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Departament de Química

PHOTOCHEMICAL STUDIES TOWARD THE SYNTHESIS OF NATURAL PRODUCTS

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Vist i plau

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Dra. Marta Figueredo Galimany

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Never say never. Because limits like fears are ofter just an illusion.

***Michael Jordan, Basketball Hall of fame, 2009**.*

Pour mes parents, pour ma famille

A l’Anna

Table of contents

Table of contents

Chapter 1:
Introduction and objectives

Il ne faut avoir aucun regret pour le passé,
aucun remords pour le présent, et une confiance
inébranlable pour l'avenir.
Jean Jaurès

1.1. Natural and nature-like cyclobutanes

Cyclobutane derivatives are remarkable compounds not only as attractive natural products,[1] as in the pheromone field where several structures bearing a cyclobutane ring are known,[2] but also for their versatility in being transformed into a variety of elaborated compounds by ring enlargement or ring-opening reactions.[3]

Some cyclobutanes play a crucial role in the pharmaceutical field, as it is the case of several nucleoside analogues that present a strong activity against the replication of some viruses (e.g. Herpes or HIV).[4]

The monoterpene (+)-grandisol, **1**, isolated in 1969 as the *major* product from the pheromone produced by boll weevil's males *Anthonomus grandis*,[5] which is an important pest affecting cotton crops, has become an important tool for the management of this species through pheromone traps (Figure 1). (+)-Grandisol has also been found to be a component of a

[1] (a) Corey, E. L. ; Cheng, X. *The Logic of Chemical Synthesis*, Wiley, New York, **1989**. (b) Bloor, S. J. *Tetrahedron Lett.* **1993**, *34*, 5617-5618. (c) Armone, A.; Nasini, G.; Vajna de Pava, O. *J. Chem. Soc, Perkin Trans I* **1993**, 2723-2725. (d) Hinkley, S. F. R.; Perry, N. B.; Weavers, R. T. *Tetrahedron Lett.* **1994**, *35*, 3775-3776. (e) Norte, M.; Fernández, J. J.; Souto, M. L. *Tetrahedron Lett.* **1994**, 4607-4610. (f) Kaiwar, V.; Reese, C. B.; Gray, E. J.; Neidle, S. *J. Chem. Soc, Perkin Trans. I* **1995**, 2281-2287. (g) Namyslo, J. C.; Haufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485-1537. (h) Iriondo-Alberdi, J.; Greaney, M. F. *Eur. J. Org. Chem.* **2007**, 4801-4815. (i) Bach, T.; Hehn, J. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 1000-1045.

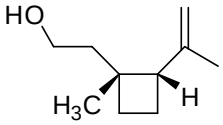
[2] Morgan, E. D.; Mandava, N. B. in *CRC Series in Naturally Occuring Pesticides, vol. IV. Part A* (Ed.: N. B. Mandava), CRC Press, Inc., Boca Raton, Florida, **1988**, 203.

[3] (a) Conia, J. M.; Robson, M. J. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 473-485. (b) Ali, S. M.; Lee, T. V.; Roberts, S. M. *Synthesis* **1977**, 155-166. (c) Brady, W. T. *Tetrahedron* **1981**, *37*, 2949-2966. (d) Oppolzer, W. *Acc. Chem. Res.* **1982**, *15*, 135-141. (e) Trost, B. M. *Top. Curr. Chem* **1986**, *133*, 3-82. (f) Wong, H. N. C.; Lau, K.-L.; Tam, K.-F. *Top Curr. Chem.* **1986**, *133*, 83-157. (g) Bellus, D. Ernst, B. *Angew. Chem. Int. Ed. Engl*. **1988**, *27*, 797-827. (h) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, New York, **1990**.

[4] (a) Ichikawa, E.; Kato, K. *Synthesis* **2002**, 1-28. (b) Ortuño, R. M.; Moglioni, A. G.; Moltrasio, G. Y. *Curr. Org. Chem.* **2005**, *9*, 237-259 and references cited therein.

[5] Tumilson, J. H.; Hardee, D. D.; Gueldner, R. C.; Thompson, A. C.; Hedin, P. A.; Minyard, J. P. *Science* **1969**, *166*, 1010-1020.

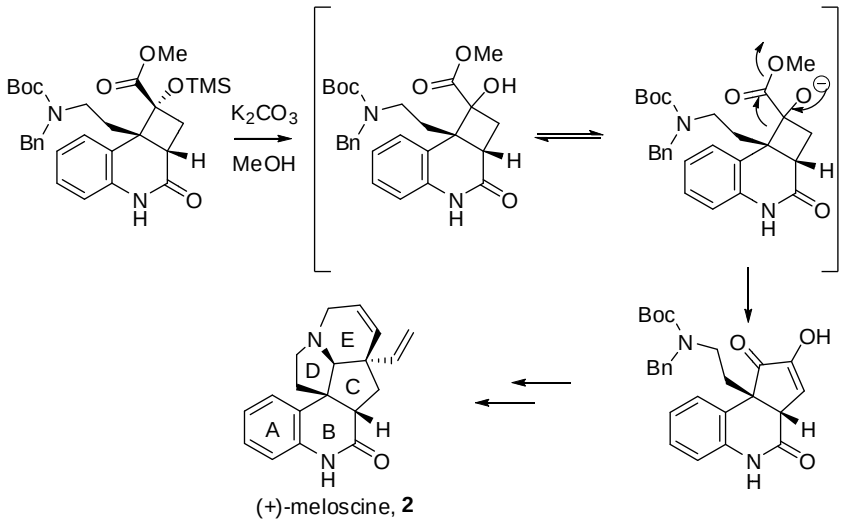
pheromone complex from bark beetles *Pityophthorus pityographus*,[6] *Pityogenes bidentatus*, *Pityogenes quadridens*, *Pityogenes calcatarus*[7] and *Curculio caryae*.[8]



1

Figure 1. Boll weevil and the main compound of its pheromone, **1**.

There are also examples of natural product syntheses in which the key step is a ring enlargement reaction or a ring opening reaction of a cyclobutane unit. For instance, the construction of the C ring of (+)-meloscine, **2**, has been performed through an enlargement of a cyclobutane core by means of a retro-benzilic acid like rearrangement (Scheme 1).[9]



Scheme 1. Synthesis of (+)-meloscine, **2**, Bach *et al.* (2009).

In the last decade, the preparation and biological activity studies of some cyclobutane nucleoside analogues such as cyclobut-A, **3**, and cyclobut-G, **4**, (Figure 2) have been

[6] Francke, W.; Pan, M.-L.; Koning, W. A.; Mori, K.; Puapoomchareon, P.; Heuer, H.; Vitè, J. P. *Naturwissenschaften* **1987**, *74*, 343-345.
[7] Francke, W.; Bartels, J.; Krohn, S.; Schulz, S.; Baader, E.; Tengo, J.; Schneider, D. *Pure & Appl. Chem.* **1989**, *61*, 539-542.
[8] Hedin, P. A.; Dollar, D. A.; Collins, J. K.; Dubois, J. G.; Mulder, P. G.; Hedger, G. H.; Smith, M. W.; Eikenbary, R. D. *J. Chem. Ecol.* **1997**, *23*, 965-977.
[9] Selig, P.; Herdtweck, E.; Bach, T. *Chem. Eur. J.* **2009**, *15*, 3509-3525.

described. These compounds present a wide range of potential pharmaceutical applications.[10]

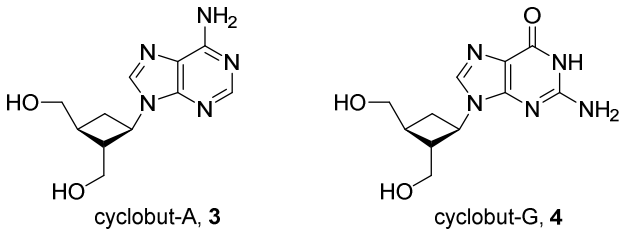


Figure 2. Cyclobutane nucleoside analogues Cyclobut-A, **3**, and Cyclobut-G, **4**.

1.2. Photochemistry as a useful tool for the synthesis of natural and unnatural compounds

Synthetic organic photochemistry has provided an extremely powerful method for the conversion of simple substrates into more complex products. [2,11] Although impressive large-scale industrial applications (for example, vitamin D synthesis)[12] are being conducted, the pharmaceutical industry has not generally embraced photochemical reactions in the routine synthesis of new drug substances. Specifically, several difficulties associated with the performance of preparative photoreactions on large scale have been perceived to be a serious problem to be solved before their routine application. [1i,13]

Some benefits of the photochemistry are the easy access to complex molecules that can be really interesting in terms of production's costs, and the possibility to open new perspectives in the synthesis of product families or libraries otherwise difficult to achieve with ground-state reactions.[14]

The first reported [2+2] photochemical reaction was published one hundred years ago in a classical work by Ciamician and Silber[15] who, using the sun as energy source, induced the

[10] (a) Norbeck, D. W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erickson, J.; Clement, J.; Swanson, R; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. *J. Med. Chem.* **1990**, *33*, 1281-1285. (b) Bisacchi, G. S.; Braitman, A.; Cianti, C. W.; Clark, J. M., Field, A. K.; Hagan, M. E.; Hockstein, D. R.; Malley, M. F.; Mitt, T.; Slusarchyk, W. A.; Sundeen, J. E.; Terry, B. J.; Toumari, A.V.; Veaver, E. R.; Young, M. G.; Zahler, R. *J. Med. Chem.* **1991**, *34*, 1415-1421. (c) Bisacchi, G. S.; Singh, J. Godfrey, J. J.; Kissick, T. P.; Mitt, T.; Malley, M. F.; Di Marco, J. D.; Gougoutas, J. Z.; Mueller, R. H.; Zahler, R. *J. Org. Chem.* **1995**, *60*, 2902-2905. (d) Blanco, J. M.; Caamaño, O.; Fernández, F.; Gómez, G.; Nieto, I. *Synthesis* **1996**, 281-285.

[11] (a) Coyle, J. D., Ed.; Royal Society of Chemistry: London, **1986**; Special Publication No. 57. (b) CRC Handbook of Organic Photochemistry and Photobiology; Horspool, W. M.; Lenci, F.; Eds.; CRC Press: Boca Raton, Florida, **2004**.

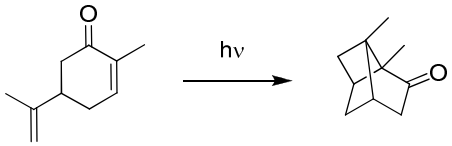
[12] Eschenmoser, A.; Wintner, C. E. *Science* **1977**, *196*, 1410-1420.

[13] (a) Van Gerven, T.; Mul, G.; Moulijn, J.; Stankiewicz, A. *Chem. Eng. Process.* **2007**, *46*, 781-789. (b) Coyle, E. E.; Oelgemöller, M. *Photochem. Photobiol. Sci.* **2008**, *7*, 1313-1322.

[14] Yoon, T. P.; Ischay, M. A.; Du, J. *Nature Chemistry* **2010**, *2*, 527-532.

[15] Ciamician, G.; Silber, P. *Ber.Dtsch. Chem. Ges.* **1908**, *41*, 1928-1935.

transformation of several organic compounds, carvone among them, although at that time the structure of the photoproducts could not be unequivocally established. About fifty years later, Büchi and co-workers exposed carvone, **5**, to California's sunlight and described the formation and characterization of a [2+2] cycloadduct, which was called photocarvone, **6**, (Scheme 2).[16]



5 **6**

Scheme 2. Intramolecular [2+2] photocycloaddition of carvone, **5**.

The latter publication brought the photochemical reactions to the spotlight and its synthetic potential was suggested in successive studies published by Corey,[17] Eaton,[18] and de Mayo.[19] Ever since, the interest for this reaction emerged from a mechanistic, theoretic and synthetic application points of view.

For more than forty years, the [2+2] photocycloaddition of cyclic enones to unsaturated substrates has been widely used in the total synthesis of natural products. Remarkable examples are annotinine,[20] caryophyllene,[21] (+)-fomannosin,[22] (-)-italicene,[23] (-)-sulcatine G,[24] and (+)-pentacycloanammoxic acid (Figure 3).[25]

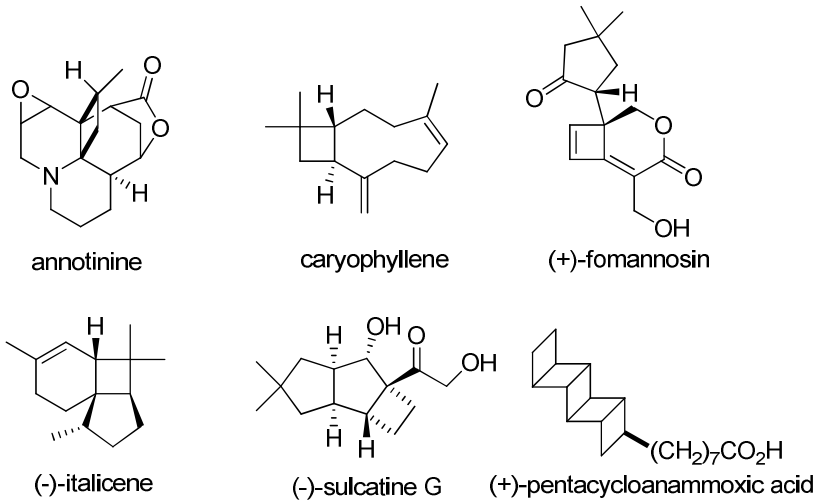
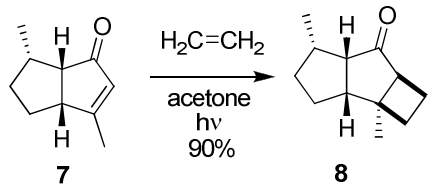


Figure 3. Natural products prepared by means of [2+2] photocycloaddition reaction of enones to unsaturated substrates.

[16] Büchi, G.; Goldman, I. M. *J. Am. Chem. Soc.* **1957**, *79*, 4741-4748.
[17] Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570-5583.
[18] Eaton, P. E. *Acc. Chem. Res.* **1968**, *1*, 50-57.
[19] (a) de Mayo, P. *Acc. Chem. Res.* **1971**, *4*, 41-47. (b) Loutfy, R. O.; de Mayo, P. *J. Am. Chem. Soc.* **1977**, *99*, 3559-3565.
[20] Wiesner, K.; Poon, L.; Jirkovsky, I.; Fishman, M. *Can. J. Chem.* **1969**, *47*, 433-444.
[21] Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485-492.
[22] Matsumoto, T.; Miyano, K.; Ohfune, Y.; Azuma, S. *Tetrahedron Lett.* **1974**, 1545-1549.
[23] Faure, S.; Piva, O. *Tetrahedron Lett.* **2001**, *42*, 255-259.
[24] Mehta, G.; Sreenivas, K. *Tetrahedron Lett.* **2002**, *43*, 3319-3321.
[25] Mascitti, V.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 3118-3119.

Considering that, in general, the biological activity of a chiral compound is associated to only one of its enantiomers, the enantioselective synthesis of cyclobutane nucleoside analogues is really a relevant objective for the pharmaceutical industry. To this purpose, different approaches can be considered: separation of diastereomers by crystallization or chromatography and/or formation of the new bonds in a stereocontrolled manner.

In recent years, many studies about induction of stereoselectivity involving photochemical reactions of enones have been performed and applied to stereoselective synthesis.[26] A stereogenic centre within a cyclic enone has been described to act as an effective control device giving good facial diastereoselectivitiy in many cases. As an example, Piers and Orellana described the preparation of the tricyclic ketone **8** with complete stereoselectivity resulting from the exclusive approach of the ethylene to the less sterically hindered face of the enone **7** (Scheme 3).[27]



Scheme 3. [2+2] Photocycloaddition of enone **7** to ethylene, Piers and Orellana (2001).

Although the [2+2] photocycloaddition of cyclic enones to alkenes has been extensively studied, less efforts have been focused on the use of α,β−unsaturated lactones in such reactions.[28] Previous to the work of our group, few studies on the photochemical behaviour, facial diastereoselectivity and asymmetric induction in the [2+2] photocycloadditions of these lactones to unsaturated substrates had been carried out.

The work of our group has been mainly focused on the use of chiral 5-substituted 2(5*H*)-furanones as suitable substrates for stereoselective synthesis through photochemically induced [2+2] cycloaddition. In this context, the *anti/syn* nomenclature that will be used in the present work describes the two alternative approaches of the unsaturated substrates to the diastereotopic faces of the 5-substituted 2(5*H*)-furanones as illustrated in Figure 4.

[26](a) Ogino, T.; Yamada, K.; Isogai, K. *Tetrahedron Lett.* **1977**, 2445-2448. (b) Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* **1982**, *104*, 1742-1744. (c) Lange, G. L.; Decicco, C.; Tan, S. L.; Chamberlain, G. *Tetrahedron Lett.* **1985**, *26*, 4707-4710. (d) Demuth, M.; Palomer, A.; Sluma, H.-D.; Dey, A. K.; Kruger, C.; Tsay, Y.-H. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1117-1119. (e) Lange, G. L.; Decicco, C.; Lee, M. *Tetrahedron Lett.* **1987**, *28*, 2833-2836. (f) Lange, G. L.; Organ, M. G. *Tetrahedron Lett.* **1993**, *34*, 1425-1428. (g) García-Expóxito, E.; Álvarez-Larena, A.; Branchadell, V.; Ortuño, R. M. *J. Org. Chem.* **2004**, *69*, 1120-1125.
[27] Piers, E.; Orellana, A. *Synthesis* **2001**, 2138-2142.
[28] (a) Fillol, L.; Miranda, M. A.; Morera, I. M.; Sheikh, H. *Heterocycles*, **1990**, *31*, 751-782. (b) Demuth, M.; Mikhail, G. *Synthesis* **1989**, 145-162.

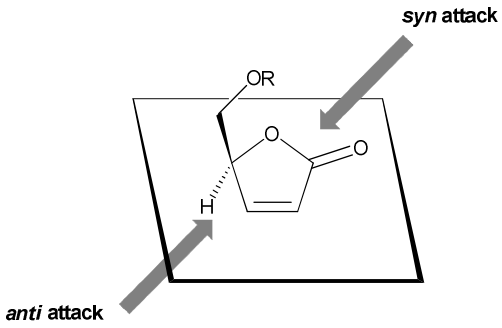
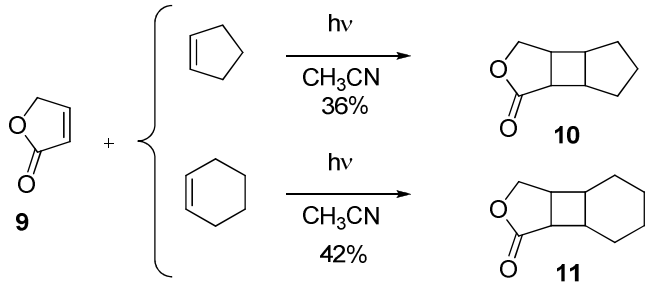


Figure 4. *Anti/syn* approaches of an unsaturated substrate to 5-substituted 2(5*H*)-furanones.

1.3. 2(5*H*)-Furanones in [2+2] photochemical reactions

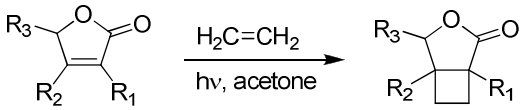
In 1972, Tada *et al.* published the first study related to the photoreactivity of 2(5*H*)-furanones with olefins.[29] They described that crotolactone, **9**, reacts with cyclopentene and cyclohexene giving the corresponding [2+2] photocycloaddition products in 36% and 42% yield, respectively, (Scheme 4) and they suggested that the photocycloaddition process occurs through the excited triplet state of the lactone.



Scheme 4. [2+2] Photocycloaddition of crotolactone with cyclopentene and cyclohexene, Tada *et al.* (1972).

Later on, Kosugi *et al.* published an article which has become an unavoidable reference for the study of [2+2] photocycloaddition reactions of 2(5*H*)-furanones with alkenes (Scheme 5).[30] In this work, they studied the effect of substituents and reaction conditions in the distribution of products of the [2+2] photocycloaddition of lactones with the general structure **9** and **12** to olefins. They found that the best solvent for the photoreaction was acetone, which seemed to play also a role as sensitizer.

[29] Tada, M.; Kokubo, T.; Sato, T. *Tetrahedron* **1972**, *7*, 2121-2125.
[30] Kosugi, H.; Sekiguchi, S.; Sekita, R.; Uda, H. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 520-528.



9, **12** **13**

9, R_1=R_2=R_3=H	70%
12a, R_1=R_3=H, R_2=Me	44%
12b, R_1=R_3=H, R_2=Ph	49%
12c, R_1=Ph, R_2=R_3=H	52%
12d, R_1=R_2=H, R_3=Me	35%

Scheme 5. Study on the [2+2] photocycloaddition of 2(5*H*)-furanones **9** and **12** to ethylene, Kosugi *et al.* (1976).

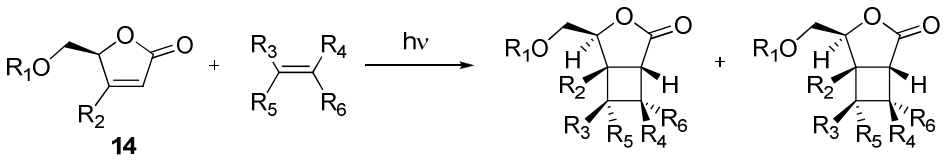
These photoreactions afforded the expected cycloadducts **13** albeit in moderate yields. In particular, the cycloadducts derived from 5-methyl-2(5*H*)-furanone, **12d**, (β-angelica lactone, R_1=R_2=H, R_3=Me) were obtained as a 60:40 *anti*:*syn* diastereomeric mixture.

A work published in 1991[31] was the first of a number of studies performed by our research group in the field of the [2+2] photocycloaddition reactions of chiral 2(5*H*)-furanones to ethylene.[32] The main aim of these studies was to get a deeper insight into the factors controlling the facial diastereoselectivity of these reactions. Thus, variables such as the 2(5*H*)-furanone substitution, the temperature, the solvent and the filter were evaluated (Table 1).

[31] Alibés, R; Bourdelande, J. L.; Font, J. *Tetrahedron: Asymmetry* **1991**, *2*, 1391-1402.

[32] (a) Alibés, R.; Bourdelande, J. L.; Font, J. *Tetrahedron Lett.* **1993**, *34*, 7455-7458. (b) Alibés, R.; Bourdelande, J. L.; Font, J. *Tetrahedron Lett.* **1994**, *35*, 2587-2588. (c) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A. *J. Braz. Chem. Soc.* **1995**, *6*, 119-121. (d) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A.; Parella, T. *Tetrahedron* **1996**, *52*, 1267-1278. (e) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M.; Rustullet, A.; Alvarez-Larena, A.; Piniella, J. F.; Parella, T. *Tetrahedron Lett.* **2003**, *44*, 69-71. (f) Racamonde, M.; Alibés, R.; Figueredo, M.; Font, J.; de March, P. *J. Org. Chem.* **2008**, *73*, 5944-5952. (g) Parés, S.; de March, P.; Font, J.; Alibés, R.; Figueredo, M. *Eur J. Org. Chem.* **2011**, 3888-3895.

Table 1. Photocycloaddition of lactones **14** to different alkenes, Font *et al.* (1991-2011).



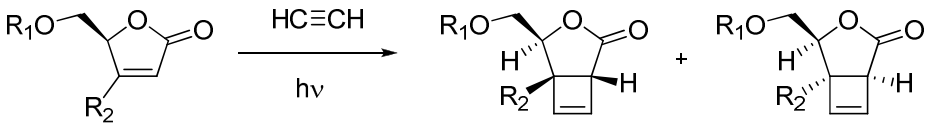
R_3=R_4=R_5=R_6=CH_3, TME
R_3=R_4=R_5=R_6=H, ethylene
R_3=R_4=OCOO, R_5=R_6=H, vinylcarbonate
R_3=R_4=H, R_5=R_6=Cl, (*Z*)-1,2-dichloroethylene
R_3=R_5=H, R_4=R_6=CH_2Cl, (*E*)-1,4-dichloro-2-butene
R_3=R_4=$CH_2OCH_2OCH_2$, R_5=R_6=H, (*Z*)-4,7-dihydro-1,3-dioxepine

	R_1	R_2	Alkene	Solvent	Filter	Yield (%)	15:16 *anti*:*syn*
14a	**H**	H	TME	ether	quartz	41	73:27
14b	**CH_3CO**	H	TME	ether	quartz	54	79:21
14c	**TBS**	CH_3	ethylene	acetone	pyrex®	89	69:31
14d	**CH_3CO**	CH_3	ethylene	acetone	pyrex®	65	56:46
14e	**CO-*t*-Bu**	CH_3	ethylene	acetone	pyrex®	70	62:38
14f	**CO-*t*-Bu**	H	vinylcarbonate	acetone	pyrex®	50	86:14
14e	**CO-*t*-Bu**	CH_3	vinylcarbonate	acetone	pyrex®	54	88:12
14f	**CO-*t*-Bu**	H	(*Z*)-1,2-dichloroethylene	acetonitrile	quartz	77	90:10
14c	**TBS**	CH_3	(*Z*)-1,2-dichloroethylene	acetonitrile	quartz	87	82:18
14e	**CO-*t*-Bu**	CH_3	(*Z*)-1,2-dichloroethylene	acetonitrile	quartz	89	88:12
14f	**CO-*t*-Bu**	H	(*E*)-1,4-dichloro-2-butene	acetonitrile	quartz	68	73:27
14f	**CO-*t*-Bu**	H	R_3=R_4=$CH_2OCH_2OCH_2$, R_5=R_6=H, (*Z*)-4,7-dihydro-1,3-dioxepine	acetonitrile	quartz	70	85:15

It was observed that increasing the size of the oxygen substituent R_1 of **14** provokes an enhancement of the antifacial diastereoselectivity. On the contrary, the substitution in R_2 decreases this stereoselectivity. No influence of the excitation type (direct or sensitized) could be highlighted.

This work was complemented with the study of the [2+2] photocycloaddition of 2(5*H*)-furanones to acetylene (Table 2).[33]

Table 2. Photocycloaddition of lactone **14** to acetylene, Font *et al.* (1998-2003).



14 **17** **18**

	R_1	R_2	Solvent	Filter	Yield (%)	17:18 *anti* : *syn*
14f	**CO-*t*-Bu**	H	acetone	pyrex®	44	70:30
14g	**COPh**	H	acetone	pyrex®	26	68:32
14h	**TBDPS**	H	acetone	pyrex®	--	--:--
14e	**CO-*t*-Bu**	CH_3	acetone	pyrex®	32	54:46
14f	**CO-*t*-Bu**	H	acetonitrile	quartz	68	66:34
14g	**COPh**	H	acetonitrile	quartz	24	66:34
14h	**TBDPS**	H	acetonitrile	quartz	--	--:--
14e	**CO-*t*-Bu**	CH_3	acetonitrile	quartz	44	53:47

Among the studied derivatives, the pivaloyl substituted furanones **14e** and **14f** gave the best overall yield and diastereofacial selectivity in these examples. The presence of a methyl group at the β position of the lactone was expected to sterically hinder the approach of acetylene but, on the other hand, the tertiary radical centre formed as a result of the attack of the alkyne of the lactone would be more stable. In fact, the presence of the methyl group diminished the rate of the photocycloaddition and led to the formation of other compounds, such as photoreduction or rearrangement products through competitive processes.[32d,34]

1.3.1. Synthesis of natural products and analogues

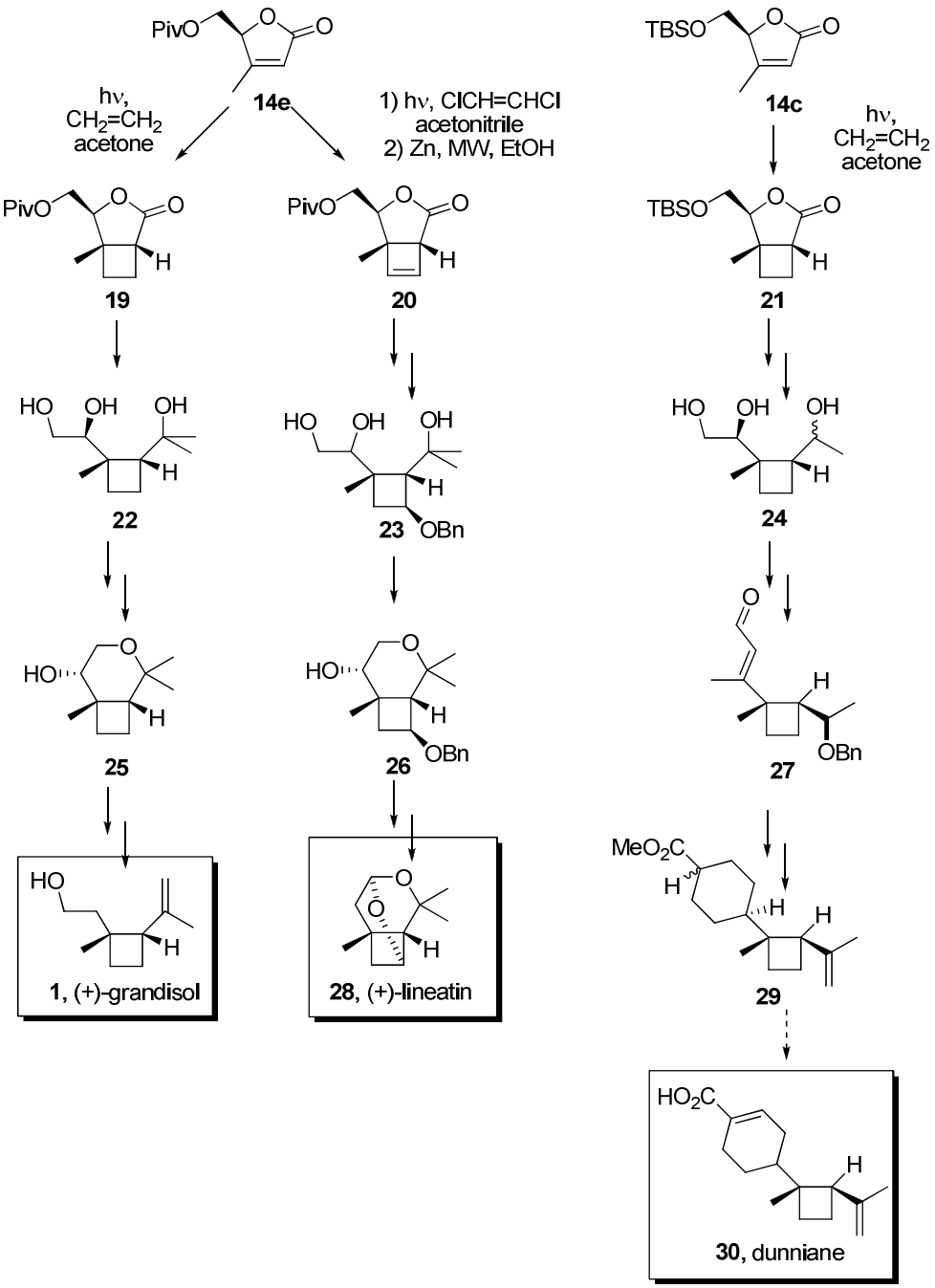
As it has been previously mentioned, our research group has been developing for a decade a research project directed to the asymmetric synthesis of cyclobutane pheromones, in which the key step is a [2+2] photocycloaddition reaction of a chiral 5-oxymethyl-2(5*H*)-furanone to an unsaturated substrate. More recently, this methodology has also been successfully applied to the synthesis of cyclobutane nucleoside analogues.

[33] (a) Gregori, A.; Alibés, R.; Bourdelande, J. L.; Font, J. *Tetrahedron Lett.* **1998**, *39*, 6961-6962. (b) Alibés, R.; de March, R.; Figueredo, M.; Font, J.; Racamonde, M. *Tetrahedron Lett.* **2001**, 42, 6695-6697. (c) Alibés, R.; de March, R.; Figueredo, M.; Font, J.; Fu, X.; Racamonde, M.; Álvarez-Larena, Á.; Piniella, J. F. *J. Org. Chem.* **2003**, *68*, 1283-1289.

[34] (a) Lange, G. L.; Organ, M. G.; Lee, M. *Tetrahedron Lett.* **1990**, *31*, 4689. (b) Lewis, F. D.; Reddy, G. D.; Elbert, J. E.; Tillberg, B. E.; Meltzer, J. A.; Kojima, M. *J. Org. Chem.* **1991**, *56*, 5311. (c) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051. (d) Capella, L.; Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1996**, *61*, 6783.

As part of this work and starting from (*S*)-4-methyl-5-pivaloyloxymethyl-2(5*H*)-furanone, **14e**, as the chiral precursor, the syntheses of (+)-grandisol, **1**,[35] and (+)-lineatin, **28**,[36] have been successfully accomplished (Scheme 6). On the other hand, furanone **14c** is the precursor of an advanced intermediate toward the sesquiterpene dunniane, **30**.[37] In those synthetic approaches, formation of the cyclobutane was achieved by [2+2] photocycloaddition of lactones **14e** or **14c** to ethylene or 1,2-dichloroethylene, which respectively delivered the *anti* cycloadducts **19**, **20** and **21** as the major products. These cycloadducts were converted into the triols **22**, **23** and **24**, which were further elaborated to the targeted compounds. Thus, the synthesis of (+)-grandisol, **1**, and (+)-lineatin, **28**, were accomplished in overall yields of 24% and 15%, respectively. The synthetic approach to dunniane required the formation of a cyclohexene moiety, which was attained by the intermediacy of enone **27** in a global yield of 7% from **14c**.

[35] (a) Alibés, R.; Bourdelande, J. L.; Font, J.; Parella, T. *Tetrahedron* **1996**, *52*, 1279-1292. (b) de March, P.; Figueredo, M.; Font, J.; Raya, J. *Org. Lett.* **2000**, *2*, 163-165.
[36] Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M.; Parella, T. *Org. Lett.* **2004**, *6*, 1449-1452.
[37] Parés, S.; Alibés, R.; Figueredo, M.; Font, J.; Parella, T. *Eur. J. Org. Chem.* **2012**, *7*, 1404-1417.

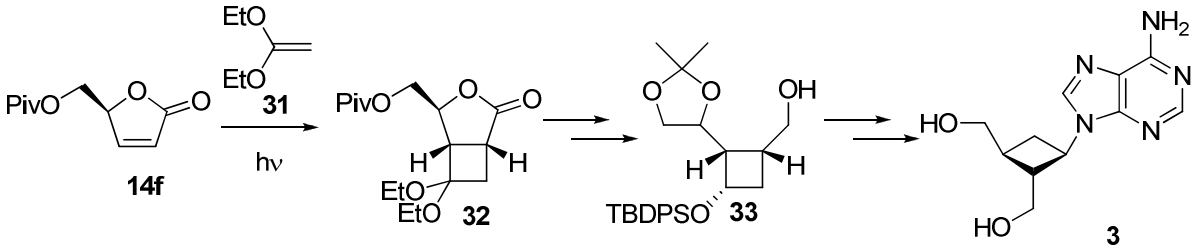


Scheme 6. Syntheses of (+)-grandisol, **1**, Alibés *et al.* (1996) and (+)-lineatin, **28**, Alibés *et al.* (2006) and approach to dunniane, **30**, Alibés *et al.* (2012).

The experience acquired in the preparation of enantiomerically pure cyclobutane compounds, as well as the biological activity displayed by some cyclobutane nucleoside analogues,[38] prompted our group to undertake a research program focussed on this field. As a result, the total synthesis of cyclobut-A, **3**,[39] a carbocyclic analogue of Oxetanocin A was

[38] (a) Ichikawa, E.; Kato, K. *Synthesis* **2002**, 1-28. (b) Ortuño, R. M.; Moglioni, A. G.; Moltrasio, G. Y. *Curr. Org. Chem.* **2005**, *9*, 237-259 and references cited therein.
[39] Rustullet, A.; Alibés, R.; de March, P.; Figueredo, M.; Font, *J. Org. Lett.* **2007**, *9*, 2827-2830.

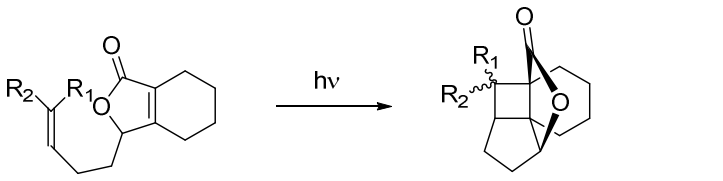
completed according to the sequence shown in Scheme 7.[40] In this case, the synthesis started from the readily available chiral 2(*5H*)-furanone **14f**, whose photochemical reaction with diethoxyethylene, **31**, provided the key cyclobutane intermediate **32** (Scheme 7).



Scheme 7. Synthesis of cyclobut-A, **3**, Alibés *et al.* (2007).

1.3.2. Intramolecular cycloadditions

The intramolecular [2+2] photocycloaddition of a cyclic α,β-enone substituted by a properly located distant alkene has proved to be an important synthetic method for the construction of polycyclic compounds including cyclobutane moieties. Coates *et al*. reported that irradiation of lactones **34** and **35** in acetone and benzene, respectively, gave the corresponding tricyclic lactones **36** and **37** in good yields (Scheme 8).[41]



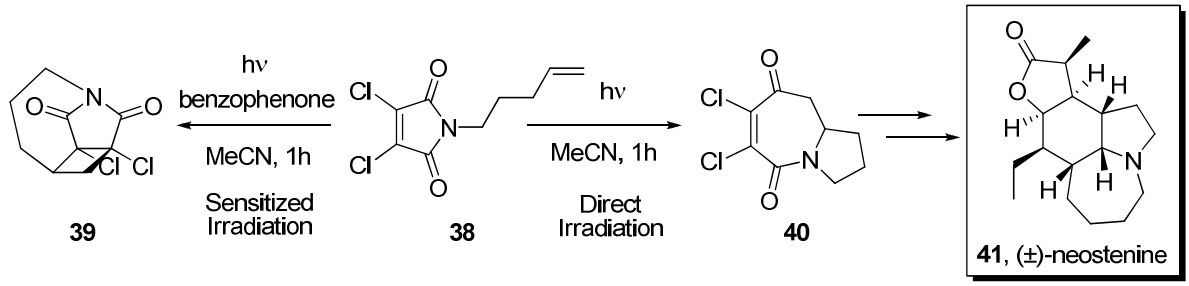
34, $R_1 = R_2 = H$
35, $R_1 = CH_3$; $R_2 = H$

36, $R_1 = R_2 = H$ 77%
37, $R_1 = CH_3$; $R_2 = H$ 66%

Scheme 8. Intramolecular [2+2] photocycloaddition of cyclic α,β-enones, Coates *et al.* (1982).

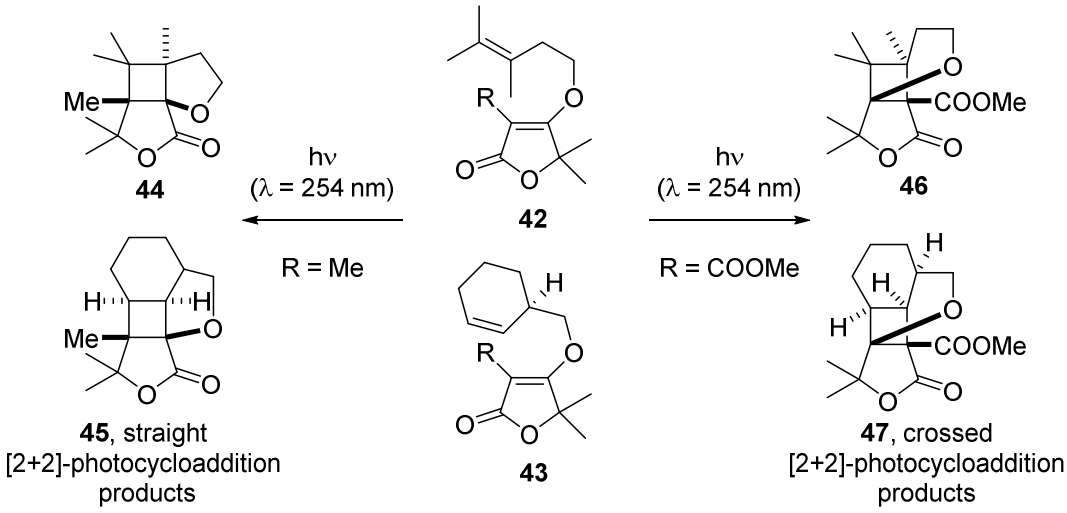
A few years ago, Booker-Milburn and co-workers described the formation of azepane derivatives by a [5+2] intramolecular photocycloaddition of specifically substituted maleimides (Scheme 9).[42] In the course on their investigations, they found that the photochemical behavior of these maleimides depends largely on the type of irradiation, and that an alternative [2+2] photocycloaddition could also take place. Thus, control of the reaction pathway was achieved by choice of either direct or photosensitized irradiation.[43] The [5+2] photocycloaddition reaction enabled them to perform a protecting group free synthesis of (±)-neostenine, **41**.

[40] Field, A. K.; Tuomari, A. V.; McGeever-Rubin, B.; Terry, B. J.; Mazina, K. E.; Haffey, M. L.; Hagen, M. E.; Clark, J. M.; Braitman, A.; Slusarchyk, W. A.; Young, M. G.; Zahler, R. *Antiviral Res.* **1990**, *13*, 41-52.
[41] Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3597-3607.
[42] Lainchbury, M. D.; Medley, M. I.; Taylor, P. M.; Hirst, P.; Dohle, W.; Booker-Milburn, K. I. *J. Org. Chem.* **2008**, *73*, 6497-6505 and references cited therein.
[43] Roscini, C.; Cubbage, K.; Berry, M.; Orr-Ewing, A. J.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed.* **2009**, *48*, 8716-8720.



Scheme 9. Photochemical behavior of maleimide **38**, Booker-Milburn *et al.* (2008).

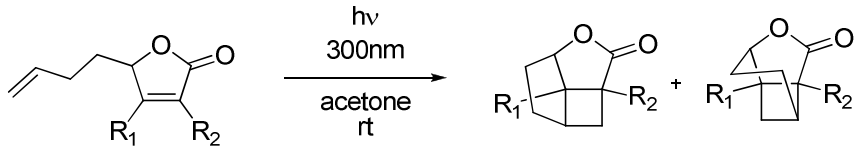
Similarly, Bach and co-workers described that an intramolecular [2+2] photocycloaddition of lactones **42** and **43** can occur either in a straight or in a crossed fashion (Scheme 10).[44] They have investigated the influence of three structural parameters: the substituent R in the α-position of the tetronate moiety, the substitution pattern at the alk-3-enyl substituent and the influence of the geminal dimethyl group in the γ-position of the tetronic acid unit. All these parameters have an effect on the type of product of the [2+2] photocycloaddition reaction: straight, affording a 5-4-5 tricylic compound or crossed, giving a 5-4-7 tricyclic product.



Scheme 10. Regioselectivity of the intramolecular [2+2] photocycloaddition, Bach *et al.* (2011).

In precedent studies of our group, the intramolecular photocycloaddition of terminal alkenes tethered to the 2(5*H*)-furanones **48-50** was investigated (Scheme 11). It was found that the regioselectivity of the photocycloaddition depends on the substitution pattern of the lactone and it was rationalized considering the relative stability and inter-radical distance of the diradical intermediates.[45]

[44] Weixler, R.; Hehn, J. P.; Bach, T. *J. Org. Chem.* **2011**, *76*, 5924-5935.
[45] Busqué, F.; de March, P.; Figueredo, M.; Font, J.; Margaretha, P.; Raya, J. *Synthesis* **2001**, 1143-1148.



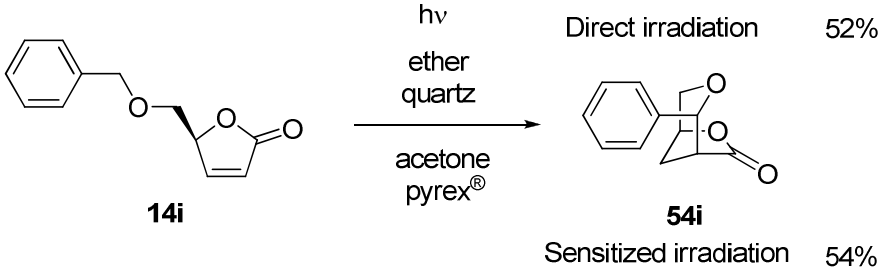
48, $R_1=R_2=H$
49, $R_1=H$, $R_2=CH_3$
50, $R_1=CH_3$, $R_2=H$

51, $R_1=R_2=H$
52, $R_1=H$, $R_2=CH_3$
53, $R_1=CH_3$, $R_2=H$

Scheme 11. Photocycloaddition of lactone **48-50**, Figueredo *et al.* (2001).

1.3.3. Formation of tetrahydropyrans

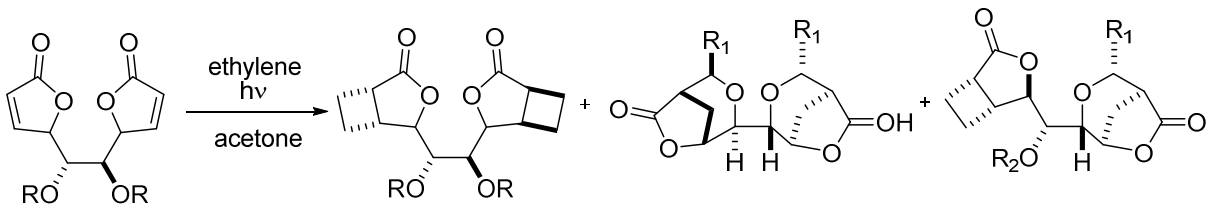
During the research of our group involving the photochemistry of 2(5*H*)-furanones, another intramolecular photoactivated process was observed.[32d] The irradiation of lactone **14i**, bearing a benzyloxymethyl substituent at the position 5, in the presence of various olefins such as ethylene, tetramethylethylene or vinylene carbonate, delivered the functionalyzed tetrahydropyran **54i**, instead of the expected cycloadducts (Scheme 12).



14i **54i**

Scheme 12. Intramolecular tetrahydropyran formation, Font *et al.* (1996).

Later, this reaction was also found to occur in other analogous substrates. In a project devoted to explore the application of C_2-symmetric bis-2(5*H*)-furanones as templates for asymmetric synthesis,[46] when the bislactones **55** and **56** were irradiated in the presence of ethylene, apart from the expected bis-photoadducts, **57** and **58**, considerable amounts of pyran photoproducts **59-62** were also formed (Scheme 13).



55, R=Et
56, R=Bn

57, R=Et 30%
58, R=Bn 5%

59, R_1=Me 10%
60, R_1=Ph 47%

61, R_1=Me R_2=Et 30%
62, R_1=Ph R_2=Bn 23%

Scheme 13. Irradiation of bis-2(5*H*)-furanones in the presence of ethylene, Figueredo *et al*. (2003).

[46] de March, P.; Figueredo, M.;Font, J.; Raya, J.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **2003**, *68*, 2437-2447.

1.4. Objectives

In this context, at the outset of our work three main objectives were targeted, all of them involving a photochemical reactivity study:

1. To investigate the scope of the photochemically induced intramolecular hydrogen abstraction leading to tetrahydropyranyl derivatives.

The tetrahydropyranyl moiety is a common framework in some biologically active natural products such as the antibiotic TMC-69,[47] and the causative agent of contact dermatitis Aplysiatoxin,[48] and it is also present in synthetic intermediates towards other natural products (for instance, Erythronolide A) (Figure 5).[49] Therefore, it is not surprising that in the last decades significant efforts have been dedicated to develop new methodologies for the construction of the tetrahydropyran ring.[50]

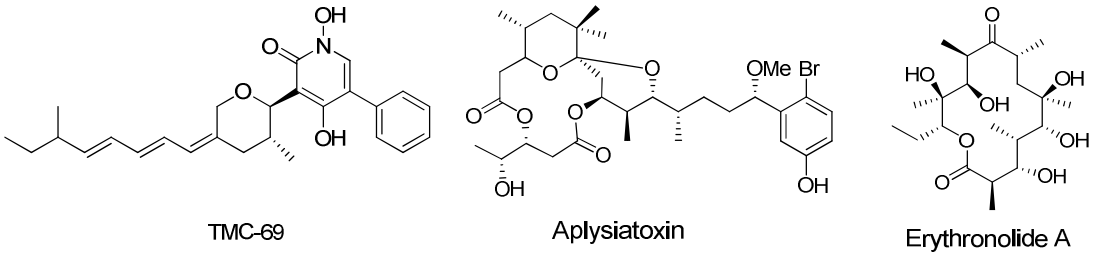
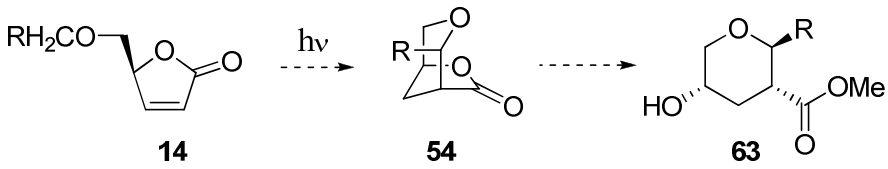


Figure 5. Naturally occurring compounds bearing a tetrahydropyran framework.

In this work, we decided to investigate the potential of different substituted 2(5*H*)-furanones **14** as precursors of bicyclic tetrahydropyrans **54**, which could give access to a family of specific trisubsituted tetrahydropyrans **63** (Scheme 14).

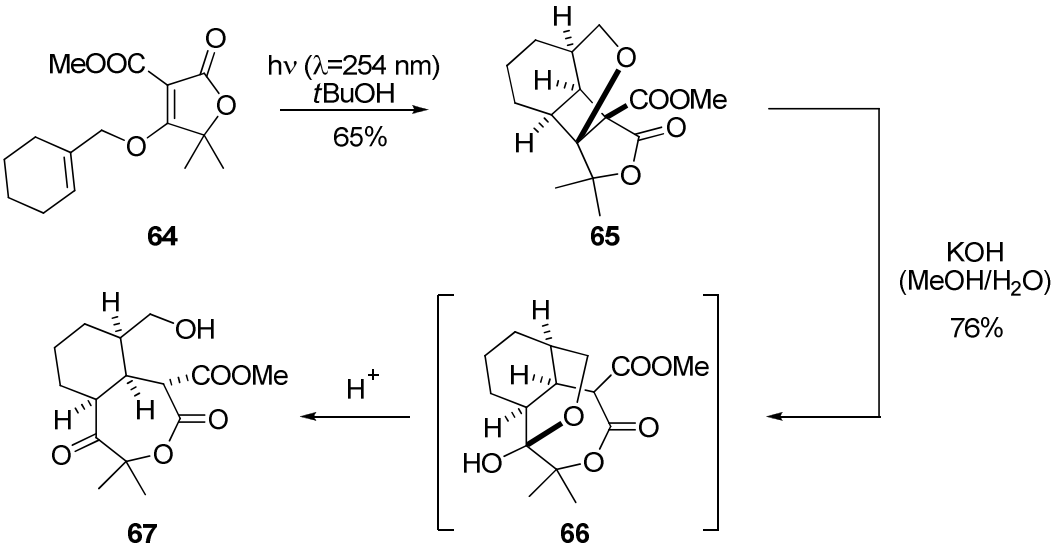


Scheme 14. 2(5*H*)-Furanones **14**, as potential precursors of tetrahydropyrans **63**.

[47] Kohno, J.; Hirano, N.; Sugawara, K.; Nishio, M.; Hashiyama, T.; Nakanishi, N.; Komatsubara, S. *Tetrahedron* **2001**, *57*, 1731-1735.
[31] Entzeroth, M. ; Blackman, A. J. ; Mynderse, J. S. ; Moore, R. E. *J. Org. Chem.* **1985**, *50*, 1255-1259.
[49] Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauvé, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2810-2814 and references cited herein.
[50] Clarke, P. A.; Santos, S. *Eur. J. Org. Chem*. **2006**, 2045-2053 and references cited therein.

2. To synthesize cyclobutane and cyclobutene tricyclic maleimide derivatives through an intramolecular [2+2] photocycloaddition process.

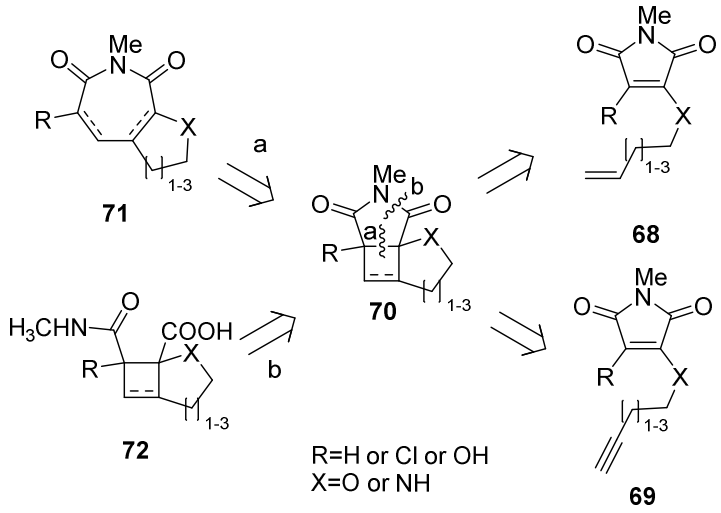
The general strategy of ring enlargement by a [2+2] photocycloaddition followed by fragmentation of the resulting cyclobutane has been largely studied over the last decade[1g,51] and more recently by Bach *et al.*, who have published a new methodology to prepare oxepanes **67** from a cyclobutane ring fragmentation (Scheme 15).



Scheme 15. Seven-membered ring formation by [2+2] photocycloaddition followed by cyclobutane ring fragmentation, Bach *et al.* (2009).

Analogously, we considered that azepane derivatives **71** could be potentially prepared by ring expansion reaction from cycloadducts **70**, coming from an intramolecular [2+2] photocycloaddition of substituted maleimides containing either an alkene (**68**) or alkyne (**69**) residue at an appropriate distance (Scheme 16). Moreover, cycloadducts **70** were also envisaged as suitable precursor of conformationally restricted amino acid derivatives **72** (X=NH). In this work, we decided to investigate the potential of different substituted maleimides **68** and **69** as precursors of derivatives **71** and **72** through the formation of the tricyclic compounds **70**.

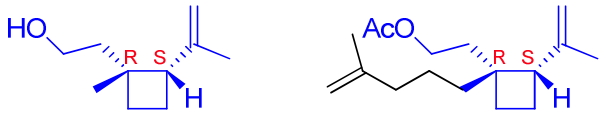
[51] Hehn, J. P.; Kemmler, M.; Bach, T. *Synlett* **2009**, *8*, 1281-1284.



Scheme 16. Retrosynthetic analysis of azepane and amino acid derivatives.

3. To investigate a synthetic approach to the sexual pheromone of *Aspidiotus nerii*.

(1*R*,2*S*)-*cis*-2-Isopropenyl-1-(4'-methyl-4'-penten-1'-yl)cyclobutaneethanol acetate, **73**, (Figure 6) has been characterized in 1998 as the major component of the sexual pheromone produced by oleander scale females, *Aspidiotus nerii*, a widespread pest, particularly in the Mediterranean area.[52] This structure was elucidated by NMR experiments (^{1}H and ^{13}C) and mass spectrometry by Einhorn and co-workers. In addition to the cyclobutane ring, this pheromone presents other structural characteristics common to (+)-grandisol, such as two of the acyclic chains linked to the cyclobutane and the configuration of the stereogenic centres.



(+)-grandisol, **1** Sexual pheromone of *Aspidiotus nerii*, **73**

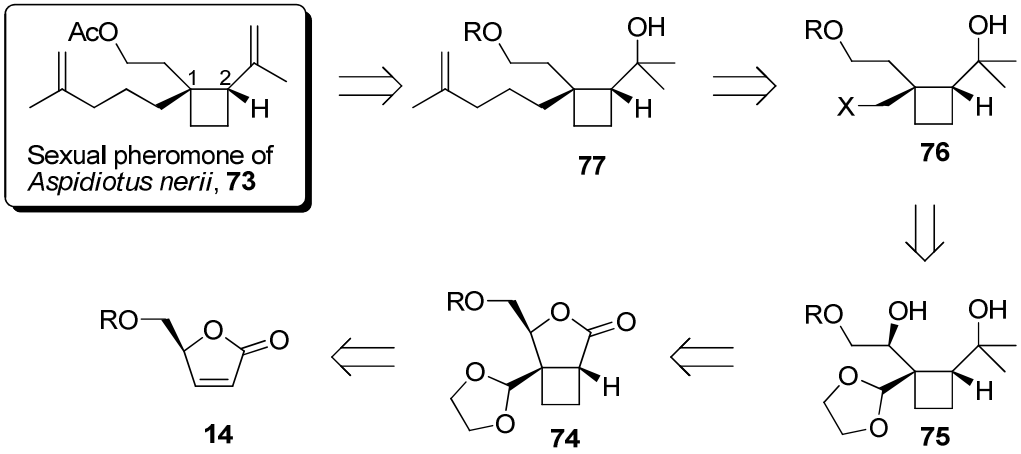
Figure 6. Similar structure of (+)-grandisol, **1**, and the sexual pheromone of *Aspidiotus nerii,* **73**.

These similarities suggested us the possibility of adapting the synthetic pathway previously designed for (+)-grandisol to the sexual pheromone of *Aspidiotus nerii*. The principal modification of the former synthesis of grandisol will be the introduction of the terpenic chain in the cyclobutane ring.

The retrosynthetic analysis proposed for **73** is shown in Scheme 17. Disconnection of the isopropenyl side chain led back to alcohol **76**, which in turn can be derived from diol **75**. We traced this intermediate back to the bicycle compound **74**. We envisioned that the

[52] Einhorn, J.; Guerrero, A.; Ducrot, P.-H.; Boyer, F.-D.; Gieselmann, M.; Roelofs, W. *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 9867-9872.

cyclobutane could be constructed from a functionalized 2(5*H*)-furanone **14** through a diastereoselective [2+2] photocyloaddition with ethylene.



Scheme 17. Retrosynthetic pathway to the sexual pheromone of *Aspidiotus nerii,* **73**.

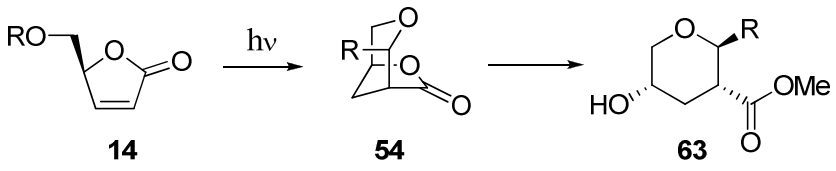
Chapter 2: Intramolecular hydrogen abstraction. Development of a new diastereoselective strategy to 2,3,5-trisubstituted pyrans

C’est la contemplation silencieuse des atlas, à plat vendre sur le tapis, entre dix et treize ans qui donne ainsi l’envie de tout planter là, […] La vérité, c’est qu’ on ne sait comment nommer ce qui vous pousse. Quelque chose en vous grandit et détache les amarres, jusqu'au jour où, pas trop sûr de soi, on s'en va pour de bon. Un voyage se passe de motifs. Il ne tarde pas à prouver qu'il se suffit à lui-même. On croit qu'on va faire un voyage, mais bientôt c'est le voyage qui vous fait, ou vous défait.

Nicolas Bouvier, écrivain-voyageur

2.1. Photochemical hydrogen abstraction reaction. Precedents

The first task of our work consisted of investigating the intramolecular photochemical reaction of 5-(oxymethyl)-2(5*H*)-furanones **14** with the aim of preparing 2,3,5-trisubstituted tetrahydropyrans of type **63** through a practical synthetic method (Scheme 18).

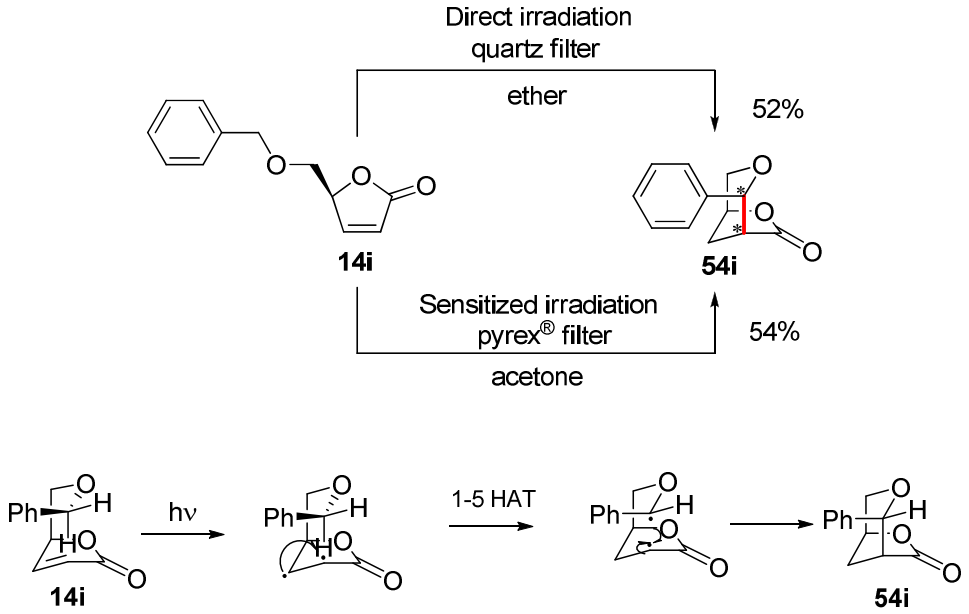


i, R=CH_2Ph
k, R=Me
l, R=*i*Pr
m, R=*n*Bu
n, R=MEM
o, R=Allyl
p, R=THP

Scheme 18. Diastereoselective synthesis of 2,3,5-trisubstituted pyrans **63**.

As it has been previously mentioned, some years ago,[32d,35a] our group reported the formation of a tetrahydropyran derivative as an unexpected by-product formed during the attempted [2+2] photochemical reaction of 5-benzyloxymethyl-2(5*H*)-furanone with different alkenes. Instead of the expected cycloadduct, the tetrahydropyran was formed in good yield. The reaction took place indistinctly under direct irradiation or under sensitization by acetone. Apparently, the product arises from a Hydrogen Atom Transfer (HAT) reaction by the β-

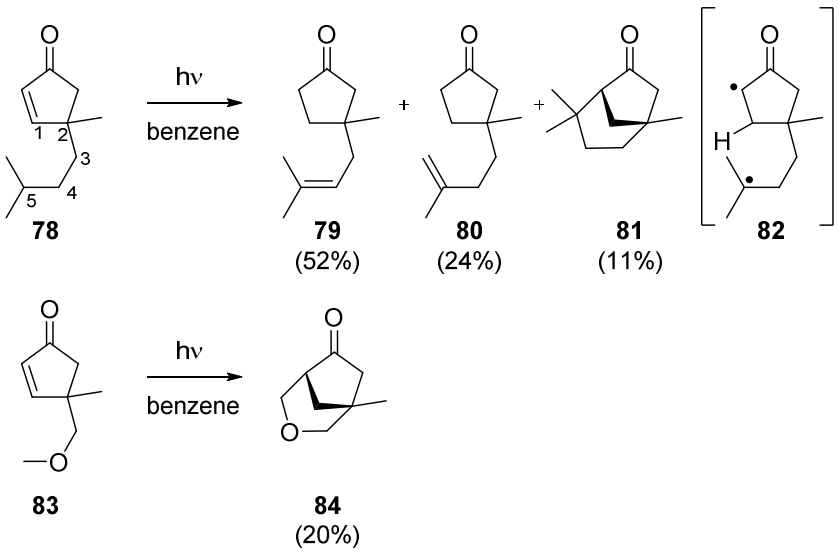
carbon of the excited enone, followed by subsequent recombination of the diradical to form the new σ C-C bond (Scheme 19).



Scheme 19. Previous reaction performed by our research group and postulated mechanism.

Similar reactions had been described in the literature. In an earlier work, Agosta and co-workers studied the photochemical isomerisation reactions of cyclopentenone **78** and **83** (Scheme 20).[53] Thus, irradiation of **78** led to **79**, **80** and **81** in nearly quantitatively total yield. These products derived from intermediate biradical **82**, formed by intramolecular 1,5-hydrogen atom abstraction of the side-chain by the β-carbon atom of the enone system. Alkenes **79** and **80** arose from intermediate **82** by a second hydrogen transfer, while simple collapse of **82** with carbon-carbon bond formation delivered **81**. In the methyl ether **83,** the ether oxygen atom provided to the adjacent radical centre stabilization similar to a tertiary centre, leading to the single isomerisation product **84** in 20% yield. It was established that formation of the biradical pairs proceeds from a readily accessible triplet state. Substrates **78** and **83** are so constructed that the abstractable hydrogen is positioned in a highly favoured 1,5-relationship to the β-carbon. Different factors may affect the possibility of a hydrogen transfer. Generally, steric and/or entropic factors combine to favour transfer to one site or the other.

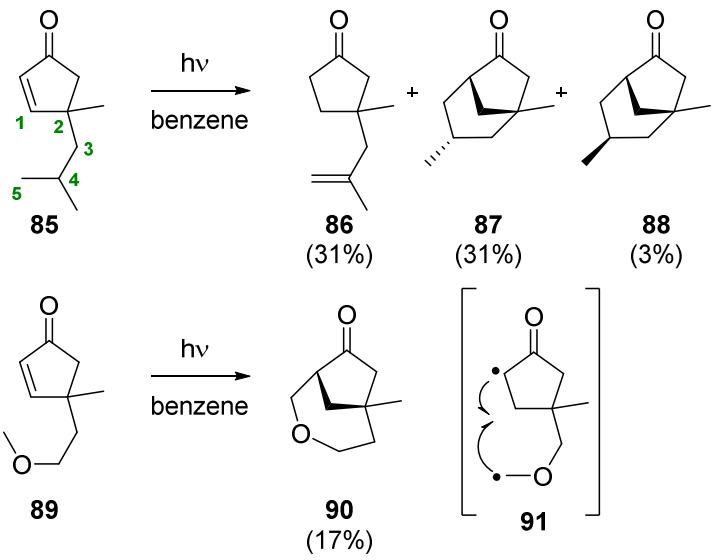
[53] Wolff, S. ; Schreiber, W. L.; Smith, A. B.; Agosta, W. C. *J. Am. Chem. Soc.* **1972**, 7797-7806.



Scheme 20. 1,5-HAT from β-carbon of enones **78** and **83**.

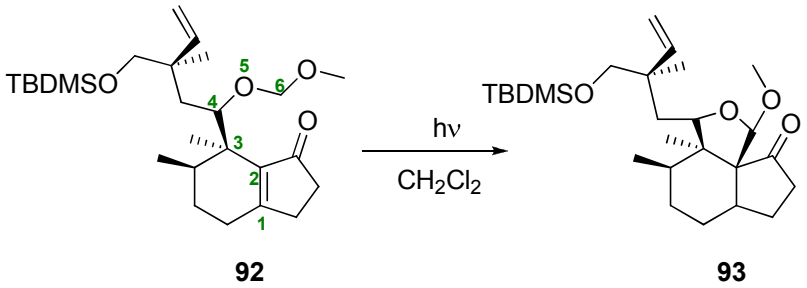
Later, the same group investigated the stereochemical effects in the photochemical isomerisation of cyclopentenones **85** and **89** (Scheme 21).[54] Photolysis of ketone **85** underwent isomerisation to products **86**, **87** and **88**, which arose from the 1,5-hydrogen atom abstraction. The differing stereochemistry at C-3 in **87** and **88** was determined by the way of hydrogen abstraction from one or the other of the two diastereotopic methyl groups of the *iso*butyl side chain. In the methyl ether **89**, 1,5-hydrogen transfer to the β-carbon atom is impossible but both 1,4- and 1,6-transfer were feasible. Irradiation of **89** led to the formation of the bicyclic compound **90** in 17% yield. From these examples, it was concluded that in these systems 1,5-transfer of hydrogen is strongly favoured over 1,6-transfer, and that there was no evidence for 1,4-transfer.[55,56]

[54] (a) Smith, A. B.; Agosta, W. C. *J. Org. Chem.* **1972**, *37*, 1259-1262. (b) Ayral-Kaloustian, S.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 598-5992.
[55] Padwa, A.; Glazer, E. *J. Am. Chem. Soc.* **1972**, *94*, 7788-7797.
[56] Herz, W.; Nair, M. G. *J. Am. Chem. Soc.* **1967**, *89*, 5474.



