Intramolecular Photoreactions of (5*S*)-5-Oxymethyl-2(5*H*)-furanones as a Tool for the Stereoselective Generation of Diverse Polycyclic Scaffolds

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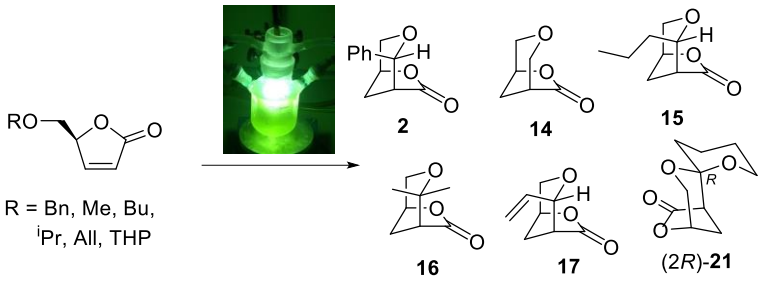


Abstract

The photoactivated evolution of a series of enantiomerically pure 5-oxymethyl-2(5*H*)-furanones has been investigated. The observed intramolecular photoreactions have proven to be a straightforward entry to diverse and stereochemically rich fragment-molecules, most of which contain the privileged tetrahydropyran (THP) scaffold. The formation of the THP involves a 1,5-hydrogen atom transfer process, leading to a diradical intermediate that recombines to form a new σ C-C bond. These reactions take place under both sensitized and non sensitized conditions and they are highly stereoselective. When

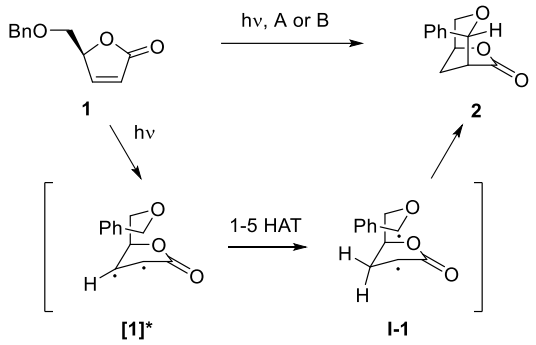
the substrate contains an allyl residue, the intramolecular [2+2] cycloaddition leading to cyclobutanes competes advantageously. When the substrate contains a THP residue, the cyclization involves the concomitant formation of [6,6]-spiroketals with non anomeric relationships.

Introduction

One of the purposes of medicinal chemistry is the discovery of new molecules for influencing biological functions. Accordingly, a main objective of drug discovery programs is to prepare diverse sets of molecules, which submitted to bioactivity tests and absorption, distribution, metabolism, excretion (ADME) screens may lead to the recognition of drug candidates among the investigated structures. In the last years, the fragment-based drug discovery (FBDD) approach[1] has emerged as a plausible alternative to other consolidated methods of hit identification, such as high throughput screening (HTS). Fragment molecules are small (typically less than 250 Da) and their binding affinity to the active site of the biological target uses to be low, but sufficient to be detected by highly sensitive techniques, as Nuclear Magnetic Resonance and X-ray crystallography. Moreover, despite their weak affinity binding, these fragment molecules may be superior to other more intricate structures in terms of ligand efficiency. Also relevant to the binding event is the lipophilic character of the ligand. Lipophilic molecules are more prone to desolvate than polar ones and hence more amenable for binding to any protein pocket, but, at the same time, water solubility is essential to conduct the bioactivity screening. A convenient compromise may result by combining in the candidate molecules a significant apolar structural fraction and one or more functional groups amenable of chemical transformation to modulate the overall polarity. Undoubtedly, the synthesis of collections of original small molecules could be an entry to important biochemical discoveries that may be essential for the treatment of many diseases. When faced to the problem of creating new druglike small molecule collections oriented to a particular target, a plausible approach makes use of the privileged scaffold concept. Privileged scaffolds are structural motifs frequently present in both natural products and pharmaceutical drugs.[2] Among them, planar aromatic heterocycles are the most frequent components of the commercially available fragment

libraries used in FBDD programs. However, it is highly probable that many privileged scaffolds are still waiting to be discovered. In this context, it would be desirable to explore fragments with higher shape diversity in order to cover a more extensive range of biological interactions.[3] The use of diversity-oriented synthesis and, in particular, the build/couple/pair strategy[4] has become a convenient approach to address this challenge. This strategy requires short reaction sequences leading to molecules with a high degree of structural and stereochemical complexity.

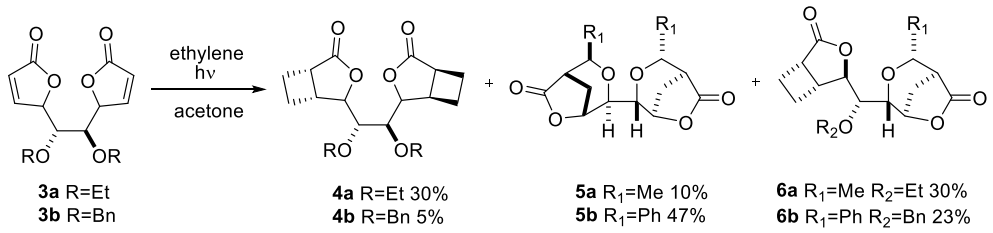
Scheme 1. Formation of bridged THP **2** by irradiation of **1**. A: ether/quartz (direct irradiation); B: acetone/Pyrex (sensitized irradiation)



Along several decades, our group has investigated the photo-induced cycloaddition of substituted 5-oxymethyl-2(5*H*)-furanones to alkenes and alkynes, in both the inter-[5] and intramolecular[6] versions, and explored its application to the synthesis of natural products or analogs, with recognized or potential biological activity.[7] In the course of these investigations, we discovered an intramolecular competitive reaction producing bicyclic tetrahydropyrans (THPs) in a stereoselective manner. Thus, the irradiation of lactone **1**, bearing a benzyloxymethyl substituent at position 5, in the presence of various alkenes such as ethylene, tetramethylethylene or vinylene carbonate, delivered, along with the expected cycloadducts, the bridged THP **2** (Scheme 1).[5b] Apparently, this product arises from a Hydrogen Atom Transfer (HAT) reaction by the β-carbon of the excited enone, followed by subsequent recombination of the diradical to form the new σ C-C bond. We reasoned that the benzylic character of the intermediate radical **I-1** could favor this alternative pathway competing with the addition of the alkene and, indeed, when lactone **1** was irradiated in the absence of any alkene, the THP **2** could be isolated in preparative

yields. However, later on this reaction was also found to occur in other analogous substrates lacking the benzyl residue. Thus, in a project devoted to explore the application of C_2-symmetric bis-2(5*H*)-furanones as templates for asymmetric synthesis, when the bislactones **3b** were irradiated in the presence of ethylene, apart from the expected bis-photoadducts **4a**, considerable amounts of THP photoproducts **5a** and **6a** were also formed (Scheme 2).[7c]

Scheme 2. Irradiation of bis-lactones **3a-b** in the presence of ethylene



Considering the occurrence of the THP ring in many natural products and drugs, including carbohydrates and macrolides as the most abundant typologies,[8] we judged worthy to explore the scope of this reaction as a straightforward access to novel, stereochemically rich fragment molecules, which may eventually lead to the discovery of new privileged scaffolds. Moreover, the lactone functionality would enable subsequent transformations to prepare monocyclic polysubstituted THPs and/or to modulate the lipophilicity of the fragments. The results of this study are presented herein.

Results and Discussion

Synthesis of the substrates

Figure 1 shows the set of 2(5*H*)-furanones **7**-**12** (complementary to **1**) selected to undertake the study. The methyl, butyl, and isopropyl derivatives, **7**-**9**, would provide evidence about the influence of the stability of the intermediate diradical in the feasibility of the process, while substrates **10**-**12** will give information concerning its compatibility with additional functionalities. The allyl derivative **11** was particularly interesting because it was expected that alternative intramolecular [2+2] cycloaddition pathways would also be at play. The photochemical behavior of the THP derivative (±)-**12** and other analogous substrates has been recently published by Hoffmann and coworkers as part of a study devoted

to investigate the stereoelectronic effects that control the HAT-cyclization process.[9] We were interested in comparing their results with our own ones.

