Intramolecular Photocycloaddition of 2(5*H*)-Furanones to Temporarly Tethered Terminal Alkenes as a Stereoselective Source of Enantiomerically Pure Polyfunctionalyzed Cyclobutanes

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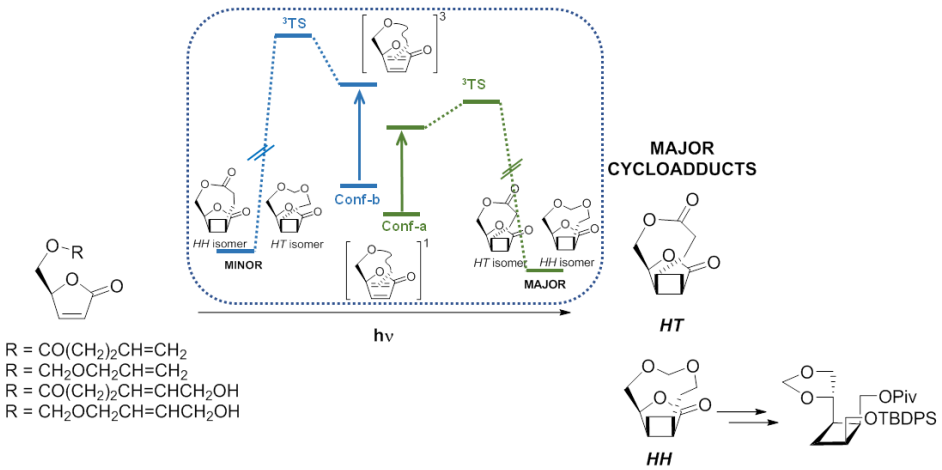
Abstract



Allyloxymethyloxymethyl and 4-pentenoyloxymethyl substituents have been used as tethered groups to study the intramolecular [2+2] photocycloaddition of chiral 5-substituted 2(5*H*)-furanones. The photoreactions proceed in good yield and provide regio- and diastereoselectively the expected tricyclic compounds with complementary regioselectivity which depends on whether the vinyl chain is attached to the furanone by an acetal or an ester linkage. Computational simulations agree with experimental observations and indicate that the origin of the different observed regioselectivity in the intramolecular photochemical reaction of lactones **5** and **6** arises from the relative stability of the initial conformers. The synthetic potential of the enantiomerically pure photoadducts is illustrated by preparing an all-*cis* 1,2,3-trisubstituted cyclobutane bearing fully orthogonally-protected hydroxyl groups.

Introduction

Cyclobutanes are found in many natural products and bioactive compounds, and also serve as useful intermediates in organic synthesis.[1] There are different methods to accomplish the preparation of these privileged building blocks.[2] Among them, [2+2] photocycloaddition reactions involving enones and alkenes have been extensively studied over the past decades.[3]

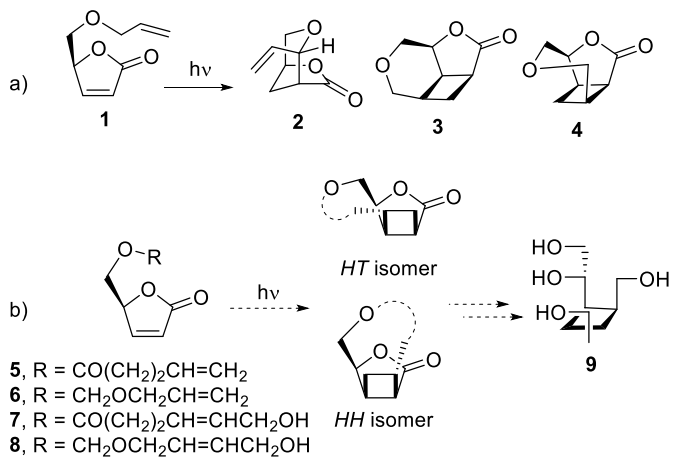
Photochemical [2+2] cycloaddition of 2(5*H*)-furanones to symmetrical alkenes have been widely used by our research group for the diastereoselective preparation of different bicyclo[3.2.0]heptanes scaffolds with acceptable yields. On the basis of these studies, some natural products and cyclobutane fused nucleoside analogues have been synthesized.[4] However, when unsymmetrical alkenes are used, the utility of the intermolecular [2+2] photocycloaddition reaction is limited as a result of the low stereo- and regioselectivity generally achieved in this process.[5]

Unlike the intermolecular version, the intramolecular [2+2] photocycloaddition reaction between two alkene moieties in the same molecule proceeds with excellent control of the regio- and stereoselectivities.[6] This is due to the decreased mobility of the reacting partners that are tethered together.[7] In recent years, increasing attention has been given to the use of temporary tethers as stereocontrol elements in the intramolecular photoreactions.[8]

Our studies on the preparation of bicyclic tetrahydropyrans (THPs) by an intramolecular photoreaction of enantiomerically pure 5-oxymethyl-2(*5H*)-furanones, showed that the photoreaction of lactone **1** bearing an allyloxymethyl substituent at C-5 delivers mainly a regioisomeric mixture of the [2+2] photocycloadducts **3** and **4,** along with the targeted THP **2** (Scheme 1a).[9] In all the assayed reactions, the head to tail (*HT*) isomer **3** was slightly favored over the head to head (*HH*) isomer **4**.[10]

The present work aims to broaden the scope of the intramolecular photochemical reactions of C-5 alkenyl substituted 2(5*H*)-furanones in order to develop an access to enantiopure *all cis* trisubstituted cyclobutane compounds. To this end, we have explored the photoactivated intramolecular cycloaddition of 2(5*H*)-furanones **5-8**, bearing an alkenyl chain attached either by an easily removable ester or ketal linkage, to prepare the corresponding [2+2] adducts, which by further modifications will lead to tri- or tetrasubstituted cyclobutanes (Scheme 1b). Herein, we give a full account of this study, which includes the preparation of several 2(5*H*)-furanones, their intramolecular [2+2]-photoreactions as well as the synthesis of a new diversely functionalyzed *(all cis*) trisubstituted cyclobutane from the photoadduct derived from **6**.

Scheme 1. Intramolecular photocycloadditions of C5-alkenyl substituted 2(5*H*)-furanones



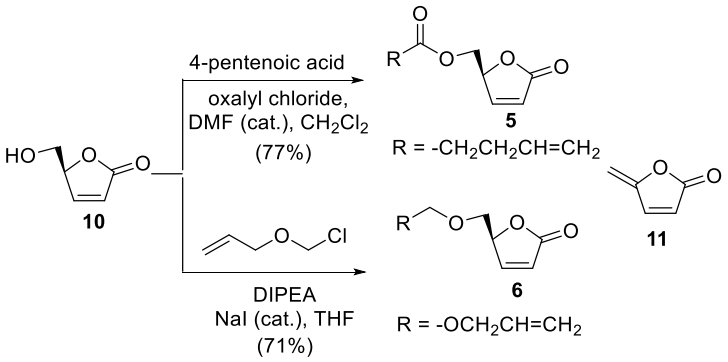
Results and Discussion

Synthesis of 2(5H)-furanones

The new furanones **5-8** selected to undertake the photochemical study were prepared starting from the known enantiomerically pure 2(5*H*)-furanone **10** (Scheme 2).[11] Initial attempts to synthesize the ester derivative **5** by applying the Steglich procedure (DMAP (cat.), DCC, CH_2Cl_2) were successful

albeit in moderate yield (52%).[12] Moreover, the formation of dicyclohexylurea in the process made its purification a tedious process. On the other hand, the condensation of **10** with freshly prepared 3-pentenoyl chloride (Cl_2SO, CH_2Cl_2) in the presence of Et_3N afforded exclusively the elimination product protoanemonin, **11,** thereby indicating that **5** is unstable in basic conditions. It was eventually found that treatment of **10** with freshly prepared chloride using oxalyl chloride and a catalytic amount of DMF in CH_2Cl_2 delivered **5** in 77% yield. The acetal **6** was synthesized in 71% yield by condensation of **10** with freshly prepared allyl chloromethyl ether,[13] DIPEA as a base and NaI as a catalyst in THF at the reflux temperature. Other reaction conditions (rt, CH_2Cl_2) proved to be less efficient.

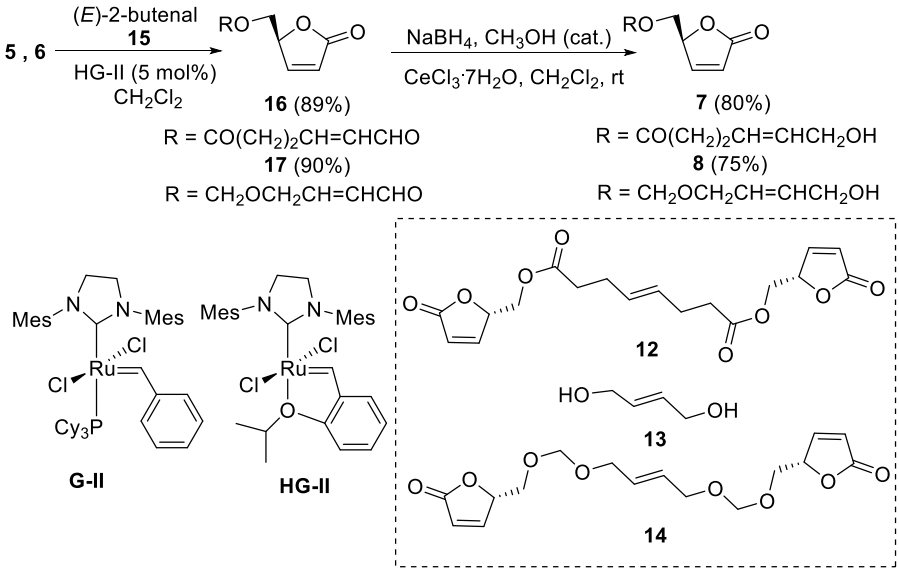
Scheme 2. Synthesis of lactones **5** and **6**



Next, the preparation of disubstituted olefins **7** and **8** was attempted through an olefin cross-metathesis (CM) reaction (Scheme 3). Initial efforts to carry out the CM reaction of **5** and **6** with allyl alcohol and 2nd generation Grubbs catalyst GII (mol 4%) in CH_2Cl_2 at rt, afforded the expected compounds **7** and **8** only in 27% and 35% yield, respectively. Substantial amount of homodimeric products **12, 13** and **14** was also obtained making the purification of **7** or **8** more difficult. Unfortunately, all attempts to suppress the formation of the homodimers failed and the yield of the desired compounds were slightly improved (up to 36% for compound **7**). Thus, we decided to prepare them by following a two-step procedure (olefin CM reaction with (*E*)-2-butenal and subsequent carbonyl reduction). The treatment of **5** with aldehyde **15** and GII (5 mol%) in CH_2Cl_2 at rt provided the desired product **16** in 54% yield. The reaction did not proceed to completion and a small amount of homodimer **12** was also observed. After considerable experimentation, it was found

that the CM reaction to produce the *E* olefin **16** proceeded in good yield (89%) by using the 2nd generation Hoveyda-Grubbs catalyst (HG-II).[14] In this case we did not observe any significant amount of homodimers arising from either olefin. The following regioselective reduction of the aldehyde moiety was achieved in 80% yield under Luche's conditions. In an analogous manner, the olefin **8** was prepared from ketal **6** by the two-step strategy in 68% overall yield.

Scheme 3. Synthesis of lactones **7** and **8**



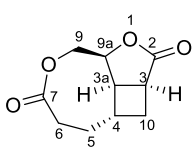
Photochemical study

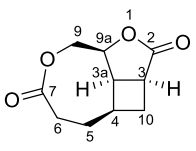
With 2(5*H*)-furanones **5-8** in hand, we next focused on their intramolecular [2+2] photocycloaddition reactions by irradiation using a 125W high-pressure mercury lamp through a quartz or Pyrex filter. Since the solvent and temperature play an important role in photochemical processes, the photoreactions were studied in acetonitrile and acetone at different temperatures. The progress of the reactions was monitored by GC analyses of aliquots of the reaction mixtures, and the irradiation was prolonged until the conversion remained constant.