Scheme 21. 1,5- and 1,6-HAT from β-carbon of enones **85** and **89**.

Another example of intramolecular hydrogen abstraction by the β-carbon of a cyclopentenone subunit with resultant α-coupling was described by Paquette and co-workers as part of the (+)-pleuromutilin synthetic studies (Scheme 22).[57] Thus, under irradiation, the cyclopentenone **92** underwent 1,6-HAT, followed by intramolecular coupling of the resulting biradical, to furnish **93** in 63% yield.



Scheme 22. Synthetic studies on (+)-pleuromutilin by Paquette *et al.* (1998).

Other works on photocyclization of α,β-unsaturated amides to β-lactams *via* hydrogen abstraction by the β-carbon atom have been also reported.[58]

With these precedents in mind, we proceeded to investigate the intramolecular photochemical reaction of a series of (*S*)-5-oxymethyl-2(5*H*)-furanones **14** and its possible future application to the synthesis of natural products.[59] The use of acetonitrile, diethyl ether or acetone was examined. The main question was whether photolysis of the furanones **14** would follow the precedent process, namely, abstraction by the β-carbon of a proximate C*H*O

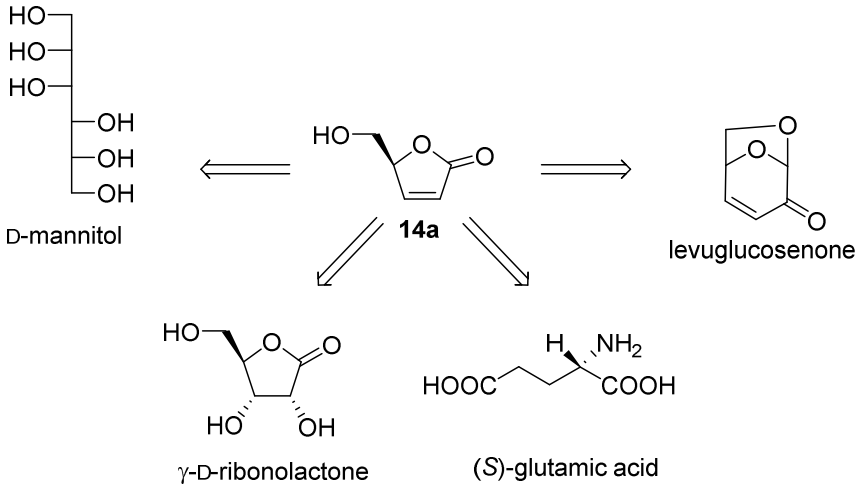
[57] Paquette, L. A.; Pansegrau, P. D.; Wiedeman, P.E.; Springer, J. P. *J. Org. Chem.* **1988**, *53*, 1461-1466.
[58] Aoyama, H.; Hasegawa, T.; Okazaki, M.; Omote, Y. *J. Chem. Soc. Perkin Trans. 1* **1979**, 263-265.
[59] Dorta, R. L. ; Martin, A.; Salazar, J. A.; Suarez, E. *J. Org. Chem.* **1998**, *63*, 2251-2261.

hydrogen atom, followed by collapse of the two resulting radical centres to give rise diastereoselectively to the corresponding tetrahydropyrans **54**.

2.2. Synthesis of (*S*)-5-(oxymethyl)-2(5*H*)-furanones

2.2.1. Preparation and alkylation of (-)-(*S*)-5-hydroxymethyl-2(5*H*)-furanone

Our group has a large experience in the preparation of chiral 2(5*H*)-furanones and its use as synthons in the synthesis of natural products that contain, or not, a γ-lactone substructure.[60] Moreover, (-)-(*S*)-5-hydroxymethyl-2(5*H*)-furanone, **14a,** (Scheme 23) and its *O*-substituted derivates have been extensively used as precursors in the enantioselective total syntheses of some biological active molecules by other researchers.[61] Different methodologies have been exploited to obtain **14a**, starting from various chiral pool materials, such as γ-ribonolactone,[60a] (*S*)-glutamic acid,[61b,62] D-mannitol,[10d] and, lately, levoglucosenone.[63]



Scheme 23. Precursors of (-)-(*S*)-5-hydroxymethyl-2(5*H*)-furanone, **14a**.

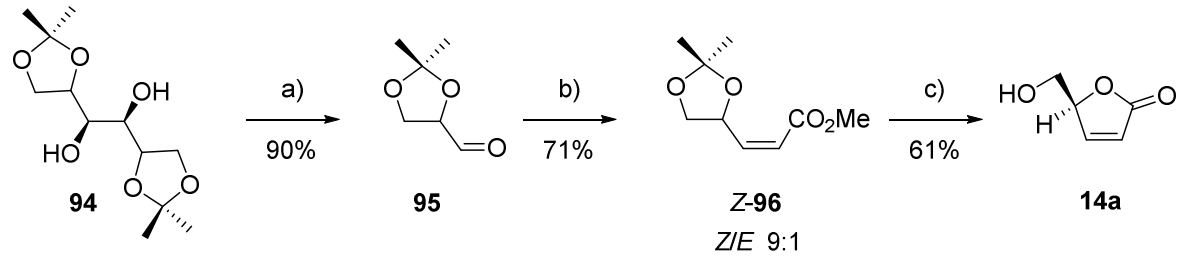
[60] (a) Camps, P.; Font, J.; Ponsatí, O. *Tetrahedron Lett*. **1981**, 22, 1471-1472. (b) Cardellach, J.; Estopa, C.; Font, J.; Moreno-Mañas, M.; Ortuño, R. M.; Sanchez-Ferrando, F.; Valle, S.; Vilamajo, L. *Tetrahedron* **1982**, *38*, 2377-2394. (c) Ortuño, R. M.; Bigorra, J.; Font, J. *Tetrahedron* **1987**, *43*, 2199-2202. (d) Ortuño, R. M.; Mercé, R.; Font, J. *Tetrahedron* **1987**, *43*, 4497-4506. (e) Ortuño, R. M.; Ballesteros, M.; Corbera, J.; Sanchez-Ferrando, F.; Font, J. *Tetrahedron* **1988**, *44*, 1711-1719. (f) Ariza, J.; Font, J.; Ortuño, R. M. *Tetrahedron* **1990**, *46*, 1931-1942. (g) Cid, P.; de March, P.; Figueredo, M.; Font, J.; Milán, S. *Tetrahedron Lett.* **1992**, *33*, 667-670. (h) Cid, P.; de March, P.; Figueredo, M.; Font, J.; Milán, S.; Soria, A. *Tetrahedron* **1993**, *49*, 3857-3870. (i) De Souza, M. V. N. *Mini-Reviews in Organic Chemistry*, **2005**, *2*, 139-145.

[61] (a) Tomioka, K.; Ishiguro, T.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 652-653. (b) Tomioka, K.; Sato, F.; Koga, K. *Heterocycles* **1982**, *17*, 311-316. (c) Tomioka, K.; Ishiguro, T.; Iitaka, Y.; Koga, K. *Tetrahedron* **1984**, *40*, 1303-1312. (d) Mann, J.; Thomas, A. *J. Chem. Soc., Chem. Commun.* **1985**, 737-738. (e) Hannesian, S.; Murray, P. *Can. J. Chem.* **1986**, *64*, 2232-2234. (f) Ferreira, J. T. B.; Marques, J. A.; Marino, J. P. *Tetrahedron: Asymmetry* **1994**, *5*, 641-648.

[62] Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547-3552.

[63] Koseki, K.; Ebata, T.; Kawasami, H.; Matsoshita, H.; Naoi, Y.; Itoth, K. *Heterocycles* **1990**, *31*, 423-426.

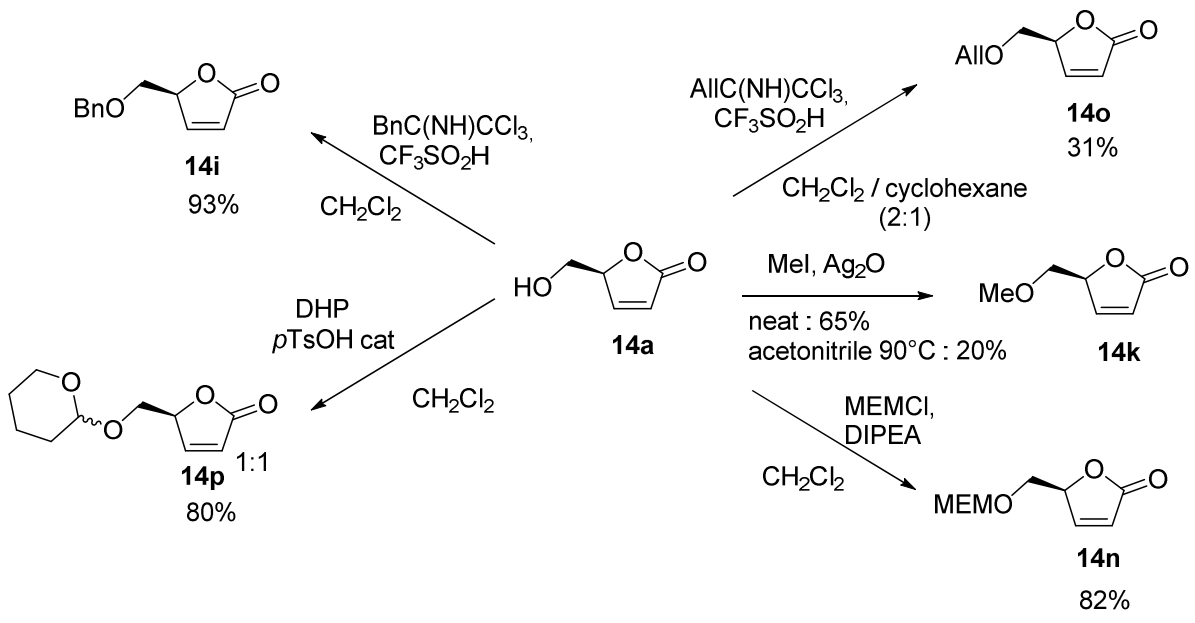
The first endeavour of this work was to prepare **14a** in a multigram scale. For its preparation, we used the well-established methodology developed by Mann and Thomas, which is depicted in Scheme 24. It started from the commercially available D-mannitol derivative **94**, which was treated with sodium metaperiodate in a mixture of THF-water at rt to deliver 2,3-*O*-isopropyliden-D-glyceraldehyde, **95**. The Wittig reaction of the aldehyde **95** with the stabilized ylide Ph_3PCHCO_2Me in methanol at 0℃ produced a chromatographically separable mixture of *Z*- and *E*-**96** (*Z*:*E* = 9:1). Finally, acid treatment in methanol, gave the desired 2(5*H*)-furanone **14a** in a global yield of 58%.



a) $NaIO_4$,THF/water, b) Ph_3PCHCO_2Me, MeOH, c) H_2SO_4 (30%), MeOH

Scheme 24. Synthesis of the 2(5*H*)-furanone **14a**.

With lactone **14a** in hands, we decided to prepare the 5-*O*-methyl, benzyl, methoxyethoxymethyl, allyl and tetrahydropyranyl derivates (Scheme 25).



Scheme 25. Preparation of the *O*-alkyl derivatives of 2(5*H*)-furanone **14a**.

We first undertook the preparation of the benzyl derivative **14i**. This reaction had been already performed in our group using benzyl bromide with silver (I) oxide to afford **14i**, albeit in a moderate 45% yield after 92 h. In order to improve this yield, we decided to attempt the benzylation step using benzyltrichloroacetimidate in dichloromethane with a catalytic amount

of trifluoromethane sulfonic acid.[64] Under these new conditions, the furanone **14i** was isolated in 93% yield.

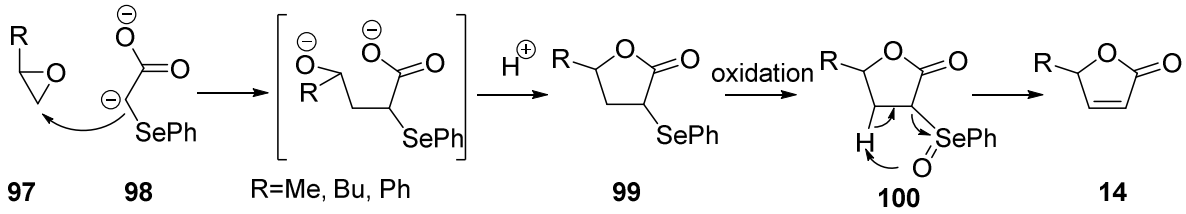
In view of the excellent yield obtained with benzyltrichloroacetimidate, we then decided to use similar conditions to prepare the allyl derivative. However, when **14a** was treated with allyltrichloroacetimidate in dichloromethane, the expected (*S*)-5-(allyloxymethyl)-2(5*H*)-furanone, **14o**, was obtained in low yield (19%), which was slightly improved (31%) by changing the solvent to a mixture of dichloromethane-cyclohexane (2:1). Next, we focused on the introduction of the MEM group by addition of methoxyethoxymethyl chloride and DIPEA to a solution of furanone **14a** in dichloromethane. This procedure afforded the desired furanone **14n** in 82% yield.

The acetal **14p** was prepared following the methodology described by Ghosh *et al.*[65] The addition of dihydropyran to a solution of **14a** in dichloromethane in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded the furanone **14p** in good yield, as a 1:1 mixture of diastereoisomers that was used as such in the subsequent photochemical studies. Then, we turned our attention to the preparation of the methyl, *iso*propyl, and *n*-butyl derivatives. Firstly, the synthesis of the methyl derivative **14k** was intended by means of a protocol previously developed in our laboratories, using iodomethane as solvent and silver (I) oxide as catalyst.[66] However, under these reaction conditions, we could only obtain the expected furanone **14k** in 20% yield, instead of the 65% previously described. In view of that, we did not intent to perform the corresponding reaction to prepare the *iso*propyl or *n*-butyl derivatives and we decided to apply a different procedure, which makes use of commercially available substituted epoxides.

2.2.2. Preparation of 2(5*H*)-furanones starting from substituted epoxides

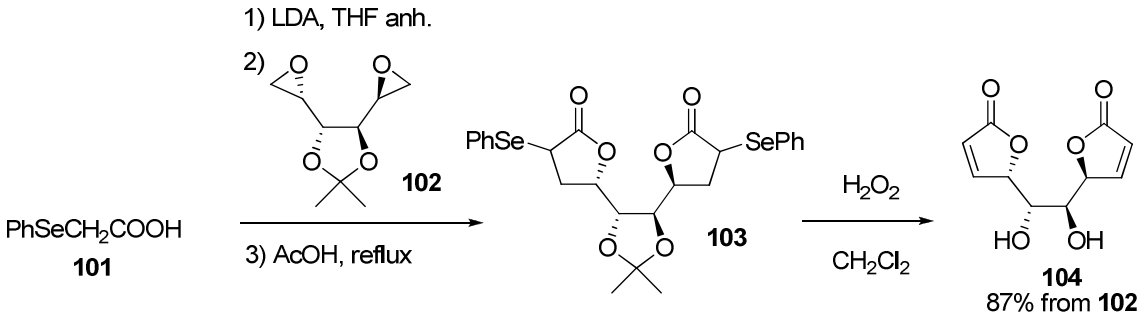
By the end of the 80's, Hanessian's group and our research group described simultaneously the preparation of 2(5*H*)-furanones by condensation of the dianion of phenylselenoacetic acid with different substituted epoxides, followed by oxidation of the selenide and concomitant β-elimination of benzeneselenic acid at 0℃ (Scheme 26).[67,68]

[64] Iversen, T.; Bundle, D. R. *J. Chem. Soc. Chem. Comm.* **1981**, 1240-1241.
[65] Ghosh, A. K.; Leshchenko, S.; Noetzel, M. *J. Org. Chem.* **2004**, *69*, 7822-7829.
[66] Estopa, C.; Font, J.; Moreno-Manas, M.; Sanchez-Ferrando, F.; Valle, S.; Vilamajo, L. *Tetrahedron Lett.* **1981**, *22*, 1467-1470.
[67] Iwai, K.; Kawai, M.; Kosugi, H.; Uda, H. *Chem. Lett.* **1974**, 385-388.
[68] (a) S. Hanessian, P. J. Hodges, P. J. Murray; S. P. Sahoo *J. Chem. Soc., Chem. Commun.* **1986**, 754-755. (b) M. Figueredo, J. Font, A. Virgili *Tetrahedron* **1987**, *43*, 1881-1886.



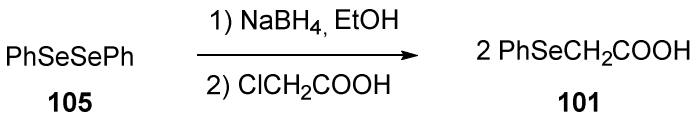
Scheme 26. Preparation of 2(5*H*)-furanones from epoxides.

This methodology has also been used in our group to prepare bis-2(5*H*)-furanone **104** in a multigram scale in 87% yield (Scheme 27).[46,68b,69]



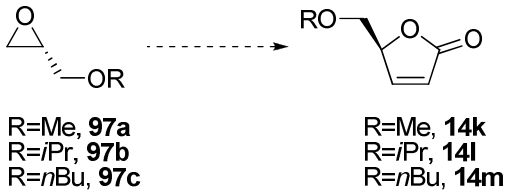
Scheme 27. Synthesis of bis-2(*5H*)-furanones **104** carried out by our group.

The starting phenyselenoacetic acid, **101**, can be easily prepared from diphenyldiselenide, **105** (Scheme 28).[70,71]



Scheme 28. Preparation of phenylselenoacetic acid, **101**.

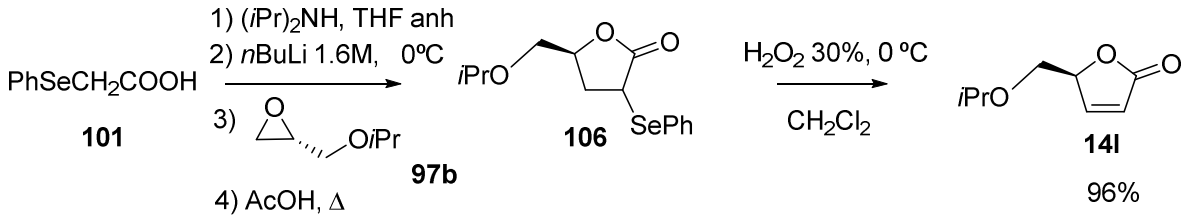
According to these precedents, we decided to apply this methodology for the preparation of **14k**, **14l** and **14m** (Scheme 29) from the corresponding epoxides, which are all commercially available.



Scheme 29. Different 2(*5H*)-furanones prepared from commercially available epoxides.

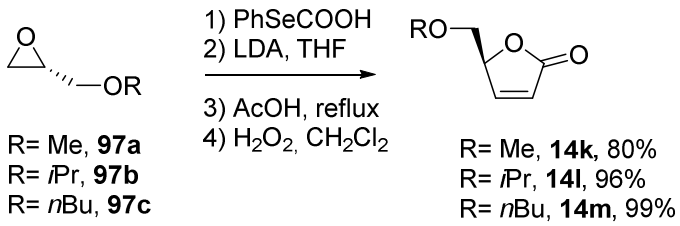
[69] (a) In Javier Raya Ph. D Thesis, *UAB*, **2005**. (b) In Montserrat Corbella Ph.D Thesis, *UAB*, **2007**.
[70] Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434-5447.
[71] Reich, H. J.; Chow, F.; Shan, S. K. *J. Am. Chem. Soc.* **1979**, *101*, 6638-6648.

First, we assayed the synthesis starting from (+)-(*S*)-glycidyl isopropyl ether, **97c**, because its availability and low price in comparison with the other two epoxides. Phenylselenoacetic acid, **101**, was transformed to the dianion by treatment with LDA in THF at 0ºC. Addition of the epoxide, treatment with acetic acid and heating afforded the expected selenide **106**, which was used in the following step without further purification. Thus, the oxidation of the selenium atom with elimination of the selenoxide was attempted using an excess of H_2O_2 and a catalytic amount of acetic acid at 0ºC in THF. However, under these conditions, selenides **106** were only partially converted to the desired 2(5*H*)-furanone, **14l**. Consequently, this last step was performed in dichloromethane at 0ºC. The solution was vigorously stirred and a solution of hydrogen peroxide (30% in water) was slowly added affording **14l** in 96% yield (Scheme 30).



Scheme 30. Preparation of 2(*5H*)-furanone **14l**.

The same methodology was then applied to prepare compounds **14k** and **14m** in good yields starting from (+)-(*S*)-glycidyl methyl ether, **97a**, and (+)-(*S*)-glycidyl *n*-butyl ether, **97c**, respectively (Scheme 31).



Scheme 31. Summary of the synthesis of alkyloxyfuranones **14k**, **14l** and **14m**.

2.3. Intramolecular hydrogen abstraction of furanones

All the photochemical reactions reported herein were conducted with a 125W high pressure mercury lamp (Cathodeon HPK125), cooling externally the reactor to -20ºC, except in specific cases. Methanol at -15ºC was used for refrigeration of the immersion well jacket (Figure 7). Evolution of the reaction was controlled by gas chromatography (GC). Irradiation was stopped in function of by-products formation. Product characterization was

accomplished by NMR analysis. The structural assignment of the synthesized cycloadducts was carried out by ^{1}H and ^{13}C NMR. Signals were assigned with the help of DEPT, COSY, HMQC, HMBC and n.O.e. differential experiments. Only some of the most significant experiments needed to determine the configuration of the compounds obtained are shown in this chapter, all the spectra are shown in the Experimental Section.

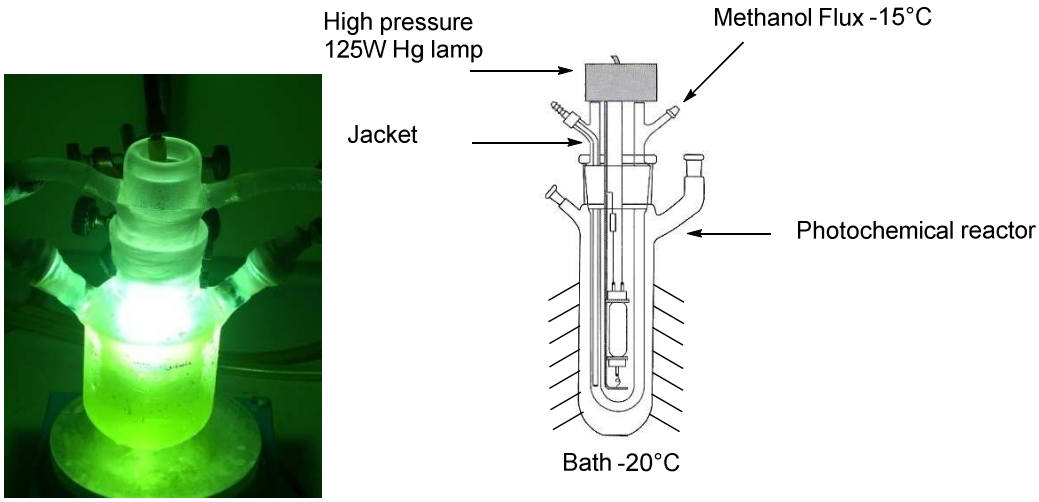
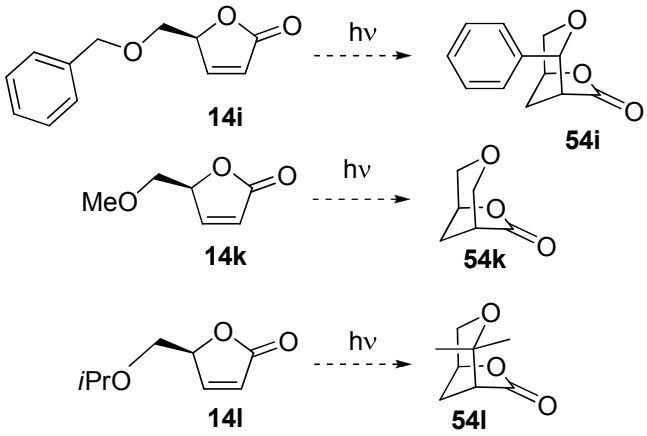


Figure 7. Typical photochemical apparatus for the reaction described herein.

The first part of the study was performed evaluating the photochemical reactivity of **14i**, **14k** and **14l** in different reaction conditions (Scheme 32). Worth to mention is that, from **14k** and **14l**, the formation of the new σ C-C bond will afford only one stereogenic centre at the α-carbonyl position, while from **14i** a second stereogenic centre will be originated in the pyran ring. For geometrical reasons, **14k** and **14l** can form a unique diastereomer with the pyran bicyclic structure.

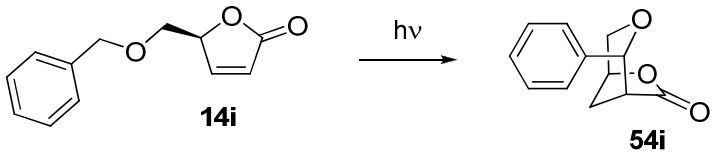


Scheme 32. Study of the intramolecular hydrogen abstraction of furanones **14i, 14k** and **14l**.

The effect of the experimental conditions (solvent, filter and reaction time) of the photoreactions on the yield and the facial diastereoselectivity was evaluated.

Initially, the previously observed photochemical reaction of lactone **14i** was reinvestigated under several conditions. The photoreactions were performed by irradiation of the furanone with a high pressure mercury lamp through a quartz or pyrex® jacket in various aprotic solvents (acetonitrile, diethyl ether and acetone) to avoid the addition of the solvent to the β-carbon. Results are reported in Table 3.

Table 3. Intramolecular photoreaction of 2(*5H*)-furanone **14i**.[a]



14i **54i**

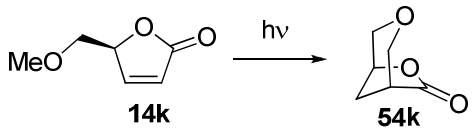
entry	mmol	[c] mmol.L^{-1}	solvent	jacket	Bath T°C	Time min	C[b] %	Yield[c] %
1	0.26	4.66	acetone	pyrex®	-20°C	180	100	38
2	0.26	4.66	CH_3CN	quartz	-20°C	50	100	44
3	0.24	4.00	CH_3CN	quartz	-40°C	70	90	70
4	0.25	4.33	Et_2O	quartz	-20°C	15	100	78
5	0.50	5.36	Et_2O	quartz	-20°C	25	100	48

[a]Irradiations were performed in a nitrogen saturated solution; the jacket was cooled down with at -15°C . [b]The substrate conversion was monitored by GC. [c]Yield of isolated products.

Under the experimental conditions previously described by our group (entry 1), irradiation of **14i** afforded the expected bicyclic product **54i** in 38% yield. Then, the conditions usually applied in our laboratory for the photoreactions of 2(5*H*)-furanones with alkenes were explored. Thus, irradiation of **14i** through a quartz filter in acetonitrile afforded **54i** in a slightly better yield (44%, entry 2). Lowering the temperature to -40°C (entry 3) gave similar results. Noteworthy, irradiation of **14i** through quartz filter in diethyl ether delivered the bicyclic compound **54i** (78% yield) in only 15 min (entry 4). Longer irradiation time provoked a decrease of the yield indicating that the photoproduct could be unstable under the reaction conditions (entry 5).

Next, we turned out our attention to the photochemical reaction of **14k** (Table 4), which under irradiation through a quartz filter in acetonitrile afforded the bicyclic compound **54k** in 52% yield after 105 min (entry 1). A similar yield was obtained using acetone as solvent (entry 3). However, when the reaction was attempted by irradiating through a quartz filter in diethyl ether, despite total disappearance of the starting material was observed after 40 min, neither the expected pyran nor any other product could be identified from the reaction mixture.

Table 4. Intramolecular photochemical reaction of furanone **14k**.[a]



entry	mmol	[c] mmol.L^{-1}	solvent	jacket	Time min	C[b] %	Yield[c] %
1	0.35	5.48	CH_3CN	quartz	105	100	52
2	0.78	10.40	Et_2O	quartz	40	100	0[d]
3	0.29	6.41	acetone	pyrex®	42	100	45

[a]Irradiations were performed in a nitrogen saturated solution. [b]The substrate conversion was monitored by GC. [c]Yield of isolated products. [d]Only degradation of the substrate was observed.

The structure of compound **54k** was established by detailed 1D and 2D NMR experiments. In particular, HMBC experiments showed interactions between H-8 and C-2 (Figure 8). ^{1}H NMR analysis shows disappearance of the alkene and the singlet signal of the methyl group.

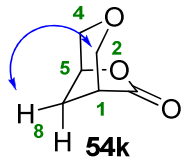
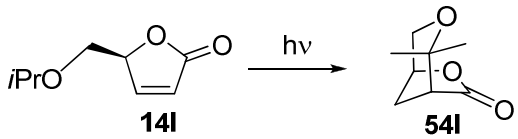


Figure 8. Interactions in HMBC experiments of bicyclic compound **54k** ($CDCl_3$, 250 MHz).

The photochemical reactions of furanone **14l** in acetonitrile, diethyl ether and acetone were also evaluated (Table 5).

Table 5. Intramolecular photochemical reaction of furanone **14l**.[a]

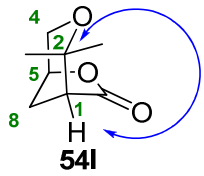


entry	mmol	[c] mmol.L^{-1}	solvent	jacket	Time min	C[b] %	Yield[c] %
1	0.66	8.80	CH_3CN	quartz	30	100	50
2	0.27	5.97	Et_2O	quartz	100	100	30
3	0.33	7.39	acetone	pyrex®	45	100	38

[a]Irradiations were performed in a nitrogen saturated solution. [b]The substrate conversion was monitored by GC. [c]Yield of isolated products.

Irradiation through a quartz filter of an acetonitrile solution of lactone **14l** afforded the corresponding pyran **54l** (50% yield, entry 1).The reaction in diethyl ether required longer time to convert all the starting material and the yield of isolated product was lower (entry 2). The photosensitized reaction in acetone (entry 3) did not present any improvement either.

The structure of compound **54l** was established by detailed 1D and 2D NMR experiments. In particular, the HMBC experiments show interactions between H-1 and C-2 (Figure 9). ^{1}H NMR shows disappearance of the alkene and of the methinic proton of the isopropyl group.

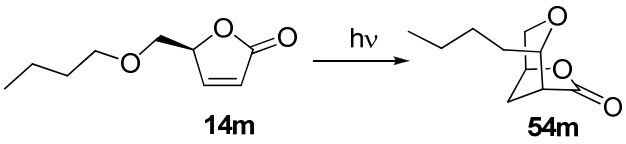


54l

Figure 9. Interactions in HMBC experiments of bicyclic compound **54l** ($CDCl_3$, 250 MHz).

Next, we focussed our attention on the photochemical behaviour of lactone **14m**, the photoinduced cyclization of which will afford two new stereogenic centres and, hence, may deliver two diastereomers (Table 6). The irradiation of furanone **14m** in acetonitrile for 40 min through a quartz filter gave the expected compound **54m** in 52% yield (entry 1). An increase of the concentration afforded the pyran **54m** in comparable yield, although it was necessary to irradiate 5 h to get a good conversion (entry 2). The yield was similar to those of **54l** and **54k**. In diethyl ether as solvent, no product could be isolated (entry 3), while the reaction by sensitive excitation with acetone delivered **54m** in 42% yield (entry 4). We also tried the direct irradiation through a quartz filter in acetone that afforded **54m** in 50% yield (entry 5). Surprisingly, the yield was slightly better than using a pyrex® filter.

Table 6. Intramolecular photochemical reactions of 2(*5H*)-furanone **14m**.[a]



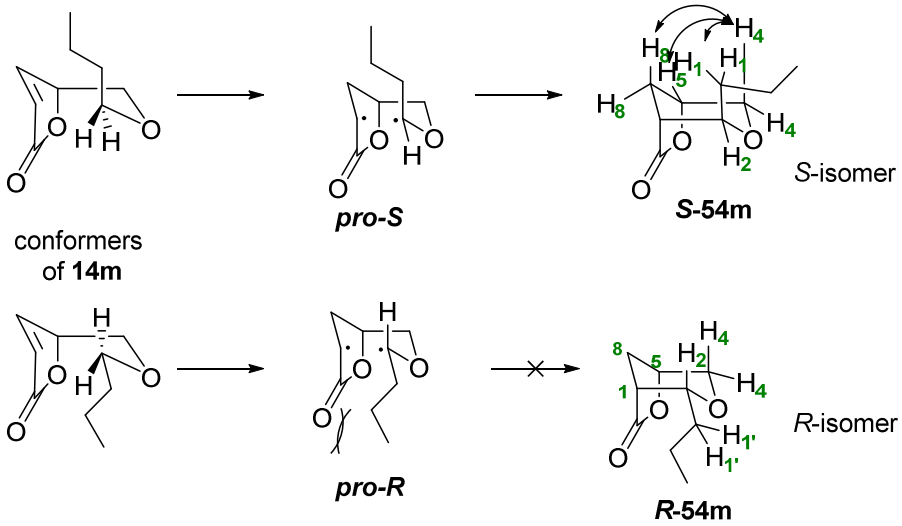
14m **54m**

entry	mmol	[c] mmol.L^{-1}	solvent	jacket	Time min	C[b] %	Yield[c] %
1	0.47	6.35	CH_3CN	quartz	40	100	52
2	1.17	15,66	CH_3CN	quartz	300	80	50
3	0.24	5.48	Et_2O	quartz	50	100	0
4	0.29	6.53	acetone	pyrex®	65	100	42
5	0.48	6.51	acetone	quartz	37	100	50

[a]Irradiations were performed in a nitrogen saturated solution. [b]The substrate conversion was monitored by GC. [c]Yield of isolated products.

The *S* configuration of the new stereogenic centre C-2 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 (Scheme 33). This configuration matches the one previously established for **14i** and it is determined by the selective abstraction of one of the two stereotopic hydrogen atoms of the butyl side chain. Apparently, when going from the

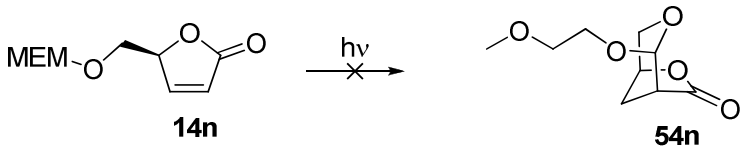
excited lactone to the subsequent diradical species, the transition state leading to the intermediate diradical ***pro-S***, with the bulky propyl chain distant from the lactone ring, is favoured over that leading to ***pro-R***, where the propyl chain is closer to the lactone. Photoreactivity is likely controlled by the relative rates at which the different diradical species are formed.



Scheme 33. Preferred conformation of the diradicals and n.O.e. observed for ***S*-54m**.

The results accomplished with **14n** are presented in Table 7.

Table 7. Intramolecular photochemical reactions of 2(*5H*)-furanone **14n**.[a]

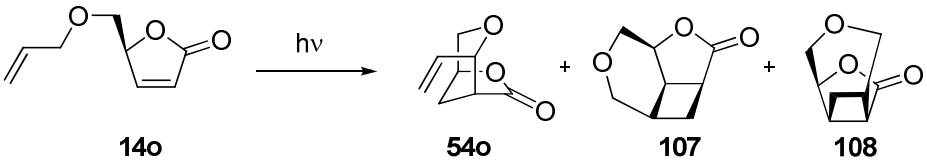


entry	mmol	[c] mmol.L^{-1}	solvent	jacket	Time min	C[b] %	Yield %
1	0.25	5.55	CH_3CN	quartz	30	100	0[c]
2	0.87	11.16	CH_3CN	quartz	45	100	0[c]
3	0.25	5.49	Et_2O	quartz	30	100	0[c]
4	0.25	5.47	acetone	pyrex®	30	100	0[c]

[a]Irradiations were performed in a nitrogen saturated solution. [b]The substrate conversion was monitored by GC.
[c]Only degradation of the substrate was observed.

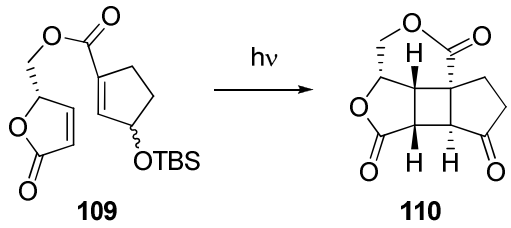
Surprisingly, the irradiation of lactone **14n** in all attempted solvents gave complex crude products. NMR analysis did not allow the identification of any compound containing the expected pyran moiety although consumption of the starting material took place during the reaction.

Then, we investigated the photoreactivity of lactone **14o** bearing an allyl group. In principle, this reaction could lead to the formation of the pyran derivative **54o**, coming from a 1,5 intramolecular hydrogen transfer followed by C-C formation, and the cyclobutanes **107** and/or **108**, arising from an intramolecular [2+2] photocycloaddition (Scheme 34).



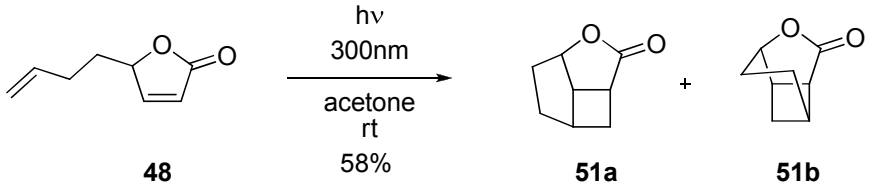
Scheme 34. Expected products from the photoreaction of **14o**.

Examples of similar intramolecular [2+2] photocycloaddition can be found in the literature. A good application of an asymmetric process of this kind was described by Koga *et al.* in the synthesis of stoechospermol.[72] This reaction was used as a key step and took place with total control of the facial stereoselectivity (Scheme 35).



Scheme 35. Step of the synthesis of stoechospermol, by Koga *et al.* (1985).

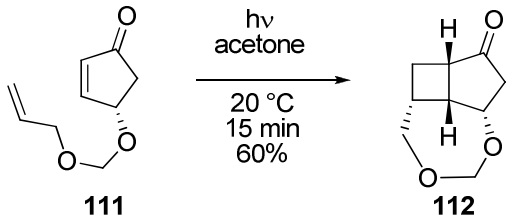
As it was already mentioned in the Introduction, our group had studied the photochemical behaviour of furanone **48** with a 3-butenyl side chain (Scheme 36).[45] It was observed that irradiation of an acetone solution of **48** delivered a 1.6:1 mixture of the regioisomeric cycloadducts **51a** and **51b** in 58% yield.



Scheme 36. Photocycloaddition of lactone **48**, Figueredo *et al.* (2001).

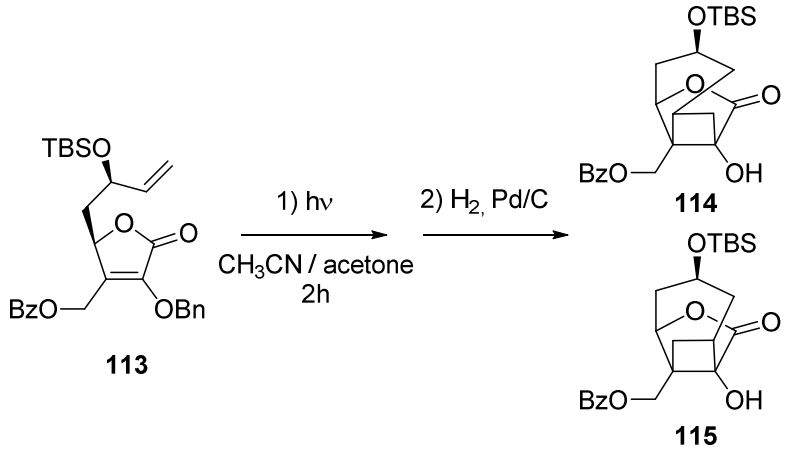
More recently, the reaction of **111** bearing an allyloxy residue attached to the core 4-hydroxycyclopenten-2-one through an acetal linkage has been also described (Scheme 37).[73] The irradiation of **111** in acetone for 15 min delivered only the tricyclic compound **112** in 60% yield.

[72] Tanaka, M.; Tomioka, K.; Koga, K. *Tetrahedron Lett*. **1985**, *26*, 3035.
[73] Le Liepvre, M. Ollivier, J. ; Aitken, D. J. *Eur. J. Org. Chem.* **2009**, *34*, 5953-5962.



Scheme 37. Photocycloaddition of cyclopentenone **111**, Aitken *et al.* (2009).

Bach and Lu have used an intramolecular [2+2] photocycloaddition as a key step in the total synthesis of (+)-lactiflorin. Thus, irradiation of substrate **113** followed by hydrogenolysis gave **114** and **115** in 18% and 53% yield, respectively (Scheme 38).[74]

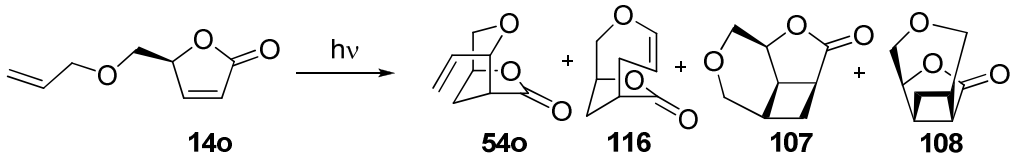


Scheme 38. Photocycloaddition of 2(5*H*)-furanone **118**, Bach and Lu (2012).

Taking into account these precedents, we focused our efforts on studying the photochemical behaviour of lactone **14o** (Table 8). The irradiation of furanone **14o** in acetonitrile through a quartz filter gave a mixture of 4 products, the expected pyran **54o**, the [2+2] adducts **107** and **108** and a fourth isomer, which was characterized as the oxepine **116**, in 36% global yield (entry 1). At the same concentration in acetone as solvent the overall yield was even lower (entry 2), but a three fold increase of the concentration increased the yield up to 70% (entry 5). The same effect was not observed when working in acetonitrile (entry 3).

[74] Lu P.; Bach. T. *Angew. Chem. Int. Ed.* **2012**, *51*, 1261-1264.

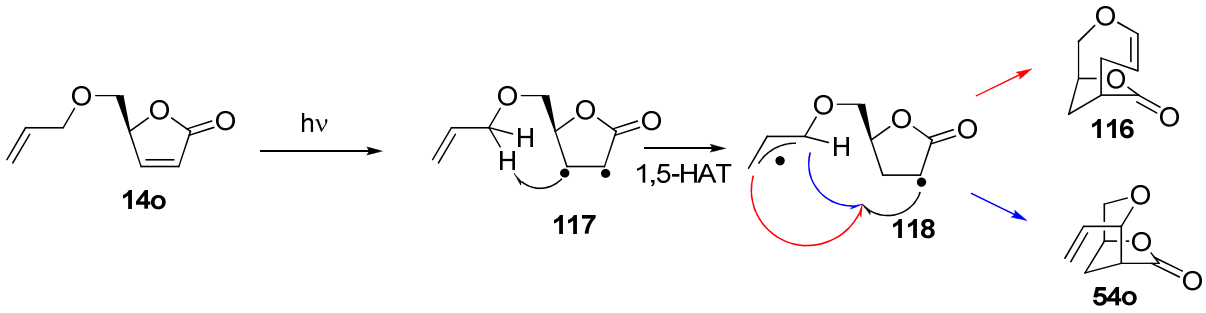
Table 8. Irradiation of 2(5*H*)-furanone **14o**.[a]



entry	mmol	[c] mmol.L^{-1}	solvent	jacket	Time min	C[b] %	Global Yield[c] %	Ratio			
										[2+2]	
								54o	**116**	**107**	**108**
1	0.28	6.34	CH_3CN	quartz	35	90	36	1	1	1.2	1.2
2	0.30	6.77	acetone	pyrex®	35	87	26	-	1	1.7	1.7
3	0.57	12.68	CH_3CN	quartz	45	70	27	-	1	1.8	2.6
4	0.67	8.99	acetone	pyrex®	72	90	39	1	2	4.4	5.7
5	1.62	21.63	acetone	pyrex®	180	92	70	1	1.5	2.2	4

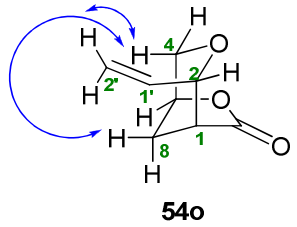
[a]Irradiations were performed in a nitrogen saturated solution. [b]The substrate conversion was monitored by GC. [c]Yield of isolated products.

The formation of **116** concomitant with **54o** can be rationalized through the occurrence of a delocalized allyl radical (Scheme 39).



Scheme 39. Intramolecular hydrogen abstraction followed by recombination of radicals upon irradiation of furanone **14o**.

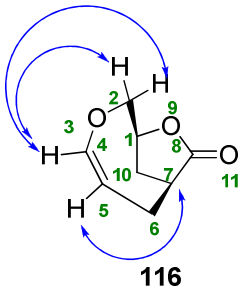
In the ^{1}H NMR spectrum of **54o**, the signals of the vinyl group remained clearly defined at δ 5.8 (H-1') and δ 5.4 (H-2'). The configuration of the stereocenter C-2 in **54o** was established through n.O.e differential experiments. Selective irradiation of the C-4 methylene protons resulted in signal enhancement of protons H-2', H-2/H-5, and H-8ax confirming the *S* configuration of C-2 (Figure 10). An HMBC experiment revealed cross-peaks between H-1' and C-1 and between H-8 and C-2. The n.O.e signal between H-4 and H-2' is only possible for an *S* configuration of C-2.



54o

Figure 10. Significant n.O.e on compound **54o** ($CDCl_3$, 250 MHz).

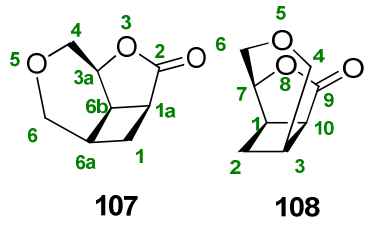
The structure of compound **116** was also determined through detailed NMR studies. Its ^1H NMR spectrum displays two signals of olefinic protons at δ 6.45 ppm and δ 5.09. An HMBC experiment showed cross-peaks between the olefinic proton H-5 and the α-carbonyl carbon atom C-7 and also between both protons H-2 and C-4 (Figure 11).



116

Figure 11. Interactions in HMBC experiments of bicyclic compound **116** ($CDCl_3$, 250 MHz).

The [2+2] photocycloaddition products **107** and **108** could not be separated by column chromatography. Thus, the analysis was performed on a 1:0.7 mixture of the two isomers, where most of the signals were clearly distinguishable (Figure 12).



107 **108**

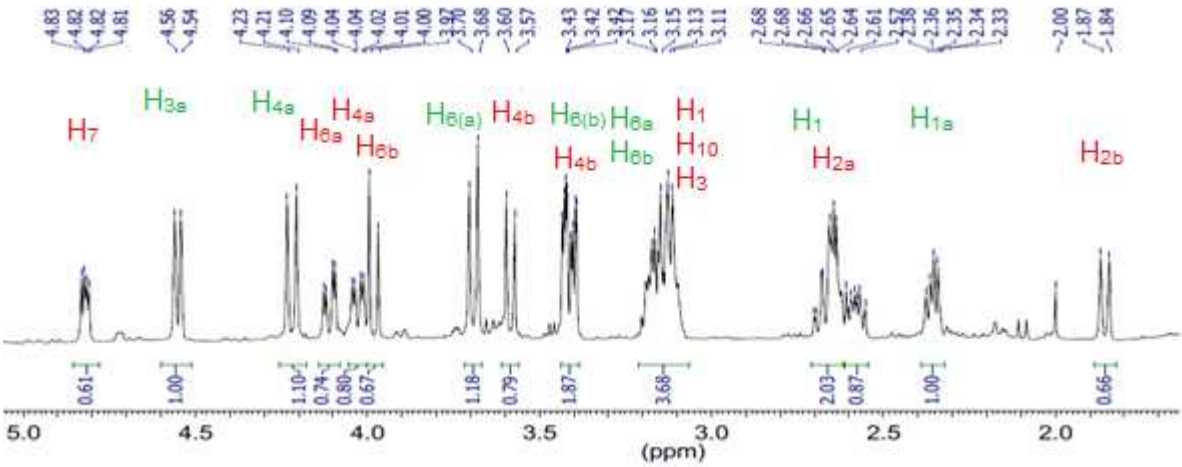


Figure 12. ^1H NMR spectrum (C_6D_6, 500 MHz) of the mixture of **107** (green) and **108** (red).

2D TOCSY experiments (Figure 13) allowed to assign a whole spin system, and were used to obtain a subspectrum of one of the isomers, through the selective irradiation of H-7 in **108**.

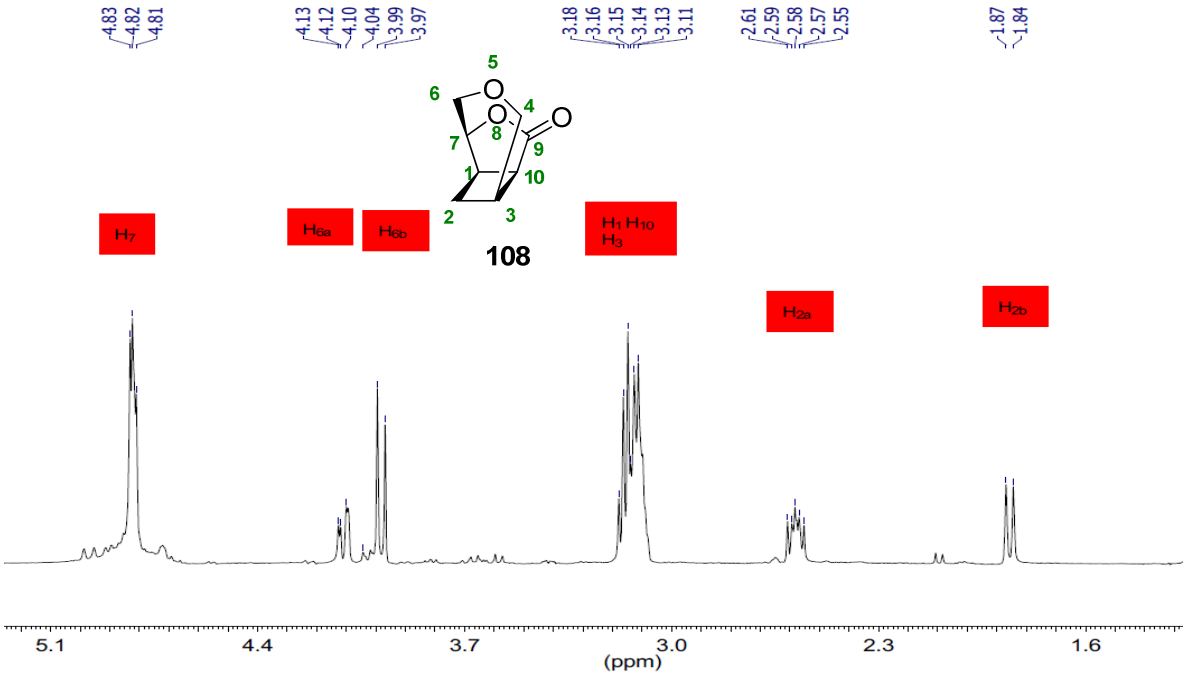


Figure 13. TOCSY experiment (C_6D_6, 500 MHz) of **108** (red).

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 C-3 and between one of the H-2 protons and C-7 (Figure 14).

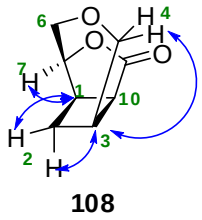
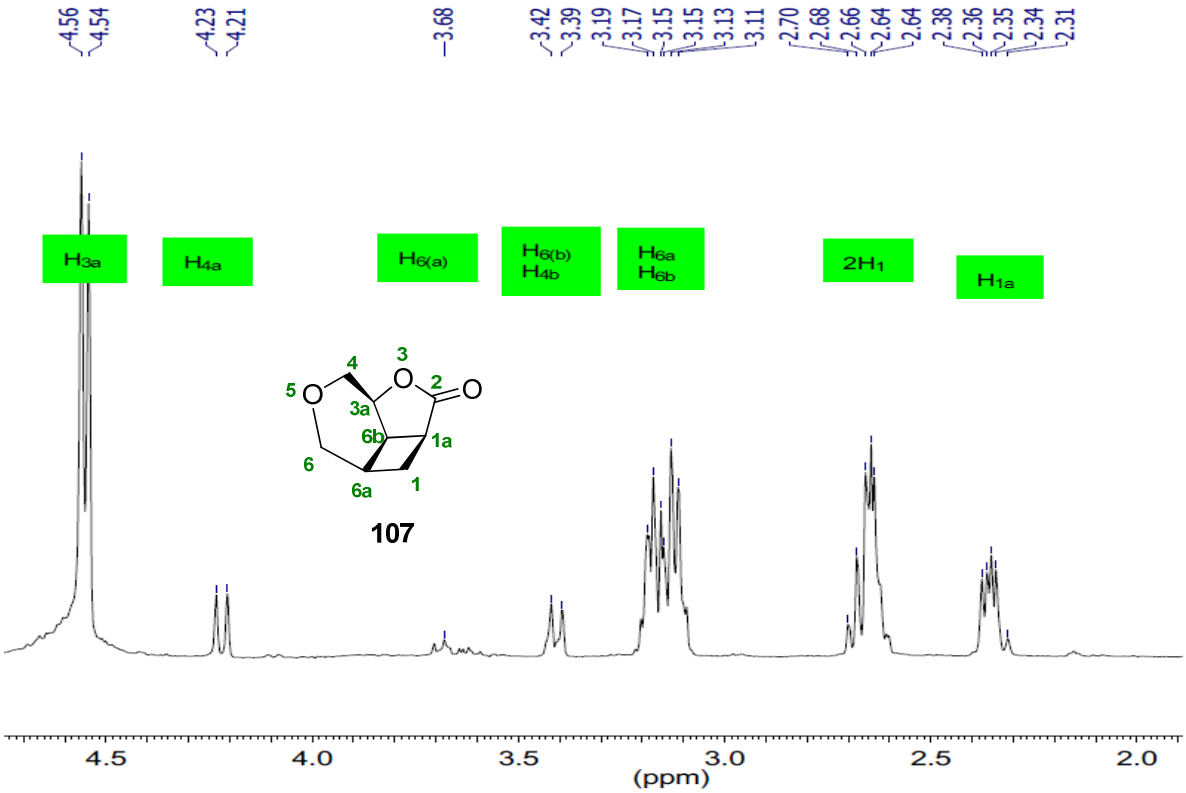


Figure 14. Interactions observed in the HMBC experiment of **108**.

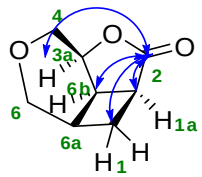
We used the same methodology to determine the structure of the isomer **107**. Again, the TOCSY experiment (Figure 15) helped us to assign the signals to each proton from the mixture of photoadducts.



107

Figure 15. TOCSY experiment (C_6D_6, 500 MHz) of **107** (green).

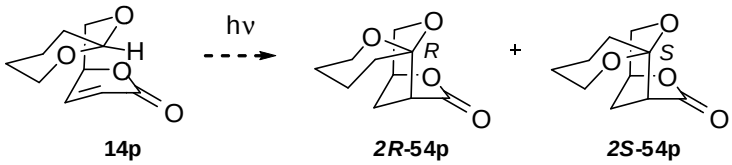
In the HMBC experiment, we observed a cross-coupling between carbon C-2 and protons H-3a, H-6b, H-1 and H-1a. The cross-coupling between one of the methylenic protons H-1 and C-2 confirms the regiochemistry shown in Figure 16.



107

Figure 16. Interactions observed in the HMBC experiment of **107**.

Finally, we investigated the photoreactivity of 2(5*H*)-furanone **14p** that would give rise to the formation of a spiranic centre between two pyran units (Scheme 40). The results are summarized in Table 9.



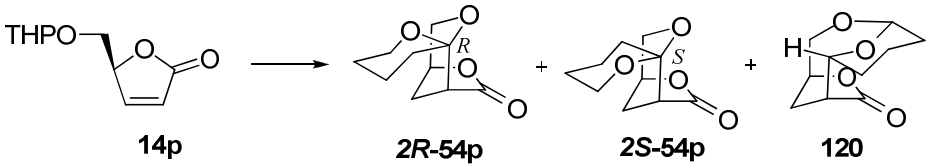
14p
1:1 mixture

***2R*-54p** **2*S*-54p**

Scheme 40. Expected products from the photoreaction of **14p**.

The photoreaction of a 1:1 diastereoisomeric mixture of **14p** in acetonitrile (entry 1) afforded a 3:1:1 mixture of three isomers ***2R*-54p**, ***2S*-54p** and **120** in overall 50% yield, after 30 min of irradiation through a quartz filter. The three cycloadducts could be isolated after purification by column chromatography. Similar results were achieved irradiating through a pyrex filter in acetone (entry 2). However, when the reaction was performed in diethyl ether (entry 3), only degradation of the subatrate was observed. By increasing the concentration of the starting furanone, the photoreaction in acetonitrile using a quartz filter (entry 4) delivered a mixture of the expected compounds **2*R*-54p**, **2*S*-54p** along with another isomer, **120**, in a 5:1:1.4 ratio and 74% yield**.**

Table 9. Irradiation of 2(5*H*)-furanone **14p**.[a]



14p **2*R*-54p** **2*S*-54p** **120**

entry	mmol	[c] mmol.L^{-1}	solvent	jacket	Time min	Conv.%[b]	Yield %[c]		
							***2R*-54p**	***2S*-54p**	**120**
1	0.24	5.43	CH_3CN	quartz	30	100	30	10	10
2	0.24	5.43	acetone	pyrex®	45	100	30	6	10
3	0.24	5.43	Et_2O	quartz	30	100	0[d]	0[d]	0[d]
4	0.75	10.09	CH_3CN	quartz	120	100	50	10	14

[a]Irradiations were performed in a nitrogen saturated solution. [b]The substrate conversion was monitored by GC. [c]Yield of isolated products. [c]Only degradation of the substrate was observed.

In 2010, during the course of the present thesis, Hoffmann and co-workers, published a study of the intramolecular photochemical reaction of several 5-hydroxymethyl-2(5*H*)-furanone derivatives protected with a tetrahydropyranyl unit, including **14p**.[75] In this work, the irradiation was carried out through a quartz filter in acetonitrile with acetone as sensitizer and it afforded a 1:1 diastereomeric mixture of **2*S*-54p** and **2*R*-54p** in moderate total yield (43%). Noteworthy, they found that the reaction does not proceed in the absence of acetone.

In our laboratories, the structure and configuration determination of the irradiation products was accomplished on the basis of their ^{1}H and ^{13}C NMR spectra with the help of 2D NMR experiments and, for **2*R*-** and **2*S*-54p**, by comparison with the NMR values described by Hoffmann.

[75] Jahjah, R.; Gassama, A.; Bulach, V.; Suzuki, C.; Abe, M.; Hoffmann, N.; Martinez, A.; Nuzillard, J.-M. *Chem. Eur. J.* **2010**, *16*, 3341-3354.

The minor product was assigned to the **2*S*-54p** isomer. The configuration of the stereocenter C-2 was established through NOESY experiments, wherein there is interaction of both protons H-8 with H-4 and one proton H-5' of the spiranic pyran moiety (Figure 17). The NMR data matched with those described by Hoffmann, who confirmed the configuration by an X-ray crystal analysis.

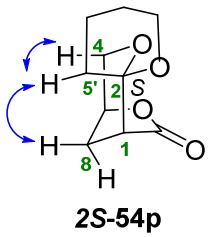


Figure 17. n.O.e interactions observed for **2*S*-54p**

On the other hand, the configuration of the major product was assigned by a NOESY experiment and by comparison between the NMR data of compounds **2*R*-** and **2*S*-54p** For **2*R*-54p**, no interaction between H-8 and any proton of the spiranic pyran unit was observed and, noteworthy, there exists cross-peaks between H-1 and one proton H-4' of the spiranic pyran unit (Figure 18).

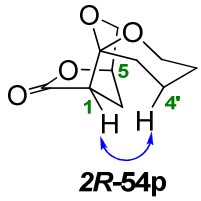


Figure 18. n.O.e interactions observed for **2*R*-54p**.

For both isomers, the connectivity was confirmed by HMBC esperiments, which showed cross peaks between both protons H-8 and proton H-1 with C-2 (Figure 19).

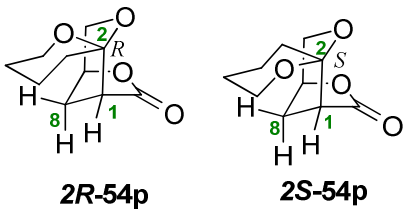
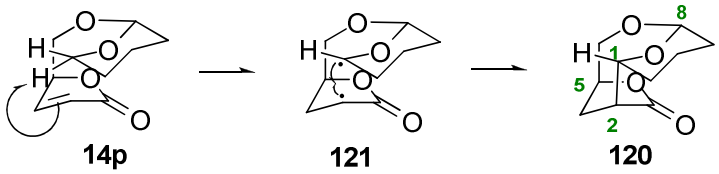


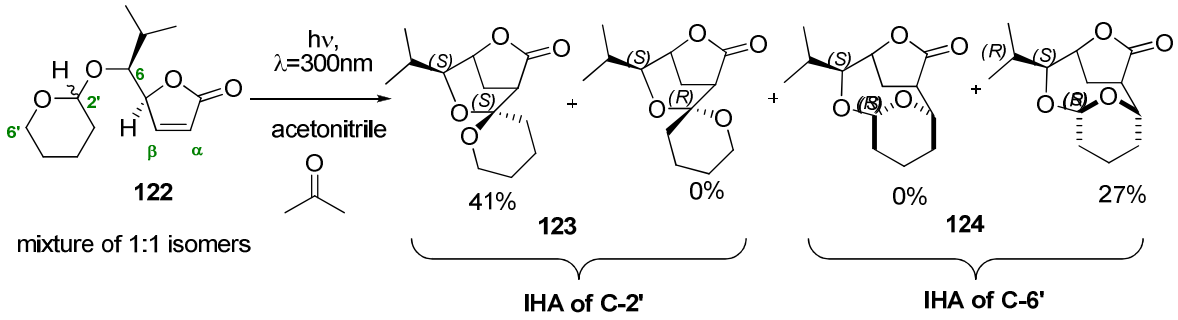
Figure 19. HMBC interactions observed for **2*R*-54p** and **2*R*-54p**.

In our study, the bicyclic compound **120**, which arises from a 1,7-IHA followed by diradical recombination, was also obtained (Scheme 41). This minor compound was isolated as a single diastereoisomer. Signals of the ketal proton at δ 4.87 ppm and of carbon atom at δ 96.25 ppm and also cross-peaks between H-1 and C=O evidence the structure of **120**.



Scheme 41. Formation of **120** from furanone **14p** by 1,7-intramolecular hydrogen abstraction

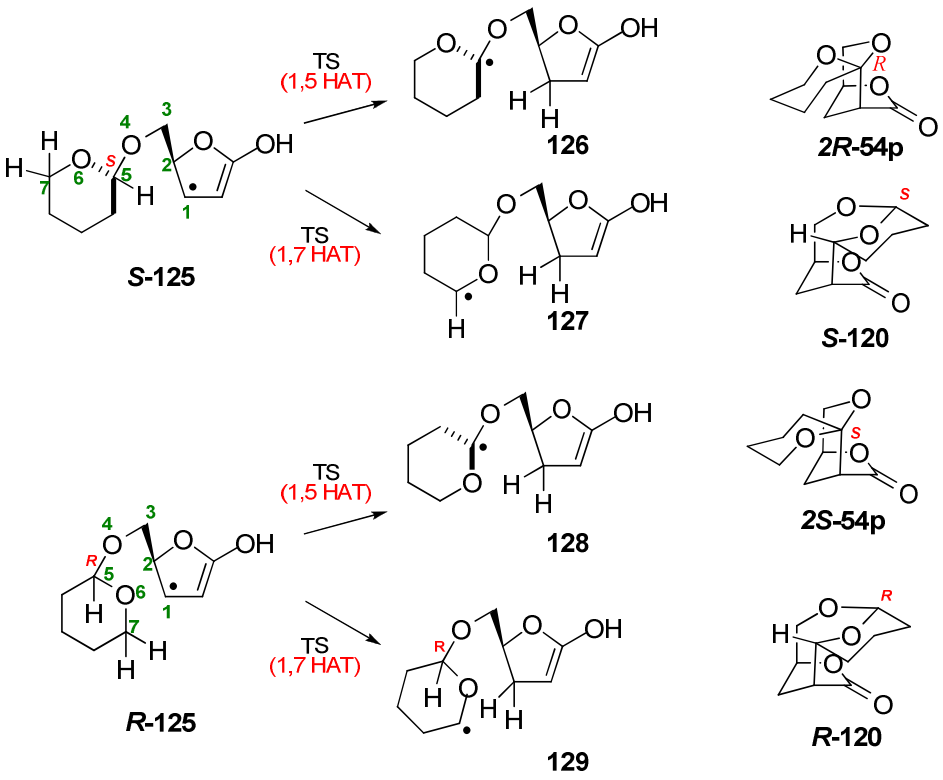
In the above mentioned work of Hoffmann, the photochemical reaction of furanone **122** containing an isopropyl moiety at the carbon atom that links the furanone and the tetrahydropyran moiety was also studied (Scheme 42). Interestingly, in this reaction, the product ***S*-124** formed by 1,7-IHA of the hydrogen H-6' was formed, along with the *S*-diastereoisomer ***S*-123**, in 27% and in 41% yield, respectively.



Scheme 42. Irradiation of furanone **122** by Hoffmann *et al.* (2010).

Therefore, our results are quite different from those described by Hofmann's group, since they neither observed reaction in the absence of acetone nor the formation of the the bicyclic compound **120**. In our experiments, we obtained better results when direct irradiation through a quartz filter was performed compared to the sensitized irradiation. A similar ratio of products **2*R*-54p**, **2*S*-54p**, and **120** was obtained when the reaction was carried out in acetone or acetonitrile.

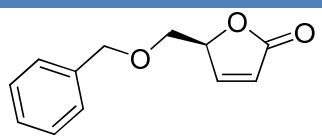
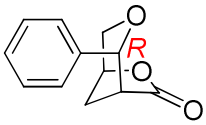
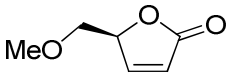
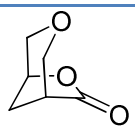
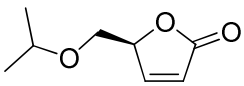
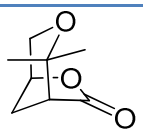
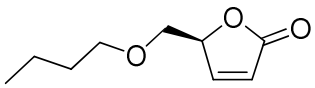
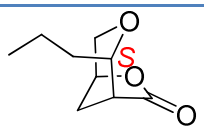
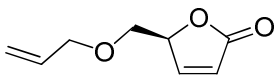
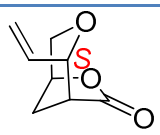
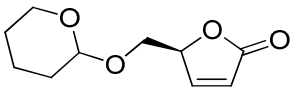
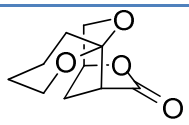
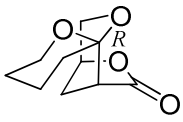
In order to obtain information about the stereoelectronic effects on the hydrogen-abstraction reaction, Hoffmann calculated the energy barriers for the possible pathways for the radical ***S*-** and ***R*-125**, which are a model for the 3ππ* excited state of **14p** (Scheme 43). These computational studies provided important information about the product selectivity observed in our experiments. According to Hoffmann's calculations, for ***S*-125** the transition state of the 1,7-hydrogen abstraction was found to have higher energy (~ 2.6 kcal/mol) to that of the 1,5-hydrogen abstraction, leading exclusively to the formation of **2*R*-54p**. While for ***R*-125**, the computational predictions are consistent with the experimental observation, since the transition state of 1,7-IHA displays only slightly higher energy (0.76 kcal/mol) of that of the 1,5-IHA, giving **2*S*-54p** and **120.**



Scheme 43. 1,5- and 1,7-Intramolecular hydrogen abstraction from furanone model **125**.

