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GRAPHICAL ABSTRACT

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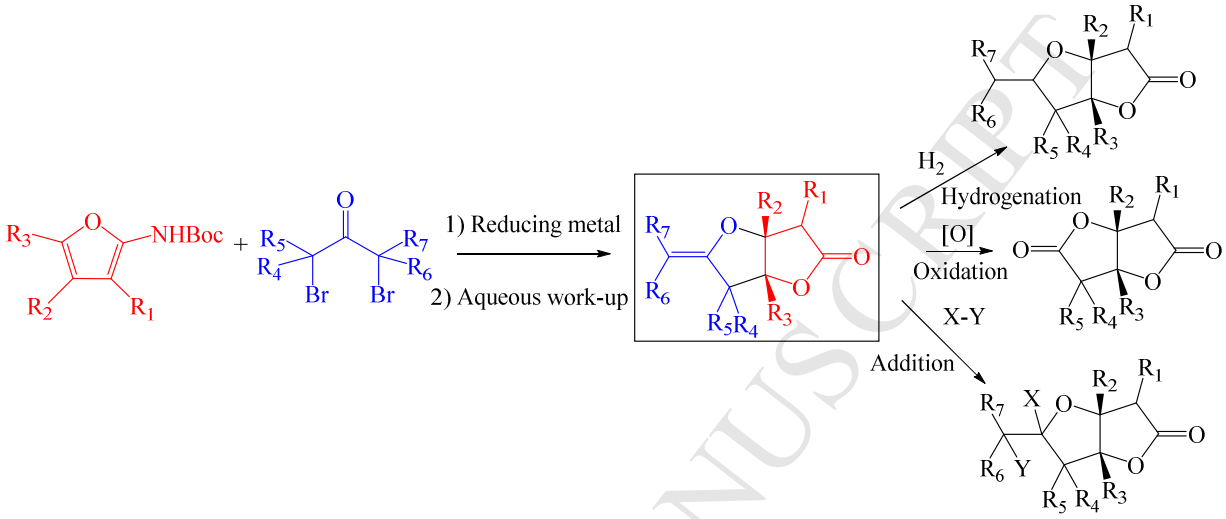

New methodology for the synthesis of tetrahydrofuro[3,2-b]furan-2(3*H*)-one derivatives, synthons of natural products with biological interest

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ABSTRACT:

A new methodology is presented to synthesize in a regio and stereoselective manner tetrahydrofuro[3,2-b]furan-2(3*H*)-one, structural subunit present in a wide variety of natural products present in plant, fungi, algae , insects and other living organisms. This secondary metabolites have important biological properties and have shown to be very active in different therapeutic areas. This method consists in the reaction of highly substituted 2-oxyallyl cations, generated *in situ* from the corresponding dihaloketone, and 2-functionalized furans (in our case 2-NHBoc-furan). It is a one-pot reaction that affords the desired furofuranones with high regio- and stereoselectivity. The new synthetic method is simple, straightforward and versatile, because a wide variety of furofuranones, and with wide molecular diversity, may be prepared by adequately designing the substituents of starting materials. The resulting furofuranones may be potentially derivatized to generate chemical libraries of high molecular diversity, which are very useful when developing structure-activity relationship studies.

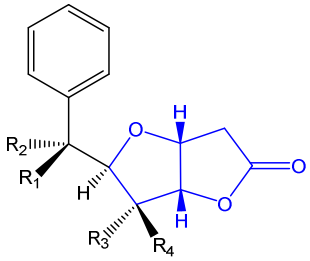
Keywords: furan, oxyallyl cation, tetrahydrofuro[3,2-b]furan-2(3*H*)-one, 2,6-dioxabicyclo[3.3.0]octan-3-one, γ-lactones, haloketones, 2-functionalized furans, [3+2]-cycloaddition, [4+3]-cycloaddition.

1. Introduction

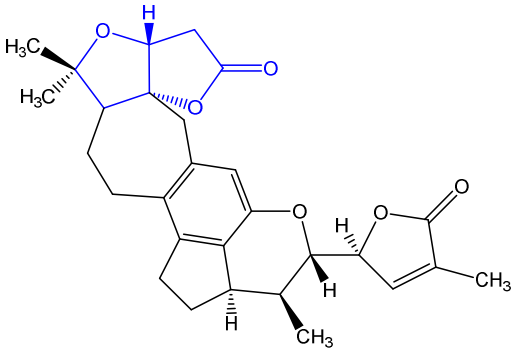
The tetrahydrofuro[3,2-b]furan-2(3*H*)-one structural subunit is present in natural products from many different living organisms: superior plants, fungi, algae, sponges, insects, etc. Some of these compounds like goniofufurone and analogues are active as cytotoxic agents against lymphocytic leukaemia and human lung carcinoma (Figure 1).[1]

Secondary metabolites from Caribbean sponges like plakortones A-F constitute a new class of activators of cardiac SR-Ca^{2+}-pumping ATPase, and are relevant to correction of cardiac relaxation irregularities. Other plakortones exhibit *in vitro* cytotoxic activity on a murine fibrosarcoma cell line, so that overall, the plakortones represent a new family of natural products of substantial pharmacological interest.[2] On the other hand, the nortriterpenoids rubriflordilactones from *Schisandra rubriflora* (Figure 1) are a class of structurally and biologically attractive compounds due to their promising anti-HIV activity.[3]

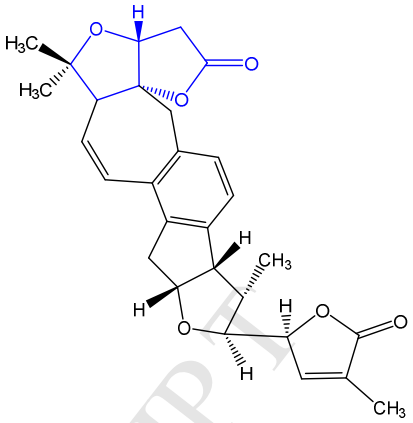
In addition, their attractive architectures represent a formidable synthetic challenge. Furthermore diachasmimorpholides secreted by abdominal glands of braconid wasps, *Diachasmimorpha longicaudata* and *Diachasmimorpha tryoni* are important fragrant volatile biological control agents acting as semiochemicals with great ecological interest.[4] It is also worth noting the interest of furofuranones derived from *D*-aldoses, as analogues of goniofufurone, with interesting cytotoxic activity.[5]



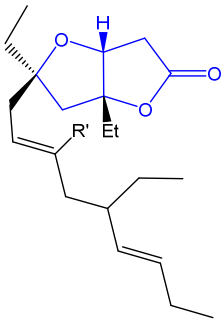
Goniofufurone:
R_1 = H, R_2 = OH, R_3 = H, R_4 = OH
7-*epi*-Goniofufurone:
R_1 = OH, R_2 = H, R_3 = H, R_4 = OH
(*Goniothalamus giganteus*)
Annonaceae



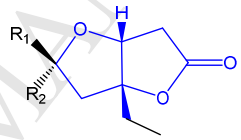
Rubriflordilactone A
(*Schisandra rubriflora*)
Schisandraceae



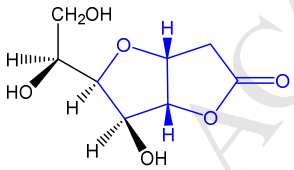
Rubriflordilactone B



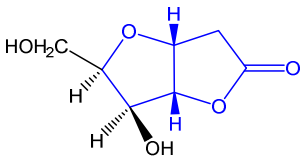
Plakortone A R' = Et
Plakortone B R' = Me
Plakortis halichondrioides and *Plakortis simplex*
(Caribbean sponges)



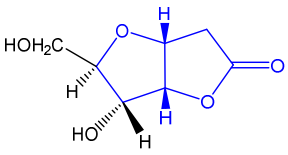
Diachasmimorpholides
R_1 = *n*-C_4H_9, R_2 = H
R_1 = *n*-C_6H_{13}, R_2 = H
R_1 = H, R_2 = *n*-C_4H_9
R_1 = H, R_2 = *n*-C_6H_{13}
Diachasmimorpha longicaudata and *Diachasmimorpha tryoni*
(Hymenoptera Braconidae, wasp parasitoid)



***cis-D*-Glucofurofuranone**



***cis-D*-Xylofurofuranone**



***cis-D*-Ribofurofuranone**

Figure 1. Examples of natural products, having the substructure tetrahydrofuro[3,2-b]furan-2(3*H*)-one, with interesting biological activities.

The structural subunit *cis*-2,6-dioxabicyclo[3.3.0]octane or perhydrofuro[3,2-b]furan is even more widely present in Nature than its furofuranone analogue. Thus, natural products like mycotoxin erythroskyrine[6] from (*Penicillium islandicum*), Laurenenines A and B from algae (*Laurentia nipponica*)[7] are good examples. On the other hand, synthetic products like isosorbide (starting material for synthesis of biobased polymers and also for pharmaceutical applications),[8] isosorbide dinitrate (vasodilator of use in cardiac therapy[9] for angina pectoris, congestive heart failure, esophageal spasms and also to treat glaucoma[10]) or even 3-(trialkylammonium)-isosorbide derived salts (used as catalysts in asymmetric synthesis)[11] are also good examples of the versatility of this structural difuran framework.

