3 (C5′), 157.2 (C2′). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 218 (9, M+N_3H_{11}), 201 (100, M+N_2H_7), 184 (100, M+NH_4), 167 (21, M+1). Anal. calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.19; H, 8.53%. GC (50°C, 1 min, 10°C/min, 290°C, 1 min): R_t=13.74 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.17.

4.3.10. (±)-*trans*-2-(2-Furyl)-1-methoxy-cyclohexane (11). Under nitrogen atmosphere (±)-*trans*-2-(2-furyl)-cyclohexan-1-ol (500 mg, 3.01 mmol) was dissolved in dry tetrahydrofuran (5 mL). A solution of 2.5 M BuLi in hexane (1.88 mL, 3.01 mmol) is added dropwise, at room temperature. The reaction mixture was stirred at room temperature for 1 h. Then, MeI (0.20 mL, 3.2 mmol) was added dropwise, and the reaction mixture was magnetically stirred overnight. The solvent was evaporated and the residue re-dissolved in diethyl ether (20 mL) and water (20 mL). The aqueous layer was extracted with diethyl ether (4×20 mL). The organic layers were combined together and dried over anh. $MgSO_4$. Finally, the solvent was distilled off obtaining a crude oil that was submitted to flash column chromatography (SiO_2, hexane/ethyl acetate), which afforded 304 mg of pure product (Yield=56%, Conv.=92%). IR (film, ν, cm^{-1}): 3116, 2934, 2859, 2822, 1597, 1506, 1451, 1091, 951, 796. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.18–2.20 (8H, m, H3, H4, H5 and H6), 2.80 (1H, dt, J_1=10 Hz, J_2=4.4 Hz, H2), 3.12–3.56 (1H, m, H1), 3.18 (3H, s, OCH_3), 6.05 (1H, dd, J_1=3.1 Hz, J_2=0.8 Hz, H3′), 6.30 (1H, dd, J_1=3.1 Hz, J_2=1.8 Hz, H4′), 7.31 (1H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H5′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 24.31 (C4), 25.19 (C5), 30.8 (C3), 30.9 (C6), 43.5 (C2), 56.6 (OCH_3), 81.69 (C1), 104.5 (C3′), 109.9 (C4′), 140.4 (C5′), 157.9 (C2′). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 215 (26, M+N_2H_7), 198 (100, M+NH_4), 181 (10, M+1), 180 (1, M^+). GC (100°C, 1 min, 10°C/min, 250°C, 1 min): R_t=8.4 min. Anal. calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.44; H, 8.90%. TLC (SiO_2, hexane/ethyl acetate): R_f=0.55 (9:1), 0.62 (8:2), 0.24 (1:0).

4.3.11. (±)-*trans*-2-(2-Furyl)-cyclohexyl benzoate (12). Under inert atmosphere, (±)-*trans*-2-(2-furyl)-cyclohexan-1-ol (500 mg, 3.01 mmol) was dissolved in dry pyridine (5 mL). Benzoyl chloride (0.365 mL, 3.08 mmol) was added dropwise, at room temperature. The reaction was magnetically stirred for 2 h. Then, the solvent was evaporated and the residue re-dissolved in diethyl ether (25 mL). The organic layer was washed with water (25 mL) and 3% aqueous HCl (3×25 mL), dried and concentrated to dryness. Finally the product was isolated as a colorless oil (700 mg, Yield=86%, Conv.=100%) by flash column chromatography (SiO_2, hexane/ethyl acetate). IR (film, ν, cm^{-1}): 2938, 2863, 1717 (C=O), 1601, 1505, 1451, 1315, 1273, 1109, 1026, 951, 920, 802, 712, 600. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.2–2.30 (8H, m, H3′, H4′, H5′, H6′), 2.97 (1H, dt, J_1=11.2 Hz, J_2=4.4 Hz, H2′), 5.13 (1H, dt, J_1=10.2 Hz, J_2=4.4 Hz, H1′), 6.03 (1H, dd, J_1=3.0 Hz, J_2=0.8 Hz, H3″), 6.20 (1H, dd, J_1=3.0 Hz, J_2=1.8 Hz, H4″), 7.23 (1H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H5″), 7.40–7.44 (3H, m, H3, H5, H7), 7.95 (2H, dd, J_1=5 Hz, J_2=1.2 Hz, H6, H4). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 24.2 (C5′), 24.9 (C4′), 30.4 (C3′), 31.7 (C6′), 42.4 (C2′), 75.2 (C1′), 104.8 (C3″), 109.9 (C4″), 128.1 (C4, C6), 129.5 (C3, C7), 130.6 (C2), 132.61 (C5), 140.9 (C5″), 156.4 (C2″), 166.2 (C1). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 288 (100, M+NH_4), 271 (3, M+1), 166 (1, MH^+−PhCO), 149 (10, M−$PhCO_2$), 105 (1, $PhCO^+$). Anal. calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.44; H, 6.92%. GC (100°C, 1 min, 10°C/min, 290°C, 1 min): R_t=17.2 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.45.

4.3.12. (±)-*trans*-[2-(2-Furyl)-1-cyclohexyloxy] methyl diphenyl silane (13). Compound **13** was synthesized following the general procedure described above, starting from (±)-*trans*-2-(2-furyl)-cyclohexan-1-ol (307 mg, 1.85 mmol), isolating the product, as a colorless oil (548 mg, Yield=83%, Conv.=100%) by flash column chromatography (SiO_2, hexane/ethyl acetate). IR (film, ν, cm^{-1}): 3069, 3040, 2932, 2859, 1589, 1506, 1446, 1429, 1254, 1119, 1092, 926, 879, 831, 793. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.39 (3H, s, Si–CH_3), 1.22–1.26 (2H, m, H4), 1.48–1.55 (2H, m, H5), 1.65–1.68 (2H, m, H3), 1.85–1.91 (2H, m, H6), 2.71–2.77 (1H, m, H2), 3.80 (1H, td, J_1=10 Hz, J_2=4.4 Hz, H1), 6.03 (1H, dd, J_1=3.4 Hz, J_2=0.8 Hz, H3′), 6.30 (1H, dd, J_1=3.4 Hz, J_2=1.8 Hz, H4′), 7.22–7.35 (4H, m, H_{meta}), 7.16–7.54 (5H, m, H_{ortho} and H5′), 7.22–7.54 (4H, m, H_{para}). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 3.0 (Si–CH_3), 24.5 (C5), 25.3 (C4), 30.6 (C3), 35.8 (C6), 45.8 (C2), 74.5 (C1), 105.5 (C3′), 110.0 (C4′), 127.5 (C_{meta}), 129.3 and 129.5 (C_{para}), 134.3 and 134.4 (C_{ortho}), 136.7 and 136.8 (C_{ipso}), 140.4 (C5′), 157.8 (C2′). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 380 (100, M+NH_4), 363 (21, M+1), 214 (29, $OSiMePh_2$+NH_4), 149 (8, M−$OSiMePh_2$). Anal. calcd for $C_{23}H_{26}O_2Si$: C, 76.20; H, 7.23. Found: C, 75.87; H, 7.12%. GC (50°C, 1 min, 10°C/min, 290°C, 1 min): R_t=27.3 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.67.

4.3.13. (*S*)-1-(2-Furyl)-ethyl benzoate (14). The ester **14** was synthesized following the previously described procedure, starting from 1-(*S*)-(2-furyl)-ethanol (0.3 mL, 2.87 mmol). The product was obtained as a white solid

(561 mg, Yield=91%, Conv.=100%). Mp 47–48°C (ether). IR (KBr, ν, cm^{-1}): 3100, 2985, 2935, 1717 (C=O, st), 1601, 1506, 1451, 1317, 1267, 1153, 1097, 1011, 926, 742, 710. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 1.71 (3H, d, J=7 Hz, H2′), 6.22 (1H, q, J=6.8 Hz, H1′), 6.36 (1H, dd, J_1=3.4 Hz, J_2=1.8 Hz, H4″), 6.41 (1H, dd, J_1=3.4 Hz, J_2=0.8 Hz, H3″), 7.41 (1H, dd, J_1=1.8 Hz, J_2=0.8 Hz, H5″), 7.42–7.50 (2H, m, H4 and H6), 7.52–7.56 (1H, m, H5), 8.04–8.08 (2H, m, H3 and H7). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 18.3 (C2′), 65.6 (C1′), 107.8 (C3″), 110.2 (C4″), 128.2 (C4 and C6), 129.7 (C3 and C7), 130.5 (C2), 132.9 (C5), 142.5 (C5″), 153.4 (C2″), 165.7 (C1). MS [GC–MS(CI), NH_3, 70 eV, 150°C, m/z, (%)]: 251 (2, M+N_2H_7), 234 (20, M+NH_4), 216 (1, M). Anal. calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.04; H, 5.91%. $[\alpha]_D^{21}$=51.4 (c=1.61%, $CHCl_3$). GC (100°C, 1 min, 10°C/min, 250°C, 1 min): R_t=12.64 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.44.