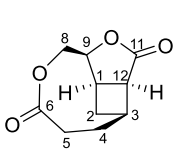
First, the intramolecular [2+2] photocycloaddition of **5** was investigated using experimental conditions usually applied in our laboratories for intermolecular photoreactions (Table 1, entry 1).[9] However, the irradiation of **5** in acetone through a Pyrex filter at different temperatures (from rt to -78 °C) did not afford any of the expected photoproducts. Instead, complex mixtures were formed in each case. Better results were found when the photoreaction was performed through a quartz filter and with acetonitrile as a solvent (entry 2). Thus, irradiation of **5** at rt furnished in 52% overall yield

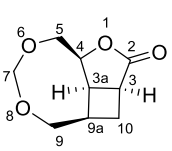
a (15:67:18) mixture of the three cycloadducts: the *HT* isomers **18, 19** and the *HH* isomer **20**. Noteworthy, the selectivity and the yield of the photochemical process were enhanced when the reaction was carried out at -20 °C (58% yield, 11:78:11) and at -40 °C (64% yield, 8:84:8) (entries 3 and 4). Finally, using acetone as solvent at -78 °C, the intramolecular photocycloaddition proceeded smoothly delivering the same mixture of compounds in higher selectivity (7:86:7) and yield (78%) (entry 5), from which the major *HT* regioisomer **19** and the minor *HH* regioisomer **20** could be isolated in 61% and 6% yield, respectively, after purification by column chromatography. Although conversion was not always complete, longer reaction times tended to produce more complex mixtures (by GC analysis) without increasing the yield of the desired photoadducts.

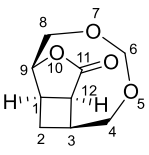
Table 1. Irradiation of 2(5*H*)-furanones **5** and **6**

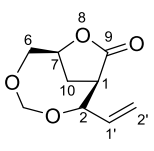

18-*HT*


19-*HT*


20-*HH*


21-*HT*


22-*HH*


23

entry	substrate[a]	solvent	filter	T (°C)	time (min)	global yield[b]	product (ratio)[c]
1	**5**	acetone	pyrex	-78	240	-	-
2	**5**	CH_3CN	quartz	25	120	52%	**18:19:20** (15:67:18)
3	**5**	CH_3CN	quartz	-20	120	58%	**18:19:20** (11:78:11)
4	**5**	CH_3CN	quartz	-40	90	64%	**18:19:20** (8:84:8)
5	**5**	acetone	quartz	-78	30	78%	**18:19:20** (7:86:7)
6	**6**	acetone	quartz	-78	25	82%	**21:22:23** (9:87:4)
7	**6**	acetone	quartz	-40	40	73%	**21:22:23** (12:82:6)
8	**6**	CH_2Cl_2	quartz	-40	40	65%	**21:22:23** (18:77:5)
9	**6**	CH_3CN	quartz	-40	40	70%	**21:22:23** (14:81:5)
10	**6**	CH_3CN	quartz	25	60	58%	**21:22:23** (18:73:9)

[a] Irradiations were performed in a nitrogen-saturated 6.3 mmol L^{-1} solution. [b] Yield of isolated mixture of products. [c] Product ratio determined by GC.

The photoreaction of **6** was next performed under similar reaction conditions (entry 6). In the event, irradiation of **6** in acetone through a quartz filter at -78 °C delivered a (9:87:4) mixture of the two regioisomeric cyclobutanes **21** and **22** and the vinylic 1,3-dioxocane **23** in 82% total yield. Purification by column chromatography allowed the isolation of the *HH* isomer **22** in 67% yield and

the dioxocane **23** in 3% yield. Enriched fractions of the *HT* isomer **21** could also be obtained allowing its structural elucidation. Compound **23** arises from a 1,7-hydrogen atom transfer (HAT) of [**6**]* to the β-carbon of the excited lactone, followed by subsequent recombination of the diradical to form a new σ C-C bond.[9] Interestingly, the regioselectivity in the photocycloaddition of **6** is completely reversed regarding that obtained in the photoreaction of **5**, thereby enabling the preparation of enantiopure cyclobutanes with different substitution patterns.

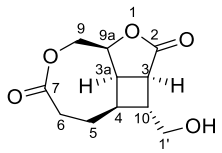
To study the selectivity of the process, irradiations of **6** were also performed at various solvents and temperatures. As previously mentioned, we observed that the increase of the temperature was accompanied by a diminution of the selectivity and the yield. Lower ratio of the major *HH* isomer **22** in similar yields was produced when the reaction was run at -40 °C in acetone, acetonitrile and CH_2Cl_2 (entries 7-9) and at rt in acetonitrile (entry 10). Therefore, the best results were achieved when the photoreactions of lactones **5** and **6** were carried out in acetone with a quartz filter at -78 °C, which furnished the *HT* isomer **19** in 61% yield and the *HH* isomer **22** in 67% yield, respectively, indicating that the regioselectivity of the process is dependent on the functionality of the tether. In both cases, the complete syn facial diastereoselectivity is cooperatively induced by the stereogenic center in the lactones.

The success of photocycloaddition of **5** and **6** prompted us to expand this study to the preparation of tetrasubstituted cyclobutanes by using the corresponding 1,2-disubstituted olefins tethered to the 2(5*H*)-furanone core. Thus, we evaluated the photochemical reactions involving lactones **7** and **8** bearing disubstituted olefins (Table 2). The intramolecular [2+2] photocycloaddition of **7** was conducted under the optimized conditions previously established above by irradiation through a quartz filter at -78 °C in acetone. Under these conditions, disappearance of the starting material was observed after 30 min to deliver a 49:27:24 mixture of the two cyclobutane compounds **24** and **25** and the bis-lactone olefin **26** in 64% overall yield (entry 1). The two cycloadducts **24** and **25** could be isolated and identified by NMR spectroscopy. Chromatographic separation of **26** was not possible, therefore, for identification purposes, it was necessary to perform NMR analysis of samples containing a mixture of isomers. When the reaction was carried out at higher temperature in

acetonitrile, both the selectivity and the yield of the process slightly decreased (entries 2-4). In all these assays, the formation of the photoadduct **24** was slightly favored. However, the low selectivity of the reaction and the difficulty to separate the components of the mixture by chromatographic means hampered its utilization as a synthetic process.

Surprisingly, the irradiation of lactone **8** in all attempted reaction conditions (acetone or acetonitrile; from rt to -78 °C) gave complex mixtures of products (entries 5-6), and NMR studies did not allow the identification of any compound containing the expected cyclobutane structures. Moreover, no starting furanone was recovered. In this case, the presence of an additional hydroxymethyl substituent in the alkene moiety along with conformational requirements demanded by the acetal linkage could favor the 1,7 and/or 1,5 hydrogen atom transfer processes over the intramolecular [2+2] photocycloaddition evolving to the formation of different unidentified decomposition products.

Table 2. Irradiation of 2(5*H*)-furanones **7** and **8**



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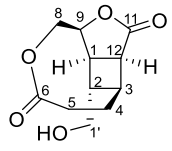

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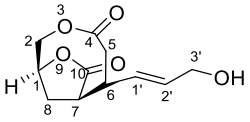


26

entry	substrate[a]	solvent	T (°C)	time (min)	global yield[b]	product (ratio)[c]
1	**7**	acetone	-78	30	64%	**24:25:26** (49:27:24)
2	**7**	CH_3CN	-40	60	58%	**24:25:26** (46:24:30)
3	**7**	CH_3CN	-20	75	52%	**24:25:26** (40:29:31)
4	**7**	CH_3CN	25	75	44%	**24:25:26** (37:29:34)
5	**8**	acetone	-78	45	-	-
6	**8**	CH_3CN	-40	75	-	-

[a] Irradiations were performed through a quartz filter in a nitrogen-saturated 6.3 mmol L^{-1} solution. [b] Yield of isolated mixture of products. [c] Product ratio determined by NMR.

The structural assignment of the photoadducts was mainly based on detailed analysis of their 1D and 2D spectra. The connectivity was established by HMBC experiments, wherein correlation between the methylenic protons H-10 and the carbonyl carbon C-2 was observed for the *HT* isomers **18, 19** and **21** while the *HH* isomers **20** and **22** showed correlation between the methylenic protons

H-2 and C-9. For the tetrasubstituted cyclobutanes **24** and **25**, the connectivity was evidenced by diagnostic cross couplings between the α-carbonylic proton H-3 and C-1' for **24** and between the β-carbonyl proton H-1 and C-1' for **25**.

The syn addition of the photoreactions was determined on the basis of the value of the coupling constant between the γ-lactone proton and its adjacent cyclobutane proton in the different cycloadducts, which due to its cis disposition is expected to be large. Indeed the ester tethered compounds display values that range from $J_{9,1}$ ~ 9.4 Hz for the *HH* regioisomers **20** and **25** to $J_{9a,3a}$ ~ 4.8 Hz for the *HT* isomers **18** and **19,** while the ketal tethered compounds show coupling constants that vary from $J_{9,1}$ ~ 10.3 Hz for the *HH* regioisomer **22** to $J_{4,3a}$ ~ 6.5 Hz for the *HT* isomer **21**. Therefore, as expected, the syn diastereoselectivity comes from the attack of the terminal alkene to the face of the 2(5*H*)-furanone to which the alkyl chain is directed by the stereogenic center at C-5.

The relative configurations between the three newly formed stereogenic centers in the cycloadducts **18-22** were established by NMR coupling patterns and by NOESY experiments. Thus, the value of the coupling constants $J_{3a,4}$ ~8 Hz for **19** and $J_{12,3}$ ~9,5 Hz for **20** and **22** indicate a *cis* disposition between both protons while the absence of coupling $J_{3a,4}$ ~0 Hz for **18** suggests a *trans* arrangement. In compound **21** the *cis* arrangement between H-3a and H-9a was assigned on the basis of a NOESY experiment, which showed cross-peaks between the H-9 protons and the cyclobutane proton H-10 *endo*, and between H-3 and H-10 *exo*. Furthermore, we were able to obtain crystals of **19** and **22** for which X-ray structures were recorded, confirming unambiguously the relative and absolute configuration of the three contiguous stereogenic centers created after irradiation.

For the tetrasubstituted cyclobutanes **24** and **25** four new stereocenters were generated and their relative configurations were determined by the coupling constant patterns and further corroborated by NOESY experiments. Thus, the *cis* arrangement between H-3a and H-4 and the *trans* disposition between H-3 and H-10 in **24** were assigned by the value of the coupling constants $J_{3a,4}$ ~7.5 Hz and $J_{3,10}$ ~2.3 Hz. In a similar way, for compound **25** the value of the coupling constants $J_{1,2}$ ~0 Hz and $J_{12,3}$ ~10.2 Hz indicate *trans* and *cis* relationships, respectively. Cross-peaks on the NOESY experiments between the methylenic protons H-1' and H-3 and H-3a in **24** and between H-1' and H-

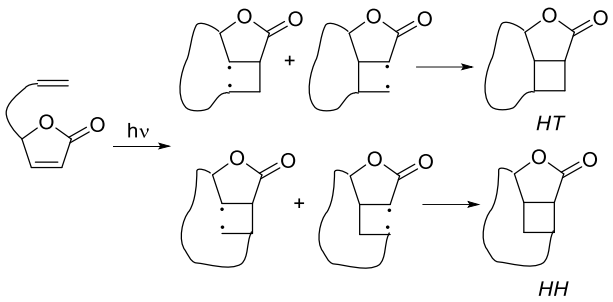
3 and H-1 and between one of the protons H-8 and H-2 in **25** validated the diagnostic value of the above parameters. Therefore, the NMR study confirmed that photocycloaddition of **7** has taken place in a *syn* sense at the lactone double bond and with preservation of the original *trans* relationship present in the unsaturated ester appendage.