For the aforementioned important properties, tetrahydrofuro[3,2-b]furan-2(3*H*)-ones have been a synthetic target since long time ago and several methodologies have been developed for this purpose.[1, 12,13,14,15,16]

Based in our previous experience in the reactivity of oxyallyl cations, [4+3]-cycloaddition reactions and related methodologies,[17] we present here a new synthetic method, which is simple, straightforward and versatile, because a wide variety of furofuranones, and with wide molecular diversity, may be prepared by adequately designing the substituents of starting materials. This method consists in the reaction of highly substituted 2-oxyallyl cations, generated *in situ* from the corresponding dihaloketone **II**, and 2-functionalized furans **I** (in our case 2-NHBoc-furan) (Figure 2) to afford alkylidene-furofuranones **III**, which can be transformed into a wide variety of derivatives (*ie.* **IV, V** or **VI**) by straightforward reactions. The key reaction leading to **III** is a [3+2] cycloaddition that takes place by a one-pot process and with high regio- and stereoselectivity.

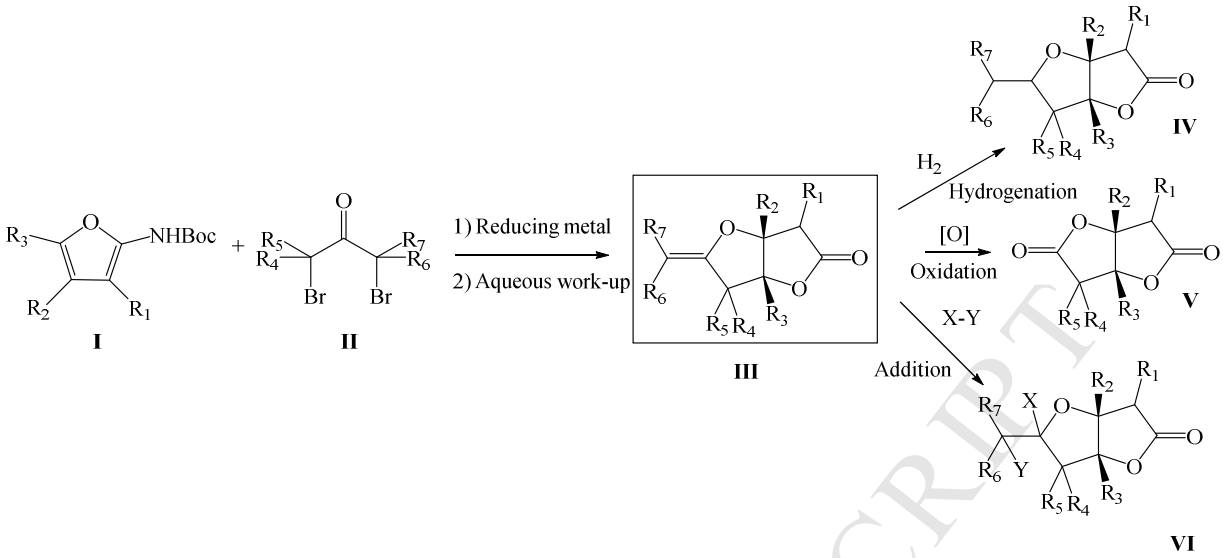


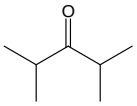
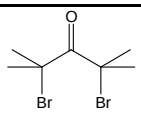
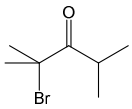
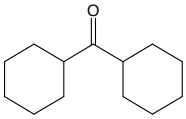
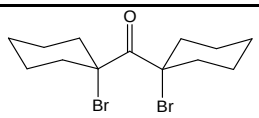
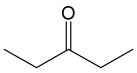
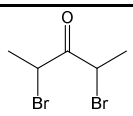
Figure 2. New methodology to prepare furofuranones and potential derivatives.

2. Results and discussion

2.1. Preparation of substrates: synthesis of dibromoketones 1 and 3 and 2-(*tert*-butoxycarbonylamino)-furan, 6

To simplify the reaction outcome in this particular study we have used symmetric dihaloketones **1** and **3**. This methodology may be applied to other tetrasubstituted dissymmetric dihaloketones **II** ($R_1 \neq R_2 \neq R_3 \neq R_4$) (Figure 2); but, a mixture of diastereoisomeric products will be formed; however, a certain degree of stereoselectivity may be expected. In any case, as it will be discussed latter on, it is of great importance that the ketone should be α,α,α',α'-tetrasubstituted and with steric demanding substituents in order to get good yields of furofuranones. Dibromoketones **1** and **3** were easily obtained by bromination of the corresponding commercially available ketones, following well described procedures.[18] The results from the synthesis of dibromoketones are quoted in Table 1.

Table 1. Reaction outcome of bromination of precursor ketones to obtain **1** and **3**.

Entry[a]	Precursor	Product[b]	Yield[c] (%)
1		 **1**	84
		 **2**	10
2		 **3**	74
3		 **4**	79[d]

(**a**) Reaction conditions: substrate/Br_2 1:2, catalytic amount of PBr_3, 0ºC, 2 h.
(**b**) Isolable by vacuum fractional distillation. (**c**) Yield on isolated product.
(**d**) *Meso/dl* ratio 4:1.

The synthesis of products **1** and **3** and in general of all tetrasubstituted ketones does not present special problems due to there are only two active positions to be halogenated. The yield in both cases was good and in the case of diisopropyl ketone only a 10% of monobrominated product **2** was formed. This byproduct was efficiently separated by vacuum fractional distillation.

The other substrate used for this methodology was the *tert*-butyl *N*-(2-furoyl)-carbamate **6**. It is of capital importance for the obtention of desired alkylidenefurofuranones that the furan ring should be functionalized on C2. Moreover, this function should exert also a certain degree of steric hindrance. In this particular work we have selected the carbamate function bur other functions like for example $(CH_3)_3C$-COO–, among other, may be used.

The non-commercial 2-(NHBoc)-furan **6** was obtained following the procedure described by Lynch *et al.*[19] This procedure involves a one-pot reaction between the 2-furoyl chloride, sodium azide and an excess of *tert*-butyl alcohol. The reaction takes place by a Curtius rearrangement of the intermediate 2-furoyl azide to obtain, in 82% yield, the desired 2-aminofuran **6**. (Figure 3). Even the reaction may be carried out by a one-pot process, the intermediate acylazide **5** may be isolated. However, due to its instability it is recommended to carry out the reaction at once.

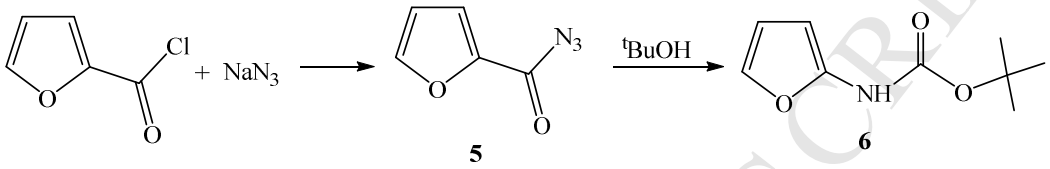


Figure 3. Formation of the *tert*-butyl *N*-(2-furoyl)-carbamate.

2.2. Generation of oxyallyl cation and its cycloaddition to C2-functionalized furan

The coupling between the dihaloketones and C2-functionalized furan takes place via a [3+2] cycloaddition reaction, where the reactive intermediates are the zwitterionic oxyallyl cations (Figure 4), which act, in first instance, as electrophiles. These oxyallyl cations are generated in situ by reaction of dihaloketones with reducing metals: Cu, Zn, Zn/Cu pair, Ag, $Fe_2(CO)_9$, etc. Nevertheless, their electrophilicity is minored by the positive inductive effects exerted by alkyl substituents, but could be increased by choosing the adequate counterion for the oxide moiety. Thus, metallic counterions that form more covalent bonds with the oxygen atom of oxyallyl cation are more electrophilic, *i.e.*: O─Fe > O─Zn > O─Cu.[20] In this particular work, we have used as reducing metal the pair Zn/Cu.