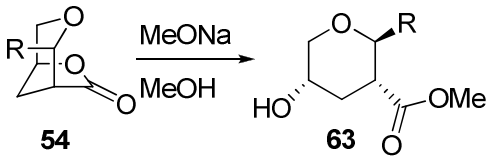
Table 10 summarizes our results concerning the photochemical study of IHA for the complete series of furanones **14i-p**. This methodology has allowed the specific and diastereoselective formation of a new C-C bond in good yield (50 to 80%).The intramolecular hydrogen abstraction of 2(5*H*)-furanones **14i-m** gave similar results. The higher yield observed for **14i** was attributed to the greater stabilization of the diradical intermediate due to the benzyl residue. Remarkably, the expected bicyclic compounds were obtained regardless of the reaction conditions: direct excitation in the case of acetonitrile through a quartz filter and sensitive excitation in the case of acetone with using a pyrex® filter. For furanone **14o**, the intramolecular [2+2] cycloaddition competes favourably with the intramolecular hydrogen abstraction. Finally, the photoreaction of **14p** afforded the expected spiro compounds **54p** along with a small amount of **120** arising from a a 1,7 intramolecular hydrogen abstraction.

Table 10. Summary of products and yields in the photoreaction of 2(5*H*)-furanones **14i-p**.

2(5*H*)-Furanone	Products	Yield (%)
 **14i**	 **54i**	78
 **14k**	 **54k**	52
 **14l**	 **54l**	50
 **14m**	 **54m**	52
 **14o**	 **54o**	8
 **14p**	 ***2S*-54p**  ***2R*-54p**	10 50

2.4. Synthesis of polysubtituted tetrahydropyrans

With the photoadducts in hands, our next endeavour was to carry out the methanolysis of the lactone to obtain, in a stereocontrolled way, polysubstituted tetrahydropyrans (Scheme 44).



Scheme 44. Pyran formation.

This methanolysis was performed with the photoadducts **54i** and **2*R*-54p** (Figure 20), which afforded the corresponding tetrahydropyrans **63i** and **63p** with the expected configuration.

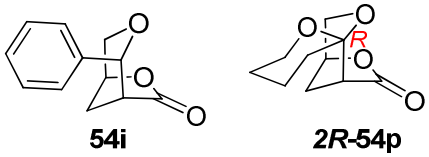
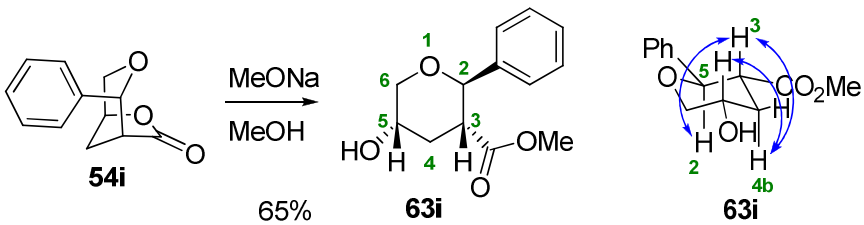


Figure 20: Selected substrates for the methanolysis reaction.

2.4.1. Methanolysis of photoadduct **54i**

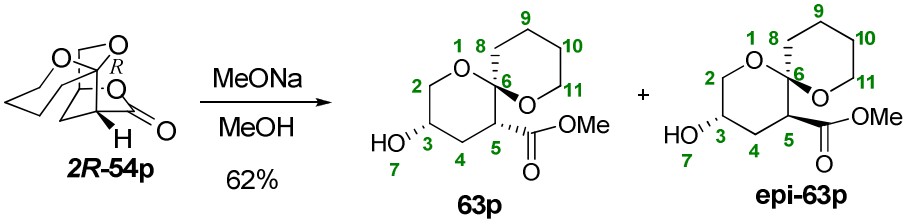
Methanolysis of **54i** was accomplished by reaction with sodium methoxide in methanol at the reflux temperature overnight (Scheme 45). After treatment of the reaction mixture with 1M HCl, the tetrahydropyran **63i** was obtained in 65% yield. The configuration of this product was established through NMR experiments. The presence of 1,2 transdiaxial couplings between H-2 and H-3 (J=10.0 Hz) and also between H-3 and H-4 (J=12.5 Hz) indicates that all substituents are placed in equatorial positions.



Scheme 45. Methanolysis of tricyclic **54i**.

2.4.2. Methanolysis of tricycle 2*R*-54p

Then, we performed the methanolysis reaction on **2*R*-54p** following the same protocol (Scheme 46). In this case, a mixture of two compounds, **63p** and **epi-63p** was obtained in 62% total yield. We speculated that compound **epi-63p** could have been formed from **63p** during the acidic work-up. To confirm this hypothesis, a milder acidic treatment of the reaction mixture was assayed, by using a saturated aqueous solution of ammonium chloride. Thus, upon these new conditions, only pyran **63p** was produced in good yield (62%).



Scheme 46. Methanolysis of **2*R*-54p**.

The identification of both products was carried out through their ^{1}H-NMR and ^{13}C-NMR spectra and NOESY experiments. In the ^{1}H NMR spectrum of **63p**, H-3 resonates at δ 3.53 and its signal appears appears as a dddd with coupling constants $J_{3,OH}$ ≈ 11.2 Hz, $J_{3,2}$ ≈ $J_{3,4}$ ≈ 4.1 Hz and $J_{3.2}$ = 2.2 Hz. The H-5 signal is a dd at δ 2.67 with two coupling constants ($J_{5,4ax}$ = 6.6 Hz and $J_{5,4eq}$ = 1.4 Hz). The absence of large diaxial coupling constants suggests a chair conformation with both the hydroxyl group and the ester moiety in axial orientations (Figure 21).

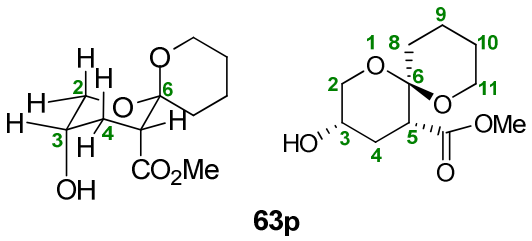
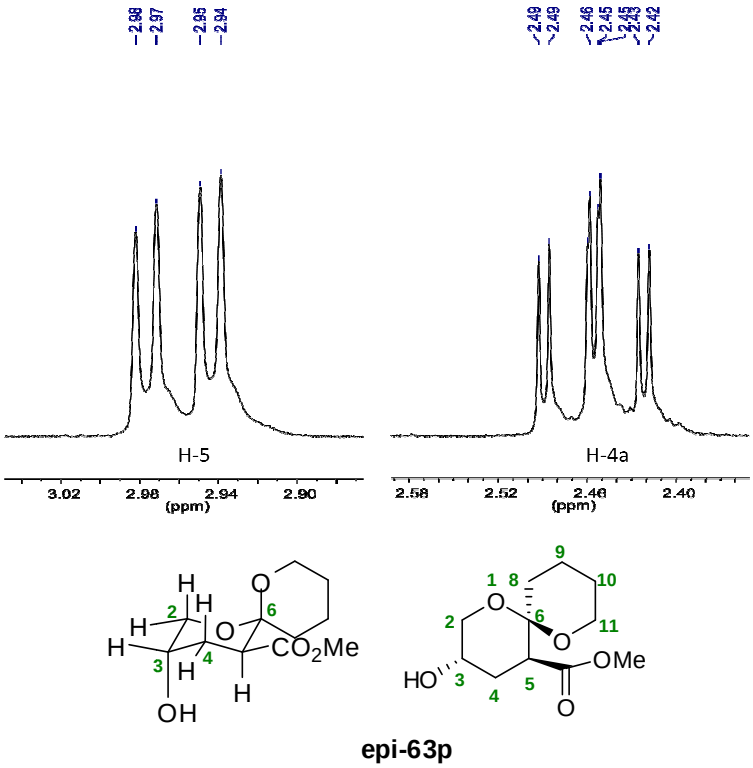


Figure 21. Structural assignment of **63p**.

In the ^{1}H NMR spectrum of **epi-63p**, H-5 resonates at δ 2.96 and its signal appears as a dd with coupling constants $J_{5,4ax}$ = 13.1 Hz and $J_{5,4eq}$ = 4.2 Hz. On the other hand, H-4ax appears as a dt at δ 2.46 with coupling constants J_{gem} ≈ $J_{4ax,5ax}$ ≈ 13.1 Hz and $J_{4ax,3eq}$ = 2.9 Hz. These data suggest a chair conformation with the ester in an equatorial orientation and the hydroxyl group in an axial orientation, which is possible only in a 1,3 trans relationship (Figure 22).



epi-63p

Figure 22. Selected 1H NMR data for **epi-63p**.

2.5. Conclusions

Tetrahydropyrans have been achieved from the intramolecular photochemical reaction of α,β-unsaturated furanones. This methodology provides a direct route to the diastereoselective synthesis of 2,3,5-trisubstituted-tetrahydropyrans **63**.

Chapter 3: Study of the intramolecular [2+2]-photochemical reaction of substituted maleimides

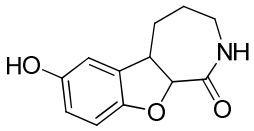
Votre temps est limité, ne le gâchez pas en menant une existence qui n'est pas la vôtre.

Steve Jobs, Discours à Stanford, 2005.

This part of the present thesis has been realized in the group of Prof. Kevin Booker-Milburn in the School of Chemistry at the University of Bristol in 2011.

3.1. Introduction

Seven membered azepane can be found in a variety of bioactive natural products, including the enzyme inhibitor CID755673[76] (Figure 23) and many stemona alkaloids.



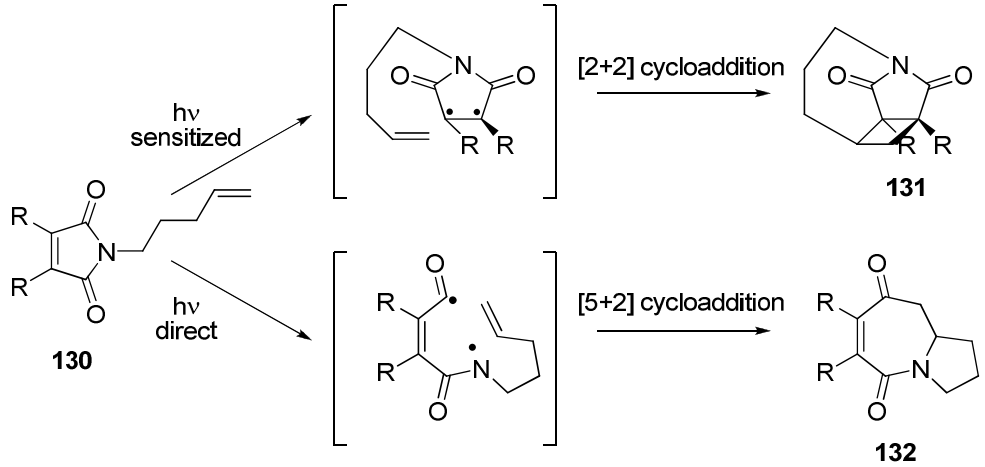
CID755673

Figure 23. A natural tricyclic azepane derivative.

Booker-Milburn's group possesses a great experience in the photochemical reactions on *N*-alkenyl substituted maleimides. Some years ago, they described how to control the reaction pathway of the two competitive synthetic evolutions, namely [5+2] and [2+2] cycloaddition.[43]

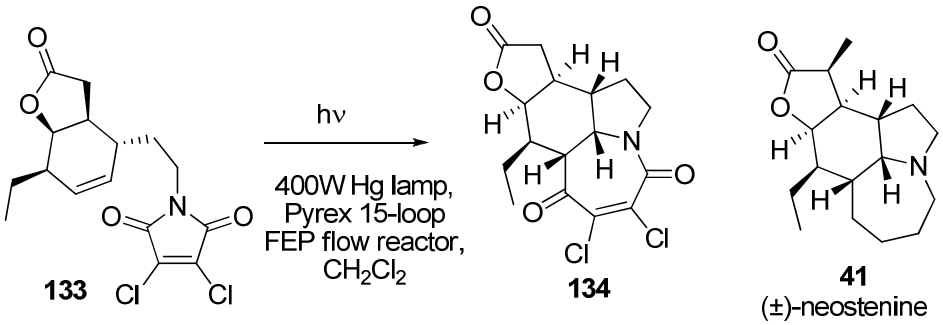
They found that the [2+2] photoreaction of the maleimide **130** led efficiently to the cycloadduct **131** in high yield (90-100%) by sensitive excitation (Scheme 47). In contrast, the direct excitative photochemical reaction of maleimide **130** afforded only the product **132**, in 94% yield, derived from the intramolecular [5+2] photocycloaddition of **130**. Moreover, they also became interested in the question whether cyclobutene frameworks may serve as precursors for azepane derivatives such as CID755673 or analogues of amino acid derivatives.

[76] LaValle, C. R.; Bravo-Altamirano, K.; Giridhar, K. V.; Chen, J.; Sharlow, E.; Lazo, J. S.; Wipf, P.; Wang, Q. J. *BMC Chemical Biology* **2010**, *10*, 5.



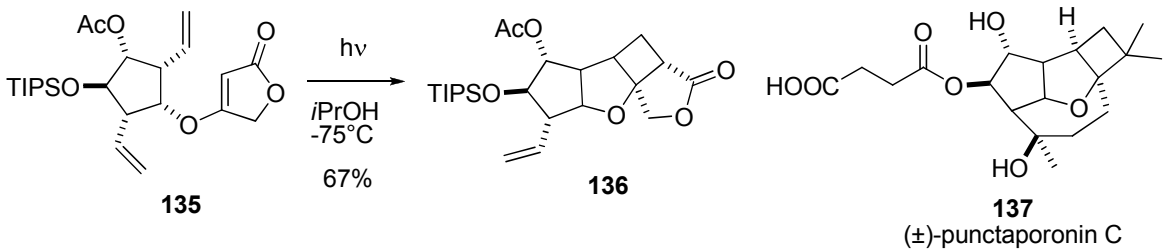
Scheme 47. Competitive intramolecular [2+2] and [5+2] photocycloaddition of maleimide derivatives.

More recently, they have focused on exploring the scope of the [5+2] cycloaddition and its application to natural product synthesis. Thus, they have published a protecting group free synthesis of (±)-neostenine[42, 77] via the intramolecular [5+2] photocycloaddition of maleimide **133**, affording advanced tetracycle **134**, which after some elaboration lead to the alkaloid (Scheme 48).



Scheme 48. Synthesis of (±)-neostenine, **41**, by Booker-Milburn *et al.* (2008).

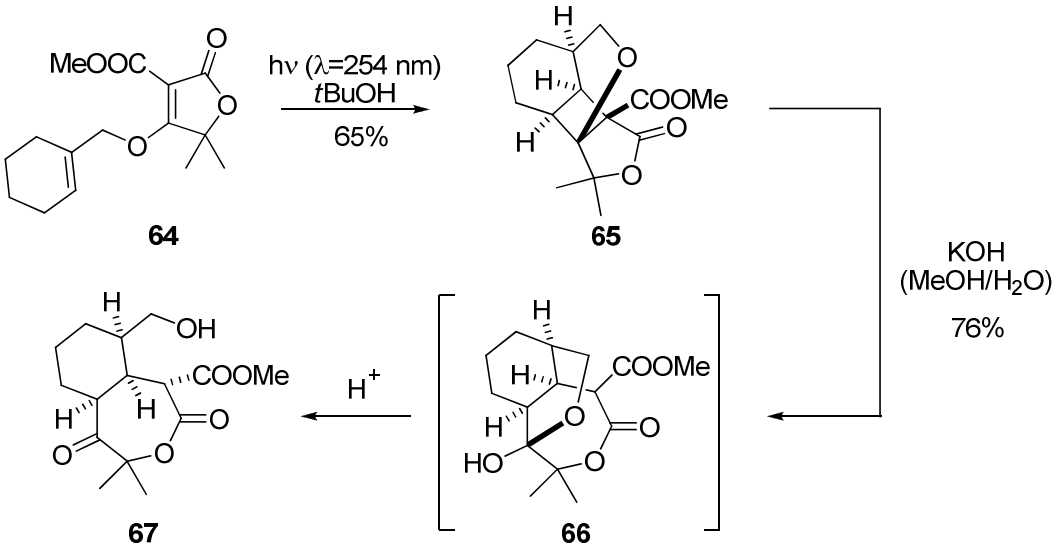
In a related area, Bach and Fleck described the total synthesis of (±)-punctaporonin C, **137**,[78] using a regio- and stereoselective intramolecular [2+2] photocycloaddition of the tetronate derivative **135** (Scheme 49).



Scheme 49. Key step of the total synthesis of (±)-punctaporonin C, by Bach and Fleck (2008).

[77] (a) Hickford, P. J.; Baker, J. R.; Bruce, I.; Booker-Milburn, K. I. *Org. Lett.* **2007**, *9*, 4681-4684.
[78] Fleck, M.; Bach, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 6189-6191.

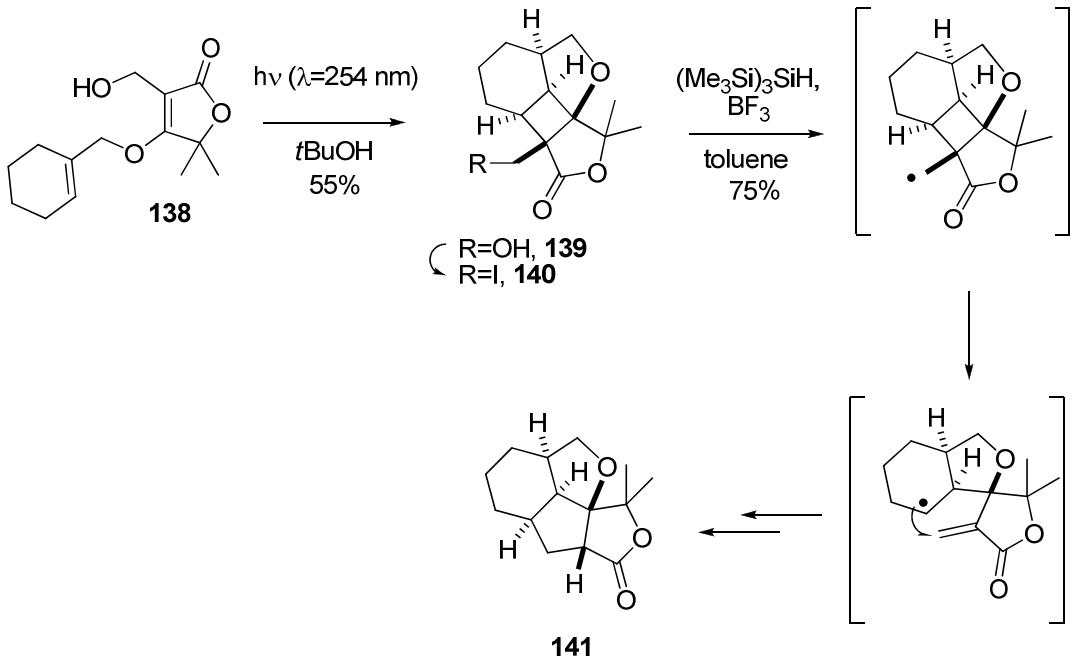
More recently, the same group has published an approach to the skeleton of several terpenoid natural products.[79] Selective cyclobutane cleavage reactions of the strained skeleton afforded from seven- to twelve-membered rings (Scheme 50) by a one-pot, two step process: [2+2] photocycloaddition/fragmentation. In particular, they synthesized the oxepane **67** by intramolecular [2+2] photocycloaddition on tetronate **64** followed by base promoted fragmentation.



Scheme 50. Seven-membered ring formation by [2+2] photocycloaddition followed by base promoted cyclobutane ring fragmentation, by Bach *et al.* (2011).

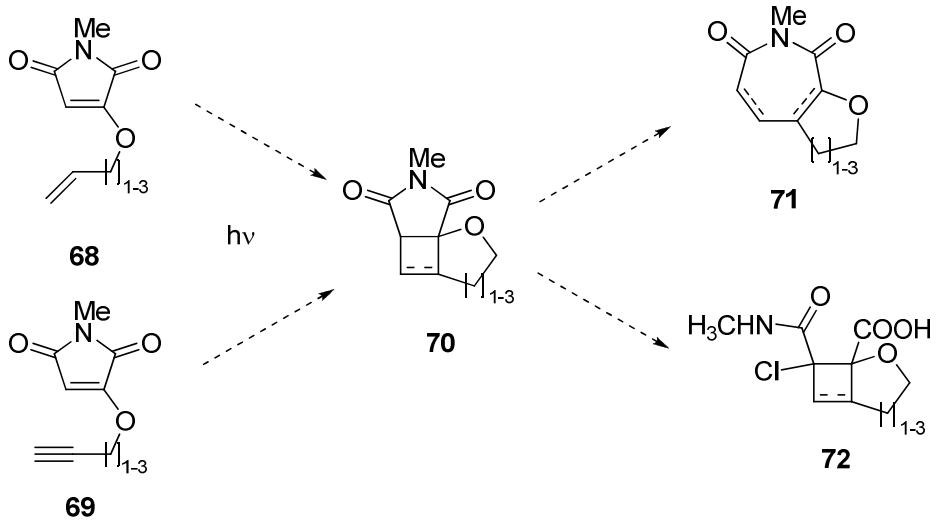
In a second example, after the intramolecular [2+2] photocycloaddition, they prepared the iodo derivative **140** to generate a radical, which trigger a cyclic rearrangement, affording the tetracycle **141** (Scheme 51).

[79] Hehn, J. P.; Herdtweck, E.; Bach, T. *Org. Lett*. **2011**, *13*, 1892-1895.



Scheme 51. Formation of the tetracycle **141** by a radical domino process, by Bach *et al.* (2011).

With all these precedents in mind, we decided to study the intramolecular [2+2] photocycloaddition of various alkene and alkyne substituted maleimide derivatives **68** and **69**, with the aim of preparing the tricyclic cycloadducts **70** (Scheme 52) which expected to be transformed into the target compound **71** and **72** by a ring opening reaction.



Scheme 52. Devised photochemical reactivity of different alkene and alkyne substituted maleimides and posterior fragmentation.

In order to carry out the photochemical study, compounds **68a-j** and **69a-f** were selected as alkenyl and alkynyl substituted maleimide derivatives (Figure 24).

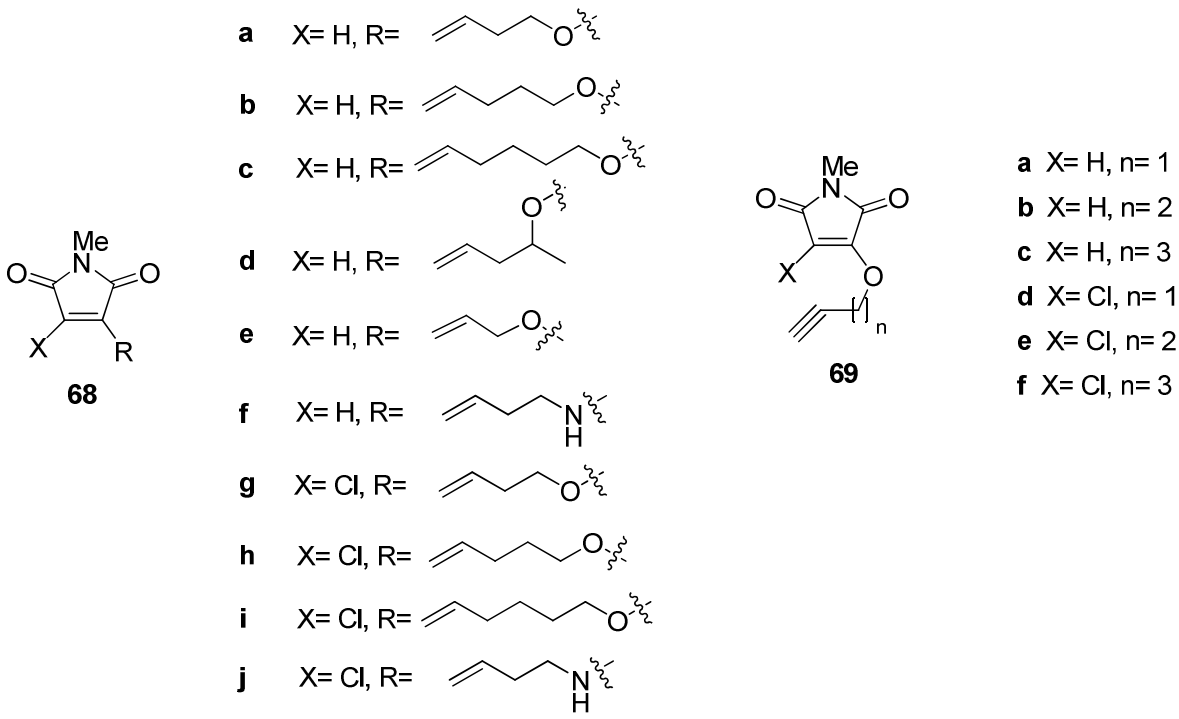


Figure 24. Structure of maleimide derivatives selected to study their photochemical reactivity.

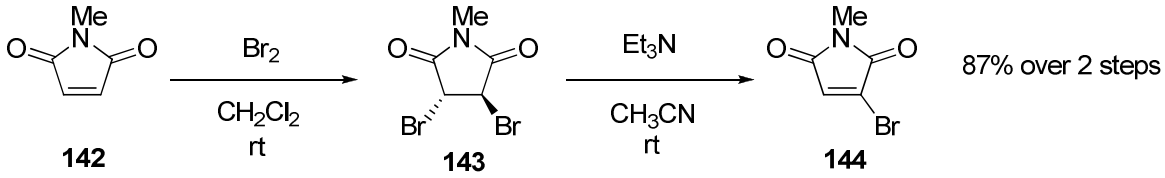
The study of these substrates will allow us to compare the difference of reactivity between alkene and alkyne substituted maleimides and the effect of the presence of chlorine atom on the conversion and the yield of the reaction. The final aim of this study was to obtain synthetically useful azepine derivatives.

All the photochemical reactions reported in this chapter were conducted with a 125W high pressure mercury lamp. The evolution of the reaction was controlled by TLC. The irradiations were stopped in function of by-product formation. Product characterization was accomplished by NMR or X-ray diffraction analyses. All the spectrum are described in the Experimental Section.

3.2. Synthesis of 1-methyl-3-(alkenyloxy)-1*H*-pyrrole-2,5-diones 68a-f and 3-chloro-1-methyl-4-(alkenyloxy)-1*H*-pyrrole-2,5-diones 68g-j

3.2.1. Synthesis of 1-methyl-3-(alkenyloxy)-1*H*-pyrrole-2,5-diones **68a-f**

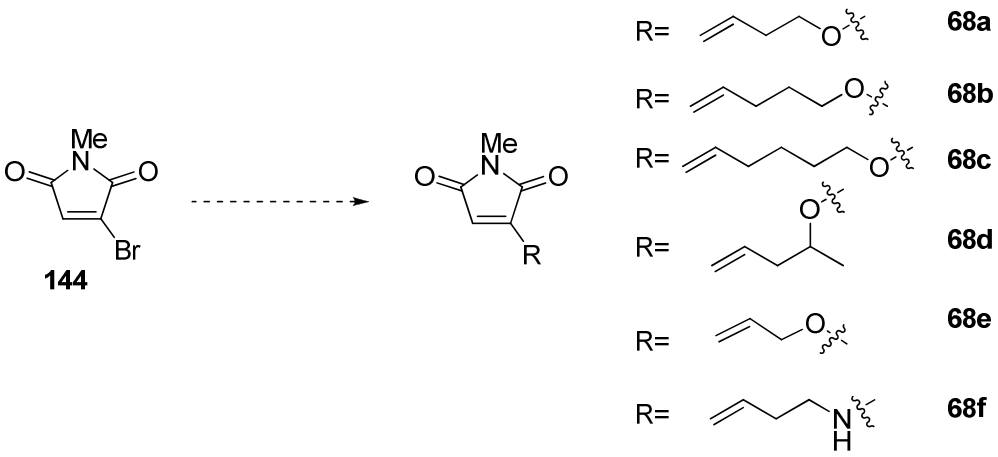
N-Methyl-3-bromomaleimide, **144**, was prepared on a multigram scale in 87% yield starting from the commercially available *N*-methylmaleimide, **142**, by bromination of the carbon-carbon double bond followed by elimination of hydrogen bromide (Scheme 53).[80]



Scheme 53. Synthesis of *N*-methyl-3-bromomaleimide, **144**.

With *N*-methyl-3-bromomaleimide, **144**, in hand, we proceeded to perform the conjugate substitution of the bromine atom with different alcohols and one amine bearing an alkenyl chain, to form 1-methyl-3-(alkenyloxy)-1*H*-pyrrole-2,5-diones **68a-f** (Scheme 54). This conjugate substitution occurs by a Michael type addition followed by elimination of the bromide. A series of different substrates were planned to be used, in order to study their behaviour in regard to the carbon chain length (from butenol to hexenol), the kind of alcohol (primary *vs*. secondary) and the atom linker (alcohol *vs*. amine). Different conditions were evaluated to prepare the alkenylmaleimides **68**.

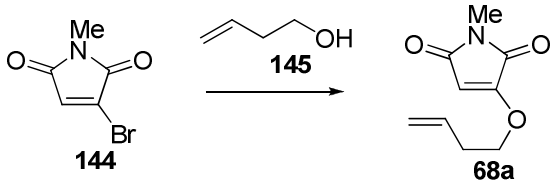
[80] Tedaldi, L. M.; Smith, M. E.; Nathani, R. I.; Baker J. R. *Chem. Commun.* , **2009**, 6583-6585.



Scheme 54. Target 1-methyl-3-subsituted-1*H*-pyrrole-2,5-diones **68a-f**.

A methodology widely used in the Booker-Milburn group laboratory was applied for introducing the alkoxy residue on bromomaleimide **144**. Firstly, the reaction of bromomaleimide **144** with 3-buten-1-ol was attempted under the usual conditions (Table 11, entry 1), namely with NaH as the base in dry dioxane at room temperature. In the event, the expected alkene **68a** was isolated, albeit in low yield (30%) and no starting material was recovered. Because of the low yield achieved in this reaction, we tried to optimize the conditions. Increasing the temperature (entry 2) or changing the solvent to DMF (entry 3) was unsuccessful, resulting only in a decrease of the yield and total decomposition of the starting materials. Using triethylamine as the base and acetonitrile as the solvent (entries 4 and 5) did not cause significant improvement. However, in these cases, the work-up and purification were easier. It must be pointed out that an increase of the temperature gave a faster reaction, but the conversion was still incomplete.

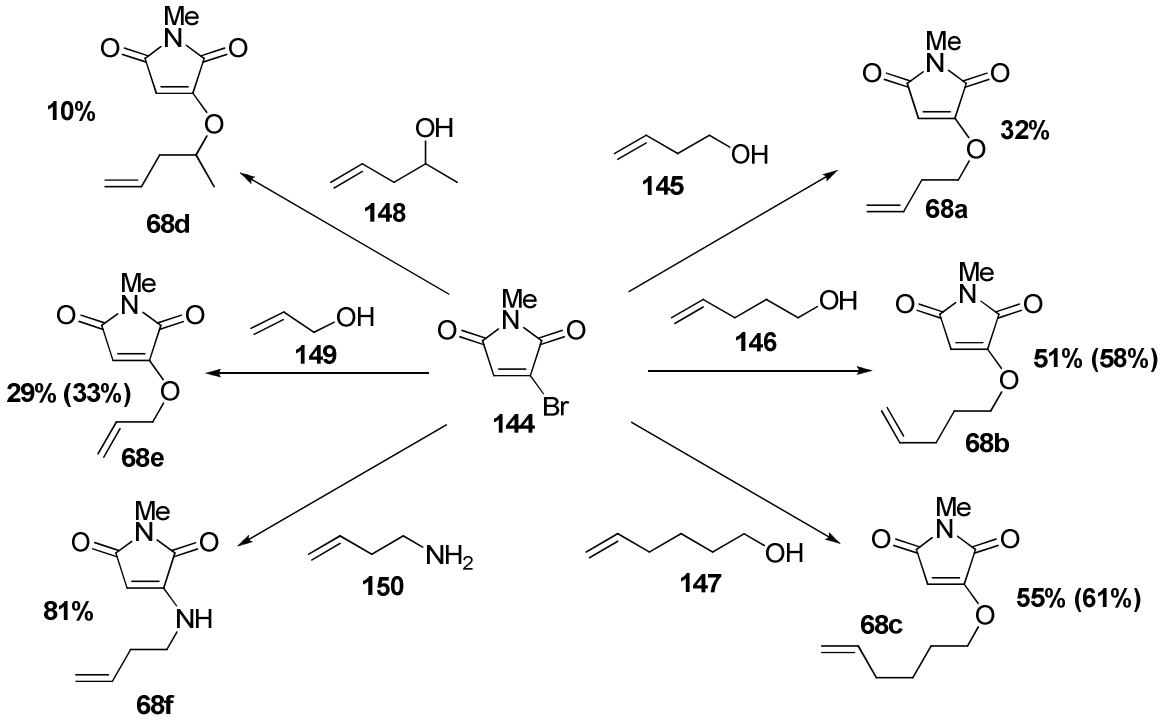
Table 11. Preparation of alkene **68a**.



Entry	Base	solvent	T℃	yield
1	sodium hydride	dioxane	rt	30%
2	sodium hydride	dioxane	101	20%
3	sodium hydride	DMF	rt	0%
4	triethylamine	acetonitrile	rt	32%
5	triethylamine	acetonitrile	40	32%

The last reaction conditions were then applied to perform the reactions with the rest of alcohols and the amine obtaining the corresponding maleimide derivatives **68b-f**, in

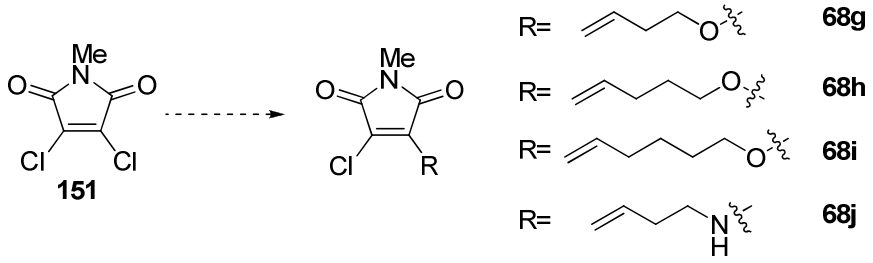
yields oscillating between 10% and 81% (Scheme 55). The worst result was observed for the secondary alcohol, showing the importance of the efficiency of the Michael type addition. On the other hand, the reaction of the amine was faster and occurred in better yield compared to its alcohol analogue (81% *vs* 32%), probably due to the higher nucleophilic character of the primary amine over the primary alcohol. The other reactions took place in yields between 29% and 55%.



Scheme 55. Synthesis of 1-methyl-3-subsituted-*1H*-pyrrole-2,5-diones **68a-f**.

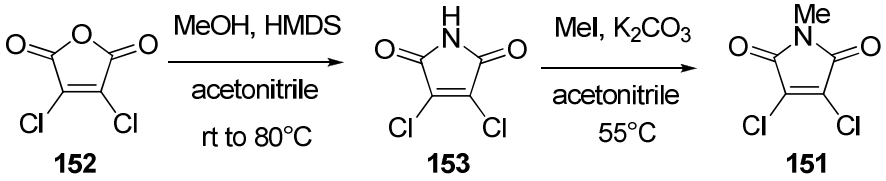
3.2.2. Synthesis of 3-chloro-1-methyl-4-(alkenyloxy)-1*H*-pyrrole-2,5-diones **68g-j**

To study the effect of the presence of a chlorine substituent, we prepared the 3-chloro-4-substituted maleimides **68g-j** (Scheme 56).



Scheme 56. Target 3-chloro-1-methyl-4-(substituted)-1*H*-pyrrole-2,5-diones **68g-j**.

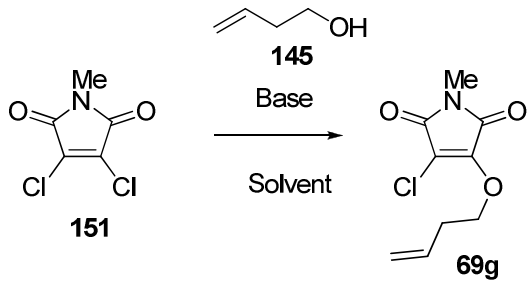
The synthesis of **151**, the common precursor of all these alkenes was achieved following a procedure used in our laboratory, which can be performed on a multi-gram scale and satisfactory yield, starting from commercially available 2,3-dichloromaleic anhydride, **152**, (Scheme 57). This procedure started with the addition of methanol to a solution of hexamethyldisilazane and 2,3-dichloromaleic anhydride in dry acetonitrile at room temperature, followed by heating at 80℃ for 10 min, and furnished the 3,4-dichloromaleimide **153** in 62% yield. Then, the reaction of imide **153** with potassium carbonate, followed by addition of iodomethane in acetonitrile at 55℃, afforded *N*-methyl-3,4-dichloromaleimide, **151**, in 49% yield.



Scheme 57. Synthesis of *N*-methyl-3,4-dichloromaleimide.

To prepare the 3-chloromaleimides **68g-j** from **151**, we applied the same procedure previously used for the synthesis of maleimides **68a-f**, except that initially less equivalents of base (from 2.2 to 1.5) and nucleophile (from 2.0 to 1.2) were added to avoid the formation of disubstitution products. However, these products were never detected. The best reaction conditions were established by using alcohol **145** as the nucleophile (Table 12). We have performed a series of reactions changing the base (Et_3N, *t*BuOK or Cs_2CO_3), the equivalents of alcohol (from 2 to 6 equiv), the solvent (acetonitrile, toluene and THF) and the reaction temperature. From the results of these experiments, we have determined the average yield for each particular factor modified to investigate which of these factors was more determining for the reaction (Tables 12 and 13).

Table 12. Studies on the reaction between maleimide **151** and alcohol **145**.



entry	T °C	Base	Base Equiv	Equiv 148	Solvent	Yield %	Conversion %
1	20	Et_3N	1.5	2	acetonitrile	25	56
2	20	*t*BuOK	1.5	4	THF	14	86
3	20	Cs_2CO_3	1.5	6	toluene	10	98
4	40	Et_3N	1.5	4	toluene	13	80
5	40	*t*BuOK	1.5	6	acetonitrile	9	89
6	40	Cs_2CO_3	1.5	2	THF	11	95
7	60	Et_3N	1.5	6	THF	33	69
8	60	*t*BuOK	1.5	4	toluene	8	88
9	60	Cs_2CO_3	1.5	2	acetonitrile	4	97

Table 13. Average yield for every factor considered.

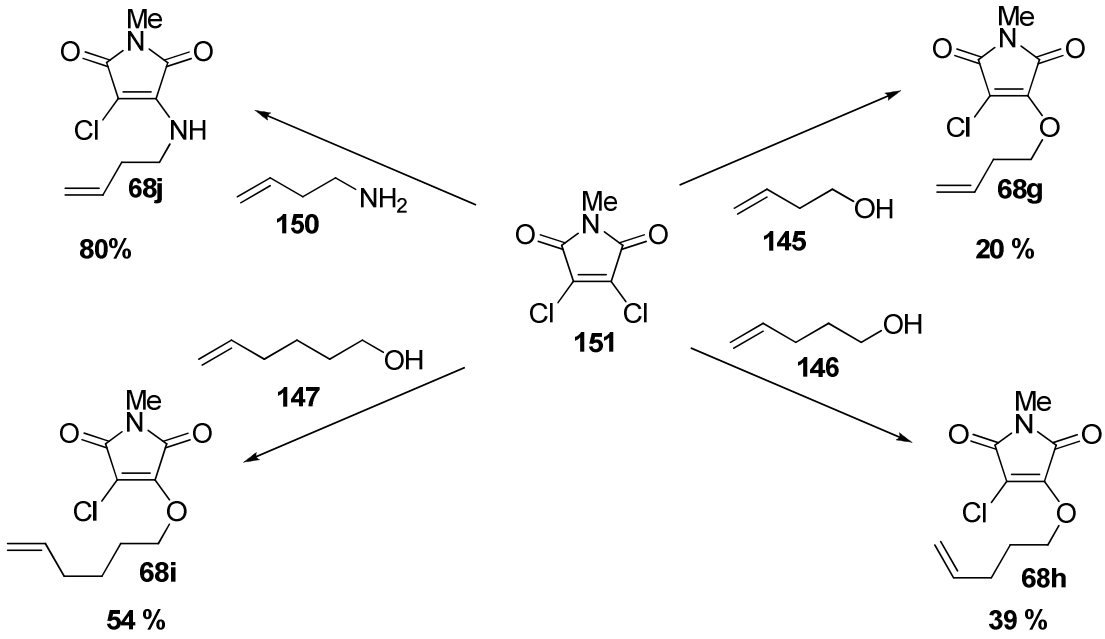
Base	Average yield	Temperature	Average yield
Et_3N	24%	20℃	16%
*t*BuOK	10%	40℃	11%
Cs_2CO_3	8%	60℃	15%
Equiv of alcohol	**Average yield**	**Solvent**	**Average yield**
2	13%	acetonitrile	13%
4	12%	toluene	12%
6	17%	THF	17%

The first parameter studied was the base. We noticed the significant role of the base for this reaction and Et_3N gave a better performance than K*t*BuO or Cs_2CO_3. The second and third parameters were the temperature and the number of equivalents of alcohol, none of which seem to play an important role over the yield. The last parameter studied was the solvent and, apparently, THF was better than toluene or acetonitrile, although the effect on the yield was not very significant.

Table 14 summarizes the optimized factors that were used to scale up the reaction between maleimide **151** and alcohol **145** and were also applied to the other nucleophiles. In general, the yields were lower than those found in the reactions of bromomaleimide **144** with the same nucleophiles. For the alcohols, the yield increased with the length of the chain, while the amine showed higher reactivity as before (Scheme 58).

Table 14. Optimized factors of the reaction between maleimide **151** and alcohol **145**.

Solvent	dry THF
Temperature	60°C
Concentration	0,278 $mmol.L^{-1}$
Base	Triethylamine (2 equiv)
Alcohol	2 equiv



Scheme 58. Synthesis of 3-chloro-1-methyl-4-(substituted)-1*H*-pyrrole-2,5-diones **68g-j**.

The lower reactivity of the dichloromaleimide **151** compared to bromomaleimide **144** in the conjugate addition might be attributed to the difference of behaviour of the two leaving groups and also to the less polarized character of the olefinic carbon atom (Figure 25).

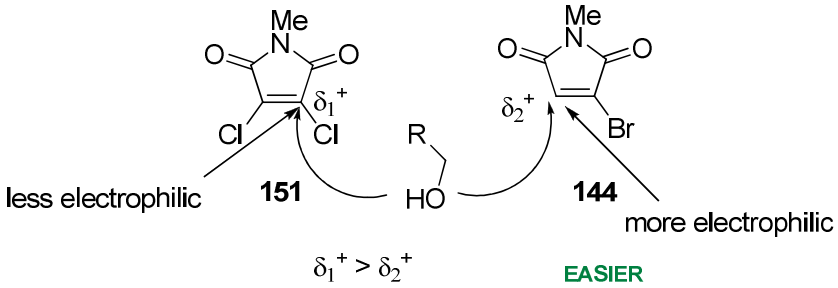
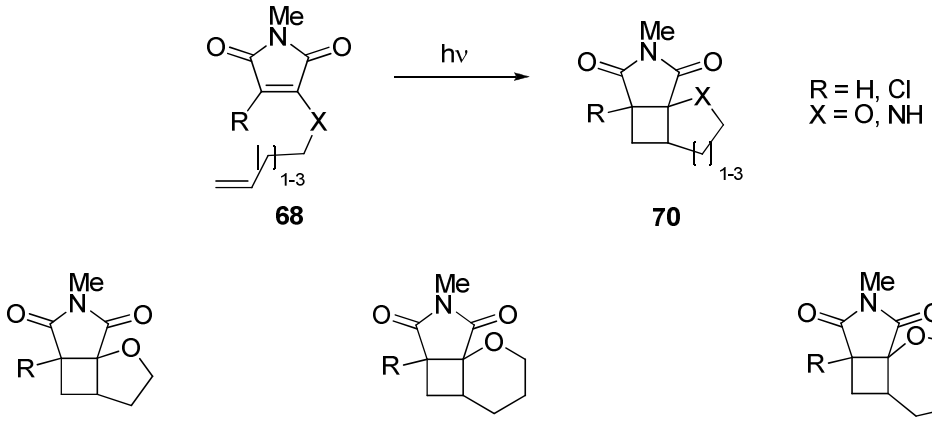


Figure 25. Difference of reactivity between maleimides **151** and **144**.

3.3. Intramolecular photochemical reaction of 1-methyl-3-(alkenyloxy)-1*H*-pyrrole-2,5-diones and 3-chloro-1-methyl-4-(alkenyloxy)-1*H*-pyrrole-2,5-diones 68

This study was performed to evaluate the photochemical reactivity of alkenes **68**, from which we expected the formation of the corresponding tricycles (Scheme 59): the 2-oxabicyclo[4.2.0]octane derivatives were anticipated to be more stable than the 2-oxabicyclo[3.2.0]heptane and 2-oxabicyclo[5.2.0]nonane derivatives.



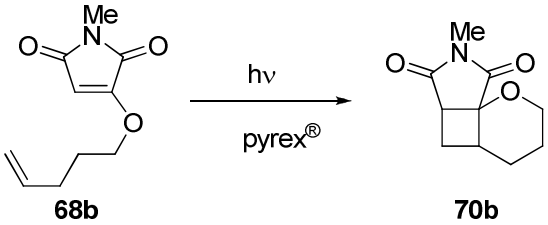
Scheme 59. Expected tricyclic products of the intramolecular [2+2] photochemical reaction of **68**.

The effect of the experimental conditions (solvents, filters) on the yield of the photoreactions was evaluated.

3.3.1. Irradiation of 1-methyl-3-(alkenyloxy)-1*H*-pyrrole-2,5-diones

In the first place, we investigated the intramolecular photochemical reaction of alkene **68b** in two solvents (Table 15). The reaction in acetonitrile (entry 1) afforded the expected cyclobutane in good yield (78%), while in acetone (entry 2) the yield was slightly lower, although the conversion was faster.

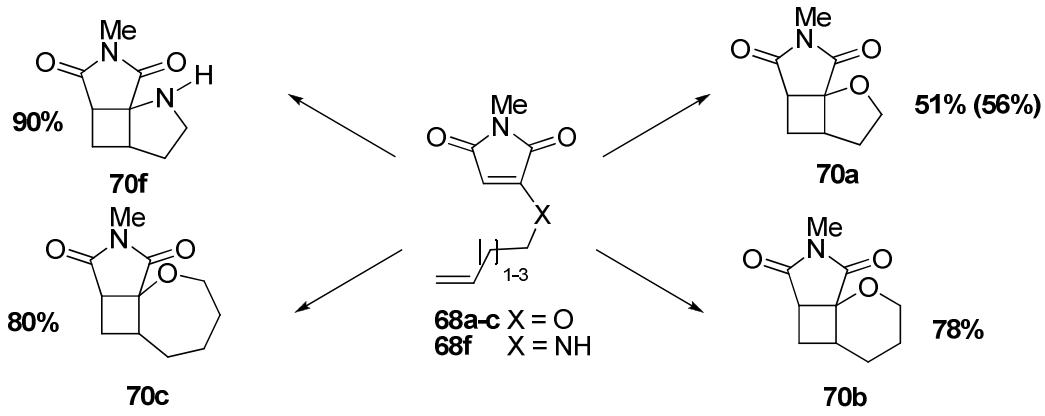
Table 15. Intramolecular [2+2] photocycloaddition of alkene **68b**.



68b **70b**

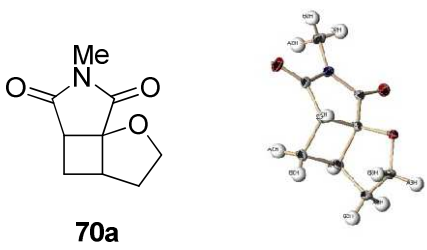
entry	Filter	Solvent	Time (min)	Temperature	Yield (%)
1	pyrex®	acetonitrile	150	20℃	78
2	pyrex®	acetone	90	20℃	69

Taking these results into account, the photochemical reactions of the other alkoxysubstrates **68a** and **68c** and the amine **68f** were carried out in acetonitrile (Scheme 60). As expected, the formation of 2-oxabicyclo[3.2.0]heptane **70a** gave lower yield (51%) than the formation of 2-oxabicyclo[4.2.0]octane **70b**, but, surprisingly, the formation of 2-oxabicyclo[5.2.0]nonane **70c** occurred in similar yield (80%), which is really a noticeable result for the generation of a seven membered ring through a photochemically activated reaction. The best performance was observed for the amine substrate **68f**, which furnished the corresponding pyrrolidine in 90% yield.



Scheme 60. Intramolecular photochemical reaction of maleimides **68**.

The configuration of tricycle **70a** was confirmed by X-ray analysis (Figure 26).



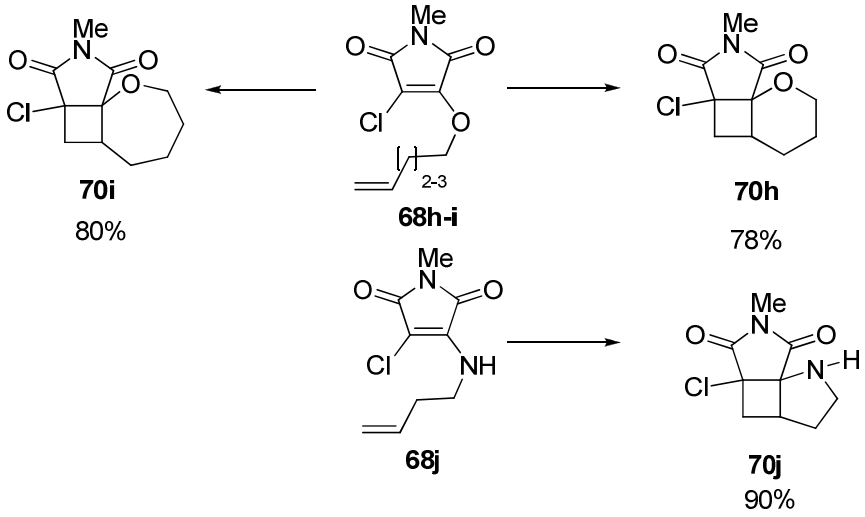
70a

Figure 26. X-ray structure of **70a**.

The same reactions were also performed using a *continuous flow* reactor and the four cyclobutanes were obtained from moderate to high yields, even working on a multigram scale. For instance, a solution of alkene **68b** (650 mg) in degassed acetonitrile (0.5 L) was irradiated with a 400W high-pressure mercury lamp under nitrogen, at room temperature, in the continuous flow reactor with a rate of 6 mL/min in a circuit of 36 mL (6 min of irradiation) to produce the expected photocycloadduct **70b** in 95% yield.

3.3.2. Irradition of 3-chloro-1-methyl-4-(alkenyloxy)-1*H*-pyrrole-2,5-diones

Then, we turned our attention to study the photochemical behavior of 3-chloro-1-methyl-4-(substituted)-1*H*-pyrrole-2,5-diones **68h-j** under the same reaction conditions (Scheme 61). Both the yield and the reaction rate were identical to those observed for the intramolecular [2+2] photocycloaddition reaction of the non chlorinated analogues.



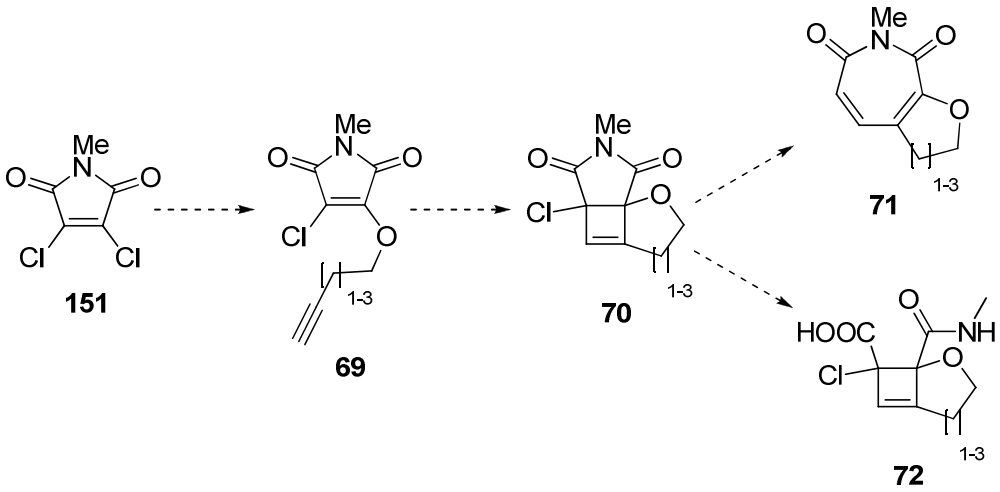
70i 80% — **68h-i** — **70h** 78% — **68j** — **70j** 90%

Scheme 61. Intramolecular [2+2] photochemical reaction of 3-chloro-1-methyl-4-(alkenyloxy)-1*H*-pyrrole-2,5-diones.

3.4. Synthesis of 1-methyl-3-(alkynyloxy)-1H-pyrrole-2,5-diones 72a-c and 3-chloro-1-methyl-4-(alkynyloxy)-1*H*-pyrrole-2,5-diones 69d-f

The formation of cyclobutene derivatives, via the intramolecular [2+2] photocycloaddition of alkynes, was an interesting challenge because we expected that the resulting photoadduct could afford a cyclobutene carboxylic acid or, after

fragmentation, an azepine derivative (Scheme 62). To our best knowledge, this kind of reaction had not been described yet.



Scheme 62. Synthetic approach to azepine derivatives **71** or cyclobutene carboxylic acid derivatives **72**.

3.4.1. Synthesis of 1-methyl-3-(alkynyloxy)-1*H*-pyrrole-2,5-diones **70a-c**

To accomplish the photochemical study of their intramolecular [2+2] cycloaddition reaction, the maleimides **69a-c** were synthesized (Figure 27).

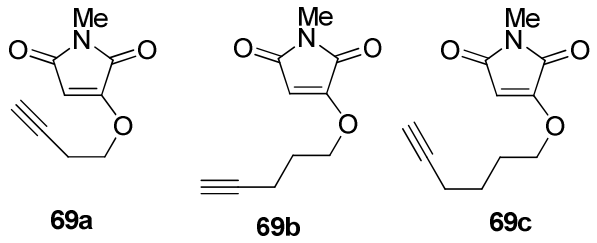
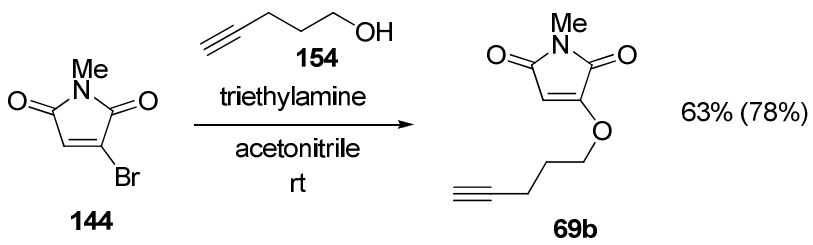


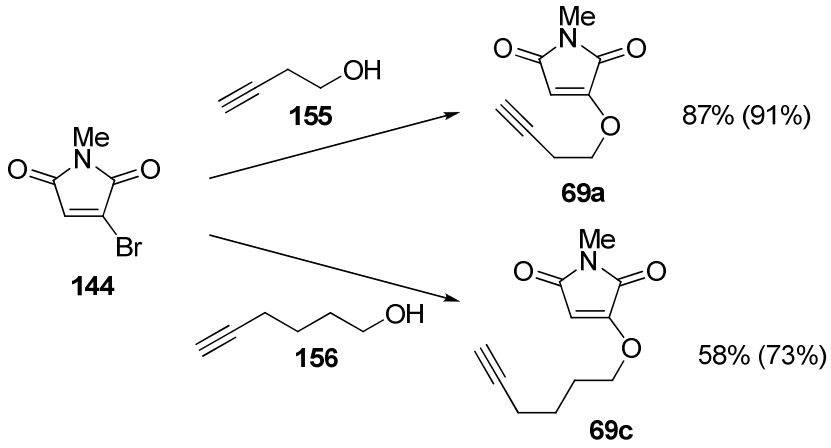
Figure 27. Targeted 1-methyl-3-(alkynyloxy)-1*H*-pyrrole-2,5-diones **69a-c**.

The synthesis of 1-methyl-3-(4-pentyn-1-yloxy)-1*H*-pyrrole-2,5-dione, **69b**, was easily achieved by treatment of **144** with 4-pentyn-1-ol and triethylamine in acetonitrile in 63% yield (78% considering the starting material recovered) (Scheme 63).



Scheme 63. Synthesis of alkynylmaleimide **69b**.

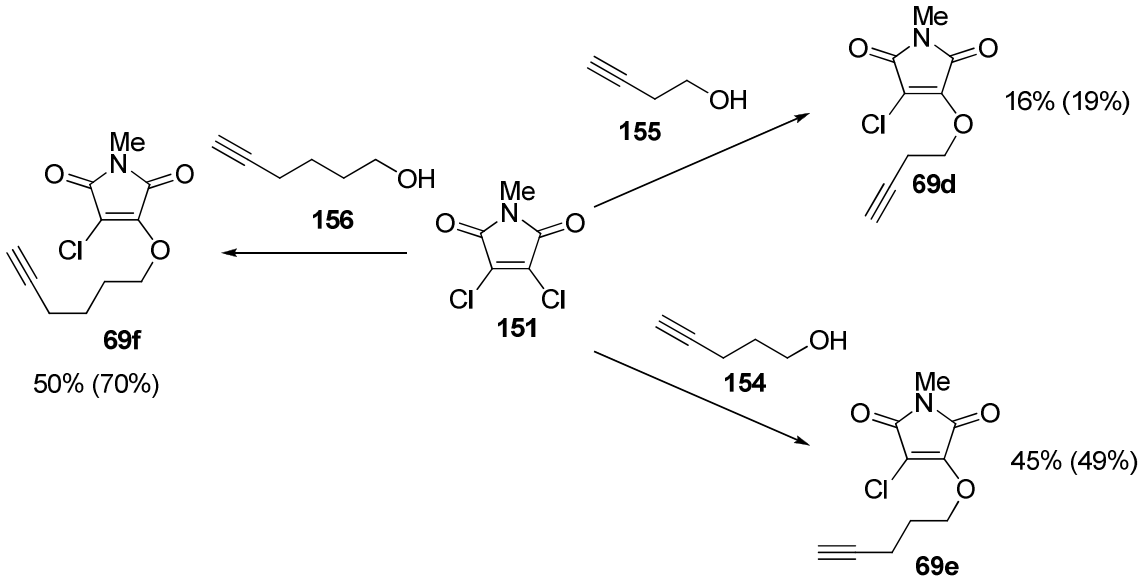
Maleimides **69a** and **69c** were synthesized following the same methodology except that in these cases the reactions were carried out at 45℃ due to slower conversion of the substrates (Scheme 64). Alkyne **69a** was obtained in good yield, while the reaction from alcohol **156** gave a moderate yield of **69c**.



Scheme 64. Synthesis of maleimides **69a** and **69c**.

3.4.2. Synthesis of 3-chloro-1-methyl-4-(alkynyloxy)-1*H*-pyrrole-2,5-diones **69d-f**

Next, we synthesized the maleimides bearing a chlorine atom. Following a similar protocol as before, the maleimides **69d-f** were prepared in low to moderate yields (Scheme 65).



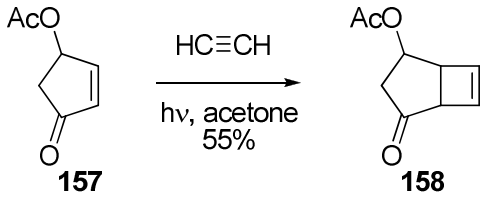
Scheme 65. Synthesis of chloroalkynyl maleimides **69d-f**.

Thereby, with the maleimides containing alkynyl groups in hands, we were able to study their intramolecular [2+2] photocycloaddition reaction.

3.5. Intramolecular photochemical reaction of 1-methyl-3-(alkynyloxy)-1*H*-pyrrole-2,5-dione 69b and 3-chloro-1-methyl-4-(alkynyloxy)-1*H*-pyrrole-2,5-dione 69e

Despite the fact that alkynes have an electronic structure very similar to that of alkenes, when irradiated they tend to produce polymeric material limiting the synthetic applicability of their photoreactions.[81]

In general, these reactions take place with a variable efficiency since the strained cyclobutene derivatives formed can also be excited to undergo many competitive reactions such as photoreductions or further cycloadditions.[82] Nevertheless, several examples of irradiation of cyclic enones with alkynes have been reported in the literature. For instance, Murata *et al.* reported in 1977 the [2+2] photocycloaddition of 4-acetoxy-2-cyclopentenone, **157**, to acetylene, which gave the cyclobutene derivative **158** in 55% yield (Scheme 66).[83]

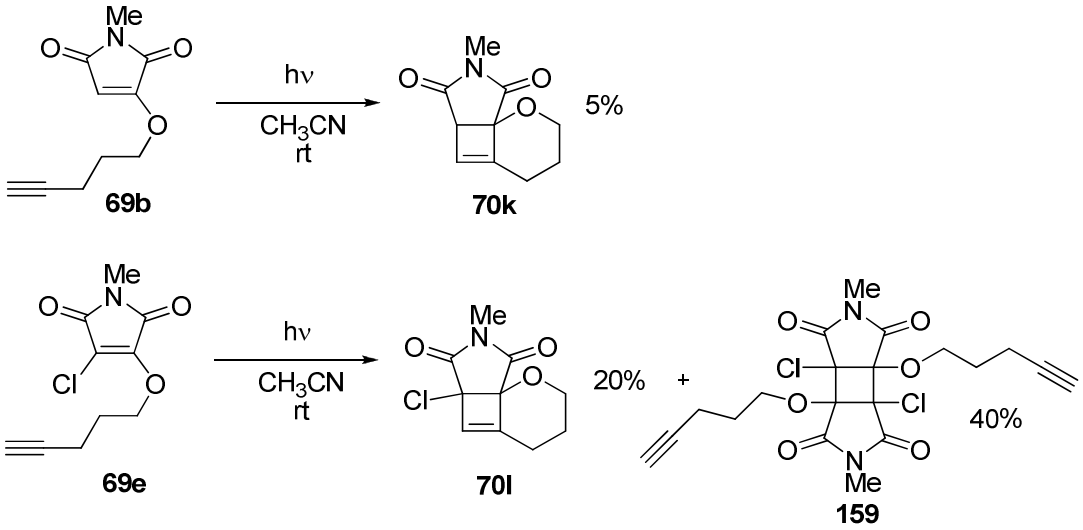


Scheme 66. [2+2] Photocycloaddition of 4-acetoxy-2-cyclopentenone, **158**, to acetylene, Murata *et al.* (1977).

In this work, we assayed the intramolecular [2+2] cycloaddition of the pentynyloxy maleimides **69b** and **69e** (Scheme 67). Irradiation of the substrate **69b**, lacking the chlorine atom, allowed the isolation of the expected cyclobutene **70k**, albeit in very low yield (5%). However, we were able to prepare crystals of this product, suitable for an X-

[81] Coyle, J. D. *Introduction to Organic Photochemistry*, John Wiley & Sons, **1989**, p. 72.
[82] (a) Houk, K. N. *Chem. Rev.* **1976**, *76*, 1-74. (b) Ninomiya, I.; Naito, T. *Photochemical Synthesis;* Academic Press; London; **1989**, chapter 6, p.79.
[83] Sugihara, Y.; Morokoshi, N.; Murata, I. *Tetrahedron Lett.* **1977**, *18*, 3887-3888.

ray analysis that unambiguously revealed its structure (Figure 28). The intramolecular [2+2] photocycloaddition of the chloromaleimide **69e** proceeded in some extension, although the competitive dimerization was also observed. Unfortunately, we were unable to separate the two products and the yield yof each product could only be estimated from the mixture.



Scheme 67. Intramolecular [2+2] photocycloaddition of alkynyl maleimides **69b** and **69e**.

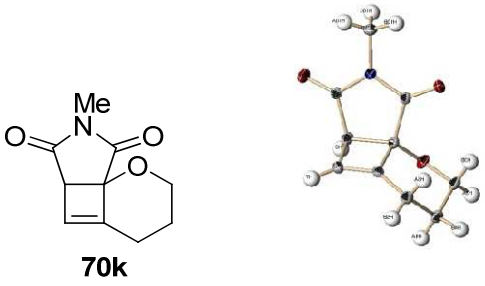


Figure 28. X-ray structure of **70k**.

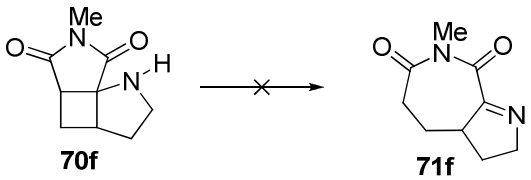
3.6. Further elaboration of the tricyclic fused maleimides

Some preliminary studies were carried out to further elaborate the tricyclic compounds **70** obtained in highest yield.

3.6.1. Attempted preparation of seven-membered ring fused reaction by opening of the cyclobutane strained ring

Cyclobutane derivatives have frequently been employed as versatile synthetic intermediates, not only as building blocks for the total synthesis of cyclobutane natural products, but also as precursors of other natural products lacking a cyclobutane. For example, cyclobutanes possessing appropriate substituents have shown to undergo a facile ring opening reaction under basic conditions to afford various synthetically useful materials. To evaluate the applicability of our tricycles on this field, we, first of all, tried to transform the tricyclic amine **70f** into an azepane derivative under different basic conditions (Table 16), but in all cases, the starting material was recovered unchanged.[84]

Table 16. Attempts to transform **70f** into an azepane derivative.



70f **71f**

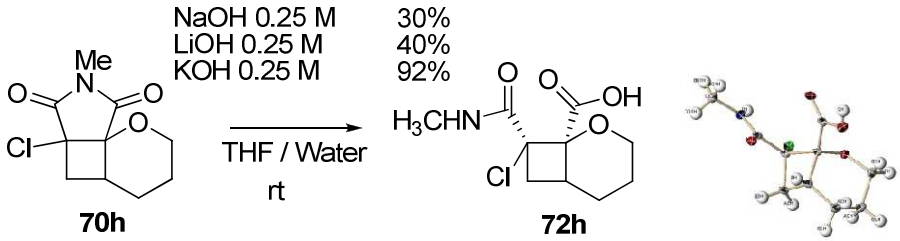
entry	Base	Solvent	Conversion (%)
1	NaH	THF	0
2	Et_3N	THF	0
3	NaOMe	methanol	0

Other methodologies for this kind of transformation have been described in the literature. For instance, Wille[85] *et al.* used nitrate radicals to cleave cyclobutane dimers of uracil, Rose*et al.* used a photosplitting methodology on a pyrimidine dimmer,[86] and Hehn *et al.* used a radical reductive agent to induce a radicalary ring opening reaction.[51b] Due to lack of time, none of these methodology were intended during the present work and the study of this issue will be continued in a near future.