The structure of compounds **23** and **26** coming from a 1,7-hydrogen atom transfer was determined through detailed NMR studies. The ^{1}H NMR spectrum of **23** displays the characteristic signals of the olefinic protons of a vinyl group at δ 5.86, 5.35 and 5.17 and the HMBC experiment showed relevant cross-peaks between the allylic proton H-2 and the carbonyl carbon C-9 and between the α-carbonylic proton H-1 and the olefinic carbon C-1'.

Compound **26** could not be obtained in pure form, and its structure was elucidated analyzing a sample containing the major cycloadduct **24**. Two olefinic protons at δ 5.67 were observed in its ^{1}H NMR spectrum and the connectivity could be established with the help of the HMBC spectrum wherein correlation between these protons and C-6 and between the methynic proton H-7 and C-1 were displayed. However, we were not able to unambiguously determine the configuration of the new stereogenic center at C-6.

In order to rationalize the origin of the different observed regioselectivity in the intramolecular photochemical reaction of lactones **5** and **6** we have carried out a computational study of the possible reaction pathways (for Computational details see the Experimental Part). Previous studies[15] on the [2 +2] photocycloaddition reaction of 2(5*H*)-furanones to ethylene indicate that the reaction involves the formation of a triplet 1,4-biradical intermediate that, after spin crossing, evolves to the cyclobutane derivative. As previously commented, in the studied intramolecular photocycloadditions two different regioisomers *HH* and *HT* are possible. For lactone **6** with the vinyl chain appended by an acetal linkage, the main observed product is the *HH* regioisomer **22**, while for lactone **5** bearing the vinyl chain appended by an ester linkage is the *HT* isomer **19**. Four different 1,4-biradical intermediates leading to the *HT* or *HH* products could be envisaged depending on the bond that it is formed in the first step of the process (Scheme 4).

Scheme 4. 1,4-Biradical intermediate species postulated for the [2+2] photocycloaddition of 2(*5H*)-furanones **5** and **6**



In addition, different low lying conformers of **5** and **6** may exist. In particular, we have identified several reactant conformers that can lead either to the final *HH* or *HT* regioisomers and explored all the possible reaction pathways connecting those conformers with the final products. Figures S3-S10 of the Supplementary Information show the schematic energy profiles obtained for all the paths considered and the optimized geometries of the stationary points involved. Since it is known that the reaction proceeds *via* the excitation of the furanone moiety,[16] we have explored the paths involving that excitation. For **6** we have found subtle differences between the possible reaction mechanisms leading to the different products and thus, reactions of **6** are presented in detail first and then reactions of **5** are also presented.

Figure 1 shows the schematic energy profile for the most stable conformers of **6** leading to the *HH* and *HT* products. Different stationary points are labelled with the number of the reactant species (**5** or **6**) plus a superscript indicating the electronic state (**1** for the singlet and **3** for the triplet), and a lower-case letter (**a** and **b**) to indicate whether the structure corresponds to the path that leads to the *HT* (**a**) or the *HH* (**b**) product. Transition structures are referred as **TS** before the two names of the interconnected intermediates and biradical species are denoted as ^{x}**BR** where x refers to the electronic spin state.

The energetic profile is essentially the same in both cases. Geometrical relaxation of the furanone centered excited triplet state leads to the ^{3}**6** intermediates which evolve to the ^{3}**BR-6** biradicals through the corresponding transition states. The Gibbs energy barrier is somewhat lower for the path leading to the *HT* product (2.1 kcal mol^{-1}) than for that leading to the *HH* product (6.3 kcal mol^{-1}). However, both transition states are isoergonic (79.4 kcal mol^{-1} with respect to the most stable

starting conformer). Finally, the intermediates **^{3}BR-6** must evolve to the singlet 1,4-biradicals **^{1}BR-6** through an intersystem crossing.[15,17,18] It can be observed in Figures S7 and S8 (Supporting Information) that the triplet and singlet biradical species present very close geometries. Moreover, their energies are also very similar (see Figure 1), thereby indicating that both stationary points sit near the intersystem crossing region between the singlet and triplet energy surfaces.

Once formed, the singlet 1,4-biradical intermediates evolve to the *HT* isomer **21** and the *HH* isomer **22**, respectively, through the associated transition state. In this case the Gibbs energy barriers do not exceed 1 kcal mol^{-1}.

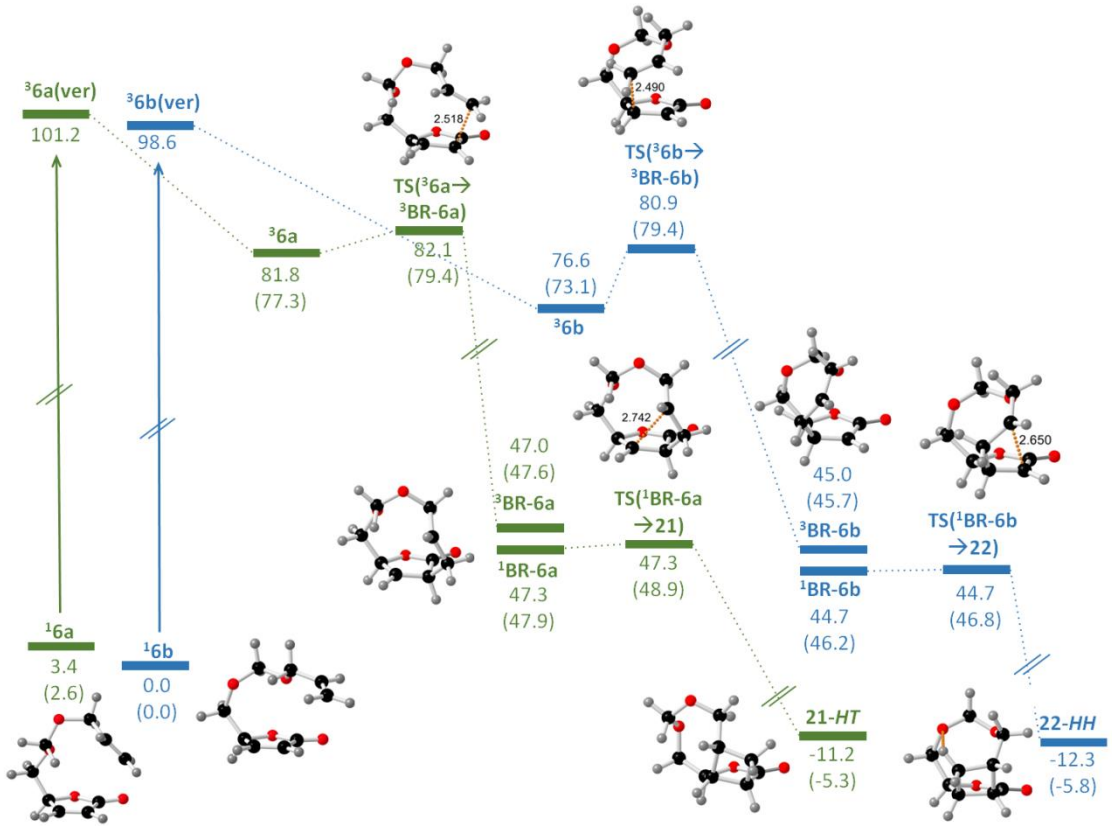


Figure 1. Schematic potential energy profile (Gibbs energies are shown in parenthesis) for the reactions of the most stable conformers of lactone **6** that lead to **21** and **22**. The green line corresponds to the formation of the *HT* product **21** and the blue line to the *HH* isomer **22**. Energies are in kcal mol^{-1}.

It should be noted that all energy barriers are accesible in the applied reaction conditions taking into account the energy provided to the system by the photoexcitation. Thus, in these conditions the observed regioselectivity would mainly be driven by the relative stability of the initial conformers.

The conformer **^{1}6b**, prone to give the *HH* product, is 2.6 kcal mol^{-1} more stable than the isomer **^{1}6a** that leads to the *HT* product. Other initial conformers have also been considered but they are all higher in energy. This relative stability is mantained in the final products although the difference is reduced (0.5 kcal mol^{-1}). The larger stability of **^{1}6b** is related to the *gauche* conformational preferences of the dihedral angles centered in the ketal moiety, [19] which is generally attributed to the so-called anomeric effect. The physical origin of this effect is controversial and several factors have been proposed to explain it such as hyperconjugation (the interaction n(O) → σ*(C-O) being the largest individual contribution) or dipole-dipole interactions.[19] In our case, **^{1}6b** presents a *gauche-gauche* conformation while **^{1}6a** shows an *anti-gauche* arrangement. Thus, the final observed regioselectivity is dictated by the *gauche* preference of the –O–CH_2–O– unit in the ketal moiety.

Figure 2 shows the schematic energy profile for the most favorable conformers of lactone **5**, with the vinyl group attached by an ester linkage, leading to the *HT* and *HH* products **19** and **20**.

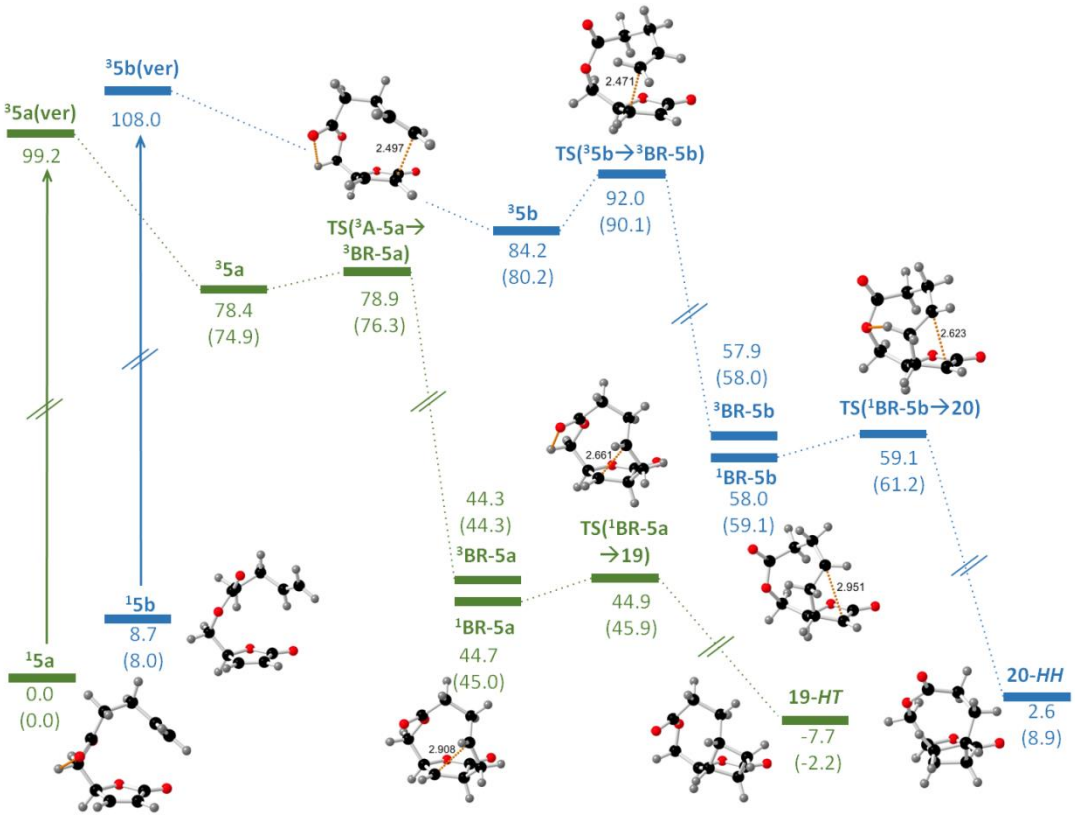


Figure 2. Schematic potential energy profile (Gibbs energies are shown in parenthesis) for the photochemical reaction involving the most stable conformers of **5** leading to **19** and **20**. The green

line corresponds to the formation of the *HT* product **19** and the blue line to the *HH* isomer **20**. Energies are in kcal mol^{-1}.