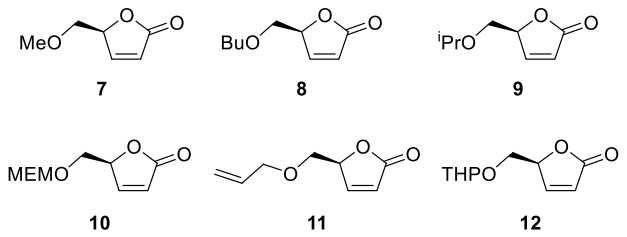
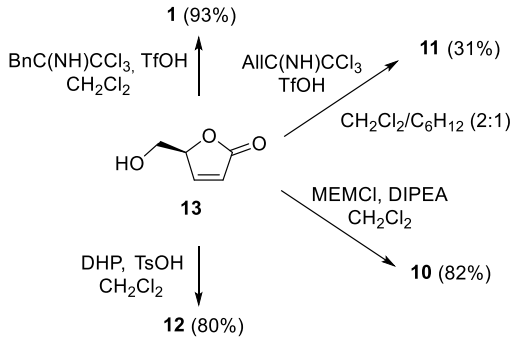


Figure 1. Selected substrates for the photo-activated Hydrogen Atom Transfer study.

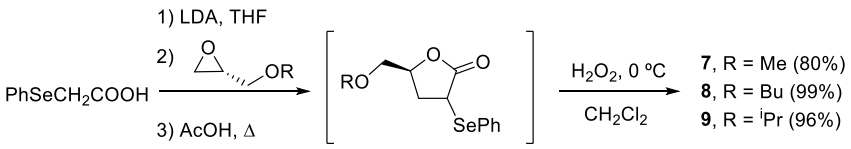
Formerly, we had prepared the benzyloxymethylfuranone **1** by reaction of the parent alcohol **13** (readily available from D-manitol)[10] with benzyl bromide and silver (I) oxide, but we have now improved the benzylation efficiency by the use of benzyltrichloroacetimidate in dichloromethane in the presence of trifluoromethanesulfonic acid.[11] Under these new conditions, furanone **1** was isolated in 93% yield (Scheme 3). An analogous protocol applied to the preparation of the allyloxy derivative **11** worked considerably worse, despite the reaction was attempted under various conditions; the best yield (31%) was obtained using a 2:1 mixture of dichloromethane and cyclohexane as solvent. The MEM, **10**, and THP, **12**, derivatives were prepared also from alcohol **13** by standard procedures in good yields.[12] Compound **12** was obtained as a 1:1 mixture of epimers at the acetal center.[13]

Scheme 3. Preparation of furanones **1** and **10-12** from **13**



The alkyloxy furanones **7-8**,[14] and **9** were more effectively synthesized by an alternative methodology,[15] involving alkylation of phenylselenoacetic acid with the appropriate epoxide, followed by acid catalyzed lactonization and then oxidation of the selenide with concomitant thermal elimination (Scheme 4).

Scheme 4. Preparation of furanones **7-9** from phenylselenoacetic acid and epoxides.

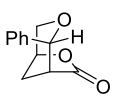


Photochemical study

The irradiations of furanones **1**, **7-12** were performed in an immersion well photochemical reactor, with a 125W high pressure mercury lamp, cooling externally the reactor to -20°C and flowing methanol at -15°C through the internal jacket. The reaction evolution was monitored by gas chromatography and the effect of the experimental conditions (solvent, filter and reaction time) was evaluated. To avoid the addition of the solvent to the β-carbonyl position of the excited furanone, all the irradiation experiments were performed in aprotic solvents.[16] The results are summarized in Table 1. Firstly, the previously observed photochemical reaction of lactone **1** was reinvestigated in several conditions. Under sensitized photo-activation (entry 1, acetone/pyrex), 3 h of irradiation were required for the full consumption of the furanone and, after chromatographic purification, the expected bicyclic THP **2** was isolated in 38% yield. The direct photo-activation (entries 2-5) proved more efficient. It was observed that, in acetonitrile (entries 2-3), a decrease in the temperature diminished the reaction rate but improved notably the yield of isolated product, suggesting that the THP **2** could partially decompose when subjected to persistent irradiation. Diethyl ether showed the best performance, furnishing 78% yield of isolated product after only 15 min of irradiation (entry 4). As before, prolonged irradiation time was detrimental to the yield (entry 5). Next, the behavior of the other alkyloxy derivatives **7-9** under similar conditions was investigated. It was somehow surprising that, under the sensitized activation (entry 6), lactone **7** bearing the methyl residue evolved faster than its benzylic analogue and furnished a superior yield of the corresponding THP **14**. However, direct activation in acetonitrile was less effective (entry 7) and the irradiation in ether lead to a complex mixture of unidentified products (entry 8). Very similar results were obtained in the photochemical experiments of the butyl derivative **8** (entries 9-11). The photochemical evolution of furanone **9** (entries 12-14), wherein the isopropyl group may originate a

more stable tertiary radical intermediate, was in good agreement with that of **1**, although the yield of the isolated THP **16** when working in ether was lower in this case (compare entries 4/5 and 14). Surprisingly, the irradiation of lactone **10** in all attempted solvents (entries 15-17) gave complex mixtures of products, which NMR analysis did not allow the identification of any compound containing the expected THP moiety.

Table 1. Irradiation of furanones **1** and **7-9**.[a]



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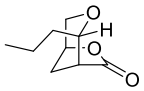

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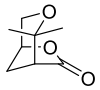

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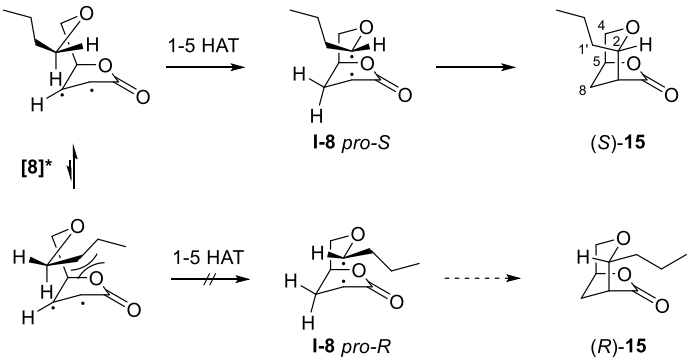
Entry	Substrate	mmol.L^{-1}	Solvent	Filter	Time (min)	Conversion (%)[b]	Product (Yield)[c]
1	1	4.7	acetone	pyrex	180	100	2 (38%)
2	**1**	4.7	CH_3CN	quartz	50	100	**2** (44%)
3[d]	**1**	4.0	CH_3CN	quartz	70	90	**2** (70%)
4	**1**	4.3	Et_2O	quartz	15	100	**2** (78%)
5	**1**	5.4	Et_2O	quartz	25	100	**2** (48%)
6	**7**	6.4	acetone	pyrex	42	100	**14** (45%)
7	**7**	5.5	CH_3CN	quartz	105	100	**14** (52%)
8	**7**	10.4	Et_2O	quartz	40	100	_[e]
9	**8**	6.5	acetone	pyrex	65	100	**15** (42%)
10	**8**	6.3	CH_3CN	quartz	40	100	**15** (52%)
11	**8**	5.5	Et_2O	quartz	50	100	_[e]
12	**9**	7.4	acetone	pyrex	45	100	**16** (38%)
13	**9**	8.8	CH_3CN	quartz	30	100	**16** (50%)
14	**9**	6.0	Et_2O	quartz	100	100	**16** (30%)
15	**10**	5.5	acetone	pyrex	30	100	_[e]
16	**10**	5.5	CH_3CN	quartz	30	100	_[e]
17	**10**	5.5	Et_2O	quartz	30	100	_[e]

[a]Irradiations were performed in a nitrogen saturated solution; unless otherwise indicated, the external cooling bath was at -20°C and the jacket cooling liquid at -15°C. [b]The substrate conversion was monitored by GC. [c]Yield of isolated products. [d]The external cooling bath was at -40°C. [e]Unidentifiable degradation products.

The stereochemical course of the photoreactions was a main concern of our study. In all the cases, the cyclization produces a new stereogenic center at the bridgehead position, whose configuration is determined by the chirality sense of the starting furanone, since the opposite facial approach would be geometrically impossible. However, in the case of lactones **1** and **8**, an additional stereogenic center is generated at C-2 of the THP products (Scheme 5). For compound **15**, the relative configuration was established through 1D NOESY experiments, which revealed an increase of the signal of one of the protons H-1', H-5 and H-8 after selective irradiation of H-4. Therefore, starting from (5*S*)-**8**, the stereochemistry of THP **15** was established as (1*R*,2*S*,5*S*). This configuration matches the one previously determined for **2** and it is probably governed by the selective abstraction of one of the two stereotopic hydrogen atoms of the butyl side chain. Apparently, when going from the excited lactone to the subsequent diradical species, the transition state leading to the intermediate diradical *pro*-*S*, with the bulky propyl chain distant from the lactone ring, is favored over that leading to intermediate diradical *pro*-*R*, where the propyl chain is closer to the lactone. Photoreactivity is likely controlled by the relative rates at which the different diradical species **I-8** are formed.

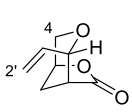
Scheme 5. Stereochemical course of the photocyclization of **8**.



