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J. Mex. Chem. Soc. **2008**, *52(2),* 145-174
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ISSN 1870-249X

γ-Lactones Upon Double Nucleophilic Additions of *Bis*(TMS)Ketene Acetals to Π-Systems and Access to New-Towards Cancer Cells Cytotoxic-Endoperoxide Lactones

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Recibido el 16 de noviembre de 2007; aceptado el 20 de mayo de 2008

Abstract. Arenechromium and cycloheptatrienechromium complexes react with (TMS)ketene acetals to give upon a double nucleophilic addition either diene-lactones or cyclohexenone-lactones. In the first case, the scope of the reaction and the stability of the dienes were examined: they could be easily transformed either in arylpropionic acids or in conjugated ketones and more interestingly, they reacted with oxygen to give new highly active cytotoxic endoperoxide lactones. Unfortunately, in the second case, no further functionalization could be achieved up to now.

Key words: Endoperoxide lactones, cytotoxic activities, γ-lactones, *bis*(TMS)ketene acetals, tricarbonylchromium complexes, double nucleophilic additions.

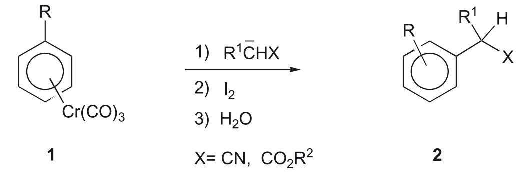
Resumen. Se describe la reacción entre complejos arentricarbonilcromo y cicloheptatrientricarbonilcromo con acetales de *bis*(trimetil silil)cetena, la cual mediante una doble adición nucleofílica conduce a la formación tanto de dieno-lactonas como ciclohexenona-lactonas. En el primer caso, se examinó la estabilidad de los dienos: pudiendo éstos transformarse fácilmente en ácidos arilpropiónicos o en cetonas conjugadas y al reaccionar con oxígeno en nuevas endoperoxolactonas con actividad citotóxica importante. Desafortunadamente, en el segundo caso, no pudo realizarse la funcionalización posterior de dichas moléculas.

Palabras clave: Endoperoxolactonas, actividad citotóxica, γ-lactonas, acetales de *bis*(trimetilsilil)cetena, complejos de tricarbonilcromo, doble adición nucleofílica.

Introduction and origin of the work

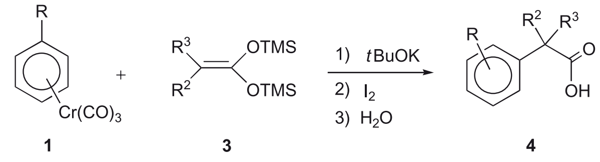
2-arylpropionic acids and their derivatives are important non-steroidal anti-inflammatory drugs [1]. Both academic and industrial efforts have been devoted to design new strategies for their synthesis. They have been obtained, on an industrial scale, by using either classical organic chemistry or transformations involving transition metals [2, 3]. Recently, promising and more direct approaches have emerged, among which successful attempts involving the *catalytic* functionalization of halogen-substituted aromatic compounds. Both Hartwig and Buchwald achieved a straightforward Pd-catalyzed addition of ester enolates originating for some of them from (OTMS)(Oalkyl)ketene acetals (TMS = trimethylsilyl) to these substrates [4, 5, 6].

Earlier attempts mainly based on academic approaches involved however the *stoichiometric* activation of the π-system of arenes by transition metals followed by nucleophilic additions of suitably functionalized nucleophiles. Pioneering work in that direction has been carried out by Trahanovsky and Semmelhack and was followed later on by many other groups [7-15]. Thus the addition of anions derived from nitriles or esters to arenetricarbonylchromium complexes **1** followed by an iodine oxidation, led indeed to 2-aryl-propionitriles or -propionic acid esters **2**, the direct precursors of the desired 2-arylpropionic acids (Scheme 1).



Scheme 1

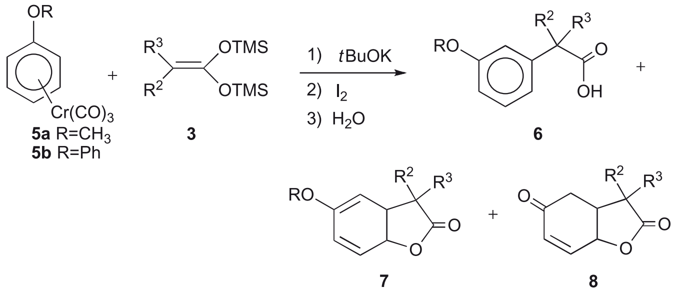
Along the same lines, we demonstrated that a large array of the *free acids* **4** could be obtained *directly*, in one pot transformations, and in amounts suitable for biological evaluations, by using instead of enolates derived from alkyl esters, enolates derived from TMS esters of carboxylic acids as nucleophiles [16-18] (Scheme 2).



Scheme 2

Thus *bis*(TMS)ketene acetals **3**, in the presence of potassium *t*-butoxide led to the corresponding (TMS)ester enolates, which upon their interaction with differently substituted arenetricarbonylchromium complexes **1** followed by an I_2 oxidation to remove the metal, directly gave, upon extraction, the free arylpropionic acids **4**. Such direct syntheses could be considered as an interesting improvement since hydrolysis using severe conditions as in the case of nitriles or esters was not necessary.

The point which focused however our attention was the observation, in some special cases, of a side reaction, the formation of γ-lactones **7** as the result of an unexpected double nucleophilic addition to a carbon-carbon double bond of the starting arene complexes, the *bis*(TMS)ketene acetals acting here as dinucleophiles [18].



Scheme 3

These double addition products were mainly isolated, in earlier attempts, in the case of complexes **5** derived from electron-rich arenes such as anisole or diphenylether, after silica gel chromatography, either as the diene-lactones **7** and (or), much more surprising, as their hydrolyzed counterparts, the corresponding conjugated ketones **8**. (Scheme 3) Although the mechanism of the second step, the closure of the lactone ring, remains the matter of speculations, this side reaction could be considered as a new example of the sequential addition of two nucleophiles to transition metal-activated arenes [19], the point being that here the two nucleophilic centers belong to the same molecule, the ketene acetal. Moreover, and in contrast to previous examples, it is a one pot transformation: no need for the isolation of the various electrophilic intermediates existed.

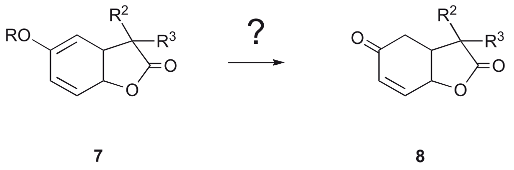
The logic and further extension of this new approach was the double nucleophilic addition of the same ketene acetals to other π-systems and especially to cycloheptatriene complexes of chromium,[20] a reaction which led again to bicyclic γ-lactones and also, *without the need of any activating metal*, to azaaromatics, giving nitrogen-functionalized δ- and γ-lactones [21-23]. As far as the two first examples were considered, and depending on the structure of the starting complexes, the addition led either to conjugated or to non-conjugated dienes.

The purpose of the present paper is first to establish the scope of the reaction between *bis*(TMS)ketene acetals and various arenechromiumtricarbonyl complexes which indeed could be driven, in all the cases examined, to the formation of bicyclic diene-lactones. Second, to demonstrate that the observed arylpropionic acids were mainly the result of a rearomatization reaction of the diene-lactones under acidic conditions. Third, to describe a method which allows for the clean transformation of the initial dienol-ethers into conjugated ketones. Fourth, to extent the new method to various cycloheptatriene complexes of chromium. And finally to describe further functionalizations of the conjugated dienes, involving cycloaddition reactions with conjugated esters and oxygen. This latter transformation provides a direct, fast access to a class of biologically important substrates, endoperoxide lactones [24-32], the cytotoxic activity towards cancer cells of which is now well established [33-35]. Finally, the results of the biological evaluation of the new endoperoxide lactones will be outlined. Preliminary reports from these Laboratories on the transformations described herein already appeared in the literature [20, 36].

Results and Discussion

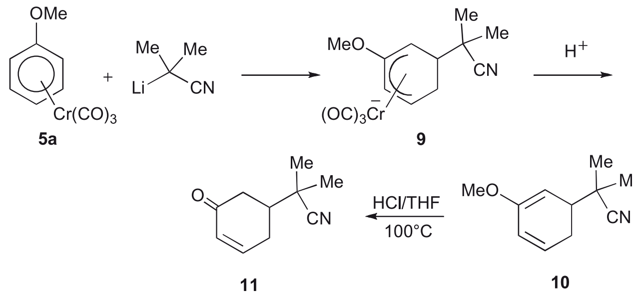
A) Formation and rearrangement of alkoxy- and aryloxydihydro-3H-benzofuran-2-ones into arylpropionic acids and tetrahydrobenzofuran-2,5-diones

A first observation indicated that the formation and isolation upon silica gel chromatography of the double nucleophilic addition products was limited to aryloxy- and alkyloxy-substituted arenes leading to lactones **7** and **8**: no lactones could be detected for example in the case of the benzenechromiumtricarbonyl complex **1** (R = H) under the same conditions.



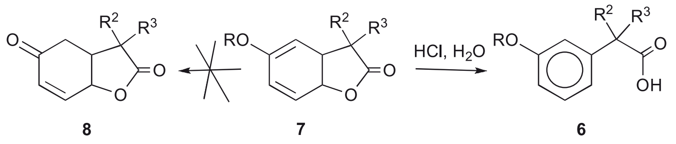
Scheme 4

A second observation was that the hydrolyzed products **8**, the conjugated ketones, *were already present* before the purification step (by TLC). The clarification of that behaviour came from attempts to transform the lactones **7**, containing also a dienol-ether, into the corresponding conjugated ketones **8**. (Scheme 4) Such compounds, containing a conjugated cyclohexadiene and in an allylic position an oxygen function behaving, due to the presence of the carbonyl group, as a good leaving group, might be prone to rearomatization. This was indeed confirmed.



Scheme 5

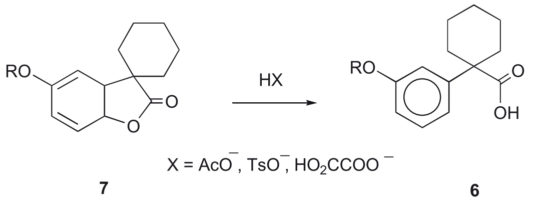
Following the procedure used by Semmelhack for the hydrolysis of the dienol-ether **10** [13, 37], derived from anisolechromiumtricarbonyl **5a** and a carbon nucleophile *via* **9**, into **11**, (Scheme 5) we submitted the lactones **7** to dilute HCl solutions, either at room temperature or below: under such conditions, no cyclohexenone-lactones **8** were detected (Scheme 6).



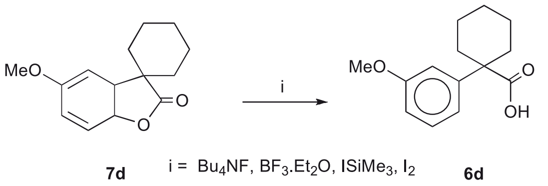
Scheme 6

Only the acids **6** resulting from a rearomatization reaction were observed. In the case of **5a** (R = Me), even the contact with silicagel for a prolonged period of time led to the rearomatized product **6**.

Many other different and popular methods from the literature known to convert ethers or enol ethers into the corresponding alcohols or ketones failed to transform these enol ethers **7** into the corresponding conjugated ketones **8**: that was the case of acetic, oxalic and π-toluenesulfonic acids, trimethylsilyliodide $ISiMe_3$, Bu_4NF/BF_3, Et_2O. [38-42] (Schemes 7 and 8).

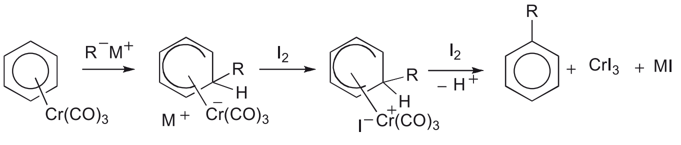


Scheme 7



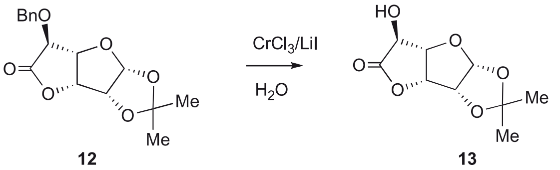
Scheme 8

What was then the origin of the conjugated ketones **8** in these reactions? Two convergent points allowed us to settle that problem. First, the addition of iodine to the intermediate chromates must lead, according to earlier mechanistic studies, besides the rearomatized products and depending on the amounts of iodine used, to oxidized chromium derivatives such as CrI_2 and (or) CrI_3 and MI.[43] (Scheme 9).



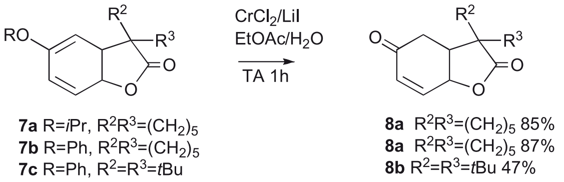
Scheme 9

Second, and interesting enough with respect to our results, it is known from the literature that a very mild, fast and clean way to promote the transformation of benzylethers into the corresponding alcohols is to react them either with $CrCl_2$ or $CrCl_3$/LiI in the presence of stoichiometric amounts of water.



Scheme 10

This allowed Mioskowski and Falck [44] to cleanly transform, at 70 °C, the α-benzyloxylactone **12** into the corresponding hydroxylactone **13** in high yield *without compromising the lactone function* (Scheme 10). The same authors mentioned also that «it was however necessary to reduce the temperature for methyl ether-containing molecules to avoid any concomitant loss of that functionality» which means that even methyl ethers could be hydrolyzed under such conditions into the corresponding alcohols.



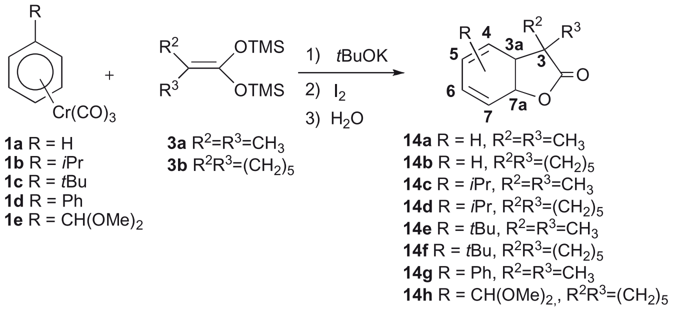
Scheme 11

Therefore, attempts were made to use that method to convert the dienol ethers **7** into the corresponding conjugated ketones **8** hopefully without affecting the lactone. To our delight this worked quite nicely. Thus, the reaction of a series of dienol ethers **7** (R = *i*Pr, Ph) using the literature conditions, at –10 °C, then at room temperature for 12h, led to the expected conjugated ketones **8** in respectively 85% (R = *i*Pr, $R^2R^3 = (CH_2)_5$), 87% (R = Ph, $R^2R^3 = (CH_2)_5$) and 47% (R = Ph, R^2 = H, R^3 = *t*Bu) yields (Scheme 11). This reagent proved thus highly efficient and selective both for aliphatic and aromatic enol ethers, no deleterious interaction with the lactone function taking place.

As a first conclusion, the direct formation of the conjugated ketones **8** can be ascribed to the formation of chromium iodide(s) during the iodine-induced oxidation step which then interact(s) with the enol ethers **7**, in the presence of water, during the extraction step. A second conclusion is related to the work-up procedure: acidic work-up procedures should be avoided as much as possible and moreover, silica gel chromatography could have a deleterious effect on the outcome of the reaction, only the more stable dienes **7** bearing alkoxy groups withstanding such a purification step.

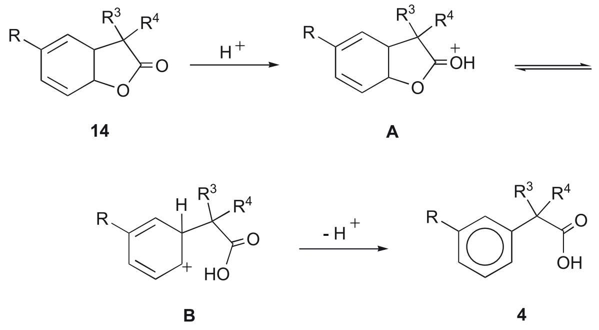
Remark: Influence of the nature of the substituents on the stability of the dienes

It was clear that if reaction conditions could be found to make the formation of the diene-lactones the major (or better) the exclusive product of that transformation, whatever the nature of the substituent R, the reaction would be of considerable synthetic interest. However, the first attempts showed, as already stated, that non-heteroatom substituted arenes only led to the monoaddition products, the arylpropionic acids. According to the above results, one could address the following question: are these acids formed directly or *via* the diene-lactones **14** (Scheme 12)?



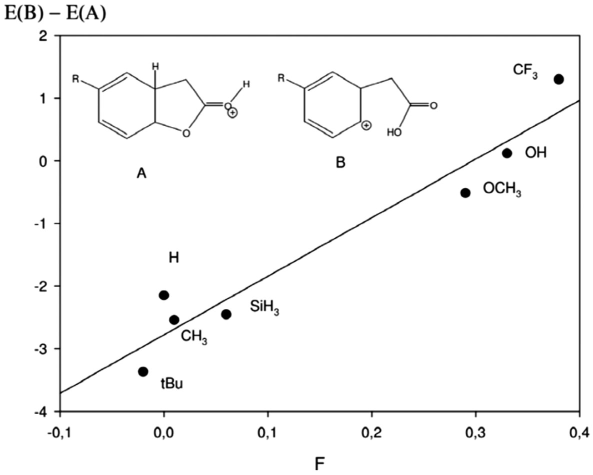
Scheme 12

Theoretical calculations carried out on various substituted diene-lactones confirmed that indeed these lactones could be considered as closed precursors of the arylpropionic acids [45, 46]. In the presence of an acid, the diene-lactones **14** are protonated and the site of protonation is indeed in all the cases the carbonyl oxygen atom of the lactone to give **A** (Scheme 13).



Scheme 13

This makes the lactone function a good leaving group promoting a fast rearomatization with abstraction of the angular proton. Moreover, the ease of the transformation should be, as one would expect, directly dependent on the nature of the substituent R of the starting arene (Eq. 12). The energies of the closed system **A** and the opened system **B**, which leads to the rearomatized systems, have been determined. No π-stabilization of **B** due to the nature of R is to be expected. However it appears, according to the graph 1, that a correlation exits between the Hansch constant *F*, which is a measure of the field or inductive effects of the substituents R, and the difference of energy ΔE between the opened and the closed forms:[47] thus the closed structure, the lactone, should be favoured for substituents such as -CF_3, -OH, -OCH_3 (*F* = 0.3), -OPh (*F* = 0.4) whereas for substituents such as H, alkyl (*F* = 0.0) the opened form, leading to the aromatic acid, would be the stable structure. The lactone with a phenyl substituent (*F* = 0.12) is at the borderline (the corresponding lactone can be chromatographed).



Graph 1. Relationship between the Hansch constant of the substituents and the difference of energy between the closed and the opened structures.

A similar conclusion might be drawn for the lactone **16a** (Fig. 1) derived from complex **15**. [48] 2-phenylpyridine, a strong σ-acceptor (*F* = 0.4), and a week π-donor destabilizes indeed the opened form **B**. Similarly, a TMS group on C-6 as in **18** obtained from **17** should also, according to the calculations (*F* = 0.01), stabilize the opened form and lead easily to the corresponding arylpropionic acid: although **18** resists a fast chromatography, it is unstable at room temperature, in the presence of air, giving over a few hours the corresponding acid **4** (R = TMS, Scheme 2). It could be concluded first, that most of these data fit with the experimental observations.