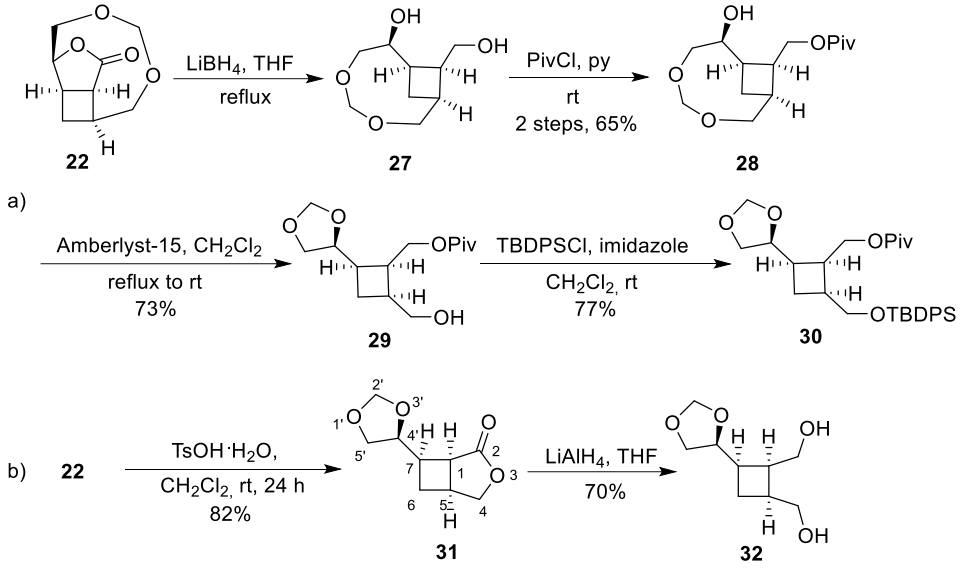
The computed pathways leading to both regioisomeric products will not be discussed in detail because they are very similar to those found for **6**. The main difference is the larger preference for one of the initial reactant conformers. Namely, conformer ^{1}**5a**, which leads to the *HT* isomer **19**, is 8 kcal mol^{-1} more stable in terms of Gibbs energy than conformer ^{1}**5b** leading to the *HH* product **20**. It should be noted that the Gibbs energy barriers of the different individual steps are also lower for the HT pathway. Thus, from a computational view, the pathway of the *HT* regioisomer is largely preferred in front of the *HH* one, in agreement with the experimental results. The larger stability of ^{1}**5a** in front of ^{1}**5b** is maintained during the whole reaction path and carried over to the final product, and is due to the different conformation of the ester moiety of the reactant, *syn* (*Z*) for ^{1}**5a** and *anti* (*E*) for ^{1}**5b**. Indeed, different experimental and computational studies on R-COO-R' molecules have shown that the *Z* rotamer is more stable than the *E* form.[20] Several factors have been proposed in the literature to contribute to this difference, such as steric interactions, dipole-dipole interactions between the C=O and –O-R' moieties,[21-23] a hyperconjugative effect due to the interaction between the σ lone pair of the "ether" oxygen and the antibonding σ*(C-O) orbital[24] or other conjugative effects.[25] On the other hand, Ferro-Costas *et al.*[20] using a QTAIM-based energy partitioning have stated that in the case of formic acid the most important factor in the stabilization of the *Z* conformer is the attraction of the carbonyl oxygen electron density by the acidic hydrogen. Replacement of hydrogens by larger groups in different positions enhances the energy difference between the *Z* and *E* rotamers due to the increase of repulsion, which destabilizes the *E* conformer, and the increase of different attractive terms that favor the *Z* conformer.

Synthesis of all-cis 1,2,3-trisubstituted cyclobutane 30

The intramolecular photocycloaddition of lactones **5** and **6** proceeds with complementary regioselectivity and good yields to furnish the photoadducts **19** and **22**, respectively. Moreover, considering the labile nature of the lactone ring and the ketal/ester moieties, these scaffolds might represent attractive precursors for the preparation of all-*cis* trisubstituted cyclobutanes. To

demonstrate some of its synthetic utility, further modifications on **22** to the cyclobutane **30,** bearing differently substituted orthogonally deprotectable groups, were undertaken (Scheme 5a).

Scheme 5. Preparation of all-*cis* 1,2,3-trisubstituted cyclobutane **30**



The ring opening lactone of **22** was performed by treatment with $LiBH_4$ delivering diol **27** whose primary hydroxyl group was selectively protected as the corresponding pivaloyl ester **28** in 65% for the two steps. Both compounds showed ^{1}H NMR spectra with wide broad signals due to the presence of the nine-membered ring. Next, a transacetalization reaction was attempted. During initial exploratory studies, it was noted that treatment of cycloadduct **22** with *p*-toluenesulfonic acid as a catalyst afforded, through a sequential translactonization and transacetalization reactions, lactone **31** in good yield which in turn was converted to diol **32** after lactone reduction (Scheme 5b). Taking this into account, ketal **28** was treated with Amberlyst-15[26] in CH_2Cl_2 to furnish the rearranged compound **29** in 73% yield. Finally, treatment of **29** with TBDPSCl and imidazole in CH_2Cl_2 delivered the target all-*cis* 1,2,3-trisubstituted cyclobutane **30**, with all the hydroxyl groups orthogonally protected, in 77% yield thus illustrating the synthetic utility of photoadduct **22**.

Conclusions

Several enantiomerically pure 2(5*H*)-furanones bearing temporary tethered alkenyl chains appendage by an acetal or ester linkage have been prepared and their photochemical reactions studied. The intramolecular [2+2] photocycloaddition reactions of lactones **5** and **6** proceed with complete syn diastereoselectivity and are complementary allowing straightforward regio-

differentiated access to the trisubstituted cyclobutanes **19** and **22** in exploitable quantities. The major cycloadduct obtained from **5** is the *HT* isomer, whereas that from **6** is the *HH* one. Calculations for the intramolecular photochemical reaction of lactones **5** and **6** agree with the experimental observations, the *HT* product being more(less) stable than the *HH* product for compounds **5(6)**. The origin of the different observed regioselectivity in the intramolecular photochemical reaction of lactones **5** and **6** arises, however, from the relative stability of the initial conformers**.** In the case of **6**, the final observed regioselectivity is dictated by the *gauche* preference of the the –O–CH_2–O– unit in the ketal moiety, whereas in the case of **5**, it is determined by the larger stability of the R-COO-R' *Z* rotamer. Furthermore, the studied photoreactions give access to new ring systems, which are difficult to prepare by other methods and open up new pathways to interesting molecular frameworks. As a proof of synthetic feasibility, photoadduct **22** has been converted to **30** which constitutes an 1,2,3-trisubstituted all-*cis* cyclobutane with the hydroxyl groups orthogonally-protected.

Experimental Section

General Methods: Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents. All reactions were performed avoiding moisture by standard procedures and under nitrogen atmosphere. Flash column chromatography was performed using silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, 360 and 90 MHz. or 400 and 100 MHz. Proton chemical shifts are reported in ppm (δ) ($CDCl_3$, δ 7.26 or acetone-d_6, δ 2.05). Carbon chemical shifts are reported in ppm (δ) ($CDCl_3$, δ 77.2). NMR signals were assigned with the help of COSY, HSQC, HMBC, and NOESY experiments. High-resolution mass spectrometry (HRMS) data were recorded on a Bruker MicroTOF-Q spectrometrer with an electrospray ionization source in positive mode, with a tandem Q-TOF analyzer. Melting points were determined on hot stage and are uncorrected. Optical rotations were measured at 22 ± 2 ˚C.

Computational details

Molecular geometries and harmonic vibrational frequencies of all the considered structures were obtained using the M06-2X density functional method[27] which encloses a large amount of exact exchange (54 %) necessary to appropriately describe radical species and reaction barriers of radical processes.[15,28-31] In addition, M06-2X is able to account for mid-range dispersion forces.[27] In order to confirm the nature (minimum or transition state) of the stationary points, harmonic vibrational frequency calculations were carried out in all cases using the same level of calculation. The minima connected by a given transition state were identified by intrinsic reaction coordinate calculations (IRC) or visual inspection. Some selected structures were optimized considering solvent (acetone) effects using the SMD[32] implicit solvation model. Open shell DFT calculations were performed using a spin unrestricted formalism. For open shell singlet states, unrestricted calculations were carried out by breaking the symmetry between the α and β spin densities. As expected, for singlet biradical intermediates the resulting $\langle S^2 \rangle$ values lie between 0.9 and 1.0; namely they are biradicals with an almost equal mixing of singlet and triplet spin states. Spin projected energies can be obtained by using the spin correction procedure of Yamaguchi *et al*.[33] This correction method was applied in some selected cases, differences between spin projected and unprojected energies being less than 0.4 kcal mol^{-1}. Thus, we only report the uncorrected values. All calculations were performed using the 6-311++G(d,p) basis set with the Gaussian 09 package.[35]

[(2*S*)-1-oxo-2,1-dihydrofuran-2-yl]methyl pent-4-enoate, 5. To an ice-cooled solution of 4-pentenoic acid (654 mg, 6.5 mmol) and DMF (2 drops) in anhydrous CH_2Cl_2 (18 mL) was added oxalyl chloride (2 M in CH_2Cl_2, 3.6 mL, 7.2 mmol), dropwise. The solution was stirred for 10 min at rt, and heated to the reflux temperature for 1 h under a N_2 flux. Then, 2(*5H*)-furanone **10** (688 mg, 6.0 mmol) was added and the resulting mixture was refluxed for 7 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane-EtOAc from 2:1 to 1:1) to afford compound **5** (909 mg, 4.6 mmol, 77% yield) as a colourless oil: $[\alpha]_D$ -114 (*c* 0.9, $CDCl_3$); IR (ATR) 2922, 1735, 1641, 1259, 1156, 1094, 819 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.41 (d, $J_{3'',4''}$=5.7 Hz, 1H, H-3´´), 6.12 (dd, $J_{4'',3''}$=5.7 Hz, $J_{4'',2''}$=1.9 Hz, 1H, H-4´´), 5.72 (ddt, $J_{4,5=}$ 16.4 Hz, $J_{4,5}$=10.4 Hz, $J_{4,3}$=6.2 Hz, 1H, H-4), 5.22-5.15 (m, 1H, H-2´´), 5.05-4.84 (m, 2H,

H-5), 4.28 (dd, J_{gem}=12.1 Hz, $J_{1',2'}$=4.4 Hz, 1H, H-1'), 2.39-2.31 (m, 2H, H-3), 2.31-2.22 (t, $J_{2,3}$=6.4 Hz, 2H, H-2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.2 (C-5′′), 172.1 (C-1), 152.4 (C-3′′), 136.0 (C-4), 122.9 (C-4′′), 115.6 (C-5), 80.7 (C-2′′), 62.2 (C-1'), 32.9 (C-3), 28.4 (C-2). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{10}H_{12}NaO_4$ 219.0628; Found: 219.0631.

(4*S*)-4-{[(allyloxy)methoxy]methyl}-2(5*H*)-furanone, 6. To a solution of **10** (796 mg, 7.0 mmol), DIPEA (4.8 mL, 28.0 mmol) and NaI (cat.) in anhydrous THF (50 mL), freshly prepared 3-(chloromethoxy)prop-1-ene[13] (3.10 g, 29 mmol) was added and the reaction mixture was heated under reflux for 3 h. Then, the solvent was removed under reduced pressure and CH_2Cl_2 (70 mL) and H_2O (70 mL) were added. The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2×70 mL). The combined organic phases were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (hexane-EtOAc 2:1 to 1:1) to afford compound **6** (907 mg, 4.9 mmol, 71% yield) as a colourless oil: $[\alpha]_D$ -76 (*c* 1.0, $CDCl_3$); IR (ATR) 2889, 1756, 1161, 1033, 776 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.46 (dd, $J_{4,3}$=4.0 Hz, $J_{4,5}$=1.8 Hz, 1H, H-4), 6.14 (dd, $J_{3,4}$=4.0, $J_{3,5}$=1.8 Hz, 1H, H-3), 5.84 (ddt, $J_{2''',3'''}$=14.4 Hz, $J_{2''',3'''}$=10.1 Hz, $J_{2''',1'''}$=4.5 Hz, 1H, H-2'''), 5.33-5.19 (m, 1H, H-5), 5.18-5.09 (m, 2H, H-3'''), 4.66 (d, J_{gem}=4.1 Hz, 2H, H-1''), 4.09-3.99 (m, 2H, H-1'''), 3.84-3.69 (m, 2H, H-1'); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.5 (C-2), 153.5 (C-4), 133.7 (C-2'''), 122.4 (C-3'''), 117.0 (C-3), 94.5 (C-1''), 81.9 (C-5), 68.2 (C-1'''), 66.7 (C-1'). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_9H_{12}NaO_4$ 207.0628; Found 207.0628.