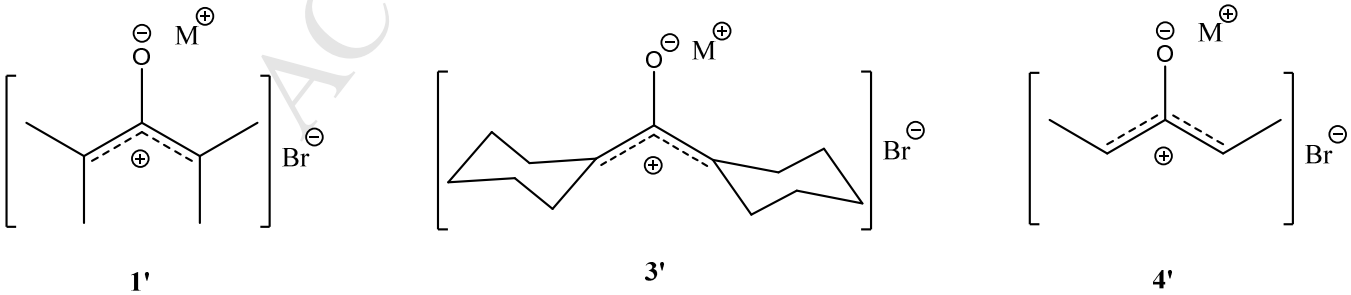
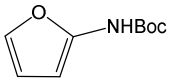
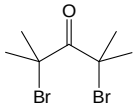
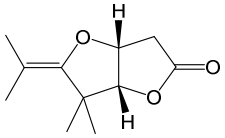
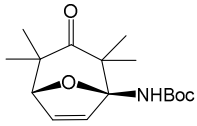
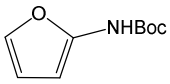
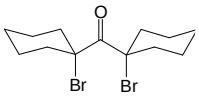
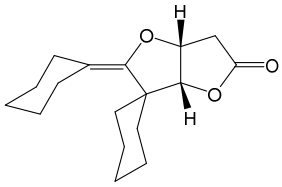
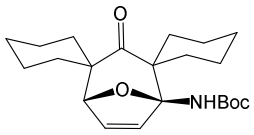
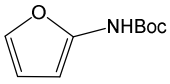
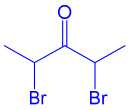
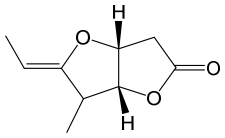
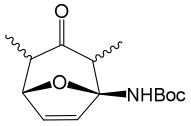
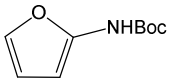
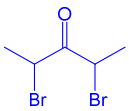
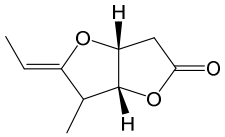
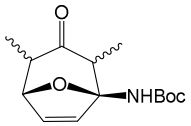
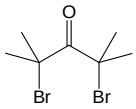
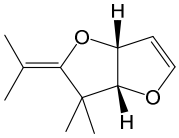
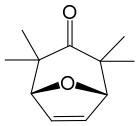
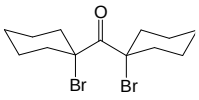
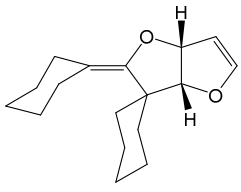
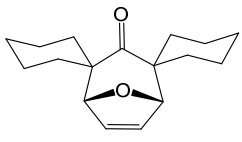


Figure 4. Oxyallyl cations generated *in situ* from dibromoketones **1** and **3**. Counterion M^+ comes from the reducing metal used in the reaction.

Table 2. Results from the cycloaddition reaction between the oxyallyl cation generated *in situ* from dihaloketones of different steric hindrance and 2-(NHBoc)-furan and/or regular furan.

Entry	Furan	Haloketone	Metal (Solvent)	T(ºC)	t_r(h)	[3+2]-Cycloadduct Yield (%)[a]	[4+3]-Cycloadduct Yield (%)[a]
1	 **6**	 **1**	Zn/Cu (ACN)	0	1.5	 **7** (56%)	 **8** (4%)
2	 **6**	 **3**	Zn/Cu (ACN)	0 to rt	5	 **9** (73%)	 **10** (0%)
3	 **6**	 **4**	Zn/Cu (ACN)	–10 to rt	5	 **11** (0%)	 **12** (33%)[b]
4	 **6**	 **4**	$Fe_2(CO)_9$ (ACN)	–10 to rt	6.5	 **11** (0%)	 **12** (76%)[c]
5		 **1**	Zn/Cu (ACN)	rt	4.5	 **13** (0%)	 **14**(57%)
6		 **3**	Zn/Cu[d] (ACN/ CH_2Cl_2 1:1)	–44	1.5	 **15** (0%)	 **16** (64%)

(**a**) Yield on isolated product. (**b**) Mixture of diastereoisomers: *trans* / *cis*-diequatorial / *cis*-diaxial: 38/55/7.[21] (**c**) Mixture of diastereoisomers: *trans* / *cis*-diequatorial / *cis*-diaxial: 55/40/5.[20] (**d**) Me_3SiCl (1:1 molar ratio respect to dihaloketone) was added to activate the metallic particles and to form silyl derivatives of oxyallyl cation.[22]

The formation of furofuranones **7** and **9** takes place by a [3C(2π)+2C(2π)] stepwise cycloaddition (Figure 5), *via* the electrophilic attack of the oxyallyl cation to the C5 position of 2-(NHBoc)-furan in a regioselective manner, as will be commented latter on. The generated intermediate **I** undergoes an intramolecular nucleophilic attack of the *O*-enolate to the allyl cation, also in a regioselective way, affording intermediates **III**/**IV**, which result hydrolyzed during the reaction work-up, forming the final product **7**. A small amount (5%) of alcohol **17** was isolated from the reaction crude, which we believe is a byproduct generated within the column chromatography during the purification process, as a result of addition of residual water (present in solvents) to the C=C double bond, catalyzed by the SiO_2 matrix. Simultaneously to the formation of furofuranone **7** a small amount (4%) of [4+3]-cycloadduct **8** was formed. For less substituted dihaloketones (*i.e.* 2,4-dibromo-3-pentanone) used as precursors of much less hindered oxyallyl cations, the [4C(4π)+2C(2π)]-cycloadduct **12** (as a mixture of three diastereoisomers) is the only product (see entries 3 and 4 in Table 2) not observing, at all, the formation of furofuranones **11**. For these particular substrates the yield of [4+3]-cycloadducts increases from 33% up to 76%, when using $Fe_2(CO)_9$ instead of Cu/Zn as reducing agent. On the other hand, when increasing the steric hindrance of oxyallyl cation (**3'**), generated from haloketone **3**, the yield of the corresponding furofuranone **9** increased up to 73% and no [4+3]-cycloadduct **10** was formed (entry 2, Table 2). Therefore, *the steric hindrance of the oxyallyl cation is a required structural condition to generate the desired furofuranones*. Finally, when reacting hindered dihaloketones **1** and **3**, with regular furan (entries 5 and 6 from Table 2), without the C2-functionalization, only [4+3]-cycloadducts **14** and **16** are formed, respectively; but no traces of the corresponding furofurans **13** or **15** are detected. Thus, *it is of capital importance that the furan diene should be functionalized at C2 to undergo a [3+2]-cycloaddition instead of a [4+3]-cycloaddition*.

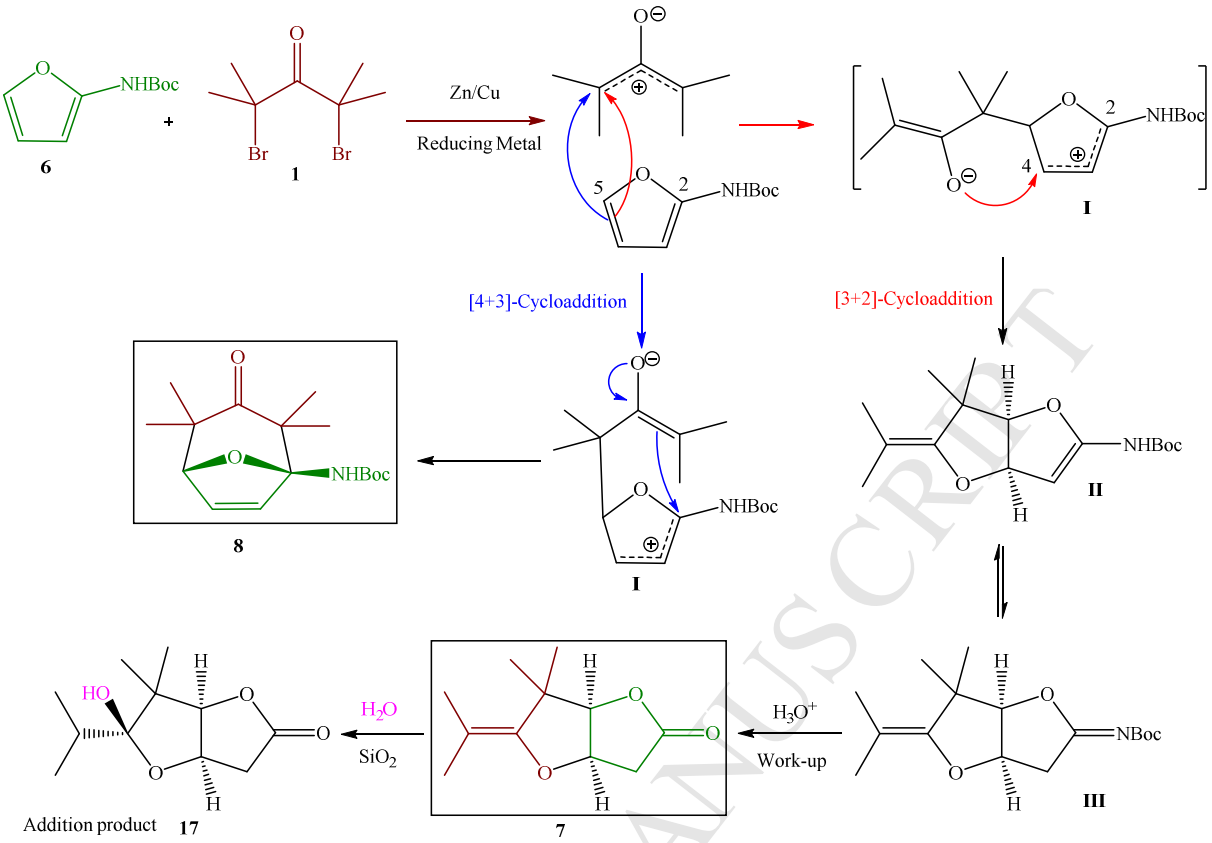


Figure 5. Mechanism proposal for the formation of products **7**, **8** and **17**.