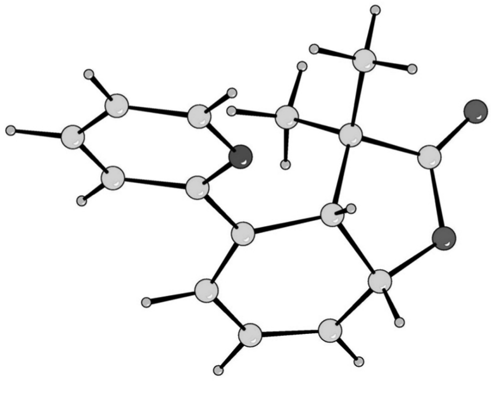
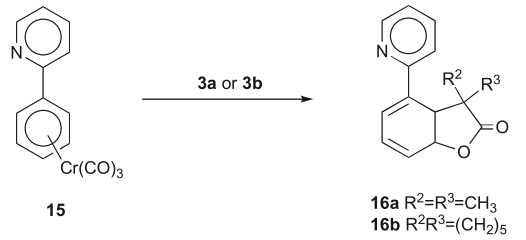
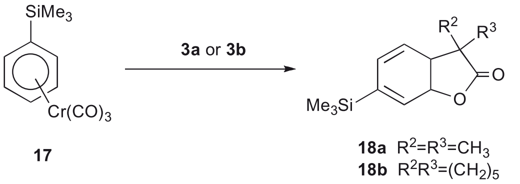


Fig. 1. X-Ray structure of compound **16a.**

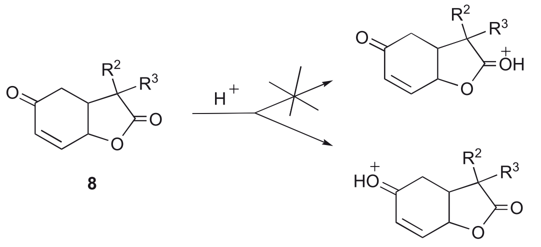


Scheme 14



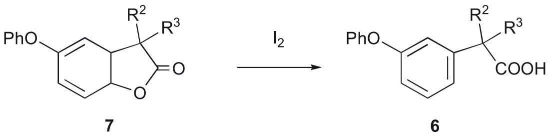
Scheme 15

Moreover, once the conjugated ketone is formed, the opening of the lactone function under acidic conditions can no longer take place, the favoured site of protonation being now, according to calculations, the oxygen of the conjugated ketone (Scheme 16).

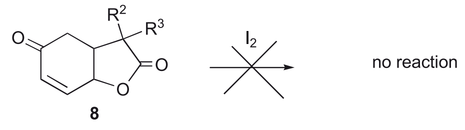


Scheme 16

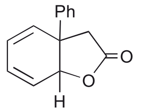
At that point, two observations warrant a comment. First, iodine itself slowly reacts with the diene-lactones at room temperature giving quantitatively the arylpropionic acids. No such a reaction takes place in the case of the conjugated ketones (Schemes 17 and 18). Second, to the best of our knowledge, only one such diene-lactone **19** has been described in the literature: however, it bears at the ring junction, in α to the oxygen a phenyl group, a feature preventing thus the rearomatization reaction to occur [49].



Scheme 17



Scheme 18



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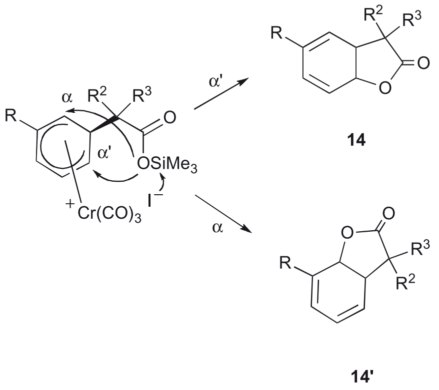
B) General access to the diene-lactones 14 : double nucleophilic addition reactions without purification of the end products

Since the success of the reaction seemed to be directly linked to the absence of acid during the work-up process, the transformations of non-substituted and of alkyl- and aryl-substituted arenes (Scheme 12, R = H, alkyl, aryl), leading, after silicagel chromatography to arylpropionic acids were repeated under exclusion of acids (base washing of the ethereal extracts, no silica gel chromatography) and avoiding the use of excess iodine.

Under such conditions, the NMR spectra of the crude reaction products confirmed that the main component of the reaction was in all the cases the diene-lactones **14** and not the acid **4**, the yields reaching 70% for R = H. The ^{1}H NMR spectrum of for example **14b** (R = H, $R^2R^3 = (CH_2)_5$) confirmed the presence of a diene, the olefinic protons giving, according to the COSY correlation spectrum, separated multiplets at δ 6.18 (H-6), 6.05 (H-5), 5.89 (H-7), and 5.79 (H-4) ppm. Moreover, as for the previous more stable lactones **5**, signals for H-7a at δ 5.13 ppm (dd) and for H-3a at δ 3.17 ppm (d), as well as at δ 180.4 ppm in the ^{13}C NMR spectrum, were observed.

In the case of the substituted arenechromium complexes **1** (R = *i*Pr, *t*Bu, Ph, $CH(OMe)_2$), two regioisomeric diene-lactones are formed, the ratios of isomers depending on the nature of both the R group and the R^2, R^3 substituents. Indeed, according to the mechanism of the ring closure, two possibilities exist for the second nucleophilic addition. It can occur either in *ortho* or in *para* with respect to the substituent *R*, depending both on the size and probably also on the electronic properties of the different substituents [18] (Scheme 19).



Scheme 19

Such a behaviour had already been observed in the case of for example the diphenylether complex **5b** which led to two stable, yet difficult to separate diene-lactones (*vide infra*) [18].

Table 1. Lactones **14** and **18**.

complex	**R**	Product(s)	**R^2**	**R^3**	First attack	Yield (%)
1a	H	**14a**	CH_3	CH_3	-	15
1a	H	**14b**	$(CH_2)_5$		-	70
1b	*i*-Pr	**14c**	CH_3	CH_3	*meta*	50
1b	*i*-Pr	**14d, 14'd**	$(CH_2)_5$		*meta*	65
1c	*t*-Bu	**14e, 14'e**	CH_3	CH_3	*meta*	36
1c	*t*-Bu	**14f, 14'f**	$(CH_2)_5$		*meta*	71
17	$SiMe_3$	**18a**	CH_3	CH_3	*para*	24
17	$SiMe_3$	**18b**	$(CH_2)_5$		*para*	60
1d	Ph	**14g, 14'g**	CH_3	CH_3	*meta*	28
1e	$CH(OCH_3)_2$	**14h, 14'h**	$(CH_2)_5$		*meta*	69

These isomers were however easily distinguishable especially by ^{13}C NMR spectroscopy since the signals of the carbon C7a appear at different fields in the two products (Table 2).

All attempts to purify further these adducts failed and led to the formation of the rearranged products, the arylpropionic acids, confirming the above hypothesis. It could thus be concluded that first in all the cases the lactones were formed, but that if none special care was taken during the work-up, most of these adducts would undergo a rearomatization reaction. Second, only in a few cases (for R = Ph, OMe, OPh, 2-pyridyl and TMS) could the diene lactones be isolated and purified by fast silicagel chromatography.

The results of these double nucleophilic addition reactions are gathered in Table 1. All those compounds for which R=H or alkyl were thus used as such for further transformations.

Table 2. ^{1}H and ^{13}C NMR data of lactones **14** and **18**.

Compound	^{1}H NMR δ (ppm)			^{13}C NMR δ (ppm)
	Hdiene	H7a	H3a	C7a
14a	6.04-5.92, 5.80-5.76, 5.71-5.66	5.33 (d, J = 10 Hz)	2.99 (dd, J = 10, 4.0 Hz)	76.6
14b	6.18, 6.05, 5.89, 5.79	5.13 (dd, J = 8.8, 4.8 Hz)	3.17 (d, J = 8.8 Hz)	72.1
14c	5.95, 5.78, 5.36	5.34 (dd, J = 10, 3.6 Hz)	2.94 (dd, J = 10, 4.5 Hz)	74.5
14d	6.08, 5.88, 5.39	5.07 (dd, J = 9, 4.8 Hz)	3.71 (dd, J = 9, 9 Hz)	72.7
14e	6.16-6.13, 5.82, 5.42	5.29 (d, J = 9.4 Hz)	2.98-2.86	74.41
14f	6.04, 5.62, 5.47	5.07 (d, J = 8.9 Hz)	3.11-3.07	72.38
18a	6.13-6.00, 5.72	5.33 (dd, J = 10, 3 Hz)	2.97 (dd, J = 10, 3 Hz)	-
18b	6.15-6.07, 5.77	5.10 (dd, J = 8.9, 4.5 Hz)	3.12 (d, J = 8.9 Hz)	-
14g	6.50, 6.24-6.20, 5.83	5.63 (d, J = 8.5 Hz)	3.18 (d, J = 8.5 Hz)	74.89
14h	6.16, 5.93-5.75	5.12-5.06	3.28 (bs)	72.37

C) Double nucleophilic additions to cycloheptatrienechromiumtricarbonyl complexes: Formation of γ-lactones

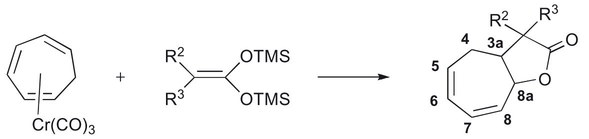
Both arene and cycloheptatriene complexes of various transition metals have been used as activated species for carrying out nucleophilic addition reactions. We described above how *bis*(TMS)ketene acetals could be used for the direct synthesis, in a stereospecific way, of a broad array of bicyclic lactones which were isolated free of the metal provided that suitable work-up procedures were applied.

Since many natural products contain also the bicyclic cycloheptane-fused γ-lactone system and moreover since such structures are found in compounds showing interesting biological properties, we focused our attention on the one pot synthesis of such structures [50-55]. The double nucleophilic addition of *bis*(TMS)ketene acetals to activated cycloheptatrienes might indeed also lead to such diene-containing lactones. Moreover, it was expected that these adducts would be more stable than the cyclohexadienes described above, since in that former case the driving force for a subsequent rearomatization reaction would not exist.

Pioneering work towards the synthesis of highly functionalized cycloheptanes, starting from activated cycloheptadiene and cycloheptatriene derivatives has been carried out by Pearson and coworkers [56-58]. Further work in that direction followed up (*vide infra*).

a) Double nucleophilic addition of *bis*(TMS)ketene acetals to cycloheptatrienechromiumtricarbonyl complexes

The known complex **20** was obtained in 90% yield (64% according to the literature)[59] by using the classical method for the preparation of arenetricarbonylchromium complexes. The addition of the various ketene acetals **3** was carried out as for arene complexes and led indeed to lactones **21a,b** ($R^2 = R^3$ = Me and $R^2R^3 = (CH_2)_5$) in very satisfactory 73% yields (Scheme 20). They were easily purified by silica gel column chromatography, and obtained as stable solids. Their structure was established both by NMR spectroscopy and by X-ray analysis. The NMR data (^{1}H, ^{13}C, DEPT, ^{1}H-^{1}H COSY) of the new products were in agreement with the structure **21**: the ^{13}C NMR spectrum of **21a** ($R_2 = R_3$ = Me) confirmed the presence of a γ-lactone (δ CO = 181.3 ppm), of two disubstituted conjugated double bonds (δ C=C, 133.0, 131.2, 128.5, 127.2 ppm) and showed the typical signal for C-8a at δ 78.3 ppm, whereas signals for five deshielded contiguous protons appeared at δ 6.15, 6.10, 5.96, 5.90, and 4.97 (H-8a) ppm.



20

3a $R^2=R^3$=Me
3b $R^2R^3=(CH_2)_5$

21a $R^2=R^3$=Me 73%
21b $R^2R^3=(CH_2)_5$ 73%

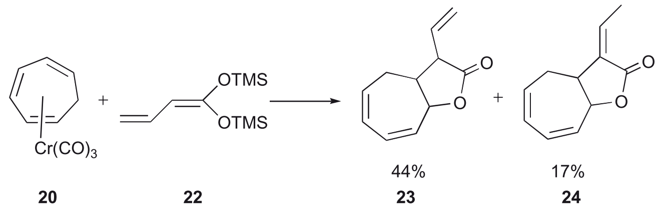
Scheme 20

In the case of the conjugated ketene acetal **22**, (Scheme 21) two compounds were isolated and separated by silica gel column chromatography: the expected lactone **23** (44% yield), (δCO 176.2 ppm) showing signals in the ^{1}H NMR spectrum for three extra deshielded protons (as compared to the spectrum of **21**), and a more polar compound (17% yield), the physical data of which were in agreement with structure **24**, a highly deshielded signal for the proton of the conjugated lactone, at δ 6.82 ppm confirming the migration of the terminal double bond of **23** towards an internal conjugated position (Table 3).

Table 3. ^{1}H and ^{13}C NMR data of lactones **21, 23** and **24.**

	^{1}H NMR δ(ppm)						
21a	H5,6	H7,8	H8a	H3a	H4		
	6.15-6.10	5.96-5.90	4.97 (dd)	2.70 (ddd)	2.13-2.00		
21b	H5,6,7,8		H8a	H3a	H4		
	6.05-5.85		4.92(td)	2.54	2.1 y 1.89		
23	H5	H6,7,8	H8a	H3a	H4	H9	H10
	6.14-6.08	6.02-5.96	5.03(d)	3.16	2.36-2.10	5.78-5.69	5.27-5.20
24	H7,6,8,5		H8a	H3a	H4	H9	H10
	6.26-6.04		5.01-4.98	3.42	2.34-2.20	6.82-6.47	2.08-1.09

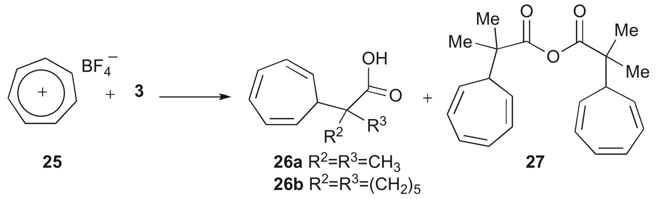
	^{13}C NMR δ(ppm)							
21a	C2	C8	C5	C7	C6	C8a	C3a	C4
	181.3	133.0	131.2	128.5	127.2	78.3	60.3	25.1
21b	C2		C5,6,7,8			C8a	C3a	C4
	180.3		133.8, 130.2, 128.0, 127.9			78.9	55.0	25.6
23	C2	C5	C8a	C9	C6,7,8			C10
	176.2	132.5	78.5	131.7	130.7, 128.7, 129.7			119.3
	C8a	C3a	C4					
	79.4	54.0	29.0					



Scheme 21

b) A ketene acetal-induced functionalization of the tropylium cation followed by a double nucleophilic addition of ketene acetals: formation of γ-lactones fused to seven-membered substituted rings

In order to extend this approach to the synthesis of more elaborate derivatives, and especially to analogs of xanthatine, a highly efficient antibiotic [55, 60], attempts were made to functionalize the cycloheptatriene ring prior to the formation of the chromium complexes. This was achieved in a very straightforward way by reacting the commercially available tropylium tetrafluoroborate **25** with a series of mono- and *bis*(TMS)ketene acetals **3** and **28** [61].

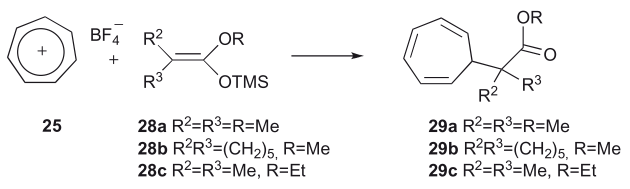


Scheme 22

Thus, the cation **25** reacted with *bis*(TMS)ketene acetals **3a** ($R^2 = R^3 = Me$) and **3b** ($R^2R^3 = (CH_2)_5$) to give in satisfactory yields (71 and 49%) the corresponding acids **26a**,**b** (Scheme 22). Their ^1H and ^{13}C NMR spectra were in agreement with such structures. In the case of **3a** ($R_3 = R_4 = Me$), a minor product, corresponding according to the NMR data to the anhydride **27**, was also isolated as white crystals in 4% yield. Both the acid **26b** ($R_2R_3 = (CH_2)_5$) and the anhydride **27** were fully characterized by an X-ray analysis. The molecular structures of the two compounds appear in Figures 2 and 3.

They confirm the equatorial position of the dimethylacetic acid substituent.

Similarly, the reaction of the tropylium cation **25** with the *mono*(TMS)ketene acetals **28** (R = Me, Et) led to the cycloheptatrienyl esters in respectively 92% ($R = R^2 = R^3 = Me$), 70% (R = Me, $R^2R^3 = (CH_2)_5$ and 64% (R = Et, $R^2 = R^3 = Me$) yields [62] (Scheme 23).



Scheme 23

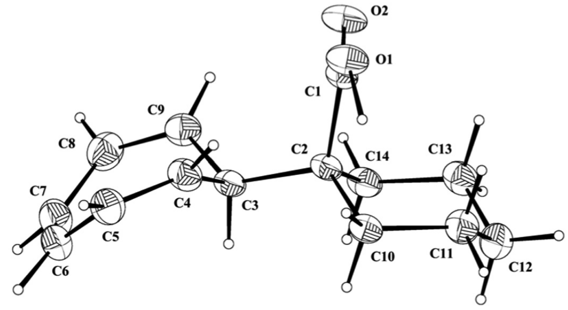


Fig. 2 X-Ray structure of compound **26b.**

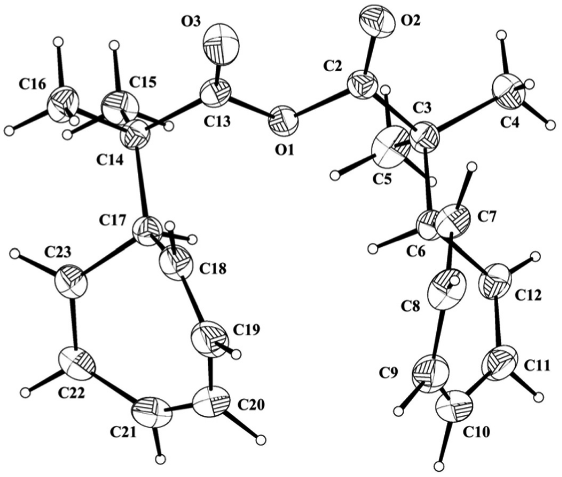
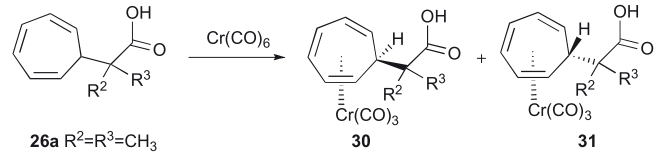


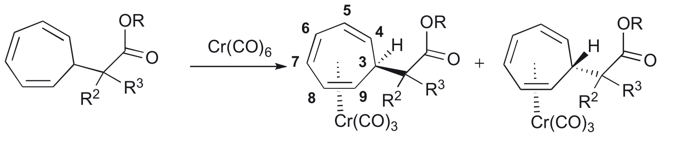
Fig. 3 X-Ray structure of compound **27.**

Although the coordination of the different trienes, under the usual conditions, led to the expected complexes, in the case of the free acid-containing product **26a**, only a poor 25% conversion was observed (Scheme 24).



Scheme 24

The ^1H NMR spectra of the crude reaction products clearly indicated that two isomeric complexes **30** and **31** were formed, one of them being in large excess (95%). The most characteristic signals appear for the hydrogens in α to the substituent, at respectively 3.17 and 3.60 ppm, in agreement with the literature data for related *endo*- and *exo*-substituted cycloheptatriene complexes [61]. Only the more abundant *endo* isomer **31** was thus characterized. Much better yields were however observed upon coordination of the corresponding esters **29a-c** (55, 89, 52% yields) (Scheme 25).