Then, we investigated the reactivity of lactone **11** bearing an allyl group under both sensitized and direct photo-activation conditions (Table 2). In previously reported photo-activated intramolecular [2+2] cycloadditions of 2(5*H*)-furanones[6,17] and conjugated enones[18] bearing a carbon-carbon double bond at a suitable distance to furnish the corresponding cyclobutanes, the competitive formation of photoproducts arising from a 1,5-HAT pathway has not been described. From our experiments we were able to isolate

and characterize four different products, the THP **17** and the oxocine **18**, coming from 1,5-HAT followed by C-C bond formation, and the cyclobutanes **19** and **20**, arising from intramolecular [2+2] photocycloadditions with head to head (HH) or head to tail (HT) orientation, respectively. In all the assayed conditions, the cycloadducts predominated, and higher substrate concentrations favored the HT regioisomer over the HH one (compare entries 1 and 2/3 and entries 4 and 5). The concomitant formation of **17** and **18** can be reasonably explained by the intermediacy of a delocalized allyl radical that seems preferentially to evolve to the formation of the eight member ring.

Table 2. Irradiation of furanone **11**.[a]



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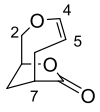

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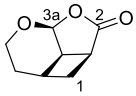

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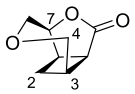

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Entry	mmol.L-[1]	Solvent	Filter	Time (min)	Conversion (%)[b]	Global Yield[c]	Product ratio **17:18:19:20**
1	6.8	acetone	pyrex	35	87	26%	–:1:1.7:1.7
2	8.9	acetone	pyrex	72	90	39%	1:2:5.7:4.4
3	21.6	acetone	pyrex	180	92	70%	1:1.5:4:2.2
4	6.3	CH_3CN	quartz	35	90	36%	1:1:1.2:1.2
5	12.7	CH_3CN	quartz	45	70	27%	–:1:2.6:1.8

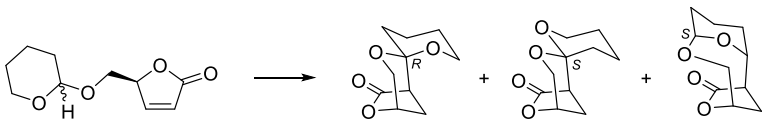
[a]Irradiations were performed in a nitrogen saturated solution; the external cooling bath was at -20°C and the jacket cooling liquid at -15°C. [b]The substrate conversion was monitored by GC. [c]Yield of isolated products.

The structure of compound **18** was determined through detailed NMR studies. Its ^{1}H NMR spectrum displays two signals of olefinic protons at δ 6.45 and 5.09 and an HMBC experiment showed relevant cross-peaks between one of this signals (H-5) and the α-carbonyl carbon atom C-7 and between both protons H-2 and C-4. As before, the stereochemical assignment of the THP **17** was unambiguously established by selective NOE experiments, that showed signal enhancement of protons H-2' when the signal corresponding to the C-4 methylene group was selectively irradiated. The cyclobutanes **19** and **20** could not be separated by column chromatography. Thus, their structural analysis was performed on a

1:0.7 mixture of the two regioisomers, where most of the signals were clearly distinguishable. Selective TOCSY experiments allowed fast assignment of whole spin systems and were used to obtain separate subspectra of each isomer, through the selective irradiation of H-3a in **19** and H-7 in **20**. For the HT regioisomer **20**, the attachment site of C-4 was established by an HMBC experiment which showed cross-peak interactions between one of the H-4 protons and the carbon atom C-3 and between one of the H-2 protons and C-7. The connectivity of the HH regioisomer **19** was evidenced by a diagnostic cross-coupling between the carbonyl carbon C-2 and one of the methylenic protons H-1.

Next, the photo-reactivity of the furanone **12** bearing the THP residue (1:1 mixture of epimers at the acetal center) was investigated (Table 3). In the above mentioned publication of Hoffmann laboratories,[9] the irradiation of (±)-**12** was performed with Rayonet reactors in quartz tubes, no transformation was observed in the absence of acetone, and the authors concluded that the reaction occurs through hydrogen transfer from the acetal center to the β-carbonyl position in the triplet (*ππ) excited state of the furanone. After irradiation of a 1:1 mixture of (±)-**12** for three hours, they isolated a 1:1 mixture of epimeric THPs (±)-**21** and (±)-**22** (entry 1).

Table 3. Irradiation of furanone **12**.[a]



Entry	mmol.L^{-1}	Solvent	Filter	Time (min)	Conversion (%)[c]	Product (yield)[d]
1[b]	35	CH_3CN/acetone (4.4:1)	quartz	180		**21** (22%), **22** (21%)
2	5.4	acetone	pyrex	45	100	**21**(30%), **22** (6%), **23** (10%)
3	5.4	CH_3CN	quartz	30	100	**21**(30%), **22** (10%), **23** (10%)
4	10.1	CH_3CN	quartz	120	100	**21**(50%), **22** (10%), **23** (14%)

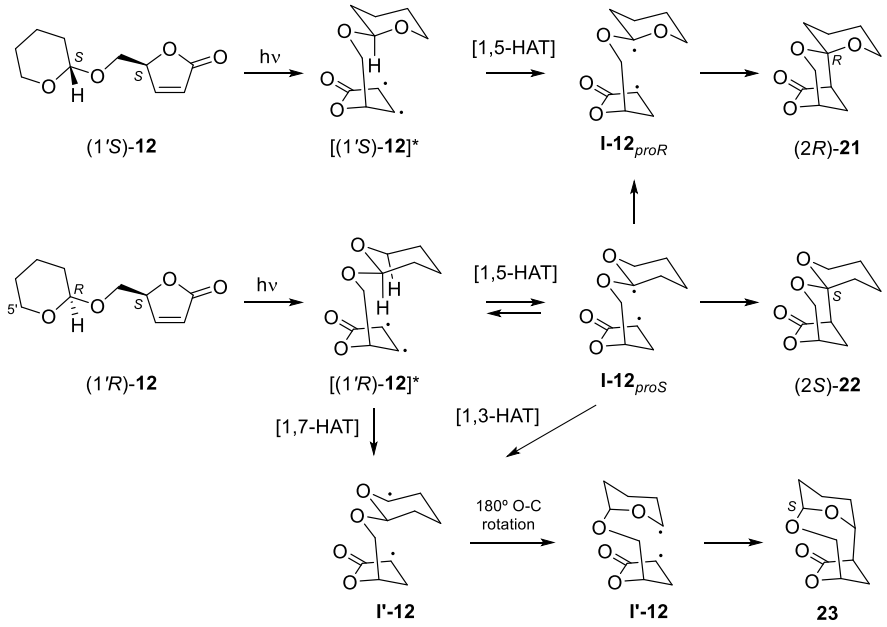
[a]Irradiations were performed in a nitrogen saturated solution; the external cooling bath was at -20°C and the jacket cooling liquid at -15°C. [b]Data reported in reference 9. [c]The substrate conversion was monitored by GC. [d]Yield of isolated products.

The experiments performed in our laboratories showed some differences with those reported. In our studies, when the photoreaction was run in acetone through a pyrex filter (entry 2), we isolated THP (2*R*)-**21** as the major product (30%), along with minor amounts of its epimer (2*S*)-**22** (6%) and a third product that was identified as the 1,3-dioxocane **23** (10%) and was a single diastereomer. Although this compound was not observed in Hoffmann laboratories, they did find photoproducts with the same skeleton as **23** after irradiation of closely related furanones bearing also tetrahydropyran moieties. Experimental data as well as theoretical calculations with model compounds led these authors to conclude that the hydrogen abstraction step determines the reactivity and regioselectivity of the process and it is strongly dependent upon the relative configuration of the substrate. Their calculations indicated that the competitive 1,5- and 1,7-HAT processes may be more or less favored by the geometry of the starting furanone. On the other hand, conversely to their observations, we discovered that irradiation of **12** in exclusively acetonitrile as the solvent (entry 3), and hence under non sensitized conditions, furnished similar results as in acetone. Interestingly, by increasing the substrate concentration in acetonitrile, the overall product yield could be improved up to 76% (entry 4). The structural assignment of the photoproducts was accomplished on the basis of their NMR data, which matched with those described by Hoffmann group.