[(2*S*)-5-oxo-2,5-dihydrofuran-2-yl]methyl (4*E*)-6-hydroxy-4-hexenoate, 7.

Method A: To a solution of **5** (50 mg, 0.26 mmol) and allyl alcohol (54 mg, 0.93 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was added 2nd generation Grubbs catalyst (9 mg, 0.011 mmol, 4%). The reaction mixture was stirred at rt for 26 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane-EtOAc1:1 to 0:1) to afford compound **7** (16 mg, 0.07 mmol, 27% yield) as a colourless oil and the dimer **12** as a white solid.

7: $[\alpha]_D$ -73 (*c* 1.0, $CDCl_3$); IR (ATR) 3409, 1736, 1159, 1095, 781, 632 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.43 (dd, $J_{3'',4''}$=5.7 Hz, $J_{3'',2''}$=1.7 Hz, 1H, H-3′′), 6.20 (dd, $J_{4'',3''}$=5.7 Hz, $J_{4'',2''}$=2.0 Hz,

1H, H-4´´), 5.69-5.61 (m, 2H, H-4 and H-5), 5.27-5.19 (m, 1H, H-2´´), 4.42 (dd, J_{gem}=12.1 Hz, $J_{1',2''}$=3.7 Hz, 1H, H-1'), 4.30 (dd, J_{gem}=12.1 Hz, $J_{1',2''}$=4.9 Hz, 1H, H-1'), 4.07 (dd, $J_{6,5}$=4.1 Hz, $J_{6,4}$=1.0 Hz, 2H, H-6), 2.46-2.37 (m, 2H, H-3), 2.39-2.31 (m, 2H, H-2), 2.07 (br, 1H, H-OH); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.4 (2C, C-1, C-5´´), 152.6 (C-3´´), 130.6 (C-5), 129.4 (C-4), 123.0 (C-4´´), 80.8 (C-2´´), 62.9 (C-1'), 62.2 (C-6), 33.3 (C-3), 27.0 (C-2). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{11}H_{14}NaO_5$ 249.0733; Found 249.0734.

Bis{[(2*S*)-5-oxo-2,5-dihydro-2-furanyl]methyl}(4*E*)-octenedioate, 12. Mp 77-78 °C (from EtOAc-hexane); $[\alpha]_D$ +11 (*c* 5.0, $CDCl_3$); IR (ATR,) 1748, 1172, 995, 632 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43 (dd, $J_{3'',4''}$=5.7 Hz, $J_{3'',2''}$=1.6 Hz, 2H, H-3´´), 6.17 (dd, $J_{4'',3''}$=5.7 Hz, $J_{4'',2''}$=2.1 Hz, 2H, H-4´´), 5.47-5.31 (m, 2H, H-4, H-5), 5.27-5.17 (m, 2H, H-2´´), 4.45-4.18 (m, 4H, H-1'), 2.39-2.28 (m, 4H, H-3, H-6), 2.31-2.18 (m, 4H, H-2, H-7); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.3 (2C-5´´), 172.2 (C-1, C-8), 152.4 (2C-3´´), 129.2 (C-4, C-5), 123.1 (2C-4´´), 80.7 (2C-2´´), 62.3 (2C-1'), 33.6 (C-3, C-6), 27.4 (C-2, C-7). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{20}NaO_8$ 387.1050; Found 387.1055.

Method B. A solution of **5** (600 mg, 3 mmol) and (*E*)-but-2-enal (1.25 mL, 15 mmol) in anhydrous CH_2Cl_2 (20 mL) was heated at the reflux temperature for 10 min. Then, 2nd Hoveyda-Grubbs catalyst (40 mg, 0.06 mmol, 2%) was added to the solution. After 2 h, more 2nd Hoveyda-Grubbs catalyst (17 mg, 0.03 mmol, 1%) was added. The solution was refluxed for another 2 h. The solvent was removed to afford a crude, which was purified by column chromatography (hexane-EtOAc 1:1 to 1:4) to deliver [(2*S*)-5-oxo-2,5-dihydrofuran-2-yl]methyl (4*E*)-6-oxo-4-hexenoate, **16**, (599 mg, 2.67 mmol, 89% yield) as a white solid. Mp 62-63 °C (from EtOAc-hexane); $[\alpha]_D$ -90 (*c* 1.0, $CDCl_3$); IR (ATR) 2359, 1745, 1685, 1161, 787 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.45 (d, $J_{6,5}$=7.8 Hz, 1H, H-6), 7.41 (dd, $J_{3'',4''}$=5.6 Hz, $J_{3'',2''}$=1.6 Hz, 1H, H-3´´), 6.79 (dd, $J_{4,5}$=15.8 Hz, $J_{4,3}$=5.9 Hz, 1H, H-4), 6.17 (dd, $J_{4'',3''}$=5.6 Hz, $J_{4'',2''}$=2.1 Hz, 1H, H-4´´), 6.06 (dd, $J_{5,4}$=15.8 Hz, $J_{5,6}$= 7.8 Hz, 1H, H-5), 5.22 (m, 1H, H-2´´), 4.39 (dd, J_{gem}=12.1 Hz, $J_{1',2''}$= 3.7 Hz, 1H, H-1´), 4.29 (dd, J_{gem}=12.1, $J_{1',2''}$=5.1 Hz, 1H, H-1´´), 2.59 (dt, $J_{3,2}$=6.1 Hz, $J_{3,4}$=5.9 Hz, 2H, H-3), 2.53 (t, $J_{2,3}$=6.1 Hz, 2H, H-2); ^{13}C NMR (90 MHz, $CDCl_3$) δ 193.6 (C-6), 172.0 (C-5´´), 171.4 (C-1), 155.2 (C-3´´), 152.2 (C-4), 133.3 (C-

4´´), 123.2 (C-5), 80.6 (C-2´´), 62.6 (C-1'), 31.6 (C-3), 27.2 (C-2). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{11}H_{12}NaO_5$ 247.0577; Found 247.0577.

To a mixture of **16** (252 mg, 1.1 mmol) and $CeCl_3{\cdot}7H_2O$ (420 mg, 1.1 mmol) in CH_2Cl_2 (5 mL), was added $NaBH_4$ (37 mg, 1 mmol) and MeOH (10 drops). After 3 h, another portion of $NaBH_4$ (15 mg, 0.4 mmol) and MeOH (10 drops) was added to the mixture and stirred for additional 20 min. Then, 3 mL saturated NH_4Cl was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5×6mL). The combined organic extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography (hexane-EtOAc 1:5) to afford compound **7** (200 mg, 0.88 mmol, 80% yield) as a colourless oil.

(5*S*)-5-[({[(2*E*)-4-hydroxy-2-buten-1-yl]oxy}methoxy)methyl]-2(5*H*)-furanone, 8.

Method A. To a solution of **6** (45 mg, 0.24 mmol) and allyl alcohol (44 mg, 0.76 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was added 2nd generation Grubbs catalyst (11 mg, 0.013 mmol, 5%). The reaction solution was stirred at rt for 24 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane-EtOAc 1:1 to 0:1) to afford compound **8** (18 mg, 0.08 mmol, 35% yield) and variable amounts of the dimer (5*S*,5*S*)-5,5-[(6*E*)-2,4,9,11-tetraoxododec-6-ene-1,12-diyl]di[2(5*H*)-hexanone], **14**, both as colourless oils.

8: $[\alpha]_D$ -102 (*c* 0. 7, $CDCl_3$); IR (ATR) 3416, 2872, 1750, 1460, 1167, 1091, 1029, 823, 632 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.51 (dd, $J_{4,3}$=5.7 Hz, $J_{4,5}$=1.6 Hz, 1H, H-4), 6.12 (dd, $J_{3,4}$=5.7 Hz, $J_{3,5}$=2.1 Hz, 1H, H-3), 5.93-5.63 (m, 2H, H-2''', H-3'''), 5.21-5.09 (m, 1H, H-5), 4.69-4.60 (s, 2H, H-1''), 4.15-4.03 (d, $J_{4''',3'''}$= 4.7 Hz, 2H, H-4'''), 4.07-3.96 (d, $J_{1''',2'''}$=5.6 Hz, 2H, H-1'''), 3.85-3.64 (m, 2H, H-1'), 2.57-2.54 (br, 1H, H-OH); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.9 (C-2), 153.6 (C-4), 132.6 (C-2'''), 126.4 (C-3'''), 122.6 (C-3), 94.7 (C-1''), 82.1 (C-5), 67.7 (C-1'''), 66.8 (C-1'), 62.4 (C-4'''). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{10}H_{14}NaO_5$ 237.0733; Found 237.0736.

14: ^1H NMR (250 MHz, $CDCl_3$) δ 7.50 (dd, $J_{4',3'}$=5.7 Hz, $J_{4',5'}$=1.9 Hz, 2H, H-4'), 6.16 (dd, $J_{3',4'}$=5.7 Hz, $J_{3',5'}$=2.0 Hz, H-3'), 5.79 (m, 2H, H-6, H-7), 5.17 (ddd, $J_{5',1}$=4.9 Hz, $J_{5',1}$=3.1 Hz, $J_{5',4'}$=1.9 Hz, 2H, H-5'), 4.68 (s, 4H, H-3, H-10), 4.08-4.03 (m, 4H, H-5, H-8), 3.79 (m, 4H, H-1, H-

12); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.7 (2C-2'), 153.4 (2C-4'), 128.9 (C-6, 7), 122.8 (2C-3'), 94.9 (C-3, C-10), 81.9 (2C-5'), 67.5 (C-5, C-8), 67.0 (C-1, C-12).

Method B. A solution of **6** (813 mg, 4.4 mmol) and (*E*)-but-2-enal (1.9 mL, 22 mmol) in anhydrous CH_2Cl_2 (15 mL) was heated at the reflux temperature for 20 min. 2nd Generation Hoveyda-Grubbs catalyst (64 mg, 0.1 mmol) was added in three portions. The solution was refluxed for 3 h. The solvent was removed to afford a crude product, which was purified by column chromatography (hexane-EtOAc 1:4) to furnish (2*E*)-4-({[(2*S*)-5-oxo-2,5-dihydro-2-furanyl]methoxy}methoxy-2-butenal, **17**, (851 mg, 4.0 mmol, 90% yield) as a colourless oil: $[\alpha]_D$ -91 (*c* 0.5, $CDCl_3$); IR (ATR) 1750, 1683, 1023, 819 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.53 (d, $J_{1,2}$=7.9 Hz, 1H, H-1), 7.44 (dd, $J_{3''',4'''}$=5.8 Hz, $J_{3''',2'''}$=5.8 Hz, 1H, H-3'''), 6.81 (dt, $J_{3,2}$=15.8 Hz, $J_{3,4}$=4.1 Hz, 1H, H-3), 6.28 (dd, $J_{2,3}$= 15.8, $J_{2,1}$=7.9 Hz, 1H, H-2), 6.14 (dd, $J_{4''',3'''}$=5.8 Hz, $J_{4,2'''}$=2.0 Hz, 1H, H-4'''), 5.21-5.11 (m, 1H, H-2'''), 4.70 (s, 2H, H-1'), 4.30 (dd, J_{gem}=4.2 Hz, $J_{1''',2'''}$= 2.0 Hz, 2H, H-1''), 3.84 (dd, J_{gem}=11.1 Hz, $J_{4,3}$=4.1 Hz, 1H, H-4), 3.73 (dd, J_{gem}=11.1 Hz, $J_{4,3}$=5.2 Hz, 1H, H-4); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 193.0 (C-1), 172.4 (C-5'''), 153.1 (C-3'''), 152.1 (C-3), 131.5 (C-2), 122.8 (C-4'''), 95.2 (C-1'), 81.8 (C-2'''), 67.1 (C-4), 66.1 (C-1''). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{10}H_{12}NaO_5$ 235.0577; Found 235.0585.