[84] (a) Smith, M. In *Reduction -Techniques and Applications in Organic Synthesis*, 1st ed.; Augustine, R. L., Ed.; E. Arnold: New York, **1968**, 95–171. (b) Dekker, J.; Martins, F. J. C.; Kruger, J. A. *Tetrahedron Lett.* **1975**, *16*, 2489. (c) Ruehle, P. H.; Dobbs, T. K.; Ansell, L. L.; van der Helm, D.; Eisenbraun, E. J. *J. Org. Chem.* **1977**, *42*, 1098. (d) Wong, H. N. C.; Fitjer, L.; Heuschmann, M. In *Houben–Weyl*, 4th ed., Vol. E17e; de Meijere, A., Ed.; Thieme: Stuttgart, **1995**, 447–609. (e) Miesch, M.; Wendling, F. *Eur. J. Org. Chem.* **2000**, 3381-3392. (f) Zhang, M.; An, H. Y.; Zhao, B.-G.; Xu, J.-H. *Org. Biomol. Chem.* **2006**, *4*, 33-35. (g) Chen, P.; Caroll, P. J.; Sieburth, S. M. *Org. Lett.* **2009,** 20,4540-4543.
[85] Krüger, O.; Wille, U. *Org. Lett.* **2001**, *3*, 1455-1458.
[86] Hartzfeld, D. G.; Rose, S. D. *J. Am. Chem. Soc.* **1993**, *115*, 850-854.

3.6.2. Preparation of **72h** by hydrolysis of **70h**

In 2005, Bach *et al.* published the synthesis of conformationally constrained β-amino acid derivatives by intramolecular [2+2] photocycloaddition of a dienamide derived from tetronic acid followed by lactone ring opening.[87] Inspired by this work, we decided to assay the basic hydrolysis of **70h** (Scheme 68), as a model reaction to be later on applied to the synthesis of amino acid derivatives. This reaction was attempted using as the base, sodium, potassium, or lithium hydroxide. Among them potassium hydroxide was the best, affording the expected product, **72h**, in 92%, with total regioselectivity, which was established by X-ray analysis.

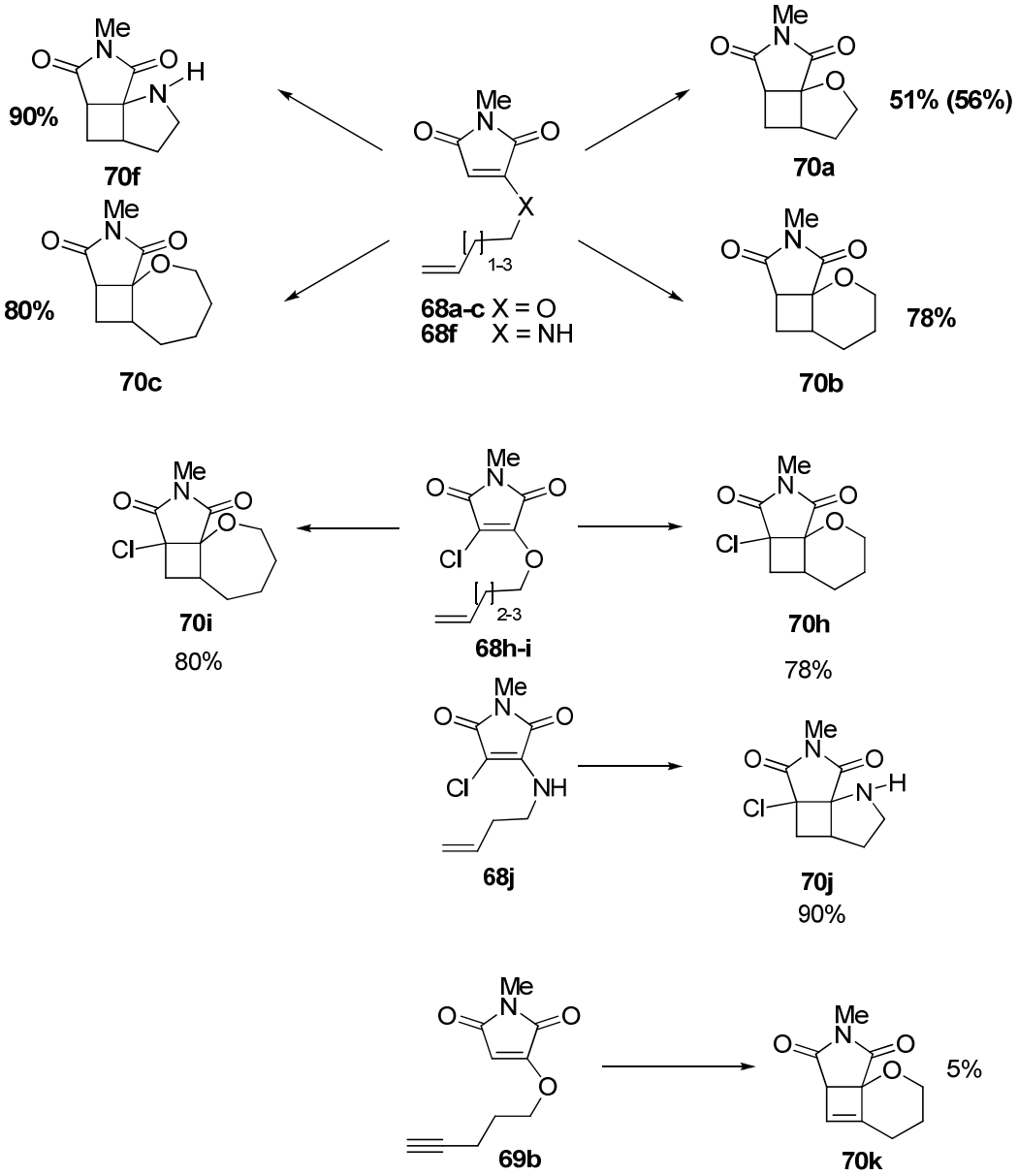


Scheme 68. Synthesis and X-ray structure of **72h**.

[87] Basler, B.; Schuster, O.; Bach, T. *J. Org. Chem.* **2005**, *70*, 9798-9808.

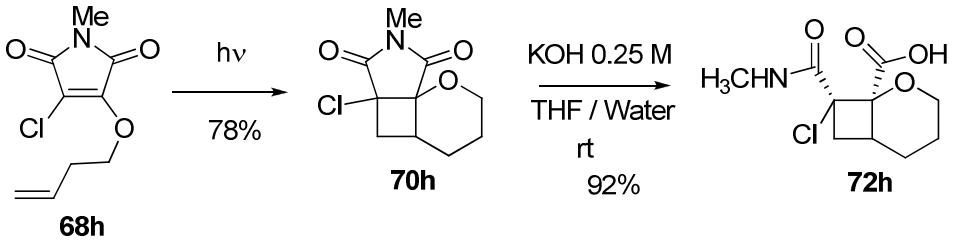
3.7. Conclusions

As a summary of this section, the intramolecular [2+2] photocycloaddition of several alkene and alkyne substituted maleimide derivatives was investigated. Relevant results obtained in this study are shown in Scheme 69.



Scheme 69. Intramolecular photochemical reaction of maleimides **68** and **69**.

Bicyclic carboxylic acid derivative **72h** have been achieved from the intramolecular photochemical reaction of maleimide **68h** in 3 steps (Scheme 70).



68h **70h** **72h**

Scheme 70. Preparation of bicyclic carboxylic acid derivative **72h**.

Chapter 4: Synthetic studies toward the sexual pheromone of oleander scale, Aspidiotus nerii

Until I realized, it is the struggle itself that is most important. We must strive to be more than we are, Lal. It does not matter that we will never reach our ultimate goal. The effort yields its own rewards.

Cmdt Data, Star Trek, the Next Generation, Paternity.

4.1. Introduction

4.1.1. Pheromones and insects

Biosphere has been drenched by pesticides without a convincing result.[88] Concerns over the potential impact of pesticides on human health and the environment have led to a priority the reduction of pesticides in agro-ecosystems by introduction of new pesticide registration procedures, such as the Food Quality Protection Act in the United States. These new regulations have reduced the number of synthetic pesticides available in agriculture. Also they have led to the development of alternative strategic pest control, such as new pesticides, including natural product-based pesticides, discovered and developed to replace the compounds lost due to the new registration[89] but also mass trapping devices utilizing *substrata* activated with specific attractants. Such traps are becoming increasingly more popular.[90]

Different sustainable ways may be used such as introduction of predators, parasites and/or pathogenic organisms, introduction of incompatible strains of pest insects, release of sterile insects or use of hormones or pheromones or a combination of them, which seems to be a remarkable safe procedure for controlling insect pest.

Pheromones (from Greek *φέρω* phero "to bear" + hormone, ὁρμή - "impetus") are chemical signals that trigger a natural response in another member of the same

[88] Silverstein, R. M. *Science* **1981**, *213*, 1326 and cited references.
[89] (a) Dayan, F. E.; Cantrell, C. L.; Duke, S. O. Natural product in crop protection, *Bioorg. Med. Chem.***2009**, *17*, 4022-4034. (b) Copping, L. G.; Duke, S. O. Natural products that have been used as crop protection agents. *Pest Manag. Sci.***2007**, *63*, 524-554. (c) Wheeler, W. B. Role of research and regulation in 50 years of pest management in agriculture. *J. Agric. Food Chem.***2002**, *50*, 4151-4155.
[90] Noce, M.; Belfiore,T.; Scalercio, S.; Vizzarri, V.; Iannotta, N.*Journal of Environmental Science and Health Part B* **2009**, *44*, 442–448.

species. There are different types of pheromones, alarm, food trail or sex. Their use among insects has been particularly well documented.[91] In particular, female sex pheromones which orient flying males to mate-finding (Figure 29). [92,93]

Figure 29. Different types of insect traps: visual lure trap (left) and pheromone trap (right).

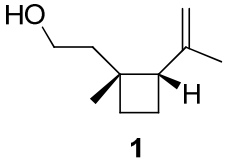
Applications of pheromones can be categorized as follows:

- Used to trap insects for monitoring and survey: insects population can be estimated and can manage the use of insecticide to treat the field only when it is necessary and not every time.
- Used as lures in which insects will become coated or infected and spread the rest of the population.
- Used in mass-trapping for population suppression
- Used to permeate the air to disrupt mate-finding.

Nowadays, there have been isolated and described more than a hundred of chiral pheromones, some of them containing a cyclobutane ring. Insects are very sensitive to the composition of their emissions, in particular the optical purity of pheromone.

Monoterpene (+)-grandisol, **1**, isolated in 1969 as the *major* product from the pheromone produced by boll weevil males *Anthonomus grandis*,[5] is an important tool for the management of this species with a pheromone trap and gives information of the number of weevils in a cotton field (Figure 30).

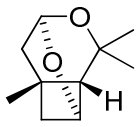
[91] Karlson, P. ; Lüscher, M. *Nature* **1959**, *183*, 55-56.
[92](a) Rice, R.E.; Moreno, D. S. *Ann.Entomol. Soc. Am.*, **1969**, *62*, 558-560. (b) Rice, R.E.; Moreno, D. S. *Ann.Entomol. Soc. Am.*, **1970**, *63*, 91-96.
[93] Beardsley, J.W.; González, R. H. *Ann. Rev. Entomol.* **1975**, *20*, 47-73.



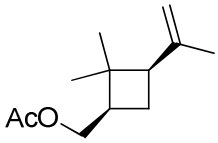
1

Figure 30. Boll weevils and the main compound of its pheromone **1**.

(+)-Lineatin, **28**, is a pheromone produced by female striped ambrosia beetle, *Trypodendron lineatum*.[94] This kind of beetles, which live in nutritional symbiosis with *ambrosia fungi*, are responsible for extensive damage on coniferous forest in Europe and North America (Figure 35). Another cyclobutane monoterpene is the acetate **160** identified as the sex attractant pheromone of the citrus mealybug, *Planococcus citri* (Figure 31).



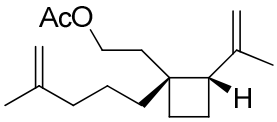
28



160

Figure 31. Female striped ambrosia beetle and citrus mealybug and the structure of their pheromones.

(1*R,*2*S*)-*cis*-2-Isopropenyl-1-(4′-methyl-4′-penten-1′-yl)cyclobutaneethanol acetate, **73**, is a sesquiterpene, which has been characterized as the *major* component of the sexual pheromone produced by oleander scale females, *Aspidiotus nerii,* a widespread pest, particularly in the Mediterranean countries (Figure 32).[95]



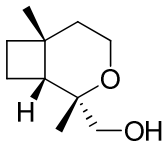
73

Figure 32. Oleander scale female and its pheromone **73**.

Discovered in 2010 by Francke *et al.*,[96] papayanol, **161**, is another molecule which can be classified along with these previous examples of pheromone containing a cyclobutane ring. Alcohol **161** has been detected as a component of a male-produced

[94] MacConnell, J. G.; Borden, J. H.; Silverstein, R. M.; Stokkink, E. *J. Chem. Ecol.* **1977**, *3*, 549-561.
[95] Einhorn, J.; Guerrero, A.; Ducrot, P.-H.; Boyer, F.-D.; Gielselmann, M.; Roelofs, W. *Proc. Nat. Acad. Sci. USA* **1998**, *95*, 9867-9872.
[96] Zarbin, P. H. G.; Moreira, M. A. B.; Haftmann, J.; Tröger, A.; Franke, S.; Kopf, J.; Mori, K.; Francke, W. *Org. Lett.***2010**, *12*, 2447-2449.

pheromone of larvae of the papaya borer, *Pseudopiazurus obesus* causing irreversible damage to papaya stalks, and in high infestations may even kill the plant (Figure 33).



161

Figure 33. Papaya tree and papayanol,**161**.

The unusual structure and the biological activity of these pheromones has led to a really important synthetic work. Although many strategies have been developed, the construction of functionnalized cyclobutanes remains a synthetic challenge. The most widely used procedures include photochemically or thermally induced [2+2] cycloaddition of alkenes and ketenes and cyclization reactions.[97]

The armoured scales (Family Diaspididae) constitute one of the most successful groups of plant-parasitic arthropods. One of them is the oleander scale, *Aspidiotus nerii*, formally *A. hederae* (Homoptera, Diaspididae). It is a cosmopolitan pest, mainly found in tropical and subtropical areas, that causes a general weakening of the tree, dicoloration of leaves, and severe deterioration of the fruit (Figure 34).[98] It has been reported to be a parasite into more than 100 plant families.[99,100] The adult female is immobile, but the male is able to fly. The sex pheromone of the scale presumably is produced by the female's pygidial glands and released through the rectum as in *Aonidiella aurantii* and *A. citrina*.[101]

[97] (a) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.***1974**, *96*, 5270-5272. (b) Brady W. T. in *The Chemistry of Ketenes, Allenes and Related Compounds*, Wiley, NewYork, **1980**, 279-308. (c) Wender, P. A in *Photochemistry inorganic Synthesis*, Royal Society of Chemistry, London, **1986** , 163-172. (d) Mori, K. *The Total Synthesis of Natural Products*, Wiley, New York, **1992**, *9*, 303-334. (e) Yamazaki, S.; Fujitsuka, H.; Yamabe, S. *J.Org.Chem.* **1992**, *57*, 5610-5619. (f) Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *Synlett* **1993**,197-198. (g) Knölker, H.-G.; Baum, G.; Graf, R. *Angew.Chem. Int. Ed. Engl.* **1994**, *33*, 1612-1615. (h) Benedetti,F.; Berti, F.; Fabrissin, S.; Gianferrara, T. *J. Org. Chem.* **1994**, *59*, 1518-1524. (i) Ramig, K.; Dong, Y.; VanArnum, S. D. *Tetrahedron Lett.* **1996**, *37*, 443-446. (j) Liu, F.; Negishi, E. *Tetrahedron Lett.* **1997**, *38*, 1149-1152. (k) Hansen, T. V.; Stenstrøm, Y. *Organic synthesis: Theory and Applications*, Elsevier, Oxford, **2001**, *5*, 1-38. (l) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449-1483.

[98] Cantoni, A.; De Maeyer, L.; Izquierdo Casas, J.; Niebes, J.-F.; Peeters, D.; Roffeni, S.; Silva, J.; Villalobos, A. *Bayer CropScience Journal* **2008**, *68*, 2, 349-376.

[99](a) Boyer, F.-D.; Ducrot, P.-H. *C. R. Acad. Sci. Paris* **1999**, 29-38. (b) Boyer, F.-D.; Ducrot, P.-H. *Eur. J.Org. Chem.* **1999**, 1201-1212.

[100] Gerson, V.; Hazan, D. *J. Nat. History* **1979**, *13*, 275-284.

[101] Moreno, D. S. *Ann. Entomol. Soc. Am.***1972**, *65*, 1283-1286.

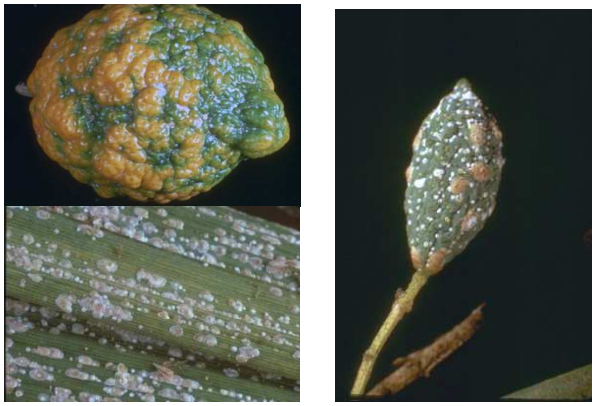


Figure 34. Damages caused by oleander scale.

Particularly important is the damage caused on lemon and olive trees (up to 100% loss of the table olive crop and 80% of the oil crop), as well as in ornamental plants, such as oleander for which[102] Spain is one of the world's largest exporters.[103] In Spain, areas such as Alicante, Murcia and Málaga are affected and the costs of plant protection products have reached a level of hundreds of million euros.

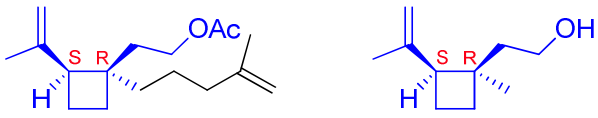
That is the reason why one of the alternative solutions for the chemical control of this scale (chlorpyrifos and some insect growth regulators such as pyriproxifen or buprofecin are the pesticide solution), is the use of its sexual pheromone to interfere the communication between the male and the female. The pheromone will trigger a perturbation of the mating and, thus, the control of the population in the infected area. To achieve this control, it is of first importance to be able to synthesize the sexual pheromone active compound.

4.1.2. Precedents of the synthesis of the sexual pheromone of *Aspidiotus nerii*

4.1.2.1. Synthesis of the sexual pheromone by Guerrero *et al.*

The structure of the sexual pheromone of *Aspidiotus nerii* was determined by NMR experiments (^{1}H and ^{13}C) and mass spectroscopy in 1998 by Guerrero *et al*.[52] This compound shares several common structural features with (+)-grandisol, such as the cyclobutane ring, the relative configuration of its stereogenic centres, and other parts of the skeleton (Figure 35).

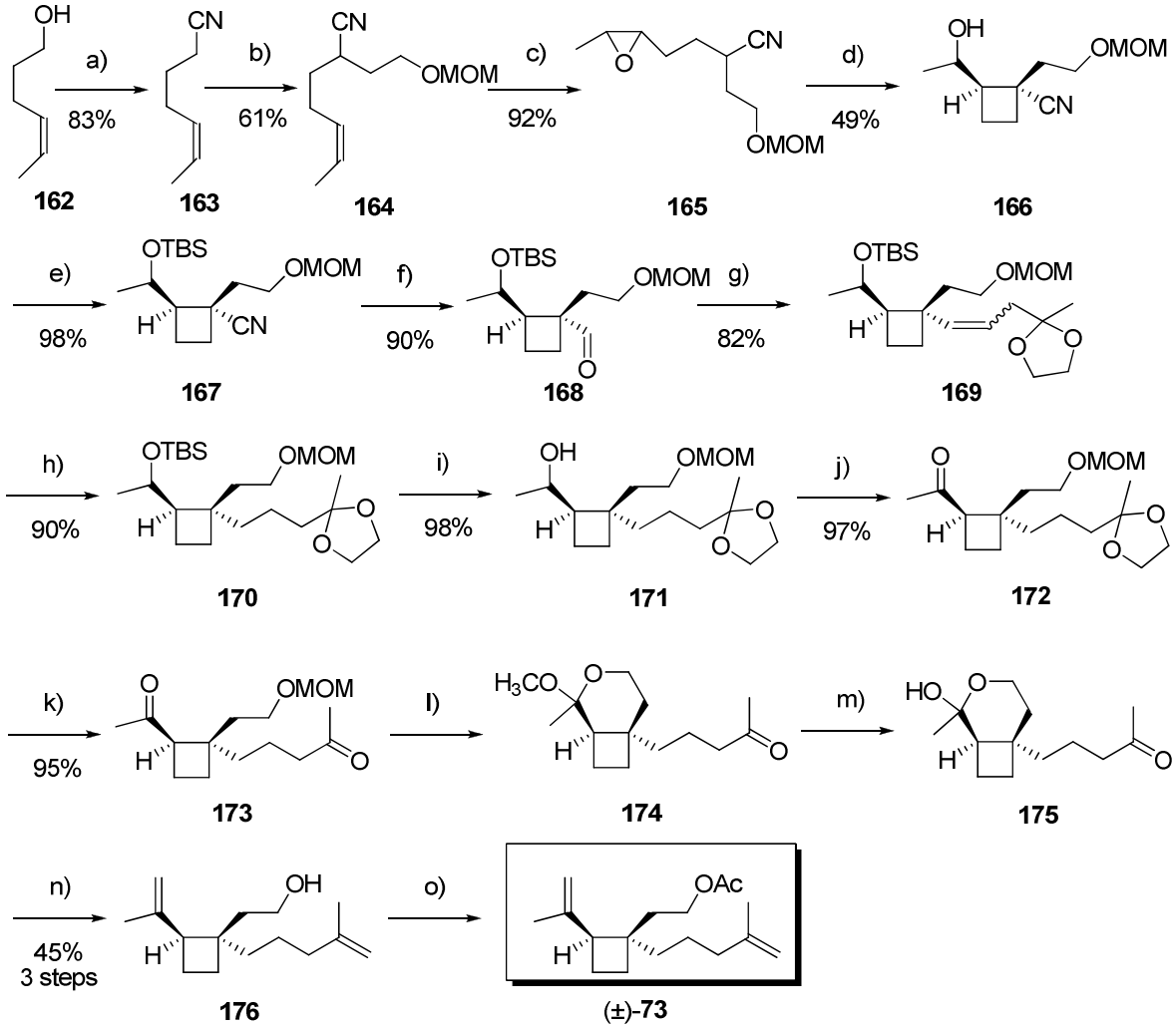
[102] Lloréns, J. M. *Homoptera I. Cochinillas de los cítricos y su control biológico*, Pisa Ed., Valencia **1990**.
[103] Food and Agriculture Organization of the United Nations **2012**, Citrus fruit fresh and processed, Annual statistics.



Sexual pheromone of *Aspidiotus nerii* **73** (+)-grandisol **1**

Figure 35. Structures of (+)-grandisol, **1**, and the sexual pheromone of *Aspidiotus nerii*, **73**.

In 1999, Guerrero and co-workers published a total synthesis of racemic **73**, wherein the key cyclobutane core was constructed by a stereocontrolled and completely regioslective cyclization of an epoxynitrile **165** (Scheme 71).[104]



a) 1) MsCl, Et_3N, 2) NaCN,DMSO; b) LDA, $Br(CH_2)_2OMOM$,THF:HMPA; c) MCPB, CH_2Cl_2; d) LiHMDS, benzene; e) TBSCl, Im,DMF; f) DIBAH, hexane; g) $Ph_3P{=}CHCH_2C(OCH_2CH_2O)CH_3$,THF; h) H_2, Pd/C, EtOH; i) TBAF;THF; j) PDC,DMF; k) Amberlist A15 resine, Acetone/H_2O; l) Dowex 50W-X4,MeOH; m) SiO_2 / hexane; n) $Ph_3P{=}CH_2$; o) Ac_2O, Et_3N, DMAP, CH_2Cl_2.

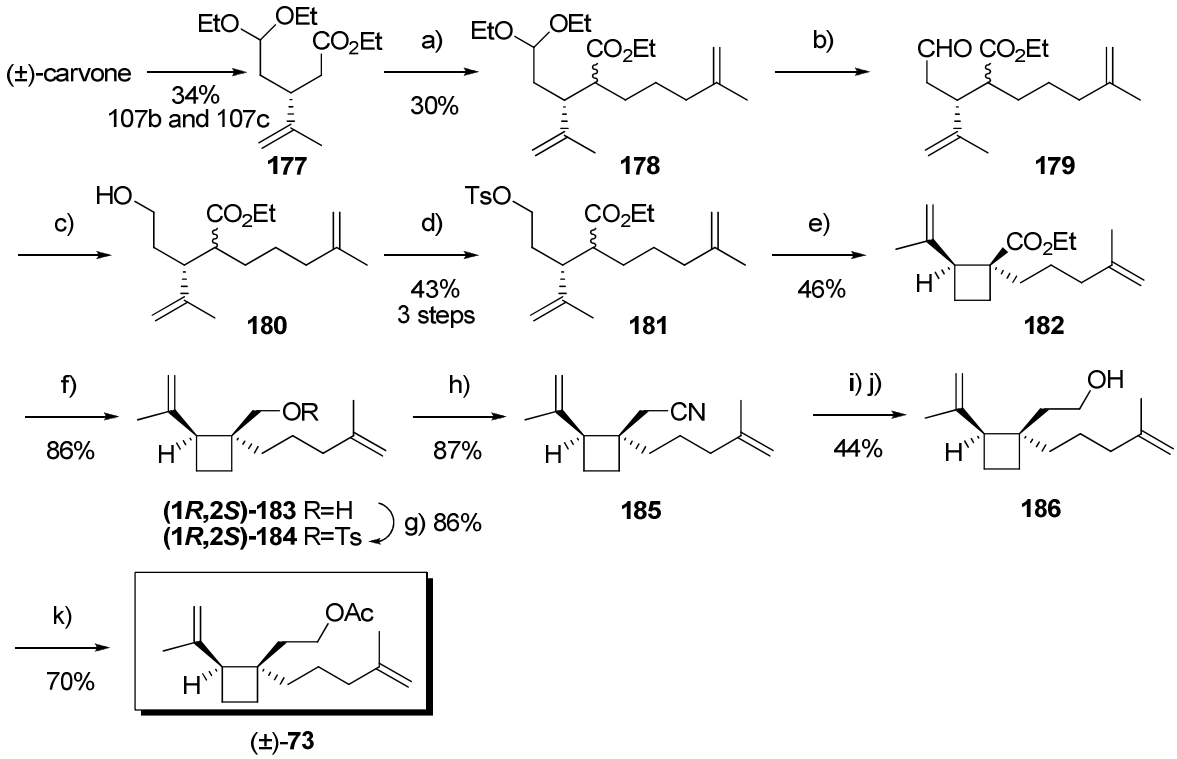
Scheme 71. Synthesis of (±)-**73** from Guerrero and co-workers (1999).

[104]Petschen, I.; Parrilla, A.; Bosch, M.P., Amela, C.; Botar, A.; Camps, F.; Guerrero, A. *Chem. Eur. J.* **1999**, *5*, 3299-3309.

Starting from the olefinic alcohol **162**, the key epoxide **165** was achieved in three steps. Then, treatment of **165** with base afforded the cyclobutane **166** with the correct configuration. The nitrile group was used as a precursor for the introduction of the alkyl chain by reduction followed by Wittig reaction of the resulting aldehyde **168**, affording **169**, which was converted to the target compound by conventional chemistry. This total synthesis of (±)-**73** was completed in 15 steps and 6% overall yield.

4.1.2.2. Synthesis of the sexual pheromone by Boyer and Ducrot

Also in 1999, Boyer and Ducrot disclosed another synthesis of the sexual pheromone of *Aspidiotus nerii* starting from racemic carvone (Scheme 72).[105a] The key step of the synthesis was the intramolecular ester enolate alkylation performed on **181** with LiHMDS in the presence of HMPA to afford the ethyl cyclobutanecarboxylate **182** in a 46% yield (10 steps from **177**, 0.4% overall yield) with a high diastereoselectivity (95:5).



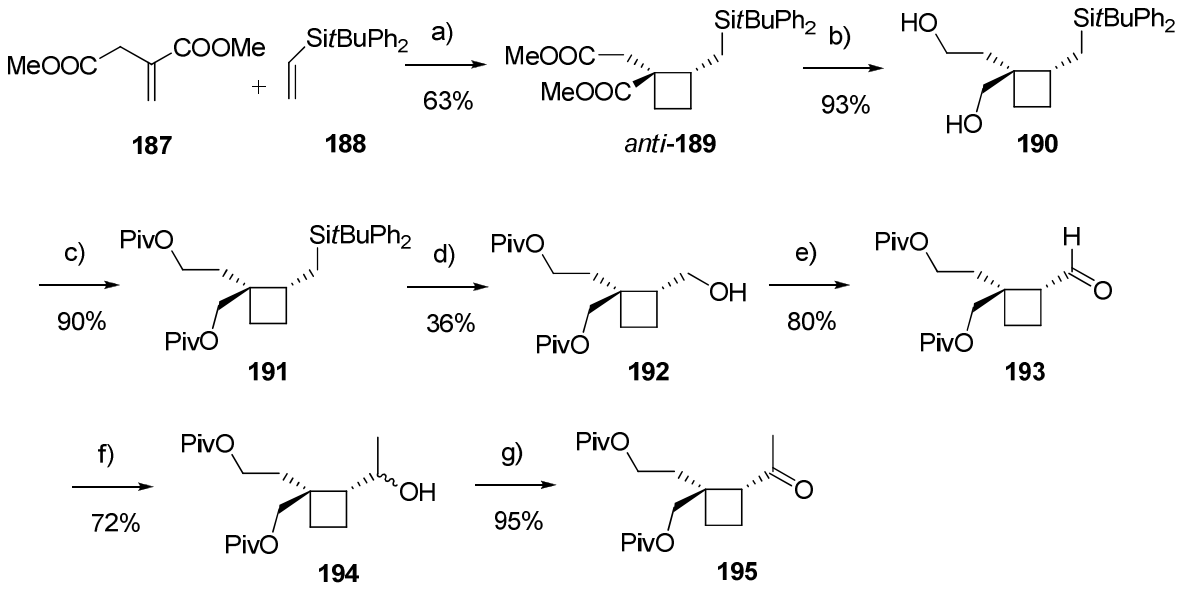
a) KHMDS, THF, HMPA, 5-iodo-2-methylpent-1-ene; b) PTSA, acetone, water; c) $NaBH_4$, EtOH d) TsCl, py.; e) LiHMDS, THF, HMPA; f) $LiAlH_4$, THF; g) TsCl, 4-DMAP, CH_2Cl_2; h) NaCN, HMPA; i) DIBAL-H, CH_2Cl_2; j) $NaBH_4$, EtOH; k) Ac_2O, pyridine.

Scheme 72. Synthesis of (±)-**73** from Boyer and Ducrot.

[105] (a) Boyer, F.-D.; Ducrot, P.-H. J *Eur. J. Org. Chem.* **1999**, 1201-1211. (b) Roelofs, W.; Gieselmann, M.; Cardé, A.; Tashiro, H.; Moreno, D. S.; Hennick, C. A.; Anderson, R. J. *J. Chem . Ecol.* **1978**, *4*, 211-224. (c) Tanida, K.; Mori, K. *J. Chem. Soc., Perkins Trans. I* **1990**, 3221-3224.

4.1.2.3. Synthetic approach to an intermediate of the sexual pheromone by Knölker et al.

In 2007, Knölker *et al.* reported a synthesis of the trisubstituted cyclobutane **195**, which the authors claimed to represent an advanced intermediate for a projected total sysnthesis of **73** (Scheme 73). In this approach, the key steps were a Lewis acid promoted [2+2] cycloaddition of the vinylsilane **188** to the acrylate **187** and a modified Fleming-Tamao oxidation of the silyl derivative **191**. Compound **195** was obtained over 7 steps in 15% overall yield .[106]



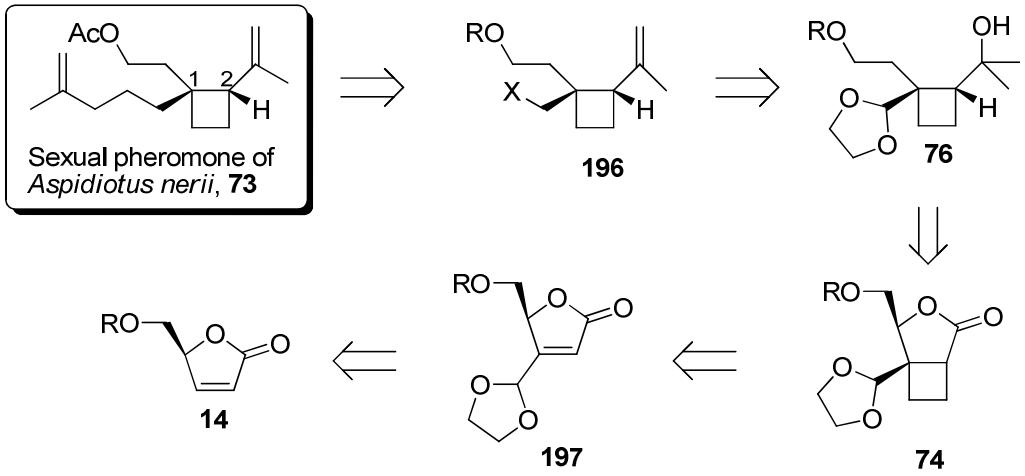
a) 1) $TiCl_4$, CH_2Cl_2; 2) **188**, (ratio *anti*-**189**:*syn*-**189** = 2:1); b) $LiAlH_4$, THF; c) PivCl, Et_3N, DMAP, CH_2Cl_2; d) 1) $BF_3{\cdot}2AcOH$, 1,2-$C_2H_4Cl_2$; 2) KF, $NaHCO_3$, H_2O_2, THF / MeOH (1:1); e) PDC, 4Å MS, CH_2Cl_2; f) MeMgBr, THF; g) TPAP, NMO, 4 Å MS, CH_2Cl_2.

Scheme 73. Synthetic approach to **195** from Knölke *et al*. (2007).

4.2. Synthesis of the initial furanones

Our retrosynthetic analysis of the sexual pheromone of oleander scale, *Aspidiotus nerii*, proceeded by deconnexion of the isopropenyl chain to the cyclobutane **196** (Scheme 74). Then we traced back to the alcohol **76**, which in turn can be derived from the bicyclic lactone **74**. Diassembly of the cyclobutane suggested the *O*-protected-2(5*H*)-furanone **197** as a chiral platform for a diastereoselective [2+2] photochemical reaction with ethylene. Finally, **197** would be prepared from a known lactone **14**.

[106] Schmidt, A. W. ; Suresh, J. R. ; Theumer, G.; Knölker, H.-J. *Chem. Lett*. **2007**, *12*, 1478-1479.



Scheme 74. Our retrosynthetic analysis for the sexual pheromone of *Aspidiotus nerii* **73**.

4.2.1. Precedent furanones synthesized in our group

As it has been already mentioned, in the last decades, our research group has been working with protected 2(5*H*)-furanones to study their reactivity and also as chiral precursors on the synthesis of natural products (grandisol, lineatin) and nucleoside analogues (cyclobut-A).

To develop the synthetic sequence, it was decided to use the (5*S*)-5-(*tert*-butyldimethylsilyloxy)-, **14j**, and (5*S*)-5-(triisopropylsilyloxy)methyl-2(*5H*)-furanone, **14q**, bearing protecting groups which were expected to be stable enough for most of the planned synthetic steps (Figure 36).

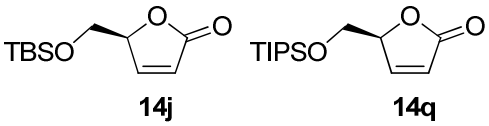
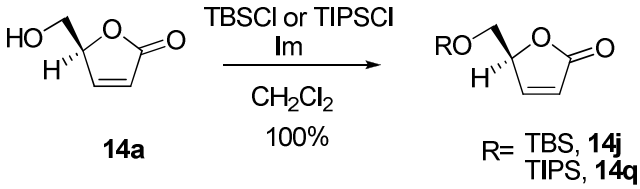


Figure 36. Starting furanones **14j** and **14q** planned for the synthesis.

4.2.2. Synthesis of 2(5*H*)-furanones **14j** and **14q**

The 2(5*H*)-furanones **14j** and **14q** were synthesized from **14a** by treatment with *tert*-butyldimethylsilyl chloride or triisopropylsilyl chloride, respectively, and imidazole in dichloromethane (Scheme 75). They were obtained in quantitative yield in a multigram scale.



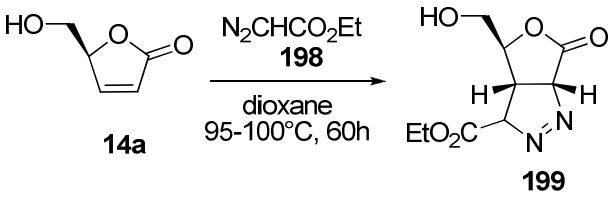
Scheme 75. Synthesis of **14j** and **14q**.

4.3. β-Alkylation of the 2(*5H*)-furanones

With 2(*5H*)-furanone **14j** and **14q** in hands, the next step involved the inclusion of a side chain at the β-position. In our synthetic strategy to the sexual pheromone of *Aspidiotus nerii*, it was decided to introduce an appropriate precursor instead of installing directly the terpenic chain that could interfere with the projected [2+2] photocycloaddition reaction for the formation of the cyclobutane ring.

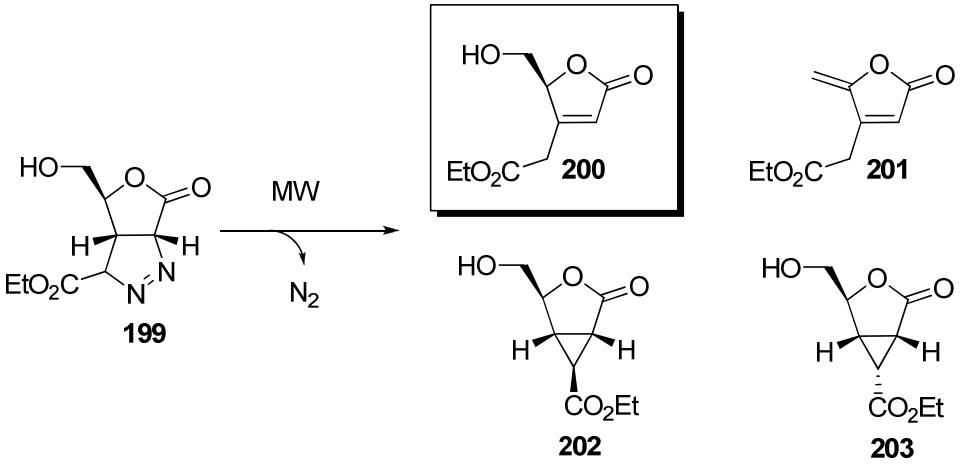
4.3.1. Precedents

The 1,3-dipolar cycloaddition of ethyl diazoacetate, **198**, to 2(5*H*)-furanones, followed by pyrolysis of the resulting pyrazolines, was one option to functionalize the β-position of the lactone. Montserrat Corbella, in her doctoral thesis, extensively studied this reaction, which was accomplished in quantitative yield (Scheme 76).[69b]



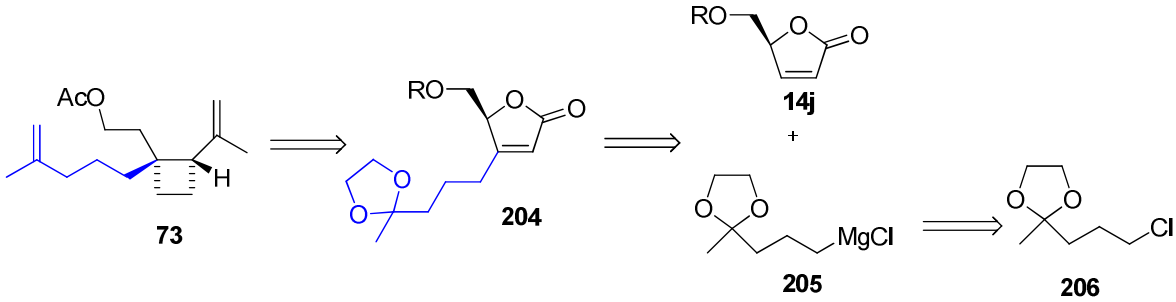
Scheme 76. 1,3-Dipolar cycloaddition of **198** to **14a**.

However, the subsequent pyrolysis was more problematic than expected (Scheme 77). The best results were obtained when the pyrolysis was performed using a microwave (60W) at 150℃ during 30 minutes. Under these condi tions, the desired olefin **200** was isolated in 58% yield, along with the dehydratation product **201** (10%) and the cyclopropanes **202** and **203** (8% and 4%, respectively). Attempts to avoid dehydration by protection of the primary alcohol as *tert*-butyldimethylsilyl ether increased the reaction time and the amount of degradation products, without avoiding the formation of cyclopropanes.



Scheme 77. Products obtained after the microwave pyrolysis of **199**.

Considering this result, studies to incorporate the β-alkenyl chain through conjugate addition of an organometallic species were initiated. It was envisioned that commercially available 2-(3-chloropropyl)-2-methyl-1,3-dioxolane, **206,** could be a suitable precursor of a masked "terpenic" cuprate (Scheme 78). However, all attempts to obtain the Grignard reagent **205** met with failure, despite many different conditions were assayed, including the use of diverse magnesium activators (iodine, dibromoethylene, mixture of mono- and dibromoethylene), different temperatures of addition of the chlorine derivative (25℃, 35℃, 45 ℃, refluxing THF), various reaction temperatures and reaction times (2h to 1 day), and different sources of magnesium (chips, grit). The formation of the Grignard reagent was monitored by addition of *p*-methoxybenzaldehyde and the corresponding alcohol was never detected.

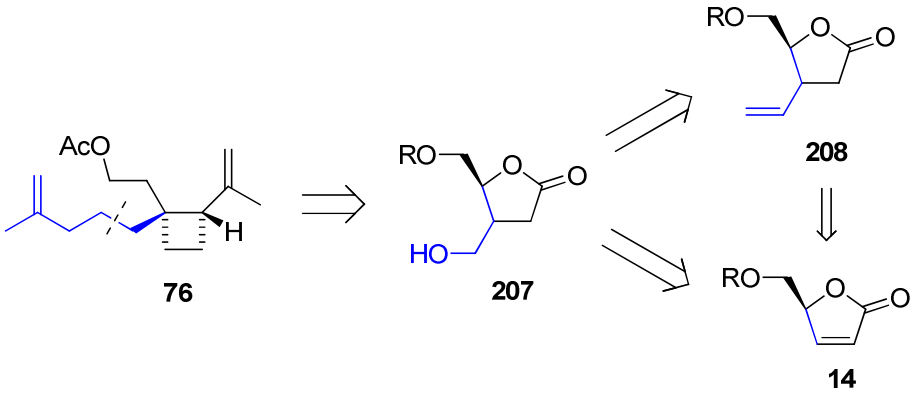


Scheme 78. Retrosynthetic analysis through furanone **204**.

Taking these results into account, in this thesis, we studied some alternative approaches for the β-alkylation.

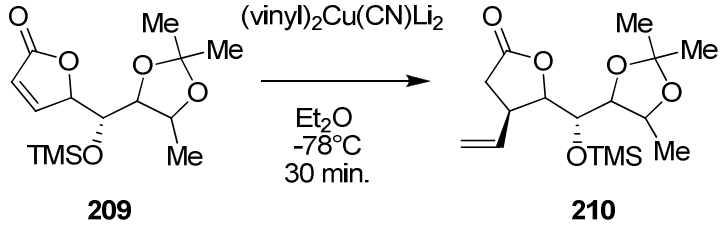
4.3.2. Nucleophilic β-alkylation

The impossibility of preparing the magnesium chloride **205** led us to the assay the addition of a vinyl group as a surrogate at the β-position of the 2(5*H*)-furanone. The subsequent manipulation of the vinyl group could allow us to build up the required side chain (Scheme 79).



Scheme 79. Retrosynthetic analysis through furanones **207** and **14**.

Different methodologies have been published for the preparation of alkenes **208** from 2(5*H*)-furanones. For example, Gilbert[107] *et al.* reported the vinylation of furanone **209** using $(vinyl)_2Cu(CN)Li_2$, a complex compound which is no more commercially available (Scheme 80).

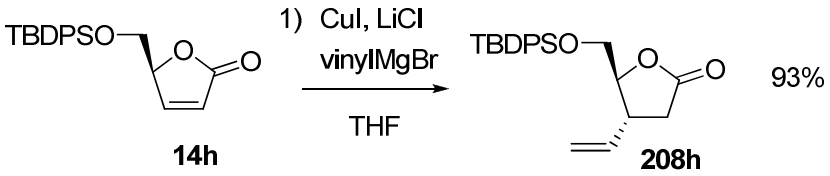


Scheme 80. Gilbert *el al.* methodology for the vinylations of **209** (1999).

Hanessian described the use of vinylmagnesium bromide in combination with copper (I) iodide and dimethyl sulfide,[108] while Theodorakis used the commercially available complex of copper (I) bromide with dimethyl sulfide.[109] In both cases, around one equivalent of magnesium reagent and from 0.2 to 1 equivalent of copper was used. Conversely, Chan and co-workers employed 2 equivalents of magnesium reagent and

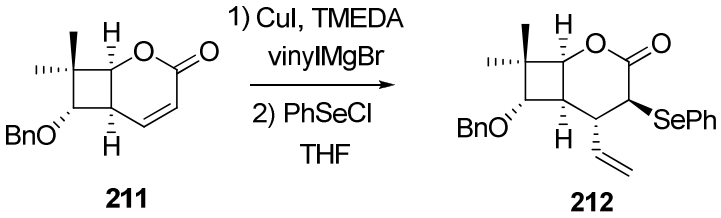
[107] Gilbert, A. M.; Miller, R.; Wulff. W. D. *Tetrahedron* **1999**, *55*, 1607-1630.
[108] Hanessian, S.; Brassard, M. *Tetrahedron* **2004**, *60*, 7621-7628.
[109] Brady, T. P.; Kim, S. H.; Wen, K;; Kim, C.; Theodorakis, E. A. *Chem. Eur. J.* **2005**, *11*, 7175-7190.

only 0.05 equivalent of copper (I) chloride with 0.1 equivalent of lithium chloride[110] to accomplish the same transformation (Scheme 81).



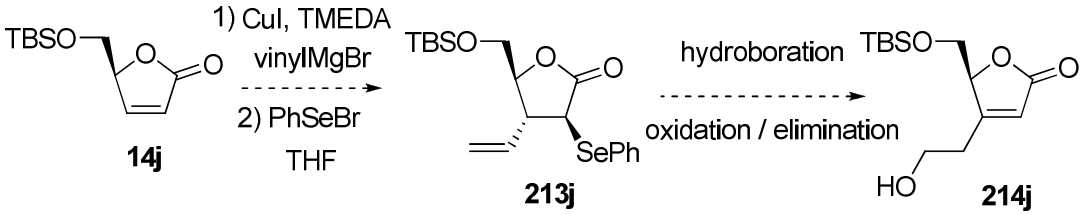
Scheme 81. Preparation of alkene **208h** by Chan *et al.* (2009).

Interestingly, Paquette *et al.* [111] described a methodology where a mixture of vinylmagnesium bromide, copper (I) iodide and tetramethylethylendiamine (TMEDA) was added on a cyclohexenone, **211**, at -78℃ affording the alkene **212** in 91% yield after treatment with phenylselenyl chloride (Scheme 82).



Scheme 82. One-pot β-vinylation/α-selenylation by Paquette *et al.* (2007).

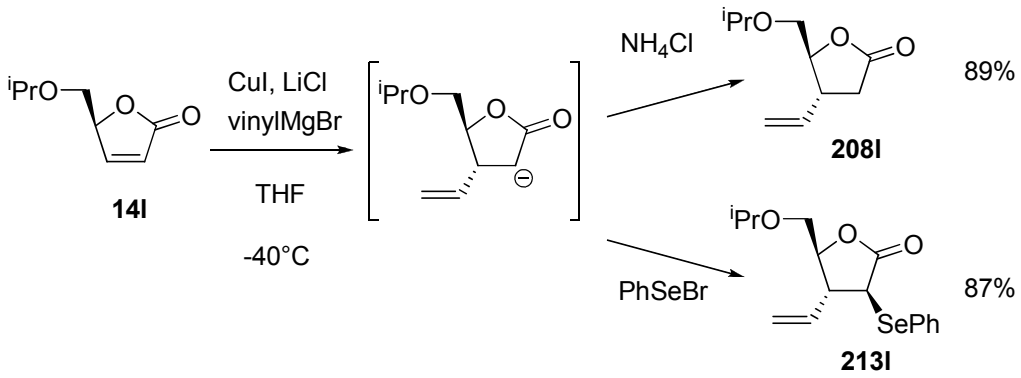
This reaction focused our attention, because it would make possible to obtain in a one-pot protocol the selenide **213j**, which, eventually, would be transformed into the 2(5*H*)-furanone **214j** (Scheme 83).[112]



Scheme 83. Intended preparation of alcohols **214j**.

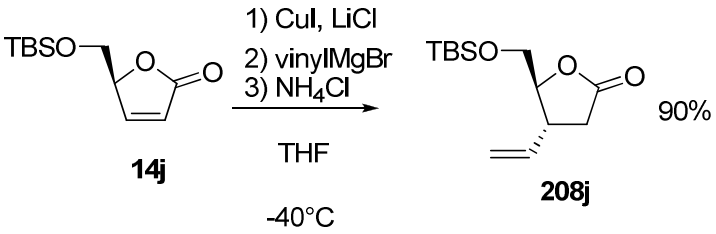
When, with a lot of expectations, we attempted to reproduce these conditions over the 2(*5H*)-furanone **14j** no reaction took place and we recovered the starting material. However, from 2(5*H*)-furanone **14l**, previously prepared as described in Chapter 2, both vinyl derivatives **208l** and **213l** were prepared in excellent yields, by applying the Chan methodology for the conjugate addition and quenching the enolate either with ammonium chloride or phenylselenium bromide, respectively (Scheme 84).

[110] Fekner, T.; Li, X.; Lee, M. M.; Chan, M. K. *Angew. Chem. Int. Ed.* **2009**, *48*, 1633-1635.
[111] Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, *72*, 7125-7134.
[112] Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434-5447.



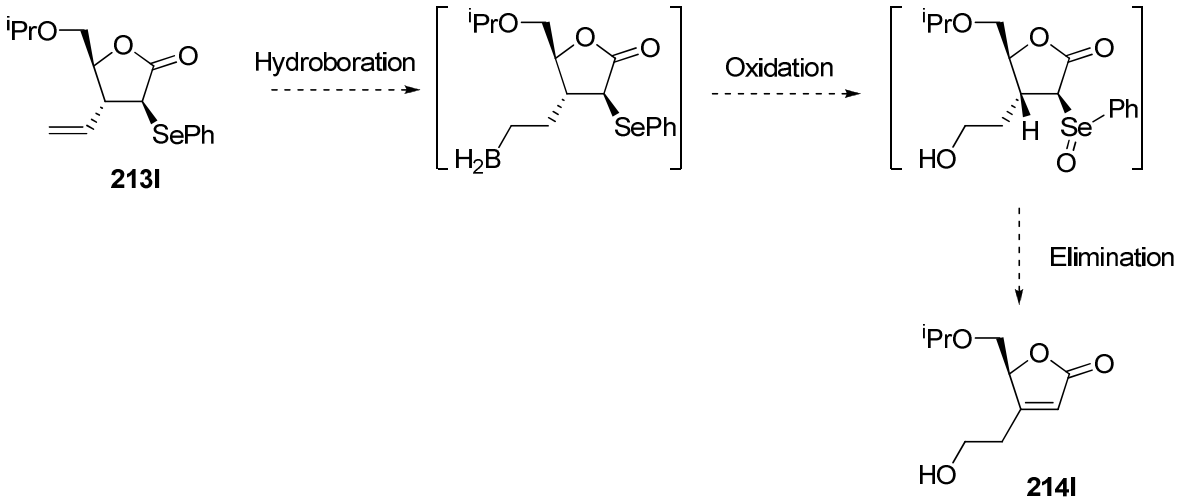
Scheme 84. Preparation of alkenes **208l** and **213l**.

The β-vinylation of furanone **14j** under the same conditions, after treatment with saturated aqueous solution of ammonium chloride, led to the isolation of alkene **208j** in 90% yield (Scheme 85), but all attempts to trap the anion with phenylselenyl bromide remained unsuccessful.



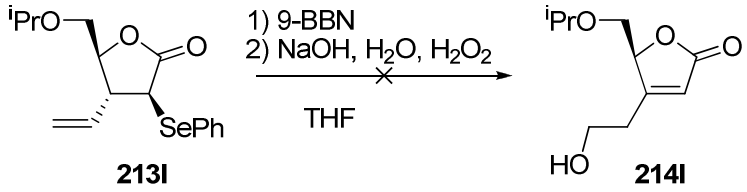
Scheme 85. Preparation of alkene **208j**.

In principle, alkene **213l** has the potential to be straightforwardly converted into furanone **214l** by simultaneous oxidation of the selenide and an intermediate borane derivative (Scheme 86).



Scheme 86. Hydroboration of alkene **213l** and further oxidation to afford furanone **214l**.

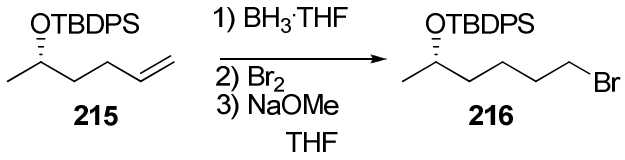
Unfortunately, the reaction of **213l** with 9-BBN and then hydrogen peroxide in basic medium did not produce the expected product (Scheme 87). NMR analysis of the crude material did not show alkene signals, neither of the starting substrate nor of a new compound, and the phenyl group was neither detected.



213l **214l**

Scheme 87. Attempted hydroboration/oxidation of alkene **213l**.

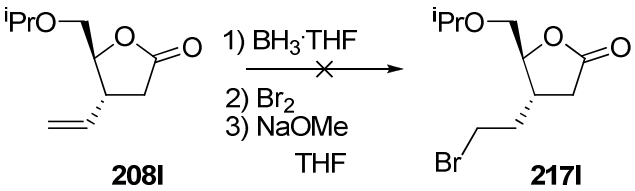
We envisaged the hydrobromination of the terminal alkene as another plausible option to introduce a convenient functionalization into the side chain. Various anti-Markovnikov hydrobrominations have been described in the literature. In a work published by Duffield and Pettit, [113] the terminal alkene of a silyl ether was regioselectively transformed into a bromide by hydroboration followed by treatment with bromine and, then, sodium methoxide (Scheme 88). The yield of the overall transformation was not described because **216** was used in the next synthetic step without purification.



215 **216**

Scheme 88. anti-Markovnikov hydrobromination described by Duffield and Pettit (2001).

We intended the application of this methodology over substrate **208l** (Scheme 89), but, unfortunately, this experiment resulted only in decomposition of the starting material.



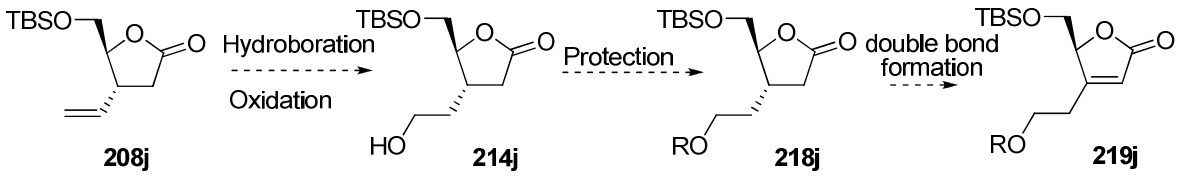
208l **217l**

Scheme 89. Attempted hydrobromination of alkene **208l**.

Next, we explored the classical hydroboration/oxidation protocol on the furanone **208j** with the aim of conducting the sequence depicted in Scheme 90. In the event, treatment of alkene **208j** with BH_3 in THF, followed by an aqueous solution of sodium

[113] Duffield, J. J.; Pettit, G. R. *J. Nat. Prod.* **2001**, *64*, 472-479.

hydroxide and hydrogen peroxide did not produce the expected alcohol. The same transformation was also intended with 9-BBN in THF, but it also met with failure.



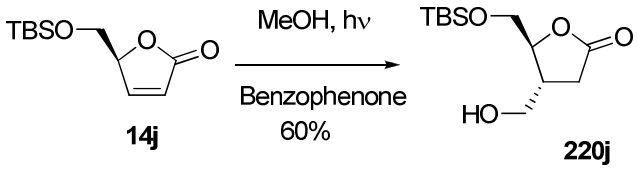
Scheme 90. Planed hydroboration of alkene **208j** and further transformations to achieve 2(*5H*)-furanone **219j**.

In view of these negative results, we moved to another type of insertion.

4.3.3. Photoinduced β-alkylation

The photochemical addition of alcohols to cycloalkenones has been studied by different groups[114] including those of Fraser-Reid[115] and Paquette[116], who used this reaction as a key step in the synthesis of (+)-pleuromutilin.

Mann and Weymouth-Wilson studied the activated photochemical insertion of methanol to 2(5*H*)-furanone.[117] This reaction seems to be general and proceeds regio- and stereoselectively. In one of their works, it was described that the addition of methanol to 2(*5H*)-furanone **14i** resulted in the formation of **220j** in 60% yield (Scheme 91).

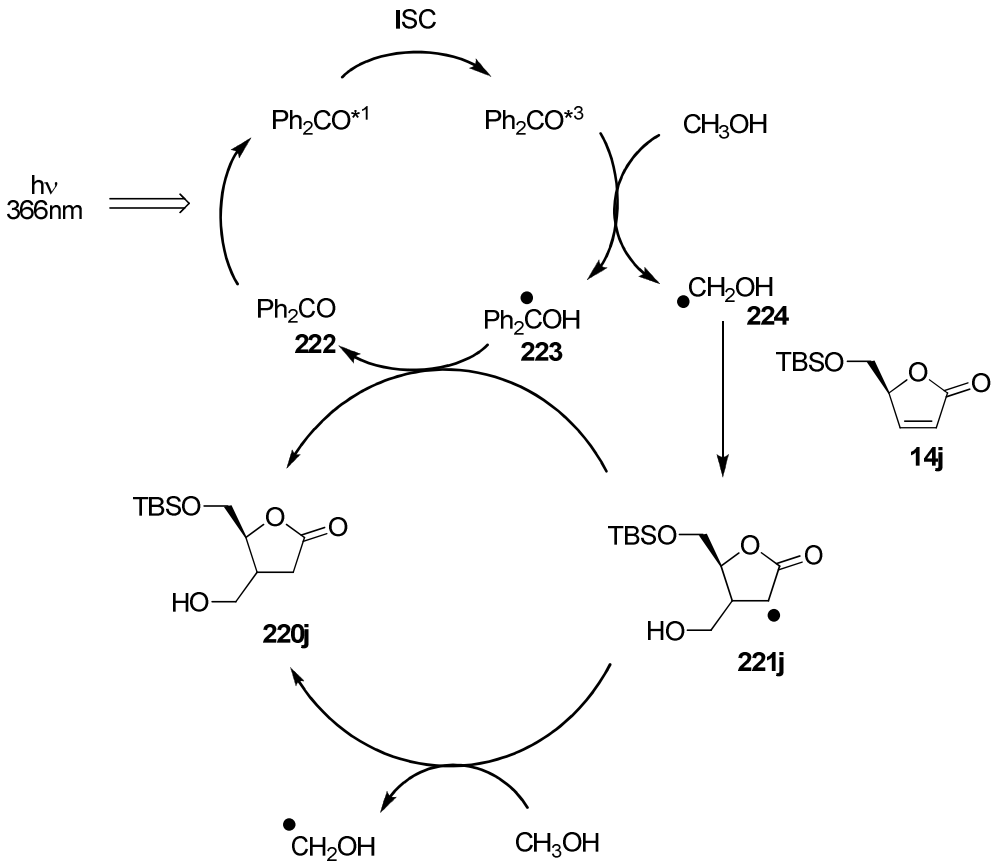


Scheme 91. Photoinduced addition of methanol to **14j**.

The mechanistic proposal for the photoinduced addition reaction of methanol to conjugated enones promoted by benzophenone is depicted in Scheme 92.[117d] In this process, the excited benzophenone abstracts one hydrogen atom of methanol

[114](a) Bundy, G. L. *Tetrahedron Lett.* **1975**, *24*, 1957-1960. (b) Buenger, G. S.; Marquez, V. E. *Tetrahedron Lett* .**1992**, *33*, 3707-3710.
[115] (a) Fraser-Reid, B.; Holder, N. L.; Yunker, M. B. *J. Chem. Soc., Chem. Commun*. **1972**, 1286-1287. (b) Fraser-Reid, B.; Hicks, D. R.; Holder, N. L.; Walter, D. L. *Can. J. Chem*. **1977**, *55*, 3978-3985. (c) Anderson, R. C.; Fraser-Reid, B.; Hicks, D. R.; Walter, D. L. *Can. J. Chem*. **1977**, *55*, 3986-3995. (d) Beckwith, A. L; Benko, Z.; Fraser-Reid, B.; Mariano, P. S. *J. Org. Chem*. **1988**, *53*, 2066-2072.
[116] Pansegrau, P. D.; Paquette, L. A.; Springer, J. P.; Wiedeman, P. E. *J. Org. Chem*. **1988**, *53*, 1461-1466.
[117] (a) Mann, J.; Weymouth-Wilson, A. C. *Organic Syntheses* **1975**, *75*, 139. (b) Mann, J.; Weymouth-Wilson, A. *Carbohydr. Res*. **1991**, *216*, 511-515. (c) Mann, J.; Weymouth-Wilson, A. C. *J. Chem. Soc., Perkin Trans. I* **1994**, 3141-3148.

generating the hydroxymethyl radical **224** and the benzhydryl radical **223**.[118] The radical insertion of **224** to enone **14j** leads to an α-carbonyl radical **221j**. This procedure is favored by the nucleophilic character of radical **224**.[119] At this point, the mechanism splits into two possible pathways, both leading to the lactone product **220j**: either abstraction of one hydrogen atom of the benzhydryl radical **223**, regenerating benzophenone, or abstraction of a hydrogen atom from another molecule of methanol, to generate a new hydroxymethyl radical **223**.[120]

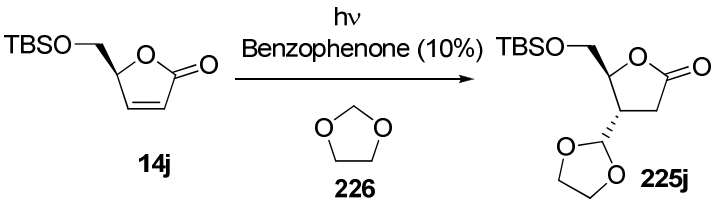


Scheme 92. Mechanistic proposal for the formation of adduct **220j**.

In previous work carried out in our group, we tried to reproduce the reaction of Scheme 79 obtaining 47% yield of **225j** after 40 h of irradiation, with incomplete conversion of the starting substrate. As an alternative for the introduction of the β chain of the target molecule, we considered inserting a dioxolane at the β-position of the furanone **14j** (Scheme 93). This reaction had been described by Ghosh and co-workers in 2004, as part of a study on the conjugated addition of 1,3-dioxolane to different protected 5-

[118] Topp, M. R. *Chem. Phys. Lett*. **1975**, *32*, 144.
[119] (a) Magnin, D. R.; Porter, N. A.; Wright, B. T. *J. Am. Chem. Soc*. **1986**, *108*, 2787-2788. (b) Cerutti, P.; Goth, H.; Schmid, H. *Helv. Chim. Acta* **1965**, *48*, 1395-1406.
[120] (a) Rubin, M. B. *Tetrahedron Lett*. **1982**, *23*, 4615-4618. (b) Grossmann, H.; Koltzenburg, G.; Schenck, G. L. *Angew. Chem.* **1957**, *69*, 177-178.

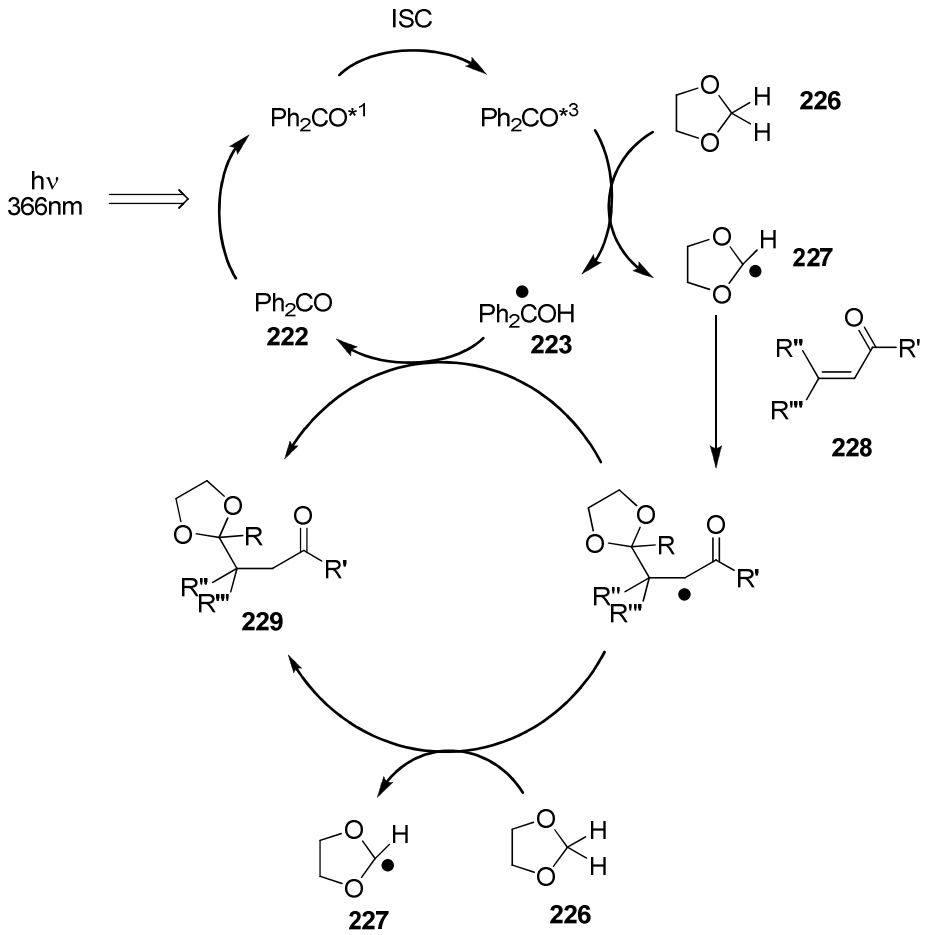
oxymethyl-2(5*H*)-furanones.[65] Hydrolysis of the ketal would render an aldehyde that could be then transformed in different functional groups.[121]



Scheme 93. Photoinduced addition of dioxolane to **14j**.

In general, the photochemical insertion of 1,3-dioxolane to α,β-unsaturated ketones occur in excellent yield.[122] The reaction mechanism is analogue to that of the photoinducted conjugated addition of methanol (Scheme 94). In this case, the 1,3-dioxolan-2-yl radical, **227**, is trapped by the α,β-unsaturated ketone, the efficiency of the alkylation process depending of the effectiveness of the dioxolanyl radical trapping. For our synthetic purpose, the facial diastereoselectivity of this reaction is not important, since the α,β-double bond has to be regenerated.