29 **32** **33** (23)

29a $R^2=R^3=R=Me$
29b $R^2R^3=(CH_2)_5$, R=Me
29c $R^2=R^3=Me$, R=Et

32a $R^2=R^3=R=Me$
32b $R^2R^3=(CH_2)_5$, R=Me
32c $R^2=R^3=Me$, R=Et

33a $R^2=R^3=R=Me$
33b $R^2R^3=(CH_2)_5$, R=Me
33c $R^2=R^3=Me$, R=Et

Scheme 25

Again, two complexes were obtained but in different ratios: thus in the case of **29c**, and according to the ^{1}H NMR spectrum, a 30/70 ratio of the *exo/endo* isomers **32c** and **33c** was present, the most important differences appearing again in the chemical shifts and coupling constances of the olefinic hydrogens close to the substituent at C(3), and of the *exo* and *endo* hydrogens on that carbon: H(3) *endo* gives a triplet at δ 3.34 ppm (J = 8 Hz), whereas H(3) *exo* appears at δ 0.89 ppm again as a triplet (J = 4 Hz), in accordance with data from the literature for similar *endo/exo* isomers.[61] In the case of **29b**, the two corresponding isomeric complexes **32b** and **33b** could be partially separated by silica gel chromatography, giving dark red crystals which were submitted to an X-ray analysis. The molecular structure of the more polar but minor compound **32b**, mp 132°C (Fig. 4) confirmed the *exo* orientation of the substituent, in agreement with its NMR spectra, the less polar, major product **33b**, mp 176 °C, showed up an *endo* orientation of the substituent (Fig 5).

Remarks on the X-ray structures of two isomeric *endo*- and *exo*-substituted cycloheptatriene complexes

The X-ray structures of these compounds warrant also a comment. Many X-ray studies carried out on complexes of substituted cycloheptatriene have been published and discussed. In the present case, high quality crystals giving small esd's were obtained for both isomeric complexes. Therefore the bond distances, and especially their multiplicities, could be discussed accurately and compared to those of the literature. As has been pointed out by Hadley [63] for the X-ray structure of the parent cycloheptatrienechromiumtricarbonyl complex, the bonding in these complexes differs deeply from that present in arenechromiumtricarbonyl complexes, the metal being no longer symmetrically linked to the triene but shifted towards the external C(6)-C(7) double bond, the chromium C(4) and C(9) distances (2.330 Å) being significantly longer than the Cr-C(5) or C(6) (2.200 Å) bond distances. Moreover, the distances of the double bonds correspond roughly to those of free cycloheptatriene. These complexes are therefore best described either as metallocyclopropanes with two weakly chelating double bonds, or as dienes C(5),C(6),C(7),C(8) coordinated to the metal with two rather long metal-carbon σ-bonds Cr-C(4) and Cr-C(9).

In the *exo* complex **32b**, the related distances are respectively 2.331(4) and 2.214(4) Å, thus comparable to those of the non-substituted cycloheptatriene complex. The question which might be risen deals with the structure of the more crowded *endo* isomer **33b**: would the proximity of the substituent to the metal induce even a more important slip of the metal towards the C(6)-C(7) double bond ? The answer is yes: as can be seen in Table 4 , the metal is even more shifted towards the external double bond, the distances being now respectively, for Cr-C(4) and Cr-C(9) 2.3774(18) and 2.3672(17) Å and for the extra metal-carbon bonds, 2.2238(17) Å thus significantly longer than in **31b**.

Double nucleophilic addition reactions

Attempts were first made to directly transform, upon a classical iodolactonization reaction [64], the polyunsaturated acids **26** into bicyclic iodolactones. However, that failed: neither reaction led to lactones. Similar negative results were observed upon attempts to add the enolates derived from ketene acetals **3** directly to the acid complexes **31**.

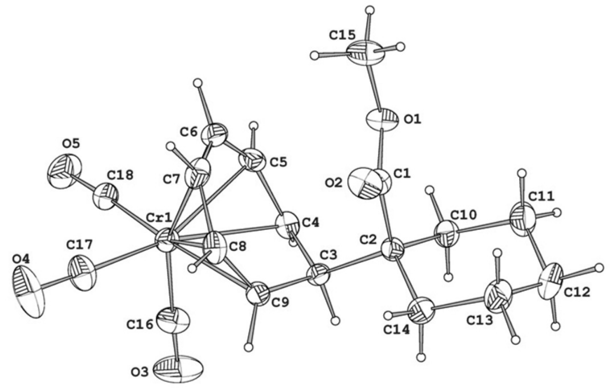


Fig. 4 X-Ray structure of compound **32b.**

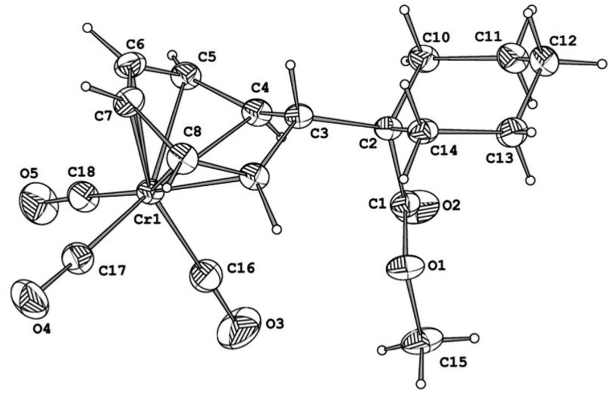
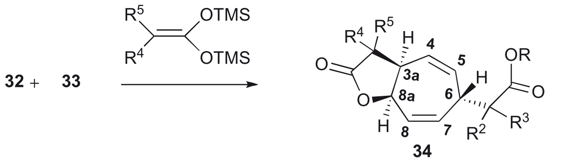


Fig. 5 X-Ray structure of compound **33b.**

Table 4. Interatomic distances (Å) for $C_{18}H_{20}CrO_5$.

Bond	Distance	Bond	Distance
Cr(1) - C(4)	2.3774(18)	Cr(1) - C(5)	2.2238(17)
Cr(1) - C(6)	2.2278(18)	Cr(1) - C(7)	2.2317(19)
Cr(1) - C(8)	2.2216(18)	Cr(1) - C(9)	2.3672(17)
Cr(1) - C(16)	1.876(2)	Cr(1) - C(17)	1.858(2)
Cr(1) - C(18)	1.858(2)	O(1) - C(1)	1.350(2)
O(1) - C(15)	1.467(2)	O(2) - C(1)	1.212(2)
O(3) - C(16)	1.150(3)	O(4) - C(17)	1.165(3)
O(5) - C(18)	1.164(3)	C(1) - C(2)	1.549(2)
C(2) - C(3)	1.561(3)	C(2) - C(10)	1.554(2)
C(2) - C(14)	1.556(2)	C(3) - C(4)	1.522(2)
C(3) - C(9)	1.531(2)	C(4) - C(5)	1.387(3)
C(5) - C(6)	1.442(3)	C(6) - C(7)	1.417(3)
C(7) - C(8)	1.442(3)	C(8) - C(9)	1.387(3)
C(10) - C(11)	1.541(3)	C(11) - C(12)	1.539(4)
C(12) - C(13)	1.537(3)	C(13) - C(14)	1.541(3)

The above standard conditions used for the conversion of activated double bonds of arenetricarbonylchromium complexes into lactones by means of a double nucleophilic addition of *bis*(TMS)ketene acetals were however again successful. In all the cases examined, lactones were isolated in satisfactory yields (Scheme 26).



34a $R^2=R^3=R^4=R^5=R=Me$ 64%
34b $R^2=R^3=R=Me$, $R^4R^5=(CH_2)_5$ 48%
34c $R^2=R^3=R^4=R^5=Me$ R=Et 27%
34d $R^2=R^3=Me$, R=Et, $R^4R^5=(CH_2)_5$, 47%
34e $R^2R^3=R^4R^5=(CH_2)_5$, R=Et 47%

Scheme 26

For example, a mixture of the complexes **32c** and **33c** led, according to the ^{13}C NMR spectrum, to a lactone, in 47% yield. Surprisingly, the NMR spectra did not agree with a structure containing two conjugated double bonds, as in **21**. Instead signals for two isolated double bonds appear in the ^1H NMR spectrum together with a signal for a highly deshielded proton which could be assaigned to C-H(8a), one of the protons at the ring junction (Table 5). Crystals of **34d** suitable for an X-ray analysis were grown from dichloromethane/hexane solutions: a molecular structure appears in Figure 6 and confirms the presence of the γ-lactone, *cis*-fused

Table 5. ^1H and ^{13}C NMR data of lactones **34**.

		^{1} H NMR δ (ppm)			
Compound	H8	H7,5	H4	H8a	H3a
34a	5.81	5.68-5.52	5.50	5.28 d (7.3 Hz)	3.09 t (6.5 Hz)
34b	5.82	5.68-5.65	5.53	5.21 d (7.3 Hz)	3.07 t (6.8 Hz)
34c	5.82	5.65	5.45	5.30 d (7.3 Hz)	3.08 S_{ancho}
34d	5.80	5.66	5.47	5.18 d (7.1 Hz)	3.03 t (6.0 Hz)
34e	5.83-5.40			5.19 d (7.3 Hz)	3.00 t (6.2 Hz)
		^{13}C NMR δ (ppm)			
	C2	CO ester	C8,C7,C5,C4	C8a	C3a
34a	181.4	176.9	131.7, 130.3 129.2, 123.4	77.6	49.6
34b	180.0	177.1	131.0, 130.9 130.7, 124.0	76.6	49.7
34c	181.9	176.9	132.0, 130.0 129.7, 123.8	50.1 78.1	
34d	180.1	176.5	130.9, 124.0	76.6	49.6
34e	180.6	176.0	131.8, 131.0 130.8, 124.6	78.1	49.6

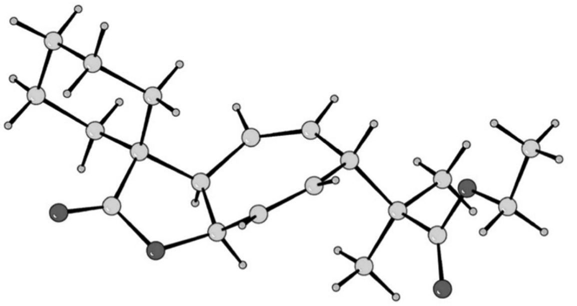
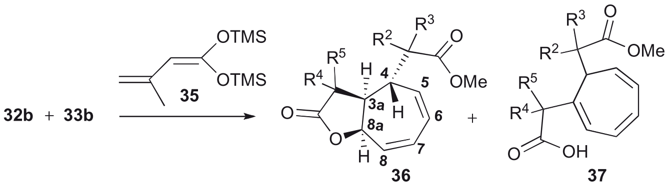


Fig. 6 X-Ray structure of compound **34d**.

to the seven-membered ring, and *trans* oriented with respect to the substituent. This bicyclic lactone results therefore from a nucleophilic addition to the internal double bond of the *endo* isomer **33c**.

In contrast, the unsaturated ketene acetal **35** interacted with complexes **32b** and **33b** to give, yet in a very low yield, two compounds which were separated by silica gel chromatography into a lactone **36** (12%) and an acid (3%), the NMR data of which agree with the structure **37** (Scheme 27).



Scheme 27

The structure of the new bicyclic lactone could also be assessed by an X-ray analysis. The molecular arrangement of **36** appears in Figure 7 and surprisingly shows that the first addition of the nucleophile took place at the terminus of the triene, in α to the substituent, a result contrasting with the above observations.

As far as the acid **37** is concerned, it results from the addition of the enolate followed by the oxidative elimination of a proton giving a conjugated cycloheptatriene, a result reminiscent of the transformation of complexes **1** into arylpropionic acids **4** (Scheme 2).

These results warrant the following comments. Highly substituted cycloheptane derivatives have been synthesized upon the interaction of various nucleophiles with suitably metal-activated precursors. Among them, three examples using chromium as the metal, are especially interesting as far as the results presented herein are concerned. First, bicyclo-(5.3.0) decane and (5.4.0) undecane derivatives were obtained by Yeh upon a two-step sequential addition of two nucleophiles [65], a functionalized zinc-copper reagent and an ester enolate, to the tropyliumchromiumtricarbonyl cation, the first step being a simple electrophile-nucleophile combination, similar to our approach, whereas the second step was a real S_N2 reaction. Removal of the metal occurred upon quenching of the intermediate chromate either with an acid or with an electrophilic alkylating agent. Second, Sheridan described the direct addition of nucleophiles to cycloheptatriene complexes of chromium and achieved the trapping of the intermediate cycloheptadienyl chromates by various electrophiles. In both examples, the addition of the nucleophiles took place at the terminus of the triene [66]. And third, more recently, Simpkins described the regioselective addition of various nucleophiles to bridged, non-conjugated trienechromiumtricarbonyl complexes: in that case, the addition took place selectively at the terminus of the diene [67].

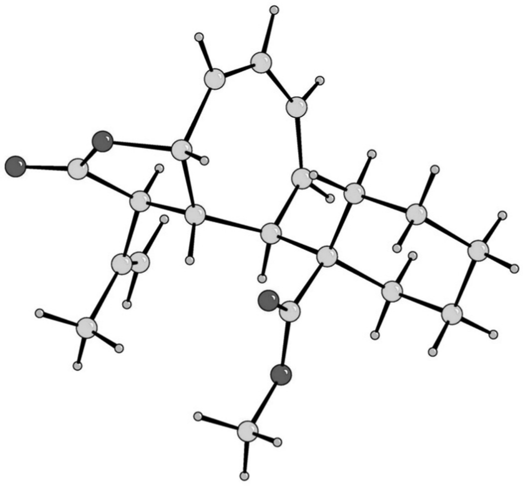
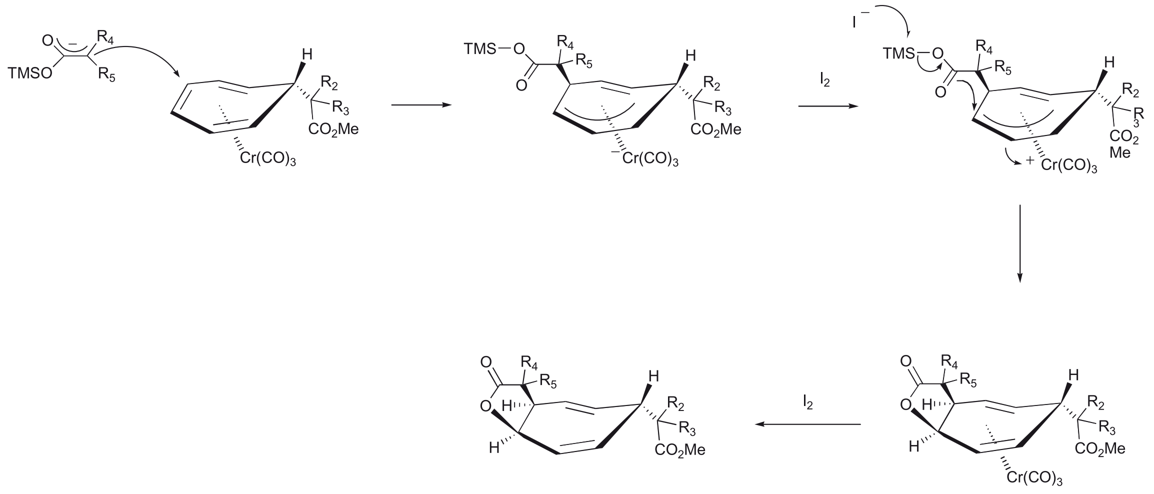


Fig. 7 X-Ray structure of compound **36**.

The transformations described herein combine all the previous approaches, and their originality could be ascribed first to the successive, two-step additions of three nucleophiles to the tropylium cation, two of them being carbon nucleophiles, the third one an oxygen nucleophile; and second, to the addition of the nucleophile, for substituted cycloheptatriene complexes, to the central double bond of the trienes.

As can be noticed herein, the yields of the reactions are however highly dependent on the structure of the starting cycloheptatriene complexes and especially on the nature of their substituents. Indeed, whereas the non-substituted cycloheptatriene complex **20** led to the lactones in rather good yields (Scheme 20), much lower yields were observed in the case of the substituted complexes **32** and **33** (Scheme 26). This is assignable both to the structure of the starting complexes and to the mechanism of the addition reaction. In the case of **20**, only one chromium complex is involved in the reaction, whereas in the latter case, two complexes, the *endo*- and *exo*- isomers in almost equal amounts, are used. The general accepted mechanism involves an *anti*-addition of the nucleophile with respect to the metal (Scheme 28).

Thus two products would be expected, in the case of **32** and **33**, one in which the lactone ring and the substitu-



Scheme 28

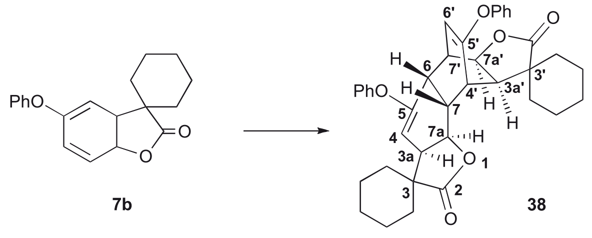
ent are *syn*, the other one in which they are *anti*. However, only one stereoisomer of the two possible lactones in which the substituent and the lactone ring are *anti* is observed: it means therefore that for steric reasons only the *endo* isomer **33** undergoes the nucleophilic addition reaction (Scheme 28), the *exo* isomer **32** giving back, upon demetallation, the substituted cycloheptatriene **29**. This leads therefore to an almost 50% loss of the starting material. Moreover, for steric reasons, the first nucleophilic addition of the bulky enolates took only place far from the substituent and from the axial hydrogen, on the carbons of the central double bond of the triene.

In the case of the conjugated ketene acetal, if the mechanism of the reaction is the same, an addition to the terminal carbon of the triene, *anti* to the metal and to the substituent must also take place, giving rise to a bicyclic lactone in which the two double bonds are conjugated. Probably, for steric reasons, the course of the reaction is again similar to what has been observed in the case of the non-substituted cycloheptatriene complex **20**: the enolate being smaller, an addition to the terminal carbon of the triene could again take place [68].

D) Reactivity of the diene-lactones

a) Stabilization of the diene-lactones 14: formation of Diels-Alder adducts

The presence of both a diene and a potential leaving group, the lactone function, are the driving forces for the easy rearomatization of these compounds. A way to avoid such a transformation would be to modify their structure by carrying out (2 + 4) cycloaddition reactions [69]. Among them, the Diels-Alder reaction and the singlet oxygen additions seemed to be the more appropriate, the latter giving possibly access to the desired peroxide lactones. Indications for the ease of such cycloaddition reactions came from the behaviour of the lactone **7b** (R = Ph). Indeed, a spontaneous dimerization of this compound was observed at room temperature, one molecule behaving as a diene, a second one as the dienophile, to give over several days, quantitatively and stereoselectivily a single cycloadduct **38** which could be fully characterized both by mass and multiple sequence NMR spectroscopies [70] (Scheme 29).

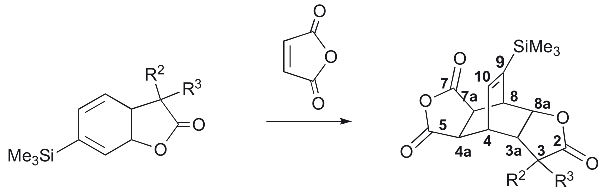


Scheme 29

Especially significant were the NMR spectra of **38**: in the ^{13}C NMR spectrum, signals due to the two lactones at δ 180.3 and 178.5 ppm, four signals for the quaternary oxygen-bearing carbons at δ 159.1, 156.7, 155.2 and 154.6 ppm together with two signals for the carbons at the ring junction bearing oxygen, at δ 77.4 and 77.3 ppm were indeed observed. Thanks to HMQS and COSY correlations, all hydrogens of the dimer could be assigned.

It is likely, since no such dimerizations are observed in the case of the lesser crowded lactones **7**, that the cycloaddition was the result of a steric decompression.

However, attempts to carry out similar cycloadditions by the use of various classical dienophiles were more tricky: for example no reaction took place at room temperature between the dienes **14a** and maleic anhydride. Attempts were therefore made at higher temperatures: unfortunately, only decomposition into the corresponding acids was observed. Only the more stable trimethylsilyl-substituted dienes **18a,b** led to significant results (Scheme 30).