2.3. Regioselectivity in the formation of [3+2]-cycloadducts 7 and 9

Analyzing the results from entries 1 and 2 of Table 2, it is worth noting the regioselectivity observed in the formation of [3+2]-cycloadducts **7** and **9**. This regioselectivity takes place at two levels: a) In the initial attack of the oxyallyl cation **1** to the C5 position of 2-(NHBoc)-furan to generate intermediate **I**; and b) In the attack of enolate (*O*-enolate) to the C4 position of intermediate **I** to generate intermediate **II** (see Figure 5). In both cases, the driving force it is not thermodynamic, in other words it is not dependent on the difference of stability between the [4+3]-cycloadduct **8** (ΔH_f = –187.07 kcal/mol) and the [3+2]-cycloadduct **II** (ΔH_f = –183.83 kcal/mol) (See Table S1). On the other hand, the initial regioselectivity (a) is consistent with the different electron density, electron charge and potential values at positions C2 or C5 of furan substrate **6**, which is favorable for the attack to C5 position by the oxyallyl cation **1'**. This C5 position has higher electron density than C2, according to the calculation of electron charges by natural population analysis (NPA) and the electrostatic potential

map (ESPM) (see Table S2). Also the different possibilities of cyclization of intermediate **I** have been evaluated: attack of *C*-enolate *versus O*-enolate and attack on C2 or on C4 ring positions. These possibilities have been studied taking into account the energy balance and the charge distribution among the different intermediates and we have concluded that none of them are responsible for the regioselectivity experimentally observed. The regioselectivity observed at this level (b) and also at initial level (a) are both mainly due to the maximum overlap of frontier molecular orbitals (FMO): HOMO from **6** and LUMO from **1'** in the initial electrophilic attack to the furan diene (see Figure S1 and Figure S2), and HOMO of *O*-enolate and LUMO of allyl cation subunit in the case of intramolecular cyclization of intermediate **I** to afford **II** (see Figure S3 and Table S3). In both cases there is a narrow HOMO-LUMO energy gap. These parameters have been calculated by Gaussian at the theory level and basis set: DFT/B3LYP/6-31G++(d,p). The founding of regioselectivity on the basis of FMO for the case of cycloadditions have many precedents in the literature.[23]

There are other factors facilitating the easy attack of *O*-enolate to the C4 position of intermediate **I**. In first place, the availability of a minimum energy conformation that allows the approach of both reactive sites, putting apart the steric demanding isopropylidene subunit and the *tert*-butoxy group. The approach is also facilitated by the Thorpe-Ingold effect[24] exerted by the gem-dimethyl group of the side chain that forces the approach of the afore-mentioned reaction sites (see Figure 6).

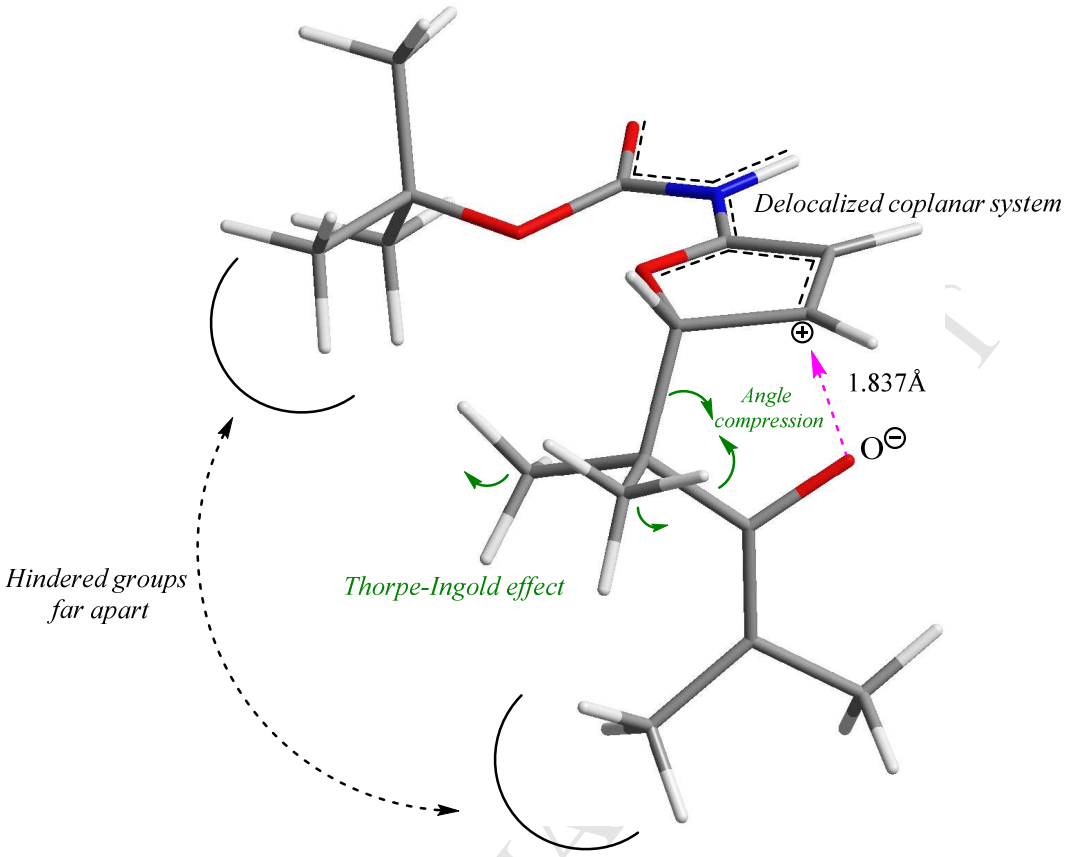


Figure 6. Minimum energy conformation for intermediate **I**. Effects facilitating the approach of the reactive sites.

2.4. Structural determination of cycloaddition products

All products, both [4+3]- and [3+2]-cycloadducts, as well as the addition product **17** were isolated, purified and physically and spectroscopically characterized. The determination of relative stereochemistry was established by ^{1}H- and ^{13}C-NMR correlation[25] after a careful analysis and signal assignment of their 1D (^{1}H and ^{13}C) and 2D NMR spectra (COSY, HSQC and NOESY). The structure of the new furofuranones was confirmed for the case of **17** by X-ray diffraction analysis of a single crystal. The ellipsoid diagram and unit cell packing for this structure are illustrated in Figure 7 and the refinement data are quoted in Table 3.

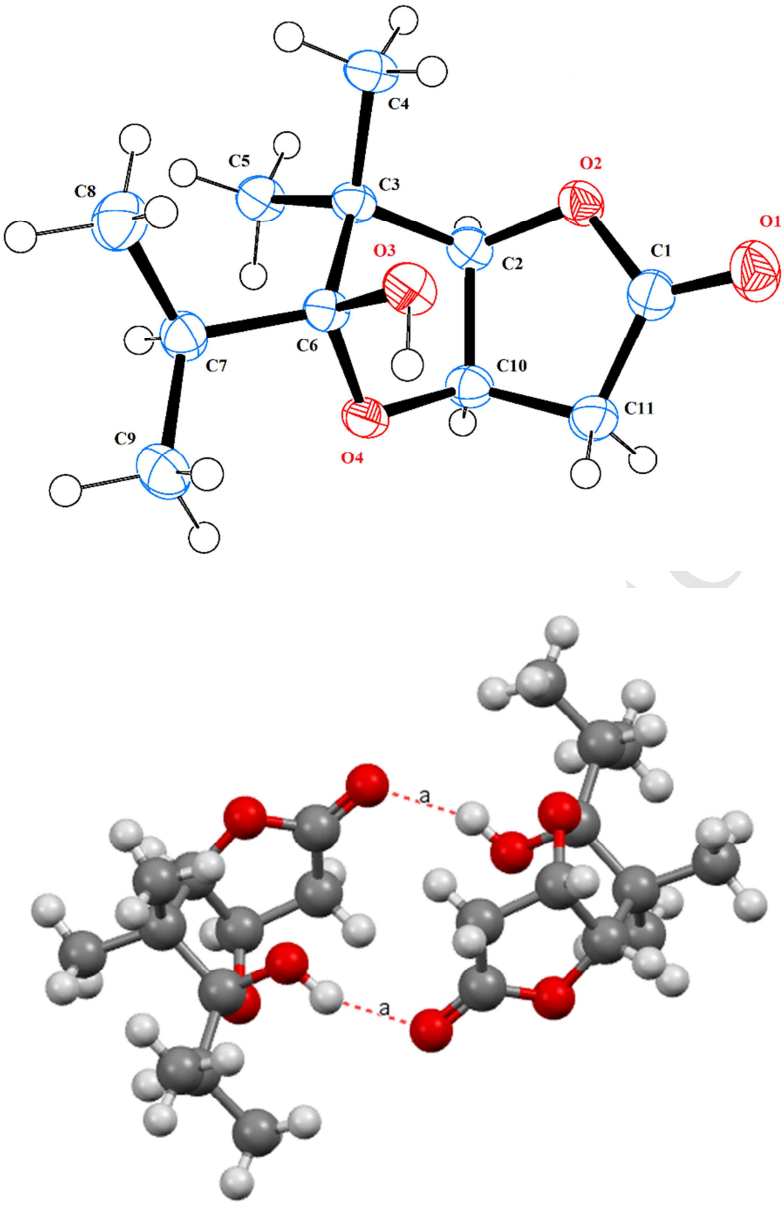


Figure 7. A) On the top: X-ray structure of **17**. Ellipsoid diagram drawn at the 50% probability level for **12**, showing the atom-labeling scheme. The numbering assigned by the X-ray data processing software is not IUPAC numbering. **B**) On the bottom. Crystal packing of **17**. Unit cell. Hydrogen bonds are observed between the hydroxyl groups (donors) and the carbonylic oxygen (acceptor) of the neighbor molecule in the unit cell.