[121](a) Ley, S. V.; Baeschlin, D. J.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2001**, *101*, 53-80; (b) Carini, S.; Cerè, V.; Peri, F.; Pollicino, S. *Synthesis* **2000**, 1756-1762.
[122]Albini, A.; Fagnoni, M.; Freccero, M.; Manfrotto, C.; Mella, M. *J. Org. Chem.* **1999**, *64*, 5024-5028.



Scheme 94. Mechanistic proposal for the photoinduced conjugate addition of dioxolane.

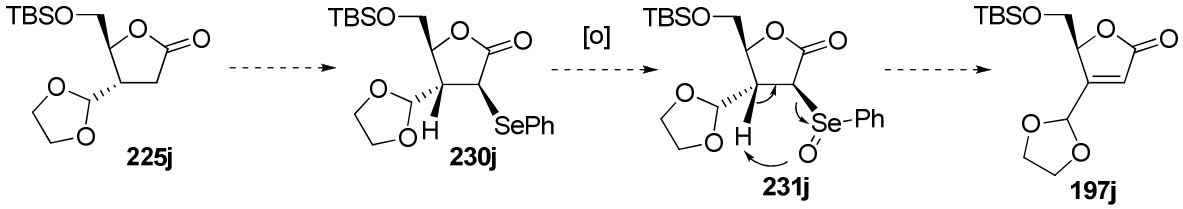
To prepare the dioxolanyl furanone **225j** we followed the protocol described by Ghosh *et al.* The reaction temperature and the quantity of benzophenone added were critical parameters in regard to the yield. The irradiation of the 2(*5H*)-furanone **14j** was performed in the presence of benzophenone (10%) in oxygen-free and commercial dioxolane through a pyrex® filter. The temperature was kept below 20℃ and the solutions were irradiated for 12h with a 125W or 400W medium pressure mercury lamp, depending of the quantity of substrate (Table 17). The adduct **225j** was purified by flash chromatography over silica gel. This reaction has been considerably scaled up respect to the work of Ghosh with good results.

Table 17. Summary of photochemical conjugated addition of dioxolane to furanone **14j**

mmol **14i**	Lamp	Exterior bath	Jacket	Interior bath	Yield
3.3[a]	125 W	0℃	pyrex®	MeOH 0℃	99%
13.2[b]	400 W	-40℃	pyrex®	MeOH -10℃	87%
16.5[c]	400 W	-45℃	pyrex®	MeOH -15℃	99%

Photochemical reactor capacity: a) 300 mL, b) 650 mL, c) 800 mL

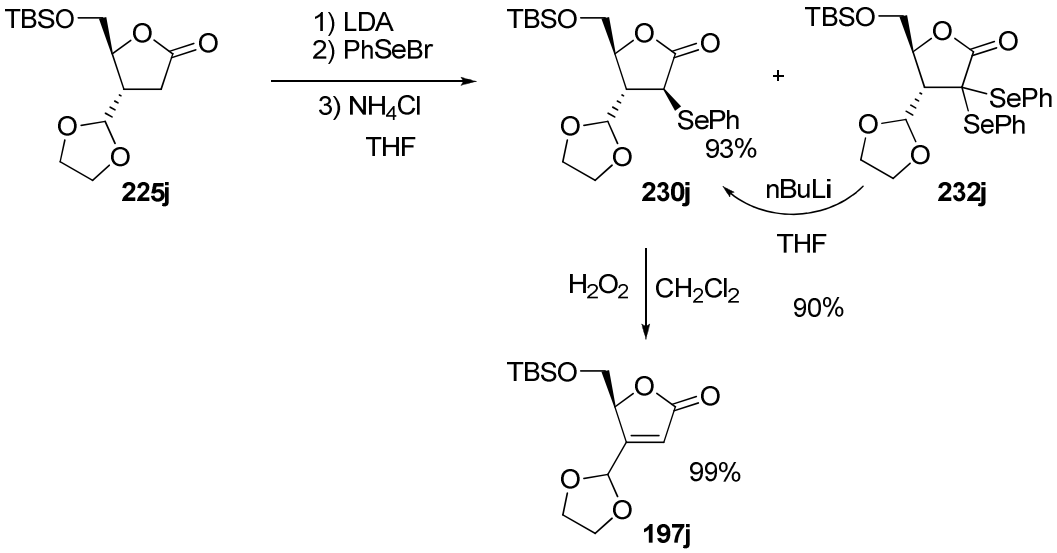
The regeneration of the α,β-double bond in **225j** to prepare **197j** was based on selenium chemistry (Scheme 95). It consisted on the preparation of the phenylselenide derivative **230j** and further *syn* β-elimination of the selenoxide. This method is based on observations made by Sharpless[123] and Reich,[124] where lithium enolate of ketones, aldehydes or esters react quickly and cleanly with phenylselenium halides to give α-phenylseleno carbonyl compounds, which can be oxidized to the phenylalkylselenoxides to undergo a *syn*-elimination.[125,126]



Scheme 95. Planed conversion of **225j** into **197j**.

Accordingly, formation of the lithium enolate by treatment of **225j** with LDA at -78℃, followed by addition of phenylselenium bromide in THF, afforded the desired 2(*5H*)-furanone **230j** in 93% yield (Scheme 96).[127] In some runs, the diaddition product **232j** was also isolated after purification by flash chromatography.[128]

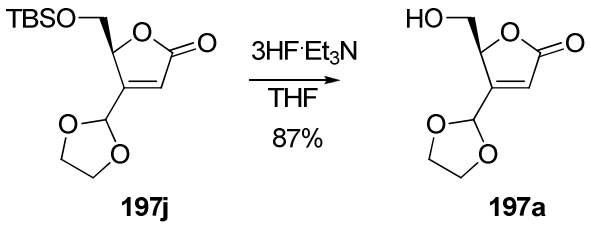
[123] Lauer, R. F.; Sharpless, K. B.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137-6139.
[124] Reich, H. J.; Reich, I. L.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813-5815.
[125] Lauer, R. F.; Sharpless, K. B.; Young, M. W. *Tetrahedron Lett.* **1973**, 1979-1982.
[126] (a) Jones, D. N.; Mundy, D.; Whitehouse, R. D. *Chem. Comm.* **1970**, 86-87. (b) Lauer, R. F.; Sharpless, K. B. *J. Am. Chem. Soc.* **1973**, *95*, 2697-2699.
[127] First methodology used: Bermejo, F.; Redero, E.; Sandoval, C. *Tetrahedron* **2001**, *57*, 9597-9608.
[128] (a) Gillissen, H. M. J.; Schipper, P.; van Ool, P. J. J. M.; Buck H.; M. *J. Org. Chem.* **1980**, *45*, 319-328. (b) Watanade, H.; Watanabe, T.; Mori, K.; Kitahara, T. *Tetrahedron Lett.* **1997**, *38*, 4429-4432.



Scheme 96. Synthesis of 2(*5H*)-furanone **197j** from **225j**.

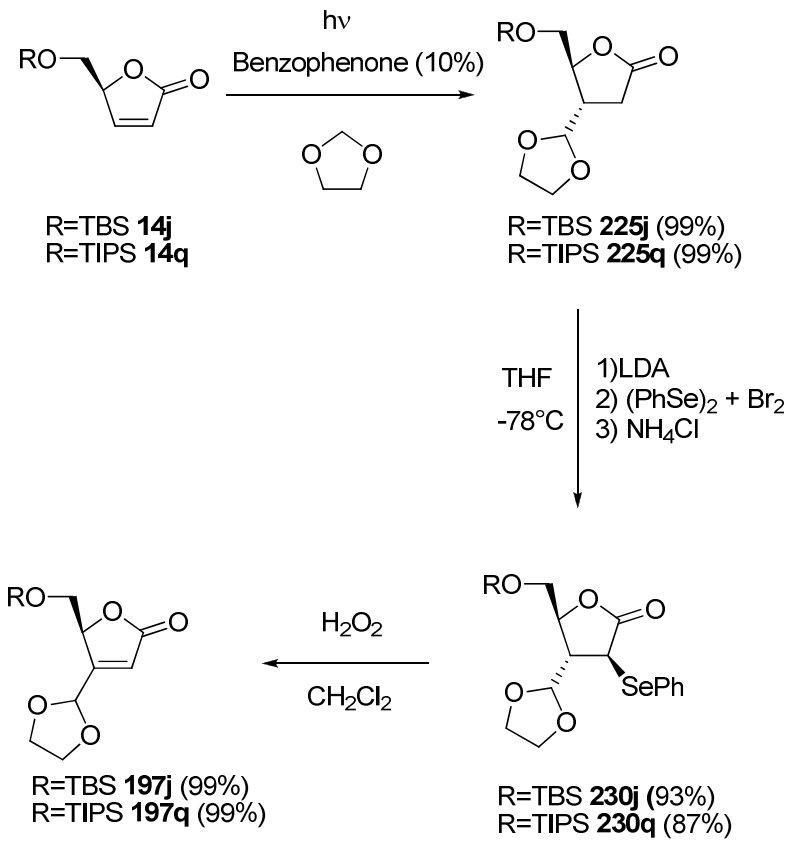
The oxidation of the phenylselenyl derivative **230j** was performed in heterophase (CH_2Cl_2-H_2O) at 0℃ and delivered **197j** in excellent yield. The ^{1}H-NMR spectrum of **197j** reveals a new signal corresponding to the olefinic proton H-3 at δ 6.09 with concomitant disappearance of H-4 and the aromatic signals. Moreover, in the ^{13}C-NMR spectrum we observed the presence of the olefinic carbon atoms, C-4 at δ 164.9 and C-3 at δ 119.2.

To compare the influence of the protecting group in the diastereoselectivity of the following [2+2] photocycloaddition reaction, we deprotected the furanone **197j** by treatment with 3HF·Et_3N in THF, which afforded furanone **197a** in good yield (Scheme 97). Its IR spectrum presents a broad band at 3429 cm^{-1}, while the ^{1}H and ^{13}C NMR spectra, except for the signals of the TBS group, are very similar to that of the precursor **197a**.



Scheme 97. Preparation of 2(*5H*)-furanone **197a**.

We also prepared the triisopropyl derivative **197q**, following a parallel methodology to that described for **197j**. The overall sequences for both furanones are summarized in Scheme 98.



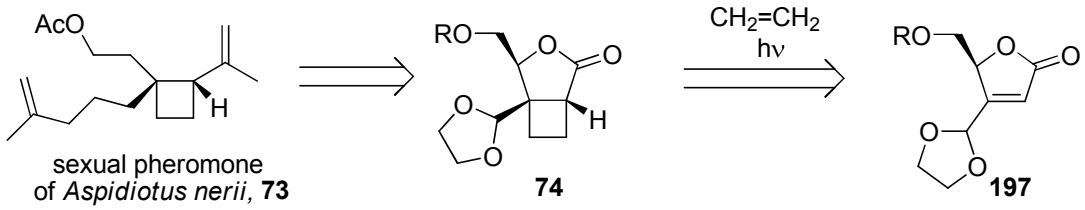
Scheme 98. Preparation of 2(*5H*)-furanones **197**.

4.4. Study of the [2+2] photocycloaddition step

4.4.1. Introduction

Photochemical reactions of cyclic enones with olefins have been successfully used in the preparation of versatile cyclobutane building blocks, which have allowed synthesizing natural products and other compounds with quite unusual structures.[129] As it was previously mentioned, one of the key steps in our synthetic pathway towards the preparation of the sexual pheromone of *Aspidiotus nerii* is the [2+2] photocycloaddition of a chiral α,β-unsaturated lactone to an alkene (Scheme 99).

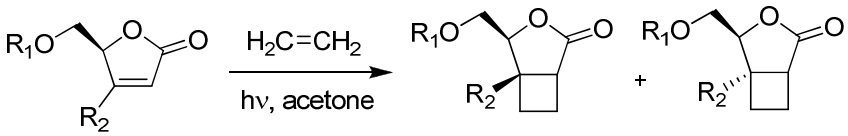
[129](a) Baldwin, S. W. *Organic Photochemistry*; Padwa, A. Ed.; Marcel Dekker: New York, **1981**; chapter 2, p 123; (b) Coyle, J. D. *Photochemistry in Organic Synthesis*; The Royal Society of Chemistry; London; **1986**, chapter 9, p 163; (c) Demuth, M.; Mikhail, G. *Synthesis* **1989**, 145-162; (d) Crimmins, M. T. *Comprehensive Organic Synthesis* **1991**, *5*, 123-150; (e) Bach, T. *Synthesis* **1998**, 683-703; (f) Lee-Ruff, E.; Madenova, G. *Chem. Rev.* **2003**, *103*, 1449-1484; (g) Namyslo, J. C.; Kaufmann, D. *Chem. Rev.* **2003**, *103*, 1485-1537. (h) Iriondo-Alberdi, J.; Greaney, M. F. *Eur. J. Org. Chem.* **2007**, 4801-4815.



Scheme 99. Partial retrosynthetic analysis of the sexual pheromone of *Aspidiotus nerii*.

Table 18 summarizes the most representative results related to the reaction of interest, formerly achieved in the photochemical reaction of several 2(*5H*)-furanones with ethylene.

Table 18. [2+2] Photocycloaddition of homochiral 2(*5H*)-furanones to ethylene, Font *et al*.



R_1	R_2	Yield (%)	*anti* :*syn* (%)
Ac	H	82	74 :26
Piv	H	59	78 :22
Ac	CH_3	65	54 :46
Piv	CH_3	70	62 :38

For those reactions, the irradiation through a pyrex filter in acetone took place with moderate to good yields. The diastereofacial differentiation is consistent with the alkene approaching to the less hindered face of the lactone, affording mainly the *anti* adducts. The highest facial diastereoselectivity was achieved when the alcohol was protected as a pivalate and decreased when a methyl group was present at C-4. It was also observed that low reaction temperatures increased the yield without influencing the stereoselectivity.

4.4.2. Results

Considering these precedents, we undertook the study of the photoinduced cycloaddition of furanones **197a**, **197j** and **197q** (Figure 37) to ethylene, with the objective of finding the best reactions conditions in terms of yield and facial discrimination.

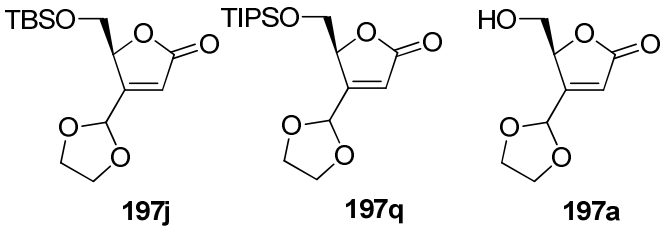
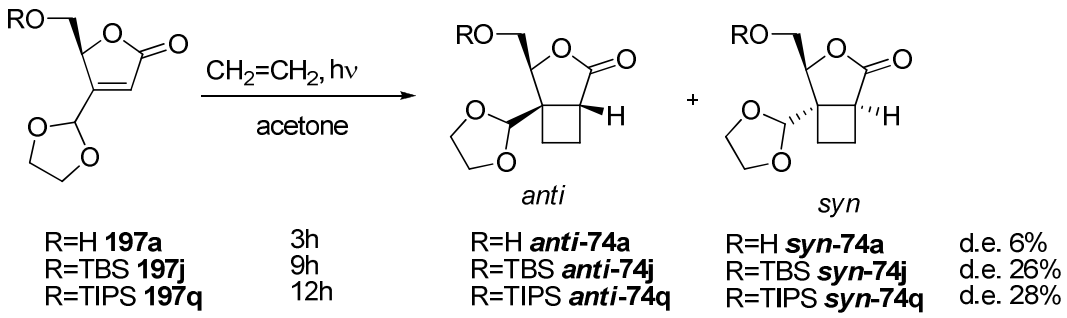


Figure 37. 2(5*H*)-furanones used in the photochemical study with ethylene.

In all the photoreactions we used a 125W high pressure mercury lamp (Cathodeon HPK125), a pyrex® filter and acetone as solvent and sensitizer, according to the best conditions described for similar substrates. The reactor was externally cooled to -20℃ and a MeOH flow at -15℃ was passed through the rea ctor refrigerant jacket. The evolution of the reaction was monitored by GC and the irradiation was stopped in function of by-products formation.

The irradiation of furanone **197a** for 3h in the presence of ethylene afforded a 53:47 mixture of cycloadducts ***anti*-74a** and ***syn*-74a** in 79% overall yield (Scheme 100). Thus, the facial diastereoselectivity was quite low (d.e. 6%) with a small predominance of the *anti* isomer.



Scheme 100. Photocycloaddition of furanones **74** to ethylene.

In a similar way, the irradiation for 9h of the 2(*5H*)-furanone **197j** delivered a 63:37 mixture of cycloadducts ***anti*-74j** and ***syn*-74j** (d.e. 26%) in 75% yield, recovering 5% of the starting material. Almost identical results were observed for compound **197q**, since, after 12h of irradiation, a 64:36 mixture of of products ***anti*-74q** and ***syn*-74q** was obtained in 70% yield without a major change in the facial diastereoselectivity (d.e. 28%). We can conclude that the bulky silyl protection is benefitial for the antifacial selectivity, but this stereoslectivity is still quite moderate, as previously observed for the β-methyl substituted furanones.

The structural elucidation of cyclobutanes **74** was performed with the help of NMR experiments. Tables 19 and 20 show the most relevant data. The chemical shift and couplig constant values, along with some NOESY experiments, allowed us to determine their relative configuration. One diagnostic observation is that the signal of the acetal carbon atom C-7, for the *anti* isomers, appears high field shifted compared to the *syn* isomers, because of the higher "steric compression" due to the *cis* arrangement of the acetal and the alkoxy groups (Figure 38). As shown in Table 20, the signal of C-7 for cycloadducts ***anti*-74a**, ***anti*-74j** and ***anti*-74q** (δ 104.3, 104.5 and 104.4,

respectively) are downfield shifted compared to cycloadducts ***syn*-74a**, ***syn*-74j** and ***syn*-74q** (δ 102.5, 102.8 and 103.1, respectively) with less steric interactions.

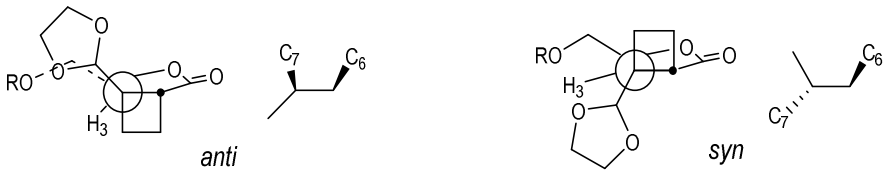


Figure 38. Steric interactions of the acetal carbon atom in cycloadducts **74**.

Table 19. Some significant ^{1}H-NMR ($CDCl_3$) data of cycloadducts **74**. The coupling constants (*J*) are in Hz and the chemical shifts are in ppm.

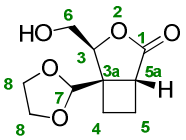
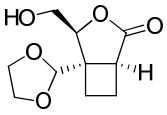
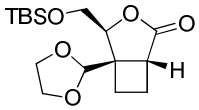
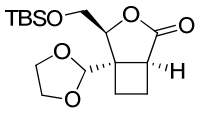
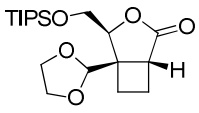
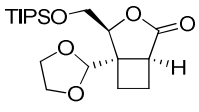
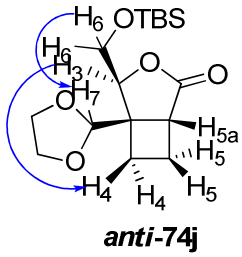
Cycloadduct	H-3	H-4	H-5	H-5a	H-6	H-7
 ***anti*-74a**	4.32 t $J_{3,6}$: 2.7	2.34 m (1H) 2.14 m (1H)	2.51 m (1H) 2.03 m (1H)	3.04 t $J_{5a,5}$: 9.6 $J_{5a,5}$: 2.8 $J_{5a,3}$: 2.8 $J_{5a,4}$: 0.9	3.81 m (2H)	5.17 s
 ***syn*-74a**	4.49 t $J_{3,6}$: 6.0	2.37 m (1H) 2.14-1.99 (1H)	2.47 m (1H) 2.14-1.99 (1H)	3.10 t $J_{5a,5}$: 9.9 $J_{5a,5}$: 2.9 $J_{5a,3}$: 2.9 $J_{5a,4}$: 1.0	4.11-3.88 (1H) 3.78 dd (1H) J_{gem}: 11.9 $J_{6,3}$: 5.7	5.00 s
 ***anti*-74j**	4.24 t $J_{3,6}$: 1.8	2.28 m (1H) 2.07 m (1H)	2.49 m (1H) 1.97 m (1H)	2.96 dddd $J_{5a,5}$: 9.4 $J_{5a,5}$: 3.4 $J_{5a,3}$: 2.3 $J_{5a,4}$: 1.0	3.82 d (2H) $J_{6,3}$: 1.8	5.24 s
 ***syn*-74j**	4.46 t $J_{3,6}$: 5.6	2.30 m (1H) 2.10 m (1H)	2.41 m (1H) 2.01 m (1H)	2.96 dt $J_{5a,5}$: 9.9 $J_{5a,5}$: 2.9 $J_{5a,4}$: 2.9	4.02-3.87 (1H) 3.80 dd (1H) J_{gem}: 11.0 $J_{6,3}$: 5.6	4.92 s
 ***anti*-74q**	4.27 b s	2.32 m (1H) 2.10 m (1H)	2.50 m (1H) 2.00 m (1H)	3.03 d $J_{5a,5}$: 8.1	3.95 m (2H)	5.35 s
 ***syn*-74q**	4.52 t $J_{3,6}$: 6.0	2.34m (1H) 2.05 m (1H)	2.45 m (1H) 2.10 m (1H)	3.07 m	3.98 m (2H)	4.97 s

Table 20. ^{13}C-NMR data of cycloadducts **74**. The chemical shifts are in ppm.

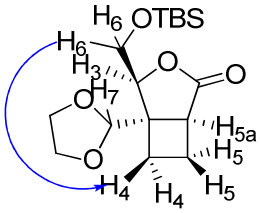
cycloadduct	C-1 (C=O)	C-7	C-3	C-6	C-3a	C-5a	C-4	C-5
***anti*-74a**	179.7	102.5	85.5	61.8	48.7	41.0	26.4	23.4
***syn*-74a**	178.4	104.3	81.5	61.4	48.9	40.9	21.7	19.9
***anti*-74j**	180.0	102.8	84.8	62.4	49.1	42.1	25.0	23.9
***syn*-74j**	179.1	104.5	81.9	62.4	49.0	39.8	20.3	21.8
***anti*-74q**	180.1	103.1	85.4	66.1	49.4	42.3	38.5	32.3
***syn*-74q**	179.1	104.4	81.9	65.6	49.2	39.9	21.9	20.5

In order to confirm the configuration assignment we performed some NOESY experiments. Two examples are highlighted, the first one corresponds to cycloadduct ***anti*-74j** (Figure 39) and the second one to ***syn*-74j** (Figure 40). For compound ***anti*-74j**, the presence of cross-peaks between protons H-6 (δ 3.82) and H-7 (δ 5.24) and between protons H-3 (δ 4.24) and H-4 (δ 2.07) confirmed *anti* stereochemistry. For compound ***syn*-74j**, its *syn* stereochemistry was confirmed by the observation of interaction between H-6 (δ 3.80 and 3.78) and H-4 (δ 2.30 and 2.10).



***anti*-74j**

Figure 39. n.O.e interactions of ***anti*-74j**.



***syn*-74j**

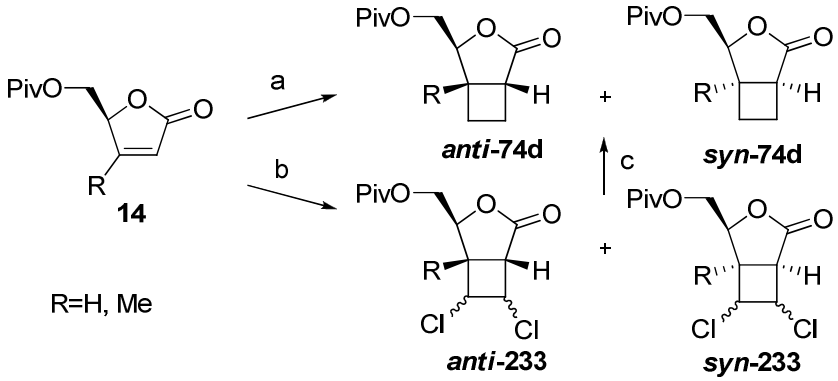
Figure 40. n.O.e interactions of ***syn*-74j**.

4.4.3. Photocycloadditions to *cis*-1,2-dichloroethylene

In 2003, our research group published a study on the [2+2] photocycloaddition reaction of (*Z*)-1,2-dichloroethylene to 2(5*H*)-furanones, demonstrating that it was possible to transform the dichloro cycloadducts into cyclobutane and cyclobutene derivatives in

high yield, with good facial selectivity and on a multigram scale.[130] Thus, the [2+2] photocycloadditon reaction of lactones **14** to (*Z*)-1,2-dichloroethylene in acetonitrile, followed by dihydrodehalogenation with tributyltin hydride in the presence of AIBN in anhydrous toluene at 100℃ afforded the correspondi ng cyclobutanes (Table 21). This protocol increased considerably the facial diastereoselectivity of the photocycloaddition in comparison to the photoreaction with ethylene and acetylene.

Table 21. Alternative preparations of ***anti*-74** and ***syn*-74**: a) photocycloaddition to ethylene or b),c) photocycloaddition to (*Z*)-1,2-dichloroethylene and posterior reduction of the dichlorocycloadducts.

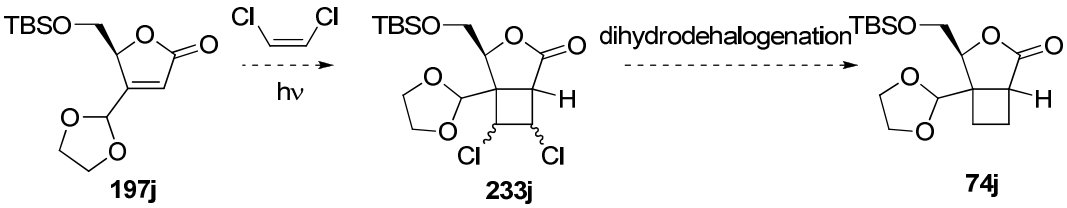


a) ethylene, hν, acetone, -20 °C ; b) hν, (*Z*)-1,2-dichloroethylene, acetonitrile; c) *n*BuSnH, AIBN, toluene, 100 °C

	Reagent	R	Yield %	*anti* : *syn*(%)	e.d. (%)
	ethylene	H	49	78 :22	56
		Me	70	62 :38	24
1)	(*Z*)-1,2-dichloroethylene	H	77[a]	95 :5	90
2)	reduction	Me	70[a]	90 :10	80

[a] Global yield

With these precedents in mind, we foresaw the possibility of applying this methodology to our dioxolanyl substrates to prepare the target cyclobutanes (Scheme 101).



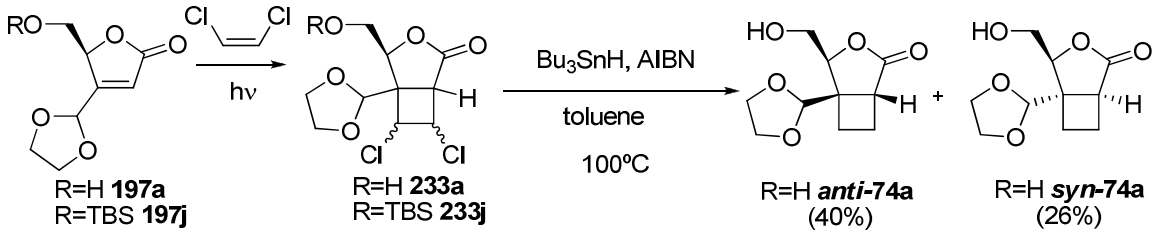
Scheme 101. Devised alternative synthetic pathway to the oxolanyl cyclobutanes.

The photochemical experiments were performed with an excess of (*Z*)-1,2-dichloroethylene, in acetonitrile as solvent, with a 125W high pressure mercury lamp, cooling the photochemical reactor with an external bath at -40℃ and the quartz filter

[130] Alibés, R.; Alvarez-Larena, A.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M.; Rustullet, A.; Parella, T.; Piniella, J. F. *Tetrahedron Lett.* **2003**, *44*, 69-71.

jacket with a flux of methanol at -15ºC. Before irr adiation, the solutions were degased by bubling a flux of nitrogen for a couple of minutes. The evolution of the reaction was monitored by GC. The crude product was filtered through a pad of silica gel using ethyl acetate as solvent and the isolated oil containig a complex mixture of different cycloadducts was used in the next dihydrodechlorination step without further purification.

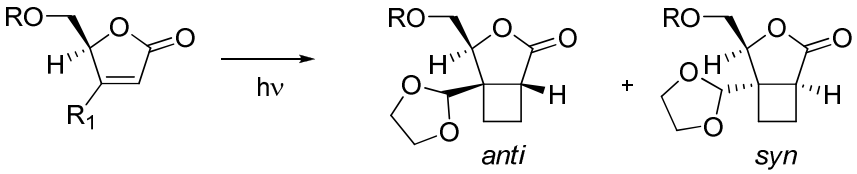
Thus, furanones **197j** and **197a** were irradiated under these conditions during 3 h and 12 h, respectively in presence of (*Z*)-1,2-dichloroethylene to afford the corresponding mixtures of dichloro cycloadducts (Scheme 102). These mixtures were then treated with tributyltin hydride, AIBN as radical initiator, in toluene at 100ºC for 1 h. The amount of tributyltin hydride and the temperature were optimized to obtain a total conversion. In the event, the hydroxycyclobutanes **74a** were isolated in 66% global yield (from furanone **14a**) in a 61:39 *anti*:*syn* ratio (d.e. 22%). However, when the same protocol was applied to the silyl protected furanone **197j**, although the photochemical process took place as expected, after the dihydrodehalogenation reaction we were not able to isolate the clean cyclobutane product, which could not be separated from the tin by-products and, hence, it was not possible to determine the exact yield and the diastereomeric excess of the process. Consequently, it was concluded that this methodology was not suitable to prepare the cyclobutanes **74j**.



Scheme 102. [2+2] Photocycloaddition of **197a** and **197j** to *cis*-1,2-dichloroethylene followed by dihydrodehalogenation.

Table 22 summarizes the results related to the preparation of the cyclobutanes bearing a dioxolanyl substituent, as required to continue with the synthesis of the target pheromone. As it can be observed, the best results combining overall yield and facial selectivity correspond to the photocycloaddition of **197j** to ethylene (entry 2). We decided to go on with the synthesis from the *anti* cyclobutanes **74j** and **74q**.

Table 22. Summary of the results of the [2+2] photocycloaddition reaction of different 2(*5H*)-furanones to ethylene and (*Z*)-1,2-dichloroethylene.

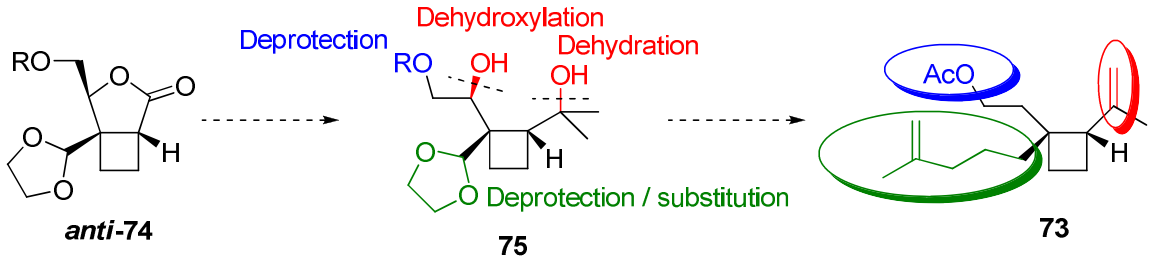


Entry	2(5*H*)-furanone	R	Reagent	Yield (%)[a]	*anti*:*syn* (%)	d.e. (%)
1	**197a**	H	ethylene	79	53:47	6
2	**197j**	TBS		75	63:37	26
3	**197q**	TIPS		70	64:36	28
4	**197a**	H	1) (*Z*)-*1,2*-dichloroethylene 2) reduction	66	61:39	22
5	**197j**	TBS		--	--	--

[a]Global yield

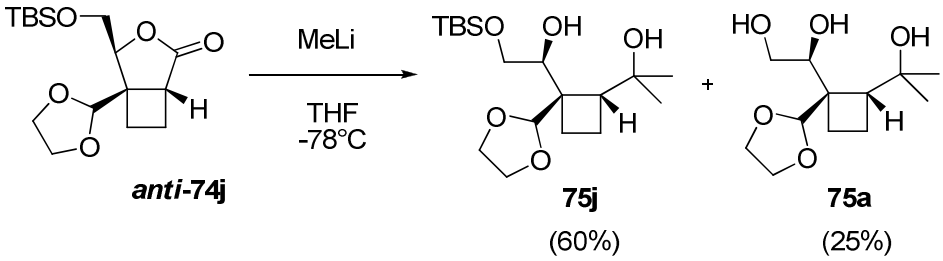
4.5. Advances in the synthesis of the pheromone

Scheme 103 summarizes the remaining transformations from the cyclobutanes ***anti*-74** to the targeted sexual pheromone of oleander scale **73**.



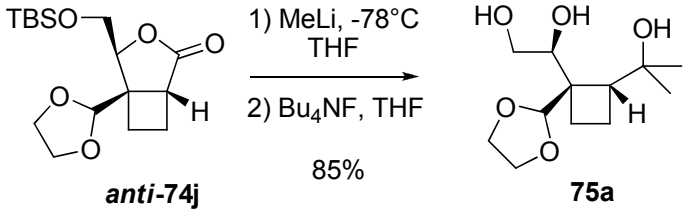
Scheme 103. Planned transformations from ***anti*-74** to the pheromoene **73**.

To incorporate the two methyl groups of the east-side chain, the TBS protected lactone ***anti*-74j** was treated with an excess of methyllithium (Scheme 104). This reaction delivered the expected dihydroxy silylether **75j** (60% yield), along with the triol **75a** (25% yield). All attempts to avoid the formation of **75a** were unsuccessful, as they were our trials to re-protect the primary alcohol of **75a** either as silyl or as *p*-metoxybenzyl ether.



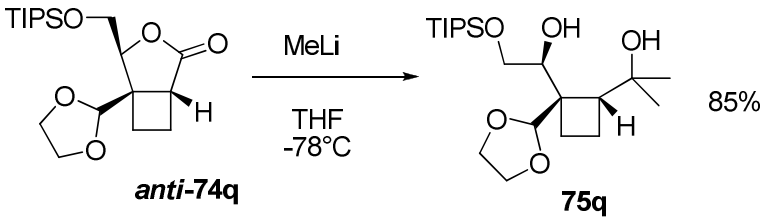
Scheme 104. Methylation of ***anti*-74j**.

Triol **75a** could be obtained in good yield by treatment of the crude product of the reaction between furanone ***anti*-74j** and methyllithium with tetrabutylammonium fluoride (Scheme 105).



Scheme 105. Synthesis of **75a**.

In contrast to ***anti*-74j**, when the TIPS protected lactone ***anti*-74q** was subjected to the same treatment with methyllithium at -78ºC, the reaction delivered a single product in 85% yield, which was identified as the diol **75q** (Scheme 106).



Scheme 106. Synthesis of diol **75q**.

The three new cyclobutane derivatives **75** (Figure 41) were used to continue the synthesis.

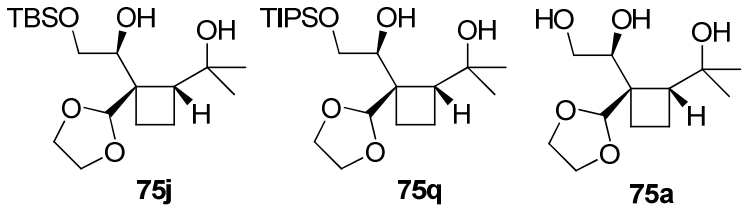
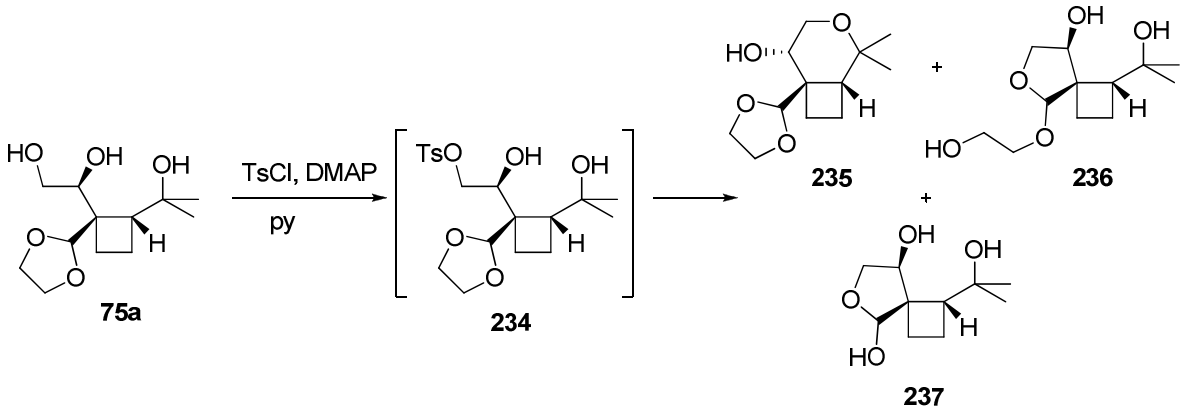


Figure 41. Synthetically available cyclobutane intermediates for the synthesis of **73**.

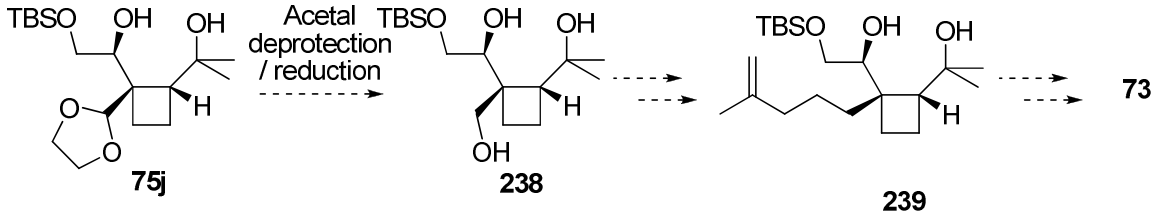
By analogy with the syntheses of grandisol and lineatin developed in our laboratories, pyran **235** (Scheme 107) was considered the next suitable intermediate en route to the

pheromone **73**. However, when in some preliminary studies, the formation of pyran **235** was attempted by tosylation of the primary alcohol of triol **75a** followed by intramolecular displacement of the tosylate intermediate, the yield of the expected pyran was low, due to the formation of considerable amounts of the hemiacetals **236** and **237** as by-products.



Scheme 107. Precedents: attempted preparation of pyran **235**.

To avoid these competitive undesired reactions, we decided to attempt the elaboration of the terpenic chain prior to the dehydration leading to the pyran (Scheme 108). This tactical modification required the reduction of the acetal group to a primary alcohol, followed by conversion of the primary free hydroxyl into a better leaving group, and subsequent coupling with an organometallic chain.[131]

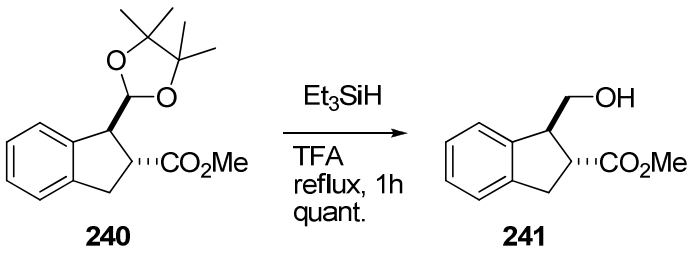


Scheme 108. Tactical modification for the synthesis of **73**.

Due to the presence of the TBS protection, a smooth methodology was required for the reduction of the acetal. In 2009, Tomioka and co-workers described that the reduction of acetal **240** with triethylsilane in trifluoroacetic acid afforded the indane derivative **241** in excellent yield (Scheme 109).[132]

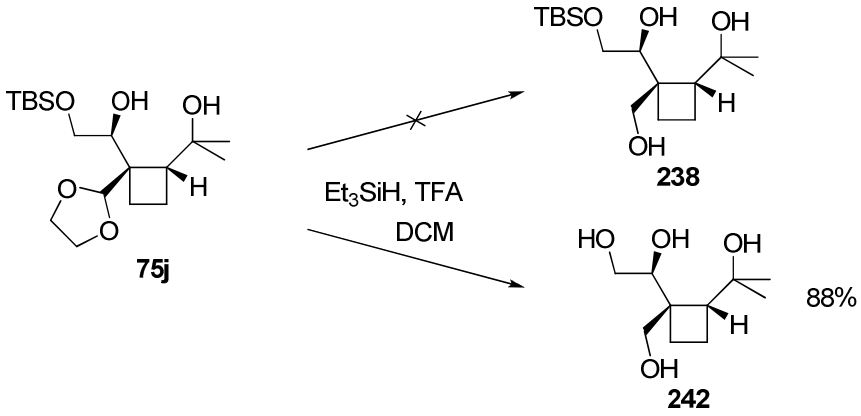
[131] (a) Prasad, K. R.; Penchalaiah, K. *Tetrahedron* **2011**, *67*, 4268-4276. (b) Chen, B.-S.; Yang, L.-H.; Ye, J.-L.; Huang, T.; Ruan, Y.-P.; Fu, J.; Huang, P.-Q. *Eur. J. Med. Chem.* **2011**, *46*, 5480-5486. (c) Zheng, J.-F.; Lan, H.-Q.; Yang, R.-F.; Peng, Q.-L.; Xiao, Z.-H.; Tuo, S.-C.; Hu, K.-Z.; Xiang, Y.-G.; Wei, Z.; Zhang, Z.; Huang; P.-Q. *Helv. Chim. Acta* **2012**, *95*, 1799-1808. (d) Herbert, M. B.; Marx, V. M.; Pederson, R. L.; Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **2013**, *52*, 310-314.

[132] Yamada, K.-I.; Maekawa, M.; Akindele, T.; Yamamoto, Y.; Nakano, M.; Tomioka, K. *Tetrahedron* **2009**, *65*, 903-908.



Scheme 109. Triethylsilane reduction of **240** by Tomioka *et al.* (2009).

When triethylsylane and trifluoroacetic acid were added to a solution of diol **75j** in dichloromethane, instead of the expected silyl ether, we obtained only one product in high yield, which was identified as the tetrol **242** by NMR analysis (Scheme 110). The deprotection was initially attributed to the presence of trifluoroacetic acid in the reaction medium, but other methodologies employing $BF_3{\cdot}OEt_2$ [133] or TMSOTf [134] as acid promoters led to the same product.



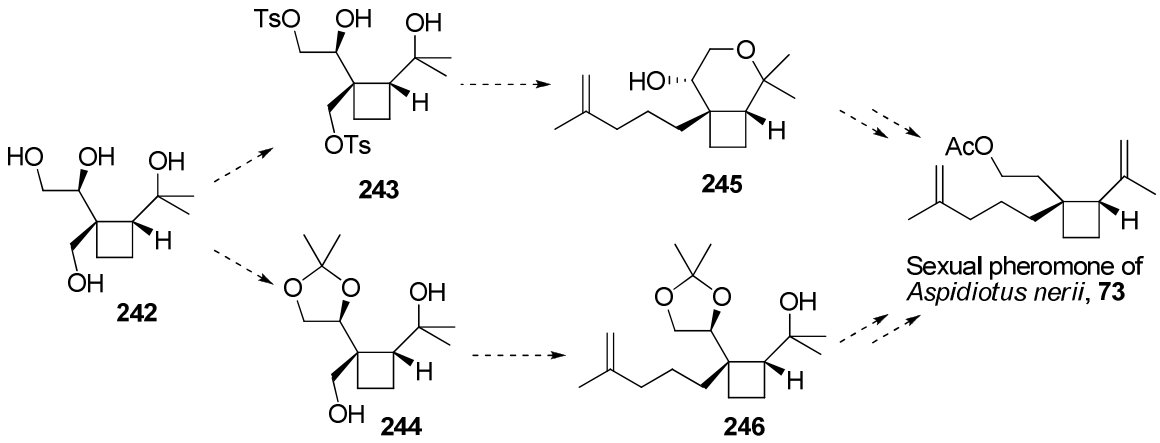
Scheme 110. Synthesis of the tetrol **242**.

Other methodologies using Et_3SiH and Lewis acids that have been described in the literature such as the use of BCl_3 by Uenishi[135]*et al.*, or $TiCl_4$ by Baltas[136]*et al.* or Cl_2AlH, or $TiCl_4$ published by Morelli[137]*et al*., also met with failure.

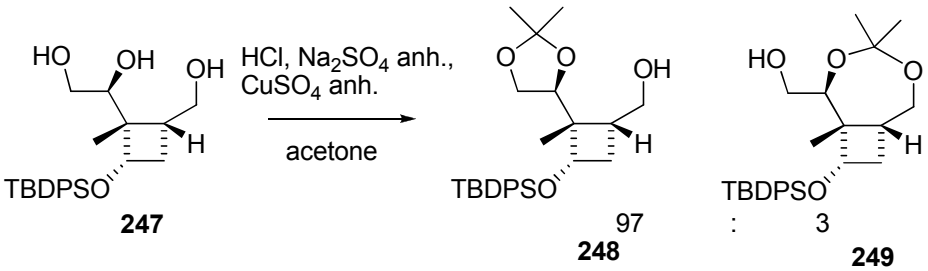
In any case, tetrol **242** opened up the possibility of continuing the synthesis of the pheromone through two alternative pathways (Scheme 111). The first one considered the preparation of pyran **245** through ditosylation of tetrol **243**, followed by regioselective cyclization and then coupling of the terpenic chain. The second one

[133] Ma, Z.; Hu, H.; Xiong, W.; Zhai, H. *Tetrahedron* **2007**, *63*, 7523-7531.
[134] Colobert, F.; Choppin, S.; Ferreiro-Mederos, L.; Obringer, M.; Luengo Arratta, S.; Urbano, A.; Carreño, M. C. *Org. Lett.* **2007**, *9*, 4451-4454
[135] Uenishi, J.; Muraoka, H.; Nameki, M.; Hata, N. *Synthesis* **2004**, *9*, 1343-1348.
[136] Dehoux, C.; Gorrichon, L.; Baltas, M. *Eur. J. Org. Chem.* **2001**, 1105-1113.
[137] Morelli, C. F.; Fornili, A.; Sironi, M.; Duri, L.; Speranza, G.; Manitto, P. *Tetrahedron Lett*. **2005**, *46*, 1837-1840.

consisted on the protection of the vicinal diol of **242** as an acetonide prior to the coupling of the terpenic chain. A similar strategy was used in the synthesis of cyclobut-A previously accomplished by our group (Scheme 112).[39]

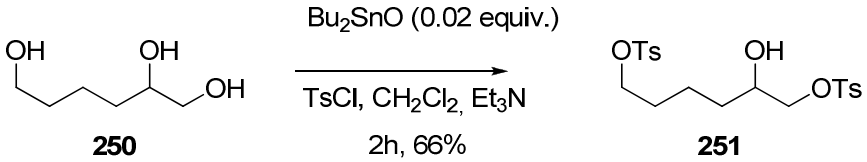


Scheme 111. Alternative pathways from tetrol **242** to the pheromone of *Aspidiotus nerii* **73**.



Scheme 112. Protection of the vicinal diol **247**, analogous to that required for **242**.

In the literature, there are some examples of one-step ditosylation of several compounds containing multiple alcohols. For instance, in 2002, Martinelli[138] *et al.* published the synthesis of the bis-tosylate **251** (Scheme 113). This bis-tosylate, containing a free secondary alcohol, was not prone to cyclise, at least under the reaction conditions.



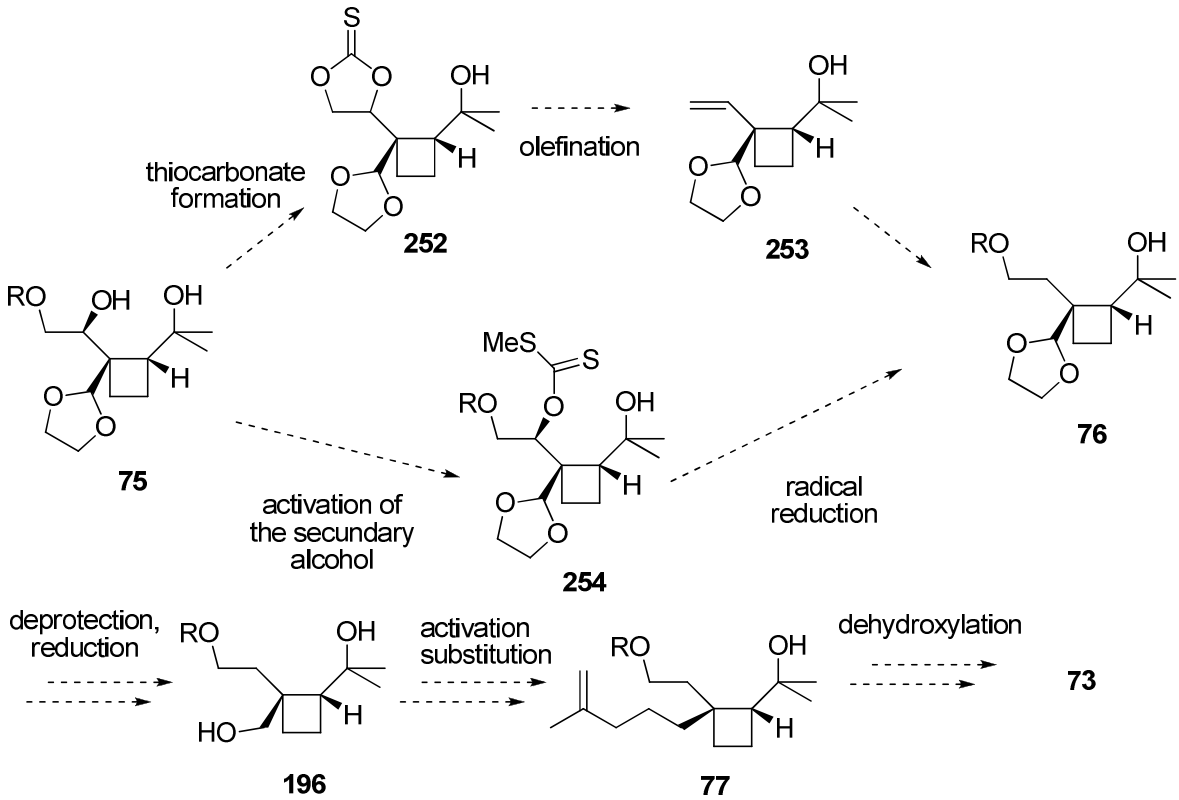
Scheme 113. Reaction of ditosylation on triol **250** by Martinelli *et al.* (2002).

The bis-tosylation of **242** was assayed under standard conditions, namely by treatment with TsCl and triethylamine in a mixture of CH_2Cl_2 and acetonitrile as the solvent and, after 5h at room temperature, the starting material remained unchanged. The addition

[138] Martinelli, M. J.; Vaidyanathan, R.; Pawlak, J. M.; Nayyar, N. K.; Dhokte, U. P.; Doecke, C. W.; Zollars, L. H. M.; Moher, E. D.; Khau, V. V.; Kosmrlj, B. *J. Am. Chem. Soc.* **2002**, *124*, 3578-3585.

of pyridine or DMAP to the reaction medium did not produce any change either. We believe that the lack of reactivity of tetrol **242** may be a consequence of a very favourable combination of intramolecular hydrogen bonding that disables the nucleophilic character of its hydroxyl groups. It was therefore not surprising that the treatment of **242** with acetone and catalytic HCl in the presence of anhydrous $CuSO_4$ and anhydrous Na_2SO_4 did not furnish the acetonide **244** either.

The impossibility of developing the sequences of Scheme 99, prompted us to postpone the introduction of the alkyl chain to a further step of the synthesis and to undertake the deoxygenation of the secondary alcohol as a previous endeavor (Scheme 114). We hoped that a change in the intramolecular hydrogen bonding scenario due to the lack of the secondary alcohol could facilitate the manipulation of our synthetic intermediates and hence the introduction of the terpenic chain. To effect the deoxygenation leading to **76**, two methodologies were considered: the Corey-Winter reaction through a cyclic thiocarbonate **252** and the Barton-McCombie radical reduction of an intermediate xanthate **254**. Both possibilities were investigated.

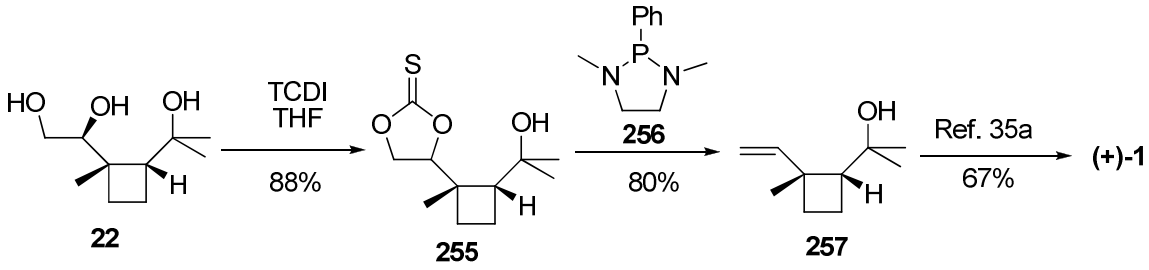


Scheme 114. Alternative synthetic design the pheromone of *Aspidiotus nerii* **73** through acetal **76**.

The Corey-Winter reaction is a methodology first described in 1963 to convert 1,2-diols into alkenes.[139] In 1982, Corey and Hopkins improved the reaction conditions, by using

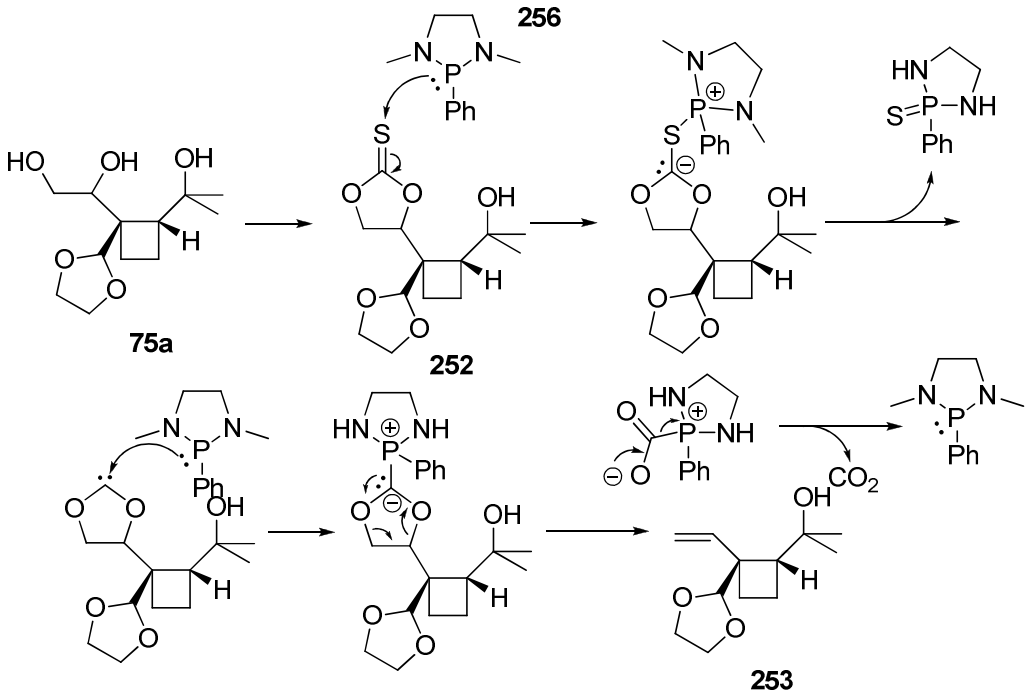
[139]Corey, E. J.; Winter, R. A. *J. Am. Chem. Soc.* **1963**, *85*, 2677-2678

1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidin instead of trialkylphosphite.[140] This reaction has been previously used by our group on compounds analogous to **75**, as a key step in the syntheses of (+)-grandisol, **1** and (-)-isolineatin, **28**, (Scheme 115).[5,141142] There, the olefinic intermediate **257** proved to be extremely volatile and the reaction had to be carried out without any solvent.



Scheme 115. Steps of the synthesis of (+)-grandisol, Font *et al.* (1996).

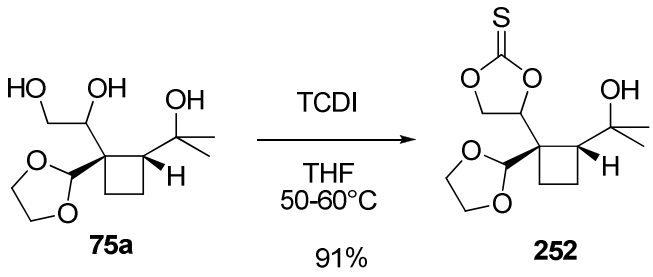
The mechanism accepted for this transformation implies the nucleophilic attack of the phosphine **256** to the sulphur atom of the thiocarbonate, leading to the formation of a carbene (Scheme 116). Then, a second molecule of **256** reacts with the carbene provoking an electronic rearrangement, which affords the carbon-carbon double bond.



Scheme 116. Mechanism of the Corey-Winter reaction with the Corey-Hopkins reagent applied to **75a**.

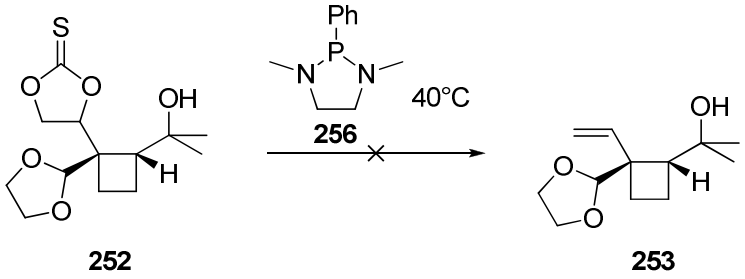
[140] Corey, E. J.; Hopkins, B. *Tetrahedron Lett.* **1982**, *23*, 1979-1982.
[141] Hoffmann, N.; Scharf, H.-D. *Liebigs Ann. Chem.* **1991**, 1273-1277.
[142] Perez, L.; Alibés, R.; de March, P.; Busque, F.; Figueredo, M.; Font, J. *J. Org. Chem.* **2013**, *78*, 4483-4489.

Treatment of triol **75a** with thiocarbonyldiimidazole (TCDI) in THF at 50-60℃ delivered thiocarbonate **252** in good yield (91%) (Scheme 117). The formation of thiocarbonate **252** was evidenced in its ^{13}C-NMR spectrum, by the signal at δ 162.8 corresponding to the C=S bond.



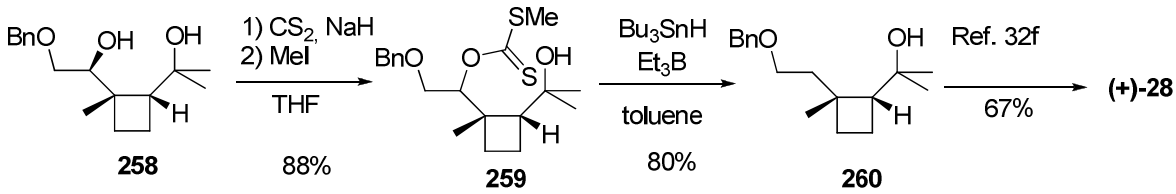
Scheme 117. Prepartion of thiocarbonate **252**.

The subsequent treatment of thiocarbonate **252** with diazaphospholidine **256** at 40℃ without any solvent (Scheme 118) consumed all the starting material. However, after purification of the crude reaction product by flash column chromatography, we were unable to isolate any product, a fact that we attributed to the extremely high volatility of **253**.



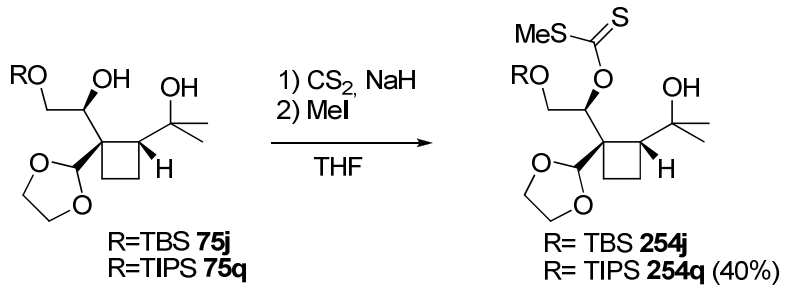
Scheme 118. Attempted preparation of alkene **253**.

In view of this difficulty, we focused on the alternative Barton-McCombie methodology. As a reference, in the synthesis of (+)-lineatin, **(+)-28**, previously developed by our group,[32f] the deoxygenation of the secondary alcohol of **258** had been accomplished in good yield (88%) through xanthate **259** (Scheme 119).



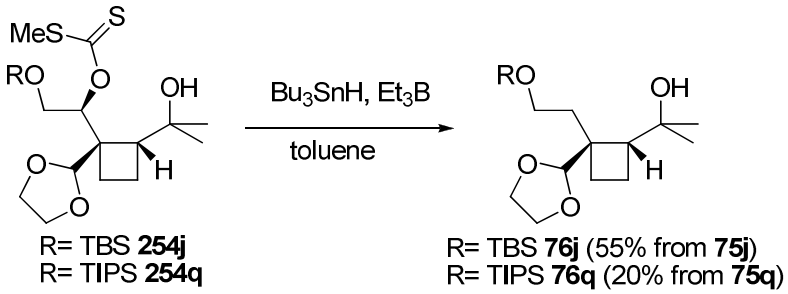
Scheme 119. Steps of the synthesis of (+)-lineatin, Alibés *et al.* (2008).

In a similar way, treatment of diol **75j** with carbon disulfide and sodium hydride in THF at room temperature and, then, with iodomethane furnished the desired xanthate **254j** in good yield (Scheme 120). For diol **75q**, bearing a TIPS protecting group, the yield was substantially lower (40%) and purification by column chromatography of the crude product was required before the next step.



Scheme 120. Preparation of xanthates **254j** and **254q**.

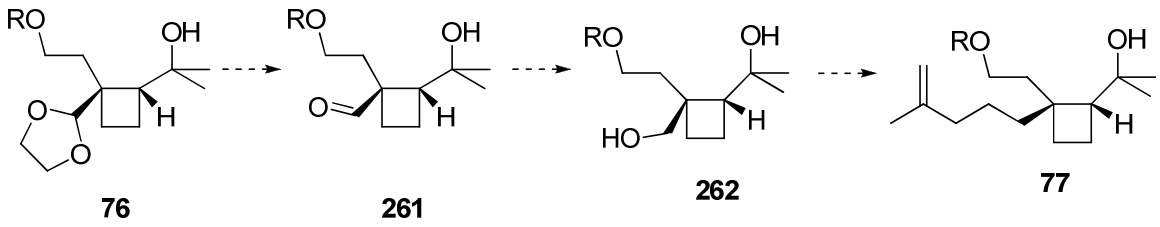
Following Okano's methodology[143] the thiocarbonyl derivatives **254** were treated with one equivalent of triethylborane and tributyltin hydride in toluene at room temperature for 3h (Scheme 121). These reactions delivered the expected alcohols **76**, although the yields were quite low. In previous investigations with similar compounds we observed that the generation of a radical species in a position contiguous to the strained ring may induce the fragmentation of the cyclobutane to deliver acyclic products. We speculated that the proximity of the acetal group may facilitate the cleavage of the cyclobutane and hence diminish the yield of the desired products. Moreover, we were not able to scale up the reaction maintaining the same degree of conversion and yields.



Scheme 121. Preparation of alcohols **76j** and **76q** by radical deoxygenation of the xanthates.

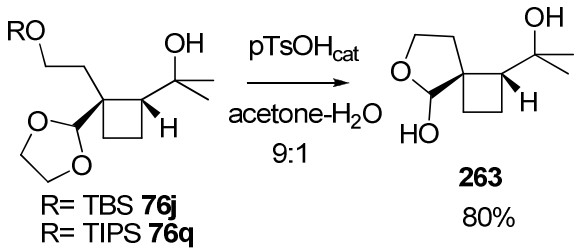
In any case, we decided to continue exploring the sequence according to the plan (Scheme 122), wherein the next step was hydrolysis of the acetal.

[143] Okano, K. ; Ebata, T. ; Koseki, K. ; Kawakami, H.; Matsumoto, K.; Matsushita, H. *Chem Pharm. Bull.* **1993**, *41*, 861-865.



Scheme 122. Synthetic plan from the acetal **76** to the immediate precursor of the pheromone, **77**.

The deprotection was attempted under different conditions. Firstly, treatment of **76j** and **76q** with a catalytic amount of *p*-toluenesulfonic acid in a mixture of acetone-water (9:1) at room temperature[144] showed very slow conversion. Therefore, after 2 h, a supplementary quantity of acid was added and, finally, the hemiacetal **263** was isolated as the sole product in 80% yield (Scheme 123). We were able to check that even under catalytic acidic conditions, the hemiacetal is the only product detected, meaning than the hydrolysis of the silyl ether is probably faster than that of the acetal.

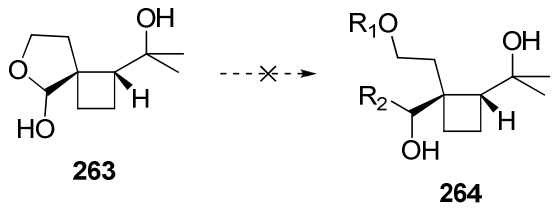


Scheme 123. Formation of hemiacetal **263** from silyl acetals **76j** and **76q**

Other methodologies were assayed, including treatment with pyridinium tosylate,[145] and Montmorillonite K10, a commercially available, acidic clay that has been extensively used in our laboratories for the hydrolysis of different kind of acetals, showing an excellent performance in most cases. However, in this case, after 24h of treatment, the starting material remained unchanged.

The hemiacetal **263** is a synthetic equivalent of the aldehyde **261** and could as well be used as the electrophilic partner for nucleophilic additions (Scheme 124). However, we anticipated that, after the additions of an organometallic nucleophile carrying the terpenic chain, [146] it would be troublesome to deoxygenate the secondary alcohol thus obtained.

[144] Paquette, L. A.; Hong, F.-T. *J. Org. Chem.* **2003**, *68*, 6905-6918.
[145] Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Tetrahedron* **2003**, *59*, 8571-8587.
[146] Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2345-2347.

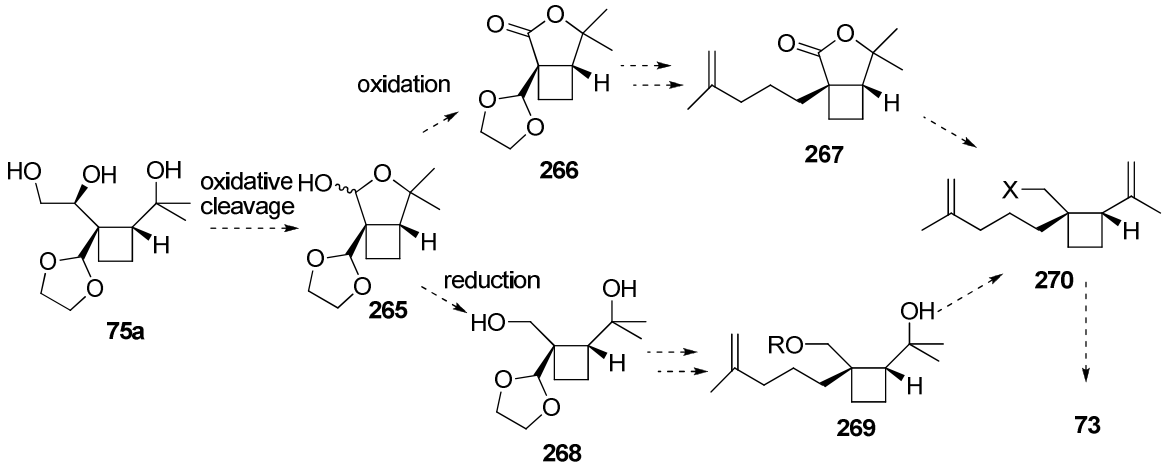


Scheme 124. Addition of a nucleophile to the hemiacetal **263**.