18a R^2=R^3=CH_3
18b R^2R^3=$(CH_2)_5$

39a R^2=R^3=CH_3
39b R^2R^3=$(CH_2)_5$

Scheme 30

Indeed, when **18a,b** were kept in the presence of maleic anhydride in diethylether, at room temperature for five days, the expected cycloadducts **39a,b** were obtained, yet in low yields (23 and 13 %), the starting material suffering, even under those mild conditions, decomposition.

These cycloadducts were stable and could easily be purified by silicagel chromatography. The NMR spectra of both compounds agreed with such structures. The ^1H NMR spectrum of **39a** depicted separated signals for all the protons, the olefinic proton appearing at δ 6.58 ppm and the proton H-8a of the lactone at δ 4.8 ppm, whereas in the ^{13}C NMR spectrum signals for the three carbonyl groups at δ 180.28, 171.35 and 171.15 ppm were observed.

The structure of the adduct **39a** was finally assessed by an X-ray diffraction analysis confirming the expected *endo* addition of the carbon-carbon double bond. The molecular structure appears in Figure 8.

b) Stabilization of the dienes 7: formation of endoperoxide lactones

Since, according to the new experimental conditions, it was easy to synthesize, in satisfactory yields the diene lactones **7** and **14**, a further step was to introduce more functionalities, and especially peroxides. It is indeed known that endoperoxide lactones could act either as antimalaria drugs or as anticancer agents or both. For example, plakortolide is known as an efficient natural anticancer agent. Such compounds were indeed easily accessible from the dienes upon their interaction with singlet oxygen [71].

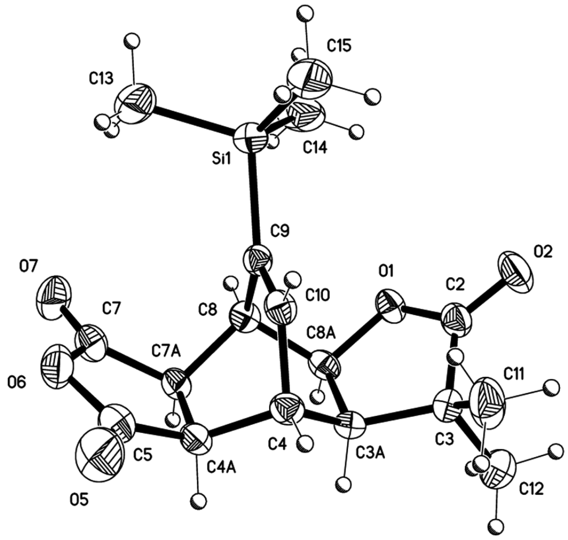
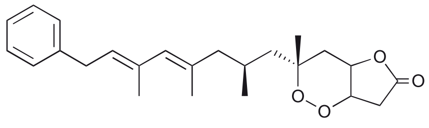
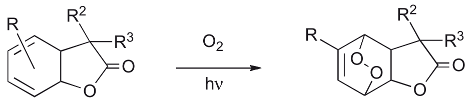


Fig. 8. X-Ray structure of compound **39a.**



Plakortolide

Thus, when a dichloromethane solution of the diene **14b** (R=H, R^2R^3=$(CH_2)_5$) was irradiated in the presence of tetraphenylporphyrin under a flow of oxygen, for 6 hrs, a more polar compound formed according to TLC. Silica gel chromatography led to a new compound **40a** in 95% yield as a white low-melting solid (Scheme 31).



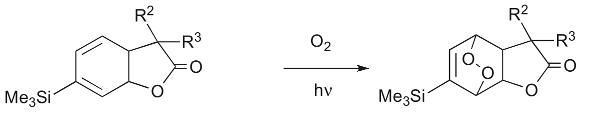
14b R=H, R^2R^3=$(CH_2)_5$
14d R=*i*Pr, R^2R^3=$(CH_2)_5$
7b R=OPh, R^2R^3=$(CH_2)_5$

40a
40b
40c

Scheme 31

The HRMS spectrum was in agreement with the incorporation of oxygen into the starting diene and thus with the presence of the expected endoperoxide. The ^1H NMR spectrum disclosed signals for two olefinic protons, at δ 6.80 and 6.60 ppm, and signals for three further deshielded protons at δ 5.10 and 4.79 ppm. The substituted diene-lactones **7** and **14** behaved similarly and led to the expected endoperoxides **40**. Such was also the case for the C-10 TMS-substituted dienes **18a**,**b** which gave the solid peroxides **41a**,**b** (Scheme 32).

The results are gathered in Tables 6 and 7.



(30)

18a R^2=R^3=CH_3
18b R^2R^3=$(CH_2)_5$

41a R^2=R^3=CH_3
41b R^2R^3=$(CH_2)_5$

Scheme 32

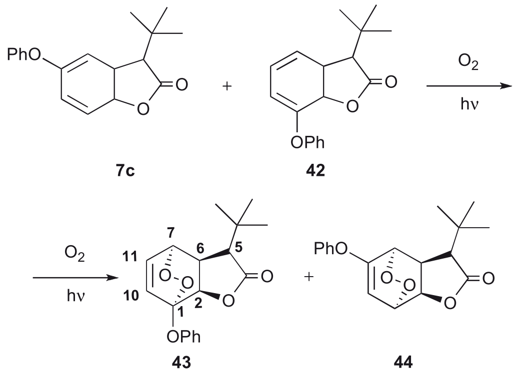
Crystals of **41a** suitable for an X-ray analysis could be grown and the structure established as shown in Figure 9. It confirms the endo addition of oxygen and, as in the previous structures, the *cis* configuration at the ring junction. The O-O distance, 1.491 Å, is typical for a endoperoxide in a six-membered ring.[72]

The peroxidation reaction was also carried out on the two regioisomeric dienes **7c** and **42**:[18] surprisingly, the regioiso-

Table 6. Synthesis of endoperoxylactones **40** and **41**.

Compound	R	Subst. C	R^2	R^3	Yield
40a	H	-		$(CH_2)_5$	95%
40b	*i*-Pr	C11		$(CH_2)_5$	32%
41a	$SiMe_3$	C10	CH_3	CH_3	40%
41b	$SiMe_3$	C10		$(CH_2)_5$	38%
40c	OPh	C11		$(CH_2)_5$	58%

mer **42** reacted much faster with oxygen than **7c** giving almost quantitatively a polar compound **43** easily separable by silica gel chromatography from **7c**, and small amounts of its isomer **44** (Scheme 33).



Scheme 33

The NMR data were again in full agreement with such structures confirming, for **43** the presence of a disubstituted double bond with signals at δ 6.74 (H_{11}, dd, *J* = 9.2 and 5.2 Hz) and at δ 6.47 ppm (H_{10}, δ, *J* = 9.2 Hz), of signals for the two methine groups bearing oxygen at δ 4.80 ppm (H_2, d, *J* = 7.8 Hz) and 4.66 ppm (H_7, m), the carbon C_1 bearing two oxygen atoms, giving a signal at δ 102.56 ppm. For **44**, a series of signals similar to those for the 11-substituted peroxides were also observed.

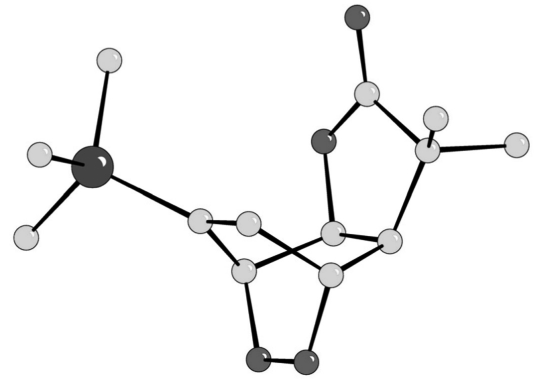
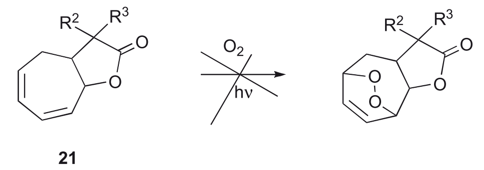


Fig. 9. X-Ray structure of compound **41a.**

c) Attempts to oxidize the diene lactones originating from cycloheptatriene

The formation of non-conjugated dienes from substituted cycloheptatrienes (Scheme 26) represented a serious drawback for one of the goals that was assigned, the synthesis of new *endo* peroxide lactones. Moreower, it appeared rapidly that even the lactones **21**, containing two conjugated double bonds, would not react with oxygen (Scheme 34).

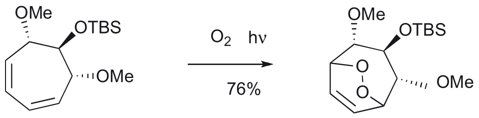


Scheme 34

This is in sharp contrast with earlier observations by Pearson concerning the photooxidation of polysubstituted cycloheptadienes (Scheme 35) which led indeed to high yields of endoperoxides [73].

Table 7. ^1H NMR data of endoperoxylactones **40** and **41**.

Compound	^1H NMR δ (ppm)					
	H10/H11		H1	H2	H7	H6
40a	6.8	H11	5.08		4.79	3.05
	6.60-6.56	H10	(d, 5.5 Hz)		(dd, J = 7, 3Hz)	(dd, J = 7, 3 Hz)
40b			4.99	4.65	4.99	3.09
	6.18	H10	(dddd, 2H, J = 7, 6, 3.4, 1.5 Hz)	(s_{ancho})		(dd, J = 7, 3.4 Hz)
41a					4.37	2.65
	6.75	H11	4.94-4.89		(s_{ancho})	(dd, J = 6.5, 3.2 Hz)
41b					4.49	2.82
	6.74	H11	4.92-4.86		(t, J = 3, 1.0 Hz)	(dd, J = 6.8, 3 Hz)
40c					4.90	3.10
			5.09-5.05 (m, 3H)		(sancho)	(dd, J = 7.3, 3.5 Hz)



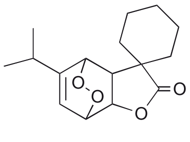
Scheme 35

The reason behind this behaviour is probably related to their geometry: indeed, examination of models of compounds **21** (and also the X-ray structure of **36**) clearly indicated that the π-system is not planar, as for the cyclohexadienes **14**, a fact confirmed by calculations since for the conformation of lowest energy, the dihedral angle between the planes containing the two double bonds is roughly equal to 37°: it is thus likely that a simultaneous overlap of the orbitals on the two terminal carbons of the diene with those of O_2 cannot take place. Introduction of a lactone function on the seven-membered ring, as in **36**, induces however a flattening of the π-system, the observed dihedral angle decreasing now to 14° (according to the X-ray analysis). However, since the yield of formation of **36** was very low, no attempts were made towards its oxidation by molecular oxygen. Thus, slight modifications of the nature of the substituents on the cycloheptadiene induced deep modifications of the reactivity of their double bonds.

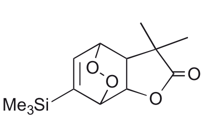
Biological evaluation of the endoperoxide lactones

Eight compounds prepared herein containing either an endoperoxide lactone or a diene-lactone (for sake of comparaison) were tested for their cytotoxicity towards several lines of human cancer cells (colon cancer HCT15; breast cancer MCF-7; leukemia K-562 CML; central nervous system U-251; prostate cancer PC-3; lung cancer SKLU-1) according to the protocole described by Monks.[74] Human cells were first treated with different concentrations (10 mM and 50 mM) of the selected compounds. As shown in Table 8, significant cytotoxicity was observed in all types of cancer cells treated with these compounds. For those three compounds **40b**, **41a**, **41b** showing the highest influence on the viability of the cells, the concentration giving 50% inhibition of the cell growth (IC_{50}) was determined and compared to the values for known, effective therapeutic agents such as doxorubicine and *cis*-platinum. Table 9. All of them appeared to inhibit at least as efficiently as *cis*-platinum the growth of cancer cells. Interestingly, these inhibitions were dependent on the structure of the peroxides and selective interactions were observed. Thus, **41b**, bearing the TMS substituent, showed the highest activity towards cancer cells of the central nervous system, **40b** and **41b** being respectively the most active against prostate and leukemia cancer cells. Moreover, **40b** is also active against colon cancer cells.

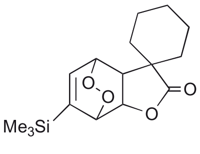
It should however be noticed that **41a** shows no selectivity since it is active towards three cell lines.



40b



41a



41b

According to these results, the activity of these compounds can be related to the presence of an endoperoxide, much lower activities being observed for the starting diene-lactones (see Table 8), the highest activities being moreover observed when they bear a voluminous substituent close to the lactone function.

Experimental

General Remarks. All reactions were performed under a dry argon or nitrogen atmosphere. All reagents were obtained from

Table 8. Preliminary evaluation of the cytotoxicity % inhibition of the cell growth.

Compound	U251 Nervous system	PC-3 Prostate	K562 Leukemia	HCT-15 Colon	MCF-7 Breast	SKUL Lung
10mM						
Endoperoxidelactones						
41a	33.5	**100**	**84.9**	**100**	**50.2**	**76.4**
41b	27	**100**	**93.4**	**94**	**68.3**	**63**
50mM						
Lactone [4.3.0]						
7a	44.49	26.67	**63.35**	22.94	**59.08**	-
Lactones [5.3.0]						
17a	9.28	22.65	20.16	4.74	21.18	-
34a	22.21	25.58	29.25	22.62	40.06	-
34b	22.59	28.29	46.96	35.8	43.8	-
34d	42.81	42.98	**62.7**	40.99	**65.5**	36.71
Endoperoxidelactones						
40b	**100**	**100**	**100**	**100**	**98.72**	-

Table 9. CI_{50} values (μM)

Compound	U251 Nervous system	PC-3 Prostate	K562 Leukemia	HCT-15 Colon	MCF-7 Breast	SKUL Lung
40b	11.45 ± 0.3	3.55 ± 0.5	9.46 ± 0.3	2.08 ± 0.8	24.49 ± 3.1	15.89 ± 0.66
41a	12.8 ± 1.7	9.4 ± 1.3	3.4 ± 0.8	5.8 ± 0.9	5.4 ± 0.4	4.6 ± 0.1
41b	4.7 ± 0.9	5.5 ± 0.7	4.6 ± 0.5	3.4 ± 0.3	6.0 ± 1.0	6.9 ± 0.3
Doxorubicine	0.09 ± 0.02	0.32 ± 0.02	0.28 ± 0.01	0.23 ± 0.01	0.10 ± 0.01	0.28 ± 0.01
***Cis*-platinum**	9.48 ± 1.7	15.90 ± 2.1	13.52 ± 0.6	13.48 ± 0.7	25.80 ± 3.7	-

commercial suppliers and used as received. Solvents were distilled from sodium/benzophenone ketyl (diethyl ether, tetrahydrofuran), phosphorous pentoxide (dichloromethane) and saturated with argon. Silica gel Merck, type 60, 0.063-0.200 mm was used for column chromatography. All NMR spectra were recorded in $CDCl_3$ unless stated otherwise with $CHCl_3$ as internal standard and the chemical shifts are given in ppm on Bruker ARX-200, Bruker AVANCE-400, JEOL GX-300. Abbreviations used for signal multiplicity are: s = singlet, d = doublet, t = triplet, q = quadruplet, m = massif. IR spectra were performed on Perkin-Elmer 1420 or Nicolet 750, MS and HRMS on Jeol MS 700 or Jeol JMS-SX102A and Jeol JMS-AX505HA, m.p. on Reichert Kofler hot bench , the reported melting points are non-corrected. X-ray data were collected on Enraf-Nonius MACH-3 and KAPPACCD, Brucker SMART APEX CCD diffractometers. Theoretical calculations have been carried out at the B3LYP/6-31G(d,p) level, using the GAUSSIAN series of programs.

The ketene acetals **3**, **22**, and **35** have been prepared according to published methods [75-79]; the arenetricarbonyl complexes according to references [80-84].

Dienol ethers deprotection

To a suspension of $CrCl_2$ (133 mg, 1.08 mmol), LiI (193 mg, 1.44 mmol) in a mixture of EtOAc / H_2O (1/0.005, 10 mL) was added the dienol ether **7a** (R=*i*Pr, R^2=R^3=$(CH_2)_5$, 100 mg, 0.36 mmol) at room temperature. The solution was stirred for 3 h then extracted with dichloromethane, the organic layer washed with a solution of sodium bisulfite, then with water and brine and dried over Na_2SO_4. Evaporation of the solvents followed by column chromatography on silica gel afforded a solid (69 mg, 85% isolated yield), the physical properties of which agreed with those of an authentic sample of the ketone **8a** (R^2=R^3= $(CH_2)_5$).

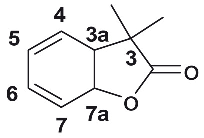
Similarly, the dienol ether **7b** led to the ketone **8a** (87%).

A 1:1 mixture of the two regioisomers of **7c** (R = Ph, R^2 = H, R^3 = *t*Bu) and **42** (400 mg, 1.4 mmol) was treated under the same conditions as above with a mixture of $CrCl_2$ (518 mg, 4.22 mmol), LiI (750 mg, 5.62 mmol) in EtOAc / H_2O (1/0.005, 40 mL) for one night at room temperature. Extraction as above afforded an oil which was chromatographed on a silica gel column to give successively the enol ether **42** (195 mg, 49%) then the ketone **8b** (R^2 = H, R^3 = *t*Bu, 137 mg, 47%) as a solid, the spectrocopic data of which agreed with those of an authentic sample.

Synthesis of the lactones

3,3-Dimethyl-3a,7a-dihydro-3*H*-benzofuran-2-one 14a

To a mixture of chromium complex **1a** (R=H, 1.15 g, 5 mmol), bis(trimethylsilyl)ketene acetal **3a** (R^2=R^3=Me, 2.49 mL, 10 mmol), DMF (6 mL) and dry THF (10 mL) stirred at –78 °C, was added 1M *t*BuOK (10 mmol) in THF. The solution was stirred at –40°C for 4 h, then a solution of I_2 (6.3 g, 25mmol) in THF (20 mL) was added at –78°C. The solution was stirred 2 h at room temperature. Diethyl ether was added, and the organic phase was washed with aqueous Na_2SO_3 (10%, 100 mL), NaOH solution (10%, 100mL), water and a saturated NaCl solution, dried over Na_2SO_4 filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel. **14a** was obtained as an oil (128 mg, 15%). Extraction of the aqueous phase with diethylether gave the corresponding acid **4a** (260 mg, 31%).

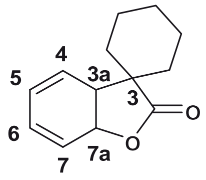


14a

^{1}H NMR ($CDCl_3$, 300MHz): δ ppm 6.04-5.92 (m, 2H, H6, H5), 5.80-5.76 (m, 1H, H7), 5.71-5.66 (m, 1H, H4), 5.33 (d, 1H, H7a, J = 10 Hz), 2.99 (dd, 1H, H3a, J = 10, 4 Hz), 1.31 and 1.27 (2s, 6H, 2 CH_3). **RMN ^{13}C** ($CDCl_3$, 75 MHz): δ ppm 181.52 (C2), 126.26, 124.83, 123.74, 121.91 (C4, C5, C6, C7); 76.64 (C7a), 44.47 (C3a), 42.26 (C3), 25.77 (CH_3), 21.67 (CH_3).

3-spiro(3-cyclohexyl)-3a,7a-dihydro-3*H*-benzofuran-2-one 14b

The same procedure was followed using complex **1a** (R=H, 700 mg, 3.2 mmol), **3b** (R^2R^3=$(CH_2)_5$, 1.7 mL (6.5 mmol)**,** a 1 M solution of *t*BuOK in THF (6.5 mmol, 20 mL), and I_2 (4.0 g,16 mmol) in THF (20 mL). Chromatography on silica gel gave **14b** (456 mg, 70%) and extraction of the aqueous phase with diethylether gave the corresponding acid **4b** (142 mg, 23%).