Table 3. Crystal data and structure refinement for **17**.

Empirical formula	$C_{11}\ H_{18}\ O_4$
Formula weight	214.25
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P $\bar{1}$
Unit cell dimensions	a = 5.9190(2) Å α = 80.919(2) deg.
	b = 7.5470(3) Å β = 85.315(2) deg.
	c = 12.6220(5) Å γ = 81.231(2) deg.
Volume	549.30(4) $Å^3$
Z	2
Calculated density	1.295 Mg/m^3
Absorption coefficient	0.097 mm^{-1}
F(000)	232
Crystal size	0.60 x 0.50 x 0.50 mm
Theta range for data collection	3.49 to 30.55 deg.
Limiting indices	$-8 \le h \le 8, -10 \le k \le 10, -17 \le l \le 18$
Reflections collected / unique	9695 / 3188 [R(int) = 0.0741]
Completeness to θ = 30.55	94.5 %
Max. and min. transmission	0.9529 and 0.9438
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3188 / 0 / 142
Goodness-of-fit on F^2	1.051
Final R indices [I > 2σ(I)]	R1 = 0.0592, wR2 = 0.1594
R indices (all data)	R1 = 0.0642, wR2 = 0.1640
Largest diff. peak and hole	0.437 and -0.274 $e.Å^{-3}$

3. Conclusions

In the present work, we describe a new methodology to generate furofuranones, which are key building blocks in many natural products with biological interest. The formation of furofuranones takes place by a [3C(2π)+2C(2π)] stepwise cycloaddition, *via* the electrophilic attack of the oxyallyl cation to the C5 position of 2-(NHBoc)-furan in a regioselective manner. The generated intermediate undergoes an intramolecular

nucleophilic attack of the *O*-enolate to the cyclic allyl cation, also in a regioselective way, affording an enamine intermediate that results hydrolyzed during the reaction work-up, forming the final product. This regioselectivity would be controlled by frontier MOs of cycloaddends. Thus, the more stable regioisomeric transition states arise through interaction of the reaction sites with the in-phase orbitals having the larger MO coefficients. It is important to mention that steric hindrance of the oxyallyl cation is a required structural condition to generate the desired furofuranones. Also, it is of capital importance that the furan diene should be functionalized at C2 to undergo a [3+2]-cycloaddition instead of a [4+3]-cycloaddition. These alkylidene-furofuranones may be potentially transformed into added-value derivatives by conventional ozonolysis, hydrogenation or addition reactions. All products have been isolated, purified and physically and spectroscopically characterized. Extension of this methodology to other synthetic objectives is under way in our laboratory.

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Notes

The authors declare neither competing financial interest nor any other conflict of interest.

5. Acknowledgements

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6. Experimental section

6.1. General procedures

NMR spectra were recorded on a Varian Inova 200 or 300 MHz, on a Varian Mercury 400 MHz and/or in a Bruker DMX 500 MHz apparatus. Chemical shifts (δ) are expressed in ppm *versus* tetramethylsilane as an internal standard. IR spectra were

recorded on a NICOLET 6700 FT-IR by film, KBr pellet or ATR (Attenuated Total Reflectance) methods. Mass spectrometry was performed on a Hewlett-Packard 5890 apparatus, generally under a CI (Chemical Ionization) method by using NH_3 or CH_4 or by direct insertion under Electron Impact at 70 eV and 150 ºC. The elemental analyses were obtained in a FISONS Elemental Analyzer, Model Na-1500. The samples were previously pyrolized al 1000 ºC in the presence of a catalyst, under oxygen atmosphere, and the content of carbon, hydrogen and nitrogen were determined by evaluation of the combustion gases by gas chromatography using a FID detector. Solvents were dried, according to standard procedures, and distilled prior to use. All other major chemicals were obtained from commercial sources and used without further purification. Gas chromatography was performed by using a Shimatzu AOC-20i apparatus with a capillary column (HP-5 Crosslinked 5% Phe-Me-Siloxane, 0.25 μm film thickness, 30 m length and 0.32 mm diameter). Used carrier gas brands and pressures were: He = 5.5 bar (Linde, Helium 5.0), Air = 3 bar (Linde, synthetic air), H_2 = 3 bar (Linde, Hydrogen 5.0). The experimental conditions are specified in each case. Ozonolysis reaction was carried out using an ozone-generator Fischer Ozone-500 apparatus, under the following conditions: Intensity = 0.25-0.40 A, P_{O2} = 0.25 bar, O_3 flow = 50-100 mL/min.

6.2. Molecular computer calculations

Geometry and energy minimization of molecules were preoptimized by molecular mechanics MM2 followed by semiempirical quantum mechanical PM7 algorithm, [26] implemented in the MOPAC-2016 software (Ver. 16.146W).[27] This software was also used to calculate the formation enthalpy and total energy of molecules. Density functional theory (DFT) based methods at the B3LYP functional level[28,29] were used for subsequent full refinements, within the Gaussian-03W (Revision E.01, version 6.1) software package[30] and using the 6–31++G(d, p) basis set.[31] All calculations were performed on isolated molecules (gas phase). The atomic charges were calculated on the basis of both Mulliken population analysis and natural population analysis (NPA), being the last one more adequate for the present study.

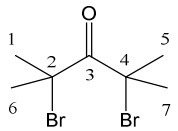
6.3. X-ray Crystal Structure Analysis of 17

Pure cycloadduct **17** was dissolved in a minimum amount of ethyl acetate at room temperature. A few drops of hexane were added and the saturated solution kept in a refrigerator at 4 °C. Suitable single crystals for X-ray diffraction studies grew over a

period of 1 week. A single crystal (0.60 x 0.50 x 0.50 mm) of **17** was mounted on a Nonius–Kappa CCD diffractometer, equipped with an Oxford Cryosystem, using graphite-monochromated Mo-*K*α radiation (λ = 0.71073 Å). Intensity data were collected at 150 K and the data were processed by using the Nonius software.[32] A symmetry-related (multiscan) absorption correction was applied. 9695 reflections were measured in the range $3.49 \leq \theta \leq 30.55$ deg. 3188 reflections were assumed as observed applying the condition $I > 2\sigma(I)$. The structures were solved by direct methods (SIR-97)[33] and refined by full-matrix least-squares techniques against *F*2 (SHELXL-2013)[34] using the program platform SHELXle.[35] Non-hydrogen atoms were anisotropically refined. Heteroatom and hydrogen atoms were located in the difference Fourier map and were isotropically refined all others were placed onto calculated positions. The final R(on F) factors were: 0.0592, wR(on $|F|^2$) = 0.1594 and goodness of fit = 1.051 for all observed reflections. The number of refined parameters was 142 and the maximum and minimum peaks in final difference synthesis was 0.437 and –0.274 e.Å^{-3}. The crystal data and a summary of the intensity data collection for **17** are summarized in Table 3. Data for crystal and structure refinements, atomic coordinates, bond lengths, bond angles, anisotropic displacement parameters, and hydrogen coordinates may be obtained from the CIF file deposited with The Cambridge Crystallographic Data Centre with the number CCDC-1487367. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* the Internet at www.ccdc.cam.ac.uk/data_request/cif. The molecular illustrations such as the thermal ellipsoid plot and the unit cell packing (Figures 7A and 7B) were made by using ORTEP-III[36] and MERCURY 3.8 software, [37] respectively.

6.4. Synthetic procedures

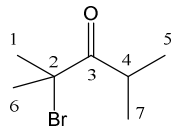
6.4.1. Synthesis of 2,4-dibromo-2,4-dimethyl-3-pentanone, (1). Isolation and characterization of minor product 2-bromo-2,4-dimethyl-3-pentanone (2)



1

In an oven-dried 100 mL three neck round-bottom flask, equipped with a stirring bar, a Dimroth condenser, a calcium chloride trap, a thermometer and a pressure equalized addition funnel, 2,4-dimethyl-3-pentanone (24.2 mL, 19.50 g, 171 mmol) and phosphorous tribromide (0.4 mL, 1.43 g, 5.27 mmol) were added. The mixture was cooled to 0 ºC and bromide (18.0 mL, 56.14 g, 351 mmol), was slowly added along 5 hours, maintaining the reaction mixture between 5 ºC and 10 ºC. During the addition of bromine, the formation of hydrogen bromide was observed. One hour after the complete addition of bromine, the conversion of 2,4-dimethyl-3-pentanone was complete as observed by GC. Then, the mixture was submitted to vacuum (20 mmHg) for 30 min at rt to eliminate the dissolved hydrogen bromide. The reaction crude was purified by fractional distillation under vacuum (10 mmHg), collecting the fraction between 85 ºC and 90 ºC. This fraction was redistilled to obtain chemically pure 2,4-dibromo-2,4-dimethy-pentan-3-one (**1**) (39.1 g, 84% yield) as a colourless oil, which freezes at –24 ºC. This product should be stored in the dark and at low temperature to avoid decomposition.

IR (film): $\bar{\upsilon}$ = 2979, 2934, 1697 (C=O, st), 1462, 1387, 1373, 1109, 1040, 993 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.15 (12H, s, H1, H5, H6 and H7) ppm. **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 32.7 (C1, C5, C6 and C7), 61.5 (C2 and C4), 188.1 (C3) ppm. **MS [**GC-MS(CI), NH_3, 70 eV, 150 ºC]: m/z (%) = 265 (16, M+N_2H_7), 248 (100, M+NH_4), 290 (100, M+NH_4), 272 (1, M). **GC** (50 ºC, 1 min, 10 ºC/min., 250 ºC, 1 min): t_R = 11.52 min.