To a mixture of **17** (207 mg, 0.92 mmol), TBAB (10 mg, 0.03 mmol) and $CeCl_3{\cdot}7H_2O$ (346 mg, 0.92 mmol) in CH_2Cl_2 (5 mL), $NaBH_4$ (25 mg, 0.65 mmol) and MeOH (5 drops) were added. After 1 h of stirring at rt, another portion of $NaBH_4$ (25 mg, 0.4 mmol) and MeOH (5 drops) were added to the mixture. After an additional hour, CH_2Cl_2 (5 mL) and H_2O (5 mL) were added to the mixture and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5×5mL), and then the combined organic extracts were dried over $MgSO_4$ and concentrated affording a crude, which was purified by column chromatography (hexane-EtOAc 1:5) to give compound **8** (147 mg, 0.69 mmol, 75% yield) as a colourless oil.

General Procedure for the Photochemical Reactions. Irradiations were performed in a small conventional photochemical reactor (two-necked vessel fitted with a Pyrex or quartz immersion type cooling jacket) using a high-pressure 125W mercury lamp. Methanol at -15 °C was used for

refrigeration of the immersion well jacket. The vessel was externally cooled at -20 °C with a dry ice-CCl_4 bath or at -40 °C with a dry ice-acetonitrile bath or a -78°C with liquid nitrogen bath. The photochemical reactions were initially degassed by passage of oxygen-free argon through the solution for 10 min and then irradiated under atmosphere of argon. The progress of the reactions was monitored by GC analysis of aliquot samples.

(3*S*,3a*R*,4*S*,9a*S*)- and (3*S*,3a*R*,4*R*,9a*S*)-hexahydro-2*H*-3,4-methanofuro[2,3-*c*]oxocine-2,1(3*H*)-dione (18) and (19) and (1*R*,3*S*,9*S*,12*S*)-dioxatricyclo[7.3.0.0^{3,12}]dodecane-6,11-dione (20). A solution of lactone **5** (80 mg, 0.41 mmol) in acetone (65 mL) was irradiated at -78 °C under an atmosphere of N_2 through a quartz filter for 30 min. Evaporation of the solvent and purification of the residue by column chromatography (hexane-EtOAc 1:1) afforded a 7:86:7 mixture of **18-20** (63 mg, 0.32 mmol, 78% global yield). Repeated column chromatography (hexane-EtOAc from 2:1 to 1:1) provided the following fractions: i) an enriched sample of the *HT* isomer **18** (6 mg), ii) the *HT* isomer **19** as a white solid (49 mg, 0.25 mmol, 61% yield), and the *HH* isomer **20** (5 mg, 0.03 mmol, 6% yield) as a white solid.

When the irradiation was performed through a quartz filter in acetonitrile at -40 °C for 90 min, from lactone **5** (80 mg, 0.41 mmol), after chromatographic purification of the crude material, a 8:84:8 mixture of **18-20** (52 mg, 0.26 mmol, 64% global yield) was obtained.

When the irradiation was performed through a quartz filter in acetonitrile at -20 °C for 2 h, from lactone **5** (80 mg, 0.41 mmol), after chromatographic purification of the crude material, a 11:78:11 mixture of **18-20** (46 mg, 0.23 mmol, 58% global yield) was obtained.

When the irradiation was performed through a quartz filter in acetonitrile at rt for 2 h, from lactone **5** (80 mg, 0.41 mmol), after chromatographic purification of the crude material, a 15:67:18 mixture of **18-20** (41 mg, 0.20 mmol, 52% global yield) was obtained.

19: Mp 87-88 °C (from EtOAc-hexane); $[\alpha]_D$ 17 (*c* 1.0, $CDCl_3$); IR (ATR) 1749, 778, 631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (dd, J_{gem}=13.3 Hz, $J_{9,9a}$=2.4 Hz, 1H, H-9), 4.46 (dt, $J_{9a,3a}$=4.8 Hz, $J_{9a,9}$=2.4 Hz, $J_{9a,9}$=2.4 Hz, 1H, H-9a), 4.32 (dd, J_{gem}=13.2 Hz, $J_{9,9a}$=2.4 Hz, 1H, H-9), 3.18 (td, $J_{3a,3}$=7.6 Hz, $J_{3a,4}$=7.6 Hz, $J_{3a,9a}$=4.8 Hz, 1H, H-3a), 3.12 (dddd, $J_{3,10}$=9.0 Hz, $J_{3,3a}$=7.6 Hz, $J_{3,4}$=2.4

Hz, $J_{3,10}$=2.4 Hz, 1H, H-3), 2.78-2.71 (m, 1H, H-10), 2.70-2.66 (m, 1H, H-6), 2.66-2.58 (m, 1H, H-4), 2.45 (tdd, J_{gem}=13.5 Hz, $J_{5,6}$=13.5 Hz, $J_{5,6}$=11.5 Hz, $J_{5,4}$=5.4 Hz, 1H, H-5), 2.16 (ddd, J_{gem}=13.0 Hz, $J_{6,5}$=11.5 Hz, $J_{6,5}$=5.7 Hz, 1H, H-6), 1.82 (dddd, J_{gem}=13.5 Hz, $J_{5,6}$=5.7 Hz, $J_{5,6}$=2.4 Hz, $J_{5,4}$=2.4 Hz, 1H, H-5), 1.78-1.73 (m, 1H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7 (C-2), 176.9 (C-7), 82.1 (C-9a), 62.5 (C-9), 40.0 (C-3a), 38.6 (C-3), 36.3 (C-4), 34.0 (C-6), 31.9 (C-5), 28.7 (C-10). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{10}H_{12}NaO_4$ 219.0628; Found 219.0626.

20: Mp 166-167 °C (from EtOAc-hexane); $[\alpha]_D$ 87 (*c* 1.1, $CDCl_3$); IR (ATR) 2923, 1725, 1172, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86 (dd, $J_{9,1}$=9.4 Hz, $J_{9,8}$=2.2 Hz, 1H, H-9), 4.69 (d, J_{gem}=12.1 Hz, 1H, H-8), 4.32 (dd, J_{gem}=12.1 Hz, $J_{8,9}$=2.2 Hz, 1H, H-8), 3.47 (br t, $J_{12,1}$=10.1 Hz, $J_{12,3}$=10.1 Hz, 1H, H-12), 3.29-3.20 (m, 1H, H-3), 3.15 (dq, $J_{1,9}$=10.1 Hz, $J_{1,12}$=10.1 Hz, $J_{1,2}$=10.1 Hz, $J_{1,2}$=1.0 Hz 1H, H-1), 2.73 (ddd, J_{gem}=17.9 Hz, $J_{5,4}$=4.6 Hz, $J_{5,4}$=2.8 Hz, 1H, H-5), 2.53-2.41 (m, 1H, H-2), 2.38-2.27 (m, 1H, H-5), 2.25-2.14 (m, 1H, H-4), 1.86-1.76 (m, 1H, H-4), 1.68 (br d, J_{gem}=14.0 Hz, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0 (C-11), 174.9 (C-6), 79.7 (C-9), 65.9 (C-8), 43.0 (C-12), 33.6 (C-1), 32.7 (C-5), 31.4 (C-3), 22.0 (C-2), 21.8 (C-4). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{10}H_{12}NaO_4$ 219.0628; Found 219.0631.

18: (90% purity) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (dd, J_{gem}=13.5 Hz, $J_{9,9a}$=4.5 Hz, 1H, H-9), 4.48 (br t, $J_{9a,3a}$=4.5 Hz, $J_{9a,9}$=4.5 Hz, 1H, H-9a), 4.25 (d, J_{gem}=13.5 Hz, 1H, H-9), 3.21-3.00 (m, 1H, H-4), 2.98 (dt, $J_{3,10}$=7.7 Hz, $J_{3,3a}$=6.4 Hz, $J_{3,10}$=1.1 Hz, J=1.1 Hz, 1H, H-3), 2.63 (br dd, $J_{3a,3}$=6.4 Hz, $J_{3,9a}$=4.5 Hz, 1H, H-3a), 2.37-2.28 (m, 2H, H-6), 2.23-2.12 (m, 1H, H-10), 2.10-1.75 (m, 3H, H-10, 2H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1 (C-2), 176.7 (C-7), 80.9 (C-9a), 63.0 (C-9), 46.0 (C-3a), 38.7 (C-3), 36.3 (C-4), 32.8 (C-6), 32.3 (C-5), 29.1 (C-10).

(3*S*,3a*R*,4*R*,9a*S*)-hexahydro-2*H*-3,4-methanofuro[2,3-*e*][1,3]dioxocin-2-one (21), (1*R*,3*S*,9*S*,12*S*)-5,7,10-trioxatricyclo[7.3.0.0^{3,12}]dodecan-11-one (22) and (1*R*,*2RS,7S*)-2-vinyl-trioxabicyclo[5.2.1]decan-9-one (23).

A solution of lactone **6** (77 mg, 0.42 mmol) in acetone (65 mL) was irradiated at -78 °C under an atmosphere of N_2 through a quartz filter for 25 min. Evaporation of the solvent and purification of the residue by column chromatography ($CHCl_3$-EtOAc 2:1) afforded a 9:87:4 mixture of **21-23** (63

mg, 0.34 mmol, 82% global yield). Repeated column chromatography ($CHCl_3$-EtOAc 3:1) provided the following fractions: i) an enriched sample of the *HT* isomer **21** (7 mg), ii) the *HH* isomer **22** as a white solid (52 mg, 0.28 mmol, 67% yield), and the vinylic compound **23** (3 mg, 0.02 mmol, 3% yield) as colorless oil.

When the irradiation was performed through a quartz filter in acetone at -40 °C for 40 min, from lactone **6** (77 mg, 0.42 mmol), after chromatographic purification of the crude material, a 12:82:6 mixture of **21-23** (56 mg, 0.30 mmol, 73% global yield) was obtained.

When the irradiation was performed through a quartz filter in CH_2Cl_2 at -40 °C for 40 min, from lactone **6** (77 mg, 0.42 mmol), after chromatographic purification of the crude material, a 18:77:5 mixture of **21-23** (50 mg, 0.27 mmol, 65% global yield) was obtained.

When the irradiation was performed through a quartz filter in acetonitrile at -40 °C for 40 min, from lactone **6** (77 mg, 0.42 mmol), after chromatographic purification of the crude material, a 14:81:5 mixture of **21-23** (54 mg, 0.29 mmol, 70% global yield) was obtained.

When the irradiation was performed through a quatz filter in acetonitrile at rt for 2 h, from lactone **6** (77 mg, 0.42 mmol), after chromatographic purification of the crude material, a 18:73:9 mixture of **21-23** (45 mg, 0.24 mmol, 58% global yield) was obtained.