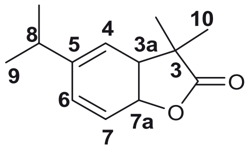


14b

^{1}H **NMR** (CDCl$_3$, 200 MHz) δ ppm: 6.18 (dd, 1H, H6, J = 9.35, 5.56 Hz,); 6.05 (td, 1H, H5 J = 12.63, 5.56, 3.03 Hz); 5.89 (dd, 1H, H7, J = 9.35, 4.8 Hz,); 5.79 (dd, 1H, H4, J = 9.6, 3.03 Hz); 5.13 (dd, 1H, H7a, J = 8.84, 4.8 Hz); 3.17 (d, 1H, H3a J = 8.84 Hz); 1.8-1.2 (m, 10H, cyclohexyl). ^{13}**C NMR** (CDCl$_3$, 75 MHz): δ ppm 180.40 (C2), 127.68 (C6), 125.10 (C4), 123.78 (C5), 120.11 (C7), 72.15 (C7a), 42.40 (C3a); 35.54, 30.20, 25.24, 22.55, 22.13 (cyclohexyl), 26.85 (C3).

3,3-Dimethyl-5-isopropyl-3a,7a-dihydro-*3H*-benzofuran-2-one 14c

The same procedure was followed using complex **1b** (R=*i*Pr, 810mg, 3.16 mmol), **3a** (R^2 = R^3= Me, 1.46 mL, 6.3 mmol)**,** a 1 M solution of *t*BuOK in THF (6.3 mmol) and I$_2$ (4.0 g,16 mmol) in THF (20 mL). Chromatography on silica gel afforded **14c** (329 mg, 50%). A total conversion of **14c** into the corresponding acid **4c** was observed after 4 days**.**

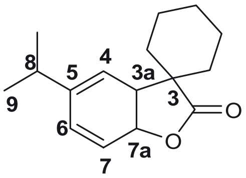


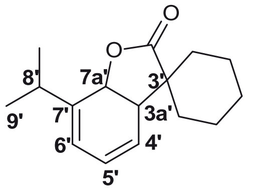
14c

^{1}H **NMR** (CDCl$_3$, 300 MHz) δ ppm: 5.95 (d, 1H, H6, J = 10Hz), 5.78 (dd, 1H, H7; J = 10, 3.6 Hz), 5.36 (d, 1H, H4; J = 10 Hz), 5.34 (dd, 1H, H7a, J = 10, 3.6 Hz), 2.94 (dd, 1H, H3a, J = 10, 4.5 Hz), 2.30-2.28 (m, 1H, H8), 1.29 (s, 3H, H10), 1.25 (s, 3H, H10'), 1.03 (s, 3H, H9), 1.01 (s, 3H, H9'). ^{13}C **NMR** (CDCl$_3$, 75 MHz) δ ppm: 181.93 (C2), 141.42 (C5), 128.42 (C6), 122.57 (C7), 115.94 (C4), 74.58 (C7a), 44.31 (C3a), 42.49 (C3), 33.51 (CH$_3$), 29.76 (C8), 25.74 (CH$_3$), 22.75 (C10). IR (n, cm^{-1}): 2961.93, 2871.64 (=CH); 1770.18 (CO lactone). **MS** (EI, 70eV): m/z (%) = 206 (7) M$^{+\cdot}$, 191 (7) [M-15]$^+$, 149 (36)[M-57]$^+$, 111(41)[M-95]$^+$, 97 (55) [M-109]$^+$, 71(79) [M-135]$^+$, 57 (100)[M-149]$^+$.

3-spirocyclohexyl-5-*i*-propyl-3a,7a-dihydro-*3H*-benzofuran-2-one 14d and 3-spirocyclohexyl-7-*i*-propyl-3a,7a-dihydro-*3H*-benzofuran-2-one 14d'

The same procedure was followed using complex **1b (**R= *i*Pr, 2.8 mmol, 720 mg), **3b** (R$_2$R$_3$=(CH$_2$)$_5$, 5.6 mmol, 1.53 mL)**,** 1M *t*BuOK in THF (5.6 mmol), I$_2$ (14 mmol, 3.5 g) in THF (20 mL). Chromatography on silica gel gave **14d** (440 mg, 65%).



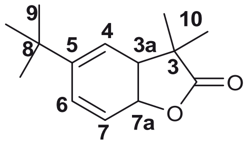


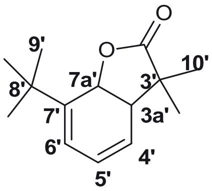
1**4d** **14d'**

^{1}**H NMR** (CDCl$_3$, 300 MHz) δ ppm: 6.08 (d,1H, H6, J = 9.8Hz), 5.88 (dd, 1H, H7, J = 9.8, 4.8 Hz), 5.39 (bs, 1H, H4), 5.07 (dd, 1H, H7a, J = 9.0, 4.8 Hz), 3.71 (dd, 1H, H3a, J = 9.0 Hz), 2.90-3.07 (m, 1H, H8), 1.82-1.60 (m, 4H, cyclohexyl), 1.55 (s, 3H, H9), 1.24 (s, 3H, H9), 1.02-1.00 (m, 6H, cyclohexyl). **RMN** ^{13}**C** (CDCl$_3$, 75 MHz) δ ppm: 180.84 (C2, 2'), 149.21(C5'), 141.10 (C5), 129.74 (C4'), 128.34 (C4), 128.22 (C6'), 124.72 (C6), 120.77 (C7'), 116.22(C7), 72.72 (C7a), 67.94 (C7a'), 51.00 (C3'), 46.66 (C3), 42.54 (C3a) 40.01 (C3a'); 32.00, 31.20, 30.06, 29.77, 25.65, 25.28, 22.55, 22.20, 21.27, 21.19 (cyclohexyl). **IR** n (cm^{-1}): 2930, 2858 (=CH), 1762 (C=O), 1173 (C-O). **MS** (EI, 70 eV) m/z (%): 246 (60) M^{+}ž, 201 (90) [M-45]$^+$, 171 (100) [M-75]$^+$.

5-*t*-Butyl-3,3-dimethyl-3a,7a-dihydro-*3H*-benzofuran-2-one 14e and 7-*t*-Butyl-3,3-dimethyl-3a,7a-dihydro-3H-benzofuran-2-one 14e'

The same procedure was followed using complex **1c (**R= *t*Bu, 2.2 mmol, 620 mg), **3a** (R^2=R^3=CH$_3$, 4.5 mmol, 1.06 mL), 1M *t*BuOK in THF (4.5 mmol), I$_2$ (11 mmol, 2.8 g) in THF (20 mL). Chromatography on silica gel gave **14e** and **14e'** as a mixture of regioisomers (174 mg, yield = 36%).



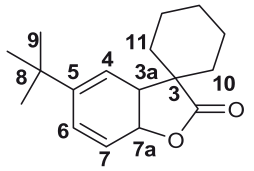


14e **14e'**

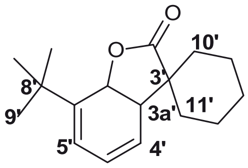
^{1}**H NMR** (CDCl$_3$, 300 MHz) δ ppm: 6.16-6.13 (d, 1H, H6, J = 10 Hz), 5.82 (bs, 1H, H7), 5.42 (bs, 1H, H4), 5.29 (d, 1H, H7a, J = 9.4 Hz), 2.98-2.86 (m, 1H, H3a),1.58-1.11 (m, 15H, H9, 10). ^{13}**C NMR** (CDCl$_3$, 75 MHz) δ ppm: 182.08 (C2), 181.52 (C2'), 151.13 (C7'), 143.79 (C5), 128.09 (C7), 127.21 (C4), 125.45 (C6), 122.75 (C4'), 122.48 (C5'), 114.81 (C6'), 74.41 (C7a), 73.32 (C7a'), 47.47 (C3), 46.47 (C3'), 44.29 (C3a), 43.04 (C3a'), 42.58 (C8), 34.35 (C8'), 31.41 (C10), 29.76 (C9'), 29.34 (C10'), 28.60 (C9). According to the signals at 74.41 and 73.32 ppm, a 7:3 ratio of the two isomers was present. **IR** (n, cm^{-1}): 2963.49, 2926.19, 2870.51 (=CH); 1771.44 (CO). **MS** (EI, 70 eV) m/z (%): 220 (30) M$^{+\cdot}$, 205 (90) [M-15]$^+$, 175 (100)[M-45]$^+$, 71 (25) [M-149]$^+$, 57 (45) [M-163]$^+$

5-*t*-Butyl-3-spirocyclohexyl-3a,7a-dihydro-*3H*-benzofuran-2-one 14f and 7-*t*-Butyl-3-spirocyclohexyl-3a,7a-dihydro-3H-benzofuran-2-one 14f’

The same procedure was followed using complex **1c** **(**R= *t*Bu, 1.9 mmol, 520 mg), **3b** (R_2R_3=$(CH_2)_5$, 3.8 mmol, 1 mL), 1M *t*BuOK in THF (3.8 mmol), I_2 (9.5 mmol, 2.4 g) in THF (20 mL). The crude furnished **14f** and **14f’** as a mixture of regioisomers (350mg, 71%).



14f

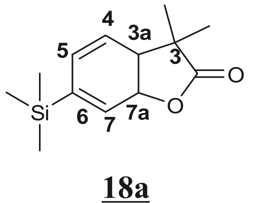


14f’

^{1}**H NMR** ($CDCl_3$, 300 MHz) δ ppm: 6.04 (bs, 1H, H6), 5.62 (bs, 1H, H7), 5.47 (bs, 1H, H4),5.07 (d, 1H, H7a, J = 8.9 Hz), 3.11-3.07 (m, 1H, H3a), 1.80-1.05 (m, 10H, cyclohexyl). ^{13}**C NMR** ($CDCl_3$, 75 MHz) δ ppm: 180.77 (C2), 148.08 (C5), 143.24 (C7’), 128.58 (C7), 127.99 (C4’), 125.30(C5’), 124.90 (C6), 120.69 (C4), 115.09 (C6’), 73.48(C7a’), 72.38 (C7a), 46.70 (C3), 41.25 (C8), 34.37, 33.89 (C3’, 8’); 31.39, 30.05, 29.76, 29.36, 28.57, 28.31, 25.28, 22.52, 22.18 (C3a, 3a’, 10, 11, 10’, 11’, 9, 9’, cyclohexyl). (4:6 mixture of two isomers). **IR** (n, cm^{-1}): 2931.20, 2858.52 (=CH); 1764 (CO lactone). **MS** (EI, 70 eV) m/z (%): 260 (35) $M^{+\cdot}$, 245(55) $[M-15]^{+}$; =215(100) $[M-30]^{+}$, 147 (70) $[M-113]^{+}$; 57 (75) $[M-203]^{+}$.

3,3-Dimethyl-6-trimethylsilyl- -3a,7a-dihydro-*3H*-benzofuran-2-one 18a (R^2=R^3=CH_3)

The same procedure was followed using complex 17 (R = $SiMe_3$, 5 mmol, 1.4 g), 10 mmol (2.3 mL), 3a (R^2=R^3=CH_3, 10 mmol, 2.3 mL), 1M *t*BuOK (10 mmol) in THF, I_2 (25 mmol, 6.3 g) in THF (20 mL). Extraction furnished 18 (284mg, 24%).

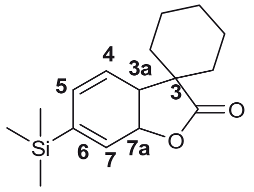


18a

^{1}**H NMR** ($CDCl_3$, 200 MHz) δ ppm: 6.13-6.00 (m, 2H, H5,7), 5.72 (dd, 1H, H4, J = 9.5, 4.2 Hz); 5.33 (dd ,1H, H7a, J = 10, 3 Hz); 2.97 (dd, 1H, H3a, J = 10, 3 Hz); 1.34-1.27 (2s, 6H, $2CH_3$); 0.13 (s, 9H, $Si(CH_3)_3$).

3-spirocyclohexyl-6-trimethylsilyl-3a,7a-dihydro-*3H*-benzofuran-2-one 18b (R^2R^3=$(CH_2)_5$)

The same procedure was followed using complex **17** (R=$SiMe_3$, 3.5 mmol,1 g), **3b** (R^2R^3=$(CH_2)_5$, 6.9 mmol,1.9 mL)**,** 1M *t*BuOK in THF (6.9 mmol), I_2 (17 mmol, 4.4 g) in THF (20 mL). The mixture was stirred at room temperature for 12 hours. Extraction furnished a crude of **18** (560 mg, 60%).

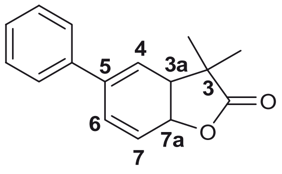


18b

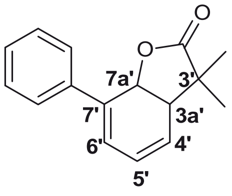
^{1}**H NMR** ($CDCl_3$, 200 MHz) δ ppm: 6.15-6.07(m, 2H, H7,5), 5.77 (dd, 1H, H4, J = 9.7, 2.7 Hz), 5.10 (dd, 1H, H7a, J = 8.9, 4.5 Hz), 3.12 (d, 1H, H3a, J = 8.9 Hz), 1.80-1.20 (m, 10H, Hcyclohexyl), 0.14 (s, 9H, $Si(CH_3)_3$).

3,3-Dimethyl-5-phenyl-3a,7a-dihydro-*3H*-benzofuran-2-one 14g and 3,3-Dimethyl-7-phenyl-3a,7a-dihydro-*3H*-benzofuran-2-one 14g’

The same procedure was followed using complex **1d** (R=Ph, 3.45 mmol, 1 g), **3a** (R_2=R_3=CH_3, 6.9 mmol,1.6 mL)**,** 1M *t*BuOK in THF (6.9 mmol), I_2 (17.2 mmol, 4.3 g) in THF (20 mL). Chromatography on silica gel gave **14g** and **14g’** as a solid mixture of regioisomers (234 mg, 28%).



14g

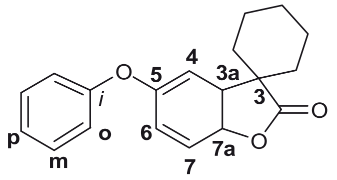


14g’

^{1}**H NMR** ($CDCl_3$, 300 MHz) δ ppm: 6.50 (d, 1H, H4, J = 6.3 Hz), 6.24-6.20 (m, 1H, H7, J = 3.3), 5.83 (dd, 1H, H6, J = 9.6, 3.3 Hz), 5.63 (d, 1H, H7a, J = 8.5 Hz), 3.18 (d, 1H, H3a, J = 8.5 Hz), 1.48 (s, 3H, $C\underline{H}_3$), 1.40 (s, 3H, $C\underline{H}_3$). ^{13}**C NMR** ($CDCl_3$, 75 MHz) δ ppm : 181.26 (C2, 2’), 138.49 (C5), 132.00 (Ci, i’), 131.00 (C7’), 128.84 (C6’), 128.68 (aromatic), 128.05 (C6), 125. 80 (aromatic), 125.07 (C5’), 124.69 (C4’), 124.38 (C7), 123.50 (C4), 74.89 (C7a), 71.50 (C7a’), 59.67 (C3a’), 46.86 (C3, 3’), 43.07 (C3a); 25.89, 22.75, 22.02, 21.09 ($(\underline{C}H_3)_4$).

3-spirocyclohexyl-5-phenoxyl-3a,7a-dihydro-*3H*-benzofuran-2-one 7b (R=Ph, R^2R^3=$(CH_2)_5$)

The same procedure was followed using complex **5b** (R=Ph, 7.3 mmol,1.7g), **3b** (R^2R^3=$(CH_2)_5$, 14.7 mmol, 4 mL)**,** 1M *t*BuOK in THF (14.7 mmol), I_2 (36.5 mmol, 9.2 g) in THF (20 mL). Extraction furnished **7b** (R=Ph, R^2R^3=$(CH_2)_5$) as an oil (1.19 g, 55%). Chromatography on silica gel gave the corresponding acid **6** ((R=Ph, R^2R^3=$(CH_2)_5$, 135 mg, yield = 6%).

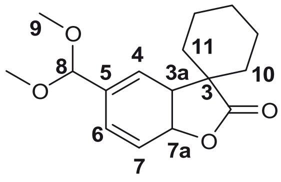


7b

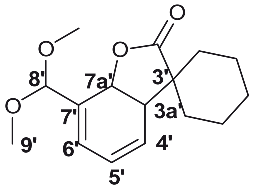
^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 7.40-7.30 (m, 2H, 2H*m*); 7.17-7.13 (m;1H, H*p*); 7.01-6.97 (m, 2H, H*o*); 6.11 (m, 2H, H6,7); 5.18 (dd, 1H, H7a, J = 8.7, 4Hz); 5.03 (m, 1H,H4); 3.33 (dd, 1H, H3a, J = 8.7, 4Hz); 1.88-1.25 (m, 10H, cyclohexyl). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ ppm: 180.21 (CO); 155.13, 149.97 (C5, *i*), 129.82 (C6), 127.61 (Cp), 123.72 (C7), 118.84 (Co, m), 102.31 (C4), 71.66 (C7a), 46.66 (C3), 42.62 (C3a); 33.45, 30.30, 25.15, 25.44, 21.96 (cyclohexyl). **HRMS** Calculated for $C_{19}H_{21}O_3$: 297.1491, found: 297.1487.

3-spirocyclohexyl-5-dimethoxydimethyl-3a,7a-dihydro-*3H*-benzofuran-2-one 14h and 3-spirocyclohexyl-7-dimethoxydimethyl-3a,7a-dihydro-*3H*-benzofuran-2-one 14h'

The same procedure was followed using complex **1e** (R=CH$(OMe)_2$, 4 mmol, 1.2 g), **3b** (R_2R_3=$(CH_2)_5$, 8 mmol, 2.1 mL), 1M *t*BuOK in THF (8 mmol), I_2 (20 mmol, 5.2 g) in THF (20 mL) and furnished **14h** and **14h'** as a mixture of regioisomers (767 mg, 69%).



14h

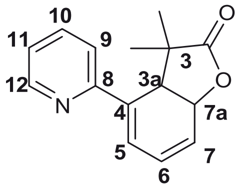


14h'

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 6.16 (d, 1H, H6, J = 9.8Hz), 5.93-5.75 (m, 2H, H7,4), 5.12-5.06 (m, 1H, H7a), 4.71 (d, 1H, H8, J = 3.2 Hz); 3.28 (bs, 1H, H3a); 3.27 and 3.23 (2s, 6H, H9); 1.80-1.21 (m, 10H, cyclohexyl). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ ppm: 180.34 (C2, 2'); 136.68 (C7'), 132.64 (C5), 128.22 (C6); 126.80 (C4); 122.83 (C5'); 121.60 (C4'); 121.21 (C7), 117.74(C6'), 103.22 (C8'), 102.75 (C8); 72.37 (C7a); 72.26 (C7a'), 53.01 (C9', 3a'), 52.95 (C9); 52.73 (C3a), 46.54 (C3'); 42.38 (C3); 33.65, 33.54, 30.31, 25.19, 22.49, 22.09 (cyclohexyl). **IR** (cm^{-1}): 2933.72, 2858.35 (=CH); 1762, 1170 (C=O). **MS** (EI, 70 eV) m/z (%): 278 (2) M$^+$; 247 (100) [M-31]$^+$; 232 (18) [M-46]$^+$; 187 (52) [M-91]$^+$; 83 (55) [M-195]$^+$.