4.3.14. (*S*)-2-(*p*-Tolylsulfinyl)-furan (15).[21] Under argon atmosphere, a solution of BuLi 1.6 M in hexane (5.05 mL, 8.08 mmol) was diluted with diethyl ether (10 mL). At room temperature, freshly distilled furan (0.60 mL, 8.08 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h and warmed up to 35°C for one additional hour. Then, a solution of anhydrous magnesium bromide (freshly prepared from magnesium and 1,2-dibromo-ethane) (8.88 mmol) in diethyl ether (5 mL) was added dropwise. The mixture was refluxed for 1 h and, the, cooled down to −78°C. At this temperature, a solution of (1*R*,2*S*,5*R*)-(−)-menthyl (S_S)-*p*-toluensulfinate (2 g, 6.73 mmol) in dry diethyl ether (10 mL) was added. The reaction mixture was stirred at −78°C for 2 h and, then, overnight at room temperature. Saturated aqueous NH_4Cl solution (30 mL) was added and the organic layer separated, dried over anh. magnesium sulfate and concentrated to dryness, obtaining 1.08 g of a white solid (Yield=78%, Conv.=100%) that was purified by flash column chromatography (SiO_2, hexane/ethyl acetate). Mp 47–49°C (ether). IR (KBr, ν, cm^{-1}): 3125–3005, 2945, 1653, 1555, 1491, 1458, 1373, 1308, 1207, 1171, 1136, 1084, 1043, 910, 811, 773. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 2.41 (3H, s, H7′), 6.43 (1H, dd, J_1=3.6 Hz, J_2=1.8 Hz, H4″), 6.78 (1H, dd, J_1=3.6 Hz, J_2=1.0 Hz, H3″), 7.31 (2H, d, J=8.2 Hz, H3′ and H5′), 7.52 (1H, dd, J_1=1.8 Hz, J_2=1.0 Hz, H5″), 7.58 (2H, d, J=8.4, H2′ and H6′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 21.4 (C7′), 111.2 (C4), 115.8 (C3), 124.8 (C2′ and C6′), 129.9 (C3′ and C5′), 138.7 (C4′), 141.8 (C1′), 147.1 (C5), 158.3 (C2). MS [GC–MS(CI), NH_3, 70 eV, 150°C, m/z, (%)]: 224 (100, M+NH_4), 207 (54, M+1). Anal. calcd for $C_{11}H_{10}SO_2$: C, 64.06; H, 4.89. Found: C, 63.53; H, 5.5%. $[\alpha]_D^{21}$=83.65 (c=1.5, $CHCl_3$). GC(1) (100°C, 1 min, 10°C/min, 250°C, 1 min): R_t=15.64 min. GC(2) (100°C, 1 min, 5°C/min, 220°C, 20 min): R_t=18.06 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.02; (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.35.

4.4. Cycloaddition procedures[12,13]

A suspension of copper bronze (210 mg, 3.3 mmol) and sodium iodide (954 mg, 6.36 mmol) in dry acetonitrile (5 mL) was placed in a round bottomed flask, fitted with magnetic stirring and under inert atmosphere. At the temperature adequate to each substrate, the diene (1.06 mmol, 1 equiv.) was added at once. A solution of freshly distilled 2,4-dibromo-3-pentanone (260 mg, 1.06 mmol, 1 equiv.) in dry acetonitrile (6 mL) was added dropwise. The reaction mixture was magnetically stirred and controlled by GC up to constant conversion of the diene. Water (5 mL) was then added to the reaction mixture and the solid was filtered out by using a no. 4 filter plate. The filtrated liquid was extracted with dichloromethane (5×15 mL). The organic layers were combined together, washed with diluted aqueous ammonia (2×25 mL) and brine (2×25 mL), dried over anh. $MgSO_4$, filtered and concentrated to dryness. The cycloadducts were purified by flash column chromatography on silica gel, using mixtures of hexane and ethyl acetate of increasing polarity as eluents.

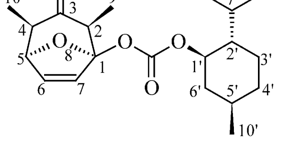
Under modified reaction conditions,[13b] zinc–copper couple was used (instead of copper bronze) and 2,4-diiode-3-pentanone (instead of 2,4-dibromo-3-pentanone). In addition, in some experiments, sodium iodide was not used as an initiator. No other changes were introduced in the reaction procedure, so, the order of addition, the reaction conditions and the method of isolation of the cycloadducts were essentially the same.

In some experiments, ultrasound was used as a metal 'activator'. The reaction mixture was sonicated by using a 1/8″ direct insertion probe from Branson (EDP no 101-148-062). The internal reaction temperature was measured by using a flexible PT-100 temperature probe.[13a]

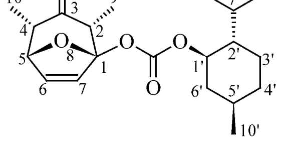
Some of the synthesized cycloadducts were obtained as mixtures of *endo* (5*R*) and *endo* (5*S*) diastereomers, which were non-separable by using typical chromatographic methods (not yet optimized). The NMR characterization of these products was possible by analyzing mixtures of them (with different ratios), which allowed us to discriminate (by 1D and 2D NMR experiments) the signals corresponding to both diastereomers. However, in some cases, the assignment of the signals was ambiguous. In these cases, we present the corresponding chemical shifts labeled by (∗). On the other hand, in some cycloadducts, it was not possible to unequivocally assign the *endo* (5*R*) or *endo* (5*S*) absolute stereochemistry to the diastereomers. In these cases, the *endo* diastereoisomers were named as *endo* A and *endo* B (without using an *R*, *S* notation), depending on the order of elution in gas chromatography analysis ($_{\mathrm{RtA}}<R_{\mathrm{tB}}$).

4.5. Characterization of cycloadducts

4.5.1. (1′*R*,2′*S*,5′*R*)-1-[(2-Isopropyl-5-methyl-1-cyclohexyloxy)-carbonyloxy]-2,4-dimethyl-8-oxabicyclo[3.2.1]-oct-6-en-3-one (16)



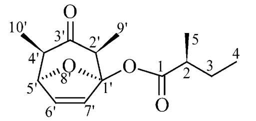
***endo* (1S, 2S, 4R, 5S)**



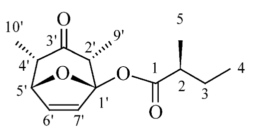
***endo* (1R, 2R, 4S, 5R)**

Mixture of diastereoisomers *endo* A and *endo* B. Colorless oil. IR (film, ν, cm^{-1}): 3090, 2955, 2869, 1759 (C=O, st), 1719 (C=O, st), 1458, 1377, 1339, 1249, 1157, 1053, 1024, 970. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): *endo* A: 0.79 (3H, d, J=7.0 Hz, H10′), 0.90 and 0.91 (6H, d, J=7.0 Hz, H8′ and H9′), 0.98 (3H, d, J=7.0 Hz, H10), 1.09 (3H, d, J=7.0 Hz, H9), 1.25–1.30 (2H, m, 1H3′ and 1H6′), 1.41–1.48 (2H, m, H7′ and H2′), 1.62–1.70 (2H, m, 1H3′ and 1H4′), 1.94–1.99 (1H, m, H5′), 2.06–2.13 (1H, m, 1H6′), 2.80 (1H, dq, J_1=7.0 Hz, J_2=4.5 Hz, H4), 3.13 (1H, q, J=6.9 Hz, H2), 4.53 (1H, td, J_1=11.0 Hz, J_2=5.0 Hz, H1′), 4.98 (1H, dd, J_1=4.5 Hz, J_2=2.0 Hz, H5), 6.31 (1H, dd, J_1=6.0 Hz, J_2=2.0 Hz, H6), 6.38 (1H, d, J=6.0 Hz, H7). *endo* B: 0.80 (3H, d, J=7.0 Hz, H10′), 0.90 and 0.92 (6H, d, J=7.0 Hz, H8′ and H9′), 0.98 (3H, d, J=7.0 Hz, H10), 1.09 (3H, d, J=7.0 Hz, H9), 1.25–1.32 (2H, m, 1H3′ and 1H6′), 1.38–1.44 (2H, m, H7′ and H2′), 1.63–1.71 (2H, m, 1H3′ and 1H4′), 1.92–2.00 (1H, m, H5′), 2.06–2.14 (1H, m, 1H6′), 2.80 (1H, dq, J_1=7.0 Hz, J_2=4.50 Hz, H4), 3.12 (1H, q, J=6.9 Hz, H2), 4.53 (1H, td, J_1=11.0 Hz, J_2=5.0 Hz, H1′), 4.98 (1H, dd, J_1=4.50 Hz, J_2=2.0 Hz, H5), 6.31 (1H, dd, J_1=6.0 Hz, J_2=2.0 Hz, H6), 6.38 (1H, d, J=6.0 Hz, H7). ^{13}C NMR (75.45 MHz, $CDCl_3$, δ, ppm): *endo* A: 8.84 (C9), 10.33 (C10), 16.18 (C10′), 20.68 (C9′ or C8′), 21.92 (C9′ or C8′), 23.40 (C3′), 26.03 (C5′), 31.40 (C7′), 34.00 (C4′), 40.53 (C6′), 46.7 (C2′), 48.12 (C4), 54.12 (C2), 79.08 (C5), 80.7 (C1′), 110.81 (C1), 132.28 (C6), 133.42 (C7), 151.78 (CO_3), 207.12 (C3). *endo* B: 8.82 (C9), 10.31 (C10), 16.38 (C10′), 20.63 (C9′ or C8′), 21.89 (C9′ or C8′), 23.2 (C3′), 26.14 (C5′), 31.4 (C7′), 34.0 (C4′), 40.51 (C6′), 46.7 (C2′), 48.13 (C4), 54.17 (C2), 79.02 (C5), 80.7 (C1′), 110.85 (C1), 132.21 (C6), 133.48 (C7), 151.78 (CO_3), 207.15 (C3). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: *endo* A: 368 (100, M+NH_4), 351 (7, M+1). *endo* B: 368 (100, M+NH_4), 351 (12, M+1). Anal. calcd for $C_{20}H_{30}O_5$: C, 68.55; H, 8.63. Found: C, 68.32; H, 8.49%. GC (50°C, 1 min, 10°C/min, 250°C, 15 min): *endo* A: R_t=23.59 min. *endo* B: R_t=23.81 min.