Consequently, a new possibility was investigated based on the cleavage of the vicinal diol in **75a** (Scheme 125). This new idea was inspired by the fact that many synthesis of grandisol were completed by a one carbon homologation.[147] Although, *a priori*, the removal and posterior reincorporation of one carbon atom at the same position is not a desirable synthetic maneuver, this additional carbon has been important in regard to the facial selectivity of the photocycloaddition leading to the formation of the cyclobutane, but now the higher density of functional groups in the synthetic intermediates seems to be detrimental compared to analogous reactions previously performed in related systems.

Again two possibilities were considered. The oxidative approach relied on the fact that the uncovering of the aldehyde in **266** and the forward nucleophilic addition of the terpenic chain should not interfere, in any case, with the lactone.

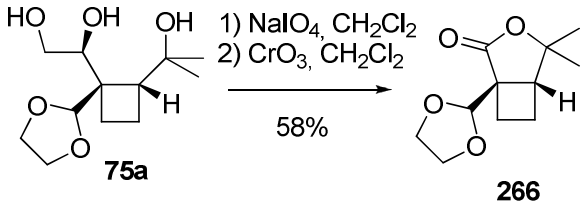
The reductive approach comes from the idea of forming diol **268**, which could be protected, and hence allow the elaboration of the acetal into the terpenic side chain. Alcohol **269** could be transformed after several step including one carbon homologation into the sexual pheromone **73**.



Scheme 125. New synthetic plan from triol **75a** based on cleavage of the vicinal diol.

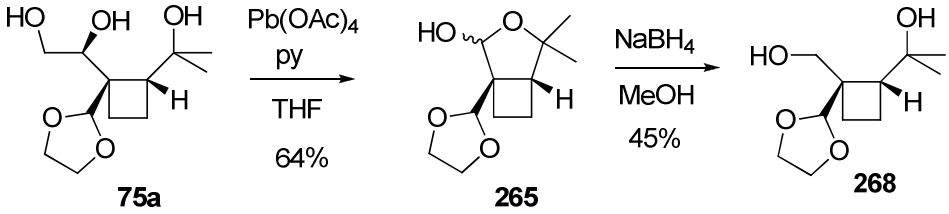
[147] (a) Clark, R. D. *Synth. Commun.* **1979**, *9*, 325-331. (b) Mori, K.;Fukamatsu, K. *Liebigs Ann. Chem.* **1992**, 489-493.

The oxidative cleavage of triol **75a** using CrO_3 furnished lactone **266** in a single step and 58% yield (Scheme 126).



Scheme 126. Preparation of lactone **266**.

In parallel, the oxidative cleavage of **75a** was carried out using $Pb(OAc)_4$ with pyridine in THF, leading to the lactol **265** in moderate 64% yield (Scheme 127). The reduction of the lactol with sodium borohydride in methanol afforded the expected diol **268** in 45% yield.

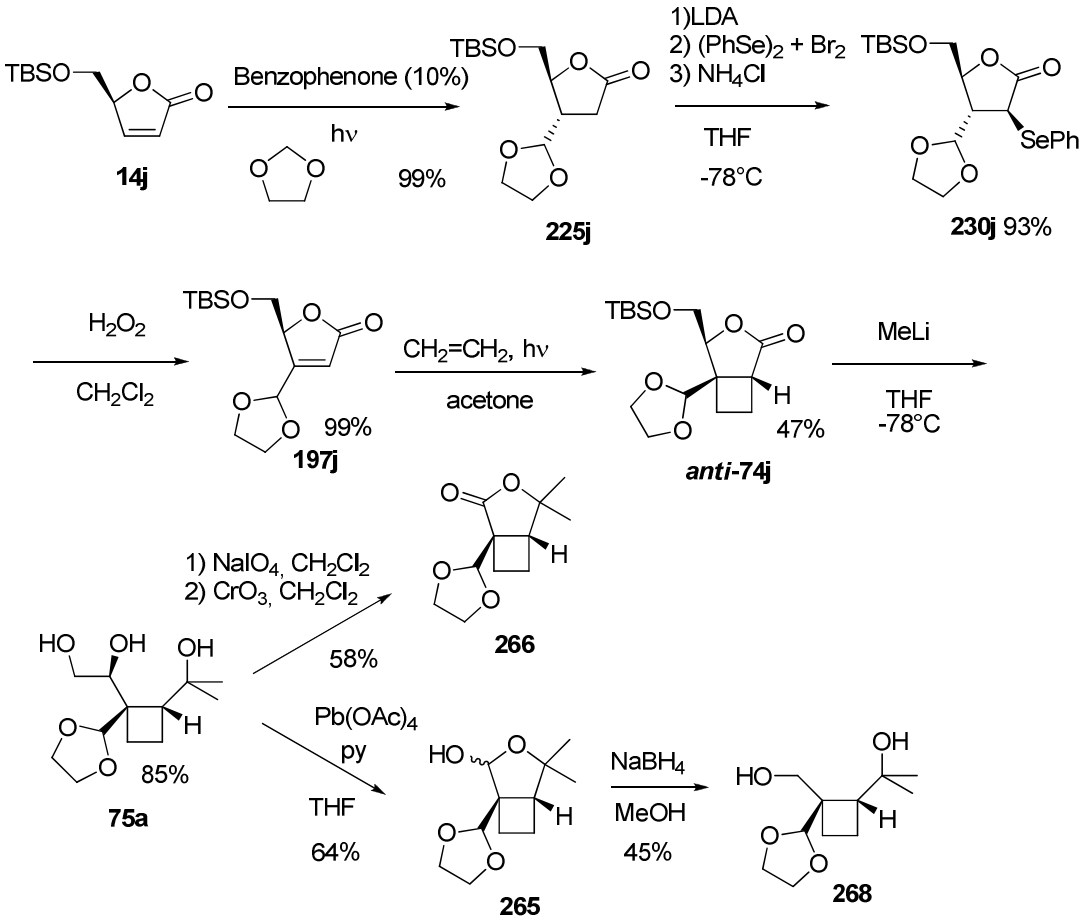


Scheme 127. Preparation of diol **268** from triol **75a**.

Due to time limitation, experiments to convert the new acetals **266** and **268** into further intermediates of the synthesis of the target pheromone were not attempted in the present thesis.

4.6. Conclusions

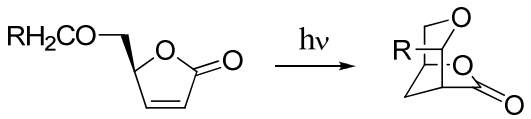
Despite the fact that the synthesis of the sexual pheromone of oleander scale was not accomplished, the preparation of lactone **266** and diol **268** was achieved. These compounds can be considered advanced intermediates, in which the introduction of the terpenic chain will probably be the most complicated task to complete (Scheme 128).



Scheme 128. Preparation of lactone **266** and diol **268**.

Chapter 5: General conclusions

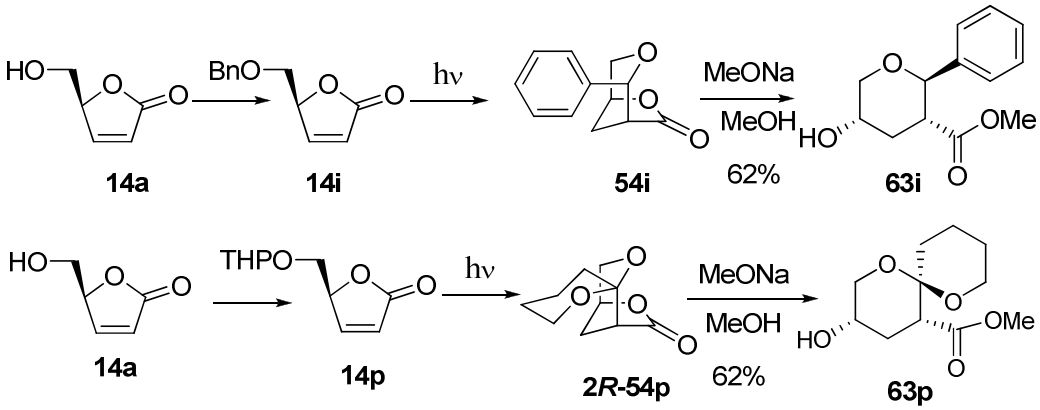
1. The photochemically induced intramolecular hydrogen abstraction of several 2(5*H*)-furanones was investigated. The effect of the filter, the solvent and the substituent of the furanone on the reaction was evaluated (Scheme 129). We can conclude that the intramolecular hydrogen abstraction is stereocontrolled and the best results were obtained in acetonitrile as solvent with a quartz filter.



14 **54**

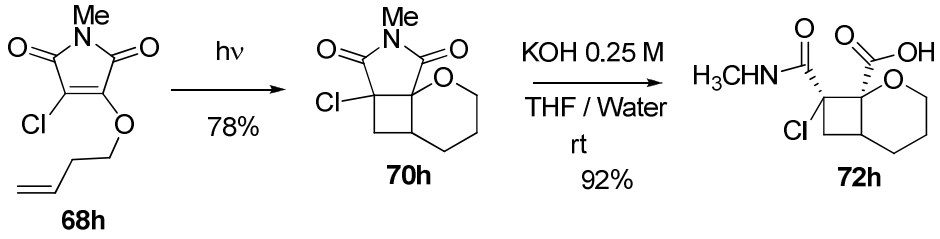
Scheme 129. Intramolecular photochemical reactivity of 2(5*H*)-furanones **14**.

The transesterification of bicycle **54** was effective to access polysubstituted tetrahydropyrans.The preparation of tetrahydropyrans **63i** and **63p** has shown that this methodology can provide a large variety of 3,5,6-trisubstituted tetrahydropyrans with a total control of the stereochemistry (Scheme 130).



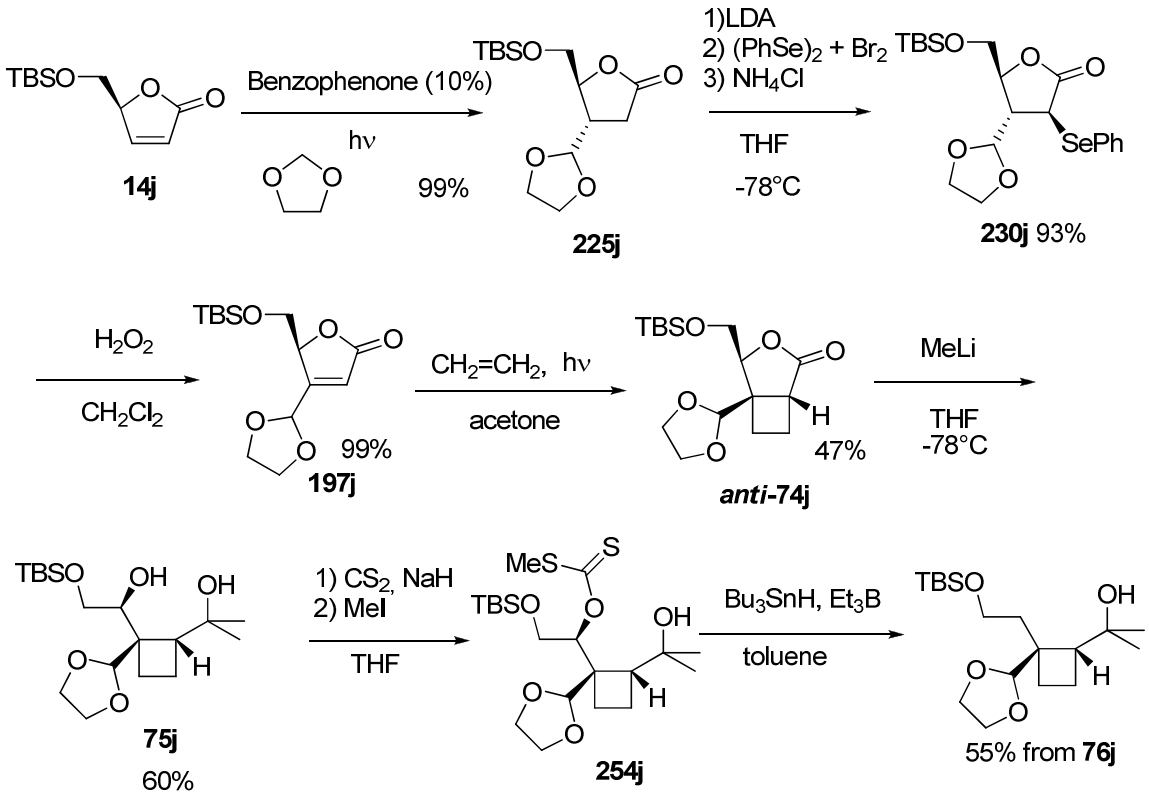
Scheme 130. Preparation of 3,5,6-trisubstituted tetrahydropyrans **63i** and **63p**.

2. The synthesis of cyclobutane and cyclobutene tricyclic compounds through an intramolecular [2+2] photocycloaddition process to afford bicyclic carboxylic acids has been investigated (Scheme 131). The preparation of the carboxylic acid derivative **72h** in 3 steps (28% yield) proved that this methodology could be applied in a synthetic strategy devised to prepare such compounds.



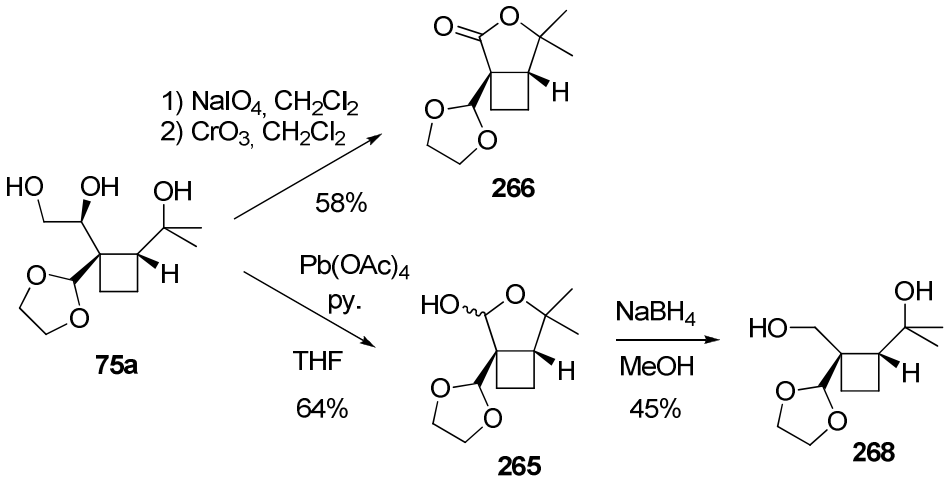
Scheme 131. Preparation of bicyclic carboxylic acid derivative **72h**.

3. Synthetic studies toward the sexual pheromone of *Aspidiotus nerii* **73**, where the key step is the [2+2] photochemical reaction of furanone **197a** to ethylene have been performed. From furanone **14j**, we prepared the advanced intermediate **76j** (Scheme 132), but the elaboration of the west-side chain met with failure and it was necessary to introduce tactical modifications.



Scheme 132. Preparation of the advanced intermediate **76j.**

We have also prepared compound **266** in 6 steps and 25% yield from **14j** and compound **268** in 7 steps and 10% yield from **14j** (Scheme 133). These acetals are potential intermediates toward the synthesis of the sexual pheromone of *Aspidiotus nerii*.



Scheme 133. Preparation of potential advanced intermediates toward the synthesis of the sexual pheromone of *Aspidiotus nerii*.

Chapter 6: Experimental Section

General Methods

Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying reagents. All reactions were performed avoiding moisture by standard procedures and under nitrogen atmosphere unless otherwise mentioned.

All the reactions were monitored by analytical thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated aluminium plates (0.25 thickness).

Column chromatography was performed using silicagel 60 Å, particule size 35-70 µm. Solutions were concentrated using an evaporator at 15-20 Torr.

Melting points were determined on a Kofler Reichert hotbanche and are uncorrected.

^{1}H-NMR at 250, 360, 400 or 500 MHz, ^{13}C-NMR at 62.9, 90.6, 100.6 or 125 MHz, were recorded at the *Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona*. NMR signals were assigned with help of DEPT, COSY, HSQC, HMBC, n.O.e. differential, NOESY experiments and TOCSY experiments.

Infrared spectra were recorded on a Sapphire-ATR Spectrophotometer. Peaks are reported in cm^{-1}.

High resolution mass spectra (HRMS) were recorded at the *Servei d'Anàlisi Química de la Universitat Autònoma de Barcelona* in a Brucker micrOTOFQ spectrometer using ESIMS (QTOF).

Optical rotations values were measured on a Propol Automatisches Dr. Kermchen polarimetre at 20 $\pm$2 ºC and through a 0.05 dm optical path length.

The photochemical reactions were conducted with a 125 W high pressure mercury lamp (Cathodeon HPK125) (Figures 47 and 48). The photochemical reactor used is equipped with a quartz or pyrex refrigeration jacket (Figure 47).

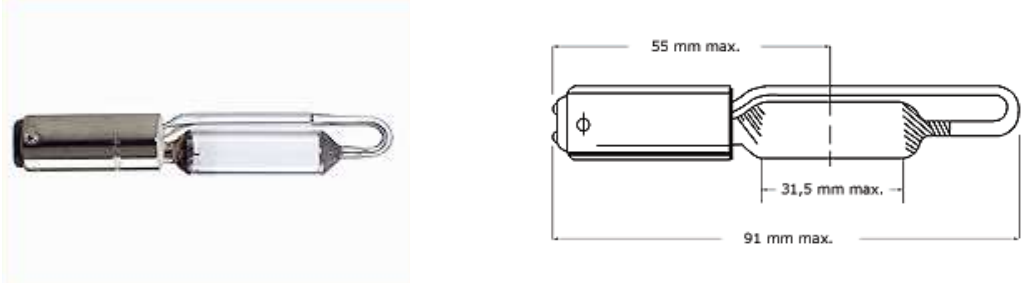


Figure 47.125 W High pressure mercury lamp.

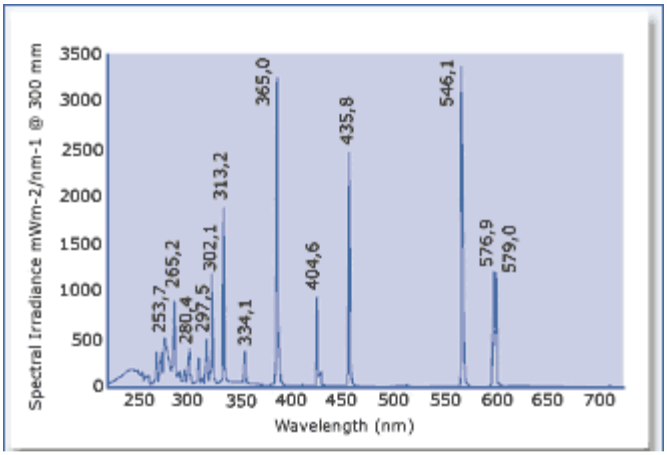


Figure 48. Spectral irradiance of the high pressure mercury lamp used in the present work.

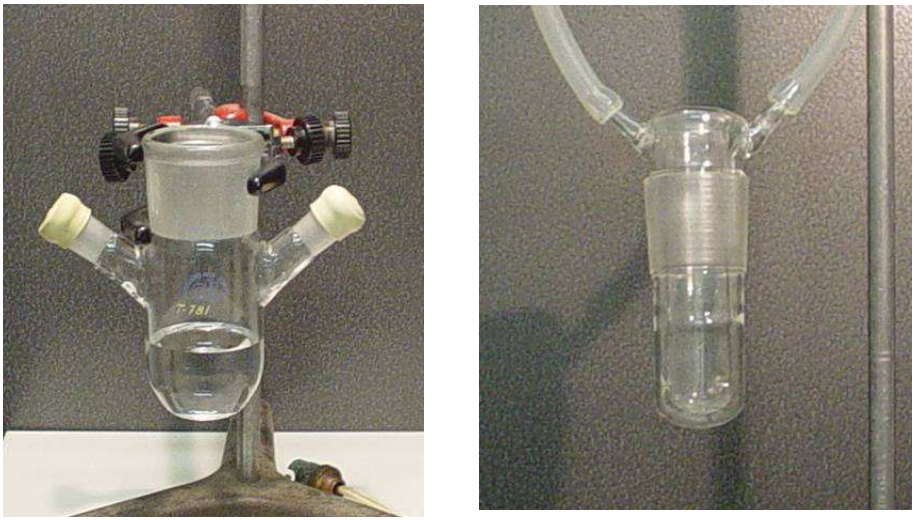
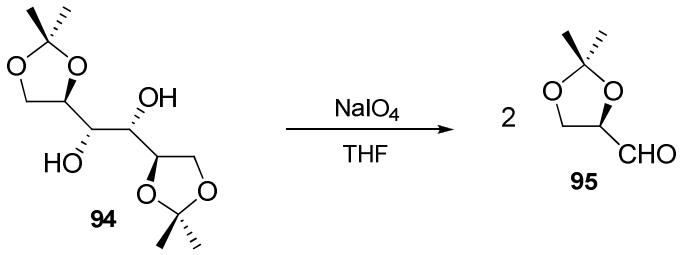


Figure 49. Photochemical reactor and refrigeration jacket.

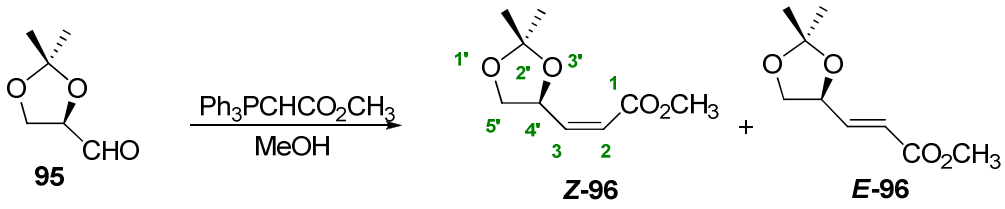
6.1. Experimental part of chapter 2:

2,3-*O*-isopropylidene-D-gliceraldehyde (95)



To a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol, **94**, (12.00 g, 45.7 mmol) in THF (100 mL), a suspension of sodium periodate (10.80 g, 50.5 mmol) in a mixture of THF (37 mL) and H_2O (17 mL) was slowly added. The resulting white suspension was stirred at room temperature for 2 h. Then, diethyl ether (170 mL) was added and the mixture was stirred for 15 min prior to filtration of a white solid. The solvent was removed under reduced pressure and extracted with CH_2Cl_2 (3x25 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was carefully removed under reduced pressure to avoid the loss of aldehyde. Thus, colourless oil (10.80 g, 83.0 mmol, 90% yield) was obtained and used in the next reaction without further purification. Variable amount of hydrated aldehyde was observed by NMR and IR.

Ethyl (2*Z*)-3-[(4*S*)-(2',2'-dimethyl-1',3'-dioxolan-4'-yl)]-2-propenoate (*Z*-96) and its isomer (*E*-96)



To an ice-cooled solution of aldehyde, **95**, (10.60 g, 81.4 mmol) in MeOH (75 mL), methoxycarbonylmethylene(triphenyl)phosphorane (27.21 g, 81.4 mmol) was carefully added in small portions. The mixture was allowed to warm to rt and stirred for 2h. Then, the solvent was removed under reduced pressure and the resulting white solid was extracted with hot hexane. The solution was cooled to 0ºC and triphenyl phosphine oxide was filtered. Evaporation of the solvent to dryness and purification by column chromatography (hexane-diethyl ether, 3:1) afforded the (*Z*)-isomer **Z-96** (10.72 g, 57.6

mmol, 71% yield) as an oil and the (*E*)-isomer ***E*-96** (2.23 g, 12.0 mmol, 15% yield) as an oil.

Spectroscopic data of ***Z*-96**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 6.35 (dd, $J_{3,2}$ = 11.7 Hz, $J_{3,4'}$ = 6.9 Hz, 1H, H-3), 5.84 (dd, $J_{2,3}$ = 11.7 Hz, $J_{2,4'}$ = 1.5 Hz, 1H, H-2), 5.48 (dddd, $J_{4',5'}$ = 6.9 Hz, $J_{4',5'}$ = 6.9 Hz, $J_{4',3}$ = 6.9 Hz, $J_{4',2}$ = 1.5 Hz, 1H, H-4'), 4.36 (dd, J_{gem} = 8.4 Hz, $J_{5',4'}$ = 6.9 Hz, 1H, H-5'), 3.70 (s, 3H, OCH_3), 3.60 (dd, J_{gem} = 8.4 Hz, $J_{5',4'}$=6.9 Hz, 1H, H-5'), 1.44 (s, 3H, CH_3), 1.39 (s, 3H, CH_3).

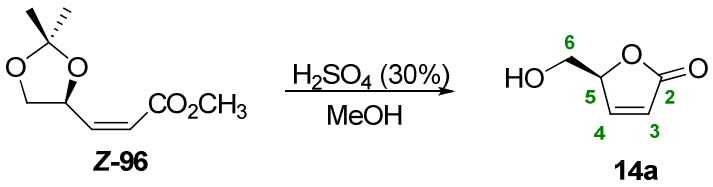
IR (ATR) 2989, 2952, 2875, 1723, 1646, 1440, 1208, 1155.

Spectroscopic data of ***E*-96**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 6.87 (dd, $J_{3,2}$ = 15.9 Hz, $J_{3,4'}$ = 5.3 Hz, 1H, H-3), 6.09 (dd, $J_{2,3}$ = 15.9 Hz, $J_{2,4'}$ = 1.5 Hz, 1H, H-2), 4.65 (dddd, $J_{4',5'}$ = 7.0 Hz, $J_{4',5'}$ = 6.6 Hz, $J_{4',3}$ = 5.3 Hz, $J_{4',2}$ = 1.5 Hz, 1H, H-4'), 4.16 (dd, J_{gem} = 8.5 Hz, $J_{5',4'}$ = 6.6 Hz, 1H, H-5'), 3.73 (s, 3H, OCH_3), 3.66 (dd, J_{gem} = 8.5 Hz, $J_{5',4}$ = 7.0 Hz, 1H, H-5'), 1.43 (s, 3H, CH_3), 1.40 (s, 3H, CH_3).

IR (ATR) 2989, 2950, 2880, 1727, 1663, 1438, 1264, 1217, 1125 cm^{-1}.

(*S*)-5-Hydroxymethyl-2(5*H*)-furanone (14a)



***Z*-96** **14a**

To a solution of ***Z*-96** (10.72 g, 57.6 mmol) in MeOH (30 mL) was added a 30% aqueous solution of H_2SO_4 (260 µl). The reaction mixture was stirred for 3 h at room temperature and the solvent was removed under reduced pressure. Purification of the crude by column chromatography (EtOAc) gave the lactone **14a** (6.23 g, 54.6 mmol, 95% yield) as a white solid.

Physical and spectroscopic data of **14a**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.46 (dd, $J_{4,3}$ = 5.8 Hz, $J_{4,5}$ = 1.5 Hz, 1H, H-4), 6.19 (dd, $J_{3,4}$ = 5.8 Hz, $J_{3,5}$ = 2.2 Hz, 1H, H-3), 5.13 (dddd, $J_{5,6}$ = 5.1 Hz, $J_{5,6}$=3.6 Hz, $J_{5,3}$=2.2 Hz, $J_{5,4}$ = 1.5 Hz, 1H, H-5), 3.98 (ddd, J_{gem} = 12.4 Hz, $J_{6,OH}$ = 6.9 Hz, $J_{6,5}$ = 3.6 Hz, 1H, H-6), 3.77 (ddd, J_{gem} = 12.4 Hz, $J_{6,OH}$ = 6.9 Hz, $J_{6,5}$ = 5.1 Hz, 1H, H-6), 2.13 (dd, $J_{OH,6}$ = 6.9 Hz, $J_{OH,6}$ = 6.9 Hz, 1H, OH).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.0 (C-2), 153.5 (C-4), 123.0 (C-3), 84.0 (C-5), 62.4 (C-6).

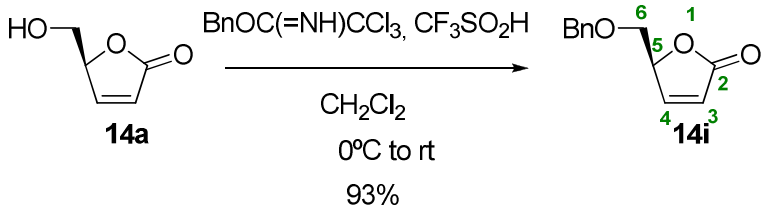
m.p. 40-41 ºC (pentane-EtOAc).

$[\alpha]_D$ -151.9 (*c* 2.4, H_2O).

IR (KBr) 3680-3200, 3107, 2930, 2880, 1743, 1602, 1170 cm^{-1}.

COSY, **HSQC**, **HMBC** and **NOESY** recorded.

(5*S*)-5-(Benzoyloxymethyl)-2(5*H*)-furanone (14i)



To a solution of (5*S*)-hydroxymethyl-2(5*H)*-furanone, **14a**, (335 mg, 2.94 mmol) in dry CH_2Cl_2 (26 mL) at 0℃ under nitrogen was added benzyltric hloroacetimidate (600µL, 3.23 mmol) and trifluoromethane sulfonic acid (26 µL, 0.3 mmol). The resulting mixture was stirred for 4h. After this period, the reaction mixture was washed with a solution of HCl (1M, 5 mL), water (5 mL) and brine (5 mL) and the organic layer was separated. The combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent followed by column chromatorgraphy (hexanes-Et_2O, 1,5:1) afforded the title compound **14i** (557 mg, 2.73 mmol, 93% yield) as a colorless solid.

Physical and spectroscopic data of **14i**:

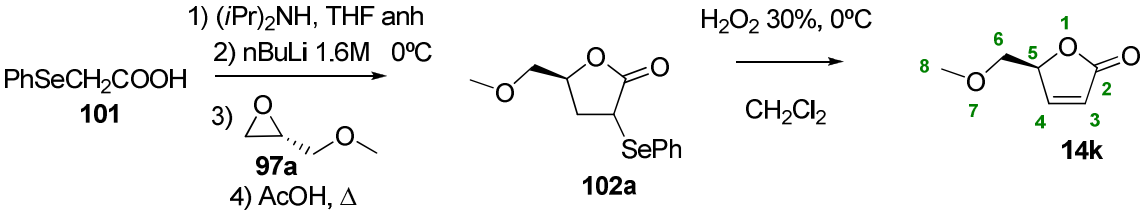
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42 (dd, $J_{4,3}$ = 5.8 Hz, $J_{4,5}$ = 1.6 Hz, 1H, H-4), 7.27 (s, 5H, C_6H_5), 6.07 (dd, $J_{3,4}$ = 5.8 Hz, $J_{3,5}$ = 1.7 Hz, 1H, H-3), 5.07 (m, 1H, H-5), 4.49 (s, 2H, H-7), 3.62 (d, $J_{6.5}$ = 5.3 Hz, 2H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 (C-2), 153.9 (C-4), 137.3 (C-3), 128.5 (C-Ph), 127.9 (C-Ph), 127.8 (C-Ph), 127.7 (C-Ph), 122.5 (C-Ph), 82.2 (C-5), 73.7 (C-6), 69.4 (C-1').

$[\alpha]_D$ -10.7 (*c* 1.6, EtOH).

IR (neat) 3120, 3050, 2920, 2890, 1750, 1600, 1500, 1460, 1270, 1160, 1130, cm^{-1}.

(*S*)-5-(methoxymethyl)furan-2(5*H*)-one (14k)



To a solution of 2-(phenylseleno)acetic acid (600 mg, 2.8 mmol) in THF (8 mL) at 0ºC, was added a solution of di-*iso*-propylamine (0.8 mL, 5.9 mmol) and *n*-butyllithium (3.7 mL, 5.9 mmol) in THF (16 mL) under nitrogen. After a couple of minutes, the epoxide **97a** (250 µl, 2.8 mmol) was added and the reaction mixture was allowed to stir for 4h at 0ºC. After this period, acetic acid glacial was added dropwise until the pH was acid and the reaction mixture was heated at the reflux temperature for 16h. Then, 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 washed with diethyl ether (3x10 mL). The combined organic extracts were concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL) and then hydrogen peroxide 30% (3 mL, 26.4 mmol) was added dropwise at 0ºC. After 2h, the reaction mixture was diluted with water (15 mL), the organic layer were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue which was purified by column chromatography (hexanes-EtOAc, 4:1) to furnish compound **14k** (287 mg, 2.24 mmol, 80% yield).

Physical and spectroscopic data of **14k**:

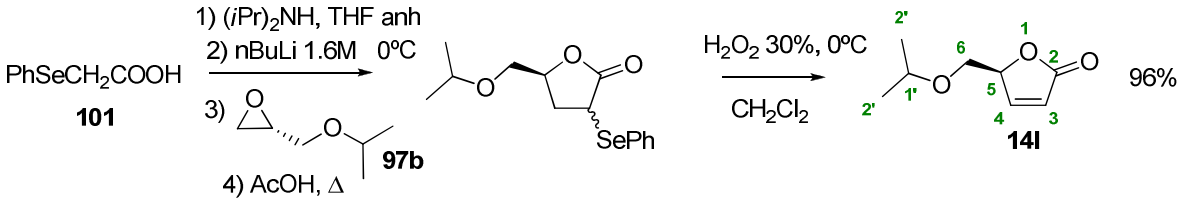
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47 (dd, $J_{4,3}$ = 5.8 Hz, $J_{4,5}$ = 1.6 Hz, 1H, H-4), 6.21 (dd, $J_{4,5}$ = 5.8 Hz, $J_{4,3}$ = 2.1 Hz, 1H, H-3), 5.19 (tdd, $J_{5,6}$ = 5.0 Hz, $J_{5,3}$ = 2.1 Hz, $J_{5,4}$ = 1.6 Hz, 1H, H-5), 3.59 (d, $J_{5,6}$ = 5.0 Hz, 2H, H-6), 3.38 (s, 3H, H-8).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.8 (C-2), 153.9 (C-4), 122.5 (C-3), 82.3 (C-5), 71.9 (C-6), 59.6 (C-8).

$[\alpha]_D$ -10.9 (*c* 0.7, $CDCl_3$).

IR (ATR) 2923, 1726, 1459, 1377, 1272, 1122, 1072 cm^{-1}.

(*S*)-5-(*iso*-Propoxymethyl)furan-2(5*H*)-one (14l).



To a solution of 2-(phenylseleno)acetic acid (1.97 g, 9.1 mmol) in THF (14 mL) at 0ºC, was added a solution of di-*iso*-propylamine (2.7 mL, 19.3 mmol) and *n*-butyllithium (12 mL, 19.3 mmol) in THF (32 mL) under nitrogen. After a couple of minutes, the commercially available epoxide **97b** (0.9 ml, 7.0 mmol) was added and the reaction mixture was allowed to stir for 4h at 0ºC. After this period, acetic acid glacial was added dropwise until pH was acid and the reaction mixture was warmed at reflux temperature during 16h. Then, the reaction was cooled and neutralized by adding a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, and the remaining aqueous phase was washed with diethyl ether (3x10 mL). The combined organic extracts were concentrated under reduced pressure to give a residue which was dissolved in CH_2Cl_2 (50 mL) and then, hydrogen peroxide 30% (4 mL, 35.3 mmol) was added dropwise at 0ºC. After 2h, the reaction mixture was diluted with water (40 mL) and the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3x10 mL). The combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue which was purified by column chromatography (hexanes-EtOAc, 4:1) to furnish compound **14l** (1.05 g, 8.7 mmol, 96% yield) as colorless oil.

Physical and spectroscopic data of **14l**:

^{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, $J_{5,6}$ = 5.5 Hz, $J_{5,4}$ = 1.8 Hz, 1H, H-5), 3.75 (dd, $J_{6a,6b}$ = 10.3 Hz, $J_{6a,5}$ = 5.5 Hz, 1H, H-6), 3.67 – 3.55 (m, 2H, H-1' and H-6b), 1.15 (d, $J_{2',1'}$ = 6.4 Hz, 3H, H-2'), 1.13 (d, $J_{2',1'}$= 6.4 Hz, 3H, H-2').

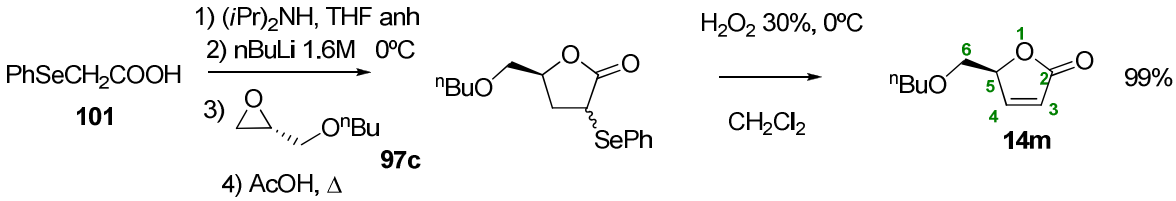
^{13}C NMR (90 MHz) ($CDCl_3$) δ 173.0 (C-2), 154.5 (C-4), 122.5 (C-3), 82.4 (C-5), 73.1 (C-6), 68.0 (C-1), 22.0 (C-2'), 21.9 (C-2').

HRMS *m/z* (ESI-TOF) $C_8H_{12}NaO_3$: calcd for $[M+Na]^+$ 179.0684, found 179.0680.

$[\alpha]_D$ -31 (*c* 0.7, $CHCl_3$).

IR (ATR) 2973, 1753, 1094, 632 cm^{-1}.

(*S*)-5-(*n*-Butyloxymethyl)furan-2(5*H*)-one (14m)



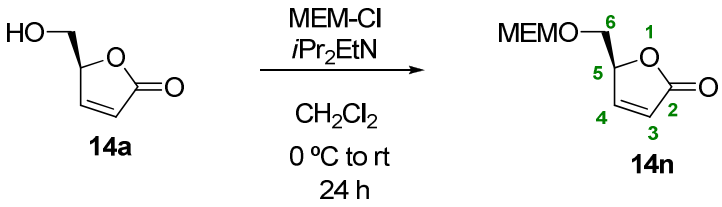
To a solution of 2-(phenylselanyl)acetic acid (1.97 g, 9.1 mmol) in THF (14 mL) at 0ºC, was added a solution of LDA in THF (32 mL, 19.3 mmol) under nitrogen. After a couple of minutes, the epoxide **97c** (1 mL, 7.0 mmol) was added and the reaction mixture was allowed to stir for 4h at 0ºC. After this period, acetic acid glacial was added dropwise until pH was acid and the reaction mixture was heated at the reflux temperature during 16h. Then, the reaction mixture was cooled and neutralized by adding a saturated aqueous solution of sodium bicarbonate (20 mL). The organic layer was separated, and the aqueous phase was washed with diethyl ether (3x10 mL). The combined organic extracts were concentrated under reduced pressure, to deliver a residue which was dissolved in CH_2Cl_2 (50 mL) and hydrogen peroxide 30% (4 mL, 35.3 mmol) was added dropwise at 0ºC. After 2h, the reaction mixture was diluted with water (40 mL) and phases were separated and the aqueous layer was extracted with $CHCl_2$ (3x20 mL). The combined organic extracts were dried over sodium sulfate. Evaporation of the solvent gave a residue which was purified by column chromatography (hexanes-EtOAc, 4:1) to furnish compound **14m** (1.18 g, 99% yield) as a yellow oil.

Spectroscopic data of **14m**:

^{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, $J_{6a,5}$ = 5.3 Hz, 1H, H-6a), 3.57 (dd, J_{gem} = 10.6 Hz, $J_{6b,5}$ = 5.6 Hz, 1H, H-6b), 3.47-3.40 (m, 2H, H-1'), 1.51-1.46 (m, 2H, H-2'), 1.38-1.16 (m, 2H, H-3'), 0.84 (t, $J_{4',3'}$ = 7.2 Hz, 3H, H-4').

IR (ATR) 1759, 1602, 1161, 1205, 1101 cm^{-1}.

(*S*)-5-(((2-methoxyethoxy)methoxy)methyl)-2(5*H*)-furanone (14n).



To a solution of (5*S*)-hydroxymethyl-2(5*H)*-furanone, **14a**, (438 mg, 3.71 mmol) in dry CH_2Cl_2 (5mL) at 0ºC, di-*iso*-propylethylamine (970 µL, 5.55 mmol) was added dropwise. The reaction mixture was cooled to 0ºC and 1-(chloromethoxy)-2-methoxyethane was added (636 µL, 5.57mmol). After 24 h, the reaction mixture was dissolved in CH_2Cl_2 (10mL) and washed with a solution of aqueous hydrochloric acid (5%) (2x5 mL), a solution aqueous saturated of bicarbonate (2x5 mL) and finally a solution aqueous saturated of sodium chloride (2x5 mL). The layers were separated and the combined organic extracts were dried over sodium sulfate. Evaporation of the solvent gave a residue which was purified by column chromatography (hexanes-EtOAc, 2:1) to furnish compound **14n** (647 mg, 82% yield) as a colorless oil.

Physical and spectroscopic data of **14n**:

^{1}H 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-8), 3.78 (dd, J_{gem} = 11.0 Hz, $J_{6b,5}$ = 4.9 Hz, 1H, H-6b), 3.74 (dd, J_{gem} = 11.0 Hz, $J_{6a,5}$ = 5.5 Hz, 1H, H-6a), 3.63 (m, 2H,H-10), 3.49 (m, 2H,H-11), 3.32 (s, 3H, H-13).

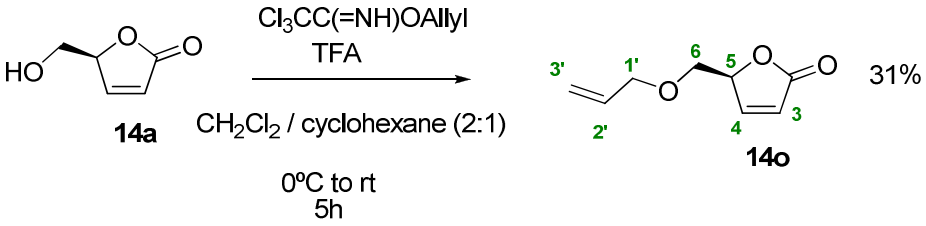
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6 (C-2), 153.0 (C-4), 122.6 (C-3), 95.6 (C-8), 81.9 (C-5), 71.5 (C-6), 67.0 (C-10), 66.9 (C-11), 58.9 (C-13).

MS (*m*/*z*) 157 (M^+-45,1), 127 (15), 98 (14), 97 (42), 89 (74), 69 (20), 59 (100), 58 (14), 45 (59).

[α]$_D$ -91.7 (*c* 2.73, $CHCl_3$).

IR (ATR) 3093, 2927, 2891, 1756, 1602, 1454, 1164, 1097, 1057, 1033 cm^{-1}.

(*S*)-5-(Allyloxymethyl)furan-2(5*H*)-one (14o)



Method A:

To a solution of (5*S*)-hydroxymethyl-2-5*H*-furanone, **14a**, (500 mg, 4.38 mmol) in dry dichloromethane (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 0ºC. After 2h of stirring at 0ºC and 3h at rt, the reaction was quenched by addition of a sodium bicarbonate solution (30 mL) and water (20 mL), dried with $MgSO_4$ and concentrated under vacuum. The resulting oil was purified by column chromatography (hexanes-EtOAc, 2:1) to give (*S*)-5-(allyloxymethyl)-2(5*H*)-furanone, **14o**, (209 mg, 1.36 mmol, 31 % yield) as a yellow oil.

Method B:

To a solution of 2-(phenylseleno)acetic acid (2.5 g, 11.6 mmol) in THF (20 mL) at 0ºC, was added a solution of di-*iso*-propylamine (3.4 mL, 24.5 mmol) and *n*-butyllithium (15.3 mL, 24.5 mmol) in THF (35 mL) under nitrogen. After a couple of minutes, the epoxide (1.05 mL, 8.9 mmol) was added and the reaction mixture was allowed to stir for 4h at 0ºC. After this period, acetic acid glacial was added dropwise until the pH was acid, the reaction mixture was heated at the reflux temperature for 16h. Then, 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 washed with diethyl ether (3x15 mL). The combined organic extracts were concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (20 mL) and hydrogen peroxide 30% (3 mL, 26.4 mmol) was added dropwise at 0ºC. After 2h, the reaction mixture was diluted with water (15 mL), the organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3x15 mL). The combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue which was purified by column chromatography (hexanes-EtOAc, 4:1) to furnish compound **14o** (1.16 g, 9.86 mmol, 85% yield) as a yellow oil.

Physical and spectroscopic data of **14o**:

^{1}H 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-2'), 5.31 (m, 3H, H-3', H-5), 4.05 (d, $J_{1',2'}$ = 5.7 Hz, 2H, H-1'), 3.70 (dd, J_{gem} = 10.5 Hz, $J_{6a,5}$ = 5.3 Hz, 1H, H-6a), 3.64 (dd, J_{gem} = 10.5 Hz, $J_{6b,5}$ = 5.1 Hz, 1H, H-6b).

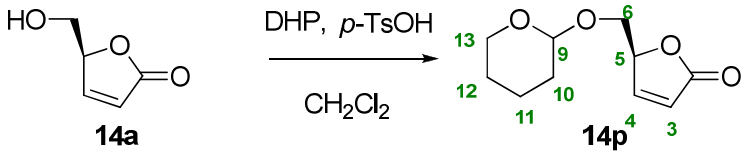
^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.9 (C-2), 154.1 (C-4), 133.9 (C-9), 122.7 (C-3), 117.9 (C-10), 82.3 (C-5), 72.8 (C-8), 69.6 (C-6).

HRMS *m/z* (ESI-TOF) ($C_8H_{10}O_3$): calcd for $[M+Na]^+$ 177.0528, found 177.0522.

$[\alpha]_D$ -71.7 (*c* 1.0, $CHCl_3$).

IR (ATR) 1745, 1261, 1167, 1086, 632 cm^{-1}.

(*S*)-5-((Tetrahydro-*2H*-pyran-2-yloxy)methyl)-2(5*H*)-furanone (14p)



14a **14p**

To a solution of (5*S*)-hydroxymethyl-2-5*H*-furanone, **14a**, (347 mg, 3.04 mmol) in CH_2Cl_2 (35 mL) at room temperature were added dihydropyran (294 µL, 3.21 mmol) and *p*-tolunesulfonic acid (34 mg, 0.17 mmol). The resulting mixture was stirred for 21h. After this period, the reaction was quenched with the addition of saturated sodium bicarbonate solution (15 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (3x5 mL). The combined organic extracts were dried over anhydrous sodium sulfate. Evaporation of the solvent followed by purification by column chromatography (hexanes-EtOAc, 3:1) afforded a mixture (1:1) of compound **14p** (537 mg, 80% yield) as a colorless oil.

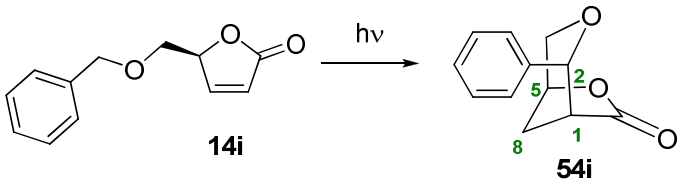
Spectroscopic data of **14p**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.47 (dd, $J_{4,3}$ = 1.1 Hz 1H, H-4), 6.09 (dd, $J_{3,4}$ = 5.9 Hz, 1H, H-3), 5.20 (m, 1H, H-5), 4.62 (dt, *J* = 6.8 Hz, *J* = 3.6 Hz, 1H, H-9), 3.94 - 3.87 (m, 1H, H-6a), 3.85 – 3.74 (m, 1H, H-11a), 3.66 - 3.60 (m, 1H, H-6b), 3.55 – 3.45 (m, 1H, H-11b), 1.90 – 1.40 (m, 6H, H-12, H-13, H-14).

^{13}C NMR (91 MHz, $CDCl_3$) δ 172.9 (C-2), 154.1 (C-4), 122.5 (C-3), 98.9 (C-9), 82.0 (C-5), 66.6 (C-7), 62.4 (C-11), 30.2 (C-14), 25.2 (C-12), 19.0 (C-13).

IR (ATR) 3070, 1240, 1753, 1618, 1154, 832 cm^{-1}.

(1*R*,2*R*,5*S*)-2-Phenyl-3,6-dioxabicyclo[3.2.1]octan-7-one (54i)



A solution of (*S*)-5-(benzyloxymethyl)-2(5*H)*-furanone **14i** (98 mg, 0.49 mmol) in diethyl ether (75 ml) was irradiated at -15ºC for 15 min. After total conversion, the solvent was evaporated and the residue was purified by column chromatography (hexanes-Et_2O, 3:1) to give compound **54i** (76 mg, 0.38 mmol, 78% yield) as a colorless oil.

Physical and spectroscopic data of **54i**:

^{1}H NMR (400 MHz, C_6D_6) δ 7.10 (m, 5H, C_6H_5), 5.30 (d, $J_{4,5}$ = 2.1 Hz, 1H, H-4), 3.81 (ddd, $J_{1,8b}$ = 5.9 Hz, $J_{1,2b}$ = $J_{1,2b}$ = 2.1 Hz, 1H, H-1), 3.61 (ddd, J_{gem} = 11.9 Hz, $J_{2a,8b}$ = 2.4 Hz, $J_{2a,1}$ = 2.1 Hz, 1H, H-2a), 3.20 (dd, J_{gem} = 11.9 Hz, $J_{2b,1}$ = 2.1 Hz, 1H, H-2b), 2.74 (ddd, $J_{5,8b}$ = 5.9 Hz, $J_{5,4}$ = 2.1 Hz, $J_{5,8a}$ = 1.2 Hz, 1H, H-5), 1.56 (dt, J_{gem} = 11.7 Hz, $J_{8b,5}$ = $J_{8b,1}$ = 5.9 Hz, 1H, H-8b), 1.36 (dd, J_{gem} =11.7 Hz, $J_{8a,5}$ =1.2 Hz, 1H, H-8a).

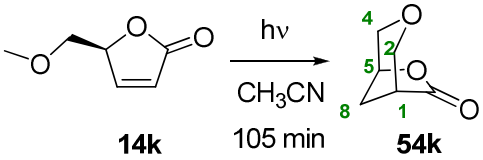
^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.9 (Ph), 129.7 (CH, Ph), 128.9 (Ph), 128.5 (Ph), 127.7 (Ph), 125.5 (Ph), 76.5 (C-4), 74.2 (C-1), 64.2 (C-2), 43.5 (C-5), 29.9 (C-8).

$[\alpha]_D$ -114.6 (*c* 1.15, $CHCl_3$).

Elemental Analysis: calcd. for $C_{12}H_{12}O_3$: 69,57% H: 5.2%; found C: 69.38%, H: 5.87%.

IR (ATR) 2256, 1785, 1454, 1352, 1159, 1025, 990, 906, 737 cm^{-1}.

(1*R*,5*S*)- 3,6-dioxabicyclo[3.2.1]octan-7-one (54k)



A solution of (*S*)-5-(methoxymethyl)-2(5*H)*-furanone, **14k**, (158 mg, 1.23 mmol) in acetonitrile (75 ml) was irradiated at -15ºC for 105 min. After total conversion, the solvent was evaporated and the residue was purified by column chromatography (hexanes-Et_2O, 2:1) to deliver **54k** (82 mg, 0.64 mmol, 52% yield) as a colorless oil.

Physical and spectroscopic data of **54k**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.72 (m, 1H, H-5), 4.11 (dt, $J_{2eq,4eq}$ = 10.7 Hz, $J_{2eq,1}$ = 2.9 Hz, 1H, H-2_{eq}), 3.94 (dt, J_{gem} = 11.6 Hz, $J_{4eq,5}$ = 2.5 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}).

^{13}C NMR (91 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).

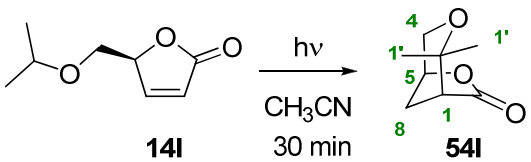
HRMS *m/z* (ESI-TOF) ($C_6H_8O_3$): calcd for $[M+Na]^+$ 151.0363, found 151.0366.

$[\alpha]_D$ -3 (*c* 0.6, $CDCl_3$).

IR (ATR) 2919, 1729, 1463, 632 cm^{-1}.

COSY, **HSQC**, **HMBC** and **NOESY** recorded.

(1*R*,5*S*)-2,2-Dimethyl-3,6-dioxabicyclo[3.2.1]octan-7-one (54l)



A solution of (*S*)-5-(isopropoxymethyl)-2(5*H)*-furanone, **14l**, (104 mg, 0.66 mmol) in acetonitrile (75 mL) was irradiated at -15ºC for 30 min. After total conversion, the solvent was evaporated and the residue was purified by column chromatography (hexanes-Et_2O, 2:1) to deliver **54l** (51 mg, 0.33 mmol, 50% yield) as colorless oil.

Physical and spectroscopic data of **54l**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.64 (m, 1H, H-5), 3.80 (m, 1H, H-4a), 3.79 (d, *J* = 0.8 Hz, 1H, H-4b), 2.38 (m, 3H, H-1 and 2 H-8), 1.40 (s, 3H, H-1'), 1.34 (s, 3H, H-1').

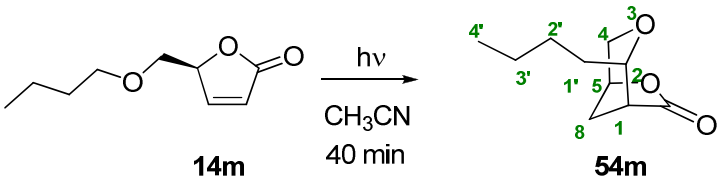
^{13}C NMR (90 MHz, $CDCl_3$) δ 176.1 (C-7), 75.8 (C-5), 72.8 (C-2), 63.5 (C-4), 48.1 (C-1), 31.4 (C-8), 27.0 (C-1'), 21.7 (C-1').

HRMS *m/z* (ESI-TOF) ($C_8H_{12}O_3$): calcd for $[M+Na]^+$ 179.0684, found 179.0683.

$[\alpha]_D^{20}$ -5.5 (*c* 0.7, $CDCl_3$)

IR (ATR) 2981, 1764, 1458, 1337, 1162, 1125, 934 cm^{-1}.

(1*R*,2*R*,5*S*)-2-Propyl-3,6-dioxabicyclo[3.2.1]octan-7-one (54m)



A solution of (*S*)-5-(butoxymethyl)-2(5*H*)-furanone, **14m**, (81 mg, 0.47 mmol) in acetonitrile (75 mL) was irradiated at -15ºC for 40 min. After total conversion, the solvent was evaporated and the residue was purified by column chromatography (hexanes-Et_2O, 2:1) to afford **54m** (42 mg, 0.24 mmol, 52%) as a colorless oil.

Physical and spectroscopic data of **54m**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.70 (dd, $J_{5,4}$ = 1.7 Hz, *J* = 4.6 Hz, 1H, H-5), 4.07 (ddd, $J_{2,1}$ = 2.5 Hz, *J* = 5.1Hz, *J* = 8.3 Hz, 1H, H-2), 3.77 (d, $J_{4,5}$ = 1.7 Hz, 2H, H-4), 2.54 (ddd, *J* = 1.2 Hz, $J_{1,2}$ = 2.5 Hz, *J* = 5.9 Hz, 1H, H-1), 2.31 (m, 2H, H-8), 1.80 (m, 1H, H-1'a), 1.54 – 1.31 (m, 3H, H-1'a and H-2'), 0.97 (t, $J_{3',2'}$ = 7.2 Hz, 3H, H-3').

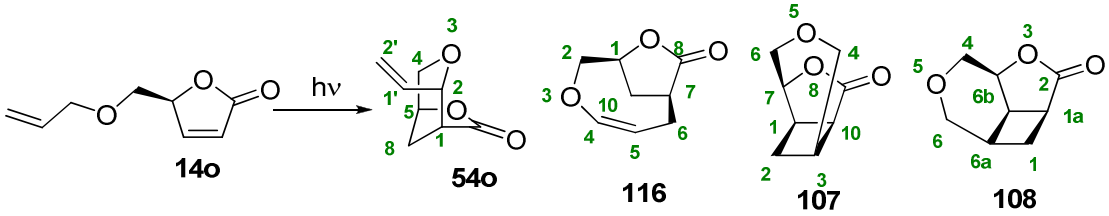
^{13}C NMR (90 MHz, $CDCl_3$) δ 177.5 (C-7), 76.56 (C-5), 73.5 (C-2), 63.7 (C-4), 43.2 (C-1), 32.3 (C-1'), 29.0 (C-8), 18.9 (C-2'), 13.8 (C-3').

HRMS *m/z* (ESI-TOF) ($C_9H_{14}O_3$): calcd for $[M+Na]^+$ 193.0838, found 193.0835.

$[\alpha]_D$ -10 (*c* 0.8, $CDCl_3$).

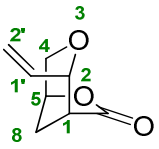
IR (ATR) 2958, 1776, 1458, 1340, 1155, 981, 924 cm^{-1}.

(1*R*,2*R*,5*S*)-2-vinyl-3,6-dioxabicyclo[3.2.1]octan-7-one (54o), (1S,7S,Z)-3,9-dioxabicyclo[5.2.1]dec-4-en-8-one (116), (1R,3S,7S,10S)-5,8-dioxatricyclo[5.3.0.0]decan-9-one (107), (1aS,3aS,6aR,6bR)-hexahydro-1H,2H-3,5-dioxacyclobuta[cd]inden-2-one (108)



A solution of (*S*)-5-(allyloxymethyl)-2(5*H*)-furanone **14o** (250 mg, 1.62 mmol) in acetone (75 ml) was irradiated at -15ºC for 180 min and the solvent was evaporated. The oily residue was purified by column chromatography (hexanes-Et_2O, 4:1) to afford **54o** (20 mg, 0.13 mmol, 8% yield), **116** (30 mg, 0.19 mmol, 12% yield) and a 1:1.8 mixture of **107** and **108** (125 mg, 0.81 mmol, 50% yield).

Physical and spectroscopic data of **54o**.



^{1}H NMR (360 MHz, $CDCl_3$) δ 5.79 (ddd, $J_{1',2}$ = 3.3 Hz, J = 10.8 Hz, J = 17.3 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_{ax}), 2.26 (d, J_{gem} = 11.8 Hz, 1H, H-8_{eq}).

^{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).

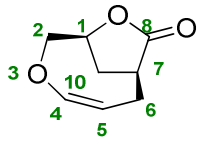
HRMS *m/z* (ESI-TOF) ($C_8H_{10}O_3$): calcd for $[M+Na]^+$ 177.0528, found 177.0522.

$[\alpha]_D$ +1 (*c* 0.9, $CDCl_3$).

IR (ATR) 3469, 2960, 2871, 1774, 1157 cm^{-1}.

COSY, **HSQC**, **HMBC** and **NOESY** recorded.

Physical and spectroscopic data of **116**



116

^{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 = 1.4 Hz, J = 5.8 Hz, J = 10.4 Hz, 1H, H-7), 2.59 (m, 2H, H-6a and H-10a), 2.43 (m, 1H, H-6b), 2.38 (m, 1H, H-10b).

^{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).

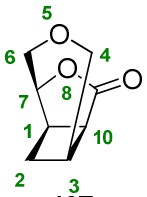
HRMS *m/z* (ESI-TOF) ($C_8H_{10}O_3$): calcd for $[M+Na]^+$ 177.0522, found 177.0525.

$[\alpha]_D$ +8 (*c* 0.7, $CDCl_3$).

IR (ATR): 3433, 2940, 2872, 1753, 1719 cm^{-1}.

COSY, **HSQC**, and **HMBC** recorded.

Spectroscopic data of **107**:



107

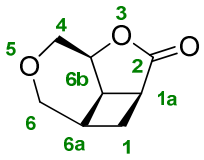
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (dd, $J_{7,6a}$ = 3.9 Hz, $J_{7,1}$ = 7.2 Hz, 1H, H-7), 4.14 (dd, J_{gem} = 13.2 Hz, $J_{6a,7}$ = 3.9 Hz, 1H, H-6a), 4.06 (dd, J_{gem} = 12.3 Hz, $J_{4,3}$ = 4.3 Hz, , 1H, H-4a), 4.00 (d, J_{gem} = 13.2 Hz, 1H, H-6b), 3.61 (d, J_{gem} = 12.3 Hz, 1H, H-4b), 3.15 (m, 3H, H-1 and H-10 and H-3), 2.58 (m, 1H, H-2a), 1.89 (d, J_{gem} =12.4 Hz, 1H, H-2b).

^{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: 154.1, 99.0, 67.0, 55.0, 41.0.

COSY, **HSQC**, **HMBC** and **NOESY** recorded.

Spectroscopic data of **108**



108

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (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, J= 1H, H-6), 3.41 (dd, $J_{4,3a}$ = 8.9 Hz , J_{gem} = 13.5 Hz, 1H, H-4), 3.15 (m, 2H, H-6a and H-6b), 2.71-2.61 (m, 2H, H-1), 2.32 (dd, *J* = 6.0 Hz, *J*= 11.2 Hz, 1H, H-1a).

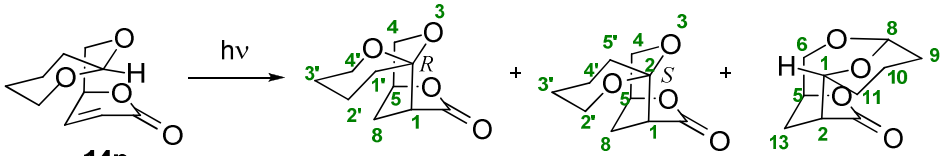
^{13}C NMR (125 MHz, $CDCl_3$) δ 179.2 (C-2), 74.8 (C-3a), 68.4 (C-6), 67.9 (C-4), 34.9 (C-6a), 29.7 (C-6b), 26.9 (C-1), 26.8 (C-1a).

GC/MS : 154.1, 83.0, 67.1, 55.0, 41.0.

COSY, **HSQC**, **HMBC** and **nOeSY** recorded.

^{1}H NMR (500 MHz, C_6D_6) δ 4.03 (d, J_{gem} = 13.4 Hz, 1H, H-4a), 3.84 (m, 1H, H-3a), 3.29 (d, J_{gem} = 12.2 Hz, 1H, H-6a), 2.83 (dd, *J* = 3.5 Hz, J_{gem} = 12.2 Hz, 1H, H-6b), 2.76 (dd, *J* = 2.0 Hz, J_{gem} = 13.4 Hz, 1H, H-4b), 2.70 (m, 1H, H-1a), 2.23 (m, 1H, H-6b), 2.12 (m, 2H, H-1), 1.72 (m, 1H, H-6a).

(1*R*,2*S*)-3,6-dioxabicyclo[3.2.1]octan-7-one (2*S*-54p) , (1*R*,5*R*)-3,6-dioxabicyclo[3.2.1]octan-7-one (2*R*-54p) and (1RS,2R,5S,8RS)-4,7,12-trioxatricyclo[6.3.1.1^{2,5}]tridecan-3-one (120).

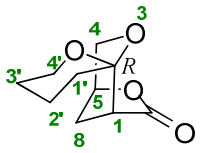


14p
1:1 mixture

2*R*-54p + **2*S*-54p** + **120**

A solution of a 1:1 mixture of (5S)-5-((tetrahydro-2*H*-pyran-2-yloxy)methyl)-2(5*H*)-furanone **14p** (150 mg, 0.76 mmol) in acetonitrile (75 ml) was irradiated at -15ºC for 120 min. After total conversion of **14p**, the solvent was evaporated and the resulting residue was purified by column chromatography (hexanes-AcOEt, 5:1) to deliver **2*R*-54p** (75 mg, 0.38 mmol, 50% yield) as a colorless oil; **2*S*-54p** (21 mg, 0.11 mmol, 14% yield) as a colorless oil and **120** (16 mg, 0.08 mmol, 10% yield) as a colorless oil.

Physical and spectroscopic data of **2*R*-54p**.



***2R*-54p**

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (d, $J_{5.8}$ = 5.7 Hz, $J_{5,8eq}$ = 2.1 Hz, 1H, H-5), 3.88 – 3.67 (m, 4H, H-4 and H-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'a), 1.78 (m, 1H, H-4'a), 1.52 (m, 4H, H-3', H-4'b, and H-5'b).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1 (C-9), 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').

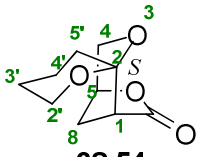
HRMS *m/z* (ESI-TOF) ($C_{10}H_{14}O_4$): calcd for $[M+Na]^+$ 221.0790, found 221.0782.

[α]$_D$ -8 (*c* 0.8, $CDCl_3$).

IR (ATR) 3431, 2941, 2873, 1764, 1720 cm^{-1}.

COSY, **HSQC**, **HMBC** and **nOeSY** recorded.

Physical and spectroscopic data of **2*S*-54p**.



***2S*-54p**

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.72 (br t, *J* = 4.7 Hz, 1H, H-5), 4.00 (d, J_{gem} = 12.6 Hz, 1H, H-4_{ax}), 3.80 (m, 3H, 2H-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, $J_{8eq,1}$ = 4.5 Hz, 1H, H-8_{eq}), 2.22 (d, J_{gem} = 11.0 Hz, 1H, H-8_{ax}), 1.98 – 1.90 (m, 1H, H-5'a), 1.81 (dt, *J* = 12.7 Hz, *J* = 3.8 Hz, 1H, H-4'a), 1.62 (m, 2H, H-3' and H-4'), 1.47 (m, 2H, H-3' and H-5').

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.3 (C-7), 94.8 (C-2), 76.4 (C-5), 63.0 (C-4), 62.4 (C-2'), 49.0 (C-1), 33.1 (C-5'), 30.4 (C-8), 25.2 (C-3'), 18.2 (C-4').

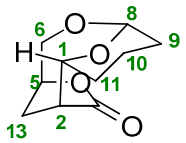
HRMS *m/z* (ESI-TOF) ($C_{10}H_{14}O_4$): calcd for $[M+Na]^+$ 221.0790, found 221.0780.

[α]$_D$ -50 (*c* 0.3, $CDCl_3$).

IR (ATR) 3433, 2941, 2872, 1754, 1719 cm^{-1}.

COSY, **HSQC**, **HMBC** and **NOESY** recorded.

Physical and spectroscopic data of **120**:



120

^{1}H 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-6a and H-1), 3.57 (d, J_{gem} = 12.4 Hz, 1H, H-6b), 2.58 (m, 1H, H-2), 2.42 (m, 2H, H-13), 2.24 (d, *J* = 12.6 Hz, 1H, H-11a), 2.00 (m, 1H, H-11b), 1.75 (m, 1H, H-9a), 1.60 (m, 2H, H-9b and H-10a), 1.40 (m, 1H, H-10b).

^{13}C NMR (90 MHz, $CDCl_3$) δ 177.9 (C-9), 96.2 (C-4), 76.8 (C-7), 69.2 (C-6), 68.2 (C-2), 44.5 (C-1), 31.0 (C-10), 29.1 (C-1'), 24.3 (C-3'), 12.7 (C-2').