All our experiments were performed with a 1:1 mixture of pure epimeric furanones **12** with *S* absolute configuration at C-5. Our results indicate that the formation of the spiranic acetal (2*R*)-**21** is clearly favored over that of its epimer (2*S*)-**22** and, on the other hand, a diastereomeric 1,3-dioxocane with *R* configuration in the acetal center was never detected. These facts support that the relative configuration of the acetal center plays indeed a primordial role in the evolution pathway of the excited furanone. Hence, the irradiation of the initial mixture of (1'*R*)-**12** and (1'*S*)-**12** should furnish the two corresponding diastereomeric excited species, which will evolve either by 1,5- or 1,7-abstraction of an axially oriented hydrogen atom (Scheme 6). When the initial configuration of the acetal center is *S*, after 1,5-HAT, recombination of the diradical **I-12**$_{proR}$ leads to the [6,6]-spiroketal system (2*R*)-**21**, which presents one anomeric and one non anomeric relationship. In contrast, when the initial configuration of

the acetal center is *S* a parallel sequence of events furnishes the spiroketal (2*S*)-**22** with two non anomeric relationships. It is therefore reasonable to expect that the cyclization of the diradical intermediate **I-12**$_{proS}$ was disfavored compared to that of **I-12**$_{proR}$ and that other alternative pathways could compete advantageously. Besides reversion to the original species, **I-12**$_{proS}$ could evolve through 1,3-HAT to give the regioisomeric diradical **I'-12**, which is also available directly from the excited enone [(1'*R*)-**12**]* by 1,7-HAT and that by cyclization furnishes the dioxecane **23**. This scenario is consistent with the experimental results and in agreement with the reported theoretical calculations.[9] It is worth mention that the preparation of [6,6]-spiroketals with one or two non anomeric relationships is not a trivial issue, since most of the standard methods of ketal formation are equilibrium processes and lead to the most stable anomeric systems.[19]

Scheme 6. Mechanistic scenario for the photochemically induced evolution of **12**.



Methanolysis of 2 and (2R)-21

To explore the lactone opening route, the bicycle **2** was transformed into the 2,3,5-trisubstituted THP **24** (Figure 2) by treatment with sodium methoxide in refluxing methanol, followed by acidification with 1M HCl, in 65% yield. When the same protocol was applied to the tricycle (2*R*)-**21**, we isolated a mixture of the expected [6,6]-spiroketal **25** and its epimer at C-5, but the epimerization could be avoided by a milder acidic work-up with saturated aqueous ammonium chloride, in which case the spirane **25**

was exclusively isolated in 62% yield. The two epimers were easily distinguished by the coupling constant pattern of the ^{1}H-NMR signal corresponding to the epimeric centre. Thus, for isomer **25** proton H-5 (δ 2.67) displays *J* values typical of an equatorial orientation (6.6 and 1.4 Hz), while for 5-*epi*-**25** these values are consistent with an axial geometry (13.1 and 4.2 Hz).

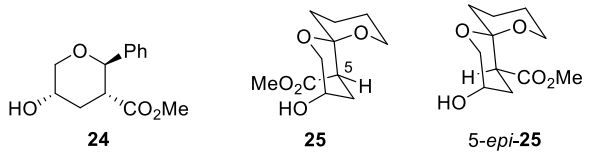


Figure 2. Methanolysis products of of **2** and (2*R*)-**21**.

Conclusions

The irradiation of a series of enantiomerically pure 5-oxymethyl-2(5*H*)-furanones has proven to be a straightforward entry to diverse and stereochemically rich fragment-molecules, most of which contain the privileged tetrahydropyran scaffold. The reactions take place under both sensitized (acetone) and non sensitized (acetonitrile, ether) conditions and they are highly stereoselective. The formation of the THP involves a 1,5-hydrogen atom transfer process in the excited state of the furanone, leading to a diradical intermediate that recombines to form a new σ C-C bond. When the substrate contains an allyl residue the cyclization is not regioselective and, besides, the intramolecular [2+2] cycloaddition leading to cyclobutanes competes advantageously. When the substrate contains a THP residue, the cyclization involves the concomitant formation of [6,6]-spiroketals with non anomeric relationships and competes with the formation of an oxecane ring. The THP derivatives prepared herein could be further elaborated to a plethora of different tetrahydropyrans and [6,6]-spiroketals.

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 250.13 and 62.5 MHz, 360.11 and 90.55 MHz, or 500.13 and 125.75 MHz. Proton and carbon chemical shifts are reported in

ppm (δ) ($CDCl_3$, δ 7.26 for ^1H; $CDCl_3$, δ 77.2 for ^{13}C). NMR signals were assigned with the help of COSY, HSQC, HMBC, and NOESY experiments. Melting points were determined on hot stage and are uncorrected. High resolution mass spectra (HRMS) and microanalyses were performed at the Servei d'Anàlisi Química de la Universitat Autònoma de Barcelona. Optical rotations were measured at 22 ± 2 °C.

*(S)-5-Benzyloxymethyl-2(5H)-furanone (**1**).*[5b] To a solution of furanone **13** (335 mg, 2.94 mmol) in dry CH_2Cl_2 (26 mL) at 0 °C under nitrogen was added benzyltrichloroacetimidate (600μL, 3.23 mmol) and trifluoromethane sulfonic acid (26 μL, 0.3 mmol). The resulting mixture was stirred for 4 h. After this period, the reaction mixture was washed with 1M HCl (5 mL), water (5 mL) and brine (5 mL) and the organic layer was separated. The organic extracts were dried over anhydrous sodium sulphate. Evaporation of the solvent followed by column chromatography (hexanes–Et_2O, 1.5:1) afforded the title compound **1** (557 mg, 2.73 mmol, 93% yield) as a colourless oil: $[\alpha]_D$ –10.7 (*c* 1.6, EtOH); ^1H NMR (250 MHz, $CDCl_3$) δ 7.42 (dd, $J_{4,3}$ = 5.8 Hz, $J_{4,5}$ = 1.6 Hz, 1H, H-4), 7.27 (s, 5H, C_6H_5), 6.07 (dd, $J_{3,4}$ = 5.8 Hz, $J_{3,5}$ = 1.7 Hz, 1H, H-3), 5.07 (m, 1H, H-5), 4.49 (s, 2H, H-3'), 3.62 (d, $J_{1',5}$ = 5.3 Hz, 2H, H-1').

General procedure for the synthesis of 2(5H)-furanones** 7-9 **from (S)-alkyl glycidil ethers. A solution of 2-(phenylseleno)acetic acid (600 mg, 2.8 mmol) in THF (8 mL) was added to a stirred solution of LDA (5.9 mmol) in THF (16 mL)) at 0 ºC under nitrogen and the mixture stirred for 30 min. Then, the corresponding epoxide (2.8 mmol) was added and the reaction mixture was stirred at 0 ºC for 4 h. The cool slurry was acidified with glacial acetic acid, and then heated at the reflux temperature for 16 h. Afterward, the reaction mixture was cooled and neutralized by adding a saturated aqueous solution of sodium bicarbonate (15 mL). The organic layer was separated and the aqueous phase was extracted with diethyl ether (3x10 mL). The combined organic extracts were concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (20 mL) and then hydrogen peroxide (30%, 3 mL, 26.4 mmol) was added dropwise at 0 ºC. After 2h, the reaction mixture was diluted with water (15 mL), the organic layer was separated, and the aqueous one was extracted with CH_2Cl_2 (3x10 mL). The combined organic

extracts were dried over anhydrous sodium sulphate and the solvent removed, furnishing a crude material which was purified by column chromatography.

*(S)-5-Methoxymethyl-2(5H)-furanone (**7**).*[14] Following the general procedure, from (*S*)-glycidyl methyl ether (250 µl, 2.8 mmol), after purification by column chromatography (hexanes–EtOAc, 4:1) furanone **7** (287 mg, 2.24 mmol, 80% yield) was obtained as an oil: $[\alpha]_D$ –90.1 (*c* 0.7, $CDCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 (dd, $J_{4,3}$ = 5.8 Hz, $J_{4,5}$ = 1.6 Hz, 1H, H-4), 6.21 (dd, $J_{3,4}$ = 5.8 Hz, $J_{3,5}$ = 2.1 Hz, 1H, H-3), 5.19 (tdd, $J_{5,6}$ = 5.0 Hz, $J_{5,3}$ = 2.1 Hz, $J_{5,4}$ = 1.6 Hz, 1H, H-5), 3.59 (d, $J_{1',5}$ = 5.0 Hz, 2H, H-1'), 3.38 (s, 3H, H-3').

*(S)-5-Butoxymethyl-2(5H)-furanone (**8**).*[14] Following the general procedure, from (*S*)-glycidyl butyl ether (400 µl, 2.8 mmol), after purification by column chromatography (hexanes–EtOAc, 4:1), furanone **8** (471 mg, 2.77 mmol, 99% yield) was obtained as an oil: $[\alpha]_D$ –125.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.48 (dd, $J_{4,3}$ = 6.4 Hz, $J_{4,5}$ = 1.2 Hz, 1H, H-4), 6.11 (dd, $J_{3,4}$ = 6.4 Hz, $J_{3,5}$ = 2.0 Hz, 1H, H-3), 5.12–5.09 (m, 1H, H-5), 3.64 (dd, J_{gem} = 10.6 Hz, $J_{1',5}$ = 5.3 Hz, 1H, H-1'), 3.57 (dd, J_{gem} = 10.6 Hz, $J_{1',5}$ = 5.6 Hz, 1H, H-1'), 3.47–3.40 (m, 2H, H-3'), 1.51–1.46 (m, 2H, H-4'), 1.38–1.16 (m, 2H, H-5'), 0.84 (t, $J_{4',3'}$ = 7.2 Hz, 3H, H-6').