4.5.2. 2,4-Dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-yl (2*S*)-2-methyl-butanoate (17)

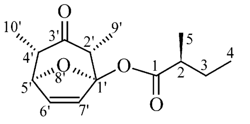


***endo* (1′S, 2′S, 4′R, 5′S)**

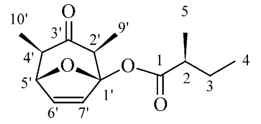


***endo* (1′R, 2′R, 4′S, 5′R)**

Mixture of *endo* A and *endo* B diastereoisomers. Colorless oil. IR (film, ν, cm^{-1}): 3110, 2973, 2938, 2880, 1755 (O–C=O, st), 1717 (C=O, st), 1599 (C=C, st), 1460, 1377, 1339, 1254, 1221, 1150, 1080, 997. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.951* and 0.956* (3H, t, J=7.5 Hz, H4), 0.95 (3H, d, J=7.0 Hz, H10′), 1.05 (3H, d, J=6.9 Hz, H9′), 1.159* and 1.162* (3H, d, J=7.0 Hz, H5), 1.48–1.56* and 1.66–1.74* (2H, m, H3), 2.43* and 2.44* (1H, tq, J_1=6.8 Hz, J_2=7.0 Hz, H2), 2.79 (1H, dq, J_1=7.3 Hz, J_2=4.7 Hz, H4′), 3.07* and 3.09* (1H, q, J=6.9 Hz, H2′), 4.94 (1H, dd, J_1=4.7 Hz, J_2=1.9 Hz, H5′), 6.26 (1H, dd, J_1=6.1 Hz, J_2=1.9 Hz, H6′), 6.40 (1H, d, J=6.1 Hz, H7′). ^{13}C NMR (75.45 MHz, $CDCl_3$, δ, ppm): 9.4 (C9′), 10.76*and 10.59* (C10′), 12.0 (C4), 16.73* and 16.82 (C5), 27.04* and 26.98* (C3), 41.9 (C2), 48.7 (C4′), 54.8 (C2′), 81.0 (C5′), 110.1 (C1′), 131.96* and 131.90* (C6′), 134.5* and 134.4* (C7′), 175.0 (C1), 207.8 (C3′). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 287 (22, M+N_2H_8), 270 (100, M+NH_4), 253 (4, M+1), 151 (77, M−$C_5H_9O_2$). Anal. calcd for $C_{14}H_{20}O_4$: C, 65.66; H, 7.99. Found: C, 65.45; H, 7.85%. GC (100°C, 1 min, 10°C/min, 250°C, 15 min): R_t=13.84 min. TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.59.



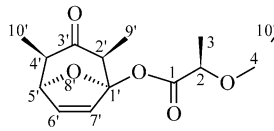
***exo* (1′S, 2′R, 4′S, 5′S)**



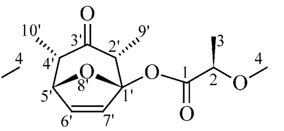
***exo* (1′R, 2′S, 4′R, 5′R)**

Mixture of *exo* A and *exo* B diastereoisomers. Colourless oil. IR (film, ν, cm^{-1}): 3100, 2980, 2935, 2890, 1756 (O–C=O, st), 1717 (C=O, st), 1601 (C=C, st), 1458, 1250, 1221, 1150, 1100. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.926* and 0.931* (3H, t, J=7.4 Hz, H4), 1.20 (3H, d, J=6.8 Hz, H5), 1.26 (3H, d, J=7.2 Hz, H10′), 1.38 (3H, d, J=7.4 Hz, H9′), 1.65*–1.82* (2H, m, H3), 2.28 (1H, q, J_1=7.4 Hz, H4′), 2.45 (1H, tq, J_1=6.8 Hz, J_2=6.9 Hz, H2), 3.05 (1H, q, J=7.3 Hz, H2′), 4.77 (1H, d, J=1.9 Hz, H5′), 6.35 (1H, dd, J_1=5.9 Hz, J_2=1.9 Hz, H6′), 6.55 (1H, d, J=5.9 Hz, H7′). ^{13}C NMR (75.45 MHz, $CDCl_3$, δ, ppm): 11.5* and 11.6* (C9′), 13.4 (C4), 16.4 (C5), 17.9 (C10′), 26.6 (C3), 41.1* and 41.4* (C2), 47.7 (C4′), 53.3 (C2′), 80.5 (C5′), 96.1 (C1′), 133.3 (C6′), 134.7 (C7′), 172.6 (C1), 212.2 (C3′). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 287 (30, M+N_2H_8), 270 (100, M+NH_4), 253 (15, M+1), 151 (80, M−$C_5H_9O_2$). Anal. calcd for $C_{14}H_{20}O_4$: C, 65.66; H, 7.99. Found: C, 65.56; H, 7.91%. GC (100°C, 1 min, 10°C/min, 250°C, 15 min): R_t=13.64 min. TLC (SiO_2, hexane/ethyl acetate, 1:1): R_f=0.59.

4.5.3. 2,4-Dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-yl (2*R*)-2-methoxy-propanoate (18)



***endo* (1′S, 2′S, 4′R, 5′S)**

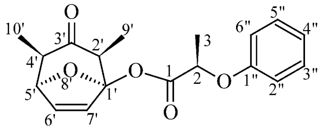


***endo* (1′R, 2′R, 4′S, 5′R)**

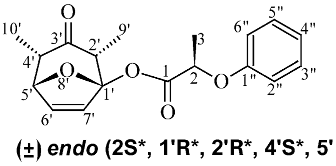
Mixture of diastereoisomers: *endo* A and *endo* B. Colorless oil. IR (film, ν, cm^{-1}): 3110, 2984, 2940, 2880, 2840, 1769 (C=O, st), 1717 (C=O, st), 1599 (C=C, st), 1452, 1377, 1339, 1246, 1148, 1128, 1080, 995. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): *endo* A: 0.982 (3H, d, J=7.0 Hz, H10′), 1.07 (3H, d, J=7.0 Hz, H9′), 1.45 (3H, d, J=7.0 Hz, H3), 2.815 (1H, dq, J_1=7.0 Hz, J_2=4.5 Hz, H4′), 3.169 (1H, q, J=7.0 Hz, H2′), 3.404 (s, 3H, H4), 3.902 (1H, q, J=7.0 Hz, H2), 4.975 (1H, dd, J_1=4.5 Hz, J_2=2 Hz, H5′), 6.325 (1H, dd, J_1=6.0 Hz, J_2=2.0 Hz, H6′), 6.411 (1H, d, J=6.0 Hz, H7′). *endo* B: 0.986 (3H, d, J=7.0 Hz, H10′), 1.07 (3H, d, J=7.0 Hz, H9′), 1.45 (3H,d, J=7.0 Hz, H3), 2.805 (1H, dq, J_1=7.0 Hz, J_2=4.5 Hz, H4′), 3.104 (1H, q, J=7.0 Hz, H2′), 3.402 (s, 3H, H4), 3.906 (1H, q, J=7.0 Hz, H2), 4.983 (1H, dd, J_1=4.5 Hz, J_2=2.0 Hz, H5′), 6.320 (1H, dd, J_1=6.0 Hz, J_2=2.0 Hz, H6′), 6.404 (1H, d, J=6.0 Hz, H7′). ^{13}C NMR

(75.45 MHz, CDCl$_3$, δ, ppm): *endo* A: 8.9 (C9′), 10.3 (C10′), 18.25 (C3), 48.2 (C4′), 54.14 (C2′), 57.76 (C4), 76.37 (C2), 80.698 (C5′), 110.29 (C1′), 132.28 (C6′), 133.53 (C7′), 170.9 (C1), 206.9 (C3′). *endo* B: 8.9 (C9′), 10.3 (C10′), 18.39 (C3), 48.2 (C4′), 54.33 (C2′), 57.88 (C4), 76.57 (C2), 80.78 (C5′), 110.15 (C1′), 132.09 (C6′), 133.44 (C7′), 170.9 (C1), 206.9 (C3′). MS [GC–MS(CI), NH$_3$, 70 eV, 150°C, *m/z*, (%)]:289 (8, M+N$_2$H$_7$), 272 (100, M+NH$_3$), 255 (4, M+1). Anal. calcd for C$_{13}$H$_{18}$O$_5$: C, 61.41; H, 7.13. Found: C, 59.96; H, 7.37%. GC (100°C, 1 min, 10°C/min, 250°C, 15 min): *endo* A: R_t=13.82 min. *endo* B: R_t=13.89 min.