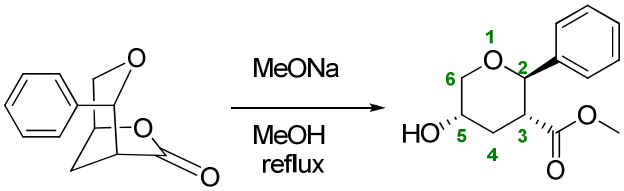
HRMS *m/z* (ESI-TOF) ($C_{10}H_{14}O_4$): calcd for $[M+Na]^+$ 221.0784; found 221.0785.

$[\alpha]_D$ -38 (*c* 1.2, $CDCl_3$).

IR (ATR) 3426, 2943, 2874, 1756, 1722 cm^{-1}.

COSY, **HSQC**, **HMBC** and **NOESY** recorded.

(2R,3R,5S)-methyl 5-hydroxy-2-phenyltetrahydro-2*H*-pyran-3-carboxylate, 63i



54i **63i**

To a solution of the furanone **54i** (55 mg, 0.269 mmol) in methanol (2 mL) was added sodium methoxyde (16mg, 0.296 mmol) and the reaction was heat up to reflux temperature. After 12h of stirring, the reaction was quenched by addition of HCl 1M, 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 **63i** 41 mg (65 % yield) as an oil.

Physical and spectroscopic data of **63i**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 5H, H-Ph), 4.45 (d, $J_{2,3}$ = 10.0 Hz, 1H, H-2), 4.15 (ddd, J_{gem} = 10.8, J = 4.9 Hz, $J_{6a,4a}$ = 2.2 Hz, 1H, H-6_{eq}), 3.90 (m, 1H, H-5), 3.47 (s, 3H, H-Me), 3.36 (dd, J_{gem} = 10.8 Hz, J = 10.2 Hz, 1H, H-6_{ax}), 2.82 (ddd, $J_{3,4b}$ = 12.5 Hz, $J_{3,2}$ = 10.0 Hz, $J_{3,4a}$ = 3.9 Hz, 1H, H-3), 2.40 (dtd, $J_{4a,6a}$ = 2.2 Hz, $J_{4a,3}$ = 3.9 Hz, J_{gem} = 12.5 Hz, 1H, H-4a), 1.87 (td, J=11.1 Hz, $J_{4b,3}$=12.5 Hz, J_{gem} = 12.5 Hz, 1H, H-4b).

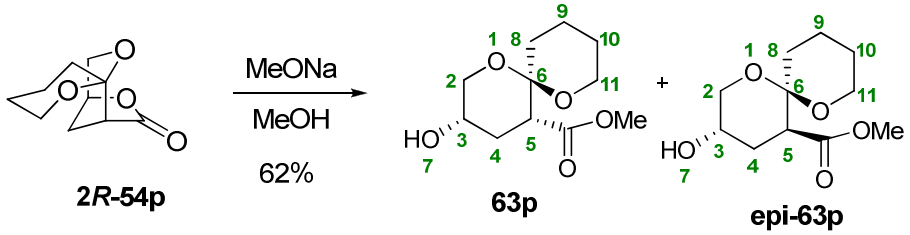
^{13}C NMR (90 MHz, $CDCl_3$) δ 172.5 (C=O), 139.3 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 128.5 (C-Ar), 126.9 (C-Ar), 81.05 (C-2), 72.95 (C-6), 65.26 (C-5), 51.84 (C-Me), 49.05 (C-3), 36.52 (C-4).

HRMS *m/z* (ESI-TOF) ($C_{13}H_{16}O_4$): calcd for $[M+Na]^+$ 259.0941, found 259.0943.

$[\alpha]_D$ +18 (*c* 0.6, $CDCl_3$).

IR (ATR) 3446, 2951, 2867, 1782, 1730 cm^{-1}.

(3S,5R,6R)-methyl 3-hydroxy-1,7-dioxaspiro[5.5]undecane-5-carboxylate, 63p



2*R*-54p **63p** **epi-63p**

To a solution of the furanone **2*R*-54p** (40 mg, 0.2 mmol) in methanol (3 mL) was added sodium methoxyde (54.5 mg, 1.01 mmol) and the reaction was heat up to reflux temperature. After 12h of stirring, the reaction was quenched by addition of aqueous ammonium chloride saturated solution, organic phases 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 **63p** (28 mg, 0.12 mmol, 62 % yield) as an oil.

Physical and spectroscopic data of **63p**:

^{1}H NMR (400 MHz, C_6D_6) δ 5.62 (d, $J_{7,3}$=11.2 Hz, 1H, H-7), 3.82 (ddd, $J_{2a,2b}$ = 11.7 Hz, $J_{2a,3}$ = 3.9 Hz, J = 1.9 Hz, 1H, H-2a), 3.61 (dd, J_{gem} = 11.7 Hz, $J_{2b,3}$ = 2.2 Hz, 1H, H-2b), 3.53 (dtd, $J_{3,7}$ = 11.2 Hz, $J_{3,2a}$ = 3.9 Hz, $J_{3,2b}$ = 2.2 Hz, 1H, H-3), 3.36 (m, 2H, H-11), 3.16 (s, 3H, H-Me), 2.67 (dd, $J_{5,4a}$ = 6.6 Hz, J = 1.4 Hz, 1H, H-5), 2.12 (ddd, J = 14.5 Hz, $J_{4a,5}$ = 6.6 Hz, J = 4.2 Hz, 1H, H-4a), 1.80 (m, 1H, H-4b), 1.64 (m, 1H, H-8a), 1.42 (m, 1H, H-8b), 1.22 (m, 3H, H-10a and H-11), 1.12 (m, 1H, H-10b).

^{13}C NMR (100 MHz, C_6D_6) δ 176.3 (C-13), 94.9 (C-6), 66.2 (C-2), 62.7 (C-7), 61.3 (C-11), 52.1 (C-ester), 47.7 (C-5), 33.6 (C-8), 27.5 (C-4), 25.4 (C-9), 19.0 (C-10).

HRMS *m/z* (ESI-TOF) ($C_{11}H_{18}O_5$) calcd for $[M+Na]^+$ 253.1046, found 253.1049.

$[\alpha]_D$ -72 (*c* 0.4, $CDCl_3$).

IR (ATR) 3468, 2952, 2870, 1775, 1731 cm-1.

COSY, **HSQC**, **HMBC** and **nOeSY** recorded.

(3*S*,5*S*,6*R*)-methyl 3-hydroxy-1,7-dioxaspiro[5.5]undecane-5-carboxylate, (epi-63p)

When the reaction was quenched with HCl 1M, another product was obtained which correspond to the epimer product.

Physical and spectroscopic data of **epi-63p**:

^{1}H NMR (400 MHz, C_6D_6) δ 3.46 – 3.37 (m, 4H, H-2a and H-11 and H-3), 3.35 (s, 3H, H-15), 3.27 (ddd, *J* = 11.9 Hz, *J* = 2.5 Hz, *J* = 1.9 Hz, 1H, H-2b), 2.96 (dd, $J_{5,4a}$ = 13.1 Hz, $J_{5,4b}$ = 4.2 Hz, 1H, H-5), 2.46 (ddd, *J* = 13.8 Hz, $J_{4a,5}$ = 13.1 Hz, *J* = 2.9 Hz, 1H, H-4b), 2.21 (td, $J_{8a\text{-}9a}$ = 13.4 Hz, *J* = 4.5 Hz, 1H, H-8a), 1.90 (dt, $J_{9a\text{-}8a}$ = 13.4 Hz, *J* = 4.0 Hz, 1H, H-9a), 1.78 (m, 1H, H-4a), 1.70 (m, 1H, H-8b), 1.40 (m, 2H, H-10a and H-9b), 1.10 (m, 1H, H-10b).

^{13}C NMR (100 MHz, C_6D_6) δ 171.9 (C-13), 96.2 (C-6), 64.8 (C-2), 64.5(C-11), 61.6 (C-3), 51.6 (C-15), 45.7 (C-5), 33.6 (C-8), 29.5 (C-4), 25.5 (C-9), 19.2 (C-10).

HRMS *m/z* (ESI-TOF) ($C_{11}H_{18}O_5$): calcd for $[M+Na]^+$ 253.1046, found 253.1048.

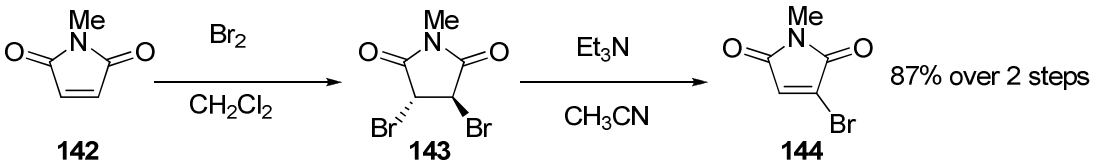
$[\alpha]_D$ -1.5 (*c* 0.3, $CDCl_3$).

IR (ATR) 3436, 2941, 2872, 1740, 1720 cm^{-1}.

COSY, **HSQC**, **HMBC** and **nOeSY** recorded.

6.2. Experimental part of chapter 3:

_N_-Methylbromomaleimide (144)



To *N*-methylmaleimide (5.5 g, 50.0 mmol) in dry CH_2Cl_2 (150 mL) was added bromine (3.1 mL, 60.0 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred at room temperature for 17 h. Solvent was removed in vacuo and the reaction mass was dissolved in dry acetonitrile (100 mL) and triethylamine (9.0 mL, 65.0 mmol, 1.3 equiv) was added, then stirred for 17h at room temperature. The material was purified by column chromatography (petroleum ether-EtOAc, 4:1) to afford **144** as a yellow powder (8.3 g, 43.7 mmol, 87% yield).

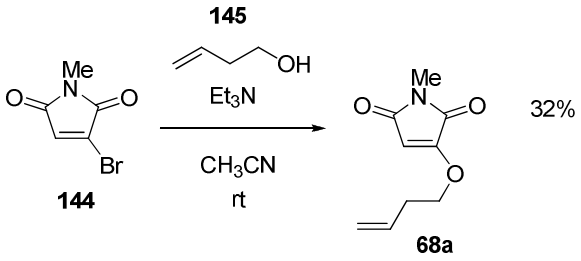
Spectroscopic data of **144**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H, H-4), 3.09 (s, 3H, H-6).

^{13}C NMR (125 MHz, MeOD) δ 168.6 (C-5), 165.4 (C-2), 131.9 (C-4), 131.4 (C-3), 24.7 (C-6).

L. M. Tedaldi; M. E. Smith; R. I. Nathani; J. R. Baker *Chem. Commun.* , **2009**, 6583-6585.

3-(but-3-enyloxy)-1-methyl-1*H*-pyrrole-2,5-dione (68a)



To a solution of bromomaleimide (1.0 g, 5.3 mmol) and 3-butenol (0.9 mL, 10.5 mmol, 2 equiv) in dry acetonitrile (15 mL) was added triethylamine (1.6 mL, 11.6 mmol, 2.2 equiv). The resulting mixture was stirred at room temperature for 24h. The reaction was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford a pale yellow powder (320 mg, 2.7 mmol) in 32% yield.

To a solution of sodium hydride (48 mg, 1.2 mmol, 2.3 equiv) in dry dioxane (3 mL) was added a solution 3-butenol (90 µL, 1.1 mmol, 2 equiv) in dry dioxane (3 mL) dropwise.

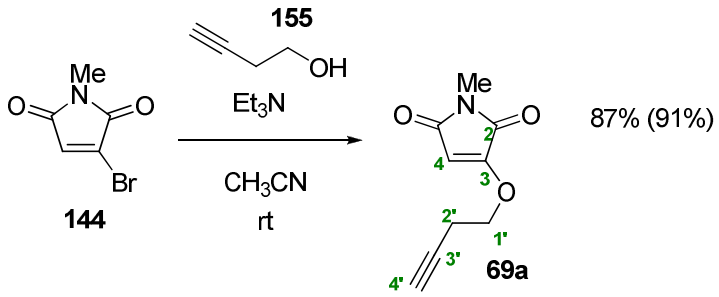
After 20 min, was added to a solution of bromomaleimide (100 mg, 0.5 mmol) in dry dioxane (3 mL). The resulting mixture was stirred at room temperature for 24h, then concentrated in vacuo and separated between EtOAc (15 mL) and NH_4Cl (5 mL). The aqueous layer was washed with EtOAc (2x6 mL), the combined organic extracts was washed with water (5 mL), brine (5 mL) and dried ($MgSO_4$). Evaporation of the solvent and purification by column chromatography (petroleum ether-EtOAc, 9:1) afforded a pale yellow powder (30 mg, 0.165 mmol, 32% yield).

Spectroscopic data of **68a**:

^{1}H NMR (301 MHz, $CDCl_3$) δ 5.75 - 5.90 (m, 1H, H-3'), 5.38 (s, 1H, H-4), 5.12 - 5.23 (m, 2H, H-4'), 4.09 (td, *J* = 6.8Hz, *J* = 1.3 Hz, 2H, H-1'), 3.00 (s, 3H, H-NMe), 2.56 - 2.65 (m, 2H, H-2').

HRMS *m/z* (CI) ($C_9H_9NO_3$): calcd for $[M+H]^+$ 180.0661, found 180.0657.

3-(But-3-ynyloxy)-1-methyl-1*H*-pyrrole-2,5-dione (69a)



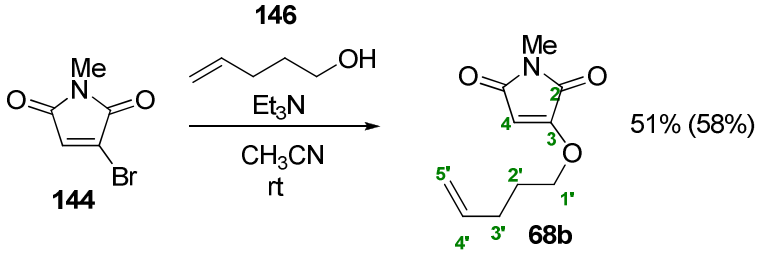
To a solution of bromomaleimide (1.0 g, 5.3 mmol) and 4-pentenol (0.90 mL, 10.5 mmol, 2 equiv) in dry acetonitrile (15 mL) was added triethylamine (1.6 mL, 11.6 mmol, 2.2 equiv). The resulting mixture was stirred at room temperature for 24h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford a pale yellow powder (816 mg, 4.6 mmol, 87% yield, 91% considering the starting material recovered).

Spectroscopic data of **69a**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43 (s, 1H, H-4), 4.15 (t, $J_{1',2'}$=7.1 Hz, 2H, H-1'), 2.99 (s, 3H, N-CH_3), 2.75 (td, $J_{2',4'}$= 2.7 Hz, $J_{2',1'}$= 7.1 Hz, 2H, H-2'), 2.06 (t, $J_{4',2'}$=2.7 Hz, 1H, H-4').

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1 (C-5), 165.5 (C-2), 159.6 (C-3), 96.9 (C-2'), 78.4 (C-4), 71.0 (C-4'), 69.7 (C-5'), 23.5 (C-3'), 18.7 (C-6).

1-Methyl-3-(pent-4-enyloxy)-1*H*-pyrrole-2,5-dione (68b)



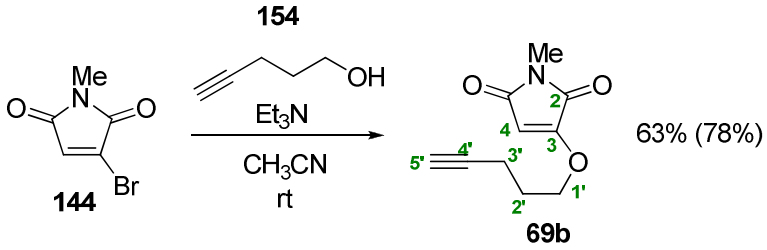
To a solution of bromomaleimide (1.0 g, 5.3 mmol) and 4-penten-1-ol (1.1 mL, 10.5 mmol, 2 equiv) in dry acetonitrile (15 mL) was added triethylamine (1.6 mL, 11.6 mmol, 2.2 equiv). The resulting mixture was stirred at room temperature for 24h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford a pale yellow powder (540 mg, 2.7 mmol, 51% yield, 58% considering the starting material recovered).

Spectroscopic data of **68b**:

^{1}H NMR (301 MHz, $CDCl_3$) δ 5.68 - 5.93 (m, 1 H, H-4'), 5.35 (d, *J* = 0.9 Hz, 1 H, H-4), 4.92 - 5.11 (m, 2 H, H-5'), 4.04 (td, *J* = 7.0 Hz, *J* = 1.1 Hz, 2 H, H-1'), 2.98 (s, 3 H, N-CH_3), 2.21 (q, *J* = 7.0 Hz, 2 H, H-2'), 1.86 - 2.00 (m, 2 H, H-3').

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C-5), 165.8 (C-2), 160.2 (C-3), 136.6 (C-4'), 115.9 (C-5'), 96.2 (C-4), 71.6 (C-1'), 29.5 (C-2'), 27.2 (C-3'), 23.4 (C-6).

1-methyl-3-(pent-4-ynyloxy)-1*H*-pyrrole-2,5-dione (69b)



To a solution of bromomaleimide (3.0 g, 15,8 mmol) and 4-pentyn-1-ol (2.9 mL, 31.4 mmol, 2 equiv) in dry acetonitrile (45 mL) was added triethylamine (4.8 mL, 34.7 mmol, 2.2 equiv). The resulting mixture was stirred at room temperature for 24h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford a pale yellow powder (1,93 g, 9.9 mmol, 63% yield, 78% considering the starting material recovered).

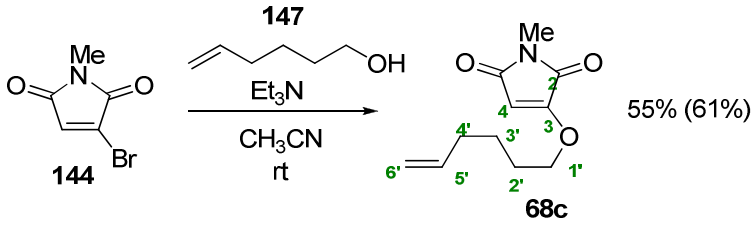
Spectroscopic data of **69b**:

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 1H, H-4), 4.04 (t, $J_{1',2'}$=6.3 Hz, 2H, H-1'), 2.80 (s, 3H, N-CH_3), 2.24 (td, $J_{2',1'}$= 6.4 Hz, $J_{2',3'}$=2.6 Hz, 2H, H-2'), 1.83 – 1.97 (m, 3H, H-5' and H-3').

^{13}C NMR (76 MHz, $CDCl_3$) δ 169.9 (C-5), 165.3 (C-2), 159.7 (C-3), 96.2 (C-4), 82.0 (C-5'), 70.2 (C-5'), 69.4 (C-1'), 26.7 (N-CH_3), 23.0 (C-2'), 14.5 (C-3').

HRMS m/z (CI) ($C_{10}H_{11}NO_3$): calcd for $[M+H]^+$ 194.0817, found 194.0820.

3-(Hex-5-enyloxy)-1-methyl-1*H*-pyrrole-2,5-dione (68c)



To a solution of bromomaleimide (1.5 g, 7.9 mmol) and 5-hexen-1-ol (1.9 mL, 15.7 mmol, 2 equiv) in dry acetonitrile (25 mL) was added triethylamine (2.5 mL, 17.4 mmol, 2.2 equiv). The resulting mixture was stirred at 45℃ for 24h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford an orange oil (950 mg, 4.3 mmol, 55% yield, 61% considering the starting material recovered).

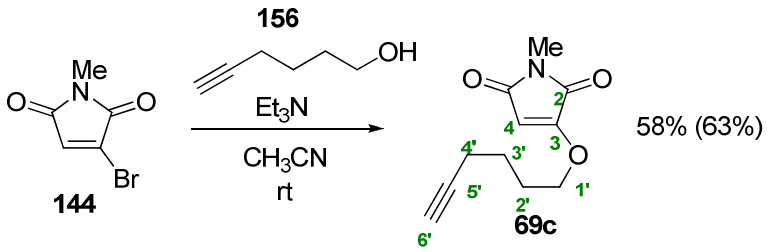
Spectroscopic data of **68c**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.70 (m, 1H, H-5'), 5.34 (s, 1H, H-4), 5.04-4.93 (m, 2H, H-6'), 4.03 (td, J_{gem} = 1.2 Hz, $J_{1',2'}$ = 6.6 Hz, 2H, H-1'), 2.97 (s, 3H, N-CH_3), 2.13-2.05 (m, 2H, H-2'), 1.83 (dtd, J_{gem} = 1.5 Hz, $J_{2',1'}$ = 6.6 Hz, $J_{2',3'}$ = 14,6 Hz, 2H, H-2'), 1.53 (dtd, J_{gem}= 1,5 Hz, $J_{3',4'}$ = 7.6 Hz, $J_{3',4'}$ = 14.6 Hz, 2H, H-3').

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C=O), 165.8 (C=O), 160.2 (C-3), 137.8 (C-4), 115.1 (C-6'), 96.1 (C-5'), 72.26 (C-1'), 33.0 (C-2'), 27.5 (C-4'), 24.8 (C-3'), 23.3 (N-CH_3).

HRMS m/z (CI) ($C_{11}H_{15}NO_3$): calcd for $[M+H]^+$ 210.1130, found 210.1133.

3-(Hex-5-ynyloxy)-1-methyl-1*H*-pyrrole-2,5-dione (69c)



To a solution of bromomaleimide (1.5 g, 7.9 mmol) and 5-hexyn-1-ol (1.7 mL, 15.7 mmol, 2 equiv) in dry acetonitrile (25 mL) was added triethylamine (2.5 mL, 17.4 mmol, 2.2 equiv). The resulting mixture was stirred at 45℃ for 24h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford a pale yellow powder (1.0 g, 4.6 mmol, 58% yield, 73% considering the starting material recovered).

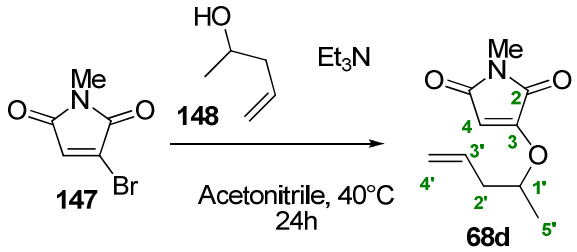
Spectroscopic data of **69c**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (s, 1H, H-4), 4.06 (t, $J_{1'\text{-}2'}$ = 6.8 Hz, 2H, H-1'), 2.96 (s, 3H, N-CH_3), 2.24 (td, *J* = 6.8 Hz, *J* = 2,6 Hz, 2H, H-2'), 2.00-1.90 (m, 3H, H-6' and H-4'), 1.71 – 1.62 (m, 2H, H-3').

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (C-5), 165.7 (C-2), 160.1 (C-3), 96.2 (C-4), 83.3 (C-5'), 71.8 (C-1'), 69.0 (C-6'), 27.1 (C-2'), 24.4 (C-4'), 23.3 (N-CH_3), 17.8 (C-3').

HRMS m/z (CI) ($C_{11}H_{13}NO_3$), calcd for $[M+H]^+$ 208.0974, found 208.0968.

1-Methyl-3-(pent-4-en-2-yloxy)-1*H*-pyrrole-2,5-dione (68d)



To a solution of bromomaleimide (1.5 g, 7.9 mmol) and 4-penten-2-ol (1.7 mL, 15.8 mmol, 2 equiv) in dry acetonitrile (25 mL) was added triethylamine (2.5 mL, 17.4 mmol, 2.2 equiv). The resulting mixture was stirred at 40℃ for 24h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford a pale yellow powder (150 mg, 0.8 mmol, 10% yield).

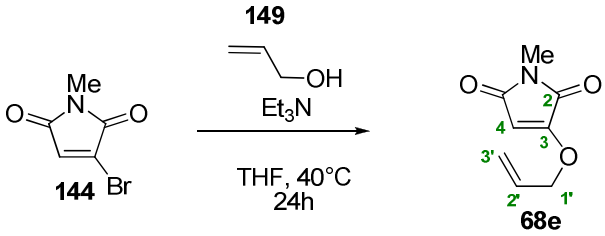
Spectroscopic data of **68d**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (ddt, *J* =17.1 Hz, *J* = 10.1 Hz, $J_{4'-3'}$ = 6.5 Hz, 1H, H-4'), 5.28 (s, 3H, H-4), 5.12 – 4.98 (m, 2H, H-5'), 4.27 (sxt, $J_{2'-3'}$= 14.4Hz, $J_{2'-1'}$=6.1 Hz, 1h, H-2'), 2.91 (s, 3H, N-CH_3), 2.49 (dt, $J_{3'-2'}$ = 14.4Hz, $J_{3'-4'}$ = 6.5 Hz, 1H, H-3'a) 2.34 (dt, $J_{3'-2'}$ = 14.4Hz, $J_{3'-4'}$ = 6.5 Hz, 1H, H-3'b). 1.32 (d, $J_{1'-2'}$ = 6.1 Hz, 3H, H-1').

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C-5), 165.8 (C-2), 158.9 (C-3), 132.2 (C-4'), 118.6 (C-5'), 95.8 (C-4), 79.0 (C-2'), 39.4 (C-3'), 23.2 (N-CH_3), 18.3 (C-1').

HRMS m/z (CI) ($C_{10}H_{13}NO_3$): calcd for $[M+H]^+$ 196.0974, found 196.0981.

3-(Allyloxy)-1-methyl-1*H*-pyrrole-2,5-dione (68e)



To a solution of bromomaleimide (1.5 g, 7.9 mmol) and prop-2-en-1-ol (1.1 mL, 15.8 mmol, 2 equiv) in dry THF (20 mL) was added triethylamine (2.5 mL, 17.4 mmol, 2.2 equiv). The resulting mixture was stirred at 40℃ f or 72h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether: ethyl acetate, 9:1) to afford a pale yellow powder (380 mg, 2.3 mmol, 29% yield, 33% considering the starting material recovered).

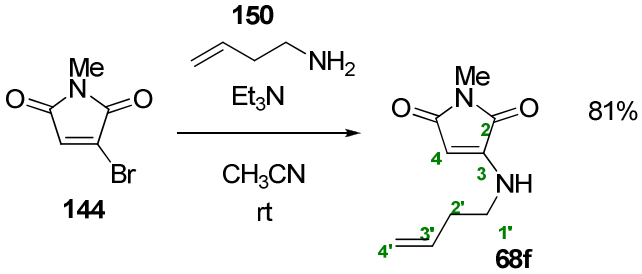
Spectroscopic data of **68e**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 – 5.91 (m, 1H, H-2'), 5.45 – 5.33 (m, 3H, H-3' and H-4), 4.58 (dt, *J* = 5.8 Hz, *J* = 1.3 Hz, 2H, H-1'), 2.95 (s, 3H, H-Me).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (C-5), 165.7 (C-2), 159.50 (C-3), 129.9 (C-2'), 120.5 (C-3'), 96.9 (C-4), 72.7 (C-1'), 23.3 (N-CH_3).

HRMS m/z (CI) ($C_8H_9NO_3$): calcd for $[M+H]^+$ 168.0661, found 168.0668.

3-(But-3-enylamino)-1-methyl-1*H*-pyrrole-2,5-dione (68f)



To a solution of bromomaleimide (1.5 g, 7.9 mmol) and 3-buten-1-amine (1.0 mL, 10.2 mmol, 1.3 equiv) in dry acetonitrile (25 mL) was added triethylamine (2.5 mL, 17.4 mmol, 2.2 equiv). The resulting mixture was stirred at 45℃ for 24h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford an orange powder (1.15 g, 6.38 mmol) in 81% yield.

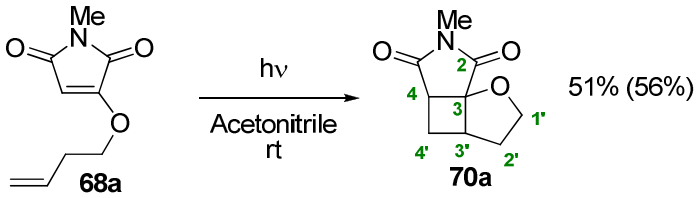
Spectroscopic data of **68f**:

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (bs, 1H, NH), 5.66 (ddt, $J_{3',2'}$= 6.7Hz, *J*=17.0 Hz, *J*=10.2Hz, 1H, H-3'), 5.13-4.90 (m, 2H, H-4'), 4.70 (s, 1H, H-4), 3.13 (q, *J*=6.7 Hz, 1H, H-1'), 2.28 (q, *J*=6.7 Hz, 2H, H-2').

^{13}C NMR (76 MHz, $CDCl_3$) δ 172.5 (C-5), 167.4 (C-2), 149.3 (C-3), 133.9 (C-3'), 118.0 (C-4'), 84.1 (C-4), 43.2 (C-1'), 32.5 (C-2'), 23.3 (N-CH_3).

HRMS m/z (CI) ($C_9H_{12}N_2O_2$): calcd for $[M+H]^+$ 181.0977, found 181.0970.

6-Methyltetrahydrofuro[2',3':1,4]cyclobuta[1,2-c]pyrrole-5,7(2*H*,6*H*)-dione (70a)



A solution of alkene **68a** (300 mg, 1.6 mmol) in degassed acetonitrile (150 mL) was irradiated with medium-pressure mercury lamp under nitrogen at room temperature through a Pyrex filter for 90 min. The resulting mixture was concentrated in vacuo and then purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford pale yellow crystals of tricycle **70a** (154 mg, 51%yield, 56% yield considering the starting material recovered)

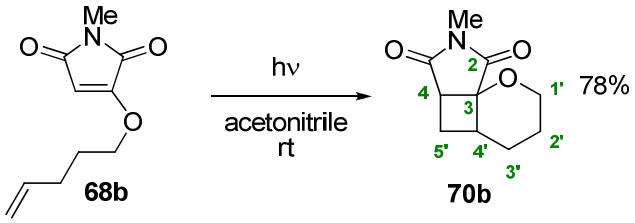
Spectroscopic data of **70a**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42 (ddd, $J_{1'a\text{-}1'b}$=9.2 Hz, *J*=7.7 Hz, *J*=1.5 Hz, 1 H, H-1'a), 4.05 (ddd, *J*=11.0 Hz, $J_{1'b\text{-}1'a}$=9.2 Hz, *J*=5.6 Hz, 1 H, H-1'b), 3.08 - 3.15 (m, 1 H, H-4), 3.02 (s, 3 H, N-CH_3), 2.99 - 3.02 (m, 1 H, H-3'), 2.14 - 2.23 (m, 1 H, H-4'a), 2.08 (m, 2 H, H-4'b and H-2'a), 1.80 - 1.88 (m, 1 H, H-2'b).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (C-5), 175.4 (C-2), 84.3 (C-3), 70.5 (C-4), 42.2 (C-1'), 41.7 (C-4'), 31.6 (C-3'), 25.0 (C-2'), 24.5 (CH_3).

HRMS m/z (CI) ($C_9H_{11}NO_3$): calcd for $[M+H]^+$ 182.0817, found 182.0814.

7-Methyltetrahydro-2H-pyrano[2',3':1,4]cyclobuta[1,2-c]pyrrole-6,8(3*H*,7*H*)-dione (70b)



A solution of alkene **68b** (200 mg, 1.0 mmol) in degassed acetonitrile (150 mL) was irradiated with medium-pressure mercury lamp under nitrogen at room temperature through a Pyrex filter for 150 min. The resulting mixture was concentrated in vacuo and then purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford pale yellow crystals of tricycle **70b** (156 mg, 78% yield)

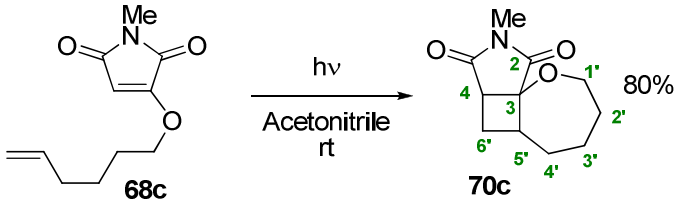
Spectroscopic data of **70b**:

^{1}H NMR (301 MHz, $CDCl_3$) δ 3.98 - 4.09 (m, 1 H, H-1'a), 3.76 - 3.87 (m, 1 H, H-1'b), 3.25 (ddd, $J_{3'\text{-}5'a}$ = 10.3, *J* = 4.7 Hz, *J* = 0.9 Hz, 1 H, H-3'), 3.02 (s, 3 H, N-CH_3), 2.52 - 2.63 (m, 1 H, H-4), 2.24 (ddd, *J* = 12.5 Hz, $J_{5'a\text{-}3'}$ = 10.3 Hz, *J* = 5.7 Hz, 1 H, H-5'a), 2.07 - 2.18 (m, 1 H, H-2'a), 1.94 - 2.04 (m, 1 H, H-5'b), 1.53 - 1.83 (m, 3 H, H-2'b and H-3').

^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6 (C-5), 177,0 (C-2), 76.1 (C-3), 64.4 (O-CH_2, C-7), 42.1 (C-10), 32.7 (C-4), 26.4 (C-9), 25.5 (C-8), 24.7 (C-6), 20.8 (C-11).

HRMS m/z (CI) ($C_{10}H_{13}NO_3$): calcd for $[M+H]^+$ 196.0974, found 196.0975.

8-Methylhexahydrooxepino[2',3':1,4]cyclobuta[1,2-c]pyrrole-7,9(2*H*,8*H*)-dione (70c)



A solution of alkene **68c** (200 mg, 0.96 mmol) in degassed acetonitrile (150 mL) was irradiated with medium-pressure mercury lamp under nitrogen at room temperature through a Pyrex filter for 150 min. The resulting mixture was concentrated in vacuo and then purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford pale yellow crystals of tricycle **70c** (160 mg, 80% yield)

A solution of alkene **68c** (650 mg, 3.1 mmol) in degassed acetonitrile (0.5 L) was irradiated with 400W medium-pressure mercury lamp under nitrogen at room temperature with a Flow continous reactor with a rate of 100 mL / min in a circuit of 30mL (6 min of irradiation). The resulting mixture was concentrated in vacuo and then purified by column chromatography (petroleum ether-EtOAc,9:1) to afford pale yellow crystals of tricycle **70c** (620 mg, 95% yield).

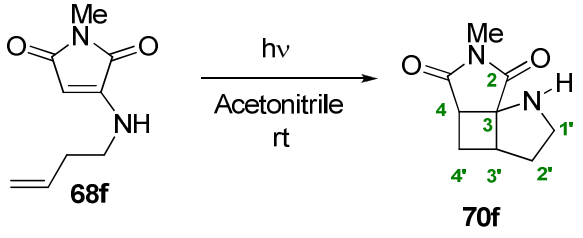
Spectroscopic data of **70c**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.39 (ddd, *J*=12.8 Hz, J=11.0 Hz, J=2.0 Hz, 1 H, H-1'a), 3.79 (dtd, *J*=12.8 Hz, J=3.4 Hz, J=2.0 Hz, 1 H, H-1'b), 3.01 - 3.06 (m, 1 H, H-3), 2.97 (s, 3 H, N-CH_3), 2.56 (ddd, *J*=8.1, 3.9, 1.0 Hz, 1 H, H-5'), 2.52 (ddd, *J*=8.3 Hz, J=4.2 Hz, J=1.0 Hz, 1 H, H-6'a), 1.57 - 2.03 (m, 7 H, H-6'b, H-4', H-2' and H-3'a), 1.32 - 1.43 (m, 1 H, H-3'b).

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6 (C-5), 177.5 (C-2), 78.5 (C-3), 69.2 (C-1'), 41.4 (C-5'), 40.0 (C-4), 33.3 (C-2'), 32.3 (C-4'), 28.2 (C-6'), 24.6 (C-3'), 24.5 (C-6).

HRMS m/z (CI) ($C_{11}H_{15}NO_3$): calcd for $[M+H]^+$ 210.1130, found 210.1125.

6-Methyltetrahydro-1*H*-cyclobuta[1,2-b:1,4-c']dipyrrole-5,7(2*H*,6*H*)-dione (70f)



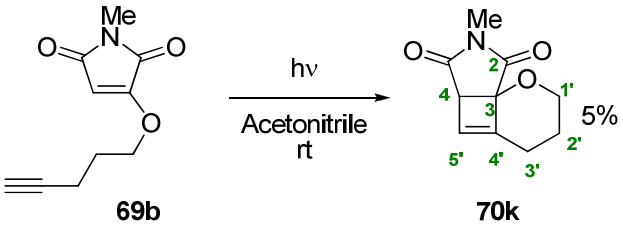
A solution of enamine **68f** (198 mg, 1.09 mmol) in degassed acetonitrile (150 mL) was irradiated with medium-pressure mercury lamp under nitrogen at room temperature through a Pyrex filter for 90 min. The resulting mixture was concentrated in vacuo and then purified by column chromatography (petroleum ether-EtOAc,9:1) to afford pale yellow crystals of tricycle **70f** (178 mg, 90% yield).

Spectroscopic data of **70f**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46-3.37 (m, 1H, H-4), 3.11 – 3.02 (m, 1H, H-3'), 2.96 (s, 3H, N-CH_3), 2.95- 2.91 (m, 1H , H-1'a), 2.85 (ddd, *J* = 10.5 Hz, *J* = 4.2 Hz, *J* =0.7 Hz, 1H, H-1'b), 2.41 (br. s., 1H, NH), 2.10 – 2.01 (m, 1H, H-4'a), 1.96-1.87 (m, 1H, H-4'b), 1.72-1.65 (m, 2H, H-2').

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (C-5), 177.9 (C-2), 69.5 (C-3), 48.2 (C-4), 43.2 (C-1'), 43.1 (C-4'), 32.8 (C-3'), 24.9 (C-2'), 24.5 (C-6).

7-Methyl-3,4-dihydro-2*H*-pyrano[2',3':1,4]cyclobuta[1,2-c]pyrrole-6,8(5a*H*,7*H*)-dione (70k)



69b **70k**

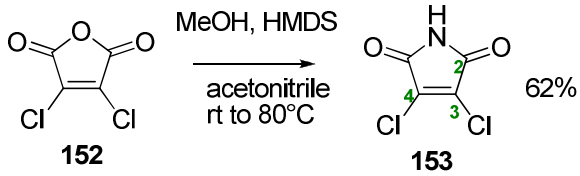
A solution of alkyne **69b** (200 mg, 1.0 mmol) in degassed acetonitrile (150 mL) was irradiated with a medium-pressure mercury lamp under nitrogen at room temperature through a Pyrex filter for 150 min. The resulting mixture was concentrated in vacuo and then purified by column chromatography (petroleum ether-EtOAc,9:1) to afford pale white oil of tricycle **70k** (5 mg, 5% yield).

Spectroscopic data of **70k**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (dd, *J* = 1.3 Hz, *J* = 2.2 Hz, 1H, H-5'), 4.54 (td, *J* = 12.2 Hz, *J* = 2.3 Hz, 1H, H-1'a), 4.04 (dddd, *J* = 12.0 Hz, *J* = 4.0 Hz, *J* = 2.6 Hz, *J* = 0.9 Hz, 1H, H-1'b), 3.42 (dd, *J* = 2.4 Hz, *J* = 1.1 Hz, 1H, H-4), 2.95 (s, 3H, H-6), 2.52-2.43 (m, 1H, H-3'), 2.43-2.29 (m, 1H, H-3'), 1.94-184 (m, 1H, H-2') 182-1.64 (m, 1H, H-2').

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 (C-5), 174.3 (C-2), 150.6 (C-4'), 126.4 (C-5'), 77.3 (C-3), 66.4 (C-1'), 50.1 (C-4), 26.2 (C-3'), 24.3 (N-CH_3), 24.1 (C-2').

3,4-Dichloromaleimide (153)



Methanol (6.0 mL, 150 mmol, 1 equiv) was carefully added to a solution of dichloromaleic anhydride (25 g, 150 mmol) and HMDS (62 mL, 300 mmol, 2 equiv) in dry acetonitrile (150 mL). The solution changed to a yellow colour and a precipitate was observed. The solution was then heated at 80℃ for 10 min, before cooling to room temperature and concentrating in vacuo. Purification by column chromatography (petroleum ether-EtOAc,10:1) gave dichloromaleimide (15.5 g, 62% yield) as pale yellow solid.

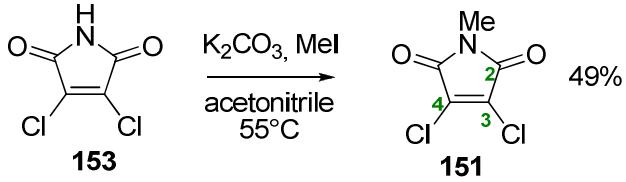
Physical and spectroscopic data of **153**:

^{13}C NMR (100 MHz, MeOD) δ 117,4 (2 x C=O), 87.0 (2 x C).

m.p. 178-180℃ (from EtOAc/petroleum ether) (lit. 178-1 80℃).

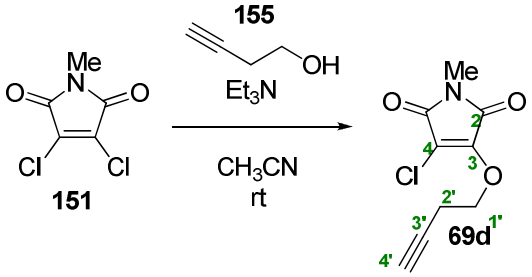
IR (neat) 3124, 1734, 735 cm^{-1}.

***N*-Methyl-3,4-dichloromaleimide 151**



To a solution of 3,4-dichloromaleimide (15.5 g, 93.4 mmol, 1 equiv) in dry acetonitrile (100 mL) were added potassium carbonate (15.5 g, 111.9 mmol, 1.2 equiv) and methyliodide (11.6 mL, 186.8 mmol, 2 equiv) dropwise. The mixture was heated until TLC analysis indicated complete conversion of the starting material. After being cooled down, the reaction mixture was concentrated in vacuo. Purification of the residue by column chromatography (petroleum ether-EtOAc, 5:1) gave *N*-methyl-3,4-dichloromaleimide as a pale yellow solid (8.7 g, 49 % yield).

3-(But-3-ynyloxy)-4-chloro-1-methyl-1*H*-pyrrole-2,5-dione (69d)

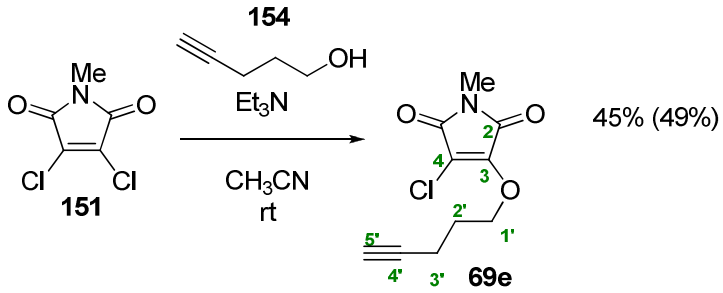


To a solution of 3,4-dichloromaleimide (0.95 g, 4.5 mmol) and 4-pentynol (0.58 mL, 7.7 mmol, 1.7 equiv) in dry acetonitrile (10 mL) was added triethylamine (1.0 mL, 7.2 mmol, 1.6 equiv). The resulting mixture was stirred at room temperature for 72h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford a dark orange oil (154 mg, 0.72 mmol, 16% yield, 19% yield considering the starting material recovered.

Spectroscopic data of **69d**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (t, $J_{1'\text{-}2'}$ = 6.9 Hz, 2 H, H-1'), 3.01 (s, 3 H, N-CH_3), 2.68 (td, $J_{2'\text{-}1'}$ = 6.9 Hz, $J_{2'\text{-}4'}$ = 2.8 Hz, 2 H, H-2'), 2.05 (t, $J_{4'\text{-}2'}$ = 2.7 Hz, 1 H, H-4').

3-Chloro-1-methyl-4-(pent-4-ynyloxy)-1*H*-pyrrole-2,5-dione (69e)



To a solution of 3,4-dichloromaleimide (1.5 g, 8.3 mmol) and 4-pentynol (0.93 mL, 9.9 mmol, 1.2 equiv) in dry acetonitrile (15 mL) was added triethylamine (1.5 mL, 10.8 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature for 72h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 20:1) to afford a yellow oil (845 mg, 3.7 mmol, 45% yield, 49% yield considering the starting material recovered).

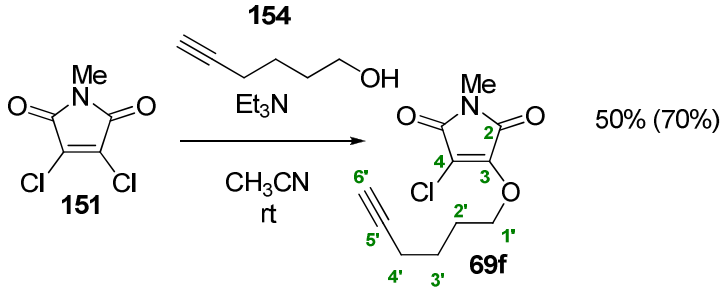
Spectroscopic data of **69e**:

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (t, $J_{1',2'}$=6.2Hz, 2H, H-1'), 3.03 (s, 3H, N-CH_3), 2.40 (d, $J_{3',2'}$=2.6 Hz, 2H, H-3'), 2.07-1.96 (m, 3H, H-5' and H-2').

^{13}C NMR (76 MHz, $CDCl_3$) δ 165.7 (C-5), 164.1 (C-2), 150.1 (C-3), 103.9 (C-4), 82.3 (C-4'), 70.9 (C-1'), 69.6 (C-5'), 28.3 (C-2'), 24.1 (C-6), 14.6 (C-3').

HRMS m/z (CI) ($C_{10}H_{10}ClNO_3$): calcd for $[M+H]^+$ 228.0435, found 228.0427.

3-Chloro-4-(hex-5-ynyloxy)-1-methyl-1*H*-pyrrole-2,5-dione (69f)



To a solution of 3,4-dichloromaleimide (1.0 g, 5.5 mmol) and 5-hexynol (0.75 mL, 6.7 mmol, 1.2 equiv) in dry acetonitrile (10 mL) was added triethylamine (1.0 mL, 7.2 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature for 48h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 4:1) to afford a yellow oil (674 mg, 2.8 mmol, 50% yield, 70% yield considering the starting material recovered).

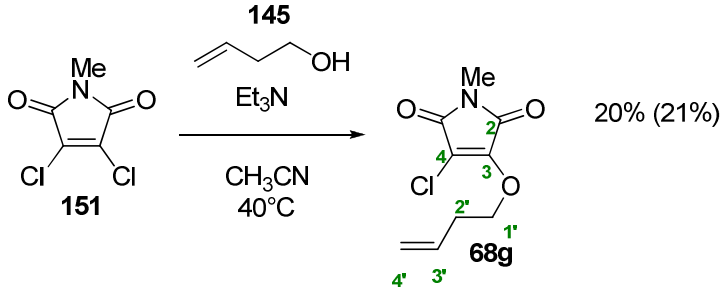
Spectroscopic data of **69f**:

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (t, $J_{1',2'}$ = 6.4 Hz, 2H, H-1'), 3.02 (s, 3H, N-CH_3), 2.26 (td, J = 6.9 Hz, J = 2.5 Hz, 2H, H-4'), 2.05-1.79 (m, 3H, H-6' and H-2'), 1.74 – 1.61 (m, 2H, H-3').

^{13}C NMR (76 MHz, $CDCl_3$) δ 165.7 (C-5), 164.2 (C-2), 150.1 (C-3), 103.5 (C-4), 83.4 (C-5'), 72.1 (C-1'), 69.0 (C-6'), 28.5 (C-2'), 24.2 (C-3'), 24.1 (N-CH_3), 17.9 (C-4').

HRMS m/z (CI) ($C_{11}H_{12}ClNO_3$): calcd for $[M+H]^+$ 242.0584, found 242.0591.

3-(But-3-enyloxy)-4-chloro-1-methyl-1*H*-pyrrole-2,5-dione (68g)



To a solution of 3,4-dichloromaleimide (0.7 g, 3.3 mmol) and 3-butenol (0.50 mL, 6.0 mmol, 1.2 equiv) in dry acetonitrile (15 mL) was added triethylamine (1.0mL, 7.26 mmol, 1.3 equiv). The resulting mixture was stirred at 40℃ for 48h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 20:1) to afford a pale yellow powder (141 mg, 0.6 mmol, 20% yield).

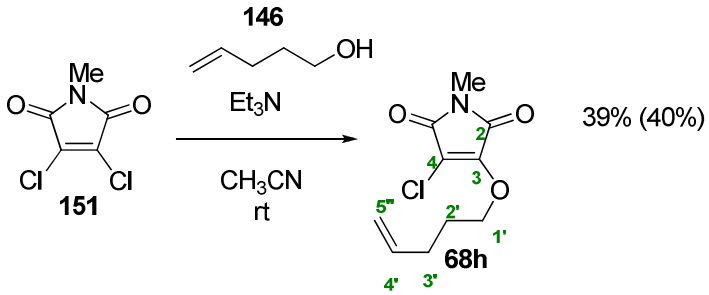
Spectroscopic data of **68g**:

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (ddt, *J* = 17.1 Hz, *J* = 10.3 Hz, $J_{3',2'}$ = 6.8 Hz, 1H, H-3'), 5.25-5.11 (m, 2H, H-4'), 4,67 (t, $J_{1',2'}$ = 6.8 Hz, 2H, H-1'), 3.03 (s, 3H, N-CH_3), 2.57 (qt, $J_{2',1'}$ = 6.8 Hz, $J_{2',3'}$ = 6.8 Hz, J_{gem} = 1.4 Hz, 2H, H-2').

^{13}C NMR (76 MHz, $CDCl_3$) δ 165.7 (C-5), 164.2 (C-2), 150.1 (C-3), 132.4 (C-3'), 118.4 (C-4'), 103.7 (C-4), 71.6 (C-1'), 33.9 (C-2'), 24.1 (CH_3)).

HRMS m/z (CI) ($C_9H_{10}ClNO_3$): calcd for $[M+H]^+$ 216.0427, found 216.0430.

3-Chloro-1-methyl-4-(pent-4-enyloxy)-1*H*-pyrrole-2,5-dione (68h)



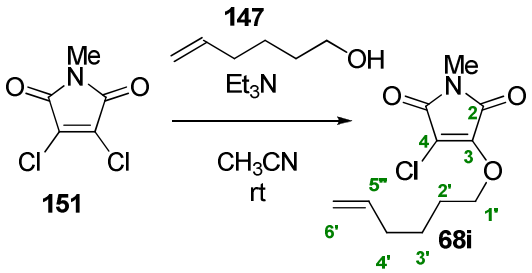
To a solution of 3,4-dichloromaleimide (1.0g, 5.5 mmol) and 4-pentenol (0.70 mL, 6.7 mmol, 1.2 equiv) in dry acetonitrile (10 mL) was added triethylamine (1.0 mL, 7.2 mmol, 1.3 equiv). The resulting mixture was stirred at room temperature for 72h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 20:1) to afford a yellow oil (493 mg, 2.1 mmol, 39% yield, 40% yield considering the starting material recovered).

Spectroscopic data of **68h**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85-5.73 (m, 1H, H-4'), 5.08-4.98 (m, 2H, H-5'), 4.61 (td, *J* = 6.6 Hz, *J* = 1.1 Hz, 2H, H-1'), 3.01 (s, 3H, *N*-CH_3), 2.19 (m, 2H, H-2'), 1.93-1.85 (m, 2H, H-3').

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (C-5), 164.1 (C-2), 150.1 (C-3), 136.7 (C-4'), 115.8 (C-5'), 103.4 (C-4), 71.9 (C-1'), 29.3 (C-2'), 28.6 (C-3'), 24.0 (C-6).

3-Chloro-4-(hex-5-enyloxy)-1-methyl-1*H*-pyrrole-2,5-dione (68i)



To a solution of 3,4-dichloromaleimide (1.5 g, 8.4 mmol) and 5-hexenol (2 mL, 16.7 mmol, 2 equiv) in dry THF (20 mL) was added triethylamine (2.5 mL, 18.4 mmol, 2.2 equiv). The resulting mixture was stirred at room temperature for 48h. The solvent was evaporated and the resulting oil was purified by column chromatography (petroleum ether-EtOAc, 20:1) to afford a yellow oil (1.0 g, 4.52 mmol, 54% yield, 58% yield considering the starting material recovered).

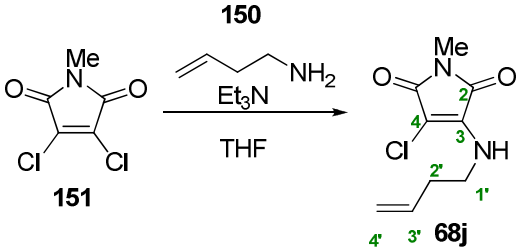
Spectroscopic data of **68i**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84-5.72 (m, 1H, H-5'), 5.05-493 (m, 2H, H-6'), 4.61 (td, *J* = 6.6 Hz, *J* = 2.0 Hz, 2H, H-1'), 3.01 (s, 3H, N-CH_3), 2.14-2.06 (m, 2H, H-2'), 1.85-1.76 (m, 2H, H-4'), 1.58-1.47 (m, 2H, H-3').

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8 (C-5), 164.2 (C-2), 150.2 (C-3), 137.9 (C-5'), 115.1 (C-6'), 103.2 (C-4), 72.6 (C-1'), 30.1 (C-2'), 28.9 (C-4'), 24.5 (C-3'), 24.1 (C-6).

HRMS *m/z* (CI) ($C_{11}H_{14}ClNO_3$): calcd for $[M+H]^+$ 244.0740, found 244.0741.

3-(But-3-enylamino)-4-chloro-1-methyl-1*H*-pyrrole-2,5-dione (68j)

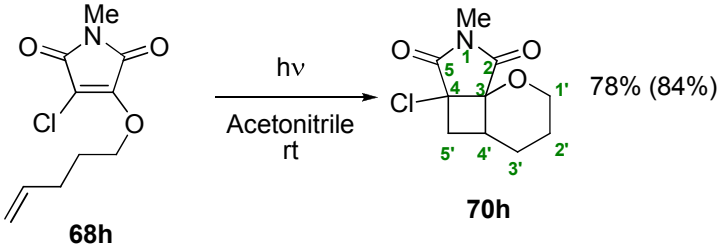


To a solution of 3,4-dichloromaleimide (2.0 g, 11.1 mmol) and but-3-en-1-amine (1.0 g, 14.1 mmol, 1.3 equiv) in dry THF (25 mL) was added triethylamine (2.5 mL, 17.3 mmol, 1.6 equiv). The resulting mixture was stirred at room temperature for 72h. The sovent was evaporated and the resulting oil was purified by column chromatography on silica gel (petroleum ether-EtOAc, 9:1) to afford a dark orange oil (154 mg, 0.72 mmol, 16% yield, 19% yield considering the starting material recovered).

Spectroscopic data of **68j**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.68 - 5.83 (m, 1 H, H-3'), 5.05 - 5.20 (m, 2 H, H-4'), 4.80 (s, 1 H, N-H), 3.16 - 3.31 (m, 2 H, H-1'), 2.94 (s, 3 H, H-NMe), 2.33 - 2.43 (m, 2 H, H-3').

5a-Chloro-7-methyltetrahydro-2H-pyrano[2',3':1,4]cyclobuta[1,2-*c*]pyrrole-6,8(3*H*,7*H*)-dione (70h)



A solution of alkene **68h** (200 mg, 1.0 mmol) in degassed acetonitrile (150 mL) was irradiated with medium-pressure mercury lamp under nitrogen at room temperature through a Pyrex filter for 150 min. The resulting mixture was concentrated in vacuo and then purified by column chromatography (petroleum ether-EtOAc, 9:1) to afford pale yellow crystals of tricycle **70h** (156 mg, 78% yield).

A solution of alkene **68h** (1.2 g, 5.2 mmol) in degassed acetonitrile (0.9 L) was irradiated with 400W medium-pressure mercury lamp under nitrogen at room temperature with a Flow continous reactor with a rate of 90 mL / min in a circuit of 30 mL (6 min of irradiation). The resulting mixture was concentrated in vacuo and then

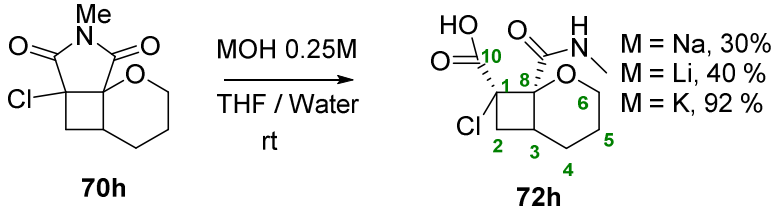
purified by column chromatography (petroleum ether-EtOAc,9:1) to afford pale yellow crystals of tricycle **70h** (800 mg, 67% yield) and dimer byproduct (350 mg, 29% yield)

Spectroscopic data of **70h**:

^{1}H NMR (301 MHz, $CDCl_3$) δ 4.09 - 4.22 (m, 1 H, H-1'a), 3.92 - 4.05 (m, 1 H, H-1'b), 3.02 - 3.06 (m, 3 H, H-NMe), 2.70 (m, 1 H, H-4'), 2.38 - 2.52 (m, 2 H, H-5'), 2.00 (s, 1 H, H-3'), 1.59 - 1.90 (m, 3 H, H-3' and H-2').

HRMS m/z (CI) ($C_{10}H_{12}ClNO_3$): calcd for $[M+H]^+$ 230.0584, found 230.0593.

(1*R*,8*R*)-8-Chloro-1-(methylcarbamoyl)-2-oxabicyclo[4.2.0]octane-8-carboxylic acid (72h)



70h **72h**

To a solution of cyclobutane **70h** (100 mg, 0.44 mmol) in 3 mL of dry THF was added 1 mL of a solution of potassium hydroxide 0.25M (0.57 mmol, 1.3 equiv) and allowed to react for 24h. After neutralization with HCl to pH 3 and addition of ethyl acetate, the organic layer was separated, dried over $MgSO_4$ and evaportated to afford 126 mg of **72h** (0.51 mmol, 90% yield).

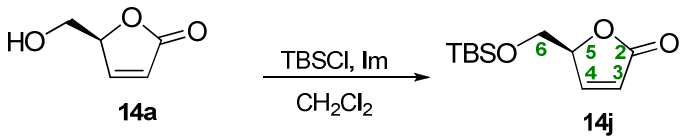
Spectroscopic data of **72h**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (dd, $J_{NH,11}$ = 4.9 Hz, 1H, N-H), 4.04 (m, 1H, H-3a), 3.59 (td, J_{gem} = 11.6 Hz, $J_{3b,4}$ = 1.7 Hz, 1H, H-3b), 3.24 (m, 1H, H-6), 2.87 (d, $J_{11,NH}$ = 4.9 Hz, 3H, H-11), 2.69 (dd, J_{gem} = 11.2 Hz, $J_{7a,6}$= 8.8 Hz, 1H, H-2a), 2.46 (t, J_{gem} = 11.2 Hz, $J_{7b,6}$ = 11.2 Hz, 1H, H-2b), 1.83 (m, 2H, H-5a and H-4a), 1.54 (m, 2H, H-5b and H-4b).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 169.8 (C-9) 169.6 (C-10), 125.5 (C-9), 80.5 (C-1), 69.3 (C-6), 64.5 (C-3), 35.9 (C-2), 30.5 (C-4), 27.1 (N-CH_3), 21.1 (C-5).

6.3. Experimental part of chapter 4:

(-)-(5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-2(5*H*)-furanone (14j)



To a solution of **14a** (5.00 g, 0.04 mol) in CH_2Cl_2 (130 mL) at 0ºC, imidazole (4.6 g, 0.07 mol) and *tert*-butyldimethylsilyl chloride (8.99 g, 0.06 mmol) were successively added. The mixture was allowed to warm to room temperature and stirred for 16h. Then, it was diluted with CH_2Cl_2 (200 mL) and water (300 mL) was added. The mixture was separated and the organic layer was washed with two more portions of water (100 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent to dryness gave a reaction crude which was purified by column chromatography (hexanes-EtOAc, 6:1) to afford **14j** (10.00 g, 0.04 mol, 99% yield) as a white solid.

Physical and spectroscopic data of **14j**:

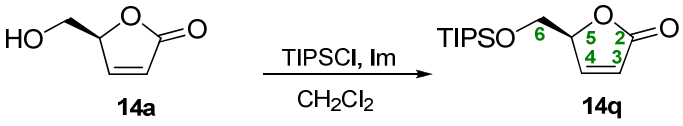
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.49 (dd, $J_{4,3}$ = 5.8 Hz, $J_{4,5}$ = 1.6 Hz, 1H, H-4), 6.15 (dd, $J_{3,4}$ = 5.8 Hz, $J_{3,5}$ = 2.0 Hz, 1H, H-3), 5.05 (dddd, $J_{5,6}$ = 5.4 Hz, $J_{5,6}$ = 4.5 Hz, $J_{5,3}$ = 2.0 Hz, $J_{5,4}$ = 1.6 Hz, 1H, H-5), 3.93 (dd, J_{gem} = 10.8 Hz, $J_{6,5}$ = 4.5 Hz, 1H, H-6), 3.79 (dd, J_{gem} = 10.8 Hz, $J_{6,5}$ = 5.4 Hz, 1H, H-6), 0.86 (s, 9H, TBDMS), 0.07 (s, 3H, TBDMS), 0.06 (s, 3H, TBDMS).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.9 (C-2), 154.3 (C-4), 122.5 (C-3), 83.3 (C-5), 62.9 (C-6), 25.7 (TBDMS), 18.2 (TBDMS), -5.5 (TBDMS), -5.6 (TBDMS).

$[\alpha]_D$ -127 (*c* 4.8, $CHCl_3$)

IR (ATR) 1747, 1605, 133 cm^{-1}.

(S)-5-((Triisopropylsilyloxy)methyl)furan-2(5*H*)-one (14q)



To a solution of **14a** (1.00 g, 8.76 mmol) in CH_2Cl_2 (45 mL) at 0ºC, imidazole (895 mg, 13.15 mmol, 1.75 equiv) and tri*iso*propyl triflate (2.94 g, 10.9 mmol, 1.5 equiv) were

successively added. The mixture was allowed to warm to room temperature and stirred for 16 h. Then it was diluted with CH_2Cl_2 (15 mL) and water (20 mL) was added. The mixture was separated and the organic layer was washed with two more portions of water (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent to dryness gave a reaction crude which was purified by column chromatography (hexanes-EtOAc 6:1) to afford **14q** (2.37 g, 8.70 mmol, 99% yield) as a colourless oil.

Spectroscopic data of **14q**:

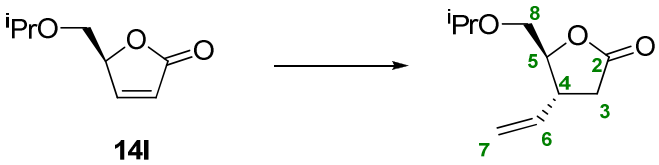
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.54 (dd, $J_{4,3}$ = 5.7 Hz, $J_{4,5}$= 1.5 Hz, 1H, H-4), 6.16 (dd, $J_{3,4}$ = 5.7 Hz, $J_{3,5}$= 1.9 Hz, 1H, H-3), 5.07 (ddt, $J_{5,6b}$ = 5.9 Hz, $J_{5,6a}$ = 4.5 Hz, $J_{5,3}$ = 1.9 Hz, $J_{5,4}$ = 1.5 Hz, 1H, H-5), 4.05 (dd, $J_{6a,6b}$ = 10.4 Hz, $J_{6a,5}$ = 4.5 Hz, 1H, H-6a), 3.86 (dd, $J_{6b,6a}$ = 10.4 Hz, $J_{6b,5}$= 5.9 Hz, 1H, H-6b), 1.09 – 0.98 (m, 21H, TIPS).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 173.1 (C-2), 154.7 (C-4), 122.5 (C-3), 83.5 (C-5), 63.6 (C-6), 18.0 (CH_3), 18.0 (CH_3), 11.9 (CH).

HMRS *m/z* (ESI-TOF) ($C_{14}H_{26}O_3Si$): calcd for ([M+Na]$^+$) 293.1543, found 293.1545.

IR (ATR) 2943, 2892, 2865, 1755, 1463, 1159, 1141, 1099 cm^{-1}.

(4*R*,5*S*)-5-(isoPropoxymethyl)-4-vinyldihydrofuran-2(3*H*)-one (208l)



A 10 mL Schlenk flask was charged with CuCl (3 mg, 0.032 mmol) and LiCl (5 mg, 0.064 mmol) and stirred under vacuum for 1h. Then, THF (2mL) was added to give a yellow-green solution. The solution was cooled to -40℃, vinylmagnesium chloride (640 µL, 0.64 mmol) was added and the solution was stirred for 10 min, after which a solution of furanone **14l** (50 mg, 0.32 mmol) in 1 mL of THF was added via cannula. After stirring for 2h, the cooling bath was removed, the solution warmed to room temperature and quenched with 1 mL of saturated ammonium chloride solution. Evaporation of the solvent, extraction with CH_2Cl_2 (3x2mL) and evaporation of the solvent afforded the desired alkene **208l** (53 mg, 0.288 mmol, 89% yield).

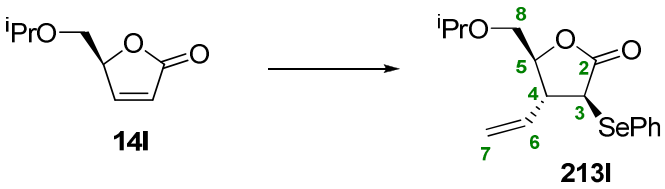
Spectroscopic data of **208l**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 17.2 Hz, *J* = 10.2 Hz, *J* = 7.9 Hz, 1H, H-6), 5.25 – 5.08 (m, 2H, H-7), 4.30 (ddd, *J* = 7.1 Hz, *J*= 4.2 Hz, *J* = 2.8 Hz, 1H, H-5), 3.73 – 3.52 (m, 3H, H-8 and H-1'), 3.18-2.99 (m, 1H, H-4), 2.79 (dd, $J_{3a,3b}$ = 17.5 Hz, $J_{3a,4}$ = 8.5 Hz, 1H, H-3a), 2.42 (dd, $J_{3b,3a}$ = 17.5 Hz, $J_{3b,4}$ = 8.5 Hz, 1H, H-3b), 1.18 (d, $J_{2',1'}$ = 1.1 Hz, 3H, H-2'), 1.16 (d, $J_{2',1'}$ = 1.1 Hz, 3H, H-2').

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.1 (C-2), 136.5 (C-6), 117.6 (C-7), 83.8 (C-5), 72.7 (C-1'), 67.9 (C-6), 41.6 (C-4), 35.1 (C-3), 22.1 (C-2'), 22.0 (C-2').

HRMS *m/z* (ESI-TOF) ($C_{10}H_{16}O_3$): calcd for $[M+Na]^+$ 207.0992, found 207.0987.

(3*S*,4*R*,5*S*)-5-(isopropoxymethyl)-3-(phenylselanyl)-4-vinyldihydrofuran-2(3*H*)-one (213l)



A 100 mL Schlenk flask was charged with CuCl (38 mg, 0.38 mmol) and LiCl (54 mg, 0.76 mmol) and stirred under vacuum for 1h. Then, THF (18 mL) was added to give a yellow-green solution. The solution was cooled to -40℃, vinylmagnesium chloride (5.1 mL, 5.1 mmol) was added and the solution was stirred for 10 min, after which a solution of furanone **14l** (400 mg, 2.56 mmol) in 9 mL of THF was added via cannula. After 1h, the reaction mixture was quenched with a solution of diphenyldiselenide (520 mg, 1.66 mmol 0.65 eq) and bromine (85 µL, 1.66 mmol, 0.65 eq) in anhydrous THF (10mL). After stirring for 2h, the cooling bath was removed, the solution warmed to room temperature and quenched with 13 mL of saturated ammonium chloride solution. Evaporation of the solvent and extraction with CH_2Cl_2 (3x2mL) afforded the desired alkene **231l** (738 mg, 2.17 mmol, 85% yield).