3,3-Dimethyl-4-(pyridin-2-yl)-3a,7a-dihydro-*3H*-benzofuran-2-one 16a (R^2=R^3=CH_3)

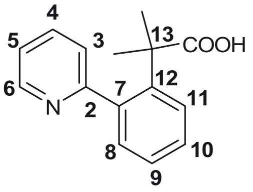
The same procedure was followed using complex **15** (3.4 mmol, 1 g), **3a** (R_2=R_3=CH_3, 6.8 mmol,1.6 mL), 1M *t*BuOK in THF (6.8 mmol), I_2 (17.2 mmol, 4.3g) in THF (20 mL) and furnished **16a** (R_2=R_3=CH_3, 110 mg, 13%) as a white solid, mp 134 °C.



16a

^{1}H NMR ($CDCl_3$, 300MHz) δ ppm: 8.55 (d, 1H, H12, J = 4.4 Hz,), 7.66 (dd, 1H, H10, J = 8, 7.2 Hz), 7.46 (d, 1H, H9, J = 8 Hz), 7.17 (dd, 1H, H11, J = 7.2, 4.4 Hz), 6.50 (d, 1H, H5, J = 5.5 Hz,), 6.05 (dd, 1H, H6, J = 10, 5.5 Hz), 5.79 (d, 1H, H7, J = 10 Hz), 5.65 (d, 1H, H7a, J = 12.2 Hz), 4.27 (d, 1H, H3a, J = 12.2 Hz), 1.07, 1.04 (s, 6H, 2CH_3). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ ppm: 182.31 (C2), 156.52 (C8), 149.15 (C12), 136.77 (C10), 136.42 (C4), 125.65 (C7), 125.15 (C6), 123.19 (C5), 122.80 (C11), 120.69 (C9), 76.92 (C7a), 42.57 (C3a), 42.46 (C3), 26.49, 21.33 ($(CH_3)_2$). **IR** n (cm^{-1}): 2978, 2934 (=CH), 1763 (C=O lactone), 1190 (C-O). **Anal.** Calcd for $C_{15}H_{15}NO_2$: C, 74.67 %; H, 6.27 %; N, 5.81 % Found: C, 74.49 %; H, 6.33 %; N, 5.77 %. **MS** (EI, 70 eV) m/z (%): 240 (16) [M-1]$^+$, 211 (12) [M-30]$^+$, 196 (100) [M-45]$^+$, 182 (22) [M-59]$^+$, 155 (34) [M-86]$^+$.

2-methyl-2-(3-pyridin-2-yl-phenyl) propionic acid 4 (R^2=R^3=CH_3)



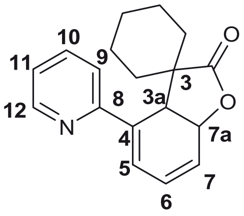
4

white solid, mp 162 °C.

^{1}H NMR ($CDCl_3$, 200MHz) δ ppm: 8.60 (d, 1H, H6, J = 4 Hz), 7.62(m, 3H, H4; 8, 9), 7.51 (m, 1H, H10), 7.38 (m, 2H, H3, 11), 7.16 (dd, 1H, H5 , J_1 = J_2 = 4 Hz) 1.54 (s, 6H, $(CH_3)_2C$). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ ppm: 180.18 (CO), 157.21 (C2) 148.8 (C6), 146.42 (C7), 138.0 (C4) 136.67 (C12), 127.46 (C9, 11), 126.39 (C3, 8), 122.47 (C5), 121.90 (C10), 46.50 (C13), 26.62 ($(\underline{C}H_3)_2C$). IR n (cm-1): 3600 (OH), 2973, 2933 (=CH), 1719 (C=O).

3-spirocyclohexyl-4-(pyridin-2-yl)-3a, 7a-dihydro-*3H*-benzofuran-2-one 16b (R^2R^3=$(CH_2)_5$)

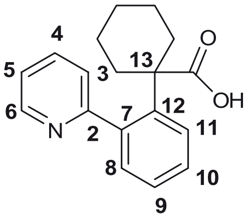
The same procedure was followed using complex **15** (5 mmol,1.5g), **3b** (R_2R_3=$(CH_2)_5$), 10 mmol, 12.5 mL), 1M *t*BuOK in THF (11 mmol), I_2 (25.6 mmol, 6.5 g) in THF (20 mL), and furnished **16b** (28 mg, 2%), mp 160 °C, and the corresponding acid **4** (19 mg, 1.7%), mp 198 °C.



16b

^{1}H NMR ($CDCl_3$, 200MHz) δ ppm: 8.50 (d, 1H, H12, J = 4.5 Hz), 7.63 (dd, 1H, H10, J = 9.3, 7.5 Hz), 7.42 (d, 1H, H9, J = 9.06), 7.17 (dd, 1H, H11, J = 7.2, 4.5 Hz), 6.42 (d, 1H, H5, J = 5.6 Hz), 5.98 (dd, 1H, H6, J = 9.4, 5.5 Hz), 5.77 (d, 1H, H7, J = 9.4 Hz), 5.58 (d, 1H, H7a, J = 11.8 Hz), 4.14 (d, 1H, H3a, J = 11.8 Hz), 1.66-1.07 (m, 10H, cyclohexyl). **^{13}C NMR** ($CDCl_3$, 50MHz) δ ppm: 179.96 (CO), 157.17 (C8), 149.20 (C12), 136.86 (C10), 136.08 (C4), 126.42 (C7) 125.01 (C6), 124.49(C5), 122.74 (C11); 120.99(C9), 77.16 (C7a), 43.77(C3a, 3), 21.10-29.24 (cyclohexyl).

1-(2-pyridin-2-yl-phenyl) cyclohexanecarboxylic acid 4 (R=pyridinyl, R^2R^3=($CH_2)_5$



4

^{1}H NMR ($CDCl_3$, 200MHz) δ ppm: 8.60 (d, 1H, H6 , J = 8 Hz), 7.74 (m, 3H, H4, 8, 9), 7.61 (m, 1H, H10), 7.45 (m, 2H, H3, 11), 7.19(m, 1H, H5), 1.22-2.47(m, 10H, cyclohexyl). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ ppm: 178.66 (CO_2H), 157.50 (C2), 148.60 (C6), 145.70 (C7), 137.81(C4), 136.85 (C12), 127.50 (C8, C11), 126.67 (C3, C9), 122.38 (C5), 121.71 (C10), 50.82 (C13), 23.74-34.66 (cyclohexyl). Anal: Calcd for $C_{18}H_{19}NO_2$: C, 76.84%; H, 6.81%; N, 4.98% Found: C, 76.26%; H,6.83%; N,4.99%.

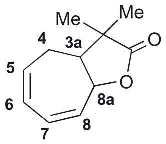
Synthesis of [5.3.0] fused lactones without substituent

General procedure

To a solution of cycloheptatrienechromiumtricarbonyl **20** and the appropriate *bis*(trimethylsilyl)ketene acetal **3** in THF (30 mL) in a 100 mL round bottom flask, maintained at –78°C, a 1M solution of *t*BuOK in THF cooled to –40 °C was added. The solution was kept at –40 °C for 4 h. Then, the solution was cooled to –78 °C and a solution of iodine in THF was added. The solution was slowly heated to room temperature then stirred for a further 12 h. The solution was then poured in a 100 mL aqueous solution of sodium bisulfite (10%), extracted with diethyl ether, the organic layer washed with a 10% NaOH solution, dried over Na_2SO_4, the solvents evaporated in vacuo, and finally the oily residue purified on silica gel.

3,3-Dimethyl-3,3a, 4,8a-tetrahydro-cyclohepta[*b*]furan-2-one 21a (R^2=R^3=CH_3)

20 (4.3 mmol, 1 g); **3a** (8.7 mmol, 2 mL); 1M *t*-BuOK 1M in THF (8.7 mmol); I_2 (21 mmol, 5.4 g) in THF (20 mL). Silica gel chromatography led to **21a** (0.55g, 73 %) as an oil.

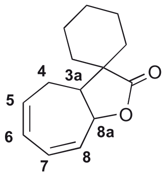


21a

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: [6.15-6.10 (m, 2H) y 5.96-5.90 (m, 2H)] H5, 6, 7, 8; 4.97 (dd, 1H, H8a, J = 7.5, 2.2 Hz), 2.70 (ddd, 1H, H3a, J = 11.6, 7.5, 3.7 Hz), 2.13-2.00 (m, 2H, H4), 1.18 (s, 3H, $C\underline{H}_3$), 1.13 (s, 3H, $C\underline{H}_3$). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 181.3 (C2), 133.0 (C8), 131.2 (C5), 128.5 (C7), 127.2 (C6), 78.3 (C8a), 60.38 (C3a), 42.6 (C3), 25.2 (CH_3), 25.1 (C4), 21.3 ($\underline{C}H_3$). **MS** (IE, 70 eV) m/z (%): 178(18) $M^{+\cdot}$, 149(37) $[M-29]^+$, 91(70) $[C_7H_7]^+$. **IR** n (cm^{-1}): 2970.8, 2932.8 (CH), 1773.0 (C=O lactone), 1101.2 (C-O lactone).

3-spirocyclohexyl-3,3a,4,8a-tetrahydro-cyclohepta[*b*]furan-2-one 21b (R^2=R^3=$(CH_2)_5$

20 (8.7 mmol,1 g); **3b** (17.5 mmol, 4.7 mL); 1M *t*-BuOK 1M in THF (17.5 mmol); I_2 (43.5 mmol, 10.9 g) in THF (20 mL). Silica gel chromatography led to **21b** (1.4 g, 73 %) as a solid mp < 50 °C.



21b

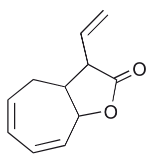
^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 6.05-5.85 (m, 4H, H5,6,7,8), 4.92 (td, 1H, H8a, J_{3a-8a} = 3.7Hz, J_{8a-8} = 5.3 Hz), 2.54 (dd, 1H, H3a , J_{3a-4} = 2.0Hz, J_{3a-8a} = 3.7 Hz), 2.1 (ddd, 1H, H4', $J_{4'-5}$ = 8.5 Hz), 1.89 (tt, 1H, H4, J_{3a-4} = 2.0, J_{4-5} = 5.3 Hz), 1.71-1.19 (m, 10H, cyclohexyl). **^{13}C** NMR ($CDCl_3$, 100 MHz) δ ppm: 180.3 (C2); 133.8, 130.1, 128.0, 127.9 (C5, 6, 7, 8); 78.9 (C8a); 55.0 (C3a); 47.3 (C3); 25.6 (C4); 33.4, 29.4, 25.3, 22.6, 22.1 (cyclohexyl). **HRMS** Calcd for $C_{14}H_{19}O_2$: 219.1385. Found: 219.1384.

3-Vinyl-3,3a, 4,8a-tetrahydro-cyclohepta[*b*]furan-2-one 23 and 3-Ethylidene-3,3a, 4,8a-tetrahydro-cyclohepta[*b*]furan-2-one 24

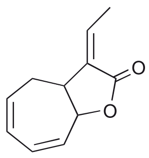
20 (6.1 mmol,1.4 g); **22** (12.3 mmol, 2.83 mL); 1M *t*-BuOK 1M in THF (12.3 mmol); I_2 (30.7 mmol, 7.82 g) in THF (20 mL). Silica gel chromatography led to the lactone **23** (0.5 g, 44 %) and **17d** (0.2g, 17%) as oils.

23 **^{1}H NMR** ($CDCl_3$, 400 MHz) δ ppm: 6.14-6.08 (m, 1H, H5), 6.02-5.96 (m, 3H, H6,H7,H8), 5.78-5.69 (m, 1H, H9), 5.27-5.20 (m, 2H, H10), 5.03 (d, 1H, H8a, J_{8a-3a} = 8.0 Hz), 3.16 (t, 1H, H3a, J_{3a-8a} = 8.0Hz), 3.0-2.92 (m, 1H, H3), 2.36-2.10 (m, 2H, H4). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 176.2 (C2); 132.5 (C5); 78.9 (C8a), 131.7 (C9); 130.7, 128.7, 127.7 (C6, C7, C8), 119.3 (C10), 79.4 (C8a), 54.0 (C3a), 43.6 (C3), 29.0 (C4).

24 **^{1}H** NMR ($CDCl_3$, 200 MHz) δ ppm: 6.82-6.74 (m, 1H, H9), 6.26-6.04 (m, 4H, H7,6,8,5), 5.01-4.98 (m, 1H, H8a), 3.42 (s, 1H, H3a), 2.34-2.20 (m, 2H, H4), 2.08-1.90 (s, 3H, H10).



23



24

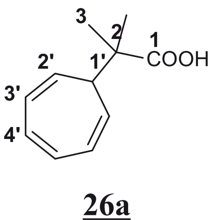
Acids derived from cycloheptatriene

General procedure

Tropylium tetrafluoroborate (TTFB) **25** was suspended in a round bottom flask containing dichloromethane (50 mL) cooled to 0 °C. A ketene acetal was then added dropwise and the mixture stirred at room temperature for a further 12 h. The reaction mixture was then poured into water, the organic layer washed with a saturated solution of brine and finally dried over Na_2SO_4. Purification *via* column chromatography on silica gel gave the expected acids.

2-(cyclohepta-2,4,6-trienyl)-2-methylpropionic acid 26a (R^2=R^3=CH_3)

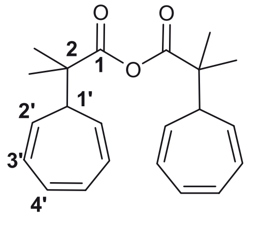
TTFB **25** (2.8 mmol, 500 mg); **3a** (4.2 mmol, 1 mL). Evaporation of the solvent followed by silica gel chromatography led first to the anhydride **27** (38 mg, 5 %, white solid, mp 76 °C) then to the acid **26** ((R^2=R^3=CH_3, 350 mg, 71 %), white solid acid, mp 86 °C.



26a

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 6.82 (m, 2H, H4',H5'), 6.4 (m, 2H, H3',H6'), 5.5 (m, 2H, H2'), 2.2 (s, 1H, OH), 1.8 (m, 1H, H1'), 1.46 (s, 6H, $(C\underline{H}_3)_2$). **^{13}C** NMR($CDCl_3$, 100 MHz) δ ppm: 184.2 (C1), 131.3 (C4', C5'), 125.5 (C3', C6'), 122.7 (C2', C7'), 47.29 (C1'), 43.6 (C2), 23.2 ($(\underline{C}H_3)_2$). **HRMS** Calcd for $C_{11}H_{15}O_2$, 179.1072; found, 179.1069.

2-(cyclohepta-2,4,6-trienyl)-2-methylpropionic anhydride 27

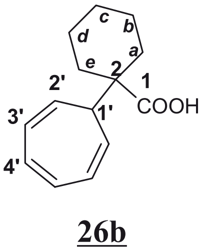


27

^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 6.64 (m, 2H, H2'), 6.21-6.15 (m, 2H, H3'), 5.24-5.16 (m, 2H, H4'), 1.65-1.60 (m, 1H, H1'), 1.30 (s; 6H, $2C\underline{H}_3$). **^{13}C** NMR ($CDCl_3$, 50 MHz) δ ppm: 172.6 (CO), 131.1 (C4'), 125.6 (C3'), 121.7 (C2'), 46.2 (C1'), 45.1 (C2), 22.1 ($2\underline{C}H_3$). **Anal.** Calcd for $C_{22}H_{26}O_3$: C, 78.10%; H 7.6 %. Found: C, 78.03%; H 7.82%.

1-(cyclohepta-2,4,6-trienyl)cyclohexanecarboxylic acid 26b (R^2R^3=$(CH_2)_5$)

-Tropylium tetrafluoroborate **25** (1.4 mmol, 250 mg); **3b** (1.8 mmol, 500 mg). Evaporation of the solvent followed by silica gel chromatography led to the acid **26b** (R^2R^3=$(CH_2)_5$), 150 mg, 49 %, white solid, mp 130°C).



26b

^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 6.70-6.67 (m, 2H, H4'), 6.25 (d, 2H, H3', J = 7.8Hz), 5.50 (dd, 2H, H2', J = 7.8Hz, J = 10.5Hz), 2.33-2.29 (m, 2H, H1', He), 1.66-1.26 (m, 9H, He', Ha-d). **^{13}C** NMR ($CDCl_3$, 50 MHz) δ ppm: 182.7 (C2), 130.9(C4'), 125.0 (C3'), 121.5 (C2'), 47.8 (C1), 47.5 (C1'), 32.2 (Ca, Ce), 25.8(Cc), 23.1 (Cb, Cd). **HRMS** Calcd for $C_{14}H_{19}O_2$, 219.1381; found, 219.1385. **Anal** for $C_{14}H_{18}O_2$, calcd: C, 77.06%;H, 8.25%. Found: C, 74.71%; H, 8.38%.

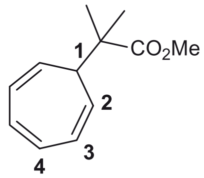
Synthesis of esters 29 derived from cycloheptatriene

General procedure

Tropylium tetrafluoroborate **25** was suspended in a round bottom flask containing dichloromethane (50 mL) cooled to

0 °C. A ketene acetal was then added dropwise and the mixture stirred at room temperature for a further 12 h. The reaction mixture was then poured into water, the organic layer washed with a saturated solution of brine and finally dried over Na_2SO_4. Purification *via* column chromatography on silica gel gave the expected esters **29**.

2-(cyclohepta-2,4,6-trienyl)-2-methylpropionic acid methyl ester 29a (R^2=R^3=R=CH_3)
Tropylium tetrafluoroborate **25** (22.5 mmol, 4 g), **28a** (R^2=R^3=R=CH_3, 26 mmol, 4.5 mL). Led to an oil after purification (3.5 g, 92%).



29a

^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 6.73-6.66 (m, 2H, H4), 6.29-6.23 (m, 2H, H3), 5.39-5.32 (m, 2H, H2), 3.71 (m, 4H, O$\underline{CH_3}$ and H1), 1.41 (s, 3H, CH_3), 1.36 (s, 3H, CH_3).

1-(cyclohepta-2,4,6-trienyl) cyclohexanecarboxylic acid methyl ester 29b (R^2R^3=$(CH_2)_5$, R=CH_3)
Method a
TTFB **25** (19 mmol, 3.85 g) , **28b** (R^2R^3= $(CH_2)_5$, R=CH_3, 21 mmol, 4.6 g). Led after purification to an oil (3.1 g, 70%).

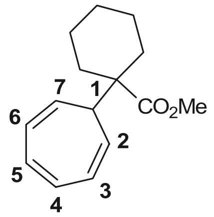
Method b

Flask 1
To a solution of THF (10 mL) and *n*BuLi 1.6 M (10.5 mL), at –78°C was added diisopropylamine (2.3 mL, 16.8 mmol). The mixture was stirred at the same temperature for 15 min.

Flask 2
28b (R^2R^3= $(CH_2)_5$, R=CH_3, 2.4 mL) was dissolved in THF (10 mL).

Flask 3
TTFB **25** (3 g) was suspended in THF (10 mL) and the mixture cooled and stirred at –78°C.

The solution of Flask 1 was transferred via a cannula into Flask 2 and the mixture stirred at –78°C for 15 mn. Then the solution of Flask 3 was added to the Flask 2. The mixture was then allowed to warm to room temperature and stirred at the same temperature until all the TTFB had disappeared. Finally, the solvent was evaporated and the mixture extracted with diethyl ether to lead to an oil which was purified by silica gel chromatography. The pure ester 29b (R^2R^3= $(CH_2)_5$, R=CH_3, 2.2 g, 59%) was obtained as an oil.



29b

^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 6.72-6.69 (m, 2H, H4, H5), 6.27-6.21 (m, 2H, H3, H6), 5.50-5.42 (m, 2H, H2, H7), 3.74 (s, 4H, H1, O$\underline{CH_3}$), 1.68-1.29 (m, 10H, cyclohexyl).

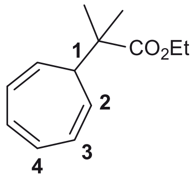
2-(cyclohepta-2,4,6-trienyl)-2-methypropionic acid ethyl ester 29c (R^2=R^3= CH_3, R=C_2H_5)
This ester was synthesized according to the aforementioned two methods:

Method a

TTFT **25** (16.3 mmol, 3 g); **28c** (R^2=R^3= CH_3, R=C_2H_5, 18 mmol, 3.3 g) ; CH_2Cl_2 (50 mL). Led to an oil (2.1 g 64.5%).