4.5.4. 2,4-Dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-yl (±)-2-phenoxy-propanoate (19)

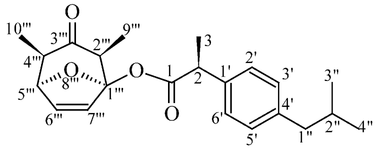


(±) *endo* (2S*, 1′S*, 2′S*, 4′R*, 5′S*)

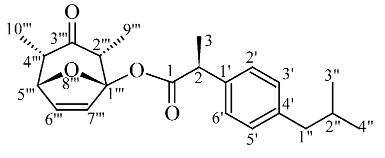


(±) *endo* (2S*, 1′R*, 2′R*, 4′S*, 5′R*)

Mixture of racemic diastereoisomers: *endo* A and *endo* B. Colorless oil. IR (film, ν, cm^{-1}): 3110, 2984, 2940, 2880, 2840, 1769 (C=O, st), 1717 (C=O, st), 1599 (C=C, st), 1452, 1377, 1339, 1246, 1148, 1128, 1080, 995. ^{1}H NMR (300 MHz, CDCl$_3$, δ, ppm): 0.91 (3H, d, J=7.0 Hz, H10′), 0.98* and 1.03* (3H, d, J=7.0 Hz, H9′), 1.67* and 1.68* (3H, d, J=6.9 Hz, H3), 2.75–2.83 (1H, m, H4′), 3.00* and 3.13* (1H, q, J=7.0 Hz, H2′), 4.75 (1H, q, J=7.0 Hz, H2), 4.97 (1H, dd, J_1=4.5 Hz, J_2=1.5 Hz, H5′), 6.31 (1H, dd, J_1=5.9 Hz, J_2=1.5 Hz, H6′), 6.34 (1H, d, J=5.7 Hz, H7′), 6.80–6.86 (3H, m, H2″, H4″ and H6″), 7.19–7.24 (2H, m, H3″ and H5″). ^{13}C NMR (75.45 MHz, CDCl$_3$, δ, ppm): 8.6* and 8.8* (C9′), 10.22* and 10.26* (C10′), 18.28* and 18.34* (C3), 48.12* and 48.17* (C4′), 54.0* and 54.3* (C2′), 72.5* and 72.8* (C2), 80.7* and 80.9* (C5′), 115.2* and 115.1* (C1′), 116.2* and 116.5* (C2″ and C6″), 121.1* and 121.7* (C4″), 129.5 (C3″ and C5″), 132.2* and 132.7* (C6′), 133.0* and 133.2* (C7′), 156 (C1″), 170.0 (C1), 206.4 (C3′). MS [GC–MS(CI), NH$_3$, 70 eV, 150°C, *m/z*, (%)]:368 (51, M+N$_3$H$_{10}$), 351 (3, M+N$_2$H$_7$), 344 (100, M+NH$_4$), 317 (1, M+1). Anal. calcd for C$_{13}$H$_{18}$O$_5$: C, 61.41; H, 7.13. Found: C, 60.99; H, 7.37%. GC (100°C, 1 min, 10°C/min, 290°C, 15 min): R_t=21.84 and 21.95 min. *exo* isomers: GC (100°C, 1 min, 10°C/min, 290°C, 15 min): R_t=21.65 and 21.71 min.



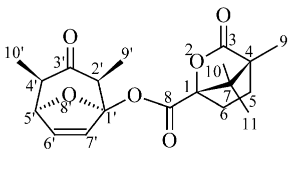
***endo* (1‴S, 2‴S, 4‴R, 5‴S)**



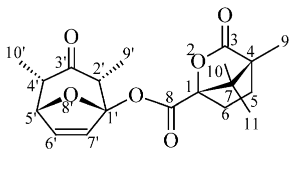
***endo* (1‴R, 2‴R, 4‴S, 5‴R)**

4.5.5. 2,4-Dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-yl (*S*)-2-(*p*-Isobutyl-phenyl)-propanoate (20). Non-separable mixture of diastereoisomers: *endo* A and *endo* B. Colorless oil. IR (film, ν, cm^{-1}): 3100, 2957, 2871, 1761 (O–C=O, st), 1717 (C=O, st), 1512, 1458, 1377, 1339, 1254, 1144, 1080, 1057, 990, 970. ^{1}H NMR (300 MHz, CDCl$_3$, δ, ppm): *endo* A: 0.76 (3H, d, J=6.9 Hz, H10‴), 0.88 (6H, d, J=5.5 Hz, H3″ and H4″), 0.96 (3H, d, J=7 Hz, H9‴), 1.53 (3H, d, J=7.0 Hz, H3), 1.80–1.88 (1H, m, H2″), 2.45 (2H, d, J=7.4 Hz, H1″), 2.73–2.81 (1H, m, H4‴), 3.13 (1H, q, J=7.0 Hz, H2‴), 3.75 (1H, q, J=7.0 Hz, H2), 4.95 (1H, d, J=4.7 Hz, H5‴), 6.26 (1H, s, H6‴), 6.30 (1H, s, H7‴), 7.14–7.20 (4H, m, H2′, H3′ H5′ and H6′). *endo* B: 0.85 (3H, d, J=6.9 Hz, H10‴), 0.88 (6H, d, J=5.5 Hz, H3″ and H4″), 0.96 (3H, d, J=7.0 Hz, H9‴), 1.50 (3H, d, J=7.0 Hz, H3), 1.81–1.89 (1H, m, H2″), 2.45 (2H, d, J=7.4 Hz, H1″), 2.72–2.80 (1H, m, H4‴), 2.90 (1H, q, J=7.0 Hz, H2‴), 3.75 (1H, q, J=7.0 Hz, H2), 4.95 (1H, d, J=4.7 Hz, H5‴), 6.26 (1H, s, H6‴), 6.30 (1H, s, H7‴), 7.14–7.20 (4H, m, H2′, H3′, H5′ and H6′). ^{13}C NMR (75.45 MHz, CDCl$_3$, δ, ppm): *endo* A: 8.48 (C9‴), 10.2 (C10‴), 18.0 (C3), 22.2 (C3″ and C4″), 30.11 (C2″), 44.9 (C1″), 45.5 (C4‴), 48.17 (C2‴), 54.4 (C2), 80.75 (C5‴), 109.9 (C1‴), 127.11 (C2′ and C6′), 129.35 (C3′ and C5′), 132.0 (C6‴), 133.7 (C7‴), 137.1 (C4′), 140.7 (C1′), 172.4 (C1), 207.2 (C3‴). *endo* B: 8.36 (C9‴), 10.14 (C10‴), 17.8 (C3), 22.5 (C3″ and C4″), 30.11 (C2″), 44.9 (C1″), 45.5 (C4‴), 48.08 (C2‴), 53.7 (C2), 80.32 (C5‴), 109.5 (C1‴), 127.06 (C2′ and C6′), 129.31 (C3′ and C5′), 131.2 (C6‴), 133.5 (C7‴), 136.7 (C4′), 140.7 (C1′), 172.4 (C1), 207.2 (C3‴). MS [GC–MS(CI), NH$_3$, 70 eV, 150°C, *m/z*, (%)]:375 (25, M+NH$_4$+1), 374 (100, M+NH$_4$), 307 (2, M+1), 306 (2, M). Anal. calcd for C$_{22}$H$_{28}$O$_4$: C, 74.12; H, 7.92%. Found: C, 74.31; H, 7.54%. GC (100°C, 1 min, 10°C/min, 290°C, 15 min): *endo* A: R_t=22.39. *endo* B: R_t=22.47. *exo* A: R_t=21.08 min. *Exo* B: R_t=22.04 min.