*(S)-5-Isopropoxymethyl-2(5H)-furanone (**9**).* Following the general procedure, from (*S*)-glycidyl isopropyl ether (354 µl, 2.8 mmol), after purification by column chromatography (hexanes–EtOAc, 4:1), furanone **9** (420 mg, 2.68 mmol, 96% yield) was obtained as a colorless oil: $[\alpha]_D$ –31 (*c* 0.7, $CHCl_3$); IR (ATR) 2973, 1753, 1094 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.54 (dd, $J_{4,3}$ = 5.7 Hz, $J_{4,5}$ = 1.8 Hz, 1H, H-4), 6.18 (dd, $J_{3,4}$ = 5.7 Hz, $J_{3,5}$ = 2.0 Hz, 1H, H-3), 5.13 (dd, $J_{5,1'}$ = 5.5 Hz, $J_{5,4}$ = 1.8 Hz, 1H, H-5), 3.75 (dd, J_{gem} = 10.3 Hz, $J_{1',5}$ = 5.5 Hz, 1H, H-1'), 3.67–3.55 (m, 2H, H-3' and H-1'), 1.15 (d, $J_{4',3'}$ = 6.4 Hz, 3H, H-4'), 1.13 (d, $J_{4',3'}$ = 6.4 Hz, 3H, H-4'); ^{13}C NMR (90 MHz) ($CDCl_3$) δ 173.0 (C-2), 154.5 (C-4), 122.5 (C-3), 82.4 (C-5), 73.1 (C-3'), 68.0 (C-1'), 22.0 (C-4'), 21.9 (C-4'). HRMS *m/z* (ESI-TOF) calcd for $[C_8H_{12}O_3 + Na]^+$: 179.0684, found: 179.0680.

*(S)-5-(2-Methoxyethoxy)methoxymethyl-2(5H)-furanone (**10**).* To a solution of furanone **13** (438 mg, 3.71 mmol) in dry CH_2Cl_2 (5mL) at 0 ºC, DIPEA (970 µL, 5.55 mmol) was added dropwise and then 1-(chloromethoxy)-2-methoxyethane (636 µL, 5.57mmol). After 24 h of stirring at rt, CH_2Cl_2 (10 mL) was added and the solution was successfully washed with 5% hydrochloric acid (2x5 mL), a solution aqueous saturated bicarbonate (2x5 mL) and brine (2x5 mL). The layers were separated and the organic extracts were dried over sodium sulphate. Evaporation of the solvent gave a residue which was purified by column chromatography (hexanes–EtOAc, 2:1) to furnish furanone **10** (647 mg, 82% yield) as a colorless oil: $[\alpha]_D$ –91.7 (*c* 2.73, $CHCl_3$); IR (ATR) 3093, 2927, 2891, 1756, 1602, 1454, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, $J_{4,3}$ = 5.5 Hz, $J_{4,5}$ = 1.2 Hz, 1H, H-4), 6.12 (dd, $J_{3,4}$ = 5.5 Hz, $J_{3,5}$ = 1.8 Hz, 1H, H-3), 5.13 (m, 1H, H-5), 4.66 (s, 2H, H-3'), 3.78 (dd, J_{gem} = 11.0 Hz, $J_{1',5}$ = 4.9 Hz, 1H, H-1'), 3.74 (dd, J_{gem} = 11.0 Hz, $J_{1',5}$ = 5.5 Hz, 1H, H-1'), 3.63 (m, 2H, H-5'), 3.49 (m, 2H, H-6'), 3.32 (s, 3H, H-8'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (C-2), 153.0 (C-4), 122.6 (C-3), 95.6 (C-3'), 81.9 (C-5), 71.5 (C-1'), 67.0 (C-5'), 66.9 (C-6'), 58.9 (C-8'). MS (*FAB*+) 157 (M^+-45,1), 127 (15), 59 (100). Anal. Calcd for [$C_9H_{14}O_5$]: C, 53.46; H, 6.98. Found: C, 53.33; H, 7.02.

*(S)-5-Allyloxymethyl-2(5H)-furanone (**11**).* To a solution of furanone **13** (500 mg, 4.38 mmol) in dry CH_2Cl_2 (85 mL) and dry cyclohexane (35 mL), allyl trichloroacetimidate (1.20 mL, 7.45 mmol) and trifluoromethanesulfonic acid (0.58 mL, 1.32 mmol) were successively added at 0 ºC. After 2 h of stirring at 0 ºC and 3 h at rt, the reaction was quenched by addition of a sodium bicarbonate solution (30 mL) and water (20 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated under vacuum. The resulting oil was purified by column chromatography (hexanes–EtOAc, 2:1) to give furanone **11** (209 mg, 1.36 mmol, 31% yield) as a yellow oil: $[\alpha]_D$ –71.7 (*c* 1.0, $CHCl_3$); IR (ATR) 1745, 1261, 1167, 1086 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.50 (dd, $J_{4,3}$ = 5.7 Hz, $J_{4,5}$ = 1.6 Hz, 1H, H-4), 6.21 (dd, $J_{3,4}$ = 5.7 Hz, $J_{3,5}$ = 2.0 Hz, 1H, H-3), 5.96–5.74 (m, 1H, H-4'), 5.31 (m, 3H, H-5', H-5), 4.05 (d, $J_{3',4'}$ = 5.7 Hz, 2H, H-3'), 3.70 (dd, J_{gem} = 10.5 Hz, $J_{1',5}$ = 5.3 Hz, 1H, H-1'), 3.64 (dd, J_{gem} = 10.5 Hz, $J_{1',5}$ = 5.1 Hz, 1H, H-1'); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.9 (C-2), 154.1 (C-4), 133.9 (C-

4'), 122.7 (C-3), 117.9 (C-5'), 82.3 (C-5), 72.8 (C-3'), 69.6 (C-1'). HRMS *m/z* (ESI-TOF) calcd for $[C_8H_{10}O_3 + Na]^+$:177.0528, found: 177.0522.

*(S)-5-(Tetrahydro-2*H*-pyran-2-yl)oxymethyl-2(5H)-furanone (**12**).*[13] To a solution of furanone **13** (347 mg, 3.04 mmol) in CH_2Cl_2 (35 mL) at rt were added dihydropyran (294 μL, 3.21 mmol) and *p*-toluensulfonic acid (34 mg, 0.17 mmol). The resulting mixture was stirred for 21 h. After this period, the reaction was quenched with the addition of saturated sodium bicarbonate solution (15 mL). The organic layer was separated and the aqueous one extracted with CH_2Cl_2 (3x5 mL). The combined organic extracts were dried over anhydrous sodium sulphate. Evaporation of the solvent, followed by purification by column chromatography (hexanes–EtOAc, 3:1), afforded a 1:1 mixture of epimeric furanones **12** (482 mg, 2.43 mmol, 80% yield) as a colorless oil: IR (ATR) 3070, 1240, 1753, 1618, 1154 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.47 (m, 2H, H-4), 6.09 (m, 2H, H-3), 5.20 (m, 2H, H-5), 4.62 (m, 1H, H-2'), 4.62 (m, 1H, H-2''), 4.59 (m, 1H, H-2''), 3.94–3.87 (m, 2H, H-1'), 3.85–3.74 (m, 2H, H-6''), 3.66–3.60 (m, 2H, H-1'), 3.55–3.45 (m, 2H, H-6''), 1.90–1.40 (m, 12H, H-3'', H-4'', H-5'').

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. The reaction mixtures were initially degassed by bubbling 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.