Method b

Diisopropylamine (111 mmol, 1 mL); *n*BuLi 2.5 M (17 mmol,7.1 mL); THF (20 mL); ethylisobutyrate (11 mmol, 1.3 g); TTFT **25** (11 mmol, 2 g). Led to the ester **29c** (1.9 g, 83%).



29c

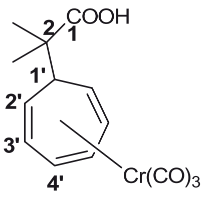
^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 6.66 (bs, 2H, H4), 6.20 (bs, 2H, H3), 5.32 (bs, 2H, H2), 4.18- 4.14 (m, 3H, $\underline{CH_2}$, H1), 1.25-1.13 (m, 9H, 3CH_3). **^{13}C** NMR ($CDCl_3$, 50 MHz) δ ppm: 177.1 (CO ester), 130.9 (C4, C5), 125.0 (C3,6), 122.6 (C7,2), 60.6 (O$\underline{C}H_3$), 47.1 (C1), 43.2 (Cq), 22.9 (($\underline{C}H_3)_2$), 14.2 ($\underline{C}H_3CH_2O$). **HMRS** Calcd for $C_{13}H_{19}O_2$ 207.1385; found, 207.1379.

Synthesis of the cycloheptatrienetricarbonylchromium complexes

General procedure

Chromium hexacarbonyl in THF (20 mL) and dibutylether (80 mL) was refluxed 4 days in the presence of the triene. After evaporation of the solvents, the residue was chromatographed on silica gel to give the expected complex.

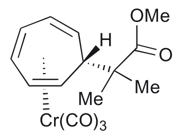
[2-(η^6-cyclohepta-2,4,6-trienyl)-2-methylpropionic acid] tricarbonylchromium 31 (R^2=R^3=CH_3)
Chromium hexacarbonyl (9.1 mmol, 2 g); **26a** (R^2=R^3=CH_3, 12.5 mmol, 2.2 g). Evaporation of the solvents followed by silica gel chromatography led with 15% AcOEt/ 85% P.E. to a red solid (723 mg, 25%) mp, 184 °C (dec).



31

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.08 (s, 2H, H4'), 4.94 (s, 2H, H3'), 3.17 (s, 2H, H2'), 1.23-1.15 (m, 7H, $(C\underline{H}_3)_2$, H$^{1'}$). **^{13}C** NMR ($CDCl_3$, 75 MHz) δ ppm: 230.5 (CO metal), 182.4 (CO acid), 98.2 (C4'), 97.9 (C3'), 54.7 (C2''), 43.6 (C2), 41.2 (C1'), 21.9 ($(\underline{C}H_3)_2$). **HRMS** Calcd for $C_{14}H_{14}O_5Cr$: 314.0246. Found, 314.0245.

_[2-(η^6-cyclohepta-2,4,6-trienyl)-2-methyl-propionic acid methyl ester] tricarbonylchromium 33a (R^2=R^3=R=CH_3).
Chromium hexacarbonyl (23 mmol, 5.2g); **29a** (R^2=R^3=R=CH_3, 23mmol, 4.5 g). Elution with 70% CH_2Cl_2 / 30% P.E. led to a red solid (4.16 g, 55%).

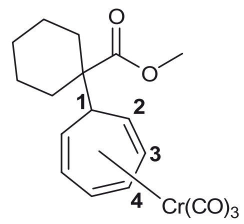


33a

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 5.83 (s, 2H, H4); 5.09 (s, 2H, H3); 3.69 - 3.61 (m, 4H, H^1, $OC\underline{H}_3$); 3.16 (s, 2H,H2), 1.27 (s, 6H, $(C\underline{H}_3)_2$). **^{13}C NMR**($CDCl_3$, 75 MHz) δ ppm: 230.54 (CO metal), 180.00 (CO ester), 98.24 (C3), 97.90 (C4), 55.09 (C2), 52.38 (C1), 46.23 ($\underline{C}(CH_3)_2$), 41.01 ($O\underline{C}H_3$), 21.98 ($(\underline{C}H_3)_2$). **HMRS** Calcd for $C_{15}H_{16}O_5Cr$, 328.0403. Found: 328.0408.

1-(η^6-cyclohepta-2,4,6-trienyl)-cyclohexancarboxy]tricarbonylchromium acid methyl ester 33b R^2R^3=(CH_2), R=CH_3)
Chromium hexacarbonyl (16.4 mmol, 3.6 g); **29b** (R^2R^3=$(CH_2)_5$, R=CH_3, 13.4 mmol, 3.1 g). Led to a red solid (4.4 g, 89%).

Silica gel chromatography allowed to obtain pure fractions of both isomers which were recrystallized from dichloromethane/hexane solutions.



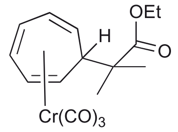
Exo isomer **32b**: red crystals, mp 132 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 5.85 (bs, 2H, H4), 4.98 (bs, 2H, H3), 3.68 (bs, 2H, H2), 3.47 (s, 3H, $OC\underline{H}_3$), 3.27 (bs, 1H, H1), 1.80-1.05 (m, 10H, cyclohexyl).

Endo isomer **33b**: red crystals, mp 176 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.80 (m, 2H, H4), 4.95 (m, 2H, H3), 3.80 (s, 3H, OCH_3), 3.32 (dd, 2H, H2), 2.25 (m, 2H, cyclohexyl), 1.63 (m, 4H, cyclohexyl), 1.23-1.06 (m, 4H, cyclohexyl), 0.86 (t, J = 4Hz, 1H, H1). **HRMS** Calcd for $C_{16}H_{18}O_5Cr$: 342.0559; found: 342.0555.

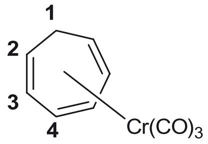
2-(η^6-cyclohepta-2,4,6-trienyl)-2-methyl-propionic acid ethyl ester]tricarbonylchromium 33c (R^2=R^3= CH_3, R=CH_2CH_3).
Chromium hexacarbonyl (22 mmol, 5 g); **29c** (R^2=R^3= CH_3, R=CH_2CH_3, 24.2 mmol, 5g). Led to a red solid (3.96g, 52 %), mp 74 °C.



Endo isomer: **32c.**

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.89 (bs, 2H, H4), 4.93 (bs, 2H, H3), 4.17-4.04 (m, 3H, H1 y $C\underline{H}_2$), 3.14-3.12 (m, 2H, H2), 1.09 (bs, 9H, $3C\underline{H}_3$). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 230.4 (CO metallic), 177.0 (CO ester), 98.2 (C4), 97.9 (C3), 61.0 (CH_2), 55.2 (C2), 45.0 ($C(CH_3)_2$), 40.7 (C^1), 21.7 ($2CH_3$), 14.2 (CH_3 ester). **HRMS** Calcd for $C_{16}H_{18}O_5Cr$: 342.0559. Found: 342.0558.

η^6-Cycloheptatrientricarbonylchromium 20
Chromium hexacarbonyl (24.8 mmol, 5.47 g); cycloheptatriene (49.6 mmol, 4 mL). Under reflux for 48 h in THF/Bu_2O. Led to a red solid (5.1g, 90 %), mp 100 °C.



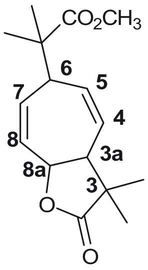
20

^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 6.1(s, 2H, H4); 4.87(s, 2H, H3); 3.44-3.36 (m, 2H, H2); 3.06-2.9 (m, 1H, H1 *exo*), 1.81-1.74 (d, 1H, H1 *endo*).

Synthesis of the [5.3.0] fused lactones

2-(3,3-dimethyl-2-oxo-3,3a, 6, 8a-tetrahydro-2H-cyclohepta[*b*]furan-6-yl)-2-methyl propionic acid methyl ester 34a (R^2=R^3=R^4=R^5= R=CH_3)

32a and **33a** (R^2=R^3=R=CH_3, 4 mmol (1.4 g); **3a (**8.5 mmol, 1.9 mL); 1M *t*-BuOK 1M in THF (8.5 mmol); I_2 (21.3 mmol, 5.42 g) in THF (20 mL). Leads to **34a** (0.7 g, 64%); white solid, mp 78 °C.

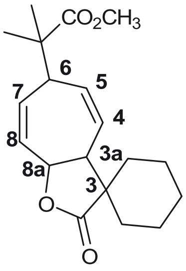


34a

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.81(d, 1H, H8, J = 12.6Hz), 5.68-5.52 (m, 2H, H7, H5), 5.50 (ddd, 1H, H4, J = 12.8, 5.5, 1.5Hz), 5.28(d, 1H, H8a, J = 7.3Hz), 3.66(s, 3H, $OC\underline{H}_3$), 3.33 (t, 1H, H6, J = 5.5Hz), 3.09 (t, 1H, H3a, J = 6.5), 1.25, 1.19, 1.17, 1.08 (4s, 12H, 4 $C\underline{H}_3$). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 181.4 (C2), 176.9 ($\underline{C}O$ ester), 131.7 (C8), 130.3 (C5), 129.2 (C7), 123.4 (C4), 77.6 (C8a), 52.0 ($O\underline{C}H_3$), 49.6 (C3a), 47.5 (C11), 47.2 (C6), 42.4 (C3); 24.0, 22.6, 22.2, 21.4 ($(\underline{C}H_3)_4$). **MS** (DCI+) m/z (%): 296 $[M+18]^+$ (100), 279 (4) $[M-1]^+$.

2-(3-spirocyclohexyl-2-oxo-3,3a,6,8a-tetrahydro-2H-cyclohepta[*b*]furan-6-yl)-2-methyl propionic acid methyl ester 34b (R^2=R^3=R=CH_3, R^4R^5=$(CH_2)_5$)

32a and **33a** (R^2=R^3=R=CH_3, 6 mmol 2 g); **3b** (12 mmol, 3.3 mL); 1M *t*-BuOK 1M in THF (12 mmol); I_2 (30 mmol, 7.6 g) in THF (20 mL). Silica gel chromatography led with 25% Et_2O/ 75% P.E.) to **34b** (0.9 g, 48%); white solid mp 126 °C.

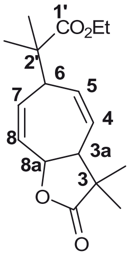


34b

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.82 (d, 1H, H8, J = 12.6), 5.68-5.65 (m, 2H, H7, H5), 5.53 (ddd, 1H, H4, J = 12.6, 5.8, 2.0Hz), 5.21 (d, 1H, H8a, J = 7.3Hz), 3.69 (s, 3H, OCH_3), 3.40 (t, 1H, H6 ,J = 5.8Hz), 3.07 (t, 1H, H3a, J = 6.8 Hz), 2.18-2.07 (m, 1H, H9), 1.80-1.35 (m, 9H, cyclohexyl); 1.16, 1.17 (2s, 6H, $(C\underline{H}_3)_2$). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 180.0 (C2), 177.1 (CO ester), 131.0 (C5), 130.9 (C8), 130.7 (C7), 124.0 (C4), 76.6 (C8a), 52.0 ($O\underline{C}H_3$), 49.7 (C3a), 47.0 (C3), 46.7 (C6), 45.4 ($\underline{C}(CH_3)_2CO_2Me$); 32.6, 30.3, 25.2 ($(\underline{C}H_2)_3$); 22.7, 22.1 ($2\underline{C}H_3$), 21.6, 21.3 ($2\underline{C}H_2$).

2-(3,3-dimethyl-2-oxo-3,3a,6,8a-tetrahydro-2*H*-cyclohepta[*b*]furan-6-yl)-2-methyl-propionic acid ethyl ester 34c (R^2=R^3=R^4=R^5=CH_3, R=C_2H_5)

32c and **33c** (R^2=R^3=CH_3, R=C_2H_5, 3 mmol 1 g); **3a** (3 mmol, 750 mg); 1M *t*-BuOK 1M in THF (3,2 mmol); I_2 (8 mmol, 2.2 g) in THF (20 mL). Silica gel chromatography led to **34c** (235 mg, 27.5 %) as an oil.

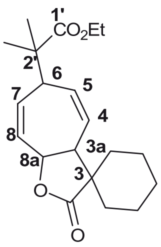


34c

^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 5.82 (d, 1H, H8, J = 12.5 Hz), 5.65 (m, 2H, H5, H7), 5.45 (ddd, 1H, H4, J = 12.5, 5.7, 1.7Hz), 5.30 (d, 1H, H8a, J = 7.3Hz), 4.09 (q, 2H, CH_2, J = 7.1Hz), 3.33 (m, 1H, H6), 3.08(m, 1H, H3a), 1.27-1.04 (m, 15H, $5CH_3$). **^{13}C NMR** ($CDCl_3$, 50 MHz) δ ppm: 181.9 (C2), 176.9 (CO ester), 132.0 (C4), 130.8 (C5), 129.7 (C7), 123.8 (C8), 78.1 (C8a), 61.1 (CH_2), 50.1 (C3a), 47.8 (C3), 47.5 (C6), 42.9 (C2'); 24.5,23.0, 22.5, 21.8 ($4CH_3$), 14.5 (CH_3 ester). **HRMS** Calcd for $C_{17}H_{25}O_4$ 293.1753; found, 293.1714.

2-(3-spiro-cyclohexyl-2-oxo-3,3a,6,8a-tetrahydro-2*H*-cyclohepta[*b*]furan-6-yl)-2-methyl-propionic acid ethyl ester. 34d (R^2=R^3=CH_3, R=C_2H_5, R^4R^5=$(CH_2)_5$)

32c and **33c** (R^2=R^3=CH_3, R=C_2H_5, 6 mmol (2 g); **3b** (9.9 mmol, 2.7g); 1M *t*-BuOK 1M in THF (10 mmol); I_2 (29 mmol, 3.81 g) in THF (20 mL). Silica gel chromatography led to **34d** (905 mg, 47%) as a solid mp, 110 °C.

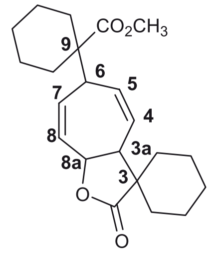


34d

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.80 (dd, 1H, H8, J = 12.2, 2.5Hz), 5.66 (m, 2H, H5, H7), 5.47(ddd, 1H, H4, J = 12.7, 6.0, 2.0 Hz), 5.18 (d, 1H, H8a, J = 7.1 Hz), 4.11 (q, 2H, CH_2, J = 7.1Hz), 3.37 (t, 1H, H6, J = 6.1Hz), 3.03 (t, 1H, H3a, J = 6.0Hz), 1.81-1.32 (m, 10H, cyclohexyl), 1.21 (t, 3H, CH_3 ester, J = 7.1Hz), 1.13-1.12 (2s, 6H, $(C\underline{H}_3)_2$). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 180.1 (C2), 176.5 (CO ester), 130.9 (C4, C5, C7), 124.0 (C8), 76.6 (C8a), 60.7 ($\underline{C}H_2$), 49.6 (C3a), 46.9 (C3), 46.5 (C6), 45.4 (C2'); 32.6, 30.3; 25.2, 22.7 (cyclohexyl); 22.0, 21.6 ($(CH_3)_2$); 21.4 (cyclohexyl); 14.1 (CH_3 ester). **Anal.** Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.06; H, 8.66.

(3-spirocyclohexyl-2-oxo-3,3a,6,8a-tetrahydro-2*H*-cyclohepta[b]furan-6-yl)-cyclohexanecarboxylic acid methyl ester 34e (R^2R^3= R^4R^5=$(CH_2)_5$, R=C_2H_5)

32b and **33b** (R^2R^3=$(CH_2)_5$, R=CH_3) 2.7 mmol 1 g); **3b** (5.1 mmol, 1.4 mL); 1M *t*-BuOK 1M in THF (5.1 mmol); I_2 (13.5 mmol, 3.4 g) in THF (20 mL). Silica gel chromatography led to **34e** (418 mg, 47 %) as a white solid.

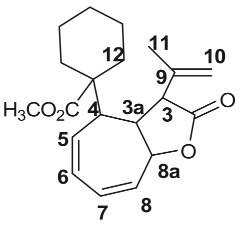


34e

^{1}H NMR ($CDCl_3$, 200MHz) δ ppm: 5.83-5.40 (m, 4H, H4, H5, H7, H8), 5.19 (d, 1H, H8a, J = 7.3Hz), 3.66 (s, 3H, $O\underline{CH_3}$), 3.14-3.11 (t, 1H, H6, J = 5.5Hz), 3.00 (t, 1H, H3a, J = 6.2Hz), 2.13-1.15 (m, 20H, cyclohexyl). **^{13}C NMR** ($CDCl_3$, 50MHz) δ ppm: 180.69 (C2), 176.02 (CO ester); 131.84, 131.01, 130.80, 124.63 (C4, C5, C7, C8), 78.13 (C8a), 52.69 (C9), 52.13 ($O\underline{C}H_3$), 49.62 (C3a), 47.53 (C6), 45.88 (C3); 32.95, 31.67, 30.87, 25.98, 23.81, 23.71, 22.09, 21.87 (cyclohexyl).

1-(3-isopropenyl)-2-oxo-3,3a,4,8a-tetrahydro-2H-cyclohepta[b]furan-4-yl)-cyclohexanecarboxylic acid methyl ester 36 (R^2R^3=$(CH_2)_5$, R=CH_3, R^4R^5=isopropenyl)

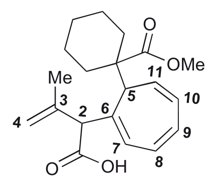
32b and **33b** (R^2R^3=$(CH_2)_5$, R=CH_3, 5.4 mmol 2 g); **35** (10.8 mmol, 1.4 mL); 1M *t*-BuOK 1M in THF (10 mmol); I_2 (21.7 mmol, 5.5 g) in THF (20 mL). Silica gel chromatography led to **36** (213 mg, 12%) as a white solid mp 132 °C.



36

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 5.97-5.91 (m, 1H, H6), 5.85-5.73 (m, 2H, H7, H5), 5.63 (dd, 1H, H8, J = 3.3,12.1 Hz), 5.30 (dd, 1H, H8a, J = 3.3, 7.3 Hz), 5.08 (s, 1H, H10), 4.84 (s, 1H, H10'), 3.66 (s, 3H, OCH_3), 2.70 (d; 1H, H3, J = 13.6 Hz), 2.45-2.40 (m, 1H, H3a), 2.28-2.15 (m, 1H, H4), 2.07-2.01 (m, 1H, H12), 1.68-1.55 (m, 6H, H11, cyclohexyl), 1.38-1.05 (m, 5H, cyclohexyl). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 175.7 (C2), 175.4 (CO ester), 137.6(C9), 130.7 (C5), 129.4 (C8), 126.9 (C6), 125.6 (C7), 118.6 (C10), 78.6 (C8a), 53.1(Cspiro), 51.9 ($O\underline{C}H_3$), 51.7 (C3), 46.2(C4), 42.8 (C3a), 33.5, 31.0, 25.4, 23.9, 23.3 (cyclohexyl), 18.4 C11).