4.5.6. 2,4-Dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-yl (1*S*,4*R*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptan-1-carboxilate (21)



***endo* (1′S, 2′S, 4′R, 5′S)**

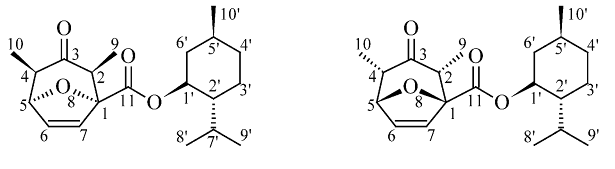


***endo* (1′R, 2′R, 4′S, 5′R)**

Mixture of diastereoisomers: *endo* A and *endo* B. Colorless oil. IR (film, ν, cm^{-1}): 3100, 2970, 2940, 1792 (C=O, st), 1750 (C=O, st), 1719 (C=O, st), 1456, 1376, 1341, 1256, 1151, 1053, 995. ^{1}H NMR (500 MHz, CDCl$_3$, δ, ppm): *endo* A: 0.97 (3H, d, J=6.0 Hz, H10′), 1.02 (3H, s, H11 or H10), 1.06 (3H, s, H11 or H10), 1.08 (3H, d, J=7.0 Hz, H9′), 1.10 (3H, s, H9), 1.68–2.43 (4H, m, H5 and H6), 2.76–2.84 (1H, m, H4′), 3.11 (1H, q, J=7 Hz, H2′), 4.98 (1H, dd,

J_1=2.5 Hz, J_2=2.0 Hz, H5′), 6.33 (1H, dd, J_1=6.0 Hz, J_2=2.0 Hz, H6′), 6.40 (1H, d, J=6.0 Hz, H7′). *endo* B: 0.97 (3H, d, J=6.0 Hz, H10′), 1.02 (3H, s, H11 or H10), 1.06 (3H, s, H11 or H10), 1.07 (3H, d, J=7.0 Hz, H9′), 1.10 (3H, s, H9), 1.68–2.43 (4H, m, H5 and H6), 2.75–2.86 (1H, m, H4′), 3.09 (1H, q, J=7.0 Hz, H2′), 4.98 (1H, dd, J_1=2.5 Hz, J_2=2.0 Hz, H5′), 6.33 (1H, dd, J_1=6.0 Hz, J_2=2.0 Hz, H6′), 6.40 (1H, d, J=6.0 Hz, H7′). ^{13}C NMR (75.45 MHz, $CDCl_3$, δ, ppm): *endo* A: 8.97 (C9), 9.6 (C9′), 10.2 (C10′), 16.0 (C10 or C11), 28.90 (C5), 29.6 (C10 or C11), 30.64 (C6), 48.2 (C4′), 54.8 (C4), 54.3 (C2′), 80.9 (C5′), 90.73 (C1), 110.9 (C1′), 132.4 (C6′), 133.3 (C7′), 165.5 (C8), 178.0 (C3), 206.60 (C3′). *endo* B: 8.92 (C9), 9.6 (C9′), 10.2 (C10′), 16.0 (C10 or C11), 28.87 (C5), 29.6 (C10 or C11), 30.60 (C6), 48.2 (C4′), 54.8 (C4), 54.5 (C2′), 80.9 (C5′), 90.69 (C1), 110.9 (C1′), 132.4 (C6′), 133.3 (C7′), 165.5 (C8), 178.0 (C3), 206.55 (C3′). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 384 (5, M+N_2H_8), 366 (66, M+NH_3), 349 (3, M+1). Anal. calcd for $C_{19}H_{24}O_6$: C, 65.49; H, 6.95. Found: C, 65.30; H, 7.31%. GC (100°C, 1 min, 10°C/min, 290°C, 15 min): *endo* A: R_t=22.52 min. *endo* B: R_t=22.63.

4.5.7. (1′*S*,2′*R*,5′*S*)-2-Isopropyl-5-methyl-cyclohexyl 2,4-dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-carboxilate (22)

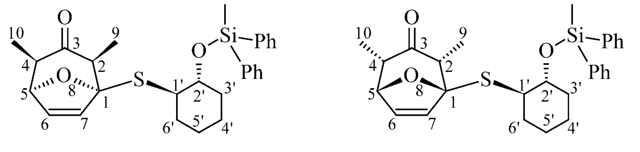


endo (1′S, 2S, 4R, 5S) *endo* (1R, 2R, 4S, 5R)

endo A. Colorless oil. IR (film, ν, cm^{-1}): 3105, 2957, 2873, 1743 (C═O, st), 1717 (C═O, st), 1456, 1379, 1335, 1248, 1159, 1134, 1070, 1034, 984. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.78 (3H, d, J=7.0 Hz, H10′), 0.91 (3H, d, J=7.4 Hz, H8′ or H9′), 0.92 (3H, d, J=6.2 Hz, H8′ or H9′), 0.98 (3H, d, J=7.0 Hz, H10), 1.00 (3H, d, J=7.4 Hz, H9), 1.07–1.11 (2H, m, 1H3′ and 1H6′), 1.49–1.52 (2H, m, H7′ and H2′), 1.66–1.70 (2H, m, 1H3′ and 1H4′), 1.90 (1H, dq, J_1=2.7 Hz, J_2=7 Hz, H5′), 2.02–2.05 (1H, m, 1H6′), 2.89 (1H, dq, J_1=4.8 Hz, J_2=7.0 Hz, H4), 2.96 (1H, q, J=7.0 Hz, H2), 4.84 (1H, td, J_1=4.4 Hz, J_2=11 Hz, H1′), 4.94 (1H, dd, J_1=4.8 Hz, J_2=1.4 Hz, H5), 6.37 (1H, dd, J_1=6.2 Hz, J_2=1.6 Hz, H6), 6.45 (1H, d, J=6.2 Hz, H7). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 8.4 (C9), 9.2 (C10), 14.9 (C10′), 19.6 and 20.8 (C9′ and C8′), 22.1 (C3′), 24.9 (C5′), 30.3 (C7′), 33.0 (C4′), 39.5 (C6′), 45.6 (C2′), 48.5 (C4), 51.3 (C2), 74.8, (C1′), 82.3 (C5), 89.7 (C1), 131.4 (C6), 133.1 (C7), 166.8 (C11), 206.0 (C3). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 196 (68, M−menthyl), 152 (12, $C_9H_{12}O_2^+$), 140 (5), 138 (22). Anal. calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.65; H, 9.12%. $[\alpha]_D^{23}$=78.3 (c=2.25, $CHCl_3$). GC (50°C, 1 min, 10°C/min, 200°C, 15 min): R_t=26.62 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.30.

endo B: Colorless oil. IR (film, ν, cm^{-1}): 3105, 2957, 2875, 1735 (C═O, st), 1717 (C═O, st), 1456, 1379, 1248, 1134, 1068, 1034, 985. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.77 (3H, d, J=7.0 Hz, H10′), 0.90 (3H, d, J=6.8 Hz, H8′ or H9′), 0.92 (3H, d, J=6.6 Hz, H8′ or H9′), 0.99 (3H, d, J=7.0 Hz, H10), 1.01 (3H, d, J=6.8 Hz, H9), 1.04–1.09 (2H, m, 1H3′ and 1H6′), 1.43–1.48 (2H, m, H7′ and H2′), 1.68–1.73 (2H, m, 1H3′ and 1H4′), 1.84–1.89 (1H, m, H5′), 2.04–2.10 (1H, m, H6′), 2.90 (1H, dq, J_1=4.6 Hz, J_2=7 Hz, H4), 2.93 (1H, q, J=7.0 Hz, H2), 4.84 (1H, td, J_1=4.4 Hz, J_2=11 Hz, H1′), 4.96 (1H, dd, J_1=4.8 Hz, J_2=1.8 Hz, H5), 6.36 (1H, dd, J_1=5.8 Hz, J_2=1.8 Hz, H6), 6.47 (1H, d, J=5.8 Hz, H7). ^{13}C NMR (75.45 MHz, $CDCl_3$, δ, ppm): 8.3 (C9), 9.1 (C10), 14.8 (C10′), 19.5 and 20.7 (C9′ and C8′), 22.0 (C3′), 24.9 (C5′), 30.2 (C7′), 32.9 (C4′), 39.4 (C6′), 45.5 (C2′), 48.4 (C4), 51.5 (C2), 74.6, (C1′), 82.1 (C5), 89.5 (C1), 131.1 (C6), 133.0 (C7), 166.6 (C11), 205.6 (C3). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 196 (47, M−menthyl), 152 (9, $C_9H_{12}O_2^+$), 140 (3), 138 (14). Anal. calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.69; H, 9.22%. $[\alpha]_D^{23}$=13.5 (c=2.52, $CHCl_3$). GC (50°C, 1 min, 10°C/min, 200°C, 15 min): R_t=26.87 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.26.