22: Mp 108-110 °C (from EtOAc-hexane); $[\alpha]_D$ 29 (*c* 0.9, $CDCl_3$); IR (ATR) 1754, 1187, 1041, 776, 631 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.72 (s, 2H, H-6), 4.62 (ddd, $J_{9,1}$=10.3 Hz, $J_{9,8}$=3.0 Hz, $J_{9,8}$=0.7 Hz, 1H, H-9), 4.30 (dd, J_{gem}=12.9 Hz, $J_{4,3}$=4.4 Hz, 1H, H-4), 4.29 (dd, J_{gem}=14.7 Hz, $J_{8,9}$=3.0 Hz, 1H, H-8), 4.03 (dd, J_{gem}=14.7 Hz, $J_{8,9}$=0.7 Hz, 1H, H-8), 3.51 (d, J_{gem}=12.9 Hz, 1H, H-4), 3.34 (t, $J_{12,1}$=8.8 Hz, $J_{12,3}$=8.8 Hz, 1H, H-12), 3.13 (ddddd, $J_{1,9}$=10.3 Hz, $J_{1,2}$=10.3 Hz, $J_{1,12}$=8.8 Hz, $J_{1,2}$=2.1 Hz, $J_{1,3}$=2.1 Hz, 1H, H-1), 2.97-2.93 (m, 1H, H-2), 2.92-2.89 (m, 1H, H-3), 2.46 (ddd, J_{gem}=12.9 Hz, $J_{2,1}$=10.3 Hz, $J_{2,3}$=9,4 Hz, 1H, H-2); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 179.5 (C-11), 95.9 (C-6), 80.7 (C-9), 73.0 (C-8), 71.3 (C-4), 39.8 (C-12), 37.9 (C-3), 34.0 (C-1), 25.1 (C-2). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_9H_{12}NaO_4$ 207.0628; Found 207.0628.

23: $[\alpha]_D$ 1.8 (*c* 1.0, $CDCl_3$); IR (ATR) 1763, 1173, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddd, $J_{1',2'}$=17.2 Hz, $J_{1',2'}$=10.4 Hz, $J_{1',2}$=5.1 Hz, 1H, H-1'), 5.35 (dt, $J_{2',1'}$=17.2 Hz, J_{gem}=1.5 Hz,

$J_{2',2}$=1.5 Hz, 1H, H-2'), 5.17 (dt, $J_{2',1'}$=10.4 Hz, J_{gem}=1.5 Hz, $J_{2',2}$=1.5 Hz, 1H, H-2'), 4.78 (d, J_{gem}=6.3 Hz, 1H, H-4), 4.71 (d, J_{gem}=6.3 Hz, 1H, H-4), 4.64 (m, 1H, H-7), 4.23 (dq, $J_{2,1'}$=5.0 Hz, $J_{2,2'}$=1.5 Hz, $J_{2,2'}$=1.5 Hz, $J_{2,1}$=1.5 Hz, 1H, H-2), 4.14 (dd, J_{gem}=12.5 Hz, $J_{6,7}$=3.9 Hz, 1H, H-6), 3.43 (d, J_{gem}=12.5 Hz, 1H, H-6), 2.71-2.64 (m, 1H, H-1), 2.39-2.33 (m, 2H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7 (C-9), 138.0 (C-1'), 115.3 (C-2'), 94.5 (C-4), 77.2 (C-7), 76.3 (C-2), 70.7 (C-6), 45.4 (C-1), 26.9 (C-10).

21: (70% purity) ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (d, J_{gem}=5.7 Hz, 1H, H-7), 4.64 (d, J_{gem}=5.7 Hz, 1H, H-7), 4.50 (ddd, $J_{4,3a}$=6.5 Hz, $J_{4,5}$=5.0 Hz, $J_{4,5}$=2.1 Hz, 1H, H-4), 4.24 (dd, J_{gem}=13.4 Hz, $J_{5,4}$=5.0 Hz, 1H, H-5), 3.82 (d, J_{gem}=11.6 Hz, 1H, H-9), 3.70 (dd, J_{gem}=13.4 Hz, $J_{5,4}$=2.1 Hz, 1H, H-5), 3.67 (dd, J_{gem}=11.6 Hz, $J_{9,9a}$=5.5 Hz 1H, H-9), 3.42-3.06 (m, 2H, H-3, H-3a), 3.02-2.81 (m, 1H, H-9a), 2.71-2.54 (m, 1H, H-10), 1.90 (ddd, J_{gem}=12.5 Hz, *J*=5.9 Hz, *J*=3.1 Hz, 1H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4 (C-2), 93.9 (C-7), 80.5 (C-4), 66.0/65.8 (C-5/C-9), 39.3 (C-3a), 37.6 (C-3), 34.8 (C-9a), 26.0 (C-10).

(3*S*,3a*R*,4*R*,9a*S*,10*R*)-10-(hydroxymethyl)hexahydro-2*H*-3,4-methanofuro[2,3-*c*]oxocine-2,7(3*H*)-dione (24), (1*R*,2*S*,3*S*,9*S*,12*S*)-2-(hydroxymethyl)-7,10-dioxatricyclo[7.3.0.0^{3,12}]dodecane-6,11-dione (25) and (1*S*,6*RS*,7*R*)-6-[(*E*)-3-hydroxy-1-propen-1-yl]-3,9-dioxabicyclo[5.2.1]decane-4,8-dione (26).

A solution of lactone **7** (104 mg, 0.46 mmol) in acetone (65 mL) at -78 °C was irradiated under an atmosphere of N_2 through a quartz filter for 30 min. Evaporation of the solvent and purification of the residue by column chromatography (hexane-EtOAc 1:5) afforded a 49:27:24 mixture of **24-26** (66 mg, 0.29 mmol, 64% global yield). Repeated column chromatography (hexane-EtOAc from 1:5 to 1:10) provided the following fractions: i) a mixture of **24** and **26** and, ii) and an analytical sample of **25** as colorless oil.

When the irradiation was performed through a quartz filter in acetonitrile at -40 °C for 1 h, from lactone **7** (104 mg, 0.46 mmol), after chromatographic purification of the crude material, a 46:24:30 mixture of **24-26** (60 mg, 0.26 mmol, 58% global yield) was obtained.

When the irradiation was performed through a quartz filter in acetonitrile at -20 °C for 75 min, from lactone **7** (104 mg, 0.46 mmol), after chromatographic purification of the crude material, a 40:29:31 mixture of **24-26** (54 mg, 0.23 mmol, 52% global yield) was obtained.

When the irradiation was performed through a quartz filter in acetonitrile at rt for 75 min, from lactone **7** (104 mg, 0.46 mmol), after chromatographic purification of the crude material, a 37:29:34 mixture of **24-26** (46 mg, 0.20 mmol, 44% global yield) was obtained.

24: $[\alpha]_D$ -2.0 (*c* 1.0, $CDCl_3$); IR (ATR) 2923, 1742, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (dd, J_{gem}=13.3 Hz, $J_{9,9a}$=2.6 Hz, 1H, H-9), 4.50 (dt, $J_{9a,3a}$=5.1 Hz, $J_{9a,9}$ =2.6 Hz, $J_{9a,9}$ =2.6 Hz, 1H, H-9a), 4.34 (dd, J_{gem}=13.3 Hz, $J_{9,9a}$=2.6 Hz, 1H, H-9), 3.79 (dd, J_{gem}=10.8 Hz, $J_{1',10}$ =5.8 Hz, 1H, H-1'), 3.72 (dd, J_{gem}=10.8 Hz, $J_{1',10}$= 6.3 Hz, 1H, H-1'), 3.15 (dddd, $J_{3a,3}$ =7.5 Hz, $J_{3a,4}$ =7.5 Hz, $J_{3a,9a}$=5.1 Hz, *J*=1.0 Hz, 1H, H-3a), 3.04 (dt, $J_{3,3a}$=7.5 Hz, $J_{3,4}$ =2.3 Hz, $J_{3,10}$=2.3 Hz, 1H, H-3), 2.70 (ddd, J_{gem}=12.2 Hz, $J_{6,5}$=5.7 Hz, $J_{6,5}$=2.1 Hz, 1H, H-6), 2.46-2.42 (m, 1H, H-5), 2.40-2.38 (m, 1H, H-4), 2.23-2.18 (m, 1H, H-6), 2.17-2.15 (m, 1H, H-10), 1.84-1.78 (m, 1H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.3 (C-2), 176.8 (C-7), 82.3 (C-9a), 64.2 (C-1'), 62.6 (C-9), 44.7 (C-10), 41.0 (C-3), 38.6 (C-3a), 38.3 (C-4), 33.9 (C-6), 31.5 (C-5).

25: $[\alpha]_D$ 101 (*c* 0.7, $CDCl_3$); IR (ATR) 2925, 1739, 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.92 (dd, $J_{9,1}$=9.5 Hz, $J_{9,8}$=2.0 Hz, 1H, H-9), 4.68 (d, J_{gem}=12.1 Hz, 1H, H-8), 4.33 (dd, J_{gem}=12.1 Hz, $J_{8,9}$=2.0 Hz, 1H, H-8), 3.72 (dd, J_{gem}=10.6 Hz, $J_{1',2}$=6.2 Hz, 1H, H-1'), 3.63 (dd, J_{gem}=10.6 Hz, $J_{1',2}$=7.0 Hz,1H, H-1'), 3.41 (t, $J_{12,3}$=10.2 Hz, $J_{12,1}$=10.2 Hz, 1H, H-12), 2.92 (br t, $J_{1,12}$=10.2 Hz, $J_{1,9}$=9.5 Hz, 1H, H-1), 2.83-2.77 (m, 1H, H-3), 2.75 (ddd, J_{gem}=18.0 Hz, $J_{5,4}$=4.3 Hz, $J_{5,4}$=2.9 Hz, 1H, H-5), 2.35 (ddd, J_{gem}=18.0 Hz, $J_{5,4}$=13.1 Hz, $J_{5,4}$=4.4 Hz, 1H, H-5), 2.22 (tt, J_{gem}=14.1 Hz, $J_{4,5}$=13.1 Hz, $J_{4,5}$=4.3 Hz, $J_{4,3}$=4.3Hz, 1H, H-4), 2.08-2.03 (m, 1H, H-2), 1.94-1.87 (m, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9 (C-11), 174.9 (C-6), 79.6 (C-9), 66.5 (C-1'), 66.1 (C-8), 41.1 (C-12), 37.3 (C-1), 37.0 (C-2), 34.9 (C-3), 32.8 (C-5), 21.8 (C-4).

26: (from the mixture **24** and **26**) ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (m, 2H, H-1',H-2'), 4.74 (dddd, $J_{1,10}$=7.7 Hz, $J_{1,10}$=6.7 Hz, $J_{1,2}$=5.4 Hz, $J_{1,2}$=3.1 Hz ,1H, H-1), 4.35 (dd, J_{gem}=12.3 Hz, $J_{2,1}$=3.1 Hz, 1H, H-2), 4.12 (dd, J_{gem}=12.3 Hz, $J_{2,1}$=5.4 Hz, 1H, H-2), 4.09-4.06 (m, 2H, H-3'), 2.61-252 (m,

1H, H-7), 2.47-2.29 (m,4H, 2H-5, H-6, H-10), 2.10-1.99 (m, 1H, H-10); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (C-10), 172.5 (C-4), 130.7/129.7 (2C, C-1'/C-2'), 77.3 (C-1), 65.2 (C-2), 63.3 (C-3'), 33.5 (C-5), 28.2 (C-7), 27.3 (C-6), 23.8 (C-8).

[(1*S*,7*S*,8*R*,9*S*)-7-hydroxy-3,5-dioxabicyclo[6.1.1]dec-9-yl-]methyl-2,2-dimethylpropenoate (28). A 2.0 M solution of $LiBH_4$ in THF (1.75 mL, 3.5 mmol) was added dropwise to a solution of **22** (210 mg, 1.14 mmol) in dry THF (16 mL) and the mixture was heated at the reflux temperature for 3.5 h. Then the reaction was allowed to cool to rt and the solvent was removed under reduced pressure. The resulting crude was taken up with CH_2Cl_2 (20 mL) and a saturated aqueous solution of NH_4Cl (5 mL) was added dropwise. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2x10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated to dryness affording the diol **27** (185 mg, 1.0 mmol), which was used in the next step without purification.