*(1R,2S,5S)-2-Phenyl-3,6-dioxabicyclo[3.2.1]octan-7-one (**2**).* A solution of furanone **1** (98 mg, 0.49 mmol) in diethyl ether (75 ml) was irradiated through a quartz filter for 15 min at -20 ºC. After total conversion, the solvent was evaporated and the residue was purified by column chromatography (hexanes–Et_2O, 3:1) to give compound **2** (76 mg, 0.38 mmol, 78% yield) as a colorless solid: mp 114–112 °C (from EtOAc-pentane); $[\alpha]_D$ –114.6 (*c* 1.15, $CHCl_3$); IR (ATR) 2256, 1785, 1454, 1352, 1159

cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.10 (m, 5H, C_6H_5), 5.30 (d, $J_{2,1}$ = 2.1 Hz, 1H, H-2), 3.81 (ddd, $J_{5,8}$ = 5.9 Hz, $J_{5,4}$ = $J_{5,4}$ = 2.1 Hz, 1H, H-5), 3.61 (ddd, J_{gem} = 11.9 Hz, $J_{4eq,8eq}$ = 2.4 Hz, $J_{4eq,5}$ = 2.1 Hz, 1H, H-4eq), 3.20 (dd, J_{gem} = 11.9 Hz, $J_{4ax,5}$ = 2.1 Hz, 1H, H-4ax), 2.74 (ddd, $J_{1,8eq}$ = 5.9 Hz, $J_{1,2}$ = 2.1 Hz, $J_{1,8ax}$ = 1.2 Hz, 1H, H-1), 1.56 (dt, J_{gem} = 11.7 Hz, $J_{8eq,5}$ = $J_{8eq,1}$ = 5.9 Hz, 1H, H-8eq), 1.36 (dd, J_{gem} =11.7 Hz, $J_{8ax,1}$ =1.2 Hz, 1H, H-8ax); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.9 (Ph), 129.7 (CH, Ph), 128.9 (Ph), 128.5 (Ph), 127.7 (Ph), 125.5 (Ph), 76.5 (C-2), 74.2 (C-5), 64.2 (C-4), 43.5 (C-1), 29.9 (C-8). Anal. Calcd. for ($C_{12}H_{12}O_3$): C, 70.58; H, 5.92. Found: C, 70.48%, H: 5.87%.

*(1R,5S)-3,6-Dioxabicyclo[3.2.1]octan-7-one (**14**).* A solution of furanone **7** (158 mg, 1.23 mmol) in acetonitrile (75 ml) was irradiated through a quartz filter for 105 min at -20 ºC. After total conversion, the solvent was evaporated and the residue was purified by column chromatography (hexanes–Et_2O, 2:1) to deliver compound **14** (82 mg, 0.64 mmol, 52% yield) as a colorless oil: $[\alpha]_D$ –3.0 (*c* 0.6, $CDCl_3$); IR (ATR) 2919, 1729, 1463 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.72 (m, 1H, H-5), 4.11 (dt, J_{gem} = 10.7 Hz, $J_{2eq,1}$ = $J_{2eq,4eq}$ = 2.7 Hz, 1H, H-2_{eq}), 3.94 (dt, J_{gem} = 11.6 Hz, $J_{4eq,5}$ = $J_{4eq,2eq}$ = 2.7 Hz, 1H, H-4_{eq}), 3.70 (d, J_{gem} = 10.7 Hz, 1H, H-2_{ax}), 3.66 (d, J_{gem} = 11.6 Hz, 1H, H-4_{ax}), 2.66 (m, 1H, H-1), 2.56 (m, 1H, H-8_{eq}), 2.09 (d, J_{gem} = 11.3 Hz, 1H, H-8_{ax}); ^3C NMR (90 MHz, $CDCl_3$) δ 176.6 (C-7), 75.8 (C-5), 68.0 (C-2), 67.3 (C-4), 40.5 (C-1), 35.8 (C-8). HRMS *m/z* (ESI-TOF) calcd for [$C_6H_8O_3$ + Na]$^+$:151.0363, found: 151.0366.

(*1R,2S,5S)-2-Propyl-3,6-dioxabicyclo[3.2.1]octan-7-one (**15**).* A solution of furanone **8** (81 mg, 0.47 mmol) in acetonitrile (75 mL) was irradiated through a quartz filter for 40 min at -20 ºC. After total conversion, the solvent was evaporated and the residue was purified by column chromatography (hexanes–Et_2O, 2:1) to afford compound **15** (42 mg, 0.24 mmol, 52% yield) as a colorless oil. $[\alpha]_D$ –10 (*c* 0.8, $CDCl_3$); IR (ATR) 2958, 1776, 1458, 1340, 1155 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.70 (m, 1H, H-5), 4.07 (ddd, *J* = 8.3 Hz, *J* = 5.1Hz, $J_{2,1}$ = 2.5 Hz, 1H, H-2), 3.77 (m, 2H, H-4), 2.54 (ddd, $J_{1,8eq}$ = 5.9 Hz, $J_{1,2}$ = 2.5 Hz, $J_{1,8ax}$ = 1.2 Hz, 1H, H-1), 2.33 (m, 1H, H-8eq), 2.28 (dd, J_{gem} = 11.8 Hz, $J_{8ax,1}$ = 1.2 Hz, 1H. H-8ax), 1.80 (m, 1H, H-1'), 1.54 – 1.31 (m, 3H, H-1', 2xH-2'), 0.97 (t, $J_{3',2'}$ = 7.2 Hz, 3H,

H-3'); ^{13}C NMR (90 MHz, $CDCl_3$) δ 177.5 (C-7), 76.6 (C-5), 73.5 (C-2), 63.7 (C-4), 43.2 (C-1), 32.3 (C-1'), 29.0 (C-8), 18.9 (C-2'), 13.8 (C-3'). HRMS (ESI-TOF) calcd for $[C_9H_{14}O_3 + Na]^+$: 193.0838, found: 193.0835.

(*1R,5S)-2,2-Dimethyl-3,6-dioxabicyclo[3.2.1]octan-7-one (**16**).* A solution of furanone **9** (104 mg, 0.66 mmol) in acetonitrile (75 mL) was irradiated through a quartz filter for 30 min at -20 ºC. After total conversion, the solvent was evaporated and the residue was purified by column chromatography (hexanes–Et_2O, 2:1) to deliver compound **16** (51 mg, 0.33 mmol, 50% yield) as a colorless oil: $[\alpha]_D^{20}$ – 5.5 (*c* 0.7, $CDCl_3$); IR (ATR) 2981, 1764, 1458, 1337, 1162, 1125 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.64 (m, 1H, H-5), 3.79 (m, *2*H, H-4), 2.38 (m, 3H, H-1 and 2xH-8), 1.40 (s, 3H, H-1'), 1.34 (s, 3H, H-1'); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.1 (C-7), 75.8 (C-5), 72.8 (C-2), 63.5 (C-4), 48.1 (C-1), 31.4 (C-8), 27.0 (C-1'), 21.7 (C-1'). HRMS (ESI-TOF) calcd for $[C_8H_{12}O_3 + Na]^+$: 179.0684, found: 179.0683.

*(1R,2S,5S)-2-vinyl-3,6-dioxabicyclo[3.2.1]octan-7-one (**17**), (1S,7S,Z)-3,9-dioxabicyclo[5.2.1]dec-4-en-8-one* (**18**), *(1aS,3aS,6aR,6bR)-hexahydro-1H,2H-3,5-dioxacyclobuta[cd]inden-2-one (**19**) (1R,3S,7S,10S)-5,8-dioxatricyclo[5.3.0.0]decan-9-one (**20**)*. A solution of furanone **11** (250 mg, 1.62 mmol) in acetone (75 mL) was irradiated through a pyrex filter for 180 min at -20 ºC. Then, the solvent was evaporated and the oily residue was purified by column chromatography (hexanes–Et_2O, 4:1) to afford **17** (20 mg, 0.13 mmol, 8% yield), **18** (30 mg, 0.19 mmol, 12% yield) and a 1.8:1 mixture of **19** and **20** (125 mg, 0.81 mmol, 50% yield).

17: $[\alpha]_D$ +10.2 (*c* 0.9, $CDCl_3$); IR (ATR) 3469, 2960, 2871, 1774, 1157 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.79 (ddd, $J_{1,2'}$ = 17.3 Hz, $J_{1,2'}$ = 10.8 Hz, $J_{1',2}$ = 3.3 Hz, 1H, H-1'), 5.45 (m, 2H, H-2'), 4.71 (br s, 2H, H-2 and H-5), 3.85 (br s, 2H, H-4), 2.68 (br s, 1H, H-1), 2.39 - 2.34 (m, 1H, H-8$_{eq}$), 2.26 (d, J_{gem} = 11.8 Hz, 1H, H-8$_{ax}$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.4 (C-7), 133.6 (C-1'), 117.8 (C-2'), 76.5 (C-5), 73.5 (C-2), 63.7 (C-4), 43.2 (C-1), 29.7 (C-8). HRMS (ESI-TOF) calcd for $[C_8H_{10}O_3 + Na]^+$: 177.0528, found: 177.0522.