4.5.8. (±)-(1′R*,2′R*)-1-[2-(Diphenylmethylsilyloxy)-1-cyclohexylthioxy]-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (23)



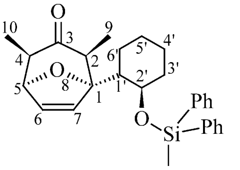
(±) *endo (1S*, 2S*, 4R*, 5S*)* (±) *endo (1R*, 2R*, 4S*, 5R*)*

(±)-*endo* A. Colorless oil. IR (film, ν, cm^{-1}): 3069, 2938, 2900, 1717 (C═O, st), 1603, 1451, 1379, 1275, 1113, 1070, 1026, 958, 746, 713. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.65 (3H, s, Si–CH_3), 0.94 (3H, d, J=7.2 Hz, H10), 1.05 (3H, d, J=7.2 Hz, H9), 1.40–1.69 (4H, m, H5′ and H3′), 1.80–1.91 (2H, m, H6′), 2.22–2.40 (2H, m, H4′), 2.68 (1H, q, J=7.2 Hz, H2), 2.74 (1H, dq, J_1=4.8 Hz, J_2=7.2 Hz, H4), 2.99 (1H, q, J=4.2 Hz, H1′), 4.06–4.11 (1H, m, H2′), 4.65 (1H, dd, J_1=4.8 Hz, J_2=1.8 Hz, H5), 6.06 (1H, d, J=6.0 Hz, H7), 6.20 (1H, dd, J_1=6.0 Hz, J_2=1.8 Hz, H6), 7.34–7.41 (8H, m, H_{meta}, H_{para}), 7.54–7.62 (2H, m, H_{ortho}). ^{13}C NMR (75.45 MHz, $CDCl_3$, δ, ppm): 2.68 (Si–CH_3), 10.38 (C9), 10.93 (C10), 20.4 (C3′), 22.6 (C5′), 29.0 (C6′), 30.0 (C4′), 45.8 (C1′), 49.6 (C4), 55.5 (C2), 71.9 (C2′), 82.5 (C5), 97.3 (C1), 127.7 (C_{meta}), 129.6 (C_{para}), 134.3 (C_{ortho}), 134.4 (C7), 135.6 (C6), 136.9 (C_{ipso}), 207.6 (C3). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]:496 (44, M+NH_4), 480 (36, M+2), 479 (100, M+1), 401 (20, M−phenyl), 265 (47, M−$OSiMePh_2$), 214 (13, $OSiMePh_2^+$). Anal. calcd for $C_{28}H_{34}O_3SSi$: C, 70.35; H, 7.16. Found: C, 70.21; H, 7.20%. GC (100°C, 2 min, 10°C/min, 200°C, 15 min): R_t=48.44 min. TLC (SiO_2, hexane/ethyl acetate, 9:1): R_f=0.31.

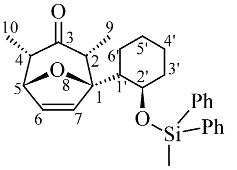
(±)-*endo* B. Colorless oil. IR (film, ν, cm^{-1}): 3069, 2938, 2900, 1717 (C═O, st), 1603, 1451, 1379, 1275, 1113, 1070, 1026, 958, 746, 713. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.68 (3H, s, Si–CH_3), 0.94 (3H, d, J=7.2 Hz, H10), 1.04 (3H, d, J=7.2 Hz, H9), 1.30–1.69 (4H, m, H5′ and H3′), 1.7–1.94 (2H, m, H6′), 2.17–2.38 (2H, m, H4′), 2.71 (1H, q, J=7.2 Hz, H2), 2.76 (1H, dq, J_1=4.8 Hz, J_2=7.2 Hz, H4), 2.83 (1H, dt, J_1=4.2 Hz, J_2=7.5 Hz, H1′), 3.75 (1H, dt,

J_1=3.3 Hz, J_2=7.2 Hz, H2′), 4.81 (1H, dd, J_1=4.8 Hz, J_2=1.8 Hz, H5), 5.96 (1H, d, J=5.7 Hz, H7), 6.19 (1H, dd, J_1=6 Hz, J_2=1.8 Hz, H6), 7.34–7.40 (6H, m, H$_{meta}$, H$_{para}$), 7.56–7.65 (4H, m, H$_{ortho}$). ^{13}C NMR (75.45 MHz, CDCl$_3$, δ, ppm): −2.34 (Si–CH_3), 10.36 (C9), 10.95 (C10), 22.2 (C3′), 24.0 (C5′), 32.1 (C6′), 32.9 (C4′), 47.6 (C1′), 49.6 (C4), 55.6 (C2), 72.9 (C2′), 82.3 (C5), 97.7 (C1), 127.7 (C$_{meta}$), 129.7 (C$_{para}$), 133.9 (C7), 134.4 (C$_{ortho}$) 136.2 (C6), 136.7 (C$_{ipso}$), 207.7 (C3). MS [GC–MS(CI), NH$_3$, 70 eV, 150°C, *m/z*, (%)]: 496 (50, M+NH$_4$), 480 (26, M+2), 479 (100, M+1), 401 (35, M−phenyl), 265 (60, M−OSiMePh$_2$). Anal. calcd for $C_{28}H_{34}O_3SSi$: C, 70.25; H, 7.16. Found: C, 70.18; H, 7.22%. GC (100°C, 2 min, 10°C/min, 200°C, 15 min): R_t=49.25 min. TLC (SiO$_2$, hexane/ethyl acetate, 9:1): R_f=0.29.

4.5.9. (±)-(1′*R**,2′*R**)-1-[2-(Diphenylmethylsilyloxy)-1-cyclohexyl]-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (24)



(±) *endo (1S*, 2S*, 4R*, 5S*)*

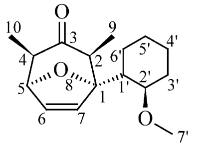


(±) *endo (1R*, 2R*, 4S*, 5R*)*

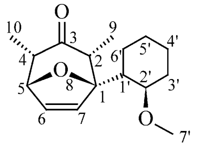
(±)-*endo* (5*R**,1′*R**). Major cycloadduct. Colorless oil. IR (film, ν, cm^{-1}): 3090, 3070, 2931, 2870, 1709 (C=O, st), 1653, 1559, 1541, 1456, 1.429, 1117, 1079, 995, 876, 827, 791. ^{1}H NMR (300 MHz, CDCl$_3$, δ, ppm): 0.70 (3H, s, Si–CH_3), 0.87 (3H, d, J=6.9 Hz, H9), 0.93 (3H, d, J=7.2 Hz, H10), 1.01–2.05 (9H, m, H1′, H3′, H4′, H5′ and H6′), 2.26 (1H, dq, J_1=4.5 Hz, J_2=6.9 Hz, H4), 3.26 (1H, q, J=6.9 Hz, H2), 4.14 (1H, dt, J_1=10.2 Hz, J_2=3.3 Hz, H2′), 4.74 (1H, dd, J_1=4.4 Hz, J_2=1.2 Hz, H5), 6.05 (1H, dd, J_1=6 Hz, J_2=1.5 Hz, H6), 6.08 (1H, d, J=6 Hz, H7), 7.30–7.45 (6H, m, H$_{meta}$, H$_{para}$), 7.54–7.62 (4H, m, H$_{ortho}$). ^{13}C NMR (75.45 MHz, CDCl$_3$, δ, ppm): −2.1 (Si–CH_3), 9.9 (C9), 10.31 (C10), 24.4 (C5′), 25.3 (C4′), 26.8 (C6′), 36.8 (C3′), 44.5 (C1′), 49.3 (C4), 53.7 (C2), 73.2 (C2′), 82.2 (C5), 92.7 (C1), 127.7 (C$_{meta}$), 129.6 (C$_{para}$), 130.4 (C7), 134.32 and 134.35 (C$_{ortho}$), 136.7 (C$_{ipso}$), 137.0 (C6), 210.7 (C3). MS [GC–MS(CI), NH$_3$, 70 eV, 150°C, *m/z*, (%)]: 464 (11, M+NH$_4$), 448 (37, M+2), 447 (100, M+1), 369 (20, M−Phenyl), 214 (3, M−OSiMePh$_2$). Anal. calcd for $C_{28}H_{34}O_3Si$: C, 75.29; H, 7.67. Found: C, 75.19; H, 7.60%. GC (50°C, 1 min, 10°C/min, 290°C, 15 min): R_t=34.9 min.

(±)-*endo* (5*S**,1′*R**): Colorless oil. IR (film, ν, cm^{-1}): 3090, 3070, 2931, 2870, 1709 (C=O, st), 1653, 1559, 1541, 1456, 1.429, 1117, 1079, 995, 876, 827, 791. ^{1}H NMR (200 MHz, CDCl$_3$, δ, ppm): 0.60 (3H, s, Si–CH_3), 0.90 (3H, d, J=7.2 Hz, H9), 0.92 (3H, d, J=7.0 Hz, H10), 1.01–2.05 (9H, m, H1′, H3′, H4′, H5′ and H6′), 2.66 (1H, dq, J_1=4.5 Hz, J_2=7.0 Hz, H4), 2.67 (1H, q, J=7.0 Hz, H2), 3.96 (1H, dt, J_1=8.7 Hz, J_2=4.5 Hz, H2′), 4.67 (1H, dd, J_1=4.5 Hz, J_2=1.5 Hz, H5), 5.64 (1H, dd, J_1=6.0 Hz, J_2=1.5 Hz, H6), 6.12 (1H, d, J=6.0 Hz, H7), 7.30–7.45 (6H, m, H$_{meta}$, H$_{para}$), 7.52–7.60 (4H, m, H$_{ortho}$). ^{13}C NMR (75.45 MHz, CDCl$_3$, δ, ppm): −2.2 (Si–CH_3), 9.0 (C9), 10.29 (C10), 24.2 (C5′), 24.6 (C4′), 25.2 (C6′), 36.3 (C3′), 45.5 (C1′), 49.5 (C4), 51.6 (C2), 71.6 (C2′), 82.1 (C5), 90.9 (C1), 126.7 (C7), 127.6 (C$_{meta}$), 129.4 (C$_{para}$), 134.3 (C$_{ortho}$), 137.0 and 137.1 (C$_{ipso}$), 139.3 (C6), 207.7 (C3). MS [GC–MS(CI), NH$_3$, 70 eV, 150°C, *m/z*, (%)]: 464 (20, M+NH$_4$), 448 (42, M+2), 447 (100, M+1), 369 (38, M−Phenyl). Anal. calcd for $C_{28}H_{34}O_3Si$: C, 75.29; H, 7.67. Found: C, 75.14; H, 7.71%. GC (50°C, 1 min, 10°C/min, 290°C, 15 min): R_t=36.05 min.