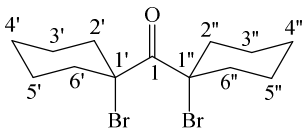


2

The fraction distilled at 70-80 ºC and 10 mmHg, from the reaction crude, consists of 2-bromo-2,4-dimethyl-3-pentanone (**2**) (3.8 g, 10% yield)

IR (film): $\bar{\upsilon}$ = 2980, 2930, 1702 (C=O, st), 1458, 1390, 1381, 1109 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 1.17 (6H, d, *J* = 7.2 Hz, H5 and H7), 1.87 (6H, s, H1 and H6), 3.45 (1H, q, *J* = 7.2 Hz, H4). **GC** (50 ºC, 1 min, 10 ºC/min., 250 ºC, 1 min): t_R = 7.54 min.

6.4.2. Synthesis of 1',1"-dibromo-dicyclohexylketone, (3).

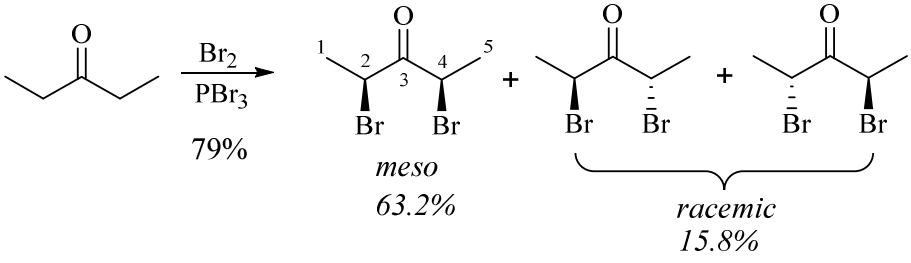


3

Dihaloketone **3** was prepared following a procedure similar to the previously described, buy using dicyclohexylketone (10.0 g, 51.5 mmol) as a starting material and phosphorous tribromide (0.2 mL, 0.57 g, 2.1 mmol). The mixture was cooled to 0 ºC and bromine (5.2 mL, 16.21 g, 101 mmol) was added along 2 h, maintaining the reaction mixture between 5 ºC and 10 ºC. During the addition of bromine, the formation of hydrogen bromide was observed. After completion, the reaction mixture was submitted to vacuum (20 mmHg) for 30 min at rt to eliminate the dissolved hydrogen bromide. The crude mixture became solid at rt and it was dissolved in CH_2Cl_2 and washed with cold aqueous 10% $Na_2S_2O_3$ solution (25 mL) and ice-water (2 x 25 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to dryness, affording dihaloketone **3** as a white solid (13.4 g, 74% yield). This solid should be stored in the dark and at low temperature to avoid decomposition.

IR (film): $\bar{\upsilon}$ = 2934, 2857, 1703 (C=O, st), 1447, 1277, 1242, 1155, 1115, 1032 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 1.30-1.79 (20H, m, H2', H3', H4', H5', H6', H2", H3", H4", H5" and H6") ppm. **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 22.8 (C4' and C4"), 24.9 (C3', C3", C5' and C5"), 38.1 (C2', C2", C6' and C6"), 72.1 (C1' and C1"), 196.6 (C1). **MS** [GC-MS(CI), NH_3, 70 eV, 150 ºC]: m/z (%) = 369 (69, M+NH_3), 292 (100, M-Br+NH_3).

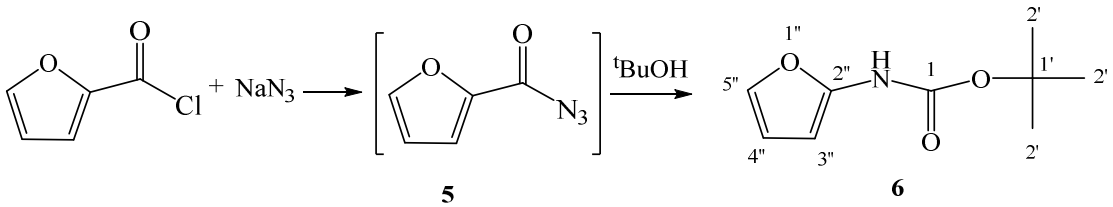
6.4.3. Synthesis of 2,4-dibromopentan-3-one, (4)



In an oven-dried 250 mL three neck round-bottom flask, equipped with a stirring bar, a Dimroth condenser, a calcium chloride trap, a thermometer and a pressure equalized addition funnel, 3-pentanone (27 mL, 22g, 0.255 mol) and phosphorous tribromide (0.5 mL, 1.43g, 5.3 mmol) were added. The mixture was cooled to 0 ºC and bromide (27 mL, 84.2g, 0.527 mol) was slowly added along 5 hours, maintaining the reaction mixture between 5 ºC and 10 ºC. During the addition of bromine, the formation of hydrogen bromide was observed. One hour after the complete addition of bromine, the conversion of 3-pentanone was complete as observed by GC. Then, the mixture was submitted to vacuum (20 torr) for 30 min at rt to eliminate the dissolved hydrogen bromide. The reaction crude was purified by fractional distillation under vacuum (10 mmHg), collecting the fraction between 65 ºC and 70 ºC. This fraction was redistilled to obtain chemically pure 2,4-dibromopentan-3-one **4** (49.15 g, 79% yield) as a colourless oily diastereoisomeric mixture: *meso* / *dl* pair 4/1.

IR (film) $\bar{\upsilon}$ = 3445 (C=O), 2980, 2920, 2875 (H─Csp^3), 1730 (C=O), 1440, 1380, 1350 (C─C, C─H), 1200, 1120, 1070, 1050, 1020 (C─O) cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$) ***pair dl***: δ = 1.88 (2H, d, *J* = 6.9 Hz, H2, H4), 4.77 (6H, q, *J* = 6.9 Hz, H1, H5); ***meso*:** δ = 1.81 (2H, d, *J* = 6.7 Hz, H2, H4), 4.99 (6H, q, *J* = 6.7 Hz, H1, H5) ppm. **^{13}C NMR** (50 MHz, $CDCl_3$) ***pair dl***: δ = 21.61 (C1, C5), 43.95 (C2, C4), 195.77 (C3) ppm; ***meso*:** δ = 19.42 (C1, C5), 43.75 (C2, C4), 195.77 (C3) ppm. **MS** (GC-MS, CI, NH_3, 70 eV, 150 ºC, t_R = 6.16-7.03 min): m/z (%) = 279 (12, M+N_2H_7), 262 (100, M+NH_4), 246 (1, M+2H), 244 (1, M), 182 (6, $C_5H_{10}O_2Br$). **GC** (T_i = 100 ºC, t_i = 2 min., r = 10 ºC/min., T_f = 200 ºC, t_f = 30 min.) ***meso*:** t_R = 5.7 min.; ***pair dl***: t_R = 6.4 min.

6.4.4. Synthesis of tert-butyl furan-2-yl-carbamate, (6)



5 **6**

In a round-bottom flask equipped with a stirring bar and a Dimroth condenser, 2-furyl chloride (20 g, 0.14 mol), *tert*-butyl alcohol (160 mL, 1.7 mol) and sodium azide (10.2g, 0.16 mol) were placed, under argon atmosphere. The mixture was stirred for 12 h at room temperature and the formation of the intermediate 2-furylazide as a white solid was observed. The mixture was heated to reflux (100 ºC) and maintained under these conditions for additional 12 h. Once 2-furoylazide **5** was completely converted (control by TLC eluted with hexane/ethyl acetate 4:6), the solvent was removed *in vacuo*, obtaining a white solid, which was submitted to a flash column chromatography on silica gel, eluting with a mixture of hexane and ethyl acetate of increasing polarity. The elution with a mixture of hexane and EtOAc (9:1), afforded the desired product as a white solid (21.6 g, 82% yield). The product **6** has to be stored in a cold place and away from light, in order to avoid its thermal or photochemical decomposition.

MP = 98-99 ºC (ethyl acetate). **TLC**: R_f = 0.66 (SiO_2, hexane/ethyl acetate 4:6, developed by ninhydrin). **IR** (film): $\bar{\upsilon}$ = 3267 (N─H, st), 2980, 1700 (C=O, st), 1546 (N─H, def), 1250 (^{t}Bu) cm^{-1}. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 1.50 (9H, s, H2'), 6.04 (1H, brs, H4''), 6.63 (1H, brs, H3''), 7.00-7.12 (1H, m, H5'') ppm. **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 28.2 (C2'), 81.3 (C1'), 95.1 (C4''), 111.2 (C3'), 136.0 (C5'), 145.4 (C2'), 151.9 (C1) ppm. **MS** (CI, NH_3, 70 eV, 150 ºC): m/z (%) = 285 (13, M+NH_4), 268 (100, M+1H), 212 (22, M+2H–^{t}Bu), 167 (36, M+1H–COO ^{t}Bu).

The intermediate 2-furoylazide **5** could be transformed, one pot, into the corresponding carbamate **6** without the necessity to isolate it. However, a pure sample of **5** was isolated and purified for its physical and spectroscopic characterization.