To a solution of alcohol **27** (185 mg, 1.0 mmol) in pyridine (6 mL) was added PivCl (0.140 mL, 1.14 mmol) and the resulting clear solution was stirred overnight at rt. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (hexane-EtOAc 3:1) to afford compound **28** (202 mg, 0.74 mmol, 65% yield) as a white solid: Mp 32-33 °C (from EtOAc-hexane); $[\alpha]_D$ 31 (*c* 0.6, $CDCl_3$); IR (ATR) 3465, 2927, 1717, 1471, 1284, 1163, 1016 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 323 K) δ 4.86 (br dd, J_{gem}=11.5 Hz, $J_{1',9}$=7.4 Hz, 1H, H-1'), 4.80-4.72 (br m, 2H, H-4), 4.59 (dd, J_{gem}=11.5 Hz, $J_{1',9}$=6.6 Hz, 1H, H-1'), 4.10-3.71 (m, 5H, 2H-6, 2H-2, H-7), 3.15-3.08 (m, 1H, H-9), 3.04-2.92 (m, 1H), 2.69-2.47 (m, 2H), 2.35-2.17 (m, 1H) 1.18 (s, 9H, ((C*H*$_3$)$_3$C); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.7 (C=O), 96.4 (C-4), 74.1 (C-7), 68.3/67.3 (C-6, C-2), 63.5 (C-1'), 39.1 (C-9), 38.7((CH$_3$)$_3$*C*), 39.1/36.0 (C-1, C-8), 27.2 ((*C*H$_3$)$_3$C), 19.5 (C-10). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{24}NaO_5$ 295.1516; Found 295.1522.

[(1*S*,2*R*,4*S*)-2-[(4*S*)-1,3-dioxolan-4-yl]-4-(hydroxymethyl)cyclobutyl]methyl pivalate (29). A solution of **28** (55 mg, 0.2 mmol) and Amberlyst-15 (220 mg) in CH_2Cl_2 (4 mL) was heated to the reflux temperature for 5 h. Then, the reaction was cooled to rt and stirred overnight. Amberlyst-15 was removed by filtration, and the solvent was removed under reduced pressure. The resulting

reaction crude was purified by column chromatography (hexane-EtOAc 2:1) to furnish compound **29** (40 mg, 0.15 mmol, 73% yield) as a colourless oil: $[\alpha]_D$ -20 (*c* 0.6, $CDCl_3$); IR (ATR) 3433, 2931, 1721, 1472, 1160, 1038 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.01 (s, 1H, H-2''), 4.85 (s, 1H, H-2''), 4.39 (d, $J_{1',1}$=7.8 Hz, 2H, H-1'), 4.09 (ddd, $J_{4'',5''}$=6.9 Hz, $J_{4'',5''}$=6.9 Hz, $J_{4'',2}$=5.4 Hz, 1H, H-4''), 3.91 (dd, J_{gem}=7.8 Hz, $J_{5'', 4''}$=6.9 Hz, 1H, H-5''), 3.72 (dd, J_{gem}=11.2 Hz, $J_{1''',4}$=8.2 Hz, 1H, H-1'''), 3.59 (dd, J_{gem}=11.2 Hz, $J_{1''',4}$=6.1 Hz, 1H, H-1'''), 3.35 (dd, J_{gem}=7.8 Hz, $J_{5'',4''}$=6.9 Hz, 1H, H-5''), 2.90-2.75 (m, 1H, H-1), 2.69-2.59 (m, 1H, H-4), 2.59-2.47 (m, 1H, H-2), 2.15-2.03 (m, 1H, H-3), 1.95-1.83 (m, 1H, H-3), 1.19 (s, 9H, (CH_3)$_3$C)); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.3 (C-2'), 95.4 (C-2''), 75.4 (C-4''), 68.2 (C-5''), 63.0 (C-1'''), 62.3 (C-1'), 38.7 (CH_3)$_3$*C*), 37.5 (C-1), 35.5 (C-4), 35.3 (C-2), 27.2 (*C*H_3)$_3$C), 23.4 (C-3). HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ Calcd for $C_{14}H_{24}NaO_5$ 295.1516; Found 295.1524.

{(1*S*,2*S*,4*R*)-2-({[*tert*-butyl(diphenyl)silyl]oxy}methyl)-4-[(4*S*)-1,3-dioxolan-4-yl]cyclobutyl}methyl pivalate (30). *tert*-Butyldiphenylsilyl chloride (0.018 mL, 0.07 mmol) was added to a solution of alcohol **29** (16 mg, 0.06 mmol) and imidazole (5.5 mg, 0.08 mmol) in anhydrous CH_2Cl_2 (0.8 mL) at rt under N_2. The reaction mixture was stirred at rt for 36 h and the solvent was removed under reduced pressure. Purification by preparative TLC (hexane-EtOAc 20:1) provided the desired compound **30** (24 mg, 0.05 mmol, 77% yield) as a colourless oil: $[\alpha]_D$ 8.7 (*c* 0.5, $CDCl_3$); IR (ATR) 2933, 2861, 1727, 1471, 1155, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70-7.59 (m, 4H, Ph-H), 7.46-7.32 (m, 6H, Ph-H), 4.97 (s, 1H, H-2'''), 4.83 (s, 1H, H-2'''), 4.39 (d, $J_{1',1}$=7.6 Hz, 2H, H-1'), 4.11 (ddd, $J_{4''',5'''}$=6.7 Hz, $J_{4''',5'''}$=6.7 Hz, $J_{4''',4}$=6.7 Hz, 1H, H-4'''), 3.91 (dd, J_{gem}=7.6 Hz, $J_{5''',4'''}$=6.7 Hz, 1H, H-5'''), 3.73 (dd, J_{gem}=10.5 Hz, $J_{1'',2}$=6.7 Hz, 1H, H-1''), 3.64 (dd, J_{gem}=10.5 Hz, $J_{1'',2}$=6.7 Hz, 1H, H-1''), 3.37 (dd, J_{gem}=7.6 Hz, $J_{5''',4'''}$=6.7 Hz, 1H, H-5'''), 2.78 (br dquint, $J_{1,1'}$=7.6 Hz, $J_{1,2}$=7.6 Hz, $J_{1,4}$=7.6 Hz, $J_{1,3}$=2.3 Hz, 1H, H-1), 2.83-2.70 (m, 1H, H-1), 2.70-2.57 (m, 1H, H-2), 2.54-2.39 (m, 1H, H-4), 2.16-2.04 (m, 1H, H-3), 2.05-1.91 (m, 1H, H-3), 1.13 (s, 9H, (CH_3)$_3$C)), 1.05 (s, 9H, (CH_3)$_3$C)); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.3 (C-2'), 135.6 (C-Ph), 133.8 (C$_{tert}$-Ph), 129.6 (C-Ph), 127.6 (C-Ph), 95.3 (C-2'''), 75.8 (C-4'''), 68.4 (C-5'''), 64.1 (C-1''), 62.6 (C-1'), 38.6 (CH_3)$_3$*C*), 37.6 (C-1), 35.8 (C-4), 35.4 (C-2), 27.2 (*C*H_3)$_3$C), 26.9

(CH$_3$)$_3$C), 24.4 (C-3), 19.2 (CH$_3$)$_3C$Si). HRMS (ESI-TOF) *m/z*: [M- C$_4$H$_9$]$^+$ Calcd for C$_{30}$H$_{42}$O$_5$Si 453.2098; Found 453.2098.

(1*S*,5*S*,7*S*)-7-[(4*R*)-1,3-dioxolan-4-yl]-7-oxa-bicyclo[3.2.0]heptan-2-one (31). A solution of **22** (31 mg, 0.17 mmol) and TsOH·H$_2$O (13 mg, 0.07 mmol) in anhydrous CH$_2$Cl$_2$ (1 mL) was stirred at rt for 24h. Then, the solvent was removed under reduced pressure affording a crude which was purified by column chromatography (hexane-EtOAc 1:5) to furnish compound **31** (25 mg, 0.14 mmol, 82% yield) as a white solid: Mp 108-110 °C (from EtOAc-hexane); [α]$_D$ 29 (*c* 0.9, CDCl$_3$); IR (ATR) 1754, 1187, 1041, 776 cm^{-1}; ^{1}H NMR (250 MHz, CDCl$_3$) δ 5.00 (s, 1H, H-2'), 4.83 (s, 1H, H-2'), 4.36 (dd, J_{gem}=9.5 Hz, $J_{4,5}$=6.1 Hz, 1H, H-4), 4.25 (dd, J_{gem}=9.5 Hz, $J_{4,5}$=1.4 Hz, 1H, H-4), 4.16 – 3.96 (m, 2H, H-4', H-5'), 3.49 (dd, J_{gem}=8.0 Hz, $J_{5',4'}$=5.3 Hz, 1H, H-5'), 3.20 – 3.11 (m, 1H, H-5), 3.11 – 3.01 (m, 1H, H-1), 2.86 – 2.69 (m, 1H, H-7), 2.64 – 2.50 (m, 1H, H-6), 2.13 – 2.03 (m, 1H, H-6); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ 177.9 (C-2), 95.3 (C-2'), 76.5 (C-4'), 74.3 (C-4), 68.2 (C-5'), 40.0 (C-1), 36.5 (C-7), 31.1 (C-5), 28.9 (C-6). HRMS (ESI-TOF) *m/z*: [M+Na]$^+$ Calcd for C$_9$H$_{12}$NaO$_4$ 207.0628; Found 207.0628.

{(1*S*,2*S*,3*R*)-3-[(4*S*)-1,3-dioxolan-4-yl]cyclobutane-1,2-diyl}dimethanol (32). To an ice-cooled solution of lactone **31** (19 mg, 0.1 mmol) in anhydrous THF (3 mL), LiAlH$_4$ (0.44 mL, 0.44 mmol, 1.0 M in THF) was added dropwise. After stirring for 2 h, a mixture of CH$_2$Cl$_2$ and H$_2$O (trace) was added until no bubbles appeared and the resulting mixture was dried over MgSO$_4$ and concentrated. The crude product was purified by column chromatography (EtOAc) to afford compound **32** (14 mg, 0.07 mmol, 70% yield) as a colourless oil: [α]$_D$ 10.2 (*c* 0.3, CDCl$_3$); IR (ATR) 3366, 2930, 1445, 1082, 1021, 935 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 4.99 (d, 1H, *J*=1.3 Hz, H-2'''), 4.87 (s, 1H, H-2'''), 4.11 (d, $J_{1'',2}$=1.3 Hz, 1H, H-1''), 4.06-4.00 (m, 1H, H-4'''), 3.91 (dd, J_{gem}=8.0 Hz, $J_{5''',4'''}$ =1.5 Hz, 1H, H-5'''), 3.75-3.71 (m, 1H, H-1'), 3.70-3.66 (m, 1H, H-1''), 3.65-3.60 (m, 1H, H-1'), 3.49 (br s, 1H, H-*OH*), 3.34 (dd, J_{gem}=8.0 Hz, $J_{5''',4'''}$ =1.5 Hz, 1H, H-5'''), 2.80-2.72 (m, 1H, H-2), 2.69-2.65 (m, 1H, H-1), 2.58-2.47 (m, 1H, H-3), 2.05-1.95 (m, 1H, H-4), 1.91-1.80 (m, 1H, H-4); ^{13}C NMR (62.5 MHz, CDCl$_3$) δ 95.3 (C-2'''), 75.5 (C-4'''), 68.1 (C-5'''), 62.4 (C-1'), 59.7 (C-1''),

41.1 (C-2), 35.6 (C-1), 35.3 (C-3), 23.0 (C-4). HRMS (ESI-TOF) *m/z*: $[M\text{-}OH]^+$ Calcd for $C_9H_{16}O_4$ 171.1021; Found 171.1021.

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Supporting Information Available: Computational details, ^1H and ^{13}C NMR spectra of all new compounds and 2D NMR spectra for compounds **18**, **19**, **20**, **21**, **22**, **23**, **24, 25**, **29**, **30**, **31** and **32** and X-ray crystal structure and crystallographic table for compounds **19** and **22.** This material is available free of charge via the Internet at http://pubs.acs.org.

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