4.5.10. (±)-(1′*R**,2′*R**)-1-(2-Methoxy-cyclohex-1-yl)-2,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (25)



(±) *endo (1S*, 2S*, 4R*, 5S*)*

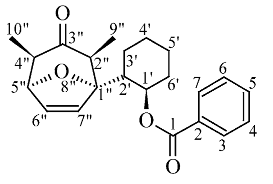


(±) *endo (1R*, 2R*, 4S*, 5R*)*

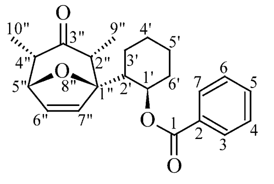
(±)-*endo* (5*S**,1′*R**). Major diastereoisomer. Colorless oil. IR (film, ν, cm^{-1}): 3105, 2984, 2870, 1718 (C=O, st), 1450, 1310, 1284, 1108, 1070, 1025, 976. ^{1}H NMR (200 MHz, CDCl$_3$, δ, ppm): 0.95 (6H, d, J=7.0 Hz, H9 and H10), 1.08–2.20 (9H, m, H1′, H6′, H5′, H4′ and H3′), 2.62–2.76 (2H, m, H2 and H4), 3.12 (3H, s, H7′), 3.15–3.25 (1H, m, H2′), 4.79 (1H, dd, J_1=4.4 Hz, J_2=1.4 Hz, H5), 5.93 (1H, dd, J_1=6.2 Hz, J_2=1.4 Hz, H6), 6.30 (1H, d, J=6.2 Hz, H7). ^{13}C NMR (50 MHz, CDCl$_3$, δ, ppm): 9.0 (C9), 10.3 (C10), 24.2 (C5′), 24.9 (C4′), 25.7 (C6′), 31.5 (C3′), 44.4 (C1′), 49.8 (C4), 51.4 (C2), 55.6 (C7′), 78.7 (C2′), 81.9 (C5), 90.9 (C1), 125.5 (C7), 138.5 (C6), 210.2 (C3). MS [GC–MS(CI), NH$_3$, 70 eV, 150°C, *m/z*, (%)]: 282 (17, M+NH$_4$), 266 (27, M+2), 265 (100, M+1). Anal. calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15%. Found: C, 72.48; H, 9.02%. GC (100°C, 1 min, 10°C/min, 290°C, 1 min): R_t=16.18 min. TLC (SiO$_2$, hexane/ethyl acetate, 8:2): R_f=0.55.

(±)-*endo* (5*R**,1′*R**). Colorless oil. IR (film, ν, cm^{-1}): 3105, 2983, 2870, 1717 (C=O, st), 1451, 1310, 1280, 1111, 1070, 1024, 976. ^{1}H NMR (200 MHz, CDCl$_3$, δ, ppm): 0.95 (3H, d, J=7.0 Hz, H9), 1.0 (3H, d, J=7.0 Hz, H10), 1.08–2.20 (9H, m, H1′, H6′, H5′, H4′ and H3′), 2.47 (1H, dq, J_1=7.0 Hz, J_2=4.8 Hz, H4), 2.74 (1H, q, J=7.0 Hz, H2), 3.24–3.33 (1H, m, H2′), 3.32 (3H, s, H7′), 4.80 (1H, d, J=4.4 Hz, H5), 6.11 (2H, s, H6 and H7). ^{13}C NMR (50 MHz, CDCl$_3$, δ, ppm): 9.9 (C9), 10.4 (C10), 24.8 (C5′), 25.5 (C4′), 26.7 (C6′), 31.2 (C3′), 42.9 (C1′), 49.6 (C4), 54.0 (C2), 55.6 (C7′), 80.3 (C2′), 82.3 (C5), 92.7 (C1), 130.5 (C7), 137.0 (C6), 211.4 (C3). MS [GC–MS(CI), NH$_3$, 70 eV, 150°C, *m/z*, (%)]:282 (14, M+NH$_4$), 266 (24, M+2), 265 (100, M+1). Anal. calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.56; H, 9.21%. GC (100°C, 1 min, 10°C/min, 290°C, 1 min): R_t=16.24 min. TLC (SiO$_2$, hexane/ethyl acetate, 8:2): R_f=0.60.

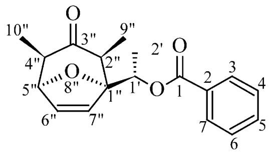
4.5.11. (±)-(1′*R,2′*R**)-2-(2,4-Dimethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-yl)-cyclohexyl benzoate (26).** (±)-*endo* (5*R**,1′*R**). Major diastereoisomer. Colorless oil. IR (film, ν, cm^{-1}): 3100, 2936, 2863, 1717 (C=O, st), 1653, 1603, 1559, 1451, 1314, 1271, 1111, 1070, 1026, 976. ^{1}H NMR (200 MHz, CDCl$_3$, δ, ppm): 0.86 (3H, d, J=7.0 Hz, H9″), 0.99 (3H, d, J=7.0 Hz, H10″), 1.1–2.4 (9H, m, H2′,



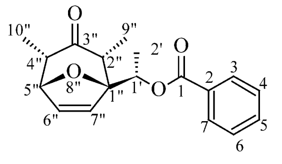
(±) endo (1″S*, 2″S*, 4″R*, 5″S*)



(±)endo (1″R*, 2″R*, 4″S*, 5″R*)



endo (1″S, 2″S, 4″R, 5″S)



endo (1″R, 2″R, 4″S, 5″R)

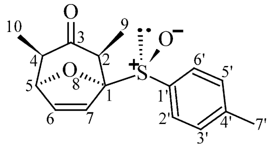
H3′, H4′, H5′ and H6′), 2.69 (1H, dq, J_1=4.4 Hz, J_2=7.0 Hz, H4″), 2.71 (1H, q, J=7.0 Hz, H2″), 4.76 (1H, dd, J_1=4.4 Hz, J_2=1.8 Hz, H5″), 5.28 (1H, dt, J_1=10.4 Hz, J_2=5.2 Hz, H1′), 5.72 (1H, dd, J_1=6.0 Hz, J_2=1.8 Hz, H6″), 6.10 (1H, d, J=6.0 Hz, H7″), 7.33–7.57 (3H, m, H3, H5 and H7), 7.67 (2H, dd, J_1=8.0 Hz, J_2=2.0 Hz, H4 and H6). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 9.1 (C9″), 10.2 (C10″), 24.0 (C4′), 24.8 (C5′), 25.1 (C3′), 32.4 (C6′), 42.9 (C2′), 49.7 (C4″), 51.3 (C2″), 72.3 (C1′), 82.0 (C5″), 90.3 (C1″), 128.3 (C4 and C6), 128.7 (C5), 129.3 (C3 and C7), 130.8 (2), 132.6 (C7″), 136.8 (C6″), 165.1 (C1), 209.8 (C3″). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 373 (26, $M+NH_4+H^+$), 372 (100, $M+NH_4$), 355 (8, M+1), 152 (M−ChexOCOPh). Anal. calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.39; H, 7.30%. GC (100°C, 1 min, 10°C/min, 290°C, 5 min): R_t=24.40 min. TLC (SiO_2, hexane/ethyl acetate, 8:2): R_f=0.48.

(±)-*endo* (5*S**,1′*R**). Colorless oil. IR (film, ν, cm^{-1}): 3100, 2936, 2863, 1717 (C═O, st), 1653, 1603, 1559, 1451, 1314, 1271, 1111, 1070, 1026, 976. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.87 (3H, d, J=7.0 Hz, H9″), 1.11 (3H, d, J=7.0 Hz, H10″), 1.1–2.4 (9H, m, H2′, H3′, H4′, H5′ and H6′), 2.63 (1H, dq, J_1=4.4 Hz, J_2=7.0 Hz, H4″), 2.81 (1H, q, J=7.0 Hz, H2″), 4.81 (1H, dd, J_1=4.4 Hz, J_2=1.8 Hz, H5″), 5.29–5.41 (1H, m, H1′), 6.10 (1H, d, J=6.2 Hz, H7″), 6.14 (1H, d, J=6.2 Hz, H6″), 7.29–7.58 (3H, m, H3, H5 and H7), 8.00 (2H, dd, J_1=8.0 Hz, J_2=1.2 Hz, H4 and H6). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 10.0 (C9″), 10.2 (C10″), 23.9 (C4′), 24.4 (C5′), 25.0 (C3′), 32.4 (C6′), 41.6 (C2′), 49.5 (C4″), 53.6 (C2″), 74.1 (C1′), 82.4 (C5″), 92.0 (C1″), 128.4 (C4 and C6), 129.4 (C3 and C7), 131.3 (C5), 130.5 (C2), 132.9 (C7″), 136.0 (C6″), 165.4 (C1), 210.1 (C3″). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 372 (100, $M+NH_4$), 355 (8, M+1), 152 (M−Chex-OCOPh). Anal. calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.42; H, 7.32%. GC (100°C, 1 min, 10°C/min, 290°C, 5 min): R_t=24.96 min. TLC (SiO_2, hexane/ethyl acetate, 8:2): R_f=0.52.