White solid. **MP** = 114.5-115 ºC. **IR** (film): $\bar{\upsilon}$ = 3129 (=C-H, st), 2145 (N=N=N, st as), 1684 (C=O, st), 1562, 1462 (C-N, st), 1393, 1290, 1231, 1190 (C-O-C, st), 1030, 1001, 916, 877, 793 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 6.55 (1H, dd, $J_{4,5}$ = 1.6, $J_{4,3}$ = 3,6, H4), 7.26 (1H, dd, $J_{3,5}$ = 0.6, $J_{3,4}$ = 3.6, H3), 7.65 (1H, dd, $J_{5,3}$ = 0.6, $J_{5,4}$ = 1.6, H5) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 112.8 (C4), 120.2 (C3), 145.6 (C2), 148.4 (C5), 162.8 (C1') ppm. **MS** (CI, NH_3, 70 eV, 150ºC): m/z (%) = 138 (9, M+H), 137 (6, M), 112 (44, M-CN), 110 (100, M-N_2), 95 (89, M-N_3), 82 (21, M-CN_3). **TLC:** R_f = 0.60 (SiO_2, hexane /ethyl acetate 4:6, developed with ninhydrin reagent).

6.4.5. Reaction of oxyallyl cations (1') and (3') with 2-tert-butoxicarbonylaminofuran (6)

6.4.5.1. Activation of reducing metals and preparation of metallic couples

6.4.5.1.1. Activation of Copper[38]

Copper powder from Sigma-Aldrich (10 g, 0.152 mol) was treated with a solution of iodine (2 g, 7.8 mmol) in acetone (100 mL). The suspension was stirred for 15 min and filtered through a Büchner funnel. The obtained violaceous solid was washed with a 1:1 mixture of conc. HCl (37 %) and cold acetone (50 mL) and then with acetone (100 mL) and diethyl ether (100 mL). The resulting solid was dried under high vacuum and kept away from light under argon atmosphere. The activated copper has metallic bright and it was promptly used.

6.4.5.1.2. Activation of Zinc[39]

Zinc powder (10 g, 0.152 mol) was suspended in diluted aqueous HCl (50 mL, 3% w/v) and vigorously stirred for 1 min, observing the release of hydrogen. The process was repeated two more times and finally the solid was filtered through a Büchner funnel and washed with distilled water (100 mL), absolute ethanol (100 mL) and diethyl ether (100 mL). The solid was then dried under vacuum in the dark for 3 hours, obtaining a fine grey solid which was used immediately. Occasionally it was stored in a desiccator under Ar atmosphere but it is preferable to activate it prior to use.

6.4.5.1.3. Preparation of the Zinc-Copper couple[40, 41, 42]

The zinc, activated as before described, (10 g, 0.152 mol) was suspended in an aqueous solution of copper(II) sulfate (100 mL, 4 % w/v) and vigorously stirred for 15 min. The zinc powder rapidly darkened turning from light grey to black, and the blue color of the copper solution completely discolored. The solid was filtered through a Büchner funnel and successively washed with distilled water (2 x 50 mL), acetone (4x 50 mL), absolute ethanol (4 x 50 mL) and diethyl ether (4 x 50 mL). Finally, the solid was dried under vacuum and in the dark for 3 h, obtaining a fine black powder that was immediately used. Occasionally it was stored in a desiccator, under Ar atmosphere and in the dark, for a short period of time. Analysis of this solid by atomic absorption showed the following composition: Zn = 72 %, Cu = 28 %.

6.4.5.2. Cycloaddition by reduction of dihaloketones with Zn/Cu pair

In a double necked flask, fitted with magnetic stirring and nitrogen atmosphere, freshly activated Zn/Cu pair (210 mg, 3.32 mmol) was added and suspended in acetonitrile (11 mL). The mixture was cooled down to 0 ºC and the furan derivative (1 mmol) was added at once. Then, dihaloketone (258 mg, 1.06 mmol) was added dropwise. The reaction mixture was homogenized by stirring and maintained at the work temperature by using a heating/cooling bath with a temperature stabilizing system. The reaction was controlled by both TLC and GC. The reaction was considered finished after observing a constant conversion in successive analyses.

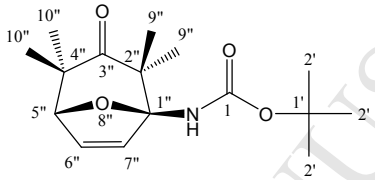
The mixture was cooled to 0 ºC and methylene chloride was added under constant stirring. The solution was poured over a 1:1 mixture of water / ice (30 mL approx.) and it was filtered through a porous sintered plate (filtering plate number 4) under vacuum to remove excess of Zn/Cu powder. The phases were decanted and the aqueous phase was extracted with methylene chloride (4 x 30 mL) until discoloration of the organic phase was observed. The organic phases were combined together and washed successively with a 3 % water solution of NH_3 (3 x 20 mL) until no blue color (due to tetraammincopper(II) complex) was observed in the washing aqueous extracts, followed by ice-water (2 x 20 mL). Finally, the organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to dryness, obtaining a product consisting of a single structure or a mixture of diastereoisomers, depending on the furan substrate. The obtained oil was submitted to a flash column chromatography on silica gel, using mixtures of hexane and ethyl acetate of increasing polarity to separate products.

6.4.5.3. Cycloaddition procedure using Fe_2CO_9

In a round bottomed flask fitted with a magnetic stirrer, under argon atmosphere, compound **6** was placed. Afterwards, inside an Atmosbag® filled with argon, the pyrophoric diironnonacarbonyl was added to the reactor, (in a molar ratio Fe_2CO_9 : furan **6** = 1.75 : 1), as a bright yellow solid. Then, anhydrous acetonitrile (in a ratio of 0.82 mL of ACN : 1 mol Fe_2CO_9) was added and the mixture was stirred for 5 min. 2,4-Dibromo-3-pentanone, **4**, freshly filtered through neutral alumina, was added dropwise at –10 ºC, (in a molar ratio of 1.2 : 1; dibromoketone : furan). The reaction mixture was stirred at room temperature for 6.5 h. The crude was concentrated to dryness and the residue was dissolved in acetone. Cerium ammonium nitrate (in a molar ratio CAN :

Fe_2CO_9 = 1 : 1) was added and the reaction mixture was stirred for 5 min. Afterwards, the solvent was evaporated under vacuum and the residue was filtered through a short path of silica gel, and then it was submitted to a flash column chromatography on silica gel, using mixtures of hexane and diethyl ether of increasing polarity to isolate cycloadduct **12** in a 76% yield and diastereoselectivity: *trans/cis-exo/cis-endo* = 55/40/5.[19]

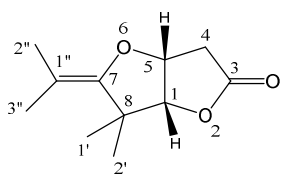
***tert*-butyl *N*-(2,2,4,4-tetramethyl-3-oxo-8-oxabicyclo[3.2.1]oct-6-en-1-yl}-carbamate, (8).**



8

Colourless oil. **IR** (film): $\bar{\upsilon}$ = 3316, 2978, 2932, 1704, 1471, 1387, 1367, 1332, 1247, 1163, 1054 cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.95 (6H, d, *J* = 6.8 Hz, H10"), 1.05 (6H, d, *J* = 6.4 Hz, H9"), 1.46 (9H, s, H2'), 1.56-1.63 (1H, m, H6a"), 1.67-1.75 (1H, m, H7b"), 1.88-1.95 (1H, m, H7a"), 1.98-2.08 (1H, m, H6b"), 2.79-2.85 (1H, m, H4"), 3.68 (1H, d, *J* = 5.6 Hz, H2"), 4.47 (1H, dd, J_1 = 4.8 Hz, J_2 = 7.6, Hz H5"), 5.24 (1H, brs, NH) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 9.0 (C9"), 9.8 (C10"), 24.2 (C6"), 28.1 (C2'), 31.6 (C7"), 49.4 (C4"), 52.9 (C2"), 78.2 (C5"), 80.1 (C1'), 94.2 (C1"), 154.0 (C1), 209.1 (C3") ppm. **MS** (CI, 70 eV, 150 ºC): m/z (%) = 296 (23, M+1), 257 (98), 240 (86, M-C_4H_8), 196 (100, M-$C_5H_8O_2$). **Anal.** Calcd for $C_{16}H_{25}NO_4$: C 65.06, H 8.53, N 4.74 %. Found: C 65.10, H 8.55, N 4.71 %. **TLC**: R_f = 0.74 (SiO_2, hexane/diethyl ether 3:7, three elutions. Developed by ninhydrin reagent).

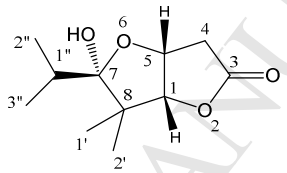
***cis*-7-Isopropylidene-8,8-dimethyl-2,6-dioxabicyclo[3.3.0]octan-3-one, (7)**



7

Colourless oil **IR** (film): ῡ = 2975 (H-Csp^3), 1786 (C=O), 1697 (C=C), 1467, 1370, 1314, 1193, 1129, 1083, 1057, 1038. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.23 (3H, s, H2''), 1.46 (3H, s, H3''), 1.59 (3H, s, H1'), 1.62 (3H, s, H2'), 2.73-2.76 (2H, m, H4), 4.44 (1H, d, *J* = 4.0 Hz, H1), 4.82-4.84 (1H, m, H5) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 17.0 (C2'), 18.9 (C1'), 22.6 (C3''), 25.1 (C2''), 37.1 (C4), 44.3 (C8), 75.4 (C5), 93.0 (C1), 101.3 (C1''), 153.5 (C7), 175.0 (C3) ppm. **MS** (CI, 70 eV, 150 ºC): m/z (%) = 197 (M+1, 100). **Anal.** Calcd for $C_{11}H_{16}O_3$: C 67.32, H 8.22 %. Found: C 67.29, H 8.25 %. **TLC**: R_f = 0.62 (SiO_2, hexane/diethyl ether 3:7, three elutions; developed by ninhydrin reagent).