2[7-(1-methoxycarbonylcyclohexyl]cyclohepta-1,3,5-trienyl]-3-methylbut-3-enoic acid methyl ester 37 (R^2R^3=$(CH_2)_5$, R=CH_3, R^4R^5=isopropenyl)



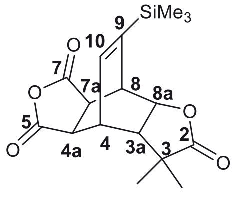
37

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 6.62-6.55 (dd, 1H, H8, J = 6.3, 10.6 Hz), 6.52-6.47 (dd, 1H, H9, J = 6.0, 10.6 Hz), 6.28 (d, 1H, H7, J = 6.3 Hz), 6.19-6.14 (dd,1H, H10, J = 6.0, 9.6 Hz), 5.17 (t, 1H, H11, J = 9.3 Hz), 4.76 (s, 1H, H4), 4.63 (s, 1H, H4'), 3.97-3.92 (m, 1H, H2), 3.52 (s, 3H, $OC\underline{H}_3$), 2.77 (d, 1H, H5, J = 9.3 Hz), 1.70 (s, 3H; CH_3), 1.67-1.20 (m, 10H, cyclohexyl). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 177.8 (C1), 174.9 (CO ester), 141.2 (C6), 137.1 (C3), 129.7 (C11), 128.9 (C8), 125.7 (C9), 121.7 (C10), 120.5 (C7), 115.8 (C4), 52.6 (C2), 51.8 ($O\underline{C}H_3$), 45.8 (C*spiro*), 35.9 (C5); 38.3, 34.5, 30.9, 25.3, 23.6 (cyclohexyl), 19.8 (C13).

Diels- Alder cycloadditions

3,3-Dimetyl-(4,8-ethene-9-trimethylsilyl-hexahydro)-1,6-dioxa-*s*-indacen-2,5,7-trienone 39a (R^2=R^3=CH_3)

A round bottom flask was loaded with lactone **18a** (R^2=R^3=CH_3, 0.4 mmol, 100 mg), maleic anhydride (1.5 mmol, 150 mg), Et_2O (10 mL) and the mixture stirred at room temperature for 120 h. Evaporation of the solvent followed by a silica gel chromatography led to **39a** ((R^2=R^3=CH_3, 31mg, 23%) as white crystals, mp 160 ºC.

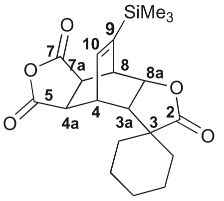


39a

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 6.57 (d, 1H, H10, J = 5.8 Hz), 4.86 (dd, 1H, H8a, J = 7.4, 3.6 Hz), 3.81 (s, 1H, H8), 3.28-3.26 (m, 1H, H4), 3.16 (td, 2H, H7a, H4a, J = 11.5, 8.8, 2.7 Hz), 2.20 (d, 1H, H3a, J = 7.4 Hz), 1.23 (s, 3H, CH_3), 1.23(s, 3H, CH_3), 0.04 (s, 9H, $(Si(C\underline{H}_3)_3)$). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ ppm: 180.28 (C2); 171.35, 171.15 (C7, C5), 147.40 (C9), 139.00 (C10), 75.65 (C8a), 49.13(C3a), 44.46 (C4a), 41.01 (C3), 40.67 (C7a), 38.92 (C8), 34.11 (C4); 29.38, 20.40$((\underline{C}H_3)_2)$, -2.66 $(Si(\underline{C}H_3)_3)$; **MS** (EI, 70 eV) m/z (%): 319 (100) $[M-15]^+$, 203 (18) $[M-131]^+$, 135 (30) $[M-199]^+$; **MS** (FAB^+) m/z (%) 335$[M-15]^+$ (65).

3-spirocyclohexyl-(4,8-ethene-9-trimethylsilyl-hexahydro)-1,6-dioxa-s-indacene-2,5,7-trienone 39b (R^2R^3=$(CH_2)_5$)

Lactone **18b** (R^2R^3=$(CH_2)_5$, 2.4 mmol, 680 mg); maleic anhydride (2.5 mmol, 250 mg). Led to **39b (**R^2R^3=$(CH_2)_5$, 90.7 mg, 10%) as a white solid.

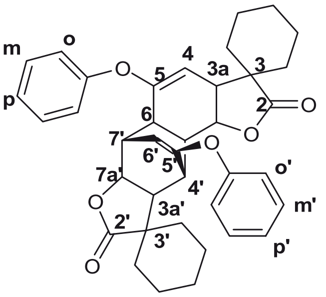


39b

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 6.56 (d, 1H, H10, J = 6.1Hz), 4.81 (dd, 1H, H8a, J = 7.0, 3.9 Hz), 3.81 (s, 1H, H8), 3.34 (s, 1H, H4), 3.17 (s, 2H, H7a, H4a), 2.32 (d, 1H, H3a, J = 7.0 Hz), 1.88-1.23 (m, 10H, cyclohexyl), 0.04 (s, 9H, $(Si (C\underline{H}_3)_3)$. **^{13}C NMR** ($CDCl_3$, 75 MHz) δ ppm: 179.56 (C2); 171.45, 171.24 (C7, C5), 147.55 (C9), 139.01 (C10), 75.50 (C8a), 46.63 (C3a), 44.70 (C4a), 40.47 (C7a), 39.07 (C8), 36.49 (C3), 33.07 (C4), 28.99, 25.18, 22.35, 22.00 $((\underline{C}H_3)_2)$, -2.68 $(Si(\underline{C}H_3)_3)$).

3-spirocyclohexyl-5-phenoxy-3a, 7a-dihydro-3*H*-benzofuran-2-one adduct 38

The lactone **7b** (R=Ph, R^2R^3=$(CH_2)_5$ was kept without solvent for a few days at room temperature. The evolution was followed by NMR which showed a complete transformation of the starting material into the adduct **38** as a white solid. Recrystallization from hexanes/ dichloromethane led to a white solid, mp 266 °C.



38

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.35 -7.37 (m, 4H, H*o*), 7.16 (t, 4H, H*m*), 6.96 (t, 2H, H*p*, J = 7.9Hz), 4.77(d, 1H, H4, J = 2.1Hz), 4.39 (dd, 1H, H7a', J = 7.1, 4.1Hz), 4.34 (dd, 1H, H6', J = 7.0, 2.4Hz), 4.25 (d, 1H, H7a, J = 4.4Hz), 3.66 (q, 1H, H4', J = 2.4Hz), 2.75 (dt, 1H, H7, J = 9.0, 2.4Hz), 2.63 (ddd, 1H, H7', J = 7.0, 4.1, 1.1Hz), 2.40 (dt, 1H, H3a, J = 4.4, 2.1Hz), 2.37 (d, 1H, H6, J = 9.0Hz), 2.22-2.14 (m, 2H, cyclohexyl), 2.10 (dd, 1H, H3a', J = 7.1, 2.4Hz), 1.98-0.95 (m, 18H, cyclohexyl). **^{13}C NMR** (C_6D_6, 100 MHz) δ ppm: 180.3, 178.7 (C2, 2'); 159.1, 156.7 (C5, C5'); 155.2, 154.6 (C*ipso,* C*ipso'*); 130.2, 130.1 (C*m,* C*m'*); 125.4, 124.8 (C*p,* C*p*'); 121.9, 121.5 (C*o,* C*o'*); 98.4, 94.9 (C4, C6'); 77.4, 77.3 (C7a, 7a'), 49.6 (C3a'), 46.8 (C3), 45.4 (C3a), 42.1 (C3'), 39.6 (C7'), 38.9 (C7, C4'), 36.1 (C6); 36.2, 31.4, 28.9, 28.1, 25.6, 25.5, 22.5, 22.3, 21.9 (cyclohexyl). **MS** (DCI^+) m/z (%): 593 (100) $M^{+\cdot}$, 547 (10) $[M-46]^+$, 499 (4)$[M-94]^+$, 297 (6) $[M-296]^+$, 251 (20) $[M-342]^+$. **HRMS** Calcd for $C_{38}H_{41}O_6$, 593.2903; found, 593.2909.

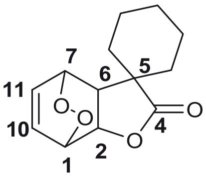
Synthesis of [4.3.0] endoperoxide lactones

General procedure

A pyrex reactor was loaded with the lactone in dichloromethane together with a catalytic amount of tetraphenylporphyrin. A steady flow of oxygen was bubbled through the solution while irradiated *via* a 400W Philipps lamp during 2 to 6 h. The purple solution was then evaporated to give an oil which was submitted to a silica gel column chromatography.

5-spirocyclohexyl-3,8,9-trioxa-tricyclo[5.2.2.0]^{2,6}undec-10-en-4-one 40a (R=H, R^2R^3=$(CH_2)_5$)

3.3 mmol (710 mg) of lactone **14b** (3.3 mmol,710 mg); TPP (0.059 mmol, 36 mg); CH_2Cl_2 (150 mL). This led after chromatography to the endoperoxide **40a** (634 mg, 95%) as a white low-melting solid.

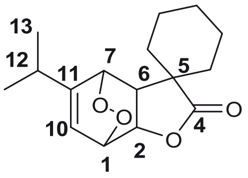


40a

^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 6.80 (t, 1H, H11, J = 7.9 Hz), 6.60-6.56 (m, 1H, H10), 5.10 (d, 2H, H2, H1, J = 5.5 Hz), 4.79 (dd, 1H, H7, J = 7.0, 3.0 Hz), 3.05 (dd, 1H, H6, J = 7.0, 3.0 Hz), 1.76-1.28 (m, 10H, H cyclohexyl). **HRMS** Calcd 254.1392; found, 254.1395 for $C_{13}H_{16}O_2 + NH_3$.

5-spirocyclohexyl-11-isopropyl-3,8,9-trioxa-tricyclo [5.2.2.0] undec-10-en-4-one 40b (R=iPr, R^2R^3=$(CH_2)_5$)

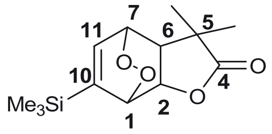
Lactone **14d (**2.9 mmol, 720 mg); TPP (5.2×10^{-5} mol, 30 mg); CH_2Cl_2 (35 mL). Gave a white solid (256 mg, 32%)



40b

^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 6.18 (d, 1H, H10, J = 6Hz), 4.99 (dddd, 2H, H1, H7, J = 7.0, 6.0, 4.8, 1.5 Hz), 4.65 (bs, 1H, H2), 3.09 (dd, 1H, H6, J = 7.0, 3.4 Hz), 2.41 (sep., 1H, H12, J = 6.7 Hz), 1.64-1.12 (m, 16H, H13, cyclohexyl). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ ppm: 180.23 (C4); 151.21 (C11); 120.58 (C10); 74.28 (C2); 71.30 (C7); 70.23 (C1); 44.80 (C6); 44.37 (C5); 35.70, 31.97, 27.92, 25.10, 23.13, 22.38, 21.91, 19.24 (C12, 13, cyclohexyl). **MS** (EI, 70 eV) m/z (%):278 (2) $M^{+\cdot}$, 246 (45) $[M-32]^+$, 201 (30)$[M-77]^+$, 123(100)$[M-155]^+$, 110 (65) $[M-168]^+$, 95 (49) $[M-183]^+$. **IR** n (cm^{-1}) : 2939, 2861 (=CH); 1768 (CO lactone), 1189 (CO), 1030 (C-O-O), 925 (O-O).

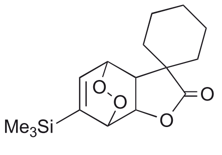
5,5-Dimethyl-10(trimethyl-silanyl)-3,8,9-trioxa-tricyclo[5.2.2.0]-undec-10-en-4-one 41a (R^2=R^3=CH_3)
Lactone **18a (**R^2=R^3=CH_3, 1.2 mmol, 284 mg); TPP (0.05 mmol,13 mg); CH_2Cl_2 (150 mL). Silica gel chromatography gave with 40% Et_2O / 60% P.E. **41a** (129 mg, 40%) as a white solid, mp 154 °C**.**



41a

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 6.75 (d, 1H, H11, J = 5.8 Hz), 4.94-4.89 (m, 2H, H2, H1), 4.37 (bs, 1H, H7), 2.65 (dd, 1H, H6, J = 6.5, 3.2 Hz), 1.15 (bs, 3H, CH_3), 0.98 (s, 3H, CH_3), 0.00 (s, 9H, Si$\underline{Me}_3$). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 180.2 (C4), 146.2 (C10), 138.1 (C11), 72.6 (C1), 70.6 (C7), 70.00 (C2), 46.2 (C6), 40.1 (C5), 28.7 (CH_3), 19.0 (CH_3), -2.6 (Si$\underline{Me}_3$). **HRMS** Calcd for $C_{13}H_{21}O_4Si$: 269.1209 found 269.1207.

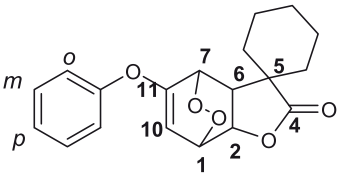
5-spirocyclohexyl-10-(trimethyl-silanyl)-3,8,9-trioxa-tricyclo[5.2.2.0]undec-10-en-4-one 41b (R^2R^3=$(CH_2)_5$)
Lactone **18b** (R^2R^3=$(CH_2)_5$), 1.36 mmol, 377 mg); TPP (0.03 mmol, 21 mg); CH_2Cl_2 (150 mL). Silica gel chromatography led with 30% Et_2O/70%P.E.) to a white solid **41** (159 mg, 38%).



41b

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 6.74 (dd, 1H, H11, J = 5.8, 1.0 Hz), 4.92-4.86 (m, 2H, H1, H2), 4.49 (t, 1H, H7, J = 3.0, 1.0 Hz), 2.82 (dd, 1H, H6, J = 6.8, 3 Hz), 1.71-1.06 (m, 10H, cyclohexyl), 0.00 (s, 9H, $Si(CH_3)_3$). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 179.6 (C4), 146.2 (C10), 138.1 (C11), 72.7 (C1), 70.0 (C2, C7), 44.3 (C5), 43.5 (C6); 35.7, 27.9, 25.0, 22.5, 21.8 (cyclohexyl), -2.6 (Si ($\underline{C}H_3)_3$. **HRMS**: Calcd for $C_{16}H_{25}O_4Si$, 309.1522; found, 309.1516.

5-spirocyclohexyl-11-phenoxy-3,8,9-trioxa-tricyclo [5.2.2.0] undec-10-en-4-one. 40c (R=OPh, R^2R^3=$(CH_2)_5$)
Lactone **7b** (R=Ph, R^2R^3=$(CH_2)_5$)**,** 2.4 mmol, 700 mg); TPP (0.02 mmol, 20 mg); CH_2Cl_2 (150 mL). Purification by silica gel chromatography led with 30% Et_2O/70% P.E. to a white solid **40c** (460 mg, 58%).



40c

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.30-7.25 (m, 1H, H*p*), 7.43-7.39 (m, 2H, H*m*), 7.10 (d, 2H, H*o*, J = 8.3 Hz), 5.09-5.05 (m, 3H, H1, H10, H2), 4.90 (bs, 1H, H7), 3.10 (dd, 1H, H6, J = 7.3, 3.5 Hz), 1.85-1.12 (m, 10H, cyclohexyl). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 180.2 (C4), 156.9 (C11), 153.0 (C*i*), 130.1 (C*m*), 125.8 (C*o*), 120.7 (C*p*), 97.1 (C10), 73.1 (C7), 72.0 (C1), 70.2 (C2), 44.9 (C5), 43.6 (C6); 35.5, 26.9, 24.9, 22.3, 21.8 (cyclohexyl). **HRMS** Calcd for $C_{19}H_{21}O_5$: 329.1389. Found: 329.1382.

5-t-Butyl-1-phenoxy-3,8,9-trioxa-tricyclo [5.2.2.0] undec-10-en-4-one 43 and 5-t-Butyl-11-phenoxy-3,8,9-trioxa-tricyclo [5.2.2.0] undec-10-en-4-one 44.
A solution of a 2:5 mixture of the enol ethers **7c** (R=OPh, R^2=H, R^3=*t*Bu) and **42** (400 mg) in dichloromethane (100 mL) was irradiated in the presence of TPP (10 mg) and a flow of oxygen for 1 h at room temperature. Evaporation of the solvent under vacuum led to a red oil which was chromatographed on silica gel. Elution with PE/ Et_2O 85:15 gave the enol ether **7**. Elution with PE/Et_2O led to **43** isolated as a solid (220 mg, 68%). mp 138 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.34-7.09 (m, 5H, ArH); 6.77 (dd, 1H, *J* = 5 and 3 Hz, H5); 6.48 (d, 1H, *J* = 5 Hz, H6); 4.79, d 1H, *J* = 4 Hz, H7^a); 4.66 *(*t, 1H, *J* = 2 Hz, H4); 3.27 (tt, *J* = 2 and 4 Hz, H3^a); 1.63 (d, 1H*, J* = 2 Hz, H3), 1.07 (s, 9H, 3 CH_3). **^{13}C NMR** ($CDCl_3$, 100 MHz) δ ppm: 175.8 (CO), 153.1 (CO), 133.31, 131.22, 129.58, 124.85, 121.36 (Ar, C=C), 102,56 (C7), 75.84 (C7^a), 74.47 (C4), 52.90 (C3^a), 41.10 (C3), 34.22 ($C(CH_3)_3$, 27.25 ($3CH_3$). **Anal**. for $C_{18}H_{20}O_5$: Calcd C, 67.39; H, 6.37. Found: C, 67.42; H, 6.52.

Elution with PE/Et_2O gave the endoperoxide **44** as an oil (30 mg).

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.38-7.05 (m, 5H, ArH), 5.01-4.96 (m, 2H, H1, H10), 4.83 (m, 1H, H2), 4.69 (m, 1H, H7), 3.14 (dt, 1H, H6), 2.08 (d, 1H, *J* = 2 Hz, H5), 1.12 (s, 9H, *t*Bu).

Determination of the cytotoxic activities

Cell cancer lines: colon cancer (HTC-15), breast cancer (MCF-7), leukemia (K-562 CML), central nervous system (U-251Glio) and prostate cancer (PC-3), were provided from the USA National Cancer Institute.

Cytotoxity data were determined using protein bonded SRB (sulphorhodamine) assay in a microculture, measuring cell growing, according with Monks method.

Cell lines were cultivated in RPMI-1640 media, 10% of foetal bovine serum, 2mM L-glutamine, 100 IU/mL penicillin G, 100mg/mL streptomycin sulphate and 0.25 mg/Ml of anphotericin B (Gibco). Incubation were done at 37 °C in a CO_2 atmosphere, 95% humidity. Following these procedure, cells were treated with 0.1% tripsine-EDTA mixture and they were counted in a hematocytometer diluted with media at a concentration of 5×10^4 cell/mL (K562, MCF-7), 7.5×10^4 cell/mL (U251, PC-3), and 10×10^4 cell/mL (HTC-15).

Microtiter plates were filled with 100 mg/mL cell suspension as well as incubated. After 24 h cells were treated with logarithmic concentrations of sample compounds employing as positive control doxorubicin. Test samples were first dissolved in DMSO to get a stock solution (40 mM) therefore diluted to 100, 31, 10, 3.1 and 1 mM solutions.

100 mg/mL of cell suspension was evaluated and added to each microtiter plate. After 48 h, cultures were fixed *in situ* adding 50 mL of 50% trichloroacetic acid (weigth/volume) and incubated 60 min at 4 °C. Supernatant was washed three times and dryed. Fixed cultures were combined with a 100 mL of 0.4% SRB solution (weigth/volume 1% acetic acid), during 30 min.

Not-linked SRB was removed upon washing with acetic acid 1% and the protein-linked dye was extracted using a 10 mM *tris*(hydroximethyl)methaneamine solution, optic densities were then registered at 515 nm wavelength. IC_{50} values were calculated according to Monks. Data points were taken in triplicate, standard error and mean of the three individual experiments were obtained.

Conclusion

The goal of this work was to get access rapidly, starting from conjugated π-systems, to new endoperoxide lactones: this has been achieved. Three major points warrant a special focus: first, the synthesis of the intermediate diene lactones has been generalized to a broad array of arenes thanks to improved, appropriate experimental procedures; second, in the case of the stable dienol-ether lactones, conditions for their clean transformation into synthetically useful conjugated ketones, have been established; and third, a series of new endoperoxide lactones, showing potent towards cancer cells cytotoxic activities, have been obtained. In the case of the cycloheptatriene derivatives, although access to new fused diene-lactones has been achieved, their further transformations remain a goal for coming research efforts.

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