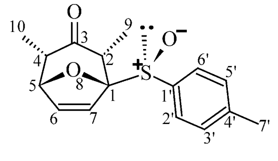
4.5.12. (1′*R*)-1-(2,4-Dimethyl-3-oxo-8-oxabicyclo[3.2.1]-oct-6-en-1-yl)-ethyl benzoate (27). *endo* A. Colorless oil. IR (film, ν, cm^{-1}): 3104, 2938, 2900, 1717 (C═O, st), 1603, 1451, 1379, 1275, 1113, 1070, 1026, 958, 746, 713. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 0.98 (3H, d, J=7 Hz, H10″), 1.08 (3H, d, J=7 Hz, H9″), 1.49 (3H, d, J=6.5 Hz, H2′), 2.81 (1H, dq, J_1=4.9 Hz, J_2=7.0 Hz, H4″), 2.91 (1H, q, J=7.0 Hz, H2″), 4.93 (1H, dd, J_1=4.5 Hz, J_2=1.5 Hz, H5″), 5.59 (1H, q, J=7.0 Hz, H1′), 6.18 (1H, d, J=6.0 Hz, H7″), 6.25 (1H, dd, J_1=6.0 Hz, J_2=1.5 Hz, H6″), 7.35–7.56 (2H, m, H6 and H4), 7.41–7.68 (1H, m, H5), 8.02 (2H, dd, J_1=7.0 Hz, J_2=1.5 Hz, H3 and H7). ^{13}C NMR (75.45 MHz, $CDCl_3$, δ, ppm): 9.5 (C9″), 10.42 (C10″), 14.2 (C2′), 49.7 (C4″), 52.0 (C2″), 69.7, (C1′), 83.38 (C5″), 91.7 (C1″), 128.3 (C6 and C4), 129.7 (C3 and C7), 130.1 (C2), 133.0 (C5), 133.6 (C7″), 133.7 (C6″), 166.0 (C1), 208.3 (C3″). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 335 (7, $M+N_2H_4$), 318 (100, $M+NH_4$), 301 (57, M+1), 179 (6, $M-C_7H_5O_2$), 122 (5, $C_7H_6O_2^+$). Anal. calcd for $C_{18}H_{20}O_4$: C, 71.97; H, 6.72. Found: C, 71.82; H, 6.65%. GC (100°C, 1 min, 2°C/min, 290°C, 15 min): R_t=68.39 min.

endo B. Colorless oil. IR (film, ν, cm^{-1}): 3105, 2940, 1717 (C═O, st), 1605, 1450, 1379, 1273, 1111, 1074, 1025, 957, 745, 710. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.98 (3H, d, J=7.0 Hz, H10″), 0.99 (3H, d, J=7.0 Hz, H9″), 1.36 (3H, d, J=6.5 Hz, H2′), 2.68 (1H, q, J=7.0 Hz, H2″), 2.85 (1H, dq, J_1=4.9 Hz, J_2=7.0 Hz, H4″), 4.99 (1H, dd, J_1=4.5 Hz, J_2=1.5 Hz, H5″), 5.51 (1H, q, J=7.0 Hz, H1′), 6.10 (1H, d, J=6.0 Hz, H7″), 6.33 (1H, dd, J_1=6.0 Hz, J_2=1.5 Hz, H6″), 7.35–7.55 (2H, m, H6 and H4), 7.40–65 (1H, m, H5), 8.09 (2H, dd, J_1=7.0 Hz, J_2=1.5 Hz, H3 and H7). ^{13}C NMR (75.45 MHz, $CDCl_3$, δ, ppm): 9.2 (C9″), 10.38 (C10″), 14.7 (C2′), 49.5 (C4″), 52.2 (C2″), 69.6, (C1′), 83.44 (C5″), 91.6 (C1″), 128.4 (C4 and C6), 129.7 (C3 and C7), 130.1 (C2), 133.4 (C7″), 133.2 (C5), 134.3 (C6″), 165.8 (C1), 209.1 (C3″). MS [GC–MS(CI), NH_3, 70 eV, 150°C, *m/z*, (%)]: 335 (2, $M+N_2H_4$), 318 (100, $M+NH_4$), 301 (17, M+1). Anal. calcd for $C_{18}H_{20}O_4$: C, 71.97; H, 6.72. Found: C, 71.83; H, 6.63%. GC (100°C, 1 min, 2°C/min, 290°C, 15 min): R_t=68.62 min.

4.5.13. (S_S)-2,4-Dimethyl-1-(*p*-tolylsulfinyl)-8-oxabicyclo[3.2.1]oct-6-en-3-one (28)



endo (1S, 2S, 4R, 5S)



endo (1R, 2R, 4S, 5R)

endo (5*R*,S_S). Major diastereoisomer. Colorless oil. IR (film, ν, cm^{-1}): 3100, 2975, 2936, 1713 (C═O, st), 1653, 1597, 1559, 1495, 1456, 1379, 1157, 1086, 1057, 1040, 1016, 985. ^{1}H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.93 (3H, d, J=7 Hz, H10), 1.30 (3H, d, J=7 Hz, H9), 2.41 (3H, s, H7′), 2.81 (1H, dq, J_1=4.8 Hz, J_2=7.0 Hz, H4), 3.21 (1H, q, J=7.0 Hz, H2), 4.85 (1H, dd, J_1=4.8 Hz, J_2=1.4 Hz, H5), 6.25 (1H, d, J=6.0 Hz, H7), 6.30 (1H, dd, J_1=6.0 Hz, J_2=1.4 Hz, H6), 7.30 (2H, d, J=8.2 Hz, H2′ and H6′), 7.53 (1H, d, J=8.2 Hz, H3′ and H5′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 9.4

(C9), 10.1 (C10), 21.4 (C7′), 49.3 (C4), 51.0 (C2), 83.6 (C5), 102.9 (C1), 126.2 (C2′ and C6′), 129.3 (C3′ and C5′), 129.8 (C6), 134.4 (C4′), 135.9 (C7), 142.0 (C1′), 207.4 (C3). MS [GC–MS(CI), CH_4, 70 eV, 150°C, *m/z*, (%)]: 291 (100, M+1), 207 (5, M−85), 151 (29, $M-SOC_7H_7$). Anal. calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25%. Found: C, 66.03; H, 6.18%. $[\alpha]_D^{21}=211.0$ (c=0.9, $CHCl_3$). GC (100°C, 1 min, 10°C/min, 290°C, 15 min): R_t=18.52 min. TLC (SiO_2, hexane/ethyl acetate, 8:2): R_f=0.1.

endo ($5S,S_S$). Colorless oil. IR (film, ν, cm^{-1}): 3100, 2977, 2936, 1715 (C═O, st), 1597, 1493, 1456, 1379, 1456, 1086, 1043, 969, 812. ^1H NMR (200 MHz, $CDCl_3$, δ, ppm): 0.93 (3H, d, J=7 Hz, H9), 1.22 (3H, d, J=7.2 Hz, H10), 2.43 (3H, s, H7′), 2.56 (1H, q, J=7.0 Hz, H2), 2.70 (1H, dq, J_1=4.8 Hz, J_2=7.2 Hz, H4), 4.98 (1H, d, J=4.8 Hz, H5), 6.47 (1H, d, J=6.2 Hz, H6), 6.50 (1H, d, J=6.2 Hz, H7), 7.32 (2H, d, J=8.0 Hz, H2′ and H6′), 7.59 (1H, d, J=8.0 Hz, H3′ and H5′). ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm): 9.7 (C9), 10.3 (C10), 21.5 (C7′), 49.5 (C4), 52.3 (C2), 83.8 (C5), 103.2 (C1), 126.5 (C2′ and C6′), 129.5 (C3′ and C5′), 130.4 (C6), 134.9 (C4′), 136.7 (C7), 142.5 (C1′), 206.4 (C3). MS [GC–MS(CI), CH_4, 70 eV, 150°C, *m/z*, (%)]: 291 (100, M+1), 167 (7), 152 (3, $M-SOC_7H_7+H^+$), 151 (23, $M-SOC_7H_7$). Anal. calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25. Found: C, 66.05; H, 6.29%. $[\alpha]_D^{23}=41.9$ (c=2.0, $CHCl_3$). GC (100°C, 1 min, 10°C/min, 290°C, 15 min): R_t=18.57 min. TLC (SiO_2, hexane/ethyl acetate, 8:2): R_f=0.1.

Acknowledgements

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