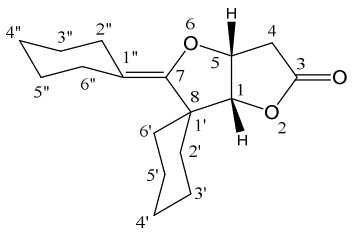
(1*R, 5*R**, 7*R**)-7-Isopropyl-7-hydroxy-8,8-dimethyl-2,6-dioxabicyclo[3.3.0]octan-3-one, (17)**



17

Colourless oil **IR** (film): ῡ = 3480 (O-H), (H-Csp^3), 1779 (C=O), 1458, 1366, 1310, 1195, 1123, 1090, 1061, 1040. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.94 (3H, d, *J* = 6.8 Hz, H2''), 0.99 (3H, d, *J* = 6.8 Hz, H3''), 1.04 (3H, s, H1'), 1.31 (3H, s, H2'), 1.95-2.04 (1H, m, H1''), 2.26 (1H, brs, OH), 2.68-2.70 (2H, m, H4), 4.50 (1H, d, *J* = 5.4 Hz, H1), 4.79-4.83 (1H, m, H5) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 16.8 (C3''), 17.3 (C2''), 18.9 (C2'), 22.3 (C1'), 33.2 (C1''), 38.7 (C4), 48.6 (C8), 74.2 (C5), 93.0 (C1), 109.8 (C7), 176.1 (C3) ppm. **MS** (CI, 70 eV, 150 ºC): m/z (%) = 214 (M, **53**, 4). **Anal.** Calcd for $C_{11}H_{18}O_4$: C 61.66, H 8.47 %. Found: C 61.70, H 8.46 %. **TLC**: R_f = 0.48 (SiO_2, hexane/diethyl ether 3:7, three elutions; developed by ninhydrin reagent).

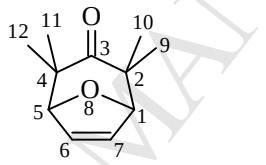
***cis*-7-Cyclohexylidene-8-spirocyclohexane-2,6-dioxabicyclo[3.3.0]octan-3-one, (9)**



9

Colourless oil. **IR** (film): ῡ = 2923, 2852, 1785 (C=O), 1686 (C=C), 1450, 1320, 1256, 1194, 1150, 1047. **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 1.23-1.29 (1H, m, cyclohexyl), 1.40-1.60 (7H, m, cyclohexyl), 1.67-1.80 (4H, m, cyclohexyl), 1.87-1.89 (1H, m, cyclohexyl), 2.02-2.24 (7H, m, cyclohexyl), 2.73 (1H, d, J = 4.0 Hz, $H4_a$), 2.73 (1H, brs, $H4_b$), 4.70 (1H, dd, $J_1 = J_2 = 3.6$ Hz, H5), 4.88 (1H, d, J = 3.2 Hz, H1) ppm. **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 23.5, 23.9, 25.4, 26.9, 27.6, 28.0, 28.2, 28.9, 30.2 and 32.7 (methylenes from cyclohexyl group); 36.8 (C4), 75.7 (C5), 88.0 (C1), 110.8 (C1"), 152.4 (C7), 175.5 (C3) ppm. **MS** (CI, 70 eV, 150 ºC): m/z (%) = 277 (M+1, 100). **Anal.** Calcd for $C_{17}H_{24}O_3$: C 73.88, H 8.75 %. Found: C 73.91, H 8.73 %. **TLC**: R_f = 0.72 (SiO_2, hexane/diethyl ether 3:7, three elutions; developed by ninhydrin reagent).

6.4.6. Cycloaddition of 2,4-dibromo-2,4-dimethyl-3-pentanone with furan (4). Synthesis of 2,2,4,4-tetramethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one, (14)



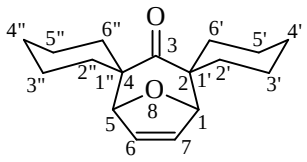
14

Following the before-described reaction procedure that uses Zn/Cu couple as reducing agent, , 2,4-dibromo-2,4-dimethyl-3-pentanone **1** (271 mg, 1.06 mmol), dissolved in dry acetonitrile (5 mL), was reacted with dry furan (770 µL, 10.6 mmol) in the presence of freshly prepared Zn/Cu pair (210 mg, 3.32 mmol) as reducing agent at 20 ºC under nitrogen atmosphere. After 4.5 h of reaction time (control by TLC and GC), the reaction mixture was submitted to the usual work-up, obtaining a crude product, which was also submitted to a flash column chromatography on silica gel, eluting with mixtures of hexane and ethyl acetate of increasing polarity. With hexane/ EtOAc 9:1 compound **14** was isolated as a pure product. Colourless oil (109 mg, 57% yield). Analysis by NMR and GC of the crude reaction product and also of the chromatographic fractions did not show the presence of [3+2]-cycloadduct **13**.

IR (KBr): ῡ = 2969, 2932, 2873, 1713 (C=O, st), 1470, 1381, 1364, 1067, 943, 926, 908 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 0.93 (6H, s, H9 y H11), 1.36 (6H, s, H10 and H12), 4.42 (2H, s, H1 and H5), 6.37 (2H, s, H6 and H7). **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 21.0 (C9 and C12), 26.7 (C10 and C11), 51.4 (C2 and C4), 86.4 (C1 and C5), 133.7

(C6 and C7). **MS** (GC-MS(CI), NH_3, 70 eV, 150ºC): m/z, (%) = 198 (8, M+NH_4), 181, (7, M+1), 180 (M^+). **Anal.** Calcd for $C_{11}H_{16}O_2$: C 73.30, H 8.95 %. Found: C 73.29, H 8.97 %.**GC** (100 ºC, 1 min, 10 ºC/min, 250 ºC, 1 min): t_R= 7.32 min. **TLC** (SiO_2, hexane/ ethyl acetate 8:2. Developed as a purple spot by anisaldehyde reagent): R_f = 0.73.

6.4.7. Cycloaddition of 1',1"-dibromodicyclohexylketone with furan (4). Synthesis of 2,4-bis(spirocyclohexane)-8-oxabicyclo[3.2.1]oct-6-en-3-one, (16)



16

In an oven-dried 50 mL flask, fitted with magnetic stirring and argon atmosphere, freshly prepare Zn/Cu couple (210 mg, 3.32 mmol) was placed suspended in dry acetonitrile (7 mL). Dry furan (770 µL, 10.6 mmol), was added by syringe at room temperature. The system was cooled down to –44 ºC and Me_3SiCl (135 µL, 1.06 mmol) was added. Afterwards, 1',1"-dibromo-dicyclohexylketone **6** (373 mg, 1.06 mmol), dissolved in a acetonitrile-dichloromethane mixture 4:1 (5 mL) were added dropwise. The reaction mixture was stirred at –44 ºC for 1h (control by GC). The resulting reaction mixture was percolated through a short pad (2 cm) of neutral alumina, in order to remove the metallic particles, washing the column with ethyl acetate. The organic phase was concentrated to dryness and submitted to a flash column chromatography on silica gel, eluting with mixtures of hexane and ethyl acetate of increasing polarity. Pure product **16** was isolated with hexane/EtOAc 95:5 as a thick oil (176.5 mg, 64% yield). Careful analysis by high field NMR and GC of both the crude reaction mixture and the chromatographic fractions did not show the presence of [3+2}-cycloadduct **15**.

IR (KBr): $\bar{\upsilon}$ = 2929, 2857, 1697, (C=O, st), 1451, 1325, 1190, 1146, 1130, 1119, 1047, 982, 910 cm^{-1}. **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 1.31-1.74 (20H, several overlapped m, H2', H2", H3', H3", H4', H4", H5', H5", H6', H6"), 4.92 (2H, s, H1, H5), 6.37 (2H, s, H6 and H7) ppm. **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 21.0, 21.3, 21.5, 25.3, 25.5, 25.6, 29.4, 29.6, 33.0, 33.7 (C2', C2", C3', C3", C4', C4", C5', C5", C6', C6"), 55.3 (C2, C4), 81.3 (C1, C5), 113.4 (C6, C7), 217.0 (C3) ppm. **MS (**GC-MS(CI), NH_3, 70 eV, 150ºC): m/z

(%) = 295 (15, M+N_2H_7), 278 (100, M+NH_4), 261 (11, M+1). **Anal.** Calcd for $C_{17}H_{24}O_2$: C 78.40, H 9.30 %. Found: C 78.18, H 9.12 %. **GC** (100ºC, 1 min, 10 ºC/min, 250C, 1 min)**:** t_R = 18.25 min. **TLC** (SiO_2, hexane / ethyl acetate, 8:2): R_f = 0.81 (developed as a purple spot by anisaldehyde reagent).

7. Supporting Information

Tables S1, S2 and S3 as well as Figures S1, S2 and S3, relative to the energy, atomic charges and HOMO-LUMO computer calculations of reacting species **1'** and **6** and also of intermediate **I** are included as supporting information. Copies of ^{1}H-, ^{13}C NMR, IR and MS spectra of the herein described products are also included. A copy of these data may be obtained free of charge from the Web page of the publisher.

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