18: $[\alpha]_D$ +8.0 (*c* 0.7, $CDCl_3$); IR (ATR) 3433, 2940, 2872, 1753, 1719 cm^{-1};^{1}H NMR (360 MHz, $CDCl_3$) δ 6.45 (d, $J_{4,5}$ = 5.4 Hz, 1H, H-4), 5.09 (q, $J_{5,4}$ = 5.4 Hz, $J_{5,6}$ = 5.4 Hz, 1H, H-5), 4.72 (m, 1H, H-1), 4.07 (br d, J_{gem} = 13.0 Hz, 1H, H-2), 3.72 (dd, J_{gem} = 13.0 Hz, $J_{2.1}$ = 2.0 Hz, 1H, H-2), 3.02 (ddd, *J* = 10.4 Hz, *J* = 5.8 Hz, *J* = 1.4 Hz, 1H, H-7), 2.59 (m, 2H, H-6, H-10), 2.43 (m, 1H, H-6), 2.38 (m, 1H, H-10); ^{13}C NMR (90 MHz, $CDCl_3$) δ 179.5 (C-8), 148.3 (C-4), 115.0 (C-5), 80.0 (C-2), 72.8 (C-1), 38.9 (C-7), 29.5 (C-6), 26.6 (C-10). HRMS (ESI-TOF) calcd for $[C_8H_{10}O_3 + Na]^+$: 177.0522, found: 177.0525.

19: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (br d, $J_{3a,4}$ = 8.9 Hz, 1H, H-3a), 4.26 (d, J_{gem} = 13.5 Hz, 1H, H-4), 3.72 (d, J_{gem} = 12.4 Hz, 1H, H-6), 3.41 (d, J_{gem} = 12.4Hz, 1H, H-6), 3.41 (dd, J_{gem} = 13.5 Hz, $J_{4,3a}$ = 8.9 Hz, 1H, H-4), 3.15 (m, 2H, H-6b, H-1a), 2.71-2.61 (m, 2H, H-6a, H-1), 2.32 (dd, J_{gem} = 11.2 Hz, *J* = 6.0 Hz, 1H, H-1); ^{1}H NMR (500 MHz, C_6D_6) δ 4.03 (d, J_{gem} = 13.4 Hz, 1H, H-4), 3.84 (m, 1H, H-3a), 3.29 (d, J_{gem} = 12.2 Hz, 1H, H-6), 2.83 (dd, J_{gem} = 12.2 Hz, $J_{6,6a}$ = 3.5 Hz, 1H, H-6), 2.76 (dd, J_{gem} = 13.4 Hz, $J_{4,3a}$ = 2.0 Hz, 1H, H-4), 2.70 (m, 1H, H-1a), 2.23 (m, 1H, H-6b), 2.12 (m, 2H, H-1), 1.72 (m, 1H, H-6a); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2 (C-2), 74.8 (C-3a), 68.4 (C-6), 67.9 (C-4), 34.9 (C-6a), 29.7 (C-6b), 26.9 (C-1), 26.8 (C-1a). GC/MS *(m/z)* 154.1 (M^+).

20: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (dd, $J_{7,1}$ = 7.2 Hz, $J_{7,6}$ = 3.9 Hz, 1H, H-7), 4.14 (dd, J_{gem} = 13.2 Hz, $J_{6,7}$ = 3.9 Hz, 1H, H-6), 4.06 (dd, J_{gem} = 12.3 Hz, $J_{4,3}$ = 4.3 Hz, 1H, H-4), 4.00 (d, J_{gem} = 13.2 Hz, 1H, H-6), 3.61 (d, J_{gem} = 12.3 Hz, 1H, H-4), 3.15 (m, 3H, H-1, H-10, H-3), 2.58 (m, 1H, H-2), 1.89 (d, J_{gem} = 12.4 Hz, 1H, H-2);^{13}C NMR (125 MHz, $CDCl_3$) δ 178.75 (C-9), 77.60 (C-7), 68.50 (C-4), 68.03 (C-6), 40.54 (C-3), 39.46 (C-10), 38.92 (C-1), 26.70 (C-2). GC/MS *(m/z)* 154.1 (M^+).

*(1R,2R,5S)-Tetrahydro-7H-spiro[3,6-dioxabicyclo[3.2.1]octane-2,2'-pyran]-7-one (2R-**21**)*, *(1R,2S,5S)-tetrahydro-7H-spiro[3,6-dioxabicyclo[3.2.1]octane-2,2'-pyran]-7-one (2S-**22**)* and *(1RS,2R,5S,8RS)-4,7,12-trioxatricyclo[6.3.1.1^{2,5}]tridecan-3-one (**23**)*. A solution of furanone **12** (1:1 mixture of epimers at the acetal center, 150 mg, 0.76 mmol) in acetonitrile (75 ml) was irradiated through a quartz filter for 120 min at -20 ºC. The solvent was evaporated and the resulting residue was

purified by column chromatography (hexanes–AcOEt, 5:1) to deliver 2*R*-**21** (75 mg, 0.38 mmol, 50% yield) as a colorless oil; 2*S*-**22** (21 mg, 0.11 mmol, 14% yield) as a colorless oil; and **23** (16 mg, 0.08 mmol, 10% yield) as a colorless oil.

2*R*-**21**: $[\alpha]_D$ –8.0 (*c* 0.8, $CDCl_3$); IR (ATR) 3431, 2941, 2873, 1764, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.67 (d, $J_{5.4}$ = 5.7 Hz, $J_{5,8eq}$ = 2.1 Hz, 1H, H-5), 3.88–3.67 (m, 4H, 2xH-4, 2xH-2'), 2.74 (d, J_{gem} = 11.6 Hz, 1H, H-8_{ax}), 2.57 (d, $J_{1,8eq}$ = 5.4 Hz, 1H, H-1), 2.23 (ddd, J_{gem} = 11.6 Hz, $J_{8eq,1}$ = 5.4 Hz, $J_{8eq,5}$ = 2.1 Hz, 1H, H-8_{eq}), 2.06 (m, 1H, H-5'), 1.78 (m, 1H, H-4'), 1.52 (m, 4H, 2xH-3', H-4', H-5'); ^1H NMR (250 MHz, C_6D_6) δ 3.71 (dd, $J_{5.8eq}$ = 5.7 Hz, $J_{5,4eq}$ = 3.0 Hz, 1H, H-5), 3.42 (td, J_{gem} = $J_{2'ax,3'ax}$ = 11.7 Hz, $J_{2'ax,3'eq}$ = 3.0 Hz, 1H, H.2ax), 3.35 (m, 1H, 2'eq), 3.42 (dt, J_{gem} = 11.4 Hz, $J_{4eq,5}$ = $J_{4eq,8eq}$ = 3.0 Hz, 1H, H.4eq), 3.11 (d, J_{gem} = 11.4 Hz, 1H, H-4ax), 2.29-2.16 (m, 3H, H-1, H-5'ax, H-8ax), 1.63 (m, 1H, H-5'eq), 1.47 (dtd, 1H, J_{gem} = 11.0 Hz, $J_{8eq,5}$ = $J_{8eq,1}$ = 5.7 Hz, $J_{8eq,4eq}$ = 3.0 Hz, 1H, H-8eq), 1.38-1.11 (m, 4H, 2xH3', 2xH-4'); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1 (C-7), 94.6 (C-2), 76.2 (C-5), 62.8 (C-4), 62.2 (C-2'), 48.8 (C-1), 32.9 (C-5'), 30.2 (C-8), 25.0 (C-3'), 18.0 (C-4'); ^{13}C NMR (62.5 MHz, C_6D_6) δ 174.1 (C-7), 94.8 (C-2), 75.5 (C-5), 62.8 (C-4), 61.9 (C-2'), 49.0 (C-1), 33.3 (C-5'), 30.0 (C-8), 25.3 (C-3'), 18.3 (C-4'). HRMS *m/z* (ESI-TOF) calcd for $[C_{10}H_{14}O_4 + Na]^+$: 221.0790, found: 221.0782.

2*S*-**22**: $[\alpha]_D$ –50.3 (*c* 0.3, $CDCl_3$); IR (ATR) 3433, 2941, 2872, 1754, 1719 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.72 (br t, $J_{5,4eq}$ = $J_{5,8eq}$ = 4.5 Hz, 1H, H-5), 4.00 (d, J_{gem} = 12.6 Hz, 1H, H-4_{ax}), 3.80 (m, 3H, 2xH-2' and H-4_{eq}), 2.67 (d, $J_{1,8eq}$ = 4.5 Hz, 1H, H-1), 2.35 (dt, J_{gem} = 11.0 Hz, $J_{8eq,1}$ = $J_{8eq,5}$ = 4.5 Hz, 1H, H-8_{eq}), 2.22 (d, J_{gem} = 11.0 Hz, 1H, H-8_{ax}), 1.96 (m, 1H, H-5'), 1.81 (m, 1H, H-4'), 1.62 (m, 2H, H-3', H-4'), 1.47 (m, 2H, H-3', H-5'); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.5 (C-7), 96.9 (C-2), 77.3 (C-5), 65.1 (C-4), 62.5 (C-2'), 49.3 (C-1), 34.3 (C-5'), 29.8 (C-8), 24.6 (C-3'), 18.8 (C-4'). HRMS *m/z* (ESI-TOF) calcd for $[C_{10}H_{14}O_4 + Na]^+$: 221.0790, found: 221.0780.