Spectroscopic data of **231l**:

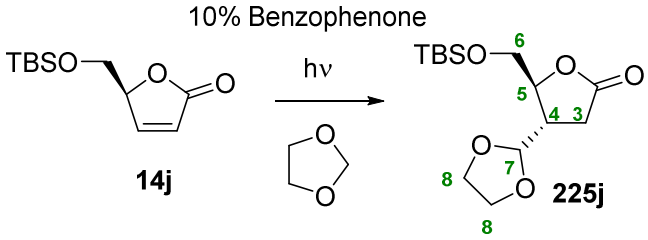
^{1}H NMR (250 MHz, $CDCl_3$) δ 7.74 – 7.62 (m, 2H, H-Ph), 7.42 – 7.30 (m, 3H, H-Ph), 5.95 (ddd, *J* = 17.0 Hz, *J* = 10.3 Hz, *J* = 8.5 Hz, 1H, H-6), 5.38 – 5.21 (m, 2H, H-7), 4.35 (ddd, *J* = 8.3 Hz, *J* = 4.1 Hz, *J* = 2.3 Hz, 1H, H-5), 4.11 (d, $J_{3,4}$ = 7.7 Hz, 1H, H-3), 3.78 – 3.47 (m, 3H, H-8 and H-1'), 3.45 – 3.26 (m, 1H, H-4), 1.17 (s, 3H), 1.14 (s, 3H).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 174.8 (C-2), 136.3 (C-Ph), 135.5 (C-6), 133.5 (C-Ph), 131.6 (C-Ph), 129.4 (C-Ph), 128.9 (C-Ph), 120.3 (C-7), 81.9 (C-5), 72.7 (C-8), 66.8 (C-1'), 46.2 (C-4), 44.1 (C-3), 22.13 (C-2'), 22.0 (C-2').

HRMS *m/z* (ESI-TOF) ($C_{16}H_{20}O_3Se$): calcd for $[M+Na]^+$ 363.0471, found 363.0460.

IR (ATR) 2970, 2927, 2863, 1768, 1743, 1666, 1477, 1369, 1126 cm^{-1}.

(4*S*,5*S*)-5-(*tert*-Butyldimethylsilyloxy)methyl-4-(1,3-dioxolan-2-yl)tetrahydro-2-furanone (225j)



A solution of furanone **14j** (17.16 mmol) in 650 mL of dioxolane with benzophenone (381 mg, 1.8 mmol, 0.1 equiv) was irradiated for 10h with a 400W medium pressure mercury lamp in a batch reactor cooled down at -40°C through a Pyrex jacket cooled down at -15℃. Evaporation of the solvent and colum n chromatography of the resulting oil (hexanes-EtOAc, 3:1) afforded 5.3 g (17.0 mmol, 99% yield) of the desired acetal **225j**.

Physical and spectroscopic data of **225j**:

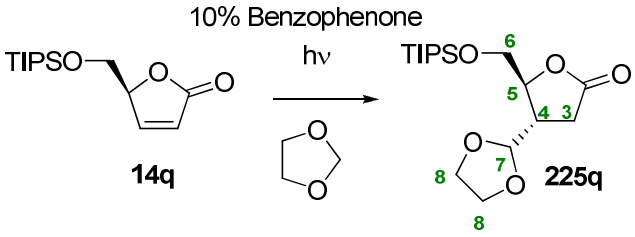
^{1}H NMR (250 MHz, $CDCl_3$) δ 4.86 (d, $J_{7,4}$ = 3.7 Hz, 1H, H-7), 4.48 (m, 1H, H-5), 3.99-3.84 (m, 5H, 4H-8, H-6), 3.65 (dd, J_{gem} = 11.3 Hz, $J_{6,5}$ = 2.6 Hz,1H, H-6), 2.80-2.60 (m, 2H, H-4 and H-3), 2.44 (dd, J_{gem} = 17.0 Hz, $J_{3,4}$ = 3.8 Hz, 1H, H-3), 0.85 (s, 9H, TBDMS), 0.04 (s, 3H, TBDMS), 0.03 (s, 3H, TBDMS).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.5 (C-2), 103.8 (C-7), 80.3 (C-5), 65.4 (C-8a), 65.3 (C-8b), 64.7 (C-6), 39.7 (C-4), 30.1 (C-3), 25.7 (TBDMS), 18.1 (TBDMS), -5.6 (TBDMS), -5.7 (TBDMS).

$[\alpha]^{23}_D$: +18.0 (*c* 1.3, $CHCl_3$) (lit., $[\alpha]^{23}_D$: +18.3 (*c* 1.3, $CHCl_3$)).

IR (ATR) 2953, 2929, 2857, 1777, 1121 cm^{-1}.

(4*S*,5S)-4-(1,3-Dioxolan-2-yl)-5-(((tri*iso*propylsilyl)oxy)methyl)dihydrofuran-2(3*H*)-one (225q)



A solution of furanone **14q** (8.8 mmol) in 400mL of dioxolane with benzophenone (160 mg, 0.88 mmol, 0.1 equiv) was irradiated for 12h 30 with a 125W high pressure mercury lamp in a batch reactor cooled down at -20°C. The jacket was cooled down at -15℃. Evaporation of the solvent and purification by column chromatography of the resulting oil (hexanes-EtOAc, 3:1) afforded 2.6 g (7,9 mmol, 90% yield) of the desired acetal **225q** and 140 mg (0.526 mmol, 6%) of the starting material.

Physical and spectroscopic data of **225q**:

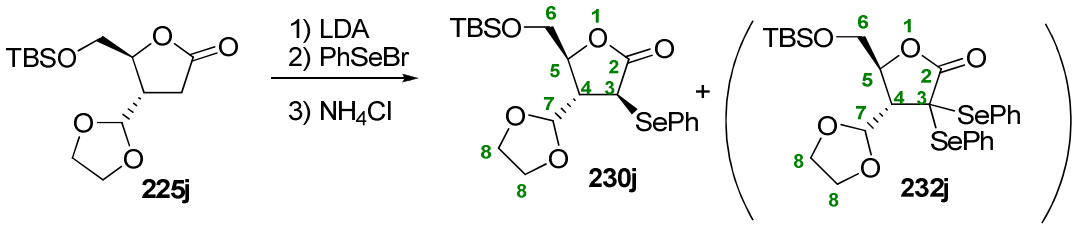
^{1}H NMR (250 MHz, $CDCl_3$) δ 4.91 (d, $J_{7,4}$ = 3.8 Hz, 1H, H-7), 4.53 (dd, $J_{5,4}$ = 6.0 Hz, $J_{5,6}$ = 2.6 Hz, 1H, H-5), 4.06 – 3.85 (m, 5H, H-8 and H-6), 3.78 (dd, J_{gem} = 11.1 Hz, $J_{6,5}$ = 2.6 Hz, 1H, H-6), 2.93 – 2.64 (m, 2H, H-3 and H-4), 2.48 (dd, J_{gem} = 17.4 Hz, $J_{3,4}$ = 4.1 Hz, 1H, H-3), 1.11 – 0.94 (m, 21H, TIPS).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.6 (C-2), 104.1 (C-7), 80.5 (C-5), 65.6 (C-8), 65.5 (C-8), 65.2 (C-6), 39.7 (C-4), 30.2 (C3), 18.0 (TIPS), 18.0 (TIPS), 12.0 (TIPS).

HRMS *m/z* (ESI-TOF) ($C_{17}H_3O_5Si$): calcd for ($[M+Na]^+$) 367.1911, found:367.1918.

IR (ATR) 2943, 2890, 2865, 1776, 1461, 1170, 1120, 881 cm^{-1}.

(3*S*,4*S*,5*S*)-5-(((tert-Butyldimethylsilyl)oxy)methyl)-4-(1,3-dioxolan-2-yl)-3-(phenylselanyl)dihydrofuran-2(3*H*)-one (230j)



To a solution of di*iso*propylamine (1.6 mL, 11.65 mmol, 1.1 equiv.) and nbutyllithium 1.6M in hexanes (7.3 mL, 11.65 mmol, 1.1equiv) in dry THF (24 mL) at -78℃ was

added dropwise a solution of **225j** (3.2 g, 10.6 mmol) in dry THF (34 mL) at -78ºC, under nitrogen. After 1h of stirring at -78 ºC, a solution of phenylselenyl bromide (PhSeBr) (3.75 g, 15.9 mmol) in dry THF (35 mL) was added dropwise and the reaction mixture was further stirred for 30 min. Then, the reaction mixture was quenched by the slow addition of a saturated NH_4Cl aqueous solution (20 mL) and allowed to warm to room temperature. The phases were separated and the aqueous layer was extracted with diethyl ether (3x30 mL). The collected organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. Purification of the crude by column chromatography (hexanes-diethyl ether, 15:1) afforded diastereomer **230j** (4.50 g, 9.83 mmol, 93% yield) as a yellow oil.

Physical and spectroscopic data of **230j**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.68 (m, 2H, H-Ph), 7.30 (m, 3H, H-Ph), 4.91 (d, $J_{7,4}$ = 3.2 Hz, 1H, H-7), 4.40 (q, $J_{5,6a} \approx J_{5,6b} \approx J_{5,4}$ =4.7 Hz, 1H, H-5), 3.95-3.81 (m, 5H, H-3 and 4H-8), 3.66 (dd, J_{gem} =11.3 Hz, $J_{6b,5}$ = 4.0 Hz, 1H, H-6b), 3.50 (dd, J_{gem}=11.3 Hz, $J_{6a,5}$=4.7 Hz,1H, H-6a), 2.79 (ddd, $J_{4,3}$ = 6.6 Hz, $J_{4,5}$ = 5.5 Hz, $J_{4,7}$ = 3.2 Hz, 1H, H-4), 0.86 (s, 9H, *t*Bu), 0.04 (s, 3H, CH_3 TBS), 0.03 (s, 3H, CH_3 TBS).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.4 (C-2), 135.5 (C-Ph), 129.3 (C-Ph), 128.8 (C-Ph), 127.9 (C-Ph), 102.8 (C-7), 78.9 (C-5), 65.5 (C-8), 65.3 (C-8), 64.3 (C-6), 46.4 (C-4), 38.0 (C-3), 25.9 (*t*Bu), 18.4 (*t*Bu), -5.3 (CH_3 TBS).

HRMS *m/z* (ESI-TOF) ($C_{20}H_{30}O_5SeSi$): calcd for $[M+H]^+$ 459.1102, found 459.1100.

$[\alpha]^{20}_D$ -19.5 (*c* 1.13, $CHCl_3$)**.**

IR (ATR) 2953, 2857, 1770, 1473, 1254, 1131 cm^{-1}.

Physical and spectroscopic data of **232j**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.72 (m, 2H, H-Ph), 7.61 (m, 2H, H-Ph), 7.20-7.42 (m, 6H, H-Ph), 5.22 (d, $J_{7,4}$ = 3.3 Hz, 1H, H-7), 4.54 (ddd, $J_{5,4}$ = 9.7 Hz, $J_{5,6b}$ = 4.1 Hz, $J_{5,6a}$ = 2.0 Hz, 1H, H-5), 3.94-3.81 (m, 5H, 4H-8, H-6a), 3.42 (dd, J_{gem} = 11.9 Hz, $J_{6b,5}$ = 4.1 Hz,1H, H-6b), 2.92 (dd, $J_{4,5}$ = 9.8 Hz, $J_{4,7}$ = 3.3 Hz, 1H, H-4), 0.74 (s, 9H, *t*Bu), -0.10 (s, 3H, CH_3 TBS), -0.15 (s, 3H, CH_3 TBS).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.0 (C-2), 138.3 (C-Ph), 137.5 (C-Ph), 130.2 (C-Ph), 129.7 (C-Ph), 129.3 (C-Ph), 128.9 (C-Ph), 127.7 (C-Ph), 126.0 (C-Ph), 102.0 (C-7),

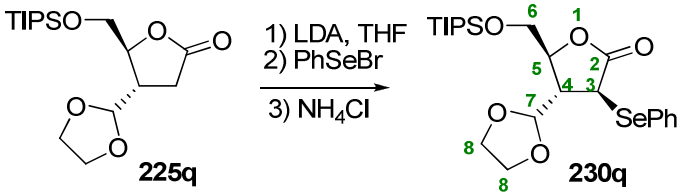
77.9 (C-5), 65.3 (C-8), 64.6 (C-8), 62.7 (C-6), 48.8 (C-3), 47.7 (C-4), 25.8 (*t*Bu), 18.4 (*t*Bu), -5.4 (CH_3 TBS), -5.5 (CH_3 TBS).

HRMS *m/z* (ESI-TOF) ($C_{26}H_{34}O_5Se_2Si$): calcd for $[M+H]^+$ 615.0584,found 615.0583.

$[\alpha]^{20}_D$ +54.9 (*c* 1.33, $CHCl_3$).

IR (ATR) 2927, 2855, 1767, 1473, 1252, 1167 cm^{-1}.

(3*S*,4*S*,5*S*)-5-((Triisopropylsilyloxy)methyl)-4-(1,3-dioxolan-2-yl)-3-(phenylselanyl)dihydrofuran-2(3*H*)-one (230q)



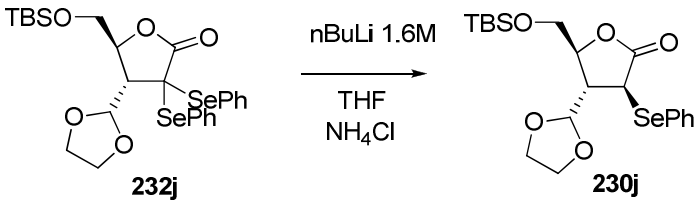
To a solution of di*iso*propylamine (3.0 mL, 21.7 mmol, 1.1 equiv) and *n*butyllithium 1.6M in hexanes (13.5 mL, 21.7 mmol, 1.1 equiv) in dry THF (60 mL) at -78℃ was added dropwise a solution of **225q** (6.8 mg, 19.7 mmol) in dry THF (60 mL) at -78ºC, under nitrogen. After 1h of stirring at -78ºC, a solution of diphenylselenide (3.99 mg, 12.81 mmol) and bromide (650 µL, 12.8 mmol) in dry THF (60 mL) was added dropwise and the reaction mixture was further stirred for 30 min. Then, the reaction mixture was quenched by the slow addition of a saturated NH_4Cl aqueous solution (60 mL) and allowed to warm to room temperature. The phases were separated and the aqueous layer was extracted with diethyl ether (3x45 mL). The collected organic layers were dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. Purification of the crude by column chromatography (hexanes-diethyl ether, 15:1) afforded diastereomer **230q** (8.6 g, 17.1 mmol, 87% yield) as a yellow oil and starting material (400 mg, 1.2 mmol, 6%).

Spectroscopic data of **230q**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.72 – 7.57 (m, 2H, Ph), 7.40 – 7.27 (m, 3H, Ph), 4.99 – 4.90 (d, $J_{7,4}$ = 3.0 Hz, 1H, H-7), 4.65 – 4.51 (m, 1H, H-5), 4.05 – 3.78 (m, 5H, H-4 and H-8), 3.58 – 3.43 (m, 1H, H-6a), 3.39 – 3.25 (dd, J_{gem} = 10.7, $J_{6b,5}$ = 5.6 Hz, 1H, H-6b), 2.85 – 2.70 (m, 1H, H-3), 1.59 – 1.51 (d, *J* = 0.7 Hz, 21H, TIPS).

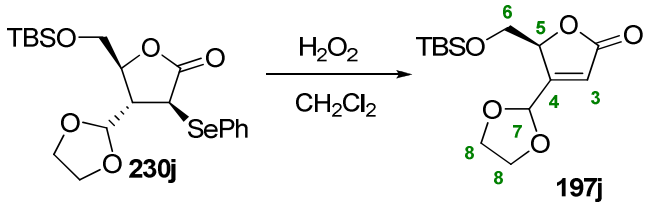
^{13}C NMR (62.5 MHz, $CDCl_3$) δ 175.7 (C-2), 136.0 (C-Ph), 129.7 (C-Ph), 129.3 (C-Ph), 128.8 (C-Ph), 127.9 (C-Ph), 103.0 (C-7), 84.6 (C-5), 70.3 (C-6), 65.9 (C-8), 65.7 (C-8), 47.3 (C-3), 38.2 (C-4), 31.9 (C-TIPS), 23.0 (C-TIPS).

(3*S*,4*S*,5*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-(1,3-dioxolan-2-yl)-3-(phenylselanyl)dihydrofuran-2(3*H*)-one (230j)



To a solution of diselenide **232j** (5.06 mmol) in dry THF (80 mL) under nitrogen at -78ºC was added dropwise 4.43 mL of *n*-butyllithium 1.6M in hexanes (7,08 mmol, 1.4 equiv). After 1h, the reaction is quenched by saturated solution of ammonium chloride (30 mL) and the reaction was allowed to warm to room temperature. The solution was evaporated, affording 2.09 g of selenide **230j** (4.55 mmol, 90% yield) which was used in the next step without further purification.

(*S*)-5-(((*tert*-Butyldimethylsilyl)oxy)methyl)-4-(1,3-dioxolan-2-yl)furan-2(5*H*)-one (197j)



To a solution of the selenide **230j** (1.00 g, 2.18 mmol) in CH_2Cl_2 (20 mL) at 0ºC, 30% H_2O_2 (1.20 mL) was added dropwise. The mixture was allowed to slowly warm to room temperature. Then, 10 mL of water were added and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2x10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. Purification of the crude by column chromatography (hexanes-diethyl ether, 6:1) afforded **197j** (637 mg, 2.12 mmol, 97% yield) as a yellow oil.

Physical and spectroscopic data of **197j**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 6.09 (t, $J_{3,7} \approx J_{3,5} \approx$ 0.7 Hz, 1H, H-3), 5.69 (bs, 1H, H-7), 5.01 (m, 1H, H-5), 4.03-3.88 (m, 6H, 2H-6, 4H-8), 0.81 (s, 9H,TBDMS), 0.02 (s, 3H, CH_3 TBDMS), 0.01 (s, 3H, CH_3 TBDMS).

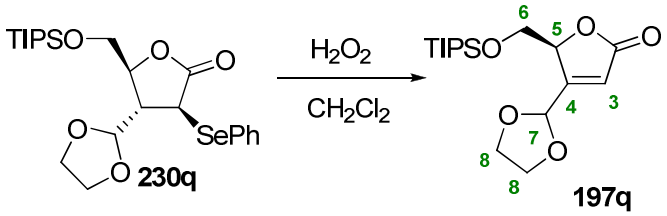
^{13}C NMR (62.5 MHz, $CDCl_3$) δ 172.0 (C-2), 164.9 (C-4), 119.2 (C-3), 98.4 (C-7), 82.7 (C-5), 65.1 (C-8a), 65.0 (C-8b), 61.8 (C-6), 25.6 (TBDMS), 18.4 (TBDMS), -5.7 (TBDMS).

HMRS *m/z* (%) (ESI) ($C_{14}H_{24}O_5Si$): calcd for $[M+Na]^+$ 323.1291, found 323.1312.

$[\alpha]^{20}_D$ +54.5 (*c* 3.91, CH_2Cl_2).

IR (ATR) 2954, 2930, 2857, 1759, 1472, 1255, 1132 cm^{-1}.

(*S*)-5-((Triisopropylsilyloxy)methyl)-4-(1,3-dioxolan-2-yl)furan-2(5*H*)-one (197q)



To a solution of the selenide **230q** (1.4 g, 2.78 mmol) in CH_2Cl_2 (20 mL) at 0ºC, 30% H_2O_2 (1.20 mL) was added dropwise. The mixture was allowed to slowly warm to room temperature. Then, 10 mL of water were added and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2x10 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. Purification of the crude by column chromatography (hexanes-diethyl ether 6:1) afforded **197q** (757 mg, 2.21 mmol, 79% yield) as a yellow oil.

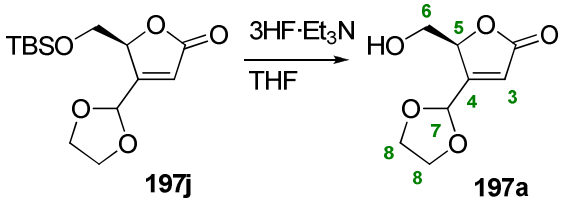
Spectroscopic data of **197q**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 – 6.10 (t, *J* = 1.5 Hz, 1H, H-3), 5.80 – 5.68 (d, *J* = 0.8 Hz, 1H, H-6), 5.08 – 5.02 (tdd, *J* = 3.1 Hz, *J* = 1.9 Hz, *J* = 0.5 Hz, 1H, H-5), 4.29 – 3.82 (m, 6H, H-8 and H-6), 1.16 – 0.92 (m, 21H, TIPS).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1(C-2), 165.3(C-4), 119.2 (C-3), 98.7 (C-5), 82.9 (C-7), 65.4 (C-8), 65.2 (C-8), 62.4 (C-6), 18.0 (TIPS), 17.9 (TIPS), 12.0 (TIPS).

HRMS *m/z* (ESI-TOF) ($C_{17}H_{30}O_5Si$): calcd for $[M+H]^+$ 365.1755, found 365.1750.

(5*S*)-4-(1,3-Dioxolan-2-yl)-5-hydroximethyl-2(5*H*)-furanone (197a)



To solution of furanone **197j** (715 mg, 2.4 mmol) in THF (18 mL) at 0ºC, was added dropwise 1,55 mL (2.52 mmol, 4 equiv) of triethylamine trihydrofluoride. After 24h, the solvent was evaporated. The resulting residue was taken in CH_2Cl_2, and washed with sodium bicarbonate, dried over magnesium sulphate. Evaporation of the solvent afforded a crude which was purified by column chromatography (hexanes-diethyl ether, 5:1) to deliver the desired alcohol **197a** (1.428 mmol, 60% yield).

Spectroscopic data of **197a**:

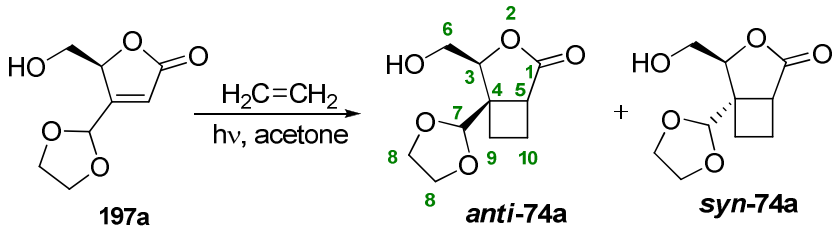
^{1}H NMR (250 MHz, $CDCl_3$) δ 6.18 (m, 1H, H-3), 5.67 (bs, 1H, H-7), 5.09 (dddd, *J*=3.9 Hz, *J* = 3.4 Hz, *J* = 1.9 Hz, *J* = 0.5Hz, 1H,H-5), 4.03-3.96 (m, 5H, H-6, 4H-8), 3.84 (ddd, *J*≈13.3 Hz, *J* ≈ 6.0 Hz, *J* ≈ 3.9 Hz, 1H, H-6), 2.31 (t, $J_{OH,6}$ = 6.9 Hz, 1H, OH).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 171.6 (C-2), 163.6 (C-4), 120.6 (C-3), 98.1 (C-7), 82.8 (C-5), 65.5 (C-8), 65.4 (C-8), 61.7 (C-6).

IR (ATR) 3429, 2896, 1752, 1151, 1097 cm^{-1}.

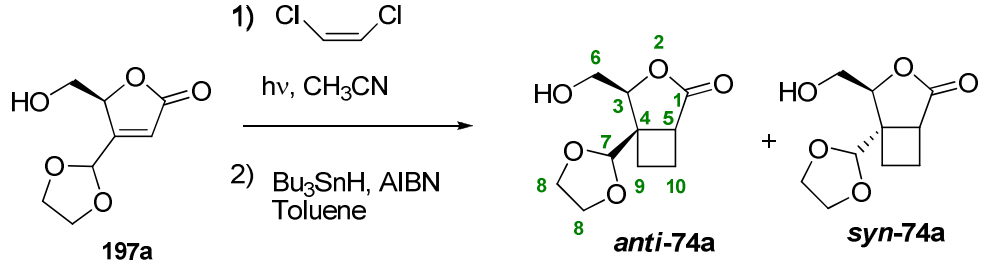
HRMS *m/z* (ESI-TOF) ($C_8H_{10}O_5$): calcd for $[M+Na]^+$ 209.0420, found 209.0420.

(1*R*,4*S*,5*R*)-5-(1,3-Dioxolan-2-yl)-4-(hydroxymethyl)-3-oxabicyclo[3.2.0]heptan-2-one (74a)



A solution of lactone **197a** (102 mg, 0.55 mmol) in acetone (60 mL) was irradiated through a pyrex filter with introduction of ethylene for 3h at -20ºC with a 125W high pressure mercury lamp. Evaporation of the solvent and column chromatography of the residue (hexanes-EtOAc, 1:4) afforded a mixture 54:46 of ***anti*-74a** and ***syn*-74a**. The

purification by column chromatography delivered the following fractions, the *anti* isomer as a white solid (49 mg, 0.23 mmol, 42% yield), starting material (8 mg, 8%) and finally the *syn* isomer (43 mg, 0.20 mmol, 37% yield).



A solution of lactone **197a** (134 mg, 0.72 mmol) and (*Z*)-1,2-dichloroethylene (0.3 mL, 3.85 mmol) in acetonitrile (60 mL) was irradiated through a quartz filter for 5h at -40ºC with a 125W high pressure mercury lamp. Evaporation of the solvent and purification of the residue by column chromatography (EtOAc) afforded a mixture of compounds which wasn used in the next step without further purification. A solution of AIBN (53 mg, 0.32 mmol) in dry toluene (3 mL) under nitrogen was heated at 90ºC. Bu_3SnH (1.4 mL, 5.05 mmol) was added dropwise and the solution was heated at 110ºC. Then, a solution of the mixture in dry toluene (2 mL) was added dropwise and the resulting solution was refluxed for 2h. After allowing the reaction mixture to cool to room temperature the solvent was removed under reduced pressure. The crude was purified by column chromatography (hexanes-diethyl ether, 30:1 to hexanes-diethyl ether, 5:1) to afford the following fractions, the *anti* isomer as a white solid (59 mg, 38% yield), starting material (4 mg, 4%) and finally the *syn* isomer (38 mg, 25% yield) also as a white solid.

Physical and spectroscopic data of ***anti*-74a**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.17 (s, 1H, H-7), 4.32 (t, $J_{3,6}$ = 2.7 Hz, 1H, H-3), 4.08-3.89 (m, 4H, H-8), 3.81 (m, 2H, H-6), 3.04 (t, $J_{5,10}$ = 9.6 Hz, $J_{5a,10}$ ≈ 2.8 Hz, $J_{5,3}$ ≈ 2.8 Hz, $J_{5a,9}$ = 0.9 Hz, 1H, H-5), 2.59 (t, 1H, OH), 2.51 (m, 1H, H-10), 2.34 (m,1H, H-9), 2.14 (m,1H, H-9), 2.03 (m,1H, H-10).

^{13}C NMR (90 MHz, $CDCl_3$) δ 179.7 (C-1), 102.5 (C-7), 85.5 (C-3), 65.5 (C-8), 61.8 (C-6), 48.7 (C-4), 41.0 (C-5), 26.4 (C-9), 23.4 (C-10).

HRMS *m/z* (ESI-TOF) ($C_{10}H_{14}O_5$): calcd for $[M+Na]^+$ 237.0733, found 237.0738.

$[\alpha]^{20}_D$ -27.6 (*c* 1.23, $CHCl_3$).

IR (ATR) 3452, 2949, 2893, 1754, 1728, 1345, 1165, 1071, 1029 cm^{-1}.

m.p. 102-103ºC (diethyl ether)

Physical and spectroscopic data of ***syn*-74a**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.00 (s, 1H: H-7), 4.49 (t, $J_{3,6}$ = 6.0 Hz, 1H, H-3), 4.11-3.88 (m, 5H, 1H-6, 4H-8), 3.78 (dd, J_{gem} = 11.9 Hz, $J_{6,3}$ = 5.7 Hz, 1H, H-6), 3.10 (t, $J_{5,10}$ = 9.9 Hz, $J_{5,10} \approx J_{5,9} \approx$ 2.9 Hz, $J_{5,3}$ = 1.0 Hz,1H, H-5), 2.47 (m,1H, H-10), 2.37 (m,1H, H-9), 2.14-1.99 (m, 2H, H-9 and H-10).

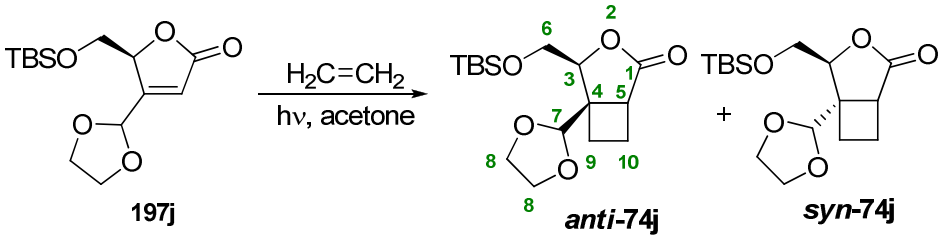
^{13}C NMR (90 MHz, $CDCl_3$) δ 178.4 (C-1), 104.3 (C-7), 81.5 (C-3), 65.7 (C-8), 61.4 (C-6), 48.9 (C-4), 40.9 (C-5), 21.7 (C-9), 19.9 (C-10).

HRMS *m/z* (ESI-TOF) ($C_{10}H_{14}O_5$): calcd for $[M+Na]^+$ 237.0733, found 237.0738.

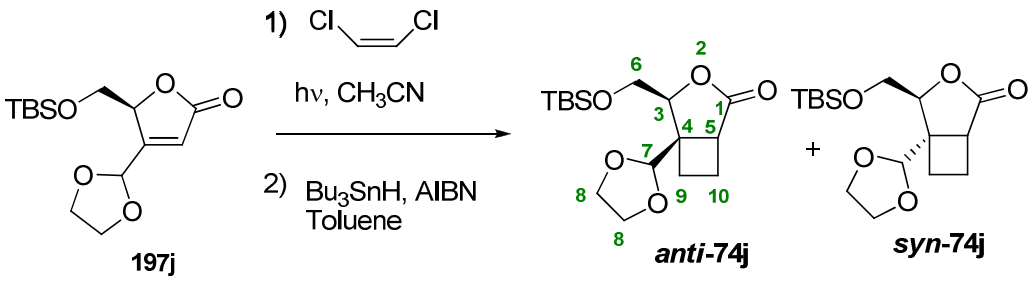
IR (ATR) 3449, 2922, 2853, 1748, 1722, 1343, 1345, 1165, 1069, 1022 cm^{-1}.

m.p. 101-103 ºC (diethyl ether).

(1*R*,4*S*,5*S*)-4-*tert*-Butyldimethylsilyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (*anti*-74j) and (1*S*,4*S*,5*R*)-4-*tert*-butyldimethylsilyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (*syn*-74j)



A solution of lactone **197j** (1.0 g, 3.32 mmol) in acetone (400 mL) was irradiated through a pyrex filter with introduction of ethylene for 9h at -20ºC with a 125W medium pressure mercury lamp. Evaporation of the solvent and column chromatography of the residue (hexanes-diethyl ether, 10:1) afforded a mixture 63:37 of ***anti*-74j** and ***syn*-74j**. The purification by column chromatography delivered the following fractions, the *anti* isomer as a white solid (515 mg, 1.57 mmol, 47% yield), starting material (76 mg, 7%) and the *syn* isomer (303 mg, 0.92 mmol, 28% yield).



A solution of lactone **197j** (1.534 mg, 5.106 mmol) and (*Z*)-1,2-dichloroethylene (2.150 mL, 28.08 mmol) in acetonitrile (400 mL) was irradiated through a quartz filter for 5h at -40ºC. Evaporation of the solvent and purification of the residue by column chromatography (hexanes-EtOAc, 2:1) afforded a reaction mixture which has been used without further purification. A solution of AIBN (164 mg, 1.0 mmol) in dry toluene (10 mL) under nitrogen was heated at 90ºC. Bu_3SnH (5.67 mL, 20.0 mmol) was added dropwise and the solution was heated at 110ºC. Then a solution of the mixture dichloroadducts (850 mg, 2.00 mmol) in dry toluene (15 mL) was added dropwise and the resulting solution was refluxed for 2 h. After allowing the reaction mixture to cool to room temperature the solvent was removed under reduced pressure. The crude was purified by column chromatography (hexanes-diethyl ether, 30:1 to hexanes-diethyl ether, 5:1) to give only decomposition products which could not be identified by NMR analysis.

Physical and spectroscopic data of ***anti*-74j**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.24 (s, 1H, H-7), 4.24 (t, $J_{3,6}$ = 1.8 Hz, 1H, H-3), 4.08-3.86 (m, 4H, H-8), 3.82 (d, $J_{6,3}$ = 1.8 Hz, 2H, H-6), 2.96 (dddd, $J_{5,10}$ = 9.4 Hz, $J_{5,10}$ = 3.4 Hz, $J_{5,3}$ = 2.3 Hz, $J_{5,9}$ = 1.0 Hz, 1H, H-5), 2.49 (m, 1H, H-10), 2.28 (m, 1H, H-9), 2.07 (m, 1H, H-9), 1.97 (m, 1H, H-10), 0.83 (s, 9H, TBDMS), 0.023 (s, 3H, TBDMS), 0.016 (s, 3H, TBDMS).

^{13}C NMR (90 MHz, $CDCl_3$) δ 180.0 (C-1), 102.8 (C-7), 84.8 (C-3), 65.7 (C-8), 65.4 (C-8), 62.4 (C-6), 49.1 (C-4), 42.1 (C-5), 25.7 (TBDMS), 25.0 (C-10), 23.9 (C-9), 18.0 (C: ^{t}Bu), -5.7 (TBDMS), -5.9 (TBDMS).

$[\alpha]^{20}_D$ -16.2 (*c* 1.05, $CHCl_3$).

IR (ATR) 2952, 2885, 2858, 1779, 1471, 1255, 1160, 1093 cm^{-1}.

Elemental analysis: Calcd for ($C_{16}H_{28}O_5Si$): C: 58.50 %, H: 8.59 %; found: C: 58.59 %, H: 8.85 %.

m.p. 64-65 ºC (pentane-diethyl ether).

Physical and spectroscopic data of ***syn*-74j**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.92 (s, 1H, H-7), 4.46 (t, $J_{3,6}$ = 5.6 Hz, 1H, H-3), 4.02-3.87 (m, 5H, H-6, 4H-8), 3.80 (dd, J_{gem} = 11.0 Hz, $J_{6,3}$ = 5.6 Hz, 1H, H-6), 2.96 (dt, $J_{5a,10}$ = 9.9 Hz, $J_{5a,10} \approx J_{5a,9} \approx$ 2.9 Hz,1H, H-5), 2.41 (m, 1H, H-10), 2.30 (m, 1H, H-9), 2.10 (m, 1H, H-9), 2.01 (m, 1H, H-5), 0.85 (s, 9H,TBDMS), 0.05 (s, 6H, CH_3 TBS).

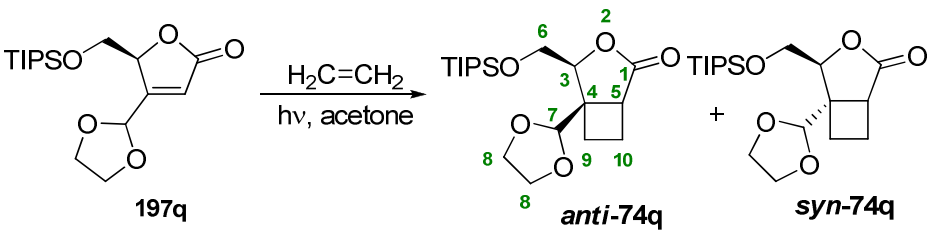
^{13}C NMR (90 MHz, $CDCl_3$) δ 179.1 (C-1), 104.5 (C-7), 81.9 (C-3), 65.6 (C-8), 62.4 (C-6), 49.0 (C-4), 39.8 (C-5), 25.8 (TBDMS), 21.8 (C-10), 20.3 (C-9), 18.2 (TBDMS), -5.4 (TBDMS), -5.5 (TBDMS).

HRMS *m/z* (ESI-TOF) ($C_{16}H_{28}O_5Si$): calcd for $[M+H]^+$ 329.1779, found: 329.1773.

IR (ATR) 2954, 2885, 2858, 1774, 1472, 1256, 1130, 1098 cm^{-1}.

$[\alpha]^{20}_D$ +40.9 (*c* 1.3, $CHCl_3$).

(1*R*,4*S*,5*R*)-5-(1,3-Dioxolan-2-yl)-4-(((triisopropylsilyl)oxy)methyl)-3-oxabicyclo[3.2.0]heptan-2-one (*anti*-74q) and (1S,4S,5S)-5-(1,3-dioxolan-2-yl)-4-(((triisopropylsilyl)oxy)methyl)-3-oxabicyclo[3.2.0]heptan-2-one (*syn*-74q)



A solution of lactone **197q** (800 mg, 2.32 mmol) in acetone (400 mL) was irradiated through a pyrex filter with introduction of ethylene for 12h at -20ºC with a 125W high pressure mercury lamp. Evaporation of the solvent and column chromatography of the residue (hexanes-diethyl ether, 10:1) afforded a mixture 64:36 of ***anti*-74q** and ***syn*-74q**. The purification by column chromatography delivered the following fractions, the *anti* isomer (388 mg, 1.05 mmol, 45% yield), starting material (90 mg, 11%) and finally the *syn* isomer (223 mg, 0.6 mmol, 26% yield).

Spectroscopic data of ***anti*-74q**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.35 (s, 1H, H-7), 4.27 (bs, 1H, H-3), 4.12 – 3.82 (m, 6H, H-8 and H-6), 3.03 (d, $J_{5,10a}$ = 8.1 Hz, 1H, H-5), 2.63 – 2.43 (m, 1H, H-10a), 2.40 – 2.24 (m, 1H, H-9a), 2.19 – 1.92 (m, 2H, H-9b and H-10b), 1.25 (s, 21H, TIPS).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 180.1 (C-1), 103.1 (C-7), 85.4 (C-3), 66.1 (C-8), 65.8 (C-8), 63.3 (C-6), 49.4 (C-4), 42.3 (C-5), 38.5 (C-10), 32.3 (C-9), 31.6 (TIPS), 30.1 (TIPS), 30.0 (TIPS).

HRMS *m/z* (ESI-TOF) ($C_{19}H_{34}O_5Si$): calcd for $[M+Na]^+$ 393.2068, found 393.2058.

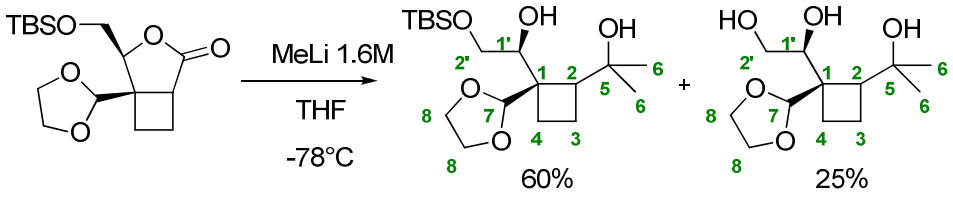
Spectroscopic data of ***syn*-74q**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.01 – 4.94 (s, 1H, H-7), 4.58 – 4.47 (t, $J_{3,6}$ = 6.0 Hz, 1H, H-3), 4.10 – 3.85 (m, 6H, 2H-6 and 4H-8), 3.13 – 3.00 (m, 1H, H-5), 2.57 – 2.26 (m, 2H, H-10a and H-9a), 2.22 – 1.96 (m, 2H, H-10b and H-9b), 1.14 – 0.94 (m, 21H, TIPS).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 179.1 (C-1), 104.4 (C-7), 81.9 (C-3), 65.6 (C-8), 65.6 (C-8), 62.8 (C-6), 49.2 (C-4), 39.9 (C-5), 21.9 (C-10), 20.5 (C-9), 18.0 (TIPS), 12.0 (TIPS).

HRMS *m/z* (ESI-TOF) ($C_{19}H_{34}O_5Si$): calcd for $[M+Na]^+$ 393.2068, found 393.2075.

2-((2*R*)-2-((*S*)-2-((tert-Butyldimethylsilyl)oxy)-1-hydroxyethyl)-2-(1,3-dioxolan-2-yl)cyclobutyl)propan-2-ol (75j)



***anti*-74j** **75j** **75a**

To a solution of ***anti*-74j** (1.14 mmol) in dry THF (10 mL) at -78℃ under nitr ogen was added dropwise 2.5 mL of methyllithium 1.6M (3.44 mmol, 3 equiv). After 1h, the reaction was allowed to warm at room temperature for 5h and the mixture was washed with a saturated solution of ammonium chloride and extracted with CH_2Cl_2. Evaporation of the sovent and purification by column chromatography (hexanes-diethyl ether, 2:1) afforded a mixture of diol **75j** (246 mg, 0.684 mmol, 60% yield) as a white solid and triol **75a** (70 mg, 0.285 mmol, 25% yield).

Physical and spectroscopic data of **75j**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.88 (s, 1H, H-7), 4.41 (bs, 1H, OH), 4.24 (m, 1H, H-1'), 3.94-3.78 (m, 4H, H-8), 3.75-3.73 (m, 2H, H-2'), 3.54 (d, J = 6.2 Hz, 1H, OH), 2.66 (dd, $J_{2,3b}$ = 11.5 Hz, $J_{2,3a}$ = 8.6 Hz, 1H, H-2), 2.00 (m, 1H, H-3), 1.82 (m, 1H, H-4), 1.68 (m, 1H, H-3), 1.37 (m, 1H, H-4), 1.22 (s, 3H, Me), 1.04 (s, 3H, Me), 0.87 (s, 9H, TBDMS), 0.05 (s, 6H, TBDMS).

^{13}C NMR (90 MHz, $CDCl_3$) δ 104.1 (C-7), 72.8 (C-1'), 70.0 (C-5), 64.8 (C-8), 63.8 (C-2'), 51.3 (C-1), 47.4 (C-2), 29.6 (CH_3), 26.8 (CH_3), 25.8 (*t*Bu), 21.4 (C-4), 18.2 (*t*Bu), 18.0 (C-3), -5.2 (CH_3TBS).

MS *m/z* (%) (ESI) ($C_{18}H_{36}O_5Si$): 383.2 ($M+Na^+$).

Elemental Analysis: Calcd for ($C_{18}H_{36}O_5Si$): C: 59.96 %, H: 10.06 %; Found: C: 59.77 %, H: 10.36 %.

$[\alpha]^{20}_D$: +5.9 (*c* 1.01, $CHCl_3$).

IR (ATR) 3353 (br), 2955, 2884, 1255, 1091 cm^{-1}.

m.p. 70-71 ºC (pentane/diethyl ether).

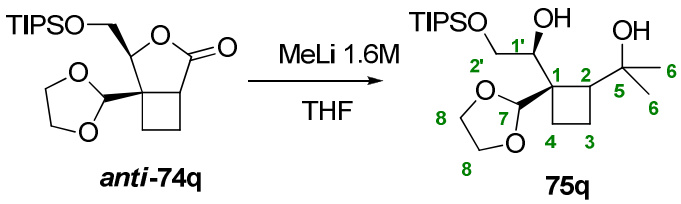
Physical and spectroscopic data of **75a**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.85 (s, 1H, H-7), 4.27 (td, $J_{1',2'}$ = 7.3 Hz, $J_{1',2'}$ = 3.7 Hz, 1H, H-1'), 4.04-3.83 (m, 4H, H-8), 3.78-3.65 (m, 2H, H-2'), 2.65 (dd, $J_{2,3}$ = 11.7 Hz, $J_{2,3}$ = 8.5 Hz, 1H, H-2), 2.54 (dd, J = 9.3 Hz, J = 3.9 Hz, 1H, OH), 2.01 (m, 1H, H-3), 1.85 (m, 1H, H-4), 1.72 (m, 1H, H-3), 1.39 (m, 1H, H-4), 1.26 (s, 3H, Me), 1.09 (s, 3H, Me).

^{13}C NMR (90 MHz, $CDCl_3$) δ 104.8 (C-7), 72.8 (C-1'), 70.6 (C-5), 65.0 (C-8), 64.8 (C-8), 62.8 (C-2'), 51.4 (C-1), 47.8 (C-2), 29.6 (CH_3), 27.1 (CH_3), 21.5 (C-4), 18.1 (C-3).

HRMS *m/z* (ESI-TOF) ($C_{12}H_{22}O_5$): calcd for $[M+Na]^+$ 269.1359, found 269.1363.

2-((2*R*)-2-(1,3-Dioxolan-2-yl)-2-((*S*)-1-hydroxy-2-((triisopropylsilyl)oxy)ethyl)cyclobutyl)propan-2-ol (75q)



To a solution of furanone ***anti*-74q** (0.432 mmol) in dry THF (3 mL) at -78℃ under nitrogen was added dropwise 0.81 mL of methyllithium 1.6M (1.29 mmol, 3 equiv). After 1h, the reaction was allowed to warm at room temperature for 5h. Addition of saturated solution of ammonium chloride (4 mL), extraction with CH_2Cl_2 (2x5 mL) and evaporation of the solvent gave a crude which was purified by column chromatography (hexanes-EtOAc, 2:1) to afford 148 mg of diol **75q** (0.367 mmol, 85% yield).

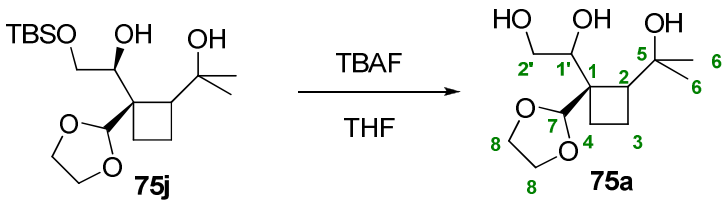
Spectroscopic data of **75q**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.95 (s, 1H, H-7), 4.32 (dd, $J_{1',2'a}$ = 6.6 Hz, $J_{1',2'b}$= 4.1 Hz, 1H, H-1'), 4.02 – 3.80 (m, 6H, 4H-8 and 2H2'), 2.71 (dd, $J_{2,3a}$ = 11.4 Hz, $J_{2,3b}$=8.5 Hz, 1H, H-2), 2.10 – 1.94 (m, 1H, H-3a), 1.93 – 1.77 (m, 2H, H-4a and H-3b), 1.77 – 1.62 (m, 1H, H-4b), 1.26 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.07 (s, 21H, TIPS).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 104.1 (C-7), 77.4 (C-5), 70.2 (C-1'), 65.02 (C-2'), 64.95 (C-8), 64.26 (C-8), 51.5 (C-1), 47.9 (C-2), 29.8 (CH_3), 26.9 (CH_3), 21.4 (C-TIPS), 18.2 (C-TIPS), 18.1 (C-4), 18.1 (C-TIPS), 18.1 (C-TIPS), 12.08 (C-3).

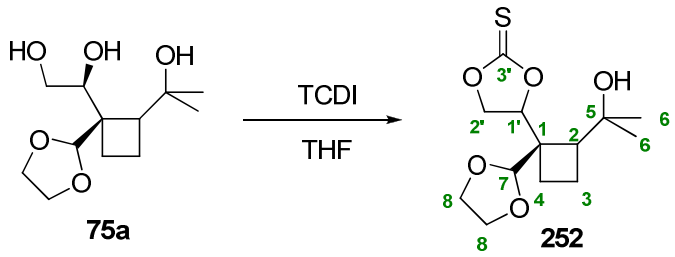
HRMS *m/z* (ESI-TOF) ($C_{21}H_{42}O_5Si$): calcd for $[M+Na]^+$ 425.2694, found 425.2703.

(1*S*)-1-((1*R*)-1-(1,3-Dioxolan-2-yl)-2-(2-hydroxypropan-2-yl)cyclobutyl)ethane-1,2-diol (75a)



To a solution of diol **75j** (0.79 mmol) in THF was added 1.6 mL of TBAF 1.0M in THF (1.6 mmol, 2 equiv). After 1h, the solvent was evaporated and the resulting residue was purified by column chromatography (hexanes-diethyl ether, 1.5:1) to deliver 163 mg of triol **75a** (0.663 mmol, 84% yield).

4-((1*R*)-1-(1,3-Dioxolan-2-yl)-2-(2-hydroxypropan-2-yl)cyclobutyl)-1,3-dioxolane-2-thione (252)



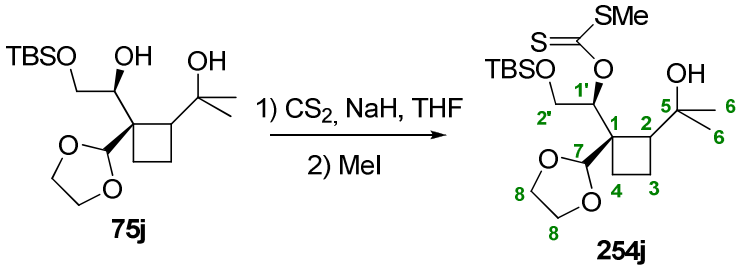
To a solution of triol **75a** (0.203 mmol) in anhydrous THF (4 mL) was added 80.4 mg of thiocarbonatediimidazole (0.406 mmol, 2 equiv). The reaction was heated to 55℃ and stirred for 24h. The solvent was removed and the resulting residue was purified by column chromatography to afford 53 mg of thiocarbonate **252** (0.185 mmol, 91% yield).

Spectroscopic data of **252**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.95 (s, 1H, H-7), 4.63 (dd, J_{gem} = 11.1 Hz, $J_{2'a,\,1'}$ = 2.7 Hz, 1H, H-2'a), 4.54 (dd, J_{gem} = 11.1 Hz, $J_{2'b,1'}$ = 8.3 Hz, 1H, H-2'b), 4.21 (dd, $J_{1',2'b}$ = 8.3 Hz, $J_{1',2'a}$ = 2.7 Hz, 1H, H-1'), 4.02 – 3.97 (m, 2H, H-8), 3.93 – 3.85 (m, 2H, H-8), 2.60 – 2.52 (m, 1H, H-2), 2.01 – 1.84 (m, 4H, H-3 and H-4), 1.26 – 1.22 (s, 3H, H-6), 1.21 – 1.15 (s, 3H, H-6).

^{13}C NMR (90 MHz, $CDCl_3$) δ 162.8 (C=S), 106.1 (C-7), 81.7 (C-5), 75.8 (C-1'), 74.7 (C-2'), 65.7 (C-8), 65.4 (C-8), 53.8 (C-1), 49.4 (C-2), 26.5 (C-6), 23.2 (C-6), 17.8 (C-4), 17.5 (C-3).

***O*-((1*S*)-1-((1*R*)-1-(1,3-Dioxolan-2-yl)-2-(2-hydroxypropan-2-yl)cyclobutyl)-2-((tert-butyldimethylsilyl)oxy)ethyl) *S*-methyl carbonodithioate (254j)**



To solution of diol **75j** (411 mg, 1.14 mmol) in anhydrous THF (25 ml) under nitrogen was added 760 µL of carbone disulfide (12.54 mmol, 11 equiv) and 120 mg of sodium hydride (3.03 mmol, 2.6 equiv). After 2h, 1.4 mL of iodomethane was added and allowed to react for an additional 1h. The reaction was quenched by addition of some drops of acetic acid. After evaporation of the solvent, the residue was taken up with

CH_2Cl_2 (2x5 mL) and washed with brine (5 mL). The organic layer was dried over Na_2SO_4 and the sovent was removed to afford the desired xanthate **254j** which was used in the next step without further purification.

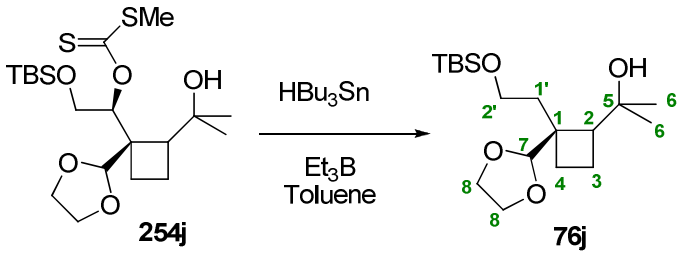
Spectroscopic data of **254j**:

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31 (t, *J* = 4.9 Hz, 1H, H-1'), 5.17 – 5.09 (s, 0H), 4.20 (dd, *J* = 11.3, 4.9 Hz, 1H, H-2'a), 4.08 – 3.88 (m, 5H, H-8 and H-2'), 2.75 (dd, *J* = 11.2, 8.9 Hz, 1H, H-2), 2.60 (s, 3H, H-2''), 2.12 – 1.92 (m, 2H, H-3a and H-4a), 1.87 – 1.68 (m, 2H, H-3b and H-4b), 1.65 – 1.57 (bs, 1H, OH), 1.22 (s, 3H, H-6), 1.12 (s, 3H, H-6), 0.89 – 0.84 (m, 9H, H-TBS), 0.06 (s, 3H, H-TBS), 0.05 (s, 3H, H-TBS).

^{13}C NMR (101 MHz, $CDCl_3$) δ 215.5 (C-1''), 104.1 (C-7), 83.9 (C-1'), 70.4 (C-5), 64.9 (C-8), 64.9 (C-8), 61.9 (C-2'), 51.9 (C-1), 47.7 (C-2), 29.2 (C-6), 27.9 (C-6), 25.7 (C-TBS), 20.9 (C-4), 18.9 (C-3), 18.6 (C-2'), -5.5 (C-TBS), -5.7 (C-TBS).

HRMS *m/z* (ESI-TOF) ($C_{20}H_{38}O_5S_2Si$): calcd for $[M+Na]^+$ 473.1822, found 473.1817.

2-((2*S*)-2-(2-((tert-Butyldimethylsilyl)oxy)ethyl)-2-(1,3-dioxolan-2-yl)cyclobutyl)propan-2-ol (76j)



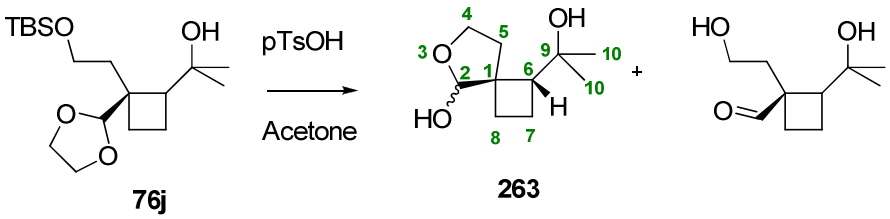
To solution of xanthate **254j** (0.15 mmol) in toluene (3.6 mL) under nitrogen was added 460 µL of triethylborane (1.0M in hexanes) (0.46 mmol, 3 equiv) and 120 µL of tributyltin hydride (0.46 mmol, 3 equiv). After 3h, the solvent was evaporated and the resulting residue was purified by column chromatography to afford 28 mg of alcohol **76j** (0.08 mmol, 55% yield over 2 steps).

Spectroscopic data of **76j**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.71 (s, 1H, H-7), 4.07 – 3.60 (m, 6H, H-8 and H-2'), 2.68 – 2.48 (m, 1H, H-2), 2.25 – 2.05 (m, 2H, H-1'), 2.01 – 1.77 (m, 2H, H-3a and H-4a), 1.82 – 1.47 (m, 2H, H-3b and H-4b), 1.24 (m, 6H, H-6), 0.92 (m, 9H, TBS), 0.05 (s, 6H,TBS).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 106.4 (C-7), 71.2 (C-5), 65.2 (C-8), 65.1 (C-8), 60.1 (C-2'), 47.8 (C-1), 46.8 (C-2), 34.0 (C-1'), 30.1 (C-6), 28.0 (C-6), 26.9 (TBDMS), 23.7 (C-4), 18.9 (C-3), 18.4 (TBDMS), 17.7 (TBDMS), 13.7 (TBDMS).

(1*R*,4*S*)-1-(2-Hydroxypropan-2-yl)-6-oxaspiro[3.4]octan-5-ol (263)



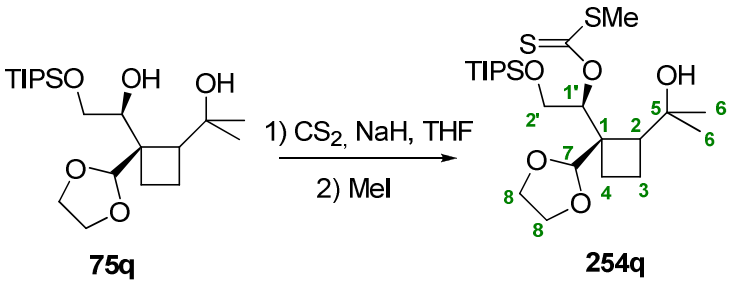
76j **263**

To a solution of acetal **76j** (87 µmol) in acetone (3 mL) was added 2 mg of *p*-toluenesulfonic acid (8.7 µmol, 0.1 equiv.) to afford 13 mg of hemiacetal **263** (80%).

Spectroscopic data of **263**:

^{1}H NMR (360 MHz, $CDCl_3$) δ 9.56 (s, 1H, H-2), 4.98 (s, 1H, H-2), 4.15 – 4.04 (m, 1H, H-4a), 4.01 (bs, 1H, OH), 3.86 – 3.72 (m, 1H, H-4b), 2.72 (s, 1H, OH), 2.69 (m, 1H, H-6), 2.52 (m, 1H, H-5a), 1.94 (dd, *J* = 11.8 Hz, *J* = 6.1 Hz, 1H, H-5b), 1.85 (m, 2H, H-7a and H-8a), 1.69 – 1.59 (m, 2H, H-7b and H-8b), 1.28 (s, 3H, H-10), 1.20 – 1.15 (s, 3H, H-10).

***O*-((1*S*)-1-((1*R*)-1-(1,3-Dioxolan-2-yl)-2-(2-hydroxypropan-2-yl)cyclobutyl)-2-((triisopropylsilyl)oxy)ethyl) *S*-methyl carbonodithioate (254q)**



75q **254q**

To solution of diol **75q** (0.675 mmol) in anhydrous THF (12 mL) under nitrogen was added 45 µL of carbone disulfide (0.74 mmol, 11 equiv) and 72 mg of sodium hydride

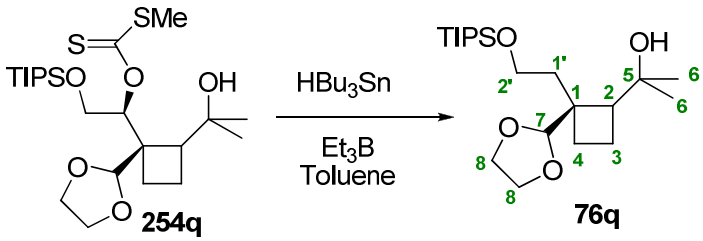
(1.8 mmol, 2.6 equiv.). After 2h, 86 µL of iodomethane (1.35 mmol, 2 equiv) was added and allowed to react for an additional 1h. The reaction was quenched by addition of some drops of acetic acid. Evaporation of the solvent gave a residue which was taken up in CH_2Cl_2 (10 mL) and washed with brine (5 mL). The organic layer was dried over Na_2SO_4 and the solvent evaporated to afford the desired xanthate **254q** (40% yield).

Spectroscopic data of **254q**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.09 (s, 1H, H-7), 4.31 (t, $J_{1',2'}$ = 6.7 Hz, 1H, H-1'), 4.05 – 3.80 (m, 7H, H-8 and H-2' and OH), 3.29 – 3.15 (t, $J_{2,3}$ = 8.9 Hz, 1H, H-2), 2.85 – 2.78 (d, J = 3.8 Hz, 1H, SH), 2.06 – 1.82 (m, 2H, H-3), 1.76 – 1.61 (m, 2H, H-4), 1.57 – 1.53 (s, 6H, CH_3), 1.11 – 1.01 (m, 24H, TIPS).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 181.9 (C-3'), 104.8 (C-7), 72.9 (C-5), 65.9 (C-8), 65.4 (C-8), 64.8 (C-1'), 51.8 (C-2'), 42.9 (C-1), 30.9 (C-2), 23.8 (C-4), 20.3 (C-6), 20.0 (C-6), 18.4 (TIPS), 18.3 (C-3), 12.3 (TIPS).

2-((2*S*)-2-(1,3-Dioxolan-2-yl)-2-(2-((triisopropylsilyl)oxy)ethyl)cyclobutyl)propan-2-ol (76q)

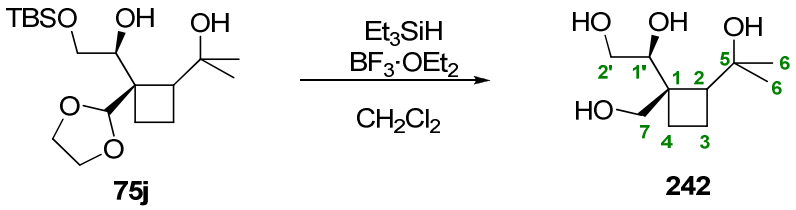


To solution of xanthate **254q** (0.675 mmol) in toluene (15 mL) under nitrogen was added 2.0 mL of triethylborane (1.0 M in hexanes) (2.0 mmol, 3 equiv) and 575 µL of tributyltin hydride (2.0 mmol, 3 equiv). After 3h, the sovent was evaporated and the resulting residue was purified by column chromatography to afford 20 mg of alcohol **76q** (0.129 mmol, 20% yield over 2 steps).

Spectroscopic data of **76q**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.04 (s, 1H, H-7), 4.19 (m, 1H, H-2'), 4.09 – 3.76 (m, 7H, H-8 and H-2' and OH), 2.72 – 2.59 (m, 1H, H-2), 2.05 (m, 2H, H-1'), 1.87 (m, 2H, H-3a and H-4a), 1.64 (m, 2H, H-3b and H-4b), 1.26 (s, 3H, H-6), 1.21 (s, 3H, H-6), 1.11 – 0.97 (m, 24H, TIPS).

(1*S*)-1-((1*S*)-1-(Hydroxymethyl)-2-(2-hydroxypropan-2-yl)cyclobutyl)ethane-1,2-diol (242)



75j **242**

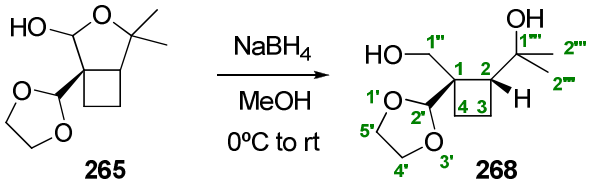
To an ice-cooled solution of **75j** (25 mg, 0.069 mmol) and Et_3SiH (35 µL, 0.210 mmol) in CH_2Cl_2 (1 mL) was added slowly $BF_3{\cdot}OEt_2$ (45 µL, 0.350 mmol). The reaction was monitored by TLC (hexanes/Et_2O 3/1). After 1h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were washed successively with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (hexanes-diethyl ether, 3:1) to afford **242** (14 mg, 95% yield) as a pale oil.

Spectroscopic data of **242**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.59 (d, $J_{1',2'}$ = 4.9 Hz, 1H, H-1'), 4.06 (d, J_{gem} = 9.9 Hz, 1H, H-7a), 3.87 (d, J_{gem} = 10.6 Hz, 1H, H-2'a), 3.61 (dd, J_{gem} = 10.6 Hz, $J_{2',1'}$ = 4.9 Hz, 1H, H-2'b), 3.40 (d, J_{gem} = 9.9 Hz, 1H, H-7b), 2.55 (dd, J = 9.8 Hz, J = 5.7 Hz, 1H, H-2), 2.47 – 2.25 (s, 2H, OH), 2.09 – 1.78 (m, 4H, H-3 and H-4), 1.31 – 1.22 (s, 3H, H-6), 1.25 – 1.17 (s, 3H, H-6).

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 90.3 (C-1'), 84.9 (C-5), 76.1 (C-2'), 75.9 (C-7), 59.6 (C-1), 56.9 (C-2), 27.8 (C-6), 23.5 (C-4), 23.1 (C-6), 18.2 (C-3).

2-((1*R*,2*R*)-2-(1,3-Dioxolan-2-yl)-2-(hydroxymethyl)cyclobutyl)propan-2-ol (268)



265 **268**

To a cold (0℃) solution of hemiacetal **265** (15 mg, 0.07 mmol) in methanol (1 mL) was added sodium borohydride (2 mg, 0.05 mmol) and the mixture was stirred at 0℃ for 30 min and was allowed to warm to room temperature. The reaction mixture was diluted with diethyl ether (3 mL), washed with saturated aqueous ammonium chloride solution, water, dried over magnesium sulftate and concentrated under reduced pressure.

Purification by column chromatography (pentane-diethyl ether, 2:1) furnished 6 mg of diol **268** (0.028 mmol, 40% yield).

Spectroscopic data of **268**:

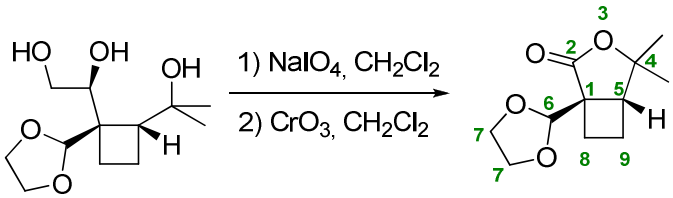
^{1}H NMR (250 MHz, $CDCl_3$) δ 4.79 – 4.77 (s, 1H, H-2'), 4.05 – 3.81 (m, 6H, H-3', H-4', H-1''), 3.75 – 3.58 (bs, 2H, OH), 2.54 – 2.41 (m, 1H, H-2), 2.10 – 1.94 (m, 1H, H-3), 1.87 – 1.63 (m, 3H, H-3, H-4), 1.29 – 1.24 (s, 3H, H-2'''), 1.14 – 1.06 (s, 3H, H-2''').

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 108.1 (C-2'), 70.7 (C-1'''), 65.1 (C-3'), 63.3 (C-4'), 49.3 (C-1), 47.6 (C-2), 29.8 (C-2'''), 27.4 (C-2'''), 21.4 (C-3), 18.4 (C-4).

HRMS *m/z* (ESI-TOF) ($C_{11}H_{20}O_4$): calcd for $[M+Na]^+$ 239.1254, found 239.1253.

IR (ATR) 3284, 2968, 2933, 2875, 1467, 1378, 1143, 1097, 1047 cm^{-1}.

(1*S*,5*R*)-1-(1,3-Dioxolan-2-yl)-4,4-dimethyl-3-oxabicyclo[3.2.0]heptan-2-one (266)



75a **266**

To a solution of triol **75a** (0.17 mmol) in CH_2Cl_2 (2 mL) was added at room temperature, 47 mg of sodium periodate (0.221 mmol, 1.3 equiv.). After 1 h, was added a solution of 32 mg of chromium (VI) oxide (0.32 mmol) and 5 drops of pyridine in CH_2Cl_2 (1 mL). Addition of water (2 mL), extraction with CH_2Cl_2 and evaporation of the solvent afforded 21 mg of the lactone **266** (0.098 mmol, 58% yield).

Spectroscopic data of **266**:

^{1}H NMR (250 MHz, $CDCl_3$) δ 5.06 – 5.00 (s, 1H, H-6), 4.09 – 3.85 (m, 4H, H-7), 2.85 – 2.71 (dd, *J* = 8.8, 6.0 Hz, 1H, H-5), 2.47 – 2.31 (m, 1H, H-9), 2.18 – 1.97 (m, 3H, H-9 and H-8), 1.41 – 1.39 (s, 3H, H-1'), 1.39 – 1.37 (s, 3H, H-1').

^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.0 (C-2), 102.7 (C-6), 85.0 (C-1), 65.60 (C-7), 65.5 (C-7), 53.9 (C-4), 43.8 (C-5), 29.8 (C-9), 28.5 (C-8), 23.8 (C-1'), 23.1 (C-1').

HRMS *m/z* (ESI-TOF) ($C_{11}H_{16}O_4$): calcd for $[M+Na]^+$ 235.0941, found 235.0938.

IR (ATR) 2950, 2887, 1758, 1388, 1296, 1110, 1097 cm^{-1}.