23: $[\alpha]_D$ –38.2 (*c* 1.2, $CDCl_3$); IR (ATR) 3426, 2943, 2874, 1756, 1722 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.87 (br s, 1H, H-8), 4.59 (ddd, *J* = 7.2Hz, *J* = 4.1 Hz, *J* = 0.6Hz, 1H, H-5), 4.07 (m, 2H, H-6 and H-1), 3.57 (d, J_{gem} = 12.4 Hz, 1H, H-6), 2.58 (m, 1H, H-2), 2.42 (m, 2H, H-13), 2.24 (d, J_{gem} = 12.6

Hz, 1H, H-11ax), 2.00 (m, 1H, H-11eq), 1.75 (m, 1H, H-9), 1.60-1.38 (m, 3H, H-9, 2xH-10); ^{13}C NMR (90 MHz, $CDCl_3$) δ 177.9 (C-3), 96.2 (C-8), 76.8 (C-5), 69.2 (C-6), 68.2 (C-1), 44.5 (C-2), 31.0 (C-13), 29.1 (C-9), 24.3 (C-11), 12.7 (C-10). HRMS *m/z* (ESI-TOF) calcd for $[C_{10}H_{14}O_4 + Na]^+$: 221.0784, found: 221.0785.

*(2R,3R,5S)-Methyl 5-hydroxy-2-phenyltetrahydro-2H-pyran-3-carboxylate (**24**).* To a solution of the bicyclic lactone **2** (55 mg, 0.269 mmol) in methanol (2 mL) was added NaMeO (16mg, 0.296 mmol) and the reaction was heated to the reflux temperature while stirring. After 12h, the reaction was quenched by addition of 1M HCl, the organic phase was separated, dried with $MgSO_4$ and concentrated under vacuum. The resulting oil was purified by column chromatography (hexanes–Et_2O, 2:1) to give compound **24** (41 mg, 0.17 mmol, 65% yield) as a colorless oil: $[\alpha]_D$ +18.2 (*c* 0.6, $CDCl_3$); IR (ATR) 3446, 2951, 2867, 1782, 1730 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34–7.28 (m, 5H, H-Ph), 4.45 (d, $J_{2ax,3ax}$ = 10.0 Hz, 1H, H-2), 4.15 (ddd, J_{gem} = 10.8 Hz, $J_{6eq,5ax}$ = 4.9 Hz, $J_{6a,4eq}$ = 2.2 Hz, 1H, H-6$_{eq}$), 3.90 (m, 1H, H-5), 3.47 (s, 3H, CH_3O), 3.36 (dd, J_{gem} = 10.8 Hz, $J_{6ax,5ax}$ = 10.2 Hz, 1H, H-6$_{ax}$), 2.82 (ddd, $J_{3ax,4ax}$ = 12.5 Hz, $J_{3ax,2ax}$ = 10.0 Hz, $J_{3ax,4eq}$ = 3.9 Hz, 1H, H-3ax), 2.40 (ddd, J_{gem} = 12.5 Hz, $J_{4eq,3ax}$ = 3.9 Hz, $J_{4eq,6eq}$ = 2.2 Hz, 1H, H-4eq), 1.87 (q, J_{gem} = 12.5 Hz, $J_{4ax,5ax}$ =12.5 Hz, $J_{4ax,3ax}$ =12.5 Hz, 1H, H-4ax); ^{13}C NMR (90 MHz, $CDCl_3$) δ 172.5 (C=O), 139.3 (C-Ar), 128.5 (4xC, C-Ar), 126.9 (C-Ar), 81.1 (C-2), 72.9 (C-6), 65.26 (C-5), 51.8 (*C*H_3O), 49.1 (C-3), 36.5 (C-4). HRMS (ESI-TOF) calcd for $[C_{13}H_{16}O_4 + Na]^+$: 259.0941, found: 259.0943.

*(3S,5R,6R)-Methyl 3-hydroxy-1,7-dioxaspiro[5.5]undecane-5-carboxylate (**25**).* To a solution of the tricyclic lactone 2*R*-**21** (40 mg, 0.2 mmol) in methanol (3 mL) was added NaMeO (54.5 mg, 1.01 mmol) and the reaction was heated to the reflux temperature while stirring. After 12h, the reaction was quenched by addition of saturated aqueous ammonium chloride; the organic phase was separated, dried with $MgSO_4$ and concentrated under vacuum. The resulting oil was purified by column chromatography (hexanes–Et_2O, 1:1) to give **25** (28 mg, 0.12 mmol, 62% yield) as a colorless oil: $[\alpha]_D$ –72.0 (*c* 0.4, $CDCl_3$); IR (ATR) 3468, 2952, 2870, 1775, 1731 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 5.62 (d, $J_{OH,3}$ =

11.2 Hz, 1H, OH), 3.82 (ddd, J_{gem} = 11.7 Hz, $J_{2eq,3eq}$ = 3.9 Hz, $J_{2eq,4eq}$ = 1.9 Hz, 1H, H-2eq), 3.61 (dd, J_{gem} = 11.7 Hz, $J_{2ax,3eq}$ = 2.2 Hz, 1H, H-2ax), 3.53 (ddd, $J_{3eq,OH}$ = 11.2 Hz, $J_{3eq,2eq}$ = 3.9 Hz, $J_{3eq,2ax}$ = 2.2 Hz, 1H, H-3eq), 3.36 (m, 2H, H-8), 3.16 (s, 3H, CH_3O), 2.67 (dd, $J_{5eq,4ax}$ = 6.6 Hz, $J_{5eq,4a}$ = 1.4 Hz, 1H, H-5eq), 2.12 (ddd, J_{gem} = 14.5 Hz, $J_{4ax,5eq}$ = 6.6 Hz, $J_{4ax,3eq}$ = 4.2 Hz, 1H, H-4ax), 1.80 (m, 1H, H-4eq), 1.64 (m, 1H, H-11), 1.42 (m, 1H, H-11), 1.22 (m, 3H, H-9, 2xH-10), 1.12 (m, 1H, H-9); ^{13}C NMR (100 MHz, C_6D_6) δ 176.3 (C=O), 94.9 (C-6), 66.2 (C-2), 62.7 (C-3), 61.3 (C-8), 52.1 (*C*H_3O), 47.7 (C-5), 33.6 (C-11), 27.5 (C-4), 25.4 (C-10), 19.0 (C-9). HRMS (ESI-TOF) calcd for $[C_{11}H_{18}O_5 + Na]^+$: 253.1046, found: 253.1049.

When the reaction was quenched with 1M HCl, the epimer *(3S,5S,6R)-methyl 3-hydroxy-1,7-dioxaspiro[5.5]undecane-5-carboxylate (epi-**25**)* was also isolated: $[\alpha]_D$ –1.5 (*c* 0.3, $CDCl_3$); IR (ATR) 3436, 2941, 2872, 1740, 1720 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 3.46–3.37 (m, 4H, H-2ax, 2xH-8, H-3), 3.35 (s, 3H, CH_3O), 3.27 (ddd, J_{gem} = 11.9 Hz, $J_{2eq,3eq}$ = 2.5 Hz, $J_{2eq,4eq}$ = 1.9 Hz, 1H, H-2eq), 2.96 (dd, $J_{5ax,4ax}$ = 13.1 Hz, $J_{5ax,4eq}$ = 4.2 Hz, 1H, H-5ax), 2.46 (ddd, J_{gem} = 13.8 Hz, $J_{4ax,5ax}$ = 13.1 Hz, $J_{4ax,3eq}$ = 2.9 Hz, 1H, H-4ax), 2.21 (m, 1H, H-11), 1.90 (m, 1H, H-10), 1.78 (m, 1H, H-4eq), 1.70 (m, 1H, H-11), 1.40 (m, 2H, H-9, H-10), 1.10 (m, 1H, H-9); ^{13}C NMR (100 MHz, C_6D_6) δ 171.9 (C=O), 96.2 (C-6), 64.8 (C-2), 64.5 (C-8), 61.6 (C-3), 51.6 (*C*H_3O), 45.7 (C-5), 33.6 (C-11), 29.5 (C-4), 25.5 (C-10), 19.2 (C-9). HRMS (ESI-TOF) calcd for $[C_{11}H_{18}O_5 + Na]^+$: 253.1046, found: 253.1048.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds and 2D NMR spectra for compounds **15**, **17**, **18**, **19**, **20, 21, 22** and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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